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Article

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DFT-Based Study of the Intramolecular Interactions of Some Aminoglycosides

The quantum chemical modeling and full geometry optimization of sisomicin and gentamicin were carried out by the correlation functional B3LYP using augmented with polarization functions for heavy atoms 6-311G(*d*) and Dunning's correlation consistent cc-pVDZ basis sets. The effect of the basis set on the calculation results of molecular structure and quantum chemical descriptors of the titled compounds was studied. Special attention was paid to the intramolecular NH…N, OH…N, OH…O, NH…O hydrogen bonds in sisomicin and gentamicin. According to theoretical calculations, the distances between hydrogen and acceptor atoms are a bit longer than a typical length due to a significant deviation of the intramolecular H-bonds from a linearity. To evaluate the extent of electron density delocalization from the lone pairs of atoms into the antibonding neighboring orbitals and inside H-bonds within the systems, NBO (Natural Bond Orbital) analysis was used at two levels of theory. The most intensive interactions between electron donor and electron acceptor in the structures under consideration are determined and their delocalization energies are evaluated. Based on the obtained data, classical electrostatic nature of the weak H-bonds and conjugation effects stabilizing the molecules are suggested.

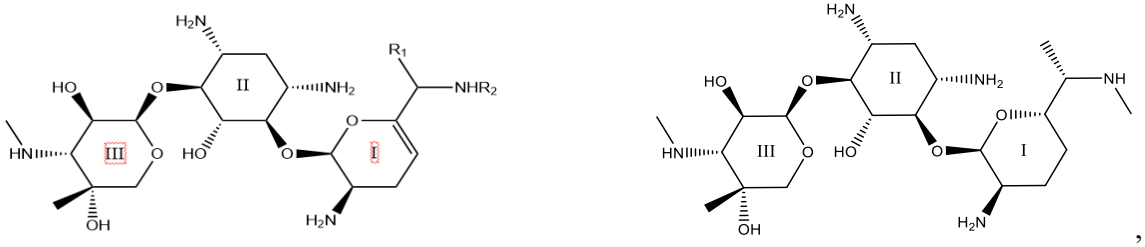
Keywords: aminoglycoside antibiotics, sisomycin, gentamicin, DFT calculation, B3LYP, NBO analysis, hydrogen bond, delocalization energy.

Introduction

Antibiotics are the antimicrobial substances for the treatment of bacterial infections [1, 2]. They can destroy or kill only bacteria with a cellular structure. Unlike bacteria, viruses do not have the cellular structure, so antibiotics do not affect them. Therefore, the use of antibiotics in the treatment of viral infections, in particular, coronavirus infection, is ineffective [3].

One of these wonderful antibiotics that can fight tuberculosis, tularemia, plague, pneumonia, brucellosis, endocarditis, staphylococcal and nosocomial infections are aminoglycoside antibiotics, a group of drugs with homogeneous pharmacokinetic properties. The first antibiotic of this group, streptomycin, was discovered in 1944 [4] and was the result of efforts to identify antibacterial agents from the fermentation products of soil microbes [5]. After a discovery of streptomycin, many additional aminoglycosides were developed. Semi-synthetic derivatives such as amikacin were created, resulting in more than 20 representatives of this class, many of which are effective antimicrobials [6].

Aminoglycosides are structurally different and consist of two or more amino-modified sugars associated with the aminocyclite core [7]. All members of this group bind to rRNA and 30s ribomes within the protein; however, interaction and binding differ depending on the chemical structure of the drug. Members of the aminoglycoside group with a 2-deoxystreptamine (2-DOS) core, such as gentamicin, sisomicin, kanamycin, and tobramycin, are particularly effective against many gram-negative bacterial pathogens [6–8]. This class of aminoglycosides is substituted at the positions 4 (ring I) and 6 (ring III) of the 2-DOS core (ring II) by the aminomodified sugars, and these substituents are called primary and double primary rings, respectively:



where R_1, R_2 = H for sisomicin (left) and CH_3 for gentamicin (right*;* cycle I is without a double bond).

Gentamicin is a bactericidal aminoglycoside that was discovered and isolated from *Micromonospora purpurea* in 1963. It is one of the most frequently prescribed aminoglycosides due to its spectrum of activity, low cost, and availability [9]. Sisomicin is a broad-spectrum aminoglycoside antibiotic and is structurally similar to gentamicin but has a unique unsaturated diamino sugar ring. Among aminoglycoside antibiotics, sisomicin has the highest activity against gram-positive bacteria [7, 8].

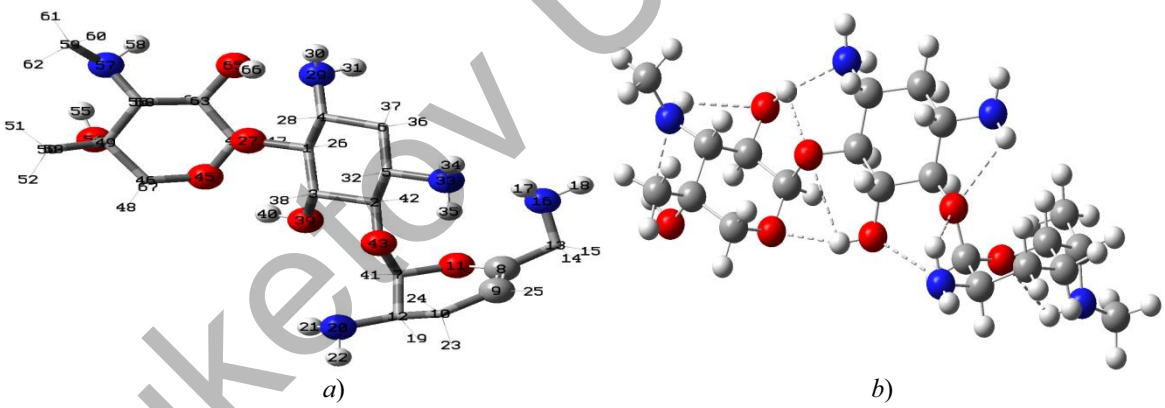
Sisomicin and gentamicin are also of interest due to a multiple hydrogen-bond (HB) network. There are the N-H…N, O-H…N, O-H…O, N-H…O intramolecular bonds. It is known that the hydrogen bonding plays an important role in many chemical and bioactive systems, and the study of structure and nature of HB is relevant. This work presents the results of a quantum chemical calculation and NBO analysis of structurally similar sisomicin and gentamicin.

Computational Details

Equilibrium molecular geometries for the ground states of the compounds studied in this work were determined in vacuum using density functional theory (DFT)-based [10] method with a split-valence 6-311G(*d*) and Dunning's cc-pVDZ basis sets [11, 12]. For the DFT calculations, the Becke three-parameter Lee–Yang–Parr (B3LYP) exchange-correlation functional [13] was employed. Sisomicin and gentamicin molecules were modeled with the GaussView 6.0.16 program, and all these calculations were performed using the Gaussian 16 computational package [14]. The local symmetry of methylene, methyl and amino groups was not taken into account because the molecules as a whole were asymmetric. All calculations converged to the optimized geometries corresponding to true minima, as revealed by the lack of imaginary values in the wavenumber calculations. NBO analysis [15] was used to explore intramolecular interactions in the optimized structures.

Results and Discussion

Molecular structure. The main thermodynamic and electrical properties of the titled compounds are listed in Table 1 that shows a comparison of the two sets of quantum chemical results. The most stable structures of sisomicin and gentamicin, atomic numbering, and the HB network are shown in Figure 1.



a) *b*)

Figure 1. The optimized structures (B3LYP/6-311G(*d*)) of the ground state of: a) sisomicin, with the numbering of the atoms; b) gentamicin, witn possible intramolecular H-bonds represented by dashed lines

The presence of hydroxyl, amino and methyl groups makes ample opportunities for conformational transformations and changes in the polarity of molecules, which can affect the implementation of biological activity. In this study, we refer to the ground state structures of entitled compounds.

In general, sisomicin calculated by two basis sets has almost the same structure. Similarly in gentamicin, the cc-pVDZ geometry slightly deviates from that optimized at the B3LYP/6-311G(*d*) level of theory. However, in the case of the last basis set, the total energies of both of these molecules are markedly lower as compared to the cc-pVDZ set (the energy differences are 170.19 and 181.11 kcal/mol for sisomicin and gentamicin, respectively) (Table 1). So, we use the B3LYP/6-311G(*d*) data during the discussion of the results.

According to the gas-phase calculations of the structures under consideration, the six-membered rings I-III in gentamicin have the form of a classic undistorted "chair". For the optimized sisomicin and gentamicin molecules, the differencies between their ring I geometries are considerable. In sisomicin, the ring I due to the presence of a double C=C-bond is distorted and other rings are identical to those of gentamicin (Fig. 2).

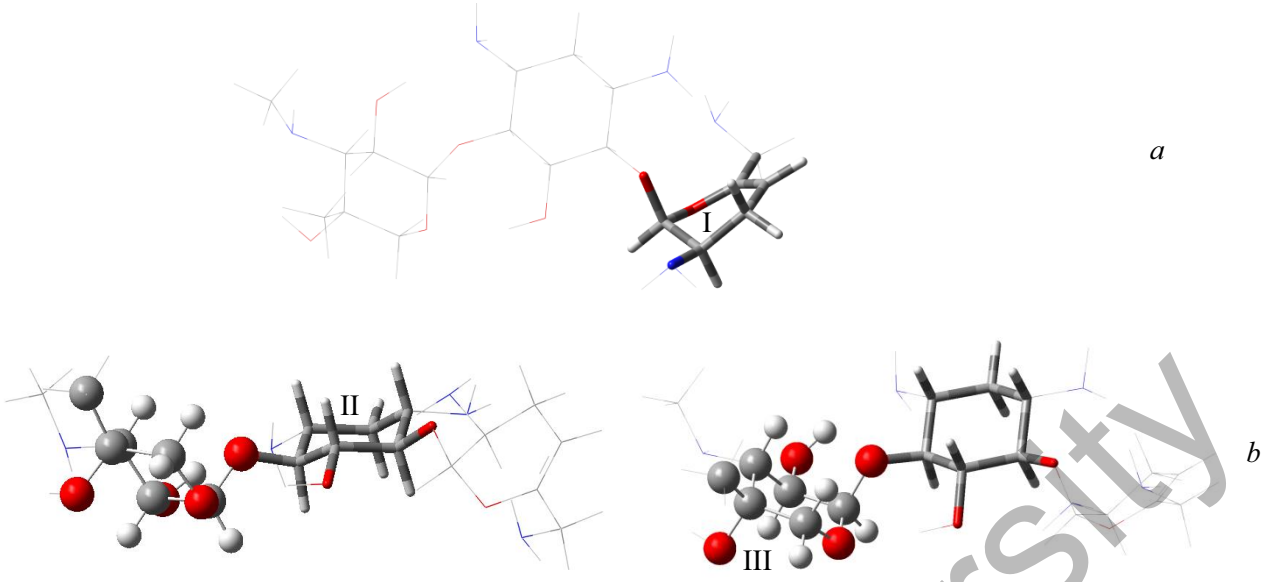


Figure 2. Optimized sisomicin molecule: a) the ring I with a partially planar conformation; b) the rings II, III with a chair conformation

The functional OH- and NH_2-groups are oriented to each other to form intramolecular H-bonds: OH-group of the ring II is directed to the O atom of the ring III and other hydroxyl groups are oriented to the N atoms etc.

Table 1

Some quantum chemical descriptors of sisomicin and gentamicin (DFT/B3LYP method)

No.	Descriptor	Basis set 6-311G(*d*) / cc-pVDZ	
		Sisomicin	Gentamicin
1	SCF energy (a.u.)	-1546.92597 / -1546.65473	-1626.789512 / -1626.500865
2	Thermal energy (kJ/mol)	393.572 / 391.006	446.075 / 442.567
3	Zero-point energy (kJ/mol)	1563.92 / 1553.35	1776.03 / 1760.21
4	Heat capacity (cal/mol·K)	124.889 / 125.220	136.329 / 137.514
5	Entropy (cal/mol·K)	198.940 / 197.444	211.606 / 215.370
6	Dipole moment (D)	5.528 / 5.091	6.684 / 6.142

Also, as one can see from Table 1, there is the changing tendency of the other calculation results with a change in the computation level. The enormous molecular dipole moments of the compounds occur due to electron density delocalization, contributions of lone pairs (LP) and indicate a high reactivity of them. The addition of electron donor methyl groups increases the dipole moment of gentamicin. Based on the NBO analysis data, the electron lone pairs of atoms located in sp^n-hybrid orbitals and contributing to the total dipole moment were determined. They are presented in Table 2.

Table 2

Contribution of lone pairs of atoms to the total dipole moment

NBO (LP)	Sisomicin	Gentamicin
N16	$sp^{4.08}$	$sp^{5.45}$
N20	$sp^{3.68}$	$sp^{4.04}$
N29	$sp^{3.96}$	$sp^{3.97}$
N33	$sp^{3.73}$	$sp^{3.73}$
N57	$sp^{4.78}$	$sp^{4.79}$

Hydrogen bonding. Both sisomicin and gentamicin have hydroxyl and amino functional groups which can form the intramolecular and intermolecular hydrogen bonds. Intramolecular H-bonding geometry parameters are collected in Table 3.

Table 3

Proposed hydrogen bonding geometry for sisomicin and gentamicin (DFT/B3LYP/6-311G(*d*) method)

H-bond	Bond length, Å			Bond angle, º
	Sisomicin (Gentamicin)			Sisomicin (Gentamicin)
	R(O(N)-H)	r(H…O(N))	r(O(N)…O(N))	φ(O- H…O(N))
N16-H17…N33	1.019	2.282	3.216	151.78
O65-H66...O27	0.981 (0.981)	*2.334 (2.347)*	2.780 (2.784)	*106.76 (106.19)*
O65-H66…N29	0.981 (0.981)	2.040 (2.038)	2.978 (2.975)	159.18 (159.09)
O54-H55...N57	0.972 (0.972)	*2.189 (2.204)*	2.781 (2.788)	*117.93 (117.39)*
O39-H40...O27	0.971 (0.971)	*2.487 (2.521)*	2.879 (2.872)	103.88 (101.21)
O39-H40…O45	0.971 (0.971)	2.141 (2.167)	3.055 (3.056)	156.55 (151.71)
N33-H35...O43	1.017 (1.015)	*2.352 (2.375)*	2.794 (2.777)	*105.03 (102.45)*
N57-H58...O65	1.015 (1.015)	*2.350 (2.353)*	2.886 (2.887)	*111.84 (111.68)*

As seen from the values of the H-bond parameters, the valence bonds are similar for the titled compounds. Also, in the case of two compounds, the bifurcated bonds with the same acceptor (donor) oxygen (nitrogen) atom can be formed in them (Fig. 1, Table 3). The N16-H17…N33 hydrogen bond is observed only in sisomicin. The H…N distance of the O65-H66…N29 hydrogen bond is the shortest among all similar bond lengths. This H-bond can be expected to be stronger than the others. The distances between donor and acceptor atoms are ideal for all hydrogen bonds, but the distances of 2.3-2.5Å between a hydrogen and the acceptor are a bit longer than a typical length due to a considerable deviation of the intramolecular H-bonds from a linearity. Accordingly, it can be conclude that such HBs may be weak.

To evaluate the extent of delocalization causing stabilization of the systems and to understand a nature of hydrogen bonding, NBO analysis was performed at the two theory levels. Table 4 lists the most significant delocalization energies, which show that the electron density delocalization occurs from the lone pairs into the antibonding neighboring orbitals and inside H-bonds.

Table 4

Delocalization energy for the titled compounds at B3LYP/6-311G(*d*) level of theory

Delocalization	Energy, kJ/mol		Delocalization	Energy, kJ/mol	
	Sisomicin	Gentamicin		Sisomicin	Gentamicin
LP(1)O11 → σ*(C8-C9)	24.83	8.58	LP(1)N33 → σ*(N16-H17)	15.95	-
LP(2)O11 → π*(C8-C9)	119.25	-	LP(2)O39 → σ*(C1-C3)	24.24	26.75
LP(2)O11 → σ*(C8-C9)	-	16.08	LP(2)O39 → σ*(C3-H38)	28.68	24.66
LP(2)O11 → σ*(C7-O43)	49.78	57.74	LP(2)O43 → σ*(C2-C3)	27.17	28.05
LP(1)N16 → σ*(C13-H15)	34.38	7.29	LP(2)O43 → σ*(C7-O11)	51.37	47.48
LP(1)N16 → σ*(C13-C15)	-	36.97	LP(2)O45 → σ*(O27-C44)	53.76	54.93
LP(1)N20 → σ*(C12-H19)	34.46	7.96	LP(2)O45 → σ*(O39-H40)	10.97	9.30
LP(1)N20 → σ*(C10-C12)	-	35.84	LP(2)O45 → σ*(C46-H67)	28.14	28.30
LP(2)O27 → σ*(C44-O45)	50.45	49.11	LP(2)O54 → σ*(C49-C50)	34.25	34.04
LP(1)N29 → σ*(C4-C6)	29.10	28.72	LP(1)N57 → σ*(C59-H60)	29.85	29.85
LP(1)N29 → σ*(O65-H66)	45.22	45.39	LP(2)O65 → σ*(C56-C63)	30.06	29.48
LP(1)N33 → σ*(C5-H32)	30.86	33.50	-	-	-

The delocalization energy was estimated from the second-order perturbation theory [16]. As can be seen in Table 4, the LP(2)O11 → π*(C8-C9) interaction in sisomicin has an enormous delocalization energy of 119.25 kJ/mol. This is the most intensive interaction between electron donor and electron acceptor in sisomicin. In the case of gentamicin, there is no such double bond, so, the electron density transfer occurs from the lone pairs LP(1)O11 and LP(2)O11 to the neighboring σ*(C8-C9) antibond. Their delocalization energy in total is equal to the energy of the LP(1)O11 → σ*(C8-C9) interaction in sisomicin. For two considered molecules, the substantial electronic delocalization is observed for LP(2)O11 → σ*(C7-O43), LP(2)O27 → σ*(C44-O45), LP(2)O43 → σ*(C7-O11), and LP(2)O45 → σ*(O27-C44) interactions.

The stabilization energy of the same order for two molecules corresponds to the through-space electron delocalization between the lone pair of nitrogen LP(1)N29 and the hydroxyl σ*(O65-H66) anti-

bonding orbital (intramolecular H-bond). Small energies were identified for the other two interactions inside hydrogen bonds: LP(1)N33 → σ*(N16-H17) and LP(2)O45 → σ*(O39-H40). All these energy values correlate with corresponding H-bond geometries: r(H…O(N)) and φ(O-H…O(N)) (Table 3). The delocalization energies of remaining H-bonds (they are represented by italics in the Table 3) are considerably smaller (< 5 kJ/mol) than that discussed above. This may indicate the classical electrostatic nature of the weak H-bonds. It should be noted that interactions with the delocalization energy of 25-35 kJ/mol, occurring from filled lone pairs of the atoms to σ* orbitals of vicinal C-C or C-H bonds, are hyperconjugative interactions.

Conclusions

In this work, a comparative analysis of the quantum chemical calculation results for the ground states of two aminoglycoside antibiotics was performed using DFT-based B3LYP method with a split-valence 6-311G(d) and Dunning's correlation consistent cc-pVDZ basis sets. Upon computation with 6-311G(d) set, the total energies of both aminoglycosides are markedly lower as compared to the cc-pVDZ set. So, we used the B3LYP/6-311G(d) data during the discussion of other results.

To explore intramolecular interactions within the sisomicin and gentamicin molecules, NBO analysis was used. The most intensive interaction between electron donor and electron acceptor in sisomicin is the LP(2)O11 → π*(C8-C9) interaction with an enormous delocalization energy of 119.25 kJ/mol. In the case of gentamicin, the most intensive interaction is observed for LP(2)O11 → σ*(C7-O43) with an energy almost two times less than the previous one. For two molecules, the stabilization energy of the same order corresponds to the through-space electron delocalization for intramolecular LP(1)N29 → σ*(O65-H66) H-bond. The delocalization energies of the remaining H-bonds are considerably smaller than above, which may indicate the classical electrostatic nature of these bonds. Interactions with the delocalization energy of 25-35 kJ/mol occuring from filled lone pairs of the atoms to σ* orbitals of vicinal C-C or C-H bonds are hyperconjugative interactions.

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