

CHE 2060: Principles of Organic Chem



4. Overview of organic reactivity

Introduction: The \$300 million reaction

4.1: A first look at some organic reaction mechanisms

4.1A: The acid-base reaction

4.1B: A one-step nucleophilic substitution mechanism

4.1C: A two-step nucleophilic substitution mechanism

4.2: A quick review of thermodynamics and kinetics

4.2A: Thermodynamics

4.2B: Kinetics

4.3: Catalysis

4.4: Comparing biological and laboratory reactions

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Introduction:

Thermophiles and the discovery of Taq polymerase

Polymerase chain reaction

<http://sites.nd.edu/bios21201/techniques/polymerase-chain-reaction-pcr/>

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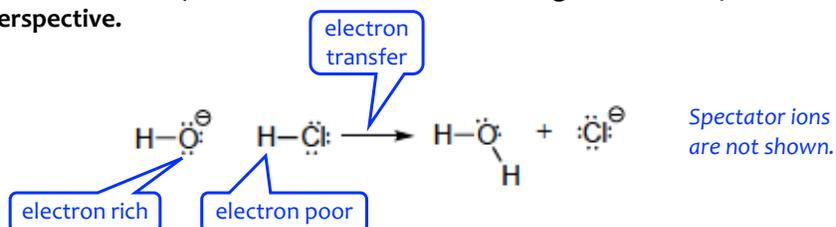
4.1A: The acid-base reaction

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Acid-base reactions (proton transfer)



Let's look at a simple **acid-base reaction** from an **organic chemistry perspective**.



Electrons are transferred from the electron-rich reactant to the electron-poor reactant to create new products.

Reaction mechanism shows the movement of electron pairs using curved arrows.

- The electron pairs are said to **'attack'** as they move simultaneously.
- Movement of electrons from a bond **breaks** that bond.



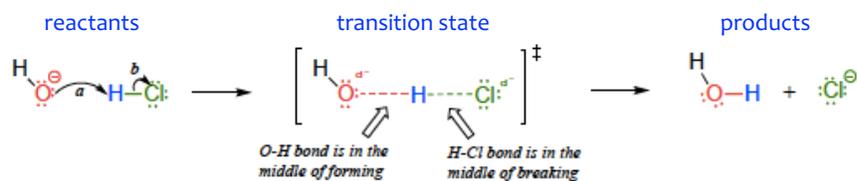
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Reaction transition states



Transition state: a very transient, short-lived form in which bonds are breaking and forming simultaneously

- Highest energy state
- Dipolar charges



Transition states are not shown for all reaction mechanisms, but they do help explain how reactions happen.

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Try this



Draw a reaction mechanism for the acid-base reaction of acetic acid (CH_3COOH) and ammonia (NH_3).

- Include all Lewis dot structures with formal charges.
- Use curved arrows to show the movement of electrons.
- Show the transition state.

Do the same for the reverse reaction!

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4.1B: One-step nucleophilic substitution

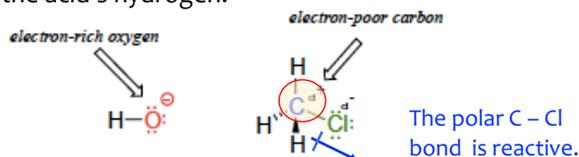
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Carbon is the electron-poor target

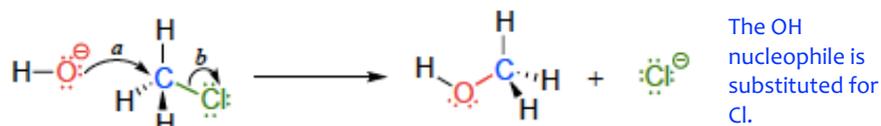


In acid base reactions, a pair of electrons from an electron-rich reactant **attacks** an electron poor hydrogen.

In this **one-step nucleophilic substitution** reaction, a **dipolar positive carbon** takes the place of the acid's hydrogen.



- A lone pair from the electron-rich oxygen attacks the electron-poor carbon.
- As the new bond forms between the oxygen and carbon a bond must break to prevent carbon from having more than an octet.
- The chlorine takes the electron pair from its bond to carbon and leaves as chloride ion.

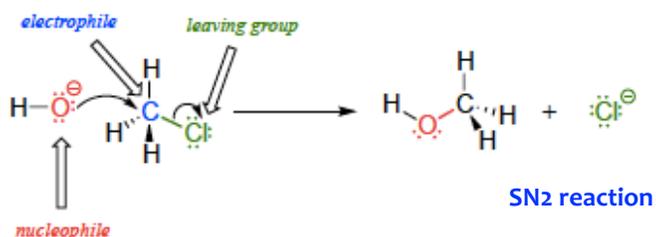


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Adding some new terms



A new set of terms labels the reactants and products according to their motives and functions.



Nucleophile (Nu): an electron-rich reactant that seeks to react with a + charge

- Has abundant : or a full - charge

Electrophile (E+): an electron-poor reactant that seeks to react with a - charge

- Has a full or partial + charge

Leaving group (LG): an electronegative group that takes the electron pair of a bond and leaves the molecule it was part of

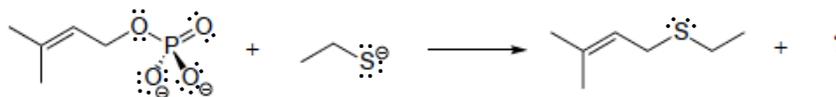
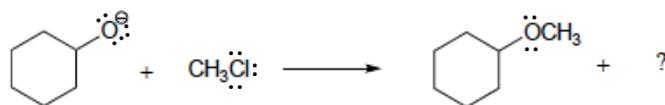
- Has a - charge or is charge neutral

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Try this



In each of the nucleophilic substitution reactions below, identify the nucleophile, electrophile, and leaving group, and fill in the missing product.



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4.1C: Two-step nucleophilic substitution

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Two-step nucleophilic substitution

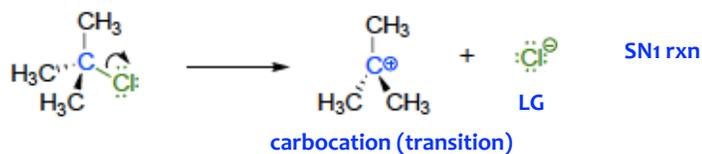


Some nucleophilic substitution reactions use two steps.

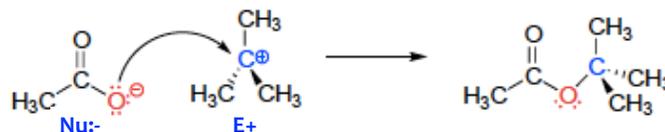


SN1 is a variant of the one-step SN2 and it's easy to identify the Nu:, E+ and LG.

Step 1: Loss of LG to form carbocation (slow)



Step 1: Resolution of the carbocation by nucleophilic attack (fast)

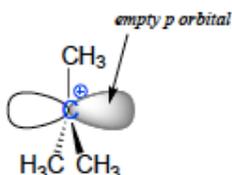


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Carbocation intermediates



The **carbocation intermediate** is a **high-energy transition state**.



Carbocations are **slow to form**, because the loss of the LG from a stable reactant creates a very unstable carbocation.

Carbocations are **quick to react** because they are so **unstable**.

- Thus, the second step of SN1 is very fast as the carbocation reacts with the first nucleophile to come along.

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Being able to see mechanism is critical

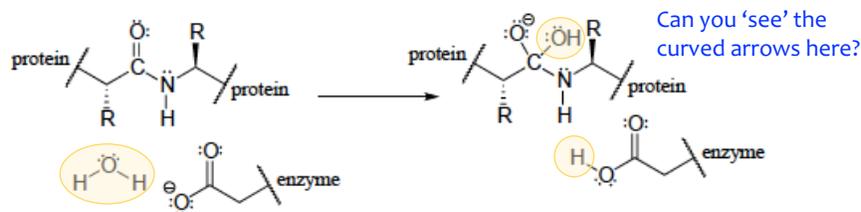


At this point in the course, you need to begin to see how reactants are related to products.

- **Where do electrons move to transform chemical structures?**

Remember that **curved arrows move electrons**, not atoms.

And practice using curved arrows properly.



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Can you?



- (1) Understand that bases are electron-rich and acids are electron-poor?
- (2) Use a curved arrow to show that the : of bases attacks to the H of acids?
- (3) Understand the concept of a transition state and why it is high-energy?
- (4) Define the terms 'nucleophile', 'electrophile, and 'leaving group' and identify these elements in reactions?
- (5) Recognize the basics of nucleophilic substitution and identify SN1 vs. SN2 reactions?
- (6) Understand why carbocations are so highly and rapidly reactive?

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4.2: A brief overview of thermodynamics & kinetics

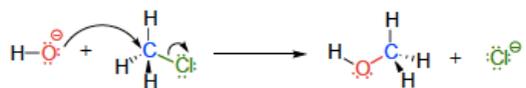
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Reaction coordinate diagrams

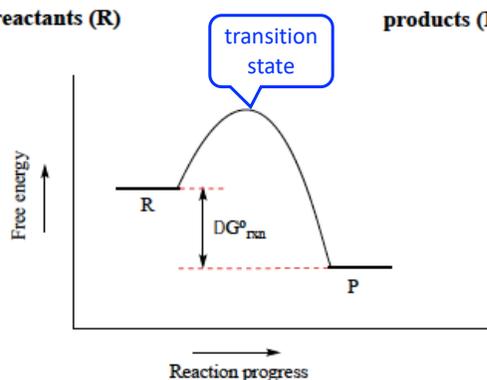


Reaction coordinate diagrams show the **energy levels** of reactants, transition states and products of a chemical reaction.

- Energy levels show why reactions happen as reactions run downhill toward stability or lower energy states.



reactants (R) transition state products (P)



Notice that:

- Energy of P < R.
- Transition states have the highest energy levels.
- Energy of R must be increased to push the reaction forward.
- G°_{rxn} is the difference between the energy of R and P.

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Gibb's free energy change (ΔG°)



Gibb's free energy change (ΔG°) is the difference between the energy states of reactants and products at standard conditions (25°C, 1 atmosphere).

$$\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$$

standard
enthalpy
change

temperature
(°K)

standard
entropy
change

Standard enthalpy change (ΔH°): *heat change during the reaction*

- + heat is absorbed (endothermic)
- heat is released (exothermic)

Standard entropy change (ΔS°): *change in disorder*

- + disorder increases; number of molecules increases
- disorder decreases; number of molecules decreases

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Equilibrium constant (Keq)



Equilibrium constant (Keq): describes the ratio of products to reactants at equilibrium for each chemical reaction

- How complete does the reaction tend to be?
(Complete means all reactants are converted to products.)

this means that w molecules of compound A react with x molecules of compound B)



$$K_{eq} = \frac{[products]}{[reactants]} = \frac{[C]^y [D]^z}{[A]^w [B]^x}$$

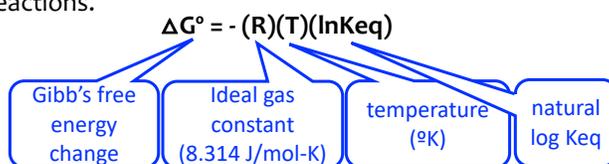
- Keq**
- > 1 Products are favored
 - = 1 Products ~ reactants
 - < 1 Reactants are favored.

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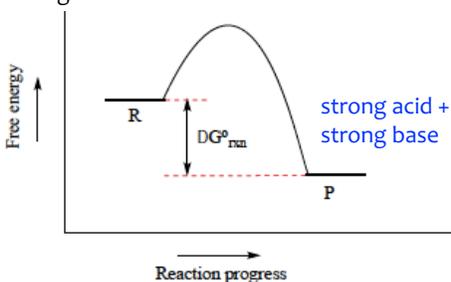
Putting thermodynamics together



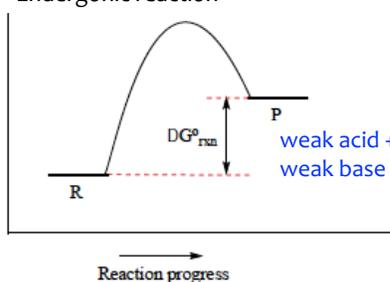
These factors can be related to each other to describe the thermodynamics of chemical reactions.



When ΔG° is negative, Keq is positive.
Products are favored.
Exergonic reaction



When ΔG° is positive, Keq is negative.
Reactants are favored.
Endergonic reaction



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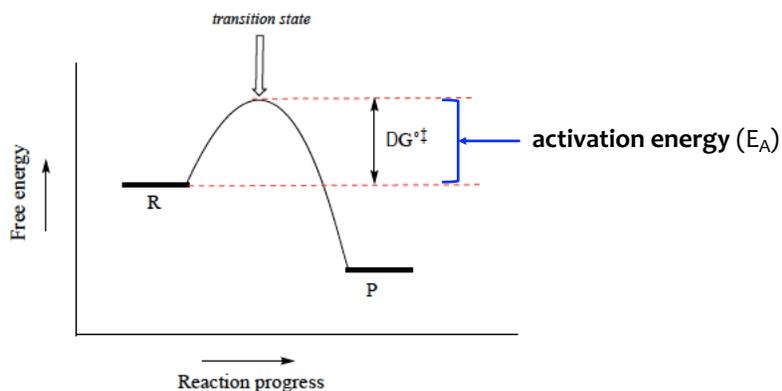
Activation energy



For a chemical reaction to proceed (go forward) from reactants to products, **energy must be added** to get reactants **up the hill** to the transition state.

Activation energy (E_A) is the amount of energy that must be added to reach the transition state.

- The 'energy barrier' that must be overcome



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Activation energy & kinetics

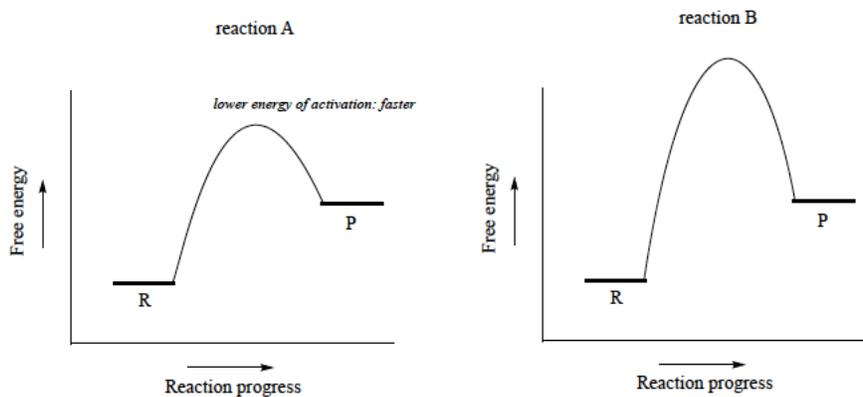


Here both reactions A & B are somewhat **endergonic**.

However, **activation energy is lower for reaction A** than for reaction B.

Therefore, **reaction A occurs more quickly** than reaction B.

- Reaction A reaches equilibrium more rapidly.



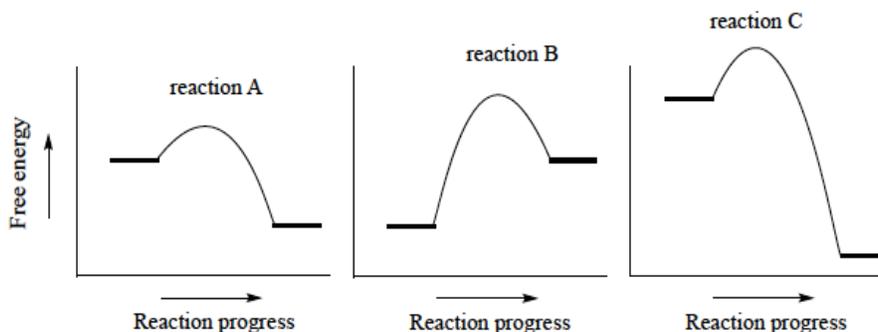
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Try this



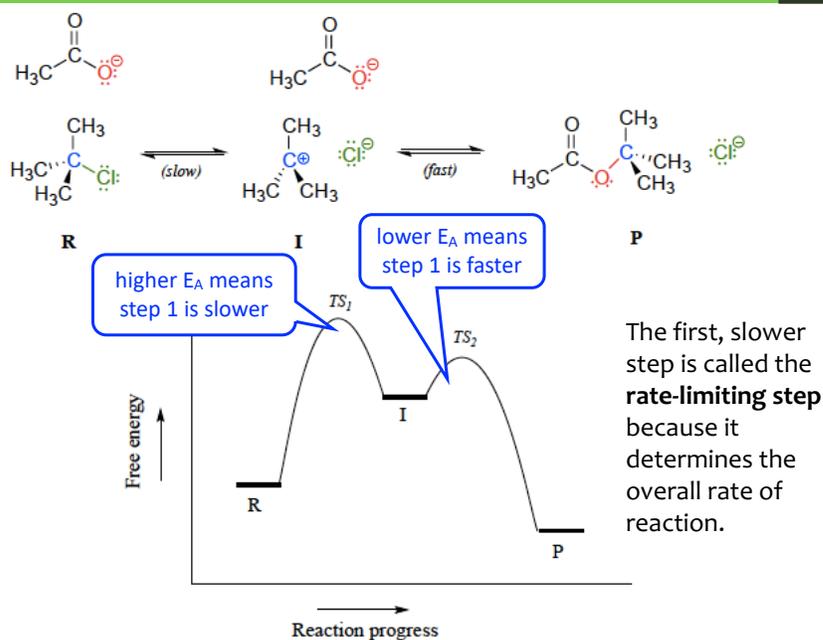
Consider the hypothetical reaction coordinate diagrams below, and assume that they are on the same scale.

- Which of the diagrams describe(s) a reaction with $K_{eq} < 1$?
- Which of the diagrams describes the fastest reaction?
- Which of the diagrams describes the reaction with the highest value of K_{eq} ?
- Which of the diagrams describes the reaction with the largest $\Delta G^\ddagger (E_A)$ for the reverse reaction?
- Copy the diagram for your answer to part (d), and add a label which graphically illustrates the value of $\Delta G^\ddagger (E_A)$ for the reaction in the reverse direction.



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Two-step reactions



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Try this



Imagine that you must extinguish a burning campfire using buckets of water filled at a faucet some distance from the fire. It takes 20 seconds to fill the bucket, 2 seconds to carry it and dump it on the flames. There are many bucket carriers but only one faucet.

- If you double the speed at which buckets are carried, what effect will this have on how fast water gets to the fire?
- If you could add a second faucet, what effect would that have?
- What is the rate-limiting step?

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Can you?



- Place reactants, products and transition states on an energy diagram?
- Compare activation energies of reactions and understand how they dictate ease and speed of reaction?
 - Understand why reactions 'run downhill'?
- Define the terms endergonic and exergonic and relate them to energy diagrams?
- Define the term 'Gibbs free energy' and how it relates to energy diagrams?
 - Describe how ΔG relates to K_{eq} ?
- Define the term 'entropy' and identify reactions in which entropy increases vs decreases?
- Understand the concept of 'rate-limiting step' for reactions with more than one step?

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4.3: Catalysis

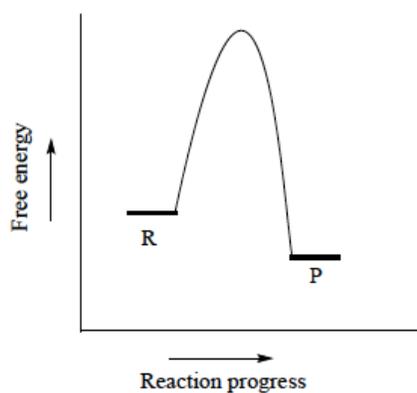
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Strategies to increase speed of rxn



Consider this reaction coordinate diagram. It's **exergonic** with a high E_A .

- How can we increase the speed of the reaction?



1. Increase temperature (add energy)
2. Increase $[R]$ (concentration of R)
3. Add a **catalyst**

What's a **catalyst**?

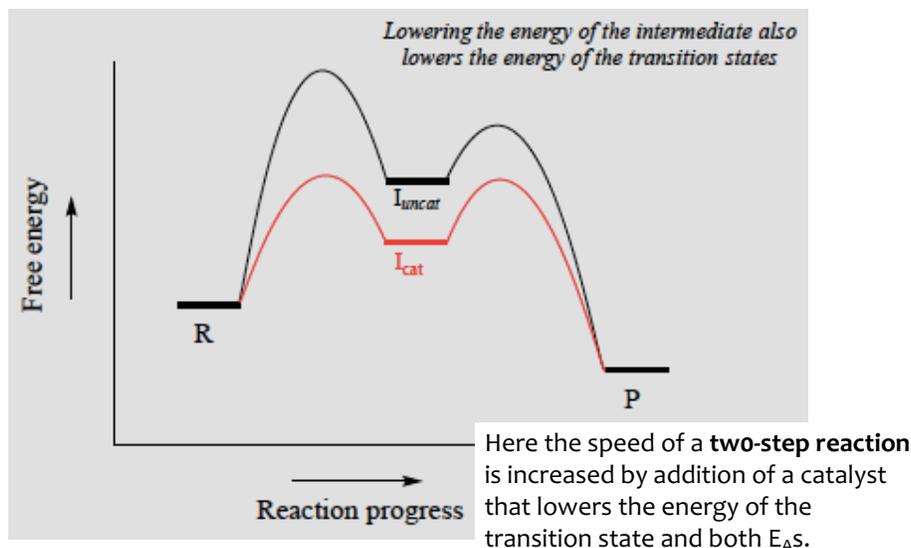
A molecule of substance that increases the speed of a chemical reaction by lowering E_A . Catalysts are not changed by the reaction and can be used many times.

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The Hammond postulate



Hammond postulate: when a catalyst lowers the energy level of an intermediate it also lowers the energy of adjacent transition states.



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How do enzymes lower E_A ?



Enzymes lower E_A by **strategies** employed at their **active sites**, where the ligand (aka substrate) is bound and chemistry is done.

1. Bring two reactants together in the proper orientation.
2. Binding substrates so that their conformation favors the reaction.
3. By increasing chemical reactivity of the substrates; increasing the strength of nucleophiles or electrophiles.
4. By stabilizing transition states of the slower, rate-limiting step.

The most efficient enzyme known, orotidine monophosphate decarboxylase, increases reaction rate by a factor of 10^{17} .

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Try this



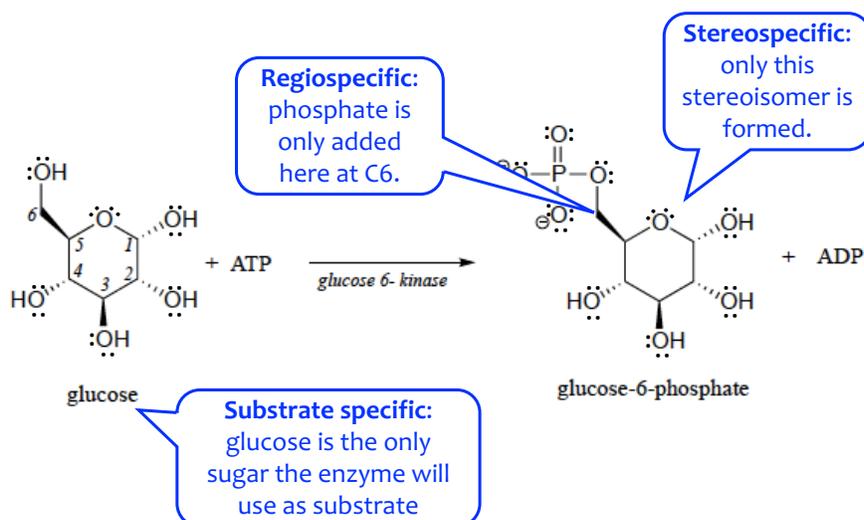
Table sugar, or sucrose, is a high-energy dietary compound, as are the fats in vegetable oil. Conversion of these compounds, along with oxygen gas (O₂), to water and carbon dioxide releases a lot of energy. If they are both so high in energy (in other words, thermodynamically unstable), how can they sit for years on your kitchen shelf without reacting?

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Enzymes are incredibly specific



Because enzymes are **chiral** molecules, they work only on the appropriate chiral substrate and produce only one chiral product, rather than both enantiomers.



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Can you?



- (1) List three methods to increase the speed of a chemical reaction?
- (2) Define the term 'catalyst'?
- (3) Draw examples of reaction diagrams with and without catalysts?
- (4) Describe means by which catalysts decrease reaction E_A ?
- (5) Understand that enzymes are catalysts that are extremely specific for one substrate molecule and even regions of that molecule and stereochemistry?

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4. Overview of organic reactivity



4.4: Comparing biological reactions to laboratory reactions

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What are the differences?



Organic chemists are often working to approximate, or circumvent, biological reactions or biochemistry. So, it's helpful to understand the differences between reactions that happen in cells and those done in chemistry labs.

Parameter	Biology	Chemical laboratory
catalyst	enzymes	acid, base, or other catalyst
solvent	water	variety: polar to nonpolar
reactant mixture	complex, low concentration	simple, high concentrations
temperature	narrow range (37C)	wide range
pH	usually 7.2 - 7.4	wide range