# CHEM 330

Topics Discussed on Sept. 11

Principle: the relative position of heteroatoms defines the kind(s) of chemical reactions that one needs to employ to construct the desired molecule.

> That is why, in charting the synthesis of a molecule, one starts by recognizing the relative position of heteroatoms (N, O, S, halogen, …) around the carbon backbone (notes of Sept 9)

Stereochemical aspects of 1,3-dioxygenated structures:

"Type A" structures possess a single stereogenic carbon; therefore, they may exist as a pair of stereoisomers that are enantiomers:
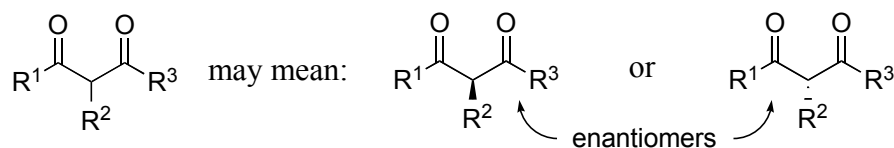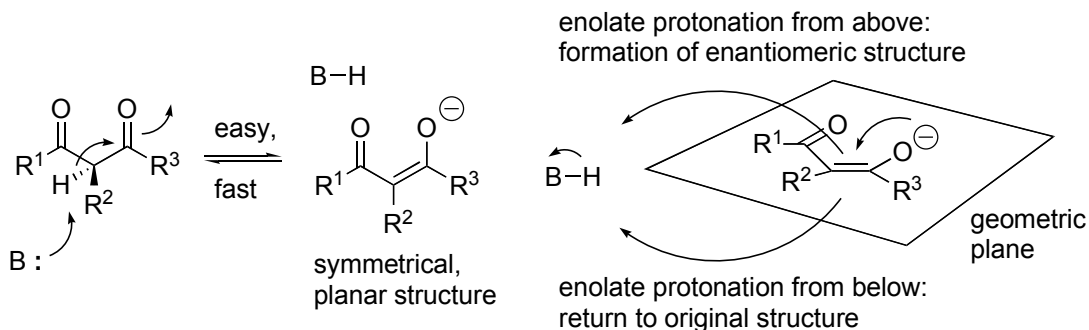

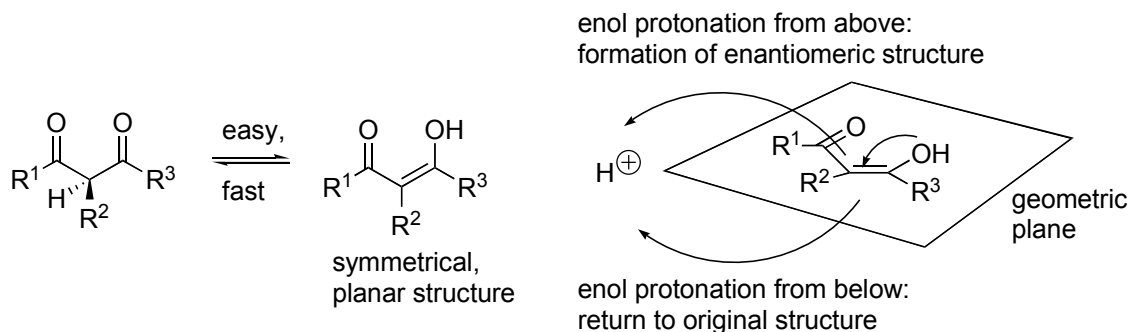Chemical properties of 1,3-dicarbonyl structures:

Low pKa (10-14, average ≈ 12) of 1,3-dicarbonyl functionalities

Facile interconversion of the enantiomers of a 1,3-dicarbonyl structure through:

(i) reversible deprotonation:
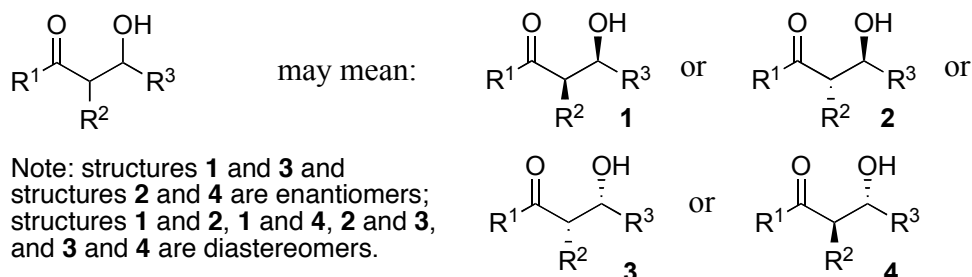

(ii) keto-enol tautomerism:

Racemization: the interconversion of two enantiomers leading to a statistical, 50:50 mixture of the two.

The configuration of a 1,3-dicarbonyl structure is not controllable.
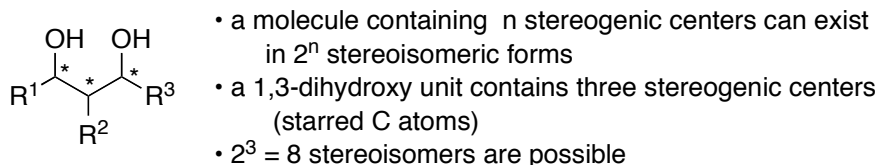
> *The preparation of 1,3-dicarbonyl structures presents no stereochemical issues, due to facile racemization.*

"Type B" structures incorporate a pair of stereogenic carbons; therefore, they may exist as a four possible stereoisomers:

R^1 ... R^3, R^2 may mean: R^1 ... R^3, R^2 **1** or R^1 ... R^3, R^2 **2** or

Note: structures **1** and **3** and structures **2** and **4** are enantiomers; structures **1** and **2**, **1** and **4**, **2** and **3**, and **3** and **4** are diastereomers.

R^1 ... R^3, R^2 **3** or R^1 ... R^3, R^2 **4**

> *the creation of 1,3-hydroxycarbonyl units presents significant stereochemical issues.*

"Type C" structures incorporate three stereogenic carbons; therefore, they may exist as a eight possible stereoisomers (pairs of which may be enantiomers or diastereomers):

R^1 OH OH R^3, R^2

- a molecule containing n stereogenic centers can exist in 2^n stereoisomeric forms
- a 1,3-dihydroxy unit contains three stereogenic centers (starred C atoms)
- $2^3 = 8$ stereoisomers are possible

> *the preparation of 1,3-dihydroxy structures also comports major stereochemical issues.*

Because the creation of 1,3-dicarbonyl compounds poses fewer / no stereochemical problems relative to the preparation of 1,3-hydroxycarbonyl or 1,3-dihydroxy structures, it is an ideal starting point to study the synthesis of 1,3-dioxygenated functionalities.

Principle: bonds between atoms, in particular carbon atoms, are created by causing atoms of opposite polarity (+ / -), or displaying radical character, to interact.

Synthons: hypothetical, often electrically charged fragments needed in bond-forming operations

"Real" molecules that behave as carriers of individual synthons: reagents

Principle: the polarity of an atom is determined by the substituent(s) attached to it

Example of a reagent that carries a C atom possessing (+) character: CH_3–I

Example of a reagent that carries a C atom possessing (–) character: CH_3–Li.

Importance of the analysis of atomic polarity in charting a synthesis (selection of + and – synthons)

A substituent induces alternating polarity along a carbon chain, e.g.:

$$(+) \overset{O}{\overset{\|}{\frown}} \; (+) \quad (+)$$
$$(-) \quad (-) \quad (-)$$
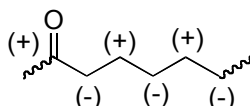
Principle: the precise oxidation state of a carbon atom bearing a heteroatomic substituent has no influence on polarity: what counts is the nature of the heteroatom. Consequently, systems **1** and **2** below are equivalent in terms of polarity:

$$(+) \overset{O}{\overset{\|}{}} \; (+) \quad (+) \qquad\qquad (+) \overset{OH}{} \; (+) \quad (+)$$
$$(-) \quad (-) \qquad\qquad\qquad (-) \quad (-)$$
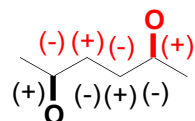$$\mathbf{1} \qquad\qquad\qquad\qquad \mathbf{2}$$

Principle: in carbon chains incorporating multiple heteroatomic substituents, each substituent polarizes individual carbon atoms independently of other substituents.

The two O functionalities of a 1,3-dioxygenated system induce matching atomic polarity in the C atoms:

$$\overset{O}{\overset{\|}{(+)}} \; (-) \; \overset{O}{\overset{\|}{(+)}}$$
$$(+) (-) (+)$$
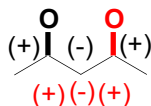
Mismatched atomic polarity in, e.g., a 1,4 dioxygenated system:

$$(-) (+) (-) \overset{O}{\overset{\|}{(+)}}$$
$$(+) \overset{}{\underset{O}{\|}} \; (-)(+)(-)$$

Principle: the construction of a polarity-matched system is easier than the assembly of a polarity-mismatched structure.

Principle: in order to build a polarity-mismatched system, one must reverse the natural polarity of an atom.

Reversal of polarity or Umpolung