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Effects of Hydrogen Bonding on the Acidity of Adenine, Guanine, and Their 8-Oxo Derivatives

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Complexes between ammonia, water, or hydrogen fluoride and adenine, guanine, or their 8-oxo derivatives are investigated using density-functional theory. The binding strengths of the neutral and (N9) anionic complexes are considered for a variety of purine binding sites. The effects of hydrogen-bonding interactions on the (N9) acidity of the purine derivatives are considered as a function of the molecule bound and the binding site. It is found that hydrogen-bonding interactions with one molecule can increase the acidity of purine derivatives by up to 60 kJ mol^{-1}. The (calculated) simultaneous effects of up to four molecules on the acidity of the purine derivatives are also considered. Our data suggest that the effects of more than one molecule on the acidity of the purines are generally less than the sum of the individual (additive) effects, where the magnitude of the deviation from additivity increases with the number, as well as the acidity, of molecules bound. Nevertheless, the increase in the acidity due to additional hydrogen-bonding interactions is significant, where the effect of two, three, or four hydrogen-bonding interactions can be as large as approximately 95, 115, and 130 kJ mol^{-1}, respectively. The present study provides a greater fundamental understanding of hydrogen-bonding interactions involving the natural purines, as well as those generated through oxidative DNA damage, which may aid the understanding of important biological processes.

Introduction

Hydrogen-bonding interactions involving biomolecules have been widely studied due to their importance in basic biological processes. Computational studies play an important role in revealing the nature of hydrogen-bonding interactions because direct information, such as the geometry of hydrogen-bonded complexes and the strength of specific binding interactions, can be more readily obtained from calculations compared with experimentation.

Researchers have also recognized the importance of understanding the effects of hydrogen bonds on the properties of biomolecules. In particular, our group has studied the effects of hydrogen bonding on the (N1) acidity of uracil and its derivatives.[1,2] Our interest in this topic mainly arises due to the proposed formation of the uracil (N1) anion during expulsion of the damaged base from DNA by a natural repair enzyme (uracil DNA glycosylase, UDG).[3] Specifically, hydrogen-bonding interactions between uracil and various active site residues have been proposed as an avenue for the enzyme to mediate glycosidic-bond cleavage.[3,4]

Although UDG is the most widely studied DNA glycosylase, many other glycosylases exist, which each remove a different type of damaged nucleobase.[3] A major form of nucleobase damage is oxidation by free radicals or other oxidizing agents.[5] DNA lesions arising from oxidative damage include thymine glycols, formamidopyrimidine derivatives of guanine or adenine, and, perhaps most importantly, 8-oxoguanine and 8-oxoadenine. Enzymes that combat the effects of 8-oxoguanine include those that directly remove 8-oxoguanine prior to DNA replication (i.e., hOGG1[6,7] or FPG (MutM)[8,9]), as well as those responsible for excising adenine that has been misincorporated opposite 8-oxoguanine (hMYH[10] and MutY[11,12]). Although it is accepted that 8-oxoadenine is also a mutagenic form of oxidative DNA damage,[13] the corresponding repair pathway is less understood as compared to that for 8-oxoguanine.[14,15]

Crystal structures of enzymes involved in repairing oxidative damage to the purines indicate that nearly all purine acceptor and donor sites are involved in hydrogen-bonding interactions with active site amino acid residues, and discrete water molecules interact with departing nucleobases.[7,9,12] Our previous research on uracil indicates that even partial protonation achieved through hydrogen bonding with one small molecule (water, ammonia, or hydrogen fluoride) can have a significant effect on the acidity of this nucleobase derivative.[1] However, due to differences in the acid−base properties of the pyrimidines and purines, as well as differences in the reactivities of the corresponding glycosidic bonds in nonenzymatic systems,[3] it is not clear whether our previous conclusions can be directly applied to damaged purines. Therefore, it is interesting to consider hydrogen-bonding interactions involving the natural and oxidized purines, as well as the effects of these interactions on the properties of these biomolecules.

Previous computational work has studied interactions between one (or more) water molecule(s) and adenine[16−22] or guanine.[16,23−28] Other studies have considered interactions between water and the natural base pairs[29] or purine tautomers.[17,21,26,27,30,31] The driving force of these studies was to better understand solvent effects on the properties of the natural nucleobases due to the importance of DNA (RNA) hydration. A few studies have also considered interactions between the natural purines and small molecules other than water, including, but not limited to, peroxide,[32] BH_3,[33] acetic acid,[34] methanol,[35] and various metals.[36−38] Although there is a large range in the

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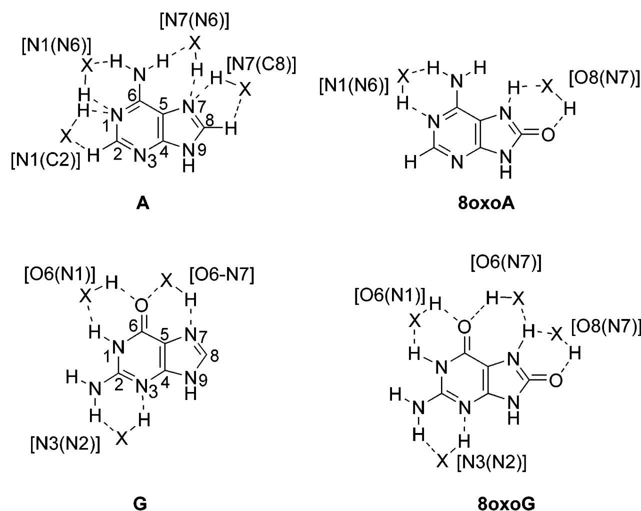

Figure 1. Complexes between adenine, guanine, or their 8-oxo derivatives and various small molecules (XH = NH_3, H_2O, or HF).

types of small molecules considered in previous studies, there has not been a systematic study performed (at the same level of theory) on the effects of different small molecules on the properties of the purines.

In the present study, we extend upon our previous work on uracil[1] and uracil derivatives[2] by considering the effects of hydrogen bonding on the (N9) acidity of adenine, guanine, and their 8-oxo derivatives (Figure 1). We are particularly interested in the effects of hydrogen bonding on the (N9) acidities of the purine derivatives due to the potential formation of (N9) anions during the glycosidic-bond cleavage by DNA repair enzymes. We consider complexes with small molecules that exhibit a range of properties (XH = NH_3, H_2O, and HF, Figure 1). Ammonia and hydrogen fluoride are considered in addition to water to provide a wider scope of binding interactions, which may lead to different effects on the properties (acidity) of the nucleobases.

Initially, complexes involving one small molecule bound to the purine are considered. However, biological molecules typically interact through more than one simultaneous hydrogen bond. Furthermore, our work on uracil derivatives considered the simultaneous effects of two small molecules on the acidity, and it was found that the combined effect of multiple hydrogen-bonding interactions is only slightly less than the sum of the individual effects.[1,2] Because a greater number of potential binding positions exist in the purines as compared to uracil, we also consider the simultaneous effects of hydrogen-bonding interactions with up to four small molecules on the acidity of the purine derivatives. Our data will complement previous studies that conclude ligand binding to adenine weakens upon addition of a second ligand,[34] and solvation at N3 and N7 in guanine and adenine modifies the intrinsic acidity or basicity of other purine sites.[16]

Because both binding strengths and the proton affinity and acidity of nucleobase sites have been shown to be correlated with the effects of hydrogen bonds on the properties of nucleobase derivatives,[1,2] the effects of multiple interactions on the properties of the purines are clearly of fundamental interest. Furthermore, although the main driving force for the present study is understanding DNA repair enzymes, we adopt a systematic approach using simplistic models, and therefore this work will lead to a more general understanding of nucleobase binding interactions, as well as hydrogen-bonding effects on nucleobase properties.

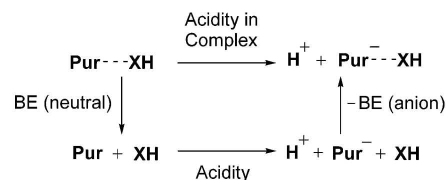

Figure 2. Thermodynamic cycle for the deprotonation of a purine (Pur) hydrogen bonded to another molecule (XH).

Computational Details

All geometries were optimized, and zero-point vibrational energy corrections obtained, in the gas phase using the B3LYP density-functional method and the 6-31+G(d,p) basis sets. Relative energies were obtained from B3LYP/6-311+G(2d,p) single-point calculations and include scaled (0.9806) zero-point vibrational energy corrections. The 6-311+G(2d,p) basis set was previously shown to yield results consistent with those obtained using larger basis sets for a similar system.[1] All energies of the hydrogen-bonded complexes include basis set superposition error corrections calculated according to the Boys and Bernardi counterpoise scheme.[39] It should be noted that the same level of theory has been previously implemented in our studies on uracil and uracil derivatives.[1,2] Furthermore, the main goal of the present work is to reveal trends in the acidities and hydrogen-bonding patterns. These trends are well reproduced at the level of theory implemented in the present work as determined through comparison with previous studies on interactions between the natural nucleobases and water.[1,2,16−28] All calculations were performed using Gaussian 98 (revision A.11.3)[40] and 03 (revisions B.05 and C.02).[41] Some calculations were performed on a Linux cluster with Linda (version 7.1).[42]

Results and Discussion

The complexes between ammonia, water, or hydrogen fluoride and the natural purines, as well as their 8-oxo derivatives, considered in the present work are displayed in Figure 1. Depending on the number of proton donor and acceptor sites in the nucleobase, two to four purine binding sites are considered. Our notation for the hydrogen-bonding sites indicates the purine hydrogen-bond acceptor and donor. For example, the adenine N1(N6) complex involves N1 as the acceptor and N6 as the donor. Because the major goal of the present work is to reveal the magnitude of the effects of these hydrogen-bonding interactions on the (N9) acidities of the purines, we do not consider hydrogen-bonding interactions involving the N9 hydrogen. Adenine and guanine complexes involving hydrogen bonding at the N9 position have been considered in previous studies.[16,21−23,26,43]

The effects of hydrogen-bonding interactions on the (N9) acidity of the purines can be calculated as the difference between the acidity of the purine-small-molecule complex and the acidity of the isolated purine. However, a complete investigation requires consideration of the individual contributions to these effects. A simple thermodynamic cycle directly relates the effects of hydrogen bonds on the acidity of the purine to the difference in the magnitudes of the binding strength between the small molecule and the neutral or anionic purine derivative (Figure 2). In turn, the binding strengths of nucleobase complexes have been shown to be a function of the proton affinity and acidity of the nucleobase acceptors and donors.[16,44] The calculated proton affinities and acidities for all sites in the purine nucleobases and their derivatives are displayed in Table 1. Our data are in good agreement with previous computational studies[16,45−47] and experimental work.[48]

TABLE 1: Calculated Gas-Phase Proton Affinities and Acidities (kJ mol^{-1}) of Various Purine Sites[a]

	proton acceptor	proton affinity	proton donor	acidity[b]
adenine	N1	938.9	N6 (near N1)	1484.0
	N3	933.3	N6 (near N7)	1482.6
	N7	906.0	C2	1669.3
			C8	1562.1
			N9	1406.8
8-oxoadenine	N1	914.6	N6 (near N1)	1450.0
	N3	914.5	N6 (near N7)	1427.8
	O8 (near N7)	850.6	C2	1641.0
	O8 (near N9)	853.5	N7	1394.7
			N9	1408.1
guanine	N3	885.7	N1	1413.3
	O6 (near N1)	899.5	N2	1431.3
	O6 (near N7)	932.3	N9	1403.6
	N7	955.3		
8-oxoguanine	O6 (near N1)	888.7	N1	1380.2
	O6 (near N7)	897.5	N2	1409.6
	O8 (near N7)	879.5	N7	1436.2
	O8 (near N9)	878.0	N9	1408.4
	N3	867.4		

[a] B3LYP/6-311+G(2d,p) single-point calculations on B3LYP/6-31+G(d,p) geometries. See Figure 1 for structure and atomic numbering. [b] It should be noted that the acidities are calculated as the deprotonation enthalpies, and therefore a small deprotonation enthalpy represents a large acidity.

In the following sections, the hydrogen-bonding interactions involving each purine derivative will be separately considered. The interaction energies within various complexes, as well as the proton affinities and acidities of purine sites, will be related to the effects of hydrogen bonding with one small molecule on the acidity of the purine. Due to the number of complexes considered that involve more than one small molecule, the discussion of simultaneous interactions at multiple purine sites will be limited to the acidity of the complexes, and the effects of multiple hydrogen bonds on the acidity. This limitation is justified because the trends in the binding strengths with respect to the small molecule bound and the binding site for complexes involving multiple small molecules parallel those discussed for the single XH-purine-derivative complexes.

Adenine. *(i) Complexes Involving One Purine Binding Site*. In our previous studies on uracil and uracil derivatives, we found that there is a delicate balance between the properties of the small molecule bound to the nucleobase and the geometries of the resulting complexes.[1,2] In particular, ammonia and water generally form bidentate hydrogen bonds with uracil derivatives by interacting with neighboring proton donor and acceptor sites within the nucleobase. Hydrogen fluoride, on the other hand, has a comparatively weak proton affinity and therefore generally forms a single hydrogen bond to a nucleobase proton acceptor.

In general, the binding arrangements observed between uracil and ammonia, water, or hydrogen fluoride are maintained upon binding with adenine. Due to the large proton affinity of ammonia, four binding sites were found to produce stable adenine−ammonia complexes (Figure 1). However, because water and hydrogen fluoride have small proton affinities and the adenine C2 and C8 sites are weak proton donors (Table 1), only the N1(N6) and N7(N6) water and hydrogen fluoride complexes were found to be stable.[49]

For all three small molecules, the binding strength of the (neutral) N1(N6) complex is slightly less (1.9−3.0 kJ mol^{-1}) than that of the N7(N6) complex (Table 2) despite the fact that the N1 proton affinity is 32.9 kJ mol^{-1} greater than that at N7, and the acidity of the two amino hydrogens differs by only 1.4 kJ mol^{-1}. This difference is directly related to geometrical

TABLE 2: Calculated Binding Strengths (kJ mol^{-1}) of Complexes between Ammonia, Water, or Hydrogen Fluoride and Adenine Derivatives[a]

	neutral			anion		
	NH_3	H_2O	HF	NH_3	H_2O	HF
adenine						
N1(N6)	18.5	24.8	49.3	18.4	43.1	90.9
N7(N6)	21.3	27.8	51.2	24.7	52.8	109.3
N7(C8)	7.1			19.8		
N1(C2)	4.1			15.6		
8-oxoadenine						
N1(N6)	20.4	25.0	46.6	17.4	40.8	86.5
O8(N7)	29.5	31.2	45.6	22.7	47.6	94.3

[a] B3LYP/6-311+G(2d,p) single-point calculations were performed on B3LYP/6-31+G(d,p) geometries. See Figure 1 for structures and notation of complexes.

effects where shorter hydrogen-bond distances are observed in the N7(N6) complexes.[50] The two additional adenine−ammonia complexes have substantially weaker binding energies (by 10−17 kJ mol^{-1}), where ammonia is found to bind slightly stronger at N7(C8) than N1(C2) due to the significantly (107.2 kJ mol^{-1}) larger acidity of the adenine proton donor (Table 1). The trends in our calculated binding strengths are in good agreement with previous computational studies of adenine−water complexes.[16,21,22]

In our previous work, the binding strengths of ammonia and water to uracil derivatives were found to be very similar at binding sites involving a strong nucleobase donor and acceptor.[1,2] This phenomenon was attributed to the formation of bidentate hydrogen bonds and a balance between the proton-donating and -accepting abilities of ammonia and water, where ammonia interacts more strongly with the nucleobase donor and water with the nucleobase acceptor. Furthermore, due to the strong acidity of hydrogen fluoride, the binding strengths of HF complexes were found to be significantly larger than NH_3 or H_2O complexes despite the fact that HF complexes contain only one hydrogen bond.

Similar trends in the binding strengths as a function of XH are found for adenine complexes. However, there is a more significant difference (6.3−6.5 kJ mol^{-1}) between the interaction energies of ammonia and water at the same adenine site than previously reported for uracil derivatives. Furthermore, hydrogen-fluoride−adenine complexes have binding strengths approximately double those calculated for the corresponding water complex, which is again a slightly larger difference than observed for the uracil derivatives.

Because we are primarily interested in the effects of hydrogen-bonding interactions on the (N9) acidity of adenine, which can be calculated as the difference between the binding strengths of the neutral and anionic complexes (Figure 2), we also consider complexes between the small molecules (XH) and the adenine (N9) anion (Table 2). Binding at N7(N6) in the adenine anion is stronger than binding at N1(N6) for all three small molecules considered in the present work (Table 2). Although this is the same trend discussed for the neutral complexes, the differences between the two binding strengths (6.3−18.4 kJ mol^{-1}) are larger for the anionic complexes, where the difference increases with an increase in the acidity of XH. Although the (neutral) ammonia N7(C8) and N1(C2) binding strengths are much smaller than those for the other sites, the binding strength of the N7(C8) anionic complex is comparable to that at N1(N6) and N7(N6), and the N1(C2) binding strength is only 2.8 kJ mol^{-1} smaller (Table 2).

In our previous work on uracil and its derivatives, we note that the small molecules migrate away from the nucleobase

TABLE 3: Calculated (N9) Acidities of Adenine and 8-Oxoadenine (kJ mol^{-1}) Complexes with Ammonia, Water, or Hydrogen Fluoride[a]

	NH_3		H_2O		HF	
	acidity	Δ (acidity)[b]	acidity	Δ (acidity)[b]	acidity	Δ (acidity)[b]
adenine						
N1(N6)	1406.9	−0.1	1388.5	18.3	1365.2	41.6
N7(N6)	1403.3	3.5	1381.8	25.0	1348.7	58.1
N7(C8)	1394.1	12.7				
N1(C2)	1395.3	11.5				
8-oxoadenine						
N1(N6)	1411.1	−3.0	1392.3	15.8	1368.2	39.9
O8(N7)	1414.8	−6.7	1391.7	16.4	1359.4	48.7

[a] B3LYP/6-311+G(2d,p) single-point calculations were performed on B3LYP/6-31+G(d,p) geometries. See Figure 1 for structures and notation of complexes. [b] The calculated (N9) acidities of isolated adenine (1406.8 kJ mol^{-1}) or 8-oxoadenine (1408.1 kJ mol^{-1}) minus the calculated acidity of the adenine-derivative complex. A positive value represents an increase in the acidity of the complex relative to the isolated purine.

proton donor and toward the proton acceptor upon anion formation, and thus the bidentate hydrogen bonds are eliminated.[1,2] These geometrical changes lead to differences in the magnitude of the binding strength of the neutral and anionic complexes. Furthermore, due to the presence of only one (strong) hydrogen bond, the binding strengths of the anionic uracil (derivative) complexes were found to increase according to $NH_3 < H_2O <$ HF, and therefore depend almost exclusively on the acidity of the small molecule bound to the nucleobase. A similar trend is observed for adenine anion complexes, where the binding strength of water is nearly twice that for ammonia, and hydrogen fluoride is doubled yet again.

As noted, comparison of the binding strengths of the neutral and anionic adenine complexes (Table 2) indicates that there is a difference in the binding properties upon anion formation. Furthermore, Figure 2 reveals that the difference in the binding strengths of the neutral and anionic complexes is directly related to the difference in the acidity of the complex and isolated adenine, which represents the effects of hydrogen bonding on the acidity of adenine. The acidity of the adenine complexes and the effects of hydrogen bonding on the acidity (Δ(acidity)) are reported in Table 3.

The largest increase in the (N1) acidity of uracil derivatives was found to occur upon binding with hydrogen fluoride, while interactions with ammonia were found to generally decrease the acidity.[1,2] Among the adenine−ammonia complexes, only the N1(N6) complex displays a slight (0.1 kJ mol^{-1}) decrease in acidity. Interestingly, the (N9) acidity of adenine is increased by 11−13 kJ mol^{-1} when ammonia binds to the N7(C8) and N1(C2) sites despite the weak binding strengths at these sites in neutral adenine complexes. This significant increase in the acidity likely arises due to the weak proton donating ability of the C2 and C8 adenine sites, which leads to stronger interactions between ammonia and the adenine acceptor (N1 or N7). Water and hydrogen fluoride increase the acidity more than ammonia, where the increase is 18−25 and 41−58 kJ mol^{-1}, respectively. The largest increase due to interactions with water or hydrogen fluoride occurs at the N7(N6) site.[51] Thus, the N7(N6) adenine−hydrogen-fluoride complex has the largest acidity (1348.7 kJ mol^{-1}), while the smallest acidity is calculated for the N1(N6) adenine−ammonia complex (1406.9 kJ mol^{-1}).

(ii) Complexes Involving Multiple Purine Binding Sites. In the present study, we consider the effects of all combinations of more than one small molecule and binding position on the (N9) acidity of adenine. However, because water and hydrogen fluoride only bind at the N1(N6) and N7(N6) sites, there are a limited number of combinations that can be considered. Furthermore, although ammonia forms stable complexes at N1(C2) and N7(C8), the properties of the adenine hydrogen-bond acceptor (N1 or N7) do not allow an additional small molecule to simultaneously bind to neighboring sites. Specifically, simultaneous complexation of any two small molecules at N1(C2) and N1(N6) or N7(C8) and N7(N6) leads to interactions between the small molecules. Although these complexes are interesting when considering the solvation patterns of nucleobases, they do not represent complexes with simultaneous interactions between two small molecules and the nucleobase that are required to consider the sum of the individual effects, which is the focus of the present work. It is noted that, although previous literature studied interactions between multiple water molecules and adenine,[19−22] the complexes investigated generally involve interactions between water molecules, and therefore it is difficult to make direct comparisons with our data.

Table S1 in the Supporting Information contains the calculated acidity for all adenine complexes that involve two XH molecules. The effects of hydrogen bonds on the acidity of adenine are also reported in Table S1 (Δ(acidity)), which are calculated as the difference between the acidity of the complex and the acidity of isolated adenine. The trends in the effects of a single small molecule on the acidity of adenine remain predominant in the effects of more than one XH moiety bound to adenine. Specifically, interactions with two hydrogen fluorides have the greatest effect on the acidity (up to 94.1 kJ mol^{-1}), while two ammonia molecules have the smallest effect (4.9 kJ mol^{-1}).

Due to similar trends in the acidities of adenine complexes involving one or two small molecules, it is intriguing to consider whether the effects of two small molecules on the acidity of adenine are additive (i.e., equal to the sum of the individual effects). Table S1 (Supporting Information) contains the additive effect on the acidity (additive). For example, water at N1(N6) increases the acidity of adenine by 18.3 kJ mol^{-1} and ammonia at N7(N6) increases the acidity by 3.5 kJ mol^{-1}, and therefore the additive effect of water at N1(N6) and ammonia at N7(N6) is 21.8 kJ mol^{-1}.

Deviations from additivity are also displayed in Table S1 (Δ), which are evaluated as the differences between the additive effect (additive) and the calculated effect (Δ(acidity)), where a negative value indicates that the simultaneous effects are less than additive. For example, the calculated simultaneous effect of water at N1(N6) and ammonia at N7(N6) is 21.0 kJ mol^{-1}, and because the additive effect is 21.8 kJ mol^{-1}, Δ equals −0.8 kJ mol^{-1} (i.e., the simultaneous effect is 0.8 kJ mol^{-1} less than additive).

Figure 3 provides a graphical comparison of the calculated effects and the additive effects of all combinations of two small molecules and binding sites on the acidity of adenine. As previously mentioned, points with the largest calculated (or additive) effects represent complexes with at least one hydrogen fluoride molecule, while those with the smallest effects contain at least one ammonia molecule. The solid line in Figure 3 represents perfect agreement between the calculated and additive effects, and therefore the simultaneous effects are increasingly less than the sum of the individual effects as the data points fall further below this line.

Figure 3 suggests that the majority of the calculated effects of two small molecules on the acidity of adenine are additive within 2 kJ mol^{-1}. Δ ranges between −1.9 and 1.5 kJ mol^{-1}

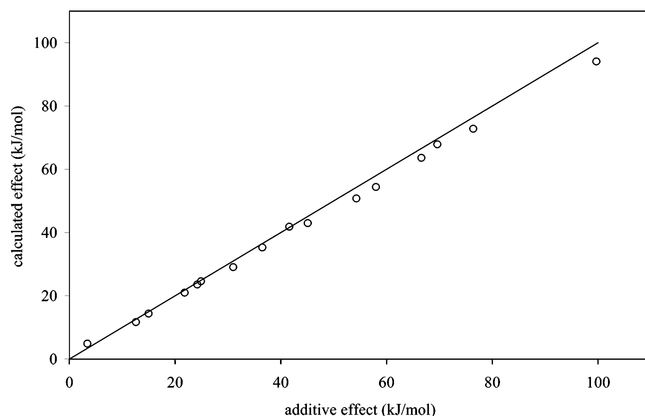

Figure 3. Comparison of the calculated and additive effects of hydrogen-bonding interactions with two small molecules on the acidity of adenine.

for complexes involving only H_2O and/or NH_3, while larger deviations from additivity (−1.7 to −5.6 kJ mol^{-1}) are found for complexes with at least one hydrogen fluoride molecule. The largest deviation from additivity (Δ = −5.6 kJ mol^{-1}) occurs when hydrogen fluoride binds at N1(N6) and N7(N6), which corresponds to a less than 6% difference between the calculated and additive effects.

In cases where significant deviations from additivity exist, the calculated effects are generally less than additive. These deviations from additivity can also be seen in geometrical changes upon binding of a second small molecule. In particular, as the number of molecules bound to adenine increases, the hydrogen-bond distances between the purine and XH increase in both the neutral and the anionic complexes as compared to the corresponding single-XH−purine complexes. This indicates that the interactions at each binding site in both neutral and anionic complexes involving more than one XH molecule are weaker as compared to complexes involving only one XH.

Our calculated hydrogen-bonding effects on the acidity are less than additive, and our calculated geometries suggest binding weakens upon addition of a second small molecule. Although others have reported (positive) cooperativity of hydrogen bonds (i.e., greater than additive binding strengths),[52] the previous studies considered complexes with two (or more) small molecules bound, where one molecule acts as a hydrogen-bond donor and the other as a hydrogen-bond acceptor. In our complexes, both small molecules bound to the nucleobase primarily act as hydrogen-bond donors, which provides competition for the hydrogen-bond acceptor sites of adenine. This leads to weaker binding (negative cooperativity or anti-cooperative binding) and therefore smaller effects on the acidity. Although strengthened binding within the complex may be expected if the small molecules interact with one another, our complexes are void of such interactions.

In summary, interactions with one small molecule can increase the acidity of adenine by up to approximately 60 kJ mol^{-1} for binding at N7(N6) and 40 kJ mol^{-1} for binding at N1(N6). The magnitude of these effects at each site decreases as XH = HF > H_2O > NH_3. When two molecules bind to different adenine sites, the acidity is increased by up to approximately 95 kJ mol^{-1}. In general, the effects of two binding interactions are additive within approximately 6 kJ mol^{-1}, where the largest deviations from additivity occur when hydrogen fluoride is bound to adenine.

8-Oxoadenine. *(i) Complexes Involving One Purine Binding Site*. Oxidation of adenine to form 8-oxoadenine changes the properties of available binding sites (Figure 1). The N7(N6) complex is no longer possible in 8-oxoadenine due to the N7 hydrogen. Although the N1(C2) 8-oxoadenine−ammonia complex can be conceptualized, this complex was not found to be a stable minimum on the surface. This difference from adenine may arise due to the smaller proton affinity of the N1 site in 8-oxoadenine as compared to adenine (by 24.3 kJ mol^{-1}, Table 1). Thus, only two stable minima have been identified for complexes between ammonia, water, or hydrogen fluoride and 8-oxoadenine (Figure 1). The N1(N6) complex is comparable to that discussed for adenine, while the other binding site involves interactions with the N7-hydrogen and C8-carbonyl that appear upon oxidation of adenine.

The O8(N7) 8-oxoadenine complexes have larger binding interactions than the N1(N6) complexes for ammonia and water. These trends arise due to the larger acidity at N7 as compared to that at N6, even though the proton affinity is larger at N1. The binding strengths for the N1(N6) and O8(N7) sites are similar for the hydrogen fluoride complexes, where binding at N1(N6) is slightly larger due to the larger acidity at N1. Binding at the O8(N7) position is larger than the N1(N6) position for all complexes with the 8-oxoadenine anion, where the binding strengths increase at each site as XH = NH_3 < H_2O < HF.

Although the N1 proton affinity is greater in adenine than 8-oxoadenine, the N6 acidity is greater in 8-oxoadenine (Table 1). The end result of these differences is slightly stronger binding strengths for ammonia or water, and slightly reduced for hydrogen fluoride, at N1(N6) upon oxidation of adenine. All anionic N1(N6) binding strengths are smaller for 8-oxoadenine as compared to adenine. Interestingly, although the hydrogen-bonding scheme at the N7 site changes significantly upon oxidation, the binding strengths at the N7 site are comparable in adenine and 8-oxoadenine.

Despite the generally stronger binding interactions between small molecules and 8-oxoadenine as compared to adenine, the effects of these interactions on the acidity of 8-oxoadenine are slightly smaller (by 2−3 kJ mol^{-1}) than the effects on adenine at comparable sites (Table 3). Because the N9 acidity of 8-oxoadenine is 1.3 kJ mol^{-1} smaller than the acidity of adenine, the 8-oxoadenine N1(N6) complexes have only slightly smaller acidities than the corresponding adenine complexes. Among 8-oxoadenine binding sites, interactions at O8(N7) lead to larger increases in acidity (by up to 9 kJ mol^{-1}) as compared to N1(N6).

(ii) Complexes Involving Multiple Purine Binding Sites. Due to the disappearance of the N1(C2) and N7(C8) complexes upon oxidation of adenine, even fewer combinations of hydrogen-bonding interactions with more than one small molecule can be considered for 8-oxoadenine. Figure 4 and Table S2 (Supporting Information) summarize the effects of all combinations of two small molecules on the acidity of 8-oxoadenine.

The trends in Δ(acidity) for 8-oxoadenine are similar to those discussed for adenine. However, because there are fewer binding sites, differences in the magnitude of the deviations from additivity (Δ) with respect to the small molecules involved in the complex are more easily identified. More specifically, although the simultaneous effect of two ammonia molecules is slightly greater than additive (by 0.6 kJ mol^{-1}), all other combinations of XH lead to less than additive effects, where the absolute magnitude of Δ increases if complexes involve one water and one ammonia ($|\Delta|$ = 0.4−0.9 kJ mol^{-1}), two waters ($|\Delta|$ = 1.6 kJ mol^{-1}), one hydrogen fluoride ($|\Delta|$ = 2.6−4.1 kJ mol^{-1}), or two hydrogen fluorides ($|\Delta|$ = 5.4 kJ mol^{-1}). However, as discussed for adenine, even the largest Δ represents a less than 7% difference in the calculated acidity.

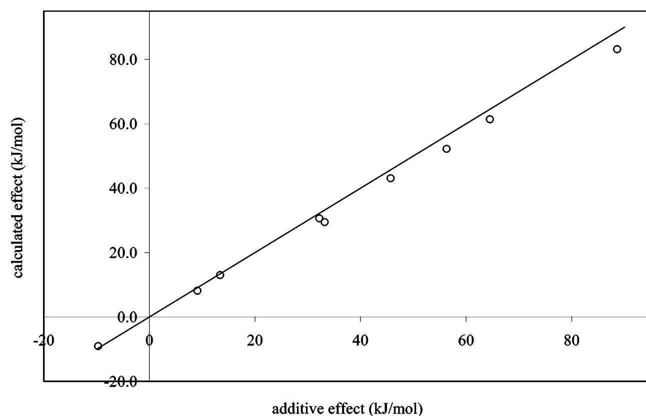

Figure 4. Comparison of the calculated and additive effects of hydrogen-bonding interactions with two small molecules on the acidity of 8-oxoadenine.

TABLE 4: Calculated Binding Strengths (kJ mol^{-1}) of Complexes between Ammonia, Water, or Hydrogen Fluoride and Guanine Derivatives[a]

	neutral			anion		
	NH_3	H_2O	HF	NH_3	H_2O	HF
guanine						
O6(N1)	30.9	35.1	53.4	21.9	44.8	88.5
N3(N2)	20.6	23.1	44.4	23.1	44.5	83.5
O6−N7	7.5	21.8	42.2	25.2	54.8	92.1
8-oxoguanine						
O6(N1)	32.6	35.8	53.3	23.5	46.1	90.5
N3(N2)	22.7	22.9	40.8	23.9	43.4	78.9
O6(N7)	28.5	32.1	50.4	15.7	38.7	79.1
O8(N7)	23.4	25.9	42.7	18.8	45.1	90.9

[a] B3LYP/6-311+G(2d,p) single-point calculations were performed on B3LYP/6-31+G(d,p) geometries. See Figure 1 for structures and notation of complexes.

In summary, 8-oxoadenine exhibits trends in the acidity, and the effects of hydrogen bonding on the acidity, similar to adenine. Comparable effects on the acidity are calculated for interactions at both (N1(N6) and O8(N7)) binding sites for ammonia and water, but hydrogen fluoride has an approximately 9 kJ mol^{-1} larger effect at O8(N7). The simultaneous effects of two small molecules on the acidity of 8-oxoadenine are found to deviate by less than approximately 5 kJ mol^{-1} from the sum of the individual effects. Clear trends in the magnitude of the deviation from additivity can be seen in the 8-oxoadenine complexes, where interactions are increasingly less than additive as the number of water molecules increases and even greater deviations from additivity are observed as the number of hydrogen fluoride molecules increases.

Guanine. *(i) Complexes Involving One Purine Binding Site.* Three guanine binding sites are characterized for complexes with one small molecule (XH) (Figure 1).[53] One binding site is characteristically different from others discussed thus far. In particular, the ammonia and water O6−N7 complexes involve interactions with two guanine hydrogen-bond acceptors. The comparable hydrogen fluoride complex involves a single hydrogen bond between HF and the N7 guanine acceptor. Due to the larger proton affinity of N7 as compared to O6 (Table 1), water binds closer to the N7 position in the O6−N7 complex. Although both the water and the hydrogen fluoride O6−N7 complexes are planar, ammonia is located out of the guanine molecular plane at this position (by 41.7°) and is situated slightly closer to O6 than N7.

The trend in the binding strengths (Table 4) with respect to the small molecule bound to guanine is similar to those discussed for adenine and 8-oxoadenine for the O6(N1) and N3(N2) complexes (i.e., $NH_3 \approx H_2O < HF$, Table 4). However, due to the unique nature of the O6−N7 complex, there is a much larger difference (14.3 kJ mol^{-1}) between the interaction energies of these water and ammonia complexes.

TABLE 5: Calculated (N9) Acidities of Guanine and 8-Oxoguanine (kJ mol^{-1}) Complexes with Ammonia, Water, or Hydrogen Fluoride[a]

	NH_3		H_2O		HF	
	acidity	Δ (acidity)[b]	acidity	Δ (acidity)[b]	acidity	Δ (acidity)[b]
guanine						
O6(N1)	1412.6	−9.1	1393.9	9.7	1368.5	35.1
N3(N2)	1401.0	2.5	1382.2	21.4	1364.5	39.1
O6−N7	1385.9	17.7	1370.6	33.0	1353.7	49.9
8-oxoguanine						
O6(N1)	1417.5	−9.1	1398.1	10.3	1371.1	37.2
N3(N2)	1407.1	1.2	1387.8	20.5	1370.3	38.1
O6(N7)	1421.1	−12.8	1401.8	6.6	1379.6	28.7
O8(N7)	1412.9	−4.6	1389.1	19.2	1360.1	48.3

[a] B3LYP/6-311+G(2d,p) single-point calculations were performed on B3LYP/6-31+G(d,p) geometries. See Figure 1 for structures and notation of complexes. [b] The calculated (N9) acidities of isolated guanine (1403.6 kJ mol^{-1}) or 8-oxoguanine (1408.4 kJ mol^{-1}) minus the calculated acidity of the guanine-derivative complex. A positive value represents an increase in the acidity relative to the isolated purine.

For all small molecules, the interaction energy decreases according to binding at O6(N1) > N3(N2) > O6−N7. These results are consistent with the proton affinities and acidities of guanine acceptor and donor sites (Table 1), as well as the nature of the complexes. Specifically, O6 (near N1) has a larger proton affinity than N3 by 13.8 kJ mol^{-1}, and N1 has a larger acidity than N2 by 18.0 kJ mol^{-1}. The O6−N7 complex has the smallest binding energies due to the competition between the O6 and N7 guanine acceptor sites for XH. The calculated trends in the interaction energies at different guanine binding sites are consistent with results previously reported in the literature for guanine−water complexes.[16,23,26]

Upon formation of the guanine anion, the trend in the binding strengths with respect to binding position changes as compared to that discussed for the neutral complexes. The O6−N7 anionic complexes have the largest binding strengths for all small molecules (by 2 kJ mol^{-1} for NH_3, 10 kJ mol^{-1} for H_2O, and 4 kJ mol^{-1} for HF). The O6(N1) and N3(N2) complexes have interaction energies within approximately 1 kJ mol^{-1} for water and ammonia, while the O6(N1) binding strength is (approximately 5 kJ mol^{-1}) larger for HF.

In addition to the trends in the binding strengths, the magnitude of the binding strengths of the guanine complexes changes significantly upon anion formation, and this difference equals the effect of the hydrogen bonds on the acidity of guanine (Figure 2). The dependence of the increase in acidity on the small molecule bound to guanine (Table 5) is consistent with our data for uracil, adenine, and their derivatives. Hydrogen fluoride and water increase the acidity of guanine by 35−50 and 10−33 kJ mol^{-1}, respectively, while ammonia decreases (by 9.1 kJ mol^{-1} at O6(N1)) or slightly increases (at N3(N2)) the acidity. Interestingly, ammonia bound at O6−N7 increases the guanine acidity by 17.7 kJ mol^{-1}. The acidity increases upon formation of this complex because two N−H ammonia bonds act as proton donors, while in the other complexes ammonia acts as a weak proton donor and a strong proton acceptor. The effects on the acidity decrease as O6−N7 > N3(N2) > O6(N1) for all small molecules considered in the present work,

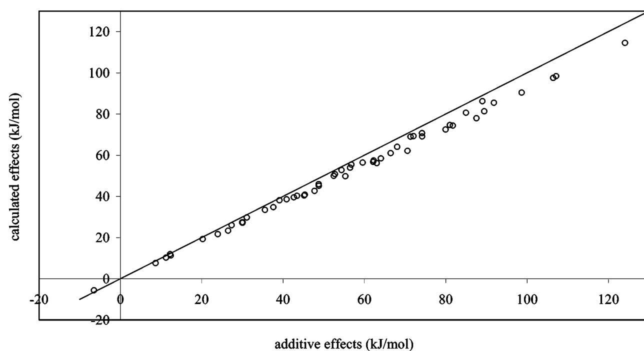

Figure 5. Comparison of the calculated and additive effects of hydrogen-bonding interactions with multiple small molecules on the acidity of guanine.

where the effect at O6−N7 is at least 10 kJ mol^{-1} larger than the other sites.

(ii) Complexes Involving Multiple Purine Binding Sites. Because guanine forms three stable complexes with one small molecule, many more combinations of two small molecules simultaneously bound to guanine can be considered as compared to adenine or 8-oxoadenine. Furthermore, numerous combinations of three small molecules bound to guanine can be considered. In the present work, a total of 54 complexes are investigated where two or three small molecules are bound to guanine. The acidities of the complexes, the effect of the hydrogen bonds on the acidity (Δ(acidity)), the additive effects of individual interactions (additive), and the deviations from additivity (Δ) are provided in the Supporting Information (Table S3).

The effects of hydrogen bonding with one small molecule on the acidity of guanine decrease according to the binding site as O6−N7 > N3(N2) > O6(N1) and XH as HF > H_2O > NH_3, and these general trends hold for all complexes considered that involve more than one purine binding site. For example, the largest effect of two small molecules on the acidity of guanine (86.2 kJ mol^{-1}) is calculated when hydrogen fluoride is located at O6−N7 and N3(N2) (Table S3, Supporting Information). The largest effect of three molecules on the acidity is calculated to be 114.6 kJ mol^{-1}, which occurs when hydrogen fluoride is present at all three guanine binding sites.

The additivity of binding interactions with two small molecules is very similar to that discussed for adenine and 8-oxoadenine. Specifically, the calculated effects of two molecules deviate by less than 4.4 kJ mol^{-1} from the sum of the individual (additive) effects (Δ, Table S3, Supporting Information), which represents a less than 6% deviation in the acidities. It is interesting to note that the maximum absolute deviation from additivity when two molecules interact with adenine ($\Delta = -5.6$ kJ mol^{-1}) is similar to that found for guanine.

Because the effects of two molecules on the acidity of adenine, 8-oxoadenine, and guanine are close to additive, it is intriguing to consider the additivity of the effects of three molecules on the acidity of guanine. Figure 5 plots the simultaneous (calculated) effect of hydrogen bonds with two or three small molecules on the acidity of guanine against the sum of the effects of the individual interactions (additive effects). Complexes with the smallest net effect on the acidity (far left of graph) represent those with two small molecules, where at least one of the molecules is ammonia. Complexes with the largest effect on the acidity (far right of graph) are those involving three small molecules and the majority of the molecules are hydrogen fluoride. The straight line in Figure 5 represents perfect agreement between the calculated and additive effects.

From Figure 5, it is clear that the calculated effects of hydrogen bonds with two molecules on the acidity of guanine are closer to additive than the calculated effects of interactions with three molecules. For example, the calculated acidity for the complex with hydrogen fluoride at O6−N7 and O6(N1) is less than additive by 4.4 kJ mol^{-1}, while the calculated effect of interactions with hydrogen fluoride at all three binding sites is 9.5 kJ mol^{-1} less than additive. In general, the effects of two or three molecules are 5 or 10 kJ mol^{-1} less than additive, respectively.

To understand why the deviation from additivity increases when three molecules are bound to guanine, we must closely consider the cause of the deviations when two molecules are bound. The largest deviations from additivity when two molecules interact with guanine occur when hydrogen fluoride and/or water simultaneously bind at the O6−N7 and O6(N1) sites. When water is located at O6−N7, the large deviation from additivity is at least in part due to the competition at the guanine O6 site for two different proton donors. Nevertheless, large deviations are also observed when hydrogen fluoride binds at O6−N7 even though HF interacts at this site solely through the N7 position. This suggests that there is a competition between the guanine acceptor sites for hydrogen-bonding interactions even when only two molecules interact with guanine and the binding sites are spatially separated.

This competition is further compounded when three molecules interact with guanine, and therefore these complexes exhibit even greater deviations from additivity. Indeed, these larger deviations can be divided into the individual contributions for each pair. For example, consider complexes involving only hydrogen fluoride. The simultaneous effects are 4.4 kJ mol^{-1} less than additive when HF binds at O6−N7 and O6(N1), 2.8 kJ mol^{-1} less than additive for binding at O6−N7 and N3(N2), and 3.4 kJ mol^{-1} less than additive for simultaneous binding at N3(N2) and O6(N1). The sum of these deviations is 10.6 kJ mol^{-1} less than additive, which is only slightly greater than the deviations from additivity calculated for the simultaneous interaction of hydrogen fluoride at all three guanine binding positions ($|\Delta| = 9.5$ kJ/mol).

In summary, the O6−N7 guanine binding site involves two purine acceptors and therefore is unique as compared to other purine binding sites. Hydrogen-bonding interactions at O6−N7 lead to the largest increases in the acidity of guanine, which are up to 50 kJ mol^{-1} when interactions with a single molecule are considered. Although the effects of two small molecules on the acidity of guanine (or adenine) are additive (within 5 kJ mol^{-1}), larger deviations from additivity (by up to 10 kJ mol^{-1}) are observed when three molecules are bound to guanine. These larger deviations are indicative of a compounded competition between guanine sites for hydrogen-bonding interactions and a decrease in the ability of guanine to accept additional hydrogen bonds. Nevertheless, the increases in acidity due to simultaneous interactions with two or three XH molecules are calculated to be up to 86 or 115 kJ mol^{-1}, respectively, and therefore binding of a second or third molecule to guanine can still lead to a significant increase in the acidity.

8-Oxoguanine. *(i) Complexes Involving One Purine Binding Site*. Upon oxidation of guanine to form 8-oxoguanine, two complexation sites that differ from those discussed for guanine are formed, which utilize the N7 hydrogen as the purine donor and the C6 (O6(N7)) or C8 (O8(N7)) carbonyl group as the purine acceptor. Because these hydrogen-bonding patterns

involve both a purine donor and an acceptor, stronger binding strengths in this region of 8-oxoguanine are observed as compared to guanine (Table 4), where the O6−N7 complex involves two purine acceptors. The O6(N1) and N3(N2) complexes are preserved upon oxidation of guanine, and the binding strengths for these 8-oxoguanine complexes are within 4 kJ mol^{-1} of the corresponding guanine binding strengths (Table 4).

For all small molecules considered in the present study, the binding strengths to neutral 8-oxoguanine decrease as O6(N1) > O6(N7) > O8(N7) > N3(N2) (Table 4). This pattern follows trends in the proton affinities and acidities of 8-oxoguanine acceptors and donors (Table 1). Specifically, O6 has a larger proton affinity than O8, which is larger than N3. The difference in the binding at O6(N1) and O6(N7) occurs because N1 has a larger acidity (by 56 kJ mol^{-1}) as compared to N7.

Upon formation of the 8-oxoguanine anion, the binding strength of ammonia complexes increases to fall between 15.7 and 23.9 kJ mol^{-1}, while those for water and hydrogen fluoride complexes fall between 38.7−46.1 kJ mol^{-1} and 78.9−90.9 kJ mol^{-1}, respectively. The trend in the binding strengths of the anionic complexes as a function of binding site is different for each small molecule. Most interestingly, when strong acids interact with 8-oxoguanine anion, the largest binding strengths occur at O8(N7) and O6(N1).

The differences in the binding strengths of the anionic and neutral 8-oxoguanine complexes are equal to the effects of hydrogen bonds on the acidity of 8-oxoguanine (Figure 2), which are displayed in Table 5. As found for guanine, ammonia at O6(N1) decreases the acidity of 8-oxoguanine (by 9.1 kJ mol^{-1}), but slightly increases the acidity at N3(N2) (by 1.2 kJ mol^{-1}). Ammonia is also found to decrease the acidity at O6-(N7) and O8(N7) (by 12.8 and 4.6 kJ mol^{-1}, respectively). Among water and hydrogen fluoride complexes, interactions at O6(N7) lead to the smallest increase in the acidity followed by O6(N1). The largest effects of water (19−21 kJ mol^{-1}) occur at O8(N7) or N3(N2). The largest effects due to hydrogen fluoride occur at O8(N7), where the effects at N3(N2) and O6(N1) are almost 10 kJ mol^{-1} smaller.

The effects of hydrogen bonds at O6(N1) and N3(N2) for 8-oxoguanine are within 2 kJ mol^{-1} of the effects calculated for guanine. Interestingly, for strong acids, the effects of binding at O8(N7) in 8-oxoguanine are almost equal to the effects at O6−N7 in guanine, a site that involves two purine acceptors. The binding strength at O8(N7) is slightly less in 8-oxoguanine as compared to the analogous site in 8-oxoadenine, which must arise due to the smaller N7 acidity in 8-oxoguanine. Nevertheless, for strong acids, the effect of binding at O8(N7) on the acidity is larger for 8-oxoguanine than 8-oxoadenine, which is likely due to the larger proton affinity at the O8 position in 8-oxoguanine.

(ii) Complexes Involving Multiple Purine Binding Sites. Due to the presence of four binding sites in 8-oxoguanine, a large number of different combinations of two, three, or four molecules simultaneously bound to 8-oxoguanine can be considered. However, in some instances, the optimized complexes involve interactions between the small molecules as discussed for adenine, and therefore these complexes were not further considered in the present work. In particular, combinations with ammonia at O6(N7) or O8(N7) and another small molecule at the other position lead to interactions between the small molecules. Complexes with hydrogen fluoride located at O6(N1) and ammonia at O8(N7) are not stable minima because ammonia migrates to the O6(N7) position. In total, 127

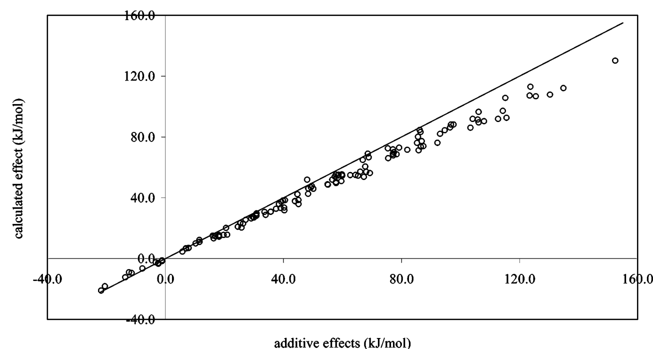

Figure 6. Comparison of the calculated and additive effects of hydrogen-bonding interactions with multiple small molecules on the acidity of 8-oxoguanine.

8-oxoguanine complexes were considered (47 complexes with two XH molecules, 66 with three XH molecules, 14 with four XH molecules).

The acidities of the 8-oxoguanine complexes involving interactions at more than one purine binding site, the effects of hydrogen bonds on the acidity (Δ(acidity)), the additive effects of the individual interactions (additive), and the deviations from additivity (Δ) are provided in the Supporting Information (Table S4). As found for adenine and guanine, the trends in the acidity and Δ(acidity) parallel those discussed when only one small molecule interacts with 8-oxoguanine.

Our calculations reveal that interactions with two HF molecules can increase the acidity of 8-oxoguanine by up to 83 kJ mol^{-1}, while two ammonia molecules decrease the acidity by up to 21 kJ mol^{-1}. Interactions with three molecules can increase the acidity by up to 113 kJ mol^{-1} or decrease the acidity by 18 kJ mol^{-1}. Interactions with four molecules increase the acidity from 56 to 130 kJ mol^{-1}. Although it appears that the effects of four molecules are generally much larger than two or three molecules, it must be recalled that some complexes could not be isolated on the potential energy surfaces due to interactions between the small molecules and therefore all complexes with four molecules involve at least one hydrogen fluoride molecule, which has been established to cause the largest effects on the acidity among the small molecules considered.

The driving force for considering a large range of complexes revolves around determining the additivity of the effects of individual hydrogen bonds on the acidity of purines. The data for 8-oxoguanine will enhance our previous discussion because up to four small molecules can simultaneously interact with this nucleobase. As mentioned for adenine, it should be noted that as the number of molecules bound to 8-oxoguanine increases, the hydrogen-bond distances between the purine acceptor and donor sites in both the neutral and the anionic complexes increase. This indicates that there is likely weaker binding in both complexes and these differences lead to the observed deviations from additivity.

Figure 6 compares the simultaneous (calculated) effects of multiple hydrogen bonds on the (N9) acidity of 8-oxoguanine to the sum of the individual (additive) effects. From the graph (and Table S4, Supporting Information), it can be seen that although hydrogen-bonding interactions with multiple small molecules can increase the acidity of 8-oxoguanine by up to approximately 130 kJ mol^{-1}, this effect is significantly smaller (by 22.1 kJ mol^{-1}) than that predicted if the effects were additive. Comparison with the deviations discussed for adenine, 8-oxoadenine, and guanine suggest that the deviation away from additivity continuously increases as the number of molecules bound to the purine increases.

To better understand the additivity of the effects of hydrogen-bonding interactions on the acidity of 8-oxoguanine, we further explore the deviations according to the number of molecules bound. The largest deviations from additivity when two molecules interact with 8-oxoguanine ($\Delta = -5.2$ to -8.7 kJ mol^{-1}) occur when two hydrogen fluoride molecules or hydrogen fluoride and water simultaneously interact at O6(N7) and O6(N1) or O6(N7) and O8(N7).[54] Larger deviations for these binding arrangements are expected due to the competition between XH for the same purine acceptor (O6) or donor (N7) site. With the exception of these combinations, the effects of two molecules deviate by less than 5.5 kJ mol^{-1} from additivity, which is similar to the Δ discussed for other purine derivatives considered in the present work.

Not surprisingly, when three molecules simultaneous interact with 8-oxoguanine, the largest deviations from additivity again occur when hydrogen fluoride and/or water are present at O6-(N7) and O6(N1). However, the magnitude of the deviation is considerably larger, ranging from approximately 12 to 17 kJ mol^{-1}. Δ is larger for complexes involving three XH molecules because it is directly related to the sum of the Δ for the corresponding pairs of binding sites. For example, consider the complex with hydrogen fluoride molecules at O6(N7), O6(N1), and O8(N7). The deviations from additivity for two hydrogen fluoride molecules simultaneously bound at O6(N7) and O6-(N1), O8(N7) and O6(N1), and O6(N7) and O8(N7) are -8.8, -5.5, and -5.3 kJ mol^{-1}, respectively. The sum of the deviations from additivity for these three complexes is -19.6 kJ mol^{-1}, which is only slightly greater in absolute value than the deviation (-17.1 kJ mol^{-1}) calculated for the complex with hydrogen fluoride simultaneously bound at all three sites. Therefore, as discussed for guanine, there is a compounded competition between the 8-oxoguanine sites for hydrogen-bonding interactions. This leads to a decrease in the magnitude of the effects of hydrogen bonds of the second and third molecule bound to the purine on the acidity.

Similarly, the effects of four hydrogen fluoride molecules on the acidity of 8-oxoguanine deviate by -22.1 kJ mol^{-1} from the sum of the individual effects (Table S4). The absolute value of this deviation is slightly smaller than the sum of the deviations in additivity for all combinations of two sites (-27.7 kJ mol^{-1}). Alternatively, the deviation from additivity of four binding interactions can be approximated by summing the Δ for three binding interactions and the Δ due to binding at the remaining site, which can be accounted for by adding the Δ for all combinations of two binding sites involving the remaining site (-25.3 to -26.9 kJ mol^{-1}). Thus, the larger deviations from additivity calculated for complexes with three or four molecules interacting with 8-oxoguanine are expected on the basis of deviations observed when two molecules bind to 8-oxoguanine.

Despite larger deviations from additivity as the number of molecules bound to 8-oxoguanine increases, there is still a significant increase in the acidity as additional molecules are complexed. For example, hydrogen fluoride at O8(N7) increases the acidity by 48 kJ mol^{-1}. A second hydrogen fluoride at N3(N2) further increases the acidity by 35 kJ mol^{-1} (83 kJ mol^{-1} total increase). A third hydrogen fluoride at O6(N1) further increases the acidity by 30 kJ mol^{-1} (113 kJ mol^{-1} total increase), and a fourth hydrogen fluoride at O6(N7) further increases the acidity by 17 kJ mol^{-1} (130 kJ mol^{-1} total increase).

In the above example, it should be noted that, although a clear decrease in the additional effect on the acidity is observed as more HF molecules are bound to 8-oxoguanine, the magnitude of the effect varies with binding site even in single XH−purine complexes (Table 5). Furthermore, it is interesting to note that an increase in the deviation from additivity as the number of XH molecules increases can be clearly seen using the above example. For example, it is noted in the previous paragraph that a second hydrogen fluoride at N3(N2) further increases the acidity by 35 kJ mol^{-1}, which is 3 kJ mol^{-1} smaller than the effect of one HF molecule at N3(N2) (38.1 kJ mol^{-1}, Table 5), or, in other words, the effect of the second HF is 3 kJ mol^{-1} less than additive. Similarly, the third HF molecule at O6(N1) is less than additive by 7 kJ mol^{-1} (10 kJ mol^{-1} total deviation), and the fourth at O6(N7) is less than additive by 12 kJ mol^{-1} (22 kJ mol^{-1} total deviation). This example provides further support to our statements regarding the compounded competition between binding sites.

In summary, interactions with 8-oxoguanine can increase the acidity by up to 48 kJ mol^{-1}, where interactions with the carbonyl group generated upon oxidation of guanine generally lead to the most significant changes. The calculated effects of two, three, or four molecules simultaneously interacting with 8-oxoguanine indicate that the effects of multiple small molecules are increasingly less than additive as the number of small molecules bound increases. In general, the simultaneous effects of two, three, or four binding interactions on the acidity are up to 9, 17, and 22 kJ mol^{-1} less than additive. However, the deviations from additivity for complexes involving three or four XH molecules are related to the sum of the deviations for the corresponding combinations of two binding interactions. Nevertheless, significant increases in the acidity are still observed with an increasing number of molecules bound, where, for example, four interactions can increase the acidity by up to 130 kJ mol^{-1}.

Conclusions

The first step to understanding the biological role of hydrogen bonds involving nucleobases is at least in part understanding the physical and chemical properties of complexes between the nucleobases and various small molecules. In the present study, we consider hydrogen-bonded complexes between ammonia, water, or hydrogen fluoride and the natural purines or their 8-oxo derivatives. We consider the binding strengths within neutral and (N9) anionic complexes and the effect of hydrogen bonds on the (N9) acidity of the purines. The (calculated) simultaneous effects of more than one small molecule bound to the purine on the acidity, as well as deviations of these effects from the sum of the effects of the corresponding individual (additive) binding interactions, are also considered.

For all purine derivatives considered in the present work, we find that the effects of hydrogen-bonding interactions on the (N9) acidity are highly dependent upon the molecule interacting with the purine, where the effect increases as $NH_3 < H_2O <$ HF. The largest increase in the acidity is approximately 50 kJ mol^{-1} for guanine, 8-oxoguanine, and 8-oxoadenine and 60 kJ mol^{-1} for adenine. The effects of two or more molecules on the acidity of the purine derivatives follow trends similar to the individual effects with respect to the nature of the molecule bound and the binding site.

The simultaneous effects of two molecules on the acidity can be as large as 85−95 kJ mol^{-1}, which represents negative deviations from additivity of approximately 5 kJ mol^{-1}. The magnitude of the deviation from additivity is found to increase with the number, as well as the acidity, of the molecules bound to the nucleobase. Less than additive effects are observed because the small molecules bound to the nucleobase primarily

act as hydrogen-bond donors, especially in anionic complexes, which provides competition for the hydrogen-bond acceptor sites of the purine. Competition between neighboring binding sites that share a common purine acceptor or donor leads to increased deviations from additivity. However, large deviations also occur when competition for binding occurs at sites that are spatially separated and therefore do not involve the same purine acceptor or donor.

As interactions between more than two molecules and the purines are considered, it becomes clear that the simultaneous (calculated) effects of multiple hydrogen-bonding interactions on the purine acidity continuously deviate to a greater extent from additivity as the number of molecules bound increases. For example, the simultaneous (calculated) effect of three or four hydrogen-fluoride molecules interacting with 8-oxoguanine are up to 17 and 22 kJ mol^{-1} less than the sum of the individual (additive) effects, respectively. Larger deviations from additivity when more than two molecules interact with the purines are indicative of a compounded competition between binding sites for hydrogen-bonding interactions and a decrease in the ability of the purine to accept additional hydrogen bonds. Nevertheless, a significant increase in the acidity of the purines is still observed upon binding additional small molecules at various sites, where the interactions with three or four molecules can increase the acidity by up to 115 and 130 kJ mol^{-1}, respectively.

The present study provides a greater understanding of hydrogen bonds involving nucleobases and the effects of these hydrogen bonds on the molecular properties of the purine derivatives. The main driving force for the present study is our interest in DNA repair enzymes that remove damaged purines, possibly through the formation of (N9) anions. Although we use small computational models and a fundamental, systematic approach, interesting trends emerge from our data that are likely relevant to the mechanism of DNA repair enzymes. Most notably, we find that hydrogen-bonding interactions with one small molecule can significantly increase the (N9) acidity of the purines in the gas phase (by up to 60 kJ mol^{-1}), and the simultaneous effects of more than one hydrogen-bonding interaction are even greater. These effects are similar to those reported in our studies of uracil derivatives[1,2] despite differences in the acid−base properties of the purines as compared to the pyrimidines.[3] Thus, although the present work must be extended to consider environmental effects and interactions with discrete active site amino acid residues, our results suggest that even partial protonation of purine derivatives accomplished through active-site hydrogen-bonding interactions may facilitate removal of damaged and mismatched purines.

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Supporting Information Available: B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d,p) acidities of the complexes, the effect of the hydrogen bonds on the acidity (Δ(acidity)), the additive effects of individual interactions (additive), and the deviations from additivity (Δ) for adenine, 8-oxoadenine, guanine, and 8-oxoguanine derivatives (Tables S1−S4). Cartesian coordinates for neutral complexes between ammonia, water, and hydrogen fluoride at each binding site within the four nucleobases (Table S5). This material is available free of charge via the Internet at http://pubs.acs.org.

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(50) The distance between XH and the purine acceptor and donor sites is 0.035 and 0.102 Å longer, respectively, for the N1(N6) water complex as compared to the N7(N6) complex. The corresponding increases in the ammonia complexes are 0.12 and 0.046 Å, while those for the hydrogen fluoride complexes are 0.001 and 0.161 Å. These changes are likely at least in part due to the formation of a six-membered hydrogen-bonded ring in N1(N6) complexes versus a seven-membered ring in N7(N6) complexes.

(51) Increases in the acidity of adenine due to interactions with water are only 3−5 kJ mol^{-1} larger than those previously discussed for uracil derivatives (see refs 1 and 2). However, increases in the adenine acidity due to hydrogen fluoride are over 10 kJ mol^{-1} larger than those observed for uracil derivatives. The larger effect of HF on the adenine acidity is at least in part due to a much larger decrease in the hydrogen-bond distance involving the nucleobase acceptor upon anion formation, which is 0.3 Å for adenine as compared to 0.2 Å for uracil derivatives.

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(53) In a previous study, a guanine−water complex was identified where water simultaneously binds to two guanine donors (N1 and N2) (see ref 26). We find that this complex is 14.5 kJ mol^{-1} higher in energy than the lowest energy (O6(N1)) complex, and 1.2 kJ mol^{-1} higher in energy than the complex involving two guanine acceptors (O6−N7). This complex is not further considered in the present work because the corresponding (N9) anionic complex is not a stable minimum, and we are primarily interested in the effects of hydrogen-bonding interactions on the (N9) acidity of guanine.

(54) It should be noted that the calculated acidity of the complex with HF at O6(N7) and H_2O at O8(N7) is greater than the sum of the individual (additive) effects (by 4 kJ mol^{-1}). The greater than additive effect may at least in part occur because the water hydrogen not involved in hydrogen-bonding interactions with 8-oxoguanine changes orientation upon addition of HF at O6(N7), where the hydrogen is directed away from the 8-oxoguanine ring when only H_2O is present and toward the ring when both HF and H_2O are present.