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Computational Analyses of Cytidine and Aza-Cytidine Molecular Structures

Roya Yaghoobi
Department of Applied Chemistry, Faculty of Pharmaceutical Chemistry, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

Mahmoud Mirzaei✉
Biosensor Research Center, School of Advanced Technologies in Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT. Structural features of cytidine and aza-cytidine were analyzed in this work by means of *in silico* approach of computational methodologies. The structures were optimized and their corresponding molecular and atomic scales properties were evaluated. The results indicated that nitrogen substitution of cytidine could lead to new properties for aza-cytidine in comparison with the original form. The trend was approved by the obtained orbital energy levels and representations. Moreover, the pyrimidine ring was the site of detection of significant changes versus the almost unchanged sugar group of the structure. Finally, the structural modification could yield meaningful changes for the structures of derivatives, which are comparable with the original structures for expected specific properties and activities. Computer-based works could reveal insightful information for such purposes.

KEYWORDS. Cytidine; Aza-cytidine; *In silico*; Density functional theory.

INTRODUCTION. The pioneering work of Watson and Crick to recognize the crystalline structure of DNA have lead the researchers to work on such important building block of life more and more.[1-5] Cytosine is one of nucleobases in addition to other adenine, guanine, thymine and uracil ones, which are all essentials of DNA and RNA architectures.[6-10] In this regard, addition of sugar group converts nucleobase to nucleoside and addition of another phosphate group converts nucleoside to nucleotide as complementary structures for constructing living systems.[11] Moreover, such original structures and their derivatives could show pharmaceutical applications of treatments of diseases.[12-14] Cytidine is nucleoside of cytosine with pharmaceutical applications of caner growth inhibition (Fig. 1).[15] Moreover, aza-cytidine is nitrogen substituted derivative of cytidine, still showing pharmaceutical applications.[16] Besides the activities, structural analyses could reveal information about the characteristic features of such small molecules.[17] In this case, computational analyses methods could provide useful *in silico* environment to study the structures at the molecular scales.[18-21] Based on such advantage, computational analyses of cytidine and aza-cytidine were performed in this work.

Structural features of molecules are important for determining their corresponding activities so called structure-activity relationship (SAR), which is very much important to determine novel activities for the investigated structures.[22] To this aim, electronic

✉ Corresponding author; *E-mail address*: mdmirzaei@pharm.mui.ac.ir (M. Mirzaei).

properties of cytidine and aza-cytidine structures were determined in this work. Orbital properties are very much important to such investigation, in which they were calculated and discussed in this work for the optimized structures (Table 1). Moreover, the graphical representations were evaluated to help better understanding the characteristic features of electronic systems (Fig. 1). The major goal of this work was to determine the structural features and properties of cytidine and aza-cytidine molecules, which were analyzed by the obtained computer-based parameters and properties.

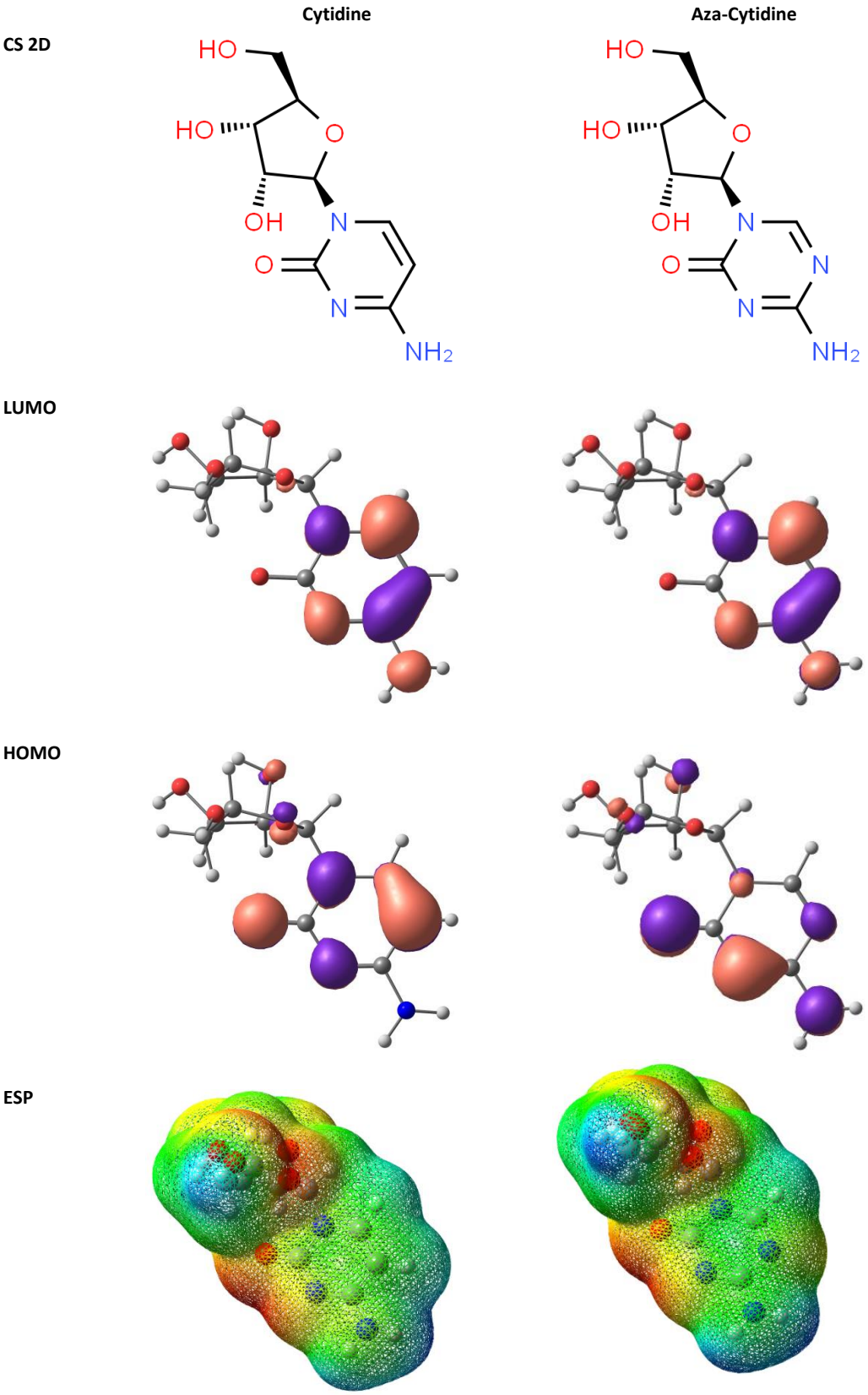

Fig. 1: Graphical representations.

METHODOLOGY. Density functional theory (DFT) calculations were performed to optimize the structures of cytidine and aza-cytidine (Fig. 1) using the B3LYP/6-31G* method as implemented in the Gaussian program.[23] After this process, the molecular properties including molar volume (MV), the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), their difference as energy gap (EG), and dipole moment (DM) were evaluated for the energy-minimized structures (Table 1). Furthermore, graphical representations were drawn for HOMO, LUMO, and ESP (Electrostatic Potential) to show the electronic environment of the investigated structures. In addition to such molecular properties, atomic-based quadrupole coupling constant were calculated for nitrogen and oxygen atoms (NQCC and OQCC) to declare the electronic changes at the atomic sites (Table 2). The procedure of such QCC calculations were described in an earlier work.[24] It is indeed an advantage of computer-based works to investigate details of structures at all possible states of molecules and atoms *in silico*.[25-29]

Table 1: Molecular properties.

Property	Cytidine	Aza-Cytidine
CS ID	5940	9072
Formula	$C_9H_{13}N_3O_5$	$C_8H_{12}N_4O_5$
MW g/mol	243	244
MV cm^3/mol	158	136
LUMO eV	-0.85	-1.05
HOMO eV	-6.22	-6.86
EG eV	5.37	5.81
DM Debye	3.68	2.03

RESULTS & DISCUSSION. Within this work, computational analyses of cytidine and aza-cytidine were performed using the *in silico* approach of computer-based studies. First the 3D models of structures both molecules were optimized to reach the minimized energy structures. Cytidine and aza-cytidine are different in nitrogen substitution of carbon atom at position number five of pyrimidine ring (Fig. 1). Earlier works indicated this position as an important atomic site for arising pharmaceutical activities for chemical structures.[24] Within this work, aza-cytidine is that of atomic site five substituted derivative of cytidine, in which its properties were investigated here by computer-based methodologies. A quick look at Fig. 1 could reveal similar 2D molecular representations for both molecules. Additional examinations could also show similar LUMO representation for both molecules but different HOMO representation parallel case. To this point, it could be mentioned here that the ionizations situation of these molecules detected the significant changes of atomic substitution in the original form and substituted derivative of cytidine. Examining the values of Table 1 indicates that difference of energy levels of HOMO for two molecules are different more significant that such difference for difference of LUMO levels. The values of EG also showed the changes of orbital properties because of the nitrogen substitution of cytidine. Comparing the values of MV shows that the carbon-hydrogen removal form cytidine to convert to aza-cytidine could reduce the corresponding volume in the derivative structure. The values of DM could show that the electronic charge distribution was moderated in the derivative structure with lower value in comparison with that of the original structure. ESP representations for cytidine and aza-cytidine could show such achievements for MV and DM, in which the site of carbon-hydrogen removal of cytidine was some smaller in aza-cytidine than that of original cytidine. Based on such molecular results, it could be concluded here that small modification of cytidine could yield significant changes in its own characteristic structural features.

Table 2: Atomic properties.

	Cytidine	Aza-Cytidine
NQCC MHz	4.54	4.39
	3.51	3.41
	3.15	3.38
		2.84
OQCC MHz	11.61	11.62
	10.93	10.92
	10.66	10.67
	10.08	10.09
	8.68	8.78

Quadrupole coupling constant is an atomic parameter describing its electronic feature detecting any perturbation to such atomic site.[30] For this work, NQCC and OQCC were calculated for nitrogen and oxygen atoms to explore the effects of derivation on the atomic site properties (Table 2). To this point, the values indicated that the atomic sites of nitrogen atoms detected more significant changes in comparison with the atomic sites of oxygen atoms. The

trend could mean that the effects of derivation were very much more significant for the pyrimidine ring, which is the place of nitrogen substitution for aza-cytidine evaluation. The environments for sugar groups were almost remains unchanged by negligible changes of OQCC in the original form and nitrogen substituted derivative of cytidine. Indeed, the atomic sites are very much important for assigning contribution of a molecule to participate in interactions with other substances, in which structural modification could yield different properties as seen by changes of NQCC and OQCC. As a concluding remark, structural modification could specify a molecule showing specific properties.

CONCLUSION. By the results of this computer-based work for analyses of cytidine and aza-cytidine derivatives, some remarkable trends could be concluded. First, the nitrogen substitution could yield significant effects in parts of molecular system whereas some parts were remained almost unchanged. Second, the HOMO levels were changed more than LUMO levels in the derivative in comparison with the original form. Third, the EG value of derivative was larger than original cytidine. Fourth, the MV and DM properties were both reduced in the derivative. Fifth, the pyrimidine ring detected more significant changes of nitrogen substitution than the sugar group based on NQCC and OQCC values. And finally, modified structures could yield specific properties according to their modification specifications, which are analyzed by details in computer-based works.

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