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Interaction of Na^+ Ion With the Solvated Gramicidin A Transmembrane Channel

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A 6-12-1 atom-atom pair potential for the interaction of a Na^+ ion with gramicidin A (GA) has been derived from *ab initio* SCF calculations on the intermolecular interaction energies between one Na^+ ion and GA molecular fragments. This potential has been used to obtain iso-energy maps, which in turn provide an energy profile of the Na^+ ion in the GA channel. We have applied this potential in Monte Carlo simulations in order to obtain i) the number of water molecules which can be placed inside the GA channel and ii) the hydration structures of the GA channel in the presence of one Na^+ ion.

INTRODUCTION

The microscopic mechanisms of transmembrane channels have been the subject of intensive investigations in recent years. Since gramicidin A (GA) ion channels are common in biological mechanisms, much effort has been devoted to determining the structure of GA, its ion transport mechanism and its selectivity by both experimental and theoretical approaches. For recent experimental reviews, see Urry[1,2], Ovchinnikov[3,4], Eisenman and Horn[5], and Anderson[6]. The primary structure of GA was determined by Sarges and Witkop[7] to be HCO — L Val[1] — Gly[2] — L Ala[3] — D Leu[4] — L Ala[5] — — D Val[6] — L Val[7] — D Val[8] — L Trp[9] — D Leu[10] — L Trp[11] — D Lue[12] — L Trp[13] — D Leu[14] — L Trp[15] — $NHCH_2CH_2OH$. Although the relevance of the crystal structures to the conformation of GA in membranes is uncertain due to the variety of conformations available to GA in various solvents[8–10], experiments

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strongly suggest a left handed β-helix of 6.3 peptide units per turn[11], with alternating D and L amino acids.

There have also been uncertainties in the number of water molecules which can be placed inside the GA channel. From osmotic and diffusional experiments, it appears that the channel holds a single file of 5—6 water molecules[12], while the electronic experiments of Rosenberg[13] suggest 7—9 water molecules and those of Levitt[14,15], 12 water molecules.

Models based on NMR chemical shifts of ion induced carbonyl carbon-13[16-17] and low resolution X-ray study[18] suggest that ion binding sites exist close to the mouth of the pore. By applying Eyring's rate theory[19-21] to the conductance measurements, experimental studies have estimated the activation barriers to ion transport through GA to be about 20—30 kJ/mol.[22-24] However, the applicability of an Eyring rate theory for GA systems have been questioned.[25,26]

GA is uniquely suited to theoretical studies of the underlying molecular basis for ion transport due to its relatively simple and well defined structure and to the wealth of experimental data. Several conformational studies investigating the local minima of the GA structure in the channel have been reported.[27-32] However, these energetic studies were performed with only selected torsional degrees of freedom of GA in the absence of ions and water molecules. Although other electrostatic calculations[33-35] have reported the activation barriers of 20—30 kJ/mol, these models (treating the membrane as a low dielectric continuous medium) are probably too simple to be reliable. A few molecular dynamics (MD) studies on a simplified GA with ion model have been reported[36-39], but the simulations imposed several restrictions such as neglecting water molecules and constraining the ion to move only along the channel axis.

Recently, Wilson and his collaborators[40] have used MD techniques to study the interaction of GA with cations and a few water molecules. Their model used vacuum instead of bulk water outside the channel, and thus it was not feasible to obtain energy profiles owing to the neglect of solvation contributions from bulk water. Furthermore, since the MD techniques have serious fluctuation in temperature for such a small number of water molecules and an ion, the static properties for given two different systems cannot be easily compared. This problem can be complemented by Monte Carlo (MC) calculations. Also of concern is the uncertainties in the potentials which, as pointed out by Wilson *et al*,. constitute one of the shortcomings in the study of ion transport through GA. Other recent theoretical studies of energy profiles of Na^+ interacting with GA have been reported by Pullman and Etchebest.[41-42] One should note that in computing the binding energy of Na^+ and GA they have chosen the parameters so as to reproduce the results of *ab initio* calculations on small systems.

We have previously reported[43] the *ab initio* interaction potential energy of H_2O with a GA channel, modeled according to Urry's atomic coordinates.[27] In this paper, we extend this work by examining the *ab initio* interaction energies of Na^+ with GA, and analyzing the resulting iso-energy maps in order to understand the niteractions of one Na^+ ion within the channel. In addition, we report preliminary MC simulation results to investigate 1)

the number of molecules which can be placed inside the GA channel and 2) the structure of the water molecules inside the channel in the presence of one Na^+ ion.

INTERACTION ENERGY OF THE Na^+ ION WITH A GA CHANNEL

The interaction energy between GA and a Na^+ ion can be written approximately as the sum of the atom-atom pair interactions. Using a minimal basis set (consisting of 4s-type gaussian functions for hydrogen atoms and 7s/3p-type gaussian functions for non-hydrogen atoms)[44-46], we have calculated the *ab initio* SCF-LCAO-MO interaction energies of a Na^+ ion with seven fragments of a GA channel, formed by a piece of polypeptide backbone connected to different amino acids, at more than 1300 different configurations (in fact, more than 3500 different configurations by the interpolation technique). In these calculations the superposition error[47-49] was not considered, after having verified that in our specific example this error was negligible.

The calculated *ab initio* interaction energies were then fitted to an analytical 6-12-1 potential energy function of the form,

$$E = \sum_j \left[\frac{-A(j,a)}{r(j)^6} + \frac{B(j,a)}{r(j)^{12}} + \frac{C(j,a)\ q(j)}{r(j)} \right]$$

where j designates an atom of GA and $r(j)$ is the distance from the Na^+ ion (with a charge equal to 1) the j-th atom with atomic charge $q(j)$ in a considered molecule. The parameters A, B and C of the potential function are characterized by two indices, j and a; the index a denotes the »class« for the atom j. A »class« is characterized by 1) the electronic environment of the j-th atom, 2) the atomic charges[50], and 3) the molecular orbital valence state (MOVS) energies.[51] Since the 6-12-1 atom-atom pair potentials using the class characterization method have been applied to many biological systems in computer simulations with good agreement with experiment or even with predictions that are later verified by experiment,[52-59] we report in Table I the A, B and C coefficients of the 6-12-1 analytic potential energy function for each class. For the details of the characterization of the class in the table, refer to Table I and Figures 2 and 3 in our recent paper[60] on the interactions of K^+ with GA.

The fitting of the *ab initio* interaction energies to the above analytical atom-atom pair potentials was carried out to a mean standard deviation of 2.5 kcal/mol. The overall quality of the fit is shown by the standard plot (fitted/*ab initio*) given in Figure 1. Note that the classes # 2, 5 and 16 in Table I were used only for the fragments (frag.) of GA, but not for the GA channel itself. These classes arise because it was necessary to attach additional atoms onto the GA fragments in order to properly simulate the chemical environment of the atoms in the GA channel.

In Figure 2 iso-energy maps are reported for the seven different molecular components of GA, the L Ala, L Val, D Val, D Leu, L Trp residues, the ethanolamine HOC—NH—CH_2 —CO—NH—CH_2 —CH_2OH) tail and the two central formyl heads. For each molecular component two plots are given: first, a two dimensional plot which contains an ORTEP projection

TABLE I

*Description of Classes Including Coefficients**

ATOM	CLASS	A	B	C	COMMENT
O	1	.7357E+01	.2011E+05	.1073E+01	O of =C=O
	2	.3493E+03	.2865E+05	.9021E+00	O of =C=O (frag.)
	3	.6916E+01	.2405E+05	.9025E+00	O of − OH
N	4	.6246E+01	.2845E+06	.9094E+00	N of − (NH) −
	5	.5461E+03	.3816E+05	.9624E+00	N of − (NH) − (frag.)
	6	.6753E+01	.6347E+05	.9086E+00	N of L.TRP
C	7	.7012E+01	.3054E+06	.9092E+00	C of − CH_3
	8	.6436E+01	.1844E+06	.9074E+00	C of L.Trp ring
	9	.6101E+01	.1332E+06	.9004E+00	C of L.Trp ring
	10	.6257E+01	.8723E+06	.9011E+00	C of − (C_αHRes.) −
	11	.6035E+01	.1188E+07	.9003E+00	C of − CHR_2
	12	.6852E+01	.8271E+06	.9754E+00	C of − CH_2OH of Tail
	13	.6311E+01	.4601E+06	.1094E+01	C of − ($C_\beta H_2$) − of L.Trp
	14	.7381E+01	.3000E+03	.9515E+00	C of − (CH_2) − of Formyl
	15	.6089E+01	.8831E+05	.9817E+00	C of − (CH_2) −
	16	.2109E+04	.5472E+06	.9771E+00	C of − (CH_2) − (frag.)
	17	− .2240E+04	.3000E+03	.9602E+00	C of =C=O,or L.Trp
	18	− .2400E+04	.3001E+03	.9094E+00	C of =CHO
	19	− .2329E+04	.2296E+06	.9100E+00	C of =C=O
H	20	.4485E+03	.2636E+05	.1086E+01	H connected to O,N
	21	.7066E+01	.1904E+04	.9099E+00	H connected to C_α
	22	.4227E+03	.1899E+05	.9099E+00	H connected to C
	23	.1129E+04	.5872E+05	.9090E+00	Aromatic H of L.Trp

* The coefficients are given so that the interaction energy and distances can be expressed in kcal/mol and Å, respectively (see the text).

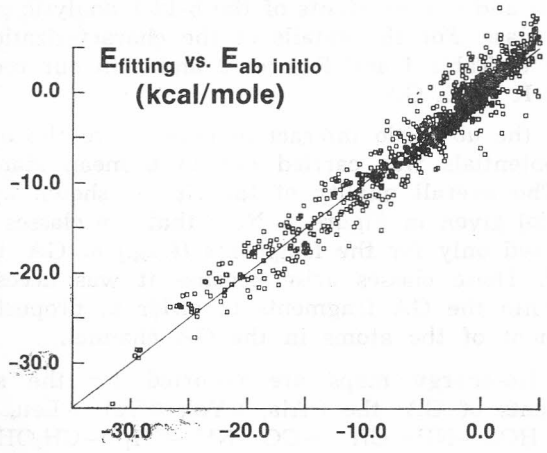

Figure 1. Plot of deviation between fitted energies and *ab initio* energies for the interaction of Na^+ with GA.

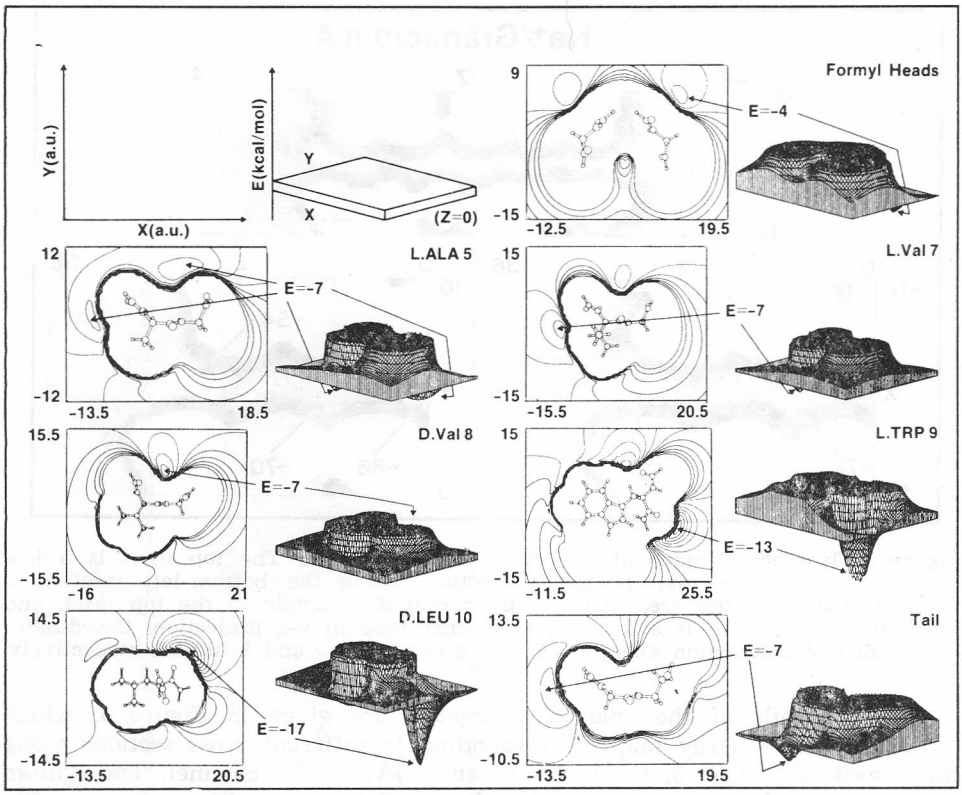

Figure 2. Iso-energy maps of the different GA residues including the formyl heads and ethanolamine tail interacting with one Na^+ ion. Coordinates (X, Y) and interaction energies (E) are given in a. u. and kcal/mol, respectively.

of the amino acid into the selected plane; and second, a three-dimensional diagram which explicitly shows both the attractive site minima and the repulsive regions (which have the appearance of a »mesa« because the repulsive energies have been cut off at 6 kcal/mol). The contour to contour interval in both plots is 2 kcal/mol. From these figures, one can notice that the D Leu and L Trp residues show strong interactions with the Na^+ ion.

After the interaction potential energy functions have been obtained for each component, the interaction energy of the Na^+ ion with the entire channel can be easily calculated. Figure 3 shows two dimensional iso-energy contour maps for a Na^+ ion interacting with the GA channel. A low resolution iso-energy map (x—z projection with a selected grid mesh of 1 a. u.) of the entire channel is given, along with two detailed views (with a grid mesh of 0.5 a. u.). The detailed views encompass the area enclosed within the dotted rectangle in the low resolution map. The left inset is the x—z projection, while the one on the the right is the y—z projection. From the detailed iso-energy contour maps the three dimensional shape of the channel can be appreciated by rotating the cross section plane by 90%. From this, helical characteristics of the channel can be noticed.

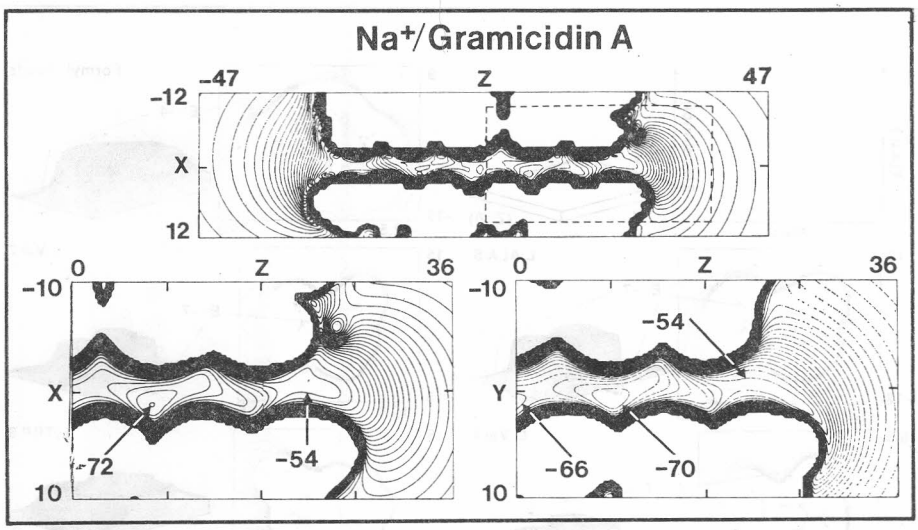

Figure 3. Iso-energy maps of Na^+ interacting with GA. The top inset is a low resolution iso-energy map in x-z projection, while the bottom-left inset is a detailed figure for the area enclosed by a dotted rectangle in the top inset, and the bottom-right inset is a detailed iso-energy map in y-z projection. Coordinates (*X*, *Y*, *Z*) and interaction energies (*E*) are given in a. u. and kcal/mol, respectively.

More details of the channel energetics are given in Figure 4, which shows eight iso-energy maps corresponding to different cross sections along the z axis ($Z = 0$, 4, 5, 8, 11, 12, 13 and 14Å) of the channel. The bottom graph reports the energy profile for the Na^+/GA system. The energy profile has been determined by finding the lowest energy in x-y cross sections generated at 0.5 a. u. intervals along the z axis. The positions a, b, c and d in the energy profiles correspond to the same positions given in the iso--energy maps. The cross section of the channel for the Na^+/GA system is *not circular,* but is rather irregular with shapes which gradually evolve and change along the z axis. The most attractive position for either water or Na^+ in each x—y cross section is *not exactly at the center, but close to it.* At $Z \leq 12$ Å, the cross section suddenly becomes large. This suggests that a narrow »channel« extends until $Z = 11$ or 12 Å, and thereafter, the channel becomes like an »estuary« which extends to about $Z = 15$ or 16Å. However, the attraction of GA with Na^+ extends much further; therefore, one cannot properly talk of ion-solvation until *Z* attains a rather large value (more than $\pm$ 20 Å). The energy profiles of Na^+/GA system show stronger interaction inside the channel than outside.

Cylindrical iso-energy maps for Na^+/GA are given in Figure 5. These maps have been obtained by selecting cylinders with a radius of either 2.0 or 2.5 a. u., and then unfolding the cylinders into the plane. For Na^+/GA the hard core region becomes conspicuous ta $R = 2.5$ a. u. The hard core region also shows the helical feature of the GA channel interacting with the Na^+ ion.

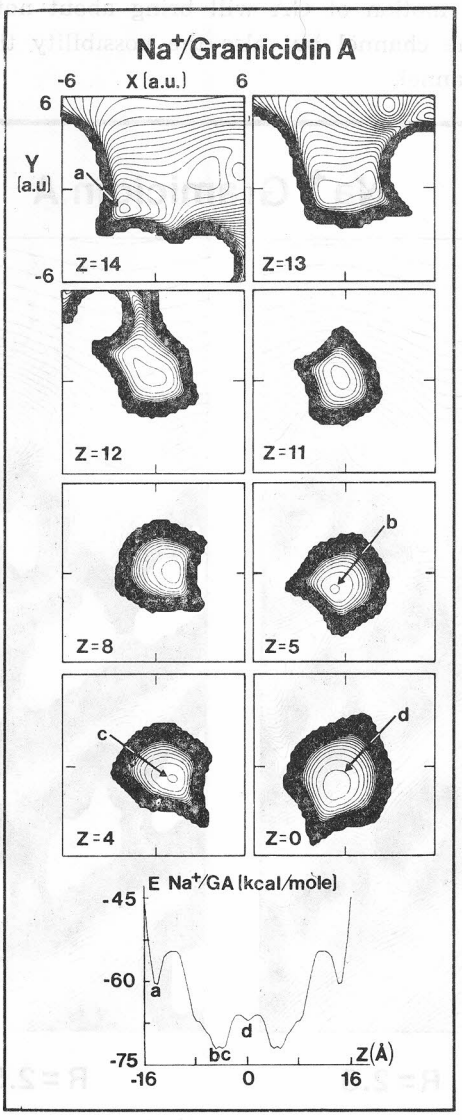

Figure 4. Iso-energy maps of Na^+ interacting with GA in x-y projection along Z axis (for $Z = 0$, 4, 5, 8, 11, 12, 13 and 14 Å), and the energy profile of Na^+/GA system. Z coordinates are in Å, while X and Y coordinates in a. u. The ion is not constrained to remain on the channel axis, but allowed to reach its energetically preferred position along the x and y axis on the plane of the given Z value.

By combining the information of Figures 3, 4 and 5, it seems clear that the channel is much more like *a spiral than a cylinder* due to the helical nature of GA. In addition, the channel is relatively very narrow with hard core inward protrusions. Any loosening or tightening of the spiral due to

the intra-molecular motion of GA will bring about not only a lengthening or shortening of the channel but also the possibility that these protrusions will occlude the channel.

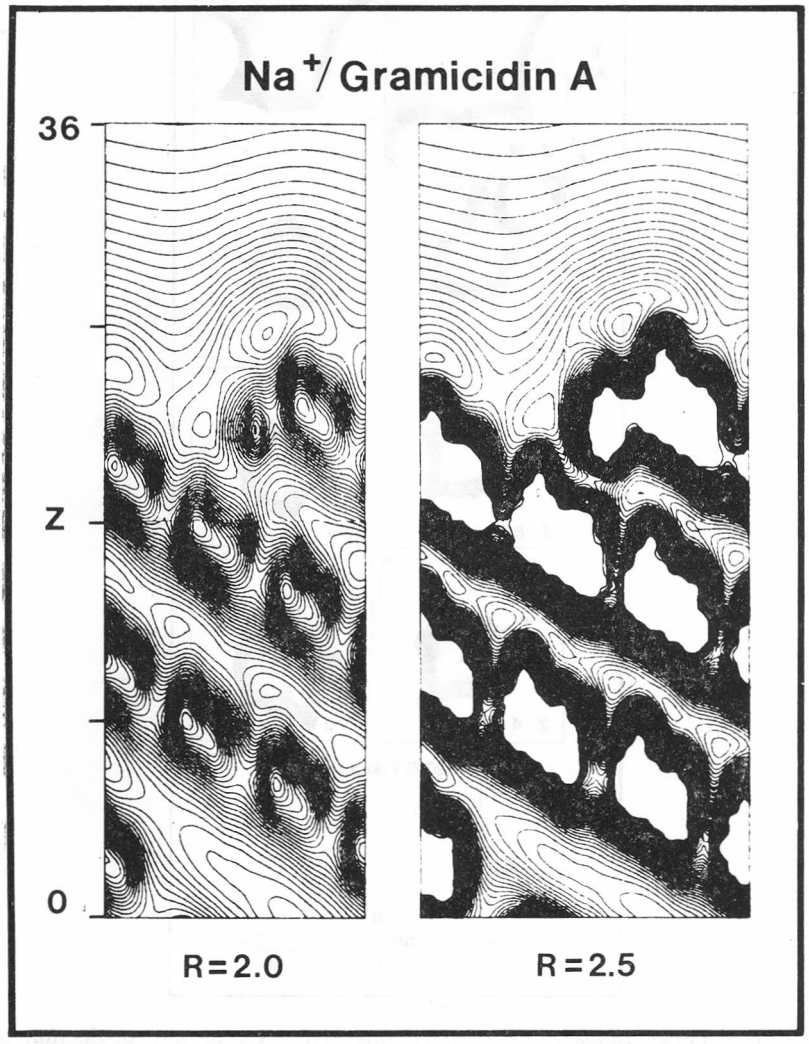

Figure 5. Cylindrical iso-energy maps flattened out for Na^+/GA in the case that the cylinder's radii are $R = 2.0$ and $R = 2.5$ a. u., respectively. Z coordinates are given in a. u.

MONTE CARLO SIMULATIONS

In order to obtain a more realistic representation of the structure and interaction of many water molecules with the GA channel in the presence of one Na^+ ion, we performed Metropolis type of Monte Carlo simulations.[61-62]

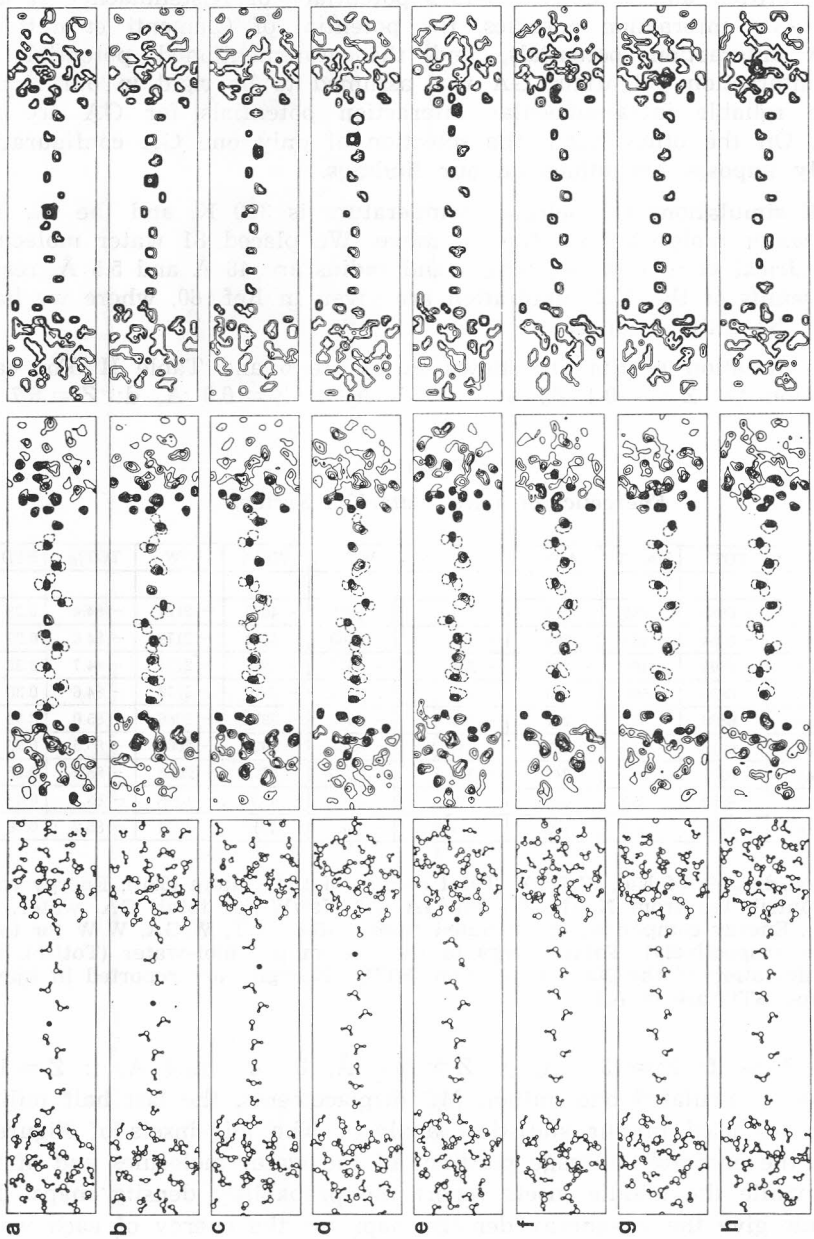

Figure 6. Ensemble average positions (1st column), probability density maps (2nd column) and iso-energy density maps (3rd column) of water molecules obtained by MC simulations for the cases that the average Z position of Na^+ is a) —0.1, b) 3.5, c) 6.0, d) 8.7, e) 11.8, f) 13.3, g) 14.0 and h) 15.4 Å, respectively.

Using this method, we can attempt to understand the energy profiles of a $Na^+/H_2O/GA$ system and the effect of the Na^+ ion on the water conformations. The potentials used were MCY potential[63] for water-water interaction energies, the refitted and simplified 6-12-1 potential[43] of Kistenmacher *et al.*[64] for water-Na^+ interaction energies, the potential of Clementi *et al.*[43] for water-GA interaction potentials, and the aforementioned potential for Na^+-GA interaction potentials. GA was assumed to be rigid in our model, since the reliable intra-molecular interaction potentials for GA are not available. On the other hand, the selection of only one GA configuration necessarily imposes limitations on our findings.

In all simulations the selected temperature is 300 K, and the Na^+ ion and the water molecules are free to move. We placed 81 water molecules in a cylindrical volume whose length and radius are 48 Å and 5.5 Å, respectively. Details of the MC simultation are given in Ref. 60, where we have considered K^+ rather than Na^+.

The simulation results are shown in Figure 6 and Table II. For each configuration (a: $Z = -0.1$ Å, b: $Z = 3.5$ Å, c: $Z = 6.0$ Å, d: $Z = 8.7$ Å,

TABLE II

*Energetics of a Na^+/Water/GA System**

	Z(NA^+)	TOT	NA^+/T	NA^+/GA	1/2 Na^+/W	W/T	W/GA	W/W	TOT/#	STD
a	− 0.1	− 6835	− 485	− 278	− 207	− 6350	− 4022	− 2121	− 84.4	0.38
b	3.5	− 6854	− 494	− 294	− 200	− 6360	− 3981	− 2179	− 84.6	0.27
c	6.0	− 6863	− 488	− 287	− 201	− 6375	− 3982	− 2191	− 84.7	0.35
d	8.7	− 6855	− 500	− 270	− 230	− 6355	− 3946	− 2178	− 84.6	0.30
e	11.8	− 6886	− 522	− 217	− 305	− 6364	− 3973	− 2086	− 85.0	0.30
f	13.3	− 6923	− 557	− 227	− 331	− 6366	− 3973	− 2063	− 85.5	0.29
g	14.0	− 6941	− 591	− 247	− 343	− 6350	− 3971	− 2036	− 85.7	0.25
h	15.4	− 6953	− 553	− 165	− 388	− 6400	− 4034	− 1978	− 85.8	0.43
i	16.6	− 6902	− 540	− 129	− 411	− 6362	− 4020	− 1932	− 85.2	0.56

* Z coordinates of Na^+, (Z(Na^+)), Total energy of the system (Tot), Energy components contributed from Na^+(Na^+/T, Na^+/GA, 1/2 Na^+/W for total, GA, water, respectively), Energy components contributed from water (W/T, W/GA, W/W for total, GA, water, respectively), Total energy of the system per mol-water (Tot/#), and Standard deviation of the Na^+ ion position (STD). (Energies are reported in kjoule, while Z and STD are in Å.).

e: $Z = 11.8$ Å, f: $Z = 13.3$ Å, g: $Z = 14.0$ Å, h: $Z = 15.4$ Å, i: $Z = 16.6$ Å), we have calculated one million MC displacements, the last half million of which are used in our statistical analyses. The left insets of Figure 6 represent the ensemble average positions of the water molecules and of the Na^+ ion, while the middle insets report the probability density maps. The right insets give the iso-energy density maps for the energy of each water molecule or ion at a given position interacting with water molecules, an ion and the gramicidin. The Na^+ ion can be easily distinguished as a filled circle (left insets), or from the conspicuously dark region (right insets).

From Figure 6 one can notice that, in general, *nine water molecules* form a well-bound filament within the channel. This number is intermediate between the two experimental values in Refs. 12—15. These nine water molecules hydrate the nearest neighboring atoms: either the atoms of other water molecules, an ion, or a carbonyl oxygen of GA. (However, also notice that sometimes one or two water molecules inside the channel are not hydrogen bonded to its neighboring water molecule). On the other hand, as can be inferred from the probability density maps, the water molecules at the two extremities of the cylinder display somewhat bulk water properties.

In Table II we report the average Z position of the Na^+ ion, the total energy of the system (Tot) (for 81 water molecules, one Na^+ ion and the GA channel), the total interaction energy for a Na^+ ion (Na^+/T), the interaction energy of a Na^+ ion with GA (Na^+/GA) and with water (Na^+/W), the total interaction energy of water (W/T), the interaction energy of water gy between Na^+ and water has been reported as 1/2 Na^+/W. From the STD of the ion coordinate. Since we define that $Na^+/T = Na^+/GA + 1/2\ Na^+/W$, $W/T = W/W + W/GA + 1/2\ W/Na^+$ and $Na^+/W = W/Na^+$, the interaction energy between Na^+ and water has been reported as 1/2 $Na/^+/W$. From the STD we note that the ion placed outside the channel is more mobile than the one placed inside the channel. It can also be noticed that the interaction energy of Na^+/GA is stronger inside the channel than outside the channel, while that of Na^+/W is just the opposite.

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SAŽETAK

Međudjelovanje Na^+ iona s transmembranskim tunelom solvatiziranog gramicidina A

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Razmatrana je interakcija iona Na^+ s gramicidinom A (GA) s pomoću atomskog potencijala 6-12-1, koji je generiran primjenom *ab initio* SCF postupka. Dobivene su iso-energijske krivulje koje određuju transport iona Na^+ kroz tunel GA. Broj molekula H_2O i hidratacijska struktura tunela GA određeni su primjenom metode Monte Carlo.