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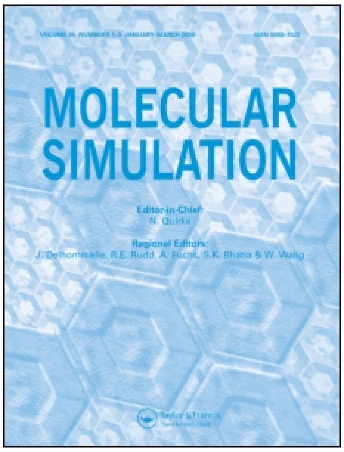

## Molecular Simulation

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# Modeling of Peptides in Implicit Membrane-Mimetic Media

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# MODELING OF PEPTIDES IN IMPLICIT MEMBRANE-MIMETIC MEDIA

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Lipid bilayer plays a crucial role in folding of membrane peptides and their stabilization in the membrane-bound state. Correct treatment of the media effects is thus essential for realistic simulations of peptides in bilayers. Previously (Volynsky *et al.*, 1999), we proposed an efficient solvation model which mimics heterogeneous membrane-water system. The model is based on combined employment of atomic solvation parameters for water and hydrocarbon, which approximate hydrated headgroups and acyl chains of lipids, respectively. In this study, the model is employed in non-restrained Monte Carlo simulations of several peptides: totally apolar 20-residue poly-L-Leu, hydrophobic peptide with polar edges, and strongly amphiphilic peptide. The principal goals are: to explore energy landscape of these peptides in membrane; to characterize the structures of low-energy states and their orientations with respect to the bilayer. Simulations were performed starting from different structures (unordered or helical) and orientations. It was found that the membrane environment significantly promotes an $\alpha$-helical conformation for all the peptides, while their energetically favourable orientations are quite different. Thus, poly-Leu was immobilized inside the membrane, the hydrophobic peptide with polar termini adapted transbilayer orientation, whereas the amphiphilic peptide stayed on the lipid-water interface in peripherial orientation. Energy barriers between different states were characterized. The computational results were compared with the experimental structural data.

*Keywords:* Protein conformation; solvation potential; molecular modeling; membrane peptides

*Abbreviations*: ASP – atomic solvation parameter; MC – Monte Carlo method; TM – transmembrane.

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## INTRODUCTION

Nowadays, a great deal is known about the physico-chemical factors driving folding of globular proteins and ensuring their stability in the folded native states (see *e.g.*, Dobson *et al.*, 1998). Although the problem of atomic-level *ab initio* prediction of the three-dimensional (3D) structure of such proteins is still unsolved, a large amount of experimental and theoretical modeling information has been accumulated. On the contrary, relatively little is known about energetics and folding of proteins in the presence of a membrane (reviewed in Booth and Curran, 1999), and general principles of their structure, stability, and mode of action are just beginning to appear (Cramer *et al.*, 1992; Haltia and Freire, 1995; Stowell and Rees, 1995; White and Wimley, 1998). This is because the amount of structural and thermodynamic data for them is scarce due to difficulties caused by their insolubility in water, large stability in the membrane-bound state, *etc.* One of the alternative approaches to address some important aspects of the problem, is employment of molecular modeling techniques. Such methods have been recently applied to simulate various membrane peptides and proteins (Tieleman *et al.*, 1997; Sansom, 1998; Efremov *et al.*, 1999a, b). The main difficulty inherent in this type of analysis is related to correct treatment of solvent effects which appear to have a fundamental importance in determining the native state. During the last years, much attention has been put on molecular dynamics (MD) and Monte Carlo (MC) simulations of 20/25-residue peptides which can either traverse membrane (preferentially – in $\alpha$-helical conformation) or stay adsorbed in the interfacial region (*e.g.*, Sansom, 1998). Such interest is caused by their biological importance – numerous peptides act autonomously having antimicrobial, fusion and channel forming activity or represent the building blocks for the membrane protein domains. In addition, the system is relatively simple to perform long-term simulations. Finally, some of the peptides, like glycophorin A (Lemmon *et al.*, 1994), magainins (Matsuzaki, 1998), melittin (Ladokhin and White, 1999), transmembrane (TM) segments of bacteriorhodopsin (Pervushin and Arseniev, 1992) were experimentally studied in membrane-mimetic media (lipid vesicles, SDS micelles, mixtures of organic solvents). This makes such systems very convinient for testing new solvation models dedicated to imitation of the effects of lipid bilayer on protein behaviour.

Various solvation models used in MC and MD studies of membrane peptides and proteins, along with their advantages and shortcomings, were discussed elsewhere (Nolde *et al.*, 1997; Efremov *et al.*, 1999a). Among them, the models with implicit consideration of the membrane effects are of a special interest because of their computational efficiency and ability to account for principal trends in protein-lipid interactions. In this approximation the bilayer is usually treated as continuous medium whose properties vary along the membrane thickness, and membrane insertion is simulated using either MC or MD methods (Milik and Skolnick, 1993; Ducarme *et al.*, 1998; Gazit *et al.*, 1998). The implicit solvation models provide a number of insights into the mechanism of peptides' insertion into membranes and result to good predictions both for the association state and peptide's orientation relative to the membrane surface. In these studies, however, the peptide's conformation was often fixed to $\alpha$-helix, and no changes of the structure were allowed during the simulations. Hence, the problems related to conformational rearrangements, like formation or destabilization of the secondary structure induced by the environment, could not be addressed.

In our previous studies (Nolde *et al.*, 1997; Efremov *et al.*, 1999a; Volynsky *et al.*, 1999) we proposed a membrane-mimetic implicit solvation model based on the concept of atomic solvation parameters (ASP). The model represents a hydrophobic core of the bilayer (described by ASPs for gas-cyclohexane transfer) surrounded by infinitive layers of polar media (approximated by ASPs for water). The width of the interfacial region and the membrane thickness are adaptable parameters and could be changed to assess their influence on peptides' behaviour. Thus, variation of the bilayer thickness in simulations of the TM segment of human glycophorin A (Volynsky *et al.*, 1999) showed that the solvation model correctly reproduces the effects of "hydrophobic match/mismatch" which are well known from the experiments (*e.g.*, Killian, 1998). In the present work we describe application of the solvation model to several model systems of different hydrophobic nature: (1) fully nonpolar peptide (20-residue poly-L-Leu); (2) hydrophobic peptide with polar groups on the termini (LA peptide); (3) amphiphilic peptide (LK peptide). Conformational space of these peptides in the presence of a bilayer is explored *via* MC simulations, and the obtained low-energy states are analyzed in terms of peptides' conformations, energetics, and orientations with respect to the membrane. The results are compared with available experimental data and the results of calculations in explicit solvent.

## METHOD OF CALCULATION

Heterogeneous three-layer membrane model used in this study is based on combined employment of ASPs for gas-cyclohexane and gas-water transfer, which mimic the hydrophobic core of a bilayer and hydrated head-groups of lipids, respectively. The all-atom potential energy function was described elsewhere (Volynsky *et al.*, 1999). Corresponding bulk-solvent ASPs were taken from our previous studies (Nolde *et al.*, 1997; Efremov *et al.*, 1999a). The width of the interface region and the bilayer thickness were taken to be 1.5 and 30 Å, respectively.

All the peptides were modelled in full-atom representation. Besides 20-residue poly-L-Leu, the following peptides were used: KLLKKLL-KLLKKLLKKLKKLLKKL (peptide LK) and KKKKKALALALALA-WALALALALAL (peptide LA). LA- and LK-peptides were built in $\alpha$-helical conformation. The starting structure of poly-Leu was generated in random coil conformation. To change during MC simulation orientation of the peptides with respect to the bilayer, fragments of 12 dummy residues were attached to their N-termini. Because of lack of force field parameters, these dummy residues did not contribute to the energy of the system. First atom of the N-terminal dummy residue was always placed in the center of the bilayer with coordinates (0,0,0). N-Methyl group was added to the C-terminus. In the beginning of MC runs the peptides were placed outside the bilayer ($|z| > 15$ Å for all atoms). Conformational space of the peptides was explored in non-restrained MC simulations in torsion angles space using the FANTOM program (von Freyberg and Braun, 1991). The $\omega$ dihedral angles were fixed (except those in dummy residues), and spherical cutoff 30 Å for nonbond interactions was used. Long-range electrostatic interactions were damped by using $\varepsilon = 4 \times \Gamma$ although the short-range ones contributing to the H-bonding term, were explicitly included.

Before the MC simulation, all structures were subjected to 50 – 100 cycles of conjugate gradients minimization. Acceptance of the conformers was done according to the Metropolis criterion (Metropolis *et al.*, 1953). No restraints were employed in the MC protocol. The simulation length for LA- and LK-peptides was 2000. At each step, one randomly selected dihedral angle was sampled, and the current structure was minimized *via* 70 conjugate gradients iterations. To cross the energy barriers between local minima, adaptive-temperature schedule protocol (von Freyberg and Braun, 1991) was employed. Simulation of poly-Leu was performed according to the following scheme: (i) Initial random structure was subjected to two MC runs of 3000 steps each with linearly decreasing temperature (initial $T = 2000$ K). At each MC step, respectively 15 and 10 randomly selected dihedrals were sampled. The variation step for each dihedral was chosen randomly on the range $-180° \div 180°$, and the current structure was minimized *via* 70 conjugate gradients iterations. (ii) Then the adaptive-temperature schedule protocol (von Freyberg and Braun, 1991) was employed during four consequtive runs (5000 iterations each) by sampling of 5, 2, 1, and 1 randomly selected dihedrals followed by 70, 70, 150, and 150 minimization steps, respectively. For each run, the initial conformation was the lowest-energy structure found at the previous stage.

Other details of the simulations could be found in (Nolde *et al.*, 1997; Efremov *et al.*, 1999a; Volynsky *et al.*, 1999). Analysis of the peptides' orientations with respect to the bilayer (angles between axes of helical segments and the bilayer normal, immersion depth ($z$ coordinate) of the center of mass, *etc.*) was done using auxiliary programs specially written for this. Hydrophobicity moment ($|\mu_{\text{max.}}|$), average hydrophobicity index ($\langle H \rangle$), indices of $\alpha$-helix ($I_\alpha$) and $\beta$-sheet ($I_\beta$) were calculated, as described in (Eisenberg *et al.*, 1984; Donnelly *et al.*, 1993). Secondary structure, ASAs and H-bonding patterns were analyzed using the DSSP program (Kabsch and Sander, 1983). Ribbon diagrams of the molecules were produced with the MOLMOL program (Koradi *et al.*, 1996).

## RESULTS AND DISCUSSION

### 20-Residue Poly-Leu

This peptide does not contain polar residues and reveal very low hydrophobicity moment (Tab. I). Apart from natural membrane peptides, it has no polar groups on its termini which often ahchor hydrophobic peptides in TM orientation. (Here and in subsequent discussion we use the term "TM orientation" for structures having at least one atom from each termini located on the opposite sides of the bilayer, with $|z| > 15$ Å). The exceptions are provided by the backbone polar N—H and C=O groups of terminal residues which are not involved in H-bonding in $\alpha$-helix. It is

TABLE I Hydrophobic characteristics of peptides calculated from their amino acid sequences

| *Peptide* | $\langle H \rangle^a$ | $\|\mu_{\text{max.}}\|^b$ | $I_\alpha{}^c$ | $I_\beta{}^d$ |
|---|---|---|---|---|
| poly-L-Leu | 1.06 | 0.022 | 0.11 | 0.08 |
| La[e] | 0.83 | 0.062 | 0.16 | 7.39 |
| LK | −0.22 | 0.853 | 4.64 | 0.17 |

[a] $\langle H \rangle$ – Average hydrophobicity.

[b] $|\mu_{\text{max.}}|$ – Maximal hydrophobicity moment (calculated for 11-residue window).

[c,d] $I_\alpha$, $I_\beta$ – Indices of $\alpha$-helix and $\beta$-sheet, respectively.

[e] LA peptide without N-terminal segment $\text{Lys}_5$. For details of calculations of $|\mu_{\text{max.}}|$, $\langle H \rangle$, $I_\alpha$ and $I_\beta$ – see (Eisenberg *et al.*, 1984; Donnelly *et al.*, 1993).

well established now from the experiments (Deber and Li, 1995; Ladokhin and White, 1999) and modeling (*e.g.*, Efremov *et al.*, 1999a, b), that nonpolar media significantly favours $\alpha$-helical conformation. This is especially true for Leu residues. Therefore, one can propose that in a bilayer poly-Leu adapts an $\alpha$-helical conformation and stays preferentially in the hydrophobic part of the membrane. On the other hand, *a priori* it is difficult to say, what are its the most energetically favourable orientations with respect to the bilayer. To answer this question, we explored the conformational space of poly-Leu using our implicit solvation model.

The results obtained are presented in Figures 1–3. The following parameters were controlled during the MC simulation: energy, secondary structure and helicity degree ($N_\alpha$ – number of residues in $\alpha$-helix), accessible surface area (ASA), angles $\theta$ between axes of helical segments and the bilayer normal, immersion depth ($z$ coordinate) of the center of mass ($z_{\mathrm{cm}}$). It is seen (Fig. 1) that already initial energy minimization of the peptide results in deep penetration of the molecule into the membrane – $z_{\mathrm{cm}}$ changes from 35.5 Å in the initial structure to 0.7 Å. Subsequently, poly-Leu stayed inside the bilayer – only in few states atoms of terminal residues had coordinates $|z| > 15$ Å. This process was accompanied by $\alpha$-helix formation (Fig. 1). Interestingly, in the high-energy conformers short $\alpha$-helical segments were detected mainly near the N-terminus (Fig. 2). In addition, on the region 11–14 some residues were observed in $3_{10}$-helix conformation.

Figure 3 shows total energy levels and conformations of the most stable structures, grouped according to their values of $N_\alpha$ and $\theta$ . We should notice that each of the states shown in Figure 3 corresponds to a local minimum on the potential energy hyper-surface for the system peptide-bilayer. It is seen that the entire helix ($N_\alpha = 18$) oriented almost parallel to the membrane plane ($\theta = 78°$) – state-1 – is the most energetically favourable. At the same time, another state (state-2) with $N_\alpha = 18$ and $\theta = 60°$ is only 1.24 kcal/mol higher in energy. Energy intervals of these states strongly overlap, thus permitting a proposal that the both could present in equilibrium. Other close in energy states have $N_\alpha = 17$, 16, *etc.*, lie parallel or perpendicular to the bilayer plane, and reveal overlapping intervals of energies (Fig. 3). In all low-energy states the N-terminus is located in the hydrophobic zone, while in some of them (states 2, 4) polar oxygen atoms on the C-terminus are exposed to the water-mimicking layer. Therefore, the results show that membrane stabilizes $\alpha$-helical conformation of poly-Leu, although the peptide has no highly preferred orientation with respect to the bilayer.

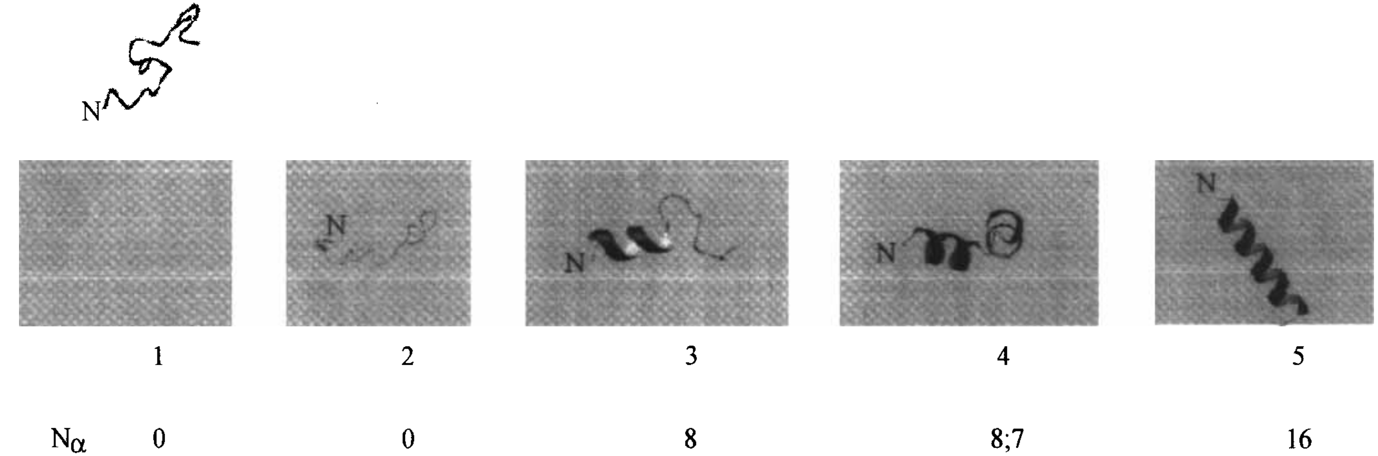

FIGURE 1 Results of Monte Carlo simulation of 20-residue poly-L-Leu in membrane-mimetic media. 1, 2: Starting structure before and after minimization. 3–5: Conformations obtained with interval of 5500 Monte Carlo steps. Nonpolar layer of membrane is grey hatched. $N_\alpha$–number of residues in $\alpha$-helical conformation (in a case of several helical regions, the corresponding numbers are given for each of them). N-terminus of the peptide is shown by symbol “N”.

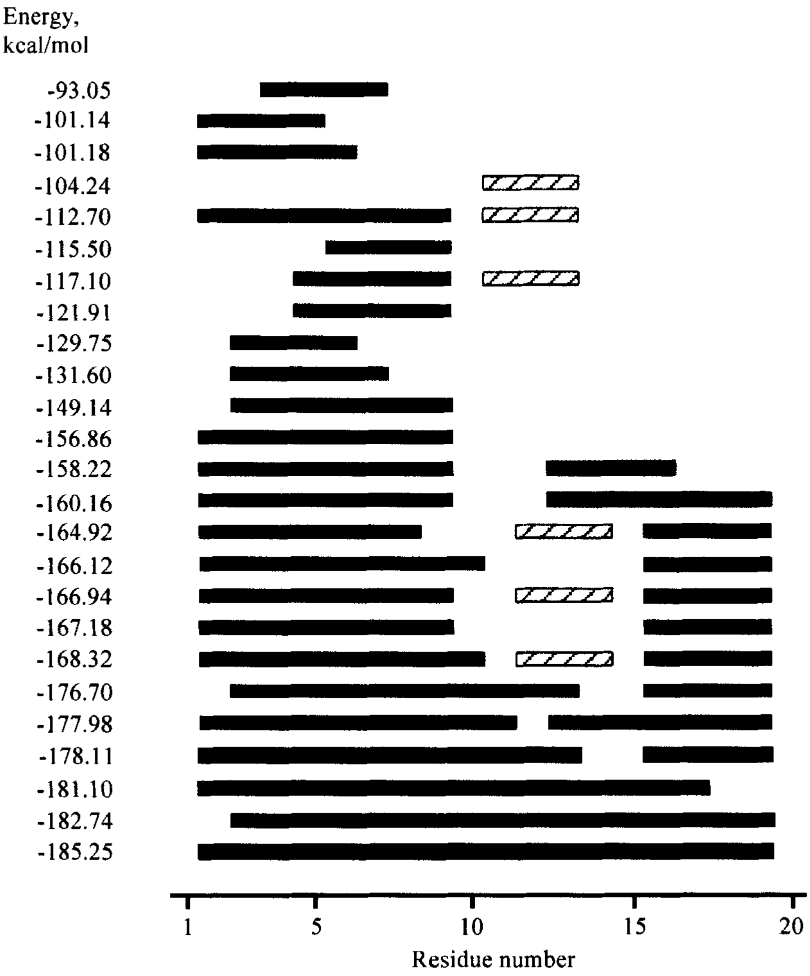

FIGURE 2 Secondary structure and total energy of conformational states obtained in the result of Monte Carlo simulation of 20-residue poly-L-Leu in membrane-mimetic media. Starting structure – random coil. Only the states with unique secondary structure are shown. For similar states the lowest energy value is indicated. $\alpha$-Helices and $3_{10}$-helices are marked with black and shaded bars, respectively.

It is interesting to compare the data with the results of MD simulation of 10-residue poly-Leu on the explicit hexane-water interface (Chipot and Pohorille, 1998). As in the present work, deca-poly-Leu was taken in initial random coil conformation and placed outside the hydrophobic zone. During the first 36 ns of MD the peptide inserted into the interfacial region and folded into an $\alpha$-helical conformation. Some short-living states with

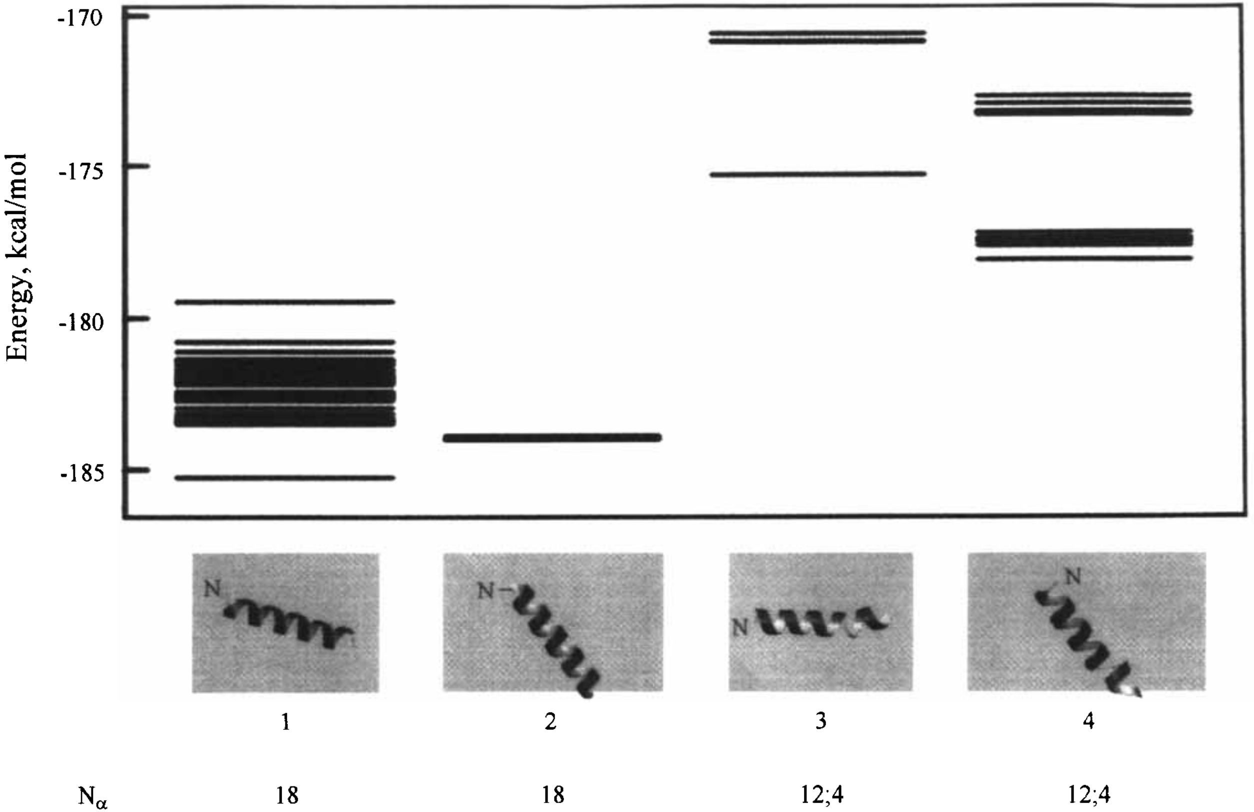

FIGURE 3 Low-energy conformers of 20-residue poly-L-Leu obtained in the result of Monte Carlo simulation in membrane-mimetic media. (**Top**). Levels of the total energy for different groups of states. (**Bottom**). Ribbon diagrams of the conformers (calculated for the minimal-energy structure from the corresponding group). The conformers are grouped according to values of $\alpha$-helical content ($N_\alpha$). Groups of the conformers are indicated by numbers 1 – 4. Other details – as in legend to Figure 1.

segments of $3_{10}$-helix were also observed. Subsequently, deca-poly-Leu stayed buried into hexane phase, although near the interface. It had no preferential stable disposition with respect to the membrane – both, parallel and perpendicular orientations were detected. In the last case, its N- and C-termini were immersed into hexane and water, respectively. Energetic analysis revealed that dehydration of N—H groups of N-terminal residues is sufficiently more favourable than that for C=O groups on the C-end. A proposal was made that this is a general feature for interactions of peptides with membranes, thus forcing the peptides to insert by their N-termini. Therefore, the results obtained in two independent approaches – with explicit and implicit solvation models – demonstrate fairly good agreement in description of principal trends of poly-Leu behaviour in the presence of a lipid-water interfaces.

## LA Peptide

Like poly-Leu, this peptide is strongly apolar in its central part Ala6-Leu25, and has no prominent asymmetry in the distribution of hydrophobic properties – corresponding values of $|\mu_{\text{max.}}|$ and $\langle H \rangle$ are equal to 0.062 and 0.83, respectively (Tab. I). On the other hand, it contains 5 sequential residues of Lys. Usually, the peptides with such polarity properties adapt TM orientation (Brasseur *et al.*, 1997). Solid state NMR data obtained for LA peptide in membrane-like environment confirm this conclusion (Bechinger *et al.*, 1996).

Starting and low-energy structures of the peptide, along with their dispositions with respect to the membrane, are shown in Figure 4. The results of MC conformational search imply that: (1) $\alpha$-Helix, initially located outside bilayer, rapidly (in terms of number of MC steps) penetrates inside the membrane and stays almost completely buried in the hydrophobic zone, except 5 N-terminal Lys residues. (2) The most energetically favourable state corresponds to $\alpha$-helix 3–23 ($N_\alpha = 21$) which has 20–23 H-bonds, including 19 H-bonds of type $CO_i \rightarrow HN_{i+4}$. This state is characterized by local energy minima on the interval $-227.54 \div -226.92$ kcal/mol, and has TM orientation ($\theta \approx 9°$). Oxygen atom of the last C=O group is located outside the membrane. (3) Several other states, similar in structure ($N_\alpha = 21$) but different in orientation ($\theta \approx 14-17°$; $2-3°$) and depth of penetration, are stable in the energy region $-226.75 \div -195.77$ kcal/mol. Increasing of $\theta$ results in exposition of the last C=O group to the hydropobic core. Also, some of these states have additional H-bonds. (4) Other stable states (3, 4, 5 in Fig. 4) also contain the only $\alpha$-helical segment (4–23, $N_\alpha = 20$;

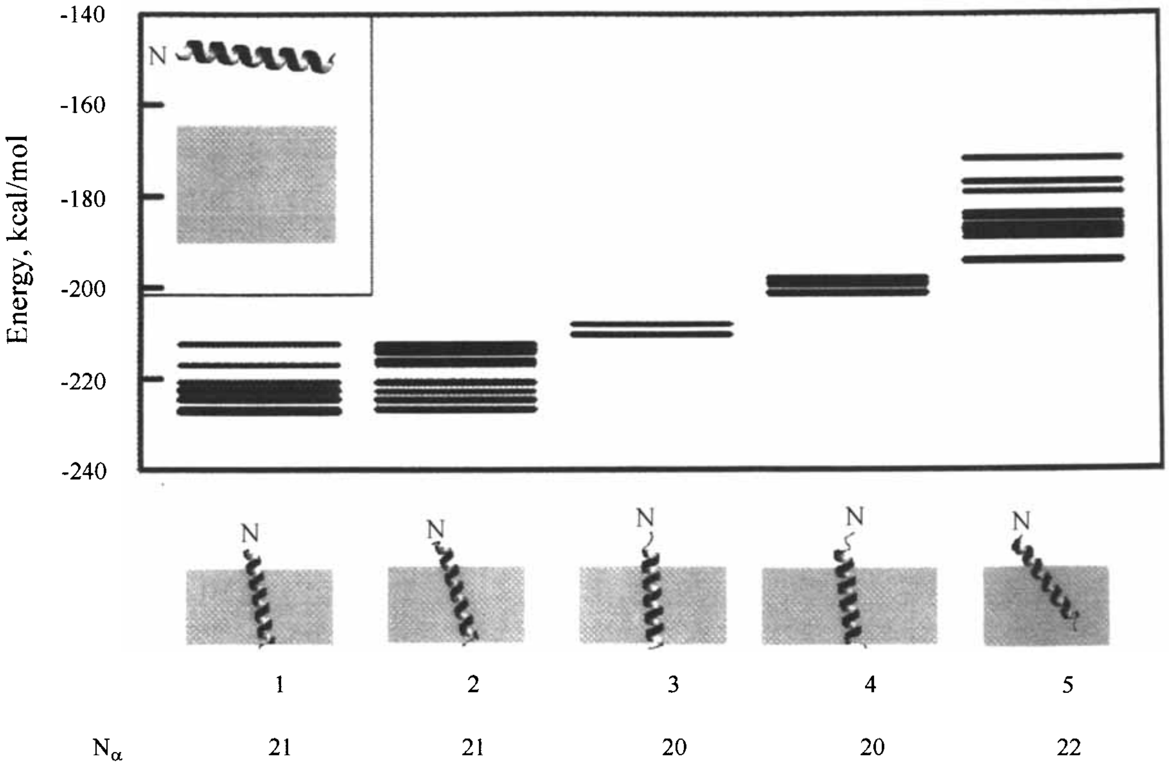

FIGURE 4 Low-energy conformers of LA-peptide obtained in the result of Monte Carlo simulation in membrane-mimetic media. (**Top**). Levels of the total energy for different groups of states. (**Bottom**). Ribbon diagrams of the conformers (calculated for the minimal-energy structure from the corresponding group). The conformers are grouped according to values of $\alpha$-helical content ($N_\alpha$). Groups of the conformers are indicated by numbers 1 – 5. (**Insert**). Starting structure of the peptide. Other details – as in legend to Figure 1.

2–23, $N_\alpha = 22$, respectively) and have energies on the intervals $-210.34 \div -198.04$ kcal/mol and $-194.40 \div -171.89$ kcal/mol. Total numbers of H-bonds in these structures are 20–21 and 21, respectively. Higher energies of such states are caused by burial of their polar C-termini to the hydrophobic region of the bilayer. Thus, although the state-3 is oriented almost perpendicular to the membrane plane ($\theta \approx 2-3°$), the length of its nonpolar region is already not sufficient to span the bilayer. On the other hand, the conformers with long hydrophobic $\alpha$-helical segment ($N_\alpha = 22$) significantly deviate from the bilayer normal ($\theta \approx 40°$).

Interestingly, because of the lack of periodicity in distribution of hydrophobic residues in the sequence, the peptide LA has low helicity index ($I_\alpha = 0.16$, Tab. I) and high index for $\beta$-sheet ($I_\beta = 7.38$, Tab. I). In spite of this, only $\alpha$-helical structures were found during the simulation, and no $\beta$-sheets were observed. This could be explained by the fact that nonpolar media stabilizes $\alpha$-helix (Deber and Li, 1995), whereas formation of isolated $\beta$-strands is energetically unfavourable because in this case some of the backbone N—H and C=O groups are not involved in H-bonding. (We should note, however, that such structures exist in water solution (Munoz *et al.*, 1997).)

## LK Peptide

Apart from the two hydrophobic peptides considered above, the sequence of the peptide LK includes polar and apolar residues alternating with a periodicity which is characteristic for $\alpha$-helix. Hydrophobic properties of the peptide LK (Tab. I) permit a proposal, that on the lipids-water interface it forms an amphiphilic $\alpha$-helix. In fact, solid-state NMR data totally confirm such a proposal (Bechinger *et al.*, 1996). Experimentally it was found that polar side chains of Lys residues are exposed to water, whereas the aliphatic ones of Leu–to hydrocarbon core of the membrane. It should be emphasized that amphiphilic peptides interacting with bilayers play an important role in many of cell processes. The examples are provided by antibacterial and fusion peptides, peptides and TM segments of proteins forming ion channels, *etc.* That is why, any theoretical model dedicated to imitate membrane effects, should be able to describe correctly behaviour of these systems in bilayers. This explains our choice of the LK-peptide as a third test system for the solvation model.

The results of exploring of its conformational space *via* MC simulation are presented in Figure 5. The following conclusions were made: (1) The lowest-energy conformers have $\alpha$-helical structure on the region 2–20.

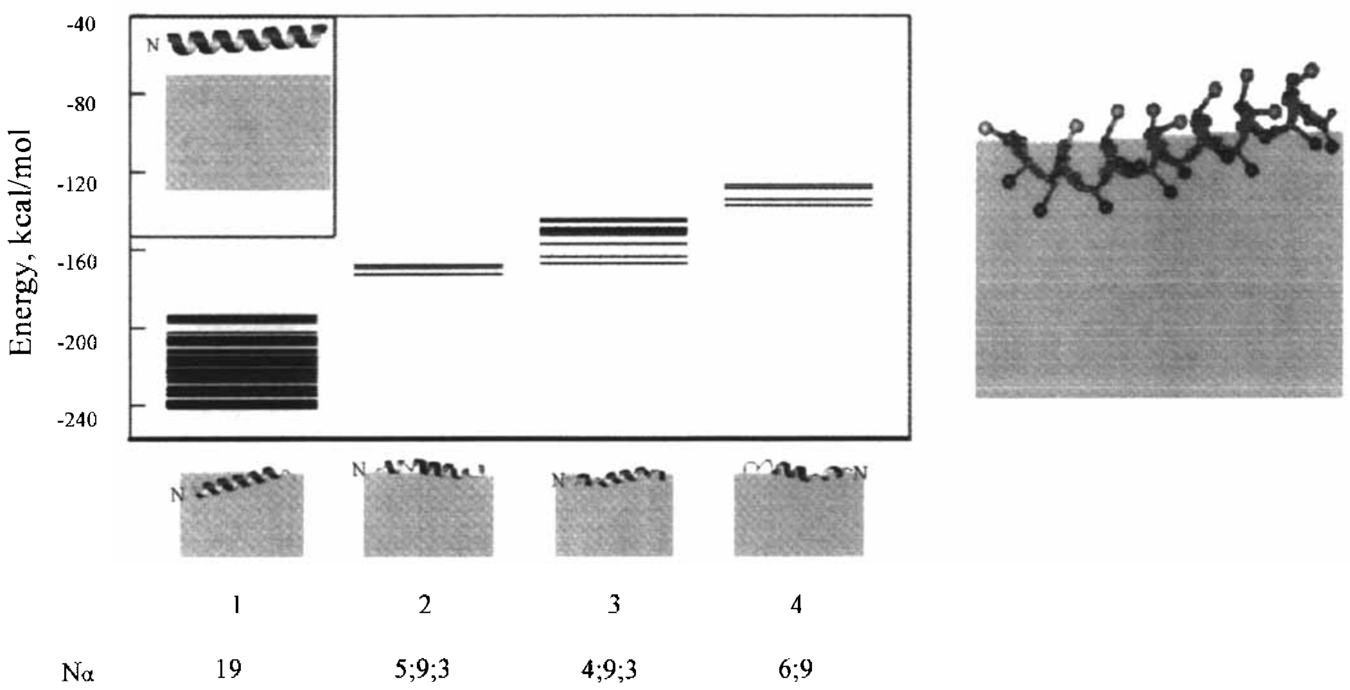

FIGURE 5 Low-energy conformers of LK-peptide obtained in the result of Monte Carlo simulation in membrane-mimetic media. (**Top**). Levels of the total energy for different groups of states. (**Bottom**). Ribbon diagrams of the conformers (calculated for the minimal-energy structure from the corresponding group). The conformers are grouped according to values of $\alpha$-helical content ($N_\alpha$). Groups of the conformers are indicated by numbers 1–4. (**Insert**). Starting structure of the peptide. (**Right**). The lowest-energy conformer. Side chains of Lys and Leu residues are shown with light and dark balls, respectively. Other details – as in legend to Figure 1.

They are located in the interfacial region ($z_{cm} \approx 12-14$ Å) and lie almost parallel to the membrane plane ($\theta \approx 80°$). Polar side chains of Lys residues are outside the bilayer, in water surrounding, while the aliphatic groups of Leu contact the hydrophobic layer. (2) These states exist in a wide energy range – from – 240.99 to – 193.85 kcal/mol. They have 18 – 21 H-bonds, including 17 bonds of type $CO_i \rightarrow HN_{i+4}$ ($N_\alpha = 19$). (3) The most stable states ($E < -238$ kcal/mol) demonstrate maximal values of ASA and have no H-bonds of type $CO_i \rightarrow HN_{i+3}$. (4) The state with $E = -214.23$ kcal/mol, which is overlapping with the most stable ones, has similar structure and disposition in the membrane, although its helicity degree is a bit less ($N_\alpha = 18$). (5) Other states are separated in energy from those considered above, by $\Delta E \geq 1.84$ kcal/mol. They have $N_\alpha$ values between 9 and 16, and the total number of H-bonds between 12 and 20. In addition, these states (excluding one with $E = -182.23$ kcal/mol and $N_\alpha = 18$) contain either segments of $3_{10}$-helix or helix breaks on the N- and C-termini. In all the cases the helical segments are oriented approximately parallel to the bilayer plane and expose side chain $NH_3^+$ groups of lysines to polar phase, and aliphatic side chains of leucines – to nonpolar media. (6) In the low-energy states N-terminus is buried in the hydrophobic layer of the membrane, while its C-terminus is outside the nonpolar zone. Interestingly, similar conclusions were reached in our previous study of glycophorin A (Volynsky *et al.*, 1999) as well as in the result of MD simulation of deca-poly-Leu with explicit water-hexane interface (Chipot and Pohorille, 1998).

Thus, in a good accord with available experimental data, the most energetically favourable state of the amphiphilic peptide LK represents an entire $\alpha$-helix lying on the membrane-water interface and exposing charged groups of lysines to polar media, while side chains of Leu residues are buried in the hydrophobic membrane core. Other states which either have distorted $\alpha$-helical conformation or contain short fragments of $3_{10}$-helix, are considerably less stable. Therefore, they do not compete with the dominant all-helical state.

## CONCLUSIONS

In this study we presented an application of the membrane-mimetic implicit solvation model to assessment of structure and energetics of three peptides of different hydrophobic nature. Comparison of the results with the experimental data showed fairly good overall agreement. This makes us confident that the model correctly reflects the principal trends of peptides' behaviour in membranes: residues with hydrophobic and hydrophilic side chains try to increase their exposure to nonpolar and polar membrane layers, respectively. According to definition of the solvation energy term employed in the model (Nolde *et al.*, 1997), this leads to decreasing of the total energy of the system. Therefore, in the low-energy conformers the hydrophobic protein segments are buried inside the bilayer, while the hydrophilic ones usually are outside. Conformation of a peptide in bilayer is determined by a subtle balance of different energy terms including van der Waals and long-range electrostatic interactions, solvation and H-bonding energies. Being located in hydrophobic protein regions and, hence, easily immersed into bilayer, polar N—H and C=O groups of the backbone exhibit a prominent tendency to form H-bonds. The most stable structure in this case is an $\alpha$-helix. Therefore, the model proposed here permits correct description of the effect of membrane-induced helix stabilization which is known from the experiments (Deber and Li, 1995; Ladokhin and White, 1999). Important features of the model – full-atom protein representation and computational efficiency (demanded CPU time is by a factor of 5–10 less than in similar explicit solvent simulations).

Current studies are centered about implication of the model to test it on various membrane-bound peptides and assess structural and energetic properties of helix-helix interactions in membrane. Our future work is also being pursued to develop a more elaborate model of a membrane which will take into account TM electrostatic potential as well as mechanistic elasticity of the natural biomembranes. This approach is believed to be useful in modeling such phenomena like *e.g.*, voltage gating of ion channels, membrane fusion, *etc.*

## *Acknowledgments*

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