Journal of Molecular Graphics and Modelling 64 (2016) 11–29

Contents lists available at ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

Theoretical studies on binding modes of copper-based nucleases with DNA

Chunmei Liu, Yanyan Zhu*, Mingsheng Tang*

College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan Province 450001, PR China

ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form
15 December 2015
Accepted 16 December 2015
Available online 22 December 2015

Keywords:
Copper nuclease
DNA
Binding mode
Molecular docking
MD simulation

ABSTRACT

In the present work, molecular simulations were performed for the purpose of predicting the binding modes of four types of copper nucleases (a total 33 compounds) with DNA. Our docking results accurately predicted the groove binding and electrostatic interaction for some copper nucleases with B-DNA. The intercalation modes were also reproduced by "gap DNA". The obtained results demonstrated that the ligand size, length, functional groups and chelate ring size bound to the copper center could influence the binding affinities of copper nucleases. The binding affinities obtained from the docking calculations herein also replicated results found using MM-PBSA approach. The predicted DNA binding modes of copper nucleases with DNA will ultimately help us to better understand the interaction of copper compounds with DNA.

1. Introduction

Artificial metallonucleases have received considerable current interest for their diverse applications not only as therapeutic agents but also for use in genomic research [1–5]. Sigman and co-workers have developed the first chemical nuclease $[Cu(phen)]^+$ that effectively cleaves DNA in the presence of reducing agent and also exhibits antiviral activity through the inhibition of proviral DNA synthesis [1,6,7]. There has been great interest in the development of various transition metal complexes serving as artificial metallonucleases [2,8,9]. Due to their unusual electronic properties and diverse chemical reactivity, artificial metallonucleases have been at the forefront of the investigations [10–12]. It is thus of importance to design and develop new molecular systems of metallonucleases with the potential to cleave DNA with damage of the sugar and/or base [13] under related conditions. Copper complexes have been preferentially used as molecules for cancer inhibition by chemotherapy in metal-based therapies because of their biologically accessible redox potential and relatively high affinity for nucleobases [14–16]. To some degree, copper complexes can bind and cleave the double-stranded DNA with high reactivity and structural selectivity [9,17–20]. Chakravarty and coworkers have reported a series of copper nucleases with promising DNA binding and DNA cleavage activity, and they also adopted the molecular docking technique to test the binding modes and affinities of the studied copper nucleases with DNA [21–23]. Some reviews [13,24,25] have summarized the relevant data of the copper complexes with different ligands with promising activity for DNA hydrolysis as well as oxidation due to its Lewis acidity and redox behavior.

However, the mechanism of copper nucleases cleaving DNA is complicated and still poorly understood. Even though experimental results have demonstrated the DNA-cleavage activity of some copper nucleases, the investigations of nuclease-DNA binding modes and cleavage mechanisms of DNA by copper nucleases at the molecular level remain limited. The theoretical approaches provide a powerful tool to evaluate the metal-based compounds interactions with DNA [26–35]. To the best of our understanding, in the light of available information, the mechanism of nuclease-DNA binding and its effect on DNA secondary structure have not been comprehensively studied in a systematic manner. In fact, stemming from the discovery of the first copper nuclease $[Cu(phen)]^+$ [36–38], it is still debated that the redox reaction causing DNA strand scission occurs via abstraction of H4' or H1' of the sugar in DNA.

DNA binding is the critical step for DNA cleavage in most cases. Interactions of copper complexes with DNA usually include electrostatic interaction, strong covalent bonding, intercalation, groove binding, hydrogen-bonding with ligands, and then cleavage of DNA [39,40]. In order to address the cleavage mechanism of DNA by copper nucleases, a better understanding of the binding modes of

* Corresponding authors.
E-mail addresses: zhuyan@zzu.edu.cn (Y. Zhu), mstang@zzu.edu.cn (M. Tang).

http://dx.doi.org/10.1016/j.jmgm.2015.12.003
1093-3263/

copper nucleases with DNA is necessary. Molecular docking technique is an important computational method to understand the drug-DNA interactions for the rational drug design and discovery and to predict the exact binding site available at the molecular target [41,42]. Different structural properties lead to different binding modes; in fact, one of the most important factors governing the binding mode is the molecular conformation. Literatures reveal that the force of interaction maintaining the stability of DNA-ligand include van der Waals, hydrogen bonding, hydrophobic charge transfer, electrostatic complementarity, and so on [43,44]. A series of copper nucleases studied in the present work were docked to the double-stranded DNA molecules in order to predict the binding energies along with preferred orientation of the copper nucleases inside the DNA groove or bases. In this work, there are thirty-three copper compounds, which are classified into four types, were studied. These nucleases are: type A are compared the aromatic ligand and side chain effect on DNA binding affinity [9,45–49]; type B focus on the effect of the macrocyclic copper nucleases with/without pendant or heterosubstituted [50,51]; type C explore the copper nucleases with tetradentate amine ligands with different pyridyl arm lengths [52–54]; type D compare the copper nucleases with ammonium/guanidinium groups by connecting different side chains [55–57].

2. Computation methods

2.1. Initial structures

According to the different ligand environments and binding modes of copper nucleases, four types of nucleases (A–D in Fig. 1) were adopted in this work. Specifically, the copper atom in type A forms squared-pyramidal coordination environment, and the functional moiety coordinating with the copper center is an N,N-donor heterocyclic base, such as, 2,2-bipyridine (bpy), 1,10-phenanthroline (phen) and 1,10-phenanthroline-5,6-dione (dione), dipyrido[3,2-*d*:2′,3′-*f*] quinoxaline (dpq), dipyrido[3,2-a:2′,3′-c]phenazine (dppz), to name a few. According to the different N,N-donor heterocyclic bases, the copper compounds in type A adopt a naming convention given by A1-bpy, A1-phen, A1-dpq, etc. for the aforementioned. For type B, the copper center atom has a square-planar coordination geometry forming macrocyclic nucleases for B1-1/2, however the remaining three nucleases B1-3/4/5 exhibit a distorted square-pyramidal environment. In type C, the coordination complex adopts a five-coordinate, trigonal bipyramidal geometry for C1 and C2-1, and that for C2-2/3/4 possesses a distorted square planar motif. For each complex in D1-R, there are four ammonium groups in the side chains, given by D1-HMe_2, D1-Me_3, D1-Et_3 and D1-Bu_3, respectively. The complex in D1 is trigonal bipyramidal, and the three copper nucleases in D2 have a square planar CuN_2Cl_2-configuration, with D2-3 possessing guanidinium groups. Initial structures of most copper nucleases are obtained from the Cambridge Crystallographic Data Centre (CCDC) and those not found were constructed from crystal structures of a similar configuration. All geometrical optimizations were carried out at the DFT (B3LYP) [58,59] level of theory with 6–31 + G* basis set for C, N, O, S, Cl, Br, H and DZpdf [60] for the copper center using Gaussian 09 program [61]. In order to check the binding modes of the copper nucleases, three DNA sequences were used in the verified docking studies: d(5′-ATATATATATAT-3′)$_2$ (assigned as DNA1) which is AT-rich sequence, d(5′-CGCGCGCGCGCG-3′)$_2$ (assigned as DNA2) which is GC-rich sequence and d(5′-CGCGAATTCGCG-3′)$_2$ (assigned as DNA3) which not only contains AT base pair but also contains CG one and is mostly used in molecular docking studies [62–65]. Three DNAs adopted in this study are B-DNA, which were built by 3DNA [66].

2.2. Molecular docking protocol

To obtain preliminary information regarding the structures of these synthesized copper nucleases, different copper nucleases are obtained from X-ray coordinates [9,45–57,67]. All the dockings were carried out with the AutoDock Vina [68]. Autodock Vina is a more recent release, and its combination of empirical and knowledge-based scoring functions with an iterated local search global optimizer which has been shown to perform at least as well as Autodock [69], yet with a reduced runtime. In the docking analysis, the binding site was assigned across all of the minor and major grooves of the DNA molecule. The centeroid of the DNA is the grid center with docking grid size of 40 Å × 38 Å × 50 Å for DNA1, 42 Å × 42 Å × 46 Å for DNA2 and 40 Å × 40 Å × 50 Å for DNA3. The charge derived for DNA and copper complex were used in the docking calculation. AutoDock Vina docking was performed using exhaustiveness value of 8 with energy range to 3. AutoDockTools is used to set up both ligand and target structure parameters. Ligands are imported, automatically merging nonpolar hydrogens, assigning atom types and Gasteiger charges, and defining non-rotatable bonds. All the other parameters were used as in defaults. The energetically most favorable conformation of the docked poses was focused on in this work.

2.3. Molecular mechanics and molecular dynamics simulation

To obtain the proper distorted DNA, intercalation binding sites on the canonical DNA d(5′-CGCGAATTCGCG-3′)$_2$ structures were formed by manually inserting a copper complex with aromatic plane between each base pairs in parallel to their aromatic moieties and then refined by subsequent energy minimization and molecular dynamics (MD) simulations [70] methods. In order to consider the effect of the different DNA base pairs on the binding energies and modes of the different intercalation modes, we choose DNA3 with C/T/A/G base as the target DNA for intercalation test. Considering all possible conformations, one copper nuclease [49] with different orientations in the major/minor grooves of DNA were minimized. Twenty-two copper nuclease-DNA intercalation adducts were performed. Initial 1000 steps of the steepest-descent minimization were performed to relax the initial strain on the molecule followed by 1000 steps of conjugate gradient minimization, to further relax the molecule and to decrease the total potential energy. In the subsequent MD simulations, the SHAKE algorithm was utilized for all bonds involving hydrogen atoms [71]. The systems were explicitly solvated using the TIP3P water potential inside a box large enough to ensure the solvent shell extended to 10 Å in all directions of each system studied. For the energy minimizations of copper nuclease-DNA adducts, harmonic restraints on DNA and nuclease positions are from 100, 75, 50 to 25 kcal mol^{-1} Å^{-2} to remove unfavorable contacts. The cut-off distance used for the nonbonded interactions was 10 Å. The energy-minimized system was heated over 100 ps from 0 to 300 K (with a temperature coupling of 0.2 ps), while the positions of DNA and copper nucleases were restrained with a small value of 10 kcal mol^{-1} Å^{-2}. Subsequently, the unrestrained equilibration of 1000 ps with constant pressure and temperature conditions was carried out for each system. The temperature and pressure were allowed to fluctuate around 300 K and 1 bar, respectively. Finally, production runs of 10 ns were performed in the NPT ensemble for each system. All MD simulations were performed using the SANDER module of AMBER 14 package [72]. Structures resulting from the MD simulations were subjected to new docking simulations using the same docking protocol.