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Binding properties and conformational dynamics of reversible amidines with DNA from a theoretical view

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ABSTRACT

We present here molecular dynamics simulations and DNA conformational dynamics for three reversible amidine-DNA adducts. Our simulation results indicated that a DNA molecule bound by a reversible amidine produced a narrow and deep minor groove. The N–H and C–H groups in binding regions from reversible amidines play important roles on functioning as H-bond donors to N or O atoms of nucleobase located on the floor of the minor groove of DNA. DNA conformational dynamics in the vicinity of binding region were influenced significantly by the reversible amidine on a nanosecond time scale. The obtained results demonstrated that influence of the central heterocycle is greater than that of tail part for reversible amidines binding affinity to DNA. All of these findings provide useful information to better understand the binding properties and conformation dynamics of the reversible amidines with DNA.

1. Introduction

There has been considerable interest in the design of aromatic dication diamidines due to their potentials as effective chemotherapeutic agents for many diseases in recent years [1–3]. Many aromatic diamidines could bind to specific base sequences in the DNA minor groove [4,5]. Especially, some reversible aromatic reversible amidines exhibit with high specificities for targeting AT-rich sequence kinetoplast DNA minicircles with disruption kinetoplast replication and cell death [6–8].

Molecular shape of diamidines is critical for its binding to DNA in the minor groove [9–11]. Even small conformation changes of diamidines have a strong effect on their affinities and specificities [12]. For instance, only a small bond angle difference for C–O–C in furan and C–S–C in thiophene of diamidine derivatives results in compounds with over 10-fold increased affinity for AT-rich sequences [13,14]. Particularly, Boykin, Wilson and Neidle group have reported that the exciting diamidines with reverse structures identify DNA with highly affinity [4,15–19]. The reversible diamidines have shown promising characteristics, such as simple structure, synthetic accessibility, and sequence-specific binding ability to base pairs in the minor groove of DNA double helix [20,21]. However, it is very difficult to make clear why the reversible diamidine present supernal affinity abilities to DNA unless we can obtain detailed information at the molecular level [22].

Understanding the structural details of DNA bound by the reversible diamidine compounds may help us delineate the features that are responsible for the remarkable potency of these reversible amidines. However, knowledge of the precise interaction mechanisms of the reversible diamidines with DNA at the molecular level is very limited [9]. Herein, we attempt to gain a more detailed understanding of the interaction mechanisms of the reversible diamidine with DNA by employing molecular dynamics (MD) simulations to examine the following aspects of the reaction: how the reversible diamidine complexe binds to a DNA molecule, how the reversible diamidine interacts with DNA, how the diamidine affects the minor goove parameters of DNA compared to the undamaged DNA, and what the important roles for reversible diamidine-DNA adducts play.

Particularly, interaction mechanisms of the reversible diamidine of DB884 and its derivatives (as shown in Scheme 1) with DNA were investigated by using MD simulations in the present work. MD simulations of three adducts were carried out, of which first one MD simulation was performed on DB884-DNA adduct (taken from Protein Data Bank) not only to investigate their binding properties but also to evaluate the accuracy of the current protocol; the second one was performed on DB613-DNA adduct to address the role of central heterocycle; the third one was performed on DB1393-DNA adduct to study the influence of tail part of diamidine on the binding properties to DNA. The present work shed light on the interaction mechanism of the reversible diamidines with DNA, and provided useful insights for a better understanding of how a DNA conformation is affected by a reversible amidine at the molecular level.

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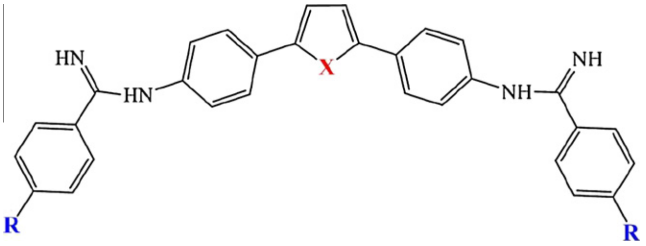

Scheme 1. Chemical structures of DB884 (X = NH, R = H), DB1393 (X = NH, R = CH_2CH_3) and DB613 (X = O, R = H).

2. Methods and computational details

2.1. Ab initio calculations

The initial structures of the three reversible diamidines, DB884, DB1393 and DB613, were optimized at the B3LYP/6-31G** level of theory [23–25]. The optimized geometries of three reversible amidines are shown in Fig. 1. It is noticeable that the optimized geometries represent a similar C2 symmetry for each complex due to the same component connecting to the both sides of five-member heterocycle center. Additionally, the computational bond lengths and angles of DB884 were selected as comparison with those available X-ray experimental data listed in Table 1. Namely, the computed parameters of bonds and angles for DB884 differ by the average percentage of 1.5 and 2.7 from those in the experiments [9,26], respectively, indicating that the theoretical calculation level used in this work is suitable.

2.2. Force field parameters

The atom types for the studied reversible amidines were generated by using the ANTECHAMBER module included in AMBER9 program package [27,28]. The electrostatic potentials of the complexes used for RESP charge calculations were calculated at the HF/6-31G(d, p) level [29–31] of theory using the Gaussian03 program [32]. RESP charges of the compounds listed in Fig. 2 were derived by the RESP program based on the calculated electrostatic potentials.

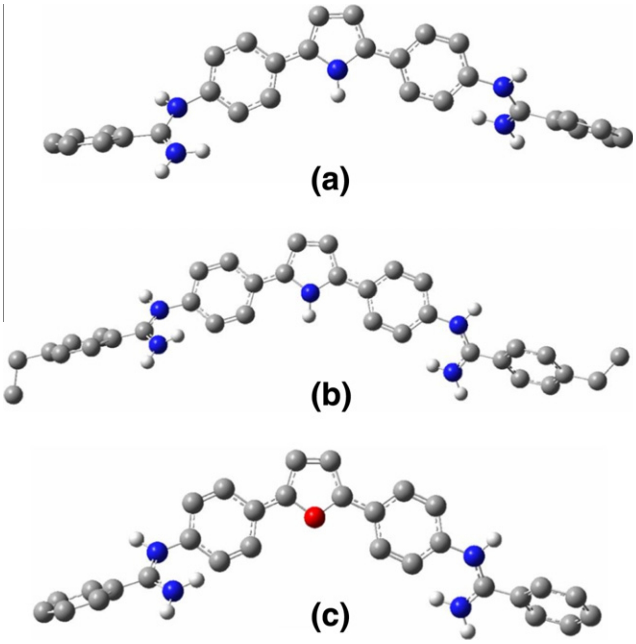

Fig. 1. Geometries of three reversible amidines optimized at the B3LYP/6-31G** level of theory. (a) DB884; (b) DB1393; (c) DB613. C (gray), N (blue), O (red), H (white). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Optimized geometrical parameters of bond distance (Å), angle (°) and dihedral (°) along with X-ray structure parameters.

Parameter		Mean optimized	Mean X-ray	Deviation[a]
Bond	CD–NA	1.399	1.408	0.6
	CA–NH	1.346	1.360	1.0
	CC–CC	1.458	1.519	4.0
	CC–CD	1.403	1.400	0.2
Angle	CD–NA–CD	110.9	107.5	3.1
	NH–CA–NH	120.1	123.0	2.3
Dihedral	NH–CA–NH–NH	162.6	168.0	3.3

[a] Denotes the change percentage (%) between optimized parameters and experimental values [9].

2.3. Starting structures

On the basis of previous experimental studies of the reversible diamidine [9], the DB884-DNA system was taken from the X-ray crystal structure of DB884-d$(C_1G_2C_3G_4A_5A_6T_7T_8C_9G_{10}C_{11}G_{12})_2$ adduct (PDB code: 2GYX) [33], assigned as 884-DNA, as the starting structure for MD simulation (as shown in Fig. 3a). Initial conformations of DB1393-DNA and DB613-DNA systems for MD simulations were obtained by docking DB1393 and DB613 into the DNA (taken from 884-DNA) using the AutoDock 3.05 program [34], assigned as 1393-DNA and 613-DNA, respectively. The grid map of 72 × 72 × 84 points and a grid-point spacing of 0.375 Å have been employed during the docking processes, using classical Lamarckian genetic

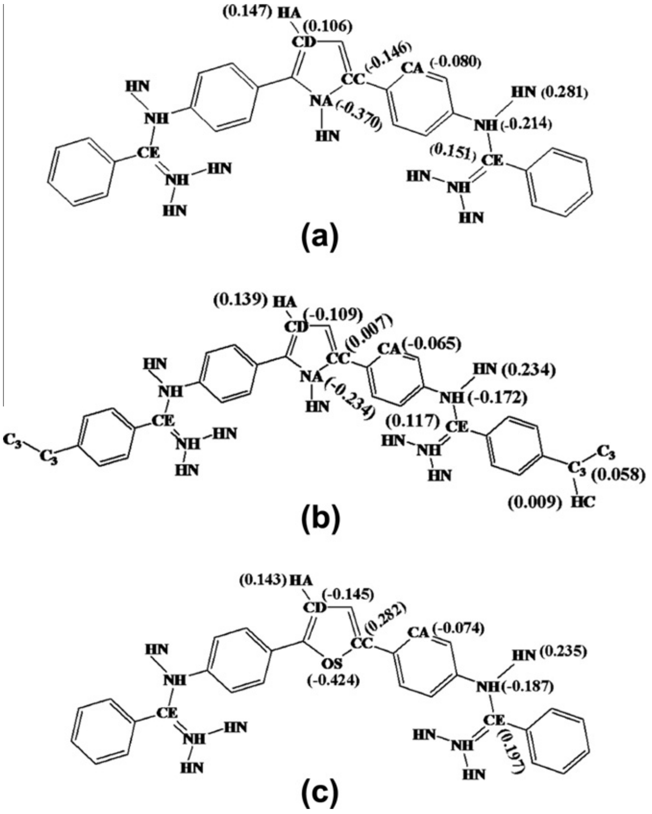

Fig. 2. AMBER atom types and RESP charges of (a) DB884, (b) DB1393, and (c) DB613.