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The intrinsic molecular potential of glyceryl monooleate layers and its effect on the conformation and orientation of an inserted molecule: example of gramicidin A

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It is shown by explicit calculation that the distribution of the atomic charges in the constituent molecules of a lipid monolayer or bilayer of glyceryl monooleate creates an intrinsic potential difference between the head region and the hydrocarbon region which tends to repel positive charges towards the exterior and attract negative charges to the interior. The analogies and differences between a bilayer and a monolayer are analyzed. The possible consequences of the intrinsic potential gradient in a lipid layer on the preferred orientation and conformation of a polar neutral molecule are illustrated on the case of a gramicidin A monomer.

Introduction

One of the major reasons of the difficulties encountered by ions to cross artificial or biological membranes is the existence of an intrinsic potential difference between the external and internal faces of lipid monolayers of the order of a few hundreds of millivolts [1] which is commonly attributed to a dipole effect, resulting from the dipolar organization of molecules at the lipid/water interface [2–4]. Attempts at the calculation of this effect have, until now, been based on models using an array of surface dipoles appropriately oriented with their positive ends towards the lipid interior [3,4], an orientation chosen essentially on a phenomenological basis. Although the possible roles in this respect of the lipid head group and/or of the ester group linking the glycerol to the hydrocarbon chain have been invoked, no attempt has been made to calculate explicitely the effect of the atomic distribution of charges in the overall structure of the lipid molecules. It is this effect, which we call the 'intrinsic molecular potential' of the lipid layer, that we consider and characterize in the present paper. A procedure is developed for its calculation, which allows further the evaluation of its possible influence on the conformation and orientation of an inserted molecule.

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Standpoint and Methodology

The lipid chosen as an example is glyceryl monooleate,

$$CH_2OH-CHOH-CH_2-O-CO-(CH_2)_7-CH=CH-(CH_2)_7-CH_3,$$

commonly used to form black films for studies of membrane conductance (see for instance, Refs. 2, 5–9). It has the advantage to contain only one hydrocarbon chain and to possess the fundamental glycerol moiety without substituents or formal charges, so that any 'dipole potential' obtained will result from the intrinsic structural features of the neutral lipid skeleton. Furthermore, detailed theoretical studies of its packing properties have been carried out [10,11] which can be used as a basis to build a monolayer: it was found by energy optimization of glyceryl monooleate isolated and in packages of two to seven molecules, that the compounds arrange themselves in a parallel fashion, with the hydrocarbon chains adopting (Fig. 1) an angular conformation with a bend of 128° at the double bond separating the two hydrocarbon fragments on each side. The torsion angles in the fragments are *trans* except for the bonds adjacent to the double bond, which are 160°. The head parts of the molecules place themselves also in a parallel fashion, making an angle with the first hydrocarbon chain and their extreme oxygens tending to be in the same plane. Utilizing these results we have built our monolayer as a bidimensional hexagonal lattice where each molecule is placed as indicated in Figs. 2 and 3,

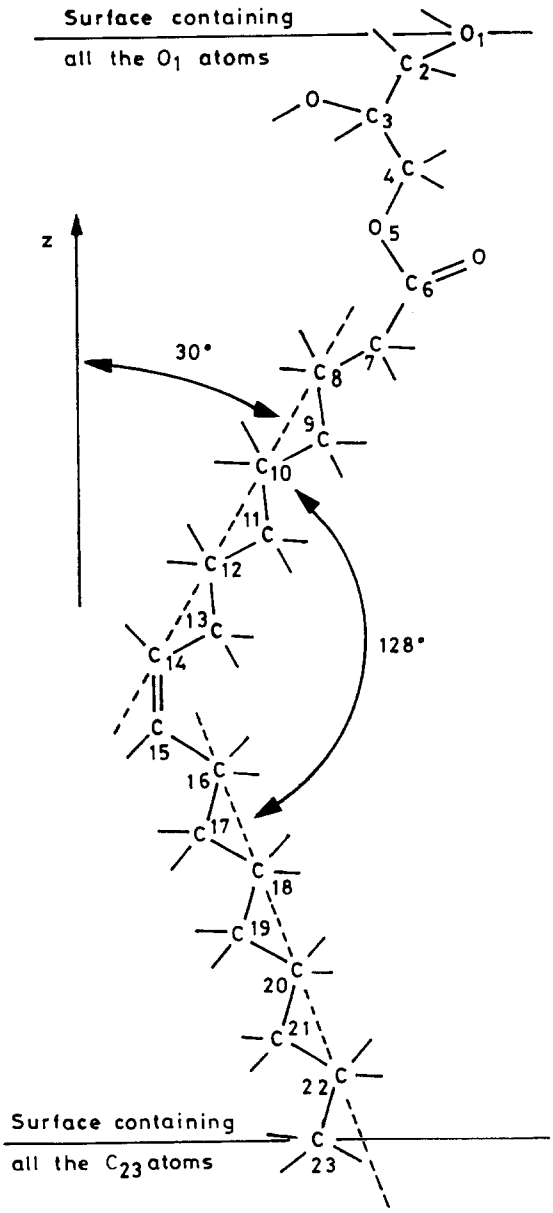

Fig. 1. The orientation and the conformation of the glyceryl monooleate molecule. Atom numbering as indicated. The end atoms O-1 of all the molecules in the layer lie in the same plane. The same is true for C-23. The Z axis is perpendicular to the surface layer.

with the lattice parameters $a = b = 5$ Å, $\gamma = 60°$, each point in Fig. 2 corresponding to one molecule. In this lattice, each molecule is in the same conformation and derives from any other by a simple translation. The conformation adopted can be considered as an idealization of the conformations observed in the bundles examined in Refs. 10 and 11 with the characteristics described above (Fig. 1). The conformations in the glycerol head are essentially extended and the torsion angle around the bond linking the ester carbonyl to the chain is 36°. The first and second part of the hydrocarbon chains make an angle of 30° and 22°, respectively, with the perpendicular to the surface of the layer.

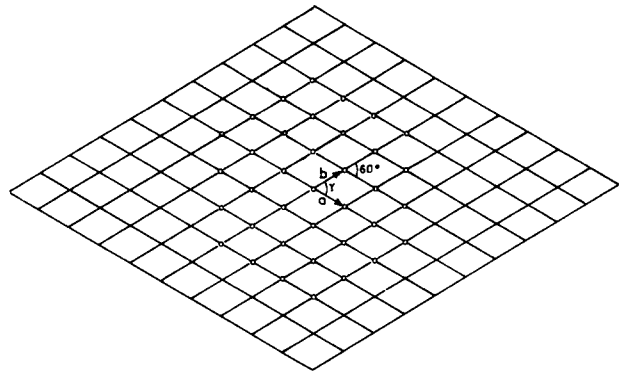

Fig. 2. The array of molecules seen from above the heads. The sites labelled with the small circles will be eliminated for inserting one gramicidin monomer (see text).

A large number (vide infra) of molecules will be considered to form the monolayer which thus presents the characteristics of Figs. 2 and 3.

The evaluation of the intrinsic potential due to this monolayer is done first by placing a point positive charge in a hole (Fig. 3) created in the center perpendicularly to its surface by eliminating the appropriate number of molecules of the lattice (Fig. 2) and computing the energy of interaction of the whole lattice with this charge.

The energy of interaction is calculated by a procedure developed in our laboratory [12–14] as a sum, over all the atoms of the system, of atom–atom interactions comprising electrostatic, polarization and repulsion/dispersion components (E_{elec}, E_{pol} and E_{LJ}). The electrostatic term [12] is calculated from atomic monopoles [14] obtained in such a way as to reproduce correctly the electrostatic properties of fundamental reference molecules; the polarization term [13] on each atom of one molecule is proportional to its polarizability [15] and to the square of the field created on it resulting from the monopoles of all the atoms of the other

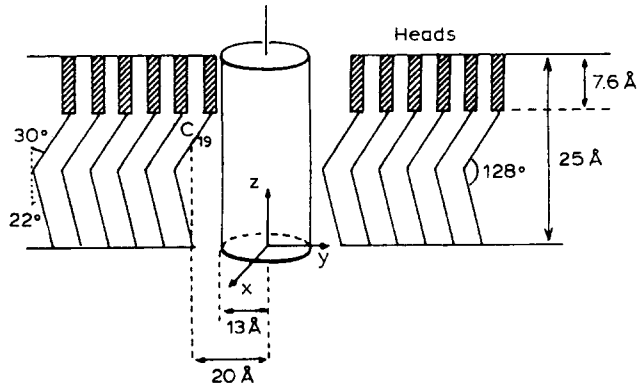

Fig. 3. The arrangement of molecules in a monolayer and the cylinder space created in the layer to introduce a gramicidin molecule and to scan the intrinsic potential distribution resulting from the surrounding lipids. The zero value of z is situated 2 Å below the plane containing the C-23 atoms.

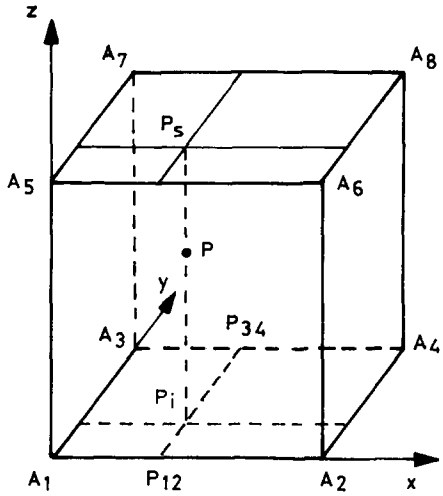

Fig. 4. The procedure of 'successive segmental interpolations' used to obtain E at point P (x, y, z) from the unit cube $A_1, A_2, \ldots, A_8$ with energy values $E_1, E_2 \ldots E_8$: $E_{12}(x, 0, 0)$ at P_{12} is first obtained by linear interpolation between E_1 and E_2; similarly $E_{34}(x, 1, 0)$ is obtained from E_3 and E_4; then $E_i(x, y, 0)$ at P_i from E_{12} and E_{34}. In the same way, $E_s(x, y, 1)$ at P_s is deduced from E_5, E_6, E_7, E_8 and finally $E(x, y, z)$ at P from E_i and E_s. The resulting distribution is continuous in all space since each cube joins with its neighbours without interruption.

molecules; the repulsion/dispersion term [12] is a Lennard-Jones potential appropriately parametrized [12,15, 16]. The test point charge carries a unit monopole and belongs to the class of a saturated carbon, a choice made for pratical reasons and which does not affect the conclusions.

In view of examining the possible effect of a monolayer upon an inserted molecule, the radius of the hole (Fig. 3) was chosen to be 20 Å so as to be able to include and let easily rotate a gramicidin A monomer in Urry's conformation [17,18], and the energy effect of the monolayer within the hole was scanned by calculating the interaction energy with a test charge placed at successive points spaced by 1 Å on a three-dimensional grid. The zone scanned in the hole is a cylinder of 13 Å radius and of 25 Å height (Fig. 3). Then in order to obtain a continuous distribution, interpolations are made for points interior to each (1 Å)^3 cube, as indicated in the caption of Fig. 4, by a successive segmental approach. The values resulting from this energy scanning are stored and then used as follows to calculate the interaction energy of the lipid monolayer with a molecule M placed anywhere in the cavity: for an atom of M placed at position r_i, carrying a monopole Q_i, the interaction energy with the monolayer (essentially electrostatic, vide infra), can be written $Q_i E(r_i)$, where $E(r_i)$ is the interaction for a unit charge. Thus the interaction energy of the lipids with the whole molecule M, E_{ML}, is obtained by summation of such terms over all its atoms at the appropriate positions. An adaptation of the CINFLEX program [12,19] used for the energy optimizations has been made to include the utilization of the stored values. When the molecule M is flexible, the total energy of the system includes its intramolecular energy E_M expressed as a sum of atom–atom electrostatic and Lennard-Jones interactions supplemented by a sum of torsion terms over the single bonds [12] and the energy minimization is carried out over the sum $E_M + E_{ML}$.

Results and Discussion

(a) The distribution of the atomic charges in glyceryl monooleate

It is instructive to examine first the distribution of the charges in the glyceryl monooleate molecule as obtained within the methodology of Ref. 14 (see section 2).

It is observed (Fig. 5) that the charge displacements in the glycerol and ester moieties are relatively large compared to those occurring in the hydrocarbon part of the molecule. Note, in particular, the strong polar character of the hydroxyl, ester and carbonyl bonds. The carbons of the glycerol skeleton and the hydrogens

TABLE I

The interaction energy and its components (kcal/mol) between the lipid monolayer and a point positive unit charge along the central axis of the hole (z defined as in Fig. 3)

For the correspondance between the z coordinate and the level of the backbone atoms in the membrane, see the upper scale in Fig. 7.

Z(Å)	E_{total}	E_{elec}	E_{LJ}	E_{pol}
0	22.6	24.7	−0.007	−2.06
1	22.4	24.6	−0.007	−2.16
2	21.9	24.2	−0.007	−2.26
3	21.3	23.7	−0.008	−2.35
4	20.7	23.1	−0.008	−2.44
5	20.0	22.5	−0.009	−2.52
6	19.1	21.7	−0.009	−2.60
7	18.2	20.8	−0.009	−2.66
8	17.1	19.8	−0.010	−2.72
9	15.9	18.7	−0.010	−2.76
10	14.6	17.4	−0.010	−2.80
11	13.1	16.0	−0.010	−2.82
12	11.5	14.4	−0.010	−2.83
13	9.7	12.6	−0.010	−2.84
14	7.8	10.7	−0.010	−2.83
15	5.8	8.6	−0.010	−2.81
16	3.6	6.4	−0.010	−2.79
17	1.3	4.1	−0.009	−2.75
18	−1.0	1.7	−0.009	−2.70
19	−3.4	−0.7	−0.009	−2.65
20	−5.8	−3.2	−0.008	−2.58
21	−8.1	−5.6	−0.008	−2.51
22	−10.4	−7.9	−0.008	−2.43
23	−12.6	−10.2	−0.007	−2.34
24	−14.6	−12.3	−0.007	−2.25
25	−16.5	−4.4	−0.006	−2.16
26	−18.3	−16.2	−0.006	−2.06

bound to them are weakly charged. In the chain part, all saturated carbons are negative while the carbons of the double bond are nearly neutral. The proximity of the double bond perturbs the saturated carbons closest to it, making them more negative. All hydrogen atoms are positively charged.

As a result of this distribution of atomic charges and of its geometry, the molecule possesses an intrinsic total dipole moment of 3.7 debye units, which is centered between C10 and C11, thus in the first part of the hydrocarbon region, and oriented with the positive end

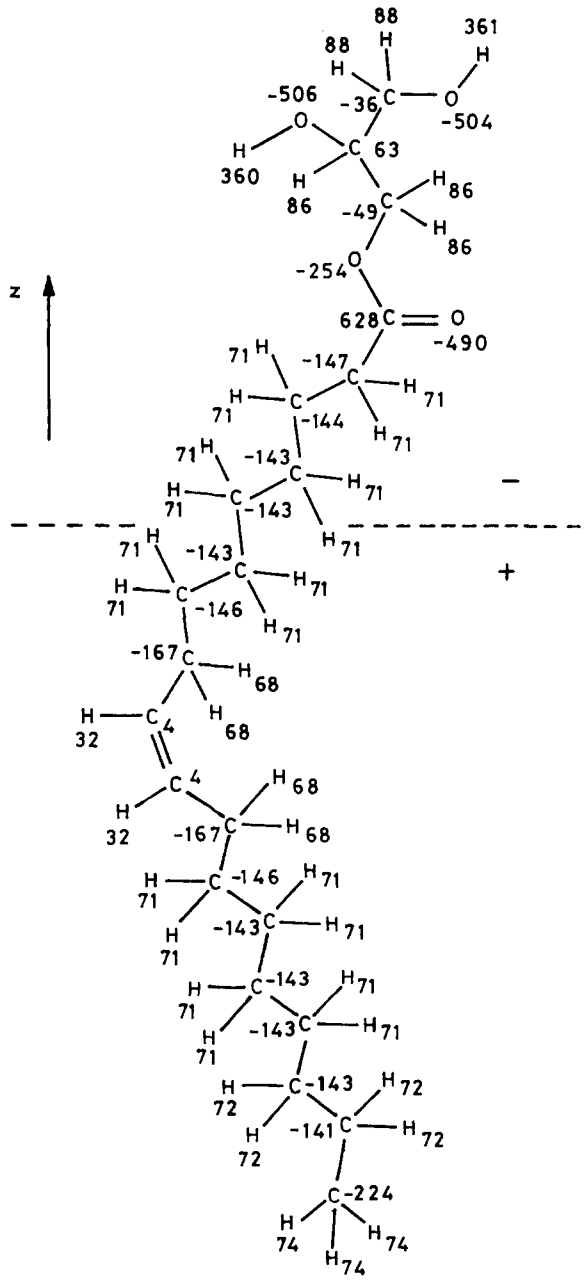

Fig. 5. The distribution of atomic net charges in the glyceryl monooleate molecule (Values in 10^{-3} electron units; ex: -504 is an excess of 0.504 e; 361 is a defect of 0.361 e).

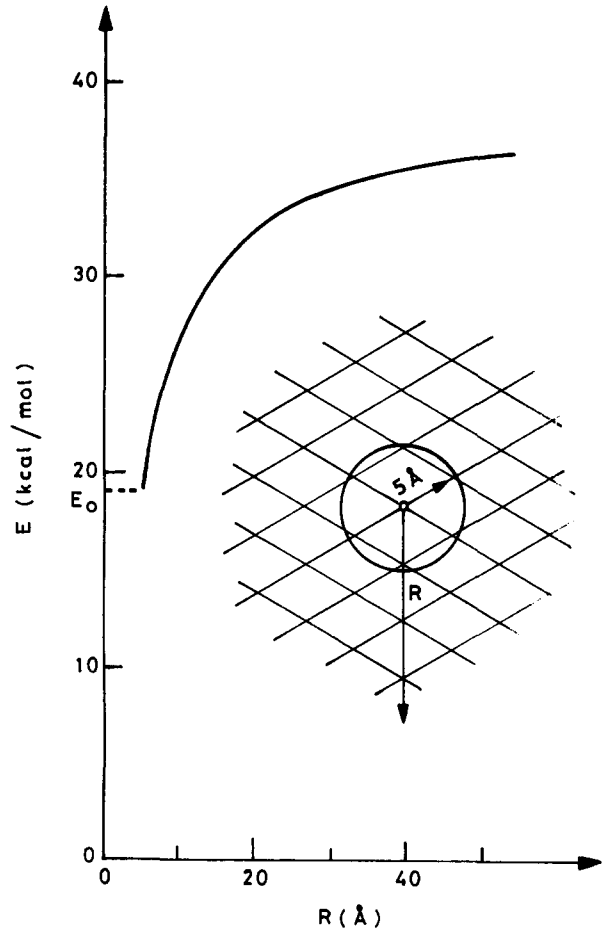

Fig. 6. The variation of the energy in the cavity at the height of C-10 according to the number of molecules included in the circle considered.

towards the chain extremity and the negative end towards the head (Fig. 5).

The atomic charges of Fig. 5 are used in the calculation of the intrinsic potential of an array of molecules in the following section.

(b) The intrinsic monolayer potential

Table I gives the values of the interaction energy of the monolayer with the test point positive charge placed at successive points on the Z axis of the hole of 20 Å radius defined in section 2, from the hydrocarbon end to the glycerol end. The external radius of the lattice used in the computation is 80 Å, enough to insure that the effect of adding more external lipids has reached saturation (Fig. 6 shows that this saturation effect on an internal charge is practically reached for $R > 50$ Å).

The values of Table I indicate that the interaction energy is negative (favorable) in the head region and becomes positive in the hydrocarbon region, a result of the strong dominance of the electrostatic component of the energy: the Lennard-Jones component is practically negligible owing to the large distances involved; the polarization term is small and nearly constant. Note

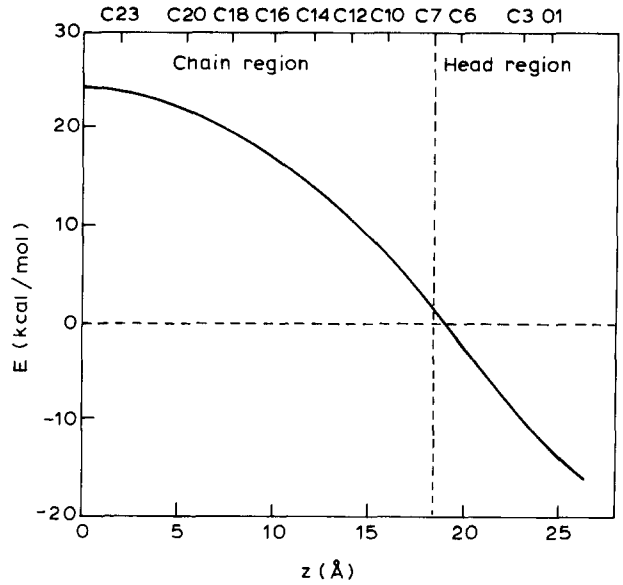

Fig. 7. Variation along the perpendicular to the surface of the interaction energy electrostatic component (see text) of a monolayer with a positive unit charge. The depth of the backbone atoms in the membrane is indicated on the upper scale.

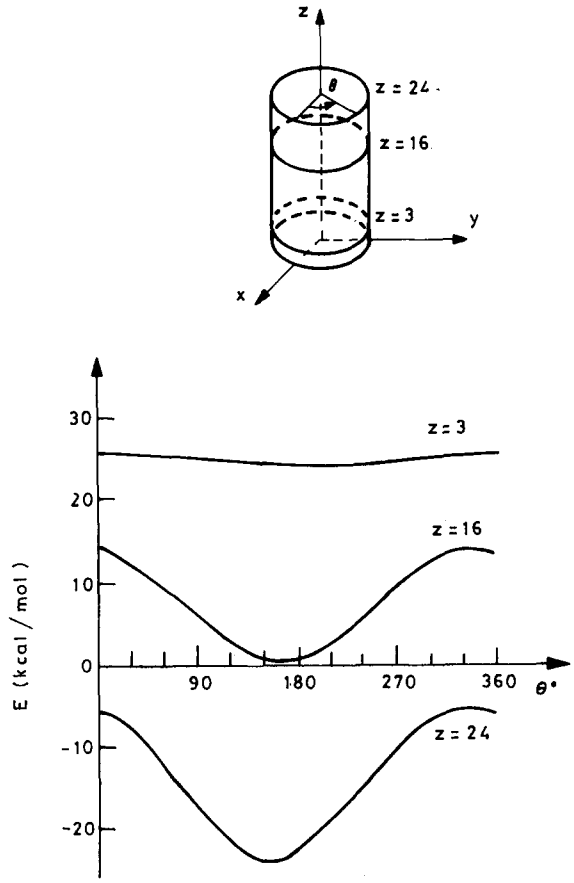

Fig. 8. The angular energy variations along a circle of 6 Å radius at different heights in the cavity.

that since this term varies as the square of the electric field produced in the lipid by the probe charge, it will be still smaller on each atom of an inserted neutral molecule. Thus, in what follows we consider only the electrostatic energy. Its evolution along Z is given in Fig. 7. It is observed that the variation of energy is rapid in the glycerol region and at the beginning of the chains, then becomes slower, reaching a plateau at the level of the chain ends.

The fact that the energy is negative in the head region and positive in the chain region can be qualitatively explained by the orientation of the total dipole moment of the molecules, the positive end of which is directed towards the chain end (Fig. 5). The above discussion shows clearly the intrinsic structural origin of this dipole, hence the corresponding largely intrinsic source of the 'dipole potential' of the monolayer.

The angular variation (Fig. 8) of the interaction energy of the lipid with a test charge on a circle of fixed radius (6 Å) at different heights ($z = 3$, 16 and 24 Å) displays minima for the same angle but with different depths according to the level, the energy varying more and more rapidly in the head region than in the hydrocarbon region. A correlation appears between the position and depth of the minima and the direction of the dipole moment: the center of gravity of this dipole is near the level of C10 (Fig. 1) and its projection on the xy plane lies at 160 degrees of the x axis.

(c) Bilayer versus monolayer

To illustrate the way in which the intrinsic potential is modified in going from a monolayer to a bilayer, the same calculations were performed for a bilayer formed

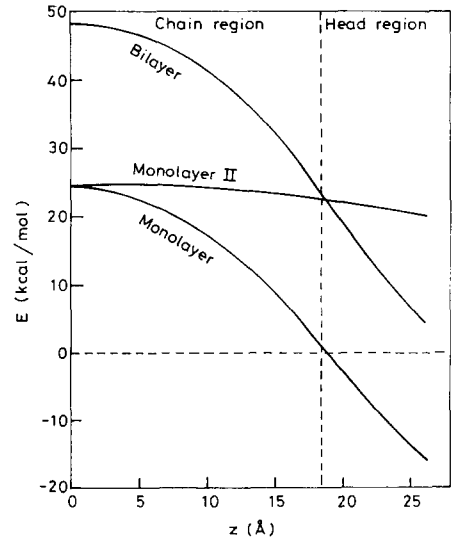

Fig. 9. Variation along the perpendicular to the surface in the upper half region of the bilayer of the interaction energy of a bilayer with a positive unit charge. The curves marked 'monolayer' and 'monolayer II' represent the components of the total energy contributed in this region by the upper and lower monolayer, respectively.

in the simplest possible fashion by juxtaposition of two monolayers in a symmetrical tail-to-tail arrangement with a separation of 4 Å between the planes of the extreme carbon atoms in each layer. The variations of the energy of interaction of the resulting bilayer with a point positive test charge along the axis of the central hole defined as before are reported in Fig. 9. We show only the energy in the upper half region because the energy in the other half is symmetrical with respect to the plane separating the two monolayers (the *x-y* plane by definition). Also given in Fig. 9 are the energy in the upper half region resulting from the upper monolayer (curve 'monolayer'), and the energy in the same region resulting from the lower monolayer (curve 'monolayer II'), the energy of the bilayer being the sum of the two.

The most notable results are that: (i) the bilayer displays no negative energy values; (ii) the bilayer energy curve is essentially parallel to that of the monolayer so that the difference in energy between the minimum and maximum is very similar in both cases.

These results can be understood using the decomposition shown in Fig. 9: the energy in the upper region resulting from the lower monolayer is very appreciably positive with little variations: its decay is slow along the *Z* axis in the upper region. This positive and slowly varying energy is superposed upon the local energy of the monolayer situated in the upper region so that the bilayer energy is more positive everywhere than that of the monolayer. The positive contribution from the farther monolayer in fact overcompensates the negative value due to the local monolayer in the head region so that no negative value remains in the bilayer case. Finally, since the decay of the contribution from the farther layer is small in all the half membrane region, the shape of the bilayer energy curve is essentially the same as that of the monolayer energy and the energy difference between the minimum (head surface) and the maximum (interplane) in a bilayer is very similar to that of the monolayer, in very satisfactory agreement with early estimations indicating that the potential of the interior of lipid bilayers with respect to the aqueous phase is very similar to the surface potentials deduced for monolayers by measurements at the air/water interface [20]. This qualitative agreement militates in favor of the validity of the calculation and indicates the major role, within the 'membrane potential', of the intrinsic component stemming from the sole molecular structure.

Caution must be exercised, however, in comparing the measured values, of the order of a few hundred millivolts [20] with our calculated values which appear too large. One of our aims being to clarify the role of the intrinsic molecular structure (heads and hydrocarbon moities) in the potential, no other contribution was considered and most importantly, the role of water is not included. Its calculation at the molecular level is not really possible at this time. However, the direction of the effect can be safely predicted: concerning the molecules of water close or bound to the heads, it is clear from the results of section B and Fig. 7 that the overall polarity of the lipid molecules will tend to orient their dipoles with the positive end essentially towards the interface, thus opposing the intrinsic dipoles of the lipids, thereby decreasing the potential difference calculated. Another global, however very approximate, view of the effect of the water phase obtains by the introduction of an effective dielectric constant varying from large values near the interface to small values near the chain ends (see, for instance, Ref. 3), thereby decreasing the potential difference calculated between the extremes. A more precise quantitation of these effects is illusory, all the more so since the boundaries at which the potential must be calculated for identification with measured values are unknown.

It remains that, both for the monolayer and the bilayer, the intrinsic tendency of the effect of surrounding lipids on a positive charge trying to cross from the head to the hydrocarbon regions is to repel the charge towards the outside. This situation is due to the intrinsic molecular characteristics of the lipid molecules in which the most negatively charged atoms are located in the esterified glycerol moiety. As mentionned in the introduction the choice of glyceryl monooleate as a test case insures that the effect is independent of the presence of formal charges in the polar head (phosphate or/and ammonium).

The corresponding effect on a test negative charge is exactly opposite. As a consequence, when a molecule is inserted in a lipid layer, it may be expected that the lipids influence its orientation and/or conformation by acting in opposite fashions on its negative and positive atoms, respectively: we illustrate this possibility in the next section, on the case of gramicidin A (upon request of a referee, the net charges on this molecule are given in the Appendix).

Effect of the lipid field on an inserted molecule

The pentadecapeptide gramicidin A (formyl-LVal[1]-Gly[2]-LAla[3]-DLeu[4]-LAla[5]-DVal[6]-LVal[7]-DVal[8]-LTrp[9]-DLeu[10]-LTrp[11]-DLeu[12]-LTrp[13]-DLeu[14]-LTrp[15]-ethanolamine), is considered to generate ion channels in membranes by forming helical $\beta^{6.3}$ dimers associated by their N-terminals (head-to-head) in the middle of the bilayer [17], so that each monomer in this dimer has its C-terminal on the side of the lipid polar heads. The conformations of the four tryptophans 9, 11, 13, 15 at this terminal are further considered [18] to be such that the dipole moments of Trp-9 and Trp-15 point towards the outside of the layer while those of Trp-11 and Trp-13 point inside [21]. Although the head-to-head structure of the dimer seems well established, the preferred orientation of a monomer itself in the lipid is

TABLE II

Characteristics of the energy minima for different orientations of the tryptophans on the gramicidin A monomer optimized in the absence of lipids

Energies in kcal/mol, $\chi_1 = NC_\alpha C_\beta C_\gamma$, $\chi_2 = C_\alpha C_\beta C_\gamma C_\delta$ of Trp, in degrees. The arrows indicate the global orientation of the dipole moments of the tryptophans with respect to the C-terminal of gramicidin. Names defined in text.

Name	Orientation of Trp		E_{tot}		χ_1	χ_2
	9↑	15↑		11	−172.5	−95.9
U_{11}			47.5			
	11↑	13↓		13	−175.8	−89.8
	9↑	15↑		11	−172.4	84.9
U			49.7			
	11↓	13↓		13	−175.8	88.5
	9↑	15↑		11	−172.9	−96.5
$U_{11,13}$			50.0			
	11↑	13↑		13	−179.5	−88.2

controversial [22,23] as are also the proposed conformations of the tryptophans [24]. To illustrate the possible influence of the lipid fields on the orientation of the monomer in the monolayer and on the conformations of the tryptophans, we proceed as follows:

(A) Three conformations of the monomer are considered first in vacuo: U, which derives from Urry's proposed conformation [17,18] by reoptimization of the backbone and side chains dihedral angles; U_{11}, in which the orientation of Trp-11 has been inverted (as proposed in [24]) followed by reoptimization; and $U_{11,13}$ where both Trp-11 and Trp-13 have been inverted, followed by reoptimization. Table II which summarizes the main characteristics of the most stable monomer obtained in each case shows that the differences in stability are small, however, slightly favoring U_{11}.

(B) Each of these conformers is then placed within the lipid and three orientations are considered: (+) with the C-terminal of the monomer oriented towards the lipid heads, (−) with the reverse orientation, (0) with the monomer lying parallel to the interface. Starting with these orientations, the energy of interaction of the monomer with the monolayer is optimized allowing three rotations and three translations of the entire molecule: the results (Table III) indicate that for U_{11} the most favorable interaction with the lipid occurs for an orientation essentially parallel to the upper layer surface with a relatively small energy difference with respect to the (+) orientation (C-terminal of the monomer towards the lipid heads), the opposite orientation being rather disfavored. For the conformation U, the same preference favors the (0) orientation but by a much larger energy difference, the next favored orientation being here the (−) one. The conformation $U_{11,13}$ displays the largest interaction with the lipid and this favors strongly the (+) orientation (N-terminal of the monomer towards the hydrocarbon end of the lipids). These results are in keeping with the fact that in $U_{11,13}$ the four tryptophan dipole moments are essentially in the same direction with their positive end towards the C-terminal of the gramicidin molecule, which thus tends to align with the negative end (the heads) of the lipids.

TABLE III

Interaction energies (E, kcal/mol) of the lipids with the monomers in the three conformations of Table II for three optimized orientations starting from $\tau = 0$, 90 and 180°, respectively

See text for details. τ is the angle between the helical axis and the axis z defined in Fig. 3.

	U_{11}		U		$U_{11,13}$	
	E	τ	E	τ	E	τ
0	−11.38	93	−13.20	93.6	−4.36	98.2
+	−8.80	13.5	−1.60	10.7	−18.64	20.1
−	+0.07	165	5.93	142.2	+2.67	159.9

(C) Assuming that the gramicidin A monomer is inserted in the monolayer in a given orientation, one may ask which is the most favorable conformation of the tryptophans. This was done by considering the monomer to be inserted in the (+) orientation defined above, thus so as to be ready to form the head-to-head dimer channel. Starting from the three conformations U, U_{11}, and $U_{11,13}$ corresponding to line 2 of Table III these were reoptimized in the lipid field, blocking the molecular axis in the (+) orientation while allowing rotation around it, translations in the hole and all dihedral angle variations. The results (Table IV) of the energy optimization indicate that the most favorable total energy occurs now for $U_{11,13}$ followed by then by U_{11}, and that the main source of this ordering resides in the much more favorable interaction with the lipid field, the intramolecular energy being very little modified with respect to the situation in vacuo (Table II).

Summarizing these results, it appears that: (i) the lipids can affect appreciably the orientation of an inserted molecule; (ii) according to the conformation of the tryptophans the preferred orientation of the monomer in the lipids appears different, and the ease of a change in orientation of the whole molecule is also different (see the large differences for $U_{11,13}$ the small ones for U_{11}); (iii) the influence of the surrounding monolayer can change the relative stabilities of the

TABLE IV

Optimal energies of the three conformers in the (+) orientation in the monolayer

Nom	E_{total}	E_{inter}	E_{intra}
$U_{11,13}$	31.43	−18.62	50.05
U_{11}	38.82	−8.69	47.51
U	48.35	−1.59	49.94

energy minima corresponding to the different tryptophan conformations, but it does not seem capable to induce the transition between the minima, at least in the case considered, probably particularly unfavorable due to the presence of the other side chains limiting the movements of the tryptophans. It appears likely that easier conformational changes could be promoted by the lipid field in more favorable cases. An influence of the membrane field on the conformation of the lipid molecules themselves has been put into evidence recently [25].

Note that, even if the differences in the interaction energies obtained were somewhat exaggerated by the (see previous section) large values of the calculated lipid potential, they are sufficiently large to remain significant even if reduced, the underlying logics of the results being that the best interaction is produced when the global monomer dipole aligns inversely with the lipid dipoles (see end of section B above).

This brings us to a last remark concerning the handedness of the gramicidin helix, a referee having suggested that parallel calculations be done for the right-handed monomer in order to provide insight into the basis for helix handedness. We do indeed intend to make such calculations. However, they represent an appreciable amount of work which will deserve a separate publication.

At present, we think that the results obtained here for the left-handed structures provide an argument in favor of the lipid preferring the right-handed form *at least insofar as this form corresponds to the orientation of the tryptophans* found by Arseniev et al. [26]. We have stressed earlier [27] the fact apparently completely overlooked, that this structure differs from the standard Urry's structure *not only by its handedness, but also by the orientation* of the side-chains, particularly that *of the four tryptophans*, all of which point the positive end of their dipole moment towards the ethanolamine terminal. We have found here (in $U_{11,13}$) that, in the left-handed structure, such an orientation of the tryptophans favors a strong interaction with the lipid field for the (+) orientation (see Table III) thereby stabilizing the structure in the lipid. It can be expected that the same phenomenon, occurring in the right-handed species, will add to its own (slightly larger) [27] stability. Aside from a more thorough theoretical study, it would be interesting to supplement the recent confirmation of the helix right-handedness [28] by experimental evidence on the tryptophan orientations.

Appendix

The net atomic charges (a), (b), (c), correspond, respectively, to the fragments: form-Val-Gly-Ala-Leu; Trp; ethanolamine terminal in the gramicidin A monomer (Fig. 10). Other peptides not shown are identical to the end ones in (a) and all Val, Ala, Leu as in (a).

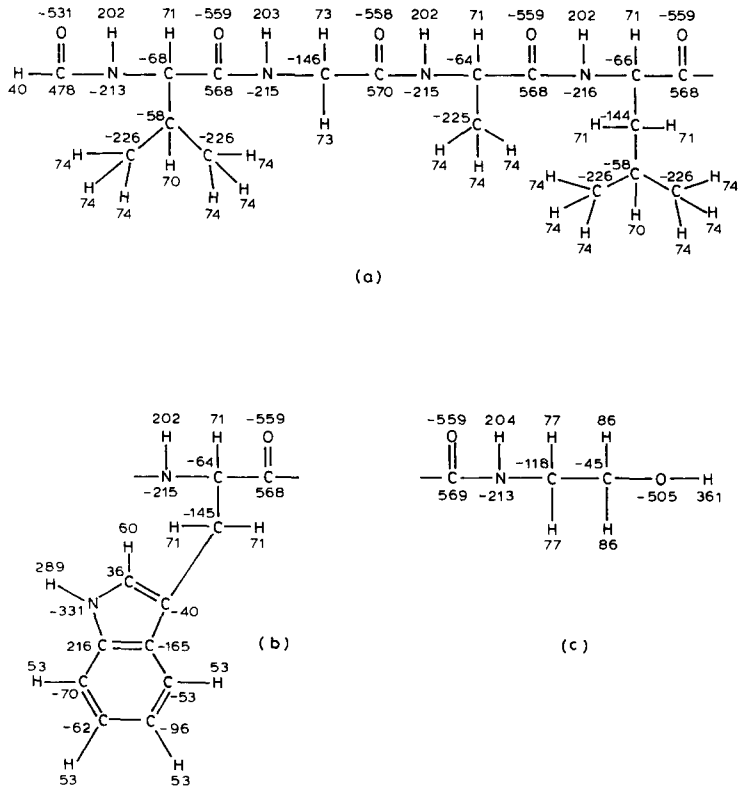

Fig. 10. Net atomic charges in the fragments: form-Val-Gly-Ala-Leu (a); Trp (b); the ethanolamine terminal in the gramicidin A monomer (c).

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