Vol. 103, No. 1, 1981 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
November 16, 1981 Pages 301-310

THEORETICAL CONFORMATIONAL ANALYSIS OF PHOSPHOLIPIDS BILAYERS

Robert Brasseur, Erik Goormaghtigh and Jean-Marie Ruysschaert

Laboratoire de Chimie Physique des Macromolécules aux Interfaces, CP 206/2. Université Libre de Bruxelles, 1050 Bruxelles, Belgium.

Received September 24,1981

SUMMARY

We present a computational approach describing the conformation of lipid molecules (1-2-dipalmitoyl-sn-glycero-3 phosphocholine (DPPC)) organized in bilayers. The classical semi-empirical method used in peptide conformational analysis has been extended successfully to lipids. The excellent agreement between our theoretical predictions and recent experimental data on the molecular organization of lipid bilayers suggests that the method could be a valuable tool in the lipid conformational analysis but also in the prediction of orientation and mode of insertion of amphiphilic molecules into the lipid bilayer.

INTRODUCTION

Phospholipids constitue a major component of biological membranes. Consideration of biological membranes at the molecular level requires a detailed knowledge of the preferred conformations of phospholipids. Surprisingly, it is only recently that neutron diffraction combined with the use of deuterated lipids has provided detailed information about the mean position of the segments constituting the lipid bilayers (1). In this report, we present the theoretical conformational analysis as another way to gain insight into the structure of the constituents of biological membranes. Other works have limited, for computer time consuming reasons, their analysis to the polar head group (2-4) or the hydrocarbon chain (5-7) constituting the lipid molecule. Here we present a theoretical approach allowing to describe the conformation of the entire lipid molecule assembled in bilayers.

METHODS AND RESULTS

The conformational energy (E_{tot}) is calculated according to an empirical scheme as the sum of two terms :

$$E_{tot} = E_{loc} + E_{int}$$

0006-291X/81/210301-10$01.00/0

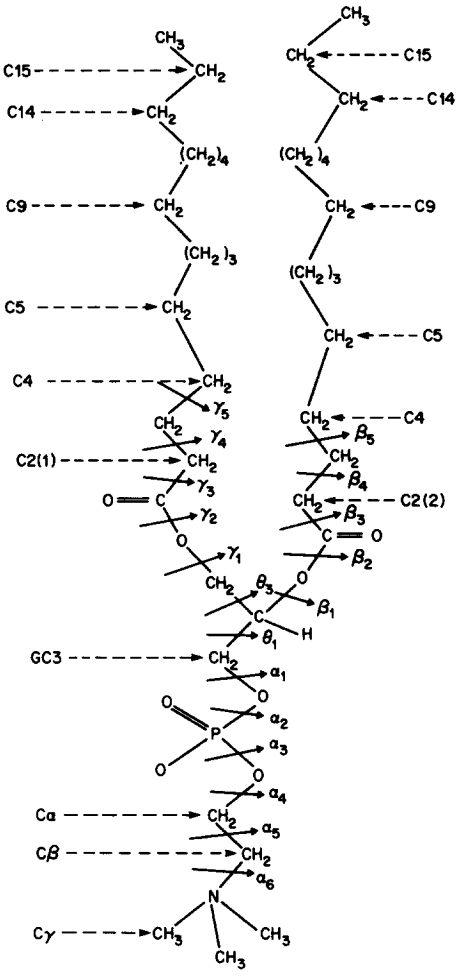

Fig.1 : Notation of the different chains and torsional angles in phospholipids (9).

The first term (E_{loc}) contains all contributions resulting from local interactions in the isolated molecule. E_{loc} is the sum of the Van der Waals energy, the electrostatic interaction and a torsional potential (8). The second term (E_{int}) which describes the interaction between molecules was only computed for conformations corresponding to the minima of E_{loc}. E_{int} is the sum of the Van der Waals energy and the electrostatic interaction (8). All parameters used in the minimization are those used in lipid structure predictions. (2,3,4,6,7). We denote the principal torsion angles of the lipid structure by the notation of Sundaralingam (9)(Fig.1). The torsion angle around bond j ($\alpha_j, \beta_j, \gamma_j, \theta_j$) is considered positive for a right-handed

Table I. Torsional angles associated to the DPPC polar head.

	Conformers		
	a	b	c
Torsional angles			
α_6	180	180	180
α_5	180	60	60
α_4	180	120	120
α_3	180	60	60
α_2	180	60	60
α_1	180	180	180
θ_1	180	300	60
Energy above minimal value (Kcal/mol)	0	2.3	2.3
Probability (%)	51	14	14

Table II. Torsional angles associated to the hydrocarbon DPPC chain.

	Conformers	
	d	e
Torsional angles		
β_1	60	180
β_2	240	180
β_3	120	300
β_4	300	300
θ_3	180	60
γ_1	180	180
γ_2	180	180
γ_3	180	180
γ_4	180	180
Energy above minimal value (Kcal/mol)	2.8	0
Probability (%)	5	85

rotation, when looking along the bond j, the far bond j+1 rotates clockwise relative to the near bond j-1 (9).

Our theoretical analysis supposes a procedure in 3 steps :

a) conformation of the isolated lipid molecule.

b) conformation of the lipid molecules assembled in monolayer.

c) conformation of the lipid molecules assembled in bilayer.

Isolated molecules

In a first systematic study, the torsional angles located in the polar head ($\alpha_6, \alpha_5, \alpha_4, \alpha_3, \alpha_2, \alpha_1, \theta_1$) were given successive increments of 60°, yielding 6^7 different conformations (279.936) from which 3 structures with maximal probability were selected (Table I).

In a second systematic study, the angles $\beta_1, \beta_2, \beta_3, \beta_4, \gamma_1, \gamma_2, \gamma_3, \gamma_4, \theta_3$ located in the hydrocarbon chain were increased by steps of 60°, yielding 6^9 different conformations (10.077.696) from which 2 more structures were selected (Table II).

Combination of the 3 structures obtained for the polar head group and of the 2 structures obtained for the hydrocarbon chain gives 6 structures for the entire isolated lipid molecule.

The energy minimum associated to each structure was obtained by application of the simplex minimization procedure (10) with a precision of 10° on the rotational angles (Table III). The 6 most probable conformations derived from the latter analysis are described in table III. The internal energy of each structure is given in Kcal/mole in excess of the lowest values.

Monolayers formation

a) The position of lipid B is modified along the X axis (Fig.2a). Each distance change is equal to 0,50 Å (the phosphate atom was used to define the distance separating 2 molecules). For each separating distance a rotation angle of 30° is imposed to lipid B around its own Z axis and around lipid A (Fig.2b). Among 14.400 possible orientations only the structure of energy minimum was considered.

b) Lipid A position is fixed and lipid B is allowed to move along the axis Z perpendicular to the lipid water interface (Fig.2c). Again, only the structure of energy minimum is considered.

c) Lipid B has the possibility to change its orientation around the Z axis as compared to lipid A (Fig.2c). This procedure allows to define

Table III. Torsional angles associated to the entire DPPC molecule. The torsional angles obtained for β_i and γ_i with $i \geq 6$ are $180° \pm 5$. The precision of the minimization is 10°.

	Conformers					
	ad	bd	cd	ae	be	ce
Torsional angles						
α_5	195	183	59	195	183	182
α_4	168	167	117	170	165	138
α_3	180	60	59	180	54	300
α_2	163	61	62	160	64	300
α_1	195	115	210	193	222	180
θ_1	231	250	70	217	237	41
θ_3	179	180	210	179	194	196
β_1	133	122	105	133	140	146
β_2	141	127	131	141	150	159
β_3	239	268	240	239	224	191
β_4	184	174	89	184	173	173
γ_1	196	232	134	196	209	217
γ_2	111	230	140	111	154	144
γ_3	126	204	200	126	216	191
γ_4	183	172	180	183	185	180
Energy above minimal value (Kcal/mol)	3.1	1.0	3.5	2.0	0	2.2
Probability (%)	0.4	14.5	0.2	2.7	80.3	1.9

finally the probable packing of the 2 lipid molecules. Addition of a third molecule to the 2 preceding one supposes a similar approach. The packing of the first two molecules is maintained and one studies the orientation of the third molecule around them.

Bilayers formation

a) Monolayer B position is modified along the Z axis. Again each separating distance is equal to 1 Å (Fig.3b). A rotation angle of 30° is imposed to monolayers B around Z axis (Fig.3a). Monolayer A is fixed.

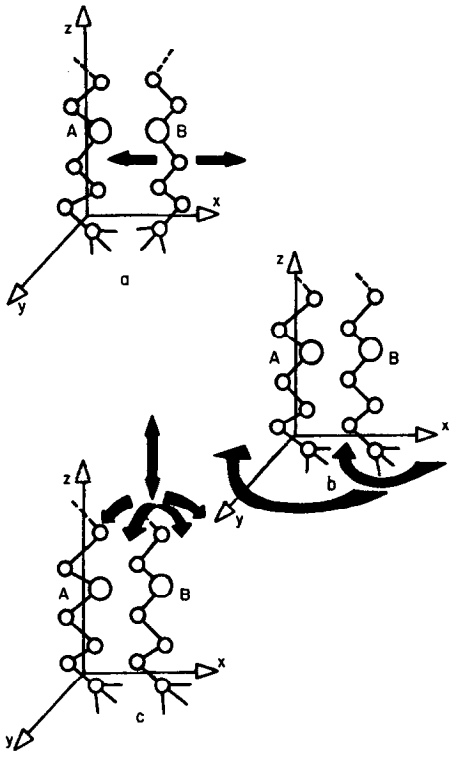

Fig.2 : Schematic presentation of the packing procedure of lipid molecules assembled in monolayers.

b) Monolayer B has the possibility to change its orientation around the Z axis (Fig.3d and Fig.3c). Monolayer A is fixed.

In each case, only the bilayer structure of energy minimum is retained. If each of the structure obtained for the isolated lipid molecule define in table III, were assembled in monolayer (for time consuming reasons we limited our approach to the assembling of 7 molecules) one structure obtained after minimization represents 95% of probability (Table IV). It is obvious that the monolayer packing stabilizes the structure cd. This conformation is characterized by the close proximity of the phosphate residue associated to the hydrophilic moeity of one lipid and the choline residue associated to the adjacent lipid (Fig.4). The electrostatic interaction between the 2 residues stabilizes the lipid structure.

From the structure of the lipid in the monolayer, the organization in the lipid bilayer was theoretically evaluated in an attempt to compare our approach with recent experimental data. Indeed, neutron diffraction combined with the use of selectively deuterated lipids can provide detailed

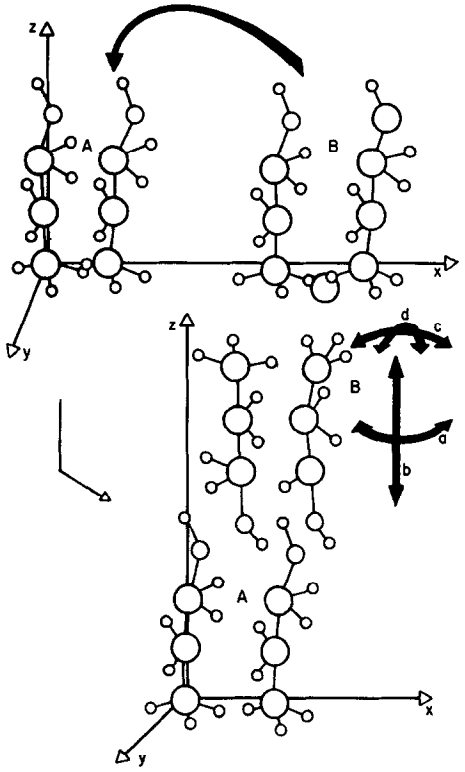

Fig.3 : Schematic presentation of the packing procedure of lipid molecules assembled in bilayers.

information about the molecular structure (1) . This approach has been recently applied to bilayer membranes of DPPC deuterated at 12 different positions in the hydrocarbon chain and polar head group. Table V compares

Table IV. Energy above minimal values and probability associated to each DPPC conformer when assembled in monolayer.

	Conformers					
	ad	bd	cd	ae	be	ce
Energy* above minimal value (Kcal/mol)	4.1	2.3	0	4.4	2.2	3.5
Probability(%)	0.09	1.97	95.1	0.06	2.49	0.29

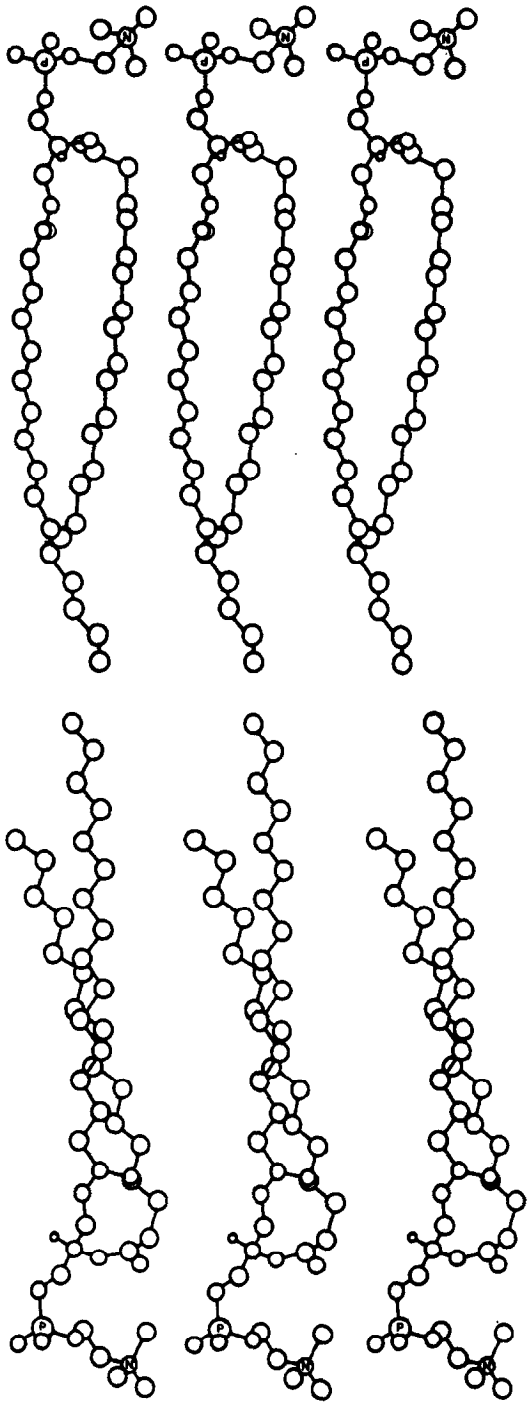

Fig.4 : Computer visualization of the lipid packing in bilayers of DPPC at 25°C. The assembling procedure was detailed in the text.

Table V. Summary of the mean carbon atom positions of DPPC in the bilayer. Atoms positions are given in Fig.1.

	Distance from the center of the DPPC bilayer (Å)										
	cγ	cβ	cα	Gc3	c2(2)	c2(1)	c4	c5	c9	c14	c15
Neutron diffraction studies (1)(20°)	25.1±0.6	24.8±0.7	24.5±0.7	23.1±1.0	20.0±1.0	18.1±1.0	16.2±0.6	15.0±0.6	10.1±1.0	4.1±0.6	2.9±0.6
Theoretical conformational analysis (25°)	25.2	25.0	24.0	22.2	20.2	17.3	15.6	14.7	10.0	4.7	3.5

the experimental and theoretical mean positions for the deuterated segment of DPPC bilayers. The given distances are measured from the center of the bilayer. For all the positions an excellent agreement was observed between the 2 approaches.The theoretical deviation is of the order of magnitude of the experimental error.

This correlation between experimental data and our theoretical predictions for a well defined system suggests that the computational approach is a valuable tool to obtain a rapid and clear picture of the orientation of any membrane constituent (cholesterol, ganglioside, lipid soluble drug) in the lipid bilayer phase of the membrane. This approach should be used in parallel with a basic experimental approach like neutron diffraction which supposes a delicate deuteration of the membrane compound.

ACKNOWLEDGMENTS

We wish to thank the Computing Center of the Université Libre de Bruxelles where the calculations were performed on a C.D.C. 6600 Computer.

REFERENCES

1. Buldt G., Gally H.U., Seelig A., Seelig J., and Zaccai G. (1978) Nature 271, 182-184.
2. Gupta S.P. and Govil G. (1975) J. Theor. Biol. 51, 13-34.
3. Pullman B., Berthod H. and Gresh N. (1975) FEBS Letters 53, 199-204.
4. Pullman B. and Berthod H. (1974) FEBS Letters 44, 266-269.
5. Nagle J.F. and Scott H.L. Jr. (1978) Biochim. Biophys. Acta 513, 236-243.
6. Belle J., Bothorel P. and Lemaire B. (1974) FEBS Letters 39, 115-117.
7. Scott H.L. (1977) Biochim. Biophys. Acta 469, 264-271.
8. De Coen J.L. and Ralston E. (1973) Peptides 335-343.
9. Sundaralingam M. (1972) An. N.Y. Acad. Sci. 195, 324-355.
10. Nelder J.A. and Mead R. (1965) Computer. J. 7, 308-313.