Duplex DNA and G-Quadruplexes

Subjects: Biochemistry & Molecular Biology
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Biomedicine may be considered the cornerstone of modern health care. It includes key enabled technologies such as molecular biology, biotechnology, nanobiotechnology, biological engineering, etc., and concerns a wide range of scientific and technological approaches that range from the understanding of molecular interactions to the study of gene therapy.

Keywords: artificial phosphoesterases ; DNA ; G-quadruplexes ; intercalation ; LS-DFT ; Mo-oxo species

1. Introduction

Biomedicine may be considered the cornerstone of modern health care. [1] It includes key enabled technologies such as molecular biology, biotechnology, nanobiotechnology, biological engineering, etc., and concerns a wide range of scientific and technological approaches that range from the understanding of molecular interactions to the study of gene therapy. According to the most recent statistics in Europe, there were 1.93 million deaths caused by cancer in Europe during 2018 (~36.3% of the total number of deaths), which means that cancer is still an important topic for biomedical research and that improvements in chemotherapy are still necessary. On the other hand, the emerging problem of bacterial antibiotic resistance (BAR) has caused 33,000 deaths per year in the EU (https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en accessed on 1 August 2021) and has become a current hot topic of research. Thus, research developed within these topics for the next years becomes important, timely, and within the priorities of the world concerning health, healthy ageing, and wellbeing. Cisplatin is the reference drug in chemotherapy treatments against cancer. Ref. [2] However, this drug may cause serious side effects due to the damage of normal tissues [3]. Research aimed at the development of more efficient alternatives is valuable.

The use of flat ligands such as 1,10-phenanthroline (phen), both in their isolated form or included in metal complexes, was devised some years ago as an alternative to cisplatin for chemotherapy treatments [4][5][6]. Their use as an innovative method to fight against BAR has been considered more recently. Refs. [7][8][9][10] They intercalate between DNA base pairs (bps) and can either inhibit the replication of DNA or cleave the DNA chain causing the death of cancer cells or bacteria. Nevertheless, some competition between intercalation and groove binding modes of interaction between these flat ligands and DNA has been proposed in the literature. Refs. [11][12][13][14][15] Indeed, whereas the groove binding occurs very fast (i.e., tenths of a millisecond), the intercalation mode of interaction takes more time to occur (i.e., in the range of few milliseconds). Ref. [12] Moreover, the intercalation mode is usually more related to cytotoxic effects. Since the cytotoxic effect of any intercalator depends on the time of residence of the drug between bps, [16] the design of any efficient drug should aim at an increased drug-DNA interaction to stabilize the intercalated state, but it should do so at less stable groove binding states to make the kinetics faster. Such modulation for the binding sites, and thus for the cytotoxicity, can be achieved by substitution of phen in number and position. For this reason, the comprehension and rationalization of the interactions between flat ligands and duplex DNA (dDNA) becomes crucial. They will give us information about how to modulate the interactions in both modes by substitution in the flat ligands and how to optimize the drug design. In this sense, the effect of substitution in phen in the intercalation process is still not clear. On the other hand, the antibacterial efficiency of phen derivatives is higher when they are coordinated to any metal than when the ligand is alone [10]. However, no satisfactory explanation has been given for it. Thus, the influence of ancillary ligands in the intercalation process is an interesting topic for study. Our contribution to state-of-the-art studies has been the analysis of the nature of the interaction and the investigation concerning how the substitution of flat ligands, such as phen, in number and position (with different kind of functional groups as $-CH_3$, -OH, $-NH_2$, =O, -Ph, -Cl, -COOH, etc.) favors the intercalation or the groove binding competitive mode of interaction. Moreover, the inclusion of metal atoms has been also analyzed.

Another alternative to overcome the problem with cisplatin is based on the stabilization of G-quadruplexes (GQ), which are alternative non-canonical quadruple-stranded helical DNA structures found in guanine rich sequences of DNA. The formation of GQ gives other singularity to the DNA, which may lead to more selective interactions. Moreover, by avoiding the abovementioned side effects, this new target could replace therapies based on cisplatin. Indeed, the formation and

stabilization of GQ were shown to decrease the activity of telomerase [17], which is the enzyme responsible for the elongation of telomeres, a phenomenon that prevents cell apoptosis. Since high telomerase activity is involved in 85% of cancers [18], it is recognized as a potential cancer specific target. Thus, inhibition of telomerase becomes a key method for stopping tumoral cell growth. The presence of GQ in promoters also represents a subject of study. Ref. [19] In this case, the presence of stable GQ in oncogene promoters can alter the expression of the gen reducing some key processes in the growth of tumor cells. Ref. [20] Thus, stabilization of GQ may also be an innovative strategy to fight against BAR since the stabilization of GQ in bacteria by small molecules may also inhibit the expression of genes responsible for BAR. Ref. [21] Several organic ligands, either alone or included in metal complexes, were reported in the literature as GQ stabilizers, inhibiting telomerase activity or disrupting the transcriptional activity of some oncogenes. Ref. [22] There are three main sites in the GQ where these stabilizing small molecules may interact: end-stacking, grooves, and loops (with the first being the most common). In order to favor such interactions, small planar molecules may induce end-stacking binding, whereas the interactions with side loops and grooves are enhanced by the presence of side chains, which are positively charged or have affinity for protons that are attached to the planar aromatic cores. These side chains participate in electrostatic interactions with the negatively charged DNA phosphate backbones. Ref. [23] Moreover, the same organic ligands bound to different metal centers may still generate different GQ affinities and interactions.

On the other hand, and trying to devise other strategies, it was only during the early-mid 2000s that systematic studies on the application of nanostructures based on polyoxometalates (POMs) for cancer treatment became a booming domain. Refs. [24][25][26] Recent advances in the use of POMs for medical applications and their antitumor activity have been reviewed by Bijelic et al. [27] In addition, Bijelic et al. and Kortz et al. also reviewed the latest developments on the use of POMs against BAR. Refs. [28][29] According to these reviews, the proposed modes of antitumoral action of POMs involve several possibilities: (1) the activation of cell death pathways; (2) inhibition of angiogenesis; (3) interaction with proteins; or (4) DNA interaction, among other mechanisms. In the case of POMs action against bacteria the proposed mechanisms considers: (a) inhibition of both PBP2a and β-lactamases; (b) targeting P-type ATPases; (c) impairment of the bacterial electron-transport chain (respiratory system); (d) POM-mediated increase of the reactive oxygen species level via oxidation; (e) interaction with important membrane-anchored proteins and enzymes; (f) disruption of the bacterial cytoskeleton dynamics by POM-interactions with cytoskeletal elements; (g) disruption of the bacterial cell wall leading to leakage of intracellular substances; or (h) interaction with cytoplasmic elements of proteins that are anion-sensitive like nucleic acid-binding proteins. In our studies, among all the processes described in the reviews of Bijelic et al. [27][28], we focused on the interaction of POMs with DNA to promote its phosphoester hydrolysis as artificial phosphoesterases. The seminal works found in the bibliography on this topic are the experimental studies of Parac-Vogt et al. based on $[Mo_7O_{24}]^{6-}$ ({Mo_7}) species, [30][31][32][33] whereas other experimental works of Abrantes et al. [34][35] were based on the MoO_2X_2L species.

2. Computational Techniques, Methods and Tools Used in Our Studies

We have used different computational approaches to carry out the different calculations for the three topics developed in these studies. In the lines of research regarding the interaction of small molecules based on phen derivatives and Mo complexes, including phen with dDNA and GQ, we used several models along with different levels of calculation. That is, in the case of sandwich models [36], we used the M06-2X/6-31+G(d,p) level of calculation [37][38][39] with Gaussian09 in order to study the intercalation of phen derivatives with dDNA. Ref. [40] The M06-2X functional is recommended to study systems in which weak interactions such as dispersion are important to explain their behavior (as the intercalation of small molecules between bps of DNA). In the case of the ring models [36] including sugar, phosphates, and Na^+ counterions, and for the study of the groove binding interactions with the $d(GTCGAC)_2$ hexamer, we used the semi-empirical Hamiltonian PM6-DH2 [41] including dispersion effects with the MOPAC software. Ref. [42] In the case of the ring model 2 ps semi-empirical MD, simulations with the PM6-DH2 Hamiltonian were also performed with a time step of 1fs. Explicit water molecules were considered by means of the TIP3PBOX solvent model for the simulations by using a rectangular box with edges no closer than 5 Å to any atom of the solute. Finally, in the case of the studies on the interaction of the $Mo[(\eta^3\text{-}C_3H_5)Br(CO)_2(phen)]$ complex with dDNA and GQ, we took into account the $d(AGACGTCT)_2$ octamer for the dDNA, coming from the 1n37 PDB structure, and the GQ coming from the 2jwq PDB structure to study the interaction of the $Mo[(\eta^3\text{-}C_3H_5)Br(CO)_2(phen)]$ with this non-canonical structure. These structures were studied at the LMKLL/DZDP level, [43][44] which includes van der Waals corrections. The core electrons were substituted by norm-conserving pseudopotentials. Refs. [45][46] Such LS-DFT computations with ~500 atoms for the dDNA and ~1000 atoms for the GQ were carried out with the Spanish Initiative for Electronic Simulations of Thousands of Atoms (SIESTA) method and associated software. Ref. [47] The cut-off radii for the atomic orbitals of each element were obtained for an energy shift [47] of 30 meV. The tolerances used for the optimizations were 10^{-5} eV for the energetics, whereas the tolerance for the forces was 0.02 eV/Å for the dDNA and 0.1 eV/Å for the GQ. In order to gain deeper insight into the interaction between the

small molecules and DNA substrates, we performed the Energy Decomposition Analysis (EDA). Refs. [48][49] To carry out the EDA, we mainly used the B3LYP-D3/TZP level of calculation [50][51][52][53] since the B3LYP-D3 functional includes an explicit Grimme's D3 correction for dispersion and, therefore, an additional ΔE_{disp} term appears in the EDA for this functional. For this reason, we thought that the discussion was simpler to visualize better the trends of the intercalated systems. It must be said that the M06-2X/TZP and M06-L/TZP levels were also checked for the EDA. In any case, the three functionals led to results comparable to the MP2/6-31G* (0.25) level of theory already used by Řeha et al. [54] which gave results comparable to the benchmark CCSD(T) data. Ref. [55] These EDA were carried out with the ADF software. Refs. [56][57][58] Another way to gain deeper insight into the interaction between the studied small molecules and DNA structures is the topological analysis of the structures. Two kinds of approaches were used, namely the classical QTAIM developed by Bader et al. [59] and the most recent approach developed by Johnson et al. [60] based on the NCI. The latter provides a rich, 3D representation for the non-covalent interactions with surfaces based on the peaks that appear in the reduced density gradient at low values of ρ. Such isosurfaces are mapped according to values of the sign of the second Hessian eigenvalue, (λ_2), and while negative values (i.e., stabilizing interactions) are depicted in blue and pale green, positive values (i.e., destabilizing interactions) are represented in yellow and red. QTAIM and NCI computations were performed with the AIM2000 [61] and AIMALL [62] software with the wave functions generated at M06-2X/6-31+G(d,p) level with Gaussian09 in all cases with the exception of the interactions of $[Pt(en)(phen)]^{2+}$ derivatives via groove binding with dDNA in which the wave function was obtained at B3LYP/6-31G(d,p) level with Gaussian09. Finally, for some of these systems in which small molecules are interacting with DNA, we studied the polarization/charge transfer for the different modes of interaction with several charge schemes arising from different approaches (Mulliken, [63] APT, [64] Hirshfeld [65] and NPA/NBO [66][67]).

In the study of the activity of Mo-oxo species as promoters and catalysts for the hydrolysis of the phosphoester bond, we carried out the DFT calculations by using ADF [56][57][58] and the Gaussian 16 Revision A.03 software. Ref. [68] In the case of ADF, geometry optimizations were carried out with the BP86 functional, which uses the Vosko-Wilk-Nusair exchange-correlation potential [69] with the generalised gradient approximation exchange correction reported by the Becke (1998) exchange functional [70] and Perdew (1986) correlation correction [71], as well as Grimme dispersion corrections (BP86-D3). Ref. [53] Relativistic effects were treated with the zero order regular approximation (ZORA) Hamiltonian. Refs. [72][73] The frozen core approximation and triple-ζ Slater-type orbitals (STO) were used to describe the valence shells of C and N (2s and 2p). One polarization function was added to C, N, O, and Mo (single-ζ, 3d, 4f). Triple-ζ STOs were used to describe the valence shells of H (1s) augmented with one polarization function (single-ζ, 2s, 2p). Solvent effects were included with the COSMO [74] and standard parameters (Water, ε = 78.39). Analytical frequencies were calculated to characterise the obtained stationary points and calculate the Gibbs free energies (standard state T = 298.15 K, p = 1 atm). Transition states were followed after a fractional displacement of the imaginary vibrational mode to both the reactant(s) and product(s). On the other hand, Gaussian calculations were carried out with the B3LYP hybrid functional. Refs. [50][51][52] The LANL2DZ effective core potential with the associated double zeta basis set supplemented with f polarisation functions was used for Mo atoms [75][76][77][78][79] and the 6-31+G(d,p) basis set [39] for the rest of the atoms. Dispersion effects were included by using the third version of Grimme dispersion with the Becke–Johnson damping approach. Ref. [80] Stationary points were characterised by means of frequency calculations, and the intrinsic reaction coordinate was followed in order to obtain the geometries of the reactants and products followed by unconstrained optimisations. Refs. [81][82] For some mechanistically relevant stationary points the energies were refined with the 6-311++G(3df,2p) basis set. Ref. [83] For these calculations with Gaussian 16 Revision A.03 the Polarisable Continuum Model (PCM) was used to take into account the solvent in an implicit way [84][85].

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