CHEM 330

Topics Discussed on Oct 5

Irreversible nature of the reaction of carbonyl enolates with the electrophiles discussed on Oct 2

Kinetic control in an irreversible reaction: the product that is obtained preferentially is the one that forms through the *fastest* reaction (i.e., the reaction with lowest activation energy: see below). Such a product is not necessarily the thermodynamically favored one

> **corollary**: the preference for C- vs. O-reactivity for a given electrophile **under kinetic conditions** is a consequence of a kinetically faster reaction at one terminus vs. the other. In turn, the rate at which C- vs. O-reactivity is expressed depends on a number factors, significant among which is the relative ease of overlap of the orbitals of E^+ with those associated with the C–and the O-terminus of the enolate. The easier the orbital overlap, the faster the reaction

Principle: the *rate* of a reaction is determined **solely** by the magnitude of the activation energy barrier, regardless of the thermodynamic properties (=thermodynamic stability) of the products:

> consider the reaction diagram below, which shows a set of reactants that could undergo conversion into either product 1 or to product 2 through transition states A and B, respectively. The diagram may thus reflect a carbonyl enolate (reactant) interacting with an electrophile (also reactant) to furnish a product of C-derivation and / or one of O-derivatization. It so happens that the activation energy for the reaction leading to product 1, $\Delta E^\ddagger$ A, is smaller that that for the reaction leading to product 2, $\Delta E^\ddagger$ B.

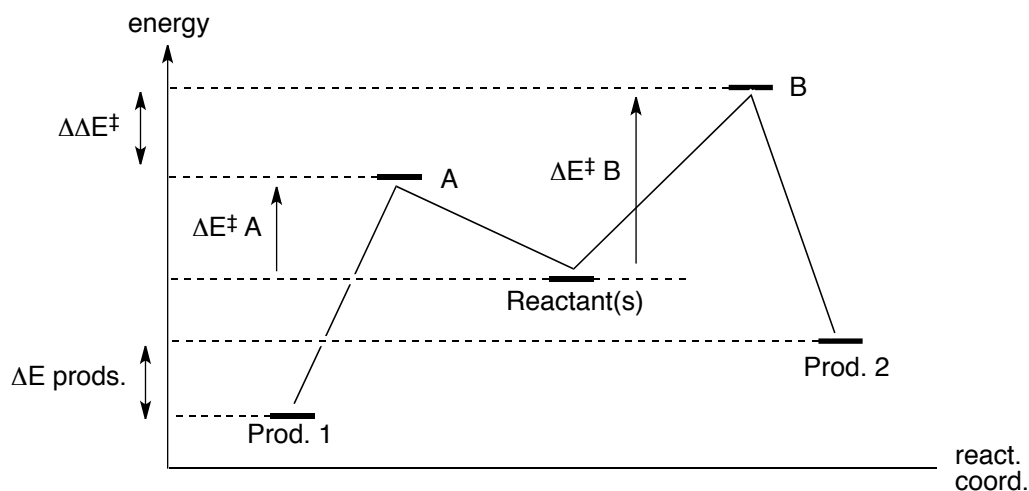### *Product 1 will form faster than product 2*.
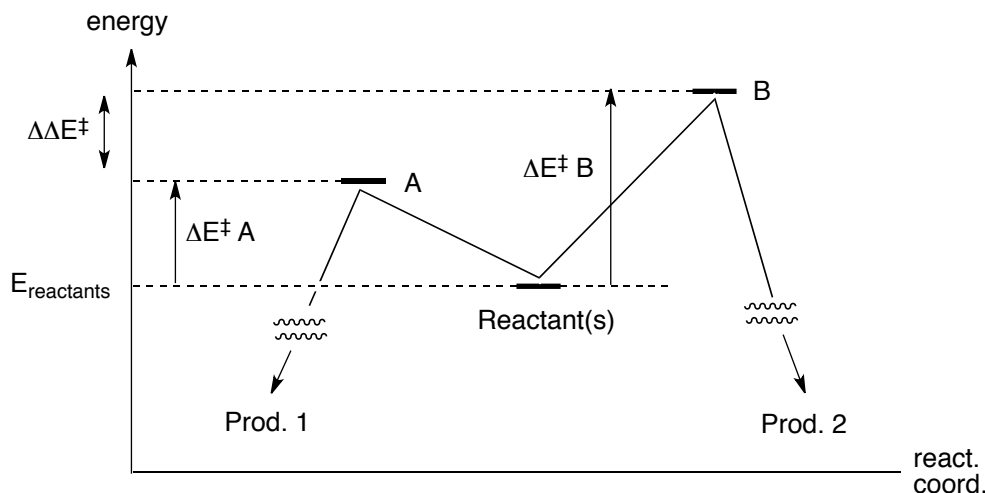
> The *absolute* rate of each reaction (= how much of each product forms per unit time under a given set of experimental conditions) will depend on $\Delta E^\ddagger$ A and $\Delta E^\ddagger$ B **only**.

> The *relative* rate of the reaction (= how much more product 1 forms per unit time relative to product 2 under the same set of conditions) will depend on $\Delta\Delta E^\ddagger$ **only**.
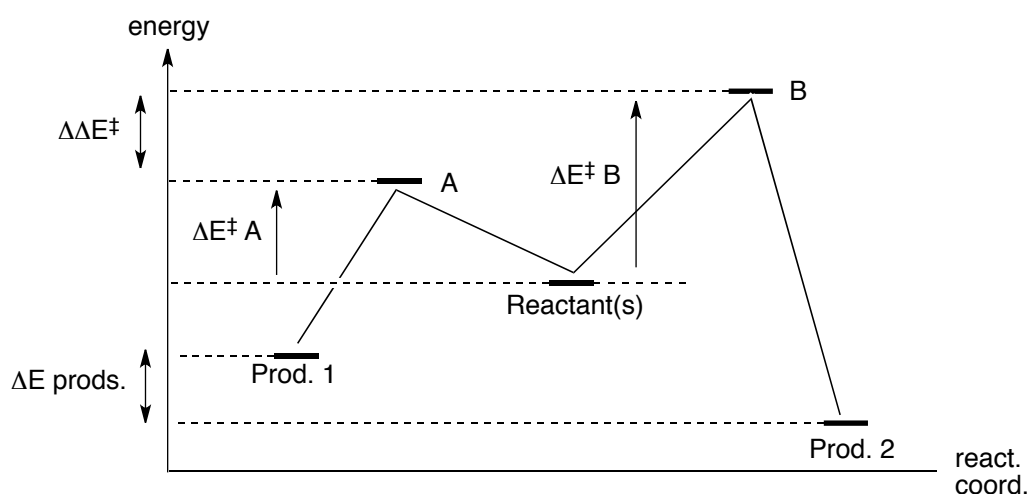
> Formulas that correlate $\Delta E^\ddagger$'s and rates (e.g., the Arrhenius equation) will be discussed in more advanced courses.

Principle: the rate of a reaction (i.e. its $\Delta E^{\ddagger}$) is independent of the relative thermodynamic stability of the products. Therefore, the fast-forming product (product 1 in the example above) may be thermodynamically more stable *or less stable* than the slow-forming one:

The reaction diagram below shows a case on which the faster-forming product happens to be thermodynamically more stable than (= thermodynamically favored over) the slower-forming one:

energy

$\Delta\Delta E^{\ddagger}$

B

A

$\Delta E^{\ddagger}$ B

$\Delta E^{\ddagger}$ A

Reactant(s)

Prod. 2

ΔE prods.

Prod. 1

react. coord.

This is a common case, *but it is by no means the norm!!!* Indeed, an equally common, and far more interesting, case is the following:

energy

$\Delta\Delta E^{\ddagger}$

B

A

$\Delta E^{\ddagger}$ B

$\Delta E^{\ddagger}$ A

Reactant(s)

Prod. 1

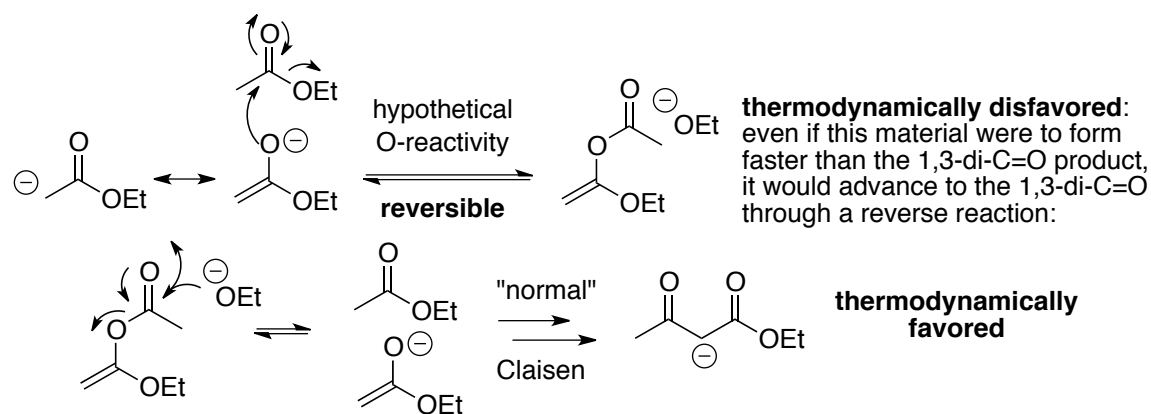ΔE prods.

Prod. 2

react. coord.

the fast-forming product is now thermodynamically less stable than (= disfavored over) the slow-forming product. If the system depicted in the above diagram were to react under conditions of irreversibility (= kinetic control, no thermodynamic equilibration of the products), it will afford largely / exclusively (depending on $\Delta\Delta E^{\ddagger}$) product 1.

Principle: if the system depicted in the above diagram reacted so that the events leading to products 1 and 2 become *reversible,* then product 1 will be converted into product 2.

Principle: the ambient reactivity of enolates (C- vs. O-reactivity) represents a significant issue only for those reactions that occur under conditions of irreversibility (kinetic control)
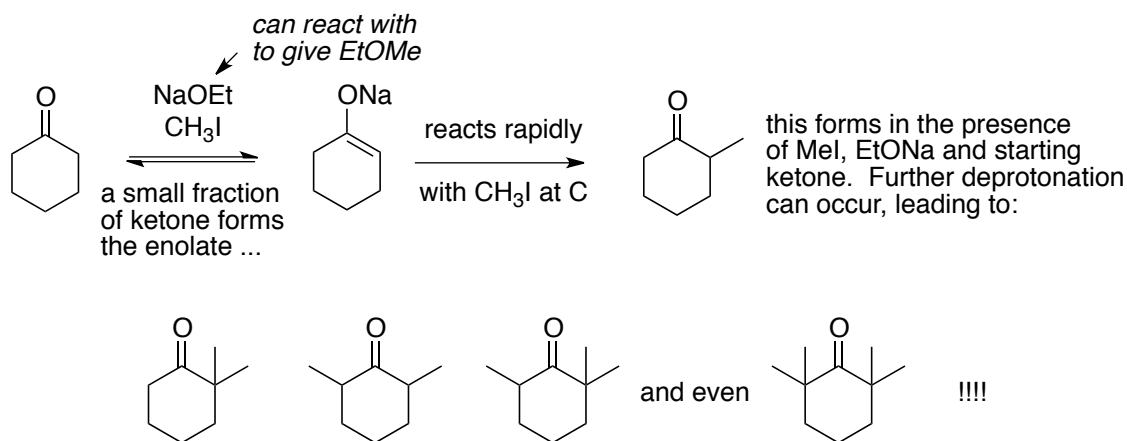
Inconsequential nature of the ambident (= C vs. O) reactivity of enolates in the context of reactions occurring under conditions of reversibility; e.g., a thermodynamically controlled Claisen condensation:

thermodynamically disfavored:
even if this material were to form
faster than the 1,3-di-C=O product,
it would advance to the 1,3-di-C=O
through a reverse reaction:

**thermodynamically
favored**

Reminder: a reversible reaction (e.g., a Claisen condensation carried out under
the conditions discussed in class) occurs under **thermodynamic control**; i.e.,
the product that is obtained preferentially is the more thermodynamic favored one

Principle: with few exceptions, it is inappropriate to derivatize — especially C-alkylate — a carbonyl compound by generating the enolate slowly and reversibly in the presence of one of the electrophiles listed in the table above. This promotes undesirable side reactions, e.g. multiple C-alkylation, as well as reaction of the basic agent (typically an alkoxide) with the electrophile.

Example: the methylation of cyclohexanone enolate. If one were to attempt methylating
cyclohexanone by treating it with, e.g., EtONa in the presence of CH_3I…

*can react with
to give EtOMe*

a small fraction
of ketone forms
the enolate ...

reacts rapidly

with CH_3I at C

this forms in the presence
of MeI, EtONa and starting
ketone. Further deprotonation
can occur, leading to:
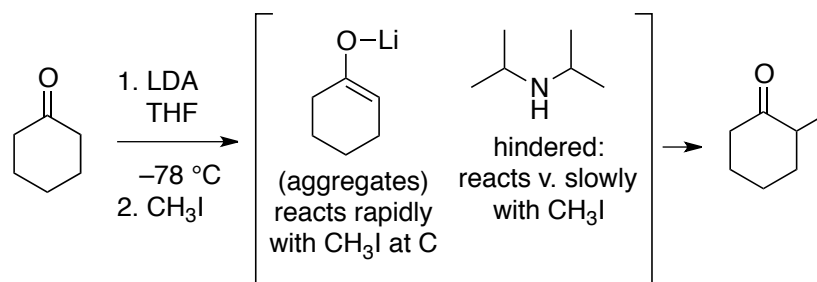
and even   !!!!

Technical aspects of the derivatization of enolates with the electrophiles listed in the table provided on Oct 1st:

• the carbonyl compound is first deprotonated <u>rapidly</u>, <u>completely</u>, and <u>irreversibly</u> with a suitably
strong base. With simple esters, ketones, nitriles, etc. (pKa ≈ 20 – 25) one commonly uses LDA
(pKa ≈ 37) or related bases, often in tetrahydrofuran (THF) as the solvent.

- both the deprotonation of the carbonyl substrate and the subsequent reaction of the enolate with a suitable electrophile are carried out at low temperature (typically −78 °C: the temperature of a Dry Ice-acetone bath) to minimize proton-transfer reactions and to ensure the survival of the highly reactive enolate

Example: the methylation of cyclohexanone is smoothly achieved by *rapidly, completely and irreversibly* converting the substrate into the enolate, at −78 °C, followed by reaction of the enolate with CH$_3$I at −78 °C:

1. LDA
   THF
   −78 °C
2. CH$_3$I

O−Li
(aggregates)
reacts rapidly
with CH$_3$I at C

hindered:
reacts v. slowly
with CH$_3$I

Interest of α-S and α-Se substituted carbonyls in modern organic synthesis:

- **enhanced C–H acidity of α-S / α-Se substituted carbonyls** (less important): more facile and/or selective deprotonation and derivatization (e.g., alkylation) of a carbonyl compound:
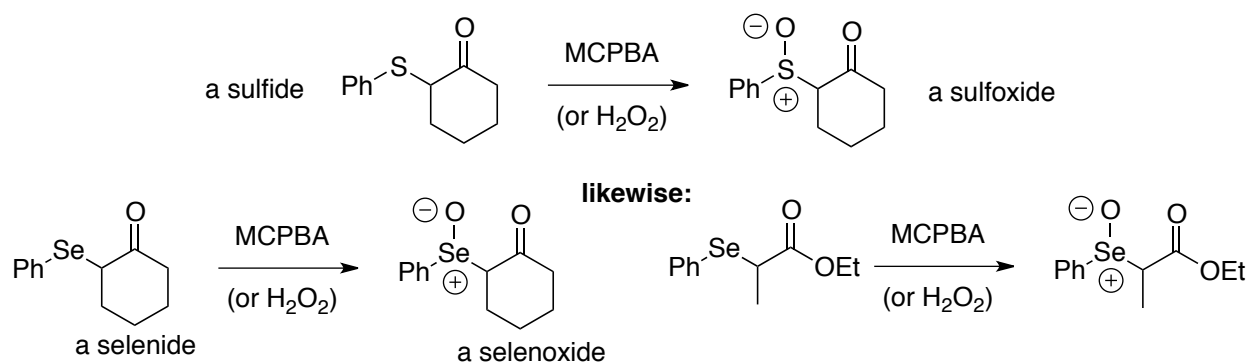
much more acidic than

1. base
2. E$^+$

much more acidic than
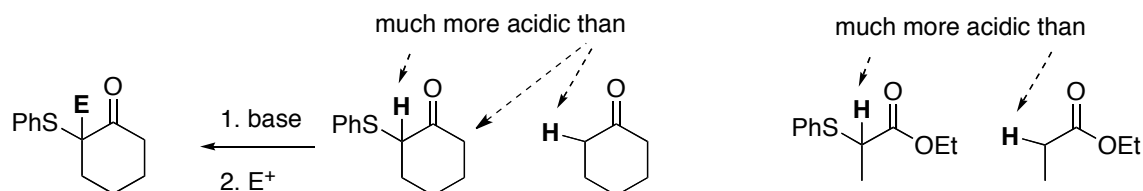
- **oxidative conversion into conjugated (= α,β-unsaturated) carbonyl compounds** (very important):

[O]

[O]
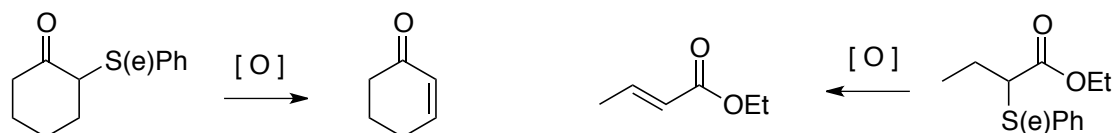
via:
a. initial oxidation of sulfides to sulfoxides and of selenides to selenoxides with MCPBA (meta-chloroperoxybenzoic acid): the same reagent that is used to form epoxides from olefins (other peroxidic oxidants, e.g., H$_2$O$_2$, may also be used):

a sulfide

MCPBA
(or H$_2$O$_2$)

a sulfoxide

likewise:

a selenide

MCPBA
(or H$_2$O$_2$)

a selenoxide

MCPBA
(or H$_2$O$_2$)

b. concerted elimination of the S or Se functionality from thermally unstable α-sulfoxy (T > 100 °C) and — especially — α-selenoxy (T < 50 °C) carbonyls, through a pericyclic mechanism:
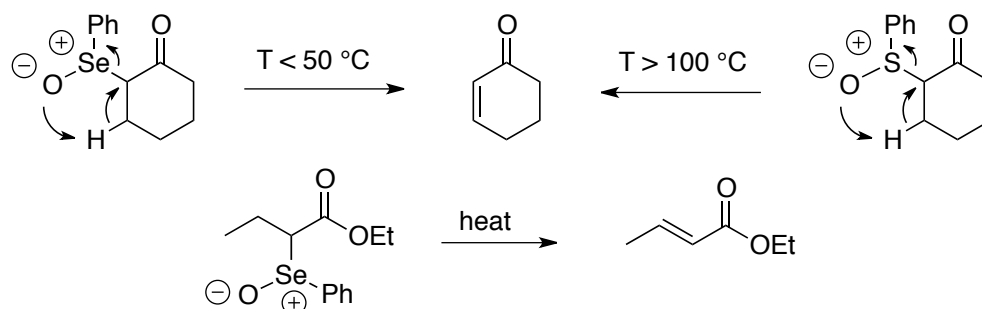

Importance of conjugated carbonyl compounds in modern organic chemistry (conjugate additions, etc.)

Enol esters and carbonates as relatively unreactive, storable enolate analogs, which nonetheless can regenerate actual enolates upon suitable activation; e.g.:
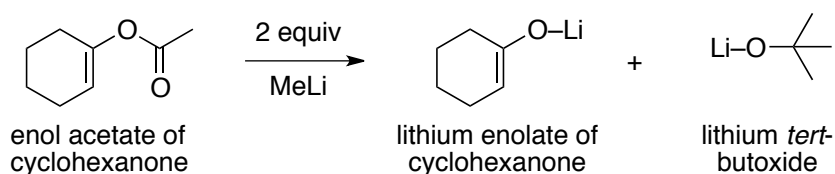
Silyl enol ethers and silyl ketene acetals: compounds obtained upon O-silylation of the enolate of a ketone and of an ester, respectively:
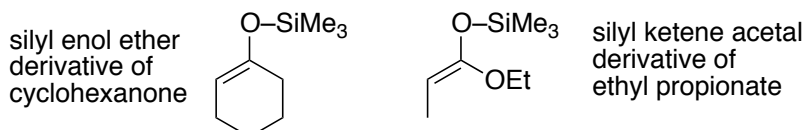
Silyl enol ethers and silyl ketene acetals as stabilized "surrogates" of carbonyl enolates

   unlike true metal enolates, silyl enol derivatives are:

   (i) somewhat tolerant of water, air (O_2), room temperature, etc. They may be stored, and in some favorable cases they may even be purified, e.g., by distillation.

   (ii) unreactive toward electrophiles such as alkyl halides, other carbonyl compounds (aldehydes, etc.).

Importance of silyl enol ethers and silyl ketene acetals in contemporary organic chemistry: these silylated carbonyl derivatives have completely replaced enol esters and carbonates as surrogates of enolates

Principle: silyl enol ethers and silyl ketene acetals are insufficiently nucleophilic to react with most of the electrophiles that are typically employed for the derivatization of true metal enolates (e.g., alkyl bromides / iodides; aldehydes, etc.). However, their nucleophilic reactivity can be expressed by activating the electrophile (= making it more electrophilic) with appropriate agents.

Example: the reaction of silyl enol ethers with aldehydes under catalysis by Lewis acids such as BF$_3$: the **Mukaiyama** variant of the aldol reaction

Me$_3$Si—O

+

H‾Ph

unreactive toward
plain aldehydes

BF$_3$ or
────────→
other suitable
Lewis acid

Me$_3$Si—O   F$_3$B⁻   O⁺   much more electrophilic   F$_3$B   O   H‾Ph   much less electrophilic

aldol-type
────────→
addition

Me$_3$Si—O⁺   O–BF$_3$⁻   Ph

⟶

O   OH   Ph