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# In Silico Studies with Substituted Adenines to Achieve Remarkable Stability of Mispairs with Thymine Nucleobase

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## **Abstract:**

DNA nucleobases are prone to undergo modification by deamination, oxidation, alkylation or hydrolysis processes because of their reactive nature. Many of these damaged DNA nucleobases are highly susceptible to mutagenesis when formed in cellular DNA and such modified nucleobases can be mispaired by a DNA polymerase during replication. The mispair formation has largely been carried out with modified uracil and guanine nucleobases. The mispair with the modified adenines are scarce in the literature. The exploration with adenine mispairs is limited due to the less number of hydrogen bonding sites and orientations of hydrogen bonding donor and acceptor in such mispairs. We have explored mispair formation between modified adenine and thymine nucleobases. The substitutions at 2-position of adenine with -NH<sub>2</sub>/-OH groups augmented the stability compared to the typical A-T base pair. Further, substituents at the remote position of adenine nucleobase also enhance the interaction energies of the mispairs. The nitrogen/oxygen-lithiated adenines showed remarkable stability for mispair with thymine base. The di-coordinated N/O-lithiated adenine and thymine mispairs were found to be stable ~12.0 kcal/mol compared to A-T base

pair. We have also studied the mispairing interaction with tetra-coordinated lithiated adenine and thymine mispair, where lithium is coordinated with two water molecules. The interaction free energies calculated with M06-2X/6-31+G(d,p) level of theory for such tetra-coordinated lithiated adenine thymine mispairs are  $\sim -30.0$  kcal/mol. The EDA analysis suggests that the electrostatic interaction energy is contributing more to the total interaction energy calculated for such mispairs. The *ab initio* molecular dynamics (ADMP) simulations show that the formation of mispairs with modified adenine is stable and the deviations in their geometries are minimal with time. This study reveals that the suitable modifications in adenine nucleobase can form very stable mispairs with the thymine nucleobase and in some cases comparable to the G-U mispairs.

**Keywords:** ADMP, AIM, EDA, DFT, DNA, Mutation, Mismatch, and Nucleobases.

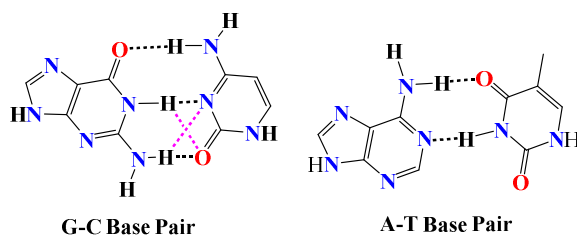
### **Introduction:**

DNA nucleobases are reactive in nature, such reactivity leads to the structural and chemical modifications with different chemical processes such as deamination, oxidation, alkylation, tautomerization or hydrolysis processes.<sup>1-2</sup> Such modifications lead to mutagenesis when modified bases formed mispair with the nucleobases in cellular DNA. These newly formed mispairs alter physical, chemical and genetic properties of DNA as well as their stability.<sup>3-7</sup> Guanine nucleobase has extensively formed mispair with the uracil, modified uracils, modified cytosines.<sup>8-14</sup> Such mispairs have shown superior mutagenic properties and achieve more stability than the natural G-C basepair. The modified uracils also forms mispair with adenine nucleobase. There are also reports on mispair formation of adenine nucleobase with modified thymines.<sup>15-16</sup> Cytosine and modified cytosines have formed mispairs either with natural nucleobases or with unnatural nucleobases.<sup>17-18</sup> DNA natural bases have also paired up with other nucleobases and leads to mispairs.<sup>17,19-21</sup> However, the mispairs with modified adenine and the thymine nucleobase is scarce in the literature.<sup>22-23</sup> Recently, the

importance of modified adenine has been demonstrated in mRNA aptamer (Riboswitch).<sup>24-25</sup>

The modified adenine molecules function as ligand molecules at the aptamer domain of riboswitch. Such riboswitches have wide range of biological applications such as gene expression and drug delivery.<sup>26-27</sup>

It has been reported that the number of hydrogen bonds between the nucleobases and the orientation of donors and acceptors for such interactions play an important role to govern the stability in DNA (Scheme 1).<sup>28</sup> The report suggests that secondary interactions are playing important role in the triply hydrogen bonded complexes. Such secondary interactions takes place in triply hydrogen bonded G-C base pair (Scheme 1). However, apart from two hydrogen bonds, additional C-H...O non-bonded interaction has been reported in A-T base pair, which is relatively much weaker than the typical H-bonds.<sup>29-33</sup> Therefore, to enhance the stability during the mispair formation; G-C would be a better choice compared to the A-T base pair.

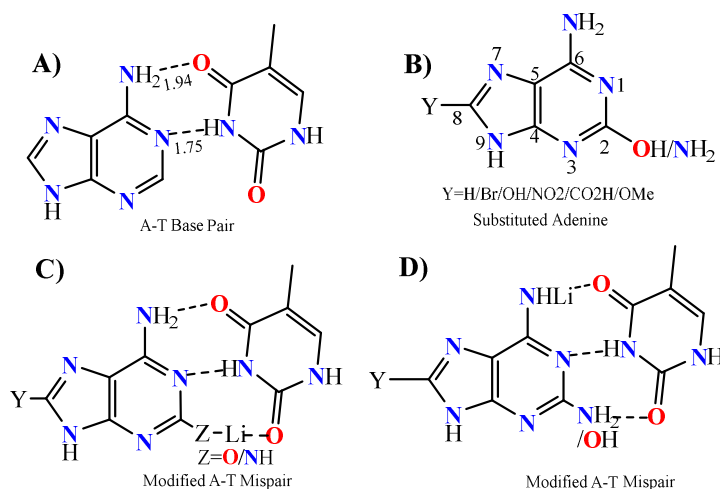


Scheme 1: Hydrogen bonding donors and acceptors orientation in A-T and G-C base pairs. G-C base pair is more stable compared to the A-T base pair due to the additional hydrogen bonding interactions and the secondary attractive interactions in G-C base pair and C-H...O interaction in A-T base pair (pink dashed line).

In this article, we have examined the mutagenesis via the mispair formation with modified adenine and thymine nucleobase. Guanine has formed variety of mispair with other modified nucleobases. The reports with modified guanines e.g. 8-oxoguanine, are also available for the mispair formation with nucleobases.<sup>34-36</sup> We have explored the mutagenesis

with modified adenine as one of the nucleobase to stabilize the typical A-T base pair. Mispairs formation at any position in cellular DNA could alter the stability, translation, replication, transcription and other properties of DNA.<sup>37-39</sup> The stability of mispairs could be achieved with different functional groups at different positions of adenine base. It is known that many DNA lesions are highly mutagenic when formed in cellular DNA, meaning they are mispaired by a DNA polymerase during replication.<sup>40</sup> Further, DNA lesions can be cytotoxic and can cause a polymerase to stall and halt DNA replication, leading to programmed cell death. To achieve higher stability with slight modification in the DNA base pairs compared to their canonical base pairs may presumably help the DNA lesions to be less cytotoxic than the other non-canonical bases. The non-canonical base pairs have also role in various processes associated with biological functions of RNAs. These non-canonical pairs govern the RNA-RNA interactions and RNA-protein, providing specific sites for drugs, antibiotics and some ions recognition processes.<sup>26-27</sup> In this regard, we have explored our study with 2-aminoadenine and thymine mispairs computationally. 2-aminoadenine is naturally found in DNA of cyanophage S-2L and can function as a modified analogue of adenine in DNA.<sup>41</sup> There is a report on 2-aminoadenine and thymine that replacement of adenine by 2-aminoadenine can modify the minor groove. The substitution of amino group in adenine enhances the stability of the Watson-Crick base pair with thymine by an additional hydrogen bond and stabilized the DNA duplexes significantly (Scheme 2).<sup>22</sup> Further, we have studied with 2-hydroxyadenine, remote position substituted adenines and lithiated adenines with thymine nucleobase to accomplish more stable mispairs (Scheme 2). The lithiated adenines showed remarkable stability as mispair compared to other substituted adenines. Various interactions in mispairs and their stability have been calculated at M06-2x/6-31+G(d,p) level of theory.<sup>42-44</sup> Atoms in Molecules (AIM) analysis, energy decomposition analysis (EDA) have also been performed to examine the nature of such interactions.<sup>45-47</sup>

Further, *ab initio* molecular dynamics calculations (ADMP) of modified adenines with thymine have also been performed.<sup>48</sup>



Scheme 2: A) The hydrogen bonding interactions in A-T base pair where the hydrogen bonding interaction distances were taken from the M06-2X/6-31+G\*\* level of theory optimized structure (Distances are given in Å). B) Structure of the 2-position and remote 8-position substituted adenine with different groups. C) Structures of the 2-position nitrogen/oxygen-lithiated adenine thymine mispairs (AOLi-T or ANHLi-T mispairs). D) Structures of the 6-position nitrogen-lithiated adenine thymine mispairs (NLiAOH-T or NLiANH<sub>2</sub>-T mispairs).

## Computational Methods:

All the structures of modified adenines and thymine have been optimized in gas phase with the M06-2X<sup>42</sup> DFT functional and 6-31+G\*\*<sup>43-44</sup> Pople basis set. The frequency calculations have been performed at the same level of theory to confirm minima of optimized geometries with no imaginary frequencies. We have chosen the M06-2X DFT functional because of extensive uses for the organic system and even for the anionic systems.<sup>49-50</sup> The interactions energy of these mispair have been calculated using the following equation

$$\Delta E_{A-B} = E_{A-B} - (E_A + E_B) \quad (1)$$

where  $E_{A-B}$  is energy of A-B mispair,  $E_A$  and  $E_B$  are energies of individual A and B base molecules, and  $\Delta E_{A-B}$  is the difference in the interaction energies. In the case of lithiated

system, we have considered lithiated adenine as fragment A and thymine as fragment B. Calculations of the free energies performed using similar equations for mispair interactions. We have also performed the basis set superposition error (BSSE) corrected energy with the Counterpoise method using the M06-2X/6-31+G\*\* level optimized structures.<sup>51</sup> The BSSE corrected (complexation) binding energies were calculated assuming that there is no structural change of monomers in complex geometry. Further, we have carried out single point calculation in the aqueous phase ( $\epsilon = 78.8$ ) using SCRF SMD solvation model with M06-2X/6-31+G\*\* level of theory using the same level of theory optimized geometries.<sup>52-53</sup> As the long-range dispersion is not considered in the M06-2X functional, we have examined the long range dispersion by using D3-zero damping parameters for M06-2X functional.<sup>54-55</sup> All calculations have been performed using the G09 package.<sup>56</sup>

AIM analysis have also been carried out with Multiwfn package using the M06-2X/6-31+G\*\* level of theory generated wave functions.<sup>57</sup>

We have performed localized molecular orbital energy decomposition analysis (LMOEDA) using the GAMESS package.<sup>58</sup> In EDA method, total interaction energy have decomposed into electrostatic energy (ES), exchange energy (EX), repulsion energy (REP), polarization energy (POL), and DFT dispersion energy (DISP).

The stability and dynamics of the mispairs are studied through *ab initio* molecular dynamics simulation, using the Atom-Centered Density Matrix Propagation (ADMP) as implemented in the Gaussian 09 program package.<sup>48</sup> The simulations are performed at B3LYP/6-31G level of theory using the M062X/6-31+G(d,p) level of theory optimized geometries. Simulation has been performed at room temperatures (298 K) to examine the dynamical nature of the mispairs as well as their structural behaviours on 300 fs time scale. In all cases, simulation has been performed by keeping the fictitious electronic mass at 0.1 amu.

## Results and Discussion:

**Non-lithiated modified adenine and thymine mispairs:**

Mutation, achieved by the mispair formation, may or may not produce recognizable changes in observable properties of the cellular DNA or various organisms, but it plays important roles in long term biological processes such as evolution, cancer and development of immune system.<sup>59-61</sup> However, report reveals that the incorrect evaluation of the mispair can cause abnormal behaviours which has been studied by Monte Carlo simulations.<sup>62</sup> We have examined mispairs formation between modified adenines and the thymine nucleobase in the present study. One of the reports with 2-aminoadenine demonstrated stable mispair with thymine compared to the typical A-T base pair.<sup>22</sup> Such studies are limited in the literature towards the modified adenine and the thymine nucleobase.

**Geometries and energetics:**

We have examined the stability of 2-aminoadenine and thymine mispairs (ANH<sub>2</sub>-T) computationally. The free energy of interaction of A-T base pair calculated at the M062X/6-31+G\*\* level of theory is -3.3 kcal/mol, whereas the free energy of interaction of the ANH<sub>2</sub>-T mispair is -5.3 kcal/mol, which corroborates the results observed experimentally with such mispair.<sup>22</sup> We have further replaced the -NH<sub>2</sub> group at 2-position of adenine base with OH group. The calculations have been performed at the same level of theory with the modified adenine and thymine. The calculated free energy for this mispair is -7.0 kcal/mol, which is much higher than the ANH<sub>2</sub>-T mispair. The enhancement in the structural features and the reactivity pattern through remote substitution is always fascinating to the researchers as such changes in the systems perturb the reactive sites least.

To improve the A-T base pair stability, we have extended our model study with the electron withdrawing and electron donating substituents at remote position of the 2-hydroxy/amino-adenine (8<sup>th</sup>-position) (Scheme 2 and Figure 1). The calculated results reveal some interesting trends with such substitutions on the adenine unit. It has been observed that

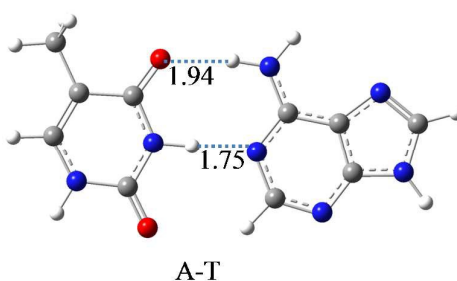


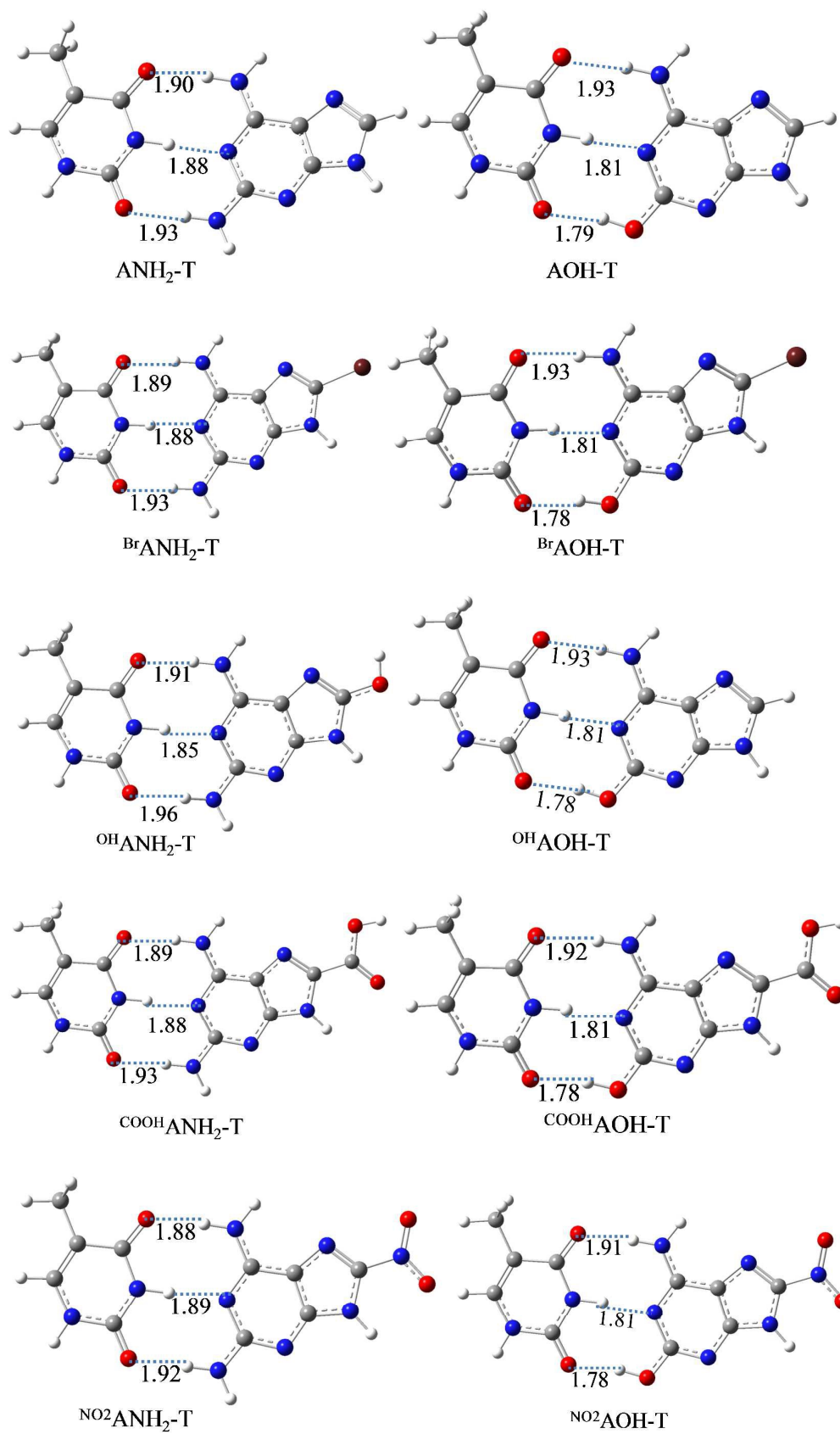
the mispairs with strong electron withdrawing groups at 8-position of adenine have shown greater stability compared to the cases, where such substitutions are absent. The free energy calculated for  $^{\text{NO}_2}\text{ANH}_2\text{-T}$  is -7.7 kcal/mol and for  $^{\text{OH}}\text{ANH}_2\text{-T}$  is -8.4 kcal/mol, respectively (Figure 1 and Table 1). We have not observed any significant change in the stability of the mispairs with Br, OH, COOH or OMe substituents. The M062X/6-31+G\*\* level of theory calculated free energy of the interactions is -7.9 kcal/mol for  $^{\text{Br}}\text{AOH-T}$ , -7.7 kcal/mol for  $^{\text{OH}}\text{AOH-T}$  and -7.7 kcal/mol for  $^{\text{OMe}}\text{AOH-T}$  mispair (Table 1). Similarly, free energy of interaction for  $^{\text{Br}}\text{ANH}_2\text{-T}$  is -5.4 kcal/mol and for  $^{\text{COOH}}\text{ANH}_2\text{-T}$  is -5.8 kcal/mol (Table 1). We have also performed the basis set superposition error (BSSE) corrected energy with the Counterpoise method using the M06-2X/6-31+G\*\* level optimized structures (Table 1). We have carried out the long range dispersion by using D3-zero damping parameters for M06-2X functional with representative systems (A-T,  $\text{ANH}_2\text{-T}$ , AOH-T, ANHLi-T, AOLi-T, ANHLi-T-2W, AOLi-T-2W, AOLi-T-2W-COOH, and AOLi-T-2W-NO<sub>2</sub>). The dispersion corrected M06-2X-D3 binding energies, free energies are somewhat higher compared to the uncorrected M06-2X binding enthalpies however, and the trend is similar for these studied systems (Supporting Info Table S1). The optimized geometries with M06-2X/6-31+G\*\* level of theory suggests that the H-bonding interactions in the  $^{\text{X}}\text{AOH-T}$  is stronger than the  $^{\text{X}}\text{ANH}_2\text{-T}$  (Figure 1). The N---H-N H-bonding in  $^{\text{X}}\text{AOH-T}$  (~1.81 Å) is much shorter compared to the N-H---N H-bonding (~1.88 Å) in  $^{\text{X}}\text{ANH}_2\text{-T}$  mispair and O---H-O H-bonding (~1.78 Å) is shorter than the O---H-N (~1.93 Å) H-bonding. It has been observed that the substituent at the remote position have not appreciably changed the hydrogen bonding distances. To understand the effect of substituent on the electronic energies, free energies and stability of the mispair, we have further performed topological analysis with the studied systems.

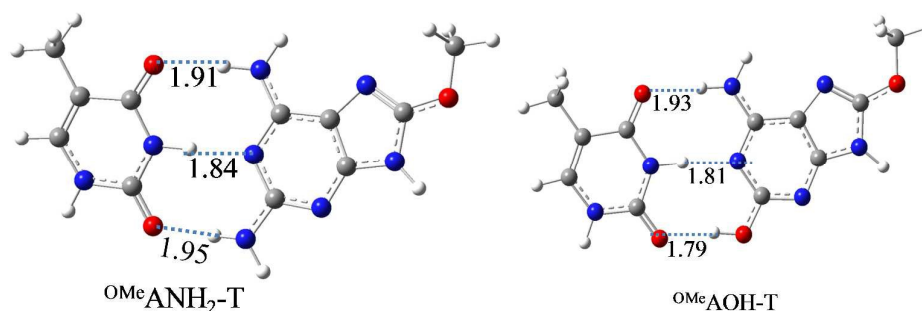
Such modified adenine nucleobase can also enhance the stability with the uracil nucleobase in DNA duplex as a replacement of thymine.<sup>14-15</sup> The calculated interaction free energy has been found to be ~3.0 kcal/mol for AOH-U compared to the typical A-T base pair (Table 1).

Table 1: Energy Values Calculated Using M062X/6-31+G\*\* Level of Theory. Energy values are given in kcal/mol.

Name	$\Delta E$	$\Delta G$	$\Delta E_{\text{BSSE}}$	$\Delta E_{\text{BSSE}}$ (Complexation)	$\Delta E_{\text{SMD}}$
A-T	-16.4	-3.3	-15.6	-15.8	-8.4
A-U	-15.1	-2.3	-14.3	-15.98	-6.7
ANH <sub>2</sub> -T	-19.3	-5.3	-18.4	-18.7	-10.0
ANH <sub>2</sub> -U	-17.8	-4.1	-16.9	-18.66	-8.4
AOH-T	-20.3	-7.0	-19.2	-20.4	-11.6
AOH-U	-18.7	-5.7	-17.6	-20.21	-9.8
<sup>Br</sup> ANH <sub>2</sub> -T	-19.5	-5.4	-18.4	-18.8	-10.2
<sup>OH</sup> ANH <sub>2</sub> -T	-19.0	-6.8	-18.1	-18.5	-9.8
<sup>COOH</sup> ANH <sub>2</sub> -T	-19.6	-5.8	-18.7	-18.9	-10.2
<sup>NO<sub>2</sub></sup> ANH <sub>2</sub> -T	-19.9	-7.7	-19.0	-19.2	-10.3
<sup>OMe</sup> ANH <sub>2</sub> -T	-19.1	-6.5	-18.2	-18.5	-9.8
<sup>Br</sup> AOH-T	-20.5	-7.9	-19.3	-20.5	-11.7
<sup>OH</sup> AOH-T	-20.1	-7.7	-19.0	-20.2	-11.6
<sup>COOH</sup> AOH-T	-20.6	-8.0	-19.5	-20.7	-11.7
<sup>NO<sub>2</sub></sup> AOH-T	-21.0	-8.4	-19.9	-21.0	-11.7
<sup>OMe</sup> AOH-T	-20.1	-7.7	-19.0	-20.2	-11.4







**Figure 1:** Hydrogen bonding interactions of  $^X\text{ANH}_2\text{-T}$  and  $^X\text{AOH-T}$  mispairs are represented in the above figure (Grey: C; blue: N; white: H; red: O; brown: Br). All geometries have been optimized with M06-2X/6-31+G\*\* level of theory. The interaction distances are given in Å.

### Topological Analysis:

We have also performed the AIM analysis to verify the strength of H-bond between these mispairs.<sup>45-46</sup> We have measured the electron density,  $\rho(r_c)$ , Laplacian of electron density  $\nabla^2\rho(r_c)$ , densities of kinetic energy,  $G(r_c)$ , and potential energy,  $V(r_c)$ , at the bond critical point. The  $|V(r_c)/G(r_c)|$  value indicates the nature and type of the noncovalent interactions, when the value of  $|V(r_c)/G(r_c)| < 1$ , then the interaction is closed shell type, when the value of  $|V(r_c)/G(r_c)| > 2$  shared type of interactions are observed and intermediate type of interactions (which are partially covalent and electrostatic in nature) are observed with  $1 < |V(r_c)/G(r_c)| < 2$ .<sup>46</sup> The hydrogen bond strength at bond critical point has been calculated with Espinosa–Molins–Lecomte (EML) formula (Half of the  $V(r_c)$  i.e.  $E_{HB}=0.5*V(r_c)$  ).<sup>63-65</sup> We have also calculated hydrogen bond energy of individual hydrogen bonds using Nikolaienko–Bulavin–Hovorun<sup>66-67</sup> (Eq-3) and Iogansen's<sup>68</sup> (Eq-2) formula.

$$E_{HB} = 0.33 * \sqrt{\Delta v - 40} \dots\dots\dots 2$$

$$E_{HB} = -2.03 + 225 * \rho \dots\dots\dots 3$$

The computed hydrogen bond strengths using these methods are slightly lower than the H-bond strengths calculated with Espinosa–Molins–Lecomte (EML) formula, however, the trend of H-bond strengths is similar in all cases (Table S4).

**Table 2:** Topological analysis of noncovalent hydrogen bonding interactions calculated using the M06-2X/6-31+G\*\* level of theory obtained wave function.

Name	Bonds	rho	lap of rho	V(r)/G(r)	H-bonding Strength (kcal/mol)
A-T	N---H-N	0.0474	0.1040	1.134	10.68
	N-H---O	0.0247	0.0768	1.006	6.10
	C-H---O	0.0062	0.0230	0.811	1.23
ANH <sub>2</sub> -T	N---H-N	0.0352	0.0815	1.062	7.23
	N-H---O(CH <sub>3</sub> )	0.0272	0.0882	0.990	6.79
	N-H---O	0.0250	0.0805	0.997	6.28
AOH-T	N---H-N	0.0416	0.0934	1.096	8.89
	N-H---O(CH <sub>3</sub> )	0.0258	0.0806	1.006	6.40
	O-H---O	0.0334	0.1118	0.955	8.01
<sup>NO2</sup> ANH <sub>2</sub> -T	N---H-N	0.0341	0.0816	1.050	7.08
	N-H---O(CH <sub>3</sub> )	0.0278	0.0894	0.990	6.86
	N-H---O	0.0253	0.0813	0.996	6.33
<sup>NO2</sup> AOH-T	N---H-N	0.0404	0.0942	1.081	8.69
	N-H---O(CH <sub>3</sub> )	0.0264	0.0819	1.005	6.49
	O-H---O	0.0343	0.1140	0.956	8.20

AIM results show that the N---H-N H-bond in the mispairs have higher  $|V(r_c)/G(r_c)|$  values ( $\sim 1.096-1.057$ ) compared to the N-H---O/O-H---O H-bond interactions. The  $|V(r_c)/G(r_c)|$  values and the hydrogen bond strength ( $1/2*V(r_c)$ ) indicate that the N---H-N interactions are stronger than the O-H---O noncovalent interactions in <sup>X</sup>AOH-T mispairs. We have observed that the N-H---O(CH<sub>3</sub>) interactions are stronger compared to the N-H---O H-bond interactions in ANH<sub>2</sub>-T mispairs. The N-H---O(CH<sub>3</sub>) hydrogen bonding interaction distance is 1.90 and the N-H---O hydrogen bonding interaction distance is 1.93 (Figure 1 and 2). The H-bond strength calculations also reveal that N-H---O(CH<sub>3</sub>) is more stronger compare to the N-H---O. The hydrogen bond strength is 6.79 for N-H---O(CH<sub>3</sub>) and 6.28 for the N-H---O hydrogen bond (Table 2 and Table S5). We have also observed similar trends for the other remote position substituted mispairs (Table 2 and Table S5). The cumulative hydrogen bond strengths calculated for each mispairs are in good agreement with the binding energies calculated for such mispair systems and the H-bond strength is also reflected in the stability of the studied mispairs (Table 1 and 2).

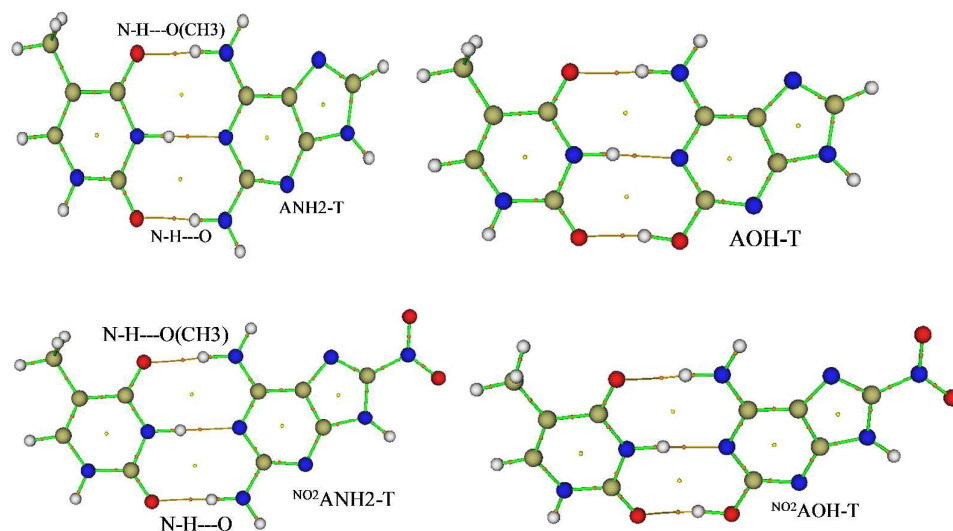


Figure 2: The molecular graph generated for the mispairs by the Multiwfn package where the orange points are the bond critical points.

### Energy Decomposition Analysis:

Localized Molecular Orbital Energy Decomposition Analysis (LMOEDA) has been employed to extend our study to decompose the H-bond interaction energies in electrostatic energy (ES), exchange energy (EX), repulsion energy (REP), polarization energy (POL), and DFT dispersion energy (DISP).<sup>47</sup> EDA is a useful method to segregate the interaction energies in non-covalent interactions. EDA analysis has been performed for representative systems. The calculated decomposition energies suggest that the electrostatic, exchange, polarization and DFT dispersion energies contribute to the hydrogen bond interaction energies in these mispairs (Table 3). The EDA analysis reveals that the contribution of electrostatic energy in the H-bonding interactions is predominant in these cases.

Table 3: Decomposition of Total Interaction Energy of various Mispairs Calculated by LMOEDA Method at M06-2X/6-31+G\*\* Level of Theory

Name of the pair	Electrostatic energy	Exchange energy	Repulsion energy	Polarization energy	DFT dispersion energy	Total interaction energy
A-T	-28.63	-21.39	61.89	-14.59	-12.85	-15.58

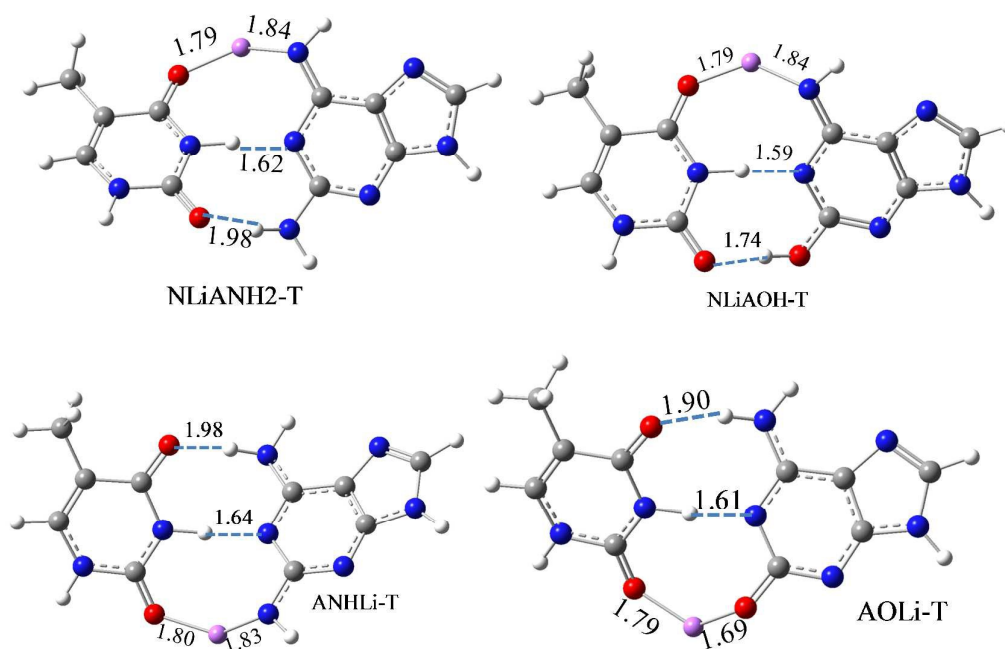
ANH <sub>2</sub> -T	-33.03	-22.80	66.58	-14.38	-15.05	-18.69
AOH-T	-45.18	-38.30	105.26	-26.96	-17.37	-22.55
<sup>Br</sup> AOH-T	-37.70	-26.88	78.52	-17.99	-16.46	-20.51
<sup>COOH</sup> ANH <sub>2</sub> -T	-33.14	-22.51	65.99	-14.24	-15.03	-18.93
<sup>COOH</sup> AOH-T	-37.76	-26.77	78.29	-17.96	-16.46	-20.66
<sup>NO<sub>2</sub></sup> AOH-T	-37.90	-26.44	77.67	-17.89	-16.46	-21.01
<sup>OH</sup> ANH <sub>2</sub> -T	-33.14	-23.40	68.08	-14.79	-15.29	-18.54
<sup>OMe</sup> ANH <sub>2</sub> -T	-34.66	-25.10	73.10	-15.43	-15.81	-17.89

### Lithiated modified adenine and thymine mispairs:

We have observed that electropositive lithium can assist to achieve stability in G-U mispairs through its multi-coordination property.<sup>11</sup> We have explored the influence of lithiation on the stability of adenine modified nucleobase with the thymine (Figure 3). Lithium is found in all organs and tissues in mammalian family. Lithium has been found to be uniformly distributed in body water, absorbed from the intestinal tract and excreted through the kidneys.<sup>69</sup> It has been reported that lithium is a non-toxic element.<sup>69</sup> However, few reports have recommended that low lithium intake can cause behavioural defects. Manic depression and other neurological and psychiatric disorders have been successfully treated with the lithium salts.<sup>70</sup>

### Geometries and energetics:

We have substituted the -NH<sub>2</sub> or -OH group of the modified adenine unit with the lithium atom to examine the strength of the mispairs (Scheme 2). The lithiation of -OH and -NH<sub>2</sub> groups is possible synthetically.<sup>71-72</sup> The lithiated adenine nucleobase with thymine unit forms very strong interaction compared to the non-lithiated mispairs (Table 4). Optimized geometries have shown that the mispairs are non-planar with respect to each other (Figure 3). The interaction free energy is almost



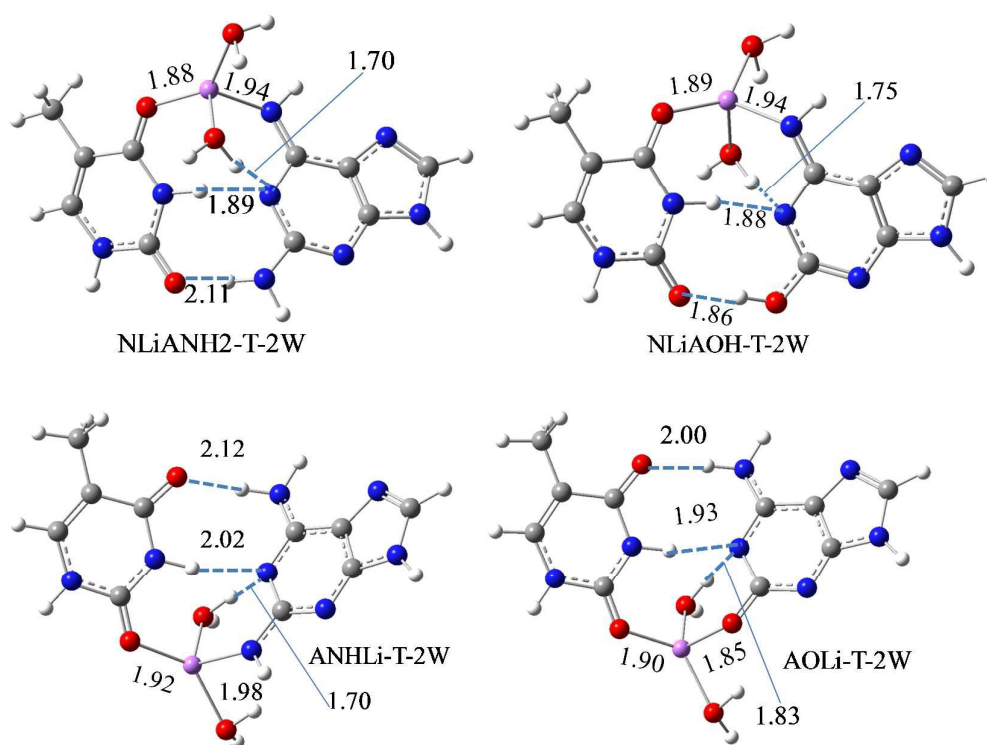
**Figure 3:** The M06-2X/6-31+G\*\* level of theory optimized geometries and hydrogen bonding interactions of di-coordinated lithiated adenine thymine mispairs are represented in the above figure (Grey: C; blue: N; white: H; red: O; brown: Br; violet: Li). The interaction distances are given in Å.

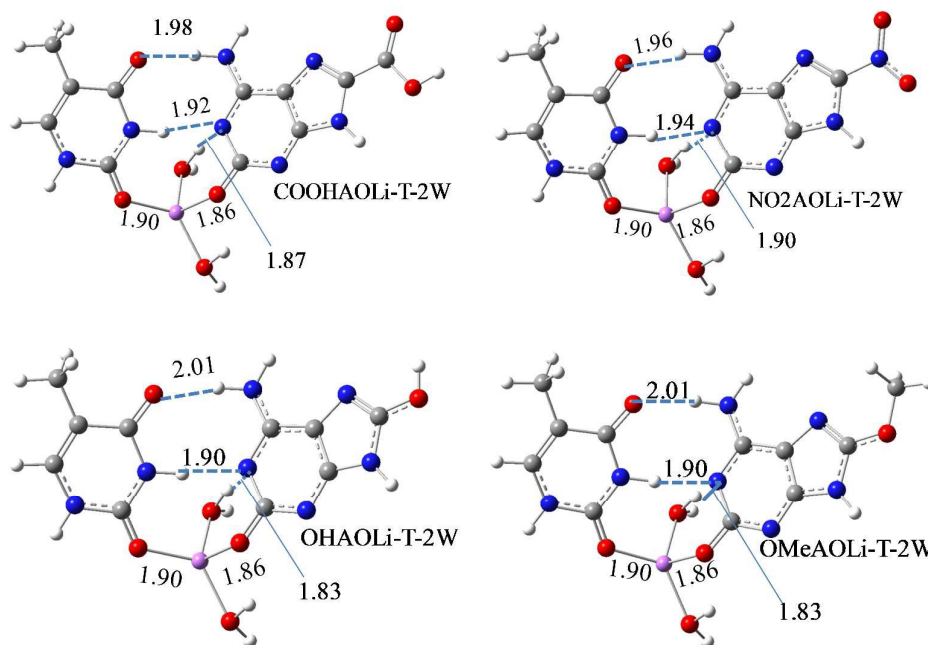
doubled for the AOLi-T mispairs (-16.4 kcal/mol) compared to the corresponding non-lithiated AOH-T (-7.0 kcal/mol) mispair (Table 1 and 4). The interaction free energies have been enhanced because of the strong lithium and oxygen/nitrogen coordination bond. Strong hydrogen bonding interaction (N-H---N  $\sim$ 1.60 Å) in lithiated mispairs also improves noncovalent interactions. Interestingly, the lithiated adenine further would help to lower the deprotonation of the C6-amino hydrogens compared to the non-lithiated adenine unit (Scheme 2 & Table S4). This finding would lower any tautomerization property for the lithiated adenine compared to the non-lithiated one while forming the mispair with thymine.

Lithium prefers to be tetra-coordinated compared to the di-coordinated situation; hence we have examined the tetra-coordination of lithium with water molecules in such mispairs.<sup>70</sup> We have seen significant enhancement in the interaction free energies of the water



coordinated lithiated adenine mispairs (Table 4). All optimized geometries prefer the mispairs to achieve more planarity with the tetra-coordinated lithium in these cases (Figure 4). AOLI-T-2W mispair exhibits strong interaction free energy (-30.3 kcal/mol) compared to the other studied mispairs. The coordinated water molecules with the lithium atom also participated for the hydrogen bonding interactions with the hetero-atom of mispairs (Figure 4). Such interactions have also augmented the stabilization of such lithiated mispairs. The interaction was further enhanced with the remote substituent effect at 8<sup>th</sup> position of adenine nucleobase with thymine in AOLI-T-2W mispair (Table 4). The interaction energies calculated in aqueous phase using SMD solvation model are in good agreement with the gas phase results and trends are also similar in both cases. The solvation free energies calculated for some representative mispairs such as ANH2-T and AOH-T showed their larger preference for formation compared to the A-T base pair (Table S2).





**Figure 4:** The M06-2X/6-31+G\*\* level of theory optimized geometries and hydrogen bonding interactions of tetra-coordinated lithiated adenine thymine mispairs are represented in the above figure (Grey: C; blue: N; white: H; red: O; brown: Br; violet: Li). The interaction distances are given in Å.

Table 4: Energy Values Calculated Using M062X/6-31+G\*\* Level of Theory. Energy values are given in kcal/mol.

Name	$\Delta E$	$\Delta G$	$\Delta E_{\text{BSSE}}$	$\Delta E_{\text{BSSE}}$ (Complexation)	$\Delta E_{\text{SMD}}$
NLiANH <sub>2</sub> -T	-26.7	-14.0	-24.8	-45.1	-16.6
NLiANH <sub>2</sub> -2W	-63.6	-26.6	-58.5	-78.2	-38.1
NLiAOH	-27.5	-16.1	-25.5	-49.8	-17.2
NLiAOH-2W	-63.7	-28.1	-59.1	-77.2	-38.4
ANHLi-T	-25.1	-13.0	-23.1	-43.1	-15.1
ANHLi-T-2W	-60.7	-24.9	-55.8	-76.2	-35.2
AoLi-T	-28.6	-16.4	-26.5	-47.6	-15.8
AoLi-T-2W	-66.0	-30.3	-61.0	-79.5	-36.5
AoLi-T-2W-COOH	-64.9	-29.0	-59.9	-79.4	-35.9
AoLi-T-2W-NO <sub>2</sub>	-67.0	-30.0	-62.0	-78.9	-36.7
AoLi-T-2W-OH	-66.1	-31.2	-61.0	-79.8	-36.8
AoLi-T-2W-OMe	-66.1	-30.2	-61.0	-80.0	-36.6

### Topological Analysis:

AIM analysis for the di-coordinated lithiated mispairs show that the N---H-N interaction exhibit higher  $|V(r_c)/G(r_c)|$  ratio ( $\sim 1.40$ ) and hydrogen bond strength ( $\sim 15-18$ ) compared to the N---H-N hydrogen bond interaction in non-lithiated mispairs (Table-XX). The  $|V(r_c)/G(r_c)|$  ratio for the N---H-N interaction is  $\sim 1.06$ . The  $|V(r_c)/G(r_c)|$  ratio for N-Li-O coordination bonds are lower than 1, which implies that interactions are closed shell type. But the bond strength calculations for Li-O/Li-N bonds indicate the strong coordination between lithium and oxygen/nitrogen atoms (Table 5 and Table S5). Energy decomposition analysis has also been performed to analyze the nature of interaction in these cases.

**Table 5:** Topological analysis of noncovalent hydrogen bonding interactions calculated using the M06-2X/6-31+G\*\* level of theory obtained wave function.<sup>a</sup>

Name	Bonds	rho	lap of rho	$V(r)/G(r)$	H-bonding Strength (kcal/mol)
NLiAOH-T-2W	N---H-N	0.0349	0.0841	1.066	7.52
	O-H---O	0.0280	0.0918	0.974	6.84
	NLi-O	0.0317	0.2315	0.763	11.19
	N---OH(W)	0.0450	0.1083	1.117	10.75
	(W)O-H---O(W)	0.0203	0.0738	0.989	5.67
NLiAOH-T	N---H-N	0.0712	0.0872	1.460	18.47
	O-H---O	0.0378	0.1228	0.977	9.20
	NLi-O	0.0422	0.3310	0.787	16.86
NLiANH <sub>2</sub> -T-2W	N---H-N	0.0339	0.0817	1.063	7.27
	N-H---O	0.0181	0.0566	1.018	4.60
	NLi-O	0.0320	0.2353	0.761	11.35
	(A)N---OH(W)	0.0519	0.1125	1.185	12.83
	(W)O-H---O(W)	0.0210	0.0750	0.997	5.85
NLiANH <sub>2</sub> -T	N---H-N	0.0661	0.0933	1.384	16.46
	N-H---O	0.0235	0.0723	1.032	6.04
	NLi-O	0.0416	0.3223	0.788	16.45

<sup>a</sup>: W in parenthesis indicates that the corresponding group/atom participates from the water molecule and A indicates adenine unit.

### Energy Decomposition Analysis:

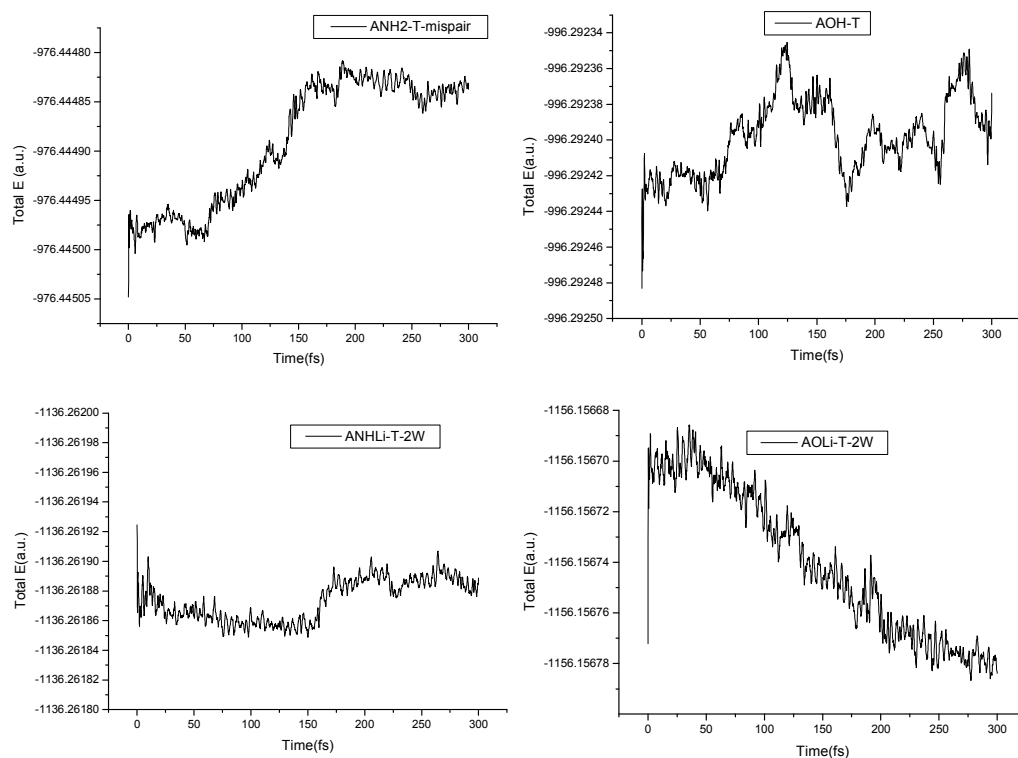
The EDA analysis revealed that the contribution of electrostatic energy for the lithiated mispairs is considerably higher than the non-lithiated species (Table 3 and 4). Electrostatic energy has been found to be the major contribution towards the total interaction energy than DFT dispersion energy, polarization energy and exchange energy.

Table 6: Decomposition of Total Interaction Energy of various Mispairs Calculated by LMOEDA Method at M06-2X/6-31+G\*\* Level of Theory

Name of the pair	Electrostatic energy	Exchange energy	Repulsion energy	Polarization energy	DFT dispersion energy	Total interaction energy
AOLi-T	-67.40	-39.41	115.78	-37.43	-19.11	-47.57
AOLi-T2W	-115.38	-56.08	168.96	-36.66	-40.36	-79.53
AOLi-T2W-COOH	-113.28	-53.14	161.94	-35.10	-39.69	-79.28
AOLi-T2W-OH	-115.59	-56.12	169.02	-36.9	-40.11	-79.71
AOLi-T2W-OMe	-116.10	-56.88	170.78	-37.39	-40.29	-79.89

### Dynamics and stability of the mispairs:

Atom-Centered density matrix propagation (ADMP) theory has been discussed that implies initial applications of an extended Lagrangian molecular dynamics method that employs atom-centered Gaussian basis functions and one-particle density matrix propagation.<sup>48</sup> This *ab initio* molecular dynamics method has been used to examine the stability and dynamics of many chemical systems.<sup>73-74</sup> The dynamical features of these mispairs have been studied with (ADMP) technique using B3LYP/6-31G level of theory. The M062X/6-31+G(d,p) level of theory optimized geometries of mispairs were considered as initial guess for ADMP simulations. We have carried out the simulations at room temperatures (298 K) to see the dynamical behaviour of the mispairs as well as the structural changes and their stability. We have performed the *ab initio* molecular dynamics simulation for some representative systems (ANH<sub>2</sub>-T, AOH-T, ANHLi-T-2W and AOLi-T-2W). The total energy plots obtained for the ADMP simulations reveal that the mispairs are stable with time (Figure 5). The energy variations were found to be minimal in all cases and the maximum deviations observed for ANH<sub>2</sub>-T mispair (0.2 kcal/mol) and the minimum deviation for ANHLi-T-2W (0.04 kcal/mol). The water coordinated lithium atom in ANHLi-T-2W and AOLi-T-2W mispairs help to stabilize the mispairs more compared to the ANH<sub>2</sub>-T and AOH-T mispairs.



**Figure 5:** Variation of the total with time during the *ab initio* molecular dynamics simulation (ADMP) for ANH<sub>2</sub>-T, AOH-T, ANHLi-T-2W and AOLi-T-2W mispairs, respectively.

A representative structural analysis of ANH<sub>2</sub>-T mispair is given in figure 6. The mispairs remain hydrogen bonded with each other with the variation of time. Similar trajectories were also obtained for the other mispairs studied here (Supporting Information, Figure S1-3).

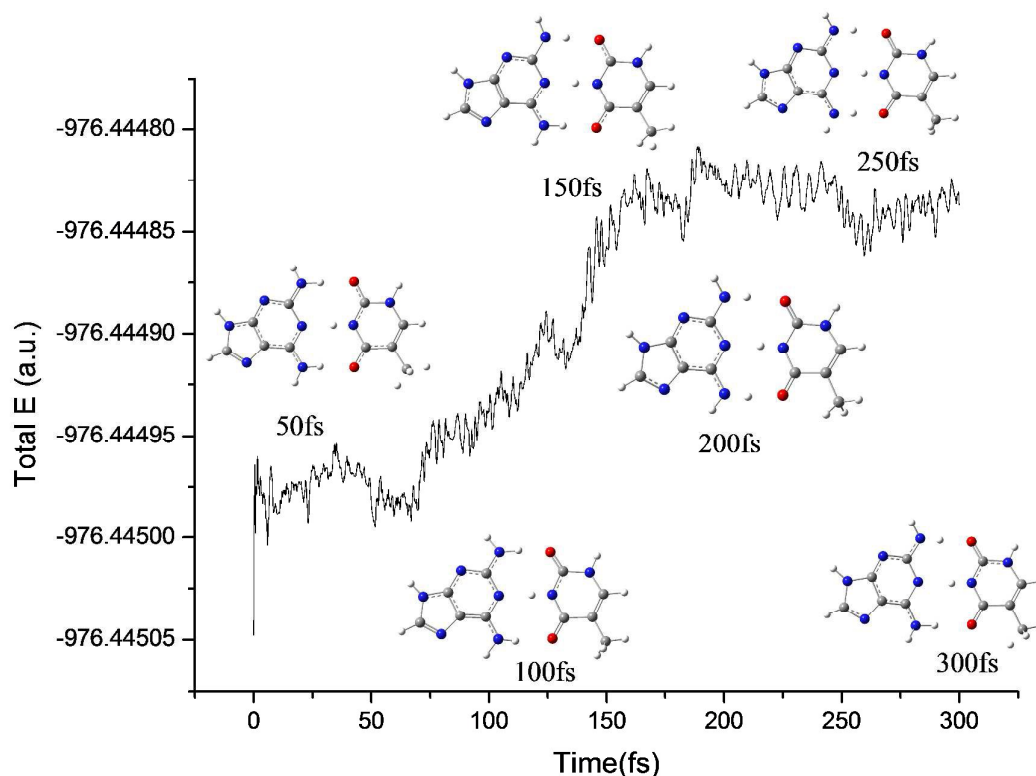


Figure 6: Trajectory analysis for the ANH<sub>2</sub>-T mispair. We have represented 50fs, 100fs, 150fs, 200fs, 250fs, and 300fs geometries in this figure.

### Conclusion:

In this work, we have examined mispairs formation with the modified adenine and thymine bases. The studies on mispair formation with the A-T are rare in the literature.<sup>14-15</sup> The stability of mispairs is primarily governed by the hydrogen bonding interactions between nucleobases. The number of hydrogen bonds between the nucleobases and the orientations of donors and acceptors for such interactions play an important role to govern the stability in DNA base pairs.<sup>22</sup> A-T base pair possesses only two hydrogen bonds, whereas, G-C base pair has three hydrogen bonds. Therefore, the studies mainly aimed to enhance the stability of mispairs using G-C compared to the A-T base pair.

We have examined the mispair formation between modified adenine with the substitutions at (2-position and the remote 8-position) and thymine nucleobase. The DFT

calculated results showed remarkable enhancement in the stability of these mispairs compared to the typical A-T base pair. The observed enhancement of mispair interaction free energies are 2.0 kcal/mol for ANH<sub>2</sub>-T and 3.7 kcal/mol for AOH-T mispair, respectively compared to A-T base pair. The substituents placed at remote position can further augment the interaction energies. The NO<sub>2</sub>AOH-T mispair stabilized by 5.8 kcal/mol than that of A-T base pair. The adenine base modified with N-lithiation or O-lithiation enhanced the interaction with thymine base significantly. AOLi-T mispair is stable by 13.1 kcal/mol than A-T base pair. The interaction energies seem to increase considerably with the coordination of water molecules with lithiated adenine thymine mispair AOLi-T-2W. The free energy of interaction in this case is -30.3 kcal/mol. The EDA analysis shows that the electrostatic interaction energies are contributing more to stabilize the mispairs than dispersion, polarization and exchange energies.

The *ab initio* molecular dynamics (ADMP) performed with these mispairs showed that the interaction between the nucleobases are strong and stable with time. ADMP results show no deviations in the energies within 300 fs time scale corroborates the results obtained with DFT calculations. These results suggest that the appropriate modifications in adenine base can lead to the stable mispair formation with thymine base, which could be comparable to the G-U mispairs.<sup>11, 75</sup> Such modified adenine nucleobase can also stabilize the mispairs with uracils as replacement of thymine. This study can guide to prepare mispairs using adenine bases as one of the nucleobase to achieve the stability, which otherwise being carried out with guanine or uracil nucleobases. 2-aminoadenine is one such example that is found naturally in DNA of cyanophage S-2L and can function as a modified analogue of adenine in vivo to enhance the stability of DNA base pairs.

**Associated Content:**

Supporting Information

SI contains M06-2X/6-31+G\*\* level of theory optimized Cartesian coordinates of all these mispairs and the M06-2X-D3 level of theory calculated energies and free energies for representative system. The ADMP trajectory analysed figures have also been given in SI. This information is available free of charge via the Internet at

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### References:

- 1) J. Cadet, T. Douki, and J. Ravanat, *Free Radical Biol. Med.*, 2010, 49, 9–21.
- 2) a) Gates, K. S. *Chem. Res. Toxicol.* 2009, **22**, 1747–1760. b) A. Furmanchuk, O. Isayev, L. Gorb, O. V. Shishkin, D. M. Hovorun and J. Leszczynski, *Phys. Chem. Chem. Phys.*, 2011, **13**, 4311–4317. c) S. P. Samijlenko, Y. P. Yurenko, A. V. Stepanyugin and D. M. Hovorun, *J. Phys. Chem. B*, 2012, **114**, 1454–1461. d) O. O. Brovarets and D. M. Hovorun, *Biopolym. Cell*, 2010, **26**, 295–298. e) O. O. Brovarets and D. M. Hovorun, *Biopolym. Cell*, 2010, **26**, 72–76.
- 3) M. D. Bick, and R. L. Davidson, *Proc. Natl. Acad. Sci. USA*, 1974, **71**, 2082-2086.
- 4) T. Brown, G. Kneale, W. N. Hunter, and O. Kennard, *Nucl. Acids Res.*, 1986, **14**, 1801-1809.
- 5) E. R. Kaufman, and R. L. Davidson, *Proc. Natl. Acad. Sci. USA*, 1978, **75**, 4982-4986.
- 6) R. M. Litman, and A. B. Pardee, *Nature*, 1956, **178**, 529-531.
- 7) S. Y. Lin, and A. D. Riggs, *Proc. Natl. Acad. Sci. USA*, 1972, **69**, 2574-2576.
- 8) B. T. Hill, A. Tsuboi, and R. Baserga, *Proc. Natl. Acad. Sci. USA*, 1974, **71**, 455-459.
- 9) C. Heidleberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzler, E. Plevan, and J. Scheiner, *Nature (London)*, 1957, **179**, 663-666.



- 10) J. A. Theruvathu, C. H. Kim, A. J. W. Darwanto, Neidigh, and L. C. Sowers, *Biochemistry*, 2009, **48**, 11312-11318.
- 11) K. Jana, and B. Ganguly, *J. Phys. Chem. A*, 2014, **118**, 9753-9761.
- 12) C. J. LaFrancois, Y. H. Jang, T. Cagin, W. A. Goddard, and L. C. Sowers *Chem. Res. Toxicol.*, 2000, **13**, 462-470.
- 13) J. Sponer, P. Jurecka, and P. Hobza, *J. Am. Chem. Soc.* 2004, **126**, 10142-10151.
- 14) A. Perez, J. Sponer, P. Jurecka, P. Hobza, F. J. Luque, and M. Orozco, *Chem. Eur. J.*, 2005, **11**, 5062-5066.
- 15) J. A. Theruvathu, C. H. Kim, D. K. Rogstad, J. W. Neidigh, and L. C. Sowers, *Biochemistry*, 2009, **48**, 7539-7546.
- 16) P. Liu, A. Burdzy, and L. C. Sowers, *Chem. Res. Toxicol.*, 2002, **15**, 1001-1009
- 17) G. Rossetti, P. D. Dans, I. Gomez-Pinto, I. Ivani, C. Gonzalez and M. Orozco, *Nucl. Acids Res.*, 2015, **43**, 4309-4321.
- 18) O. O. Brovarets, and D. M. Hovorun, *J. Comput. Chem.*, 2014, **35**, 451-466.
- 19) O. O. Brovarets, and D. M. Hovorun, *Phys. Chem. Chem. Phys.*, 2014, **16**, 15886-15899.
- 20) O. O. Brovarets, and D. M. Hovorun, *Phys. Chem. Chem. Phys.*, 2013, **15**, 20091-20104.
- 21) O. O. Brovarets, R. O. Zhurakivsky and D. M. Hovorun, *J. Mol. Model.*, 2013, **19**, 4223-4237.
- 22) A. Chollet, and E. Kawashima, *Nucl. Acids Res.*, 1988, **16**, 305-317.
- 23) V. Valinluck, P. Liu, A. Burdzy, J. Ryu, and L. C. Sowers *Chem. Res. Toxicol.*, 2002, **15**, 1595-1601.
- 24) M.-C. Wu, P. T. Lowe, C. J. Robinson, H. A. Vincent, N. Dixon, J. Leigh, and J. Micklefield, *J. Am. Chem. Soc.*, 2015, **137**, 9015-9021.
- 25) C. A. Kellenberger, C. Chen, A. T. Whiteley, D. A. Portnoy, and M. C. Hammond, *J. Am. Chem. Soc.* 2015, **137**, 6432-6435.
- 26) M. Mandal and R. R. Breaker, *Nat. Cell Biol. Rev.*, 2004, **5**, 451-463.
- 27) K. F. Blount<sup>1</sup> and R. R. Breaker, *Nat. Biotechnol.*, 2006, **24**, 1558-1564.
- 28) W. L. Jorgensen, and J. Pranata, *J. Am. Chem. Soc.*, 1990, **112**, 2008-2010.

- 29) O. O. Brovarets, Y. P. Yurenko and D. M. Hovorun, *J. Biomol. Struct. Dyn.*, 2014, **32**, 993-1022.
- 30) O. O. Brovarets, and D. M. Hovorun, *J. Biomol. Struct. Dyn.*, 2014, **32**, 127-54.
- 31) S. Scheiner, *Crystals*, 2015, **5**, 327-345.
- 32) C. F. Matta, N. Castillo, and R. J. Boyd, *J. Phys. Chem. B*, 2006, **110**, 563-578
- 33) O. O. Brovarets, Y. P. Yurenko, I. Ya. Dubey and D. M. Hovorun, *J. Biomol. Struct. Dyn.*, 2012, **29**, 1101-1109.
- 34) E. D. Larson, K. Iams, and J. T. Drummond, *DNA Repair*, 2003, **2**, 1199–1210
- 35) J. Reynisson, and S. Steenken, *J. Mol. Struct. THEOCHEM*, 2005, **723**, 29–36.
- 36) C. M. Crenshaw, J. E. Wade, H. Arthanari, D. Frueh, B. F. Lane, and M. E. Núñez, *Biochemistry*, 2011, **50**, 8463–8477.
- 37) C. D. James, G. Jianmin, L. Haibo, S. Nidhi, E. M. John, and T. E. Kool, *Angew. Chem. Int. Ed.*, 2009, **48**, 4524-4527.
- 38) R. Mogens, and T. Rudolf, *Hereditas* (Lund, Sweden), 1983, **99**, 245-250.
- 39) J. Bode, S. Goetze, H. Heng, S. A. Krawetz, and C. Benham *Chromosome Research*, 2003, **11**, 435-445.
- 40) K. M. Schermerhorn and S. Delaney, *Acc. Chem. Res.*, 2014, **47**, 1238–1246.
- 41) M.D. Kirnos, I.Y. Khudyakov, N.I. Alexandrushkina, and B.F. Vanyushin, *Nature*, 1977, **270**, 369-370.
- 42) Y. Zhao, and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215-241.
- 43) P. C. Hariharan, and J. A. Pople, *Mol. Phys.*, 1974, **27**, 209–214.
- 44) P. C. Hariharan, and J. A. Pople, *Theor. Chem., Acc.* 1973, **28**, 213-222.
- 45) P. Popelier, *Atoms in Molecules*; Pearson Education Ltd.: Essex, U.K., 2000.
- 46) N. J. M. Amezaga, S. C. Pamies, N. M. Peruchena, and G. L. Sosa *J. Phys. Chem. A*, 2010, **114**, 552–562.
- 47) P. Su, and H. Li, *J. Chem. Phys.* 2009, **131**, 14102–14115.

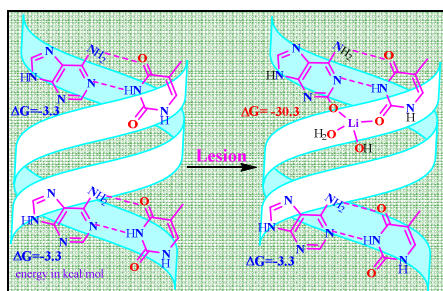
- 48) S. S. Iyengar, H. B. Schlegel, J. M. Millam, G. A. Voth, G. E. Scuseria, and M. J. Frisch, *J. Chem. Phys.*, 2001, 115, 10291-302.
- 49) R. J. O'Reilly, A. Karton, and L. Radom, *J. Phys. Chem. A*, 2013, 117, 460-472.
- 50) H. Z. Yu, Y. M. Yang, L. Zhang, Z. M. Dang, and G. H. Hu, *J. Phys. Chem. A*, 2014, 118, 606-622.
- 51) S. F. Boys, and F. Bernardi, *Mol. Phys.*, 1970, 19, 553-566.
- 52) A. V. Marenich, C. J. Cramer, and D. G. Truhlar, *J. Phys. Chem. B*, 2009, 113, 6378-96.
- 53) R. Constanciel, and R. Contreras, *Theoretica chimica acta*, 1984, 65, 1-11.
- 54) L. Goerigk, H. Kruse, and S. Grimme, *ChemPhysChem*, 2011, 12, 3421-3433.
- 55) S. Grimme, *Chem. Eur. J.*, 2012, 18, 9955-9964.
- 56) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian 09, Revis. B01*, Gaussian, Inc., Wallingford, CT., 2010.
- 57) T. Lu, and F. Chen, *J. Comput. Chem.*, 2012, 12, 580-592
- 58) M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.*, 1993, 14, 1347-1363.
- 59) M. Nei, *Mutation-Driven Evolution.*, 1<sup>st</sup> Edition, Oxford Press, 2013,

- 60) G. Alfred, and J. R. Knudson, *Proc. Natl. Acad. Sci. USA*, 1971, **68**, 820-823
- 61) C. A. Janeway, J. P. Travers, M. Walport, and M. J. Shlomchik, *Immunobiology: The Immune System in Health and Disease.*, 5th edition, New York: Garland Publication, 2001
- 62) S. Alcaro, F. Ortuso, and R. S. Coleman, *J. Med. Chem.* 2002, **45**, 861-870.
- 63) E. Espinosa, E. Molins and C. Lecomte, *Chem. Phys. Lett.*, 1998, **285**, 170–173.
- 64) M. Malecka, *Struct. Chem.*, 2010, **21**, 175-184.
- 65) M. K. Si, R. Lo, and B. Ganguly, *Chem. Phys. Lett.*, 2015, **631-632**, 6-11.
- 66) T. Y. Nikolaienko, L. A. Bulavin and D. M. Hovorun, *Phys. Chem. Chem. Phys.*, 2012, **14**, 7441–7447.
- 67) O. O. Brovarets, and D. M. Hovorun, *Phys. Chem. Chem. Phys.*, 2014, **16**, 9074–9085
- 68) V. Iogansen, *Spectrochim. Acta, Part A*, 1999, **55**, 1585–1612
- 69) H. Aral, and A. Vecchio-Sadus, *Ecotoxicology and Environmental Safety* 2008, **70**, 349– 356
- 70) U. Olshe, *Chem. Rev.*, 1991, **91**, 137-164.
- 71) A. R. Katritzky, and K. Akutagawawa, *Organic Preparations and Procedures International: The New Journal for Organic Synthesis*, 1988, **20**, 585-590.
- 72) R. Luisi, and V. Capriati, *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*; Wiley-VCH: Weinheim, Germany, 2014.
- 73) F. Wang, D. Zhang, X. Xu, and Y. Ding, *J. Phys. Chem. C*, 2009, **113**, 18032–18039.
- 74) S. Mondal, and P. K. Chattaraj, *Phys. Chem. Chem. Phys.*, 2014, **16**, 17943-17954.
- 75) R. V. Solomon, S. A. Vedha, and P. Venuvanalingam, *Phys. Chem. Chem. Phys.*, 2014, **16**, 7430-7440.

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### In Silico Studies with Substituted Adenines to Achieve Remarkable Stability of Mispairs with Thymine Nucleobase

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The modified adenine and thymine mispair achieves remarkable stability presumably help the DNA lesions to be less cytotoxic.