

# Conformational analysis and intramolecular hydrogen bonding of *cis*-3-aminoindan-1-ol: a quantum chemical study

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**Abstract** In the present work, we carried out a conformational analysis of *cis*-3-aminoindan-1-ol and evaluated the role of the intramolecular hydrogen bond in the stabilization of various conformers using quantum mechanical DFT (B3LYP) and MP2 methods. On the basis of relative energies, we have found nine conformational minima, which can interchange through the ring-puckering and the internal rotation of the OH and NH<sub>2</sub> groups on the five-membered ring. The intramolecular hydrogen bonds such as OH⋯π, NH⋯π, NH⋯OH and HN⋯HO are expected to be of critical importance for the conformational stabilities. The intramolecular interactions of the minima have been analyzed by calculation of electron density (ρ) and Laplacian (ρ) at the bond critical points (BCPs) using atoms-in-molecule (AIM) theory. The existence or absence of OH⋯π and NH⋯π in *cis*-3-aminoindan-1-ol remains unclear since the geometrical investigation has not been confirmed by topological criteria. The results of theoretical calculations demonstrate that this compound exists predominantly in one ring-puckering form stabilized by strong hydrogen bond HN⋯HO Interaction.

**Keywords** Atoms-In-Molecule · *cis*-3-aminoindan-1-ol · Conformational stability · DFT · Ring-puckering

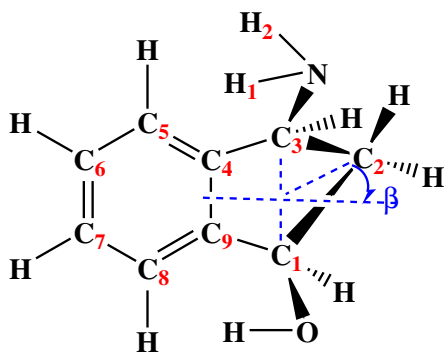
## Introduction

1,3-disubstituted indane moiety is one of the most interesting structures of indan derivatives and several therapeutically important compounds contain this skeleton [1]. This structural subunit is present in some HIV protease inhibitors [2, 3], in drugs used for cocaine abuse treatment [4], as well as in polyamine derivatives used against neurodegenerative diseases [5]. Among the 1,3-disubstituted indane derivatives, *cis*-3-aminoindan-1-ol illustrated in Scheme 1 is of particular interest [1]. This compound belongs to the 1,3-amino alcohol family found in a large variety of biologically important compounds and represents a large contribution to the pharmaceutical industry [6, 7]. Furthermore 1,3-amino alcohols have also been used as ligands for asymmetric catalysis, as chiral auxiliaries, as resolving agents, and as phase transfer catalysts [8]. The 1,3-amino alcohols are still undergoing development and remain a challenge [9, 10]. The synthesis of *cis*-3-aminoindan-1-ol was reported by López-García [1] and Kinbara [11] using a chemoenzymatic strategy and moderately selective reductions of 3-aminoindan-1-one derivatives, respectively. As seen in Scheme 1, the five-membered ring moiety of *cis*-3-aminoindan-1-ol is flexible around C<sub>2</sub> carbon atom (envelope forms). In addition, there are numerous sites in the structure of *cis*-3-aminoindan-1-ol that can potentially act as donors and/or acceptors of protons. Indeed, the presence of OH, NH<sub>2</sub> groups and the π electronic density of the aromatic ring allow for a wide range of hydrogen bonding combinations such as NH⋯π, OH⋯π, N-H⋯O and O-H⋯N. Consequently a large number of stable conformers are expected for *cis*-3-aminoindan-1-ol.

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**Scheme 1** Labeling scheme for *cis*-3-aminoindan-1-ol

Previous works have already investigated the structures of substituted indan molecules and the factors that govern their conformational stabilities using several spectroscopic techniques and high-level quantum mechanical methods [12–17]. In these studies the electronic and infrared spectroscopy of indan derivatives have been examined to get a detailed understanding of the large amplitude motions such as puckering, butterfly and ring twisting vibrations both in the  $S_0$  and  $S_1$  states [12–17].

The non-classical  $\text{NH}\cdots\pi$  and  $\text{OH}\cdots\pi$  “weak” hydrogen bonds expected in *cis*-3-aminoindan-1-ol compound have attracted considerable attention since they are able to affect the chemical and physical properties of flexible molecules and may have some contribution during the interaction with biological receptors [18]. More recently, our group has been studying the conformational properties and non-covalent interactions of *cis*-1,3-indanediol using *ab initio* and density functional theory (DFT) [19]. It emerges from this study that the formations of intramolecular  $\text{OH}\cdots\text{OH}$  and nonconventional  $\text{OH}\cdots\pi$  hydrogen bonds have a very pronounced effect on molecular structure and properties [19]. Nikhil Guchhait and co-workers [20] have investigated the structure of isolated *cis*-1-amino-indan-2-ol in a supersonic jet using laser-induced fluorescence excitation. The two observed conformers of *cis*-1-amino-indan-2-ol, assigned with the aid of density functional theory (DFT) calculation, present an intramolecular hydrogen bond interaction between OH and  $\text{NH}_2$  groups [20].

To the best of our knowledge, a systematic theoretical conformational analysis of *cis*-3-aminoindan-1-ol has not been reported so far. Therefore, the main goal of the present study is to examine in detail the conformational preference of *cis*-3-aminoindan-1-ol which arises from the ring-puckering of the cyclopentenyl moiety and the internal rotation of the hydroxyl and amine groups using DFT and MP2 levels of theory. Another main point of this investigation is to explore the influence of the non-covalent interactions such as  $\text{NH}\cdots\pi$ ,  $\text{OH}\cdots\pi$ ,  $\text{N}\cdots\text{O}\cdots\text{H}$  and  $\text{O}\cdots\text{H}\cdots\text{N}\cdots\text{H}$  to obtain precise knowledge about the relative stabilities of different conformers of this biologically important 1,3-amino alcohol. In order to have a deeper information of the nature of the possible hydrogen bonding

interactions present in conformers of *cis*-3-aminoindan-1-ol, topological analysis of the electron density distribution within Bader’s atoms in molecules theory (AIM) was performed [21, 22].

We hope that this conformational study on the parent compound will prove useful for providing insight regarding the chemistry of the 1,3-disubstituted indane derivatives.

## Computational methods

All quantum calculations reported in this paper were executed with the Gaussian03 software package [23]. The geometry optimization of all conformers reported in the present work was performed with second-order Møller-Plesset (MP2) [24] and the hybrid Becke three parameter Lee–Yang–Parr DFT B3LYP functional [25]. Basis set of 6-31+G(d) was used for both methods, while large basis set 6-311+G(d,p) was used only for B3LYP DFT level.

The use of correlation-consistent polarize basis sets at MP2 calculations are fundamental to adequately describe molecular properties of weakly bound hydrogen-bonded system [26]. Therefore geometry optimization at MP2 level in conjunction with cc-pVTZ basis set were carried out for comparison purpose.

Geometry optimizations convergence criteria were tightened using the keywords SCF=Tight and Int=Ultrafine. Furthermore, harmonic vibrational frequencies were evaluated at the same levels to confirm the nature of the stationary points found and also to account for the zero point vibrational energy correction. Due to the limited computer resources available in our laboratory no frequency calculation at MP2/cc-pVTZ level were carried out.

To evaluate the nature of hydrogen-bonding interactions in *cis*-3-aminoindan-1-ol conformers, the electron density of the systems has been analyzed by the atoms in molecules (AIM) methodology [21, 22] using the Multiwfn program [27] at the B3LYP/6-311+G(d,p) level. It is well-known that the relative strength of bond could be obtained in terms of electron density ( $\rho$ ), and Laplacian ( $\nabla^2\rho$ ) [28, 29].

## Results and discussion

### Relative energies of the conformers

The quantum chemical calculations and the conformational information available from our investigation on *cis* 1,3-indanediol [19] provided a good starting point to predict the plausible conformations of *cis*-3-aminoindan-1-ol. The atom numbering scheme of *cis*-3-aminoindan-1-ol is shown in Scheme 1. This molecule can adopt “ $\text{C}_2$ -up” or “ $\text{C}_2$ -down” conformations, in which, the  $\text{C}_2$  atom is located on the same

side of OH and NH<sub>2</sub> groups above C<sub>1</sub>C<sub>3</sub>C<sub>4</sub> plane or in the opposite side of the OH and NH<sub>2</sub> groups below C<sub>1</sub>C<sub>3</sub>C<sub>4</sub> plane, respectively. Each of these envelope conformations can again form a number of conformers due to the different internal rotation of the hydroxyl and amine groups. The study of the conformational species of *cis*-3-aminoindan-1-ol generated from the ring-puckering of the cyclopentenyl group as well as the internal rotation of the hydroxyl and amine groups is carried out using B3LYP and MP2 levels of theory. It should be mentioned that the discussion refers to the optimum orientation of the OH and NH<sub>2</sub> groups either toward or outside the phenyl ring.

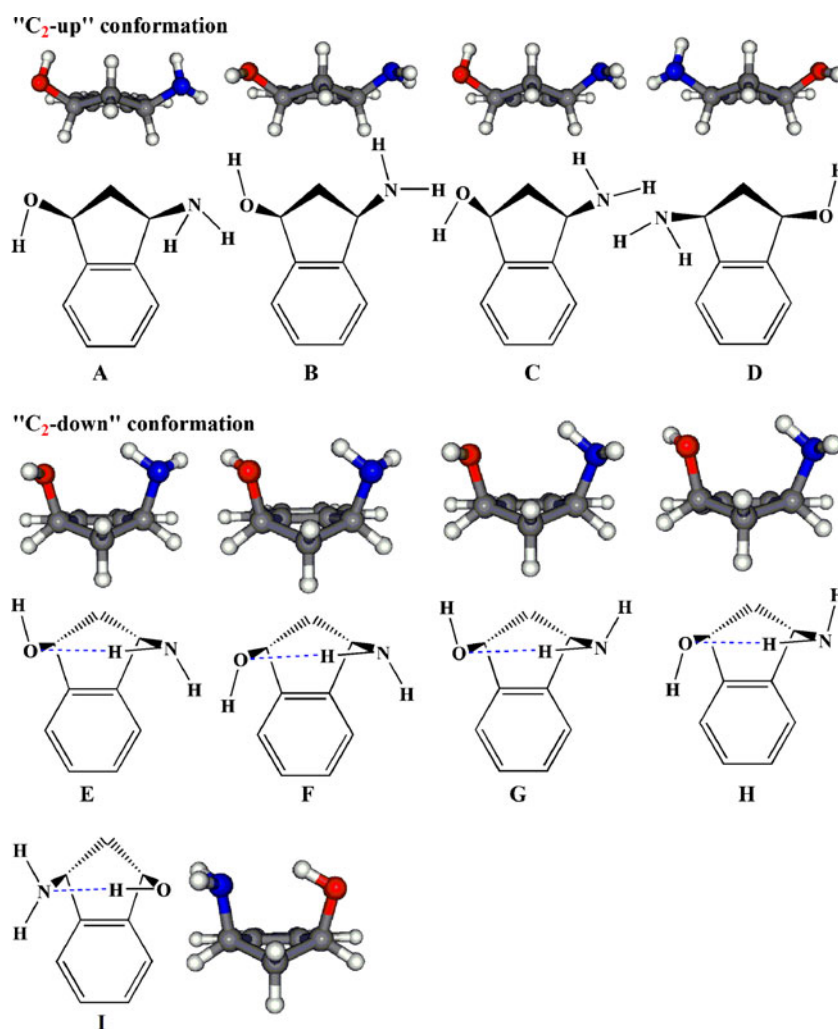
Figure 1 illustrates the fully optimized structures of *cis*-3-aminoindan-1-ol calculated at the B3LYP/6-311+G(d,p) together with the nomenclature employed and used throughout the text. It is worth mentioning that all systems considered here correspond to energy minima since no imaginary frequencies were observed. We found nine energy minima, four possible rotamers for the “C<sub>2</sub>-up” conformation and five rotamers for the “C<sub>2</sub>-down” conformation (see Fig. 1). The

“C<sub>2</sub>-up” conformers **A**, **B**, **C** and **D** present the same puckered conformation of the cyclopentane ring where C<sub>2</sub> atom is located on the same side as the OH and NH<sub>2</sub> groups above C<sub>1</sub>C<sub>3</sub>C<sub>4</sub> plane and differ only by the OH and NH<sub>2</sub> orientation with respect to phenyl ring. The interconversion between “C<sub>2</sub>-up” and “C<sub>2</sub>-down” conformations is investigated using the ring-puckering parameter  $\beta$  (see Scheme 1). The conformational analysis lead to the “C<sub>2</sub>-down” ring-puckering conformers **E**, **F**, **G**, **H**, **I**. These structures are envelope conformations with C<sub>2</sub> atom puckered out of plane and located on the opposite side of the OH and NH<sub>2</sub> groups.

Table 1 provides the absolute and relative energies of the nine *cis*-3-aminoindan-1-ol conformers computed at B3LYP level in conjunction with 6-31+G(d) and 6-311+G(d,p) as well as MP2 level in conjunction with 6-31+G(d) and cc-PVTZ basis set. The relative energies are corrected for zero-point energies (ZPE) except for MP2/cc-PVTZ for which vibrational frequencies were not computed because of lack of resources.

As is obvious from Table 1, unanimously all levels of theory predict the conformer **I** which belongs to “C<sub>2</sub>-down”

**Fig. 1** Schematic representation and the corresponding optimized structures of the nine stable conformers of *cis*-3-aminoindan-1-ol obtained at B3LYP/6-311+G(d,p)



**Table 1** Zero-point corrected total energies  $E_0 + \text{ZPE}$  (a.u) and relative energies  $\Delta E_{(\text{ZPVE})}$  (kcal mol<sup>-1</sup>) in gas phase. No frequency calculation at MP2/cc-pVTZ level were carried out

Conformers		B3LYP				MP2			
		6-31+G(d)		6-311+G(d,p)		6-31+G(d)		cc-pVTZ	
		$E_{(\text{ZPVE})}$	$\Delta E_{(\text{ZPVE})}$	$E_{(\text{ZPVE})}$	$\Delta E_{(\text{ZPVE})}$	$E_{(\text{ZPVE})}$	$\Delta E_{(\text{ZPVE})}$	E	$\Delta E$
C <sub>2</sub> -up	A	-479.378314	00.93	-479.501086	00.45	-477.857452	02.88	-478,588608	02,51
	B	-479.374648	03.23	-479.497420	02.75	-477.854056	05.01	-478,584461	05,11
	C	-479.376530	02.04	-479.499186	01.64	-477.855850	03.88	-478,586708	03,69
	D	-479.377373	01.52	-479.500172	01.02	-477.856692	03.35	-478,587317	03,32
C <sub>2</sub> -down	E	-479.376513	02.05	-479.498985	01.77	-477.857763	02.68	-478,588067	02,85
	F	-479.377108	01.68	-479.499598	01.38	-477.858272	02.36	-478,588780	02,40
	G	-479.375903	02.44	-479.498373	02.15	-477.856991	03.17	-478,586768	03,66
	H	-479.377312	01.55	-479.499738	01.29	-477.858494	02.22	-478,588411	02,63
	I	-479.379790	00.00	-479.501807	00.00	-477.862039	00.00	-478,592604	00,00

conformation to be the most stable one. This stability is mainly due to the formation of a relatively strong OH $\cdots$ N intramolecular hydrogen bond, which appears also assisted by one weak non-bonded NH $\cdots$  $\pi$  interaction (see Fig. 1). Theoretical studies carried out at the MP2 and DFT B3LYP levels establish clearly the importance of the intramolecular OH $\cdots$ N interaction in *cis*-3-aminoindan-1-ol. A similar hydrogen bond (OH $\cdots$ N) has already been observed for the most stable conformer of *cis*-1-amino-indan-2-ol using spectroscopic techniques and DFT calculation [20]. Our finding is also well supported by the microwave spectroscopic results obtained for 3-amino-propanol [30], which show that in the gas phase only the lowest energetic conformer with OH $\cdots$ N intramolecular hydrogen bond exists. Therefore, the observation of relatively strong intramolecular OH $\cdots$ N hydrogen bonding in *cis*-3-aminoindan-1-ol would provide credible evidence for the presence of this compound in “C<sub>2</sub>-down” conformation in gas phase. As can be seen on Fig. 1, the intramolecular NH $\cdots$ OH interaction appear to be present in four of the minima found in “C<sub>2</sub>-down” conformation, but one can conclude that it was a weak interaction compared to OH $\cdots$ N H-bond present in **I** conformer. This result confirms the fact that the NH<sub>2</sub> group is a good proton acceptor and a less effective proton donor.

From the values in Table 1, the order in the relative stability among the nine conformers obtained at B3LYP/6-31+G(d) level in gas phase should be as follows: **I**>**A**>**D**>**H**>**F**>**C**>**E**>**G**>**B**. Using the large basis set 6-311+G(d,p), the same order in the relative stability is still kept. Increasing the size of the B3LYP basis set from 6-31+G(d) to 6-311+G(d,p) decreased the energy differences among the conformers considerably. From the *ab initio* MP2 calculations the order of conformer stability is predicted to be **I**>**H**>**F**>**E**>**A**>**G**>**D**>**C**>**B** at MP2/6-31+G(d). Using the Dunning correlation consistent basis set cc-pVTZ at MP2 level, the order in the

relative stability becomes: **I**>**F**>**A**>**H**>**E**>**D**>**G**>**C**>**B**. As can be seen, the calculated energies at B3LYP and MP2 methods do not show the same stability order.

The B3LYP method predict conformer **A** corresponding to “C<sub>2</sub>-up” conformation to be the second most stable structure. The optimized geometry of conformer **A** (Fig. 1) has a structural arrangement that could facilitate an intramolecular OH $\cdots$  $\pi$  and NH $\cdots$  $\pi$  hydrogen bonding interactions. When the MP2 method was used, the conformer **A** becomes the fifth lowest energy conformation at MP2/6-31+G(d). On the other hand, the MP2/cc-pVTZ level predict conformer **A** of “C<sub>2</sub>-up” conformation to be the third most stable structure, which converge slightly to the result obtained by B3LYP level (second most stable structure). Hence, considerably larger basis sets (cc-pVTZ or larger) appear to be essential at MP2 level of theory to evaluate the real energetic order somewhat better. It should be emphasized that, the Dunning correlation consistent basis set such as cc-pVTZ are known to be adequate to describe hydrogen bonded systems [26].

Notice that the relative energies displayed in Table 1 reveal the clear preference of the “C<sub>2</sub>-down” conformations over the “C<sub>2</sub>-up” conformations at MP2 level, as expected from our previous study on *cis* 1,3-indanediol [19]. It is necessary to mention that both DFT and MP2 methods predict the structure **B** to be the least favorable conformer among the *cis* 3-aminoindan-1-ol structures considered in this study, probably due to the absence of intramolecular hydrogen bond giving rise to high repulsion between the lone pair electrons of the hydroxyl oxygen and nitrogen amine with the  $\pi$  electrons of the phenyl ring.

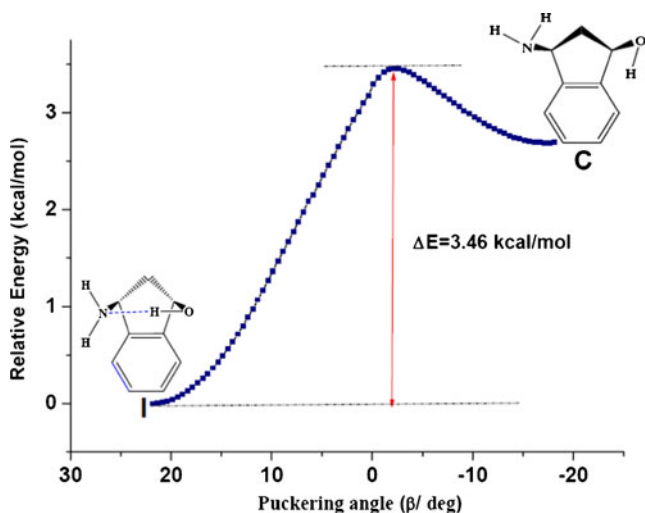
Among “C<sub>2</sub>-down” conformers, the structure **G** presenting NH $\cdots$ OH hydrogen bond has the highest electronic energy. The instability of the “C<sub>2</sub>-down” conformer **G** is probably caused by the repulsive non-bonded interactions between the lone pair (oriented toward the phenyl ring) of oxygen and

nitrogen atoms and the  $\pi$ -electron cloud of an aromatic moiety of the indan ring. This observation shows clearly that the orientation of the hydrogen atoms of O-H and N-H bonds toward the  $\pi$  electron cloud of aromatic ring contributes to the stabilization of the “C<sub>2</sub>-down” conformers.

Notice that the dispersion interaction is the major source of the attraction for OH $\cdots\pi$  and NH $\cdots\pi$  interactions and it is well known that B3LYP cannot account for dispersion in a quantitative way [31]. One can conclude that the MP2 relative energies are therefore likely to be the more accurate.

#### The barrier of interconversion “C<sub>2</sub>-down” $\leftrightarrow$ “C<sub>2</sub>-up”

Barrier energy to interconversion between “C<sub>2</sub>-down” and “C<sub>2</sub>-up” conformation appear to be one of the major factors controlling the conformations of *cis*-3-aminoindan-1-ol. The interconversion between “C<sub>2</sub>-down” and “C<sub>2</sub>-up” conformations is investigated using the ring-puckering parameter  $\beta$  (see Scheme 1). The potential energy curves (PEC) corresponding to this motion was generated by freezing the dihedral angle  $\beta$  at different values in steps of 1.0°, and fully optimizing the geometry with respect to all other coordinates. Calculations were done at the B3LYP/6-31+G(p) level and the obtained PEC is illustrated in Fig. 2. Starting with structure **I** of “C<sub>2</sub>-down” conformation, the second ring-puckering conformer **C** of “C<sub>2</sub>-up” conformation were found. According to the PEC, the barrier for interconversion between these two conformations is very small. The transition state is only about 3.46 kcal mol<sup>-1</sup> above the most stable conformer **I**. Our calculations predict that *cis*-3-aminoindan-1-ol is a flexible system which can adopt “C<sub>2</sub>-up” or “C<sub>2</sub>-down” conformations easily. Furthermore, this very low barrier of interconversion could be taken to suggest that OH $\cdots$ N intramolecular interaction, present in conformer **I**, is not very strong.



**Fig. 2** Potential energy curve (PEC) for conformer **I**, along the puckering angle  $\beta$  (see Scheme 1) calculated at B3LYP/6-31+G(p) level

#### Optimized structures

Since the B3LYP method is well known to give reliable geometrical parameters, then we will only present some structural data obtained at B3LYP/6-311+G(d,p) level of theory. For comparison, some significant bond lengths, bond angles and dihedral angles predicted for the different conformers of *cis*-3-aminoindan-1-ol by B3LYP/6-311+G(d,p), are summarized in Table 2, while the atom labeling is given in Scheme 1. According to these optimized parameters, those which involve C<sub>2</sub> atom show great sensitivity to the orientation of the OH and NH<sub>2</sub> groups as well as to the puckered conformation adopted by C<sub>2</sub> atom of the five-membered ring. On the other hand, as can be seen in Table 2 the double bonds of the benzene ring C<sub>4</sub>-C<sub>5</sub>, C<sub>4</sub>-C<sub>9</sub> and C<sub>9</sub>-C<sub>8</sub> are affected by the orientation adopted by the OH and NH<sub>1</sub> groups. Effectively, in conformer **A** these double bonds are slightly longer than their counterpart obtained in conformer **B**, about 0.001 Å.

The dihedral angle  $\beta$  is of significant importance, it defines the degree of puckering of the five-membered ring. The optimized structural parameters reported in Table 2 show clearly that the degree of puckering  $\beta$  obtained for **I** “C<sub>2</sub>-down” conformer is the higher value ( $\beta = -34.8^\circ$ ) which makes the OH and NH<sub>2</sub> groups sufficiently close thereby facilitating the formation of intramolecular hydrogen bonds OH $\cdots$ N.

#### Intramolecular hydrogen bonding in *cis*-3-aminoindan-1-ol

Another noteworthy feature of the structure of *cis*-3-aminoindan-1-ol is the probable hydrogen bonds NH $\cdots\pi$ , OH $\cdots\pi$ , N-H $\cdots$ O-H and O-H $\cdots$ N-H, visible in the conformers represented in Fig. 1. In this investigation, hydrogen bonding is discussed in terms of observable properties such as geometrical parameters. The geometric criteria of the various possible H-bonds present in the different conformers of *cis*-3-aminoindan-1-ol obtained at B3LYP/6-311+G(d,p) are reported in Table 3.

The intramolecular NH<sub>1</sub> $\cdots$ OH and O-H $\cdots$ N hydrogen bonding plays a prominent role in stabilizing the “C<sub>2</sub>-down” conformations. The formation of an intramolecular H-bond O-H $\cdots$ N is favored in **I** structure of “C<sub>2</sub>-down” conformation. We have shown that the conformer **I** with an intramolecular O-H $\cdots$ N bond strongly predominates in the gas phase. As can be seen in Table 3, our calculation delivers O-H $\cdots$ N distance of 2.298 Å at B3LYP/6-311+G(d,p). The non-linear hydrogen bridges were found, the  $\angle$ O-H $\cdots$ N angle is 135.7° in **I**. Careful conformational analyses of the optimized geometries of the “C<sub>2</sub>-down” structures (see Fig. 1) show that the NH<sub>1</sub> $\cdots$ OH intramolecular hydrogen bond takes part in a four structures **E**, **F**, **G** and **H** of “C<sub>2</sub>-down” conformation. It is especially noted that the nonbonded NH<sub>1</sub> $\cdots$ OH distance (2.608 Å) obtained in **F** conformer is the shorter one. Notice the very

**Table 2** Calculated structural parameters for different conformers of *cis*-3-aminoindan-1-ol at B3LYP/6-311+G(d,p), for numbering of the atoms see Scheme 1

Parameters	“C <sub>2</sub> -up” conformers				“C <sub>2</sub> -down” conformers				
	A	B	C	D	E	F	G	H	I
Bond lengths (Å)									
C <sub>1</sub> -C <sub>2</sub>	1.544	1.545	1.544	1.543	1.545	1.536	1.545	1.535	1.547
C <sub>2</sub> -C <sub>3</sub>	1.547	1.545	1.546	1.548	1.547	1.549	1.559	1.560	1.544
C <sub>4</sub> -C <sub>9</sub>	1.396	1.395	1.395	1.395	1.396	1.398	1.394	1.396	1.398
C <sub>4</sub> -C <sub>5</sub>	1.392	1.391	1.392	1.392	1.392	1.391	1.392	1.391	1.390
C <sub>9</sub> -C <sub>8</sub>	1.392	1.390	1.392	1.391	1.391	1.391	1.393	1.393	1.390
Bond angles (°)									
C <sub>1</sub> -C <sub>2</sub> -C <sub>3</sub>	106.0	105.3	105.8	105.7	105.7	105.7	106.2	106.0	104.1
C <sub>1</sub> -O-H	108.2	108.7	108.1	108.7	108.2	108.5	108.2	108.5	106.1
C <sub>3</sub> -N-H <sub>1</sub>	110.8	110.2	110.2	110.6	109.4	109.5	110.3	109.9	110.9
C <sub>3</sub> -N-H <sub>2</sub>	111.6	110.8	110.8	111.6	110.4	110.7	110.8	110.4	110.5
Dihedral angles (°)									
C <sub>1</sub> -C <sub>9</sub> -C <sub>4</sub> -C <sub>3</sub>	0.0	0.1	1.1	0.9	-1.0	0.7	0.2	2.2	0.5
C <sub>2</sub> -C <sub>3</sub> -C <sub>1</sub> -C <sub>9</sub>	152.4	150.6	152.7	151.5	209.2	209.6	206.1	208.1	214.8
.β	27.6	29.4	27.3	28.5	-29.2	-29.6	-26.1	-28.1	-34.8
H-O-C <sub>1</sub> -C <sub>9</sub>	-56.0	166.8	-55.7	-168.0	177.0	54.6	172.7	53.0	64.7
H <sub>1</sub> -N-C <sub>3</sub> -C <sub>4</sub>	48.0	179.3	179.4	-48.5	54.4	59.3	60.7	64.2	56.6
H <sub>2</sub> -N-C <sub>3</sub> -C <sub>4</sub>	-71.9	-62.8	-62.8	71.2	-63.0	-58.9	179.9	-177.6	175.6

bent bridges <N-H<sub>1</sub>⋯O (116–124°) found in **E**, **F**, **G** and **H** “C<sub>2</sub>-down” conformers indicating weaker interactions.

The assumption of a weak -X-H⋯π-electron interaction could be verified by analyzing the variation of the X-H bond length (X=O, N). Inspection of the results reported in Table 3 shows that the O-H and N-H bond lengths of conformer **A** that has the OH and NH<sub>1</sub> pointing directly toward the phenyl ring are slightly longer (about 0.002 Å) than corresponding ones in conformer **B**. The result points to the existence of weak NH⋯π and OH⋯π interactions in conformer **A**.

Another significant feature of the conventional H-bonds N-H⋯O and O-H⋯N is the O⋯⋯N distance. Inspection of the results reported in Table 3 shows that “C<sub>2</sub>-down” conformers show shorter O⋯⋯N distance making the hydroxyl and

amine groups sufficiently close to form an intramolecular hydrogen bonds NH<sub>1</sub>⋯OH or O-H⋯N. It is especially noted that the most stable conformer **I** is characterized by an O⋯⋯N distance of 3.067 Å, which is the shorter distance. The O⋯⋯N distances in other structures of “C<sub>2</sub>-down” conformation are increased in comparison to **I**, from 3.285 to 3.564 Å. The greatest contraction of O⋯⋯N distance in conformer **I** is an effect of the creation of strong O-H⋯N hydrogen bond, making clear great stability of this conformer.

More strict evaluation of the intermolecular hydrogen bonds in *cis*-3-aminoindan-1-ol conformers will be presented below on the basis of topological parameters calculated using AIM analyses based on Bader’s atoms in molecules theory [21, 22].

**Table 3** Optimized hydrogen bonds of *cis*-3-aminoindan-1-ol conformers, bond lengths (Å) and bond angle (°) obtained at B3LYP/6-311+G(d,p). For numbering of the atoms see Scheme 1

Parameters	“C <sub>2</sub> -up” conformers				“C <sub>2</sub> -down” conformers				
	A	B	C	D	E	F	G	H	I
N-H <sub>1</sub>	1.016	1.015	1.015	1.016	1.017	1.017	1.016	1.016	1.015
N-H <sub>2</sub>	1.014	1.016	1.016	1.014	1.016	1.016	1.015	1.015	1.016
O-H	0.964	0.962	0.964	0.962	0.963	0.963	0.963	0.963	0.970
NH <sub>1</sub> ⋯O	–	–	–	–	2.690	2.608	2.961	2.814	–
OH⋯N	–	–	–	–	–	–	–	–	2.298
O⋯⋯N	4.807	4.752	4.764	4.773	3.353	3.285	3.564	3.440	3.067
<N-H <sub>1</sub> ⋯O	–	–	–	–	122.9	123.8	118.9	120.3	–
<O-H⋯N	–	–	–	–	–	–	–	–	135.7

**Table 4** Analysis of bond critical points between hydrogen bond acceptors and hydrogen bond donors in *cis*-3-aminoindan-1-ol conformers. All quantities are in atomic unit

Conformers	A		B		C		D		E		F		G		H		I	
	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$	$\rho$	$\nabla^2\rho$
NH <sub>1</sub> ⋯O	—	—	—	—	—	—	—	—	0.007	0.023	0.007	0.025	—	—	—	—	—	—
OH⋯N	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.0162	0.0472
NH <sub>1</sub> ⋯ $\pi$	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
OH⋯ $\pi$	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

### Atoms-in-molecule (AIM) topological analysis

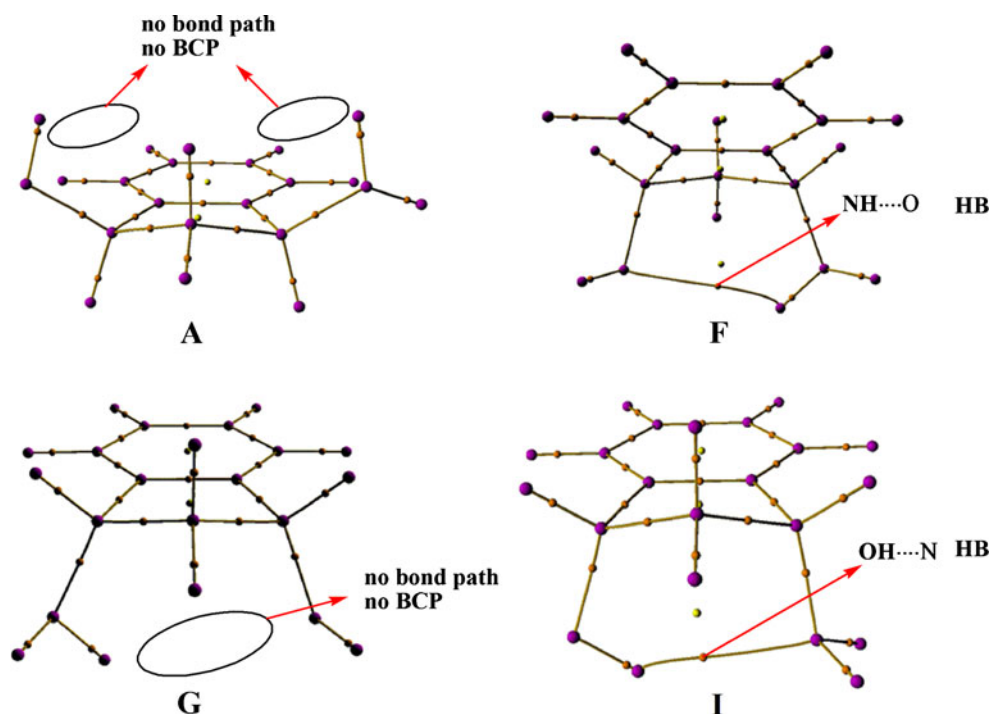
Since the geometrical criteria are frequently considered as insufficient to decide if hydrogen bonding exists, the presence of hydrogen bond in different conformers of *cis*-3-aminoindan-1-ol could be supported further by the atoms in molecules (AIM) theory. According to AIM methodology, the hydrogen bonds (HB) are characterized by the presence of bond critical points (BCPs) associated with a bond path between an HB acceptor (oxygen, nitrogen and  $\pi$ -electrons of the benzene) and the hydrogen atom of the HB donor moiety (hydroxyl and amino groups) [21, 22]. The values of the charge density ( $\rho$ ) and its Laplacian ( $\nabla^2\rho$ ) at these critical points give valuable information about the strength of the hydrogen bonds [21, 22]. Two quantitative criteria have been suggested by Koch and Popelier [28, 29] to characterize the strength of a hydrogen bond: the electron density ( $\rho$ ) should be within the range 0.002–0.040 a.u. and its Laplacian ( $\nabla^2\rho$ ) should be within the range 0.024–0.139 a.u.

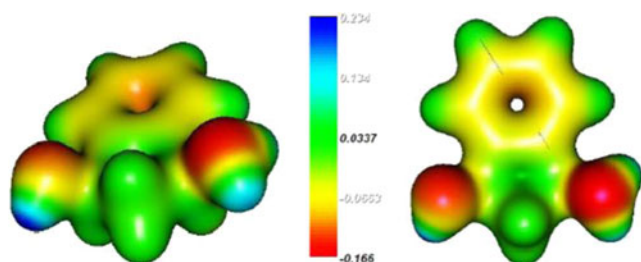
The structural parameters obtained for *cis*-3-aminoindan-1-ol show that up to four intramolecular hydrogen bonds (OH⋯ $\pi$ , NH⋯ $\pi$ , NH⋯OH and HN⋯HO) are possible. To get a deeper insight into the characteristics of these intramolecular hydrogen bonding, AIM analysis was carried out for the optimized structures reported in Fig. 2.

The topological parameters (density  $\rho$  and Laplacian  $\nabla^2\rho$ ) of some important bond critical points (BCPs) at expected hydrogen bond locations are all listed in Table 4. Figure 3 shows the molecular graphs, which include the critical points and bond paths of the selected conformations of *cis*-3-aminoindan-1-ol.

A point to be noted with regard to the results reported in Table 4 is that no bond critical points (BCPs) are found between the proton in the OH and/or NH<sub>2</sub> groups and the region around the  $\pi$ -electron of benzene ring (see also Fig. 3). This is somewhat surprising as for example, the conformer A in which the OH and NH<sub>2</sub> groups oriented toward the phenyl ring is more stable than conformer B. In addition, as

**Fig. 3** Molecular graphs for conformers A, F, G and I. Small red spheres, small yellow spheres, and lines correspond to the bond critical points (BCP), ring critical points (RCP), and bond paths, respectively as calculated using Multiwfn program





**Fig. 4** MEP for **B** conformer of *cis*-3-aminoindan-1-ol obtained at B3LYP/6-311+G(d,p). The value of electron density of the isosurface on which electrostatic potential was mapped is 0.03 a.u.

indicated above all of the conformers that have the OH and/or NH<sub>2</sub> groups pointing toward  $\pi$ -electron density of the benzene ring (**A**, **C**, **D**, **E**, **F**, **H** and **I**) have a longer OH and NH bond length compared to those conformers (**B** and **G**) where the OH and/or NH<sub>2</sub> groups points away from the  $\pi$ -electron density.

The absence of BCPs at OH $\cdots\pi$  and NH $\cdots\pi$  leads to the conclusion that the implication of these types of hydrogen bonds is less clear. Precisely, the no direct AIM evidence of OH $\cdots\pi$  and NH $\cdots\pi$  interactions indicate probably that the conformational stability of the conformers might be influenced more by avoiding energetically unfavorable electrostatic repulsion between the  $\pi$ -cloud of the benzene ring and the lone pair of electrons on the oxygen and nitrogen atoms than creating an energetically favorable OH $\cdots\pi$  and NH $\cdots\pi$  intramolecular hydrogen bonds. This interpretation is also supported by the results obtained by Miller [32] for prop-2-yn-1-ol and prop-2-en-1-ol which show no BCP between the OH group and the  $\pi$ -electrons of C $\equiv$ C and C=C bonds, respectively.

In a very recent paper published by Lane and coworkers [33], entitled “*Are bond critical points really critical for hydrogen bonding?*”, have shown that the stringent criteria of AIM theory controversially exclude some systems that otherwise appear to exhibit weak hydrogen bonds. In the same direction, Contreras-Garcia [34] has concluded that AIM theory is blind to intermolecular interactions that occur in the absence of a critical point and hence potentially gives rise to false negative results for weak hydrogen bonds.

**Table 5** Theoretical rotational constants (MHz) and dipole moment (Debye) components for the conformers of *cis*-3-aminoindan-1-ol predicted at the B3LYP/6-311+G(d,p) level

Parameters	“C <sub>2</sub> -up” conformers				“C <sub>2</sub> -down” conformers				
	A	B	C	D	E	F	G	H	I
I <sub>a</sub>	1484.8	1491.5	1494.2	1487.5	1816.8	1836.9	1760.0	1795.9	1902.3
I <sub>b</sub>	1152.2	1164.0	1155.3	1158.3	1037.4	1029.6	1054.1	1042.7	1023.6
I <sub>c</sub>	681.2	683.7	683.4	682.8	762.3	761.6	756.1	759.0	777.6
$\mu_a$	-1.52	-1.45	-0.09	0.02	0.31	2.49	-1.67	-0.53	-0.41
$\mu_b$	1.62	0.80	-2.06	0.37	-0.44	-0.70	-0.95	-1.00	2.92
$\mu_c$	0.53	2.37	0.71	1.11	1.14	0.32	1.63	-0.93	1.10
$\mu_{\text{Total}}$	2.29	2.89	2.18	1.17	1.26	2.61	2.52	1.47	3.15

As shown in Table 4, the BCPs at NH<sub>1</sub> $\cdots$ OH interaction expected in four conformers of “C<sub>2</sub>-down” was found only in two conformations, namely **E** and **F**. The AIM analyses indicated no evidence for NH<sub>1</sub> $\cdots$ OH hydrogen bond in the conformers **G** and **H** (see e.g., conformer **G** in Fig. 3). This may be easily explained by the very large proton-acceptor distance NH $\cdots$ OH (2.961 Å and 2.814 Å see Table 3) obtained for **G** and **H** compared to **E** and **F** structures. It is evident from Table 4, the values of  $\rho$  and  $\nabla^2\rho$  of BCPs at NH<sub>1</sub> $\cdots$ OH interaction, observed in **E** and **F** conformers, are (0.007 a.u. and 0.07 a.u.) and (0.023 a.u. and 0.025 a.u.) respectively. Notice that for **E** and **F** conformers, both  $\rho$  and  $\nabla^2\rho$  at BCPs of NH<sub>1</sub> $\cdots$ OH interaction are close to the lower limits of the criteria proposed by Koch and Popelier [28, 29]; thus our calculations reveal that the hydrogen bond NH<sub>1</sub> $\cdots$ OH is of low strength, which is consistent with the geometrical analysis reported above.

In the case of HN $\cdots$ HO interaction present in the most stable conformer **I**, its value of electron density  $\rho$  is 0.0162 a.u., and its Laplacian  $\nabla^2\rho$  is 0.0472 a.u. (see Table 4 and Fig. 3) fulfilling the topological criteria proposed by Koch and Popelier [28, 29] for hydrogen bond. The AIM analysis reveals that HN $\cdots$ HO type of hydrogen bond has higher electron density  $\rho$  and electron density laplacian  $\nabla^2\rho$ , than NH<sub>1</sub> $\cdots$ OH interaction. The relatively high values of the charge density and Laplacian at BCPs of HN $\cdots$ HO indicate that this interaction is quite a bit stronger, which is also consistent with the given above geometrical characterization. This finding indicates that nitrogen is a better proton acceptor than oxygen.

#### Molecular electrostatic potential

The molecular electrostatic potential (MEP) provides important information about the reactive sites for electrophilic attack and nucleophilic reactions as well as hydrogen-bonding interactions [35, 36]. To understand the nature of practical reaction regions in *cis*-3-aminoindan-1-ol the MEP surfaces were generated at B3LYP/6-311+G(d,p) and visualized using the MOLEKEL 5.4 program [37]. The conformer **B** of *cis*-3-



aminoindan-1-ol has been chosen to illustrate the MEP of parent compound, because in **B** conformation both hydroxyl and amine groups are free and non-interacting. Figure 4 shows the 3D of molecular electrostatic potential of conformer **B**. The red and blue regions in the MEP map refer to the electron-rich and electron-poor areas, respectively, whereas the green color signifies the neutral electrostatic potential. The regions of negative electrostatic potential (denoted by red) are generally used to identify hydrogen-bond-acceptor sites, whereas the regions of positive electrostatic potential (denoted by blue) describe the hydrogen-bond-donating sites. Figure 4 clearly shows that the H atom of the hydroxyl group displays a deeper blue color than the amino hydrogens. As a result, the H atom of OH group is the most positive electrostatic potential. On the other hand, the nitrogen atom appears to be the site that exhibits the highest negative (dark red) electrostatic potential. This result indicates clearly the great predisposition of the H atom of the hydroxyl group and the azote atom of the amine group for noncovalent hydrogen bonding. Considering these calculated results, it is expected that the most stable conformer **I** of *cis*-3-aminoindan-1-ol is mainly driven by the electrostatic attraction between the H and N atoms of OH and NH<sub>2</sub> groups, respectively.

#### Rotational constants

The predicted rotational constants appear to be a useful source of information for the structure of molecules, helping the interpretation of the experimental spectra arising from different conformers. Indeed, the rotational constants depend directly on the mass distribution and geometry [38]. The predicted rotational constants and dipole moments of the nine conformers of *cis*-3-aminoindan-1-ol calculated at the B3LYP/6-311+G(d,p) level of theory are listed in Table 5. These theoretical rotational constants may be helpful in searching of gas phase *cis*-3-aminoindan-1-ol conformers by means of the microwave spectroscopy. The variation of predicted rotational constants on-going from “C<sub>2</sub>-up” conformation to a “C<sub>2</sub>-down” conformation is worthy of mention. The rotational constants are found to increase significantly in going from a given “C<sub>2</sub>-up” conformer to a “C<sub>2</sub>-down” conformer. Therefore, this difference could be used to distinguish unambiguously between “C<sub>2</sub>-up” and “C<sub>2</sub>-down” conformations using micro-wave spectrum.

The rotational constants of the conformer **I**, which belongs to the “C<sub>2</sub>-down” family, is very unique and different from those of all other species. As can be seen on Table 5, despite the I<sub>a</sub> and I<sub>b</sub> rotational constants are particularly equivalent in the conformers of “C<sub>2</sub>-down” conformations, the I<sub>c</sub> rotational constant of **I** conformer is sufficiently large to make unambiguous discrimination. The quantum chemical calculations reported in Table 5 indicate that the rotational constants of “C<sub>2</sub>-up” conformers **A**, **B**, **C** and **D** are very close to each

**Table 6** Some low-frequency vibrational modes (cm<sup>-1</sup>) obtained from theoretical calculations at B3LYP/6-311+G(d,p) level for *cis*-3-aminoindan-1-ol conformers and their tentative assignments

“C <sub>2</sub> -up” conformers		“C <sub>2</sub> -down” conformers		E		F		G		H		I	
A	B	C	D	E	F	G	H	I	J	K	L	M	N
Freq	Freq	Freq	Freq	Freq	Freq	Freq	Freq	Freq	Freq	Freq	Freq	Freq	Freq
Assign	Assign	Assign	Assign	Assign	Assign	Assign	Assign	Assign	Assign	Assign	Assign	Assign	Assign
102.0	97.9	91.4	100.0	87.9	100.6	70.2	72.6	117.6	117.6	72.6	111.6	123.3	123.3
Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering	Ring puckering
113.3	114.6	112.1	114.9	112.2	114.1	108.6	111.6	123.3	123.3	111.6	111.6	123.3	123.3
two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting	two rings twisting
163.1	163.4	163.3	163.7	145.9	147.2	148.0	145.4	148.6	148.6	145.4	145.4	148.6	148.6
ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly	ring butterfly
223.8	170.4	183.4	225.7	243.6	242.8	243.7	237.6	238.4	238.4	237.6	237.6	238.4	238.4
two ring deformation	two ring deformation	NH <sub>2</sub> torsion	two ring deformation	two ring deformation	two ring deformation	two ring deformation	two ring deformation	two ring deformation	two ring deformation	two ring deformation	two ring deformation	two ring deformation	two ring deformation
OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion	OH and NH <sub>2</sub> torsion

other. In this case the rotational constants alone do not allow a full discrimination of the “C<sub>2</sub>-up” conformers.

As listed in Table 5, the dipole moment of *cis*-3-aminoindan-1-ol is slightly sensitive to conformational changes. Interestingly, the structure **I** identified as the most stable conformer has a remarkably higher  $\mu_{\text{Total}} = 3.15\text{D}$  at B3LYP/6-311+G(d,p), while for other conformers the dipole moment range between 1.17D and 2.89D. This result indicates that the conformer **I** should be better stabilized in polar environments and could also be a valid reason why we could observe the spectrum of **I** conformer experimentally.

### Vibrational spectra

It is well known that indan derivatives have some important low-frequency vibrational modes such as puckering and butterfly vibrational vibrations, giving an insight to the conformational preferences [39]. The ring-puckering is essentially the movement of the CH<sub>2</sub> group out of the five-membered ring while the flapping is the bending of the five-membered ring relative to the benzene ring in a butterfly-like motion [40]. These two out-of-plane vibrations have been observed in most of the published electronic spectra of jet-cooled indan and its derivatives [12–17]. The vibrational frequency analysis at the B3LYP/6-311+G(d,p) level was carried out. The assignments of the relevant low-frequency vibrational modes and their frequencies obtained for the nine conformers are summarized in Table 6. The vibrational descriptions of the low-frequency vibrational modes were done using Gaussview software.

It should be mentioned that “C<sub>2</sub>-up” and “C<sub>2</sub>-down” conformations give rise to slightly different puckering frequency modes, which facilitates their identification. In the case of conformer **A** of “C<sub>2</sub>-up” series and the most stable conformer **I** of the “C<sub>2</sub>-down” group the puckering vibration appears at 102.2 cm<sup>-1</sup> and 117.6 cm<sup>-1</sup>, respectively. The increase of the puckering frequency is probably due to the strong hydrogen bond interaction O-H⋯N present in the most stable conformer **I**. One can conclude that the puckering frequency could be experimentally resolved from “C<sub>2</sub>-up” to “C<sub>2</sub>-down” conformation and be analyzed independently.

The calculated ring butterfly mode in the nine conformers can be seen to follow the same variation as that of puckering vibrations. As can be seen in Table 6, the ring butterfly mode has values of 163.1, 163.4, 163.3 and 163.7 cm<sup>-1</sup> for **A**, **B**, **C** and **D** conformers of “C<sub>2</sub>-up” structure, respectively. While, the calculated values for “C<sub>2</sub>-down” conformers **E**, **F**, **G**, **H** and **I** are 145.9, 147.2, 148.0, 145.4 and 148.6 cm<sup>-1</sup>, respectively. Another lowest frequency vibration is the twisting motions which involve both rings. This mode of vibration is calculated at slightly similar frequency for all the conformers except the most stable structure **I**, which shows the highest value.

### Conclusions

Nine stable conformers of *cis*-3-aminoindan-1-ol have been identified by quantum mechanical B3LYP and MP2 methods. Their relative energies, optimized geometry, dipole moments, rotational constants and vibrational spectra are presented. Our calculations predict that *cis*-3-aminoindan-1-ol is a flexible system which can adopt “C<sub>2</sub>-up” or “C<sub>2</sub>-down” conformations.

The expected intramolecular hydrogen bonds OH⋯ $\pi$ , NH⋯ $\pi$ , NH⋯OH and HN⋯HO have been investigated by geometrical and topological criteria. The existence or absence of OH⋯ $\pi$  and NH⋯ $\pi$  in *cis*-3-aminoindan-1-ol remains unclear since the geometrical investigation has not been confirmed by topological criteria. Indeed, no direct AIM proof has been found for  $\pi$ ⋯hydrogen bond between the benzene ring and the hydroxyl and/or amine groups in *cis*-3-aminoindan-1-ol conformers. The nonexistence of BCPs at OH⋯ $\pi$  and NH⋯ $\pi$  interactions could be attributed to the fact that the carbon atoms that carry the hydroxyl and amino groups are not flexible enough to overcome structural constraints that prevent favorable arrangement between the OH and NH<sub>2</sub> groups and the  $\pi$ -cloud of benzene ring. Using AIM methodology, the NH⋯OH hydrogen bond was identified as true in two conformers **E** and **F** not in **G** and **H** conformers. According to AIM theory, the HN⋯HO interaction present in the most stable conformer **I** is quite a bit stronger than NH⋯OH interaction. This hydrogen bond was found to be the lead factor in determining the molecular configuration of the most stable species of *cis*-3-aminoindan-1-ol.

Finally, the calculated dipole moments, rotational constants and vibrational frequencies presented in this study are of real interest and may be useful for the future experiments in searching for gas phase *cis*-3-aminoindan-1-ol conformers.

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