

# 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.

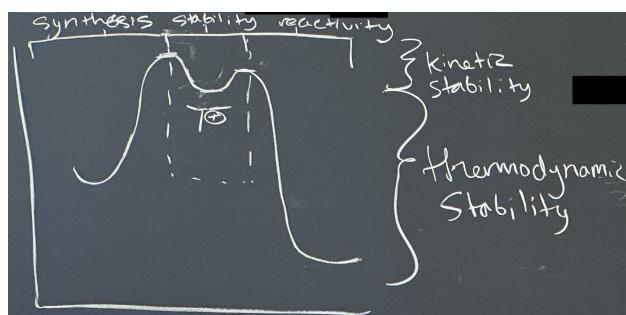


Figure 4.1: Phases in the life of a cation.

- 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.

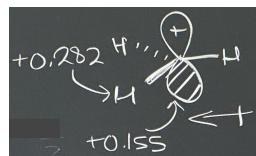


Figure 4.2: Cation structure.

- Figure 4.2 depicts a methyl cation ( $\text{CH}_3^+$ ).
- 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  $\delta^+$  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.

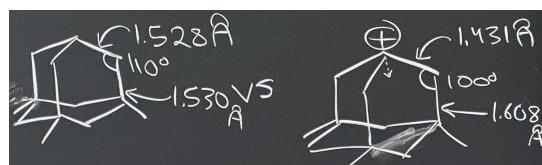


Figure 4.3: Evidence that carbocations exist.

- 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  $\alpha, \beta$  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*



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

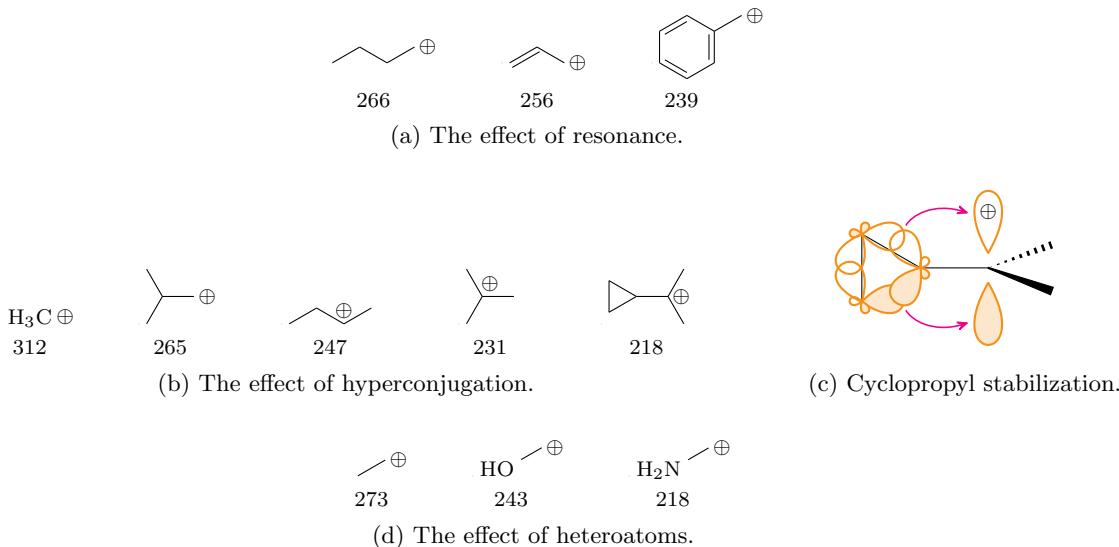


Figure 4.4: Hydride ion affinity examples.

- 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  $\sigma$ -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).

<sup>1</sup>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.

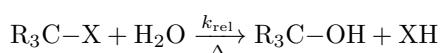
- Rates of **solvolysis**.

- Used all the time.

- 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*

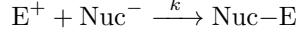


- Rates of solvolysis are reported as a relative rate constant  $k_{\text{rel}}$ .
- Comparing HIAs to rates of solvolysis.

	Bn-Br	All-Br	<i>i</i> Pr-Br
HIA ( $R^+$ )	239	256	249
$k_{\text{rel}}$	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.<sup>[2]</sup>
- 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*



- 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 “ $\text{Nuc}^-$ ” indicates a nucleophile, just like the more commonly used  $\text{Nu}^-$ .
  - 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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<sup>2</sup>Clarify??

- Example Mayr electrophilicities.

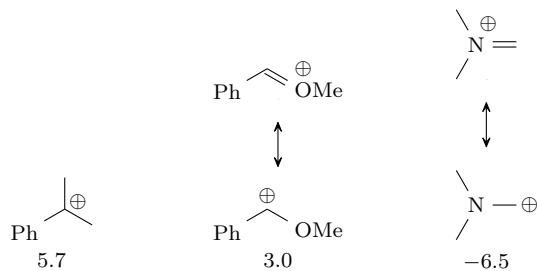
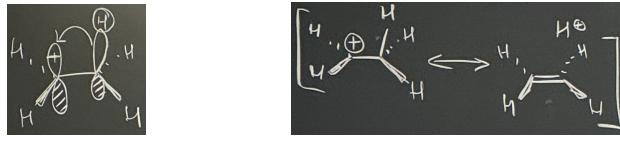


Figure 4.5: Mayr electrophilicity examples.

- 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  $3^\circ$  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  $\beta$ -silicon effect.
  4. The neighboring group effect.
- **Hyperconjugation:** The delocalization of electrons through  $\sigma$ -bonds.



(a)  $\sigma_{\text{CH}} \rightarrow p_{\text{C}}$  donation.

(b) No-bond resonance.

Figure 4.6: Stabilizing carbocations: Hyperconjugation.

- Hyperconjugation explains why substituted cations are more stable.
- Recall from 5.13<sup>[3]</sup> that the ethyl cation is stabilized by  $\sigma_{\text{CH}} \rightarrow p_{\text{C}}$  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.

<sup>3</sup>Figure 4.6a is just Figure 2.3a from Labalme (2024a).

- 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  $\sigma$ -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.

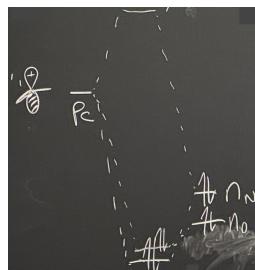


Figure 4.7: Stabilizing carbocations: Adjacent heteroatoms.

- 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.
- **$\beta$ -silicon effect:** The stabilization of positive charge at the position  $\beta$  to a silicon atom.
  - Caused by hyperconjugation.
  - Specifically, silicon is a better  $\sigma$ -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.<sup>[4]</sup>
  - Silicon is better because...
    - Silicon is less electronegative than other common  $\sigma$ -donors;
      - Indeed,  $EN_C = 2.55$  and  $EN_{\text{C}} = 2.20$ , but  $EN_{\text{Si}} = 1.90$ .
      - 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.

<sup>4</sup>Note that we do *not* mean that silicon is a better  $\sigma$ -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  $\sigma_{\text{CSi}}$  orbital is higher in energy than  $\sigma_{\text{CC}}$  orbital.
  - Thus, like in Figure 4.7, we get closer to the  $p_{\text{C}}$  energy level and have more effective overlap.
- Example HIA differences caused by the  $\beta$ -silicon effect.

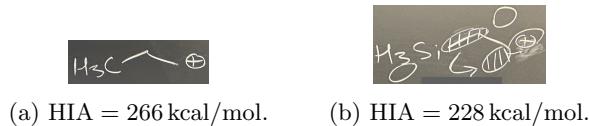


Figure 4.8: Hydride ion affinities subject to the  $\beta$ -silicon effect.

- Changing an alkyl cation to the direct silicon analogue alters the HIA by nearly 40 kcal/mol.
- Examples of how the  $\beta$ -silicon effect alters reactivity.

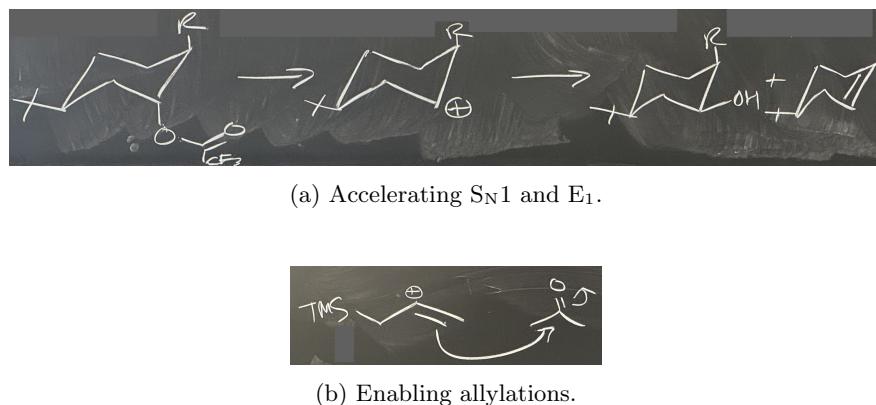


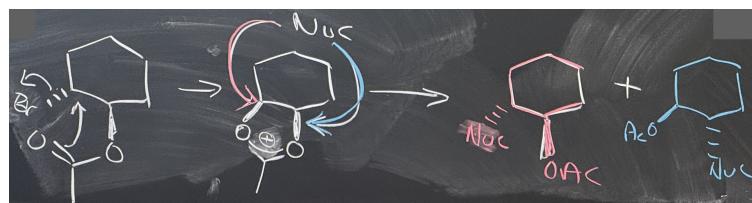
Figure 4.9: The  $\beta$ -silicon effect enables cationic reactivity.

- 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  $\text{F}_3\text{CCO}_2^-$  in the axial position with an equatorial *tert*-butyl group aids departure.
    - Specifically, if  $\text{R} = \text{SiMe}_3$ , the anomeric effect will significantly weaken the C–O bond.
  - Once  $\text{F}_3\text{CCO}_2^-$  leaves, the reaction completes through hydration ( $\text{S}_{\text{N}}1$ ) or elimination ( $\text{E}_1$ ).
  - If  $k_{\text{rel}} = 1$  when  $\text{R} = \text{H}$ , then  $k_{\text{rel}} = 2.4 \times 10^{12}$  when  $\text{R} = \text{SiMe}_3$ .
    - 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  $\beta$ -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<sub>N</sub>2: We'll see 100% *syn* and 0% *anti* product because S<sub>N</sub>2 is stereospecific.
    - The *syn* product will be enantiopure due to the stereoinverting nature of the attack.
  - If S<sub>N</sub>1: 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  $\pi$ -electrons. *Also known as anchimeric assistance.*
  - Note that the intramolecular pair of  $\pi$ -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  $\pi$ -system.<sup>[5]</sup>
- Example of homoconjugation.



Figure 4.11: Homoconjugation.

<sup>5</sup>This definition is consistent with the definition of homoconjugation as “an overlap of two  $\pi$ -systems separated by a non-conjugating group” because the carbocation counts as a  $\pi$ -system and the carbocation in Figure 4.11 is separated from the  $\pi$ -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  $\pi$ -orbitals can donate into the carbocation.
  - Something like 5 orders of magnitude faster.<sup>[6]</sup>
  - We're now done with carbocation stability, and we'll begin discussing their synthesis and reactivity.
  - Acidity.

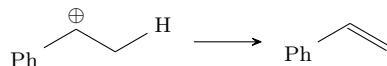
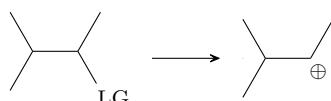
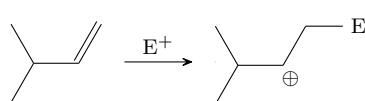


Figure 4.12: Carbocations acidify  $\beta$ -protons.

- Carbocations induce a dramatic acidification of  $\beta$  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)  $\pi$ -activation.

Figure 4.13: Synthesis of carbocations.

### 1. Ionization.

- This is just the departure of a leaving group.

## 2. Activation of a $\pi$ -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.

<sup>6</sup>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  $k_{1,2} = 3 \times 10^7 \text{ s}^{-1}$ , even at  $-139^\circ\text{C}$ .
    - The activation energy  $\Delta G_{1,2}^\ddagger \approx 3 \text{ kcal/mol}$ , 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.



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  $\sigma$ -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 stake.
- Takeaway from our discussion of nonclassical cations: Cations exist on a spectrum.

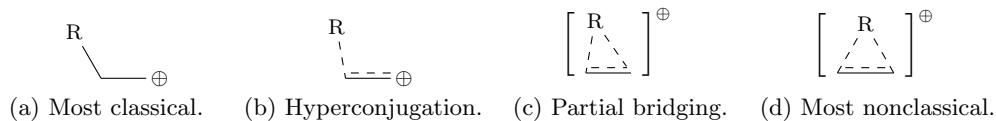


Figure 4.16: A spectrum of cations.

- 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.

## 4.2 Anions

9/26:

- Lecture 6 recap: Modes of cation stabilization.
  - Heteroatoms: Through lone-pair resonance.
  - Anchimeric assistance: With neighboring lone pairs (Figure 4.10b).
  - Homoconjugation: With nearby  $\pi$ -electrons (Figure 4.11).
  - Hyperconjugation: With adjacent  $\sigma$ -bonding orbitals. (Figure 4.6a).
- Announcements.
  - Don’t cheat on the PSet.
    - You can probably find papers or the key online, but be responsible academics instead.
    - PSets give you a chance to engage with the material; you will not learn if you cheat.
  - Ask for help if you can’t make the deadline.

- Today: Anions.
  - Lecture outline.
    - Acidity.
      - Gas phase.
      - Solution phase.
    - $pK_a$ 's.
      - Common ones.
      - Solvent effects.
      - Misc. influencing factors.
    - Anion structure and inversion.
    - Synthesis of carbanions.
    - Reactions of carbanions.
    - Kinetic vs. thermodynamic acidity.
  - Thermodynamic stability of an anion.
  - **Acidity** (gas phase): The extent to which anions want to bind a proton in the gas phase. *Given by*
- $$\text{R}-\text{H} \rightleftharpoons \text{R}^- + \text{H}^+ \quad \Delta H^\circ = \text{acidity}$$
- Similarities between this definition and that of the HIA!
    - Acidity is also always measured in the gas phase.
    - It is also more useful as a measure of relative stability.
  - Trends in (gas-phase) acidity are not always the same in solution.
  - Example gas-phase acidities.

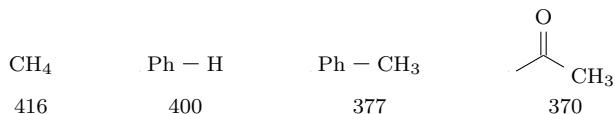


Figure 4.17: Gas phase acidity examples.

- We can intuitively rationalize these with resonance/EWG stabilization of the conjugate base.
  - **Acidity** (solution phase): The extent to which anions want to bind a proton in the solution phase. *Given by*
- $$\text{R}-\text{H}_{(\text{aq})} \rightleftharpoons \text{R}_{(\text{aq})}^- + \text{H}_{(\text{aq})}^+ \quad pK_a = \text{acidity}$$
- A refresher on what exactly “ $pK_a$ ” means.
    - The dissociation of an Arrhenius acid (exemplified by the above chemical equation) obeys the following mass action expression, where  $K_a$  is the **dissociation constant**.

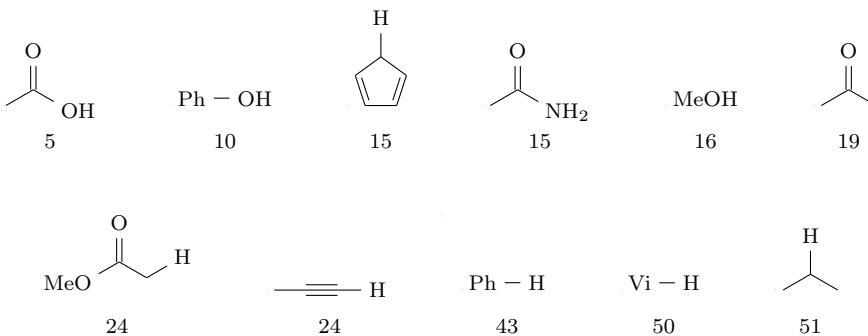
$$K_a = \frac{[\text{R}_{(\text{aq})}^-][\text{H}_{(\text{aq})}^+]}{[\text{RH}_{(\text{aq})}]}$$

- To look at the  $K_a$ 's in more human-readable units, we transform them to a log scale using the **p function**:

$$pK_a = -\log K_a \approx \Delta G$$

- Solution-phase acidity is a quantitative measure of anion stability.

- Some  $pK_a$ 's to know. (Memorize these!! These are the baseline, and they are a common qual question.).



- These are all measured in  $H_2O$ .
- These all come from the [Evans  \$pK\_a\$  table](#).<sup>[7]</sup>
- We should bookmark this page and refer to it regularly when we're trying to work out plausible mechanisms!!
- Solvent effects on the  $pK_a$ .

<b>R–H</b>	<b><math>pK_a</math> (<math>H_2O</math>)</b>	<b><math>pK_a</math> (DMSO)</b>
H–Cl	–8	1.8
PhCOOH	4.2	11.1
CH <sub>3</sub> NO <sub>2</sub>	10	17.2
H <sub>2</sub> O	15.7	32
H <sub>3</sub> CCN	25	31.3
CH <sub>2</sub> (CN) <sub>2</sub>	11	11

Table 4.2:  $pK_a$ 's in  $H_2O$  vs. DMSO.

- The  $pK_a$  of  $H_2O$  is about 15, so it is hard to get accurate measurements in  $H_2O$  for anything less acidic (higher  $pK_a$ ).
- One solution to this problem is to use DMSO as an alternate solvent.
  - The  $pK_a$  of DMSO is  $\approx 35$ .
  - This allows you to characterize a greater range of things.
  - DMSO is also very polar (like water), minimizing conflicting aggregation effects.
- All data on DMSO acidity comes from the [Bordwell  \$pK\_a\$  table](#).
- $pK_a$ 's are typically higher in DMSO than in water, as we can see in Table 4.2.
  - This is because  $H_2O$  is better at anion stabilization than DMSO, so the equilibrium is easier to access.
  - The trends are not always consistent, e.g., CH<sub>2</sub>(CN)<sub>2</sub>.
    - When  $pK_a$ s are similar in different solvents, this tends to be because the anion is being stabilized internally.
    - For example, the (CN)<sub>2</sub>HC<sup>–</sup> anion is stabilized by both resonance and  $\sigma$ -EWG inductive effects. Since it is internally stabilized, its stabilization is less dependent on solvent effects.

<sup>7</sup>Not all of Masha's values match the Evans table (e.g., cyclopentadiene is 18.0, not 15). Whose value should we memorize??

- Factors influencing a compound's solution-phase acidity.

1. Electronegativity.

- More electronegative atoms make acids stronger.
  - This is because electronegative atoms inductively (i.e., through the  $\sigma$ -network) withdraw electron density, stabilizing the negative charge through delocalization.
  - Example: HOAc and TFA have  $pK_a = 4.76$  and 0.52, respectively.

2. Hybridization.

- More  $s$ -character leads to a stronger acid.
  - Essentially, orbital electronegativity (and hence stability) decreases  $s > sp > sp^2 > sp^3$ .
  - This is because  $p$ -orbitals "feel" the  $\delta^+$  nuclear charge less, owing to their node at the nucleus. Therefore,  $s$ -orbitals are a better place for  $\delta^-$  charge to reside in.
  - Example:  $-\equiv H$ , Ph-H, and  ${}^iPr-H$  have  $pK_a = 24$ , 43, and 51, respectively.
  - This effect also extends to nitrogen.
    - Example: Protonated imines are more acidic than protonated amines because their conjugate bases (the neutral imine and amine) have lone pairs in  $sp^2$  vs.  $sp^3$  orbitals.
    - Example: Piperidine is more basic than pyridine because its lone pair is in a relatively destabilized  $sp^3$  orbital.
    - Good qual question: Use a hybridization argument to differentiate basicities/acidities!!

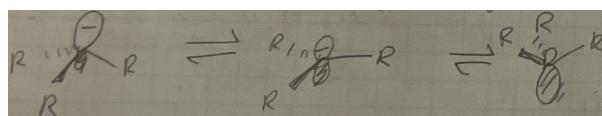
3. Delocalization and aromaticity.

- A more delocalized anion means a stronger acid.
- Example: Cyclopentadiene and cyclopropene have  $pK_a = 15$  and 61 because the former deprotonates to an aromatic anion and the latter deprotonates to an antiaromatic anion.

4. Orbital overlap with adjacent atoms.

- Donation into adjacent  $d$ - or  $\sigma^*$ -orbitals stabilizes anions.
- Example:  $R_3P^+ - \text{CH}_2^-$ .
  - This ylide has a relatively stable anion.
  - Ylides are especially stable when the adjacent atom is S or P; such ylides are synthetically useful (e.g., Swern oxidation and Wittig olefination).

- Anion structure.



(a) Rapid inversion.



(b) Resonance stabilized anions.

Figure 4.19: Anion structure.

- In general, anions are  $sp^3$ -hybridized, trigonal pyramidal species.
  - Recall that Figure 2.5 explains why anions are trigonal pyramidal instead of planar.
- Inversion is possible through a trigonal planar structure (Figure 4.19a).
  - The inversion barrier for carbanions is an *extremely* low 1-2 kcal/mol.
  - Because of this rapid inversion, anions behave as if they are planar even though they are not!
- Exception: Resonance stabilized anions are *actually* planar (Figure 4.19b).
  - This is because in these cases, the negative charge localizes to a  $p$ -orbital to have better overlap with the  $\pi$ -system with which it resonates.
  - This gives the carbanion atom an orbital structure of  $sp^2 + p$ .

- Some factors can raise the inversion barrier.
  1. Geometric constraints (i.e., incorporation into a small ring) raise the inversion barrier.
    - The planar structure of the ring requires some bond angles (e.g., between the anion lone pair and a substituent) to be larger than in the pyramidal structure.
    - Example: The cyclopropanide anion.
  2. More electronegative substituents raise the inversion barrier.
    - VBT explanation.
      - Electronegative groups prefer to bind to orbitals with more *p*-character (**Bent's rule**) since it's easier to "steal" those electrons because they're further from the nucleus.
    - MO theory explanation.
      - Consider the **D**-MO in Figure 2.5, which is the HOMO for an anion.
      - In the pyramidal structure, the *p*-AO in **D** will hybridize into an *sp*<sup>3</sup>-orbital, shedding some of its *p*-character. But per the "conservation of bonding character" discussed in Figure 2.14, this *p*-character will infuse the bonds to the (now electronegative) substituents.
      - Electronegative substituents then want this influx of *p*-character, lowering the energy.
      - Is this it, or am I missing something else??
- Other XR<sub>3</sub> structures with 8 electrons.
  - Consider H<sub>3</sub>C<sup>-</sup>, H<sub>3</sub>N, F<sub>3</sub>N, and H<sub>3</sub>P.
  - Their respective inversion barriers are 1-2 kcal/mol, 5 kcal/mol, 50 kcal/mol, and 35 kcal/mol.
  - Thus, H<sub>3</sub>C<sup>-</sup> and H<sub>3</sub>N are effectively planar, and F<sub>3</sub>N and H<sub>3</sub>P are pyramidal.
    - F<sub>3</sub>N is pyramidal due to its electronegative substituents.
    - H<sub>3</sub>P is pyramidal due to the HOMO of P being even more stabilized by its larger 3*p*-orbital.
    - Implication: We can have chirality at P, but rarely at N.
- Synthesis of carbanions: Two main ways.

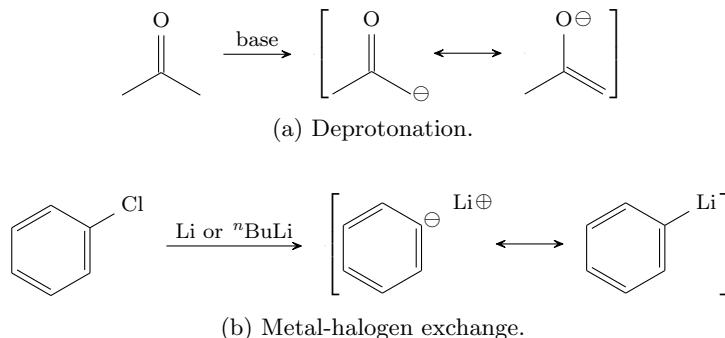


Figure 4.20: Synthesis of carbanions.

- A carbanion created by base deprotonation typically must be stabilized (e.g., by resonance).
- Metal-halogen exchange is typically used to create aryl, vinyl, and primary alkyl anions.
- Proton transfer and lithium-halogen exchange are among the fastest *intermolecular* reactions common in organic chemistry.
  - Some *intramolecular* reactions can be faster, e.g., 1,2-hydride shifts.
  - It is important to know such relative rates for reaction planning.
  - Caveat: Proton transfer from heteroatoms is much faster than proton transfer from carbon ( $k_{\text{rel}} \approx 10^6$ ). This is why we often talk about acidic X-H bonds, e.g., RCOOH.
- Note: B-H bonds are **hydridic** (think inorganic), not protic??

- Reactions of carbanions.

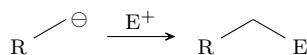
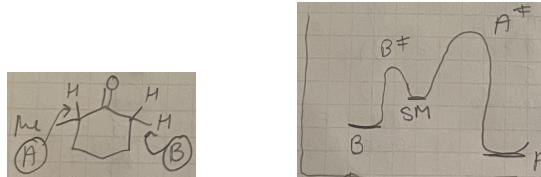


Figure 4.21: Reactions of carbanions.

- Anions are nucleophilic and basic.
- They react with electrophiles, such as protons and metals.
- Kinetic vs. thermodynamic acidity.



(a) Two deprotonation sites. (b) The energy diagram.

Figure 4.22: Energy differences governing kinetic and thermodynamic acidity.

- Rate of deprotonation varies based on whether our base attacks site A or B (Figure 4.22a).
- Site B has less steric clutter, so deprotonation is easier there.
  - This ease of deprotonation manifests as a lower energy  $\text{B}^\ddagger$  relative to  $\text{A}^\ddagger$  (Figure 4.22b).
  - To form this enolate, we should use a base such as LDA that is sterically bulky and has essentially irreversible deprotonation, so we will be under kinetic control.
- On the other hand, **Zaitsev's rule** tells us that the tetrasubstituted enolate we obtain by deprotonating at site A is more thermodynamically stable than the trisubstituted one we obtain by deprotonating at site B.
  - This difference in thermodynamic stability manifests as a lower energy  $\text{A}^\ddagger$  relative to  $\text{B}^\ddagger$  (Figure 4.22b).
  - To form this enolate, we should use a base such as an amine or alkoxide that has reversible deprotonation, so we eventually form the thermodynamic product.
- Great explanation of this phenomenon in Figures 5.3-5.7 (esp. Figures 5.5-5.6) of Labalme (2024b).
- **Zaitsev's rule:** The more substituted alkene is the more stable one.