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Dispersion Interactions between Urea and Nucleobases Contribute to the Destabilization of RNA by Urea in Aqueous Solution

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Abstract

Urea has long been used to investigate protein folding and, more recently, RNA folding. Studies have proposed that urea denatures RNA by participating in stacking interactions and hydrogen bonds with nucleic acid bases. In this study, the ability of urea to form unconventional stacking interactions with RNA bases is investigated using *ab initio* calculations (RI-MP2 and CCSD(T) methods with the aug-cc-pVDZ basis set). A total of 29 stable nucleobase-urea stacked complexes are identified in which the intermolecular interaction energies (up to -14 kcal/mol) are dominated by dispersion effects. Natural bond orbital (NBO) and atoms in molecules (AIM) calculations further confirm strong interactions between urea and nucleobases. Calculations on model systems with multiple urea and water molecules interacting with a guanine base lead to a hypothesis that urea molecules along with water are able to form cage-like structures capable of trapping nucleic acid bases in extrahelical states by forming both hydrogen bonded and dispersion interactions, thereby contributing to the unfolding of RNA in the presence of urea in aqueous solution.

Keywords

chemical denaturation; RNA folding; dispersion interaction; nonbonded interactions; π -stacking; protein folding

Introduction

Extensive studies during the last two decades have provided insights into the involvement of RNA molecules in a number of cellular functions such as gene regulation and catalysis in addition to their role in the transcription and translation processes.^{1–2} RNA is capable of

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Supporting Information Available: Figures of optimized structures, correlation between RI-MP2 and CCSD(T) interaction energies, distributions of the interaction energies, and AIM analysis, and tables of interaction energies, NBO analysis data, AIM analysis data and coordinates of optimized geometries of all structures. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

performing diverse functions due to its ability to fold to form a variety of complex non-canonical structures. Accordingly, it is important to establish structure-function relationships of RNA, including understanding their folding. Experimental studies have shown that RNA undergoes denaturation in the presence of urea, and such studies are useful in monitoring the unfolding pathways and the associated thermodynamic changes.^{3–7} Chemical denaturants such as urea, guanidinium chloride, and alcohols have been commonly used to elucidate protein folding pathways and also to probe the intramolecular interactions that stabilize the native state of proteins.^{8–17} While the molecular mechanism by which urea destabilizes proteins has been a subject of several investigations, how urea facilitates RNA unfolding is not well understood.

Molecular dynamics (MD) simulations studies by MacKerell, Thirumalai and coworkers on RNA molecules in urea solution proposed that urea forms stacking interactions and multiple hydrogen bonds with nucleic acid bases resulting in destabilization of the RNAs.^{18–19} A recent MD study on urea induced unfolding of flavin adenine dinucleotide reported the presence of stacking interactions between the adenine moiety of FAD and urea.²⁰ However, the nature of such stacking interactions and their role in stabilizing the nucleic acid bases in the unfolded state are not clear. A better understanding of how urea interacts with RNA, especially via stacking, is essential for reliable interpretation of the experimental studies. In the present study, we employ quantum mechanical methods to substantiate and comprehend the novel mode by which urea has been proposed to interact with nucleobases.^{18–19} It is observed that urea indeed forms strong stacking interactions with nucleobases dominated by dispersion. A hypothesis on how urea along with water can form supramolecular cage like structures and trap nucleobases in their extrahelical states stabilizing unfolded states is put forth. In addition, the present results will be of utility for the optimization of empirical force fields.²¹

Methods

Initial models for nucleobase-urea stacked complexes were systematically generated from the individually optimized planar structures of the bases (GUA, ADE, CYT and URA) and urea molecule. The common structural features of all the initial geometries are (a) the planes of the urea and the base molecules are parallel to each other, and (b) the interplanar distance is 3.0 Å. For every atom in the six-/five-membered rings of the bases, three models were generated corresponding to three different orientations of the urea molecule. For example, for N1 of guanine, urea was positioned with respect to guanine such that the vector joining N1 of guanine, and C atom of urea is normal to the both the molecular planes; three orientations (as given in Chart 1) of the urea molecule were considered for each case, which vary from each other based on the orientation of the carbonyl group with respect to guanine. This gave rise to 90 putative models (27 (9 ring atoms * 3 orientations) each for GUA and ADE, and 18 (6 ring atoms * 3 orientations) each for CYT and URA), which were initially optimized using the MP2 level of theory using the resolution of identity (RI) approximation²² referred to as the RI-MP2 method implemented in the TURBOMOLE 6.2 program.²³ Dunning's correlation consistent double- ζ basis set augmented with diffuse functions, namely the aug-cc-pVDZ basis set, used for all the calculations reported here is expected to adequately model the geometries of the stacking interactions. Single point

energy calculations were performed at the CCSD(T) level of theory employing the aug-cc-pVDZ basis set using the GAMESS program²⁴. Basis set superposition errors (BSSE) have been corrected using the counterpoise method at both the RI-MP2 and CCSD(T) levels of theory. The dispersion component of the interaction energies were estimated as the difference in the interaction energies obtained using the Hartree-Fock and RI-MP2 methods.²⁵ Dispersion interaction energies have also been computed as the difference in the interaction energies obtained using the density functional theory B2PLYP²⁶ and B2PLYP-D (includes Grimme's D2 dispersion correction²⁷) methods for comparison. AIM²⁸ and NBO²⁹ analyses were performed at the RI-MP2 level using the AIMALL³⁰ and the NBO 5.9³¹ programs, respectively. The hydrogen-bonded complexes comprising the nucleobases and urea were modeled using the RI-MP2/aug-cc-pVDZ level of theory and the interaction energies were corrected for BSSE.

Results and Discussion

Nucleobases and urea form π -stacking type interactions

Geometry optimizations of 90 putative initial models of the nucleobase-urea stacked structures (Chart 1) at the RI-MP2 level resulted in 29 unique stationary points (8 for GUA, 11 for ADE, 3 for CYT and 7 for URA) where the nucleobase and the urea molecule stacked against each other. In all these complexes, the molecular planes of the urea molecule and the nucleobase are nearly parallel to each other. However, the hydrogen atoms connected to the nitrogen atoms of the nucleobase and urea deviate from planarity in a number of structures. Such deviations of the hydrogen atom positions with respect to the corresponding molecular plane involve both shifting towards or away from the other molecule due to pyramidalization about the nitrogens. All eight structures corresponding to the guanine-urea stacked complexes along with select distances between non-hydrogen atoms of urea and the base are given in Figure 1a (see Figures S1 and S2 in the Supporting Information for complexes involving ADE, CYT and URA). The distances between base and urea were found to be in the range of 2.83 to 3.12 Å. These values are similar to interplanar distances between molecules stabilized by π -stacking (eg. benzene dimer).^{32–33} Figure 1b depicts the orientations of the urea molecule with respect to the nucleobases in all the 29 structures, which shows that urea can interact with all four RNA bases via stacking interactions in a number of ways with respect to its position and orientation. This substantiates the results from previous MD studies that reported stacking interactions between nucleobases and urea.^{18–19}

The interaction energies between the nucleobase and the urea molecule in the 29 complexes were calculated at the CCSD(T) and the RI-MP2 levels of theory. Excellent correlation ($r^2 = 0.98$) between the BSSE corrected interaction energies obtained using the two methods was observed (Figure S3 in Supporting Information) validating the adequacy of the RI-MP2 method. The stabilization due to stacking interactions is slightly, but systematically, overestimated by the RI-MP2 level of theory by about 1 kcal/mol. It has been shown previously that dispersion effects are slightly overestimated by the MP2 method in general.³⁴ Further discussions on the interaction energies and analyses will be based on the RI-MP2 calculations.

Figure 2 depicts the interaction energies (shown in blue) of all the stacked complexes. Substantial stabilization corresponding to the complex formation was observed with the interaction energies ranging from -3.8 to -14.5 kcal/mol with a mean value of -7.6 kcal/mol. These values are more favorable or comparable to those obtained for commonly known π -stacked structures such as benzene dimer (-2.6 kcal/mol), stacked cytosine dimers (-2.6 kcal/mol), stacked adenine-thymine (-12.8 kcal/mol) and stacked guanine-cytosine (-16.9 kcal/mol) indicating substantial stabilization due to nucleobase-urea stacking.³²⁻³⁴ In addition to the stacking interactions, urea is capable of forming conventional hydrogen-bonded interactions with nucleobases. The interaction energies corresponding to all possible in-plane hydrogen-bonded interactions were calculated using the same level of theory (Figure 3). Such in-plane interactions give rise to stabilization energies in the range between -6 and -21 kcal/mol. As expected, the magnitudes of stabilization associated with hydrogen-bonded interactions are more favorable than stacking effects in general. However, there is a significant overlap in the distributions of the stabilization energies between the two modes of interactions (Figure S4 in the Supporting Information). Thus, if gas phase energies were considered alone, hydrogen-bonded interactions would be typically favored over stacked interactions. However, the situation is much more complex in aqueous solution where desolvation energies and entropic effects play a significant role in the context of the hydrophobic effect, which may favor stacked conformations, such as those observed in the MD simulations.¹⁸⁻¹⁹ In addition, the possibility of cooperative interactions between urea and water with the bases may contribute to the overall destabilization of RNA as discussed below.

Nucleobase-urea interactions in stacked structures are primarily dispersive in nature

The HF and the dispersion components of the RI-MP2 interaction energies along with the total interaction energies corresponding to all the stacked complexes are given in Figure 2. The interaction energies are also tabulated in Table S1 of the supporting information. Dispersion contributions are estimated based on the difference between the RI-MP2 and HF energies. Dispersion interactions dominate the total interaction energy in all the complexes with the exception of interaction **G1**. Out of the 29 structures, the HF energy of only five complexes exhibit a value of -2 kcal/mol or less (**G1**, **C1**, **C3**, **U1** and **U6**), while in the rest of the complexes the HF components of the interaction energies are destabilizing (16 complexes) or marginally stabilizing (8 complexes). Such low contribution of the HF components to the total interaction energies indicates dispersive forces to be dominant. It has been previously showed that dispersion effects highly contribute to the significant differences in the nonbonded interaction energies calculated using the MP2 and HF levels of theory because of the inability of the HF to account for dispersion interactions.²⁵ The dispersion contributions in the stacked complexes were also calculated as the differences in the interaction energies calculated at the B2PLYP and B2PLYP-D levels of theory, which confirm the dispersive nature of the stacking interactions (Figure S5 in the Supporting Information). Despite falling short of reproducing the total interaction energies obtained using the CCSD(T) method unlike the RI-MP2 method, the energies are predicted to be dominated by dispersion type interactions. Similar analysis for the hydrogen-bonded interactions (Figure 3) showed the HF contribution to be in the range of about 60 to 88% percent of the favorable interaction in the various complexes (Table S2 of the Supporting

Information) further indicating the importance of the dispersion contributions to stabilization of the stacking interactions.

In structures where the HF energy is stabilizing, one or more hydrogen atoms covalently bound to a nitrogen atom of either the nucleobase or urea are shifted out-of-plane towards an N or O of the other molecule to form weak hydrogen-bond like conformations. The second order stabilization energy corresponding to the donor and the acceptor natural bond orbitals (NBO) were calculated using the NBO analysis,²⁹ and are given in the Supporting Information (NBO section). In most of the structures, a considerable overlap between the π and π^* NBOs were observed. Additionally, weak hydrogen bond like interactions ($\pi \rightarrow \sigma^*$ and lone pair (LP) $\rightarrow \sigma^*$) were also observed corresponding to the interaction of N-H of one molecule with O or N atoms of the other molecule. For example, in **G6**, one of the most stable guanine-urea stacked complexes, a second order perturbation energy corresponding to the interaction between donor π -NBO (C4-C5 of GUA) and acceptor π^* -NBO (C-O of urea) is about 2.3 kcal/mol. The next significant interaction between donor and acceptor NBOs correspond to π (C6-O6 of the base) and σ^* (N-H of urea) with an energy of 0.8 kcal/mol, which correspond to weak hydrogen bond type interaction. Similarly in the other structures, such tertiary interactions between π - and π^* -orbitals dominate the stabilization energies.

Bader's atoms in molecules (AIM) theory, using which parameters such as bond/ring/cage critical points, total electron energy density values at these points, electron density and Laplacian are calculated, has been extremely useful for studying nonbonded interactions.²⁸ Several bond critical points, and ring critical points corresponding to 4 to 7 membered rings involving atoms of both nucleobase and urea were observed, substantiating the nonbonded interaction between the two molecules (see 'AIM analysis' section in the Supporting Information). For example, a ring critical point corresponding to atoms N1, C6 and C5 of the guanine base and C and O atoms of urea was found in **G6** in addition to three such points. Additionally, cage critical points were also observed in several of the stacked complexes further confirming strong associations. **G6** exhibits a cage critical point corresponding to the five membered ring of the guanine base and all the non-hydrogen atoms of the urea. Previously, cage critical points have been used to explain favorable stacking interactions between nucleobases.³⁵ Thus both NBO and AIM analyses further substantiates the strong nonbonded interactions between nucleobases and urea. The following section explores the possibility of multiple urea molecules interacting with the base, and the role of water.

Urea along with water may potentially form cage like complexes that trap nucleobases

The above discussions reveal that urea is capable of forming stable π -stacked structures with all the nucleobases. It is possible that multiple urea molecules may favorably interact with the base. To test this hypothesis, two additional model systems were considered: one with two urea molecules stacked above and below a guanine base (urea orientations as in **G5** and **G6** in Figure 1a), and a second with five urea molecules having both hydrogen bonded (as in **hG1**, **hG3** and **hG5** in Figure 3) and stacking interactions (as in **G5** and **G6** in Figure 1a) with a guanine base. Both were subjected to geometry optimizations at the RI-MP2/aug-cc-pVDZ level of theory, which yielded stable minimum energy structures (Figure 4a and b).

Both the structures were found to be stable with BSSE corrected interaction energies of -20.5 and -70.3 kcal/mol between the guanine and the two or five urea molecules, respectively. Similar to the binary complexes, the interaction energies are found to be mostly due to dispersion interactions in both the complexes (system 1: -19.5 and system 2: -37.6 kcal/mol). Thus, both hydrogen bonding and stacking interactions can coexist in guanine-urea complexes, yielding stable cage like structures in the gas phase.

Nucleobases of unfolded states of RNA are exposed not only to urea but also to water. A third system was therefore conceived to examine the role of water in the formation of cage-like structures. The optimized geometry of the second, 5 urea-guanine model system was subjected to a short MD simulation in a pre-equilibrated water box with positional restraints on the non-hydrogen atoms of guanine and the urea molecules. From the simulation, a system that included twelve bridging water molecules along with the guanine-five urea molecular cluster was obtained and subjected to geometry optimization at the density functional M06/aug-cc-pVDZ level. This exercise involved full optimization of the eighteen-molecule system with no restrictions on any degrees of freedom in the system. Visual inspection of the optimized structure reveals a guanine molecule engulfed in a supramolecular cage-like architecture formed by urea and water molecules (Figure 4c). While the complex in Figure 4c represents a single local minimum from a large ensemble of accessible configurations, it represents an example of the cooperative pattern of hydrogen bonds and stacking interactions stabilizing the flipped out conformation of a nucleobase. Interestingly, recent base flipping studies using the fully polarizable Drude force field³⁶ showed the presence of explicit polarizability to yield quantitatively improved agreement with experiment due to more favorable interactions of the bases with solvent.³⁷ It is anticipated that presence of polarizability in a force field may be important for forming clusters such as that in Figure 4c, which may contribute to the ability of urea to destabilize RNA. Currently, force field optimization studies primarily use hydrogen bonded structures and stabilities obtained from quantum chemical calculations in addition to experimental free energies of solvation as target data. The nucleobase-urea complex structures and their energetics obtained in this study are expected to serve as reliable model chemistries for further refinement of force field parameters.²¹

Conclusions

Knowledge of the nature of nonbonded interactions between urea and RNA is essential for proper understanding of the RNA unfolding process facilitated by urea. The current study addresses a novel and unconventional interaction mode between urea and nucleobases using high level *ab initio* quantum chemical calculations (RI-MP2 and CCSD(T)). Unconstrained optimizations revealed all four RNA nucleobases to be capable of forming stable stacking interactions with urea. Model systems corresponding to multiple urea molecules interacting with a guanine base yielded stable structures with significant interaction energies between the urea molecules and guanine dominated by dispersion. In addition, a stable structure comprising five urea and twelve water molecules interacting with a guanine base was obtained, which is suggested to be representative of a cage of urea and water that may stabilize nucleobases in their extrahelical state, hence stabilizing the unfolded states of RNA. The role of such stacking interactions between urea and aromatic moieties may

contribute to other biological systems such as in nucleic acids with urea lesions,³⁸ and in regulation of urea diffusion across urea transporters.³⁹ Future studies are needed to quantify the contribution of dispersion interactions to these and other biological systems in which urea plays an important role.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Zamore PD, Haley B. Ribo-gnome: The Big World of Small RNAs. *Science*. 2005; 309:1519–1524. [PubMed: 16141061]
2. Mercer TR, Dinger ME, Mattick JS. Long Non-Coding RNAs: Insights into Functions. *Nat. Rev. Genet.* 2009; 10:155–159. [PubMed: 19188922]
3. Ralston CY, He Q, Michael B, Chance MR. Stability and Cooperativity of Individual Tertiary Contacts in RNA Revealed through Chemical Denaturation. *Nat. Struct. Biol.* 2000; 7:371–374. [PubMed: 10802732]
4. Shelton VM, Sosnick TR, Pan T. Applicability of Urea in the Thermodynamics Analysis of Secondary and Tertiary RNA Folding. *Biochemistry*. 1999; 38:16831–16839. [PubMed: 10606516]
5. Emily JG, Jeffrey JS, Hyo KC, Joseph LM, Wolf EM, Ryan R, Gregory WM, Samuel WE, Kathryn EM, Perry JT, Michael JK, Record MT Jr. Quantifying Functional Group Interactions that Determine Urea Effects on Nucleic Acid Helix Formation. *J. Am. Chem. Soc.* 2013; 135:5828–5838. [PubMed: 23510511]
6. Erik DH, David JN. Single-Molecule Fluorescence Resonance Energy Transfer Studies of the Human Telomerase RNA Pseudoknot: Temperature-/Urea-Dependent Folding Kinetics and Thermodynamics. *J. Phys. Chem. B*. 2014; 118:3853–3863. [PubMed: 24617561]
7. Dominic L, David ED. Denaturation of RNA Secondary and Tertiary Structure by Urea: Simple Unfolded State models and Free Energy Parameters Account for Measured *m*-Values. *Biochemistry*. 2012; 51:9014–9026. [PubMed: 23088364]
8. Canchi DR, Paschek D, Garcia AE. Equilibrium Study of Protein Denaturation by Urea. *J. Am. Chem. Soc.* 2010; 132:2338–2344. [PubMed: 20121105]
9. Rossky PJ. Protein Denaturation by Urea: Slash and Bond. *Proc. Natl. Acad. Sci. USA*. 2008; 105:16825–16826. [PubMed: 18974225]
10. Hua L, Zhou R, Thirumalai D, Berne BJ. Urea Denaturation by Stronger Dispersion Interactions with Proteins than Water Implies a 2-Stage Unfolding. *Proc. Natl. Acad. Sci. USA*. 2008; 105:16928–16933. [PubMed: 18957546]
11. Stumpe MC, Grubmuller H. Interaction of Urea with Amino Acids: Implications for Urea-Induced Protein Denaturation. *J. Am. Chem. Soc.* 2007; 129:16126–16131. [PubMed: 18047342]
12. Berteotti A, Barducci A, Parrinello M. Effect of Urea on the β -Hairpin Conformational Ensemble and Protein Denaturation Mechanism. *J. Am. Chem. Soc.* 2011; 133:17200–17206. [PubMed: 21854002]
13. Huang J-R, Gabel F, Jensen MR, Grzesiek IS, Blackledge M. Sequence-Specific Mapping of the Interaction between Urea and Unfolded Ubiquitin from Ensemble Analysis of NMR and Small Angle Scattering Data. *J. Am. Chem. Soc.* 2012; 134:4429–4436. [PubMed: 22309138]
14. Emily JG, Wayne SK, Oleg VT, Irina S, Record MT Jr. Probing the Protein-Folding Mechanism Using Denaturant and Temperature Effects on Rate Constants. *Proc. Natl. Acad. Sci. USA*. 2013; 110:16784–16789. [PubMed: 24043778]

15. Carr JK, Buchanan LE, Schmidt JR, Zanni MT, Skinner JL. Structure and Dynamics of Urea/Water mixtures Investigated by Vibrational Spectroscopy and Molecular Dynamics Simulation. *J. Phys. Chem. B.* 2013; 117:13291–13300. [PubMed: 23841646]
16. Stumpe MC, Grubmuller H. Interactions of Urea with Amino Acids: Implications for Urea Induced Protein Denaturation. *J. Am. Chem. Soc.* 2007; 129:16126–16131. [PubMed: 18047342]
17. Lan H, Zhou R, Thirumalai D, Berne BJ. Urea Denaturation by Stronger Dispersion Interactions with Protein than Water Implies a 2-Stage Unfolding. *Proc. Natl. Acad. Sci. USA.* 2008; 105:16928–16933. [PubMed: 18957546]
18. Priyakumar UD, Hyeon C, Thirumalai D, MacKerell AD Jr. Urea Destabilizes RNA by Forming Stacking Interactions and Multiple Hydrogen Bonds with Nucleic Acid Bases. *J. Am. Chem. Soc.* 2009; 131:17759–17761. [PubMed: 19919063]
19. Yoon J, Thirumalai D, Hyeon C. Urea-Induced Denaturation of PreQ1-Riboswitch. *J. Am. Chem. Soc.* 2013; 135:12112–12121. [PubMed: 23863126]
20. Sengupta A, Singh KR, Gavvala K, Koninti KR, Mukherjee A, Hazra P. Urea Induced Unfolding Dynamics of Flavin Adenine Dinucleotide (FAD): Spectroscopic and Molecular Dynamics Simulation Studies from Femto-Second to Nanosecond Regime. *J. Phys. Chem B.* 2014; 118:1881–1890. [PubMed: 24456234]
21. MacKerell AD Jr. Empirical Force Fields for Biological Macromolecules: Overview and Issues. *J. Comput. Chem.* 2004; 25:1584–1604. [PubMed: 15264253]
22. Weigend F, Häser M, Patzelt H, Ahlrichs R. RI-MP2: Optimized Auxiliary Basis Sets and Demonstration of Efficiency. *Chem. Phys. Lett.* 1998; 294:143–152.
23. Ahlrichs R, Bär M, Häser M, Horn M, Kölmel C. Electronic Structure Calculations on Workstation Computers: The Program System TURBOMOLE. *Chem. Phys. Lett.* 1989; 162:165–169.
24. Schmidt MW, Baldridge KK, Boatz JA, Elbert ST, Gordon MS, Jensen JH, Koseki S, Matsunaga N, Nguyen KA, Su SJ, Windus TL, Dupuis M, Montgomery JA. General Atomic and Molecular Electronic Structure System. *J. Comput. Chem.* 1993; 14:1347–1363.
25. Su P, Li H. Energy Decomposition Analysis of Covalent Bonds and Intermolecular Interactions. *J. Chem. Phys.* 2009; 131:014102. [PubMed: 19586091]
26. Grime S. Semiempirical Hybrid Density Functional with Perturbative Second-Order Correlation. *J. Chem. Phys.* 2006; 124:034108. [PubMed: 16438568]
27. Schwabe T, Grimme S. Double-hybrid Density Functionals with Long-Range Dispersion Corrections: Higher Accuracy and Extended Applicability. *Phys. Chem. Chem. Phys.* 2007; 9:3397. [PubMed: 17664963]
28. Bader, RFW. *Atoms in Molecules: A Quantum Theory.* Oxford: Oxford University Press; 1990.
29. Reed AE, Curtiss LA, Weinhold F. Intermolecular Interactions from a Natural Bond Orbital, Donor-Acceptor viewpoint. *Chem. Rev.* 1988; 88:899–926.
30. Todd, A.; Keith, TK. *AIMALL (Version 11.12.19).* Overland Park KS, USA: Gristmill Software; 2011.
31. Glendening, ED.; Badenhoop, JK.; Reed, AE.; Carpenter, JE.; Bohmann, JA.; Morales, CM.; Weinhold, F. *NBO 5.9.* Madison, WI: Theoretical Chemistry Institute, University of Wisconsin; 2011.
32. Mahadevi AS, Rahalkar AP, Gadre SR, Sastry GN. *Ab Initio* Investigation of Benzene Clusters: Molecular Tailoring Approach. *J. Chem. Phys.* 2010; 133:164308. [PubMed: 21033789]
33. Bloom JW, Wheeler S. Taking the Aromaticity out of Aromatic Interactions. *Angew. Chem. Int. Ed.* 2011; 50:7847–7849.
34. Šponer J, Riley KE, Hobza P. Nature and Magnitude of Aromatic Stacking of Nucleic Acid Bases. *Phys. Chem. Chem. Phys.* 2008; 10:2595–2610. [PubMed: 18464974]
35. Matta CF, Castillo N, Boyd RJ. Extended Weak Bonding Interactions in DNA: π -Stacking (Base–Base), Base–Backbone, and Backbone–Backbone Interactions. *J. Phys. Chem. B.* 2006; 110:563–578. [PubMed: 16471569]
36. Savelyev A, MacKerell AD Jr. All-Atom Polarizable Force Field for DNA Based on the Classical Drude Oscillator Model. *J. Comput. Chem.* 2014; 35:1219–1239. [PubMed: 24752978]

37. Lemkul JA, Savelyev A, MacKerell AD Jr. Induced Polarization Influences the Fundamental Forces in DNA Base Flipping. *J. Phys. Chem. Lett.* 2014; 5:2077–2083. [PubMed: 24976900]
38. Lukin M, Santos C. NMR Structures of Damaged DNA. *Chem. Rev.* 2006; 106:607–686. [PubMed: 16464019]
39. Levin EJ, Quick M, Zhou M. Crystal Structure of a Bacterial Homologue of the Kidney Urea Transporter. *Nature.* 2009; 462:757–776. [PubMed: 19865084]

Figure 1.

(a) RI-MP2/aug-cc-pVDZ optimized geometries of the eight guanine-urea complexes. Distances (Å) between each of the urea non-hydrogen atoms and the closest non-hydrogen atom of guanine are also given. (b) Representations of the orientations of urea molecules with respect to the nucleobases in the RI-MP2/aug-cc-pVDZ optimized structures of the nucleobase-urea binary complexes. Only the carbonyl groups of the urea molecules (oxygen represented by a small sphere) are depicted for clarity.

Figure 2.

Total interaction energies (blue), HF contributions (green), and dispersion energies (orange) between urea and nucleobase (a: GUA, b: ADE, c: CYT, and d: URA) in the 29 binary complexes. All values are given in kcal/mol. Dispersion contribution was calculated as the difference between the MP2 and HF energies.

Figure 3. All possible in-plane hydrogen bonded structures of each of the nucleobase with urea. The interaction energies (kcal/mol) with respect to each orientation of urea are also given.

Figure 4.

(a) RI-MP2 optimized geometry of the guanine base sandwiched between two urea molecules. The distances (Å) between each of the non-hydrogen atoms of the urea molecules and the closest non-hydrogen of the base are given. (b) RI-MP2 optimized geometry of the guanine base interacting with five urea molecules. All distances between non-hydrogen atoms that are less than 3.5 Å are denoted by dotted lines. (c) M06 optimized geometry of the guanine base interacting with a cluster of five urea and twelve water molecules. Those interatomic (non-hydrogen atoms) distances less than 3.5 Å within the

cluster of urea and water molecules are depicted by dotted lines in the left side representation. In the right side representation, the interactions between the base and the molecular cluster (urea/water) are given.

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Chart 1.

Molecular representations of the three model systems of stacked complexes conceived for N1 of guanine base. Guanine is given in ball and stick, and urea is given in stick (orange color) representations.