Dehydroalanine

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summary

Dehydroalanine (DHA) is a significant amino acid derivative characterized by its unique ±,²-unsaturated carbonyl structure, with the molecular formula CƒH…NO, and a molar mass of 87.08 g/mol.[1][2] This compound is notable for its electrophilic properties, allowing it to participate in various chemical reactions that are not typical of standard amino acids. Dehydroalanine's reactivity and structural characteristics have established its prominence in synthetic organic chemistry, where it serves as a key building block in the development of complex molecules, particularly in peptide synthesis and modification.[3][4][5]

DHA is particularly relevant in biological contexts, being found in naturally occurring peptides such as nisin and other lantibiotics, which underscores its role in the formation of bioactive compounds.[5][6] Its formation in living organisms occurs through enzymatic processes and can influence post-translational modifications (PTMs) of proteins, thereby impacting cellular metabolism and protein functionality.[7][8] Moreover, its incorporation into peptides can enhance their stability and bioavailability, making it a valuable modification for therapeutic applications in drug design and development.[9][10]

The synthesis of dehydroalanine has garnered attention due to its dual pathways—both enzymatic and non-enzymatic—along with advancements in efficient synthetic methodologies, including one-pot reactions that streamline the production of DHA derivatives.[6][11] These derivatives are increasingly utilized in bioconjugation techniques, enabling the development of targeted therapies and enhancing the efficacy of peptide-based drugs.[12][13] In addition, DHA's applications extend to agriculture, where it contributes to the formulation of antimicrobial peptides aimed at combating plant pathogens, showcasing its broad relevance across multiple fields.[14][15]

Controversies surrounding dehydroalanine primarily relate to its potential implications in disease processes, such as cancer, where its accumulation and effects on protein biosynthesis have been linked to pathological changes in cellular functions.[16][15] As research progresses, the integration of DHA into innovative therapeutic strategies continues to evolve, highlighting its critical role in advancing both chemical biology and medical science.[6][15]

Chemical Structure

Dehydroalanine (DHA) is a chemical compound with the molecular formula CƒH…NO, and a molar mass of 87.08 g/mol[1][2]. Its structure features an ±,²-unsaturated carbonyl group, which is responsible for its electrophilic character, allowing it to react with nucleophiles[3]. This unique property distinguishes dehydroalanine from most amino acids, which are typically unreactive in such contexts[3].

Molecular Characteristics

The chemical structure of dehydroalanine consists of a carbon skeleton that includes a carboxylic acid functional group, an amino group, and the distinctive ±,²-unsaturated carbonyl[4][5]. The presence of this unsaturated carbonyl makes dehydroalanine an important building block in synthetic organic chemistry, particularly for the formation of complex structures like lanthionine[3][6].

Reactivity

Due to the reactivity of its ±,²-unsaturated carbonyl moiety, dehydroalanine can alkylate other amino acids, contributing to its utility in the synthesis of various biologically active compounds[3][17]. The residue has been identified in natural peptides such as nisin and certain lantibiotics, further highlighting its biological significance[5].

Synthetic Applications

Dehydroalanine is commonly utilized in peptide synthesis and modification processes. It serves as a precursor for the incorporation of unnatural amino acids through techniques such as late-stage functionalization, which leverages its electrophilic nature[17]. This capability allows for the development of novel peptides with enhanced properties for drug design and discovery[17].

Synthesis

Overview

Dehydroalanine (Dha) is an important amino acid derivative that can be synthesized through various chemical pathways, showcasing its significance in organic synthesis and biochemistry. Recent advancements have focused on the efficient synthesis of dehydroalanine esters and derivatives, providing practical methods that enhance the scalability and utility of these compounds in research and application.

Enzymatic and Non-Enzymatic Pathways

Interestingly, dehydroalanine can be formed through both enzymatic and non-enzymatic processes. In eukaryotic systems, the key enzyme SepSec synthase converts phosphoserine to selenocysteine, with the formation of a dehydroalanine intermediate being a crucial step in the mechanism.[11] This intermediate is produced via a spontaneous non-enzymatic elimination of phosphoserine, a process that has been observed during protein aging in human cells.[11][6] Moreover, in prokaryotes, Dha is also generated during the biosynthesis of lantipeptide natural products, highlighting its biochemical relevance across different life forms.[11]

One-Pot Synthesis Methodology

A notable advancement in the synthesis of dehydroalanine involves a practical one-pot method that utilizes a Cs2CO3-mediated simultaneous esterification and elimination process. This method starts from commercially available N-protected serines and haloalkanes, simplifying the operational steps compared to traditional synthesis methods.[6] The efficiency of various inorganic carbonates in facilitating this reaction has been evaluated, demonstrating that alkaline conditions promote the elimination of ²-hydroxyl groups, leading to the formation of ±,²-unsaturated carbonyl compounds.[6] The optimization of this reaction revealed that using Cs2CO3 as a base significantly increases the yield of N-phthaloyldehydroalanine isopropyl ester, thereby establishing a robust framework for synthesizing diverse dehydroalanine esters.[6]

Applications

Dehydroalanine (Dha) is a versatile amino acid derivative that plays a significant role in various fields, particularly in peptide synthesis, drug development, and bioconjugation techniques. Its unique properties facilitate the creation of bioactive compounds and improve therapeutic potentials.

Peptide Synthesis and Drug Development

Dha has gained attention in peptide synthesis due to its ability to enable the incorporation of non-canonical amino acids into peptide chains. This incorporation is crucial for the development of novel therapeutic peptides with enhanced stability and bioavailability[10][16]. For instance, studies demonstrate that Dha can be utilized in the synthesis of peptides with rigid secondary structures, which are often more effective as drugs[9][18]. Moreover, the modification of natural peptides, such as the polycyclic antibiotic Nisin A, using Dha can enhance their biophysical properties and functionality[19][17].

Bioconjugation Techniques

In the realm of bioconjugation, Dha serves as a reactive site for attaching biomolecules to drugs or imaging agents. This modification significantly enhances the efficacy and specificity of targeted therapies[12][20]. Recent advancements in coupling methods involving Dha allow for precise modifications that can improve the therapeutic application of peptides and proteins[21][13]. The incorporation of Dha into bioconjugation strategies has shown promise in accelerating drug discovery by facilitating the synthesis of complex peptide structures[22].

Agricultural Applications

Dha-based peptides also hold potential in agriculture, where they can be used to develop antimicrobial peptides (AMPs) to combat plant pathogenic infections caused by bacteria and fungi[15]. The application of AMPs derived from Dha may provide a sustainable solution to reduce crop losses due to various agricultural diseases[14]. However, challenges remain in the practical implementation of these peptides due to cost considerations in the transportation and preservation of agricultural products[-23].

Biological Role

Dehydroalanine (Dha) plays a significant role in various biological processes, particularly as a key component in post-translational modifications (PTMs) of proteins. It is formed through the ²elimination reaction of cysteine, serine, or phosphoserine residues, which can lead to protein cross-linking and aggregation over time[7][24]. This accumulation of modifications, including Dha, influences protein functionality and stability, which is crucial in cellular metabolism and the integrity of cellular structures[8].

Dha is particularly noteworthy for its ability to enable the labeling of proteins, facilitating the synthesis of modified proteins and their analogs[25][26]. This capability is increasingly valuable in therapeutic applications, as modified proteins can be utilized for probing and modulating functions, as well as for tracking within biological systems[14]. Furthermore, the incorporation of Dha into peptides can enhance their structural stability and bioavailability, making it a desirable modification in peptide drug discovery[9].

Additionally, Dha's presence in proteins has been linked to various pathophysiological conditions, including the development of diseases such as cancer[16]. Studies have indicated that dehydroalanine residues can affect transcription and translation processes, thereby influencing protein biosynthesis pathways essential for cellular health[15]. In summary, dehydroalanine is not only a crucial element in protein chemistry but also plays a significant role in regulating various biological functions and disease processes.

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Analytical Methods

Liquid Chromatography and Tandem Mass Spectrometry

Liquid chromatography tandem mass spectrometry (LC-MS/MS) is a pivotal analytical technique utilized in the study of dehydroalanine (DHA) and its derivatives. This method enables the identification and quantification of specific DHA-modified peptides in biological samples, particularly in the context of aging and cataractous lenses. A recent study demonstrated the application of LC-MS/MS to analyze lens tissue samples, where the samples underwent a series of preparation steps including homogenization, centrifugation, and extraction to isolate water-soluble and urea-soluble fractions for further analysis[24][27].

During the LC-MS/MS analysis, it was revealed that multiple cysteine-based DHA sites exist, along with a few dehydrobutyrine (DHB) sites formed through water loss. Notably, among the dataset, a tandem mass spectrum highlighted a DHA-modified peptide sequence derived from BFSP2 (phakinin), providing critical insights into the site-specific consequences of protein modifications associated with cataracts[24]. The quantification of relative levels of modification on numerous unique peptides further underscores the utility of this method in proteomic studies[24].

Sample Preparation Techniques

Effective sample preparation is crucial for accurate LC-MS/MS results. For dehydroalanine analysis, lens tissues are typically subjected to homogenization in a buffer consisting of Tris, NaCl, and EDTA. Following centrifugation, the supernatant is collected to represent the water-soluble fraction (WSF), while the pellet is processed to yield urea-soluble (USF) and urea-insoluble fractions (UIF) through additional solubilization and centrifugation steps[24]. These preparation techniques ensure that the samples are clean and free of contaminants that may interfere with subsequent mass spectrometric analysis.

Reaction Kinetics and Characterization

The kinetics of reactions involving DHA have also been studied using high-performance liquid chromatography (HPLC). For instance, a reaction involving a dehydroalanine-containing peptide demonstrated rapid consumption when reacted with a reducing agent, with a significant percentage of conversion achieved within a short timeframe. This reflects the reactivity of DHA and its potential applications in peptide chemistry[19]. Such kinetic studies are instrumental for understanding the behavior of DHA in different chemical environments and its implications in biological processes.

Research and Development

Dehydroalanine (Dha) is increasingly recognized for its potential in various therapeutic applications and as a key structural component in antimicrobial peptides. Recent research has focused on the unique properties of Dha and its derivatives, particularly in the context of developing novel antimicrobial agents and peptide-based drugs.

Future Directions

Ongoing research is focused on optimizing the synthesis of Dha-containing peptides and exploring their application in fields such as food preservation, agriculture, and medical treatments[6][24]. As the low success rate of clinical applications for antimicrobial peptides is a pressing challenge, continued advancements in peptide design and modification, particularly through the incorporation of Dha, are essential for the development of effective therapeutic strategies[15][6]. This area of research not only aims to combat antibiotic resistance but also seeks to expand the potential uses of antimicrobial peptides in diverse sectors.

Antimicrobial Peptides and Bacteriocins

Dha plays a significant role in the structure of several antimicrobial peptides, including the bacteriocin nisin, which contains three dehydro amino acid residues, two of which are dehydroalanine residues[6]. These modifications enhance the bioactivity of antimicrobial peptides by influencing their interactions with microbial membranes, thereby increasing their efficacy against a range of pathogens[6][24]. Research indicates that Dha-containing peptides, such as temporin-SHd, exhibit potent antibacterial and leishmanicidal activities, highlighting the importance of post-translational modifications in enhancing peptide functionality[15].

Design and Application

The design of new antimicrobial peptides often incorporates dehydroalanine to leverage its unique structural characteristics. Various studies have employed transcriptome analysis to understand the cellular responses to Dha-modified peptides, leading to insights into their mechanisms of action and potential therapeutic applications[15]. The evolution of peptide design informed by these studies suggests that integrating Dha can create peptides with improved specificity and reduced toxicity, making them suitable candidates for clinical use[15][24].

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