Journal of Molecular Structure: THEOCHEM 939 (2010) 44–52

Contents lists available at ScienceDirect

Journal of Molecular Structure: THEOCHEM

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

Theoretical study of the interaction pattern and the binding affinity between procaine and DNA bases

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ARTICLE INFO

Article history:
Received 29 June 2009
Received in revised form 17 September 2009
Accepted 17 September 2009
Available online 24 September 2009

Keywords:
Procaine
DNA bases
Hydrogen bonding
Binding affinity
AIM
NBO

ABSTRACT

The interacting patterns and mechanism of the binding affinity between the local anaesthetic procaine and four DNA bases (adenine, cytosine, guanine and thymine) in neutral form have been investigated in gas phase using the Austin Model l and density functional methods. The results show that the complexes are mainly stabilized by the H-bonding interactions. The bond critical point properties of the optimized complexes were analyzed by using the atoms in molecules theory with DFT method and the results show that the presence of the C–H···O or C–H···N hydrogen bonding. The natural bond orbital analysis was performed to quantitatively evaluate the hydrogen bonding interaction. The interacting energy shows that the binding of procaine with guanine is the most strong, whereas its binding to cytosine exhibits relatively weaker stability. The strength order of the relevant transferred charge between procaine and DNA base with natural population analysis are consist with the HOMO–LUMO gap results for each complex. And the order is accord with the relevant electrochemical experimental results.

1. Introduction

As one kind of quick-action local anaesthetics (LAs) and the first derivative of cocaine, procaine hydrochloride ($C_{13}H_{20}N_2O_2{\cdot}HCl$) mainly interacts with both peripheral and integral components of membrane proteins, thus represses the depolarization and inhibits the generation of action potential [1] and produces a reversible loss of sensation by diminishing the conduction of sensory nerve impulses. Despite considerable advances in experiments [2–5] and theories [6–8], its molecular structure and pharmacological mechanism still remains to be clarified. Therefore, a number of experimental [9–12] and theoretical [13–15] studies of procaine have been performed on its structural and functional properties.

Generally speaking, the procaine contains three groups: an amine group, an aromatic group, and an intermediate alkyl chain, in which the latter is a flexible unit and easy to undergo conformational changes in different solutions. Therefore the configuration of the procaine has been investigated extensively. The crystal structures of the procaine [9] and procaine hydrochloride [10] have been resolved by X-ray crystallography method [9,14]. Rothchild et al. investigated the procaine hydrochloride in neutral and protonated conjugate acid forms by using one and two dimensional proton and carbon-13 NMR technique and HF/6-31G* *ab initio* calculation [12]. Neto et al. studied the procaine in neutral and protonated forms both in gas and solvent phases with the Austin Model l (AM1) method, and calculated the gas-phase absorption spectra with the semi-empirical INDO method [13].

On the other hand, the toxic side effects of the LAs on biological organism should be also taken in account in clinic applications. Apart from their adverse effects on the central nervous and cardiovascular systems, there still exist potential hazards when the DNA exposes to the LAs for a long time and induce baneful effects [15]. Therefore a number of relevant studies on the procaine and DNA have been taken in recent years [16,17]. The relevant ionic strength and viscosity experiments showed that the procaine may bind to DNA in groove-binding mode [16]. Meanwhile, the binding behaviors of procaine with DNA bases by atomic force microscopy and differential pulse voltammetric method showed that the binding of purines with procaine hydrochloride is much stronger than that of pyrimidines and the binding affinity exhibits the sequence dependent, i.e., the binding ability for the four DNA bases adenine (A), cytosine (C), guanine (G), thymine (T) to procaine is in the order of P·G > P·A > P·T > P·C [17].

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doi:10.1016/j.theochem.2009.09.039

Although the observed binding specifities have improved fundamental understanding on the specific binding behavior to DNA bases, the lack of their structural knowledge presents a challenge for experiments to obtain an insight into the DNA base-related molecular recognition. These intermolecular interactions, including the hydrogen bonding (H-bonding), van der Waals interaction, and hydrophilic or hydrophobic interaction, etc, which are poorly understood to date, play important roles in determining the structures and dynamics of large biomolecules and small ligands [18–23]. Therefore, in this study, the AM1 and density functional theory (DFT) were used to study the interacting pattern and the origin of the binding affinity of the different procaine–DNA base complexes in neutral state, for which only the neutral procaine is able to diffuse through tissues and membranes [24,25]. The aims of this work were mainly focused on the following points: (i) to explore the main intermolecular interaction underlying the procaine–DNA complexes; (ii) to investigate the binding affinity of the different procaine–DNA base complexes; (iii) to study the origin of the relation between the binding affinity and relevant theoretical parameters.

2. Computational details

As a first step, the initial procaine structure obtained from X-ray data [9,14] was optimized with AM1 methods [26,27]. Then the Becke3–Lee–Yang–Parr (B3LYP) hybrid density functional theory and the medium-sized polarized 6-31G(d,p) basis sets were used to refine the monomer structures obtained from the AM1 method considering its suitability and reasonable accuracy [28]. The geometries of the four procaine–DNA complexes in gas phase were fully optimized with the same AM1//DFT strategy. All optimizations were carried out in gas phase with tight convergence criteria by using the "Tight" and "Int = Ultrafine" keywords without imposing any molecular symmetry constraints. The harmonic vibrations were calculated in order to characterize the reliability of the structures of the complexes and further analyze their thermodynamic properties. The interaction energies (ΔE) of the most stable complexes were calculated with the zero-point energy (ZPE) and basis-set superposition error (BSSE) correction [29]. To examine the accuracy of the results and determine the suitability of the methods in the present studies, single-point calculations of the optimized geometries were carried out at the second-order Møller–Plesset level (MP2) levels by using the 6-31G(d,p) basis set for comparison. Meanwhile, the standard entropies (ΔS), enthalpies (ΔH), and Gibbs free energies changes at the 298 K of all the optimized complexes have been derived from the frequency calculations at B3LYP/6-31G(d,p) level. These energies were corrected with zero-point energy but not scaled.

To obtain a deeper insight into the nature of H-bonded interactions, the atoms in molecules (AIM) analysis was performed using AIMALL [30]. The BCPs of the X–H bonds as well as the H···Y interactions were found and their features were analyzed. Furthermore, the complexes were analyzed by using natural bond orbital (NBO) method to obtain an insight into the bonding features and the nature of the intermolecular interactions [31,32]. All calculations were performed using the Gaussian98 program (Pittsburgh, PA, USA) [33]. And the Molekel5.3 program was employed for the molecule visualization [34] and the molecular electrostatic potential (MESP).

3. Results and discussion

3.1. Optimized geometry of procaine

The structures and the label scheme of the four DNA bases and procaine are depicted in Fig. 1. The geometric parameters of procaine calculated by AM1 and DFT methods are listed in Table 1, compared with Kashino et al.'s X-ray crystal data [9]. The final optimized structure of the neutral procaine with the lowest energy in gas phase (−767.100 a.u. with ZPE correction) at the B3LYP/6-31G(d,p) level shows a folding configuration and the detailed coordinates are given in Tables S1 in Supplementary material. The intramolecular distance r(O14···N26) between O14 and N26 is of special interest because it could be used as a structure parameter to characterize the configuration of the alkyl chain group [14]. The r(O14···N26) in the present work is 4.940 Å, larger than the X-ray data of 4.382 Å by about 12.73%.

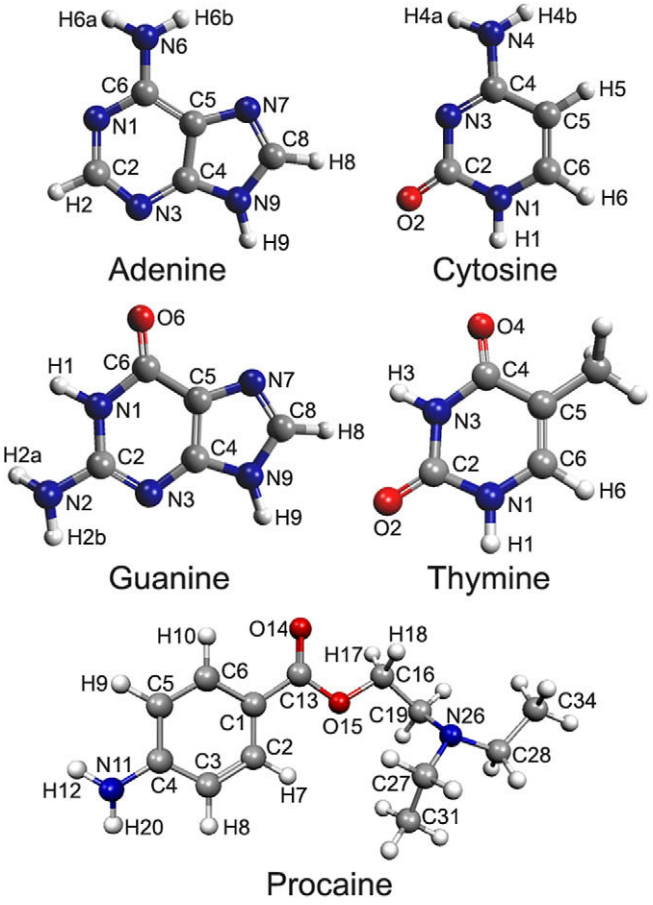

Fig. 1. Structures and atom numbering schemes of the procaine and DNA bases.

As shown in Table 1, the bond lengths and bond angles calculated by both AM1 and B3LYP methods are consistent with experimental data with less than 6% and 8% deviation, respectively. The largest difference by both method lies in r(N1–H20), i.e., by about 14.14% for AM1 and 16.09% for DFT compared with the corresponding X-ray data. The errors may origin from the influence of the hydrogen atom H20 involved H-bonding which is formed with the O14 on the other procaine molecule in the experimental crystal structure. The calculated bond length of r(C27–C31) by AM1 method is 1.521 Å and the bond length of r(C27–C31) calculated by the DFT method is 1.539 Å, which differs from the corresponding experimental values of 2.36% and 3.57%, respectively. The torsion angle ∠(C13–O15–C16–C19) differs from the crystal data remarkably and exhibits the opposite trend caused by the flexible amine group. The dihedral angle of ∠(C13–O15–C16–C19) and ∠(O15–C16–C19–N26) at the B3LYP/6-31G(d,p) level are −177.4° and −79.9°, respectively, displaying a folding configuration.

The optimized geometrical parameters of the bonds and angles of the four DNA bases are given in Fig. S1 in Supplementary mate-