TOPIC 5. ORGANIC REACTIONS: ACIDS AND BASES

OBJECTIVES

1. Classify types of reaction:
   -Addition, Substitution, Elimination, Rearrangement
2. Define the concept of “Mechanism”
3. Discuss the thermodynamics (equilibrium) and kinetics (rate) of organic reactions
4. Describe acid-base reactions
5. Develop relationships between structure and acidity/basicity
6. Take a first look at acid-promoted reactions

CLASSIFYING REACTIONS

Reactions are conveniently classified as substitutions, additions, eliminations and rearrangements. These terms describe the *overall* process, simply comparing the structure of starting materials and products. They do not indicate anything about the *pathway* (“mechanism”) by which the reaction proceeds.

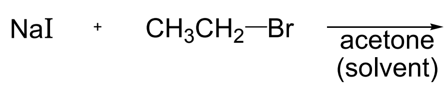
Substitutions

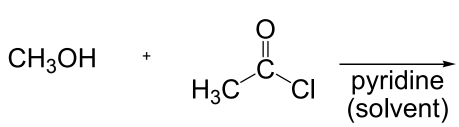
Additions

Eliminations

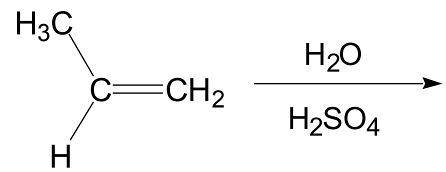
Rearrangements
(often in combination
with another type of reaction)

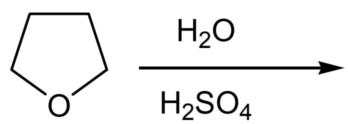
Substitution



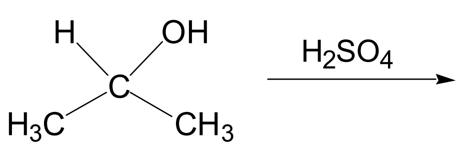


Addition

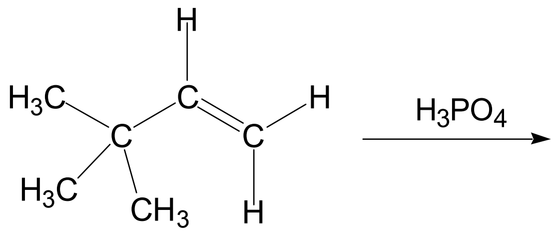




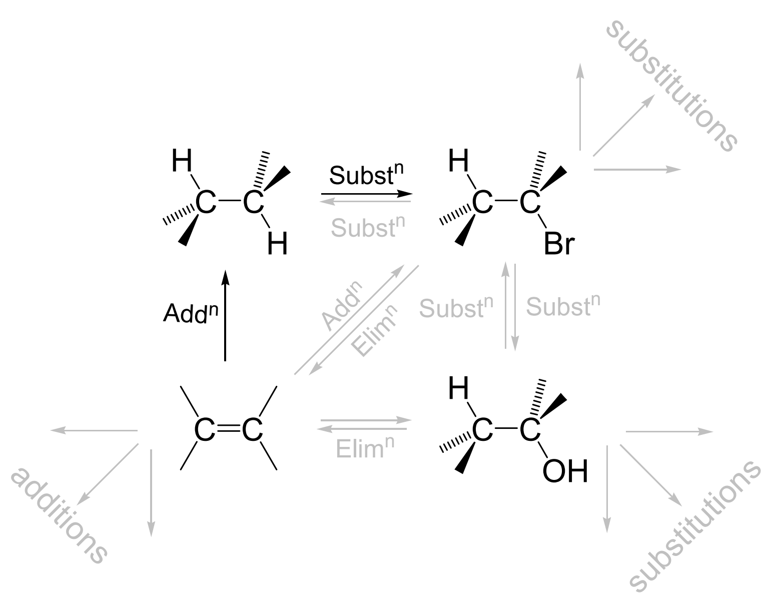
Elimination



Rearrangement



A Preview of Reactivity



Practical Aspects of Running a Reaction

BEGINNING

Starting material
("substrate")
Reagents
Catalysis
(lowers activation energy)
Solvent
(allows for mixing)

Mode of addition

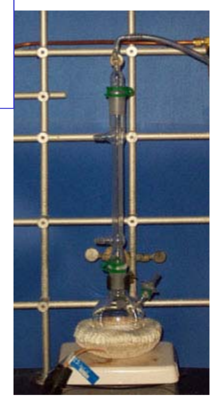
→

Time
Temperature
(heating/cooling)
Environment
(avoid O_2, H_2O?)
Stirring

END

Product
Byproducts
Unreacted reactants
Catalyst
Solvent

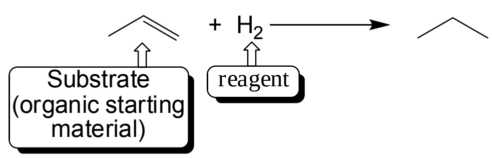
SEPARATION
PURIFICATION
IDENTIFICATION



$$\% \text{ yield} = \frac{\text{moles of product}}{\text{moles of limiting reactant}} \times 100$$

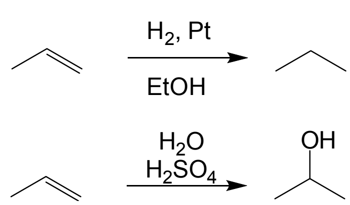
Representations of reactions

Reactant(s) ⟶ Product(s)



...more commonly written as....

Substrate (organic starting material) $\xrightarrow[\text{solvent(s)}]{\text{reagent(s), catalyst(s)}}$ Product (+ byproduct(s))



WHAT IS A MECHANISM?

A mechanism is a *proposal* for a step-by-step pathway by which a reaction proceeds. Each step involves bond making and/or breaking. The mechanism takes into account all currently available evidence (kinetics, formation of byproducts, effect of structure on reactivity). Any new data collected must be consistent with the proposed mechanism, or the mechanism itself must be modified to account for the new finding.

An understanding of common mechanistic steps can be applied to new combinations of reagents to *predict* the outcome of a new reaction. As such, development of an understanding of mechanisms will save you from memorizing a huge amount of material.

While you must develop a familiarity with reactions, do not try to pass this course by just memorizing the outcome of reactions!

Electrophiles and Nucleophiles

Nucleophile
Electron-rich, “nucleus-loving” species

Electrophile
Electron-deficient, “electron-loving” species

CURVED ARROWS

examples of $2e^-$ processes

A—B

$\ddot{\text{Nu}}$ E^+

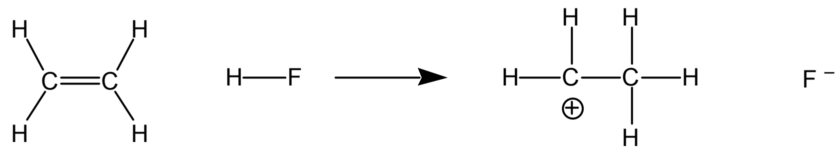
A=B H^+

Polarity and Heterolytic Bond Cleavage

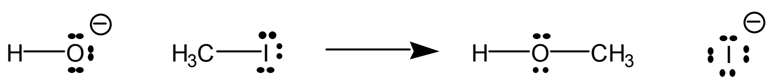
$$(CH_3)_3C\text{—}Br \longrightarrow (CH_3)_3C \quad Br$$

$$H_3C\text{—}Li \longrightarrow CH_3 \quad Li$$

Problem: Provide curved arrows to account for the changes in bonding in the following reaction step.



Problem 3.31(d). Show the curved arrows to account for the following reaction step.



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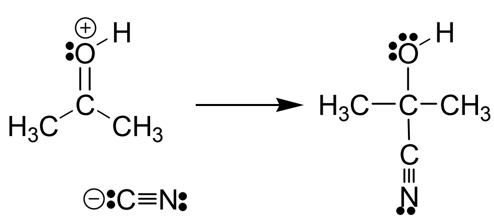
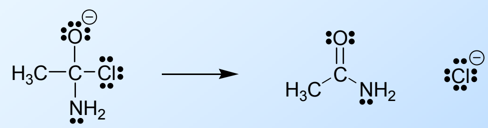
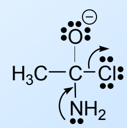


Which curved arrows account for the following reaction step?



1



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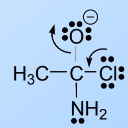

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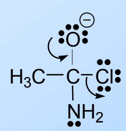

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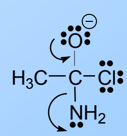
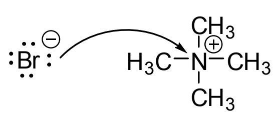
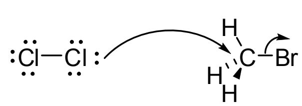
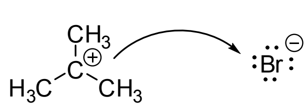


Problem: What is wrong with each of the following mechanistic steps, suggested by students in previous classes? *[consider what the curved arrow is meant to depict, or draw the products of the suggested flow of electrons and comment on why that product is not stable]*







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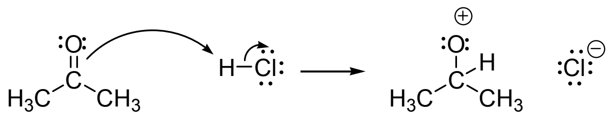
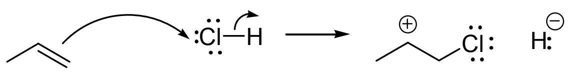




ACID-BASE REACTIONS

Definitions

Brønsted Acidity: ability to donate a proton
  Brønsted Acid: proton donor
  Brønsted Base: proton acceptor

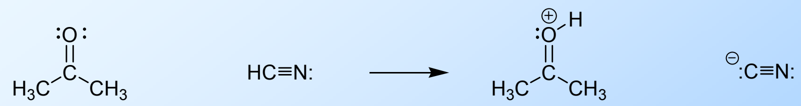
H—A + :B ⟶

Strong acids have weak conjugate bases
e.g., Acid strength: HBr > H_2O Conjugate base strength: Br^- < HO^-

Lewis Acidity
  Lewis Acid: electron pair acceptor
  Lewis Base: electron pair donor

Ph_3P: + BF_3 ⟶

Which species in the following acid base reaction is the acid, base, conjugate acid and conjugate base?



1	acid	base	conjugate acid	conjugate base
2	acid	base	conjugate base	conjugate acid
3	base	acid	conjugate acid	conjugate base
4	base	acid	conjugate base	conjugate acid

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pK_a and Acid Strength

$$\underset{\text{acid}}{\text{A–H}} + \underset{\text{base}}{H_2O} \overset{K_{eq}}{\rightleftharpoons} \underset{\text{conjugate base}}{\text{A}} + \underset{\text{conjugate acid}}{H_2O\text{–H}}$$

$$K_{eq} = \frac{[A^-][H_3O^+]}{[HA][H_2O]}$$

since H_2O is solvent, $[H_2O]$ = 55 M

$$K_a = \frac{[A^-][H_3O^+]}{[HA]}$$

$K_a \uparrow$, acid strength $\uparrow$

pK_a = –logK_a

<u>Bottom line:</u> pK_a $\downarrow$, acid strength $\uparrow$

THE STRENGTH OF ACIDS

pK_a values

	Acid	pK_a
➢	HI	-10
	H_2SO_4	-9
➢	HBr	-9
➢	HCl	-7
	$(CH_3)_2C{=}O\mathbf{H}^+$	-2.9
	$CH_3O\mathbf{H}_2^+$	-2.5
	H_3O^+	-1.74
	HNO_3	-1.4
	CF_3CO_2H	0.18
➢▶	HF	3.2
	H_2CO_3	3.7
⇨	$CH_3CO_2\mathbf{H}$	4.75
	$CH_3COC\mathbf{H}_2COCH_3$	9.0

	Acid	pK_a
	NH_4^+	9.2
	$C_6H_5O\mathbf{H}$	9.9
	HCO_3^-	10.2
	$CH_3NH_3^+$	10.6
▶	H_2O	15.7
⇨	$CH_3CH_2O\mathbf{H}$	16
	$(CH_3)_3CO\mathbf{H}$	18
	CH_3COCH_3	19.2
➜	$HC{\equiv}CH$	25
	H_2	35
▶	NH_3	38
➜	$CH_2{=}CH_2$	44
▶➜	CH_3CH_3	55

Predicting Equilibrium Constants

$$\underset{\text{acid}}{\text{A–H}} + \underset{\text{base}}{\text{B:}^-} \xrightleftharpoons{K_{eq}} \underset{\text{conjugate base}}{\text{A:}^-} + \underset{\text{conjugate acid}}{\text{B–H}}$$

Equilibrium lies of side of the weaker acid and weaker base (the weaker acid and weaker base will always be on the same side)

$$\log K_{eq} = pK_a\text{ (conjugate acid)} - pK_a\text{ (acid)}$$

$$\underset{pK_a = -7}{HCl} + NaOH \xrightleftharpoons{K_{eq} =} NaCl + \underset{pK_a = 15.7}{H_2O}$$

$$CH_3OH + \underset{pK_a = -9}{H_2SO_4} \xrightleftharpoons{K_{eq} =} \underset{pK_a = -4}{CH_3\overset{+}{O}H_2} + HSO_4^-$$

Species that can act as either an acid or as a base

$$CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^+ + HO^-$$

$pK_a = 38$ $pK_a = 15.7$ $pK_a = 10.6$

versus

$$CH_3NH_2 + H_2O \rightleftharpoons CH_3NH^- + H_3O^+$$

$pK_a = 38$ $pK_a = 15.7$ $pK_a = -1.74$

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

$pK_a = 5.5$ $pK_a = 15.7$ $pK_a = -1.74$

versus

$$CH_3COOH + H_2O \rightleftharpoons CH_3COOH_2^+ + HO^-$$

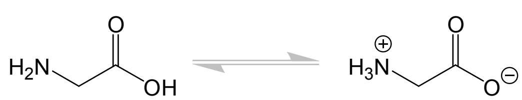
$pK_a = 5.5$ $pK_a = 15.7$

Amine + Acid

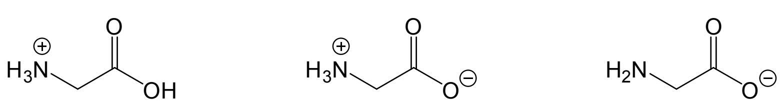
$$CH_3COOH + CH_3NH_2 \rightleftharpoons CH_3COO^- + CH_3NH_3^+$$

$pK_a = 5.5$ $pK_a = 38$ $pK_a = 10.6$

Amino acids



Amino acids in aqueous solution



STRUCTURE-ACIDITY RELATIONSHIPS

In order to assess the relative strengths of acids, consider the ability of the acid to donate a proton (ability to break the H-A bond) and for the conjugate base to accommodate negative charge. Stronger acids have weaker conjugate bases...

$$A{-}H + B{:}^- \rightleftharpoons A{:}^- + H{-}B$$

We have ways to assess the ability of ions (anions and cations) to accommodate negative charge based on:

- Inductive effects (substituents donate or withdraw electron density *via* sigma bonds)
- Resonance effects (electron donation or withdrawal by pi-bonds)
- Hybridization

Acidity: Across a Row of the Periodic Table

	$H{-}CH_3$	$H{-}NH_2$	H–OH	H–F
pK_a	48	38	15.7	3.2
conjugate bases				
	CH_3^-	NH_2^-	OH^-	F^-

- Bonds strengths are similar:
  Acidity primarily depends on electronegativity

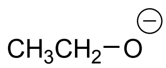
Acidity: Down a Column of the Periodic Table

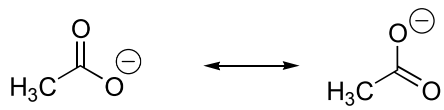
	pK_a	conjugate base
H–F	3.2	F^-
H–Cl	-7	Cl^-
H–Br	-9	Br^-
H–I	-10	I^-

- Bonds strength decreases dramatically from H-F to H-I:
  Acidity primarily depends on bond strength.

The Effect of Resonance

	pK_a	conjugate base
CH_3CH_2OH	16	$CH_3CH_2O^-$
CH_3CO_2H	4.75	$CH_3CO_2^-$





⇨ *Resonance stabilization of conjugate base and increases acidity*

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pKa values

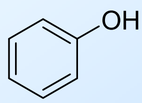
acid strength ↑ (left to right across a row)

acid strength ↑ (down a group)

H H-H 55								He
Li	Be		B	C H-CH_3 35	N H-NH_2 38	O H-OH 15.7	F H-F 3.2	Ne
Na	Mg		Al	Si	P	S H-SH 7.04	Cl H-Cl -7	Ar
K	Ca		Ga	Ge	As	Se H-SeH 3.9	Br H-Br -9	Kr
						Te H-TeH 2.6	I H-I -10	

Which of the following is the strongest acid?

1 CH_3NH_2

2 

3 CH_3OH

The Effect of Hybridization

Acidity

$$R-C\equiv C-H \quad > \quad R-CH=CH-H \quad > \quad R-CH_2-CH_2-H$$

$$pK_a=25 \qquad pK_a=44 \qquad pK_a=50$$

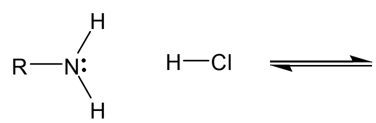
Conjugate bases

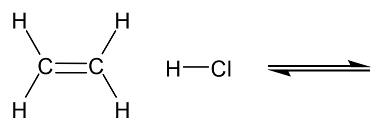
$$R-C\equiv \ddot{C}^{\ominus} \qquad R-CH=\ddot{C}H^{\ominus} \qquad R-CH_2-\ddot{C}H_2^{\ominus}$$

Lone pair in lower energy hybrid orbital stabilizes conjugate base and increases acidity

ORGANIC BASES

Organic bases have either lone pairs of electrons or pi-bonding electrons



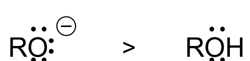


Strong bases commonly used in organic chemistry:

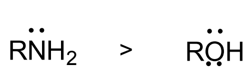
potassium *tert*-butoxide: $K^{+-}OC(CH_3)_3$
sodium amide: $Na^+NH_2^-$
sodium hydride: Na^+H^-

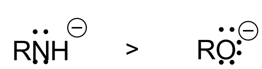
The Effect of Structure on Basicity

Effect of charge

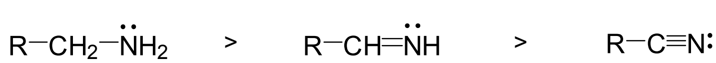


Effect of electronegativity

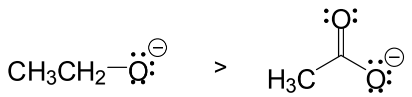


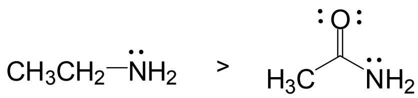


Effect of hybridization



Effect of resonance





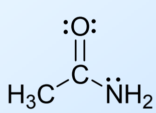
Effect of alkyl substituents

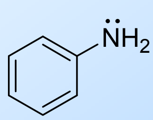
$R_3N > R_2NH > RNH_2 > NH_3$

(gas phase basicity)

Which of the following is the strongest base?

1 CH_3NH_2

2 

3 

4 CH_3F

ACID-BASE REACTIONS IN AQUEOUS AND NON-AQUEOUS MEDIA

H_3O^+ is the strongest acid, and HO^- is strongest base, that can be present in water.

$$\underset{pK_a = -7}{HCl} + \underset{pK_a = 15.7}{H_2O} \rightleftharpoons \underset{pK_a = 1.74}{H_3O^+} + Cl^-$$

$$NaH + \underset{pK_a = 15.7}{H_2O} \rightleftharpoons HO^- + \underset{pK_a = 35}{H_2}$$

In *any* solvent, the strongest acid [base] which can be present is the *conjugate acid [base] of the solvent*. The choice of solvent for acid-base reactions is important…

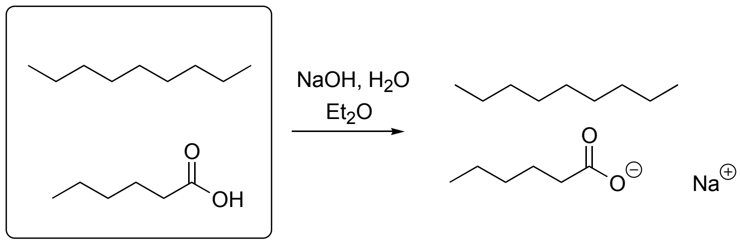
				conjugate acid	conjugate base
$R-C\equiv C-H$ (pK_a=25)	$NaNH_2$	hexane (pK_a=55)	$\longrightarrow$	NH_3 (pK_a=38)	
$R-C\equiv C-H$ (pK_a=25)	$NaNH_2$	H_2O (pK_a=16)	$\longrightarrow$	NH_3 (pK_a=38)	

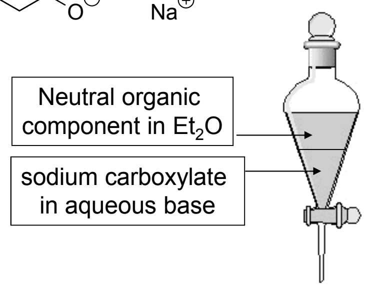
e.g., $CH_3OH_2^+$ is the strongest acid possible in methanol (i.e., H_2SO_4, a stronger acid, is completely dissociated in methanol). CH_3O^- is the strongest base present in methanol (i.e., NH_2^-, a stronger base, is completely protonated by methanol).

PRACTICAL APPLICATIONS OF ACID-BASE CHEMISTRY

Separation of Neutral, Acidic and Basic Compounds

Challenge: Separate a mixture of hexanoic acid and nonane.



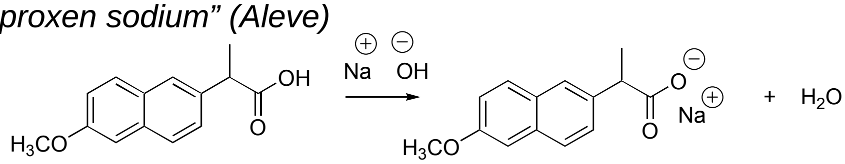


1. Separate the layers, distill off the ether to isolate nonane
2. Acidify the separated aqueous solution, extract neutral hexanoic acid into another portion of ether. Separate these two layers, remove ether.

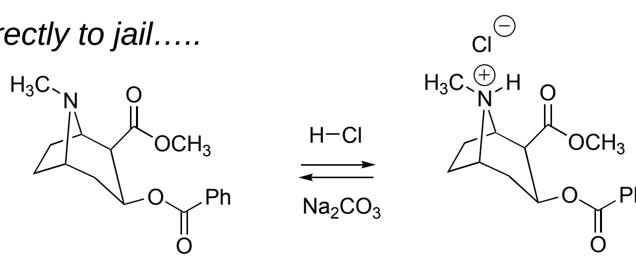
Problem: Design a procedure to separate hexylamine ($C_6H_{13}NH_2$) from nonane.

Provide Greater Water-solubility to Drugs

Naproxen sodium" (Aleve)



Go directly to jail…..



Catalysis of Reactions

Proton transfer is usually fast. Protonation (or deprotonation) of an organic starting material with an acid (or base) often catalyzes reactions which do not take place in the absence of catalyst.

Bases *deprotonate* molecules and make them better (*i.e.*, more reactive) *nucleophiles*

Acids *protonate* molecules and make them better *electrophiles*

ENERGY CHANGES AND EQUILIBRIA: THERMODYNAMICS

Equilibria

$$\text{Reactants (R)} \underset{}{\overset{K_{eq}}{\rightleftharpoons}} \text{Products (P)} \qquad K_{\text{eq}} = \frac{[\text{products}]}{[\text{reactants}]}$$

Enthalpy

$\Delta H° = H°_{\text{products}} - H°_{\text{reactants}}$

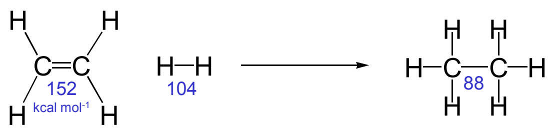
based on changes in bonding

Representative Bond Lengths and Strengths

	bond length Å	bond strength kcal/mol	bond strength kJ/mol
H-H	0.74	104	435
H-F	0.92	136	571
H-Cl	1.27	103	432
H-Br	1.41	87	366
H-I	1.61	71	289
H-O	0.97	110	460
H-C	1.10	99	414
C-C	1.55	88	368
C=C	1.33	152	636
C≡C	1.20	200	837
C-O	1.43	80	355
C=O	1.21	191	799
C-F	1.38	110	461
C-Cl	1.77	79	330
C-Br	1.95	67	280
C-I	2.14	57	240

1 Å = 10^{-10} m = 100 pm   1 kcal = 4.18 kJ

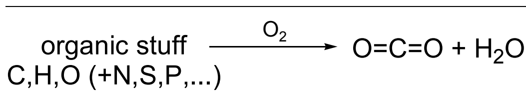
Calculating Heats of Reaction, Δ*H*



bonds broken (energy *IN*)

bonds made (energy *OUT*)

net change



Relationship Between K_{eq} and $\Delta G°$

Equilibrium constant depends on changes in enthalpy and entropy (change in disorder)

Change in Gibbs free energy for a reaction:
$\Delta G° = \Delta H° – T\, \Delta S°$

$\Delta G° = G°_{products} – G°_{reactants}$

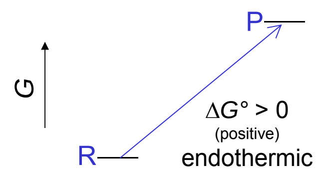
$\Delta G° = –RT \ln K_{eq} = –2.303\, RT \log K_{eq}$

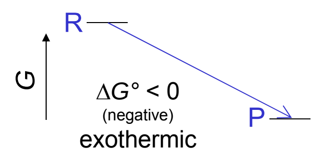
R = 8.314 J/K.mol = 1.987 cal/K.mol
T = temperature (in K)

$K_{eq} = {}^{[products]}/_{[reactants]}$

When $\Delta G° = 0$; K_{eqm}
When $\Delta G° > 0$; K_{eqm}
When $\Delta G° < 0$; K_{eqm}

If $\Delta G° < -13$ kJ mol^{-1}, $K > 100$



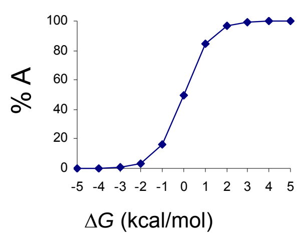


For the equilibrium:

$$A \rightleftharpoons B$$

$$\Delta G° = –RT \ln K_{eq} = –2.303\, RT \log K_{eq}$$

$\Delta G°$(kcal/mol)	K_{eq}	% A at equilibrium
+5	0.0002	99.98
+4	0.001	99.88
+3	0.006	99.38
+2	0.03	96.71
+1	0.2	84.42
0	1	50
-1	5	16
-2	29	3.3
-3	159	0.63
-4	862	0.12
-5	4670	0.02



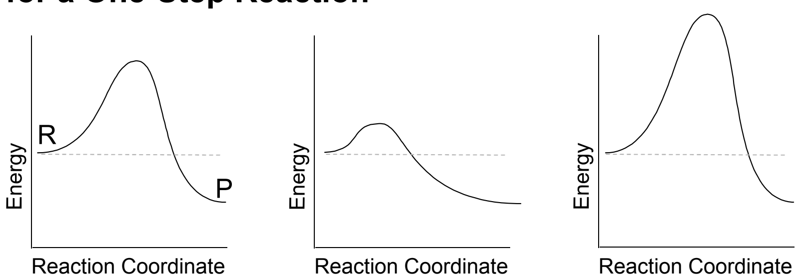
» A small change in the ΔH of a reaction has a large influence on K_{eq}

If $\Delta G° < -13$ kJ mol^{-1}, $K > 100$

Thermodynamics tells us the extent to which a reaction ***CAN*** occur, but nothing about how ***FAST*** it will be

KINETICS

Transition State Theory: Energy-Reaction Coordinate Diagram for a One-Step Reaction



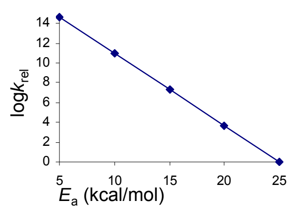
Rate constant: $k = Ae^{-E_a/RT}$

Catalysis -

$k = Ae^{-E_a/RT}$

Effect of E_a on Rate (at 25 °C)

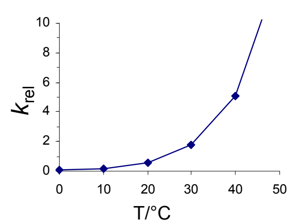
E_a kcal/mol	log$k$
5	14.7
10	11.0
15	7.3
20	3.7
25	*0 (i.e., krel=1)*



Effect of Temperature on Rate

For reaction: A → B (for E_a = 25 kcal/mol)

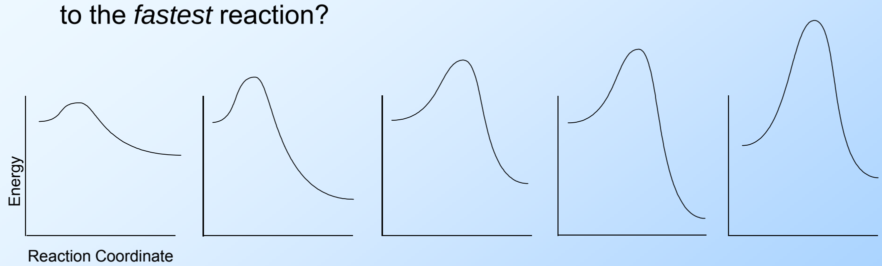
T/°C	k_{rel}
0	0.05
10	0.17
20	0.56
25	*1*
30	1.75
40	5.05
50	13.7
60	34.9
70	84.2
80	193
90	424
100	893



» A small change in the E_a of a reaction has a very large influence on k

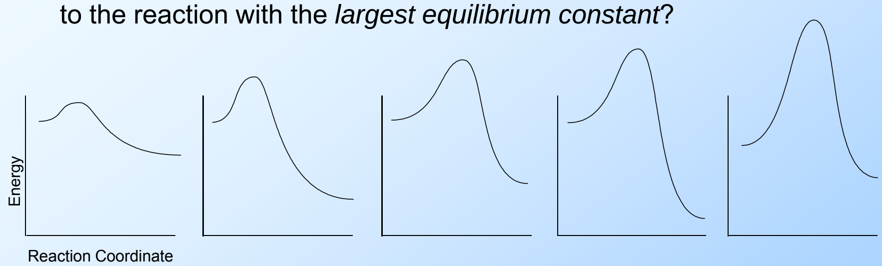
» A small increase in temperature can have a large influence on k

Which of the following reaction coordinate diagrams corresponds to the *fastest* reaction?



1 2 3 4 5

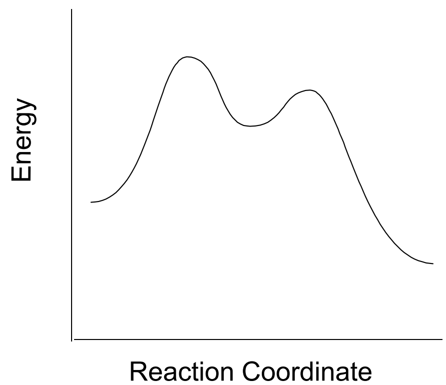
Which of the following reaction coordinate diagrams corresponds to the reaction with the *largest equilibrium constant*?



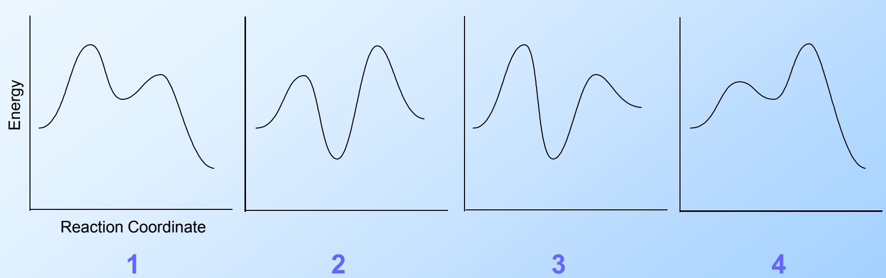
1 2 3 4 5

Energy-Reaction Coordinate Diagram for Two-Step Reaction

Reactants ⇌ Intermediate ⇌ Product



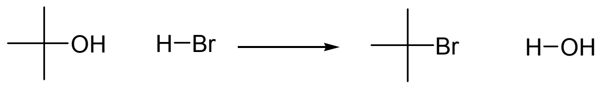
Which of the following reaction coordinate diagrams corresponds to a slow reaction followed by an fast reaction?



A MULTISTEP MECHANISM IN WHICH THE FIRST STEP IS AN ACID-BASE REACTION

Substitution of *tert*-Butyl Alcohol

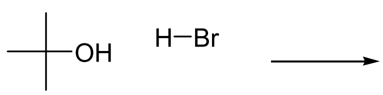
Overall Reaction



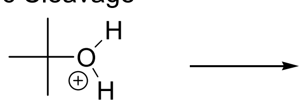
How do changes in bonding take place?

Mechanism

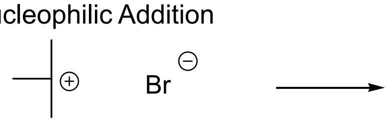
– Protonation



– Heterolytic Cleavage



–Nucleophilic Addition



TOPIC 5

Key concepts

- Classify organic reactions
- Compare acid (or base) strength; understand relationship of acid or base strength as related to structure
-Show movement of electrons (nucleophiles attacking electrophiles)
-Understand thermodynamics and kinetics of organic reactions, including interpretation of reaction coordinate diagrams