Biophysical Chemistry 42 (1992) 195–200
Elsevier Science Publishers B.V., Amsterdam

BIOCHE 01627

Monte Carlo simulation of the conformational behaviour of a polypeptide chain near a charged surface

F. Elhebil and S. Premilat

Laboratoire de Biophysique Moléculaire, URA CNRS 494, Faculté des Sciences, Université de Nancy I, BP 239, 54506 Vandoeuvre les Nancy (France)

(Received 21 December 1990; accepted in revised form 15 July, 1991)

Abstract

The conformational behaviour of a short polypeptide chain in the neighbourhood of a charged plane is simulated using a Monte Carlo method. In this approach, the plane is taken as a model of an interface separating a hydrophobic region from a hydrophilic one. It is shown that in the neighbourhood of the plane, folded molecular conformations are prevailing whilst stretched conformations are preferred far from the interface. When the plane is not charged, the molecule adjusts itself parallel to the interface. For a given position of the molecule with respect to the plane, when the charge density of the plane is increased, the molecule tends to turn perpendicular to the plane. The surface may either attract or repulse the molecule depending on the value of the charge density (the plane is always negatively charged).

Keywords: Enkephalin conformation; Monte Carlo calculations; Charged surface; Electric images

1. Introduction

The study of the behaviour of charged particles in the neighbourhood of a charged plane is a very important problem in physical chemistry. The response of these particles to the electric field created by the plane is linked to the problem of electric bilayer. The bilayers are presented in electrochemistry as an interface electrode/electrolyte and they play a very important role in the stability of lipidic films and in biological membranes. The first theory for such systems, based on Boltzmann's equation, has been developed by Gouy and Chapman. It had great success and several other models have been proposed on the basis of their model to study the configuration of polyelectrolytes in the neighbourhood of surfaces [1–3].

The surface of cell membranes essentially carries negative charges [4,5] and the effect of this surface on the conformation adopted by molecules of biological interest is therefore very important [4,5]. Cellular membranes contain molecules known as receptors (generally proteins). Their function is to receive the information conveyed by the so-called "messenger molecules", which are hormones or neurotransmitters secreted by special cells or nervous cells, respectively. When these messenger molecules move towards the target cells, it is likely that they should first be

---

Correspondence to: Dr. F. Elhebil, Laboratoire de Biophysique Moléculaire, URA CNRS 494, Faculté des Sciences, Université de Nancy I, BP 239, 54506 Vandoeuvre les Nancy (France).

0301-4622/92/$05.00 © 1992 - Elsevier Science Publishers B.V. All rights reserved

oriented by the membrane and then directed towards the receptors [6,7].

Several recent studies concerning the simulation of the behaviour of polyelectrolytes near an interface have been carried out using Monte Carlo methods [2,3,8,9]. In these approaches no effect due to the part of the space situated in the other side of the plane are taken into account. In the present paper an approach, is proposed to examine the effect of the charged surface on the molecular conformation of a short polypeptide chain when it gets closer to this surface.

2. Method of calculation

We consider a plane dividing the space into two different media with dielectric constants ε_1 and ε_2 respectively equal to 3.5 and 78. $\varepsilon_1 = 3.5$ corresponds to the organic medium (hydrophobic) of the membrane essentially composed of phospholipids while $\varepsilon_2 = 78$ represents the extracellular medium which is mainly water (hydrophilic). The charge density of the plane is given values near $-0.02\ e/A$ (e is the electronic charge, A is equal to 1 Å^2). This value is of the order of the mean charge density of membranes [6]. A simplified molecular model, namely the chain of enkephalin Tyr–Gly–Gly–Phe-Leu(Met) where methyl groups are substituted for side chains, has been chosen as an example in this present approach. This molecule, with terminal groups NH_3^+ and COO^-, is placed in the region corresponding to $\varepsilon_2 = 78$ (water).

The Monte Carlo procedure which allows us to obtain samples of molecular conformations taking the orientation of the molecule with respect to the plane into account comprises mainly the two following steps:

2.1 Calculation of molecular conformation and conformational energy

Atomic coordinates of molecular structures are computed according to Eyring's method [10,11]. To generate new molecular conformations values, chosen at random in energy maps, are given to the (ϕ, ψ) angles of every residue [12,13]. The conformational energy EA, calculated with standard parameters [14], it is the sum of all pairwise nonbonded and electrostatic interactions between atoms and the torsional energy. In the present Monte Carlo simulation short range interactions (between nearest neighbours) are taken into account by means of statistical weight matrices but long range interactions are completely calculated following a procedure already explained elsewhere [15].

2.2 Orientation of the molecule and interaction energy with the plane

The orientation of the molecule with respect to the charged plane is defined by the angle between the plane and the vector joining the N terminal to the CO terminal of the molecule. This angle is therefore positive when the CO terminal is farther from the plane than the N terminal.

In order to reduce computation time, only six different orientations with respect to the plane are considered for every new molecular conformation obtained from the preceding step. They are defined as follows: suppose that the molecule is placed in a cube; the six positions of the molecule with respect to the six faces of the cube must correspond to the different orientations actually considered. The centre of the enkephalin backbone is placed in coincidence with the centre of the cube. The distance of the molecule with respect to the plane is therefore maintained constant for the different orientations.

The potential function for the interaction of one charged particle with a plane separating two dielectric media, is given by the classical method of the electric images [16,17]. The expression of the interaction energy is then given by:

$$EB = \frac{-2C\pi\sigma}{\varepsilon_2} \sum_{i=1}^{N} Q_i Z_i + \frac{C(\varepsilon_2 - \varepsilon_1)}{\varepsilon_2(\varepsilon_1 + \varepsilon_2)} \sum_{\substack{i=1 \\ j=1}}^{N} \frac{Q_i Q_j}{r'_{ij}}$$

The first term is the interaction energy of the charged wall with the molecule; Z_i is the distance between the charged plane and the charge Q_i, and σ is the charge density of the plane. This potential expression has already been used in many simulations [18,19]. The second term represents the interaction energy of the charges with their electric images, r'_{ij} is the distance between the image of Q_i and the charge Q_j, and C is a constant depending on the units used (here we have $C = 332$ in order to get energy values in kcal/mol).

Among the six orientations of the molecule, with respect to the plane, the one corresponding to the lowest energy EB is selected for the Monte Carlo sampling procedure which is performed with the energy $E = EA + EB$. Samples of 30000 chain conformations are calculated for every simulation.

3. Results

3.1 Conformational behaviour

Figure 1 represents the distribution function $w(r)$ of the end-to-end distance (C_α terminals) for a few different positions of the molecular model with respect to the plane. The chain is folded in the neighbourhood of the plane; (the peak of $w(r)$ is situated around $r = 5$ Å for $D = 6$ Å, with $\sigma = -0.01$ e/A (see Fig. 1a) whereas stretched structures appear when the molecule is moved away from the plane (for $D = 8.5$ Å we find $r = 5$ Å for relative maxima of $w(r)$; (see Fig. 1b, $\sigma = -0.01$ e/A). For larger distances, for instance $D = 15$ Å, we find peaks of $w(r)$ at $r = 6$ Å and $r = 12$ Å; (see Fig. 1c, $\sigma = -0.01$ e/A). The same behaviour of the molecular conformation is noticed for other values of σ.

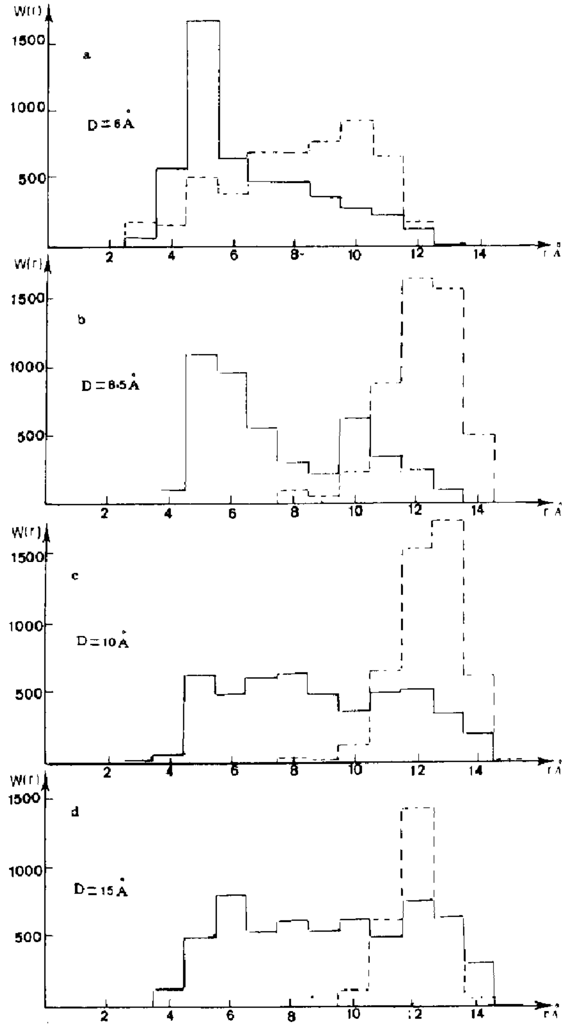

Fig. 1. Distribution function of the end-to-end distance of enkephalin. D is the distance of the center of the molecule to the surface of the plane. (———): $\sigma = -0.01$ e/A, and (- -): $\sigma = -0.03$ e/A.

Table 1 gives results corresponding to the behaviour of the enkephalin model in the neighbourhood of a charged plane. D is the distance between the plane and the centre of the molecule, E is the mean energy and C_n is Flory's ratio defined by $C_n = \langle r^2 \rangle / nl^2$ where $\langle r^2 \rangle$ is the mean square of the end-to-end distance for a chain of n units of length l. This ratio characterizes the degree of folding of the chain. The mean orientation θ_M of the molecule with respect to the plane, is defined by the following expressions [20]:

$$C_M = \frac{1}{n}\sum_{i=1}^{n} f_i \cdot \cos\theta_i, \quad S_M = \frac{1}{n}\sum_{i-1}^{n} f_i \cdot \sin\theta_i$$

where f_i is the statistical weight corresponding to the orientation θ_i, and n the number of calculated orientations. Then:

$$\theta_M = \begin{cases} \mathrm{arctg}(S_M/C_M) & \text{if } S_M > 0,\ C_M > 0 \\ \mathrm{arctg}(S_M/C_M) + \pi & \text{if } C_M < 0 \\ \mathrm{arctg}(S_M/C_M) + 2\pi & \text{if } S_M < 0,\ C_M > 0 \end{cases}$$

Table 1

Mean energy E, Flory's ratio and orientation of enkephalin as a function of the distance D to the plane. Results obtained using the partial charges given in Momany et al. [14]

Conformation	D(Å) 6	8	10	12
Mean energy, E (kcal/mol)				
a	−6.25	−5.30	−5.19	−5.66
b	−7.25	−7.17	−6.05	−6.07
c	−7.85	−7.98	−7.60	−7.55
d	−8.07	−8.78	−8.65	−8.28
e	−8.84	−8.85	−8.90	−9.12
f	−10.40	−11.71	−11.98	−11.88
Flory ratio, C_n				
a	0.78	1.02	0.86	0.86
b	0.87	1.10	1.48	1.52
c	1.23	1.74	2.37	2.44
d	1.26	1.67	2.23	2.60
e	1.37	1.95	2.52	2.51
f	1.54	2.56	2.65	2.72
Orientation angle, θ_M (°)				
a	−359	−358	−354	−358
b	−54	−60	−62	−66
c	−63	−71	−72	−72

Charge density, σ (e/A), $A = 1$ Å^2
a 0.000; b −0.010; c −0.018
d −0.020; e −0.022; f −0.030

We can clearly notice in Table 1 a decrease of Flory's ratio when the molecule is near the charged plane. The present results show also that for a given position, D, of the molecular model with respect to the plane, a decrease of the absolute value of the charge density leads to the folding of the chain (decrease of Flory's ratio). For instance, for a position $D = 6$ Å, with $\sigma = -0.03$ e/A or $\sigma = 0.01$ e/A, we find $C_n = 1.54$ and $C_n = 0.87$, respectively.

This effect may also be noticed with the distribution functions $w(r)$ of end-to-end distance of the chain which present a maximum around $r = 5$ Å and $r = 10$ Å respectively with $\sigma = -0.01$ and -0.03 (see Fig. 1a). Moreover, the following example shows that the extension of the chain is larger when the plane is more charged.

The relative extension of the molecular chain for a given position D and for two different charge densities σ_1 and σ_2 can be defined by:

$$EX = C_n(\sigma_2)/C_n(\sigma_1)$$

where $C_n(\sigma_1)$ and $C_n(\sigma_2)$ are Flory's ratio corresponding to σ_1 and σ_2, respectively. For instance, we have (Table 1) $C_n(0.00) = 0.78$ and $C_n(-0.03) = 1.54$ and thus $EX = 2$ for $D = 6$ Å.

Values of the average energy for very low charge densities (given in Table 1) show that the molecule tends to remain close to the plane. But it can be noticed that the molecular conformation of lowest average energy is situated at increasing distances from the plane as soon as the charge density is increased from a value near to -0.02 e/A.

As the interaction energy of the charged plane with the molecule is essentially electrostatic, values given to partial atomic charges are therefore very important for the behaviour of the molecule. One has to verify if results presently obtained are directly related to the choice of a set of charges or if it is a general phenomenon. Consequently calculations have been performed with another set of partial atomic charges — the one proposed by Weiner et al. [21].

Results obtained with this last set of charges (Table 2) show that the values of Flory's ratio, corresponding to different distances D of molecule to the plane, are practically equal to those obtained with the partial atomic charges

Table 2

Mean energy E, Flory's ratio of enkephalin as a function of the distance D to the plane. Results obtained using the partial charges given in Weiner et al. [21]

Conformation	D(Å) 6	8	10	12
Mean energy, E (kcal/mol)				
a	−6.85	−6.76	−6.48	−6.25
b	−8.19	−7.42	−7.87	−7.47
c	−9.01	−8.94	−9.27	−9.45
d	−9.80	−10.88	−11.41	−11.43
Flory ratio, C_n				
a	0.90	1.14	1.23	1.41
b	1.70	1.75	2.09	2.23
c	1.37	2.18	2.41	2.50
d	1.56	2.48	2.61	2.78

charge density, σ (e/A)
a −0.010 c −0.024
b −0.018 d −0.030

given in Momany et al. [14]. For instance, at $D = 12$ Å with the charge density -0.01 e/A, Flory's ratio, C_n, is now equal to 1.41 while it was equal to 1.52 previously. Moreover, in the vicinity of the charged wall ($D = 6$ Å), with the same charge density, C_n is now equal to 0.90 instead of 0.87 obtained before.

We can also note that the distance D between the molecule and the plane corresponding to the lowest conformational energy depends, as previously, on the charge density σ. For example, with $\sigma = -0.01$ e/A, the lowest molecular energy corresponds to $D = 6$ Å and the energy minimum is obtained for a distance D larger than 12 Å when the charge density is equal to -0.03 e/A. This result is equivalent to that obtained with the other set of partial charges.

We do not present the distribution functions of the end-to-end distance for these last calculations because the corresponding curves present the same behaviour as that obtained when using the charges given in Momany et al. [14]. Let us only note that when $D = 6$ Å (with $\sigma = 0.01$ e/A), the maxima of distribution functions are situated near 5 Å and 6 Å, respectively, for the two sets of partial atomic charges. For $D = 10$ Å, with $\sigma = -0.03$ e/A, the maxima are at $r = 12$ Å with the charges of Momany et al. and at $r = 13$ Å with those of Weiner et al. [21]. Therefore, we can conclude that the molecular conformation is not very dependent on the precise values of the partial atomic charges. However, note that the molecular model presently used is zwitterionic and the contribution of the charged terminal groups to the electrostatic energy is of main importance.

3.2 Orientation effect

Several studies [22–24] have shown that hydrophilic–hydrophobic interfaces have an orientation effect on molecules placed in their neighbourhood. In the present work, results show that the molecule remains parallel to the plane as long as it is not charged; this orientation effect is only due to image interactions. However, for charge densities different from zero, an other orientation effect appears. Indeed, when the molecule moves away from the plane, it tends to be perpendicular (see Table 1) and this effect becomes more important when the charge density of the plane is increased.

4. Discussion

Monte Carlo calculations were performed in order to determine the conformational behaviour of an enkephalin molecular model placed in the vicinity of a charged plane separating two different media with dielectric constants respectively equal to 3.5 and 78 (water). The molecule is placed in the "water" side of the plane and the charged plane can be considered as a model of a cellular membrane surface [5,25]. The present simulation shows that effects of the image potentials and of the charged plane play an important role on the conformation and orientation adopted by the enkephalin backbone. The importance of electrostatic interactions between polyelectrolytes and a charged wall has already been recognized [9,19]. In accordance with these studies, it has already been noted [22,23] that before any interaction of the receivers with the message molecule, this last one is likely to be oriented by the membrane and takes a conformation which favours this interaction.

Presently, the peaks of distribution functions of the chain end-to-end distance, determined for different positions of the molecule with respect to the plane, are indeed different depending on the relative position to the plane. They are situated around 5 and 12 Å when the molecule is in the neighbourhood and far from the plane, respectively. Accordingly, the present results also show that Flory's ratio decreases when the molecule gets closer to the plane. These two observations clearly demonstrate that the molecule adopts folded conformations in the neighborhood of the wall and stretched ones far from it. Moreover, we noted that the folding of the molecule and the orientation effect depend on the value of the charge density of the plane.

Using high resolution ^{1}H and ^{13}C NMR spectroscopy, Deber and Behnam (26) have proposed a model for the encounter of enkephalin with a phospholipid membrane. These authors have shown that the molecule adopts a folded structure when it is in contact with the membrane. In the aqueous medium extended conformations are adopted. The present study gives the same general features for the behaviour of enkephalin near a charged surface.

References

1 F. Akoum and O. Parodi, J. Phys. (Paris) 46 (1985) 1675.

2 D.A. Hoagland, Macromolecules 23 (1990) 2781.

3 I.S. Graham and A. Georgallas, M.J. Zuckermann, J. Chem. Phys. 85 (1986) 10.

4 R.M. Friedenberg, The electrostatics of biological cell membranes. Vol. 8, eds. A. Neuberger and E.L. Tatum (North-Holland, Amsterdam, 1967).

5 T.Y. Tsong and R. D. Astumian, Progr. Biophys. Mol. Biol. 50 (1987) 1.

6 A. Kepes, Aspects moléculaires des fonctions membranaires (Masson, Paris, 1978).

7 P.W. Schiller, Specialist periodical reports amino-acids, peptides and proteins, Vol. 11, ed. R.C. Scheppard (Royal Society of Cambridge, London, 1981).

8 A. Yethiraj and C.K . Hall, Macromolecules 23 (1990) 1865.

9 S.K. Kumar, M. Vacatello and D.Y. Yoon, J. Chem. Phys. 89 (1988) 8.

10 H. Eyring, Phys. Rev. 39 (1932) 746.

11 J. Hermans and D. Ferro, Biopolymers 10 (1971) 1121.

12 S. Premilat and J. Hermans, J. Chem. Phys. 59 (1973) 2602.

13 S. Premilat and B. Maigret, J. Chem. Phys. 66 (1977) 3418.

14 F.A. Momany, R.F. McGuire, A.W. Burgess and H.A. Scheraga, J. Phys. Chem. 79 (1975) 2361.

15 S. Premilat, J. Chem. Phys. 88 (5) (1988) 3385.
S. Premilat, J. Chem. Phys. 90 (9) (1989) 5128.

16 E. Durand, Electrostatique et Magnétostatique (Masson, Paris, 1953).

17 L. Landau and E. Lifchitz, Electrodynamique des milieux continus. (Mir, Moscow, 1969).

18 C.H. Hodges and H.J. Stot, Solid State Commun. 12 (1973) 1153.

19 G. Aloisi, M.L. Foresti and R. Guidelli, J. Chem. Phys. (9) (1989) 91.

20 K.V. Mardia, Statistics of Directional Data (Academic Press, New York, NY, 1972).

21 S.J. Weiner, P.A. Kollman, D.A. Case, U. Chandra Singh, C. Ghio, G. Alagona, S. Profeta Jr. and P. Weiner, J. Am. Chem. Soc. 106 (1984) 765.

22 R. Schwyzer, Biochemistry 25 (1986) 4281.

23 D.F. Sargent, J.W. Bean, H.W. Kosterlitz and R. Schwyzer, Biochemistry, 27 (14) (1988) 4974.

24 R. Schwyzer, EMBO J. 6 (8) (1987) 2255.

25 S.J. Singer and G.L. Nicolson, Sciences, 175 (1972) 720.

26 C.W. Deber and B.A. Behnam, Biopolymers 24 (1985) 105.