Method of synthesis of Amides and its Biological significance

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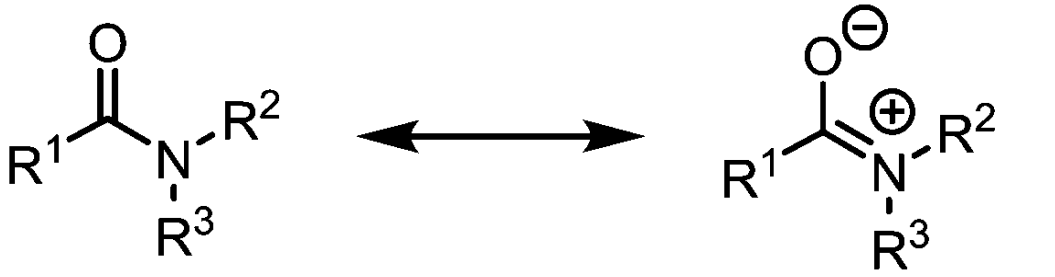
Abstract: An **amide functional group** consists of a carbonyl **group** bonded to a nitrogen. In simple **amides**, two hydrogen atoms are bonded to the nitrogen (-CONH2) while in more complex **amides**, the nitrogen is bonded to one or two aliphatic or aromatic **groups** (-CONR2).

Keywords: - Amide , Benzamide ,Amino acid, Isopeptide.

Introduction: In organic chemistry, an **amide**, also known as an **organic amide** or a **carboxamide**, is a compound with the general formula RC(=O)NR′R″, where R, R', and R″ represent organic groups or hydrogens atoms.(1-2) The amide group is called a peptide bond when it is part of the main chain of a protein, and isopeptide bond when it occurs in a side chain, such as in the amino acids asparagine and glutamine. It can be viewed as a derivative of a carboxylic acids RC(=O)OH with the hydroxyl group –OH replaced by an amine group –NR′R″; or, equivalently, an acyl group RC(=O)– joined to an amine group.

Common examples of amides are acetamide $H_3C–CONH2$, benzamide $C_6H_5–CONH2$, and dimethylformamide $HCON(–CH_3)_2$.



classical representation of an amide *zwitterionic amide mesomer*

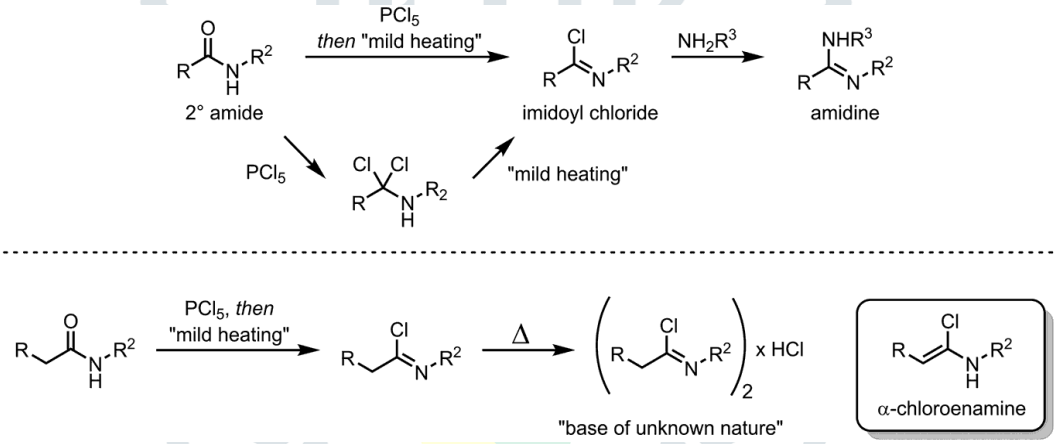
Pic-1

In their classical representation, carboxamides comprise a central carbon atom possessing a double bond to oxygen and a single bond to nitrogen. This representation, however, is grossly incomplete given that nitrogen lone-pair delocalization plays a crucial role in dictating the structure and reactivity of amides (Pic -1). Indeed, this delocalization imparts an increased stabilization to the electrophilic carbonyl carbon, especially when compared to other carbonyl and carboxyl derivatives, resulting in considerably reduced reactivity towards nucleophiles.(3-5) It has therefore long been textbook knowledge that, in contrast to acyl halides, anhydrides and esters, amides do not readily undergo addition of, for example, alcohols, amines or mild hydride sources, thereby precluding any chemo selective amide-transformations in the presence of other carbonyl functional groups. In addition, primary and secondary amides will not undergo addition of Grignard reagents or similar strong nucleophiles, but will rather be deprotonated at nitrogen. This difference in reactivity has led to a

perception of amides as significantly less useful functional handles than their ester and acid chloride counterparts. To the same extent that amides are weak electrophiles at carbon, they have historically been shown to be powerful nucleophiles at oxygen, leading to the emergence of the field of "amide activation". (6-10)

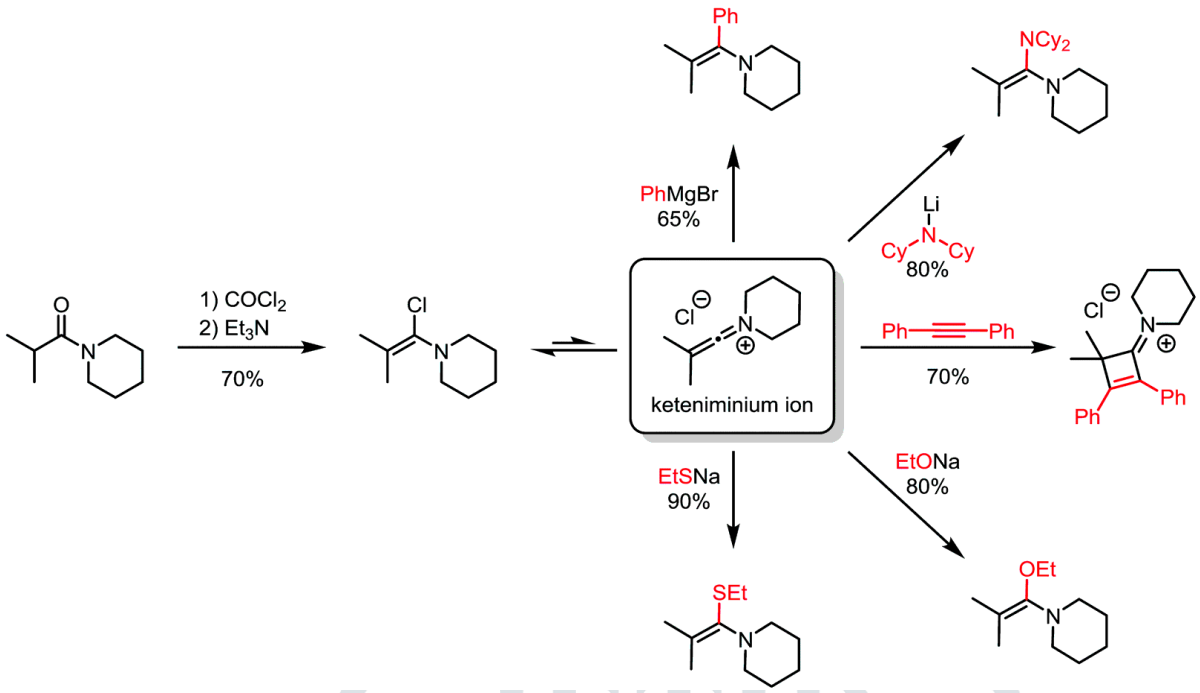
The origins of electrophilic amide activation date back to the 19th century: as early as 1877 it was common knowledge that primary (NH_2) amides can be converted to the corresponding nitriles through treatment with dehydration agents. (11) However, all dehydration attempts of secondary and tertiary amides using phosphoric anhydride failed.

In 1877 Wallach et.al prepared a secondary amide in presence of phosphorus pentachloride.(12) In this preparation several ground-breaking discoveries were detailed: first, the observed formation of α-dichloroamines, which decomposed smoothly to the corresponding α-chloroimines (imidoyl chlorides); second, the demonstration that the imidoyl chloride of *N*-phenyl acetamide dimerized under loss of hydrogen chloride to "base(s) of unknown nature" which contained chlorine. The latter was most likely the first instance of intermediate preparation of an α-chloroenamine (pic-2). Moreover, Wallach recognized the highly electrophilic character of imidoyl chlorides and showed that they can be converted generally and easily to the corresponding amidines by treatment with amines.



Pic-2

The formation of an α-chloroenamine was claimed: a tertiary amide was treated with phosphorus pentachloride to yield a compound, whose hydrolysis to the corresponding amide, unlike the related imidoyl chloride, was shown to be relatively difficult. (13) H. G. Viehe, L. Ghosez and co-workers published a new method for the preparation of alkyl and aryl α-chloroenamines from the corresponding 3° amides, using phosgene with subsequent deprotonation of the cationic imidoyl chloride salt. (14) The chemical behaviour of these compounds was partly predictable based on knowledge gained from previous studies: the hydrolysis to the amide, the addition of elemental bromine or hydrogen chloride and subsequent elimination to the corresponding enamines. However, the outstanding ability for nucleophilic substitution of the chloride seemed to surprise the authors: Grignard reagents, organolithium compounds, thiolates, alkoxides and lithium amides (deprotonated amines) yielded the substitution products in moderate to high yields. (pic-3) Viehe *et al.* were able to show that α-chloroenamines can be readily employed in formal [2+2] cycloadditions with acetylenes, forming the corresponding cyclobutenone derivatives in good yields. The extraordinary reactivity was believed to be due to an equilibrium of the α-chloroenamine with the corresponding keteniminium chloride. This report marked the beginning of modern electrophilic amide activation in organic synthesis.



Pic-3

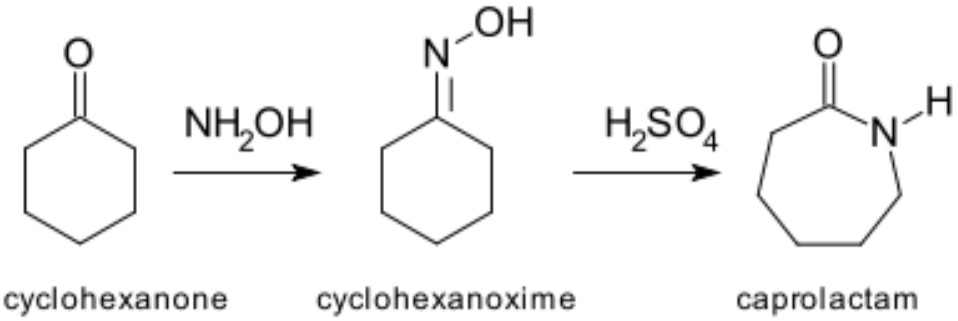
In the 1970s, the Ghosez group initiated further investigations into the preparation of α-chloroenamines and their reactivity in cycloaddition reactions. They observed that, in contrast to ketenes, particularly electron-rich unsaturations are not necessary to perform cycloadditions with keteniminium ions: even the simplest alkene, ethylene, is a competent reaction partner in the [2+2]-cycloaddition of keteniminium ions at ambient temperature.(15-16) Those reagents thus surpass ketenes in their reactivity, as ketenes require elevated temperatures to react with simple alkenes. (17)

In the same year, [2+2]-cycloadditions of *in situ* formed keteniminium ions with conjugated dienes and alkenes were reported. (18) The reactions were generally clean: the Diels–Alder product was absent, and the only observable side product was the parent amide. For non-symmetrical dienes, the least substituted double bond was favoured for the cycloaddition and both *cis*- and *trans*-alkenes formed the desired products with high stereospecificity. (18) The scope was quickly extended to the synthesis of cyclobutenones using simple alkynes, (19) and to the synthesis of 2-amino-1-azetines, (20) and β-lactams using imines as cycloaddition partners. (21)

Beckmann rearrangement : The **Beckmann rearrangement**, named after the German chemist Ernst Otto Beckmann (1853–1923), is a rearrangement of an oxime functional group to substituted Amides .(22-23) The rearrangement has also been successful performed on haloimines and nitrones. Cyclic oximes and haloimines yield lactums.

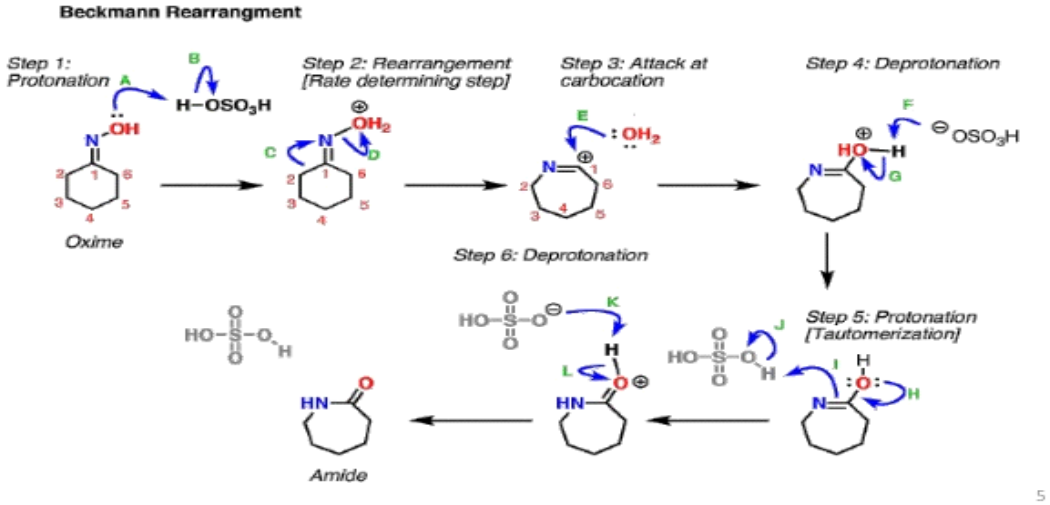
The Beckmann rearrangement is often catalyzed by acid, however other reagents have been known to promote the rearrangement. These include tosyl chloride, thionyl c, PCl5, phosphorous pentoxide, triethylamine, NaOH, trimethylsilyl iodide among others.(24) The **Beckmann fragmentation** is another reaction that often competes

with the rearrangement, though careful selection of promoting reagent and solvent conditions can favor the formation of one over the other, sometimes giving almost exclusively one product. The rearrangement occurs stereospecifically for ketoxime and N-chloro/N-fluoro imines, with the migrating group being anti-periplanar to the leaving group on the nitrogen. Certain conditions have been known to racemize the oxime geometry, leading to the formation of both regeoisomers. The rearrangement of aldoximes occurs with stereospecificity in the gas-phase and without stereospecificity in the solution phase. A few methodologies allow for the rearrangement of aldoximes to primary amides, but fragmentation commonly competes in these systems. Nitrone rearrangement also occurs without stereospecificity; the regioisomer formed has the amide nitrogen substituted with the group possessing the greatest migratory aptitude.



Reaction mechanism

This rearrangement take place an alkyl migration with expulsion of the hydroxyl group to form a nitrilium ion followed by hydrolysis.



The archetypal Beckmann rearrangement (25) is the conversion of cyclohexanone to caprolactum via the oxime. Caprolactam is the feedstock in the production of Nylon 6. (26)

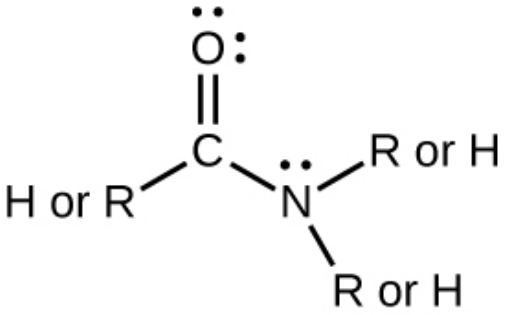
The **Beckmann solution** consists of acetic acid, hydrochloric acid and acetic anhydride, and was widely used to catalyze the rearrangement. Other acids, such as sulfuric acid, polyphosphoric acid, and hydrogen fluoride have all been used. Sulfuric acid is the most commonly used acid for commercial lactam production due to its formation of

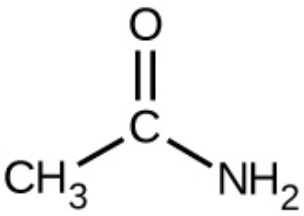
an ammonium sulfate by-product when neutralized with ammonia. Ammonium sulphate is a common agricultural fertilizer providing nitrogen and sulfur.

Biological significance of amides:

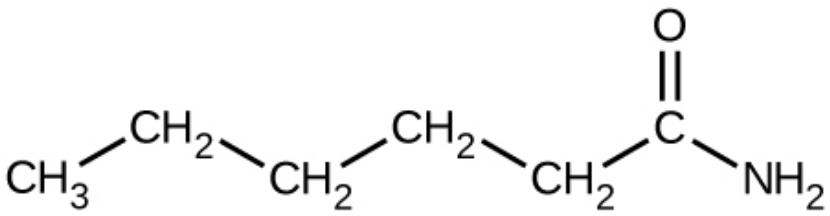
The **Amide bond formation reactions are among the most important transformations in organic chemistry and biochemistry** because of the widespread occurrence of amides in pharmaceuticals, natural products and biologically active compounds. The amide group is widely present in the drugs, intermediates, pharmaceuticals, and natural products.

Amides are molecules that contain nitrogen atoms connected to the carbon atom of a carbonyl group. Like amines, various nomenclature rules may be used to name amides, but all include use of the class-specific suffix -*amide*:



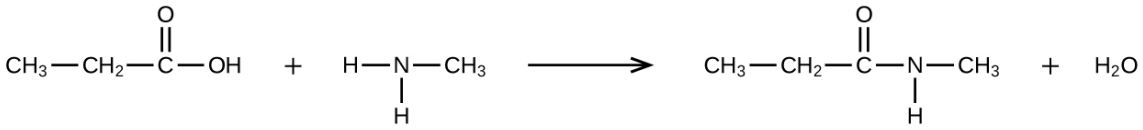


acetamide



hexanamide

Amides can be produced when carboxylic acids react with amines or ammonia in a process called amidation. A water molecule is eliminated from the reaction, and the amide is formed from the remaining pieces of the carboxylic acid and the amine (note the similarity to formation of an ester from a carboxylic acid and an alcohol discussed in the previous section):



carboxylic acid amine amide water

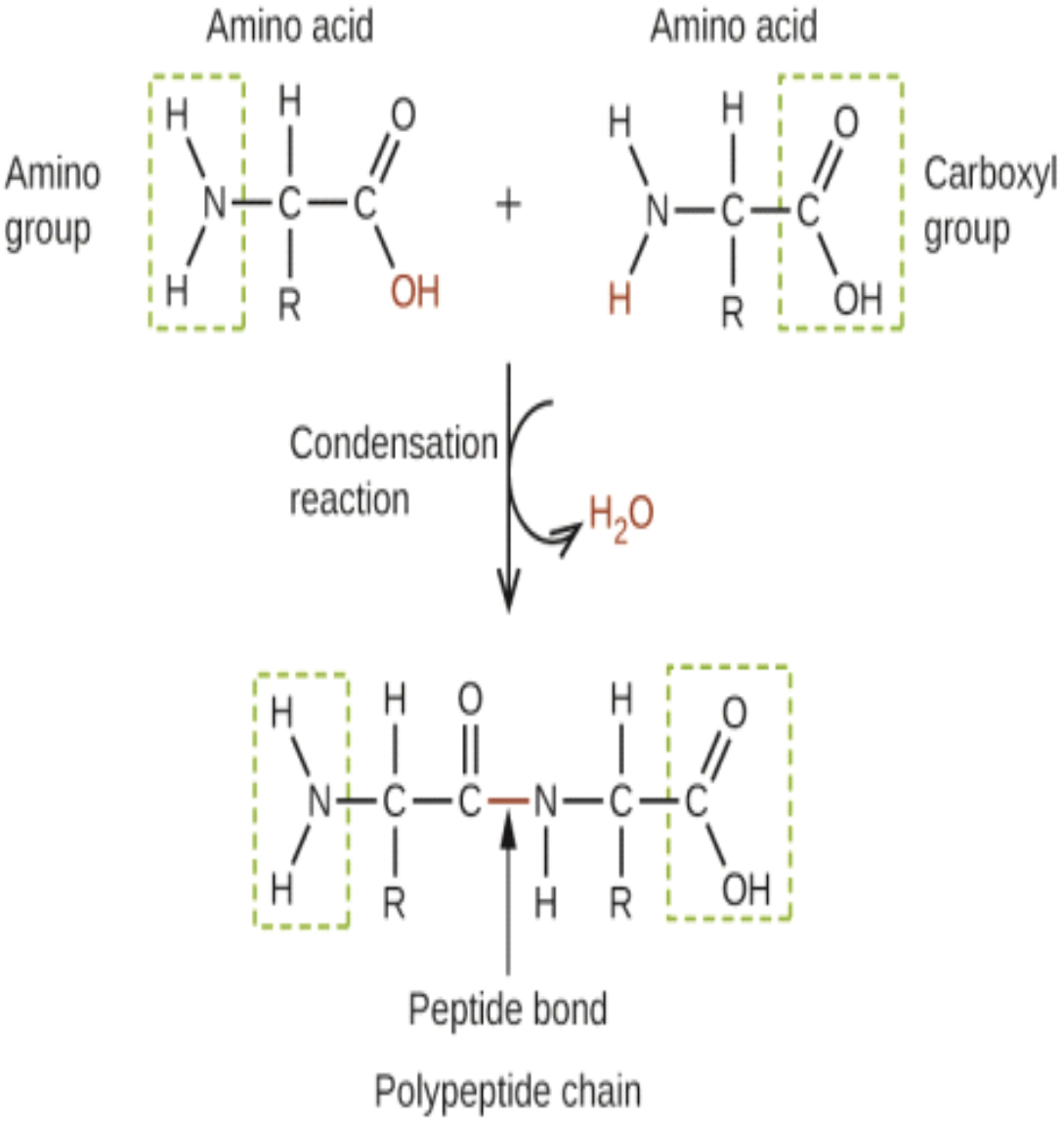
The reaction between amines and carboxylic acids to form amides is biologically important. It is through this reaction that amino acids (molecules containing both amine and carboxylic acid substituents) link together in a polymer to form proteins.

Proteins and Enzymes

Proteins are large biological molecules made up of long chains of smaller molecules called amino acids. Organisms rely on proteins for a variety of functions—proteins transport molecules across cell membranes, replicate DNA,

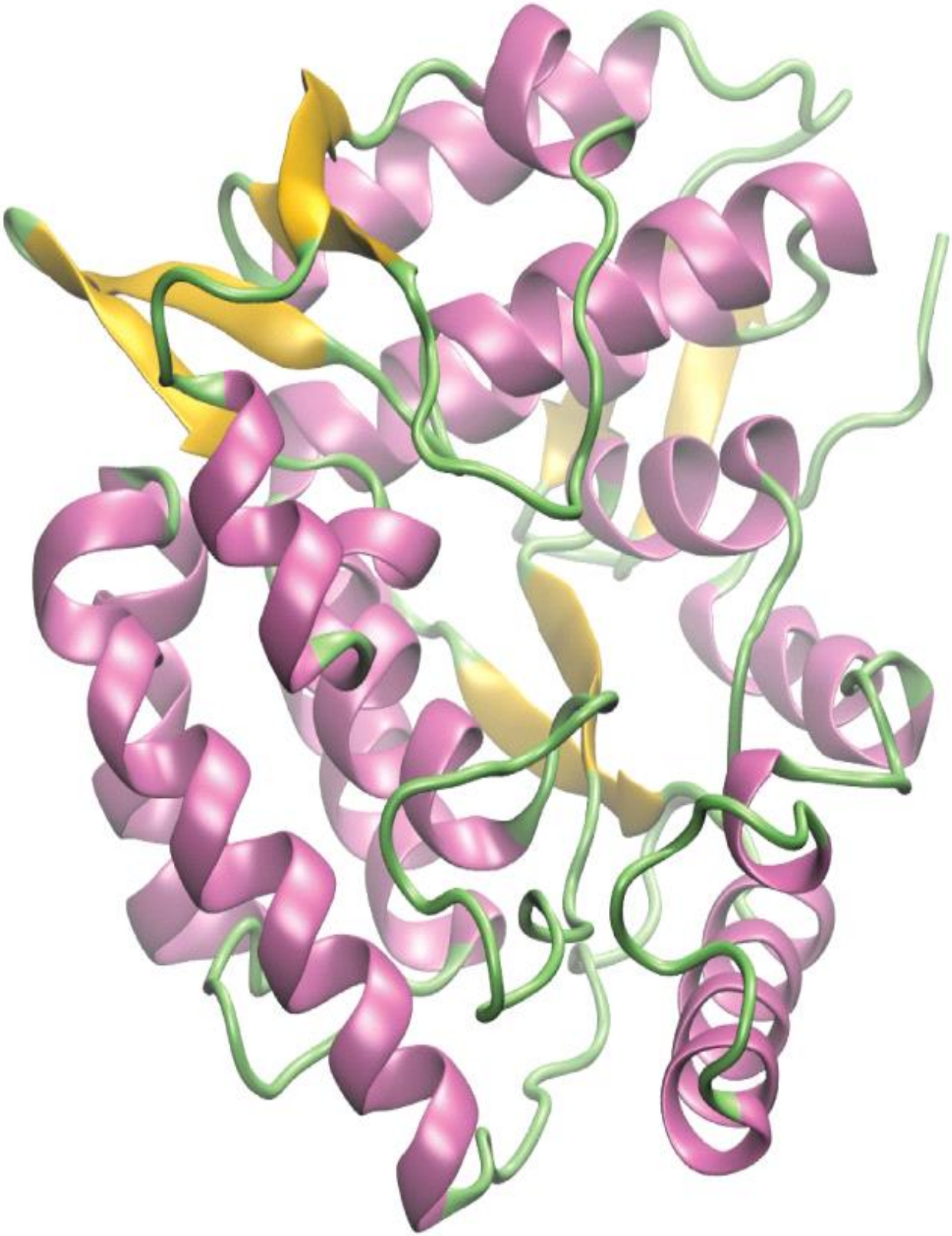
and catalyze metabolic reactions, to name only a few of their functions. The properties of proteins are functions of the combination of amino acids that compose them and can vary greatly. Interactions between amino acid sequences in the chains of proteins result in the folding of the chain into specific, three-dimensional structures that determine the protein's activity.

Amino acids are organic molecules that contain an amine functional group (–NH2), a carboxylic acid functional group (–COOH), and a side chain (that is specific to each individual amino acid). Most living things build proteins from the same 20 different amino acids. Amino acids connect by the formation of a peptide bond, which is a covalent bond formed between two amino acids when the carboxylic acid group of one amino acid reacts with the amine group of the other amino acid. The formation of the bond results in the production of a molecule of water (in general, reactions that result in the production of water when two other molecules combine are referred to as condensation reactions). The resulting bond—between the carbonyl group carbon atom and the amine nitrogen atom is called a peptide link or peptide bond. Since each of the original amino acids has an unreacted group (one has an unreacted amine and the other an unreacted carboxylic acid), more peptide bonds can form to other amino acids, extending the structure. (pic 4) A chain of connected amino acids is called a polypeptide. Proteins contain at least one long polypeptide chain.



Pic 4. This condensation reaction forms a dipeptide from two amino acids and leads to the formation of water.

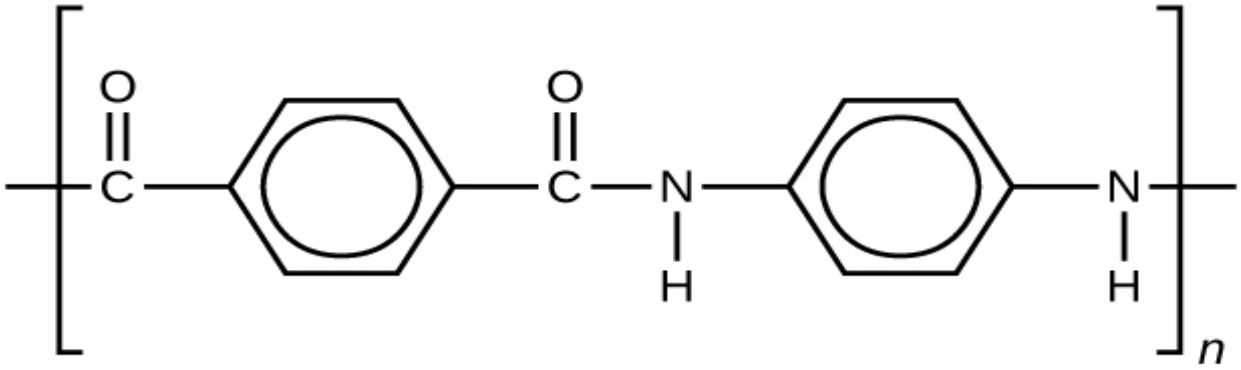
Enzymes are large biological molecules, mostly composed of proteins, which are responsible for the thousands of metabolic processes that occur in living organisms. Enzymes are highly specific catalysts; they speed up the rates of certain reactions. Enzymes function by lowering the activation energy of the reaction they are catalyzing, which can dramatically increase the rate of the reaction. Most reactions catalyzed by enzymes have rates that are millions of times faster than the noncatalyzed version. Like all catalysts, enzymes are not consumed during the reactions that they catalyze. Enzymes do differ from other catalysts in how specific they are for their substrates (the molecules that an enzyme will convert into a different product). Each enzyme is only capable of speeding up one or a few very specific reactions or types of reactions. Since the function of enzymes is so specific, the lack or malfunctioning of an enzyme can lead to serious health consequences. One disease that is the result of an enzyme malfunction is phenylketonuria. In this disease, the enzyme that catalyzes the first step in the degradation of the amino acid phenylalanine is not functional (Pic-5). Untreated, this can lead to an accumulation of phenylalanine, which can lead to intellectual disabilities.



Pic 5. A computer rendering shows the three-dimensional structure of the enzyme phenylalanine hydroxylase. In the disease phenylketonuria, a defect in the shape of phenylalanine hydroxylase causes it to lose its function in breaking down phenylalanine.

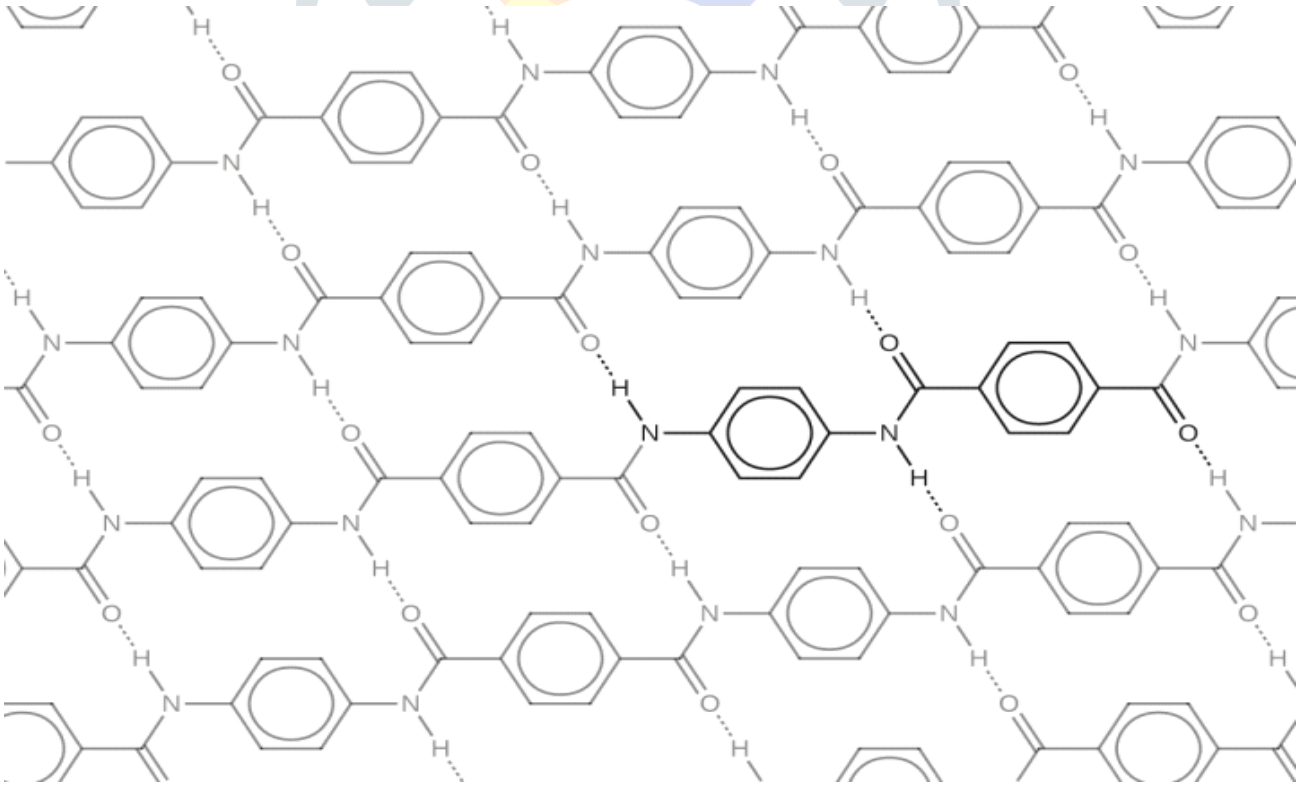
Kevlar

Kevlar (Pic- 6) is a synthetic polymer made from two monomers 1,4-phenylene-diamine and terephthaloyl chloride (Kevlar is a registered trademark of DuPont). Kevlar's first commercial use was as a replacement for steel in racing tires. Kevlar is typically spun into ropes or fibers. The material has a high tensile strength-to-weight ratio (it is about 5 times stronger than an equal weight of steel), making it useful for many applications from bicycle tires to sails to body armor.



Pic-6. This illustration shows the formula for polymeric Kevlar.

The material owes much of its strength to hydrogen bonds between polymer chains (refer back to the chapter on intermolecular interactions). These bonds form between the carbonyl group oxygen atom (which has a partial negative charge due to oxygen's electronegativity) on one monomer and the partially positively charged hydrogen atom in the N–H bond of an adjacent monomer in the polymer structure (see dashed line in Pic- 7). There is additional strength derived from the interaction between the unhybridized *p* orbitals in the six-membered rings, called aromatic stacking.



Pic -7. The diagram shows the polymer structure of Kevlar, with hydrogen bonds between polymer chains represented by dotted lines.

Kevlar may be best known as a component of body armor, combat helmets, and face masks. Since the 1980s, the US military has used Kevlar as a component of the PASGT (personal armor system for ground troops) helmet and vest. Kevlar is also used to protect armored fighting vehicles and aircraft carriers. Civilian applications include protective gear for emergency service personnel such as body armor for police officers and heat-resistant clothing for fire fighters. Kevlar based clothing is considerably lighter and thinner than equivalent gear made from other materials (Pic-8).

(a) (b) (c)

Pic-8. (a) These soldiers are sorting through pieces of a Kevlar helmet that helped absorb a grenade blast. Kevlar is also used to make (b) canoes and (c) marine mooring lines. (credit a: modification of work by "Cla68"/Wikimedia Commons; credit b: modification of work by "OakleyOriginals"/Flickr; credit c: modification of work by Casey H. Kyhl)

Conclusion: From above discussion it is confirmed that amides are very important compounds not only for organic chemists but also for biologists. Natural products and their derivatives represent more than 50% of the drugs in clinical use in the world and amides are one of them. Amides constitute an important class of plant secondary metabolites and are involved in their development and their defense against environmental stresses. Their importance lies in their biological activities like antitumor, anthelmintic, antispasmodic, antifungal, antibacterial, insecticidal, and herbicidal activities. Isobutyl amine, phenylethylamine, piperidine, pyrrolidine, putrescine, spermidine, and tryptamine are the predominant amine components of natural amides, which are mainly distributed in Piperaceae and Rutaceae families. Several sulfur-containing amides have also been found to show antifungal and insecticidal activities.

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