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Theoretical study of the structural and optical properties of cytosine analogues

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ABSTRACT

Fluorescent nucleoside analogues have attracted much attention in studying the structure and dynamics of nucleic acids in recent years. In the present work, we use theoretical calculations to investigate the structural and optical properties of four cytosine analogues (termed as C1, C2, C3, and C4), and also consider the effects of aqueous solution and base pairing. The results show that the fluorescent cytosine analogues can pair with guanosine (G) to form stable H-bonded WC base pairs. The excited state geometries of cytosine analogues are similar to the ground geometries. The absorption maxima of the cytosine analogues are greatly red shifted compared with nature cytosine (C). The calculated absorption peaks of modified deoxyribonucleosides are in good agreement with the experimental data. The solvent effects can induce a small blue shift for C1 and C2 but a little red shift for C3 and C4, and can increase the oscillator strengths in both the absorption and emission spectra. With regard to the WC base pairs, the B3LYP functional reveals that the lowest energy transitions of GC base pairs are charge transfer excitation while the CAM-B3LYP functional predicts that they are localized excitation. The M062X and CAM-B3LYP functional show good agreement with respect to both the value of the lowest energy transitions as well as the oscillator strengths.

1. Introduction

Fluorescence is widely used in probing the structure and dynamics of nucleic acids and their interactions with other biomolecules. For example, the adenine analogue 2-aminopurine is strongly fluorescent and has been used as a site – specific probe of nucleic acid structure and dynamics [1–3] because it can form base pairs with thymine in Watson–Crick (WC) geometry or with cytosine in a wobble configuration. However, the use of fluorescence to study nucleic acids requires fluorescent marker such as fluorescent dyes [4–6] and nucleobase analogues [7] since the natural nucleobases are virtually non-fluorescent ($\Phi_f \sim 10^{-4}$) [8]. Fluorescent nucleoside analogues (FBAs) resemble the natural nucleobases, retain their Watson–Crick (WC) hydrogen bonding (H-bonding) faces, minimally perturb the natural DNA or RNA structure, and most importantly, are significantly fluorescent [7]. Over recent decades several research groups have focused on the development of FBAs with the above-mentioned properties. Saito and co-workers [9–12] produced a series of base-discriminating analogues, Tor et al. [13–16] reported pyrimidine analogues, Sandin et al. [17,18] designed tricyclic cytosine analogues tC and tC^O, Hawkins et al. [19,20] developed pteridines which comprise guanine analogues and adenine analogues, Kool's group [21–28] synthesized a range of size-expanded nucleobases, Shin et al. [29] synthesized four thieno modified RNA nucleosides. However, there are no many theoretical studies on photophysical characteristics of FBAs. Theoretical studies of novel FBAs will hopefully lead to a more complete understanding of the relationship between their structural and fluorescence properties. Until recently, Zhao et al. [30–32] studied photophysical characteristics of size-expanded nucleobases, Liu et al. [33,34] studied Janus-type AT nucleobases analogues and adenine analogues in theory. In this work, we turn our attention to the cytosine analogues, four types of cytosine analogues, benzopyridopyrimidine (BPP) [10], naphthopyridopyrimidine (NPP) [11], 1,3-diaza-2-oxophenoxazine (tC^o) [17], 1,3-diaza-2-oxophenothiazine (tC) [18], have been chosen as the objects. For convenience, these four cytosine analogues are termed as C1, C2, C3, and C4, respectively. We use ab initio calculations to obtain the structural and optical properties of these cytosine analogues, and also consider the effects of aqueous solution and base pairing. We find that the calculated low-energy peaks in the

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absorption spectra are in good agreement with the experimental data. We hope our theoretical studying is helpful to design new fluorescent base analogues in the future.

2. Computational details

All calculations were performed using the Gaussian 09 program package [35]. The ground state (S_0) geometries of cytosine analogues (termed as C1, C2, C3, and C4, respectively), the free deoxyribonucleosides (dC1, dC2, dC3, and dC4, respectively), and the WC base pairs (GC1, GC2, GC3, and GC4, respectively) were optimized using both B3LYP and HF [36,37] methods with the 6-31+G** [32] basis set. The lowest singlet excited state (S_1) geometries were optimized by the ab initio configuration interaction singles method (CIS) [38]. These fully optimized stationary points were further characterized by harmonic vibrational frequency analysis to ensure that real local minima had been found without imaginary vibrational frequency. The electronic absorption and emission spectra [39,40] were carried out using the time-dependent density functional theory (TD-DFT) theory with the B3LYP hybrid functional on the basis of the optimized ground and excited structures, respectively. For the hydrogen-bonded WC base pairs, the vertical transition energies were also computed using long-range corrected (LC) density functional CAM-B3LYP [41] and M06-2X [42] on the basis of the corresponding optimized ground structures. The solvent effect on the transition energies was considered using the polarized continuum model (PCM) of the self-consistent reaction field (SCRF) theory [43,44].

3. Results and discussion

3.1. Optimized geometries

3.1.1. Properties of the ground state

The optimized geometries and atomic numbering scheme of cytosine analogues are shown in Fig. 1, the selected bond lengths and bond angles of these cytosine analogues obtained by B3LYP/6-31+G** calculations are listed in Table 1. From Fig. 1, it can be clearly seen that the cytosine analogues retain the Watson–Crick (WC) hydrogen bonding (H-bonding) faces and the cytosine is modified via fusing diverse aromatic ring linked to N4 and C5 atoms to yield rigid and conjugate structure. C1, C2, and C3 are

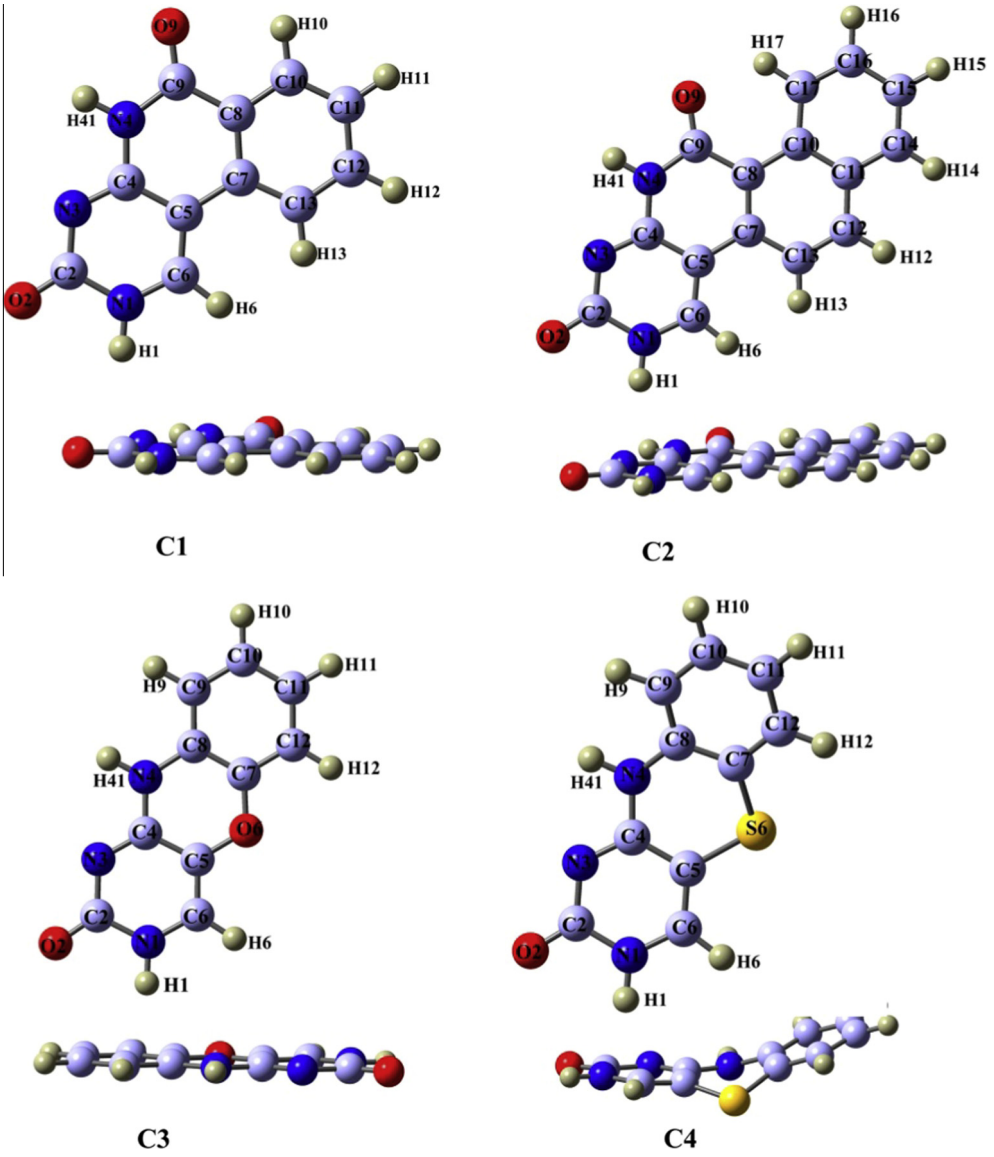

Fig. 1. The optimized ground state geometries and atomic numbering scheme of the cytosine analogues calculated at the B3LYP/6-31+G** level.