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DNA–phospholipid recognition: modulation by metal ion and lipid nature. Complexes structure and stability calculated by molecular mechanics

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Abstract

The structures and formation energies of nucleic acid–phospholipid complexes both in the absence and in the presence of Mg^{2+} ions were calculated taking double-stranded trinucleoside diphosphates NpNpN or heptanucleotides ApAp(NpNpN)pApA, composed of 64 possible combinations of genetic code, and phosphatidylcholine (PC) and sphingomyelin (SM) as model compounds. The dependence of intramolecular interactions on the primary structure of nucleic acid molecules and on the presence of a cationic bridge was revealed. The formation energies and structure of oligonucleotides were found by molecular mechanics calculations with the AMBER force field. The structures of phospholipid and $MgCl_2$ molecules were calculated by the semiempirical PM3 method, while the energies of phospholipid–oligonucleotide complexes were calculated by the molecular mechanics method. Calculations of complexes were carried out with consideration of solvation effects. Considerable gain in the formation energy of triple complexes is achieved due to the presence of the electroneutral metal bridge. A tendency toward increasing the stability of "triple" PC complexes (but not SM ones), containing guanosine- and cytidine-enriched triplets was revealed. Depending on the structure of NpNpN trinucleotides, the formation energy values of NpNpN–$MgCl_2$–PC and ApAp(NpNpN)pApA–$MgCl_2$–PC complexes differ by 1.7–2.6 kcal mol^{-1}, which can be considered as the atomic-scale manifestation of the recognition phenomenon. Presence of metal (II) ion bridge results in a greater stabilization of the phospholipid–nucleic acid complexes for SM in comparison to PC (the total energy difference equals to 4–16 kcal mol^{-1}). Depending on the structure of NpNpN trinucleotides, the formation energies of NpNpN–$MgCl_2$–SM and ApAp(NpNpN)pApA–$MgCl_2$–SM complexes differ by 1.7–2.1 kcal·mol^{-1}, which is essential at physiological conditions and can also be considered as the recognition effect.

Keywords: Phospholipid–nucleic acids complexes; Formation energy; Computer simulation; Molecular mechanics; Quantum-chemical calculations

1. Introduction

Four main classes of biopolymers, namely, proteins, nucleic acids, polysaccharides, and lipids are known. Only lipid–protein and nucleic acid–protein interactions, recognition and corresponding complexes were studied in detail [1]. Interactions of nucleic acids with (phospho)lipids and corresponding recognition phenomena have been poorly studied. Almost no information on structural–conformational and energy characteristics of nucleic acid–phospholipid complexes is available. At the same time, complexes of DNA with an internal nuclear membrane can be isolated and studied [2,3]. The formation of DNA and RNA complexes with phospholipid liposomes in model systems was studied in more detail [4–6]. It is known that DNA-bound lipids (neutral and phospholipids; weakly and tightly bound) take part in genome expression [7], and phospholipid vesicles can affect stability of the double DNA helix by causing its local unwinding [8]. Direct nucleic acid–phospholipid binding is hampered because of the electrostatic repulsion between negatively charged phosphate groups of lipids and DNA. However, it can be strengthened by introducing cationic bridges (e.g., metal (II) ions, M^{2+}) or positively charged fragments of polypeptides or proteins [9,10].

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The aim of this work is to evaluate a possible recognition phenomenon using the calculations of the structure and formation energy values of nucleic acid–phospholipid complexes with phosphatidylcholine (PC) and sphingomyelin (SM) as phospholipids both in the absence and in the presence of the Mg^{2+} ions. The recognition phenomenon can follow from the dependences of intermolecular interactions on the primary structure of nucleic acid and the nature of phospholipid molecule. Similar complexes of double-stranded nucleic acids with phosphatidylcholine liposomes have been studied turbidimetrically [5], by differential scanning microcalorimetry [8,11,12] and by spin and fluorescent labels [6,8]. The phase behavior of the lipid–DNA complexes aqueous salt solutions was studied theoretically [13–15]. Using a simplified model, in which the electrostatic and elastic interactions between the macromolecules were taken into account, a relative stability of a variety of the lipid–DNA aggregates such as the flat-bilayer, honeycomb, and cylindrical ones was determined [13–15]. However, a particular atomic structure of the lipids and DNA molecules was not considered in Refs. [13–15], this molecules being considered as the macroscopic phases. In this paper, an atomic-scale model of these complexes is presented.

To calculate structural and energy characteristics of such complexes, we determined energetically favorable mutual arrangements of the lipid and oligonucleotides, as well as the formation energies of lipid–nucleic acid complexes between phospholipids and oligonucleotides, containing various sequences of nitrogen bases using the molecular mechanics method. All calculations were performed under the assumption that nucleic acid molecules have the B-form and that the carbohydrate core has the 2′-*endo*-conformation. We chose the Mg^{2+} ion from all cations present in the cell as it is the only divalent metal ion whose concentration in the nucleus can reach high values.

2. Calculation procedure

Calculations were performed using the HYPERCHEM program (Version 4.5). The formation energies and structures of oligonucleotides were found by the molecular mechanics method with the AMBER force field developed for proteins and nucleic acids [16]. The structures of phospholipid and $MgCl_2$ molecules were calculated by the semiempirical PM3 method [17], whereas the energies of phospholipid–oligonucleotide complexes were calculated by molecular mechanics with fixed lipid geometry. The structures of the complexes were optimized using an original program written in the Visual Basic programming language, which made it possible to move the lipid molecule (with retention of its preliminarily optimized geometry) with respect to nucleotides and cationic bridge. The complexation energies were determined as differences between the total energies of the complexes and corresponding isolated molecules.

3. Results and discussion

We began the simulation of nucleic acid–phospholipid complexes with calculating the diethyl phosphate–Mg^{2+}–diadenosine monophosphate (ApA) complex, whose components served as phospholipid, bridging metal ion, and nucleic acid models, respectively. It was assumed that such a model will in some degree reflect the interaction between the phosphate groups of the phospholipid and nucleic acid molecules and Mg^{2+} ions. The calculated formation energy of the complex was 392 kcal mol^{-1}. However, lipid–nucleic acid interactions belong to much weaker intermolecular interactions, so the value indicated seems to be strongly overestimated. This is likely due to oversimplification of the bridge structure in this model. Structures with an electroneutral magnesium chloride bridge, which are described below, appeared to be more adequate to the weak interactions model. According to the different estimates, the formation energies of such complexes do not exceed 1–2 kcal mol^{-1} (with respect to 1 mol of phospholipid per pair of bases) [8,18].

Next we performed a molecular mechanics simulation of nucleic acid–phospholipid complexes with phosphatidylcholine as phospholipid (Fig. 1). Phosphatidylcholine plays an important role in the DNA–phospholipid interaction (for simplicity, hydrophobic residues of PC were shortened up to butyric acid fragments). Here, double-stranded trinucleoside

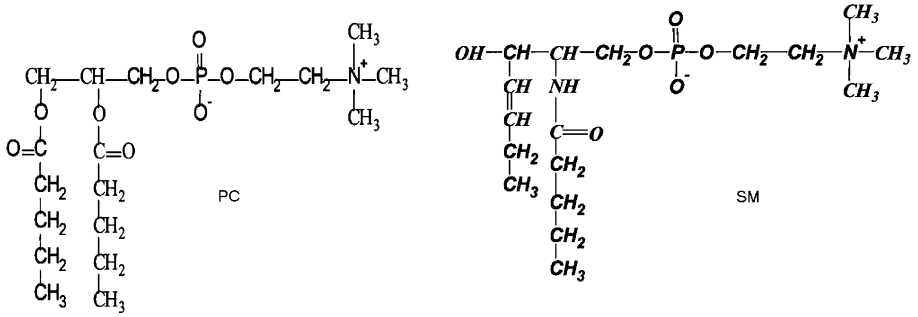

Fig. 1. Structures of phosphatidylcholine and sphingomyelin.

Table 1
Formation energies E (kcal mol^{-1}) of nucleic acid–phosphatidylcholine complexes d.s. NpNpN–PC, d.s. NpNpN–$MgCl_2$–PC, and d.s. ApAp(NpNpN)pApA–$MgCl_2$–PC depending on the oligonucleotides and on the presence of a bridging metal ion (Mg^{2+})

Complexes d.s. NpNpN–PC		Complexes d.s. NpNpN–$MgCl_2$–PC		Complexes d.s. ApAp(NpNpN)pApA–$MgCl_2$–PC	
Triplet	$-E$	Triplet	$-E$	Triplet	$-E$
GCC	13.6	GTC	27.1	CCC	16.3
GTC	13.3	GGC	27.1	TCC	15.9
TCC	13.3	GAC	27.0	CCA	15.9
ACC	13.2	GCC	27.0	GCC	15.8
GCT	13.1	GTT	26.9	CTC	15.7
TTC	13.1	GGT	26.9	CCG	15.7
GAC	13.1	GAT	26.8	CCT	15.6
ATC	13.0	GCT	26.8	CGC	15.6
GCA	12.9	GTA	26.8	TCA	15.6
GTT	12.9	GGA	26.8	GCA	15.5
TCT	12.9	GAA	26.7	CAC	15.5
TAC	12.8	GCA	26.7	ACC	15.3
CCC	12.8	GTG	26.6	CGA	15.3
ACT	12.8	AGC	26.6	CTA	15.3
GGC	12.8	GGG	26.6	TCG	15.3
AAC	12.7	ATC	26.5	TGC	15.3
GTA	12.7	TTC	26.5	TTC	15.3
TCA	12.7	TGC	26.5	GGC	15.3
TTT	12.7	GAG	26.5	TCT	15.3
GAT	12.6	AAC	26.5	GCG	15.2
CTC	12.6	GCG	26.5	CAA	15.2
ACA	12.6	ACC	26.4	GTC	15.2
ATT	12.6	TAC	26.4	TAC	15.1
TGC	12.5	ATT	26.4	GCT	15.1
AGC	12.4	AGT	26.4	CTG	15.0
GAA	12.4	TCC	26.4	GAC	15.0
TTA	12.4	TTT	26.4	CGG	15.0
TAT	12.4	TGT	26.4	ACA	15.0
CCT	12.4	AAT	26.3	TGA	15.0
ATA	12.4	ACT	26.3	CGT	15.0
GGT	12.3	ATA	26.3	TTA	14.9
GCG	12.3	AGA	26.3	CTT	14.9
CAC	12.3	TAT	26.3	CAG	14.9
AAT	12.3	TCT	26.3	GGA	14.9
TAA	12.2	TTA	26.2	GTA	14.8
CCA	12.2	TGA	26.2	TAA	14.8
CTT	12.2	AAA	26.2	CAT	14.8
GGA	12.1	ACA	26.2	GAA	14.7
GTG	12.1	TAA	26.1	ACG	14.7
TGT	12.1	TCA	26.1	AGC	14.7
AAA	12.1	ATG	26.0	TGG	14.7
TCG	12.1	AGG	26.0	TTG	14.7
CGC	12.0	CTC	26.0	GGG	14.6
ACG	12.0	TTG	26.0	ATC	14.6
AGT	12.0	CGC	26.0	TGT	14.6
CTA	11.9	TGG	26.0	GTG	14.6
CAT	11.9	AAG	26.0	ACT	14.5
TGA	11.9	ACG	25.9	TTT	14.5
TTG	11.9	CAC	25.9	GGT	14.5
GAG	11.9	CCC	25.9	TAG	14.5
AGA	11.8	TAG	25.9	AAC	14.5
ATG	11.8	TCG	25.9	GTT	14.5
CAA	11.7	CTT	25.9	GAG	14.4
TAG	11.6	CGT	25.9	TAT	14.4
CGT	11.6	CAT	25.8	AGA	14.3
CCG	11.6	CCT	25.8	GAT	14.3
GGG	11.6	CTA	25.7	ATA	14.3
AAG	11.5	CGA	25.7	AAA	14.2
CGA	11.4	CAA	25.6	AGG	14.0
CTG	11.4	CCA	25.6	ATG	14.0
TGG	11.3	CTG	25.5	AAG	13.9
AGG	11.2	CGG	25.5	AGT	13.9
CAG	11.1	CAG	25.4	ATT	13.8
CGG	10.8	CCG	25.4	AAT	13.7

diphosphates (NpNpN) composed of 64 possible combinations of guanosine (G), adenosine (A), cytidine (C), and thymidine (T), which are constituents of genetic code, were used as models of nucleic acid molecules. Na^+ ions were added to meet the condition of electroneutrality of the entire system. The complementary chain of nucleic acid molecule stabilizes the complex, thus making it possible to increase similarity between the model complex and that existing in solution. The parameters of (NpNpN)–PC and (NpNpN)–$MgCl_2$–PC complexes listed in Table 1 were calculated. Solvation effects were taken into account by placing the complex molecules into a cubic unit cell containing up to 1668 water molecules; the minimum distance between the complex and solvent molecules was 0.46 Å.

The most complex model is corresponded to ApAp(NpNpN)pApA–$MgCl_2$–PC complexes. In this case, two adenylic acid molecules were added in positions 3′ and 5′ of NpNpN trinucleotide in order to reduce the influence of boundary effects on the formation energies of the complexes. The sequence of three neutral nitrogen base molecules was varied to obtain 64 possible heptanucleotides.

We calculated the formation energies of all complexes with the above-mentioned trinucleotides or heptanucleotides. The results of calculations are listed in Table 1. In each column of Table 1, NpNpN trinucleotides are listed in descending order of complex stabilities. It follows from the data in Table 1 that the NpNpN–$MgCl_2$–PC derivatives, in which nucleic acid–phospholipid interactions occur with participation of a bridging metal ion, are 13–14 kcal mol^{-1} more stable than NpNpN–PC complexes, in which the choline group serves as a bridge. It should be noted that the mutual arrangement of the constituents of a bridge-containing complex at the energy minimum corresponds to the location of the Mg^{2+} ion between phosphate groups of the PC and DNA molecules. Such a structure obtained as a result of computer experiments indicates the possibility of the formation of a DNA–phospholipid contact at which the phosphate groups of interacting molecules form chemical bonds with the Mg^{2+} ion, which plays the role of a bridge. This model requires that Mg^{2+} cations necessarily be shielded by anions (e.g., Cl^-); otherwise it corresponds to extremely stable compounds similar to inorganic phosphates.

Table 2
Formation energies E (kcal mol^{-1}) of nucleic acid–sphingomyelin complexes d.s. NpNpN–SM, d.s. NpNpN–$MgCl_2$–SM, and d.s. ApAp(NpNpN)pApA–$MgCl_2$–SM depending on the oligonucleotides and on the presence of a bridging metal ion (Mg^{2+})

Complexes d.s. NpNpN–SM		Complexes d.s. NpNpN–$MgCl_2$–SM		Complexes d.s. ApAp(NpNpN)pApA–$MgCl_2$–SM	
Triplet	$-E$	Triplet	$-E$	Triplet	$-E$
GGC	10.3	GGT	31.1	CCC	30.2
GGT	10.2	GGG	31.1	TCC	30.1
GTC	10.1	GGA	31.0	GCC	29.9
GAC	10.0	GGC	31.0	CGC	29.9
GTT	10.0	GAT	30.7	CTC	29.8
GGA	10.0	GTT	30.7	CCA	29.8
GAT	10.0	GAG	30.7	TGC	29.8
GCC	9.9	GTG	30.7	GGC	29.7
GCT	9.8	GAA	30.6	CAC	29.7
GTA	9.8	AGT	30.6	TCA	29.7
GGG	9.8	GAC	30.6	TTC	29.6
GAA	9.8	GTA	30.6	CCG	29.6
AGC	9.7	GTC	30.6	GCA	29.6
GTG	9.6	AGG	30.6	CCT	29.6
GCA	9.6	AGA	30.6	CGA	29.5
TGC	9.6	AGC	30.6	TAC	29.5
GAG	9.6	TGT	30.5	GTC	29.5
AGT	9.6	TGG	30.5	TCG	29.4
TGT	9.5	TGA	30.5	TGA	29.4
ATC	9.5	TGC	30.4	ACC	29.4
AAC	9.4	GCT	30.4	TCT	29.4
TTC	9.4	GCG	30.3	CTA	29.4
GCG	9.4	GCA	30.3	GAC	29.4
ATT	9.4	GCC	30.3	CAA	29.3
TAC	9.4	AAT	30.2	GCG	29.3
AGA	9.4	ATT	30.2	CGG	29.3
TTT	9.4	AAG	30.2	GGA	29.3
AAT	9.3	ATG	30.2	TTA	29.3
ACC	9.3	CGT	30.2	GCT	29.2
TGA	9.3	CGG	30.2	CGT	29.2
TAT	9.3	AAA	30.2	TGG	29.2
TCC	9.3	AAC	30.2	AGC	29.2
ACT	9.2	ATA	30.2	CTG	29.2
ATA	9.2	ATC	30.2	TAA	29.1
AGG	9.2	TAT	30.2	TGT	29.1
TCT	9.2	TTT	30.2	ACA	29.1
AAA	9.1	CGA	30.1	GTA	29.1
TTA	9.1	CGC	30.1	GGG	29.1
TGG	9.1	TAG	30.1	CAG	29.1
TAA	9.1	TTG	30.1	CTT	29.1
ATG	9.0	TAA	30.1	GAA	29.0
ACA	9.0	TAC	30.1	TTG	29.0
AAG	9.0	TTC	30.1	GGT	29.0
TCA	9.0	TTA	30.1	ATC	29.0
TTG	9.0	ACT	29.9	CAT	29.0
TAG	8.9	ACG	29.9	TAG	28.9
CGC	8.9	ACA	29.8	TTT	28.9
ACG	8.8	ACC	29.8	AAC	28.9
CGT	8.8	CAT	29.8	ACG	28.9
TCG	8.8	CTT	29.8	GTG	28.9
CTC	8.7	TCT	29.8	AGA	28.8
CAC	8.7	CAG	29.8	TAT	28.8
CTT	8.6	CTG	29.8	GTT	28.8
CGA	8.6	TCG	29.8	GAG	28.8
CAT	8.5	CAA	29.7	ACT	28.7
CCC	8.5	TCA	29.7	GAT	28.7
CCG	8.5	CAC	29.7	ATA	28.6
CCT	8.4	CTA	29.7	AGG	28.6
CTA	8.4	CTC	29.7	AAA	28.5
CGG	8.4	TCC	29.7	ATG	28.4
CAA	8.3	CCT	29.5	AGT	28.4
CCA	8.2	CCG	29.4	AAG	28.3
CTG	8.2	CCA	29.4	ATT	28.1
CAG	8.2	CCC	29.4	AAT	28.1

Depending on the structure of NpNpN trinucleotides, the formation energy values of NpNpN–$MgCl_2$–PC and ApAp(NpNpN)pApA–$MgCl_2$–PC complexes differ by 1.7–2.6 kcal mol^{-1}, which can be considered as the atomic-scale manifestation of the recognition phenomenon. A tendency toward increasing the stability of PC complexes with guanosine-enriched triplets can be pointed out (see Table 1). For instance, complexes containing GGT, GGG, GGA, and GGC nucleotide sequences are by not less than 0.3 kcal mol^{-1} more energetically favorable than other complexes. The formation energies of ApAp(NpNpN)-pApA–$MgCl_2$–PC complexes are 10–13 kcal mol^{-1} lower than those of NpNpN–$MgCl_2$–PC complexes. This is likely due to changes in the packing of acyl residues upon elongation of the oligonucleotide chain, probably, in the large groove. From the data in Table 1, it follows with certainty that the phospholipid–nucleic acid structures containing oligonucleotides with three or two guanosine residues are the most energetically favorable.

Table 2 shows the results of the calculations of formation energy of complexes between the SM (Fig. 1b) and oligonucleotides. Sphingomyelin is selected for the second step of calculations, because of its comparatively high content in the nuclear membrane. Comparison of the formation energies of the NpNpN–SM and NpNpN–PC complexes points that the direct (phospho)lipid–nucleic acid interactions are weaker in the former case than in the latter one. However, presence of metal (II) ion bridge results in a greater stabilization of the phospholipid–nucleic acid complexes for SM in comparison to PC (the total energy difference equals to 4–16 kcal mol^{-1}). The greater stability of ternary SM complexes in comparison to PC ones explains well-known facts of high SM content in nuclear membrane and chromatin attachment to inner nuclear membrane [2,3,7]. Depending on the structure of NpNpN trinucleotides, the formation energies of NpNpN–$MgCl_2$–SM and ApAp(NpNpN)pApA–$MgCl_2$–SM complexes differ by 1.7–2.1 kcal mol^{-1}, which can also be considered as the recognition effect.

The calculations of ternary cardiolipin–DNA complexes, which are of great interest because of key role of cardiolipin in the structure and function of active chromatin, are in progress [7].

4. Conclusion

(i) Structural models for nucleic acid–phospholipid complex were proposed, and formation energy and the stabilities values for these complexes both with and without a bridging metal ion were estimated.

(ii) It is shown that a considerable gain in the formation energy of ternary complexes is obtained because of the presence of the electroneutral metal bridge as compared with the case of direct DNA–phospholipid interaction.

(iii) The stability of ternary PC complexes containing guanosine- and cytidine-enriched triplets grows up.

(iv) Depending on the structure of NpNpN trinucleotides, the formation energy values of NpNpN–$MgCl_2$–PC and ApAp(NpNpN)pApA–$MgCl_2$–PC complexes differ by 1.7–2.6 kcal mol^{-1}, which can be considered as the atomic-scale manifestation of the recognition phenomenon.

(v) Presence of metal (II) ion bridge results in a greater stabilization of the phospholipid–nucleic acid complexes for SM in comparison to PC (the total energy difference equals to 4–16 kcal mol^{-1}).

(vi) Depending on the structure of NpNpN trinucleotides, the formation energies of NpNpN–$MgCl_2$–SM and ApAp(NpNpN)pApA–$MgCl_2$–SM complexes differ by 1.7–2.1 kcal mol^{-1}, which is essential at physiological conditions and can also be considered as the recognition effect.

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