

Azidoalanine

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summary

Azidoalanine is a non-canonical amino acid derivative of alanine, characterized by the presence of an azido functional group (-N₃) attached to its side chain. With the chemical formula C₃H₆N₄O₂, azidoalanine plays a pivotal role in organic synthesis and biochemistry, particularly in the formation of complex peptides and drug development applications.[\[1\]\[2\]](#) The unique reactivity of the azido group enables azidoalanine to engage in various chemical reactions, including click chemistry, making it a valuable building block in medicinal chemistry and protein labeling.[\[3\]\[4\]](#)

The synthesis of azidoalanine can be accomplished through both biological and chemical methodologies. These include recombinant DNA technology and advanced chemical techniques such as nucleophilic substitution and copper-catalyzed azide-alkyne cycloaddition (CuAAC), which are crucial for producing azidoalanine and its derivatives efficiently.[\[5\]\[6\]\[7\]](#) Recent advancements in synthesis have further enhanced its utility, allowing for more precise incorporation into peptides and other biomolecules, expanding its applicability in research and therapeutic contexts.[\[8\]](#)

Azidoalanine's biological implications extend to its potential roles in metabolic pathways, protein interactions, and even mutagenesis. Its incorporation into proteins may influence enzymatic activity and receptor signaling, while emerging studies suggest it could impact cancer biology, particularly through interactions with cancer-associated fibroblasts.[\[9\]\[10\]](#) These properties make azidoalanine a significant subject of study in both biochemical research and cancer therapeutics.

Despite its advantages, the use of azidoalanine is not without controversy, particularly regarding its mutagenic potential and the implications of using azido-containing compounds in biological systems. Continued research is necessary to fully understand the impacts of azidoalanine on metabolism, protein function, and its overall safety in biomedical applications.[\[11\]\[9\]](#)

Chemical Structure

Azidoalanine, specifically D-Alanine with the chemical formula C₃H₆N₄O₂, incorporates an azido group (-N₃) which significantly influences its chemical behavior and reactivity[\[1\]\[2\]](#). The structure consists of an amino acid backbone that features both an amino group (-NH₂) and a carboxyl group (-COOH), typical of amino acids, with the azido group attached to the side chain[\[12\]\[13\]](#).

Molecular Configuration

The azido group serves as a notable functional modification that enhances the molecule's utility in organic synthesis, particularly in the formation of complex pep-

tides[13]. The presence of the azido group makes the amino acid less bulky than other protecting groups, allowing for more effective coupling reactions, especially in challenging peptide bond formations[13].

Interaction and Reactivity

In terms of molecular interactions, the azido radical derived from azidoalanine can establish strong covalent bonds with surrounding amino acids in hydrophobic environments. This interaction is facilitated by the azido moiety, which can promote intramolecular electrostatic interactions among neighboring peptide bonds[14][15]. As a result, azidoalanine not only acts as a building block in peptide synthesis but also plays a pivotal role in stabilizing molecular structures through these interactions.

Synthesis

The synthesis of azidoalanine and related compounds can be achieved through various methods, predominantly utilizing both biological and chemical synthesis techniques.

Biological Synthesis

Biological synthesis methods for unnatural amino acids (UAAs), such as azidoalanine, typically involve the incorporation of specific amino acids into peptides or proteins through recombinant DNA technology or through the use of engineered enzymes. These methods leverage the natural enzymatic processes to produce amino acids with modified side chains, making them suitable for various applications in biotechnology and pharmacology[3].

Chemical Synthesis

Chemical synthesis has emerged as a robust approach to produce azidoalanine and its derivatives, with several methodologies reported:

Two-Step Synthesis

A notable two-step synthesis involves starting with readily available Fmoc-protected asparagine and glutamine. This method efficiently transforms these compounds into Fmoc-protected L-azidoalanine and L-azidohomoalanine. This scalable approach is characterized by its simplicity and adaptability, allowing for modifications to accommodate different substrates[5][16].

Nucleophilic Substitution

One of the foundational reactions employed in the synthesis of azidoalanine is nucleophilic substitution. For instance, the azide group can be introduced through an SN2 reaction, where an azide ion displaces a suitable leaving group on an amino

acid derivative. This method has been optimized to enhance yields and selectivity, demonstrating the versatility of azidoalanine synthesis[6][17].

Click Chemistry

Click chemistry techniques have also been utilized to incorporate azido groups into peptides. The copper-catalyzed azide-alkyne cycloaddition (CuAAC) allows for the formation of stable triazole linkages, which is essential for the functionalization of azidoalanine in complex biomolecules. This reaction is notable for its high efficiency and selectivity, often referred to as a "click" reaction due to its reliability and simplicity[7][17].

Advanced Methodologies

Recent advancements have introduced novel reagents and strategies for the diazo transfer process, including the use of imidazole-1-sulfonyl azide hydrochloride, which has shown superiority over traditional reagents. This alternative provides a more efficient pathway for the synthesis of azides, thereby streamlining the incorporation of azido groups into amino acids and peptides[8][17].

Properties

Physical Properties

Azidoalanine, specifically D-azidoalanine, possesses distinct physical properties that are crucial for its application in medicinal chemistry and biochemistry. The standard enthalpy of formation for D-azidoalanine in its solid state is measured to be approximately -1621.00 kJ/mol[18]. Additionally, the enthalpy of fusion is estimated to be 10.89 kJ/mol[18]. The compound exhibits a decomposition temperature below 80 °C, indicating stability as a crystalline solid at room temperature but potential reactivity at elevated temperatures[17].

Chemical Properties

D-azidoalanine is characterized by the presence of an azide functional group, which significantly enhances its reactivity, particularly in click chemistry applications. This reactivity is primarily exploited in copper-catalyzed azide-alkyne cycloaddition reactions, where D-azidoalanine can form stable triazole linkages with alkyne-containing molecules[19]. The azide group facilitates unique interactions in biochemical processes, making it a valuable building block in drug development and chemical biology[11].

Comparisons with Other Amino Acids

Azidoalanine's properties can be contrasted with those of other amino acids. For instance, cysteine, another amino acid containing a functional group, exhibits polar characteristics due to its thiol group, which differs fundamentally from the reactivity

of the azide[12]. The thiol of cysteine is significantly more reactive than the hydroxyl group found in serine, highlighting the diverse reactivity patterns across amino acids[12].

Energetic Properties

The energetic contributions of D-azidoalanine are essential for understanding its behavior in biological systems. The enthalpy of formation ($\Delta H^\circ_{\text{gas}}$) is reported to be -414.70 kJ/mol[18], illustrating the stability of its gaseous form under standard conditions. The Gibbs free energy of formation (ΔG°) is noted to be -227.35 kJ/mol, which further supports its thermodynamic favorability in biochemical reactions[18].

Biological Role

Azidoalanine, a derivative of alanine, plays a significant role in various biological processes, particularly in the context of protein interactions and metabolic pathways.

Role in Metabolism

In mammals, alanine, from which azidoalanine is derived, plays a pivotal role in the glucose-alanine cycle. This cycle facilitates the transport of nitrogen from peripheral tissues to the liver, where alanine can be converted back to glucose, thereby aiding in energy metabolism.[20] The presence of azidoalanine in metabolic pathways could potentially alter this cycle, although further research is needed to clarify its specific impacts on metabolism and energy homeostasis.

Protein Interactions

Many proteins, including those involved in critical functions such as enzymatic activity and receptor signaling, engage in interactions with small ligands, which can include azidoalanine. These interactions are governed by several key factors, including shape complementarity, the chemical nature of interacting moieties, and the free energy of binding.[21] Azidoalanine may serve as a useful probe in understanding these interactions, providing insights into the energetics and dynamics of protein-ligand complexes.

Mutagenesis and Research Applications

Azidoalanine has also been implicated in mutagenesis processes, particularly in bacterial and plant systems. Research has shown that sodium azide, a related compound, mediates mutagenesis through metabolic intermediates, suggesting that azidoalanine may participate in similar pathways.[9] Understanding its biological roles could lead to advancements in genetic research and the development of therapeutic strategies targeting metabolic and mutagenic processes.

Implications in Cancer Biology

Emerging studies indicate that azidoalanine could play a role in cancer biology, particularly in the tumor microenvironment (TME). Cancer-associated fibroblasts (CAFs) are known to be influenced by various ligands that could potentially include azidoalanine. These interactions may drive the differentiation of CAFs and affect their interactions with tumor cells, ultimately influencing tumor progression and response to therapies.[\[10\]](#) Thus, azidoalanine represents a molecule of interest for further investigation in cancer research, especially in understanding its contributions to tumor cell signaling and metabolism.

Applications

Azidoalanine, a non-canonical amino acid, has gained attention for its diverse applications in biochemistry and medicinal chemistry. Its unique azide functional group enables it to participate in various chemical reactions, making it a valuable tool in protein labeling, drug delivery, and molecular imaging.

Protein Labeling and Imaging

Azidoalanine is frequently used in the genetic encoding of proteins, allowing for the incorporation of this amino acid into specific locations within a protein structure. This property facilitates the development of fusion proteins that can be used for molecular imaging applications. For example, azidoalanine can be incorporated into proteins to create azide-tagged biomolecules that are amenable to click chemistry, enabling researchers to visualize protein dynamics and localization in live cells[\[3\]](#).

Therapeutic Applications

The structural versatility of azidoalanine allows it to be employed as a chiral building block in the design of therapeutic agents. Research indicates that azidoalanine-modified peptides and proteins can exhibit enhanced stability and bioactivity, making them promising candidates for drug development. For instance, azidoalanine can be utilized to construct targeted drug delivery systems where the azide group can react with specific drug conjugates, potentially improving therapeutic efficacy while minimizing off-target effects[\[3\]\[4\]](#).

Biocatalysis and Chemical Synthesis

Azidoalanine's reactivity makes it a suitable substrate in biocatalytic processes, where it can be utilized for the synthesis of various bioactive compounds. Its incorporation into peptide libraries expands the possibilities for discovering new pharmacological agents, particularly in the realm of cancer therapeutics. For example, peptides containing azidoalanine have shown potential in the development of site-specific drug carriers that can selectively target cancer cells, thereby enhancing the delivery of chemotherapeutic agents[\[21\]\[4\]](#).

History

Azidoalanine, a notable derivative of the amino acid alanine, has garnered attention for its unique chemical properties and applications in various fields of research. The history of azidoalanine can be traced back to the synthesis of amino acids and the exploration of their derivatives.

Discovery and Synthesis

The structural representation of azidoalanine allows for unique biochemical interactions, particularly due to the azide functional group, which is capable of participating in click chemistry reactions with alkyne-containing molecules. D-azidoalanine, one of its isomers, has been specifically recognized for its ability to undergo the copper-catalyzed azide-alkyne cycloaddition, leading to the formation of stable triazole linkages with alkyne-modified compounds[22][19].

Applications in Biochemistry

The biochemical significance of azidoalanine has prompted research into its mutagenic properties. Although the mechanisms behind azidoalanine-induced mutagenesis are not fully understood, its utility in studying interactions at a molecular level has made it a subject of interest in medicinal chemistry and biochemical research[11][19]. Additionally, the compound's synthesis and utilization have been highlighted in various scientific literature, emphasizing its role in advancing organic synthesis techniques and contributing to the field of organocatalysis[6][22].

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