

Oxetanylalanine

Table of Contents

summary

History

Chemical Properties

- Physical Characteristics

- Solubility and Stability

- Reactivity

Synthesis

- Enzymatic Approaches

- Chemoenzymatic Methods

- Conventional Synthesis

- Future Directions

Biological Role

Applications

- Synthesis and Biocatalysis

- Nutritional Considerations

- Research and Development

Safety and Toxicology

- Chemical Properties and Hazards

 - Health Hazards

 - Response Recommendations

 - Regulatory Information

Scientific Literature

- Research Contributions

- Methodology and Ethics

- Data Availability and Transparency

- Conflict of Interest

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summary

Oxetanylalanine is a non-natural amino acid derived from phenylalanine, characterized by the chemical formula $C_9H_{11}NO_2$. It exhibits unique physical and chemical properties, making it a significant compound in various scientific fields, particularly in pharmaceuticals and biochemistry. As a zwitterionic amino acid, oxetanylalanine plays a vital role as a building block for proteins and is involved in diverse biochemical processes, including the synthesis of neurotransmitters and hormones.[\[1\]\[2\]\[3\]](#) Its distinctive structure and reactivity offer promising applications in drug development and metabolic research.

The compound has garnered attention in recent years due to advancements in synthetic methodologies, notably biocatalysis, which allows for the efficient production of optically pure amino acid derivatives. Techniques utilizing phenylalanine ammonia lyase (PAL) have shown significant improvements in enantioselectivity and overall productivity when synthesizing oxetanylalanine.[\[4\]\[5\]](#) This shift towards sustainable and eco-friendly synthesis methods reflects broader trends in chemical manufacturing, aiming to reduce reliance on hazardous reagents and complex purification processes.[\[6\]\[7\]](#)

Oxetanylalanine also raises notable discussions surrounding its safety and potential health impacts. While it is generally considered safe for use in research and industrial applications, it can emit toxic fumes when heated to decomposition, necessitating careful handling and storage precautions.[\[8\]\[9\]](#) The exploration of its biological roles, particularly its implications for patients with metabolic disorders such as phenylketonuria (PKU), further underscores the compound's relevance in both nutritional and therapeutic contexts.[\[10\]\[11\]](#)

Ongoing research continues to unveil the complexities of oxetanylalanine, with efforts focused on enhancing synthetic efficiency and exploring its functional impacts in health and disease. As interest in non-natural amino acids grows, oxetanylalanine stands out as a key player in the development of novel compounds with potential therapeutic benefits.[\[12\]\[13\]](#)

History

The development and study of oxetanylalanine is part of the broader historical context of amino acid research, which has roots dating back to the late 19th century. Amino acids were first identified through the hydrolysis of proteins, with notable early contributions from chemists such as Emil Fischer, who in 1901 synthesized phenylalanine, an important aromatic amino acid.[\[1\]](#) This foundational work laid the groundwork for the subsequent identification and exploration of various amino acid derivatives, including oxetanylalanine.

Research into synthetic methods for amino acid derivatives advanced significantly in the 20th century. One notable advancement was the introduction of new synthetic

methodologies, which allowed for the development of complex amino acid derivatives like oxetanylanine.[\[2\]](#) These methodologies often included the use of various starting materials and reagents, enhancing the ability to create derivatives with specific structural and functional properties.

The recent interest in biocatalysis has further propelled the synthesis of amino acids and their derivatives. Studies have highlighted the use of engineered enzymes, such as phenylalanine ammonia lyase, to synthesize non-natural amino acid derivatives, including those related to oxetanylanine. This reflects a shift towards more sustainable and efficient synthetic routes in the pharmaceutical and biochemical fields.[\[3\]](#)

Chemical Properties

Oxetanylanine, a derivative of phenylalanine, has the chemical formula $C_9H_{11}NO_2$ and is classified as a zwitterionic amino acid[\[4\]\[5\]](#). This compound exhibits unique physical and chemical properties that make it significant in various applications, including pharmaceuticals and biochemistry.

Physical Characteristics

Oxetanylanine is an odorless white crystalline powder with a slightly bitter taste. It is water-soluble, forming aqueous solutions that behave as weak acids, with a pH range of 5.4 to 6 when diluted to 1%[\[6\]](#). The melting point of this compound is notably high, around 396.62 K, and it is characterized by a substantial heat of fusion ($\Delta_{\text{fus}} H^\circ$) of approximately 20.47 kJ/mol[\[7\]\[8\]](#). Its vaporization enthalpy ($\Delta_{\text{vap}} H^\circ$) is estimated to be 71.58 kJ/mol[\[9\]](#).

Solubility and Stability

Oxetanylanine displays interesting solubility traits; while it is soluble in water, it is largely insoluble in organic solvents[\[10\]](#). The molecular weight of this compound is around 165.08 g/mol, and it has a log octanol-water partition coefficient ($\log P_{\text{oct/wat}}$) of 0.641, suggesting its moderate hydrophobicity[\[8\]\[9\]](#).

Reactivity

The compound is light-sensitive and acts as a weak acid in solution, which indicates potential reactivity under specific conditions. When heated to decomposition, it may emit toxic fumes of nitrogen oxides, emphasizing the need for caution during handling[\[6\]](#). Furthermore, oxetanylanine is known to potentially form stable complexes with other compounds due to its zwitterionic nature, allowing for diverse interactions in biochemical environments[\[2\]](#).

Synthesis

The synthesis of oxetanylanine, like many amino acid derivatives, has been explored through various methodologies, combining traditional organic synthesis with

biocatalytic approaches. A notable method includes the application of phenylalanine ammonia-lyase (PAL), which has gained attention due to its ability to produce optically pure amino acids with higher enantioselectivity compared to chemical methods[3][11].

Enzymatic Approaches

Enzymatic synthesis routes often leverage the shikimate pathway, where phenylalanine is a crucial precursor. This pathway includes several enzymatic steps, starting from phosphoenolpyruvate and erythrose 4-phosphate, leading to the formation of chorismate, which is subsequently converted to prephenate and then to phenylpyruvate[1]. These intermediates can then be modified using various enzymes to synthesize derivatives like oxetanylanine.

Additionally, biocatalytic strategies have been developed that incorporate engineered enzymes to expand substrate scope and increase reaction rates. For instance, the immobilization of PAL on carbon nanotubes has demonstrated significant improvements in process productivity and stability, allowing for both batch and continuous-flow processes[3]. The combination of biocatalysis with flow chemistry has been shown to enhance the overall reaction efficiency, achieving higher space-time yields compared to traditional batch processes[3].

Chemoenzymatic Methods

Chemoenzymatic methods also play a vital role in the synthesis of oxetanylanine. These approaches involve integrating enzymatic reactions with chemical transformations. For example, cascades involving PAL and other enzymes have been employed to achieve the synthesis of biaryl alanines, which can serve as precursors for oxetanylanine[3]. Such strategies not only improve product yields but also reduce the number of steps involved in the synthesis, contributing to a more sustainable and efficient production process.

Conventional Synthesis

While enzymatic methods are preferred for their selectivity and environmental benefits, conventional chemical synthesis techniques still exist. The traditional multi-step organic synthesis starting from phenylalanine or its derivatives often faces challenges, such as the use of toxic reagents and complex purification processes[12]-[13]. These methods may also yield less optically pure products compared to their enzymatic counterparts.

Future Directions

Ongoing research is focused on enhancing the efficiency of the enzymatic synthesis of oxetanylanine. Efforts such as directed evolution and systematic protein engineering are being explored to increase enzyme activity and substrate specificity, further optimizing production pathways and potentially leading to the development of more efficient synthetic routes[11][14]. As the demand for optically pure amino

acid derivatives continues to grow in pharmaceutical and therapeutic applications, advancements in both enzymatic and chemoenzymatic synthesis methods will be crucial for meeting these needs.

Biological Role

Oxetanylalanine, like other amino acids, plays a crucial role in biological systems primarily as a building block for proteins. While there are hundreds of amino acids, only 20 are utilized in the synthesis of proteins, which are essential macronutrients in the human diet and serve numerous functions within living organisms[15]. Proteins not only contribute to the structure of cells and tissues but also facilitate a wide array of biological processes including enzymatic reactions, hormone signaling, and nutrient transport[1].

In the context of protein synthesis, oxetanylalanine can function as a precursor in the formation of various peptides, contributing to the diversity of protein structures and functions through its incorporation into polypeptide chains. Proteins, formed from long chains of amino acids, undergo a two-phase process of transcription and translation, during which amino acids, including oxetanylalanine, are linked together in sequences that can vary significantly in length[15][16].

Moreover, amino acids like oxetanylalanine are not exclusively found in proteins; they can also serve as precursors for the synthesis of important biomolecules such as neurotransmitters and hormones. For instance, certain amino acids are critical for the production of neurotransmitters like dopamine, norepinephrine, and epinephrine, which are vital for various physiological functions[17][18]. This versatility underscores the importance of oxetanylalanine not just in structural roles but also in regulatory and signaling capacities within biological systems.

After protein synthesis, amino acids within proteins, including oxetanylalanine, can undergo chemical modifications that enhance the functional diversity of proteins. These modifications can include phosphorylation, acetylation, and glycosylation, which can alter the protein's activity, stability, and interactions with other cellular molecules[16][2].

Applications

Oxetanylalanine, a non-natural amino acid, has garnered interest for its potential applications in the pharmaceutical and agrochemical industries. Its unique structural properties make it an important building block for the development of novel drug compounds and therapeutic agents.

Synthesis and Biocatalysis

The use of phenylalanine ammonia lyases (PALs) in the synthesis of amino acid derivatives, including oxetanylalanine, has been extensively researched. This approach leverages the advantages of biocatalysis for higher enantioselectivity and chemoselectivity, which are essential for producing optically pure compounds.[3] Continuous

flow biocatalysis combined with immobilized PALs has demonstrated significant improvements in process productivity and efficiency. Compared to traditional batch reactions, continuous flow methods reduce reaction times and increase space-time yield (STY) by three-fold, showcasing the potential of integrating biocatalysis with flow chemistry for industrial applications.[\[3\]](#)

Nutritional Considerations

In terms of dietary applications, phenylalanine, which is structurally related to oxetanylanine, plays a vital role in human nutrition. While most individuals can obtain sufficient phenylalanine from a balanced diet, those with phenylketonuria (PKU) must manage their intake carefully. Dietary interventions often need to be scientifically validated through controlled studies to ensure efficacy and safety, particularly for those on restrictive diets.[\[1\]\[19\]](#) Consequently, the development of oxetanylanine and similar compounds could lead to safer dietary alternatives that fulfill the nutritional needs of patients with metabolic disorders.

Research and Development

Oxetanylanine's unique properties also make it a candidate for further research into new therapeutic pathways and drug formulations. Ongoing studies are focused on understanding the functional and neurometabolic impacts of various phenylalanine derivatives, which could enhance treatment strategies for metabolic diseases, including PKU.[\[19\]](#) Furthermore, innovative applications of oxetanylanine in metabolomics are being explored, with companies like MetwareBio providing advanced analysis services to unravel the complexities of amino acid metabolism in health and disease.-[\[1\]](#)

Safety and Toxicology

Chemical Properties and Hazards

Oxetanylanine, commonly referred to as L-phenylalanine, is an odorless white crystalline powder that has a slightly bitter taste and a pH of approximately 5.4 to 6 in a 1% aqueous solution[\[6\]](#). It is classified as a weak acid when in solution and is water-soluble[\[6\]](#). The compound is known to be light-sensitive and can emit toxic fumes of nitrogen oxides when heated to decomposition[\[6\]](#).

Health Hazards

Acute exposure to Oxetanylanine may lead to several health hazards. Skin contact requires immediate action; affected areas should be flooded with water, and all contaminated clothing should be removed. If symptoms like redness or irritation develop, medical attention is necessary[\[6\]](#). Inhalation of the substance may cause respiratory symptoms, and those affected should seek fresh air immediately and call

for medical assistance if symptoms persist[6]. The substance is likely combustible, although specific flash point data is not available[6].

Response Recommendations

In the event of a spill, it is recommended to dampen the solid spill material with water and transfer it to a suitable container. Remaining material should be picked up using absorbent paper that is also dampened with water[6]. Proper storage involves protecting Oxetanyllalanine from exposure to light and maintaining it at ambient temperatures[6]. For firefighting, it is advisable to use a dry chemical, carbon dioxide, or Halon extinguisher to control any fires involving this material[6].

Regulatory Information

No specific regulatory information is available concerning Oxetanyllalanine from the Environmental Protection Agency (EPA) or the Occupational Safety and Health Administration (OSHA)[6]. Alternate names for the chemical include ALANINE, PHENYL-, L-, and L-PHENYLALANINE among others[6].

Scientific Literature

Research surrounding oxetanyllalanine has seen contributions from various institutions and scholars, focusing on its biochemical properties and potential applications. The Department of Chemistry, Biochemistry and Pharmaceutical Sciences at the University of Bern and the Novartis Institutes for Biomedical Research are key contributors to the ongoing research in this area[3].

Research Contributions

The scientific community has published several notable studies exploring the implications of oxetanyllalanine in biocatalysis and enzyme coupling reactions. For example, a study highlighted the application of enzyme coupling reactions to shift thermodynamically limited biocatalytic reactions, demonstrating significant advancements in the understanding of this compound's capabilities[20].

Methodology and Ethics

Recent projects investigating oxetanyllalanine have adhered to strict ethical guidelines, with research approved by relevant ethics committees, such as the one in Bern, Switzerland[19]. All modifications to study protocols are reported to ensure transparency and compliance with established standards. The research has also been registered on platforms like clinicaltrial.gov, promoting accountability in scientific inquiry.

Data Availability and Transparency

The original contributions from studies on oxetanylanine, including supplementary material, are accessible online. This emphasis on data availability allows for further inquiries and verification of research findings, promoting transparency within the scientific community[20][21]. The authors have acknowledged the importance of collaboration and support from various staff in the delivery of their research findings, underscoring the collective effort required in scientific studies[20].

Conflict of Interest

In conducting this research, the authors have declared the absence of any commercial or financial relationships that could pose a potential conflict of interest, thereby reinforcing the integrity of their findings[20]. Such declarations are crucial in maintaining the trust of the scientific community and the public in published research.

This body of literature not only contributes to the fundamental understanding of oxetanylanine but also lays the groundwork for its practical applications in the pharmaceutical sciences and related fields.

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