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BINDING ACTIVITY OF THE QUADRUPLE BONDING DIRHENIUM(III) COMPOUND WITH BENZIMIDAZOLE LIGANDS TO NON-CANONICAL DNA

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Abstract

The aim of the work was to investigate the binding activity of the quadruple bonding dirhenium(III) compound with benzimidazole ligands to G4 DNA. Dirhenium(III) complexes with an unique quadruple bond are especially promising candidates for clinical development due to their very low toxicity, anticancer and antioxidant activity The binding affinity of G4 DNA to Re(III) complexes was obtained from UV–vis absorption titration. We have obtained data about the considerable hyperchromism and significant shift of the absorption maximum to the low wave side (blue shift) in UV-region usually correlating with a conformational change for G4 DNA on binding or complex formation for substances-groove binders. The electronic absorption titrations indicate that dirhenium complex compound with benzimidazole ligands interacts relatively strongly with G4 (Kb = $5.258 \cdot 10^4$ for c-kit1 and $4.653 \cdot 10^4$ for HTelo22). We have found, that addition of the G4-quadruplexes (ckit-1 or HTelo22) led to the intensive increase of the absorption maximum in visible region, that was the same for both nucleotides. This increasing of intensity can't describe formation of any other complex without containing the quadruple bond. We may assume that this absorption appeared due to di(tri, poly)-merization of the nucleotide-complex compound. Hyperchromicity and binding constant of dirhenium(III) complex compound is higher for c-kit1 in comparison to HTelo22, thus suggesting that c-kit displays enhanced interaction. The HTelo22 sequence contains no free guanines besides those participating in the G4 fold whereas c-kit1 features three non-stacked guanines, making them potentially accessible for an easier covalent binding of dirhenium(III) compound with benzimidazole ligands.

Keywords: dirhenium(III) complexes; G4 DNA; benzimidazole; binding constant.

ЗВ'ЯЗУЮЧА АКТИВНІСТЬ БЕНЗІМІДАЗОЛЬНОГО КОМПЛЕКСУ ДИРЕНІЮ(III), ЩО МІСТИТЬ ЧЕТВЕРНИЙ ЗВ'ЯЗОК, ДО НЕКАНОНІЧНОЇ ДНК

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Антоація

Метою роботи було дослідження зв'язуючої активності сполук диренію(III) з бензімідазольними лігандами, до складу яких входить четверний зв'язок метал-метал, з ДНК G4-квадруплексами. Комплекси диренію(III) з унікальним четверним зв'язком є особливо багатообіцяючими кандидатами для клінічного застосування через їх дуже низьку токсичність, протипухлинну та антиоксидантну активності. Зв'язування ДНК G4 з комплексами Re(III) було досліджено за допомогою електронної абсорбційної спектроскопії шляхом титрування. Ми отримали дані про гіперхромізм та зсув максимуму поглинання у бік низьких хвиль (синій зсув) в УФ-області, що корелює з конформаційною зміною ДНК G4 за умови зв'язування або комплексоутворення речовин, які не належать до інтеркаляторів, а проявляють жолобочне зв'язування. Спектральні дані показали, що комплексна сполука диренію(III) з бензімідазольними лігандами досить сильно взаємодіє з G4 (Kb = $5.258 \cdot 10^4$ для c-kit1 та $4.653 \cdot 10^4$ для HTelo22). Ми виявили, що додавання G4-квадруплексів (ckit-1 або HTelo22) призводило до інтенсивного збільшення максимуму поглинання у видимій області, що було однаковим для обох нуклеотидів. Таке збільшення інтенсивності не може описати утворення будь-якого іншого комплексу без четверного зв'язку реній-реній. Можна припустити, що таке поглинання виникло за рахунок ді(три, полі)-мерізації нуклеотид-комплексної сполуки. Гіперхромізм і константа зв'язування комплексної сполуки диренію(III) вище для c-kit1 у порівнянні з HTelo22, що дозволяє припустити, що c-kit демонструє більш інтенсивну взаємодію. HTelo22 не містить вільних гуанінів, крім тих, які беруть участь в утворенні G4, в той час як c-kit1 містить три неупакованих гуаніна, що робить їх потенційно доступними для більш легкого ковалентного зв'язування сполукою диренію(III) з бензімідазольними лігандами.

Ключові слова: комплекси диренію(III); ДНК G4; бензімідазол; константа зв'язування.

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СВЯЗУЮЩАЯ АКТИВНОСТЬ БЕНЗИМИДАЗОЛЬНОГО КОМПЛЕКСА ДИРЕНИЯ(III), КОТОРЫЙ СОДЕРЖИТ ЧЕТВЕРНУЮ СВЯЗЬ, К НЕКАНОНИЧНОЙ ДНК

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Аннотация
Целью работы было исследование связывающей активности соединений дирения(III) с бензимидазольными лигандами, в состав которых входит четверная связь металл-металл, с ДНК G4-квадруплексами. Комплексы дирения(III) с уникальной четверной связью являются особенно многообещающими кандидатами для клинической разработки из-за их очень низкой токсичности, противоопухолевой и антиоксидантной активности. Связывание ДНК G4 с комплексами Re(III) было исследовано с помощью электронной абсорбционной спектроскопии путём титрования. Мы получили данные о гиперхромизме и значительном смещении максимума поглощения в сторону низких волн (синий сдвиг) в УФ-области, что коррелирует с конформационным изменением ДНК G4 при связывании или комплексообразовании веществ, которые не относятся к интеркаляторам, а проявляют желобочное связывание. Спектральные данные показали, что комплексное соединение дирения с бензимидазольными лигандами достаточно сильно взаимодействует с G4 (Kb = $5.258 \cdot 10^4$ для c-kit1 и $4.653 \cdot 10^4$ для HTelo22). Мы обнаружили, что добавление G4-квадруплексов (ckit-1 или HTelo22) приводило к интенсивному увеличению максимума поглощения в видимой области, что было одинаковым для обоих нуклеотидов. Это увеличение интенсивности не может описать образование какого-либо другого комплекса без четверной связи рений-рений. Можно предположить, что это поглощение возникло за счет ди (три, поли) -меризации нуклеотид-комплексное соединение. Гиперхромизм и константа связывания комплексного соединения дирения(III) выше для c-kit1 по сравнению с HTelo22, что позволяет предположить, что c-kit демонстрирует более интенсивное взаимодействие. HTelo22 не содержит свободных гуанинов, кроме тех, которые участвуют в образовании G4, тогда как c-kit1 содержит три неупакованных гуанина, что делает их потенциально доступными для более лёгкого ковалентного связывания соединения дирения(III) с бензимидазольными лигандами.

Ключевые слова: комплексы дирения(III); ДНК G4; бензимидазол; константа связывания.

Introduction

In recent years, significant attention was devoted to the role of metal complexes as anticancer drugs targeting the non-canonical sequences of DNA [1–5]. These non-canonical DNA patterns were found in some important regulatory points of DNA processing, for example, in telomers. In telomeric DNA, the four bases of the rich sequence of guanine form a square planar structure through eight hydrogen bonds and establish a G-quadruplex (G4) structure in the presence of sodium or potassium ions [6]. In new anticancer chemotherapy, telomerase inhibition and G4 stabilization are considered as some crucial pharmacological targets.

The stabilization of G4 DNA can prevent telomere elongation because G4 is an effective inhibitor of telomerase enzyme action, which has greater activity in 85% of cancer cells. So far, some experiments have been conducted on G4 stabilization by connecting them to suitable compounds such as metal complexes [7]. The metal center effect on enhancing the interaction of ligands with G4 DNA was clearly shown [7]. Among the N-heterocyclic derivatives, benzimidazoles have been reported to show a variety of valuable biological activities [8].

Dirhenium(III) complexes with a unique quadruple bond are especially promising candidates for clinical development due to their very low toxicity, anticancer and antioxidant activity [9]. Recently we have synthesized and characterized a new compound containing both benzimidazole ligands and dirhenium moieties [10].

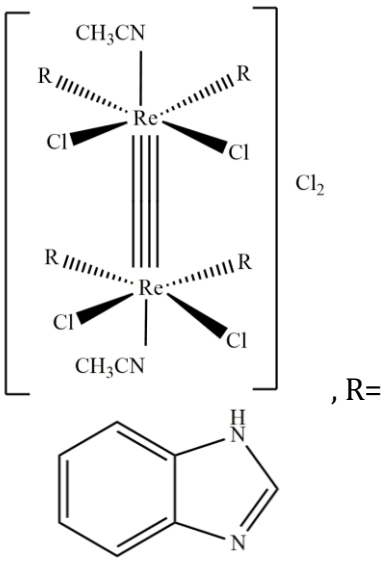

Fig. 1. Structure of the $[Re_2(Benzim)_4Cl_4(CH_3CN)_2]Cl_2$ (I)

Spectral investigations of some low-molecular weight substances and biological molecules were conducted, which brought information about possible mechanisms of interactions between these molecules [11]. Taking all of the above into account, the purpose of the following investigation was exploring the interaction of **I** with two DNA G4 using electronic absorption spectra (EAS).

Results and discussion

Electronic absorption spectroscopy in DNA-binding studies is one of the most useful techniques [12; 13]. Due to the intercalative mode involving a strong stacking interaction between an aromatic chromophore and the base pairs of DNA, the binding of small molecules to DNA through intercalation usually results in hypochromic (or hyperchromic) effect, a broadening of the envelope, and a red shift (or blue shift) of the complex absorption band. In the case of groove binders, a large wavelength shift is usually correlated with a conformational change on binding or complex formation.

According to the procedures described above, the interaction between DNA and **I** was investigated in two zones: 220–270 nm and 500–700 nm. The obtained spectra in the first zone for c-kit were presented on the Figure 2 and are typical for titration of DNA in this absorption region.

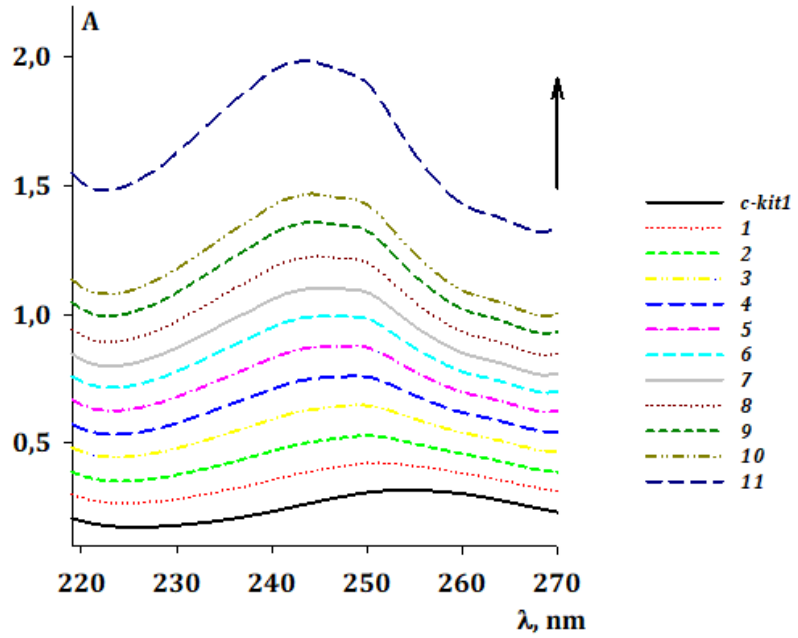

Fig. 2. UV–Vis titration spectra in the region 220-270 nm of c-kit1 (1 μM, constant concentration) with Re(III) cluster compound (0-15 μM) in cacodylate buffer: 1 μM complex (1); 2 μM complex (2); 3 μM complex (3); 4 μM complex (4); 4 μM complex (4); 5 μM complex (5); 6 μM complex (6); 7 μM complex (7); 8 μM complex (8); 9 μM complex (9); 10 μM complex (10); 15 μM complex (11).
The arrows show the intensity changes corresponding to an increase of complex concentration.

We have obtained data on essential hyperhromism and a significant shift of the absorption maximum to the low wave side (blue shift). Plots of $A_0(A_0–A)$ versus 1/[**I**] for c-kit1 and HTelo22 are presented on the Figure 3 and the calculated parameters from these measurements are presented in the Table.

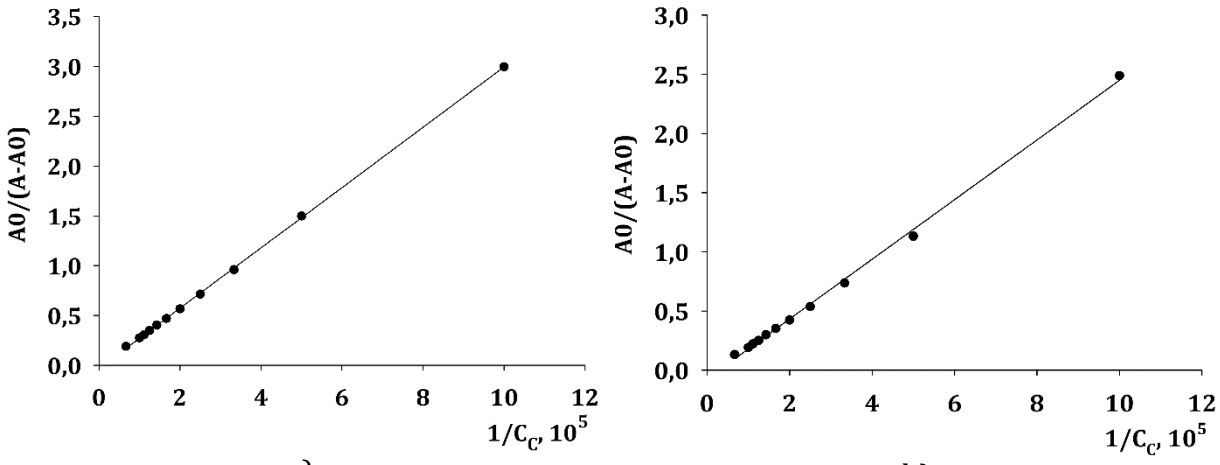

Fig. 3. The plots of $A_0(A_0-A)$ versus 1/[Complex] for c-kit1 (a) and HTelo22 (b)

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Table

Parameters calculated from the obtained UV spectra

Compound	Δλmax	%Hyperchromism	K_b, l/mol
c-kit1 (constant) + **I**	-10 nm	88.27	$5.258 \cdot 10^4$
HTelo22 (constant) + **I**	-12 nm	84.08	$4.653 \cdot 10^4$

These binding constants (Kb = $5.258 \cdot 10^4$ for c-kit1 and $4.653 \cdot 10^4$ for HTelo22) are lower than those observed for intercalating compounds (10^6-10^7 M^{-1}) [14]. The blue shift data presented in the Table 1, which were approximately the same for both nucleotides, were discovered from the first additions of the complex **I** (molar ratio DNA : **I** was 1 : 1) and could indicate the formation of a new complex nucleotide-**I** with covalently bound dirhenium fragment to guanine through the axial positions of **I**. The structure of such complexes with both purine bases was confirmed previously [15].

The hyperchromism was very large for both nucleotides and reached more than 80 %. A series of mono- and bimetallic complexes (with Cu(II), Pt(II) and Zn(II)) with substituted polypyridyl ligands have been prepared and their binding affinities towards some quadruplexes have been determined using UV/vis spectroscopic titrations [16]. Red shifts (4–6 nm) in absorption bands above 300 nm (those corresponding to metal-to-ligand charge-transfer (MLCT) or intraligand π–π* transitions) were considered as characteristic of π–π* interaction with DNA bases. The maximal hypochromism in this zone reached 38 %. These studies have shown that the number of aromatic rings play an important role in defining the DNA binding abilities of the resulting metal complexes; the prepared bi-metallic complexes had a higher affinity towards G-quadruplex DNA compared to their mono-metallic counterparts. Large values of shifts and hyperchromicity obtained in our work may be explained by the existence of bimetallic dirhenium(III) core and four aromatic rings in the structure of **I**.

Analyzing the proposed mechanisms of G4-metal compounds interactions [1], we consider that the binding mode of **I** to DNA is not exclusively a result of a combination of π–π stacking interactions, an electrostatic and covalent interaction. Indication of more than one binding mode can be rationalized by the multiple targeting nature of the complex: via π–π stacking interactions at the top of the DNA quadruplex (with the metal-benzimidazole core), as well as through electrostatic or covalent interactions via axial positions to bases/phosphate backbone in the loops.

Hyperchromicity and binding constant of **I** is higher for c-kit1 in comparison to HTelo22 (Table 1), thus suggesting that c-kit displays enhanced interaction. The HTelo22 sequence contains no free guanines besides those participating in the G4 fold (Fig. 4A), [17] whereas c-kit1 features three non-stacked guanines (Fig. 4B), making them potentially accessible for easier covalent binding of **I**.

a) b)

Fig. 4. 3D structures of hTelo (A) and (B) c-Kit1 G4s, generated with Chimera using PDB 2HY9 and 2O3M, respectively. Guanines belonging to G-tetrads are highlighted in orange and unpaired guanines are shown in green [18].

From our point of view, the most interesting result was found during the spectral picture investigation in the visible area where the quadruple bond absorbs, Figure 5.

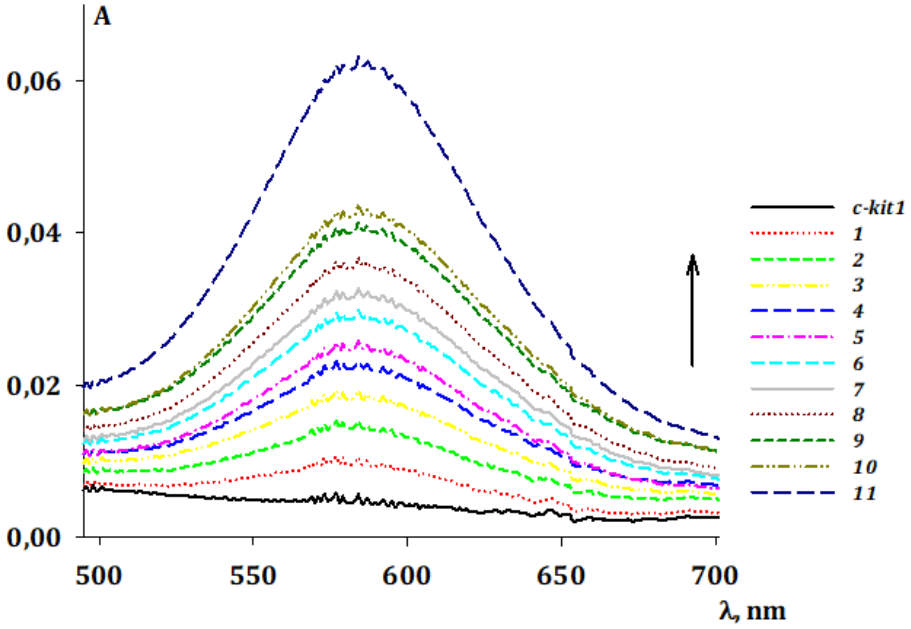

Fig. 5. UV–Vis titration spectra in the region 500-700 nm of c-kit1 (1 μM, constant concentration) with Re(III) cluster compound (0-15 μM) in cacodylate buffer: 1 μM complex (1); 2 μM complex (2); 3 μM complex (3); 4 μM complex (4); 4 μM complex (4); 5 μM complex (5); 6 μM complex (6); 7 μM complex (7); 8 μM complex (8); 9 μM complex (9); 10 μM complex (10); 15 μM complex (11). The arrows show the intensity changes corresponding to increase of complex concentration.

Absorption in this region is the well-studied property of the dirhenium(III) clusters [19]. The analysis of the energy position and intensity of the most long-waved band in EAS solutions of the rhenium compounds let to assign it to $\delta\rightarrow\delta^*$ electron transition. We have found out that addition of the quadruplex (ckit-1 or HTelo22) led to an intense increase in this region, which was the same for both nucleotides. This increase in intensity can't describe the formation of any other, quadruple bond-free complex. Based on the state of our knowledge we can only assume that this absorption appeared due to di(tri, poly)-merization of the nucleotide-**I** complex. This assumption is based on the known fact that unwinding of oligonucleotides leads to their concomitant hybridization, as it was shown for ruthenium derivatives of some oligonucleotodes [20]. Also, it was shown that the interactions of some binders with G4s led to intermolecular aggregation between the molecule and DNA [21]. But this mechanism requires additional investigations.

Experimental section

Chemicals and reagents. The complex of Re(III) with benzimidazole was synthesized according to [10; 15; 22]. All the oligonucleotides and cacodylate buffer components were purchased from Eurogentec. The sequences for the unlabelled oligonucleotides were c-kit1 (5'-AGGGAGGGCGCTGGGAGGAGGG-3') and HTelo22 (5'-AGGGTTAGGGTTAGGGTTAGGG-3').
Rhenium(III) complex compound was dissolved in cacodylate buffer to give 2 mM stock solution. All solutions were stored at –20°C. Before use, they were defrosted and diluted to yield the appropriate concentrations.

UV–vis absorption titration. The G4 DNA was dissolved in potassium or sodium cacodylate buffer (10 mM KCl/90 mM LiCl/10 mM LiCac, pH 7.4) to give 20 μM stock solutions. The solutions were then further diluted to 0.4 μM with theappropriate buffer and annealed at 95 ˚C for 5 min. Finally, they were allowed to cool slowly to room temperature overnight. The concentration of G4 DNA was checked using their molar extinction coefficients. The ligands were diluted from stock solutions in the same buffer as the tested sequence to yield specific final concentrations.

The binding affinity of G4 DNA to Re(III) complexes was obtained from UV–vis absorption titration from 230 to 900 nm on a Cary 300 (Varian) spectrophotometer at room temperature (constant G4 DNA concentration). 1–15 μM of the complex were added to 1 μM G4 DNA solution in a sample 1-cm methacrylate cuvette and the mixture was incubated for 7 min prior to recording the absorption spectra.

The titration was continued until only small changes in the absorption spectra were observed

upon successive addition of rhenium complex compound. The binding data obtained from spectrophotometric were analyzed according to Eq. 1 [6; 23], plotting ($A_0/A–A_0$) vs $1/C_C$, gives the binding constant (Kb) as the ratio of the intercept to the slope. Table 1 shows the corresponding values.

$$\frac{A_0}{A\text{-}A_0} = \frac{\varepsilon_f}{\varepsilon_b} + \frac{\varepsilon_f}{\varepsilon_b K_b} \frac{1}{C_C} \quad (1)$$

where A_0 and A are the absorbances of G4 DNA in the absence and presence of the complex at 256 nm, respectively. ε_f and ε_b are the extinction coefficients of free and bounded G4 DNA, respectively, and C_C is the concentration of the complex.

The hyperchromism was calculated according the formula: %Hyperchromism = [(A_b, max – A_b, min)/A_b, max] × 100 %.

Conclusion

We have investigated the binding activity of the quadruple bonding dirhenium(III) compound with benzimidazole ligands to G4 DNA by UV–vis absorption titration. The electronic absorption titrations indicate that dirhenium complex compound with benzimidazole ligands interacts relatively strongly with G4 (Kb = $5.258 \cdot 10^4$ for c-kit1 and $4.653 \cdot 10^4$ for HTelo22). We have found out that addition of the G4-quadruplexes (ckit-1 or HTelo22) led to intensive increase in visible region, that was the same for both nucleotides. This absorption appeared due to di(tri, poly)-merization of the nucleotide-complex compound. The hyperchromicity and binding constant of dirhenium(III) complex compound is higher for c-kit1 in comparison to HTelo22, thus suggesting that c-kit displays enhanced interaction. The HTelo22 sequence contains no free guanines besides those participating in the G4 fold whereas c-kit1 features three non-stacked guanines, making them potentially accessible for easier covalent binding of dirhenium(III) compound with benzimidazole ligands. These results are the experimental evidence of the interaction of the quadruple-bonding dirhenium(III) compounds with G4 DNA showing their possible valuable applications as compounds with strong biological activity.

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