

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.

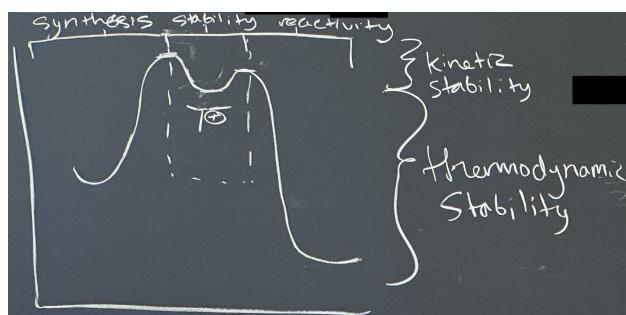


Figure 4.1: Phases in the life of a cation.

- 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 (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.

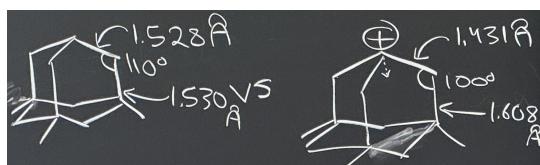


Figure 4.3: Evidence that carbocations exist.

- 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*



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

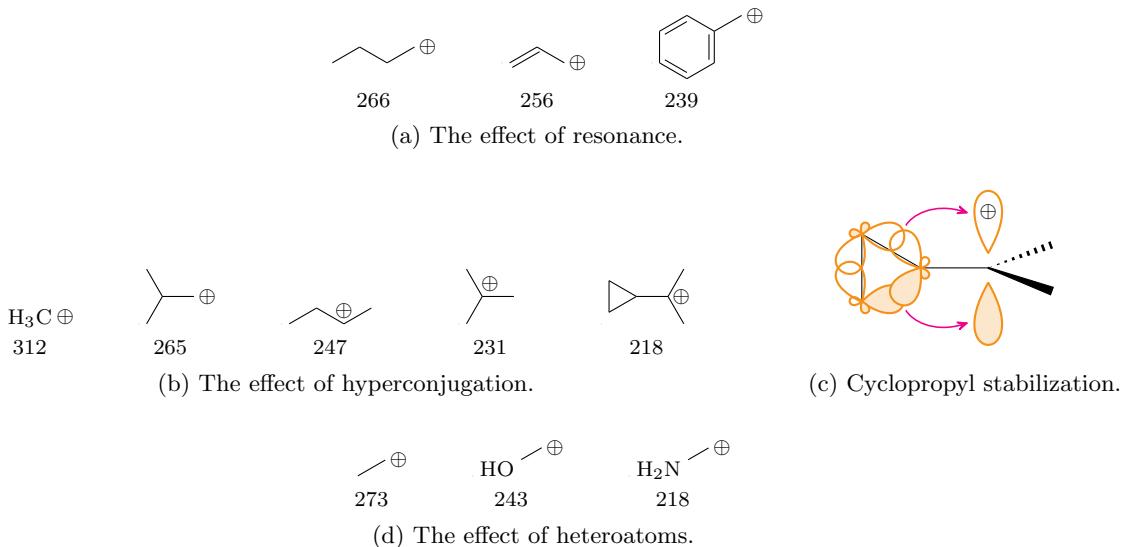


Figure 4.4: Hydride ion affinity examples.

- 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 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).

¹Relative 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.

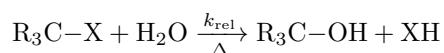
- Rates of **solvolysis**.

- 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_{rel} .

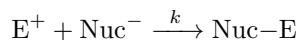
- Comparing HIAs to rates of solvolysis.

	Bn-Br	All-Br	<i>i</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*



- 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).

²Clarify??

- Example Mayr electrophilicities.

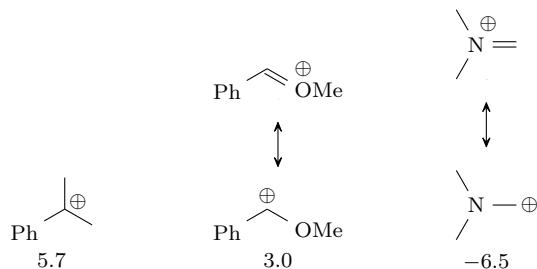
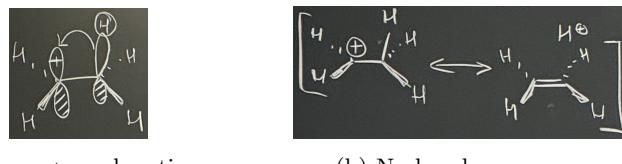


Figure 4.5: Mayr electrophilicity examples.

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

(b) No-bond resonance.

Figure 4.6: Stabilizing carbocations: Hyperconjugation.

- Hyperconjugation explains why substituted cations are more stable.
- Recall from 5.13^[3] 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.

³Figure 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 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.

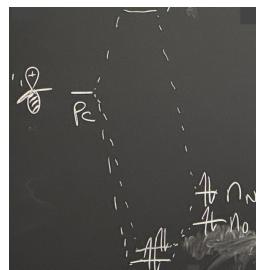


Figure 4.7: Stabilizing carbocations: Adjacent heteroatoms.

- 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, $EN_C = 2.55$ and $EN_C = 2.20$, but $EN_{Si} = 1.90$.
 - 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.

⁴Note 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.

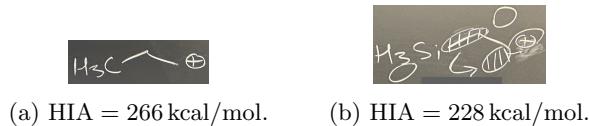


Figure 4.8: Hydride ion affinities subject to the β -silicon effect.

- 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.

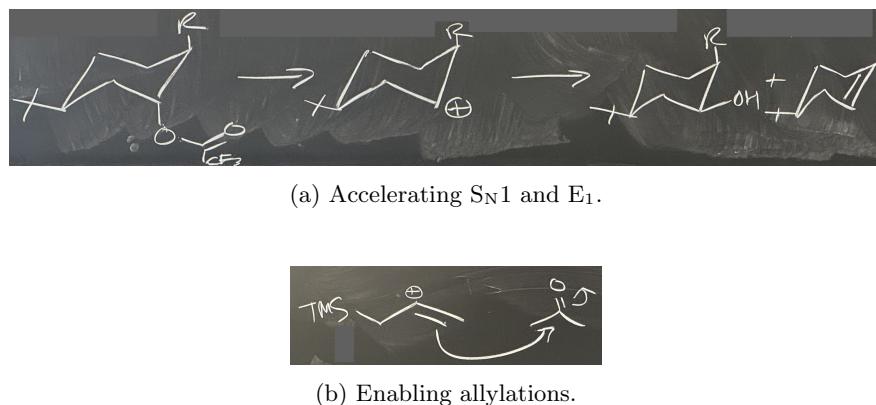


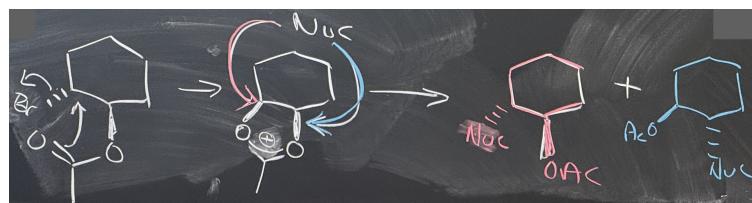
Figure 4.9: The β -silicon effect enables cationic reactivity.

- 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 $\text{R} = \text{SiMe}_3$, 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 $\text{R} = \text{H}$, 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 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.

⁵This 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.

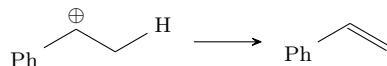
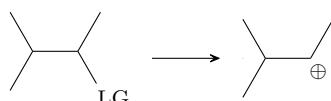
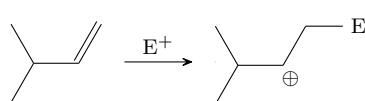


Figure 4.12: Carbocations acidify β -protons.

- 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.

⁶Actually 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°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.

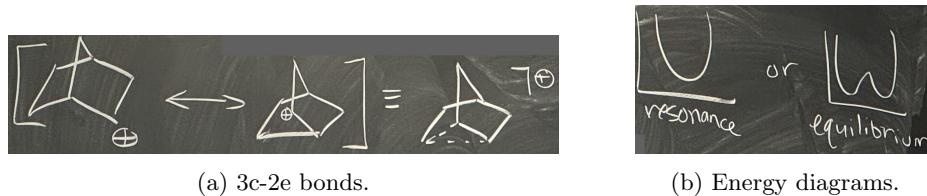


Figure 4.15: Nonclassical cations.

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

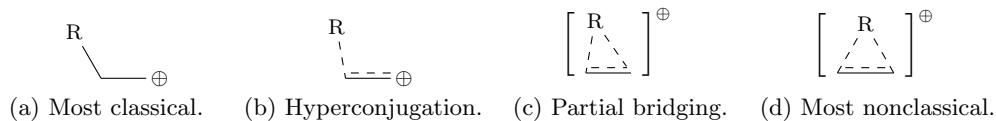


Figure 4.16: A spectrum of cations.

- 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 π -electrons (Figure 4.11).
 - Hyperconjugation: With adjacent σ -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.

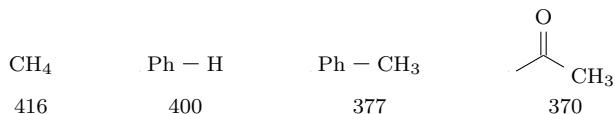


Figure 4.17: Gas phase acidity examples.

- 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**.

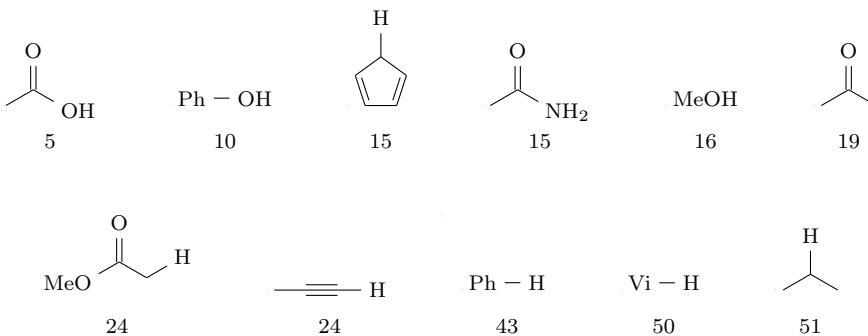
$$K_a = \frac{[\text{R}_{(\text{aq})}^-][\text{H}_{(\text{aq})}^+]}{[\text{RH}_{(\text{aq})}]}$$

- 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](#).^[7]
- 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 .

R–H	pK_a (H_2O)	pK_a (DMSO)
H–Cl	–8	1.8
PhCOOH	4.2	11.1
CH ₃ NO ₂	10	17.2
H ₂ O	15.7	32
H ₃ CCN	25	31.3
CH ₂ (CN) ₂	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 ≈ 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., CH₂(CN)₂.
 - When pK_a s are similar in different solvents, this tends to be because the anion is being stabilized internally.
 - For example, the (CN)₂HC[–] anion is stabilized by both resonance and σ -EWG inductive effects. Since it is internally stabilized, its stabilization is less dependent on solvent effects.

⁷Not 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 σ -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 δ^+ nuclear charge less, owing to their node at the nucleus. Therefore, s -orbitals are a better place for δ^- 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!!

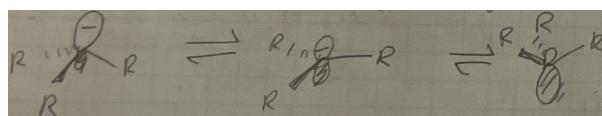
3. Delocalization and aromaticity.

- 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 σ^* -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 π -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*³-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 XR₃ structures with 8 electrons.
 - Consider H₃C⁻, H₃N, F₃N, and H₃P.
 - Their respective inversion barriers are 1-2 kcal/mol, 5 kcal/mol, 50 kcal/mol, and 35 kcal/mol.
 - Thus, H₃C⁻ and H₃N are effectively planar, and F₃N and H₃P are pyramidal.
 - F₃N is pyramidal due to its electronegative substituents.
 - H₃P 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.

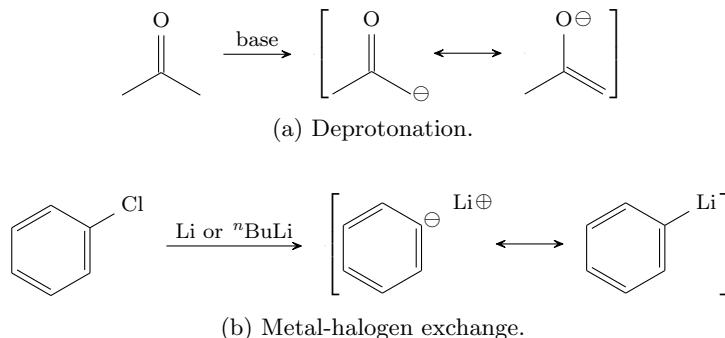


Figure 4.20: Synthesis of carbanions.

- 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.

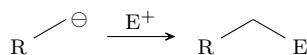
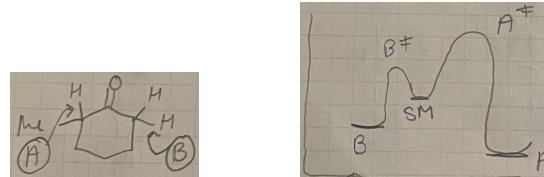


Figure 4.21: Reactions of carbanions.

- 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 B^\ddagger relative to 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 A^\ddagger relative to 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.