COMPUTER SIMULATION OF THE INTERACTION OF PROSTAGLANDINS $PGF_{2\alpha}$ AND PGB_1 WITH DIPALMITOYLPHOSPHATIDYLCHOLINE

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ABSTRACT

Computer-aided model building, using the empirical potential energy function and the energy minimization technique, was used to study the interaction of prostaglandins (PGs) $PGF_{2\alpha}$ and PGB_1 with dipalmitoylphosphatidylcholine (DPPC). $PGF_{2\alpha}$ can interact with the DPPC molecule in two different ways. In the first model (model I) 9α- and 11α-hydroxy groups could make hydrogen bonds with the phosphate oxygens and neutralize them. In the second model (model II) 15-(S)-hydroxy group makes bifurcated hydrogen bonds with the phosphate oxygens. The 9α- and 11α-hydroxy groups are free to interact with the cation (Ca^{2+}) and neutralize its positive charge. For PGB_1 model I was energetically unfavourable, and model II had energy 30.11 kcal mol^{-1} higher than model II for $PGF_{2\alpha}$. In addition to these two binding sites, both the molecules could make hydrophobic contacts with the DPPC chains and loosely embed in the membrane (model III). The binding energy in model III was higher than that in model II. The influence of these interactions on prostaglandin-induced contractile activity of smooth muscle is discussed. An explanation for the higher activity of $PGF_{2\alpha}$ compared to that of PGB_1 is offered.

INTRODUCTION

PROSTAGLANDINS (PGs) elicit contractile response in smooth muscle[1-3] and have therapeutic value. The biological effectiveness of different PGs depends on their chemical nature[1,4-7]. Although the physiological pathway of PG action is quite complex and not well understood[8], there is enough evidence for an ionophoric effect of PG on Ca^{2+} ions in the plasma membrane[9-13].

The plasma membrane is a multicomponent system of lipids and proteins organized into functional domains[14,15]. It is possible that PGs interact directly with specific sites on receptor molecules in the membrane or perturb the dynamic properties of the lipid part of the membrane, which in turn may perturb specific proteins. It has been shown[15] that chemically active molecules can trigger a cascade of events by adsorption on membranes via electrostatic or dispersive forces. Rearrangement of phospholipids in erythrocytes in the presence of small amounts of PGE_1 was noted by Manevich *et al*[16]. Interaction of several drugs (propranolol, epinephrine, norepinephrine, vitamin D and *n*-akanols) with different lipid molecules has been studied using physicochemical techniques[17-21]. The drug molecules have been shown to interact with the hydrophobic core or the polar head, to be partly immobilized between the hydrophobic core and the polar head, or to make hydrogen bonds with the phosphate groups of the lipid molecule.

The 'form' specificity in PG action depends on the initial event in their interaction with the membrane and is related to the stereochemical aspects of different PGs. Many studies have therefore been directed at understanding the three-dimensional structures of the molecules[22-34]. As a result, many structural details are available for the PGs. Several factors, such as conformation of five-membered ring[27] and orientation of α and ω chains, have been shown to be related to activity[24-34]. However, nothing definite has been said about the primary target of PG action in membranes.

We undertook a systematic study of the interaction of PGs with membrane lipids. In earlier papers[35,36], we demonstrated that $PGF_{2\alpha}$ can bind to dipalmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylcholine (DMPC) vesicles and cause fluidization of the membrane. There is also a reduction in the gel–liquid-crystalline-phase transition temperature. The fluidization effect is enhanced in the presence of Ca^{2+} ions[36]. These observations suggest the necessity of a detailed examination of the mode of interaction of PGs with lipid molecules.

In the present paper we describe possible models for the interaction of $PGF_{2\alpha}$ and PGB_1 with DPPC

using computer modelling, allowing full (conformational and motional) freedom to the drug molecule. This technique yields, simultaneously, information regarding the stereochemical aspects of the complexes and the forces involved in the interaction.

MATERIALS AND METHODS

Initial geometry

The initial geometry of the DPPC molecule was generated from the bond length, bond angle and torsional angle data given in reference 37 on 3-lauroylpropanediol-1-phosphorylcholine monohydrate (LPPC) and by attaching fatty acyl chain to glycerol C_2. The cartesian co-ordinates of $PGF_{2\alpha}$ were generated on the basis of crystallographic co-ordinates of $PGF_{2\alpha}$ tri-*p*-bromobenzonate[22], with the difference in the orientation of the 9-OH group and the 5–6 *cis* double bond. The torsional angles given in reference 25 were incorporated in these data. Structural data for PGB_1 were generated from bond length and bond angle data given in reference 26. The torsional angles C_6–C_7–C_8–C_9 (α1), C_{11}–C_{12}–C_{13}–C_{14} (α9) and C_{13}–C_{14}–C_{15}–C_{16} (α10) were also fixed according to the results of a conformational study of PGB_1[31] (see figure 1a–c for nomenclature).

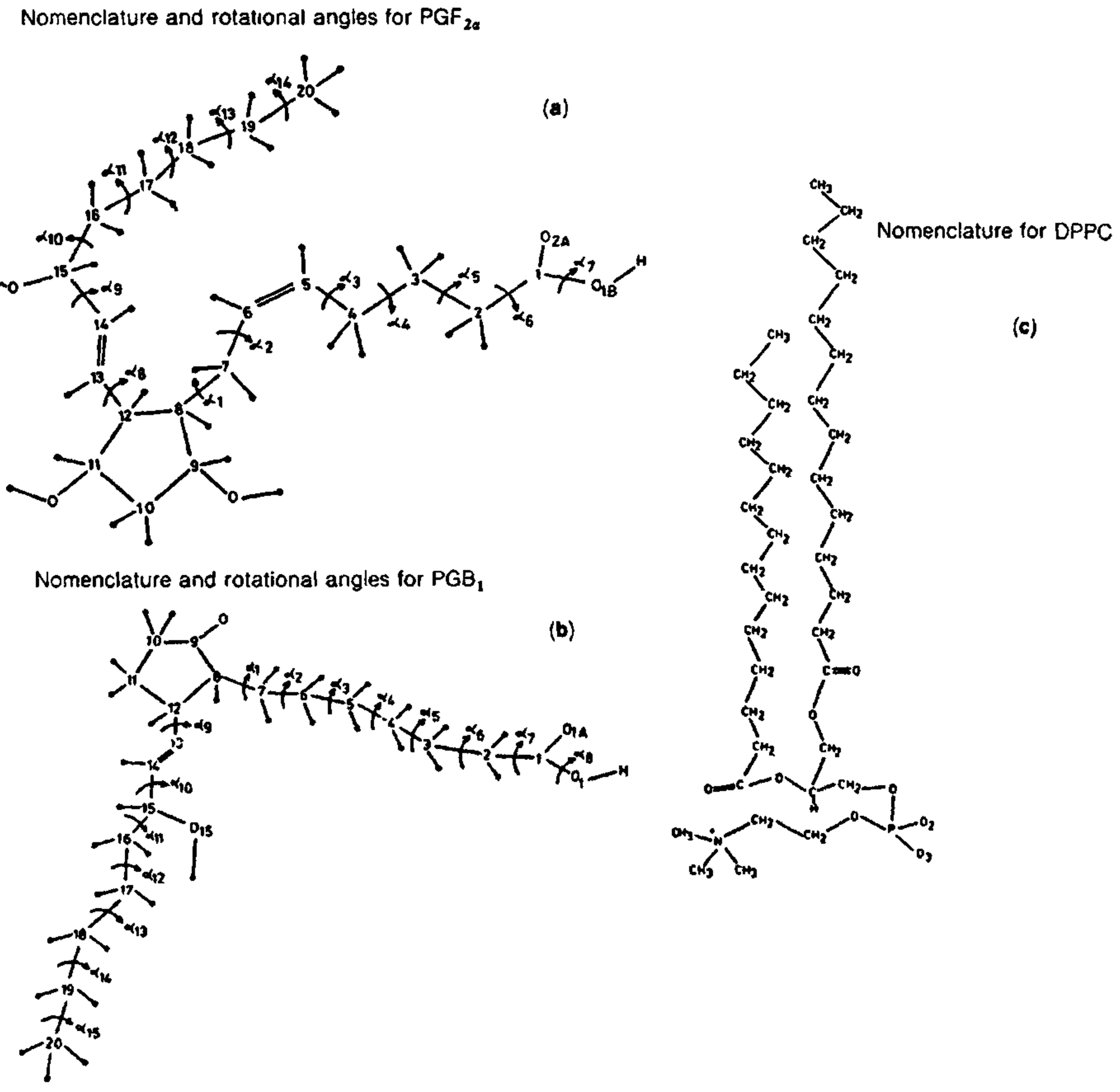

Figure 1a–c. Nomenclature for $PGF_{2\alpha}$, PGB_1 and DPPC, showing different rotational angles. The four-atom sequence for the rotational angles is described in table 2.

Potential energy function

Pair-wise (atom–atom) additive potential, comprising attractive, repulsive, electrostatic, polarization, H-bonding and torsional contributions, was used. Details are described in an earlier paper[34].

Rigid body docking of the PGs with DPPC

For the initial docking, both the molecules were considered to be rigid. The DPPC molecule was oriented such that its aliphatic chains were directed along the z-axis (figure 1c). The PG molecule was allowed to rotate around the DPPC molecule and translated in the z direction. We also allowed rotation of the PG around its own axis. Interaction energy for PG and DPPC was calculated. The energetically stable position was taken as the tentative initial binding site for further refinement. An energy constraint, viz. that for each atom–atom pair the attractive contribution should be more than the repulsive, was used for obtaining the crude models.

Refinement of the model

Refinement of the model of the complex was done in two steps. In the first step the H-bonding donors were oriented towards the phosphate oxygens. The PG molecule was allowed to translate and rotate along the H-bonds. Rotations were allowed along various single bonds to remove unnecessary short contacts. The molecule was also allowed to have limited translational freedom. Lowest energy position at a particular binding site was obtained. In the second step the technique of successive infinitesimal rotation (SIR) of Sklenar[38] was used to solve complicated inhomogeneous, highly nonlinear equations of energy. Translatory movements were frozen in this step. Rotations were allowed along all the single bonds shown in figures 1a,b. Change in conformation and interaction energy for rotation of the nth torsional angle was calculated. The next increment in the torsional angle was given proportionate to the gradient of the energy[39].

Any number of angles can be moved simultaneously in this technique. There is also a provision for changing the relative weightage for different angles. The procedure refines the geometry very fast. It has been employed efficiently in the case of DNA conformation and for drug–DNA interactions[40,41].

Energy analysis

The different contributions (attractive, repulsive, electrostatic, polarization, H-bonding and torsional) to the interaction energy for the five-membered ring and carboxy and hydroxy chains of PGs and the polar head and aliphatic chains of DPPC were calculated.

Geometry analysis

The final geometries of the complexes, and stereochemical factors such as H-bonding geometries, distances between functional groups, etc. were also analysed.

All calculations were done on a HP 1000 A series computer using programs specially developed for the purpose.

RESULTS AND DISCUSSIONS

The rigid body docking procedure suggested that the polar head group of the DPPC molecule is the main binding site for the PGs. $PGF_{2\alpha}$ could bind to the polar head in two different ways. In model I (figures 2a–c) 9α- and 11α-hydroxy groups are oriented towards the phosphate groups of DPPC and bifurcated H-bonds are formed between O_2 and O_3 atoms of DPPC with 9α- and 11α-hydroxy hydrogens. The O...H distances in this case were 2.43 Å, 1.81 Å, 3.33 Å and 2.66 Å, and the O...H–O angles 143°, 159°, 139° and 105°, all well within the H-bonding limits (table 1). The carboxy and hydroxy chains of PG run parallel to the aliphatic chains of DPPC on both sides (figure 2c). The five-membered ring overlaps a portion of the polar head close to them.

In model II the five-membered ring of PG is shifted away (figures 3a, b) from the phosphate group, and the 15-(S)-hydroxy group is directed towards O_2 and O_3, making bifurcated H-bonds with H-bond lengths 1.85 Å and 2.23 Å and O...H–O angles 155° and 98° (table 1). The hydroxy chain and the five-membered ring overlap the polar head. The carboxylic chain runs parallel to the aliphatic chain of DPPC. There is a good amount of overlap between the two molecules (figure 3b). Moreover, 9α and 11α, which are specific for PG activity, are oriented away from the polar head (figure 3a). This region, as mentioned earlier[30], has the lowest electrostatic potential, compared to other PGs. It can serve as an ideal cation-binding site.

In the case of PGB_1 the carbonyl oxygen at the 9th position shows electrostatic repulsion with the DPPC phosphate oxygens O_2 and O_3. Model I

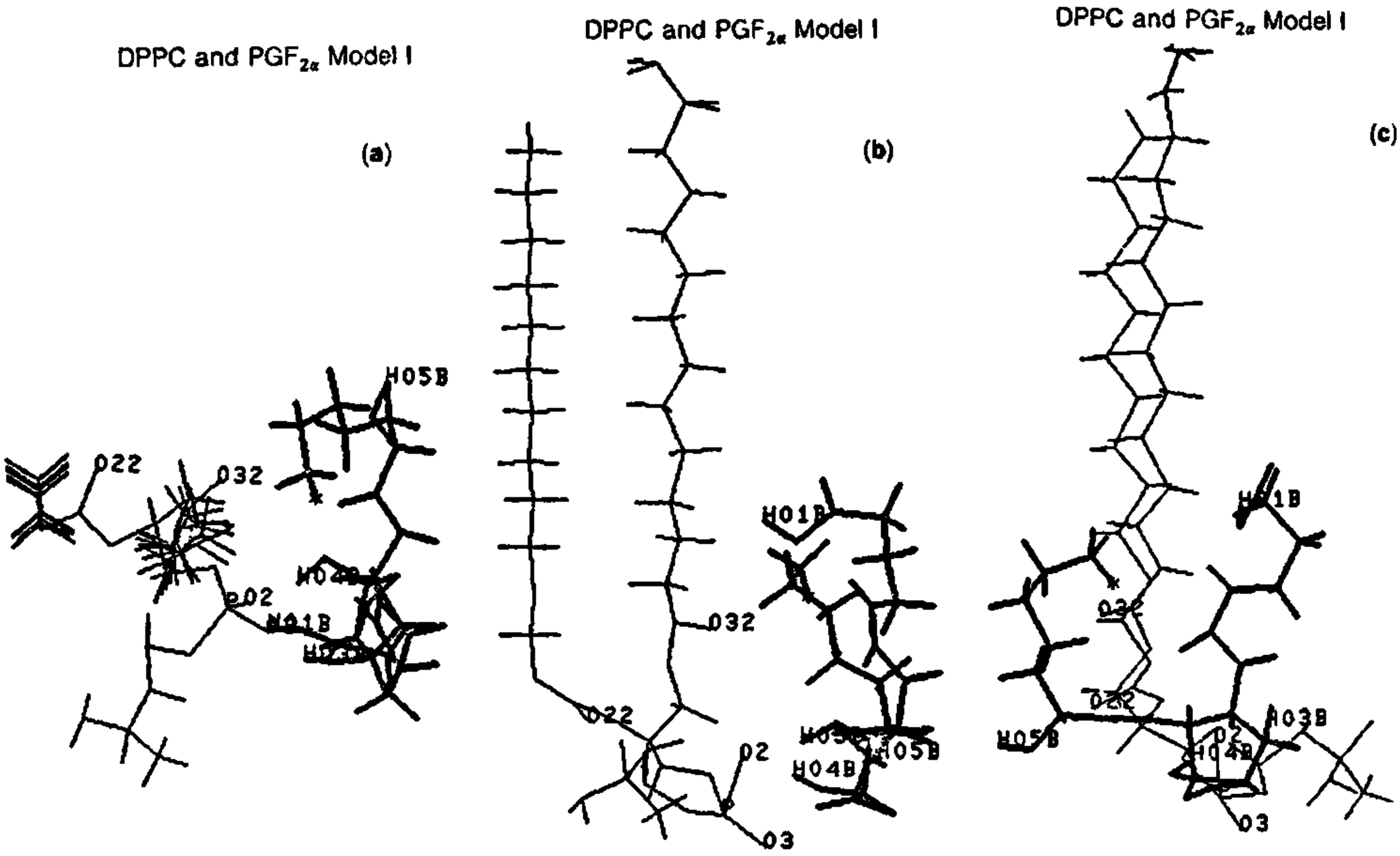

Figure 2a–c. **a,** Computer-built model for the interaction of DPPC with $PGF_{2\alpha}$ (model I) in *xy* plane. Hydrogen bonding is between O_2 and O_3 of the polar head of DPPC with 11α- and 9α-hydroxy groups of $PGF_{2\alpha}$. **b,** The same model in *xz* plane. **c,** The same model in *yz* plane.

Table 1 *Interatomic distances and angles between H-bonding donors and acceptors in PG–DPPC models*

Model	Phosphate oxygens of DPPC	Hydroxy hydrogens of PGs	O...H distance (Å)	Angle O...H–O (degrees)
$PGF_{2\alpha}$ (model I)	O_2	OH_9	2.43	143
	O_2	OH_{11}	1.81	159
	O_3	OH_9	3.33	139
	O_3	OH_{11}	2.66	105
$PGF_{2\alpha}$ (model II)	O_2	15-(S)-OH	1.85	155
	O_3	15-(S)-OH	2.23	98
PGB_1 (model III)	O_2	15-(S)-OH	3.42	90
	O_3	15-(S)-OH	1.96	144

could be realized only after the molecule was taken sufficiently away from the DPPC molecule (figure 4a). We attempted interaction of the 15-(S)-hydroxy group with the polar head using the crystallographic conformation of PGB_1[26] as the starting point. However, because the 15-(S)-hydroxy group was pointed in between the hydroxy and carboxy chains, the model was sterically not possible. We then attempted modelling this interaction starting from the conformationally optimized structure of PGB_1[31]. Torsional angles C_9-C_8-C_7-C_6 (χ1), C_{11}-C_{12}-C_{13}-C_{14} (α9) and C_{13}-C_{14}-C_{15}-C_{16} (χ10) in this case were fixed at 120°, 120° and 270° respectively. The optimized model (model II), with the 15-(S)-hydroxy group making bifurcated H-bonds with O_2 and O_3 with O H distances 1.96 and 3.43 Å, was obtained

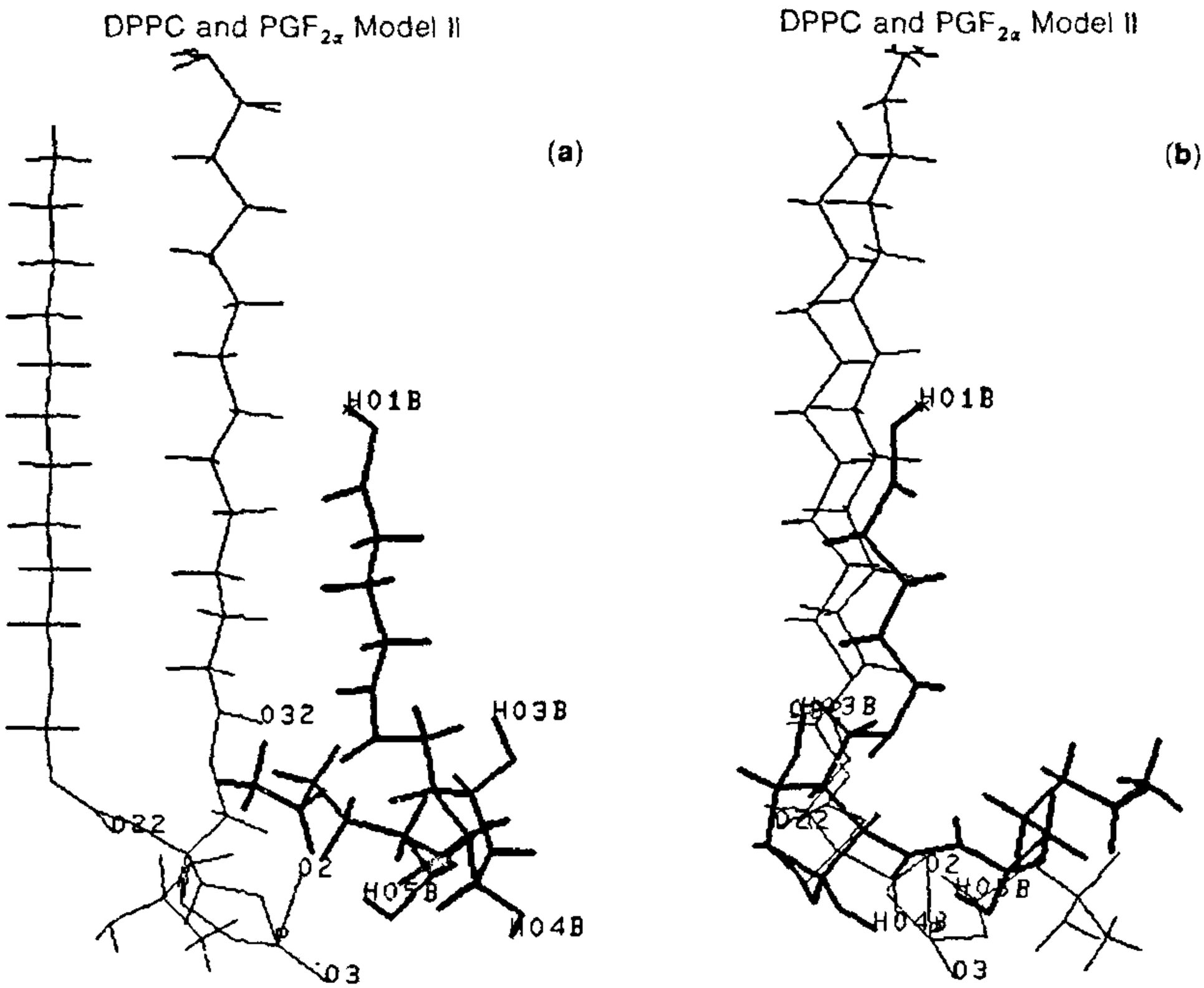

Figure 3a, b. **a,** Computer-built model for the interaction of DPPC with $PGF_{2\alpha}$ (model II). showing bifurcated hydrogen bonding between O_2 and O_3 of DPPC with 15-OH of $PGF_{2\alpha}$. In this model 9α- and 11α-hydroxy groups are free to interact with the cation. **b,** The same model in *yz* plane. The model shows stereochemical compatibility of $PGF_{2\alpha}$ with DPPC.

(figure 4b). As in the case of $PGF_{2\alpha}$, model II for PGB_1 also showed a good amount of overlap with the DPPC conformation. However, there was no specific cation-binding site in this case.

A third model (model III) could be obtained both with PGB_1 and $PGF_{2\alpha}$ with no specific H-bonding contacts with the DPPC molecule. The PG molecule in this case was deeply embedded in the aliphatic chains of DPPC (figure 4c), similar to the 'walking-stick model' of Finean[42]. The complex was stabilized in the hydrophobic region formed by the aliphatic chains of DPPC.

PG conformation

Because we allowed rotations around various single bonds (figure 1b) the conformation of PG in the optimized models was different from the crystallographic or conformationally minimized starting conformation (table 2). The conformation energy with respect to crystallographic structure could be lower and higher (table 2), because it depended on the degree of refinement in the optimized models. Comparison of the torsional angles of the final models with the crystallographic as well as energy-minimized conformations obtained in our earlier studies[25, 34] is shown in table 2. Considerable differences were observed in the torsional angles around the C_7–C_8, C_{12}–C_{13} and C_{15}–C_{16} bonds.

Inter-oxygen distances

Reduction in the distances O_9–O_{1B} and O_{11}–O_{1B} by 3 and 4 Å respectively was found in model I for

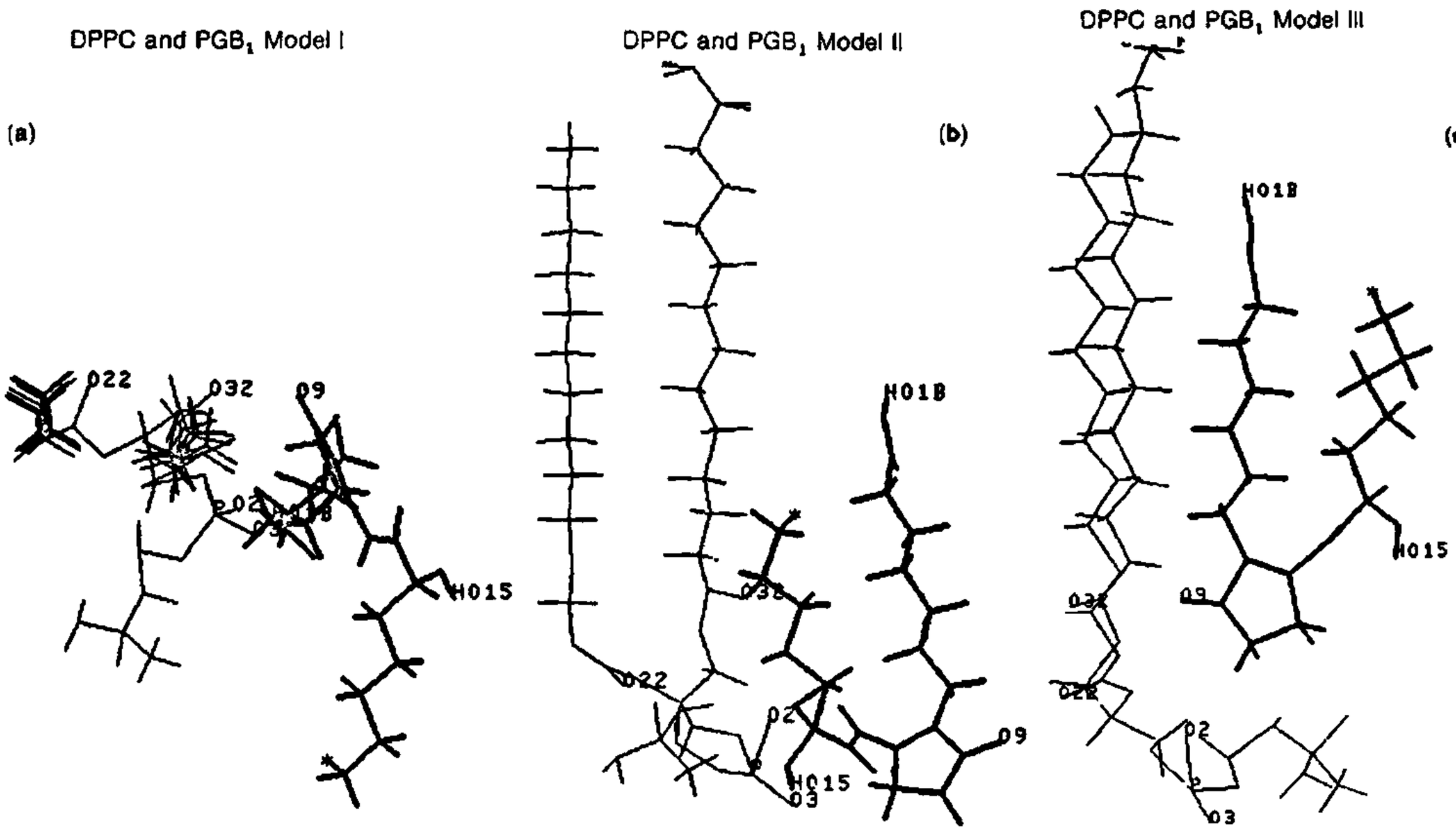

Figure 4a–c. **a,** Computer-simulated model interaction of DPPC with PGB_1 (model I). Here hydrogen bonding is not possible because O_9 of PGB_1 ring repels the two oxygens of the polar head of DPPC. The hydroxy chains and ring are turned away from the DPPC molecule. **b,** Computer-simulated model for the interaction between DPPC and PGB_1 (model II), depicting bifurcated hydrogen bonding between O_2 and O_3 of DPPC and 15-hydroxy group of PGB_1. Note the difference between this model and model II for $PGF_{2\alpha}$ (figure 3a, b). **c,** PGB aligned along with the aliphatic chains of DPPC (model III). The figure clearly depicts the hydrophobic interactions between the chains.

$PGF_{2\alpha}$. The O_{1B}–O_{15} distance was reduced here by 1.72 Å. Inter-oxygen distances in model II for both $PGF_{2\alpha}$ and PGB_1 were of the same order as those found in the crystallographic study.

Energetics

In the case of $PGF_{2\alpha}$, model I was the most preferred model. The interaction energy in this case is lower by 12.73 kcal mol^{-1} compared to model II (table 3). Stabilization of the complex is mainly by H-bonding interaction. The dispersion contribution of 11.94 kcal mol^{-1} is compensated by electrostatic repulsion (16.6 kcal mol^{-1}) between O_2 and O_3 atoms of DPPC and ring oxygens of PG. In model II there is reduction in the electrostatic repulsion by 7 kcal mol^{-1} and increase in the dispersion by 10.5 kcal mol^{-1}. As a result both dispersion and H-bonding interactions contribute towards stabilization of the PG–DPPC complex.

The maximum contribution to the stabilization energy in model I for $PGF_{2\alpha}$ is due to interaction of the five-membered ring with the polar head of DPPC (figure 5). The aliphatic chains show a small interaction with the hydroxy chain. In model II, the maximum interaction is between the polar head of DPPC and the hydroxy chain of $PGF_{2\alpha}$. A 15% contribution to the total interaction comes from the interaction of the carboxy chain of $PGF_{2\alpha}$ with the aliphatic chains of DPPC.

In the case of PGB_1, model II is preferred over models I and III (table 3). It is stabilized by dispersion and H-bonding forces. There is a 5 kcal mol^{-1} electrostatic repulsion between O_2 and O_3 of DPPC and O_{15} of PG. The maximum contribution to interaction energy is by the polar head of DPPC and the hydroxy chain of PGB_1. Interactions between the polar head and the five-membered ring, and between the aliphatic chains

Table 2 *Optimized values of the torsional angles in the different models for $PGF_{2\alpha}$ and PGB_1*

Angle	Atom atom–atom atom	Model I	Model II	a	b
$PGF_{2\alpha}$					
χ_1	C_9–C_8–C_7–C_6	−103.88	167.47		157.39
χ_2	C_8–C_7–C_6 C_5	156.07	176.57	142	167.61
χ_3	C_6–C_5–C_4–C_3	185.08	167.45	153	167.36
χ_4	C_5–C_4–C_3 C_2	−36 01	−176.53		182.16
χ_5	C_4–C_3–C_2–C_1	96.04	−179.73		175.18
χ_6	C_3–C_2–C_1–O_{2A}	107.33	−41.35		−27.29
χ_7	C_2–C_1–O_1–HO_1	178.11	−177.23		177.78
χ_8	C_{11}–C_{12}–C_{13}–C_{14}	84.06	−49.62		117.09
χ_9	C_{13}–C_{14}–C_{15}–C_{16}	−111.56	−87.54	−150, −118	247.84
χ_{10}	C_{14}–C_{15}–C_{16}–C_{17}	−29.15	−6.42		61.06
χ_{11}	C_{15}–C_{16}–C_{17}–C_{18}	178.19	−177.75		178.96
χ_{12}	C_{16}–C_{17}–C_{18}–C_{19}	167.65	−64.64		−178 07
χ_{13}	C_{17}–C_{18}–C_{19}–C_{20}	64.54	−159.12		−180.96
χ_{14}	C_{18}–C_{19}–C_{20}–C_{200}	−52.89	−66.06		−61.34

Angle	Atom-atom-atom-atom	Model I	Model II	Model III	c	d
PGB_1						
χ_1	C_9–C_8–C_7–C_6	110.0	128 87	129.99	−91.9	120
χ_2	C_8–C_7–C_6–C_5	165.59	167.44	170.59	170.59	
χ_3	C_7–C_6–C_5–C_4	172.29	175.91	177.29	177.3	
χ_4	C_6–C_5–C_4–C_3	168.49	176.33	173.49	173.5	
χ_5	C_5–C_4–C_3–C_2	146.41	178.86	176.39	176.4	
χ_6	C_4–C_3–C_2–C_1	−179 60	176 90	170.39	170.4	
χ_7	C_3–C_2–C_1–O_{1B}	154.09	156.22	154.09	154.1	
α_8	C_2–C_1–O_1–O_{1A}	179 99	179.13	179.99	180.00	
χ_9	C_{11}–C_{12}–C_{13}–C_{14}	149.98	85.77	90.01	5.0	120
χ_{10}	C_{13}–C_{14}–C_{15}–C_{16}	−60 01	−76 61	−75.01	123.3	270
χ_{11}	C_{14}–C_{15}–C_{16}–C_{17}	166.69	144.65	141.71	166.7	
χ_{12}	C_{15}–C_{16}–C_{17}–C_{18}	179.99	−149.78	−150.01	180.0	
χ_{13}	C_{16}–C_{17}–C_{18}–C_{19}	−175.19	155.18	154.81	−175.2	
χ_{14}	C_{17}–C_{18}–C_{19}–C_{20}	177.59	193.09	177.59	177.6	
χ_{15}	C_{18}–C_{19}–C_{20}+d_{200}	−59.99	−57.67	−59.99	60.0	

a, Crystallographic data from reference 20; b, Conformational data from reference 29; c, Crystallographic data from reference 21; d, Conformational data from reference 26.

Table 3 *Partitioning of interaction energy (kcal mol^{-1}) in the different models for interaction of PGs with DPPC*

		E_{non}	$E_{ele+pol}$	E_{Hyd}	E_{Int}	ΔE_{Conf}	Total
$PGF_{2\alpha}$	Model I	−11 94	16.60	−80 67	−76.01	−0.35	−75.66
$PGF_{2\alpha}$	Model II	−22.47	9.53	−50.35	−63.28	−7.27	−70.55
PGB_1	Model I	−16.47	−3.59	0.0	−20.06	+8.72	−11.34
PGB_1	Model II	−14.52	5.21	−40.25	−49.56	+9.12	−40.44
PGB_1	Model III	−23.17	0.53	0 0	−22.64	+6.19	−16 45

E_{non}, Lennard Jones 6–12 potential; $E_{ele+pol}$, Electrostatic + polarization; E_{Hyd}, H-bonding contribution calculated using 10–12 potential; E_{Int}, Total interaction energy; E_{Conf}, Difference in conformation energy with respect to crystallography.

and hydroxy chain contribute 10% of the interaction energy.

In model III, where there are no specific H-bonds, the maximum contribution to the energy comes from the interaction between the aliphatic chains of DPPC and the carboxy chain of PG. It is purely of dispersive nature. There is some interaction between the five-membered ring and the aliphatic chains,

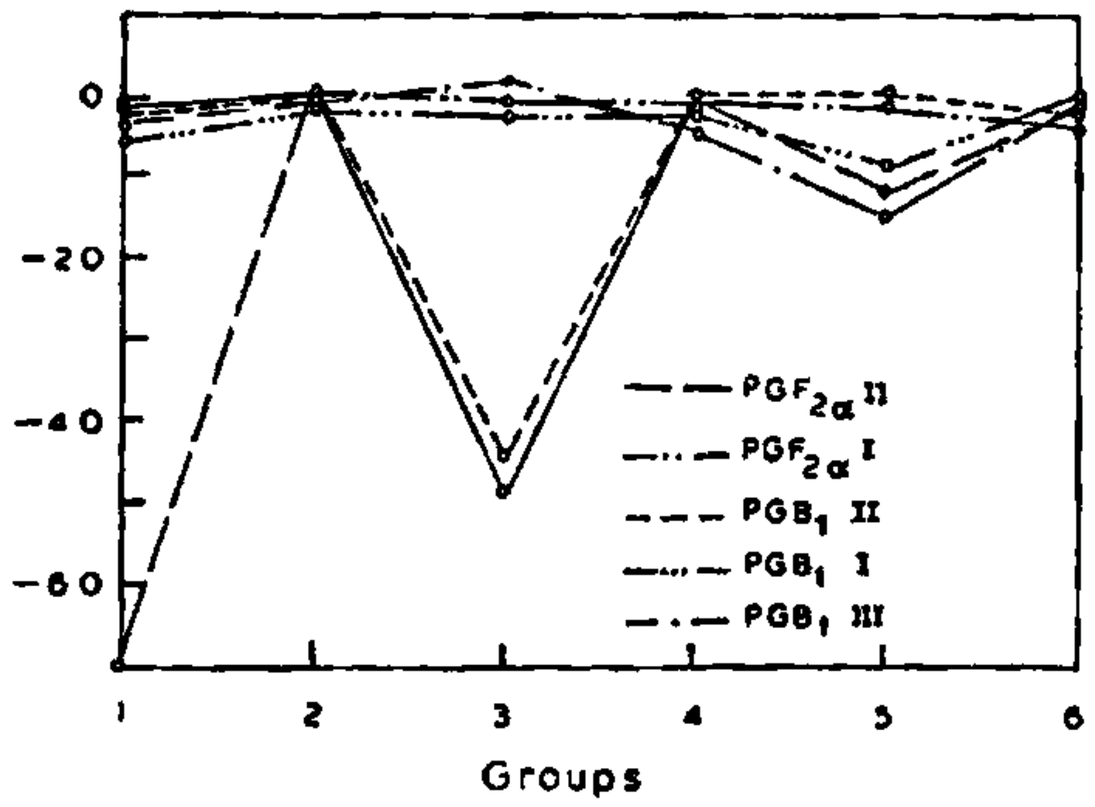

Figure 5. Partitioning of the total interaction energy for $PGF_{2\alpha}$ (models I and II) and PGB_1 (models I–III) with the DPPC molecule. The numbers 1 to 6 on the *x*-axis refer to contributions by interaction between (1) polar head of DPPC and five-membered ring of PG, (2) polar head and carboxylic chain of PG, (3) polar head and hydroxy chain of PG, (4) aliphatic chains of DPPC and five-membered ring of PG, (5) aliphatic chains and carboxy chain of PG, and (6) aliphatic chains of DPPC and hydroxy chain of PG.

which is of dispersive nature. A small amount of electrostatic interaction is found between the polar head and the hydroxy chain (figure 5).

CONCLUSIONS

The main site of interaction of PGs with membrane lipids is the polar head. The ring OH and the 15-(S)-OH groups make H-bonds with phosphate oxygens.

The conformation of $PGF_{2\alpha}$ is more suitable for interaction with the DPPC molecule. A very stable complex can be formed when 9α- and 11α-hydroxy groups of $PGF_{2\alpha}$ H-bond with O_2 and O_3 of DPPC. This interaction is stereo-specific.

It is possible that $PGF_{2\alpha}$ binds to DPPC non-specifically through the 15-hydroxy group. The 9α- and 11α-hydroxy groups in such a case point away from DPPC. Because of low-energy electrostatic potential around them, this region can serve as a good cation-binding site. Although PGB_1 can also bind to DPPC through the 15-(S)-OH group, the electrostatic potential around the ring is not suitable for binding to Ca^{2+}. The binding energy of PGB_1–DPPC is also much higher than that of $PGF_{2\alpha}$–DPPC and the former complex is energetically less favoured.

The present results show that the specificity in the molecular mechanism of action of PGs can be interpreted on the basis of their interaction with the polar head group of the lipid molecule. The orientation of the fatty acid chain of the lipid depends upon torsional angles $\theta 1$ and $\theta 3$ (as defined in reference 43). X-ray crystallography, NMR spectroscopy and theoretical conformation analysis[44–47] show considerable variation (from g^- to g^+) in these angles. Although these changes would modify the interaction of flexible fatty acid chains, they would have no direct influence on drug specificity since their total contribution to the stabilization energy is less than 15% (see figure 5).

To sum up, we believe that $PGF_{2\alpha}$ shows higher contractile activity because of its stereochemical compatibility with the DPPC molecule, which leads to proper orientation of functional groups. The trigger is offered by binding of PGs to DPPC through 15-(S)-hydroxy groups followed by binding of the cation to the ring hydroxy groups. PGB_1 is an antagonist because of the absence of this initial triggering interaction.

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