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Plausible lipid-like peptides: prebiotic molecular self-assembly in water

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Introduction

Life as we know it today completely depends on water. Without water, life would be either impossible or totally different. Thus, a deep understanding of the relationship between water and other simple building blocks of life is crucial to gain insight into how prebiotic life forms could have originated and evolved and whether the physical laws of this universe are in any way predisposed to the emergence of life (Henderson, 1913, 1917; Eisenberg and Kauzmann, 1985; Ball, 2001).

It is unlikely that under prebiotic conditions the complex and sophisticated biomacromolecules commonplace in modern biochemistry would have existed. Thus, research into the origin of life is intimately associated with the search for plausible systems that are much simpler than those we see today. However, it is also plausible that these simple building blocks of life might have been amphiphilic molecules in which water could have had an enormous influence on their prebiotic molecular selection and evolution, because water can either form clathrate structures or drive these simplest molecules together (Ball, 2001).

Structure of water

Water is both simple and complex. It is simple because it consists of only one oxygen atom and two hydrogen atoms (see Figure 20.1). But at the same time it exhibits highly complex molecular behavior (far exceeding the many-body problem in mathematics, planetary science, and astrophysics) wherever numerous water molecules interact dynamically (Eisenberg and Kauzmann, 1985; Ball, 2001). Indeed, this behavior becomes even more complex when water molecules interact with other atoms and molecules (Eisenberg and Kauzmann, 1985; Ball, 2001).

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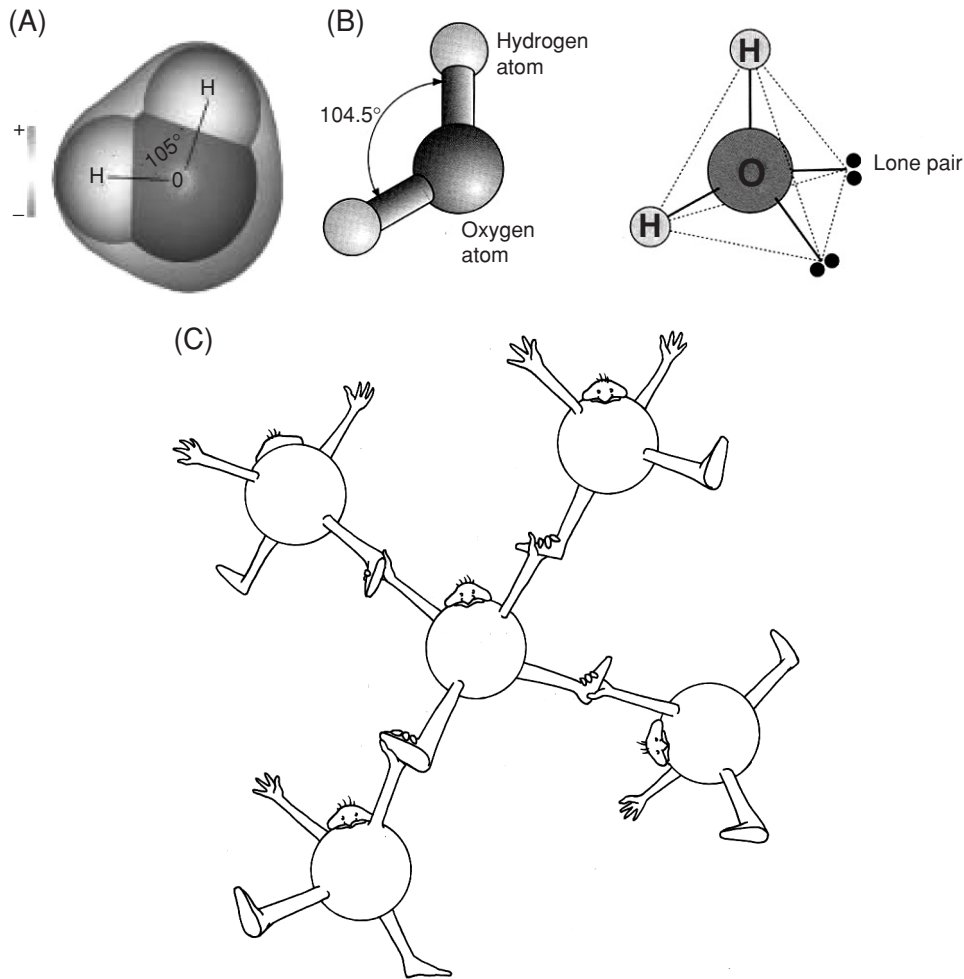
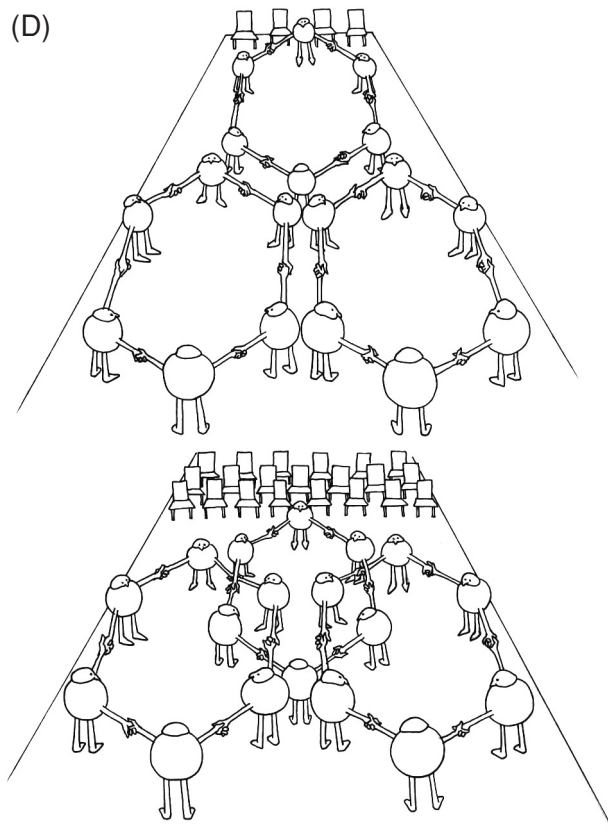


Figure 20.1. Molecular structure of water. (A) Each water molecule has a typical dipole with one oxygen atom covalently sharing bonds with two hydrogens at $104.5\text{--}105^\circ$ in an asymmetric manner. (B) The remaining two lone pairs of the oxygen atom can form additional weak hydrogen bonds with other water molecules or other substances. (C) Thus, each water molecule can form four hydrogen bonds: two covalent bonds as hydrogen donors, like hands; and two non-covalent bonds as hydrogen acceptors, like feet. (D) Structure of ice formation. When temperature decreases, water molecules repack themselves to form a tighter structure. (The images and drawings are courtesy of Philip Ball and reprinted with permission.)

The root of this complexity is that the oxygen can form up to four chemical bonds with other atoms or molecules. In water, oxygen forms two covalent bonds with hydrogen, leaving two electron lone pairs that can form hydrogen bonds with the hydrogen atoms of neighboring water molecules or with other atoms. In other words, water is a strongly dipolar molecule, wherein negatively charged oxygen

Figure 20.1. (*cont.*)

attracts positively charged hydrogens with an angle of $104.5\text{--}105^\circ$ (Ball, 2001). It is this dipole property that makes water very interactive with other neighboring molecules.

The human form serves as an analogy for representing the structure of a single water molecule: the arms represent hydrogen donors that can hold things, and the legs are hydrogen acceptors that can be held by other “arms” (Ball, 2001). Wherever numerous water molecules co-exist, they form a dynamic network, constantly connecting and disconnecting with extreme rapidity, much like constantly and rapidly exchanging dance partners at a densely populated dance party (see Figure 20.1).

When temperature decreases, the length of bonds between different atoms diminishes. The water molecules pack together more and more tightly and eventually form an ice structure (see Figure 20.1). On the other hand, when temperature increases, bond lengths increase as atoms are stretched farther and farther apart, like receding stars and galaxies in the universe. Beyond a certain threshold, the hydrogen bonds

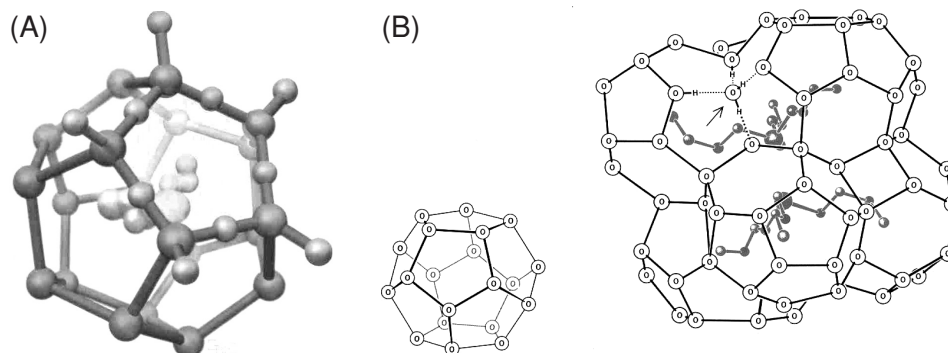


Figure 20.2. Structure of water clathrates. When water molecules interact with non-water substances, water molecules form a cage-like structure to surround them. Depending on the size of the substance, water molecules pack in different ways to solubilize or to form an interface with the materials.

between water molecules eventually break, and water forms vapor. Without a doubt, this “physics of water” operated billions of years ago, just as it does today. Thus, cyclical temperature fluctuations not only could have driven numerous prebiotic molecular interactions in an unpredictable way, but could also have generated predictable synthesis reactions (Henderson, 1913, 1917).

As water molecules exhibit a dipolar moment that allows them to interact with one another and with other atoms and molecules, they can encase other molecules within cage-like (“clathrate”) structures. These multifaceted balls resemble viral protein-coats by encapsulating molecules within them (see Figure 20.2). In fact, we now know of diverse clathrate structures that vary considerably, depending on the non-water molecules involved. When non-water molecules become too large, water molecules cease to encase them, such that they aggregate and either precipitate out of water or form macromolecular interfaces with water. Precipitated aggregates exhibit little structure, but the latter systems (multimolecular interfaces between water and biopolymers) are often found in biological membranes. Many researchers have pointed out that some simple kind of membrane would have been a requirement for the earliest metabolism to form partitions and enclosures that optimized specific reactions or sequestered important metabolites (see, for example, Morowitz, 1992; Chakrabarti and Deamer, 1994).

Simplest enclosure system in water

In the summer of 1992 at the “Origin of Life” Gordon Conference in New Hampshire, I asked two simple questions. What might be the simplest amphiphilic

biopolymers that could self-organize to enclose other biological molecules in a primarily aqueous prebiotic environment? Could such structures be constructed from the simplest of molecular building blocks? I reasoned that the biopolymers could be neither phospholipids nor nucleic acids because they are relatively complex multicomponent molecules containing several distinctive parts (Hargreaves *et al.*, 1977). Likewise, proteins seem unlikely because the polymerization of any specific (or even semi-specific) sequence from a “soup” of possible monomers brings in unavoidable problems of combinatorial mathematics (moreover, most extant proteins also require chaperone molecules to facilitate folding into the correct three-dimensional shape). In short, abiotic syntheses of all three types of complex molecule in the prebiotic environment seem rather unlikely. I therefore asked whether it were plausible that the simplest peptides, comprising just two or three of the simplest amino acids, could function in this membrane/enclosure-forming capacity. Although several groups had studied the chemistry of various amino acids and amino acid biopolymers (Fox and Harada, 1958; Brack and Orgel, 1975; Brack and Spach, 1981; Yanagawa *et al.*, 1988), distinctive structures and enclosures were not reported or observed at that time.

Simplest amino acids

Glycine with a side chain ($R=H$), alanine ($R=CH_3$), and aspartic acid ($R=CH_2COOH$) are among the chemically and structurally simplest amino acids. They are of particular interest to prebiotic molecular evolution because of their presence not only in the products of biochemical simulations of earth’s presumed prebiotic environment (Miller, 1953; Miller and Urey, 1959; Oro and Kamat, 1961; Bada *et al.*, 1994), but also in the CI-type carbonaceous chondrites, including the Orgueil, Ivuna, and Murchison meteorites (Kvenvolden *et al.*, 1970; Wong and Bronskill, 1979; Anders, 1989; Chyba and Sagan, 1992; Ehrenfreund *et al.*, 2001). Specifically, glycine is the simplest possible amino acid (it is an achiral molecule without any true side chains and is universally indicated to have been the most abundant amino acid in abiotic environments).

Beyond synthesis of the amino acids themselves, it has been experimentally demonstrated that these amino acids (and their derivatives) can form peptides when subjected to repeated hydration–dehydration cycles under microwave heating, in aqueous ammonia, or on heated clays that mimic various hypothesized conditions of early life on the planet (Oro and Guidry, 1961; White *et al.*, 1984; Yanagawa *et al.*, 1988). Indeed, oligo-glycine appears even more easy to produce abiotically, as it has been synthesized by subjecting glycine monomers to extended exposure (more than forty hours) of supercritical water conditions, that is under high temperature

(several hundred degrees celsius) and high pressure (tens of atmospheres) (Goto *et al.*, 2004).

These high-temperature and high-pressure conditions are similar to those found in deep-sea volcanoes and hydrothermal vents, a favorite hypothesized venue for the origin of life. It is plausible that some of the simplest biochemical building blocks could have produced complex life forms over eons of natural selection and evolution. The challenge, however, is to explain how sufficiently complex proteins, or ribozymes, could have been produced in the lipid membranes necessary for the metabolism of their own catalysis.

If, instead of lipid membranes, simple peptides with hydrophobic tails and hydrophilic heads (made up of merely a combination of these robust, abiotically synthesized amino acids) could self-assemble into nanotubes or vesicles, they would have the potential to provide a primitive enclosure for the earliest RNA-based (Beaudry and Joyce, 1992; Wilson and Szostak, 1995) or peptide enzymes and other primitive molecular structures with a variety of functions.

In other words, if such structures can be demonstrated to exist, then this renders plausible the idea that in the prebiotic world lipid-like peptides of various lengths could form and self-organize into distinct vesicles and tubes that could act as naturally formed enclosures, isolated from the broader environment, for prebiotic rudimentary enzymes and ribozymes to accumulate. From this starting point, it is far easier to envisage how a diverse population of peptides and RNA not only could condense into complex structures, but also could evolve increasing sophistication, stimulating their own synthesis and replication and evolving ultimately into the wondrously efficient chemical and biological catalysts we encounter today (Zhang and Egly, 1994, 1995).

Lipid-like peptides that form nanotubes and nanovesicles

To this end, I focused on designing a class of simple amphiphilic lipid-like peptides that consist exclusively of plausible prebiotic amino acids. One class of these molecules comprises peptides that exhibit lipid-like or surfactant properties (Vauthey *et al.*, 2002; Santoso *et al.*, 2002a,b; von Maltzahn *et al.*, 2003; Yang and Zhang, 2006; Nagai *et al.*, 2007). I designed such peptides with computer modeling, linking amino acids together one at a time to achieve a length and shape similar to those of lipids. Although individual chemical species within this population of peptides have completely different composition and sequence, they share a crucial common feature: a hydrophilic head comprising one or two charged amino acids and a hydrophobic tail comprising four or more consecutive hydrophobic amino acids (see Figure 20.3). In other words, although it would be possible to design peptides with non-charged hydrophilic heads using serine and threonine, those that

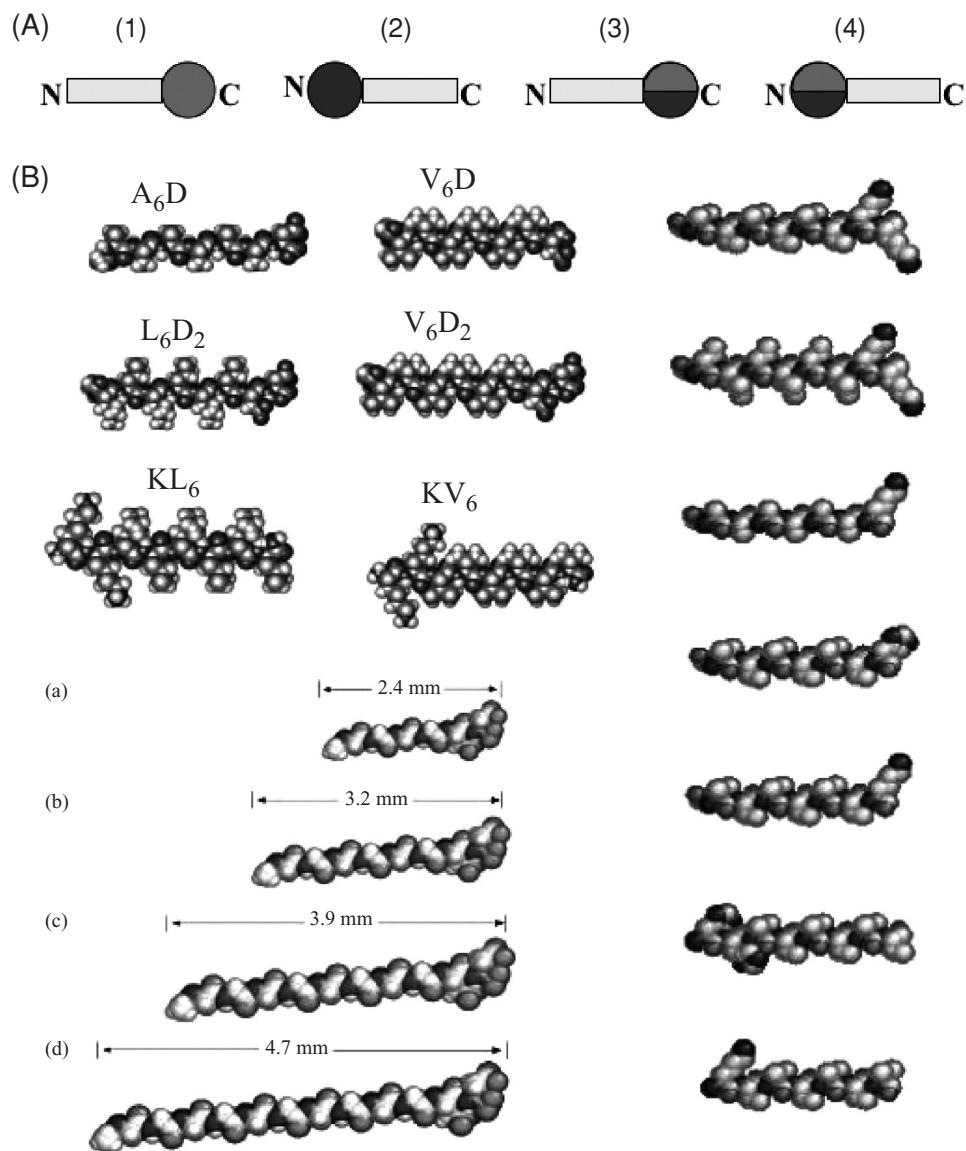


Figure 20.3. Models of the simplest diphasic peptides. (A) Schematic illustrations of four types of diphasic (hydrophobic tail and hydrophilic head) peptide. Hydrophilic heads can exhibit either negative charges (aspartic acid and glutamic acid) or positive charges (lysine, arginine, and histidine). (B) Selected molecular models of diphasic peptides: G_4D_2 , G_6D_2 , G_8D_2 , $G_{10}D_2$, A_6D , V_6D , V_6D_2 , V_6K_2 , L_6D_2 , KL_6 , KV_6 , A_6H , HA_6 , and H_2A_6 . Note: The glycine tail has no side chain, as glycine's R-group is a single hydrogen atom. Alanine's tail has a methyl side chain, and valine's tail has an *n*-isopropyl side chain. The hydrophobicity increases as the hydrocarbon side chains become large, as in this case. G_6D_2 , A_6D , and V_6D have a negatively charged head, but V_6K_2 has a positively charged head.

Table 20.1. *Aspartic acid head at N- or C-termini with variation in hydrophobic tails*

When an aspartic acid is placed at the C-terminus of a peptide, the resulting molecule possesses two negative charges, one from the side chain and the other from the C-terminus. On the other hand, when an aspartic acid is placed at the N-terminus of the peptide, it bears one negative charge from the side chain and one positive charge from the N-terminus.

Name	Sequence	Name	Sequence
G ₆ D	GGGGGGD	DG ₆	DGGGGGG
A ₆ D	AAAAAAD	DA ₆	DAAAAAA
V ₆ D	VVVVVVD	DV ₆	DVVVVVV
I ₆	IIIIID	DI ₆	DIIIIII
L ₆ D	LLLLLLD	DL ₆	DLLLLLL
F ₆ D	FFFFFFD	DF ₆	DFFFFFF

Table 20.2. *Lysine head at N- or C-termini with variation in hydrophobic tails*

When a lysine is placed at the C-terminus of a peptide, it possesses one positive charge from its side chain and one negative charge from its C-terminus. On the other hand, when lysine is placed at the N-terminus of a peptide, it bears two positive charges from the side chain and a positive charge from the N-terminus.

Name	Sequence	Name	Sequence
G ₆ K	GGGGGK	KG ₆	KGGGGGG
A ₆ K	AAAAAK	KA ₆	KAAAAAA
V ₆ K	VVVVVK	KV ₆	KVVVVVV
I ₆ K	IIIIK	KI ₆	KIIIIII
L ₆ K	LLLLLK	KL ₆	KLLLLLL
F ₆ K	FFFFFK	KF ₆	KFFFFFF

I designed resemble lipids (or other organic surfactants) in their possession of a hydrophobic tail and a charged hydrophilic head (see Figure 20.3).

Not only do the shape and physical structure of these lipid-like peptides resemble lipids and other organic surfactants, but their chemical properties do as well. For example, peptides have six hydrophobic either alanine or valine residues from the N-terminus, followed by a negatively charged aspartic acid residue (A₆D = Ac-AAAAAAD; V₆D Ac-VVVVVVD); thus, they possess two negative charges, one from the charged terminal side chain and the other from the C-terminus (Vauthey *et al.*, 2002). In contrast, several simple peptides, G₄DD (Ac-GGGGDD), G₆DD (Ac-GGGGGDD), G₈DD (Ac-GGGGGGGDD), have four, six, and eight

Table 20.3. *Aspartate (⁻) head with various hydrophobic tail lengths at N- or C-termini*

When an aspartate is placed at the C-terminus of a peptide, it has two negative charges, one from the side chain and the other from the C-terminus. On the other hand, when an aspartate is placed at the N-terminus of a peptide, it bears one negative charge from its side chain and one positive charge from the N-terminus.

Name	Sequence	Name	Sequence
G ₄ D	GGGGD	A ₃ D	AAAD
G ₅ D	GGGGGD	A ₄ D	AAAAD
G ₇ D	GGGGGGGD	A ₅ D	AAAAAD
V ₂ D	VVD	I ₂ D	IID
V ₃ D	VVVD	I ₃ D	IIID
V ₄ D	VVVVD	I ₄ D	IIIID
V ₅ D	VVVVVD	I ₅ D	IIIIID
L ₂ D	LLD	F ₂ D	FFD
L ₃ D	LLLD	F ₃ D	FFFD
L ₄ D	LLLLD	F ₄ D	FFFFD
DG ₄	DGGGG	DA ₃	DAAA
DG ₅	DGGGGG	DA ₄	DAAAA
DG ₇	DGGGGGGG	DA ₅	DAAAAA
DV ₂	DVV	DI ₂	DII
DV ₃	DVVV	DI ₃	DIII
DV ₄	DVVVV	DI ₄	DIIII
DV ₅	DVVVVV	DI ₅	DIIIII
DL ₂	DLL	DF ₂	DFF
DL ₃	DLLL	DF ₃	DFFF
DL ₄	DLLLL	DF ₄	DFFFF

glycines, followed by two aspartic acids with three negative charges (Santoso *et al.*, 2002a,b). Similarly, A₆K (Ac-AAAAAAK) or KA₆ (KAAAAAA) has six alanines as the hydrophobic tail and a positively charged lysine as the hydrophilic head (von Maltzahn *et al.*, 2003). These lipid-like peptides can self-organize to form well-ordered nanostructures, including micelles, nanotubes, and nanovesicles in water. Furthermore, the structure formation is concentration-dependent: namely, at low concentration, there are no defined structures. These structures spontaneously form at a critical aggregation concentration (CAC) (Yang and Zhang, 2006; Nagai *et al.*, 2006), in a way similar to that of lipids and other surfactants.

Six amino acids of varying hydrophobicity (Gly, Ala, Val, Ile, Leu, and Phe) can be used to generate the non-polar tails. Such hydrophobic tails never exceed six residues, so that the total length of the peptide detergents will be seven, about 2.4 nm in length; interestingly, this is a size similar to that of the phospholipids

Table 20.4. *Lysine head with various hydrophobic tail lengths at N- or C-termini*

When a lysine is placed at the C-terminus of the peptide, it has one positive charge from its side chain and one negative charge from its C-terminus. On the other hand, when a lysine is placed at the N-terminus of a peptide; it bears two positive charges from its side chain and another from the N-terminus.

Name	Sequence	Name	Sequence
G ₄ K	GGGGK	A ₃ K	AAAK
G ₅ K	GGGGGK	A ₄ K	AAAAK
G ₇ K	GGGGGGK	A ₅ K	AAAAAK
V ₂ K	VVK	I ₂ K	IIK
V ₂ K	VVK	I ₃ K	IIIK
V ₄ K	VVVVK	I ₄ K	IIIIK
V ₅ K	VVVVK	I ₅ K	IIIIK
L ₂ K	LLK	F ₂ K	FFK
L ₃ K	LLLK	F ₃ K	FFFK
L ₄ K	LLLLK	F ₄ K	FFFFK
KG ₄	KGGGG	KA ₃	KAAA
KG ₅	KGGGGG	KA ₄	KAAAA
KG ₇	KGGGGGGG	KA ₅	KAAAAA
KV ₂	KVV	KI ₂	KII
KV ₃	KVVV	KI ₃	KIII
KV ₄	KVVVV	KI ₄	KIIII
KV ₅	KVVVVV	KI ₅	KIIIII
KL ₂	KLL	KF ₂	KFF
KL ₃	KLLL	KF ₃	KFFF
KL ₄	KLLLL	KF ₄	KFFFF

abundant in membranes, although this in part reflects the fact that the first peptide detergent was designed by modeling the peptide using the phosphatidylcholine as a size guide. However, when more than six hydrophobic residues (except glycine) are used, the peptide detergents themselves become less soluble in water. Although Tables 20.1–20.4 list only Asp (–) and Lys (+) as the hydrophilic head groups, it must be emphasized that Glu (–), Arg (+), and His (+) can also be used the same combinatorial ways. Therefore, they can broaden the spectra of variations and increase the possible number of peptide detergents.

Moreover, similar to the dynamic behavior of phospholipid vesicles and other microstructures (Wick *et al.*, 1996), these simplest of peptide nanostructures appear to behave as dynamic entities in water: they can fuse, divide, and change shape as a function of time and environmental influence (see Figures 20.4–20.7) (Vauthey *et al.*, 2002; Santoso *et al.*, 2002a,b; von Maltzahn *et al.*, 2003).

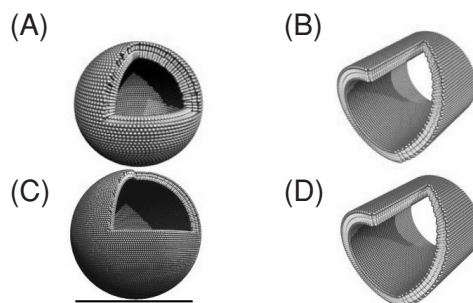


Figure 20.4. Molecular models of cutaway structures formed from the lipid-like peptides with negatively charged heads and glycine tails. Each peptide is *c.* 2 nm in length. (A, C) Peptide vesicle with an area sliced away. (B, D) Peptide tubes. The glycines are packed inside the bilayer away from water, and the aspartic acids are exposed to water, much like other lipids and surfactants. The modeled dimension is 50–100 nm in diameter. Preliminary experiments suggest that the wall thickness may be *c.* 4–5 nm, implying that the wall may form a double layer, similar to phospholipids in cell membranes.

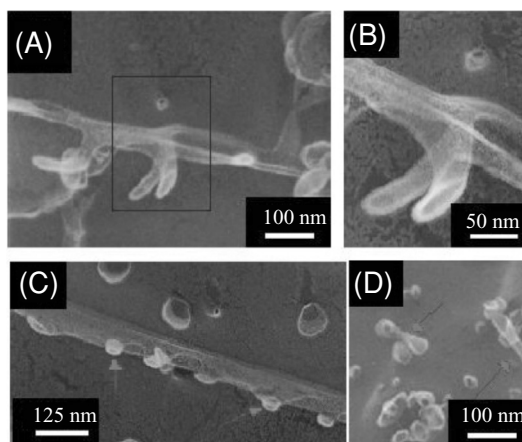


Figure 20.5. Transmission electron microscopic (TEM) images of lipid-like glycine peptide enclosures. Glycine tail and aspartic acid head peptides formed tube and vesicle structures. Note the growth of the tube opening (A, B, C) and the presumed vesicle division (D). If these dynamic enclosures can encapsulate other biomolecules, this may be one step closer for prebiotic molecular evolution.

It is thus plausible that in the prebiotic world, under the influence of water, lipid-like peptides of various lengths might self-organize into distinct vesicles and tubes (regardless of sequence) that could enclose prebiotic rudimentary enzymes to isolate them from the environment. Thus, a diverse population of peptides and RNA might condense into complex structures that evolve to perform different functions.

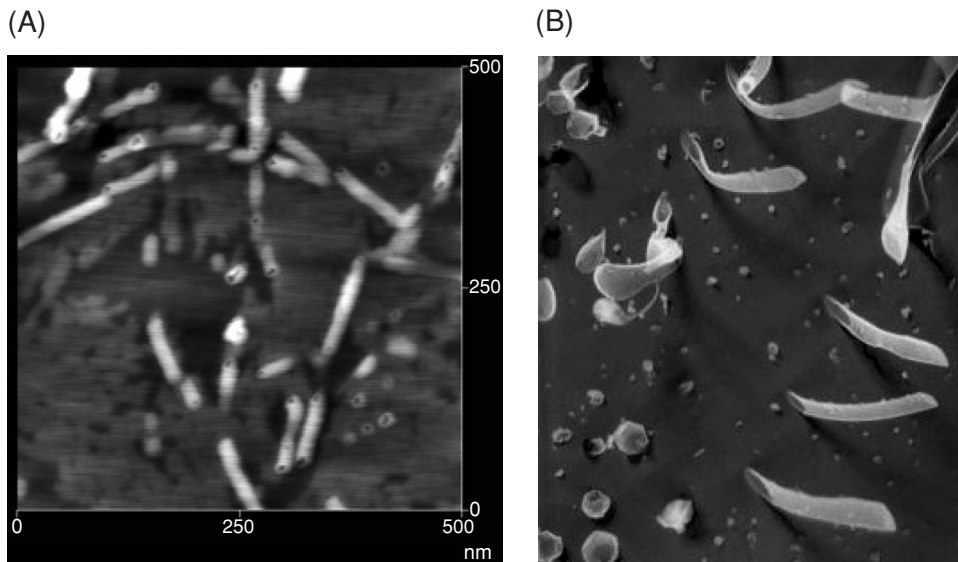


Figure 20.6. Images of lipid-like alanine and valine peptide enclosures. (A) Atomic-force microscopic (AFM) image of alanine tail and lysine head lipid-like peptide; note the tube structures. (B) Transmission electron microscopic (TEM) image of valine tail and aspartic acid head lipid-like peptide; note the tube structure with open and closed ends as well as vesicles.

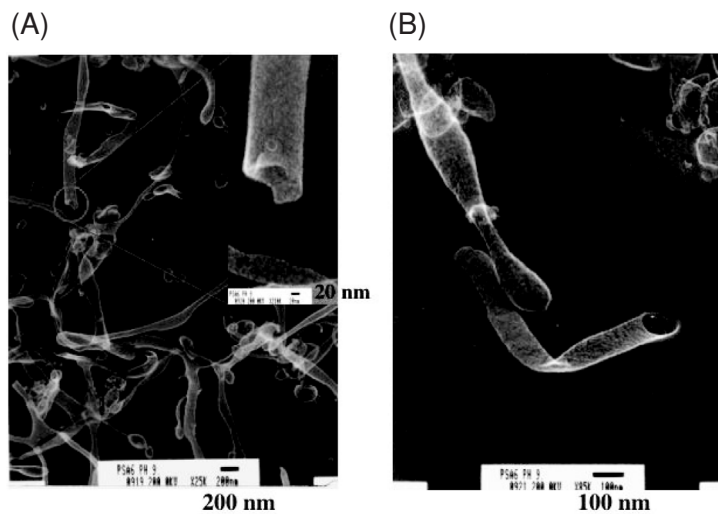


Figure 20.7. pSA6, a lipid-like peptide. Images of lipid-like phosphoserine head and alanine tail peptide enclosures. (A) Low magnification of structures; insert shows the high magnification of the single tube with opening. (B) High magnification of structures; note the life-like complexity and the vesicles.

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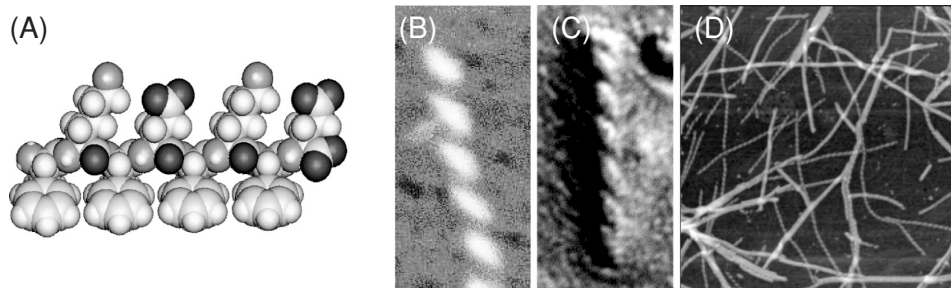


Figure 20.8. An amphiphilic peptide FKE8 (FKFEFKFE). A single FKE8 peptide is shown with a hydrophobic side, phenylalanine and hydrophilic side, lysine (positive charge), and glutamic acid (negative charge) (A). Atomic-force microscopic (AFM) (B) and transmission electron microscopic (TEM) (C) images of FKE8; note the distinctive left-handed helices in high magnification and overall fibrous structure with defined diameter (D).

Other simple amphiphilic peptides

A number of simple alternating peptides have a few amino acids. These peptides, like Lego[®] bricks, have two distinctive side-pegs and holes. The hydrophilic part bears charged residues, either positive charges – lysine, arginine, histidine – or negative charges – aspartic acids and glutamic acids. On the other side are hydrophobic residues – alanine, valine, isoleucine, leucine, phenylalanine, tyrosine, and tryptophan. Some of them can form well-ordered helical and other fibrous structures (Zhang *et al.*, 1993, 2002; Marini *et al.*, 2002; Hwang *et al.*, 2003; Zhang, 2003) (see Figures 20.8–20.10). Others form non-helical fibrous structures (Zhao and Zhang, 2004). They form many stable structures, as either double-layered helical or non-helical tapes that sequester hydrophobic parts because the hydrophobic residues must move away from water and leave the hydrophilic side exposed to water. Water is the driving force that sequesters the hydrophobic part of a molecule, regardless of whether it is a protein, alipid, a nucleic acid, or some other small molecule.

To summarize, this provides one vision of a crucial bridge between the physicists' claim of a "fine-tuned universe" (one predisposed to the production of water, carbon, and nitrogen) and the reality of life on earth. The existence of stable nanotube structures demonstrates how biochemical molecular fine-tuning could give rise to complex entities, presumably through a process of prebiotic molecular selection applied to primitive, quasi-living autocatalytic networks.

Put more simply, when considering prebiotic selection and evolution in the context of the origin of life, the enormously powerful force of water must never be underestimated. As all life is based on water, all molecules in living systems interact with it, and water likely has driven molecular evolution from the very beginning, here on earth or plausibly elsewhere in the universe – or multiverse.

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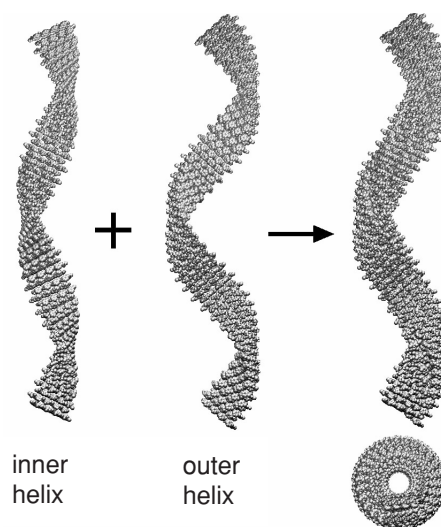


Figure 20.9. Molecular simulations of numerous FKE8 peptides, with hydrophobic phenylalanine on one side and hydrophilic lysines and glutamic acids on the other, undergo self-assembly to form left-handed helical fibers that contain 97 peptides per helical turn, 7 nm in diameter with a 19 nm pitch. The molecular simulated structures are consistent with the experimental observations. Water drives the hydrophobic phenylalanine pack inside the left-handed peptide double helix (Marini *et al.*, 2002; Hwang *et al.*, 2003).

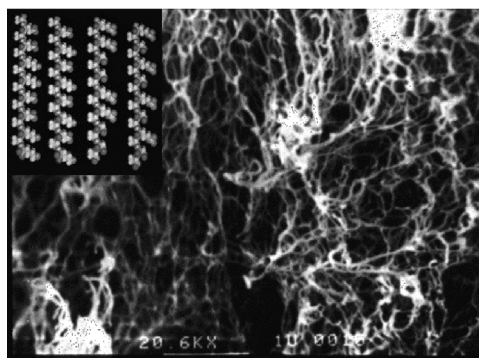


Figure 20.10. Amphiphilic ionic self-complementary peptides. This class of peptides has 16 amino acids, *c.* 5 nm in size, with an alternating polar and non-polar pattern. They form stable β -strand and β -sheet structures; thus, the side chains partition into two sides, one polar and the other non-polar. They undergo self-assembly to form nanofibers with the non-polar residues inside; positively and negatively charged residues form complementary ionic interactions, like a checkerboard. These nanofibers form interwoven matrices that further form a scaffold hydrogel with a very high water content (>99.5%). The simplest peptide scaffold may form compartments to separate molecules into localized places where they can not only have high concentration, but also form a molecular gradient, one of the key prerequisites for prebiotic molecular evolution.

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