Environmental Effects on the Enhancement in Natural and Damaged DNA Nucleobase Acidity Because of Discrete Hydrogen-Bonding Interactions

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The present study uses density functional theory to carefully consider the effects of the environment on the enhancement in (natural and damaged) DNA nucleobase acidities because of multiple hydrogen-bonding interactions. Although interactions with one small molecule can increase the acidity of the nucleobases by up to 60 kJ mol^{-1} in the gas phase, the maximum increase in enzymatic-like environments is expected to be approximately 40 kJ mol^{-1}, which reduces to approximately 30 kJ mol^{-1} in water. Furthermore, the calculated (simultaneous) effects of two, three, or four molecules are increasingly less than the sum of the individual (additive) effects with an increase in the number and acidity of the small molecules bound or the dielectric constant of the solvent. Regardless of these trends, our calculations reveal that additional hydrogen-bonding interactions will have a significant effect on nucleobase acidity in a variety of environments, where the exact magnitude of the effect depends on the properties of the small molecule bound, the nucleobase binding site, and the solvent. The maximum increase in nucleobase acidity because of interactions with up to four small molecules is approximately 80 kJ mol^{-1} in enzymatic-like environments (or 65 kJ mol^{-1} in water). These results suggest that hydrogen-bonding interactions likely play an important role in many biological processes by changing the physical and chemical properties of the nucleobases.

Introduction

Weak interactions involving biomolecules have many roles in fundamental processes in nature, such as DNA replication and repair, and therefore must be understood on a molecular level. Since information about discrete interactions is difficult to obtain directly from experimental measurements, computer calculations of the strength of hydrogen-bonding and stacking interactions involving biomolecules can provide a wealth of important information. Indeed, computational studies have characterized the hydrogen-bonding[1−4] and stacking[4−6] interactions between natural and modified DNA nucleobases, as well as their interactions with water[7−15] or other small molecules.[7−11,16−21] A smaller number of articles have considered the effects of solvation on the hydrogen-bonding or stacking interactions of the nucleobases.[3a,6a,6c,12e,13f−g,13n−o,14g,15e,15g,21c−e] Furthermore, to the best of our knowledge, no articles have studied the effects of weak (hydrogen-bonding or stacking) interactions on the physical and chemical properties of nucleobases in solution.

We are particularly interested in the hydrogen-bonding interactions between natural or damaged nucleobases and a variety of small molecules, as well as the effects of these interactions on the acidity of the nucleobases. Our interest stems from the potential role of hydrogen-bonding interactions between nucleobases and amino acid residues in the natural DNA repair process (base excision repair),[22] which is initiated by the DNA glycosylases.[23] Specifically, the proposed mechanism of action of the best studied DNA glycosylase (uracil DNA glycosylase, UDG) involves the formation of a nucleobase anion upon cleavage of the base-sugar bond, and it has been hypothesized that the enzyme stabilizes the anionic intermediate through hydrogen-bonding interactions with active site residues.[23,24] Furthermore, although some glycosylases (MutY) have been proposed to protonate purines (adenine) prior to base departure,[23,25] there is evidence that other (damaged) purines (8-oxoguanine) may be repaired through anionic intermediates.[26] Indeed, crystal structures of DNA glycosylases suggest that almost all nucleobase hydrogen-bond donor and acceptor sites interact with active site amino acids.[24,28] Therefore, to better understand the enzymatic behavior of the DNA glycosylases, we must first understand the acidity of the (natural and damaged) nucleobases, as well as how external factors, such as hydrogen-bonding interactions, influence this property. In our previous work, we carefully considered the effects of hydrogen-bonding interactions with hydrogen fluoride, water, or ammonia on the acidity of the natural nucleobases (thymine,[8] cytosine,[9] adenine,[11] guanine[11]), as well as a selection of damaged nucleobases (uracil,[7] 5-substituted uracils,[8] 8-oxo purine derivatives[11]).[29] The three small molecules were chosen because of the range in their proton affinities and acidities, and therefore because of their hydrogen-bonding abilities, which span those of the natural amino acids. Furthermore, consideration of interactions between the nucleobase and small molecules allows us to gain insight into the ability of hydrogen bonding to stabilize nucleobase anions without biasing our model to a particular active site.

Our previous calculations revealed that the acidity of natural and damaged nucleobases can be enhanced by up to 60 kJ mol^{-1} when the nucleobase is complexed with one small molecule[7−11] and up to 130 kJ mol^{-1} when the nucleobase is simultaneously complexed with two, three, or four small molecules.[7,11] We also found that the effects of two hydrogen-bonding interactions are

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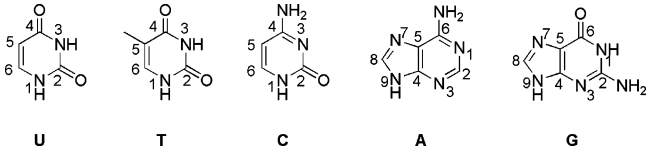

Figure 1. Structure and chemical numbering of the natural (DNA and RNA) nucleobases: uracil (U), thymine (T), cytosine (C), adenine (A), and guanine (G).

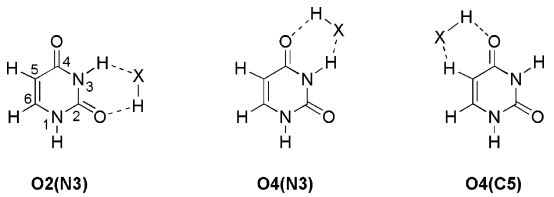

Figure 2. Structure and nomenclature for uracil hydrogen-bonding sites, where XH = HF, H_2O, or NH_3.

close to additive (i.e., equal to the sum of the two individual effects),[7,11] although greater deviations from additivity were noted for the simultaneous binding of three or four molecules.[11]

The goal of the present study is to consider the effects of solvation on the increase in the nucleobase acidity because of discrete hydrogen-bonding interactions with small molecules. One of the driving forces of this study is to account (in bulk) for the environment within biological systems or, more specifically, enzymatic active sites. This is important since the enzymatic environment likely affects the acidity of the nucleobase. Indeed, previous studies have shown, for example, that the relative acidity of the N1 and N3 sites in uracil[30] and 5-substituted uracil derivatives[31] is different in solution compared with the gas phase (see Figure 1 for the structure and numbering of the natural nucleobases). Additionally, the preferred tautomers of guanine[32] and 8-oxoguanine[33] can be drastically different depending on the environment.

In addition to directly affecting the acidity of nucleobase sites, changes in the environment may affect how small molecules interact with the nucleobase. For example, previous studies have shown that binding discrete molecules to the nucleobase affects the acid−base properties and, therefore, the hydrogen-bonding ability of other sites.[7,11,12b,13h,14b,15a] Thus, the environment in biological systems may also change the effects of hydrogen-bonding interactions on the nucleobase acidity, and the magnitude of this change is not immediately clear. The present work accounts for both distinct hydrogen-bonding interactions and the bulk environment at the same time and thereby allows us to determine the synergy of these effects on the nucleobase acidity.

Computational Details

Prior to considering the effects of hydrogen bonding on the acidity of various nucleobases, we performed a systematic study on the (N1) acidity of uracil (Figure 1) and the uracil−water O2(N3) complex (Figure 2) to identify an appropriate level of theory (Tables S1 and S2, Supporting Information). B3LYP/6-311+G(2d,p) single-point calculations on B3LYP/6-31+G(d,p) gas-phase geometries were performed on uracil and the uracil anion using the Onsager[34] and polarizable continuum (PCM)[35] self-consistent reaction field (SCRF) methods (Table S1). Eleven different solvents were used that have dielectric constants ranging from the gas phase ($\epsilon = 1$) to water ($\epsilon = 78.39$). The acidities are reported as deprotonation enthalpies, and therefore an increase in (absolute) magnitude represents a decrease in the acidity.

We found that the Onsager method incorrectly predicts greater stabilization of neutral uracil than the uracil anion, which leads to a net decrease in the acidity. In contrast, PCM single-point calculations on gas-phase geometries lead to an increase in the acidity of uracil, which increases with the dielectric constant of the solvent. Since PCM provides a more accurate description than the Onsager method, acidities from PCM optimized geometries were considered and were within 4 kJ mol^{-1} of those calculated with gas-phase geometries. Thus, we conclude that accurate estimates of the acidity of isolated uracil in different media can be obtained by performing PCM single-point calculations on gas-phase geometries.

PCM solvent-phase 6-31+G(d,p) optimizations of the uracil−water (O2(N3)) neutral and anionic complexes require greater computational time than gas-phase calculations and sometimes fail to converge when larger dielectric constants are used (Table S2). However, results obtained for geometries optimized with the 6-31G(d) basis set suggest that the acidities, and therefore the estimated effects of solvation on the acidity, calculated using gas- or solvent-phase geometries are very similar. Additionally, single-point calculations on gas-phase geometries yield similar results with the 6-31G(d) and 6-31+G(d,p) basis sets. Furthermore, when complexes could be optimized in solution with 6-31+G(d,p), small differences between the two basis sets, as well as small differences between single-point calculations on gas- and solvent-phase (6-31+G(d,p)) geometries, were found. Thus, we conclude that PCM single-point calculations on 6-31+G(d,p) gas-phase geometries can be used to reliably assess solvation effects on the acidity of the nucleobases and nucleobase−small molecule complexes.

On the basis of the above results, all nucleobases, as well as their complexes with hydrogen fluoride, water, and ammonia, were optimized in the gas phase using B3LYP/6-31+G(d,p). B3LYP/6-311+G(2d,p) single-point calculations were performed on these geometries in the gas phase, ether, and water, where the latter calculations were performed with PCM. Water was chosen because of its abundance in biological systems, while ether ($\epsilon = 4.335$) was chosen since dielectric constants around $\epsilon = 4$ have been shown to provide a suitable compromise between the environment within enzymatic active sites and the surrounding water.[36] Furthermore, data from a wider range of dielectrics (Table S1 and S2, Supporting Information) suggests that the gas, ether, and water data span that obtained from studying a greater number of solvents.

All reported energies include scaled (0.9806) zero-point vibrational corrections, and energies of all complexes include basis set superposition error (BSSE) corrections.[37] It is not possible to obtain BSSE corrections using the PCM method. However, solvent-phase BSSE corrections were calculated for a variety of complexes and solvents using the Onsager method, and the differences between the gas- and solvent-phase BSSE were less than 1 kJ mol^{-1} in all cases. Therefore, for consistency, energies of all complexes in the solvent phase were corrected using the gas-phase BSSE values. All calculations were performed with Gaussian 03.[38]

Results and Discussion

I. Effects of Solvation on the Increase in Nucleobase Acidity Because of Discrete Hydrogen-Bonding Interactions with One Small Molecule. *(1) Uracil.* Although we are interested in all of the nucleobases, we begin our analysis of the effects of solvation on the acidity of nucleobase (hydrogen-bonded) complexes by considering uracil. In particular, we will consider the effects of solvation on the (N1) acidity of

TABLE 1: Acidity, the Effect of Hydrogen Bonding on the Acidity (Δ_{XH}), and the Effect of Solvation on the Acidity (Δ_{solv}), as well as Δ_{XH} ($(\Delta_{XH})_{solv}$), for Complexes between Uracil and One Small Molecule (kJ mol^{-1})[a]

			gas[b]		ether[c]				water[c]			
O2(N3)	O4(N3)	O4(C5)	acidity	Δ_{XH}	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$
			1389.4		1251.9	137.5			1214.8	174.6		
HF			1338.0	51.4	1213.1	124.9	38.8	−12.6	1181.2	156.8	33.6	−17.8
	HF		1346.7	42.7	1219.8	126.9	32.1	−10.6	1184.3	162.4	30.5	−12.2
		HF	1342.5	46.9	1222.3	120.2	29.6	−17.3	1191.3	151.2	23.5	−23.4
H_2O			1369.2	20.2	1240.4	128.8	11.5	−8.7	1204.0	165.2	10.8	−9.4
	H_2O		1373.7	15.7	1243.2	130.5	8.7	−7.0	1204.7	169.0	10.1	−5.6
		H_2O	1366.4	23.0	1241.2	125.2	10.7	−12.3	1207.1	159.3	7.7	−15.3
NH_3			1392.6	−3.2	1258.4	134.2	−6.5	−3.3	1218.1	174.5	−3.3	−0.1
	NH_3		1394.8	−5.4	1258.2	136.6	−6.3	−0.9	1217.2	177.6	−2.4	3.0
		NH_3	1380.3	9.1	1248.4	131.9	3.5	−5.6	1210.6	169.7	4.2	−4.9

[a] See Figure 2 for definition of the uracil binding sites. All acidities refer to the N1 acidity of uracil. [b] Reference 7. [c] PCM-B3LYP/6-311+G(2d,p) single-point calculations on gas-phase B3LYP/6-31+G(d,p) geometries.

complexes between uracil and hydrogen fluoride, water, or ammonia. The small molecule (XH) can bind at three different uracil sites (Figure 2), which involve both a nucleobase proton donor and acceptor. Our notation for these complexes uses brackets to identify the uracil proton-donor site.

The gas-phase acidity of uracil, as well as the effects of hydrogen bonding with small molecules on the acidity (Δ_{XH}), are displayed in Table 1. As mentioned in the Computational Details, the acidities are reported as deprotonation enthalpies, and therefore an increase in (absolute) magnitude represents a decrease in the acidity. The gas-phase acidity of uracil (1389.4 kJ mol^{-1})[39] is generally increased upon binding of small molecules by up to 51.4 kJ mol^{-1}. Hydrogen fluoride leads to the largest increases in acidity, while ammonia sometimes decreases the acidity compared with isolated uracil. This trend follows the acidity of the small molecule bound to the nucleobase. In regard to the binding site, the increase in the acidity is largest when HF binds at O2(N3), while the greatest enhancement upon binding of water or ammonia occurs at O4(C5). This interesting trend with respect to the binding sites can be explained by considering differences in the (neutral and anionic) binding strengths of the individual complexes, as previously discussed in the literature.[7] Nevertheless, the nature of the small molecule bound affects Δ_{XH} to a greater extent than the binding site.

The acidities of uracil and uracil−XH complexes in solution are also displayed in Table 1, where Δ_{solv} represents the increase in acidity because of the solvent. The acidity of uracil increases significantly (Δ_{solv} = 137.5 kJ mol^{-1}) upon solvation with ether, which reflects greater stabilization of the uracil anion in solution. The effects of solvation on the acidity of uracil−XH complexes are smaller (by 1−17 kJ mol^{-1}) than the effect on isolated uracil, where Δ_{solv} for uracil complexes in ether ranges from 120.2−136.6 kJ mol^{-1}. The solvent does not stabilize the uracil−XH anionic complexes as much as the isolated uracil anion since the discrete hydrogen-bonding interactions with the small molecule already provide some stabilization to the uracil anion prior to solvation. This suggests that the combined effects of one small molecule and the extreme of full solvation are less than the sum of the individual effects. This agrees with previous observations that there is a clear decrease in the enhancement in acidity provided by each additional hydrogen-bonding interaction when more than two small molecules are simultaneously bound to the purines.[11]

For any binding site, Δ_{solv} decreases with XH as NH_3 > H_2O > HF, which suggests that the net stabilization afforded by subsequent solvation decreases with an increase in the acidity of the small molecule bound or, in other words, an increase in the stabilization provided to the uracil anion by the small molecule. Indeed, ammonia leads to very small changes in the acidity of uracil, and therefore the effects of solvation on the acidity of uracil−ammonia complexes are almost equal to the effects of solvation on the acidity of (isolated) uracil. Interestingly, for each small molecule, the effect of solvation decreases with binding site according to O4(N3) > O2(N3) > O4(C5), which implies that the solvent provides a different net stabilization according to the binding site regardless of the properties of XH.

Increasing the dielectric constant of the solvent is anticipated to increase the net stabilization provided to the uracil anion and thereby increase the acidity. Indeed, Δ_{solv} for the acidity of uracil is greater for water (174.6 kJ mol^{-1}) than ether (137.5 kJ mol^{-1}), which is in agreement with results previously presented in the literature.[30] The stabilization provided to the uracil−XH complexes also increases upon consideration of an aqueous environment. Nevertheless, the trends in Δ_{solv} discussed for ether continue to predominate upon solvation with water.

One of the main driving forces of the present study is to understand how solvation changes Δ_{XH} the effect of discrete hydrogen-bonding interactions on the acidity of the nucleobase. Differences in the effect of solvation on the uracil−XH complexes compared with (isolated) uracil, as well as the relatively small dependence of the gas-phase Δ_{XH} on the binding site (compared with XH), lead to changes in the trends in Δ_{XH} with respect to the binding site upon solvation. For example, in the gas phase, the effect of hydrogen bonding with one water molecule on the acidity of uracil decreases as O4(C5) > O2(N3) > O4(N3), while the trend changes upon solvation with ether to O2(N3) > O4(C5) > O4(N3) and to O2(N3) > O4(N3) > O4(C5) in an aqueous environment. Perhaps more importantly, the large dependence of Δ_{XH} on the molecule bound to uracil noted in the gas phase (i.e., decrease as HF > H_2O > NH_3) still dominates in solution, which reemphasizes that the molecule bound has a greater influence on the acidity of uracil than the binding site.

The greater effects of solvation on the acidity of isolated uracil compared with the acidity of uracil complexes lead to a net decrease in the effect of the small molecule on the acidity of uracil in solution compared with the gas phase. Specifically, the difference between the gas and solvent phase Δ_{XH}, which is represented as $(\Delta_{XH})_{solv}$, is up to 17 kJ mol^{-1} in ether (Table 1). Furthermore, the absolute magnitude of $(\Delta_{XH})_{solv}$ generally increases with the dielectric constant of the solvent, where water can decrease the gas-phase Δ_{XH} by up to 23 kJ mol^{-1}. These effects can once again be understood in terms of the stabilization provided to the uracil anion. In particular, the greater the

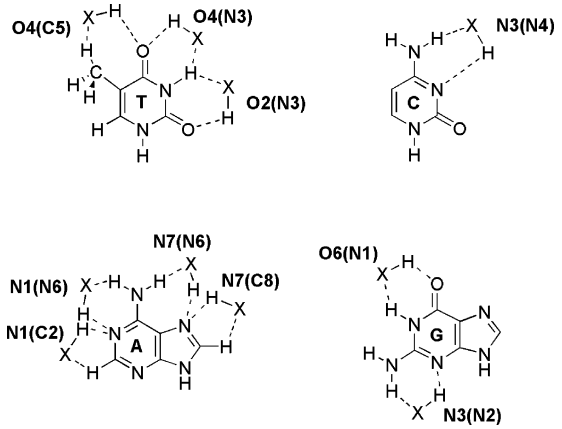

Figure 3. Structure and nomenclature for bidentate hydrogen-bonding sites in the natural DNA nucleobases, where XH = HF, H_2O, or NH_3.

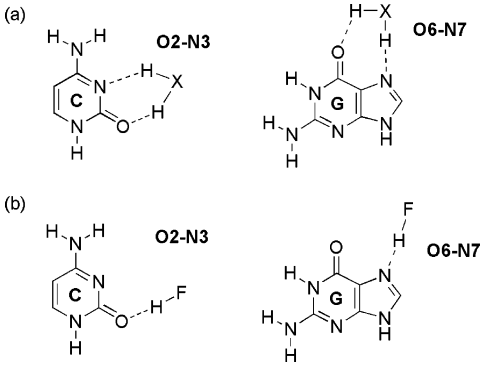

Figure 4. Structure and nomenclature for hydrogen-bonding sites in cytosine and guanine involving (a) two nucleobase acceptor sites (X = O or NH) and (b) only one nucleobase acceptor site.

stabilization provided by the solvent, which increases with the dielectric constant, the smaller the additional stabilization provided by discrete hydrogen-bonding interactions.

Interestingly, the gas-phase Δ_{XH} decreases rapidly with initial changes in the environment. For example, the gas-phase Δ_{XH} due to water at O2(N3) (20.2 kJ mol^{-1}) decreases to 11.5 kJ mol^{-1} in ether, which represents a 45% reduction. However, the corresponding Δ_{XH} in water is 10.8 kJ mol^{-1} and therefore changing the solvent from ether to water causes only a further 10% decrease. Indeed, comparing the acidity of (isolated) uracil (Table S1) to the acidity of the uracil−water O2(N3) complex (Table S2) calculated in a variety of solvents suggests that Δ_{XH} changes rapidly as the solvent dielectric increases from 1 (gas) to 2.247 (benzene), but further increases in ϵ to 78.39 cause much smaller variations in Δ_{XH}. This suggests that there exists a plateau in the net stabilization of the uracil anion provided by the (bulk) solvent.

Table 1 clearly shows that the effect of solvation on the acidity of uracil or uracil complexes (Δ_{solv}) is much larger than the effect of one small molecule on the acidity of uracil (Δ_{XH}). Nevertheless, the effects of discrete hydrogen-bonding interactions with uracil in solution are significant. Indeed, hydrogen-bonding interactions with small molecules can increase the acidity of uracil by up to approximately 40 kJ mol^{-1} in ether and 35 kJ mol^{-1} in water. Although these effects are smaller than those in the gas phase (approximately 50 kJ mol^{-1}), our results suggest that discrete hydrogen-bonding interactions may have important roles within biological systems.

In summary, our results indicate that there is a balance between the effects of discrete hydrogen-bonding interactions and the (bulk) solvent on the acidity of uracil. Specifically, the greater the increase in acidity provided by a discrete hydrogen-bonding interaction (i.e., because of the acidity of the small molecule or binding site), the smaller the enhancement due to the solvent. Alternatively, the greater the stabilization of the uracil anion provided by the solvent (i.e., because of an increase in the dielectric constant), the smaller the stabilization due to hydrogen bonds with small molecules.

(2) Natural DNA Nucleobases. Because of differences in the hydrogen-bonding patterns of the natural DNA nucleobases, we now compare the effect of solvation on the increase in the acidity of the four (natural) DNA bases due to hydrogen-bonding interactions with XH = HF, H_2O, or NH_3.[29] Figure 3 displays the hydrogen-bonding patterns between the natural nucleobases and XH and provides the nomenclature for the sites.[7−11] The majority of the binding sites considered in the present work involve one nucleobase proton acceptor and one nucleobase proton donor, which affords a bidentate hydrogen-bonding arrangement in the nucleobase−XH complex. However, a binding arrangement involving two nucleobase proton acceptors interacting with two small molecule donors was also found for cytosine and guanine when XH = H_2O or NH_3 (see Figure 4a),[40] while a binding arrangement involving only one nucleobase acceptor was found when XH = HF (Figure 4b).

Prior to considering the nucleobase complexes, the effects of solvation on the acidity of the isolated nucleobases must be considered (Tables 2−5).[39] Cytosine is the least acidic nucleobase. As a result, the effects of solvation (Δ_{solv}) are larger for cytosine, and the span in the nucleobase acidity is reduced from approximately 55 kJ mol^{-1} in the gas phase to 37 kJ mol^{-1} in ether. The gap in nucleobase acidities is further reduced (to approximately 32 kJ mol^{-1}) in water. A change in the relative acidity of nucleobase sites has been previously reported in the literature.[30−31]

The effects of solvation on the acidity of nucleobase−XH complexes involving both a nucleobase proton donor and acceptor (Tables 2−5) generally follow the same trends as those previously outlined in detail for uracil (Table 1). Specifically, the effects of solvation on the acidity of the nucleobase−XH complexes generally decrease with an increase in the acidity of XH or with a decrease in the dielectric constant of the solvent. Most importantly, solvation decreases the acidity of the nucleobase to a greater extent than the nucleobase−XH complex. As a result, the effects of discrete hydrogen bonds on the nucleobase acidity (Δ_{XH}) are smaller in solvation compared with the gas phase ($(\Delta_{XH})_{solv}$ is negative). Nevertheless, the effects of hydrogen bonds are still significant in solution. Indeed, the largest effect of discrete hydrogen-bonding interactions on the acidity of the natural nucleobases is 43 kJ mol^{-1} in ether and 37 kJ mol^{-1} in water (a maximum increase of 58 kJ mol^{-1} in the gas phase was previously reported).[7−11]

As discussed for uracil, the effects of discrete hydrogen-bonding interactions on the acidity of the nucleobases in both the gas phase and solution depend more significantly on the molecule bound than on the binding site. Indeed, Δ_{XH} decreases as HF > H_2O > NH_3 for all nucleobases in all media. However, the range in the effects of each small molecule for different nucleobases is quite large. For example, the effect of hydrogen fluoride in the gas phase ranges from 35 to 58 kJ mol^{-1}, which decreases to 23−43 kJ mol^{-1} in ether and 17−37 kJ mol^{-1} in water. For comparison, the effects of hydrogen bonds with a discrete water molecule in the gas phase, ether, and water range from 15 to 33, from 8 to 12, and from 5 to 11 kJ mol^{-1}, respectively. Interestingly, although there is a large range in Δ_{XH} for each small molecule, which reflects differences in the

TABLE 2: Acidity, the Effect of Hydrogen Bonding on the Acidity (Δ_{XH}), and the Effect of Solvation on the Acidity (Δ_{solv}), as well as Δ_{XH} ($(\Delta_{XH})_{solv}$), for Complexes between Thymine and One Small Molecule (kJ mol^{-1})[a]

			gas[b]		ether[c]				water[c]			
O2(N3)	O4(N3)	O4(C5)	acidity	Δ_{XH}	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$
			1396.5		1257.6	138.9			1219.4	177.1		
HF			1345.3	51.2	1220.5	124.8	37.1	−14.1	1188.5	156.8	30.9	−20.3
	HF		1354.2	42.3	1227.8	126.4	29.8	−12.5	1193.8	160.4	25.6	−16.7
		HF	1351.1	45.4	1234.9	116.2	22.7	−22.7	1204.0	147.1	15.4	−30.0
H_2O			1376.1	20.4	1245.8	130.3	11.8	−8.6	1208.2	167.9	11.2	−9.2
	H_2O		1380.5	16.0	1248.9	131.6	8.7	−7.3	1208.9	171.6	10.5	−5.5
		H_2O	1366.6	29.9	1242.3	124.3	15.3	−14.6	1208.2	158.4	11.2	−18.7
NH_3			1399.1	−2.6	1263.9	135.2	−6.3	−3.7	1221.9	177.2	−2.5	0.1
	NH_3		1401.4	−4.9	1265.0	136.4	−7.4	−2.5	1221.5	179.9	−2.1	2.8
		NH_3	1384.7	11.8	1255.0	129.7	2.6	−9.2	1217.5	167.2	1.9	−9.9

[a] See Figure 3 for definition of the thymine binding sites. All acidities refer to the N1 acidity of thymine. [b] Reference 8. [c] PCM-B3LYP/6-311+G(2d,p) single-point calculations on gas-phase B3LYP/6-31+G(d,p) geometries.

TABLE 3: Acidity, the Effect of Hydrogen Bonding on the Acidity (Δ_{XH}), and the Effect of Solvation on the Acidity (Δ_{solv}), as well as Δ_{XH} ($(\Delta_{XH})_{solv}$), for Complexes between Cytosine and One Small Molecule (kJ mol^{-1})[a]

		gas[b]		ether[c]				water[c]			
O2−N3	N3(N4)	acidity	Δ_{XH}[d]	acidity	Δ_{solv}	Δ_{XH}[d]	$(\Delta_{XH})_{solv}$	acidity	Δ_{solv}	Δ_{XH}[d]	$(\Delta_{XH})_{solv}$
		1442.7		1292.2	150.5			1246.8	195.9		
HF		1387.4	55.3	1255.4	132.0	36.8	−18.5	1214.8	172.6	32.0	−23.3
	HF[e]	1394.0	48.7	1256.1	137.9	36.1	−12.6	1215.4	178.6	31.4	−17.3
H_2O[f]		1405.3	37.4	1280.5	124.8	11.7	−25.7	1244.8	160.5	2.0	−35.4
	H_2O[e]	1422.2	20.5	1282.4	139.8	9.8	−10.7	1238.9	183.3	7.9	−12.6
NH_3		1422.3	20.4	1290.9	131.4	1.3	−19.1	1248.7	173.6	−1.9	−22.3
	NH_3	1441.2	1.5	1294.4	146.8	−2.2	−3.7	1247.9	193.3	−1.1	−2.6

[a] See Figure 3 for definition of the cytosine binding sites. All acidities refer to the N1 acidity of cytosine. [b] Reference 9. [c] PCM-B3LYP/6-311+G(2d,p) single-point calculations on gas-phase B3LYP/6-31+G(d,p) geometries. [d] Relative to 6-31+G(d,p) geometries. [e] Values estimated using 6-31G(d,p) geometries. [f] Geometry taken from reference 10.

TABLE 4: Acidity, the Effect of Hydrogen Bonding on the Acidity (Δ_{XH}), and the Effect of Solvation on the Acidity (Δ_{solv}), as well as Δ_{XH} ($(\Delta_{XH})_{solv}$), for Complexes between Adenine and One Small Molecule (kJ mol^{-1})[a]

				gas[b]		ether[c]				water[c]			
N1(N6)	N7(N6)	N7(C8)	N1(C2)	acidity	Δ_{XH}	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$
				1406.8		1264.1	142.8			1222.8	184.0		
HF				1365.2	41.6	1238.1	127.1	25.9	−15.7	1202.4	162.8	20.4	−21.2
	HF			1348.7	58.1	1220.9	127.8	43.1	−15.0	1185.7	163.0	37.1	−21.0
H_2O				1388.5	18.3	1255.1	133.4	8.9	−9.4	1216.5	172.0	6.3	−12.0
	H_2O			1381.8	25.0	1251.9	129.9	12.1	−12.9	1214.7	167.1	8.1	−16.9
NH_3				1406.9	−0.1	1266.3	140.6	−2.3	−2.2	1224.6	182.3	−1.8	−1.7
	NH_3			1403.3	3.5	1265.6	137.7	−1.6	−5.1	1224.2	179.1	−1.4	−4.9
		NH_3		1394.1	12.7	1260.7	133.4	3.3	−9.4	1221.8	172.3	1.0	−11.7
			NH_3	1395.3	11.5	1262.5	132.8	1.5	−10.0	1223.9	171.4	−1.1	−12.6

[a] See Figure 3 for definition of the adenine binding sites. All acidities refer to the N9 acidity of adenine. [b] Reference 11. [c] PCM-B3LYP/6-311+G(2d,p) single-point calculations on gas-phase B3LYP/6-31+G(d,p) geometries.

properties of nucleobase binding sites, there is little overlap between the effects of the different small molecules.

As mentioned above, unique binding patterns involving one (XH = HF) or two (XH = H_2O or NH_3) nucleobase acceptor sites have been previously identified for cytosine (O2−N3) and guanine (O6−N7). In the gas phase and solution, binding HF at these sites leads to similar increases in acidity as binding HF at bidentate nucleobase sites. On the other hand, since water and ammonia have two hydrogen-bond donors, binding either small molecule to these unique sites in cytosine or guanine leads to significantly larger increases in the nucleobase acidity in the gas phase (33−37 kJ mol^{-1} for water and 18−20 kJ mol^{-1} for ammonia) compared with other sites involving only one acceptor. However, the benefits of this binding is significantly reduced in the solvent phase, where Δ_{XH} decreases by up to 35 kJ mol^{-1}.

In summary, as discussed for uracil, the effects of discrete hydrogen-bonding interactions on the acidity of the natural DNA nucleobases are reduced in solvent compared with the gas phase. Nevertheless, these hydrogen-bonding interactions can still lead to significant increases in the nucleobase acidity, where the magnitude of the effect depends on the molecule bound, the binding site, and the solvent.

II. Effects of Solvation on the Increase in Nucleobase Acidity Because of Discrete Hydrogen-Bonding Interactions with More Than One Small Molecule. In our previous work, we considered the effects of simultaneous interactions with two small molecules on the gas-phase acidity of several nucleobases.[7,11] It is important to consider the simultaneous binding of more than one small molecule since it is very common for nucleobases to interact with multiple amino acid residues within the active sites of enzymes. Indeed, multiple interactions have been identified to be important for substrate identification, binding, and catalysis in natural DNA repair processes.[24−28] To understand how these interactions can affect the reactivity (acidity) of the nucleobases, we must determine whether the simultaneous effects are additive (equal to the sum of the

TABLE 5: Acidity, the Effect of Hydrogen Bonding on the Acidity (Δ_{XH}) and the Effect of Solvation on the Acidity (Δ_{solv}), as well as Δ_{XH} ($(\Delta_{XH})_{solv}$), for Complexes between Guanine and One Small Molecule (kJ mol^{-1})[a]

			gas[b]		ether[c]				water[c]			
O6−N7	N3(N2)	O6(N1)	acidity	Δ_{XH}	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$	acidity	Δ_{solv}	Δ_{XH}	$(\Delta_{XH})_{solv}$
			1403.6		1265.3	138.3			1226.1	177.5		
HF			1353.7	49.9	1232.7	121.0	32.6	−17.3	1198.9	154.8	27.2	−22.7
	HF		1364.5	39.1	1241.8	122.7	23.5	−15.6	1208.8	155.7	17.3	−21.8
		HF	1368.5	35.1	1241.6	126.9	23.7	−11.4	1206.4	162.1	19.7	−15.4
H_2O			1370.6	33.0	1254.1	116.5	11.2	−21.8	1221.4	149.2	4.7	−28.3
	H_2O		1382.2	21.4	1255.2	127.0	10.1	−11.3	1221.2	161.0	4.9	−16.5
		H_2O	1393.9	9.7	1257.3	136.6	8.0	−1.7	1219.4	174.5	6.7	−3.0
NH_3			1385.9	17.7	1264.7	121.2	0.6	−17.1	1229.7	156.2	−3.6	−21.3
	NH_3		1401.0	2.5	1268.5	132.5	−3.2	−5.8	1231.4	169.6	−5.3	−7.9
		NH_3	1412.6	−9.1	1270.7	141.9	−5.4	3.6	1229.9	182.7	−3.8	5.2

[a] See Figure 3 for definition of the guanine binding sites. All acidities refer to the N9 acidity of guanine. [b] Reference 11. [c] PCM-B3LYP/6-311+G(2d,p) single-point calculations on gas-phase B3LYP/6-31+G(d,p) geometries.

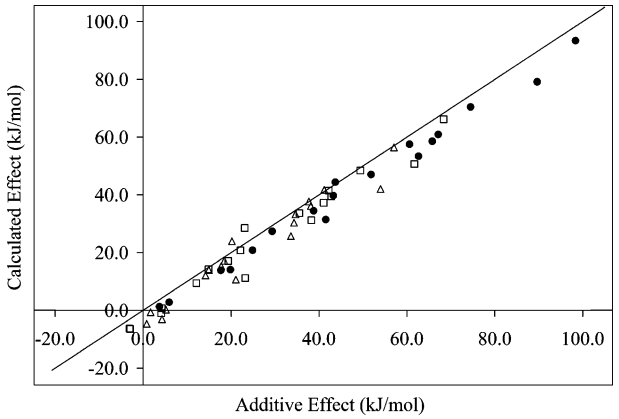

Figure 5. Comparison of the calculated (simultaneous) and additive (sum of the individual) effects of hydrogen-bonding interactions with two small molecules on the (N1) acidity of uracil in the gas phase (circles), ether (squares), or water (triangles).

individual effects) or whether the individual effects decrease (or increase) with each subsequent interaction.

In the present study, we consider 18 combinations of two small molecules at three uracil binding sites. Complexes with molecules simultaneously bound at O2(N3) and O4(N3) are neglected from the discussion because of changes in the number and type of nucleobase hydrogen bonds upon binding of the second molecule.[7] The effects of solvation on the acidity (Δ_{solv}) of complexes between uracil and two small molecules (105−130 kJ mol^{-1} for ether and 130−170 kJ mol^{-1} for water, see Table S3, Supporting Information) are slightly smaller than the solvation effects on the acidity of complexes involving one small molecule (120−140 kJ mol^{-1} for ether and 150−180 kJ mol^{-1} for water) or uracil (137 kJ mol^{-1}). As previously noted, Δ_{solv} also decreases with an increase in the acidity of the small molecules bound. The net effect of the solvent (Δ_{solv}) decreases with the number (acidity) of small molecules bound since two (more acidic) small molecules provide greater stabilization to the uracil anion than one (more basic) molecule.

Figure 5 compares the simultaneous (calculated) effect of two small molecules on the acidity of uracil to the sum of the individual (additive) effects calculated in the gas phase, ether, and water (Table S3, Supporting Information, contains the raw data). The straight line in Figure 5 represents perfect agreement between the calculated and additive effects. As was discussed for complexes involving one small molecule, the difference in the effects of solvation on the acidity of uracil complexes involving two small molecules compared with uracil leads to a decrease in the effects of hydrogen bonding on the nucleobase acidity upon solvation. Furthermore, Δ_{XH} decreases with an increase in the dielectric constant of the solvent. This can be seen in Figure 5, where the gas-phase data points (circles) have the largest effect (maximum effect of 95 kJ mol^{-1}) and water data points (triangles) have the smallest effect (maximum effect of 56 kJ mol^{-1}). Figure 5 also shows that although the spacing between the gas, ether, and water data points systematically decreases with an increase in the dielectric constant, the interspatial pattern within each data set is constant. This indicates that the same trends with respect to the small molecule bound and the binding site hold in the gas phase and various solvents.

Since the majority of the gas-phase data points fall close to or slightly below the straight line, the simultaneous effect of two small molecules on the acidity of uracil is close to or slightly less than the sum of the individual (additive) effects. For the majority of these uracil complexes, the simultaneous (calculated) effects exhibit greater additivity in solution. However, the reverse is true for some complexes, such as those with ammonia bound at O2(N3) or O4(N3) or hydrogen fluoride bound at O4(N3) and O5(C5). The most important conclusion is that the deviations from additivity in solution are different from the gas-phase deviations by less than 5 kJ mol^{-1}. Therefore, additivity holds in all phases, which suggests that binding of the first molecule does not greatly affect the properties of the nucleobase and that additional discrete hydrogen bonds can still play an important role in enhancing the acidity when the bulk environment is taken into account. Indeed, two small molecules can increase the acidity of uracil by up to 66 kJ mol^{-1} in ether or 56 kJ mol^{-1} in water (compared with 95 kJ mol^{-1} in the gas phase).

Unfortunately, although more than two amino acid residues often simultaneously interact with nucleobases in the active sites of enzymes, the limited number of binding sites in uracil means that it is only possible to consider the true additivity of the simultaneous effects of two small molecules. Therefore, 54 complexes with two or three small molecules simultaneously bound to guanine were considered (see Table S4, Supporting Information, for the raw data).

As discussed for uracil, the effects of solvation on the acidity (Δ_{solv}) of the guanine complexes decrease with an increase in the number and acidity of the molecules bound to the nucleobase, as well as an increase in the dielectric constant of the solvent. These differences reduce the effect of hydrogen bonding on the acidity with an increase in the dielectric constant of the solvent (Figure 6). Thus, complexes with the smallest net effects on the acidity are those involving two small molecules bound in water, where at least one of the molecules is ammonia, while complexes with the largest effects are those involving three

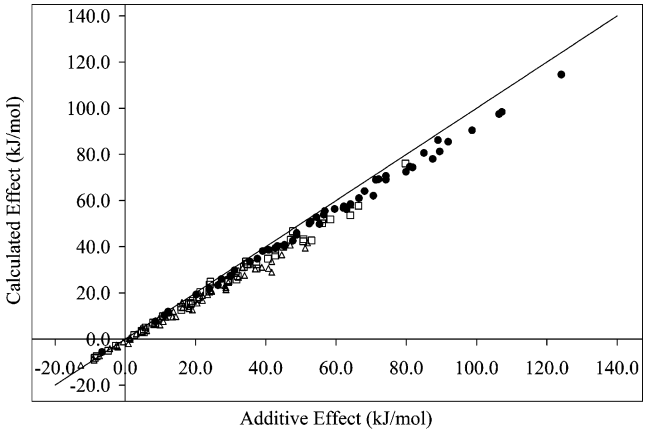

Figure 6. Comparison of the calculated (simultaneous) and additive (sum of the individual) effects of hydrogen-bonding interactions with two or three small molecules on the (N9) acidity of guanine in the gas phase (circles), ether (squares), or water (triangles).

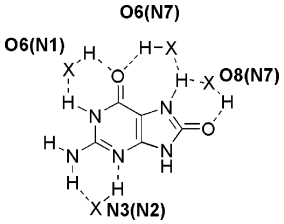

Figure 7. Structure and nomenclature for hydrogen-bonding sites in 8-oxoguanine, where XH = HF, H_2O, or NH_3.

molecules bound in the gas phase, where the majority of the molecules are hydrogen fluoride.

Similar to uracil, the calculated effects of multiple hydrogen bonds on the acidity of guanine in solution are sometimes more additive and sometimes less additive than the gas-phase data. However, a general trend begins to prevail. Specifically, the deviation from additivity typically increases with the number of molecules bound and the dielectric constant of the solvent. Nevertheless, the acidity of guanine can increase by up to 76 (58) kJ mol^{-1} when three molecules are bound in ether (water).

To test our conclusions about the changes in additivity with the dielectric constant and the number of small molecules bound, we examined 8-oxoguanine, which has an even greater number of binding sites (Figure 7). A total of 127 8-oxoguanine complexes were considered (47 complexes with two XH molecules, 66 with three XH molecules, 14 with four XH molecules). In addition to having a greater number of binding sites, 8-oxoguanine is of interest since this is one of the major products of DNA damage because of oxidation by free radicals or other oxidizing agents[41] and therefore, like uracil, is involved in DNA repair processes.[23,26,28]

Consideration of 8-oxoguanine confirms our suggestion that increasing the number of small molecules bound or the dielectric constant of the solvent leads to greater deviations from additivity (Table S5, Supporting Information). To best illustrate this point, Figure 8 separates the data points according to the phase considered and the number of molecules bound. Even in the gas phase (Figure 8a), it is clear that there are greater deviations from additivity as the number of molecules bound increases (i.e., data points corresponding to four molecules bound (triangles) fall further from true additivity (straight line) than those corresponding to two molecules bound (circles)). Indeed, the slopes of the best-fit lines between data points representing complexes with two (0.944), three (0.894), or four (0.855) small molecules bound to 8-oxoguanine systematically decrease from

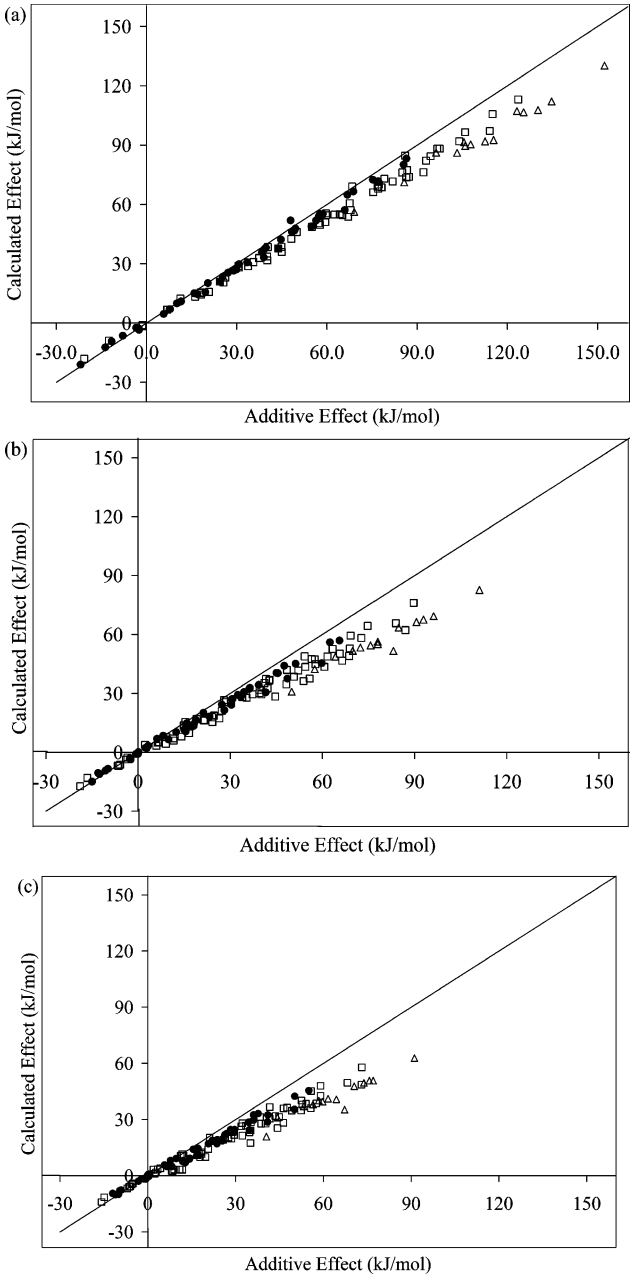

Figure 8. Comparison of the calculated (simultaneous) and additive (sum of the individual) effects of interactions with two (circles), three (squares), or four (triangles) small molecules on the (N9) acidity of 8-oxoguanine in (a) the gas phase, (b) ether, or (c) water.

true additivity (1). Comparing the results for different solvents shows that deviations from additivity (slopes) also increase (decrease) with an increase in the dielectric constant, where the slopes of the best-fit lines that connect data points corresponding to two, three, or four XH bound in ether (Figure 8b) are 0.862, 0.798, and 0.768, respectively, while the corresponding slopes in water (Figure 8c) are 0.812, 0.743, and 0.716, respectively.

In addition to showing the decreased additivity in Δ_{XH}, Figure 8 clearly shows that the effects of the small molecules on the acidity of 8-oxoguanine decrease with an increase in the dielectric constant. Specifically, the acidity of 8-oxoguanine can be increased by up to 56, 76, or 82 kJ mol^{-1} in ether but only up to 42, 58, or 63 in water when two, three, or four molecules are bound, respectively. The small enhancements in the acidity for discrete hydrogen-bonding interactions with the fourth molecule in solution provide another clear indication of

increased deviations from additivity with the number of molecules bound to 8-oxoguanine in solution.

In summary, increases in the deviation from additivity with the number of molecules bound and the dielectric constant of the solvent are generally observed. This occurs because of a decrease in the ability of the nucleobase to accept additional hydrogen-bonding interactions with an increase in the number of small molecules bound or a decrease in the ability of more than one discrete hydrogen-bonding interaction to provide further stabilization to the anion in environments that already provide good stabilization. Nevertheless, despite greater deviations from additivity in ether or water compared with the gas phase, the effects of more than one small molecule on the acidity of the nucleobase (uracil, guanine, 8-oxoguanine) are significant in different environments, including those that mimic biological systems.

Conclusions

The present study considers the effects of both distinct hydrogen-bonding interactions and the (bulk) environment on nucleobase acidity. It was determined that changes in the environment decrease the effects of discrete hydrogen-bonding interactions on the nucleobase acidity. These decreases occur since the acidity of the isolated nucleobase increases to a greater extent in solution than the acidity of the nucleobase−small molecule complex. In other words, the solvent stabilizes the isolated nucleobase anion more significantly than the anionic nucleobase complex. Indeed, there is a balance between the effects of discrete hydrogen-bonding interactions and the (bulk) solvent on the acidity, where an increase in the stabilization provided by one decreases the stabilization provided by the other. The largest increases due to interactions with one small molecule are 40 kJ mol^{-1} in environments that mimic enzyme active sites and 30 kJ mol^{-1} in water.

Although the effects of hydrogen-bonding interactions with two small molecules are equal to the sum of the individual (additive) effects in the gas phase, greater deviations from additivity are generally found in solution. The deviations increase with the dielectric constant of the solvent as well as the number and acidity of the small molecules bound. Nevertheless, the combined effects of interactions with up to four small molecules on the acidity of the nucleobases can be as large as approximately 80 kJ mol^{-1} in enzymatic-like environments and 65 kJ mol^{-1} in water. Thus, discrete hydrogen-bonding interactions can significantly affect the reactivity of the natural and damaged nucleobases in enzyme-active sites. The general nature of this study ensures that the results will provide useful insight into how weak (hydrogen-bonding) interactions influence the properties of nucleobases within biological systems.

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Supporting Information Available: Acidity of uracil in various media (Table S1), acidity of the uracil−water O2(N3) complex in various media (Table S2), acidities of uracil complexes with two small molecules (Table S3), acidities of guanine complexes with two or three small molecules (Table S4), and acidities of 8-oxoguanine complexes with two, three, or four small molecules (Table S5). This information is available free of charge via the Internet at http://pubs.acs.org.

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