In the previous two segments we have examined the acidity of hydrogen atoms attached to a carbon atom $\alpha$ to a carbonyl group, as reflected in the facile deuterium exchange reaction observed for such hydrogen atoms, both in base and in acid. Our conclusion was that the exchange, and hence the acidity, is the direct result of the possibility of the formation of the enolate anion (in base) or the enol (in acid). The net result is that we convert our carbonyl compounds (here, aldehydes and ketones) into nucleophiles — again, the enolate anion (in base) or the enol (in acid). But we know also that the carbonyl group is vulnerable to attack by nucleophiles. Putting these two phenomena together, we come up with a new idea, that a carbon-carbon bond can be formed when the nucleophile is an enolate anion (in base; attacking a carbonyl group), or an enol (in acid; in that case, attacking a protonated carbonyl group). Broadly speaking, the multitude of variants and manifestations of this reaction constitute as a group the most frequently used method of carbon-carbon bond formation, both in Nature and in the laboratory.

The archetype of these transformations is the aldol condensation, in its simplest form the reaction between two molecules of acetaldehyde. Indeed, this single chemical change has lent its name to the entire manifold. Initiated by the formation of the acetaldehyde enolate anion (in base) or acetaldehyde enol (in acid), the reaction proceeds by subsequent interaction of the enolate with acetaldehyde itself (in base), or of the enol with protonated acetaldehyde (in acid), to form 3-hydroxybutanal, for which the long-standing common name is "aldol." The constitutional hallmark of the aldol condensation, whether it takes place with aldehydes or ketones, is the $\beta$-hydroxy carbonyl functionality of the product, although — particularly in acid — there may occur a subsequent dehydration, so that the final product then possesses instead the $\alpha,\beta$-unsaturated carbonyl functionality, as shown in the following figure. Thus, the constitutional outcome of the aldol
condensation in base amounts to the addition of one molecule of acetaldehyde, divided as \( \text{H—} \) and \( \text{—CH}_2\text{—CHO} \), across the carbonyl group of the other. The figure also makes clear that schematically (but not mechanistically!) in the acid case the product may be envisioned simply as deriving from the loss of a molecule of water, obtained from the carbonyl oxygen atom of one molecule of the condensing pair and from two hydrogen atoms activated by the adjacent carbonyl group of the other:

\[
\begin{array}{c}
\text{H}_3\text{C—O—H} \\
\text{H—C—O—H} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{H}_3\text{C—OH—CH}_2\text{—O} \\
\text{H—C—O—H} \\
\end{array}
\]

**functional hallmarks of the aldol condensation:**
- \( \beta \)-hydroxy carbonyl or \( \alpha,\beta \)-unsaturated carbonyl

Although here we do not enter into detail concerning the transition state for the reaction, the next figure presents a more mechanistic picture, the general "Bürgi-Dunitz" trajectory of attack reflecting the directionality of the empty \( \text{C—O} \pi^* \) electron-accepting antibonding orbital. It should be noted that in 3-hydroxybutanal a new stereogenic center is created; however — in the absence of a controlling chiral influence — both members of the enantiomeric pair must form in equal amount, as a result of attack by the enolate or enol form of one acetaldehyde molecule on either the Re or the Si face of the carbonyl group of the other acetaldehyde molecule involved in the condensation:
Examination of the case of propanal (next figure) makes clear that in this case, which at first glance might appear to be only slightly more complicated, in fact we must deal with a considerably more complex stereochemical problem:
Each of the two species interacting in the condensation now has a Re face and a Si face, and so the net result must be the possibility of two (diastereoisomeric) enantiomeric pairs. Although again on this point we do not enter into detail, suffice it
to say that in related cases there has been important progress made on aspects both of diastereoselectivity and of enantioselectivity, but at the same time that a general chemical solution for this exceedingly interesting, but intricate, problem has not yet appeared in practice. It should be noted that, in the general case, the attacking enolate or enol can possess either E or Z stereochemistry. If one considers only the starting materials and the products, enol stereochemistry does not seem to be a factor that should affect the ultimate stereochemical result, which depends on relative facial combinations. However, further reflection brings the realization that this additional stereochemical dichotomy must have an influence on the relative energies of transition state geometries, and hence on final stereofacial outcomes in any kinetically controlled situation.

The intramolecular variant of the aldol condensation, exemplified by the self-condensation of heptanediol (next figure), also deserves mention here. Comparison with the previous figure for acetaldehyde makes apparent that the only difference is in the addition a tether of three methylene groups, the consequence of which is that a ring forms as a result of the same aldol reaction:
heptanediial

enolate formation at one aldehyde functionality

enolate (here the E-isomer is shown)

condensation

enol (here the E-isomer is shown)

protonated aldehyde functionality

in base

in acid

intramolecular aldol condensation of heptanediial, showing the Re - Re absolute stereochemical interaction mode
Acid-catalyzed dehydration of the β-hydroxy carbonyl products to α,β-unsaturated carbonyl compounds always is a possibility:

A last point that should be made is a variant of one we already have mentioned in analogous cases (for example, in Segment 18.01). From a kinetic standpoint a hypothetical best-case scenario for the aldol condensation could come about, were an enolate anion to attack a protonated carbonyl group, a circumstance forbidden to us in the test tube, because it involves having acid and base as catalysts "in the same pot." However, once again this is precisely the method by which an enzyme may enhance the rate of a reaction, if at its reactive site one carbonyl function may be held as the enolate or its equivalent by means of a basic group in the enzyme cavity, while at the same time the other carbonyl may be activated by an acidic grouping elsewhere in the cavity.

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