Probing the Influence of Solvent Effects on the Conformational Behavior of 1,3-Diazacyclohexane Systems

Ajeet Singh and Bishwajit Ganguly*

Central Salt Marine & Chemicals Research Institute, (CSIR) Bhavnagar 364002, Gujarat, India

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The conformational behavior of a 1,3-diazacyclohexane system has been investigated using the DFT B3LYP/6-311+G** level of theory. The structural parameters and relative energies predicted that anomeric effects are operative in the conformations of 1,3-diazacyclohexane. The stability of conformers predicted in the solvent continuum model (water and acetonitrile) is similar to the gas-phase results. The explicit water molecules stabilized the least-stable conformer, and the predictive trend is opposite to that of the gas-phase results. The stability of the conformers in the gas phase is a compromise between avoiding repulsions and maximizing hyperconjugative stabilization. The NBO analysis suggests that the interactions of explicit solvent molecules with 1,3-diazacyclohexane conformers attenuate the anomeric stabilization. The hydrogen-bonding interactions of explicit solvent molecules with 1,3-diazacyclohexane swamped the anomeric effects to alter the conformational stability compared to the gas-phase and solvent continuum model studies.

Introduction

The stereoelectronic behavior of X−C−Y-containing systems (X,Y = OR, NR_2, Hal), known as the anomeric effect, and that of the X−C−C−Y molecular unit, known as the gauche effect, have been studied extensively.[1−4] The anomeric effect in an X−C−Y system is due to an $Xn_p-\sigma^*_{C-Y}$ two-electron−two-orbital interaction[2] (negative hyperconjugation[3] in valence bond terms) and is to be manifested as follows:[4] (1) structural parameters, for example, shorter or longer anomeric bonds and larger anomeric bond angles; (2) relative energy, that is, greater stability of gauche (axial) forms over anti (equatorial) forms; and (3) stereoselective reactivity. The anomeric effect is no longer an anomaly and proved to be an important factor toward the stability of substituted conformers of cyclohexanes and other heterocyclic compounds.[4k,l] In this regard, molecules containing the N−C−N moiety have been explored less than the analogous oxygen systems. Only one electron diffraction (ED) study was performed on *N*,*N*,*N′N′*-tetramethyldiaminomethane,[5] and there are few really reliable (^{13}C NMR)[6e,f] conformational equilibrium studies of the highly relevant 1,3-diazane system.[6,7] The complexity of the systems containing N−C−N moieties is a result of a combination of steric and stereoelectronic effects and hydrogen bond-type interactions. It has been indicated that the anomeric effects in N−C−N systems are smaller than in O−C−O systems, but the structural manifestations were borne out as expected.[4e] Salzner has performed ab initio HF/6-31G* level calculations on the stability of conformers of 1,3-diazacyclohexane in the light of examining the conformational behavior of 2-hydroxyhexahydropyrimidine.[8a] Recently, Locke et al. have examined the stability of 1,3-diazacyclohexane with the DFT (B3LYP/6-311+G**) level while quantifying the contributions and interplay of steric and electronic factors for 5-hydroxyhexahydropyrimidine.[8b] The NBO energy decomposition analysis showed that the hyperconjugative stabilization was important for the stability of 1,3-diazacyclohexane conformers.[8] Though the studies are limited on N−C−N systems, the 1,3-diazacyclohexane derivatives are nevertheless important for the preparation of neuroblocking-active drugs such as clothianidin and high-energy materials.[9,10] The wide application of 1,3-diazacyclohexane and its derivatives in studies from biology to materials make these compounds candidates for the detailed conformational study in both the gas and solution phases. To the authors' knowledge, the conformational preference in solvent for 1,3-diazacyclohexane conformers was not studied previously. In this article, we report a density functional (DFT) study of 1,3-diazacyclohexane conformers (Scheme 1) in the gas phase, in water, and in acetonitrile. The solvent calculations have been performed using the quantum chemical solvent continuum model and explicit solvent molecules. Employing NBO analysis, the hyperconjugative energetic contribution can be separated from that due to steric and electrostatic effects on the conformers of 1,3-diazacyclohexane. We have shown that the conformer with larger anomeric interactions stabilizes more in the polar solvent; however, the explicit solvent molecules suggested a reversal in the trend of stability for 1,3-diazacyclohexane conformers. Second-order perturbative NBO analysis has shown that the binding of explicit water and acetonitrile molecules with the nitrogen atoms of 1,3-diazacyclohexane largely unperturbed the anomeric effect.

Computational Methods

All calculations were performed with the Jaguar program package[10] using Becke's three-parameter exchange functional with the correlation functional[11] of Lee, Yang, and Parr (B3LYP).[12] All species were fully optimized with the 6-31+G* basis set, and harmonic vibrational frequency calculations were used to confirm that the optimized structures were minima, as characterized by positive vibrational frequencies. Single-point calculations were then carried out with the 6-311+G** basis set. The NBO calculations have been carried out employing the B3LYP/6-311+G** level using B3LYP/6-31+G* geometries. According to the NBO method,[13,14] E_{tot} represents the total SCF relative energy, and E_{Lew} is the energy associated with the

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* Corresponding author. Fax: (+91)-278-2567562. E-mail: ganguly@csmcri.org.

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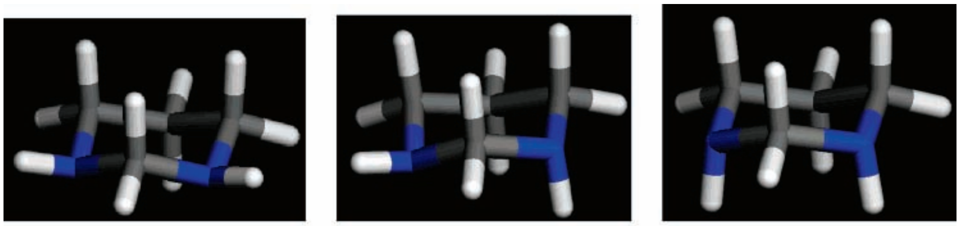
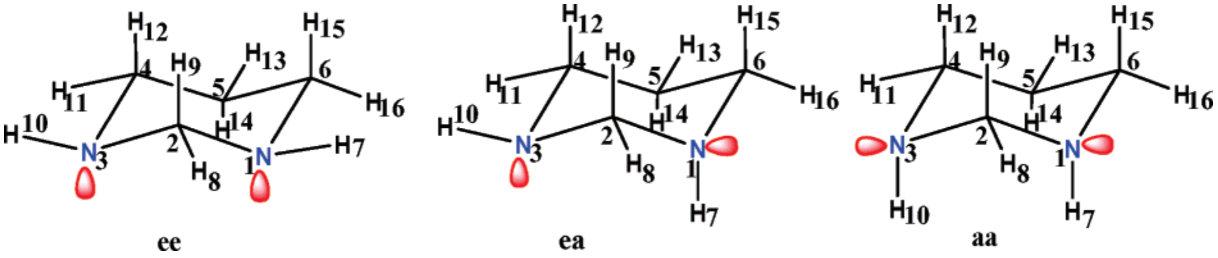


ee **ea** **aa**

Figure 1. B3LYP/631+G* optimized geometries for 1,3-diazacyclohexane conformers.

SCHEME 1



localized part of the wave function (corresponding essentially to a Lewis structure, although its interpretation is not direct). The Lewis energy is obtained by zeroing all the orbital interactions, that is, deleting the off-diagonal elements of the Fock matrix. Finally, the delocalization energy, which corresponds to all the possible interactions between orbitals, is calculated as $E_{\mathrm{del}} = E_{\mathrm{tot}} - E_{\mathrm{Lew}}$. The B3LYP/6-31+G*-optimized geometries were used to calculate the solvation energies at the B3LYP/6-311+G** level employing the Poisson−Boltzmann continuum (PB) solvent model[15,16] as implemented in the Jaguar program.[10] In PB-based calculations of solvation energies, the dielectric interface between solvent and solute is taken to be the molecular surface, which is the contact surface between the van der Waals enevelope of the solute and a probe solvent molecule (for aqueous solution, a probe radius is 1.4 Å). The internal dielectric constant in the PB calculations is set equal to unity, as molecular polarizability is treated explicitly with quantum chemical calculations. All regions outside of the molecular surface are assigned the experimental solvent dielectric ($\epsilon = 78.4$ for aqueous solution and $\epsilon = 36.64$ for acetonitrile). Water and acetonitrile molecules have been considered for the explicit interactions with 1,3-diazacyclohexane conformers. The basis-set superposition error (BSSE) was corrected by the counterpoise method.[17]

Results and Discussion

The relative energies, the energetic contributions in the NBO model, and selected values of the B3LYP/6-31+G* geometrical parameters of each 1,3-cyclohexane conformers (Figure 1) are given in Tables 1 and 2. 1,3-Diazacyclohexane was optimized in three conformations which differ by the orientation of N−H bonds: axial/axial (**aa**), equatorial/axial (**ea**), and equatorial/equatorial (**ee**). Conformations **ee**, **ea**, and **aa** were fully optimized without any symmetry constraints.

The calculated relative energies and NBO results for these three conformers are summarized in Table 1. The **ea** and **aa** conformers are close in energy and significantly more stable than the **ee** form in the gas phase.[8b] According to valence-shell electron pair repulsion theory (VSEPR), **ee** with axial lone pairs should be expected to be highest in energy, since lone pairs require more space than bond pairs. This situation has been borne out in the calculated results (Table 1). However, if it is assumed that the polar N−H bonds also cause dipole repulsion but that these are smaller than those between lone pairs, **aa** was lowest in energy. The similar energies of **ea** and **aa** can thus be rationalized by additional 1,3-diaxial steric repulsions between the axial N−H bonds in **aa**. In Table 1, the dipole moments are also included because it has been suggested that the most stable conformers in the gas phase correspond with the lowest dipole.[18] The dipole moment increase **aa** < **ea** < **ee** is in agreement with earlier reports;[18] however, this trend is found to be different from the HF/6-31G* calculated results.[8] The NBO decomposition energy suggests a different interpretation. In the **ee** conformation, the nitrogen lone pairs are antiperiplanar with the adjacent C−H axial hydrogen. In the **aa** conformation, both nitrogen lone pairs are antiperiplanar with the adjacent C−N bonds. Since $n_N-\sigma^*_{C-N}$ interactions are stronger than $n_N-\sigma^*_{C-H}$ interactions, a preference due to hyperconjugation for **aa** over **ea** and **ee** results.

This is borne out in the NBO deletion energies (E_{del}, Table 1). E_{Lew} (Table 1) shows that, after removal of the hyperconjugation energy contribution, **aa** is highest in energy. This result points to repulsions between the N−H bonds. Thus, according to NBO analysis, dipole repulsions between the lone pairs are much smaller than repulsions between the N−H bonds and do not explain the relative energies of 1,3-diazacyclohexane. The similar energies of **aa** and **ea** result as a compromise between avoiding repulsions and maximizing hyperconjugative stabilization. The selection of geometrical parameters listed in Table 2 permits us to deduce that **aa**, **ae**, and **ee** show the tendencies associated with the anomeric effect and were discussed in many studies.[1,6] Briefly, the bonds are elongated when they are in a position anti to the lone pair of nitrogen, and the angles which these bonds form are widened (Scheme 1 and Table 2). For example, due to the delocalization of lone pairs, the N−C−N bond angles are larger in **aa** than in **ee** and **ea**. The C−H bonds antiperiplanar to the lone pairs are relatively longer than the bonds that are not satisfying such arrangements.

To continue further, the second-order perturbative analysis in the NBO procedure has been used to estimate the individual hyperconjugative effect, namely, the lone pair of nitrogen antiperiplanar to σ^*_{C-N} and σ^*_{C-H} orbitals. Table 3 gives the

TABLE 1: B3LYP/6311+G//B3LYP/631+G* Relative Energies (E_{rel}) (in kcal/mol) in the Gas Phase, Water, and Acetonitrile for ee, ea, and aa Conformers of 1,3-Diazacyclohexane; Lewis Energies (E_{Lew}) (in kcal/mol) and Hyperconjugative Contributions (E_{del}) (in kcal/mol) to the Total Energy Differences for the Conformers in the Gas Phase at the Same Level of Theory; and Dipole Moments (in Debye)**

	ee	ea	aa
E_{rel}(gas)	2.6	0.0	−0.1
E_{Lew}	1.0	0.0	4.4
E_{del}	1.6	0.0	−4.5
E_{water}	3.3	1.6	0.0
$E_{acetonitrile}$	3.4	1.6	0.0
dipole moment (gas)	1.88	1.23	1.10

TABLE 2: Selected B3LYP/6-31+G* Geometrical Parameters for ee, ea, and aa (bond lengths in angstroms, and bond angles in degrees)

	ee	ea	aa
C6−H15	1.110	1.100	1.109
C6−H16	1.096	1.096	1.096
N1−C2	1.460	1.454	1.466
N3−C2	1.460	1.470	1.466
C4−H12	1.110	1.109	1.100
C4−H11	1.096	1.096	1.096
N3−C4	1.467	1.468	1.470
N1−C6	1.467	1.472	1.476
N1−C2−N3	108.9	112.0	116.8
N3−C2−N1	108.9	112.0	116.8
N1−C6−H15	112.1	107.2	107.2
N3−C4−H12	112.1	112.0	107.3
N3−C2−H9	111.1	111.9	107.2
N1−C2−H9	111.1	106.9	107.2

TABLE 3: Hyperconjugative Interaction Energies (E_2) Calculated at B3LYP/6311+G//B3LYP/6-31+G* for ee, ea, and aa (in kcal/mol)**

	ee	ea	aa
N1−C2−N3	1.97	9.88	10.91
N3−C2−N1	1.97	2.03	10.93
N1−C6−H15	7.85	2.07	2.33
N3−C4−H12	7.85	7.77	2.32
N3−C2−H9	7.53	7.48	2.14
N1−C2−H9	7.53	1.66	2.14
N1−C6−H16	1.27	0.83	0.76
N3−C4−H11	1.27	1.13	0.76
N1−C2−H8	1.29	0.94	0.70
N3−C2−H8	1.29	1.05	0.70

hyperconjugative interaction energies (E_2) of such orbitals in **ee**, **ea**, and **aa** at the B3LYP/6-311+G**//B3LYP/6-31+G* level.[19] The interaction energies clearly show that the antiperiplanar σ^*_{C-N} and σ^*_{C-H} orbitals overlap much more strongly compared to the antibonding orbitals that are not antiperiplanar to the nitrogen lone pairs in **ee**, **ea**, and **aa** conformers (Scheme 1 and Table 3). For example, in the case of the **aa** conformer, N_1 and N_3 lone pairs interact with antiperiplanar σ^*_{C2-N3} and σ^*_{C2-N1} orbitals; as a result, the interaction energies are much larger than the corresponding interactions in the **aa** conformer, where the interacting orbitals are not antiperiplanar to each other. These results corroborate the earlier NBO delocalization analysis performed for these conformers. This perturbative analysis will be a particularly useful tool to access the hyperconjugative effects when the explicit solvent molecules interact with these conformers and are discussed later.

The preference for the **aa** conformer is increased in water and acetonitrile with the Poisson−Boltzmann continuum (PB) solvent continuum model (Table 1). Importantly, in the solvent phase the **aa** conformer is significantly more stable than the **ea** conformer, in contrast to the gas-phase calculations. These calculated results suggest that the conformer with larger anomeric interactions is even more stabilized by the solvent. Numerous cases have been reported on attenuation of the anomeric effect to the presence of a polar solvent;[20] however, this feature is not clearly appreciable for the conformers of 1,3-diazacyclohexane. Recently, some studies have shown that the anomeric effects are not attenuated in the presence of a polar solvent.[21] Furthermore, the influence of the polar solvent to stabilize the conformers with larger dipole moments is not significant. There is a relationship between the variation in dipole moments and relative energies of these conformers. The conformer of 1,3-diazacyclohexane with the smaller dipole moment is stabilized in the solvent phase. This suggests that the interaction of the total dipole of each conformer with solvent is not the factor responsible for the solvation energy, and those local dipolar interactions or even multipole components can be important.[22]

TABLE 4: BSSE-Corrected Relative Energies (E_{rel}) at the B3LYP/6311+G//B3LYP/631+G* Level (in kcal/mol) and Selected Geometrical Parameters for ee, ea, and aa Conformers of 1,3-Diazacyclohexane with Water Molecules at the B3LYP/631+G* Level (bond lengths in angstroms, and bond angles in degrees)**

	ee	ea	aa
E_{rel}	0.0	1.4	3.4
C6−H15	1.106	1.099	1.098
C6−H16	1.095	1.095	1.095
N1−C2	1.469	1.456	1.470
N3−C2	1.460	1.481	1.467
C4−H12	1.107	1.106	1.098
C4−H11	1.095	1.096	1.095
N3−C4	1.473	1.477	1.476
N1−C6	1.479	1.477	1.478
N1−C2−N3	108.8	111.5	116.8
N3−C2−N1	108.8	111.5	116.8
N1−C6−H15	111.5	107.3	107.2
N3−C4−H12	111.1	111.0	107.3
N3−C2−H9	111.4	111.4	107.2
N1−C2−H9	110.4	107.6	107.2

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 1,3-diazacyclohexane conformers. Interestingly, the hydrogen bonding of solvent molecules with the nitrogen lone pairs can affect the anomeric stabilizations in these cases, and hence the stability of the conformers can be different from the gas-phase and continuum model results. In the present study, we have considered two water and acetonitrile molecules in each case for the interactions with 1,3-diazacyclohexane conformers.

The relative energies, selected values of the B3LYP/6-31+G* geometrical parameters, and the second-order perturbative analysis (E_2) NBO of each 1,3-diazacyclohexane conformer with two water molecules are given in Tables 4 and 5. Figure 2 shows the interaction of two water molecules with the nitrogen lone pairs of 1,3-diazacyclohexane conformers. The calculated relative energies suggest that the **ee** conformer is more stable than the **aa** and **ea** conformers at the B3LYP/6-311+G**//B3LYP/6-31+G* level (Table 4), which is contrary to the gas-phase and continuum model results (Table 1). The water molecules form strong hydrogen bonds with the nitrogen atoms of 1,3-diazacyclohexane. In the case of **ee**, the water molecules also interact with each other and form a strong hydrogen bond (Figure 2). The N−H···O type hydrogen bonding is possible for **ea**, and that presumably leads to the extra stabilization compared to **aa**. The other orientations of N···O−H type interactions with water molecules were also attempted in each

TABLE 5: Hyperconjugative Interaction Energies (E_2) Calculated at B3LYP/6-311+G//B3LYP/6-31+G* for ee, ea, and aa with Water Molecules (in kcal/ mol)**

	ee	ea	aa
N1−C2−N3	1.93	9.27	9.93
N3−C2−N1	1.54	1.67	10.25
N1−C6−H15	6.92	1.97	2.08
N3−C4−H12	6.16	6.45	1.92
N3−C2−H9	6.32	5.97	1.82
N1−C2−H9	6.24	1.53	1.94
N1−C6−H16	1.20	0.74	0.66
N3−C4−H11	1.21	1.03	0.77
N1−C2−H8	1.21	0.87	0.63
N3−C2−H8	1.21	0.96	0.72

TABLE 6: BSSE-Corrected Relative Energies (E_{rel}) at the B3LYP/6311+G//B3LYP/631+G* Level (in kcal/mol) and Selected Geometrical Parameters for ee, ea, and aa Conformers of 1,3-Diazacyclohexane with Acetonitrile Molecules at the B3LYP/631+G* Level (bond lengths in angstroms, and bond angles in degrees)**

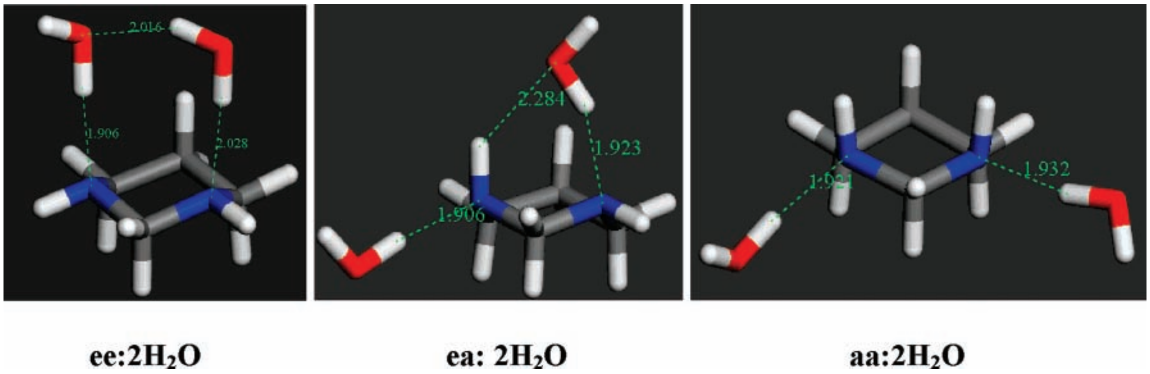
	ee	ea	aa
E_{rel}	3.4	0.0	1.7
C6−H15	1.111	1.100	1.100
C6−H16	1.096	1.096	1.095
N1−C2	1.460	1.453	1.462
N3−C2	1.460	1.474	1.468
C4−H12	1.111	1.109	1.101
C4−H11	1.096	1.097	1.097
N3−C4	1.464	1.469	1.472
N1−C6	1.464	1.469	1.469
N1−C2−N3	109.3	112.7	117.3
N3−C2−N1	109.3	112.7	117.3
N1−C6−H15	112.1	107.5	107.6
N3−C4−H12	112.1	111.7	107.2
N3−C2−H9	110.9	111.3	106.8
N1−C2−H9	110.9	107.0	107.8

case, but the optimizations led to the geometries shown in Figure 2. The computed structural parameters for **ee**, **ea**, and **aa** suggest that the anomeric effects are operational in these cases. The bonds are elongated when they are in a position anti to the lone pair of nitrogen, and the angles which these bonds form are widened (Scheme 1 and Table 4) in a manner similar to that observed in the gas-phase studies. To examine further, the second-order perturbative analysis (E_2) has been performed to estimate the hyperconjugative effect, namely, the lone pair of nitrogen antiperiplanar to σ^*_{C-N} and σ^*_{C-H} orbitals in these cases.[19] The interaction energies show that the antiperiplanar σ^*_{C-N} and σ^*_{C-H} orbitals overlap much more strongly compared to the antibonding orbitals which are not antiperiplanar to the nitrogen lone pairs in **ee**, **ea**, and **aa** conformers (Scheme 1 and Table 5). The second-order perturbative energies (E_2) predicted that the hyperpconjugative effects with water molecules for **ee**, **ea**, and **aa** are slightly attenuated compared to the gas-phase results; however, the trend predicted is similar to that obtained in the perturbative analysis of the **ee**, **ea**, and **aa** gas-phase conformers (Tables 3 and 5). Therefore, it appears that the structural parameters are not significantly affected with the interaction of explicit water molecules, but such interactions are reflected in the hyperconjugative interaction energies (E_2). The calculated results suggest that the reversal in the conformational stability of **ee**, **ea**, and **aa** with water molecules compared to that in the gas phase is primarily dictated by hydrogen-bonding interactions (Tables 1 and 4). Further, the study was extended to examine the interaction of water molecules with amino hydrogens of 1,3-diazacyclohexane conformers **ee**, **ea**, and **aa**. However, the interaction of two water molecules with the **aa** conformer could not converge after several trials with different orientations. Therefore, a direct comparison is not possible for this type of interactions of water molecules with **ee**, **ea**, and **aa** conformers. Earlier reports have demonstrated that the NH_2 is a good proton acceptor but a less effective proton donor,[23] and that is also evident in this study. Studies were extended with four water molecules as well (two with the available lone pairs of nitrogen and two with the N−H hydrogens), but the **aa** conformer did not converge in this case either. Presumably, the steric factor is not favored for the interaction of water molecules with the axial N−H hydrogens in the **aa** conformer. It is important to note that the additional water molecules can have an influence on the relative stability of conformers compared to the two-water model study; however, it is difficult to comment in the absence of such results.

Moving to the conformational stability of **ee, ea**, and **aa** conformers with acetonitrile molecules, the hydrogen-bonding interactions have been considered between the amino hydrogens of 1,3-diazacyclohexane and the −CN group of acetonitrile. The interaction of nitrogen lone pairs with the CH_3 hydrogen (C−H···N) of acetonitrile is not stable in these cases. Hence, we could not locate such complexation geometries for **ee, ea**, and **aa** conformers with acetonitrile.

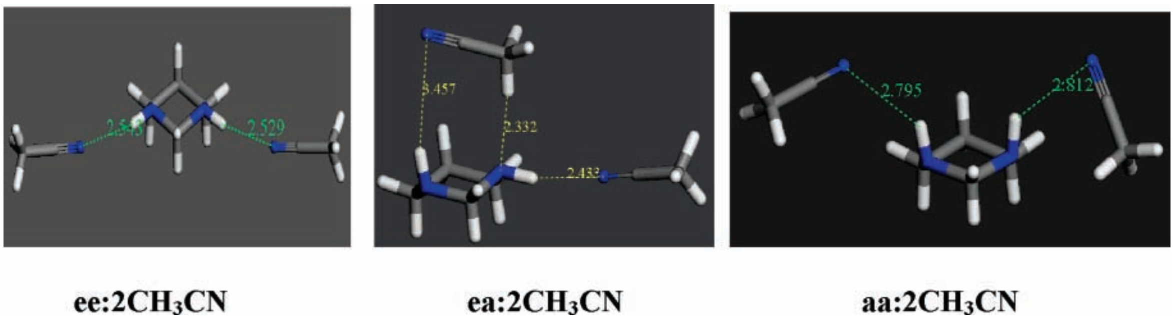
The relative energies, selected values of the B3LYP/6-31+G* geometrical parameters, and the second-order perturbative analysis (E_2) NBO of each of the 1,3-diazacyclohexane conformers with two CH_3CN molecules are given in Table6 and Table S1 (Supporting Information). Figure 3 shows the interaction of two CH_3CN molecules with the −N−H moieties of 1,3-diazacyclohexane conformers. The calculated geometries show that the hydrogen-bonding interactions are much weaker in these cases. The calculated hydrogen-bonding distances are around 2.4 Å and deviate from linearity. In the case of the **ea** conformer, a N···H−C type interaction takes place (2.33 Å) with the acetonitrile molecule and the amino nitrogen of 1,3-diazacyclohexane (Figure 3). For **ee** and **aa**, it appears that the 1,3-diazacyclohexane conformers form a van der Waals complex with acetonitrile molecules as the hydrogen-bonding distances are larger than ∼2.5 Å (Figure 3). It is known that acetonitrile forms a hydrogen bond with phenol, alcohols, and water molecules.[24] However, to the authors' knowledge, the interaction of CH_3CN with amines is not known. Thus, we have computed the relative interaction energies for acetonitrile with methyl alcohol and methylamine at the B3LYP/6-31+G* level. The calculated results suggest that methanol forms a strong hydrogen bond (5.2 kcal/mol) with acetonitrile, whereas, the methylamine forms a much weaker hydrogen bond (2.5 kcal/mol) with acetonitrile (Supporting Information; Figure S1).

The relative energies calculated for the interaction of acetonitrile molecules with 1,3-diazacyclohexane conformers suggest that the **ea** is more stable than that of **ee** and **aa** with CH_3CN molecules (Table 6). The three weak attractive interactions of acetonitrile molecules with the **ea** conformer presumably makes it energetically more stable than **ee** and **aa** conformers (Table 6). The calculated results for **ee** and **aa** with acetonitrile molecules show that the energy difference has been reduced compared to the gas-phase results (Table 1). It appears that the greater stability of the **aa** conformer than **ee** due to the anomeric effect is partially attenuated by the weak attractive interactions of acetonitrile molecules with the latter conformer (Figure 3). Importantly, the trend predicted for the stability of conformers of 1,3-diazacyclohexane conformers with acetonitrile molecules is different from the gas-phase and acetonitirile continuum model results (Table 1). Expectedly, the computed structural parameters for **ee**, **ea**, and **aa** are largely unperturbed in these



ee:2H$_2$O **ea: 2H$_2$O** **aa:2H$_2$O**

Figure 2. The optimized geometries of **ee, ea**, and **aa** conformers with two water molecules at the B3LYP/6-31+G* level. Hydrogen-bonding distances are shown with (···) in angstroms. (Red: oxygen; blue: nitrogen; grey: carbon; white: hydrogen.)



ee:2CH$_3$CN **ea:2CH$_3$CN** **aa:2CH$_3$CN**

Figure 3. The optimized geometries of **ee**, **ea**, and **aa** conformers with two acetonitrile molecules at the B3LYP/6-31+G* level. Hydrogen-bonding distances are shown with (···) in angstroms. (Blue: nitrogen; grey: carbon; white: hydrogen.)

cases because the nitrogen lone pairs are not directly involved in the interaction with the solvent molecules. The bonds are elongated when they are in a position anti to the lone pair of nitrogen, and the angles which these bonds form are widened (Table 6) in a manner similar to that observed in the gas-phase and aqueous-phase studies. The second-order preturbative energies (E_2) calculated for **ee**, **ea**, and **aa** conformers with acetonitrile molecules are similar to that obtained in the gas phase and with water molecules (Supporting Information; Table S1).

Overall, the DFT-calculated results suggest that the anomeric effects play an important role toward the stability of 1,3-diazacyclohexane conformers. The solvent continuum model results enhanced the stability of conformers with larger anomeric interactions. However, the explicit solvent molecules reverted the stability pattern for 1,3-diazacyclohexane conformers. The nonbonding interactions (hydrogen-bond, N···H−C) dictate the stability of **ee**, **ea**, and **aa** conformers though the anomeric interactions prevail in such situations. These results warrant an experimental study to verify the trends predicted by the DFT calculations.

Conclusions

We have reported the stability of 1,3-diazacyclohexane conformers in both the gas-phase and solvent-phase conditions. The stability of conformers **ee**, **ea**, and **aa** arises due to a compromise between avoiding repulsions and maximizing hyperconjugative interactions in the gas phase. The high energy of **ee** is due to attenuated hyperconjugative effects. The continuum solvent model calculations with water and acetonitrile dielectrics enhanced the stability of **aa** compared to that of **ee** and **ea** conformers. The stability trend for **ee**, **ea**, and **aa** was reversed with the explicit water molecules. The anomeric effects were largely unperturbed for **ee**, **ea**, and **aa** while interacting with the water molecules. Thus, the reversal of stability arises due to the hydrogen-bonding interactions of water molecules. The explicit acetonitrile molecules also predicted a different stability trend for **ee**, **ea**, and **aa** conformers compared to the gas-phase results. The hydrogen-bonding interactions are much weaker in the case of acetonitrile and, in general, forms a van der Waals complex with 1,3-diazacyclohexane conformers.

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Supporting Information Available: Optimized geometries and hyperconjugative interaction energies for conformers **ee**, **ea**, and **aa**. This material is available free of charge via the Internet at http:// pubs.acs.org.

References and Notes

(1) (a) *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series No. 539; American Chemical Society: Washington, DC, 1993. (b) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019. (c) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: Berlin, 1983. (d) *Anomeric Effect. Origins and Consequences*; Szarek, W. A., Horton, D., Eds.; ACS Symposia Series No. 87; American Chemical Society: Washington, DC, 1979. (e) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Wiley: New York, 1983. (f) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527. (g) Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 39. (h) Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373. (i) Smits, G. F.; Krol, M. C.; Altona, C. *Mol. Phys.* **1988**, *65*, 513. (j) Lemieux, R. U. In *Molecular Rearrangements*; De Mayo, P., Ed.; Interscience Publishers: New York, 1964; p 709.

(2) (a) Altona, C. Ph.D. Thesis, University of Leiden, 1964. (b) David, S.; Eisenstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1973**, *95*, 3806.

(3) (a) Reed, A. E.; Schleyer, P. v. R. *Inorg. Chem.* **1988**, *27*, 3969. (b) Salzner, U.; Schleyer, P. v. R. *J. Org. Chem.* **1994**, *59*, 2138 and references cited therein.

(4) (a) Schleifer, L.; Senderowitz, H.; Aped, P.; Tartakovsky, E.; Fuchs, B. *Carbohydr. Res.* **1990**, *206*, 21. (b) Fuchs, B.; Schleifer, L.; Tartakovsky, E. *Nouv. J. Chim.* **1984**, *8*, 275. (c) Fuchs, B.; Ellencweig, A.; Tartakovsky, E.; Aped, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 287. (d) Aped, P.; Apeloig, Y.; Ellencweig, A.; Fuchs, B.; Goldberg, I.; Karni', M.; Tartakovsky, E. *J. Am. Chem. Soc.* **1987**, *109*, 1486. (e) Aped, P.; Fuchs, B.; Schleifer, L.; Wolfe, S. *J. Comput. Chem.* **1989**, *10*, 265. (f) Senderowitz, H.; Aped, P.; Fuchs, B. *Helv. Chim. Acta* **1990**, *73*, *2113*. (g) Senderowitz, H.; Aped, P.; Fuchs, B. *J. Comput. Chem.* **1993**, *14*, 944. (h) Senderowitz, H.; Aped, P.; Fuchs, B. *Tetrahedron* **1993**, *49*, 3879. (i) Senderowitz, H.; Fuchs, B. *J. Mol. Struct. (THEOCHEM)* **1997**, *395*, 123. (j) Reany, O.; Goldberg, I.; Abramson, S.; Golender, L.; Ganguly, B.; Fuchs, B. *J. Org. Chem.* **1998**, *63*, 8850. (k) Kleinpeter, E.; Taddei, F.; Wacker, P. *Chem. Euro. J.* **2003**, *9*, 1360. (l) Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910.

(5) Van der Does, H.; Mijlhoff, F. C.; Reres, G. H. *J. Mol. Struct.* **1981**, *74*, 153.

(6) (a) Riddel, F. G.; Williams. F. G. *Tetrahedron Lett.* **1971**, 2073. (b) Blackbume, I. D.; Katritzky, A. R.; Read, D. M.; Chivers, P. J.; Crabb, T. A. *J. Chem. Soc., Perkin Trans. II* **1976**, 418. (c) Chive, P. J.; Crabb, T. A. *Tetrahedron* **1970**, *26*, 3369. (d) Katritzky, A. R.; Brito-Palma, F. M. S.; Baker, V. J. *J. Chem. Soc., Perkin Trans. II* **1980**, 1739. (e) Katritzky, A. R.; Baker, V. J.; Brito-Palma, F. M. S.; Ferguson, I.; Angiolini, J. L. *J. Chem. Soc., Perkin Trans. II* **1980**, 1746. (f) Jones, R. A. Y.; Katritzky, A. R.; Snarey. M. *J. Chem. Soc. B* **1970**, 131. (g) Katritzky, A. R.; Baker, V. J.; Ferguson, I. J.; Pate, R. C. *J. Chem. Soc., Perkin Trans. II* **1979**, 143. (h) Armarego, W. L. F.; Jones. R. A. Y.; Katritzsky, A. R.; Read, D. M.; Scattergood, R. *Aust. J. Chem.* **1975**, *28*, 2323. (i) Armarego, W. L. F.; Kobayishi, T. *J. Chem. Soc. C* **1971**, 1912.

(7) (a) Crabb, T. A.;. Katritzky, A. R. *Adv. Heterocycl. Chem.* **1983**, *36*, 1 and references cited therein. (b) Kleinpeter, E. *Adv. Heterocycl. Chem.* **2004**, *66*, 42.

(8) (a) Salzner, U. *J. Org. Chem.* **1995**, *60*, 986. (b) Locke, J. M.; Crumbie, R. L.; Griffith, R.; Bailey, T. D.; Boyd, S.; Roberts, J. D. *J. Org. Chem.* **2007**, *72*, 4156.

(9) (a) Kagabu, S.; Hibi, M.; Nishimura, K. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 705. (b) Axenrod, T.; Sun, J.; Das, K. K.; Dave, P. R.; Forohar, F.; Kaselji, M.; Trivedi, N. J.; Gilardi, R. D.; Flippen-Andersen, J. L. *J. Org. Chem.* **2000**, *65*, 1200.

(10) *Jaguar*, 5.5 ed.; Schrodinger, Inc.: Portland, OR, 2004.

(11) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(12) Lee, C. T.; Wang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(13) (a) Brunck, T. K.; Weinhold, F. *J. Am. Chem. Soc.* **1978**, *102*, 1700. (b) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211. (c) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 1736. (d) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (e) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (f) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066.

(14) (a) Salzner, U.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1993**, *115*, 10231. (b) Carballeira, L.; Perez-Juste, I. *J. Org. Chem.* **1997**, *62*, 6144.

(15) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honig, B. *J. Am. Chem. Soc.* **1994**, *116*, 11875.

(16) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775.

(17) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

(18) (a) Perrin, C. L.; Young, D. B. *Tetrahedron Lett.* **1995**, *36*, 7185. (b) Perrin, C. L.; Armstrong, K. B.; Fabian, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 715. (c) Wiberg, K. B.; Murcko, M. A. *J. Chem. Phys.* **1987**, *91*, 3616.

(19) The second-order perturbation energy is expressed as the following formula: $E_2 = q_i F(i,j)^2/\epsilon_j - \epsilon_i$ where q_i is the electron population of the ith donor orbital, ϵ_i and ϵ_j are the energy levels of the ith and jth orbital, respectively, and $F(i,j)$ is the (i,j) element of the Fock matrix.[13e,f]

(20) (a) Cramer, C. J. *J. Org. Chem.* **1992**, *57*, 7034. (b) Montagnani, R.; Tomais, J. *Int. J. Quantum Chem.* **1991**, *39*, 851.

(21) (a) Carballeira, L.; Perez-Juste, I. *J. Org. Chem.* **1997**, *62*, 6144. (b) Carballeira, L.; Perez-Juste, I. *J. Comput. Chem.* **2000**, *21*, 462.

(22) Alagona, G.; Ghio, C. *J. Mol. Struct.* (*THEOCHEM*) **1992**, *254*, 287.

(23) (a) Hu, C.-H.; Shen, M.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1993**, *115*, 2923. (b) Barone, V.; Adamo, C.; Lelji, F. *J. Chem. Phys.* **1995**, *102*, 364.

(24) (a) Doo-Sik, A.; Lee, S.; Cheong, W. J. *Bull. Kor. Chem. Soc.* **2004**, *25*, *1161*. (b) Cringus, D.; Yeremenko, S.; Pshenichnikov, M. S.; Wiersma, D. A. *J. Phys. Chem. B* **2004**, *108*, 10376. (c) Chaudhari, A.; Lee, S.-L. *Int. J. Quantum Chem.* **2005**, *102*, 106. (d) Kryachko, E. S.; Nguyen, M. T. *J. Phys. Chem. A* **2002**, *106*, 4267.