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.

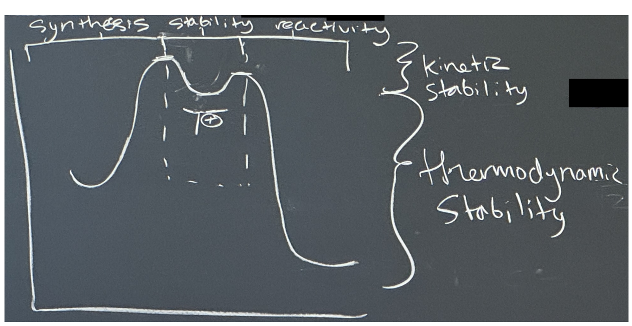


Figure 4.1: Phases in the life of a cation.

- 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.

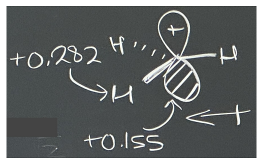


Figure 4.2: Cation structure.

- 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.

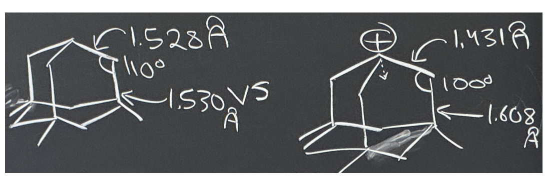


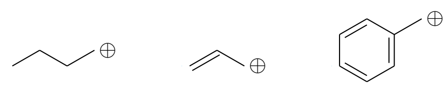
Figure 4.3: Evidence that carbocations exist.

- 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*

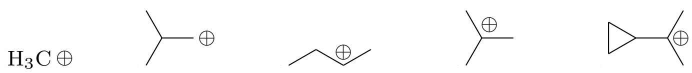
$$\mathrm{RH} \rightleftharpoons \mathrm{R}^+ + \mathrm{H}^- \qquad \Delta H^\circ = \mathrm{HIA}$$

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



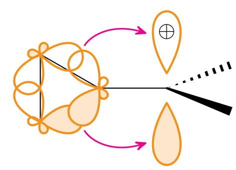
266 256 239

(a) The effect of resonance.

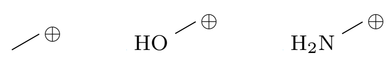


312 265 247 231 218

(b) The effect of hyperconjugation.



(c) Cyclopropyl stabilization.



273 243 218

(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).

[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.

	Bn−Br	**All−Br**	**^{i}Pr−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*

$$E^+ + Nuc^- \xrightarrow{k} Nuc{-}E$$

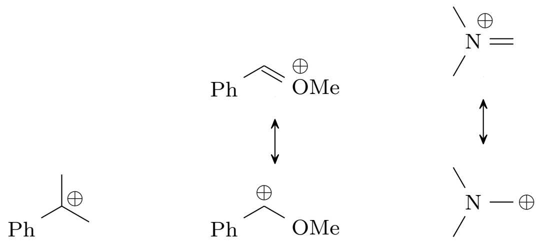
    - By Herbert Mayr from 5.47!
    - Mayr defined three parameters (S, N, and E) via the equation.

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

        - 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).

[2] Clarify??

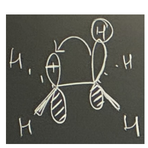
- Example Mayr electrophilicities.



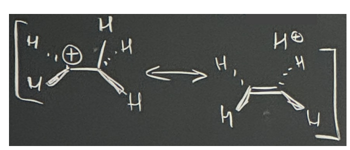
5.7 3.0 -6.5

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) $\sigma_{\text{CH}} \to p_{\text{C}}$ 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 $\sigma_{\text{CH}} \to p_{\text{C}}$ 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.

[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.

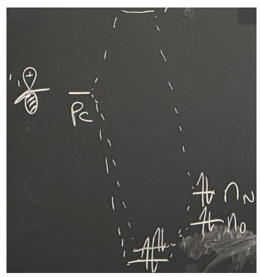


Figure 4.7: Stabilizing carbocations: Adjacent heteroatoms.

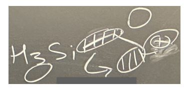
  - The high-energy empty *p*-orbital on carbon and low-energy heteroatom lone pair interact to form new bonding and antibonding MOs.
    - The bonding MO will be lower energy than the lone pair AO, so the electrons in that lone pair will be stabilized.
  - Nitrogen vs. oxygen stabilization: Rationalizing 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, $\text{EN}_{\text{C}} = 2.55$ and $\text{EN}_{\text{C}} = 2.20$, but $\text{EN}_{\text{Si}} = 1.90$.
      - 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.

[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.



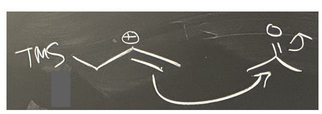
(b) HIA = 228 kcal/mol.

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 $\text{S}_\text{N}1$ and E_1.



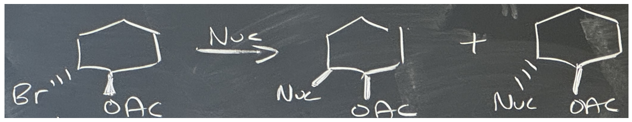
(b) Enabling allylations.

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

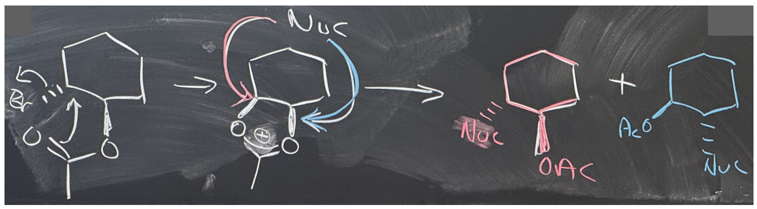
  – It can accelerate the departure of a leaving group by orders of magnitude (Figure 4.9a).
    - Suppose we have a trifluoroacetate leaving group on a cyclohexane ring in aqueous solution.
    - Locking $F_3CCO_2{}^-$ in the axial position with an equatorial *tert*-butyl group aids departure.
      - ➢ 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 ($\text{S}_\text{N}1$) or elimination (E_1).
    - If $k_{\text{rel}} = 1$ when R = H, then $k_{\text{rel}} = 2.4 \times 10^{12}$ 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.

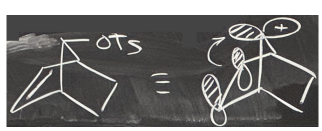


Figure 4.11: Homoconjugation.

[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.

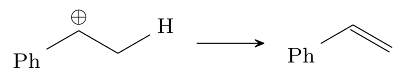


Figure 4.12: Carbocations acidify β-protons.

  - 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.

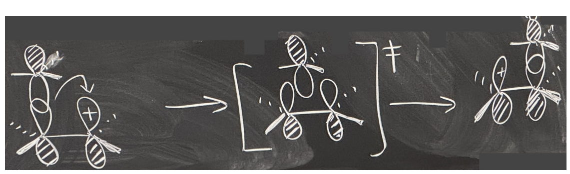
- Synthesis of carbocations: Two main ways.

(a) Ionization. (b) π-activation.

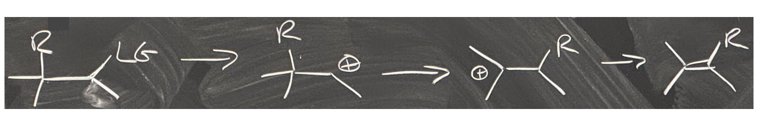
Figure 4.13: Synthesis of carbocations.

  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.



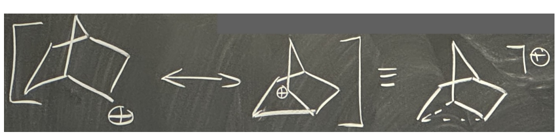
(b) General form of a rearrangement.

Figure 4.14: Reactions of cations.

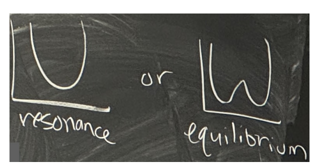
[6]Actually 11 orders of magnitude per Wikipedia.

- 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 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.