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A REVIEW ON CHEMISTRY OF PEPTIDES

Satyam Tiwari*, Nitin Rajan , Udit Sagar Dwivedi

INTRODUCTION

Peptide is compound consisting of two or more amino acids linked in a chain, the carboxyl group of each acid being joined to the amino group of the next by a peptide bond. The word "peptide" itself comes from πέσσειν (peptós), the Greek word meaning "to digest." Peptides are an essential part of nature and biochemistry, and thousands of peptides occur naturally in the human body and in animals. In addition, new peptides are being discovered and synthesized regularly in the laboratory as well. Indeed, this discovery and innovation in the study of peptides holds great promise for the future in the fields of health and pharmaceutical development.

Polypeptide consist of 10-50 amino acids residues are called peptides; peptides contain more than 50 amino acids often refer as protein. Peptides can be naturally or synthetically obtained, comprising of two or more amino acids linked through an amide formation. The chemical bond (covalent bond) formed between a nitrogen atom of one amino acid to a carboxyl group of another amino acid. Peptides can be distinguished with protein on the basis of number of amino acids. The dipeptides are known as shortest peptides which contained of two amino acids connected to each other through a single bond known as peptide bond. Peptides often classified by function or by synthesis.

Glycine is the simplest amino acid. There is no stereo form of glycine because in glycine the side-chain is another hydrogen atom. While glycine is not a chiral compound, still for all other amino acids has two structural configuration or substituents arrangement around the central α-carbon atom are possible, so each exists in two stereochemical forms, known as the L-isomers for the amino acids found in proteins and the D-isomers for those with the opposite configurations. The natural amino acids & glyceraldehyde have the same configuration, which arbitrarily had been designated the L-form. Two isomers of opposite configuration or chirality (handedness) have the relationship of mirror images and are referred to as enantiomers. According to the Cahn–Ingold–Prelog system of nomenclature, L-amino acids are of the (S)-configuration, except for cysteine and its derivatives. In discussion, when the configuration of an amino acid residue is not indicated, it is assumed to be the L-enantiomer.

Synthetic peptides becoming crucial in commercial and pharmaceutical industry, from the dipeptide sugar substitute aspartame to hormones which are clinically used such as oxytocin, adrenocorticotropic hormone, and calcitonin. The epitope-specific antibodies development against pathogenic proteins is the application of different using synthetic peptides, synthetic peptides are also used in the study of enzyme-substrate interactions within enzyme categories such as proteases and kinases, which has a key role in cell signalling.

In biology of cell, binding on receptors or the recognition of substrate specificity of newly developed enzymes can be studied using sets of homologous synthetic peptides. Synthetic peptides having similar chemical structure as naturally occurring peptides and act as drugs against carcinogenic diseases and other major diseases. In spectrometry synthetic peptides are also used as reagents and standards in mass spectrometry and Mass Spectrometry-based applications. In MS-based discovery, characterization and quantitation of proteins, synthetic peptides play a major role, especially in case of early biomarkers for diseases.

IMPORTANT TERMS OF PEPTIDE

There are some basic peptide-related terms that are key to a general understanding of peptides, peptide synthesis, and the use of peptides for research and experimentation:

Amino Acids – Peptides are composed of amino acids. An amino acid is any molecule that contains both amine and carboxyl functional groups. Alpha-amino acids are the building blocks from which peptides are constructed.

Cyclic Peptides – A cyclic peptide is a peptide in which the amino acid sequence forms a ring structure instead of a straight chain. Examples of cyclic peptides include melanotan-2 and PT-141 (Bremelanotide).

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Peptide Sequence – The peptide arrangement is basically the request in which amino corrosive deposits are associated by peptide bonds in the peptide.

Peptide Bond – A peptide bond is a covalent bond that is formed between two amino acids when a carboxyl group of one amino acid reacts with the amino group of another amino acid. This reaction is a condensation reaction (a molecule of water is released during the reaction).

Peptide Mapping – Peptide mapping is a process that can be used to validate or discover the amino acid sequence of specific peptides or proteins. Peptide mapping methods can accomplish this by breaking up the peptide or protein with enzymes and examining the resulting pattern of their amino acid or nucleotide base sequences.

Peptide Mimetics – A peptide mimetic is a molecule that biologically mimics active ligands of hormones, cytokines, enzyme substrates, viruses or other bio-molecules. Peptide mimetics can be natural peptides, a synthetically modified peptide, or any other molecule that performs the aforementioned function.

Peptide Fingerprint – A peptide fingerprint is a chromatographic pattern of the peptide. A peptide fingerprint is produced by partially hydrolysing the peptide, which breaks up the peptide into fragments, and then 2-D mapping those resulting fragments.

Peptide Library – A peptide library is composed of a large number of peptides that contain a systematic combination of amino acids. Peptide libraries are often utilized in the study of proteins for biochemical and pharmaceutical purposes. Solid phase peptide synthesis is the most frequent peptide synthesis technique used to prepare peptide libraries.

PEPTIDE TERMINOLOGY

Peptides are generally classified according to the amount of amino acids contained within them. The shortest peptide, one composed of just two amino acids, is termed a "dipeptide." Likewise, a peptide with 3 amino acids is referred to as a "tripeptide." Oligopeptides refer to shorter peptides made up of relatively small numbers of amino acids, generally less than ten. Polypeptides, conversely, are typically composed of more than at least ten amino acids. Much larger peptides (those composed of more than 40-50 amino acids) are generally referred to as proteins.

While the number of amino acids contained is a main determinate when it comes to differentiating between peptides and proteins, exceptions are sometimes made. For example, certain longer peptides have been considered proteins (like amyloid beta), and certain smaller proteins are referred to as peptides in some cases (such as insulin). For more information about the similarities and differences among peptides and proteins.

CLASSIFICATION OF PEPTIDES

Peptides are generally divided into several classes. These classes vary with how the peptides themselves are produced. For example, ribosomal peptides are produced from the translation of mRNA. Ribosomal peptides often function as hormones and signalling molecules in organisms. These can include tachykinin peptides, vasoactive intestinal peptides, opioid peptides, pancreatic peptides, and calcitonin peptides.

Antibiotics like microcin's are ribosomal peptides produced by certain organisms. Ribosomal peptides often go through the process of proteolysis (the breakdown of proteins into smaller peptides or amino acids) to reach the mature form.

Conversely, non-ribosomal peptides are produced by peptide-specific enzymes, not by the ribosome (as in ribosomal peptides). Non-ribosomal peptides are frequently cyclic rather than linear, although linear non-ribosomal peptides can often occur. Non-ribosomal peptides can develop extremely intricate cyclic structures. Non-ribosomal peptides frequently appear in plants, fungi, and one-celled organisms. Glutathione, a key part of antioxidant defines in aerobic organisms, is the most common non-ribosomal peptide.

Milk peptides in organisms are formed from milk proteins. They can be produced by enzymatic breakdown by digestive enzymes or by the proteinases formed by lactobacilli during the fermentation of milk. Additionally, peptones are peptides derived from animal milk or meat that have been digested by proteolytic digestion. Peptones are often used in the laboratory as nutrients for growing fungi and bacteria.

Peptide fragments, moreover, are most commonly found as the products of enzymatic degradation performed in the laboratory on a controlled sample. However, peptide fragments can also occur naturally as a result of degradation by natural effects.

PEPTIDES FORMATION

Peptides are formed both naturally within the body and synthetically in the laboratory. The body manufactures some peptides organically, such as

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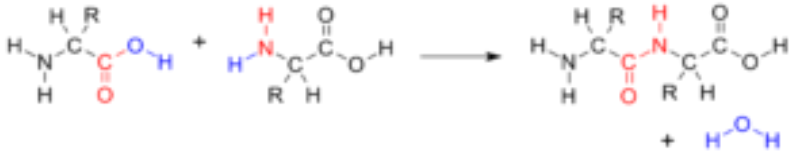
ribosomal and non-ribosomal peptides. In the laboratory, modern peptide synthesis processes can create a virtually boundless number of peptides using peptide synthesis techniques like liquid phase peptide synthesis or solid phase peptide synthesis. While liquid phase peptide synthesis has some advantages, solid phase peptide synthesis is the standard peptide synthesis process used today.



The first synthetic peptide was discovered in 1901 by Emil Fischer in collaboration with Ernest Fourneau. Oxytocin, the first polypeptide, was synthesized by Vincent du Vigneaud in 1953.

METHODS OF PEPTIDE SYNTHESIS

In the old style arrangement stage technique, all the functionalities other than the α-amino gathering of one of the amino acids and a-carboxyl gathering of the other amino are reversibly secured and afterward the alpha-carboxy bunch is enacted and couple utilizing a reasonable strategy. Ensuing evacuation of the N-amino shielding bunch from the dipeptide in this way got and the coupling of the following N-ensured amino corrosive delivers a tripeptide. This pattern of tasks kept on getting the ideal peptide. Since this technique includes the partition, refinement and characterisation of the intermediates at each progression. This is an exceptionally monotonous, difficult and tedious system. The capricious insolubility of the secured peptide sections particularly hydrophobic peptides at different phases of combination is the ordinary, task frequently experienced in this method. Union of β-amyloid plaque protein is the best model for solvency issues. Also, an outstanding test aptitude is needed for the fruitful get together of the peptide. Notwithstanding, the technique has the upside of acquiring profoundly unadulterated items in enormous amounts.

The cycle of SPPS, includes the stepwise joining of N-and side chain secured amino acids into an insoluble strong help utilizing appropriate substance strategies, typically in the C to N course of the ideal peptide to evade the risk of racemisation. Notwithstanding, combination in the N to C course (opposite amalgamation) was likewise endeavoured. At the point when the grouping get together was finished, the security holding the peptide to the help was specifically severed and the peptide was freed in arrangement. The overall highlights and steps associated with the strong stage amalgamation of peptides. This method can be stretched out to the combination of any polymer particle from bifunctional monomers. Depsipeptides, polyamides, polysaccharides, polynucleotides, epoxides and lactones have been integrated by this technique. Despite the fact that this technique appreciates the benefits of simple manufactured control it faces a difficult issue of collection of firmly related contaminations as cancellation and shortened successions alongside the objective peptide.

Solid supports (resins and linkers)

The right choice of resins and linkers is prime for a hit peptide synthesis. The strong guide has to provide balance to mechanical stirring in a large variety of solvents and temperatures. In addition, the strong guide has to be capable of swell in order that the reagents can without difficulty get admission to the energetic sites. A collection of resins and linkers has been advanced withinside the beyond permitting a huge variety of applications. Selection of defensive groups, coupling reagents, and cleavage situations are without delay related to the choice of the polymer guide and the linker. The first polymer guide utilized by Merrifield become polystyrene, which continues to be in use. Later, resins primarily based totally on polystyrene incorporating polyethylene glycol (PEG) chains and resins composed of PEG chains sporting precise go linkers had been advanced. Linkers in SPPS play a pivotal position. Firstly, they offer a reversible linkage among the peptide chain and the strong guide and secondly, they play a shielding position towards aggregation. In addition, the linker acts as a defensive institution for the C-terminus carboxy institution. Furthermore, the linker is used for the C-terminus change of the peptide and determines the foremost choice of the protective groups, coupling reagents and the cleavage situations.

RESINS

Based at the polymer aspect group, there are 3 varieties of resin:

(i) **Polystyrene(PS)-primarily based totally resins;**
(ii) **PS-functionalized polyethylene glycol (PS-PEG) resins, and**

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(iii) natural crosslinked PEG resins.

PS resins were broadly used with extraordinary fulfillment withinside the synthesis specially of short- to medium-period peptides. For medium- to long-peptides or peptides with "hard sequences" PEG-primarily based totally resins regularly display higher overall performance ensuing in peptides with excessive purity and yield.

PEPTIDE APPLICATIONS IN BIOMEDICINE, BIOTECHNOLOGY AND BIOENGINEERING

In the case of polystyrene resin, the polymer is commonly crosslinked with 1% of divinylbenzene (DVB). The resin is produced via way of means of suspension polymerization of styrene withinside the presence of divinylbenzene. This sort of polymer help swells properly in non-polar solvents together with dichloromethane (DCM) or toluene however it's also like minded with solvents like N,N-dimethylformamide (DMF), dioxane, or tetrahydrofuran (THF), or N-methyl-2-pyrrolidone (NMP). However, this resin isn't always like minded with water or different polar solvents. In the case of syntheses regarding pretty hydro-phobic amino acids, tough peptide sequences, or peptides with a bent to aggregate, greater hydrophilic strong helps must be selected.

Tenta Gel (TG) then again behaves nicely in each polar and non-polar solvents and famous notable swelling houses in maximum solvents well matched with PEG chains. The extrade of the solvent from non-polar to polar ought to be executed step by step to be able to maintain the most effective swelling houses of the polymer. Tenta Gelis the maximum nicely studied PEG-PS resin today[10]. TG resins are organized via way of means of grafting of PEG chains (50p%) to low pass connected polystyrene via way of means of ether linkages. The 0.33 institution of polymer helps is the hydrophilic PEG-primarily based totally resins, which include no polystyrene or a totally low quantity of it. This institution consists of polymers that swell thoroughly in water supplying the gain to look at peptide proteins inter-moves while the protein is as much as 3570 kDa.

Poly(ethylene glycol)-poly-(N, N-dimethyl acrylamide) copolymer (PEGA) are the main achievements of this category which was developed by Meldal, and the cross linked ethoxylate acrylate resin(CLEAR) which was given by Kempe. PEGA resins are very sophisticated when dried and therefore they are supplied swollen in ethanol. A new variety of polymer support called Chem Matrix (CM), which was developed by Cote, with the advantages of the two previous polymers, namely, the chemical stability of polystyrene resins and the versatility of the PEG grafted resins, making it a powerful tool for the synthesis of large peptides or difficult sequences with many hydrophobic amino acids. As well, many polar solvents including water, DMF, THF, methanol, and acetonitrile, as well as trifluoroacetic acid (TFA) could be used with Chem Matrix because the polymer is highly polar and therefore it retains its excellent swelling properties in the presence of polar solvents. Most of the polymer supports enlisted above are marketed with different types of linkers, such as PAL linker, Fmoc-Rink linker, HMBA linker, etc.

LINKERS FOR FMOC-BASED SPPSA

Linker plays a twin role throughout amide synthesis. It offers protection to beat aggregation during the elongation of the peptidic sequence whereas it provides a reversible linkage between the peptide chain and also the solid support. Linkers are simply classified into low and high acid-labile linkers supported the conditions that are used for cleavage, sometimes TFA solution. Another classification is predicated on their linkage with solid support. during this case, the linkers are classified as integral or non-integral. a 3rd classification is based on the ultimate C-terminal practicality of the peptide, usually peptide acid or peptide amide. The classical Rink-amide linker or other aminomethyl-based linkers are bound onto the rosin with a chemical bond exploitation normal coupling procedures. On the opposite hand, trityl sort linkers, just like the 2-chlorotrityl chloride resin (Barlos resin), are tethered to the compound support (e.g., polystyrene) by direct synthesis. The aryl hydrazide linkers are among the foremost helpful resin-linkers for the synthesis of a good style of with chemicals changed peptides, head-to-tail cyclic peptides, yet as lipidated peptides. These linkers will be cleaved beneath gentle aerophilous conditions to supply protected peptides whereas they're absolutely compatible with each Boc- and Fmoc-based methodologies. Also, the backbone organic compound linker (BAL) allows for the synthesis of C-terminal changed amides, peptide aldehydes, or thioesters whereas once cleavage the C-terminal remains free for more reactions. Another form of linker is that the "safety catch linker" that is especially helpful for the synthesis of peptide thioesters, which are free from the rosin exploitation and more than thiol in DMF or NMP. The term "safety catch" was introduced by Kenner in1971 for peptide chemistry to explain a method that enables a linker to stay stable till it's activated for cleavage by chemical modification. because of several disadvantages, appreciate poor loading and low reactivity as compared to alternative well-known

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normal linkers, this linker ne'er found a widespread application. However, today it presents a helpful and broadly speaking applicable tool for the synthesis of a series of changed amides upon treatment with different nucleophiles. Linker plays a twin role throughout peptide synthesis. It offers protection to beat aggregation during the elongation of the peptidic sequence whereas it provides a reversible linkage between the peptide chain and also the solid support. Linkers are simply classified into low and high acid-labile linkers supported the conditions that are used for cleavage, sometimes TFA solution. Another classification is predicated on their linkage with solid support. during this case, the linkers are classified as integral or non-integral. a 3rd classification is predicated on the ultimate C-terminal practicality of the amide, sometimes peptide acid or peptide amide. The classical Rink-amide linker or other aminomethyl-based linkers are bound onto the rosin with a chemical bond exploitation normal coupling procedures. On the opposite hand, trityl sort linkers, just like the 2-chlorotrityl chloride resin (Barlos resin), are tethered to the compound support (e.g., polystyrene) by direct synthesis. The aryl hydrazide linkers are among the foremost helpful resin-linkers for the synthesis of a good style of with chemicals modified amides, head-to-tail cyclic peptides, yet as lipidated peptides. These linkers will be cleaved beneath gentle aerophilous conditions to supply protected peptides whereas they're absolutely compatible with each Boc- and Fmoc-based methodologies. Also, the backbone organic compound linker (BAL) permits for the synthesis of C-terminal changed peptides, peptide aldehydes, or thioesters while once cleavage the C-terminal remains free for further reactions. Another form of linker is that the “safety catch linker” that is especially helpful for the synthesis of peptide thioesters, which are free from the rosin exploitation an more than thiol in DMF or NMP. The term “safety catch” was introduced by Kenner in1971 for amide chemistry to explain a method that enables a linker to stay stable till it's activated for cleavage by chemical modification. because of several disadvantages, appreciate poor loading and low reactivity as compared to alternative well-known normal linkers, this linker ne'er found a widespread application. However, today it presents a helpful and broadly speaking applicable tool for the synthesis of a series of changed peptides upon treatment with different nucleophiles.

GREEN PEPTIDE SYNTHESIS

Solid-phase amide synthesis is one in all the foremost polluting and least inexperienced chemical processes. DMF, NMP, or DCM are toxic, polar aprotic solvents movement environmental threats as a result of they combine with water. Disposal of those solvents to waste water treatment facilities results a high BOC/COD and N loading that may be drawbackatic with the added problem of Roman deity emissions. they're among the chemicals of highest concern below the laws of EU REACH (Registration, analysis and Authorization of Chemicals). Therefore, there's a good have to be compelled to replace DMF with green alternatives.

Recently, Albericio and his co-workers published the elimination of the sham group by using γ-Valero lactone instead of DMF during SPPS in PS resins and Chem Matrix. Another alternative for DMF during Fmoc was N-formyl morpholine, which only performed excellently when the polymer carrier Chem Matrix was used. Previously, the same group had published the synthesis of the Aib-enkephalin pentapeptide (H-Tyr-Aib-Aib-Phe-Leu-NH2) using 2-methyltetrahydrofuran (2-MeTHF) as an alternative solvent that can be obtained from renewable raw materials ; In addition, they have reported the substitution of AcN and THF with DMF in the synthesis of the hindered peptides Aib-enkephalin-pentapeptide and Aib-ACP-decapeptide using the SPPS methodology on Chem Matrix resin. This work showed a better coupling efficiency than when using DMF. The development of solid phase peptide synthesis in water using Fmoc-protected amino acids is still a topic of research interest. Most of these new approaches are limited to laboratory research areas. Hojo and his team developed an environmentally friendly method using water-dispersible amino acid nanoparticles. It can be easily applied to His-containing peptides that are sensitive to racemization. Other recently introduced processes use alternative solid supports in place of conventional resins. Sarma et al. Demonstrated the synthesis of small dipeptides, mainly with aliphatic amino acids, at room temperature using banana water extract (WEB) / ethylene glycol as an aqueous medium with and without an external base. The peptide synthesis technique (MEPS) could be an alternative method for peptide synthesis on an industrial scale, using the RADA tetramer as a model.

CONCLUSION

Taken together, these results illustrate the applicability of multiple peptide synthesis methods for obtaining large amounts of peptides, which can then be cleaved in solution under mild conditions. The purity of the peptide is comparable to that obtained by conventional solid-phase peptide synthesis. In addition, the purity can be achieved through simple processing steps after protection, without the need for complicated chromatography.

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The amount of digestion is sufficient to characterize and perform several biological analyses. In addition, the lytic peptide solution is non-toxic to cells and should be suitable for other biological agents. The method we describe should make it possible to conduct research projects requiring hundreds or thousands of peptides or peptide analogs in a short period of time without special equipment. The study included an alpha-alanine spacer for comparison with the diketopiperazine study described above. Terminal peptide. By replacing one of the 20 amino acids with P-ala-9, a natural C-terminal peptide can also be obtained.

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