Carbonyl group and Total Synthesis: Targets, Strategies – A Study

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Abstract

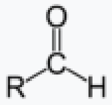
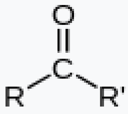
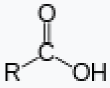
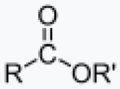
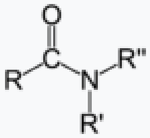
This paper attempts to study how **carbonyl group** a functional group composed of a carbon atom double-bonded to an oxygen atom: C=O is employed in **total synthesis** with several classes of organic compounds, as part of many larger **functional groups targets.** A compound containing a carbonyl group is often referred to as a carbonyl compound. Oxygen is more electronegative than carbon, hence carbonyl compounds often have resonance structures which affect their reactivity. This relative electronegativity draws electron density away from carbon, increasing the bond's polarity, therefore making carbon an electrophile (i.e. slightly positive). Carbon can then be attacked by nucleophiles (e.g. negatively charged ions, like the cyanide ion) or a negatively charged part of another molecule (e.g. the lone pair electrons of nitrogen in the ammonia molecule). During the reaction, the carbon-oxygen double bond is broken, and the carbonyl group may experience addition reactions. This reaction is known as addition-elimination (because a water molecule is often lost) or condensation. The electronegative oxygen also can react with an electrophile; for example a proton in an acidic solution or with Lewis acids to form an oxocarbenium ion. The polarity of oxygen also makes the alpha hydrogens of carbonyl compounds much more acidic (roughly 1030 times more acidic) than typical sp3 C-H bonds, such as those in methane. For example, the pKa values of acetaldehyde and acetone are 16.7 and 19 respectively, while the pKa value of methane is extrapolated to be approximately 50. This is because a carbonyl is in tautomeric resonance with an enol. The deprotonation of the enol with a strong base produces an enolate, which is a powerful nucleophile and can alkylate electrophiles such as other carbonyls.

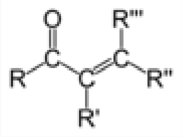
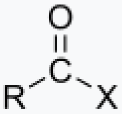
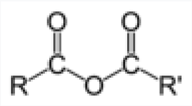
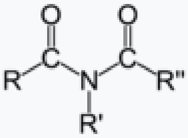
Amides are the most stable of the carbonyl couplings due to their high resonance stabilization between the nitrogen-carbon and carbon-oxygen bonds. In case of multiple carbonyl types in one molecule, one can expect the most electrophilic carbonyl carbon to react first. Acyl chlorides and carboxylic anhydrides react fastest, followed by aldehydes and ketones. Esters react much more slowly and amides are almost completely unreactive due to resonance of the amide nitrogen towards the carbonyl group. This reactivity difference allows chemoselectivity when a reactant contains multiple carbonyl groups. The total synthesis of quinine, a naturally-occurring antimalarial drug, was developed over a 150-year period. The development of synthetic quinine is considered a milestone in organic chemistry although it has never been produced industrially as a substitute for natural occurring quinine.

Key words: Carbonyl group , chemoselectivity , carboxylic Total Synthesis, double-bonded

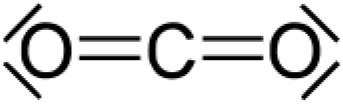
Introduction

A carbonyl group characterizes the following types of compounds:

Compound	Aldehyde	Ketone	Carboxylic acid	Carboxylate ester	Amide
Structure					
General formula	RCHO	RCOR'	RCOOH	RCOOR'	RCONR'R"

Compound	Enone	Acyl halide	Acid anhydride	Imide
Structure				
General formula	RC(O)C(R')CR"R"'	RCOX	(RCO)2O	RC(O)N(R')C(O)R"

Carbon dioxide



Other organic carbonyls are urea and the carbamates, the derivatives of acyl chlorides chloroformates and phosgene, carbonate esters, thioesters, lactones, lactams, hydroxamates, and isocyanates. Examples of inorganic carbonyl compounds are carbon dioxide and carbonyl sulfide.[citation needed]

Industrial chemical needs often differ from academic focuses. Typically, commercial entities may pick up particular avenues of total synthesis efforts and expend considerable resources on particular natural product targets, especially if semi-synthesis can be applied to complex, natural product-derived drugs. Even so, for decades there has been a continuing discussion regarding the value of total synthesis as an academic enterprise. While there are some outliers, the general opinions are that total synthesis has changed in recent decades, will continue to change, and will remain an integral part of chemical research. Within these changes, there has been increasing focus on improving the practicality and marketability of total synthesis methods. The Phil S. Baran group at Scripps, a notable pioneer of practical synthesis have endeavored to create scaleable and high efficiency syntheses that would have more immediate uses outside of academia. Friedrich Wöhler discovered that an organic substance, urea, could be produced from inorganic starting materials in 1828. That was an important conceptual milestone in chemistry by being the first example of a synthesis of a substance that had been known only as a byproduct of living processes. Wöhler obtained urea by treating silver cyanate with ammonium chloride, a simple, one-step synthesis:

$AgNCO + NH4Cl \rightarrow (NH2)2CO + AgCl$

Camphor was a scarce and expensive natural product with a worldwide demand. Haller and Blanc synthesized it from camphor acid; however, the precursor, camphoric acid, had an unknown structure. When Finnish chemist Gustav Komppa synthesized camphoric acid from diethyl oxalate and 3,3-dimethylpentanoic acid in 1904, the structure of the precursors allowed contemporary chemists to infer the complicated ring structure of camphor. Shortly thereafter, William Perkin published another synthesis of camphor. The work on the total chemical synthesis of camphor allowed Komppa to begin industrial production of the compound, in Tainionkoski, Finland, in 1907.

The American chemist Robert Burns Woodward was a pre-eminent figure in developing total syntheses of complex organic molecules, some of his targets being cholesterol, cortisone, strychnine, lysergic acid, reserpine, chlorophyll, colchicine, vitamin B12, and prostaglandin F-2a.

Vincent du Vigneaud was awarded the 1955 Nobel Prize in Chemistry for the total synthesis of the natural polypeptide oxytocin and vasopressin, which reported in 1954 with the citation "for his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone."

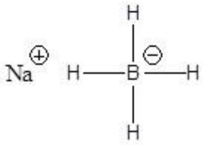
Another gifted chemist is Elias James Corey, who won the Nobel Prize in Chemistry in 1990 for lifetime achievement in total synthesis and for the development of retrosynthetic analysis. The subject has also been attended with some controversy: Gilbert Stork published the first stereoselective total synthesis of quinine in 2001, meanwhile shedding doubt on the earlier claim by Robert Burns Woodward and William Doering in 1944, claiming that the final steps required to convert their last synthetic intermediate, quinotoxine, into quinine would not have worked had Woodward and Doering attempted to perform the experiment. A 2001 editorial published in Chemical & Engineering News sided with Stork, but the controversy was eventually laid to rest once and for all when Williams and coworkers successfully repeated Woodward's proposed conversion of quinotoxine to quinine in 2007.

Objective:

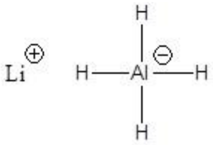
This paper intends to explore and analyze **Carbonyl groups** that are found in a variety of organic compounds, and they can be structured as synthetic steroids like norethindrone with **total synthesis** of optically active lycopladine by utilizing diastereoselective protection.

Reduction of Aldehydes and Ketones

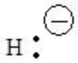
The most common sources of the hydride nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.



Sodium Borohydride

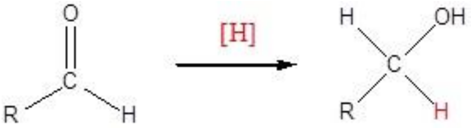


Lithium Aluminum Hydride

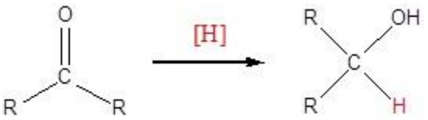


Hydride Nucleophile

Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which upon protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols.



Aldehyde **1° Alcohol**



Ketone **2° Alcohol**

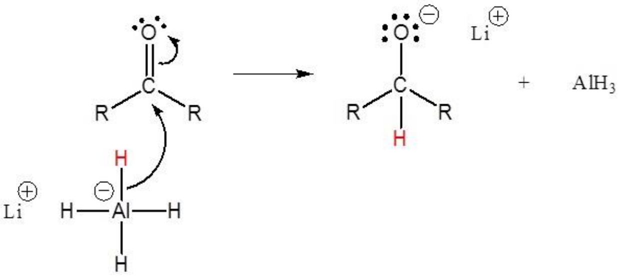
In metal hydrides reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. A carbonyl (aldehyde or ketone) plus two electrons and two protons becomes an alcohol.

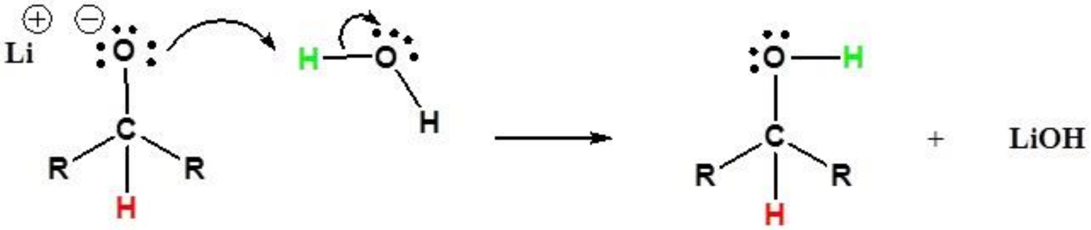
Mechanism

This mechanism is for a $LiAlH_4$ reduction. The mechanism for a $NaBH_4$ reduction is the same except methanol is the proton source used in the second step.

1) Nucleopilic hydride anion reacts with the electrophilic carbonyl carbon forcing the pi electrons onto the electronegative oxygen atom.

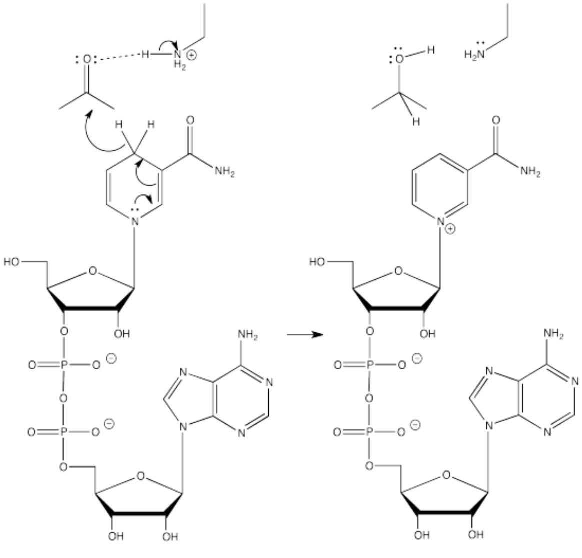


2) The alkoxide is protonated.



Biological Reduction

Addition to a carbonyl by a semi-anionic hydride, such as $NaBH_4$, results in conversion of the carbonyl compound to an alcohol. The hydride from the BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.



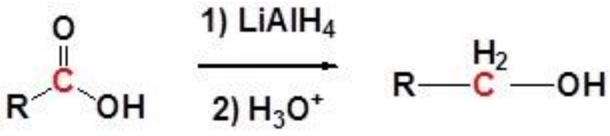
NADH NAD+

Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

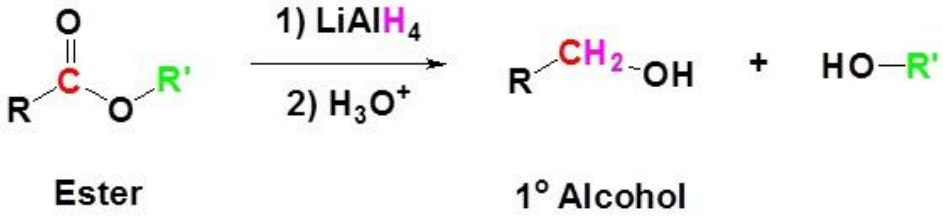
NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Insetad of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.

Reduction of Carboxylic Acids and Esters

Carboxylic acids can be converted to 1° alcohols using Lithium aluminum hydride ($LiAlH_4$). Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.

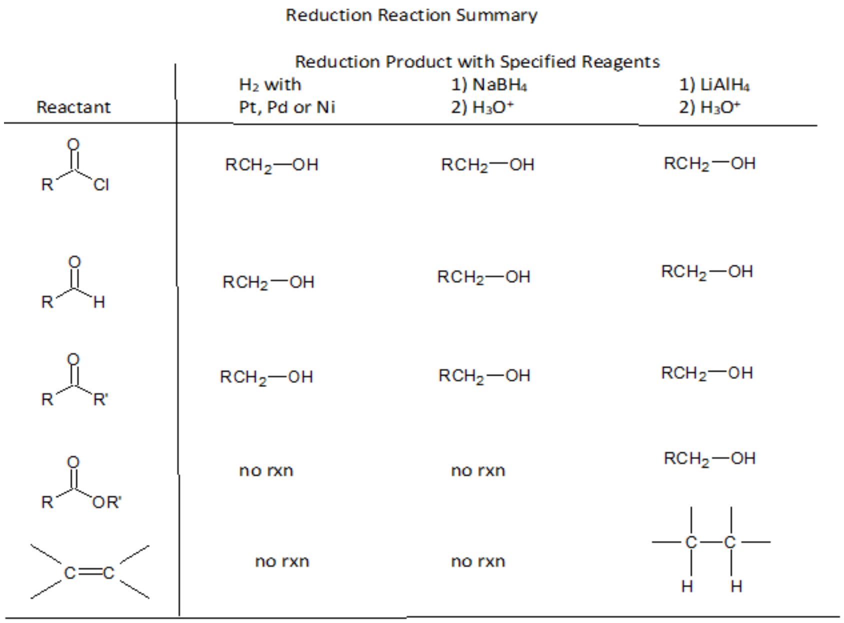


Esters can be converted to 1° alcohols using $LiAlH_4$, while sodium borohydride (NaBH4NaBH4) is not a strong enough reducing agent to perform this reaction.



Reduction Reaction Summary

The table below summarize the reduction reactions covered so far in our text. It is important to distinguish between functional group reactivity as we add more multiple-step synthetic pathways.



Reduction Reaction Summary

Reactant	Reduction Product with Specified Reagents H_2 with Pt, Pd or Ni	 1) $NaBH_4$ 2) H_3O^+	 1) $LiAlH_4$ 2) H_3O^+
$RCOCl$	RCH_2-OH	RCH_2-OH	RCH_2-OH
$RCHO$	RCH_2-OH	RCH_2-OH	RCH_2-OH
$RCOR'$	RCH_2-OH	RCH_2-OH	RCH_2-OH
$RCOOR'$	no rxn	no rxn	RCH_2-OH
$C=C$	no rxn	no rxn	$-\underset{H}{C}-\underset{H}{C}-$

A special group of carbonyl compounds are **1,3-dicarbonyl compounds** that have acidic protons in the central methylene unit. Examples are Meldrum's acid, diethyl malonate and acetylacetone. Total synthesis is the complete chemical synthesis of a complex molecule, often a natural product, from simple, commercially-available precursors. It usually refers to a process not involving the aid of biological processes, which distinguishes it from semisynthesis. Syntheses may sometimes conclude at a precursor with further known synthetic pathways to a target molecule, in which case it is known as a formal synthesis. Total synthesis target molecules can be natural products, medicinally-important active ingredients, known intermediates, or molecules of theoretical interest. Total synthesis targets can also be organometallic or inorganic, though these are rarely encountered. Total synthesis projects often requires a wide diversity of reactions and reagents, and subsequently requires broad chemical knowledge and training to be successful.

Often, the aim is to discover a new route of synthesis for a target molecule for which there already exist known routes. Sometimes, however, no route exists and chemists wish to find a viable route for the first time. Total synthesis is particularly important for the discovery of new chemical reactions and new chemical reagents, as well as establishing synthetic routes for medicinally important compounds. There are numerous classes of natural products for which total synthesis is applied to. These include (but are not limited to): terpenes, alkaloids, polyketides, and polyethers. Total synthesis targets are sometimes referred to by their organismal origin such as plant, marine, and fungal. The term total synthesis is less frequently but still accurately applied to the synthesis of natural polypeptides and polynucleotides. The peptide hormones oxytocin and vasopressin were isolated and their total syntheses first reported in 1954. It is not uncommon for natural product targets to feature multiple structural components of several natural product classes. Although untrue from a historical perspective (see the history of the steroid, cortisone), total synthesis in the modern age has largely been an academic endeavor (in terms of manpower applied to problems).

Conclusion

The carbonyl group is C=O with the carbon atom bonded to two other atoms. Carbonyl compounds with only hydrogen, alkyl, or aryl groups bonded to the carbonyl carbon atom are aldehydes or ketones. Aldehydes have one hydrogen atom and one alkyl or aryl group bonded to the carbonyl carbon atom. Ketones have only alkyl or aryl groups bonded to the carbonyl carbon atom.Carbonyl groups not adjacent to a heteroatom are less stabilized by resonance and react with the relatively weakly nucleophilic ‘ketonic’ reagents. If carbonyl groups of both types are present, as in (Z = O, NH), then the carbonyl group not adjacent to the heteroatom is preferentially attacked. Thus, isatin and indoxyl and their O- and S-analogues. Carbonyl groups with lower reactivities can be transformed in the presence of more reactive ones by treatment with PPhand TMSOTf prior to the reaction (TMS=trimethylsilyl, Tf=trifluoromethanesulfonyl). This methodology can be applied to reduction and alkylation reactions, and enabled the short asymmetric total synthesis of (+)-centrolobine with the highest overall yield reported to date.

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