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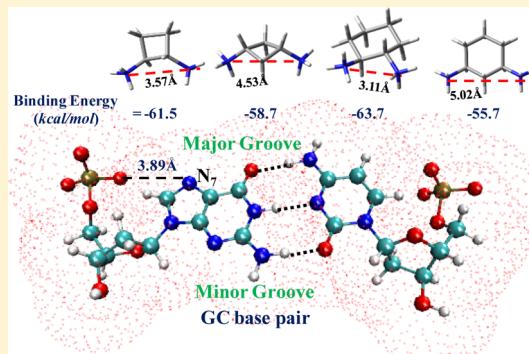
# In Silico Studies toward Understanding the Interactions of DNA Base Pairs with Protonated Linear/Cyclic Diamines

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<sup>6</sup> Supporting Information

**ABSTRACT:** Protonated amino groups are ubiquitous in nature and important in the fields of chemistry and biology. In search of efficient polyamine analogues, we have performed DFT calculations on the interactions of some simple cyclic and constrained protonated diamines with the DNA base pairs and compared the results with those obtained for the corresponding interactions involving linear diamines, which mimic biogenic polyamines such as spermine. The interactions are mainly governed by the strong hydrogen bonding between the ligand and the DNA base pairs. The DFT calculations suggest that the major-groove N7 interaction (GC base pair) with linear diamine is energetically more favored than other possible interactions, as reported with spermine. The cyclic diamines exhibited better interactions with the N7 site of the AT and GC base pairs of DNA than the linear diamines. The net atomic charges calculated for the protonated amine hydrogens were higher for the cyclic systems than for the linear diamines, inducing better binding affinity with the DNA base pairs. The stable conformers of cyclic diamines were predicted using the MP2/aug-cc-pVQZ level of theory. The positions of the protonated diamine groups in these cyclic systems are crucial for effective binding with the DNA base pairs. The DFT-calculated results show that diequatorial (ee) 1,2-cyclohexadiamine (CHDA) is a promising candidate as a polyamine analogue for biogenic polyamines. Molecular dynamics simulations were performed using explicit water molecules for the interaction of representative ligands with the DNA base pairs to examine the influence of solvent molecules on such interactions.



## INTRODUCTION

Deoxyribonucleic acid (DNA) is one of the fundamental units of living organisms, containing the genetic instructions, and is the pharmacological target of different drug molecules. In particular, the recognition of DNA by small molecules is an important problem in drug design.<sup>1,2</sup> The interaction of a drug or a binding agent with DNA can occur through alkylation, intercalation, minor-/major-groove binding, or outside binding to DNA or through dependent enzymes.<sup>3–11</sup> Low-molecular-weight ligands such as polyamines show good interactions with the polyanionic DNA molecule, stabilizing double-stranded DNA,<sup>12</sup> and such interactions cause a variety of significant biological responses.<sup>1</sup> Natural polyamines such as putrescine, spermidine, and spermine are essential in many aspects, including cell replication, modulation of gene expression and enzyme activities, activation of DNA synthesis, and facilitation of protein–DNA interactions;<sup>13–17</sup> they are also involved in neurological diseases<sup>18</sup> and anticancer<sup>19–30</sup> and anti-AIDS drugs.<sup>31</sup> The interactions of spermine with nucleic acids are still under debate.<sup>32–43</sup> Previous studies with <sup>23</sup>Na NMR<sup>34</sup> and X-ray<sup>35</sup> spectroscopies suggested that spermine interacts with the DNA minor groove through hydrogen-bonding and electrostatic interactions, but later, it was reported that spermine interacts with the major groove of the DNA molecule

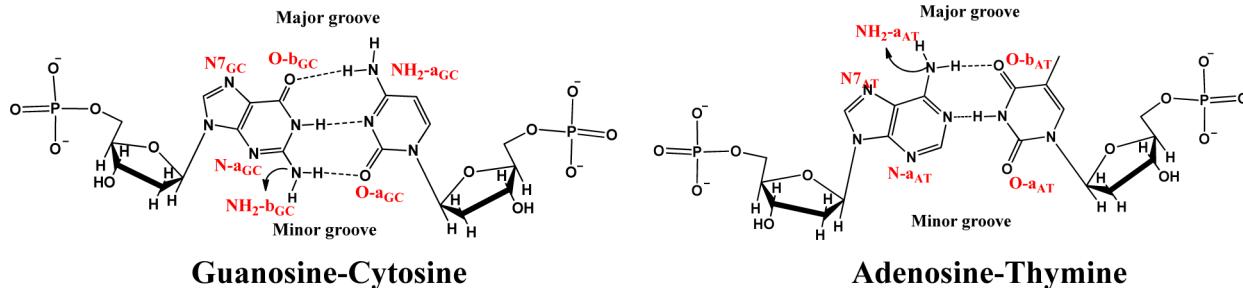
through similar interactions, involving the N7 atom of the GC base pair (Scheme 1) and the phosphate oxygen.<sup>32,36–39</sup> Molecular dynamics studies combined with grand canonical Monte Carlo simulations of DNA revealed the presence of more spermine molecules in the minor groove than in the major groove.<sup>40</sup> Recently, infrared studies showed favorable binding of spermine in the major groove of DNA through the purine N7 atom, with the outer primary amino groups of spermine binding with the phosphate groups of DNA.<sup>41</sup> Further, Raman studies revealed that the interactions with spermine occur across the major grooves involving contacts between the inner amino groups and the purine-N7 and thymine-O4 atoms, which also permit hydrophobic contact between the CH<sub>2</sub> group of thymine and the methylene group of spermine.<sup>42,43</sup>

For decades, there has been a continuous search for synthetic polyamines that can serve as alternatives to biogenic polyamines. Many such synthetic polyamines act as good anticancer agents or prevent neurological diseases<sup>9,10</sup> but cannot mimic such activities of biogenic polyamines as cell replication and

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Scheme 1



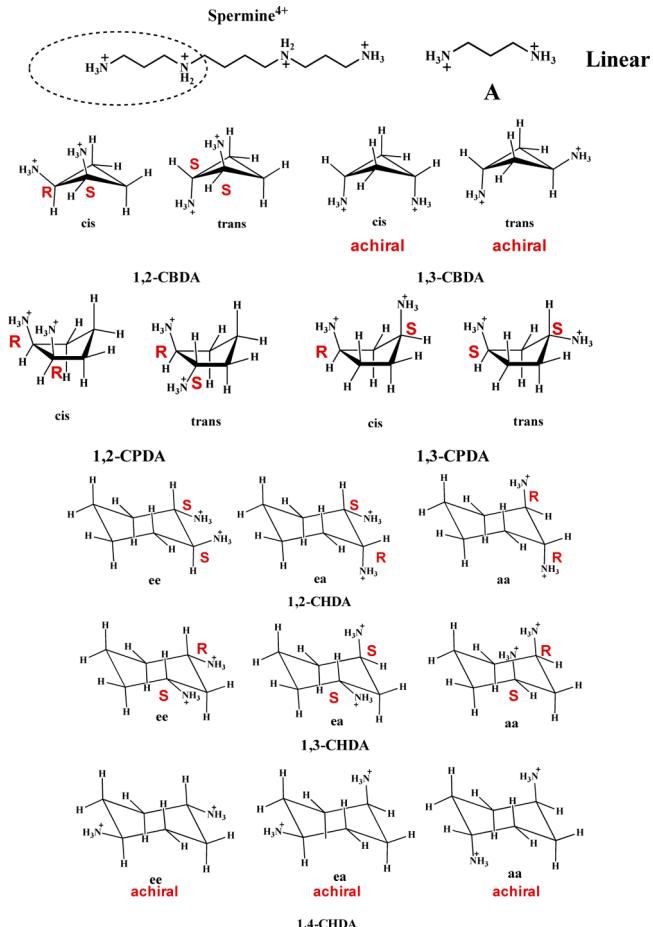
71 enzymatic activity, primarily because of the lower binding  
72 affinities of synthetic polyamines with DNA.<sup>9,44</sup> Recently,  
73 synthesized branched polyamines were found to exhibit good  
74 binding with DNA.<sup>45,46</sup> The search for amines with higher  
75 binding affinities with DNA is very important because no metal  
76 ion is involved, resulting in lower toxicity. The cyclic analogues  
77 of linear amines have been employed for better association with  
78 DNA molecules and to control the cytotoxicity of such  
79 ligands.<sup>47</sup>

80 In this article, we have explored the role of cyclic analogues  
81 of linear amines in terms of their ability to associate with the  
82 DNA molecule and the influence of the spatial separation of  
83 such amine groups. The study was performed with model DNA  
84 AT and GC base pairs (Scheme 1) using higher-level quantum  
85 chemical calculations. Spermine was modeled with linear  
86 diamines, and small cyclic analogues were chosen for the  
87 study. Cyclic diamines are rigid structures and can induce  
88 chirality in the system. Further, cyclic diamines can also have  
89 different positional isomers. The constrained diamines, namely,  
90 cyclobutadiamine (CBDA), cyclopentadiamine (CPDA), and  
91 cyclohexyldiamine (CHDA), and their corresponding position-  
92 al isomers were examined for their interactions with the DNA  
93 base pairs (Scheme 2). Cyclohexadiamine (CHDA) has been  
94 used as a ligand to prepare [dichloro(1,2-diaminocyclohexane)-  
95 platinum(II)], an oxaliplatin-important anticancer drug.<sup>48</sup>  
96 Recently, improved anticancer drugs have also been synthesized  
97 from 1,2-CHDA using metal centers.<sup>49–51</sup> The chiral  
98 constraints induced in ligands have been suggested for better  
99 anticancer activity than linear polyamines with chiral  
100 DNA.<sup>49–51</sup> The ring size of polyamine analogues has been  
101 suggested to be important during binding with DNA.<sup>49–51</sup>

102 We have performed a systematic study with protonated  
103 diamines having different ring sizes and the nature of their  
104 binding with the DNA molecule. The use of higher-level  
105 density functional theory (DFT) calculations can reveal the  
106 mode of binding of such cyclic diamines compared to that of  
107 acyclic linear amines, which can provide insights for researchers  
108 attempting to design efficient analogues of biogenic polyamines.  
109 The interactions between protonated diamines and the DNA  
110 base pairs observed in this study were found to be primarily  
111 governed by strong hydrogen-bonding interactions.

112 Molecular dynamics simulations were performed using  
113 explicit water molecules for the interaction of representative  
114 ligands such as linear and diequatorial (ee) 1,2-CHDA with the  
115 guanine base of DNA employing periodic boundary conditions  
116 to examine the interference of solvent molecules with such  
117 interactions. The solvent molecules were not found to affect the  
118 binding affinity of these ligands with the bases of DNA.

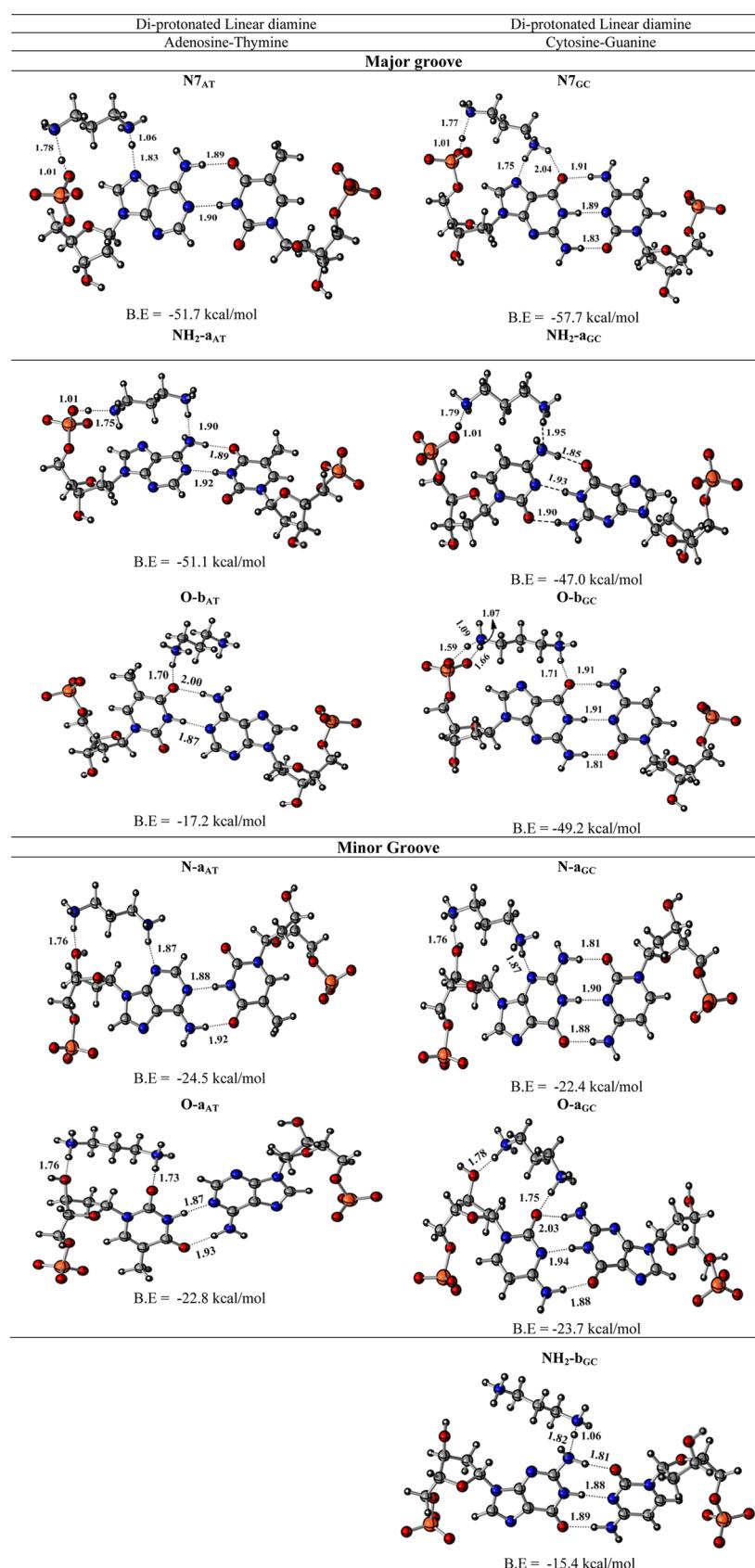
Scheme 2



## ■ COMPUTATIONAL METHODS

119 All reactants and complexes were fully optimized using the  
120 polarizable continuum model (PCM)<sup>52,53</sup> with water as a  
121 solvent to mimic *in vivo* conditions with the B3LYP/6-  
122 31G(d)<sup>54–56</sup> level of theory. Harmonic vibrational frequency  
123 calculations were used to confirm that the optimized structures  
124 were minima, as characterized by positive vibrational  
125 frequencies. Water was used as the solvent with dielectric  
126 constant ( $\epsilon = 78.36$ ). Single-point energy calculations were  
127 performed at the MP2/aug-cc-pVQZ<sup>57,58</sup> level for the  
128 conformational analyses of CBDA, CPDA, and CHDA.<sup>59,60</sup>  
129 The binding energies of the diamine ligands with the DNA base  
130 pairs were calculated with Grimme's B3LYP-gCP-D3/6-  
131 31G(d) method. Single-point calculations were performed  
132 with Grimme's method on B3LYP/6-31G(d)-optimized geo-  
133 metries.<sup>61,62</sup> This newly developed geometrical counterpoise  
134

**Table 1.** B3LYP-gCP-D3/6-31G(d)//B3LYP/6-31G(d)-Calculated Geometries of Diprotonated Linear Diamine Interactions with Different Sites of DNA Base Pairs (AT and GC) and Their Relative Energies<sup>a</sup>



<sup>a</sup>Relative energies are in kcal/mol; distances are in angstroms.

**Table 2.** MP2/aug-cc-pVDZ//B3LYP/6-31G(d)-Calculated Conformational Geometries of (1,2 and 1,3 Positional) Buta- and Pentacyclic Diamine Rings and Their Relative Energies<sup>a</sup>

	CBDA	
	1,2-position	1,3-position
<i>cis</i>		
	6.4	0.0
<i>trans</i>		
	0.0	2.5
CPDA	CPDA	
	<i>cis</i>	<i>trans</i>
<i>cis</i>		
	4.0	0.0
<i>trans</i>		
	0.0	0.8

<sup>a</sup>Relative energies are in kcal/mol.

135 (gCP) correction can account for inter- and intramolecular  
136 basis set superposition error (BSSE) and the missing London  
137 dispersion at the same time.<sup>63</sup>

138 To examine the energies obtained with Grimme's B3LYP-  
139 gCP-D3/6-31G(d) method, additional calculations were  
140 performed with smaller model systems, namely, protonated  
141 methylamine with methyl phosphate, imidazole, and amino-  
142 pyrimidine. Such calculated results were compared with the  
143 results obtained using the CBS-QB3 method, which is known  
144 to predict energies within  $\pm 1$  kcal/mol.<sup>64</sup> Fair agreement  
145 between the results calculated with Grimme's method and the  
146 CBS-QB3 method was obtained (Table S1, Supporting  
147 Information).

148 The DFT-D3 energy is given by

$$149 E_{\text{DFT-D3}} = E_{\text{KS-DFT}} - E_{\text{disp}} \quad (1)$$

150 where  $E_{\text{KS-DFT}}$  is the usual self-consistent Kohn-Sham (KS)  
151 energy as obtained from the chosen density functional and  $E_{\text{disp}}$   
152 is the dispersion correction, given as the sum of two- and three-  
153 body contributions.<sup>61,62</sup>

$$154 E_{\text{disp}} = E^{(2)} + E^{(3)} \quad (2)$$

155 All calculations were performed with the Gaussian 09 suite of  
156 programs.<sup>65</sup> The CHelpG charges<sup>66,67</sup> were calculated at the  
157 B3LYP/6-31G(d) level of theory in solvent medium. All three-  
158 dimensional structures are given with the CYLview.<sup>68</sup> Binding  
159 energies were calculated using the equation

$$160 \text{binding energy } (\Delta E) = E_{\text{complex}} - E_{\text{reactant}} \quad (3)$$

The IR spectra for free AT and GC base pairs and diamine- 161  
base pair adducts were calculated and plotted against 162  
absorbance. Specific IR spectral data (C=O stretch, symmetric 163  
stretch of  $\text{PO}_2^-$ , and H-bond stretch of interacting diamine) 164  
were observed to understand the diamines that interact better 165  
with the base pairs according to the equation 166

$$167 E = hc\nu \quad (4)$$

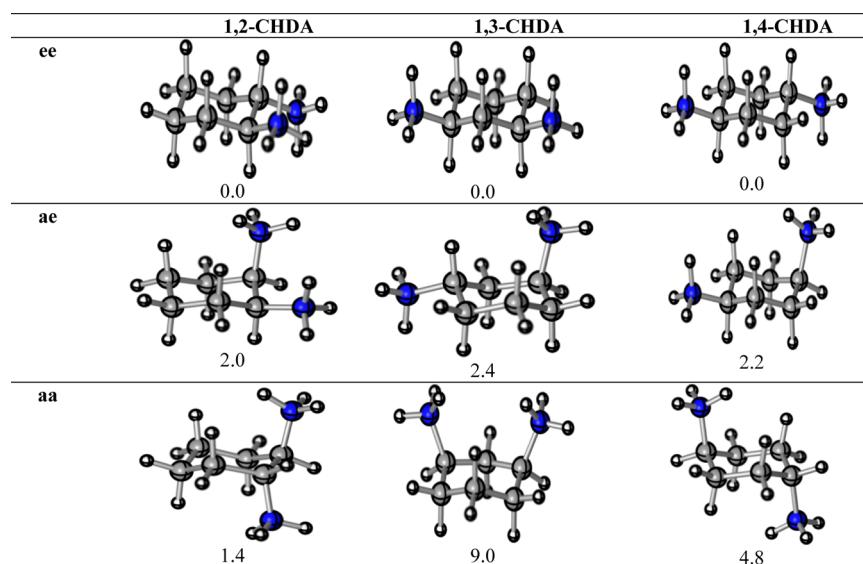
where  $h$  is Planck's constant,  $c$  is the velocity of light in a 168  
vacuum, and  $\nu$  is the wavenumber ( $\text{cm}^{-1}$ ). 169

Molecular dynamics calculations were performed with 170  
DMol3 software (version 4.1) in Materials Studio from 171  
Accelrys Inc.<sup>69-72</sup> with the local spin density approximation 172  
and the Perdew-Wang correlation (LDA/PWC).<sup>73</sup> We used 173  
the DNP double-numerical basis set, which is comparable to 174  
the 6-31G\*\* basis set. All molecular dynamics simulations for 175  
the interactions of linear and diequatorial (ee) 1,2-CHDA with 176  
the guanine base in the presence of explicit water molecules 177  
were performed using periodic boundary conditions with a 178  
cubic box of 20-Å size in the canonical NVT ensemble, and the 179  
system temperature was kept at around 300 K using a Nosé- 180  
Hoover chain thermostat.<sup>74,75</sup> Six solvent molecules ( $\text{H}_2\text{O}$ ) 181  
were placed inside the periodic box, interacting with the 182  
guanine base as well as the ligand molecule. The simulations 183  
were carried out for 1 ps with a time step of 1 fs. 184

## RESULTS AND DISCUSSION

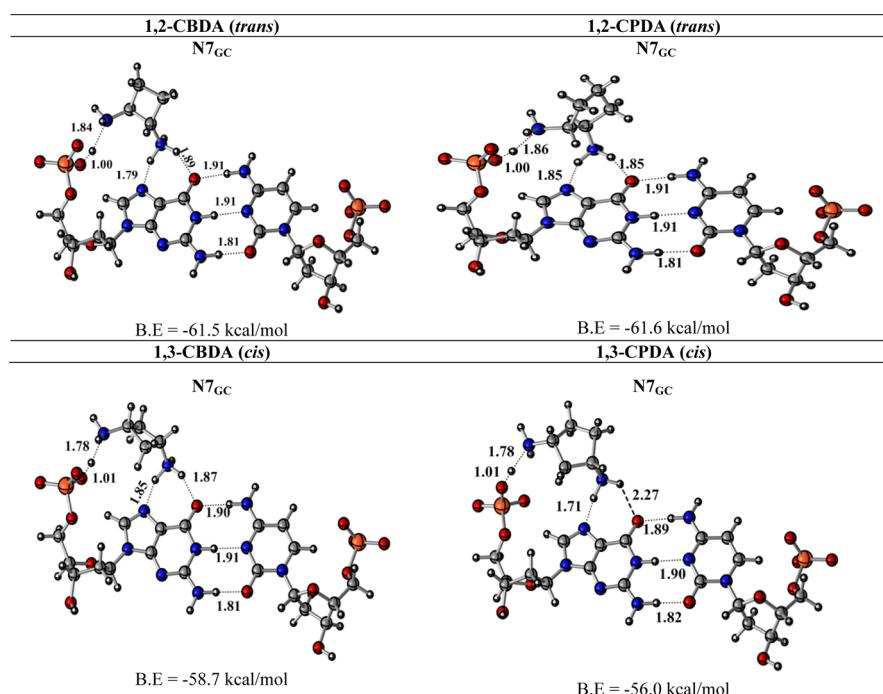
**A. Linear Diamine Interactions.** The interactions of 186  
diprotonated linear diamine with the different sites of the AT 187  
and GC DNA base pairs are reported in Table 1. The binding 188 t1  
energies were calculated using eq 1. The diprotonated linear 189

**Table 3.** MP2/aug-cc-pVDZ//B3LYP/6-31G(d)-Calculated Conformational Geometries (ee, ae, and aa) of 1,2, 1,3, and 1,4 Cyclic Diamine Rings and Their Relative Energies<sup>a</sup>



<sup>a</sup>Relative energies are in kcal/mol.

**Table 4.** B3LYP-gCP-D3/6-31G(d)//B3LYP/6-31G(d)-Calculated Geometries of Diprotonated Trans-1,2 and Cis-1,3 Isomers of CBDA and CPDA with the N7 and Phosphate Sites of the GC Base Pair and Their Relative Energies<sup>a</sup>

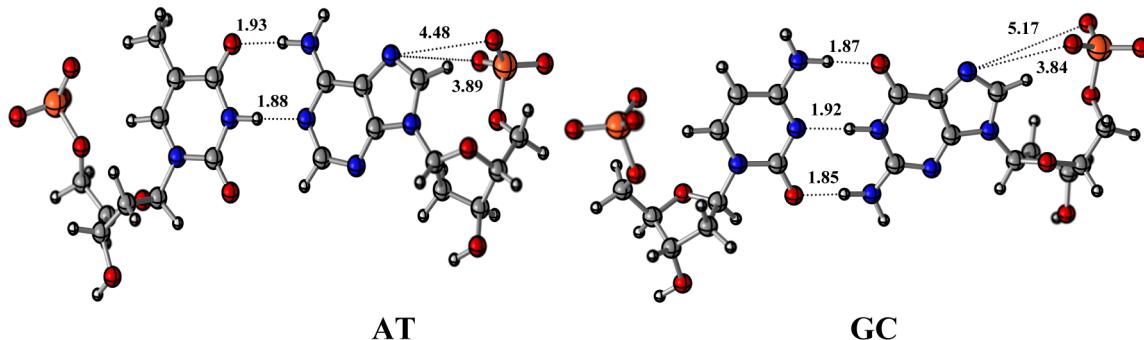


<sup>a</sup>Relative energies are in kcal/mol; distances are in angstroms.

190 diamine (A) prefers to interact with the N7 site (Scheme 1)  
 191 and the phosphate group attached to the GC base pair, as  
 192 observed for biogenic polyamines such as spermine.<sup>32,36–39</sup> The  
 193 calculated binding energy of A with the GC base pair is -57.7  
 194 kcal/mol (Table 1). The similar binding mode of the  
 195 diprotonated linear diamine with the AT base pair is 6.0  
 196 kcal/mol weaker than that with the GC base pair. The  
 197 hydrogen bonding of A with the carbonyl group of the guanine  
 198 base leads to the additional stability for the GC base pair (Table  
 199 1).<sup>76</sup> The negatively charged phosphate group in the base pair  
 200 abstracts the proton from the  $\text{—NH}_3^+$  group of the diamine

(A) (Table 1). The interactions of A with other major- and 201 minor-groove sites of the AT and GC base pairs were also 202 examined. The highest binding affinity was achieved when the 203 phosphate group was involved in the binding with A (Table 1). 204 Therefore, these calculated results corroborate the general 205 preferential binding of biogenic polyamines to the major groove 206 of DNA compared to the minor-groove site.<sup>32,36–39</sup> 207

The nucleic acids are chiral in nature; hence, introducing 208 chirality into the polyamines is beneficial to the activity of the 209 polyamines.<sup>49–51</sup> Chirality was introduced within the poly- 210 amines through restricted chain flexibility and the formation of 211



**Figure 1.** N7–phosphate distances (in angstroms) in the B3LYP/6-31G(d)-optimized geometries of the AT and GC DNA base pairs.

cyclic geometries. However, information on the influence of the constrained ring size and their positional isomers for binding with DNA is limited. Cyclic rings (CBDA, CPDA, and CHDA) with their positional isomers were considered in this work to examine their binding with the DNA base pairs. Some of these cyclic isomers exhibit intrinsic chirality and, hence, can provide a fair comparison with their achiral analogues. A conformational analysis was performed for these cyclic protonated diamines to predict the most stable conformers in each case, before they were considered for interactions with the DNA base pairs.

### B. Conformational Analysis of Cyclic Diamines.

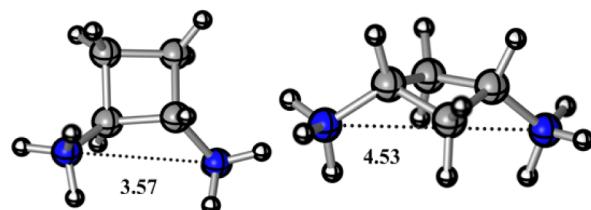
Conformational searches were performed with diprotonated cyclobutadiamine, cyclopentadiamine, and cyclohexadiamine at the MP2/aug-cc-pVDZ level of theory with the PCM solvation model in the aqueous phase. In the case of CBDA, the 1,2 and 1,3 positional isomers were considered. The trans form of the 1,2 isomer was found to be relatively stable compared to the cis form, whereas in the case of the 1,3 isomer, the cis form was predicted to be more stable than the trans form (Table 2). The 1,2 isomer of CBDA exhibits chirality, whereas the 1,3 isomer is achiral in nature. Going from the cyclobutyl ring to the cyclopentyl ring, the stabilities of the 1,2 and 1,3 positional isomers of CPDA also showed trend similar to that observed for the CBDA isomers (Table 2). All 1,2- and 1,3-CPDA isomers exhibit intrinsic chirality in the systems.

The conformational analysis extended to diprotonated CHDA showed that the diequatorial (ee) conformers of the 1,2, 1,3, and 1,4 isomers are energetically more stable than their corresponding axial-equatorial (ae) and diaxial (aa) conformers (Table 3). This conformational analysis of CHDA isomers is in good agreement with earlier reports in aqueous media.<sup>59,60</sup> The 1,2 and 1,3 isomers of CHDA are chiral, whereas the 1,4 positional isomer does not exhibit any chirality.

### C. Cyclic Diamine Interactions with Major-Groove Sites.

Recent studies and our computational results on the interactions of linear diamines with the DNA base pairs suggest that the major groove is the preferred site for such interactions; hence, the calculations for CBDA, CPDA, and CHDA were performed with the major-groove N7 site of the AT and GC base pairs.

Grimme's B3LYP-gCP-D3/6-31G(d)-calculated results show that the interaction of *trans*-1,2-CBDA with the N7 site and the phosphate group of the GC base pair is energetically preferred to the corresponding interaction with the *cis*-1,3 isomer (Table 4). The diprotonated amine nitrogen resides at a distance of 3.57 Å in the *trans*-1,2 isomer of CBDA, which better matches the distance between the N7 site and the phosphate group of the optimized GC base pair (3.84 Å) than the N–N distance of the *cis*-1,3 isomer (4.53 Å) (Figures 1 and 2). Hence, the

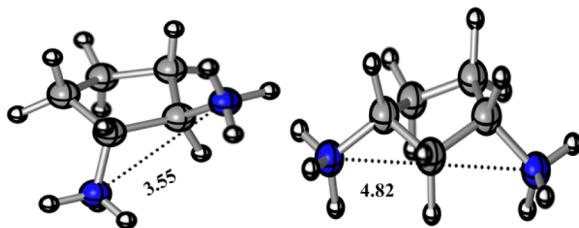


**Figure 2.** N–N distances (in angstroms) in the B3LYP/6-31G(d)-optimized geometries of the diprotonated *trans*-1,2 and *cis*-1,3 isomers of CBDA.

appropriate fit of *trans*-1,2-CBDA with the DNA GC base pair seems to be important for stronger hydrogen binding in this case. We also examined the interactions of the *trans*-1,2 and *cis*-1,3 conformers of CBDA with the N7 site at the major-groove sites of the AT base pair. The interaction energy was found to be lower in this case than that for the GC base pair, as the  $\text{C}=\text{O}\cdots\text{H}-\text{N}$  hydrogen-bonding interaction is not possible in the AT base pair (Table S2, Supporting Information). The preference for the *trans* isomer of synthetic cyclobutyl amine analogues to bind with DNA has also been observed experimentally, which corroborates the calculated results.<sup>49–51</sup> These DFT calculated results show that the chiral *trans*-1,2 isomer of CBDA is better in term of binding with the DNA base pairs than the achiral *cis*-1,3 isomer. The CHelpG charges calculated for the linear and the *trans*-1,2-CBDA suggests that the net atomic charges on the amine hydrogens are higher in *trans*-1,2-CBDA than in the linear diamine (Figure S1, Supporting Information). The ring carbons bear more s character than the carbons in the corresponding linear systems,<sup>77,78</sup> which consequently enhances the polarization in the bonds.<sup>77,78</sup> Such polarization in the substituted amine groups can cause better binding for cyclic systems than for the corresponding linear amines.

To examine the influence of ring strain on the binding with the DNA base pairs, cyclopentadiamine (CPDA) was examined. The strain energy in the cyclopentane ring is lower than that in the cyclobutane ring.<sup>79,80</sup> The calculated interaction energy of the *trans*-1,2 isomer of CPDA with the GC base pairs of DNA is comparable to the interaction energy computed for the *trans*-1,2 isomer of CBDA (Table 4). Furthermore, the binding energy computed for *cis*-1,3-CPDA with the GC base pair is ~5.6 kcal/mol lower than that computed for the *trans*-1,2 isomer (Table 4). The interaction energy for the *cis*-1,3 isomer of CPDA is even lower than that for the *cis*-1,3 isomer of CBDA (Table 4). The weaker interaction of the *cis*-1,3 isomer of CPDA is due to the larger N···N distance of diamine groups (4.82 Å) compared to the

298 distance between the N7 site and the phosphate group of the  
299 GC base pair ( $3.84 \text{ \AA}$ ) (Figures 1 and 3). Cyclopentyl amines



**Figure 3.** N—N distances (in angstroms) in the B3LYP/6-31G(d)-optimized geometries of the diprotonated trans-1,2 and cis-1,3 isomers of CPDA.

300 with longer chains were studied previously for the binding  
301 studies with DNA, and these ligands were found to be rather  
302 inactive in terms of inhibitory effects on human prostate cancer  
303 cells.<sup>49–51</sup> Our calculated results suggest that the trans-1,2  
304 isomer of the CPDA ligand employed in the present study  
305 might be a better candidate for effective binding with the DNA  
306 base pairs, as it showed binding energies similar to those  
307 computed for CBDA. The experimental observations reported  
308 with the cyclobutyl groups are rather promising, although this  
309 system has not been explored much.<sup>49–51</sup> The interactions of  
310 CPDA with the N7 site of the AT base pair at the major groove  
311 exhibited a much lower interaction energy because of the  
312 absence of  $-\text{C}=\text{O}\cdots\text{H}-\text{N}-$  hydrogen-bonding interactions  
313 (Table S3, Supporting Information). The calculated results  
314 showed that *trans*-1,2-CPDA and *trans*-1,2-CBDA bind  $\sim 3.0$   
315 kcal/mol more strongly with the GC base pair of DNA than the  
316 linear diamine (Tables 1 and 4).

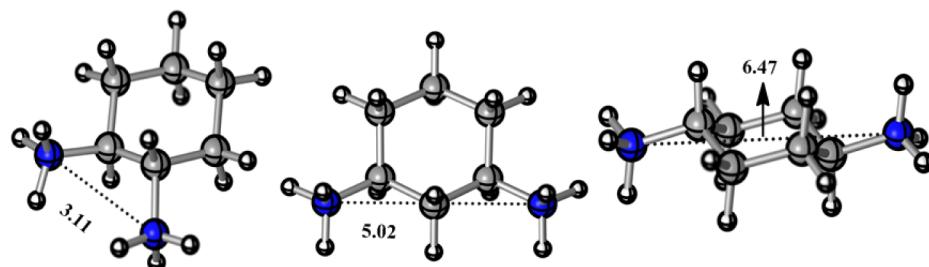
317 The ee-1,2 isomer of CHDA showed a better interaction  
318 with the N7 site of the GC base pairs than did CPDA and  
319 CBDA. The N—N distance of amine groups in the ee-1,2  
320 isomer of CHDA is  $3.11 \text{ \AA}$ , which is slightly less than the N7—  
321 phosphate distance ( $3.84 \text{ \AA}$ ) of the GC base pair (Figures 1 and  
322 4); however, the larger flexibility in the cyclohexyl ring enables  
323 it to interact strongly with the base pair (Figure 4). The  
324 calculated binding energy of the ee-1,2 isomer of CHDA with  
325 the GC base pair was found to  $-63.7 \text{ kcal/mol}$ , which is much  
326 higher than the values calculated for the CBDA and CPDA  
327 cyclic systems (Table 5). The binding energy of the ee-1,3  
328 isomer of CHDA was predicted to be much lower than that of  
329 the ee-1,2 isomer of CHDA (Table 5). The ee-1,4 isomer of  
330 CHDA showed the lowest affinity for binding with the GC base  
331 pair. The geometric mismatch between the ee-1,4 isomer of  
332 CHDA and the N7 and phosphate sites of the GC base pair is a  
333 maximum, and hence, no amine···phosphate interaction occurs,

334 resulting in a weaker binding energy of  $-25.0 \text{ kcal/mol}$ . The  
335 binding energies thus suggest that the ee-1,2-CHDA has  
336 stronger binding ( $\sim 6.0 \text{ kcal/mol}$ ) with the GC base pair than  
337 the linear diamine (Tables 1 and 5). CHelpG charges calculated  
338 for CPDA, CHDA, and *trans*-1,3-CBDA are also provided in  
339 the Supporting Information (Figure S1).  
339

The AT base pair of the major groove showed a markedly  
340 higher interaction energy with the ee-1,2 isomer of CHDA  
341 (Table 6). The B3LYP-gCP-D3/6-31G(d)-calculated interac-  
342 tions suggest that the ee-1,2 isomer of CHDA binds 4  
343 kcal/mol more strongly with the AT base pair than with the 344  
345 GC base pair of the major groove (Tables 5 and 6). Two N—H  
346 hydrogens of an amine group in the ee-1,2 isomer of CHDA  
347 interact with two oxygen atoms of the phosphate group, and  
348 the other amine N—H hydrogen interacts with the N7 site of  
349 the AT base pair (Table 6). The additional interaction between  
349 the phosphate and amine groups augments the interaction  
350 energy in this case compared to that for the corresponding GC  
351 base pair (Tables 5 and 6). In contrast, 1,3- and 1,4-CHDA  
352 showed much weaker interactions with the AT base pair (Table  
353 6). The chiral ee-1,2 and ee-1,3 isomers of CHDA interact with  
354 the DNA base pairs strongly compared to the achiral ee-1,4  
355 isomer of CHDA. These representative calculations with chiral  
356 ligands showed better binding abilities with the DNA base pairs  
357 than the calculations with achiral ligands. The better interaction  
358 of chiral ligands seems to arise from the more appropriate  
359 geometrical fit with the DNA base pairs than for the achiral  
360 systems in these cases. The calculations support the selection of  
361 chiral analogues of biogenic polyamines in earlier reports, but  
362 should be considered in a qualitative sense.<sup>49–51</sup> ee-1,2-CHDA  
363 showed an effective interaction of  $-67.7 \text{ kcal/mol}$ , which is  
364  $\sim 16$  kcal/mol stronger than the interaction of the linear  
365 diamine ( $-51.7 \text{ kcal/mol}$ ) with the AT base pair of DNA  
366 (Tables 1 and 6). Further, the interaction of ee-1,2-CHDA with  
367 the AT base pair was also found to be  $4.0 \text{ kcal/mol}$  stronger  
368 than the interaction with the GC base pair (Table 6).  
369

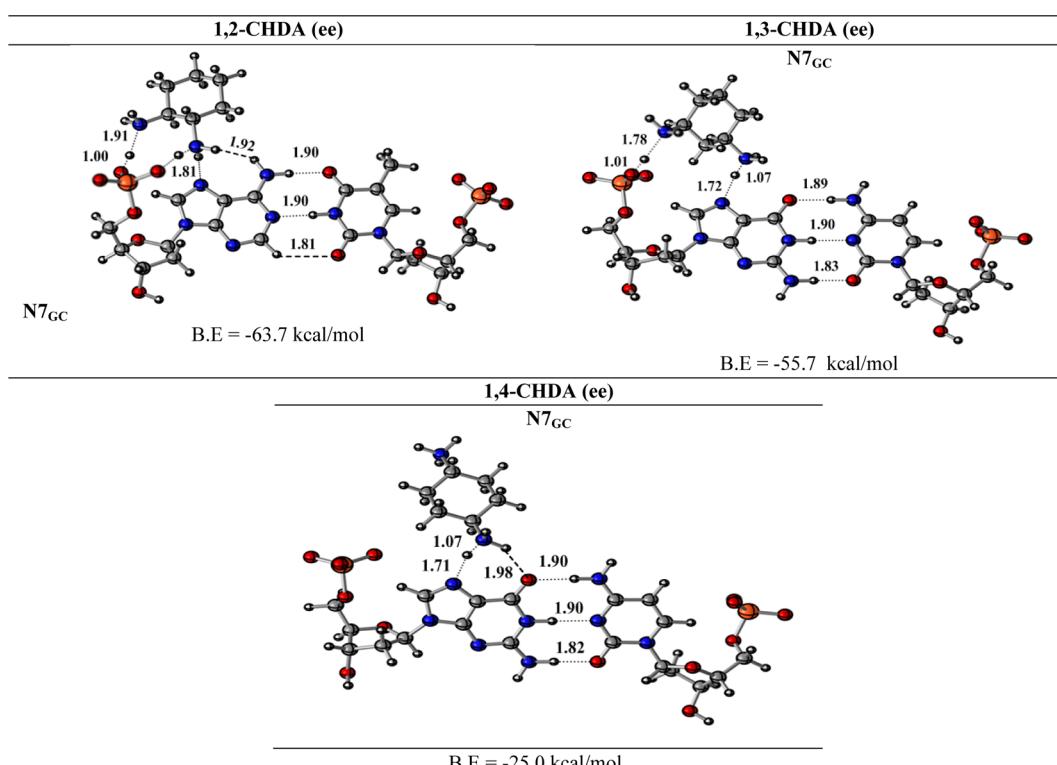
#### D. Diamine–Base Pair Interactions Studied by Theoretical IR Spectra.

In an earlier report, the interactions between calf thymus DNA and polyamine analogues were studied using the Fourier transform infrared, circular dichroism, and UV-vis methods.<sup>9</sup> Evidence for the binding and stability of analogue–DNA complexation was observed in these studies. Therefore, the calculated infrared spectral results for the interactions of the linear diamines (A) and the cyclic diprotonated diamines are provided in Table 7. In this table, we compare the spectral changes of the free GC base pair with the diamines bound to this base pair. The guanine C=O stretching frequency, symmetric stretch of the  $\text{PO}_2^-$  group, and the hydrogen-bonded stretching frequency of the ligand N—H



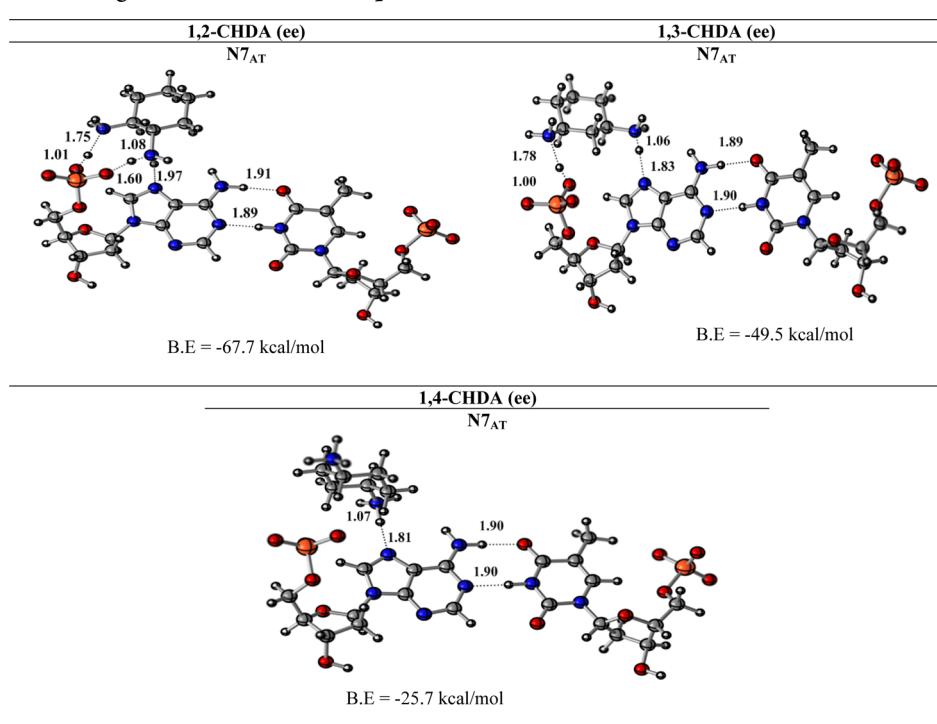
**Figure 4.** N—N distances (in angstroms) in the B3LYP/6-31G(d)-optimized geometries of the diprotonated ee-1,2, ee-1,3, and ee-1,4 isomers of CHDA.

**Table 5.** B3LYP-gCP-D3/6-31G(d)//B3LYP/6-31G(d)-Calculated Geometries of the Diprotonated ee-1,2, ee-1,3, and ee-1,4 Isomers of CHDA with the N7 and Phosphate Sites of the GC Base Pair and Their Relative Energies<sup>a</sup>



<sup>a</sup>Relative energies are in kcal/mol; distances are in angstroms.

**Table 6.** B3LYP-gCP-D3/6-31G(d)//B3LYP/6-31G(d)-Calculated Geometries of the Diprotonated ee-1,2, ee-1,3, and ee-1,4 Isomers of CHDA Interacting with the N7 and Phosphate Sites of the AT Base Pair and Their Relative Energies<sup>a</sup>



<sup>a</sup>Relative energies are in kcal/mol; distances are in angstroms.

383 hydrogen with the GC base pair during the interactions show  
384 some interesting trends in the IR data. In the case of the AT

base pair, similar stretching frequencies are also included in 385  
Table 7.  
386

**Table 7.** B3LYP/6-31G(d)-Calculated Specific IR Spectral Bands ( $\text{cm}^{-1}$ ) for Free AT and GC Base Pairs and the Base Pairs Interacting with Different Diamines in Aqueous Medium

	guanine C=O stretch	$\text{PO}_2^-$ symmetric stretch	H-bond stretch in the interaction	
			N7···H—N stretch	phosphate···H—N stretch
free GC base pair	1736.51	935.43	—	—
linear diamine GC interaction	1678.43	1075.80	2848.61	3006.46
<i>trans</i> -1,2-CBDA—GC interaction	1676.85	1074.68	2915.00	3223.96
<i>cis</i> -1,3-CBDA—GC interaction	1677.70	1073.40	3001.63	3074.41
<i>trans</i> -1,2-CPDA—GC interaction	1677.00	1073.81	3012.68	3239.54
<i>cis</i> -1,3-CPDA—GC interaction	1680.20	1068.87	2700.92	3054.08
1,2-CHDA (ee)—GC interaction	1679.94	1082.44	2968.87	3308.09
1,3-CHDA (ee)—GC interaction	1680.25	1073.86	2668.35	3039.24
1,4-CHDA (ee)—GC interaction	1677.60	932.11	2710.24	—
free AT base pair	—	936.61	—	—
1,2-CHDA (ee)—AT interaction	—	1074.70	3159.87	2600.20, 3027.75
1,3-CHDA (ee)—AT interaction	—	1086.67	2845.62	3081.91
1,4-CHDA (ee)—AT interaction	—	935.32	2772.19	—

The changes in the spectral pattern of the guanine C=O stretch from the free GC base pair confirm the interaction between the ligands and the base pair (Table 7). The  $\text{PO}_2^-$  symmetric stretch increased for the bonded GC base pairs in all cases, except for the ee-1,4 isomer of CHDA, as there is no interaction between the phosphate group and the ligand in this case (Table 5). The fact that a larger shift in the symmetric stretch of  $\text{PO}_2^-$  ( $1082.44 \text{ cm}^{-1}$ ) was observed for the ee-1,2 isomer of CHDA suggests a much better interaction with the base pair (Table 6). A shift in the N—H stretching frequencies for the N7···H—N (diamine) and phosphate···H—N (diamine) interactions with the GC base pair was also observed compared to those of the free base pair. A larger shift in the stretching frequency was observed for the phosphate···H—N (diamine) interaction of the ee-1,2 isomer of CHDA ( $3308.09 \text{ cm}^{-1}$ ), which further corroborates the much stronger interaction for this cyclic diamine. The interaction of the ee-1,4 isomer of CHDA was weaker because of the absence of any phosphate···H—N (diamine) stretching (Tables 5 and 7). In the case of the AT base pair, the strong interaction observed for the ee-1,2 isomer of CHDA correlated well with the shifts in the IR frequencies for the N7···H—N (diamine) ( $3159.87 \text{ cm}^{-1}$ ) and phosphate···H—N (diamine) (2600.20 and  $3027.75 \text{ cm}^{-1}$ ) interactions. The calculated IR results will be valuable in experimental studies examining the binding affinities of these cyclic diamines and their potential roles in the stability, aggregation, precipitation, and conformation of DNA.

Ab initio molecular dynamics calculations performed using explicit water molecules with the linear and ee-1,2-CHDA ligands and the guanine base of DNA revealed that the explicit water molecules did not influence the ionic hydrogen bonds

formed between the ligand and the base (Figures S2 and S3, Supporting Information).

## CONCLUSIONS

In this work, we have examined the binding affinities of linear and cyclic diamines with the DNA base pairs using DFT. The B3LYP-gCP-D3/6-31G(d) method predicted the better binding of linear diamine with the N7 atom and phosphate group at the major site of the GC base pair, which is in good agreement with earlier studies performed with biogenic polyamines such as spermine.<sup>32,36–39</sup> The interactions of rigid cyclic diamines with the N7 sites of the AT and GC base pairs were examined. The calculated results suggest that chiral cyclic diamines generally exhibit stronger interactions ( $\sim 3.0$ – $16.0 \text{ kcal/mol}$ ) with the DNA base pairs than the linear diamines. The cyclic rings induce a change in the hybridization of the carbon centers (i.e., the s character increases), which influences the bond polarization and results in better binding with the DNA base pairs.<sup>49–51</sup> Furthermore, the calculated results suggest that the binding affinities of ligands with the DNA base pairs can be efficient with geometric match of the binding sites of the ligands with those of the base pairs. The larger flexibility in cyclohexadiamine (CHDA) allows this protonated amine to interact much more strongly than the smaller cyclic diamines. In general, the additional  $—\text{C}=\text{O}\cdots\text{H—N—}$  hydrogen bonding interactions between the GC base pair and the cyclic diamines provides a stronger interaction with the GC base pair than with the AT base pair. The calculated IR spectral data corroborate well the binding energies calculated for such cyclic systems. The molecular dynamics simulations suggest that the strong ionic hydrogen-bonding interactions between the ligands and the base pairs of DNA are not influenced by explicit solvent molecules. This study will shed light on the design of more efficient synthetic polyamine analogues that can bind DNA more effectively.

## ASSOCIATED CONTENT

### Supporting Information

Additional information as noted in text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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