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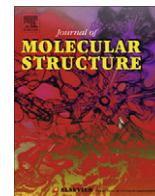


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Probing the influence of solvent effects on the conformational behavior of 1,4-diazacyclohexane systems

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ABSTRACT

Structural and energetic consequences of replacing one or more carbon atoms in small cyclic hydrocarbons with electronegative atoms have been observed due to stereoelectronic anomeric and gauche effects. We have reported the influence of gauche effect on the conformational behavior of a 1,4-diazacyclohexane system using the DFT B3LYP/6-311 + G** level of theory. Factors which are found to control the conformational preferences of a 1,4-diazacyclohexane system include steric, dipolar repulsions and hyperconjugative interactions. The stability order of the 1,4-diazacyclohexane conformers was predicted to be similar in the gas phase and solvent continuum model (aqueous phase). The interactions of explicit water molecules with 1,4-diazacyclohexane conformers however predicted a different order of stability compared to the gas phase and continuum phase results. Ab initio molecular dynamics (AIMD) study showed the minor perturbation in the orientation of explicit water molecules compared to the DFT results and no dramatic changes was observed during the simulation with 1,4-diazacyclohexane conformers.

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1. Introduction

Conformational analysis has always been an important topic of research in physical organic chemistry [1] as most of the properties like reactivity [2], spectroscopic behaviors etc. depends on the conformation. Sachse was the first to recognize the existence of two kinds of C–H bonds for cyclohexane [3]. However, it is a matter of controversy, that, what mostly controls the properties or stabilities for even the simple systems and hence studies on conformational analysis is still actively pursued.

The stereoelectronic behavior of X–C–Y containing systems known as the anomeric effect and that of X–C–C–Y known as gauche effect, where X and Y are any electronegative atoms containing lone pairs have been studied widely [4–20]. The anomeric effect in an X–C–Y system is due to $Xn_p-\sigma_{C-Y}^*$ two electron–two orbital interaction. The gauche effect was originally defined as the tendency for a molecule to adopt that structure which has the maximum number of *synclinal* (sc, gauche, 60°) interactions between adjacent electron pairs and/or polar bonds in a molecular fragment X–C–C–Y, where X and Y are two electronegative substituents [19]. Both gauche and anomeric effects are absent when X and Y do not contain any interacting lone pair. In the recent studies interpretations of gauche effect are based on hyperconjugation effect [16,18,21–23]. The hyperconjugation approach states a two

electron/two orbital interaction which depends on the donor–acceptor ability of the orbitals, on the energy difference between them and on overlap symmetry [24].

Ethylenediamine (EDA) is one of the most studied structures for the conformational analysis for its vast number of structures available. Van Alsenoy et al. [25] and Radom et al. [26] reported that EDA consists of 10 minimum energy structures. Electron diffraction experiments in the gas phase have shown that nonprotonated EDA is predominantly (95%) in a gauche conformation with a dihedral angle φ_{NCCN} of 64° [27] and r_{CC} and r_{NC} bond lengths of 1.545 Å and 1.469 Å [26] respectively. Moreover microwave study [28] showed that in the dominant gauche form, one of the NH₂ groups may assume either two positions, depending on the hydrogen atom involved in the hydrogen bonding. A number of theoretical studies have also been performed in order to investigate the conformational properties of EDA in the gas phase including empirical [27], semi-empirical calculations [29,30]. These studies shed light on the most stable structural conformers, their relative energies and electronic properties. The factors stabilizing the gauche conformers are assumed to be both ‘gauche effect’ and intramolecular hydrogen bonding between two amine groups. Kazerouni and Hedberg [31] estimated 0.20 kcal/mol stabilization through the gauche effect. Lee et al. [32] proposed 1.1 kcal/mol stabilization through the hydrogen bonding and a 2.4 kcal/mol destabilization for the lone pair repulsions. DFT calculations performed by Corte et al. [33] also showed that gauche conformers are the most stable conformers in both gas and aqueous phase. The structural stabilities of

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such types of molecules depend upon stereoelectronic effect, steric effect and hydrogen bonding. Muray et al. calculated computationally the energies of different aza cyclic, acyclic systems and observed that σ -delocalization of nitrogen pair or anomeric effects are responsible for their extra stability than the simple cyclic or acyclic systems [34]. Recent efforts on the conformational stability of 1,3-diazacyclohexane conformers with different solvents [35,36] prompted us to examine the conformational preference of 1,4-diazacyclohexane in the gas and solvent phase. 1,4-diazacyclohexane is also known as piperazine and is used in preparing anticancer drugs like Pibobroman [37]. It is also used in the production of pharmaceuticals and for human and veterinary medicinal drugs. Further, it is used as catalyst in urethane production and also as raw material for preparing antibiotics. Aqueous solution of piperazine also helps to remove the corrosive gases like CO_2 , H_2S etc. [38,39].

In this article, we report a density functional (DFT) study of 1,4-diazacyclohexane conformers (Scheme 1) in the gas and aqueous phase. The solvent study has been performed both with implicit solvent continuum model and explicit solvent molecules. We have examined the stability of conformers of 1,4-diazacyclohexane with two and four water molecules. We have also performed molecular dynamics study using atom-centered density matrix propagation (ADMP) for 1,4-diazacyclohexane conformers interacting with four water molecules. Natural bond orbital analysis (NBO) was performed to obtain the hyperconjugative and steric contributions towards the stability of 1,4-diazacyclohexane in the gas and solvent phase.

2. Computational details

The structures were fully optimized at Becke's three parameter exchange functional with the correlation functional [40] of Lee et al. (B3LYP) [41] with 6-31 + G^* basis set. Positive harmonic vibrational frequencies confirmed that the optimized structures were minima. Single point calculations were carried out with B3LYP/6-311 + G^{**} level of theory [35,42–44]. The relative energies were calculated using the electronic energies obtained with B3LYP/6-311 + G^{**} level of theory. NBO calculations were carried out at B3LYP/6-311 + G^{**} level of theory using B3LYP/6-31 + G^* optimized geometries [45–47]. According to the NBO method, the total SCF energy (E_{tot}) can be decomposed in two terms. The Lewis energy (E_{Lew}) is associated with the localized Hatree Fock (HF) wave function (corresponding essentially to a Lewis structure, although its interpretation is not direct), and is obtained by zeroing all the orbital interactions, that is deleting the off-diagonal elements of the Fock matrix. The delocalization energy (E_{del}) corresponding to all the possible interactions between orbitals, is calculated as:

$$E_{\text{del}} = E_{\text{tot}} - E_{\text{Lew}} \quad (1)$$

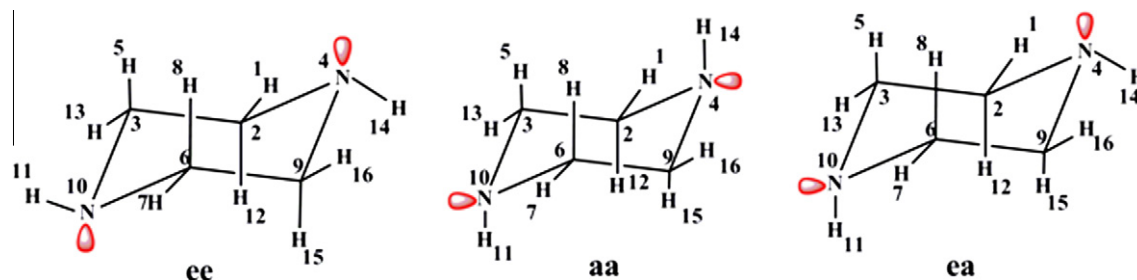
The B3LYP/6-31 + G^* optimized geometries were used to calculate the solvation effect at B3LYP/6-311 + G^{**} level employing the polarizable continuum (PCM) solvent model [48–50]. The solvent

dielectric constant was set to be the experimental value ($\epsilon = 78.4$ for aqueous solution). For explicit interactions between the solute and solvent, water has been considered as solvent molecules. The energies reported for the interaction of water molecules with 1,4-diazacyclohexane were corrected with basis set superposition error (BSSE) employing the counterpoise method [51]. All calculations were carried out with the Gaussian 03 suite of programs [52]. To examine the relative orientations of explicit water molecules with 1,4-diazacyclohexane conformers, the atom-centered density matrix propagation (ADMP) method [53–55] was carried out at the B3LYP/6-31G(d) level of theory using the Gaussian 03 suite of programs [52]. To compromise with the computational cost, these calculations were carried out with 6-31G* basis set instead of 6-31 + G^* basis set. The default time step of 0.1 fs was used for the trajectories. The default fictitious electron mass of 0.1 amu was used throughout. ADMP simulations were carried out for 100 fs with each conformer in presence of water molecules. Selected snapshots were registered with larger changes in the trajectories in each case.

3. Results and discussion

1,4-Diazacyclohexane (**1**) was optimized in three conformations which differ by the orientation of N–H bonds: equatorial/equatorial (**ee**), axial/axial (**aa**) and equatorial/axial (**ea**) (Fig. 1). Conformations were fully optimized without any symmetry constraints. Relative energies and NBO results for **1** are summarized in Table 1. The relative energies of 1,4-diazacyclohexane in implicit solvent phase (water with dielectric constant = 78.4) using the gas phase computed geometries with B3LYP/6-311 + G^{**} level are given in Table 1. The **1aa** and **1ea** conformers are higher in energy than that of **1ee** form. The stability order of these conformers was further calculated with MP2/6-311 + G^{**} and B3LYP/6-31G* levels to examine the influence of basis sets and the methods. The calculated relative energies were found to be similar to that of B3LYP/6-311 + G^{**} level of theory (Table S1 in Supplementary data). Further free energy calculations were computed for these conformers and similar preference was observed (Table S2 in Supplementary data). According to valence-shell electron pair repulsion theory (VSEPR), **1ee** with axial lone pairs should be expected to be highest in energy, since lone pairs require more space than bond pairs. However, this situation has not been borne out in the calculated results (Table 1).

The NBO energy decomposition suggests that the E_{Lew} energy contributes predominantly towards the stability of 1,4-diazacyclohexane **1** (Table 1). The hyperconjugative type interactions in **1aa** is stronger compared to **1ee**, however, the overall stabilization in the later case is due to the lower E_{Lew} energy (Table 1). The higher E_{Lew} term for **1aa** shows that the dipole repulsion between bond pairs is larger than that of the repulsion between the lone pair and bond pair in **1ee**. The conformer **1ea** is a result of compromise between avoiding repulsions and the hyperconjugative stabilization. The highest energy for **1ea** is due to attenuated hyperconjugative effects. The importance of steric effect and dipolar repulsions



Scheme 1. 1,4-diazacyclohexane **ee**, **aa** and **ea** conformers.

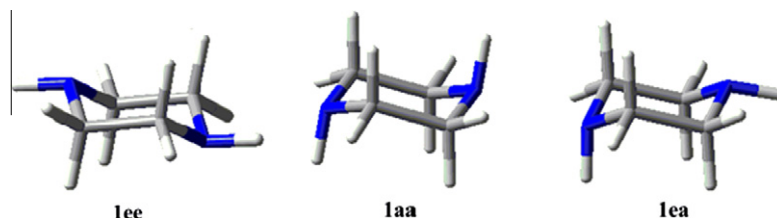


Fig. 1. B3LYP/6-31 + G* optimized structures for **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane [nitrogen: blue; carbon: grey; hydrogen: white]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

B3LYP/6-311 + G**//B3LYP/6-31 + G* relative energies (E_{rel}) for the conformers of 1,4-diazacyclohexane in gas and aqueous phase. Relative energies after removal of hyperconjugative interaction (E_{Lew}), contributions from hyperconjugation (E_{del}) to the total energy differences and dipole moment for **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane in the gas phase are given. Energies are in kcal/mol.

	ee	aa	ea
E_{rel} (gas)	0.0	1.5	3.0
E_{rel} (water)	0.0	0.8	2.6
E_{Lew}	0.0	7.0	5.8
E_{del}	0.0	−5.5	−2.8
Dipole moment (gas)	0.002	0.004	1.60

towards the stereoelectronic effect in the conformational analysis of 2-methoxy-1,3-dimethylhexahydropyrimidine was also observed [56]. Polarizable continuum model (PCM) calculations show that the relative stability of 1,4-diazacyclohexane **1** conformers in aqueous phase is similar to the gas phase results. The relative energy differences are smaller in the solvent medium than that of the gas phase calculated results. These calculated results suggest that the conformer with larger hyperconjugative interactions is stabilized more by the solvent. Numerous cases have been reported on attenuation of the stereoelectronic effect to the presence of a polar solvent [57,58]; however, this feature is not clearly appreciable for the conformer of 1,4-diazacyclohexane. Recently, some studies have shown that the stereoelectronic effects are not attenuated in the presence of a polar solvent [59,60]. Furthermore, the influence of the polar solvent to stabilize the conformers with larger dipole moments is not significant. The conformer **1ea** with larger dipole moment is less stabilized than that of **1aa** with smaller dipole moment (Table 1).

The selection of geometrical parameters listed in Table 2 permits us to deduce that **1ee**, **1aa** and **1ea** show the tendencies associated with gauche effect and were discussed in many studies. Briefly, the bonds are elongated when they are in a position anti to the lone pair of nitrogen, and the angles are widened (Scheme 1 and Table 2). For example, due to the delocalization of lone pairs, the N–C–C bond angles are larger in **1aa** than in **1ee** and **1ea**. The C–H bonds antiperiplanar to the lone pairs are relatively longer than the bonds that are not satisfying such arrangements.

The influence of hydrogen bonding of polar solvent molecules with the substrates is absent in the continuum model calculations. Therefore, it is important to examine the effect of hydrogen bonding of solvent molecules on the stability of 1,4-diazacyclohexane conformers. Interestingly, the hydrogen bonding of solvent molecules with nitrogen lone pairs can affect the gauche stabilizations in these cases, and hence the stability of the conformer can be different from the gas phase and continuum model results. The interaction of water molecules with each conformer of 1,4-diazacyclohexane has been considered. The DFT B3LYP/6-311 + G**//B3LYP/6-31 + G* level relative energies for two explicit water molecules with **1ee**, **1aa** and **1ea** are given in Table 3. Fig. 2 shows the interaction of two water molecules with the nitrogen lone pairs of

Table 2

Geometrical parameters for **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane in the gas phase. All distances are in angstroms; angles and dihedrals are in degrees.

Parameters	ee	aa	ea
C6–C9	1.530	1.540	1.530
C2–C3	1.530	1.540	1.530
C6–H7	1.096	1.097	1.096
C6–H8	1.106	1.101	1.106
C3–H5	1.106	1.101	1.106
C3–H13	1.096	1.098	1.096
C9–H15	1.105	1.101	1.105
C9–H16	1.096	1.098	1.096
C2–H1	1.096	1.098	1.096
C2–H12	1.105	1.101	1.106
N4–C9–H15	112.50	107.38	111.39
N4–C2–H12	113.54	107.34	111.43
N4–C9–C6	108.90	113.33	109.30
N4–C2–C3	108.95	113.35	109.23
N10–C6–H8	112.51	107.43	107.80
N10–C3–H5	112.49	107.38	107.77
N10–C6–C9	108.94	113.32	112.69
N10–C3–C2	108.93	113.31	112.75

1,4-diazacyclohexane conformers. The calculated results suggest that the **1ee** conformer is more stable than the **1aa** and **1ea** conformers (Table 3). The water molecules form strong hydrogen bonds with the nitrogen atoms of 1,4-diazacyclohexane. The conformational stability order changed for **1aa** and **1ea** conformers with explicit water molecules compared to the gas phase and continuum model results. **1aa** conformer was found to be least stable, while interacting with two water molecules. Comparing the NBO calculated E_{Lew} and E_{del} energies for **1ee**, **1aa** and **1ea** show that the Lewis energy is even more detrimental for **1aa** with water molecules, which contributes to make it unstable than **1ee** and **1ea** conformers (Tables 1 and 3). Hence, earlier reports have demonstrated that the —NH_2 is a good proton acceptor but a less effective proton donor [61,62], and that is evident in this study. The interaction of water molecules with —NH_2 as a proton donor was found to be less stable compared to the case where —NH_2 is a proton acceptor for 1,4-diazacyclohexane conformers (Fig. S1 in Supplementary data). In the case of **1aa**, water molecules moved away from —NH donor side to —N acceptor side.

Extending the study with explicit solvent molecules, the conformational stabilities of 1,4-diazacyclohexane conformers was examined with four water molecules. The relative energies

Table 3

B3LYP/6-311 + G**//B3LYP/6-31 + G* relative energies (E_{rel}) for **1ee**, **1aa**, **1ea** conformers of 1,4-diazacyclohexane with two water molecules. Relative energies after removal of hyperconjugative interaction (E_{Lew}), contributions from hyperconjugation (E_{del}) to the total energy differences for **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane with two water molecules are given in kcal/mol. BSSE corrected relative energies are given in parenthesis.

	ee	aa	ea
E_{rel}	0.0 (0.0)	3.8 (3.7)	1.1 (1.0)
E_{Lew}	0.0	9.4	3.9
E_{del}	0.0	−5.6	−2.8

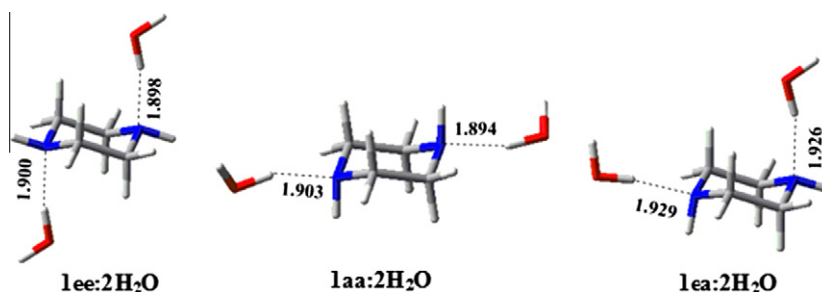


Fig. 2. B3LYP/6-31 + G^* optimized structures of the **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane with explicit two water molecules are given [nitrogen: blue; carbon: grey; oxygen: red; hydrogen: white] Hydrogen bond-distances are given in angstroms. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

calculated with DFT B3LYP/6-311 + G^{**} //B3LYP/6-31 + G^* level for four water molecules with **1ee**, **1aa** and **1ea** are given in Table 4. The water molecules can either interact with the nitrogen's of 1,4-diazacyclohexane in a cluster form or can interact in a chain form with the advantage of more number of hydrogen bonding (Fig. 3). We have examined both situations for each conformer of 1,4-diazacyclohexane. The calculated relative energies for the interaction of four water molecules in a cluster form with the nitrogen atoms of 1,4-diazacyclohexane show that the **1ee** and

1ea are energetically similar, whereas, the **1aa** conformer is slightly higher in energy by 0.7 kcal/mol (Table 4). The water molecules form strong hydrogen bonds with the nitrogen atoms of 1,4-diazacyclohexane and also with each other. The NBO calculations indicate that the contributions of E_{lew} and E_{del} energies are smaller with four water molecules compared to the two water molecules and contributions of both the energies are largely comparable in the former case (Tables 3 and 4). Further, to take the advantage of hydrogen bonding within the water molecules, calculations have been performed with the chain of water and 1,4-diazacyclohexane conformers (Fig. 3). The relative energies calculated with the chain of water molecules show that the **1ee** and **1aa** conformers are isoenergetic in this case (Table 3). Interestingly, the **1ea** conformer was found to be much higher in energy than **1ee** and **1aa** conformers, which is mainly dictated by the unfavored hyperconjugative type interaction energy (E_{del}). To note that both the nitrogen lone pairs are engaged in **1ea** while interacting with the four water chain, however, this is not the case with **1ee** and **1aa**. Therefore, there is a possibility that the nitrogen lone pair not engaged in hydrogen bonding can interact with one more water molecule. Additional calculations performed with five water molecules also showed that **1aa** is 3.0 kcal/mol energetically preferred over **1ea** conformer (Fig. S2 in Supplementary data).

Table 4

B3LYP/6-311 + G^{**} //B3LYP/6-31 + G^* relative energies for the **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane with four water molecules in cluster form and four water molecules in chain form. Relative energies after removal of hyperconjugative interaction (E_{lew}), contributions from hyperconjugation (E_{del}) to the total energy differences for **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane in four cluster form and four chain form are given in kcal/mol. BSSE corrected relative energies are given in parenthesis.

	4:H ₂ O cluster			4:H ₂ O chain		
	ee	aa	ea	ee	aa	ea
E_{rel}	0.0 (0.0)	0.7 (0.6)	0.2 (0.2)	0.0 (0.0)	0.0 (0.1)	2.1 (2.6)
E_{lew}	0.0	3.4	3.8	0.0	9.7	−6.9
E_{del}	0.0	−2.7	−3.6	0.0	−9.7	9.0

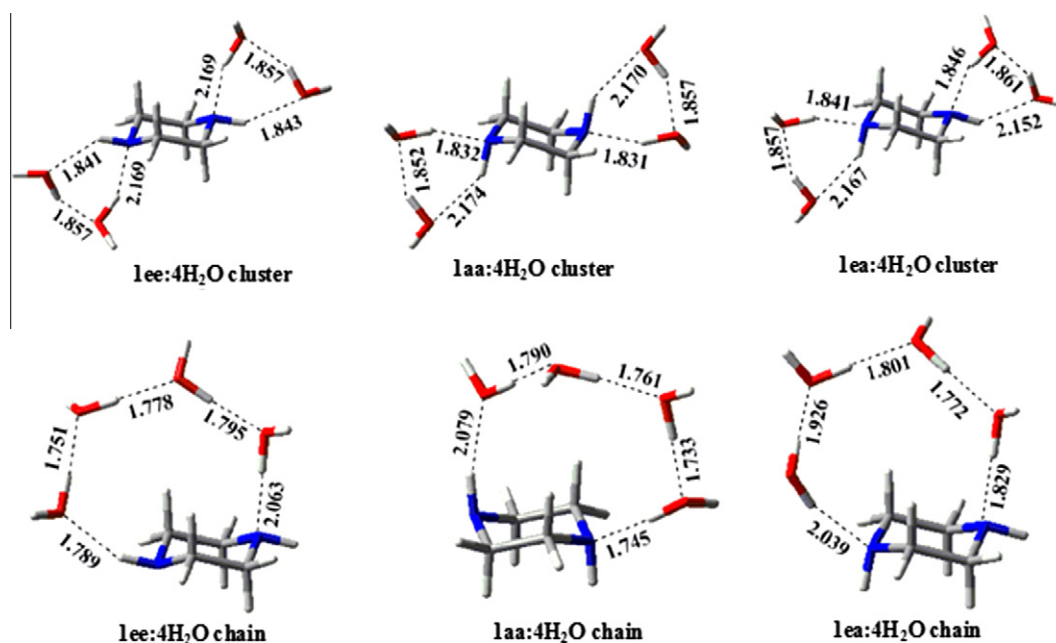


Fig. 3. B3LYP/6-31 + G^* optimized structures of the **1ee**, **1aa** and **1ea** conformers of 1,4-diazacyclohexane with explicit four water molecules in cluster form and in chain form are given [nitrogen: blue; carbon: grey; oxygen: red; hydrogen: white]. Hydrogen bond-distances are given in angstroms. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

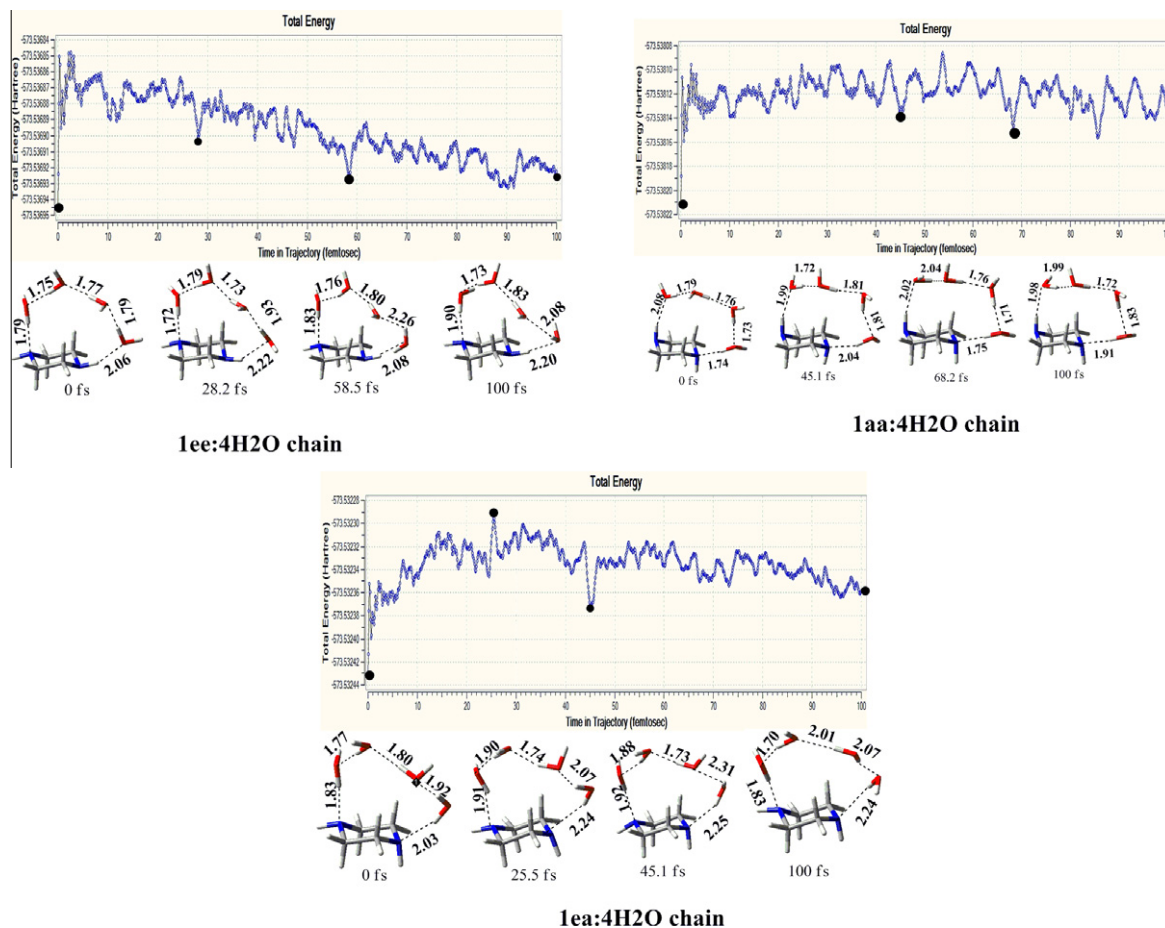


Fig. 4. B3LYP/6-31G* trajectories for the interaction of **1ee**, **1aa**, **1ea** conformers of 1,4-diazacyclohexane with four water in chain form with AIMD/ADMP simulations. Snapshots of the conformers for each case are given at specific time marked in black in the time trajectory. [nitrogen: blue; carbon: grey; oxygen: red; hydrogen: white]. Hydrogen bond-distances are given in angstroms. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

DFT calculations with four water molecules showed that the clustered water interacting with 1,4-diazacyclohexane conformers are energetically less stable than the corresponding situations where water molecules form a chain (Table S3 in Supplementary data). Therefore, it appears that four water molecules would prefer to interact with **1ee**, **1aa** and **1ea** conformers while taking advantage of more number of hydrogen bonding i.e., in the chain form. To examine the orientations of four water molecules in the chain form observed in DFT calculations with time—ab initio molecular dynamic simulations (AIMD) were performed at B3LYP/6-31G* level using the atom-centered density matrix propagation (ADMP) method. The AIMD simulations performed for 100 fs showed that the orientations of water molecules are largely unperturbed in each case. The total energy vs. the time step plots are given in Fig. 4 for **1ee**, **1aa** and **1ea** conformers. The snapshots with the maximum fluctuations of water molecules in the time trajectory marked as black are also given in Fig. 4. Comparing the snapshots taken for each conformer it appears that there are minor perturbations in the orientations of water molecules with 1,4-diazacyclohexane.

4. Conclusions

The present article demonstrates the conformational stability of 1,4-diazacyclohexane in gas phase, implicit and explicit solvent molecules. The stability of conformers was found to be an interplay of steric, dipolar repulsions and hyperconjugative $n_N-\sigma_{C-C}^*$ interactions for 1,4-diazacyclohexane conformers. The NBO analysis suggests that the hyperconjugative type interactions (E_{del}) seem to

be weaker for such $-N-C-C-N-$ systems compared to the steric effects (E_{Lewis} energy). The solvent continuum model (PCM) with water also predicted the similar conformational stability: **1ee** > **1aa** > **1ea**, however with reduced preferences. The explicit water molecules, however, showed the change in the conformational stability order of 1,4-diazacyclohexane conformers compared to gas and continuum model results. The chain of water molecules around **1ee**, **1ea**, **1aa** conformers are more stable than the cluster form of water molecules. In the chain form, the conformers **1ee** and **1aa** are isoenergetic and are expected to be equally populated in the polar solvents like water, which is different from the gas phase results. Ab initio molecular dynamics study showed the minor perturbation in the orientation of water molecules and no dramatic changes was observed during the simulation with 1,4-diazacyclohexane conformers.

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Appendix A. Supplementary material

Cartesian coordinates of the optimized conformers of 1,4-diazacyclohexane in gas phase and with explicit water molecules are given. Supplementary data associated with this article can be

found, in the online version, at [doi:10.1016/j.molstruc.2010.09.045](https://doi.org/10.1016/j.molstruc.2010.09.045).

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