CHEMISTRY OF NATURAL COMPOUNDS

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Contents

Summary

Natural products have attracted chemists and biologists. The structures of most natural products are extremely varied and often very complex, showing a wide reactivity range and different physiological properties. However, they appear to originate from general biosynthetic schemes, common to all or nearly all species populating our planet. Natural compounds can be divided into two main classes: primary metabolites and secondary metabolites; primary metabolites are the fundamental building blocks common to all living matter. Secondary metabolites reflect the differentiation of the species and are natural products typical of only specific groups of organisms. This contribution will cover basic biosynthetic topics, such as fundamental biogenetic pathways to primary metabolites, the reaction mechanisms most frequently involved in enzyme-catalyzed processes, the key roles played by coenzymes. Main pathway for the biosynthesis of main classes of biomolecules such as lipids, carbohydrates, nucleic acids, and amino acids, peptides and proteins will be considered, together with their biological relevance and activity.

1. Introduction

This chapter will give groundwork in natural product chemistry, by considering their biosynthesis. All organisms need to synthesize and interconvert a vast array of organic molecules, in order to grow, live and reproduce. Some of the crucially important molecules of life are carbohydrates, proteins, fats, and nucleic acids. Apart from fats, these are polymeric material. Carbohydrates are composed of monosaccharide units, while proteins are built up from amino acids, and nucleic acids are based on nucleotides. Organisms vary widely in their capacity to synthesize and transform chemicals. Despite the wide variety of living organisms, the metabolic pathways (network of enzyme-mediated chemical reactions) for the modification of carbohydrates, nucleic acids, proteins and fats are essentially the same in all organisms, apart from minor variations. These processes are collectively indicated as primary metabolism, with the compounds involved in the pathways termed primary metabolites. Thus, for example, degradation of

carbohydrates generally proceeds via the glycolysis, and the Krebs/citric acid/tricarboxylic acid cycle, accompanied by release of energy. Proteins taken in as food provide amino acids, but in different proportions from the organism requirements. Hence, metabolic pathways will interconvert amino acids, or degrade those not required, providing an additional source of energy. In contrast to these primary metabolic pathways, which synthesize, degrade, and interconvert compounds generally encountered in all organisms, a metabolism concerned with compounds which have a much more limited distribution in Nature also exists. Such molecules, indicated as secondary metabolites, are found in only specific groups of organisms, and are an expression of the individuality of species. In this chapter we will focus especially on primary metabolites, such as carbohydrates, fats, amino acids and proteins.

2. Chemistry of natural products: a general perspective

Natural products are synthesized in living organisms by a sequence of reactions generally catalyzed by enzymes. Enzymes are biochemical catalysts composed of amino acids, which facilitate chemical modifications by lowering the energy of activation. In many cases a suitable cofactor is required for affecting the biotransformation. Relatively few building blocks are routinely employed in Nature. The most frequently encountered building blocks in producing the carbon and/or nitrogen skeleton of a natural compound are included in Figure 1.

The simplest of the building blocks is composed of a unique carbon atom, usually in the form of a methyl group, derived from L-methionine (Figure 1.A). A two carbon atom unit is frequently supplied by acetyl coenzyme A (acetyl-CoA, Figure 1.B). The acetyl group is the building block of choice for the construction of a long alkyl chain (as in fatty acids) or may be part of aromatic systems (phenols). The isoprene unit (Figure 1.C) is a branched chain five carbon unit, derived from acetyl-CoA, via the mevalonate pathway, or from deoxyxylulose phosphate; this C_5 unit is a fundamental building block for terpene and steroid biosynthesis. More complex building blocks can be found; a C_6C_3 unit (Figure 1.D) can be derived from the carbon skeleton of L-phenylalanine or L-tyrosine, after loss of the amino function. The C_3 side chain can be saturated, unsaturated or even oxygenated; in addition this is precursor of the C_6C_2 or C_6C_1 unit after one or two carbons are removed; also C_6C_2N units are derived from L-phenylalanine or L-tyrosine (Figure 1.D), after decarboxylation, or the indole-C_2N unit obtained from L-triptophan (Figure 1.E), after decarboxylation as well, the C_4N usually found as a heterocyclic pyrrolidine system, derived from the non-proteinogenic amino acids L-ornithine (Figure 1.F), and finally the C_5N unit produced from L-lysine to form usually the piperidine ring system (Figure 1.G). No oxygenated building blocks have been taken into account, since oxygen atom can be introduced and removed by many different processes, which cannot be easily summarised.
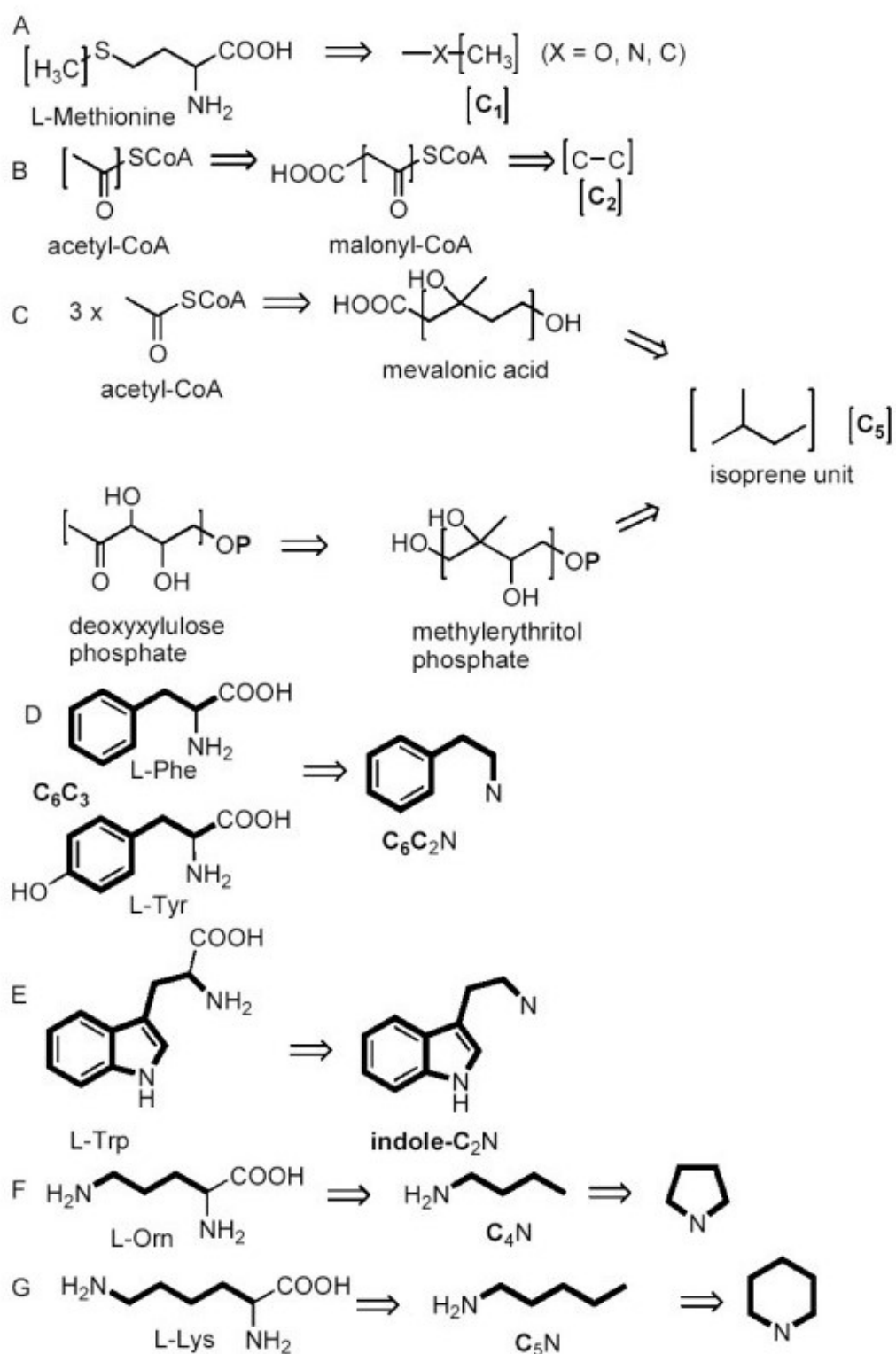
Figure 1: Building blocks frequently encountered in the synthesis of natural compounds.

Chemistry of the reactions catalyzed by enzymes for the synthesis of natural products present many analogies and can be grouped in terms of chemical reaction; in many cases, a suitable cofactor may be bound to the enzyme and needed for the chemical transformation.

2.1. Alkylation Reactions

2.1.1. Nucleophilic Substitution

Nucleophilic substitution is encountered in methylation reaction; the C_1 unit is supplied by L-methionine which is converted to S-adenosylmethionine (SAM, Figure 2.A) in order to form a better leaving group. The positively charged sulfur atom then facilitates the SN_2 type nucleophilic substitution; thus, nitrogen and oxygen nucleophiles can be methylated (Figure 2.B). Also carbon atoms can function as nucleophiles. This is the case of position ortho or para in a phenol ring (Figure 2.C), or carbons adjacent to one or more carbonyl groups.
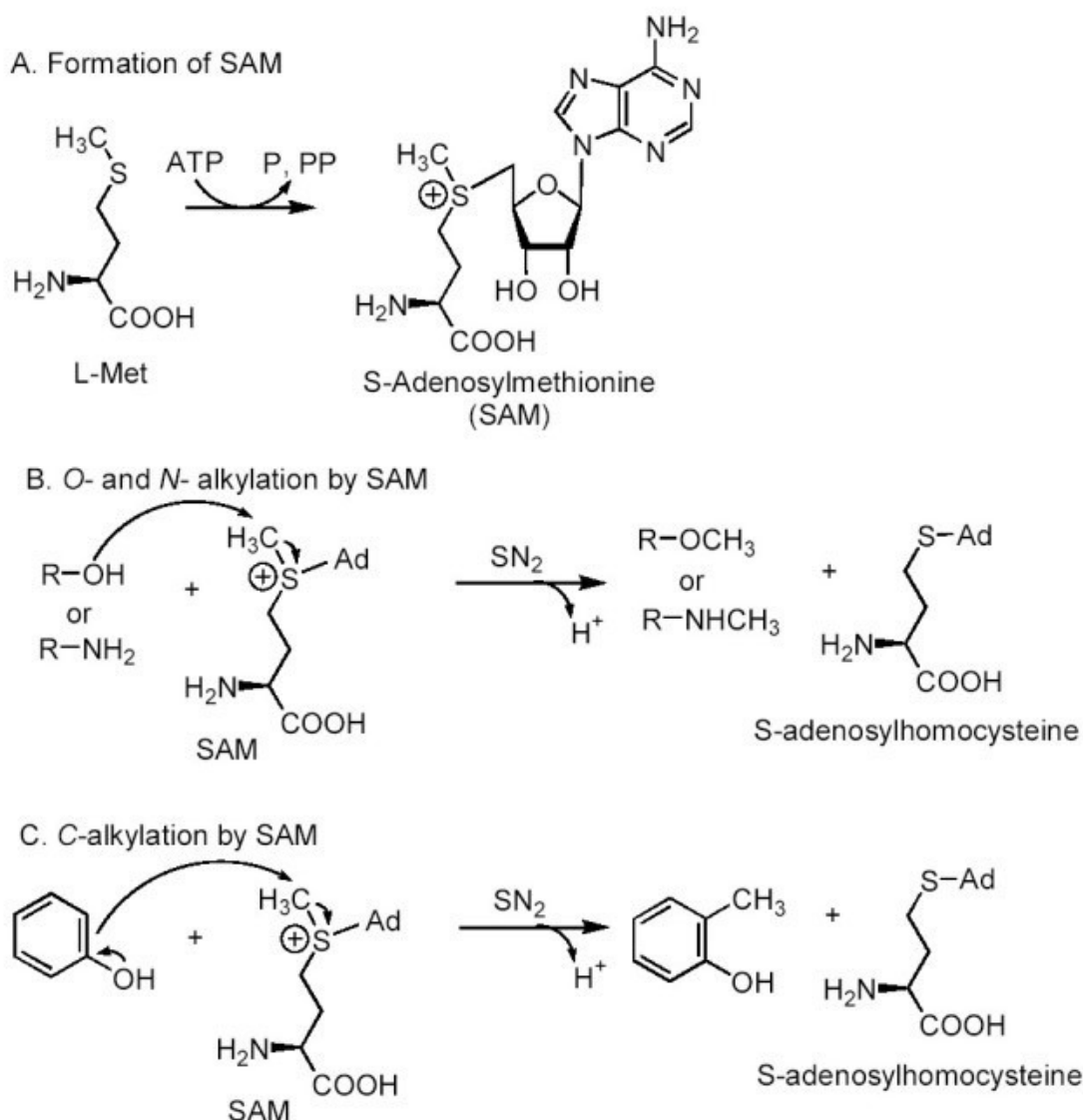

Figure 2: Alkylation reaction by SAM.

A C5 isoprene unit in the form of dimethylallyl diphosphate (DMAPP) may also act as an alkylating agent, the diphosphate being a good leaving group. In this case there are evidence that both SN_2 or SN_1 type substitution (where a resonance stabilized allylic carbocation is formed) can operate (Figure 3).
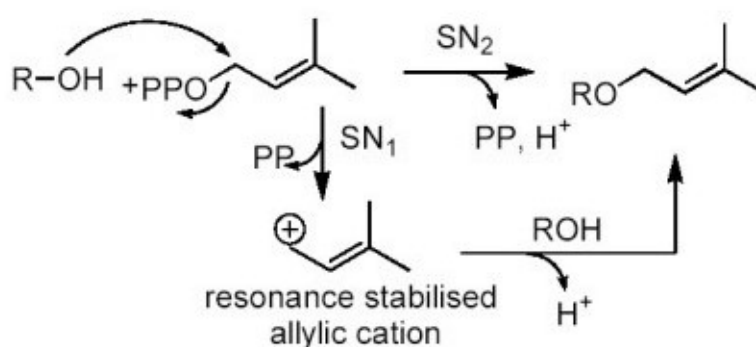
Figure 3: Alkylation reaction mediated by DMAPP

2.1.2. Electrophilic Addition

Electrophilic additions can be rationalized in terms of carbocation chemistry, such as electrophilic addition of carbocations to alkenes. In general, initial carbocations giving electrophilic attack can be generated by a number of mechanisms. These include the loss of a good leaving group, especially diphosphate (PP), protonation of an alkene, and protonation/ring opening of epoxides, or by alkene methylation mediated by SAM (Figure 4.A). The electrophilic addition of the carbocation will lead to a new carbocation which can evolve essentially in two different ways (Figure 4.B): by loss of a proton, sometimes after a Wagner-Meerwein rearrangement, giving a new alkene, or more rarely a cyclopropane ring, or by attack of a suitable nucleofile, especially water.
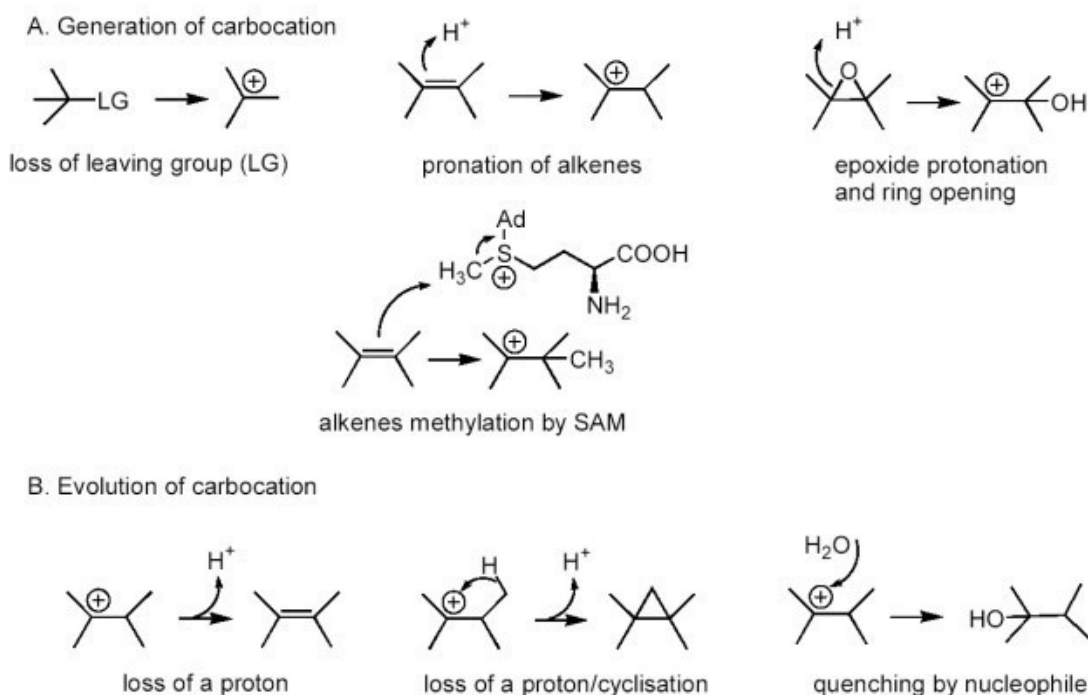

Figure 4: General mechanisms for the generation of electrophiles

In the biosynthesis of terpenoids and steroids DMAPP is ionized to the corresponding allylic carbocation and gives electrophilic addition to alkenes; the alkene which

undergoes electrophilic addition is isopentenyl diphosphate (IPP, Figure 5). The resultant carbocation then can lose a proton, to give the uncharged geranyl diphosphate (GPP, route a), or give an intramolecular addition affording cyclic products (route b).
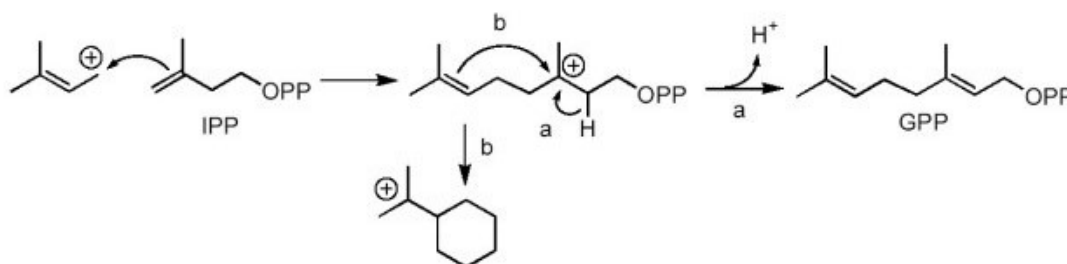

Figure 5: Alkylation reaction of IPP

2.2. Wagner-Meerwein Rearrangements

The biosynthesis of a wide range of natural products, such as steroids or terpenoids, can only be explained as originating after fundamental rearrangement process has occurred. These rearrangements are almost always consistent with the participation of carbocation intermediates, generated by SN_1 mechanisms or by loss of a suitable leaving group. They typically consist of 1,2-shifts of hydride, methyl, or alkyl groups; occasionally, 1,3- or longer shifts are encountered. These shifts, termed Wagner-Meerwein rearrangements, are readily rationalized in terms of generating a more stable carbocation, or relaxing ring strain (Figure 6).
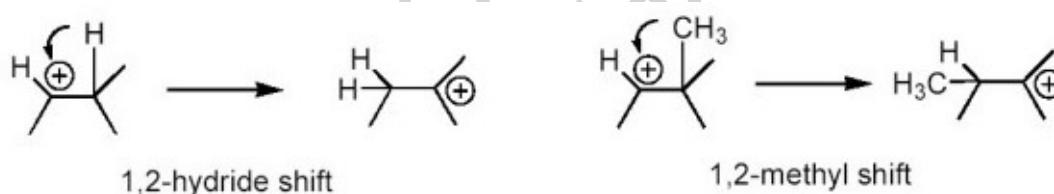

Figure 6: Wagner-Meerwein rearrangments.

Hence, tertiary carbocation are preferred over secondary ones; however a tertiary to secondary transition might be favored if the rearrangements allows ring strain release. One should be aware that these general concepts are not always respected in Nature, and it must be remembered that all reactions are enzyme-mediated and that carbocations may not exist as discrete entities.

2.3. Aldol and Claisen Reactions

Carbon-carbon bond formation is frequently obtained by aldol and Claisen condensations, based on the enolate formation of a suitable carbonyl system. An aldol type reaction occurs on aldehydes and ketones, while Claisen condensation occurs on esters and thioesters (Figure 7).
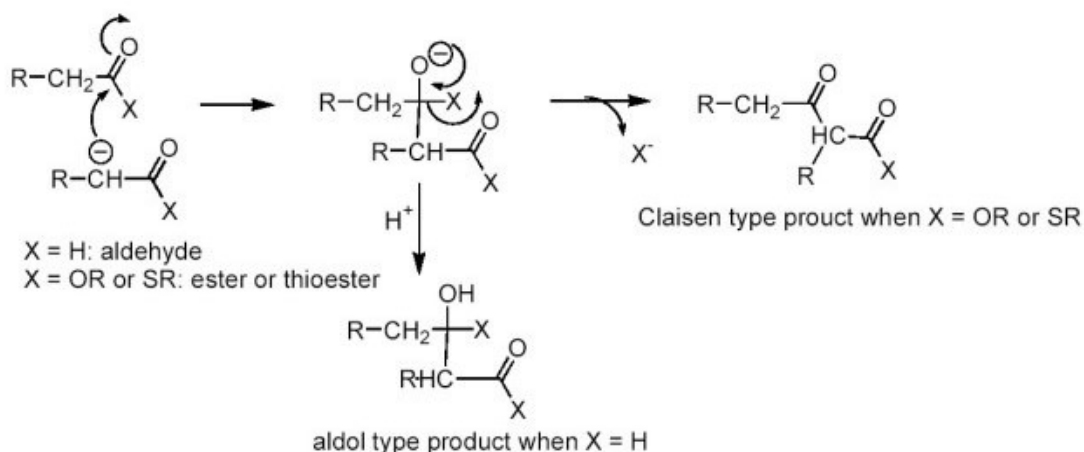
Figure 7: Aldol and Claisen condensation reactions.

When a thioester is involved in the enzymatic reaction, in most cases this is a coenzyme A ester, such as acetyl-CoA (Figure 8).
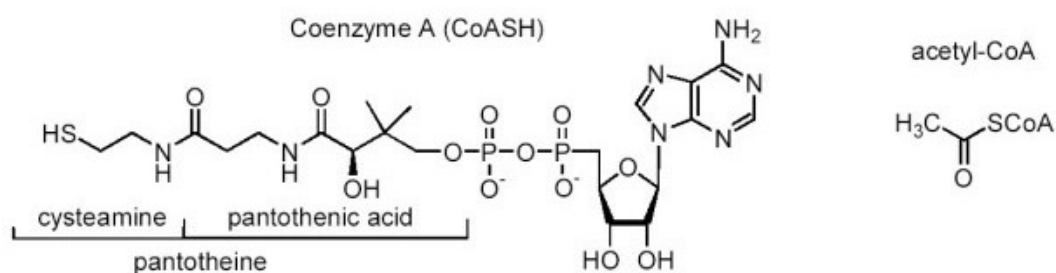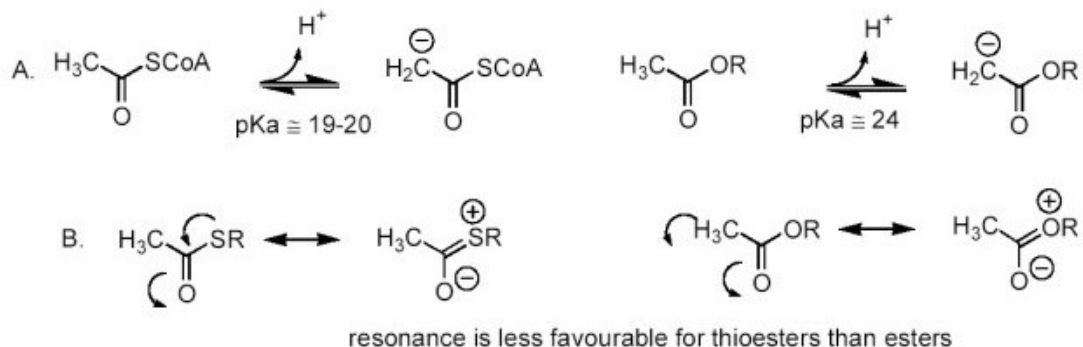

Figure 8: Structure of Coenzyme A and its acetyc thioester.

These processes are fundamental both for the synthesis of primary and secondary metabolites. A thioester has significant advantages: α-methylene hydrogens are more acidic then in the corresponding oxygen esters, comparable to the equivalent ketone (Figure 9.A). This can be explained in terms of electron delocalization (Figure 9.B): this resonance is more important in the oxygen ester, then in the thioester, due to oxygen's smaller size and thus closer proximity of the lone pair to overlap with carbon's orbitals.

Figure 9: Comparison of thioester and ester α-hydrogen acidity.

Furthermore, the thioester is a better leaving group then the oxygen ester, giving a combined effect of increased reactivity. Claisen reactions involving acetyl-CoA, are rendered even more favorable by first converting acetyl-CoA into malonyl-CoA, via a carboxylation reaction with CO_2, mediated by biotin as coenzyme, and ATP (Figure 10). CO_2 is activated as mixed anhydride by ATP, then carboxylates the coenzyme in a biotin-enzyme complex. Fixation of carbon dioxide by biotin occurs also in the generation of oxaloacetate from pyruvate in the biosynthesis of glucose from non-carbohydrate sources (gluconeogenesis). Then, the carboxybiotin-enzyme forms malonyl-CoA. α-Hydrogens of malonyl-CoA, flanked by two carbonyl groups, have enhanced acidity then the acetyl-CoA; in this way, a better nucleophile is provided for the Claisen reaction.
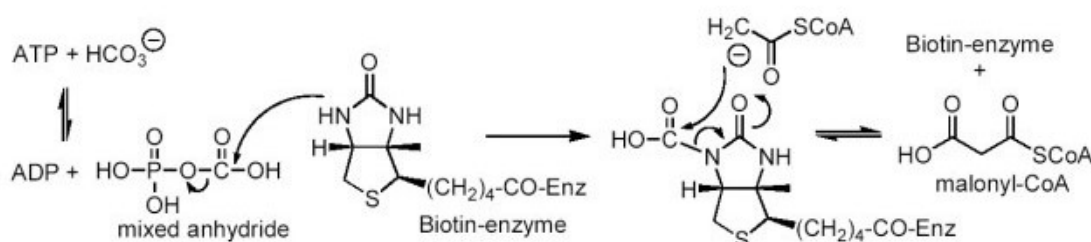

Figure 10. Synthesis of malonyl-CoA

The carboxylic group of malonyl-CoA is immediately lost by a decarboxylation reaction during the Claisen condensation (Figure 11).
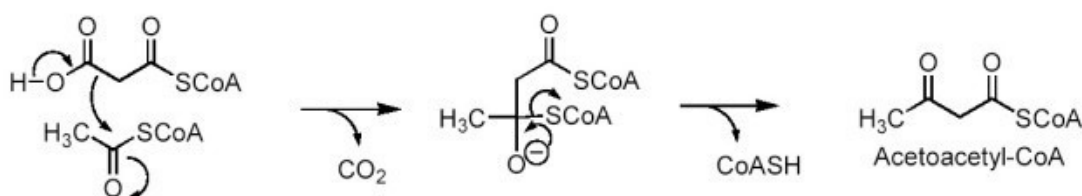

Figure 11: Claisen condensation to acetoacetyl-CoA

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Bibliography

Binckley R.W. (1988) *Modern Carbohydrate Chemistry*. Marcel Dekker Inc, New York. [Exhaustive book on carbohydrate chemistry].

Collins P.M. and ferrier R.J. (1995) *Monosaccharides-Their Chemistry and Their Roles in Natural Products*. John Wiley & Sons, Ltd. [Exhaustive book on carbohydrate chemistry].

Davis B.J. and Fairbanks A.J. (2003) *Carbohydrate Chemistry*. Oxford University Press Inc, New York, vol 99. [Exhaustive book on carbohydrate chemistry].

Dewick P.M. (2001). *Medicinal Natural Products-A Biosynthetic Approach* John Wiley & Sons, Ltd. [This book present a comprehensive outline of biosynthetic pathway and mechanisms, focusing on secondary metabolites].

Gunstone F.D. and Herslof, B.G. (2000). *Lipid Glossary 2*. The Oily Press, Bridgwater TA7 0YZ England [Source of information on lipid structures available at no cost on the Internet http://www.pjbarnes.co.uk/op/lg2.htm].

Hamilton R.J. (1995) *Waxes: Chemistry, Molecular Biology and Functions*. The Oily Press, Bridgwater TA7 0YZ England. [Source of information on natural waxes].

Kolattukudy P.E. (1976) *Chemistry and Biochemistry of Natural Waxes*. Elsevier, Amsterdam. [Source of information on natural waxes].

Mann J. (1994) *Chemical Aspects of Biosynthesis*. Oxford Chemistry Primers, Oxford. [This book focuses on chemical mechanisms encountered in biosynthetic pathways].

Biographical Sketch

Cipolla, Laura was born in Milan in 1968, graduated in Chemistry at the University of Milan in 1993, in 1996 received her Ph.D in Chemistry at the University of Milan (Mentor Prof. F. Nicotra). In 1997 she worked as a post-doc fellow at the Carlsberg Research Laboratory, Copenhagen, Denmark, Claus Bock being the supervisor. In 1998 and 1999 she came back to University of Milan with a post-doc fellowship (Supervisor Prof. F. Nicotra). In October 1999 she joined the Biotechnology and Biosciences Department of the University of Milano-Bicocca as researcher. In April 2005 she got an Associate Professor position in Organic Chemistry. Co-author of more then forty publications on international scientific journals, three book's chapter on carbohydrate and peptidomimetic chemistry, and more then 70 communications at national and international meetings.
Application reviewer for international funding agency (Netherlands Organisation for Scientific Research-NOW-Chemical Sciences.
Current scientific interests focus on the synthesis and biological activity of carbohydrate analogues and peptidomimetics.