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# Effect of organic ligands with conjugated $\pi$-bonds on the structure of iodine–$\alpha$-dextrin complexes

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## Abstract.

Using X-ray data for iodine–$\alpha$-dextrin complexes and the results of quantum chemical *ab initio* restricted Hartree–Fock/3-21G** level calculations, a model of drug active complex (AC) Armenicum with anti-HIV action was proposed. It was suggested that the drug AC contains molecular iodine allocated inside of $\alpha$-dextrin helix and coordinated by lithium halogenides and a protein component of lymphocyte ribosomes. The electronic structure of $I_2$ in this complex differs from its characteristics in complexes with organic ligands or the free $I_2$. In the considered ACs, the molecular iodine displays acceptor (donor) properties toward the $\alpha$-dextrins (lithium halogenides). A mechanism of Armenicum anti-HIV action is suggested. Under the influence of molecular iodine-containing drug AC, the structure of HIV DNA is modified—it becomes more $\pi$-donor-active against proteins and peptide nucleotides of viral DNA form a stable complex with molecular iodine and lithium halogenides.


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**Keywords:** molecular iodine complexes, $\alpha$-dextrins, HIV, quantum chemical *ab initio* method

## 1. Introduction

Quite a number of iodine–polymer complexes with a broad spectrum of antimicrobic and antiviral action, including HIV infection, are well known. Among them there is "Armenicum," the drug aimed at HIV infection treatment [1–3]. The distinctive drug feature is that its active substance includes not only iodine-containing polymeric complex, but also potassium and lithium halogenides. Active substance "Armenicum" contains $LiI_5$–$\alpha$-dextrin complex. Lithium salts have potentially expressed antiviral action. In *in vitro* experiments using murine AIDS models, it was shown that lithium prevents the emergence of nearly every clinical immunodeficiency symptom [4].

Currently, a new anti-infective drug (AD) composed of polypeptides along with $LiI_5$–$\alpha$-dextrin complex is patented [5].

Under molecular iodine action, the whole of known microflora is killed, as iodine has antimicrobic and antiviral properties. However, all known iodine-containing drugs are characterized as highly toxic substances and therefore are not in fact used in medical practice for parenteral introduction.

Toxicological research of "Armenicum" and AD has shown that the classification "Globally Harmonized Classification System" can be attributed to four categories [6].

According to X-ray data, the secondary structure of $\alpha$-dextrin is represented by a left-handed helix with six glucose residues per turn. The cavity diameter of every turn amounts to ~5 Å with an ~8 Å pitch [7]. $Li^+I_5^-$–$\alpha$-dextrin complex structure was determined as well. In this structure $I_5^-$ ion was located along the helix; the distance between central $I^-$ ion and molecules of $I_2$ reaches ~3.6–3.7 Å, at which point the distance between atoms in $I_2$ rises up to 2.8–2.88 Å [8],[9].

Findings of experimental and clinical investigation of iodine ($^{131}J$) pharmacokinetics as the constituent of "Armenicum" showed the drug's ability to bind with blood lymphocytes and erythrocytes [10].

Lymphocytes have a spheroidical form and an oval nucleus surrounded by abundant ribosomes in the cytoplasm. On the basis of their chemical nature, ribosomes are nucleoproteins. Polypeptides enter into the AD drug.

In the present study, the influence of the amide component of peptides or nucleoproteins on $Li^+I_5^-$–$\alpha$-dextrin complex's structure and stability was studied within the framework of an *ab initio* method restricted Hartree–Fock (RHF)/3-21G** and a model of the drug active complexes (ACs) was proposed.

HIV belongs to the series of retroviruses whose gene within the virion is represented by an RNA molecule. After the

Abbreviations: AC, active complex; AD, anti-infective drug; HOMO, highest occupied molecular orbital; MO, molecular orbital; PIC, pre-integration complex; RHF, restricted Hartree–Fock; SB RAS, Siberian Branch of Russian Academy of Sciences.

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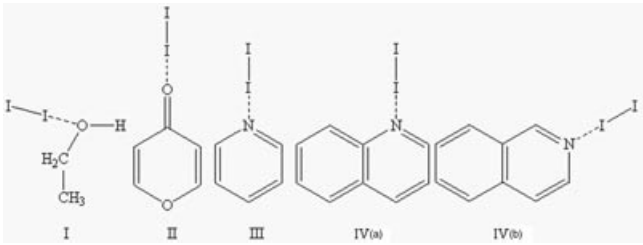

Fig. 1. Complexes of molecular iodine with organic ligands.

virus penetrates a human cell, a DNA copy of the virus genome is synthesized and this viral DNA is integrated into the genome of the human cell. Both processes are produced by the viral enzymes transcriptase and integrase.

It is typical for a family of enzymes such as HIV integrase to produce very stable complexes with a viral DNA. To be integrated, it is necessary for integrase to bind both—virus and cell—DNA molecules at the same time. The integration proceeds in two stages and begins in the cytoplasm of HIV-infected cells, where, upon completion of the reverse transcription of the virus DNA genome, integrase binds the viral DNA copy, producing the so-called pre-integration complex (PIC), which can be isolated from the HIV-infected cells [11].

The intercalation of the drug active substance into the viral DNA structure is considered to be a possible cause of inhibition of HIV DNA replication enzyme activity [12],[13].

In [13], the interaction of molecular iodine with HIV DNA nucleotide is studied by an *ab initio* RHF/3-21G** method. It is shown that molecular iodine prevents the formation of PIC and inhibits HIV-1 integrase enzyme inside the nucleoprotein complex, where $I_2$ interacts both with the viral DNA and the active center of the catalytic domain of the HIV-1 integrase, exhibiting acceptor properties with respect to the nucleotides of the viral DNA and donor properties with respect to $Mg^{2+}$ ions.

Among the recently developed drugs inhibiting the activity of HIV-1 integrase, there are those whose inhibiting activity is connected with the formation of coordination bonds with two $Mg^{2+}$ ions of the catalytic fragment of HIV-1 integrase [14]. The calculations revealed that the molecular iodine contained in iodine polymer complexes could be referred to this class of compounds; however, unlike the known inhibitors of HIV-1 integrase, $I_2$ also changes the structure of the viral DNA [13].

In the present study, the model of the proposed AC model of "Armenicum" and AD interaction with viral DNA nucleotides (guanosine and adenosine) was carried out.

The results of the study are summarized in three sections. In the first section, the selected calculation method was tested using model structures in accordance with X-ray data and experimental values of iodine complex's heat of formation energy with saturated and unsaturated organic compounds. In the second section, the influence of the amide component of polypeptides or nucleoproteins of lymphocyte ribosome on $LiXI_4$ (X = Cl, I)–$\alpha$-dextrin complex structure was studied, and an AC model of "Armenicum" and AD was proposed. In the third section, the interaction of drug AC with HIV DNA is discussed.

**Table 1**
**Interatomic distances: coordination bond length [O(N)—I, Å], bond length in molecule of $I_2$ (I—I, Å), experimental ($\Delta H^{exp}$, kcal/mol), and theoretical ($\Delta H^{theor}$, kcal/mol) heats of formation for iodine complexes with organic compounds, including atoms of nitrogen and oxygen**

| | I | II | III | IV(a) | IV(b) |
|---|---|---|---|---|---|
| $\Delta H^{exp}$ | 2.1–4.7 | 3.2 | 7.4–8.6 | 7.2 | 8.3 |
| $\Delta H^{theor}$ | 8.03 | 8.19 | 8.62 | 7.86 | 8.73 |
| O(N)—I | 2.72 | 2.72 | 2.68 | 2.75 | 2.68 |
| I—I | 2.72 | 2.72 | 2.74 | 2.74 | 2.74 |

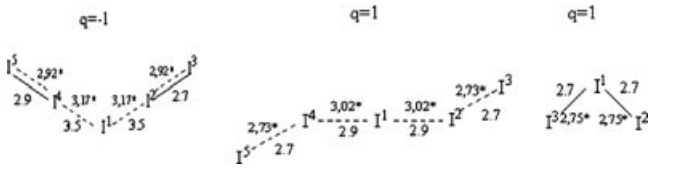


Fig. 2. X-ray data and calculation results obtained by method RHF/3-21G** (*) for iodine polycations and polyanions (Å).

## 2. Method

Iodine complexes as constituents of "Armenicum" and AD in human organism interact with a great number of bioorganic compounds; their functional donor-active fragments that might interact with molecular iodine groups include nitrogen and oxygen heteroatoms connected with functional group atoms by saturated or unsaturated bonds.

The ability of the RHF/3-21G** method to properly reproduce iodine complex formation energy with saturated and unsaturated organic ligands including nitrogen and oxygen atoms was tested using structures I–IV (Fig. 1; Table 1).

The theoretical heat of formation $\Delta H^{theor}$ was calculated for the temperature 298.15 K. Theoretical $\Delta H^{theor}$ calculated by the RHF/3-21G** method is close to the experimental values [15–19].

According to X-ray data for $I_2$–methylpyridine complex, $R_{N—I} = 2.31$ Å, whereas $R_{I—I}$ varies from 2.67 Å in free $I_2$ molecule up to 2.83 Å in complex [20]. The RHF/3-21G** method overestimates N—I bond length, whereas for the I—I bond, it gives close to experimental values in free iodine molecule (2.68 Å) and in complex (Table 1).

The RHF/3-21G** method's ability to properly reproduce the molecular parameters in charged iodine polycation and polyanion geometry was tested using structures V–VII. The RHF/3-21G** method properly reproduces the geometry of ions of $I_5$ ($q = -1$), $I_5$ ($q = 1$), and $I_3$ ($q = 1$), and the calculated bond lengths are close to the experimental X-ray data (Fig. 2) [21].

Calculations were performed using the Gaussian 03 program.

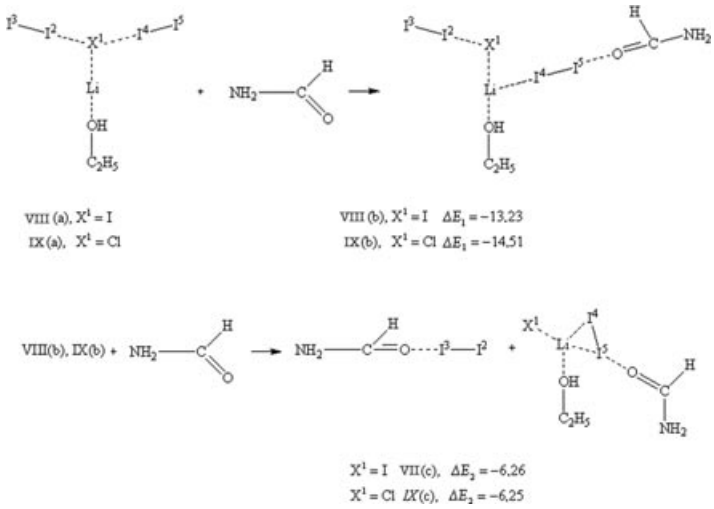


Fig. 3. Mechanism of formation of the active complex drugs Armenicum and AD. Energy of formation ($\Delta E_1$, kcal/mol) and energy of reorganization ($\Delta E_2$, kcal/mol) of complexes VIII (b) and IX (b) for process interaction of complex VIII(a)–IX(a) with peptides or protein components of the ribosome lymphocytes.

**Table 2**
**Interatomic distances (Å) in iodine complexes with organic ligands and lithium halogenides VIII(a,c)–IX(a,c)**

| | Li–O | Li–$X^1$ | Li–$I^4$ | $X^1$–$I^2$ | $X^1$–$I^4$ | $I^2$–$I^3$ | $I^4$–$I^5$ |
|---|---|---|---|---|---|---|---|
| VIII(a) | 1.80 | 2.64 | 3.05 | 3.58 | 3.54 | 2.72 | 2.72 |
| VIII(b) | 1.82 | 2.66 | 2.90 | 3.24 | 4.79 | 2.80 | 2.75 |
| VIII(c) | 1.80 | 2.60 | 2.94 | – | 4.85 | – | 2.75 |
| IX(a) | 1.81 | 2.24 | 3.02 | 3.28 | 3.25 | 2.72 | 2.72 |
| IX(b) | 1.82 | 2.22 | 2.94 | 3.06 | 4.63 | 2.75 | 2.77 |
| IX(c) | 1.80 | 2.21 | 2.94 | – | 4.43 | – | 2.76 |

## 3. Drug AC model

By use of the RHF/3-21G** method, calculation of structures for the model $LiXI_4$–α-dextrin complexes VIII(a)–IX(a) was performed (Fig. 3). In the calculations, the hydrocarbon glucose fragment, including an oxygen atom, was replaced with ethanol. Interaction of VIII(a)–IX(a) complexes with polypeptides or ribosome protein component was modeled by VIII(b)–IX(b) structures (Fig. 3).

Interatomic distances for structures VIII(a,c)–IX(a,c) are given in Table 2. Calculations provide interatomic distances in complex VIII(a) close to X-ray values for $Li^+I_5^-$–α-dextrin complexes [7–9].

The calculated data show that in the presence of protein, a transition of VIII(a)–IX(a) structures to more stable VIII(c)–IX(c) structures, including $Li^+I_3^-$, is possible. This process may be carried out in two steps. At the first step of coordination, bond formation between amide and $I^4$–$I^5$ is energy profitable and results in a change in $LiXI^4$–$I^5$ spatial structure; in complexes VIII(b)–IX(b), $Li^+$ is coordinated with negative ion $I^3$–$I^2X^1$ and iodine ($I^4$–$I^5$). In these structures, molecular iodine ($I^4$–$I^5$) displays acceptor properties relative to amide, forming a complex with charge transfer, and donor properties relative to ion pair LiX. At the next step, iodine molecule $I^3$–$I^2$ may be also coordinated by an amide protein component. It results in destruction of complexes VIII(b)–IX(b) and formation of charge-transfer complex $NH_2CHO$–$I_2$ and complexes VIII(c)–IX(c).

Figure 3 displays complex formation energies ($\Delta E_1$) for VIII(b)–IX(b) under amide interaction with VIII(a)–IX(a) at the first process step. In addition, complex reconstruction energies ($\Delta E_2$) for VIII(b)–IX(b) at the second step under amide interaction with VIII(b)–IX(b) are also provided. The $\Delta E_1$ and $\Delta E_2$ energies are calculated as follows:

$$\Delta E_1 = E^{tot}_{VIII(b),IX(b)} - E^{tot}_{VIII(a),IX(a)} - E^{tot}(NH_2CHO) \quad (1)$$

where $E^{tot}_{VIII(b),IX(b)}$ is the total energy of complexes VIII(b)–IX(b), $E^{tot}_{VIII(a),IX(a)}$ is the total energy of complexes VIII(a)–IX(a), and $E^{tot}(NH_2CHO)$ is the total energy of amide.

$$\Delta E_2 = E^{tot}_{VIII(c),IX(c)} + E^{tot}(NH_2CHO{-}I_2) - E^{tot}_{VIII(b),IX(b)} - E^{tot}(NH_2CHO) \quad (2)$$

where $E^{tot}_{VIII(c),IX(c)}$ is the total energy of complexes VIII(c)–IX(c), $E^{tot}_{VIII(b),IX(b)}$ is the total energy of complexes VIII(b)–IX(b), and $E^{tot}(NH_2CHO{-}I_2)$ is the total energy of amide–molecular iodine complex.

Energy and electronic parameters (charges were calculated by the Mulliken scheme) of complexes VIII(a,c)–IX(a,c) are well coordinated with each other. At every subsequent process step, the charge transfer to a $LiXI^4$–$I^5$ fragment increases (Table 3).

Energy and electronic parameters of complexes VIII(c)–IX(c) demonstrate that in these structures, molecular iodine displays acceptor properties toward amide and donor properties toward halogenides. The formation of complexes VIII(c)–IX(c) from two complexes, $LiXOHC_2H_5$ and $I_2$–amide complex, is energy favorable [$\Delta E = -25.09$ kcal/mol for VIII(c) and $\Delta E = -27.44$ kcal/mol for IX(c)]; at that charge transfer to ion pair LiX, coordinated by $I_2$, in complexes VIII(c)–IX(c) is significantly greater compared to complex $LiXOHC_2H_5$ (Table 3).

Pharmacokinetic studies revealed that under "Armenicum" intrablood infusion, iodide ion is detected in blood; at the same time, its concentration varies in proportion to the introduced drug dose [22]. Calculations demonstrated that in the presence of $I^-$ (their blood content is determined by KI as the drug constituent), the $NH_2CHO$–$I_2$ complex decomposition into amide and iodide ion $I_3^-$ is energy profitable ($\Delta E = -16$ kcal/mol). Iodide ion present in the blood is probably a consequence of this process.

Complexes VIII(c)–IX(c) are also calculated with the most donor-active (with respect to molecular iodine) fragments of amino acid residues of polypeptides or proteins (Fig. 4).

Energy of formation AC $\Delta E_3$ is calculated as follows:

$$\Delta E_3 = E^{tot}(AC) - E^{tot}(LiXet) - E^{tot}(complex\ I_2) \quad (3)$$

where $E^{tot}$ (AC) is the total energy of AC, $E^{tot}$ (LiXet) is the total energy of lithium halogenide ethanol complex, and $E^{tot}$ (complex $I_2$) is the total energy of iodine complex with amino acid.

**Table 3**
**Charge distribution in iodine complexes with organic ligands and lithium halogenides VIII(a,c)–IX(a,c)**

| | $\Delta Q$ ($LiX^1I^4I^5$) | $\Delta Q$ ($LiX^1$) | Li | $X^1$ | $I^2$ | $I^3$ | $I^4$ | $I^5$ |
|---|---|---|---|---|---|---|---|---|
| VIII(a) | −0.193 | −0.171 | 0.374 | −0.545 | 0.085 | −0.080 | 0.079 | −0.101 |
| VIII(b) | −0.225 | −0.232 | 0.357 | −0.589 | −0.278 | 0.098 | −0.141 | 0.148 |
| VIII(c) | −0.273 | −0.255 | 0.372 | −0.627 | −0.148 | 0.064 | 0.173 | −0.191 |
| IX(a) | −0.210 | −0.219 | 0.453 | −0.672 | 0.099 | −0.073 | 0.098 | −0.089 |
| IX(b) | −0.221 | −0.191 | 0.487 | −0.678 | 0.107 | −0.190 | −0.208 | 0.178 |
| IX(c) | −0.279 | −0.248 | 0.480 | −0.728 | −0.148 | 0.064 | 0.180 | −0.211 |

$\Delta Q$ (LiI) $= -0.148$ for $LiIOHC_2H_5$ and $\Delta Q$ (LiCl) $= -0.145$ for $LiClOHC_2H_5$.

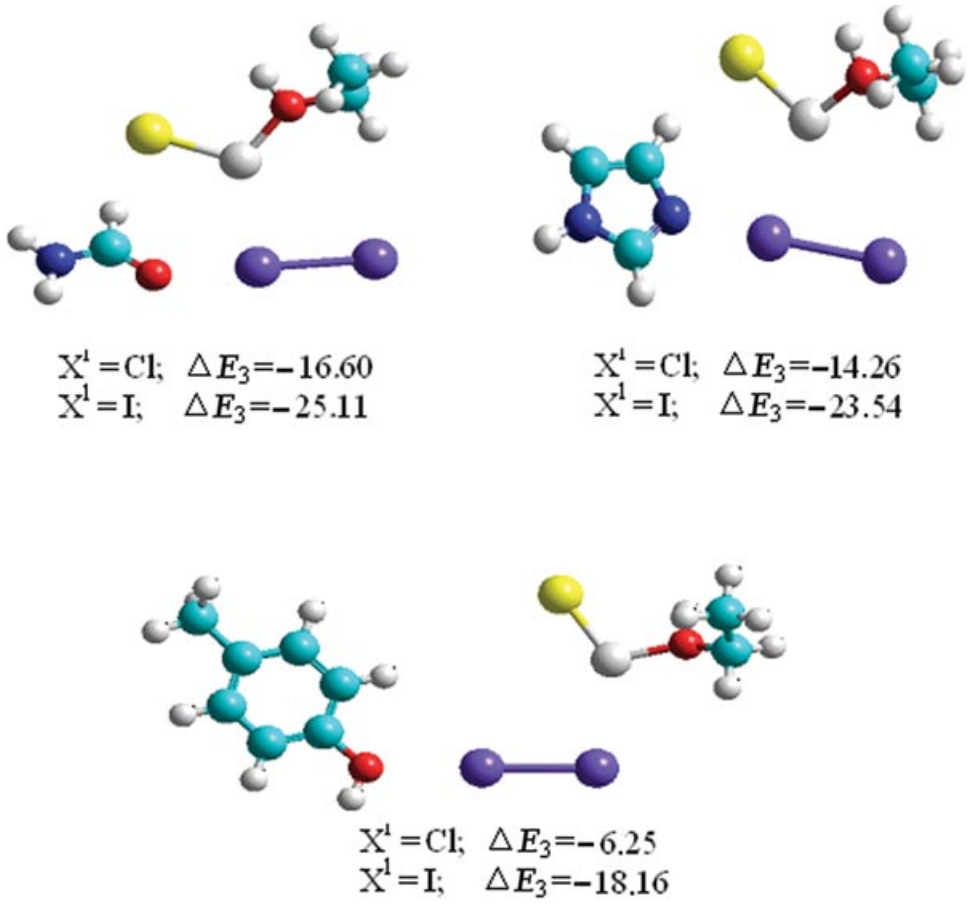


Fig. 4. Energy of formation ($\Delta E_3$, kcal/mol) of active complex (amino acid residues, molecular iodine, lithium halogenides ethanol complex; red, oxygen; blue, carbon; dark blue, nitrogen; violet, iodine; white, lithium; yellow, halogen (X = I, Cl).

The data of calculations indicate that the most stable structure is formed when the amino acid residues contain the amide fragment. Amino acid residues asparagine and glutamine contain amide fragment.

Thus, X-ray data for lithium halogenides–$\alpha$-dextrins complexes and calculated results suggest that the AC of AD and "Armenicum" include $Li^+XI_2$, located inside of $\alpha$-dextrin helix and in addition are coordinated by the amide polypeptide component in the case of AD and the protein ribosome component in the case of "Armenicum."

## 4. Drug AC interaction with nucleotide bases of HIV DNA

The AC complex located inside of $\alpha$-dextrin helix molecular iodine, coordinated by lithium halogenides and amide protein

**Table 4**
**Complex formation energy ($\Delta E$, kcal/mol) and electronic structure parameters: energies HOMO in free ligands ($E^{HOMO}$, eV) and charge transfer to molecular iodine ($\Delta Q$) for molecular iodine complexes with amide and nucleotide purine bases**

| | X | XI | XII |
|---|---|---|---|
| $-\Delta E$ | 10.07 | 10.93 | 11.50 |
| $-E^{HOMO}$ | 10.94 | 8.39 | 7.96 |
| $-\Delta Q$ | 0.084 | 0.107 | 0.110 |

component, appears to be hard to reach for interaction with bioorganic compounds. Bioorganic compounds are able to compete with $I_2$ only in complexes; their donor activity is greater as against amide.

In Table 4, energetic and electronic parameters of molecular iodine complexes with amide and nucleotide purine bases (Fig. 4) are displayed. In the calculations, a model complex is considered and the sugar–phosphate fragment is replaced by a $CH_3$ group on the assumption that the sugar–phosphate fragment of the nucleotides should not significantly affect the donor properties of the bases.

The results of calculations demonstrate that $I_2$ complexes with adenosine and guanosine are more stable in comparison with $I_2$–amide complex (Fig. 5).

In the electronic structure of complexes X–XII, not only molecular orbital (MO) could be defined with the contribution of $I_2$ $\sigma$-orbitals and *n*-pair of heteroatoms, specific for iodine complexes with saturated organic ligands, but MO as well with contribution of ligand $\pi$-orbitals and $I_2$ $\pi$-orbitals.

In the $I_2$ molecule, the highest occupied molecular orbitals (HOMO) are represented by two degenerate $\pi_g$-orbitals with an energy of–9.61 eV. The next two degenerate $\pi_u$-orbitals are characterized by an energy of –11.72 eV. In HOMO of the amide molecule, the main contribution is provided by $\pi_u$-orbitals of carbonyl group double bond, whereas in adenosine and guanosine molecules, by $\pi_{u,g}$-orbitals of heterocycles. Amide HOMO is located higher than the $I_2$ $\pi_u$-orbital and thus under III complex formation, $\pi$-electron density transfer from amide HOMO to $I_2$ $\pi_u$-orbital is possible. HOMO of adenosine and guanosine are allocated higher than $I_2$ HOMO; thus under the formation of complexes IV and V, the electron density transfer from HOMO of adenosine and guanosine to $I_2$ $\pi_g$- and $\pi_u$-orbitals is feasible.

As seen from the data in Table 4, the higher the energy of ligand HOMO, more charge transfer to $I_2$ is carried out. This process stabilizes the complex.

Within the framework of the RHF/3-21G** method, the calculations of structures XIII–XVI that approximate the proposed AC model interaction with nucleotide purine bases (Fig. 6) were performed. Nitrogen atom of a pentamerous ring was selected as a site for complex formation because in the Watson–Crick pairs, this atom does not take part in hydrogen bond formation. In addition, the sugar–phosphate fragment was replaced by a $CH_3$ group.

Two ligands with conjugated $\pi$-bonds competing for complex formation with $I_2$ are the constituents of the structures XIII–XVI. Spatial and energy characteristics of the structures XIII–XVI obtained as a result of geometry optimization demonstrate that nucleotide interaction with AC is energy profitable. Within these species, the purine bases of adenosine and guanosine replace amide and form a complex with molecular iodine and lithium halogenides (Fig. 6).

Complex formation energy for XIII–XVI $\Delta E_3$ was calculated as follows:

$$\Delta E_4 = E^{tot}_{XIII-XVI} - E^{tot}_{VIII(c),IX(c)} - E^{tot}_{aden,guan} \qquad (4)$$

where $E^{tot}_{XIII-XVI}$ is the total energy of structures XIII–XVI, $E^{tot}_{VIII(c),IX(c)}$ is the total energy of structures of model drug AC, and $E^{tot}_{aden,guan}$ is the total energy of nucleotides.

In complexes XIII–XVI as well as in VIII(c)–IX(c), the $I_2$ molecule forms a coordination bond with ion pair LiX (Fig. 6).

## 5. Conclusion

Based on the X-ray data for iodine–$\alpha$-dextrin complexes and calculated results, it is possible to conclude that AC of AD and "Armenicum" contains molecular iodine located inside of an $\alpha$-dextrin helix and coordinated by lithium halogenides and amide protein component. In this complex, the electronic structure of $I_2$ differs from that of $I_2$ in complexes with organic ligands or in free molecule. In AC of these drugs, molecular iodine displays acceptor properties relative to $\alpha$-dextrins and donor characteristics relative to lithium halogenides.

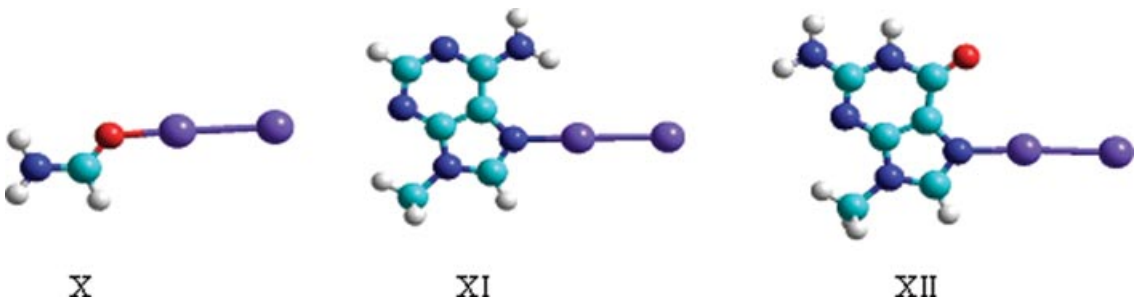


Fig. 5. Complexes of molecular iodine with amide and purine bases of nucleotides; red, oxygen; blue, carbon; dark blue, nitrogen; violet, iodine; white, lithium.

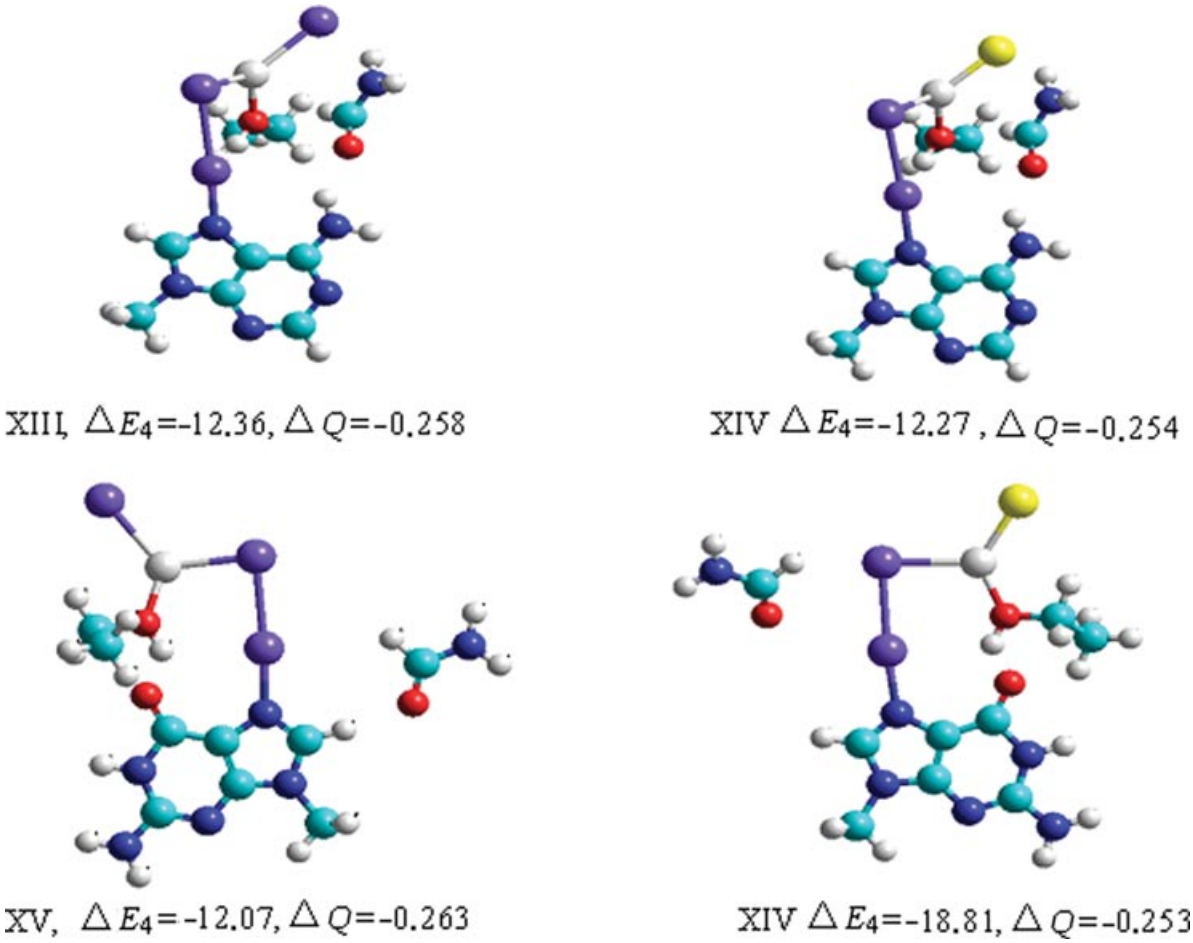


Fig. 6. Model of interaction of the active complex Armenicum and AD with nucleotides of HIV DNA. Energy of formation of complexes XIII–XVI ($\Delta E_4$, $\Delta$kcal/mol) and charge transfer ($\Delta Q$) in ion pair LiX (X = Cl, I); red, oxygen atoms; blue, carbon; dark blue, nitrogen; violet, iodine; yellow, chlorine; white, lithium.

Perhaps after the penetration of drug AC into the cytoplasm of infectious cells under the influence of AC, the structure of HIV DNA changes and becomes more $\pi$-donor active as against proteins, and peptide nucleotides of viral DNA form a stable complex with molecular iodine and lithium halogenides.

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