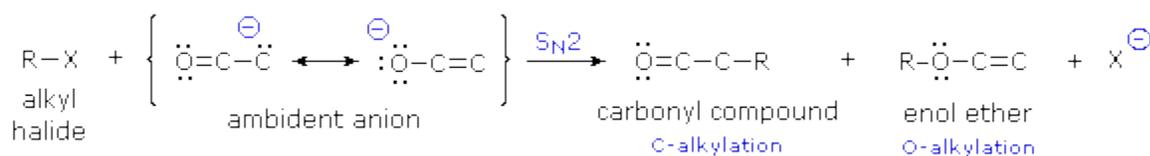


Irreversible Substitution Reactions of Aldehyde and Ketone

In its simplest form the aldol reaction is reversible, and normally forms the thermodynamically favored product. To fully appreciate the complex interplay of factors that underlie this important synthesis tool, we must evaluate the significance of several possible competing reaction paths.

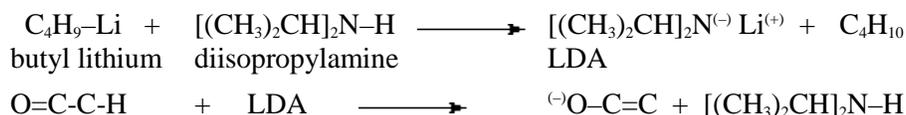
A. The Ambident Character of Enolate Anions

Since the negative charge of an enolate anion is delocalized over the alpha-carbon and the oxygen, as shown earlier, electrophiles may bond to either atom. Reactants having two or more reactive sites are called **ambident**, so this term is properly applied to enolate anions. Modestly electrophilic reactants such as alkyl halides are not sufficiently reactive to combine with neutral enol tautomers, but the increased nucleophilicity of the enolate anion conjugate base permits such reactions to take place. Because alkylations are usually irreversible, their products should reflect the inherent (kinetic) reactivity of the different nucleophilic sites.

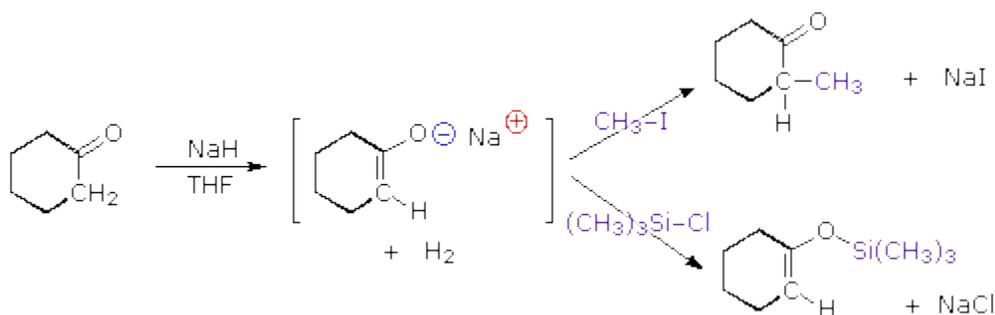


If an alkyl halide undergoes an $\text{S}_{\text{N}}2$ reaction at the carbon atom of an enolate anion the product is an alkylated aldehyde or ketone. On the other hand, if the $\text{S}_{\text{N}}2$ reaction occurs at oxygen the product is an ether derivative of the enol tautomer; such compounds are stable in the absence of acid and may be isolated and characterized. These alkylations (shown above) are irreversible under the conditions normally used for $\text{S}_{\text{N}}2$ reactions, so the product composition should provide a measure of the relative rates of substitution at carbon versus oxygen. It has been found that this competition is sensitive to a number of factors, including negative charge density, solvation, cation coordination and product stability. For alkylation reactions of enolate anions to be useful, these intermediates must be generated in high concentration in the absence of other strong nucleophiles and bases. The aqueous base conditions used for the aldol condensation are not suitable because the enolate anions of simple carbonyl compounds are formed in very low concentration, and hydroxide or alkoxide bases induce competing $\text{S}_{\text{N}}2$ and $\text{E}2$ reactions of alkyl halides. It is necessary, therefore, to achieve complete conversion of aldehyde or ketone reactants to their enolate conjugate bases by treatment with a very strong base ($\text{pK}_{\text{a}} > 25$) in a non-hydroxylic solvent before any alkyl halides are added to the reaction system. Some bases having pK_{a} 's greater than 30 were described earlier, and some others that have been used for enolate anion formation are: NaH (sodium hydride, $\text{pK}_{\text{a}} > 45$), NaNH_2 (sodium amide, $\text{pK}_{\text{a}} = 34$), and $(\text{C}_6\text{H}_5)_3\text{CNa}$ (trityl sodium, $\text{pK}_{\text{a}} = 32$). Ether solvents like tetrahydrofuran (THF) are commonly used for enolate anion formation. With the exception of sodium hydride and sodium amide, most of these bases are soluble in THF. Certain other strong bases, such as alkyl lithium and Grignard reagents, cannot be used to make enolate anions

because they rapidly and irreversibly add to carbonyl groups. Nevertheless, these very strong bases are useful in making soluble amide bases. In the preparation of lithium diisopropylamide (LDA), for example, the only other product is the gaseous alkane butane.



Because of its solubility in THF, LDA is a widely used base for enolate anion formation. In this application one equivalent of diisopropylamine is produced along with the lithium enolate, but this normally does not interfere with the enolate reactions and is easily removed from the products by washing with aqueous acid. Although the reaction of carbonyl compounds with sodium hydride is heterogeneous and slow, sodium enolates are formed with the loss of hydrogen, and no other organic compounds are produced. The following equation provides examples of electrophilic substitution at both carbon and oxygen for the enolate anion derived from cyclohexanone.

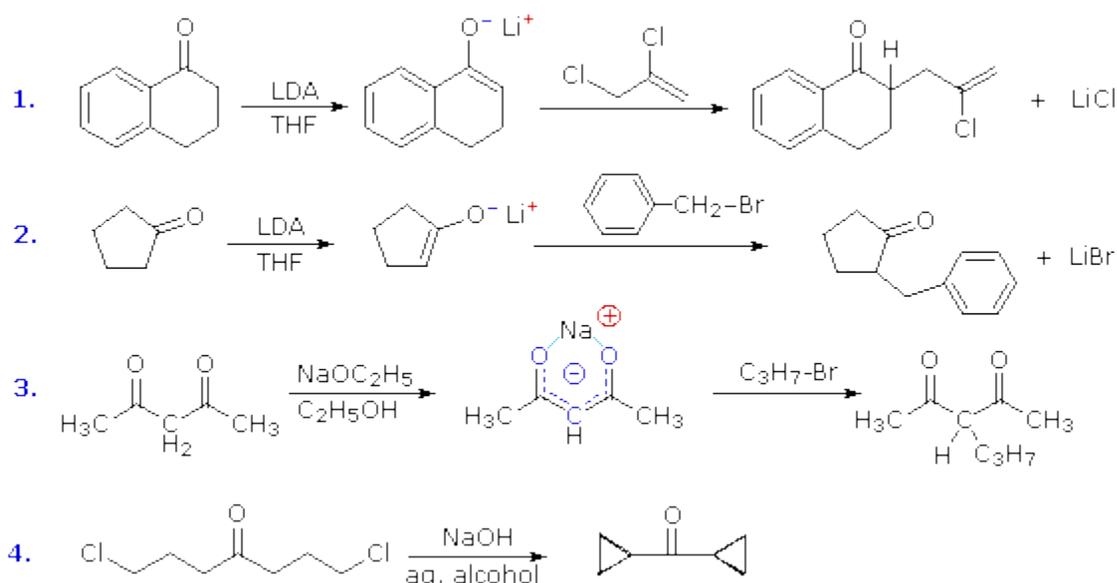


A full analysis of the factors that direct substitution of enolate anions to carbon or oxygen is beyond the scope of this text. However, an outline of some significant characteristics that influence the two reactions shown above is illustrative.

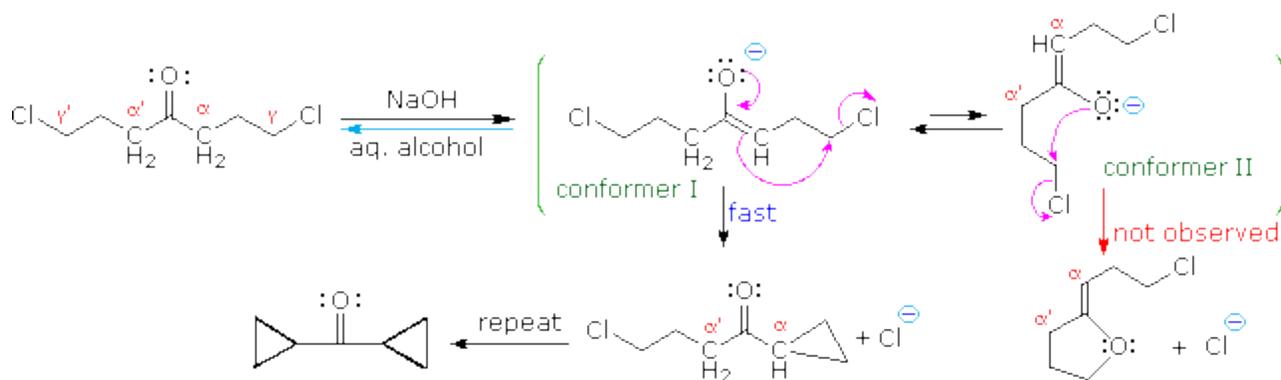
Reactant	Important Factors
CH ₃ -I	The negative charge density is greatest at the oxygen atom (greater electronegativity), and coordination with the sodium cation is stronger there. Because methyl iodide is only a modest electrophile, the S _N 2 transition state resembles the products more than the reactants. Since the C-alkylation product is thermodynamically more stable than the O-alkylated enol ether, this is reflected in the transition state energies.
(CH ₃) ₃ Si-Cl	Trimethylsilyl chloride is a stronger electrophile than methyl iodide (note the electronegativity difference between silicon and chlorine). Relative to the methylation reaction, the S _N 2 transition state will resemble the reactants more than the products. Consequently, reaction at the site of greatest negative charge (oxygen) will be favored. Also, the high Si-O bond energy (over 25 kcal/mole greater than Si-C) thermodynamically favors the silyl enol ether product.

B. Alkylation Reactions of Enolate Anions

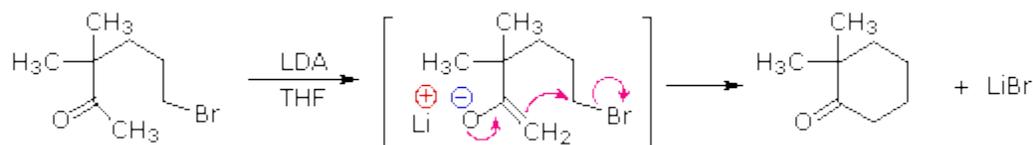
The reaction of alkyl halides with enolate anions presents the same problem of competing S_N2 and $E2$ reaction paths that was encountered earlier in the alkyl halide chapter. Since enolate anions are very strong bases, they will usually cause elimination when reacted with 2° and 3° -halides. Halides that are incapable of elimination and/or have enhanced S_N2 reactivity are the best electrophilic reactants for this purpose. Four examples of the C-alkylation of enolate anions in synthesis are displayed in the following diagram. The first two employ the versatile strong base **LDA**, which is the reagent of choice for most intermolecular alkylations of simple carbonyl compounds. The dichloro alkylating agent used in reaction #1 nicely illustrates the high reactivity of allylic halides and the unreactive nature of vinylic halides in S_N2 reactions.



The additive effect of carbonyl groups on alpha-hydrogen acidity is demonstrated by reaction #3. Here the two hydrogen atoms activated by both carbonyl groups are over 10^{10} times more acidic than the methyl hydrogens on the ends of the carbon chain. Indeed, they are sufficiently acidic ($pK_a = 9$) to allow complete conversion to the enolate anion in aqueous or alcoholic solutions. As shown (in blue), the negative charge of the enolate anion is delocalized over both oxygen atoms and the central carbon. The oxygens are hydrogen bonded to solvent molecules, so the kinetically favored S_N2 reaction occurs at the carbon. The monoalkylated product shown in the equation still has an acidic hydrogen on the central carbon, and another alkyl group may be attached there by repeating this sequence. The last example (reaction #4) is an interesting case of intramolecular alkylation of an enolate anion. Since alkylation reactions are irreversible, it is possible to form small highly strained rings if the reactive sites are in close proximity. Reversible bond-forming reactions, such as the aldol reaction, cannot be used for this purpose. The use of aqueous base in this reaction is also remarkable, in view of the very low enolate anion concentration noted earlier for such systems. It is the rapid intramolecular nature of the alkylation that allows these unfavorable conditions to be used.



The five-carbon chain of the dichloroketone can adopt many conformations, two of which are approximated in the preceding diagram. Although conformer II of the enolate anion could generate a stable five-membered ring by an intramolecular S_N2 reaction, assuming proper orientation of the α and γ' carbon atoms, the concentration of this ideally coiled structure will be very low. In this case O-alkylation of the enolate anion, rather than C-alkylation, is preferred from stereoelectronic arguments (see Baldwin rules). On the other hand, conformations in which the α and γ -carbons are properly aligned for three-membered ring formation are much more numerous, the result being that as fast as the enolate base is formed it undergoes rapid and irreversible cyclization. Ring closures to four, five, six and seven-membered are also possible by intramolecular enolate alkylation, as illustrated by the following example. In general, five and six-membered rings are thermodynamically most stable, whereas three-membered ring formation is favored kinetically.



Source : <http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/aldket2.htm#rx5>