Hans-Dieter Jakubke and Norbert Sewald

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A Concise Encyclopedia

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Preface

The versatility of peptides with respect to structure, biological activity, and potential application has led to a renaissance of peptides, also in a pharmaceutical context and a growing interest in the chemistry and biology of peptides. Recent progress in peptide research is documented by numerous scientific contributions, both in the primary literature and patents. Peptides exert impact not only onto chemistry and biochemistry, but also influence biology, pharmacology, medicinal chemistry, biotechnology, and gene technology. The ubiquitous and trans-disciplinary relevance of peptides for the life sciences calls for reference works in a handy, compact volume providing an informative overview of all types of aspects of peptides, either as natural products or synthetic compounds.

The overwhelmingly positive review and feedback for the glossary of our previously published monograph *"Peptides: Chemistry and Biology"* fostered the idea to produce this specific concise encyclopedia. We faced the difficult task of selecting and processing the vast knowledge in the peptide field and presenting it within one volume. This approach cannot be free of subjective decisions, but we hope to have collected the most relevant issues. Care has been taken to compile a concise, clearly presented scientific definition of the keywords among more than 2000 entries. A task such as this, of course, can never be completed and should not replace a textbook. Rather, this compendium is meant to provide a useful first reference tool, an "information mine" with key information and up-to-date references on a specific peptide topic. Besides covering important biologically active peptides, the book also provides basic information on general and specific topics of modern peptide research.

This encyclopedia will be useful to scholars, professors, lecturers, laboratory technicians, science teachers and students that are interested in certain aspects of peptides – occasionally or permanently. Readers belonging to the disciplines chemistry, biosciences, physics, pharmacy, biology, medicine or even beyond the academic community will profit from using the encyclopedia either when searching for specific issues or by just browsing through the topics.

We appreciate contributions by our colleagues Gunter Fischer (Max Planck Research Unit for Enzymology of Protein Folding, Halle/S., Germany), John D. Wade (University of Melbourne, Australia), Siegmund Reißmann (Friedrich Schiller University, Jena, Germany), Frank Bordusa (Martin Luther University, Halle-Wittenberg, Germany) on topics related to their research fields. Helpful discussions with Paul Cordopatis (University of Patras, Greece), Gerd Gäde (University of Cape Town, South Africa), Ferenc

Hudecz (Eötvös Loránd University, Budapest, Hungary), John H. Jones (Balliol College, Oxford, U.K.), Luis Moroder (Max-Planck Institute of Biochemistry, Martinsried, Germany), Robin E. Offord (University of Geneva, Switzerland), and Dirk Ullmann (Evotec, Hamburg, Germany) are gratefully acknowledged. We express our special thanks to the Protein Research Foundation (Osaka, Japan) for providing the biweekly journal *Peptide Information* to one of us (H.-D. J.) over many years, which has been a very useful source for conceiving the latest developments in peptide research.

The editorial team at Wiley-VCH took care that the manuscript was converted into this book in a rather short period of time without complications.

Bielefeld **Norbert Sewald**
and
Dresden-Langebrück **Hans-Dieter Jakubke**

How to use this book

Entries

Entries are listed in alphabetical order. The main entry title is printed in bold type, followed by synonyms in bold italics. Numbers, Greek letters and configurational numbers/letters at the beginning of the name are ignored when allocating in alphabetical order, e.g. O-Acyl isopeptide method is listed under A, α_2-macroglobulin is listed under M, while 8-quinolyl ester is listed under Q.

Abbreviations

The standard abbreviations and symbols in peptide science are mainly used according to the previously published recommendations in Journal of Peptide Science (J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 1-12) and many of them have been included as entries in the appropriate alphabetical positions. The three-letter code is used for peptides with up to ten amino acid residues. For larger peptide sequences the one-letter symbols are used. In the latter case, a C-terminal amide is symbolized by "a".

Other abbreviations

abbr.	abbreviation
[α]	optical rotation
b	bovine
b.p.	boiling point
c	concentration
°C	degrees Celsius/degrees centigrade
Da	dalton
3D	three dimensional
ee	enantiomeric excess
E. coli	*Escherichia coli*
h	human

IC	inhibitory concentration
i.c.v.	intracerebroventricular(ly)
i.p.	parenteral(ly)
i.t.	intrathecal(ly)
i.v.	intravenous(ly)
kb	kilo base pair
kDa	kilodalton
K_M	Michaelis constant
LD_{50}	lethal dose 50%
m.p.	melting point
M	molar
M_r	relative molecular mass
N	refractive index
o	sheep (*ovinus*)
p	porcine
pI	isoelectric point
r	rat
®, ™	trade mark
rac.	racemic
syn.	synonym

Cross References

Cross references to other keywords are indicated by → .

References

Key references are given at the end of most entries to suggest further reading in the form of recent review articles, important original publications or even the first publication to communicate the discovery. They are meant to illustrate recent developments or important aspects of the keyword.

Trademarks, Patents

Trademarks (®, ™) are normally not marked, simply to refrain from using the encyclopedia for product advertising purposes. Patents are cited to international conventions and the following abbreviations are used: DE for Germany, US for United States, GB for Great Britain, FR for France, EP for European Patent.

The use of registered names and trademarks in this book does not imply that such names are exempt from protective laws and regulations and, hence, free for general use.

Further Reading

A comprehensive bibliography on peptide research until the end of the last century was published by John H. Jones (*J. Peptide Sci.* **2000**, 6, 201). The same author has published a useful commentary on the confusing nomenclature and bibliography of serial publications which use the term 'peptide' in their titles (*J. Peptide Sci.* **2006**, 12, 503). The Houben-Weyl volumes E22a to E22e "*Synthesis of Peptides and Peptidomimetics*" (Thieme, Stuttgart, **2002**), edited by Murray Goodman (Editor-in-Chief), Arthor Felix, Luis Moroder and Claudio Toniolo, represents the most up-to-date and exhaustive general treatise in the field of peptide synthesis. In addition, the *Handbook of Biologically Active Peptides* (Elsevier, San Diego, **2006**), edited by Abba J. Kastin, presents a tremendous body of knowledge in the field of biologically active peptides.

A

aa, amino acid.

AA, antamanide.

Aad, α-aminoadipic acid.

β-Aad, β-aminoadipic acid.

AAP, antimicrobial animal peptides.

Aart, a designed Cys2-His2 → zinc finger protein (190 aa, M_r 21.4 kDa). It was designed and constructed based on the application of zinc-finger domains of predetermined specificity to bind a 22-base-pair duplex DNA. The aart protein was expressed in *E. coli* as a C-terminal fusion to maltose-binding protein (MBP). The fusion protein contained a factor Xa protease cleavage site for the MBP tag. Aart complexed with its DNA target was crystallized followed by X-ray analysis. Aart binds its DNA target with picomolar affinity. The 1.96 Å structure of Aart was described in 2006 [B. Dreier et al., *J. Biol. Chem.* **2001**, *276*, 29466; J. W. Crotty et al., *Acta Crystallogr.* **2005**, *F61*, 573; D. J. Segal et al., *J. Mol. Biol.* **2006**, *363*, 405].

AatRS, amino acyl tRNA synthetase.

Aβ, amyloid-β.

Ab, antibody.

A_2bu, 2,4-diaminobutyric acid.

Abderhalden, Emil (1877–1950), professor of physiology (1908–1910) at Berlin, of biochemistry (1911–1945) at Halle/S. (Germany), and of physiological chemistry (1946/47) at Zurich (Switzerland). From 1931–1950 Prof. Abderhalden was President of the German Academy of Natural Scientists Leopoldina in Halle/S. In 1902, Abderhalden had joined → Emil Fischer's group and worked on protein hydrolysates and proteolytic enzymes which led, in 1904, to *Habilitation*. Further scientific activities were mainly directed towards the chemistry of proteins and physiological chemistry of metabolism [J. Gabathuler (Ed.), *Emil Abderhalden, Sein Leben und Werk*, Ribaux, St. Gallen, **1991**].

Abrin, a highly toxic protein isolated and crystallized from the red seeds of *Abrus precatorius*. It consists of an A-chain ($M_r \sim$ 30 kDa) and a B-chain ($M_r \sim$35 kDa), joined by disulfide bridges. The A-chain is a highly specific *N*-glucosidase acting as ribosome-inactivating protein (RIP), whereas the B-chain is a glycoprotein responsible for anchoring at the cell surface. One of the carbohydrate chains forms a bridge between two neighboring molecules, whereas another sugar chain covers the surface of the B-chain. A disulfide-cleaving system of the cell releases the A-chain, which enters the cell by endocytosis. RIP cleaves a single adenine residue from the rRNA, resulting in inhibition of protein synthesis followed by cell death. Similar action and structure are possessed by → ricin. The A-chain coupled with a monoclonal antibody directed against a tumor antigen is used in drug targeting [J. Y. Lin et al., *J. Formosan Med. Assoc.* **1969**, *68*, 32; J. Y. Lin et al., *Nature* **1970**, *227*, 292; A. J. Cumber et al., *Methods Enzymol.* **1985**, *112*, 207; T. H. Tahirov et al., *J. Mol. Biol.* **1995**, *250*, 354].

Abu, α-aminobutyric acid.

Abz, aminobenzoic acid.

Abzyme, *catalytic antibody*, a monoclonal antibody with catalytic activity. An antibody raised against a transition-state analogue of a particular reaction can catalyze that reaction. The first abzyme to be generated was capable of catalyzing the hydrolysis of esters. Abzymes have been described that catalyze, e.g., acyl transfer, C–C bond cleavage, β-elimination, and C–C bond formation. From X-ray analyses it could be concluded that antibodies bind peptides of various length in elongated grooves using hydrogen bonding, van der Waals forces, and ionic contacts for recognition. Abzymes are also an interesting choice for → abzyme-catalyzed peptide synthesis [L. Pauling, *Am. Sci.* **1948**, *36*, 51; W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, **1969**; R. A. Lerner et al., *Science* **1991**, *252*, 659; D. Hilvert et al. in: *Bioorganic Chemistry: Peptides and Proteins*, S. M. Hecht (Ed.), Oxford University Press, Oxford, **1998**].

Abzyme-catalyzed synthesis, the application of catalytic antibodies as catalysts for formation of the peptide bond. If an abzyme could bind a substrate already in the transition-state conformation, it might act as an enzyme catalyzing the reaction to which the transition-state conformation is predisposed. Analogues of the transition state were used as haptens to induce abzymes (catalytic antibodies) with the correct arrangement of catalytic groups. At present, the main disadvantage of the abzyme approach is the requirement of a large number of abzyme catalysts to accommodate the wide specificity pattern of amino acids in coupling reactions. However, these first interesting results in this field provide an impetus for producing further generations of abzymes capable of catalyzing the ligation of longer, unprotected fragments, combined with a general strategy for the development of sequence-specific abzyme ligases [R. Hirschmann et al., *Science* **1994**, *265*, 234; J. R. Jacobson, P.G. Schultz, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 5888; D. W. Smithrud et al., *J. Am. Chem. Soc.* **1997**, *119*, 278; S. N. Savinov et al., *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1321].

Ac, acetyl.

ACE, angiotensin-converting enzyme.

ACE 2, angiotensin-converting enzyme 2.

ACE inhibitors, pharmaceuticals for the treatment of hypertension, congestive heart failure, and myocardial infarction. Different types of synthetic ACE inhibitor have been designed. Synthetic ACE inhibitors are grouped by their ligand for the active site of the → angiotensin converting enzyme (ACE). The major representative of this group is → captopril bearing a sulfhydryl moiety, whereas → enalapril and lisinopril have a carboxyl moiety, and fosinopril a phosphorous group. The beneficial effects of this group of ACE inhibitors in hypertension and heart failure result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE causes a decrease in plasma angiotensin II (→ angiotensins) level, which leads to decreased vasopressor activity and to a small decrease in aldosterone secretion. However, these synthetic ACE inhibitors are known to have strong adverse side effects, such as cough, skin rashes, and angioedema. Attempts to use → angiotensin-converting enzyme 2 and its proteolysis product angiotensin-(1–7) for the regulation of blood pressure are under investigation. Naturally occurring → ACE inhibitory peptides have been reported to

have potential as antihypertensive components in functional foods or nutraceuticals. However, the development of ACE inhibitors was greatly influenced by natural products, e.g., by special members of the → bradykinin-potentiating peptides. The 9-peptide *teprotide*, <Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro-OH (BPP_{9a}, SQ20, 881) was the most active ACE inhibitor *in vivo*, whereas the 5-peptide <Glu-Lys-Trp-Ala-Pro-OH (BPP_{5a}, SQ20, 475) showed *in vitro* the highest activity. The proposed binding of BPP_{5a} to the active site of ACE led to the rational design of the first marketed, orally active ACE inhibitor → captopril [M. A. Ondetti et al., *Biochemistry* **1971**, *10*, 4033; M. A. Ondetti et al., *Science* **1977**, *196*, 441; D. W. Cushman et al., *Biochemistry* **1977**, *16*, 5484; M. L. Cohen, *Annu. Rev. Pharmacol. Toxicol.* **1985**, *25*, 307; G. Lawton et al., in: *Advances in Drug Research*, B. Testa (Ed.), Volume 23, p. 161, Academic Press, New York, **1992**; T. F. T. Antonius, G. A. Macgregor, *J. Hypertens.* **1995**, *13*, S11].

ACE inhibitory peptides, naturally occurring peptides derived, for example, from the venoms of the Brazilian pit viper *Bothrops jararaca* and other snakes, known as → bradykinin-potentiating peptides, have significantly influenced the development of synthetic → ACE inhibitors based on rational drug design. Surprisingly, peptides from the enzymatic partial hydrolysis of proteins, such as milk, maize, gelatin, soybean, wheatgerm, serum, hemoglobin, porcine and chicken muscle have a potential as antihypertensive compounds in functional foods and nutraceuticals. It is interesting to note that some of these peptides not only show ACE inhibitory activity *in vitro*, but also exhibit *in-vivo* antihypertensive activity in spontaneously hypertensive rats [H. Kato, T. Suzuki, *Experientia* **1969**, *25*, 694; *Biochemistry* **1971**, *10*, 972; L. Vercruysee et al., *J. Agric. Food Chem.* **2005**, *53*, 8106].

Acetaldehyde/chloranil test, a monitoring method for the control of complete coupling reaction in → solid-phase peptide synthesis [T. Voikovsky, *Peptide Res.* **1995**, *8*, 236].

Acetamidomethyl group (Acm), a type of thiol protecting group with an *N*-acyl *N*,*S*-acetal moiety, compatible with both Boc and Fmoc chemistry. The Acm group is completely stable towards acidolysis, and is cleaved with mercury(II) salts at pH 4, thallium(III) trifluoroacetate, or iodine. Oxidizing agents such as iodine simultaneously induce disulfide formation. Structural analogues of the Acm group are the chloroacetamidomethyl group, the isobutyrylamidomethyl group, and the → trimethylacetamidomethyl group.

Achatin, a 4-peptide isolated from the ganglia of the African giant land snail *Achatina fulica*. The neuroexcitatory peptide *achatin I* (H-Gly-D-Phe-Ala-Asp-OH) contains a D-amino acid (→ dermorphin, → deltorphins, → fulicin) in position 2, whereas *achatin-II* with the L-isomer in the same position shows neither physiological nor pharmacological activities. Because of Na^+, achatin I induced a voltage-dependent inward current on the giant neuron. It has been assumed that D-Phe in achatin-I is a prerequisite for forming a 15-membered ring with a unique turn conformation structure, which may be the active conformation suitable for interactions with the receptor. The characterization of a cDNA encoding a precursor polypeptide of achatin-I have been described [Y. Kamatani et al., *Biochem. Biophys. Res. Commun.* **1989**, *160*, 1015; T. Ishida et al., *FEBS Lett.* **1992**, *307*, 253; H. Satake et al., *Eur. J. Biochem.* **1999**, **261**, 130].

AchR, acetylcholine receptor.

Acm, acetamidomethyl.

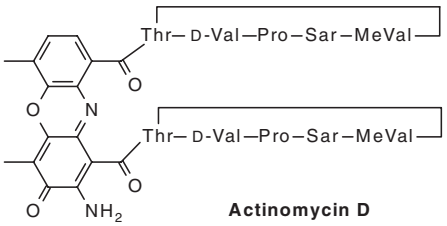
ACP, acyl carrier protein.

ACTH, acronym of adrenocorticotropic hormone, → corticotropin.

Actin, a contractile protein occurring in many eukaryotic cell types. Actin and → myosin are the major components of the muscle. Both proteins account for 60–70% and 20–25% of the total muscle protein, respectively. Actin and its filaments are the major components of the cytoskeleton in eukaryotic cells. Besides thrombomyosin and → troponin, actin is the major constituent of thin filaments. The fibrous *F-actin* forms the core of the thin filament and is formed under physiological conditions by polymerization of the globular *G-actin* ($M_r \sim 42$ kDa; 375 aa). The regulation of the polymerization/depolymerization of F-actin is essential for cytokinesis, cell mobility, and the control of cell shape and polarity. The monomeric G-actin consists of two domains, each of which is divided into two subdomains. G-actin normally binds one molecule of ATP, which is hydrolyzed during polymerization to F-actin, and the resulting ADP remains bound to the F-actin monomer unit. ATP and ADP bind in a cleft between the two domains. The F-actin helix (diameter 100 Å) has 2.17 actin monomers per left-handed helix turn (13 subunits in six turns) and a rise per turn of 60 Å. The monomeric unit of each F actin is capable of binding a single myosin S 1 fragment [R. A. Milligan et al., *Nature* **1990**, *348*, 217; P. Sheterline, J. C. Sparrow, *Protein Profiles* **1994**, 1, 1; P. Sheterline et al., *Actin*, Oxford University Press, New York, **1998**; J.-W. Chu, G. A. Voth, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13111].

Actinohivin (AH), a sugar-binding anti-human immunodeficiency virus protein produced by an actinomycete *Longispora albida* gen. nov, sp. nov. AH consists of 114 aa and is composed of highly conserved three-tandem repeats. Each repeat unit is built of 38 aa containing a Gln-Xaa-Trp motif at the *C*-terminus. It has been reported that AH inhibits the infection of susceptible cells by various strains of T-lymphocyte (T)-tropic and macrophage (M)-tropic HIV types 1 and 2, and both T- and M-tropic syncytium formation via AH binding to the high-mannose-type saccharide chains of HIV gp120. The three tandem-repeat structure of AH is essential for potent anti-syncytium formation activity and gp120-binding [H. Chiba et al., *J. Antibiot.* **2001**, *54*, 818; *Biochem. Biophys. Res. Commun.* **2004**, *316*, 203; A. Takahashi et al., *Arch. Biochem. Biophys.* **2005**, *437*, 233].

Actinomycins, peptide antibiotics produced by various strains of *Streptomyces*. Actinomycins are orange-red bacteriostatic and cytostatic, but highly toxic, chromopeptides. The chromophore *actinocin*, 2-amino-4, 6-dimethyl-3-oxo -phenoxazine-1,9-dicarboxylic acid, is linked to two five-membered peptide lactones by the amino groups of two threonine residues. The various naturally occurring and synthetic actinomycins differ mostly in the amino acid sequence of the lactone moieties. *Actinomycin D* is one of the well-known actinomycins with known 3D structure. Actinomycin D is a useful antineoplastic agent that binds tightly to ds-DNA, and in this manner strongly inhibits both transcription and DNA replication. It presumably interferes as an intercalating agent with the passage of RNA polymerase and DNA polymerase, respectively. Actinomycin D is used as a cytostatic in the treatment of the rare types of cancer, e.g.,



Actinomycin D

Wilms' carcinoma, chorion carcinoma, and Hodgkin's disease [A. B. Mauger, *Topics Antibiot. Chem.* **1980**, *5*, 223].

Active ester, R-CO-XR′, an amino acid or peptide ester bearing an electron-withdrawing substituent XR′ that promotes the nucleophilic attack of the amino component during the formation of a peptide bond. The acylating power of an ester moiety increases with the ability of its leaving group $^{-}$XR to depart, which in turn is related to the strength of the acid HXR′. A very large number of different types of active esters have been described, but only some of these, e.g., thiophenyl-, pentafluorphenyl- and 4-nitrophenyl esters, have been used much. New types of active ester are mechanistically based on intramolecular base catalysis. Efforts to minimize racemization have led to studies of neighboring effects (anchimeric assistance) which led to the development of active esters capable of discriminating effectively between aminolysis and racemization first indicated by 8-quinolyl ester and *N*-hydroxypiperidinyl ester. The same situation applies to other active esters of high practical importance, such as derivatives of *N*-hydroxysuccinimide (HOSu), 1-hydroxybenzotriazole ((HOBt), and the 7-aza analogue of HOBt, commonly referred to as 1-hydroxy-7-azabenzotriazole (HOAt; the correct name is 1-hydroxy-1,2,3-triazolo[5,4-b] pyridine) [H.-D. Jakubke et al., *Chem. Ber.* **1967**, *106*, 2367; M. Bodanszky, in: *The Peptides: Analysis, Synthesis, Biology*, Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York **1979**, 105].

Activins, members of the transforming growth factor-β protein family, originally discovered in the follicular fluid from ovaries and in leukemic cells. They stimulate the release of → follitropin. *Activin A* is a homodimer of the β-chains of → inhibin-A, whereas *activin B* consists of the β-chains of inhibin-A and inhibin-B. Activin is involved in the regulation of a couple of biological events, ranging from early development to pituitary function. It has numerous functions in both normal and neoplastic cells. Several different cells synthesize activin and have a specific binding site for this protein. It has been described that the activin-binding protein in rat ovary is → follistatin. Another activin-binding protein in biological fluids is → α_2-macroglobulin. cDNAs coding for an activin receptor were cloned in order to obtain more information on the cellular mechanisms of activin actions. The resulting cDNAs code for a receptor protein consisting of 494 aa comprising a ligand-binding extracellular domain, a single membrane-spanning domain, and an intracellular kinase domain with predicted Ser/Thr specificity. Recently, regulated production of activin A and activin B throughout the cycle of seminiferous epithelium in the rat have been described [T. Nakamura et al., *Science* **1990**, *247*, 836; L. S. Mathews, W. W. Vale, *Cell* **1991**, *65*, 973; P. G. Knight et al., *J. Endocrinol.* **1996**, *148*, 267; Y. Okuma et al., *J. Endocrinol.* **2006**, *190*, 331].

Activity-dependent neurotrophic peptides (ADNP), peptides derived from the neuroprotective protein, named *activity-dependent neuroprotective factor* (*ADNF*). ADNF ($M_r \sim 14$ kDa; pI 8.3) is a glia-derived

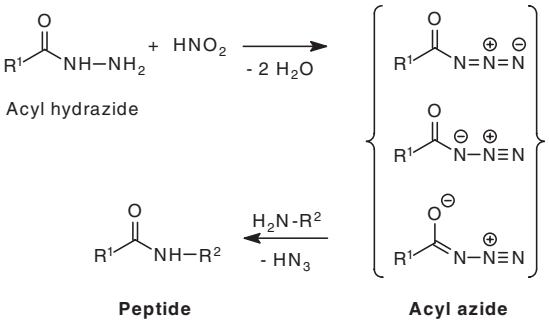
protein and is neuroprotective at femtomolar concentrations. Besides ADNF, even the related peptide fragment ADNP-14, VLGGGSALLR[10]SIPA, protects neurons from multiple neurotoxins. From structure–activity studies it follows that ADNP-9, SALLRSIPA, shows greater potency and a broader effective concentration range (10^{-16}–10^{-13} M) compared with ADNF and ADNP-14 in preventing cell death with tetrodotoxin treatment of cerebral cortical cultures [D. E. Brenneman, I. Gozes, *J. Clin. Invest.* **1996**, *97*, 2299; D. E. Brenneman et al., *Pharmacol. Exp. Ther.* **1998**, *285*, 619].

Aculeacins, antifungal peptides affecting glucan synthesis. Aculeacins A to G are produced by *Aspergillus aculeantus*. The peptides A through D, F, and G show good *in-vitro* activity against *C. albicans* and *Saccharomyces cerevisiae*, but reduced the growth of only a few filamentous fungi [K. Mizuno et al., *J. Antibiot.* **1977**, *30*, 297].

Acyl azide method, one of the oldest coupling methods in peptide synthesis, introduced by Theodor → Curtius in 1902. Starting compounds are amino acid or peptide hydrazides (R-CO-NH-NH_2), easily accessible from the corresponding esters by hydrazinolysis, which are transformed into azides (R-CO-N_3) by *N*-nitrosation at –10°C. The azide is extracted from the aqueous layer with ethyl acetate, washed, dried and reacted with the amino component. The azide method is still important, especially for segment condensations, because of its low tendency towards racemization [J. Meienhofer, in: *The Peptides: Analysis, Synthesis, Biology*, Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York, **1979**, 197].

Acyl enzyme, an intermediate in the catalytic mechanism of serine proteases, such as trypsin and chymotrypsin. After the serine protease has bound a peptide substrate to form the Michaelis complex, Ser^{195} (in the case of chymotrypsin) nucleophilically attacks the peptide bond in the rate-determining step, forming a transition-state complex, known as a tetrahedral intermediate. The latter decomposes to the acyl enzyme, an extremely unstable intermediate, that bears the acyl moiety at the hydroxy group of Ser^{195}. The acyl enzyme intermediate is deacylated by water during proteolysis, or the attacking nucleophile is an amino component in case of kinetically controlled → enzymatic peptide synthesis.

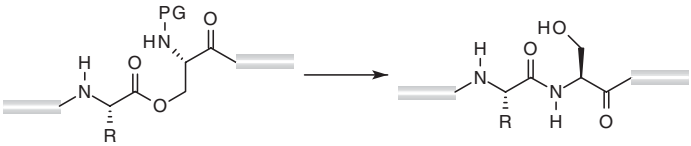
***O*-Acyl isopeptide method**, an approach to the efficient synthesis of peptides containing → difficult sequences via the *O*–*N*



intramolecular acyl migration reaction of *O*-acyl isopeptides. Such intermediates have also been termed → click peptides or → switch peptides. The sequence-specific formation of stable β-strands that aggregate and consequently prevent further deprotection or acylation reactions in SPPS is a major problem in peptide synthesis. Depending on the amino acid sequence present in the target peptide, the synthetic accessibility may be hampered or even rendered impossible. Such → difficult sequences require special consideration when planning a synthesis. Besides the introduction of → backbone amide protecting groups or serine/threonine derived → pseudo-prolines building blocks, the application of the *O*-acyl isopeptide method provides appropriate measures for obtaining difficult sequences. It relies on an *O*–*N*-intramolecular acyl migration at serine or threonine residues in strategic positions. During the peptide synthesis, a serine or threonine residue protected at N^{α} is incorporated, involving the β-hydroxy functionality and giving rise to a depsipeptide bond (*O*-acyl isopeptide). Such a single isopeptide moiety prevents the undesired formation of secondary structures. The method allowed, e.g., the synthesis of the Alzheimer's disease-related → amyloid β peptide (1-42) [Aβ (1-42)]. The water soluble Aβ (1-42) isopeptide precursor with Gly^{25}-Ser^{26} replacement by the corresponding β-depsipeptide undergoes, upon Ser^{26} N^{α} deprotection, an *O*–*N* acyl migration forming the target Aβ (1-42). Because of this property, the names → click peptide and → switch peptide have been coined. As there is a protecting group at the N^{α} of the isopeptide bond, the *O*–*N* acyl migration can not only be triggered by acidolytic cleavage of the N^{α}-Boc group, but also, e.g., by the photolysis of photolabile N^{α}-protecting groups. Such compounds will certainly facilitate the investigation of, e.g., β-sheet formation. Besides Aβ (1-42), other difficult sequences such as the Jung-Redemann 10-peptide and 26-peptide, H-$(VT)_{10}NH_2$ and the 37-peptide of the FEP28 WW-domain have been synthesized [Y. Sohma et al., *Biopolymers* **2007**, *88*, 253; M. Mutter et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 4172; L. Carpino et al., *Tetrahedron Lett.* **2004**, *45*, 7519].

***O*-Acylisourea**, a reactive intermediate of the → carbodiimide method.

Acyl halides, derivatives of amino acids in which the hydroxy group in the carboxyl group is replaced by a halogen atom. Acyl halides are reactive compounds suitable as acylating agents. First, Fmoc-protected amino acid chlorides have been used as stable derivatives for rapid peptide coupling reaction without the danger of racemization. However, their general application is somewhat limited, as not all Fmoc-protected amino acid derivatives are accessible. In contrast, Fmoc-protected amino acid fluorides do not suffer from such limitations. Further advantages of fluorides relative to the chlorides include their greater stability towards water, including moisture in the air, and their relative lack of conversion to the corresponding oxazolones on treatment with tertiary



O-Acyl isopeptide method

organic bases. The Fmoc-protected amino acid fluorides are suited both for solution peptide synthesis and for SPPS [L. A. Carpino et al., *J. Org. Chem.* **1986**, *51*, 3732; L. A. Carpino et al., *Acc. Chem. Res.* **1996**, *29*, 268; L. A. Carpino et al., *Tetrahedron Lett.* **1998**, *39*, 241].

Acyltransfer, the transfer of an acyl group R-CO- between two molecules in the course of a reaction as takes place, for example, in a serine protease-catalyzed cleavage of a peptide bond (→ acyl enzyme).

AD, Alzheimer's disease.

Ada, adamantyl.

Adaptins, accessory proteins thought to bind the membrane-spanning receptors for those specific proteins that the coated vesicle clathrin sequester.

Adhesion molecules, proteins responsible for interactions between cells and their environment, especially, the extracellular matrix and other cells. Several different molecules act as cell adhesion receptors such as → integrins, intercellular adhesion molecules (ICAM), leukocyte LFA-1, Mac-1 and p150/95 molecules, the fibronectin receptor complex (→ fibronectin), tenascin, and the position-specific (PS) antigens of *Drosophila*.

Adipokinetic hormones (AKH), peptide hormones belonging to the → AKH/RPCH peptide hormone family. As early in the 1960s, it was observed that extracts of the corpus cardiacum (CC) from either the American cockroach or the migratory (*Locusta migratoria*) and desert locust show metabolic effects such as elevation of the blood sugar trehalose or of the blood lipids (adipokinetic or hyperlipemic effect). In 1976, the complete sequence of the locust's AKH, today denoted as *Locmi-AKH-I*, pGlu-Leu-Asn-Phe-Thr-Pro-Asn-Trp-Gly-Thr-NH_2, was elucidated. Insecta contain up to three AKH peptides (isoforms) as demonstrated by the other two peptides produced by the African migratory locust: *Locmi-AKH-II*, pGlu-Leu-Asn-Phe-Ser-Ala-Gly-Trp-NN_2, and *Locmi-AKH-III*, pGlu-Leu-Asn-Phe-Thr-Pro-Trp-Trp-NH_2. The mobilization of substrates for high-energetic phases is the major function of AKH in insects. AKH are involved in the regulation of the level of circulating metabolites such as lipids, carbohydrates and proline by activating phosphorylases or lipases in the fat body cells. However, AKH peptides play also a multifunctional role and exert pleiotropic actions. For example, in certain insects (firebug, cricket) AKH show an effect on the locomotory activity, and are also involved in the immune response of locusts. Beside the members listed above, a huge number of AKHs such as Phymo-AKH (from *Phymateus morbillosus*), Emppe-AKH (from *Empusa pennata*), Manto-CC (*Mantophasmatodea*), and others (Psein-AKH, Grybi-AKH) are known. Recently, a novel member in a water boatman (*Heteroptera*, *Corixidae*), named Corpu-AKH, and its bioanalogue in a saucer bug (*Heteroptera*, *Naucoridae*), code-name Anaim-AKH, have been described. Interestingly, a glycosylated AKH, denoted Carma-HrTH (hypertrehalosemic hormone)-I, synthesized in the CC of the stick insect, is characterized by an unique modification. The hexose moiety is thought to be linked by *C*-glycosylation to the C-2 atom of the indole ring of tryptophan. On the other hand, Trifa-CC isolated of an extracts of CC from the protea beetle, *Trichostetha fascicularis*, is the first report of a phosphorylated invertebrate neuropeptide [J. V. Stone et al., *Nature* **1976**, *263*, 207; L. Schoofs et al., *Peptides* **1997**, *18*, 145; M. J. Lee et al., *Regul. Pept.* **1997** *69*, 69; G. Gäde, *Annu. Rev. Entomol.* **2004**, *49*,

93; G. Gäde et al., *Biochem. Biophys. Res. Commun.* **2005**, *330*, 598; G. Gäde et al., *Biochem. J.* **2006**, *393*, 705; G. Gäde et al., *Peptides* **2007**, *28*, 594].

Adiponectin, *adipocyte complement-related protein of 30 kDa (ACRP30), adipoQ, adipose most abundant gene transcript 1(apM1), gelantin-binding protein of 28 kDa (GBP28)*, an adipose-tissue-derived protein with important effects in glucose and lipid homeostasis. The molecular structure of adiponectin is characterized by an *N*-terminal collagen-like domain and a *C*-terminal globular domain with similarities to the complement factor C1q. It assembles into homotrimers, and higher-order oligomeric structures resulting by interactions between the collagen-like domains. The production and/or secretion of adiponectin is regulated by various mechanisms; e.g., it is increased by both IGF-1 and insulin in white adipose tissue. The synthesis and secretion of adiponectin are decreased by TNF-α, β-adrenergic agonists, glucocorticoids, and cAMP. With AdipoR1 and AdipoR2 two receptors for adiponectin have been cloned. AdipoR1 occurs primarily in skeletal muscle, whereas AdipoR2 is primarily produced in hepatic tissues. It may act also directly on bone, since receptors are found in osteoblasts and these cells also secrete adiponectin [L. Shapiro, P. E. Scherer, *Curr. Biol.* **1998**, *12*, 335; A. H. Berg et al., *Trends Endocrinol. Metab.* **2002**, *13*, 84; H. S. Berner et al., *Bone* **2004**, *35*, 842; U. Meier, A. M. Gressner, *Clin. Chem.* **2004**, *50*, 1511].

Adoc, 1-adamantyloxycarbonyl.

Adrenocorticotropic hormone (ACTH), → corticotropin.

Adrenocorticotropin, → corticotropin.

Adrenomedullin (AM), YRQSMNNFQG[10] LRSFGCRFGT[20]CTVQKLAHQI[30]YQFTD KDKDN[40]VAPRSKISPQ[50]GYa (disulfide bond: C^{16}–C^{21}), a vasoactive 52-peptide amide which is a member of the → calcitonin/calcitonin gene-related peptide family and shares 24% sequence homology with → calcitonin gene-related peptide (CGRP). AM was first discovered in human pheochromocytoma tissue in 1993, and later found in the normal adrenal medullae, kidneys, lungs, and blood vessels. AM has been reported to be synthesized and secreted by various types of cell, such as vascular endothelial and smooth muscle cells, cardiomyocytes, macrophages, fibroblasts, neurons, glial cells, and retinal pigment epithelial cells. In humans, its gene is situated in a single locus on chromosome 11p15.4. The amino acid sequence is highly conserved across species. The gene contains four exons separated by three introns and codes for a longer preprohormone of 185 aa, which is processed post-translationally, originating AM and *proadrenomedullin N-terminal 20-peptide* (*PAMP*). Both peptides participate in many physiological functions, including vasodilatation, bronchodilatation, neurotransmission, regulation of hormone secretion, brain functions, renal homeostasis, and antimicrobial activities. Apart from vasodepressive effects in mammals, caused by decreasing peripheral vascular resistance, AM shows diuretic and bronchodilatory effects and plays a regulatory role on aldosterone and ACTH (→ corticotropin) release. In renal failure, hypertension, heart failure, pregnancy loss, and septic shock plasma, the AM level has been found to be increased. The biological actions of AM are mediated through the calicitonin receptor-like receptor (CRLR) complexed with → receptor activity-modifying proteins (RAMPs),

especially via both CRLR/RAMP2 and CRLR/RAMP3 receptors, respectively (→ calcitonin/calcitonin gene-related peptide family). Plasma AM concentration is increased in patients with cardiovascular diseases. It has been shown that the source of increased AM levels in cardiac failure is the heart. AM has hypotensive, diuretic and natriuretic properties that are in common with → natriuretic peptides; however, the role of AM in cardiac pathologies is less clear. Sequence analysis of the *Fugu rubripes* genome led to the identification of three AM orthologues characterized by a 31 aa *C*-terminal domain sharing 50, 38, and 35% sequence identity with hAM in the mature area. The sequence *N*-terminal to the cystine ring varies greatly among species. Recently, it has been reported that AM and PAMP might be potent inducers of angiogenesis which is required for the maintained growth of solid tumors [K. Kitamura et al., *Biochem. Biophys. Res. Commun.* **1993**, *192*, 553; C. J. Charles et al., *Am. J. Hypertens.* **1999**, *12*, 166; S. J. Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, *11*, 167; M. Jougasaki, J. C. Burnett, Jr., *Life Sci.* **2000**, *66*, 855; T. Eto et al., *Regul. Pept.* **2003**, *112*, 61; M. T. Rademaker et al., *Regul. Pept.* **2003**, *112*,51; C. L. Chang et al., *Peptides* **2004**, *25*, 1633; A. Martinez, *Cancer Lett.* **2006**, *236*, 157].

Adrenorphin, → metorphamide.

Advanced glycation end products (AGEs), a heterogeneous group of non-enzymatically glycated and oxidized proteins or lipids. AGEs are present and accumulated in many different cell types, and affect extracellular and intracellular structure and function. Microvascular and macrovascular complications are caused through the formation of crosslinks between molecules in the basement membrane of the extracellular matrix. AGCs are prevalent in the diabetic vasculature, and contribute to the development of atherosclerosis. The concentrations of AGEs are altered in the body, particularly in relation to changes occurring with age. AGEs contribute to amyloidosis in → Alzheimer's disease, and AGEs formation is also stimulated by oxidative stress, e.g., in uremia. A decrease in renal function increases circulating AGE concentrations by reduced clearance [M. P. Vitek et al., *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4766; R. Singh et al. *Diabetologia* **2001**, *44*, 129; J. M. Bohlender et al., *Am. J. Renal Physiol.* **2005**, *289*, F645; A. Goldin et al., *Circulation* **2006**, *114*, 597].

Aequorin, a calcium-sensitive photoprotein originally obtained from the jellyfish *Aequorea victoria*. This bioluminescent jellyfish produces a greenish luminescence from the margin of its umbrella using aequorin and a chromophore-bearing → green fluorescent protein (GFP). Aequorin is a Ca^{2+}-binding protein (M_r ~21 kDa), and undergoes an intramolecular reaction on binding Ca^{2+}, yielding a blue fluorescent protein in the singlet excited state, transferring its energy by resonance to GFP. Aequorin consists of four helix-loop-helix "EF-hand" domains, of which three can bind Ca^{2+}. It also contains coelenterazine as its chromophoric ligand. The addition of Ca^{2+} causes decomposition of the protein complex into apoaequorin, coelenteramide and CO_2, accompanied by the emission of light. Regeneration of apoaequorin into active aequorin takes place in the absence of Ca^{2+} by incubation with coelenterazine, oxygen, and a thiol agent. Aequorin is widely used as a probe to monitor intracellular levels of Ca^{2+}. The crystal structure of recombinant aequorin at 2.3 Å resolution shows a globular molecule containing a hydrophobic core cavity accommodating the ligand

coelenterazine-2-hydroperoxide [O. Shimomura et al., *J. Cell. Comp. Physiol.* **1962**, *59*, 223; H. Morise et al., *Biochemistry* **1974**, *13*, 2656; M. Brini et al., *J. Biol. Chem.* **1995**, *270*, 9896; J. F. Head et al., *Nature* **2000**, *405*, 291].

Aeruginosins, a main class of → cyanobacterial peptides characterized by a derivative of hydroxyphenyl lactic acid (Hpla) at the *N*-terminus, 2-carboxy-6-hydroxyoctahydroindole (Choi) and the arginine derivative agmatine at the *C*-terminus. The aeruginosins 98-A and B from the blue-green alga *Microcystis aeruginosa* act as trypsin inhibitors [M. Murakami et al., *Tetrahedron Lett.* **1995**, *36*, 2785].

Aet, aminoethyl.

Affinity chromatography, a special variant of adsorption chromatography in which the adsorbent is biospecific. A molecule, known as the ligand, that specifically binds, for example to the protein of interest, is covalently attached to an inert porous matrix, e.g., agarose gel, glass beads, cellulose, polyacrylamide, crosslinked dextrans. The impure protein solution is passed through this stationary phase and the desired protein with selective affinity to the ligand is retained, while other proteins and substances are immediately eluted. The bound substance can then be recovered in highly purified form by changing the elution conditions such that the desired protein is released from the stationary phase. Specific interactions between, e.g., antibodies and antigens, enzymes and their inhibitors, nucleic acids of complementary sequences, lectins and polysaccharides, receptors and hormones, avidin and biotin can be utilized [P. Cuatrecasas et al., *Proc. Natl. Acad. Sci. USA* **1968**, *61*, 636].

Ag, antigen.

AG3, AYSSGAPPMP^{10}PF, an inorganic-binding peptide (→ silver-binding peptides) that specifically and selectively binds to silver. AG3 was immobilized on the surface of protonated poly(ethylene terephthalate) (PET) film which was prepared for biomimetic synthesis of silver particles *in vitro*. Silver crystallites have been formatted on the surface of the AG3-PET film showing various shapes 1 to 4 μm in size [Z. Xu et al., *J. Inorg. Biochem.* **2005**, *99*, 1692].

AGaloc, tetra-*O*-acetyl-β-D-galactopyranosyloxycarbonyl.

AGE, advanced glycation end product.

Agloc, tetra-*O*-acetyl-D-glucopyranosyloxycarbonyl.

Agonist, a term given for analogues of native peptide hormones that trigger the hormone signal in the same manner.

Agouti protein, a 131 aa protein encoded by the murine agouti gene and expressed in the skin. During hair growth, agouti acts to regulate coat coloration, and abnormal expression of the agouti protein causes the yellow phenotype. The agouti protein is a paracrine signaling molecule that regulates coat coloration via competitive antagonism of α-MSH (→ melanocortin peptides) binding to its receptor (→ melanocortin receptors, MCR). The antagonistic action of agouti protein prevents the α-MSH-mediated increase in intracellular cAMP that results in the cell switching from the production of black pigment, eumelanin, to yellow pigment, phaemelanin. Pharmacologically, agouti is a high-affinity, competitive antagonist of the melanocortin peptides at melanocortin receptors MC1R, MC3R, MC4R, and the adrenocortical ACTH (→ corticotropin) receptor, MC2R, respectively [D. Lu et al., *Nature* 1994, *371*,

799; D. M. Dinulescu, R. D. Cone, *J. Biol. Chem.* **2000**, *275*, 6695].

Agouti-related protein (AGRP), a 132 aa protein first identified by database searches for molecules with homology to → agouti protein in 1997. AGRP is expressed predominantly in the adrenal gland, hypothalamus, and at low levels in the lung, testis, and kidney. AGRP has been physiologically implicated in the regulation of food intake, body weight, and energy homeostasis. It is acting as a brain melanocortin-4 (MC4R) and melanocortin-3 (MC3R) receptor (→ melanocortin receptor) antagonist. It has been reported that AGRP has additional targets in the hypothalamus and/or physiologically functions through a mechanism in addition to competitive antagonism of α-MSH at the brain melanocortin receptors. AGRP is a orexigenic (appetite-stimulating) peptide that promotes food intake and is coexpressed with another potent orexigenic neuropeptide, → neuropeptide Y. The human AGRP gene is relatively short, spanning 1.1 kb on chromosome 16q22. Most investigations on the *in-vivo* function of AGRP have used *C*-terminal AGRP peptide sequences that mimic the effect of the full-length protein. Human AGRP-(87–132): CVRLH ESCLG^{10}QQVPCCDPCA^{20}TCYCRFFNAF ^{30}CYCRKLGTAM^{40}NPCSRT (disulfide bonds: C^1–C^{16}/C^8–C^{22}/C^{15}–C^{33}/C^{19}–C^{43}/ C^{23}–C^{31}), a synthetic 46-peptide was capable of binding the melanocortin receptors MC3R, MC4R, and MC5R, thus, inhibiting binding of α-MSH. NMR structure analysis of AGRP-(87–132) revealed an inhibitor cysteine-knot structure which makes possible contact with the MC3R and MC4R with two loops which are present in this structure. The appetite-boosting AGRP-(87–132) may be both an important tool for elucidating the mechanism of obesity, and a potentially interesting drug target in combating obesity and related co-morbidities [M. M. Ollman et al., *Science* **1997**, *278*, 135; J. R. Shutter et al., *Genes Dev.* **1997**, *17*, 75; R. D. Rosenfeld et al., *Biochemistry* **1998**, *37*, 16041; E. J. Bures et al., *Biochemistry* **1998**, *37*, 12172; C. Haskell-Luevano, E. K. Monck, *Regul. Pept.* **2001**, *99*, 1].

AGRP, agouti-related protein.

Ahx, 2-aminohexanoic acid (norleucine).

ε Ahx, 6-aminohexanoic acid.

AHZ, β-alanyl-histidinato zinc.

Aib, α-aminoisobutyric acid (α-methyl-alanine).

AIDS, acquired immunodeficiency syndrome.

alle, allo-isoleucine (2*S*,3*R* in the L-series).

Aimoto thioester approach, a polypeptide synthesis method characterized by converting an *S*-alkyl thioester moiety in the presence of a silver salt into an active ester derived from HOBt or HODhbt, followed by segment condensation of partially protected segments [S. Aimoto, *Biopolymers* **1999**, *51*, 247].

Akabori Conference, called in honor of Shiro Akabori, a series of conferences with Japanese and German peptide chemists held every two years, alternating between the two countries, founded by Erich Wünsch and Shumpei Sakakibara.

Akabori method, an approach to *C*-terminal amino acid end group analysis of peptides using hydrazine. By treatment of the peptide under investigation with anhydrous hydrazine for 90–100 h at 90°C in the presence of an acidic ion-exchange resin, only the *C*-terminal amino acid residue

is released as free amino acid, whereas all other amino acids are converted into hydrazides. The resulting *C*-terminal free amino acid can be identified chromatographically [S. Akabori et al., *Bull. Chem. Soc. Japan* **1956**, *29*, 507].

Akabori, Shiro (1900–1992), professor of organic chemistry at Osaka University (1939–1966), known as the father of peptide chemistry in Japan, with outstanding international achievements in peptide research, inter alia → Akabori method. From 1960 onwards, and even after his retirement in 1966, Professor Akabori continuously served the scientific community for over 20 years as president of the Protein Research Foundation Japan.

AKH, adipokinetic hormone.

AKH/RPCH peptide hormone family, *adipokinetic hormone/red pigment-concentrating hormone family*, peptide hormones produced in the neurosecretory organs of crustacean and insects, and named after the first fully characterized members and their most prominent functions. These include the aggregation of pigment in the epidermal cells of crustaceans by the → red pigment-concentrating hormone (Pando-RPCH), whereas the → adipokinetic hormones (AKH) in insects regulate the levels of circulating metabolites such as lipids, carbohydrates and proline by activating phosphorylases or lipases in the fat body cell. The resulting substrates can subsequently be used during intense muscular work, e.g., flight, swimming, or running. At present, only Pando-RPCH have been found in a relatively large number of crustaceans, whereas about 40 analogues (isoforms), including Panbo-RPCH, have been isolated from all major orders of insects. The members of this peptide hormone family consist of 8 to 10 amino acid residues bearing both a blocked *N*-terminus (pyroglutamate residue) and *C*-terminus (amide) respectively. They are characterized by aromatic amino acids at position four (Phe or Tyr) and eight (Trp). Besides the well-known members of this family, some AKH/RPCH peptides are produced in the brain and not in the retrocerebral corpora cardiaca (CC), for example in the migratory locust and the African malarial mosquito. In addition to the modified termini of the peptides, additional post-translational modifications comprise *C*-glycosylations at Trp and phosphorylation at Thr residues [G. Gäde, *Z. Naturforsch.* **1996**, *51*, 333; G. Gäde, H. G. Marco, in: *Studies in Natural Product Chemistry (Bioactive Natural Products)*, Atta-ur-Rahmann (Ed.), Vol. 33, pp. 69–139, Elsevier Science Publishers, The Netherlands, **2005**].

Al, allyl

Ala, alanine

Alanine (Ala, A), α-aminopropionic acid, $H_3C\text{-}CH(NH_2)\text{-}COOH$, $C_3H_7NO_2$, M_r 89.09 Da, a proteinogenic amino acid.

Alanine scan, systematic substitution of each amino acid residue of a native peptide by a simple amino acid such as alanine. A first step in structure–activity relationship studies.

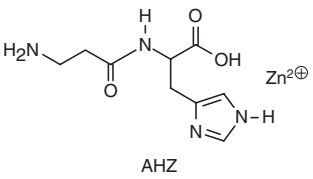
β-Ala, β-alanine

β-Alanine (β-Ala), β-aminopropionic acid, a naturally occurring non-proteinogenic amino acid occurring, e.g., in → carnosine, → anserine, and coenzyme A.

Alamethicin, a member of the → peptaibols produced by the fungus *Trichoderma viride*. This is one of the most extensively investigated member of the long peptaibol antibiotics. Alamethicin consists of a natural microheterogeneous peptaibol mixture

of which 23 members have been sequenced up to 2004. All alamethicins are 19-peptides blocked at the *N*-terminus by an acetyl moiety, and at the *C*-terminus by the 1,2-aminoalcohol L-phenylalaninol (Fol). The acidic alamethicins bear a Glu^{18} residue, whereas this building block is replaced by Gln^{18} in the neutral alamethicins. The alamethicins are classified into two groups. The major group is called F50 and is composed of neutral peptides (Gln^{18}), whereas the minor group, termed F30, consists of acidic peptides (Glu^{18}). Only the F30/6 analogue bears two acidic amino acids (Glu^{7},Glu^{18}), while in all other alamethicins Gln^{7} is conserved. The alamethicins are rich (7–10 aa) on the strongly helicogenic, non-coded α-aminoisobutyric acid (Aib), and contain two well-spaced proline residues in positions 2 and 14. A major component of the natural alamethicin mixture is the F50/5 analogue with the following sequence: Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Val-Aib^{10}-Gly-Leu-Aib-Pro-Val-Aib-Aib-Glu-Gln-Phe-ol, the total synthesis of which in solution by an easily tunable segment condensation approach was described in 2004. Besides this approach, more than 20 other synthesis variants of alamethicin have been reported. Alamethicin is amphiphilic, but of high overall hydrophobicity. It is known to generate voltage-dependent pores in biological membranes, and to insert spontaneously into lipid bilayers. Some more or less convincing models have been postulated. From the crystal structure it could be revealed that alamethicin is preferentially α-helical, with a bend in the helix axis at Pro^{14}. This structure is in agreement with an early model for the mode of action, in which a certain number (6–12) of molecules form aggregates, like the staves of a barrel. However, there are also other models for channel formation. One model, based on a voltage-dependent flip-flop of α-helix dipoles, postulates that the membrane-inserted helices attract each other when oriented in anti-parallel fashion. In contrast to the flip-flop model, another model assumes that the gating charge transfer is involved in the opening-closing mechanisms. The mechanisms of membrane permeability by alamethicin remain the subject of debate [R. Nagaray, P. Balaram, *Acc. Chem. Res.* **1981**, *14*, 356; E. Benedetti et al., *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 7951; R. O. Fox, F. M. Richards, *Nature* **1982**, *300*, 325; H. Brückner, H. Graf, *Experientia* **1983**, *39*, 528; G. Boheim et al., *Biophys. Struct. Mech.* **1983**, *9*, 181; D. T. Edmonds, *Eur. Biophys. J.* **1985**, *13*, 31; H. Wenschuh et al., *J. Org. Chem.* **1995**, *60*, 405; M. S. P. Sansom, *Mol. Biol.* **1991**, *55*, 139; J. Kirschbaum et al., *J. Peptide Sci.* **2003**, *9*, 799; C. Peggion et al., *Biopolymers (Pept. Sci.)* **2004**, *76*, 485].

β-Alanyl-histidinato zinc (AHZ), a zinc-chelated dipeptide for the exogenous administration of zinc. The zinc delivery potential of AHZ is more effective on bone metabolism than zinc sulfate. In-vitro studies have established that AHZ causes complete inhibition of the decrease of bone calcium in a bone tissue culture system, as well as in the formation of osteoclast-like cells in mouse marrow culture [M. Yamaguchi, *Gen. Pharmacol.* **1995**, *26*, 1179].

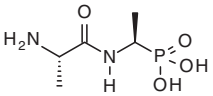


AHZ

β-Alanyl-histidinato zinc

Alaphosphin, L-alanyl-L-1-aminoethylphosphonic acid, a → phosphopeptide acting as an antibacterial agent. It selectively inhibited peptidoglycan biosynthesis in both

Gram-negative and Gram-positive bacteria. Alaphosphin was selected from a range of phophonopeptides for studies in humans on the basis of its antibacterial activity, pharmacokinetics, and stability against intestinal and kidney proteases. *In vitro*, it proved active against the majority of about 50 strains of *Serratia marcescens* [J. G. Allen et al., *Antimicrob. Agents Chemother.* **1979**, *15*, 684; F. R. Atherton et al., *Antimicrob. Agents Chemother.* **1979**, *15*, 696; W. H. Traub, *Chemotherapy* **1980**, *26*, 103].



Alaphosphin

Albomycins, natural siderophores and antibiotics first isolated from *Streptomyces griseus* and named grisein in 1947. Some years later, another microbial iron-transport compound, named albomycin, was isolated from *Streptomyces subtropicus* which had the same structure as grisein. In 1982, the structure of the albomycins was firmly established. The linear tripeptide built of N^5-acetyl-N^5-hydroxy-L-ornithine is the hexadentate, octahedral ligand for ferric ion responsible for intracellular transport of iron. The albomycins are used for treatment of iron metabolism disorders [G. Benz et al., *Angew. Chem. Int. Ed.* **1982**, *21*, 527; G. Benz, *Liebigs Ann. Chem.* **1984**, 1408].

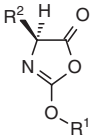
Albumins, a group of water-soluble proteins occurring in body liquids, animal tissues and in some plant seeds. They are rich in both Glu and Asp (20–25%) as well as Leu and Ile (up to 16%). Albumins have a low molecular mass, are easily crystallizable, and their isoelectric points are in the weakly acid range. High concentrations of neutral salts are necessary for "salting out." Albumins have been used as a model protein for diverse biophysical, biochemical, and physico-chemical studies. *Serum albumins* ($M_r \sim 67.5$ kDa) are the most abundant of these proteins in blood plasma. These proteins have been one of the most investigated proteins for many years, and show interesting properties of binding a variety of hydrophobic ligands, e.g., fatty acids, warfarin, anesthetics, bilirubin, steroids, lysolecithin, and several dyes. Furthermore, a high binding capacity for Ca^{2+}, Na^+, K^+ must be mentioned. Serum albumins comprise up to 60% of the dry mass of blood serum, corresponding to a concentration of 42 g L^{-1}, and provide about 80% of the osmotic pressure of blood. The single peptide chain of about 580 aa forms a secondary structure characterized by 67% of α-helix, six turns, and 17 disulfide bridges. The X-ray structure of *human serum albumin* (HSA) shows three domains I, II, and III, which confer to the protein a heart-shaped molecular form. Each domain consists of two subdomains, named IAB, IC, IIAB, IIC, IIIAB, IIIC, respectively. Interestingly, the domains exhibit a certain degree of binding specificity. Domain I, also named the warfarin binding site, binds predominantly indole derivatives, several dyes, long-chain fatty acids, and compounds with alicyclic ring structures, whereas domain II, termed the indole or benzodiazepine binding site, is specific for the binding of short-chain fatty acids, bilirubin, indole derivatives, several dyes, and steroids. Domain III is specific for indole derivatives, long-chain fatty acids, diazepam and other drugs. *Bovine serum albumin* (BSA) shows 76% sequence identity with HSA. BSA contains two tryptophan residues (W^{214}, W^{131}), while HSA has only one (W^{214}). The consequences are different spectroscopic properties of the two proteins. Bovine and human serum

albumin contain 16% nitrogen, and are used as standard proteins for calibration. Further important animal and plant albumins are → lactalbumin, → ovalbumin and → ricin [J. R. Brown, P. Shockley, *Lipid-Protein Interactions*, Vol. 1, Wiley, New York, **1982**; D. Carter, J. X. Ho, *Advances in Protein Chemistry*, Vol. 45, Academic Press, New York, **1994**, p. 153; E. L. Gelano et al., *Biochim. Biophys. Acta* **2002**, *1594*, 84].

Alkanesulfonamide linker, → safety-catch linker.

Alkene peptidomimetics, peptides, where an amide bond has been replaced to give E-alkene [M. M. Hahn et al., *J. Chem. Soc. Commun.* **1980**, 234; M. Kranz, H. Kessler, *Tetrahedron Lett.* **1996**, *37*, 5359].

2-Alkoxy-5(4*H*)-oxazolones, *azlactones*, stereochemically labile intermediates that occur during coupling reactions and can cause → racemization at the stereogenic center of an α-amino acid. The propensity toward oxazolone formation strongly correlates with the activation potential of the activating group X in the carboxy component, R^1-CO-NH-CHR^2-CO-X, and with the electronic properties of the *N*-acyl moiety R^1-CO- [M. Goodman, L. Levine, *J. Am. Chem. Soc.* **1964**, *86*, 2918].



Oxazolone

Alkyl-type protecting groups, protecting groups for the amino function of amino acids during peptide synthesis based on alkyl moieties. The most popular protecting group of the alkyl type is the → triphenylmethyl (Trt) group.

All, allyl

Allatostatins (AST), a family of neuropeptides first isolated from the brain of the cockroach *Diploptera punctata*. There are three allotostatin families according to *C*-terminal sequence homology: (a) the *cockroach type* (>70 peptides, consensus sequence FGLa), comprising e.g. Dippu-AST 1 (LYDFGLa), Dippu-AST 2 (AYSYVSEYKR^{10}LPVYNFGLa), Dippu-AST 5); (b) the *cricket type* (consensus sequence WX_6Wa), with Grybi-AST 1 (H-Gly-Trp-Gln-Asp-Leu-Asn-Gly-Gly-Trp-NH_2) and Grybi-AST 5 (H-Ala-Trp-Asp-Gln-Leu-Arg-Pro-Gly-Trp-NH_2); and (c) the *Manduca type* (consensus sequence PISCF). Members of the latter family are highly homologous (<EXRZRQCYFN^{10}PISCF with X = V,I and Z = F,Y) between the species *Manduca sexta*, *Drosophila melanogaster*, and *Anopheles gambiae*. AST inhibit the synthesis of the juvenile hormone in the *corpora allata*, which regulates insect metamorphosis. However, it has been proposed that this effect appeared secondarily, and that the ancestral function was the modulation of myotropic activity. Further effects of the different AST include endocrine and interneuronal functions, neuromodulatory effects, and direct action on biosynthetic pathways; mostly being species- or order-specific. Picomolar concentrations of the *Drosophila melanogaster* Drome-AST 3 (H-Ser-Arg-Pro-Tyr-Ser-Phe-Gly-Leu-NH_2) from the head of *Drosophila* activate a fruit-fly G protein-coupled receptor that shows striking sequence similarities to mammalian galanin and somatostatin/opioid receptors [A. P. Woodhead et al., *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 5997; W. G. Bendena et al., *Ann. N. Y. Acad. Sci.* **1989**,

897, 311; J. G. Yoon, B. Stay, *J. Comp. Neurol.* **1995**, *363*, 475; N. Birgul et al., *EMBO J.* **1999**, *18*, 5892].

Alloc (Aloc), → allyloxycarbonyl group.

Allom, Alom, → allyl-type protecting groups.

Allopeptide, a word derived from the noun "peptide" that means in immunology a peptide from different individual (Greek *allos*, other) of the same species [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, *12*, 79].

Allyl ester, → allyl-type protecting groups.

Allyloxycarbonyl group (Alloc, Aloc), an urethane-type protecting group for the amino function during peptide synthesis. The Alloc group is completely orthogonal to Boc and Fmoc, and is especially suited for the synthesis of labile derivatives. The group can be smoothly removed by treatment with a suitable nucleophile, e.g., amines, amine-borane complexes, organosilanes, in the presence of a palladium catalyst (palladium(0)-catalyzed allyl transfer) [H. Kunz, C. Unverzagt, *Angew. Chem. Int. Ed.* **1984**, *23*, 436; A. Loffet, H. X. Zhang, *Int. J. Pept. Protein Res.* **1993**, *42*, 346; F. Guibe, *Tetrahedron* **1998**, *54*, 2967].

Allyl-type protecting groups, protecting groups used in peptides synthesis bearing the allyl moiety. This type of protecting group has the advantage of being completely orthogonal to most other protecting groups, and provides an excellent tool for temporary reversible protection in glycopeptide synthesis. Beside the → allyloxycarbonyl group, *allylester* (OAll) of amino acids are very easy to obtain, are stable under glycosylation conditions, and can be cleaved by Rh^{I} catalysis. An even milder method for the selective cleavage of allyl esters utilizes palladium(0)-catalyzed allyl transfer to morpholine. Allyl-type linker moieties are also suited for the solid-phase synthesis of complex glycopeptides. The *allyloxycarbonylaminomethyl* (Allocam) group was described as a thiol-protecting group in 1999, while the N^{π}-allyl moiety was suggested as an imidazole-protecting group by the same authors one year later. Last, but not least, the N^{π}-*allyloxymethyl* (Allom) group has also been described as an imidazole-protecting group [A. Loffet, H. X. Zhang, *Int. J. Pept. Protein Res.* **1993**, *42*, 346; A. M. Kimbonguila et al., *Tetrahedron* **1997**, *53*, 12525; A. M. Kimbonguila et al., *Tetrahedron* **1999**, *55*, 6931; S. J. Harding, J. H. Jones, *J. Peptide Sci.* **1999**, *5*, 368; H. Herzner et al., *Chem. Rev.* **2000**, *100*, 4495].

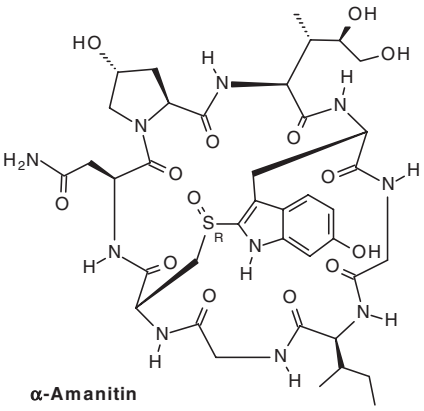
Alterobactin, a 19-membered macrocyclic → depsipeptide containing two types of unusual building block, two L-*threo*-β-hydroxyaspartic acids and one (3*S*,4*S*)-4,8-diamino-3-hydroxyoctanic acid attached to a catechol carboxylate at the N^{ω}-site. It was isolated from a open-ocean bacterium *Alteromonas luteoviolacea* collected off Chub Cay, Bahamas. Alterobactin is a depsipeptide → siderophore exhibiting extraordinary affinity for ferric ion. The total synthesis has been described [R. T. Reid et al., *Nature* **1993**, *366*, 455; J. Deng et al., *Synthesis* **1998**, 627].

Alytensin, <EGRLGTQWAV^{10}GHLMa, a 14-peptide amide belonging to the → bombesin family. Alytensin was isolated from the skin of the European amphibian *Alytes obstetricans* in 1971. It is structurally very similar to → bombesin, and displays similar biological activities when applied to mammals [A. Anastasi et al., *Experientia* **1971**, *27*, 166; V. Erspamer, P. Melchiorri, *Trends Biochem. Sci.* **1980**, *1*, 391].

Alzheimer's disease (AD), the most prominent severe dementia in the elderly population, first described by Alzheimer in 1907. AD is a widespread, neurodegenerative,

dementia-inducing disorder characterized mainly by amyloid deposits surrounding dying neurons (senile plaques), neurofibrillar degeneration with tangles, and cerebrovascular angiopathies. AD is clinically characterized by a progressive loss of cognitive abilities, progressive memory and intellectual deficits. In 1998, it was estimated that 25 million people worldwide suffered from AD. Amyloid-β and tau protein are responsible for the formation of the plaques and tangles of AD. The mechanism of neurodegeneration caused by → amyloid-β in AD is controversial. The primary pathogenic event of AD is the progressive cerebral accumulation of amyloid-β (Aβ), a proteolytic product of the β-amyloid precursor protein (APP). Tau protein is the major component of paired helical filaments that form a compact filamentous network described as "neurofibrally tangles." From culture experiments there was derived the existence of a relationship between fibrillary amyloid and the cascade of molecular signals that trigger tau hyperphosphorylations. The cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3beta are the two main protein kinases involved in the anomalous tau phosphorylations. Inhibitors of both kinases and antisense oligonucleotides exert protection against neuronal death. On the other hand, it has been reported that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells. In brain tissue from AD patients, some major species of soluble Aβ have been identified: the full-length form Aβ(1–42), and at residues Glu^3 and Glu^{11}, respectively, truncated Aβ peptides, such as Aβ(3–40/42) and Aβ(11–40/42). The shortened forms bear at the *N*-terminus a pyroglutamic acid residue which might be result from the corresponding Glu residues catalyzed by the glutamyl cyclase activity of → glutaminyl cyclase. It has been reported that, *in vitro*, these smaller peptides are more neurotoxic and aggregate more rapidly than the full-length isoforms. A rational design of inhibitors against glutaminyl cyclase-associated disorders has been started [R. B. Maccioni et al., *Arch. Med. Res.* **2001**, *35*, 367; T. Hashimoto et al., *EMBO J.* **2002**, *21*, 1524; C. Morgan et al., *Prog. Neurobiol.* **2004**, *74*, 323; S. Schilling et al., *FEBS Lett.* **2004**, *563*, 191; K.-F. Huang et al., *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13117; S. Schilling et al., *Biochemistry* **2005**, *44*, 13415; M. Goedert, M. G. Spillantini, *Science* **2006**, *314*, 777].

Amanitins, a group of toxic components of *Amanita phalloides* (→ amatoxins).



α-Amanitin

Amatoxins, heterodetic bicyclic 8-peptides from *Amanita* species, but also detected in *Galerina* and *Lepiota* species, which are responsible for the fatal intoxications by the mentioned toadstools. The toxic peptides are readily absorbed by the intestine, and in humans the lethal dose of amatoxin is ~ 0.1 mg kg^{-1} body weight, or even lower. The gut cells of humans seem to be the first cells affected, and the intestinal phase begins about 9 h after