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Further evidence for redox activation of the plasmid – dirhenium(III) complexes interactions

K.V. Zeleniuk, O.A. Golichenko, A.V. Shtemenko, N.I. Shtemenko

The DNA-interactions *in vitro* are still necessary investigations for determination of the possible anticancer properties of the compounds, candidates for application in cancer therapy. The aim of the present work was to realize if the interaction of *cis*-dicarboxylates of dirhenium(III), with pivalato- (**I**), isobutirato- (**II**) and adamanthyl- (**III**) ligands cleaves the plasmid in the same manner and what is the influence of the ligands on this process. For experiments we used the prokaryotic plasmid which is good model to analyze DNA-cleaving ability of different substances that exists in supercoiled conformation and turns to nicked and linear forms. It was shown that gradual conversion of the supercoiled Form I to a mixture of supercoiled (Form I) and nicked (Form II) DNA takes place and increasing amounts of Form II are produced with higher concentrations of **I–III** under increasing of concentration that showed the DNA-cleaving abilities of all investigated dirhenium complexes. This process was taking place with different intensity in the range **I** > **II** > **III**, that demonstrates the influence of the organic radical on the cleaving activity of the dirhenium(III) complexes. Under hydrogen peroxide conditions, **I** and **II** showed close results, demonstrating more intensive process of cleaving, including formation of the linear plasmid (Form III) under higher concentration, witnessing about redox-activation of the DNA-cleaving reaction. Cleaving activity of **III** was approximately the same in all experiments, that was demonstrated only by decreasing of the supercoiled form I and increasing of the nicked form II of the plasmid and by absolutely absence of the linear form III of the plasmid. The electrophoresis mobility shift assays showed that rhenium cluster compounds have nuclease activity and confirmed that natural DNA may be their target in the living cells. The conclusion was made that the mechanism of DNA-cleavage reaction of the dirhenium(III) complexes is multiple in which the electron donating (withdrawing) effects of the ligands and catalytic activity of the metal core should be taken in consideration.

Key words: *dirhenium(III) clusters, plasmid, DNA-cleavage, redox-activation*.

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Introduction

Earlier using the method of UV-titration we have shown that the rhenium(III) quadruple bonding compounds interacted with supercoiled Calf Thymus DNA (CT DNA) (Paramonova et al., 2016; Polokhina et al., 2016) and that the mechanism of the interaction was redox-activated. Also, bis-dimethylsulfoxide-*cis*-tetrachlorodi-*μ*-pivalatodirhenium(III) cis–$Re_2((CH_3)_3CCOO)_2Cl_4$•2DMSO (**I**) was shown to cleave plasmid DNA by electrophoretic mobility shift assay (Shtemenko et al., 2013) in different manner depending from the redox state of the medium. The DNA-interactions *in vitro* are still necessary investigations for determination of the possible anticancer properties of the compounds, candidates for application in cancer therapy (Ismail et al., 2019). It is known, that anticancer properties of the dirhenium(III) dicarboxylates *in vivo* depended on the length of the alkyl ligands (Leus et al., 2012).

Thus, the aim of the present work was to realize if the interaction of other two dicarboxylates of dirhenium(III), with shorter (isobutirato-) and longer, bulkier (adamantyl-) ligands cleave the plasmid in the same manner and what is the influence of the ligands on this process.

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Materials and methods

Materials.

Cis–$Re_2(i\text{-}C_3H_7COO)_2Cl_4$•2DMSO bis-dimethylsulfoxide-cis-tetrachlorodi-μ-isobutyratodirhenium(III) (**II**) and cis–$Re_2(C_{10}H_{15}COO)_2Cl_4$•2DMSO bis-dimethylsulfoxide-cis-tetrachlorodi-μ-adamantylcarboxylatodirhenium(III) (**III**) were synthesized according to (Golichenko, Shtemenko, 2006, 2015). Supercoiled plasmid pUC18 and DNA ladder were purchased from Fermentas, Life Science (USA).

Electrophoretic Mobility Shift Assays.

The mobility assays were performed according to (Keck, Lippard, 1992; Mitra et al., 1997) by using aliquots (10 μl) of native supercoiled plasmid pUC18 (20 μg/ml) and increasing concentrations of complex (0 to 80 μM). Electrophoresis experiments were carried out using 1 % agarose gel and buffer solution (40 mM Tris-acetate and 1 mM EDTA, pH 8.2). The applied voltage was 250 V and the gels were run for a period of 20 min. After electrophoresis, the gels were stained with 0.5 mg/L ethidium bromide and imaged under UV light. The efficiency of the DNA cleavage was measured by determining the ability of the complex to form open circular or nicked circular DNA from its supercoiled forms. The same assays were also carried out in the presence of H_2O_2 (experiment b) and 2-mercaptoethanol (experiment c) (25 μM). Gel image analysis was made with the help of free LabImage 1D – Software for 1D Gels and Western Blots (https://www.kapelanbio.com/products/).

Results and discussion

To study cleavage ability of metal-containing substances and their cleavage pathway, an assay is widely used, which employs a special type of DNA, a plasmid DNA (Wang et al., 2015; Kettenman et al., 2018; Kadoya et al., 2019). Single strand DNA cleavage (SSC) is the process, in which one scission is introduced in one of the two DNA strands in one cleavage event. Double strand DNA cleavage (DSC) denotes the process, in which two scissions are introduced to each of the strands of the DNA double helix in a single cleavage event. Although both pathways introduce double strand breaks ultimately, it is important to note that these are two inherently different processes. The pathway that is responsible for the induction of strand breaks is of more interest, as the direct double strand cleavage pathway is considered to be responsible for the cytotoxicity of the initiating substances to cancer cells.

Typically, the quaternary structure of plasmids is superhelical, which means that the double stranded DNA forms a compact folded structure. When one of the DNA strands is broken, a swivel, i.e. a free rotation site in the complementary strand opposite to the break, relieves the strain in the twisted molecule. This causes the supercoiled structure to relax into an uncoiled form, which is referred to as nicked DNA. When both strands of the DNA are cleaved opposite to each other, linear DNA is observed. Supercoiled DNA is often referred to as form I, nicked DNA as form II and linear DNA as form III. These forms are good resolved by electrophoresis (Sears et al., 2013; Kadoya et al., 2019).

We used these good described phenomena to investigate cleaving activity of the investigated substances **II** and **III** (Fig. 1, 2) and to compare the results with previously obtained data for the substance **I**.

The intensity of the bands obtained by scanning procedure is presented on the Fig. 3.

As it is clear from obtained results, the gradual conversion of the supercoiled Form I to a mixture of supercoiled (Form I) and nicked (Form II) DNA takes place and increasing amounts of Form II are produced with higher concentrations of **I**–**III** under increasing of concentration that showed the DNA-cleaving abilities of all investigated dirhenium complexes (Experiment a). This process was taking place with different intensity in the range **I** > **II** > **III,** that demonstrates the influence of the organic radical on the cleaving activity of the dirhenium(III) complexes. This range coincides with the binding constants, obtained from the UV-titration experiments (Paramonova et al., 2016; Polokhina et al., 2016).

Under hydrogen peroxide conditions (Experiment b) **I** and **II** showed close results, demonstrating more intensive process of cleaving, including formation of the linear plasmid (Form III) under higher concentration, witnessing about redox-activation of the DNA-cleaving reaction. Cleaving activity of **III** was approximately the same in Experiments a–c, that was demonstrated only by decreasing of the supercoiled form I and increasing of the nicked form II of the plasmid and by absolutely absence of the linear form III of the plasmid.

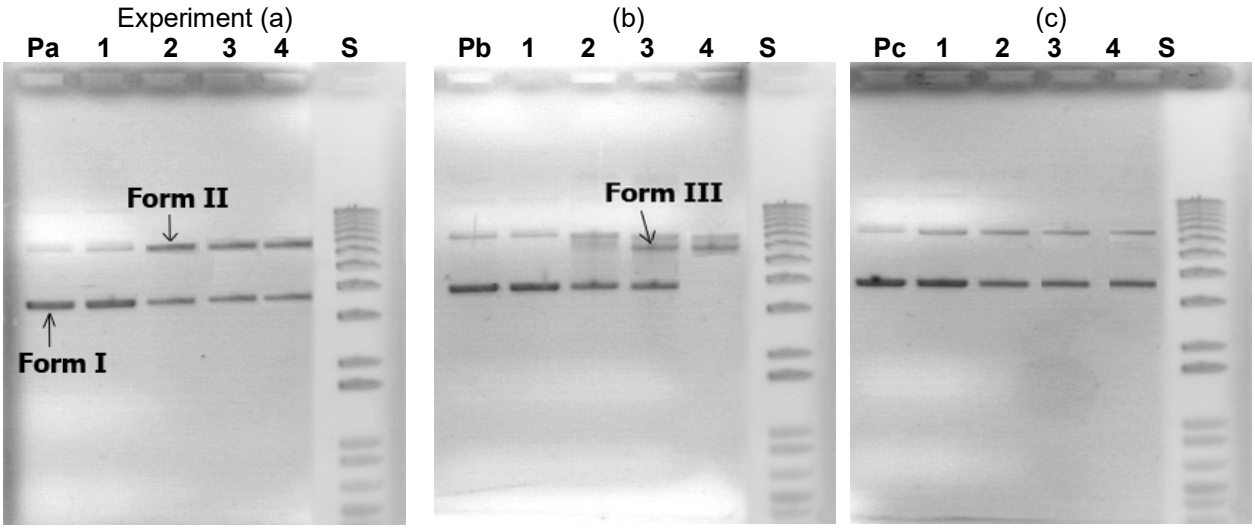

Fig. 1. Ethidium stained agarose gel electrophoresis depicting pUC18 mobility and effects (a) in the presence of increasing concentrations of II; (b) pUC18 with II in the presence of hydrogen peroxide; (c) pUC18 with II in the presence of mercaptoethanol. Lane Pa – untreated plasmid, Pb – plasmid with hydrogen peroxide; Pc – plasmid with mercaptoethanol; lanes 1: 10 μM; 2: 20 μM; 3: 40 μM; 4: 80 μM (concentration of II); S – standard

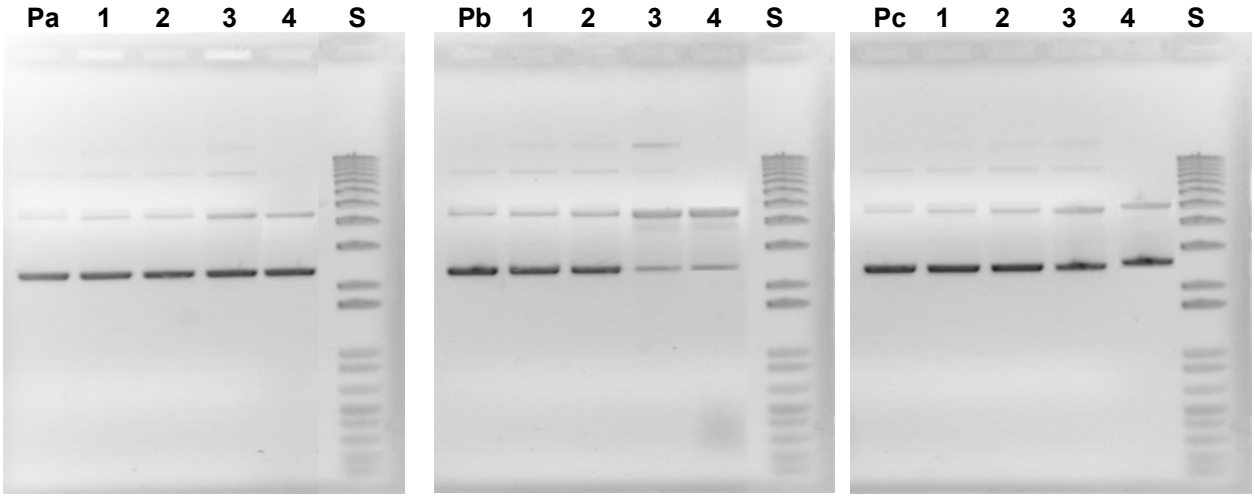

Fig. 2. Ethidium stained agarose gel electrophoresis depicting pUC18 mobility and effects (a) in the presence of increasing concentrations of III; (b) pUC18 with III in the presence of hydrogen peroxide; (c) pUC18 with III in the presence of mercaptoethanol. Lane Pa – untreated plasmid, Pb – plasmid with hydrogen peroxide; Pc – plasmid with mercaptoethanol; lanes 1: 10 μM; 2: 20 μM; 3: 40 μM; 4: 80 μM (concentration of III); S – standard

In the presence of mercaptoethanol (Experiment c), the activation of the cleaving abilities of **I–III** are also evident but no Form III is observed as compared to the activity of **I–III** only.

The presence of the slowest moving bands in Fig. 1, 2 (slower than Form II) indicates formation of high molecular weight adducts that may be explained by the ability of unwound plasmids to polymerize (Vilfan et al., 2006) or to form unwound DNA-**I** intra-strand adducts similar to cisplatin and dirhodium compounds (Dunham et al., 2005).

The mechanism of the SSC and DSC of plasmids was in detail studied for bleomycin (BLM), an iron-containing natural nuclease (Decker et al., 2006). The experimental and computational studies presented here on the reaction coordinate of activated BLM strongly support the low-spin (BLM)Fe^{III}-OOH

complex as the active oxidizing species and a direct hydrogen-atom abstraction as the reaction mechanism for the initial attack on DNA. The mechanism for double-strand cleavage by a single BLM molecule would then involve the Fe^{IV} intermediate generated by the first reaction as the active species for the initial second H-atom abstraction reaction damaging the second DNA strand. A hydroperoxo species of the dicopper(II) was also identified as the active species and spectroscopically identified in the reaction of the complex with plasmids (Kadoya et al., 2019). Analogical investigations for the dirhenium(III) complexes are absent, but acceleration of the nuclease reaction by hydrogen peroxide shown by us makes possible to think that the same hydroperoxo species may play definite role in the investigating processes with rhenium substances.

It is well-known that the microenvironment in the cancer cells is significantly different from that in normal cells (Zhou et al., 2014) and the concentration of reactive oxygen species (ROS) including H_2O_2 is relatively higher in cancer cells than in normal cells (Nogueira, Hay, 2013), that is mainly caused by mitochondrial malfunction (Aykin-Burns et al., 2009). Thus, redox activating of the process of cleavage by H_2O_2 shown by us in the Experiment b, is of great value as could work in cancer cells but not so extensively in normal cells and this phenomena could be used to reduce the side-effects of anticancer drugs.

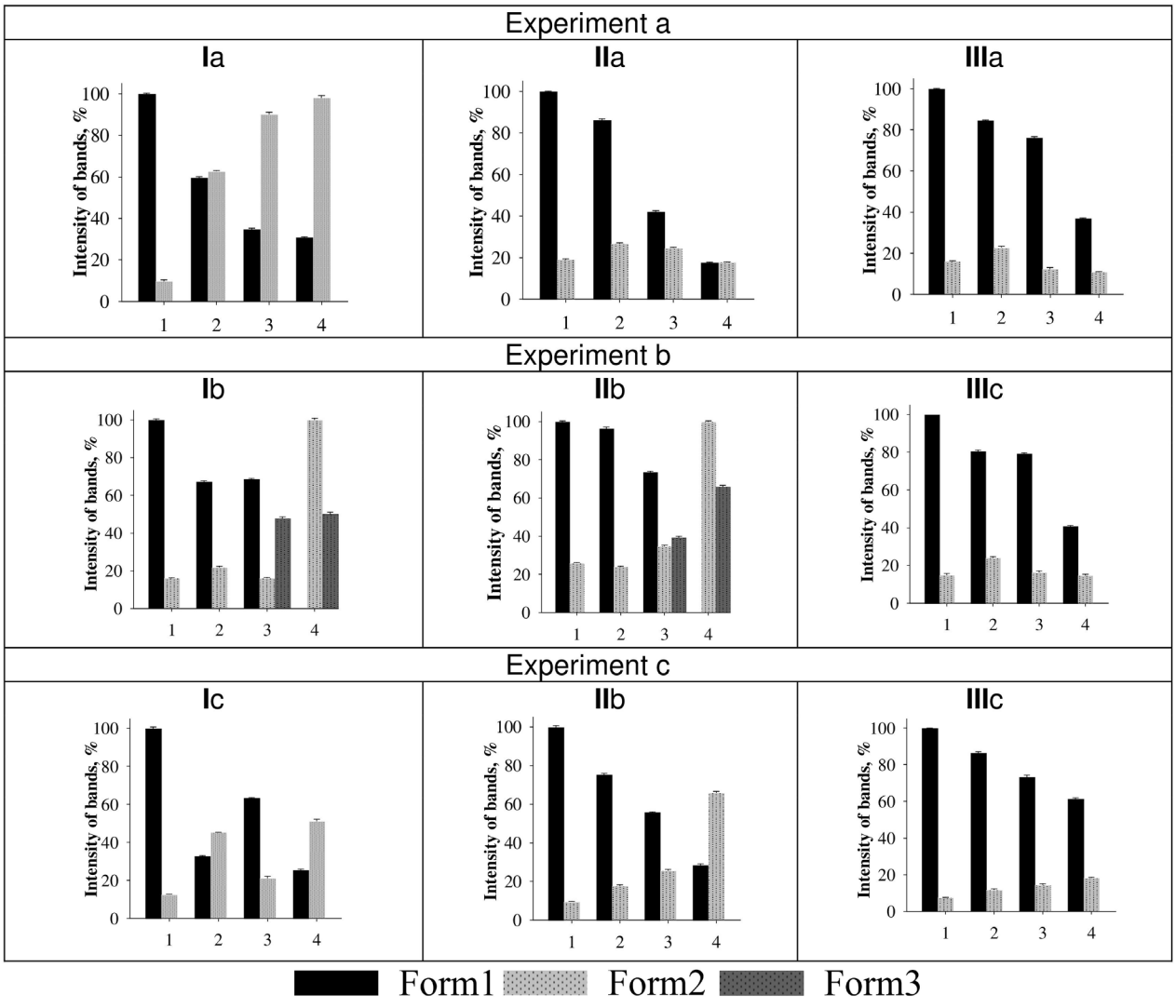

Fig. 3. Intensity of bands of different forms of plasmid pUC 18 under influence of I, III, III in % to intensity of Pa, Pb, Pc accordingly

The influence of ligands surrounding the active center of metal-containing artificial nucleases was investigated on the copper – dipicolamine complexes (Wang et al., 2015). It was shown that replacement of a hydrogen atom of the dipicoyl ligand with a benzyl group enhanced the efficiency both of SSC and DSC cleavage; also introducing an electron donating group resulted in further increase in efficiency, whereas the presence of electron withdrawing group reduced the efficiency; the introducing of different ROS-inhibitors decreased the intensity of cleavage. In our experiments **I** (pivalic derivative) and **II** (isobutiric derivative) are homologues, **I** has two longer alkyl ligands, that we may note that they are more electron donating and thus agree with previously made conclusions about possible formation of the intermediate complex for which electron donation is a stabilization factor. As for **III**: recently we have shown that some dirhenium complexes with diadamanthyl ligands had catalase-like activity (Shamelashvili et al., 2016); thus, **III** could act as inhibitor of ROS-formation in the nuclease event. Nuclease activity of the dirhenium(III) clusters to our mind is of great interest and requires additional deep investigations.

Conclusions

The electrophoresis mobility shift assays showed that compounds **I–III** have nuclease activity and confirmed that natural DNA may be their target in the living cells. The redox-activation of DNA cleavage, observed in the electrophoresis experiments, may explain the anticancer activity of dirhenium(III) compounds as well as the positive effects of combined therapy, that includes their simultaneous introduction together with cisplatin. The present study and our other recent reports showed the dependence of the DNA-cleaving activity of dirhenium clusters on the nature of the ligands in the coordination sphere of the Re_2^{6+} clusters. The obtained data showed the multiple mechanism of DNA-cleavage reaction of the dirhenium(III) complexes in which the electron donating (withdrawing) effects of the ligands and catalytic activity of the metal core should be taken in consideration.

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Додаткові докази редокс-активації взаємодій плазміда – комплекси диренію(III)

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Дослідження взаємодії з ДНК *in vitro* є необхідним для визначення можливих протипухлинних властивостей сполук – кандидатів на застосування у терапії раку. Мета цієї роботи полягала у тому, щоб зрозуміти, чи однаково розщеплюють плазміду цис-дикарбоксилати диренію(III) з півалатними (**I**), ізобутіратними (**II**) та адамантилкарбоксилатними (**III**) лігандами, і як впливають ліганди на цей процес. Для експериментів ми використовували прокаріотичну плазміду, яка є придатною моделлю для аналізу здатності розщеплювати ДНК різними речовинами та існує у суперспіралізованій конформації і перетворюється у деспіралізовану і лінійну форми. Було показано, що відбувається поступове перетворення суперспіралізованої форми I у суміш ДНК із суперспіралізованою (форма I) і деспіралізованою (форма II) формами, при більш високих концентраціях комплексних сполук **I–III** (при підвищенні концентрації) збільшуються кількості форми II, що показує здатність всіх досліджених диренієвих комплексів розщеплювати ДНК. Цей процес відбувався з різною інтенсивністю в ряду **I** > **II** > **III**, що свідчить про вплив органічного радикала на нуклеазну активність комплексів диренію(III). За наявності гідроген пероксиду **I** і **II** показали близькі результати, демонструючи більш інтенсивний процес розщеплення, який включає утворення лінійної плазміди (форма III) при більш високій концентрації, що свідчить про редокс-активацію реакції розщеплення ДНК. Розщеплююча активність **III** була приблизно однаковою у всіх експериментах, що було продемонстровано зменшенням суперспіралізованої форми I і збільшенням деспіралізованої форми II плазміди, а також повною відсутністю лінійної форми III плазміди. Аналіз зсуву рухливості при електрофорезі показав, що кластерні сполуки ренію володіють нуклеазною активністю, і підтвердив, що природна ДНК може бути їх мішенню в живих клітинах. Був зроблений висновок про те, що механізм реакції розщеплення ДНК комплексами диренію(III) є багатогранним, при цьому слід брати до уваги електронодонорні ефекти лігандів і каталітичну активність кластерного диренієвого ядра.

Ключові слова: *кластери диренію(III), плазміда, розщеплення ДНК, редокс-активація.*

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Дополнительные доказательства редокс-активации взаимодействий плазмида – комплексы дирения(III)

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Изучение взаимодействия с ДНК *in vitro* всё ещё является необходимым исследованием для определения возможных противоопухолевых свойств соединений – кандидатов на применение в терапии рака. Цель настоящей работы состояла в том, чтобы понять, одинаково ли расщепляют плазмиду цис-дикарбоксилаты дирения(III) с пивалатными (**I**), изобутиратными (**II**) и адамантилкарбоксилатными (**III**) лигандами, и какое влияние оказывают лиганды на этот процесс. Для экспериментов мы использовали прокариотическую плазмиду, которая является хорошей моделью для анализа способности расщеплять ДНК различными веществами, существует в суперспирализованной конформации и превращается в деспирализованные и линейные формы. Было показано, что происходит постепенное превращение суперспирализованной формы I в смесь ДНК со суперспирализованной (форма I) и деспирализованной (форма II) формами, при более высоких концентрациях **I–III** (при повышении концентрации) увеличивается количество формы II, что показывает способность всех исследованных дирениевых комплексов расщеплять ДНК. Этот процесс происходил с различной интенсивностью в ряду **I** > **II** > **III**, что свидетельствует о влиянии органического радикала на расщепляющую активность комплексов дирения(III). При наличии перекиси водорода **I** и **II** показали близкие результаты, демонстрируя более интенсивный процесс расщепления, который включает образование линейной плазмиды (форма III) при более высокой концентрации, что свидетельствует о редокс-активации реакции расщепления ДНК. Расщепляющая активность **III** была примерно одинаковой во всех экспериментах, что было продемонстрировано уменьшением суперспирализованной формы I и увеличением деспирализованной формы II плазмиды, а также полным отсутствием линейной формы III плазмиды. Анализ сдвига подвижности при электрофорезе показал, что кластерные соединения рения обладают нуклеазной активностью, и подтвердил, что природная ДНК может быть их мишенью в живых клетках. Сделан вывод о том, что механизм реакции расщепления ДНК комплексами дирения(III) является многогранным, при этом следует принимать во внимание электронодонорные эффекты лигандов и каталитическую активность кластерного дирениевого ядра.

Ключевые слова: *кластеры дирения(III), плазмида, ДНК-расщепление, редокс-активация.*

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