

A DFT COMPUTATIONAL INVESTIGATION OF MONO-SILA-SUBSTITUTED DNA NUCLEOBASES AND THEIR HYDROGEN-BONDED WATSON-CRICK DIMERS WITH THE PARENT PURINES AND PYRIMIDINES

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Abstract

The theoretical potential for the existence of mono-sila-substituted DNA nucleobases has been addressed through density functional theory (DFT) calculations at the ω B97X-D/6-311++G** level of theory. These sila-purines and sila-pyrimidines included the sila-analogs of adenine (2-Si^H-A, 4-Si-A, 5-Si-A, 6-Si-A, and 8-Si^H-A), guanine (2-Si-G, 4-Si-G, 5-Si-G, 6-Si-G, and 8-Si^H-G), thymine (2-Si-T, 4-Si-T, 5-Si-T, 6-Si^H-T, and 7-Si^{H3}-T), and cytosine (2-Si-C, 4-Si-C, 5-Si^H-C, and 6-Si^H-C). When the sila-purines or sila-pyrimidines contained a silicon-hydrogen bond (indicated by the superscript "H" in the symbols for the sila-analogs), the methylsila-derivatives (2-Si^{Me}-A, 8-Si^{Me}-A, 8-Si^{Me}-G, 6-Si^{Me}-T, 5-Si^{Me}-C, and 6-Si^{Me}-C, indicated by the superscript "Me") were also investigated, as was the exocyclic trimethylsilyl-derivative of thymine (7-Si^{Me3}-T). With the exceptions of 5-Si-A and 5-Si-G, all of the sila-purines optimized as planar molecules; the most stable were 6-Si-A and 6-Si-G. For the pyrimidines, each of the sila-thymines optimized with a planar ring and, save for 5-Si^H-C and 5-Si^{Me}-C, each of the sila-cytosines also optimized with a planar ring; the most stable were 2-Si-T and 2-Si^H-C. Each of the sila-nucleobases were then investigated as part of a hydrogen-bonded dimer with the appropriate parent purine or pyrimidine to determine the effect of silicon substitution on the strength of the hydrogen bonds formed, after correcting for basis set superposition error. The hydrogen-bonded pairs investigated were A \cdots Si-T, Si-A \cdots T, G \cdots Si-C, and Si-G \cdots C for each of the sila-substituted nucleobases. The dimers with the greatest hydrogen bond energy were calculated to be A \cdots 4-Si-T, 6-Si-A \cdots T, G \cdots 4-Si-C, and 2-Si-G \cdots C. In all cases, the dimers with the greatest hydrogen bond energy exhibited stronger hydrogen bond energies than those calculated for any of the analogous unsubstituted DNA base pairs, which were also calculated at the same level of theory for comparative purposes. In most cases, the substitution of a silicon atom for a carbon atom did not change the hydrogen bond energy significantly. However, the presence of unprotected Si-C, Si-N, and Si-O multiple bonds may make these silicon-containing monomers and Watson-Crick dimers too reactive to be synthesized and isolated (with the exception of 7-Si^{H3}-T and 7-Si^{Me3}-T, which do not contain these reactive bonds).

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Introduction

Watson-Crick deoxyribonucleic acid (DNA) base pairing¹ describes the interaction, through hydrogen bonds, of the nitrogenous bases adenine (A), bound by two hydrogen bonds to thymine (T), and guanine (G), bound by three hydrogen bonds to cytosine (C), to form the base pairs A \cdots T and G \cdots C, and is integral to information storage in DNA. Hydrogen bonding between nucleotides is not the main contributor to nucleic acid stability; other interactions, such as the hydrophobic effect and π - π stacking also contribute² to the stability of double-stranded DNA (dsDNA). The sequence of base pairs (and, hence, information storage) is preserved by the phospho-diester linkage between deoxyribose on one nitrogenous base and phosphate on the next even when the two strands denature from each other to form single-stranded DNA (ssDNA) chains. Maintaining the nucleotide sequence in each strand preserves the integrity of the information encoded; a high degree of fidelity³ is necessary if the ssDNA information code is to interact properly with and allow for the specific recognition required by biomolecular machinery, such as transcription factors.⁴ In addition, the difference in stability between the three hydrogen bonds in the G \cdots C base pair and the two hydrogen bonds in the A \cdots T base pair affects the sites at which the dsDNA duplexes denature. For example, A \cdots T-rich regions in which only two hydrogen bonds hold most of the nitrogenous base pairs together are areas in dsDNA that will melt — denature — first.⁵

atom in the nitrogenous bases is expected to provide insight into the applications of organosilicon chemistry to fundamentally-important biomolecules, despite the concurrent production of either silicon-carbon, silicon-nitrogen, or silicon-oxygen multiple bonds (*vide infra*). However, no such experimental investigations have been reported for the purines or pyrimidines essential to the structures of DNA. Silicon-based life may currently be a far-fetched work⁶ of fiction, but the discovery⁷ of phosphates in the oceans of Enceladus, a moon of Saturn, indicated that these extraterrestrial oceans contain the elements thought to be necessary for life (but not including silicon, unfortunately). However, incorporating silicon into organic molecules to change the structure and properties of those molecules is well-documented. For example, there are enzymes⁸⁻¹⁰ that can be engineered to catalyze carbon-silicon bond formation.

Because silicon is directly below carbon in column 14 of the Periodic Table of the Elements, some of the chemical properties of silicon resemble, but are not equivalent with, the properties of carbon. Thus, the substitution of silicon for carbon in an organic molecule is often expected to yield a stable product, but with properties that are altered to a greater or lesser extent. This is often the reason many mono-sila-analogs of organic molecules^{11,12} have been able to be synthesized. There is a vast amount of information in the literature concerning organosilicon compounds, both experimental¹³ and computational.¹⁴⁻¹⁶

substituted analogs of DNA bases have been reported. However, no information concerning experimental or computational studies of sila-substituted analogs of the adenine, guanine, thymine, or cytosine, monomers, or their dimers with the parent or with sila-substituted DNA bases, is extant in the published literature. A single, brief mention of “silaguanine” was uncovered, but with no experimental or explanatory data, in the proceedings²⁰ of a conference on the origins of life on earth.

In order to address the dearth of information and the potential synthetic accessibility of sila-substituted DNA nucleobases and, perhaps, the potential for such sila-purines and sila-pyrimidines to provide a basis for silicon-based life, herein are reported the results of the density functional computational investigation at the ω B97X-D/6-311++G** level of theory of the structures and properties of the mono-sila-analogs of adenine, guanine, thymine, and cytosine and the determination of the total strengths of the hydrogen bonds formed when these mono-sila-DNA bases form Watson-Crick dimers with the appropriate unsubstituted parent DNA bases. In addition, for those mono-sila-substituted DNA bases in which an Si–H bond exists because of the position of the silicon atom substituent, additional calculations on the derivative of that base in which a methyl group replaces the hydrogen atom (or in the case of thymine, all three hydrogen atoms on the exocyclic methyl group) bound to the silicon have been carried out to further investigate the effect of this “methyl-protected” structure on the strength of the hydrogen bonds in the dimer species.

Computational Methods

The Gaussian '09 program package²¹ was used for all calculations, performed at the ω B97X-D/6-311++G** level of density functional theory (DFT)^{22,23} for all molecules. This method includes polarization and diffuse functions on all atoms, and reportedly performs well for the investigation^{24,25} of isolated biomolecules in general, and has been recommended²⁶ for main-group kinetics and thermochemistry. (No attempt was made to determine whether this method was optimal for the computational investigation of the sila-purines or sila-pyrimidines, as being beyond the scope of this study.) Similar studies investigating the base pairs in DNA have successfully used the ω B97x-D method^{27–29} for describing hydrogen bond environments, and this method has been reported to exhibit greater correlation between theoretical and experimental structures.

All calculations, whether for the purines, pyrimidines, mono-sila-analogs of these molecules, or for the Watson-Crick dimers, were initiated from planar ring geometries. Vibrational frequencies were calculated for all molecules to ascertain when local minima had been located on the relevant potential energy surfaces. Calculations were performed without the imposition of any symmetry constraints during optimization. Basis set superposition error (BSSE) counterpoise corrections^{30–32} were performed for all hydrogen-bonded dimers, and hydrogen bond energies were determined based on the BSSE corrections. In the BSSE calculations, the single point energy of each individual parent or sila-substituted nitrogenous base (such as **A** or **2-Si^H-A**) was calculated from the fixed, optimized structure of the hydrogen-bonded dimer (such as **A**...**T** or **A**...**2-Si-T**) with the atoms of **A** or **T** or **2-Si-T** replaced by ghost atoms, as appropriate, to calculate the corrected

energies of the monomers. These nucleobase-ghost pairs provided the BSSE-corrected energies for the individual nitrogenous bases when hydrogen-bonded to the appropriate counterpart nitrogenous bases.

The numbering of the mono-sila-substituted DNA bases follows the same numbering as in the parent molecules, as illustrated in Figure 1 for reference purposes. When a silicon atom replaces a carbon atom having an attached hydrogen atom, the resulting molecule was investigated both with an Si–H moiety and an Si–CH₃ moiety to probe the effect of an electron-donating methyl group compared to that of a hydrogen atom and to mimic the steric “protection” of the silicon atom by the methyl group. In thymine, when silicon was substituted for the exocyclic methyl group carbon (arbitrarily numbered “7”) to form an SiH₃ group, an additional calculation in which all three of the hydrogen atoms were replaced by methyl groups, to form a trimethylsilyl group, was also carried out.

Adenine, guanine, and cytosine could exist as different isomeric structures, based on prototropic tautomerism, with respect to the positions of the N–H bonds. In adenine, these two potential tautomers are the **A(N⁷–H)** and **A(N⁹–H)** structures, while for guanine, four tautomers may be envisioned: **G(N¹–H,N⁷–H)**, **G(N¹–H,N⁹–H)**, **G(N³–H,N⁷–H)**, and **G(N³–H,N⁹–H)**. No such tautomerism is possible with thymine, but cytosine also has two potential tautomers, the **C(N¹–H)** and **C(N³–H)** structures. However, only the tautomers that are of biological importance, **A(N⁹–H)**, **G(N¹–H,N⁹–H)**, and **C(N¹–H)**, as depicted in Fig. 1, and the mono-sila-derivatives of these tautomers, were investigated in this report. The numbering of the sila-substituted molecules employed the same numbering as in the parent molecules regardless of whether the substitution of a silicon atom for a carbon atom would alter the molecular numbering priorities.

Results and Discussion

The calculated structures and properties of the mono-sila-substituted DNA nucleobases, sila-adenine, sila-guanine, sila-cytosine, and sila-thymine, the parent purines and pyrimidines, and the hydrogen-bonded dimers, are discussed herein, beginning with the purines, followed by the pyrimidines and concluding with the hydrogen-bonded dimers.

When a single silicon atom was substituted for a single carbon atom in adenine (**A**), five sila-adenine isomers are possible: 2-sila-adenine (**2-Si^H-A**, with the superscript “H” used to distinguish this molecule from the methylsila-derivative, **2-Si^{Me}-A**, denoted by the superscript “Me”), 4-sila-adenine (**4-Si-A**), 5-sila-adenine (**5-Si-A**), 6-sila-adenine (**6-Si-A**), and 8-sila-adenine (**8-Si^H-A** and **8-Si^{Me}-A**). Similarly, based on guanine (**G**), there are five sila-derivatives, *i.e.*, 2-sila-guanine (**2-Si-G**), 4-sila-guanine (**4-Si-G**),

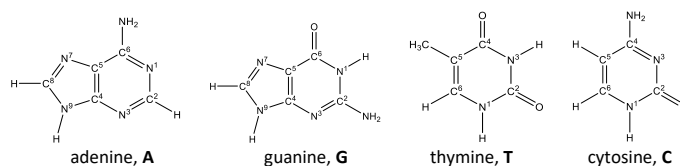


Figure 1. The parent DNA purines and pyrimidines, illustrating the numbering system in the parent molecules which was also used for the sila-purines and sila-pyrimidines.

5-sila-guanine (**5-Si-G**), 6-sila-guanine (**6-Si-G**), and 8-sila-guanine (**8-Si^H-G** and **8-Si^{Me}-G**). With cytosine (**C**), only four sila-cytosines are possible, 2-sila-cytosine (**2-Si-C**), 4-sila-cytosine (**4-Si-C**), 5-sila-cytosine (**5-Si^H-C** and **5-Si^{Me}-C**), and 6-sila-cytosine (**6-Si^H-C** and **6-Si^{Me}-C**), but five possible sila-thymine isomers (when the exocyclic methyl group, herein arbitrarily numbered “7” in thymine (**T**), was included). These five are 2-sila-thymine (**2-Si-T**), 4-sila-thymine (**4-Si-T**), 5-sila-thymine (**5-Si-T**), 6-sila-thymine (**6-Si^H-T** and **6-Si^{Me}-T**), and 7-sila-thymine (**7-Si^H3-T** and **7-Si^{Me}3-T**). The structures and properties of each of these molecules are discussed below, beginning with the purine analogs (**Si-A** and **Si-G**) and followed by the pyrimidine analogs (**Si-T** and **Si-C**).

The sila-purines

The computed electronic and structural properties of adenine and the sila-adenines, as well as the two methylsila-derivatives, are listed in Table 1. The most stable sila-adenine was calculated to be **6-Si-A**, and, although not directly comparable to the un-methylated sila-adenines, **2-Si^{Me}-A** was calculated to be more stable than **8-Si^{Me}-A**, just as **2-Si^H-A** was calculated to be more stable than **8-Si^H-A**. (See Fig. 2. Note: All molecular structure illustrations in the following figures were prepared from the Gaussian-calculated coordinates using the Spartan '18 computational package³³ for reasons of clarity.) For the parent adenine, an experimental gas-phase electron diffraction structural investigation³⁴ (supplemented with MP2/cc-pVTZ computational results) has been reported. In addition, solid-state x-ray diffraction studies have been carried out for the mono-hydrochloride^{35,36} and di-hydrochloride³⁷ salts of adenine, and these data, along with the experimental gas-phase electron diffraction results, are reported in Table 1. As detailed in the table, the calculated structure of adenine corresponds closely to the experimental electron diffraction data; protonation of adenine — as in the hydrochloride salts — results in structural changes.

Apart from **5-Si-A**, the least stable of the sila-adenines, adenine and the sila- and methylsila-adenines optimized as planar molecules with the exocyclic amino group also optimizing as coplanar with the planar ring system. Bond lengths not involving silicon in these molecules exhibited little change from the parent adenine. On the other hand, bonds to silicon in the sila-adenines are significantly longer than the corresponding bonds in **A**, leading to ring distortions, compared to the structure of **A**, due to the presence of the larger silicon atom and longer bond lengths, although the distorted rings remain planar, again apart from **5-Si-A**. The average Si–C single bond length has been reported³⁸ to be ~187 pm.

Based on the tetrahedral covalent bond radii³⁹ for carbon (77.3 pm), nitrogen (68.9 pm), and silicon (117.6 pm), bond lengths for Si–C and Si–N bonds can be calculated to be less than or equal to ~194.9 pm and ~186.5 pm, respectively. While molecules containing Si=C double bonds (sometimes termed monosilenes, silenes, or sila-ethylenes) are much less common than those containing Si–C single bonds, some molecules have been structurally characterized. Thus, for monosilenes, experimental silicon-carbon double bond lengths established through x-ray crystallography have been reported. For example, Si=C bond lengths appear to range from ~170 pm to ~177 pm: 176.4 pm in [((CH₃)₃Si)₂Si=C(OSi(CH₃)₃) (1-adamantyl)]⁴⁰, 170.2 pm in [(CH₃)₂Si=C(Si(CH₃)₃)(Si(CH₃)(*t*-butyl)₂)]⁴¹, and 174.1 pm in [((CH₃)₃Si)((CH₃)₂(*t*-butyl)Si)Si=(2-adamantyl)]⁴². (In the latter structure, the “carbon-half” of the silene was derived from 2-adamantanone such that the double bond to oxygen was replaced by a double bond to silicon.) The sila-adenines exhibited Si–C bond lengths approximating the experimentally-reported distances, or, in **5-Si-A**, the distances were closer to Si–C single bond distances.

Structurally characterized examples of Si=N double bonds (silaketimines or sila-imines) are likewise somewhat rare and, like the molecules with a Si=C double bond, are often heavily-substituted. For example, in the first structurally-characterized sila-imine, a Si=N bond length of 156.8 pm was reported using x-ray crystallography in [(*t*-butyl)₂Si=N(Si(*t*-butyl)₃)]⁴³, while in [(HCNDipp)₂Si=C(2,6-di(2,4,6-trimethylphenyl)phenyl)]⁴⁴, in which HCNDipp was a stable cyclic silylene, a Si=C bond length

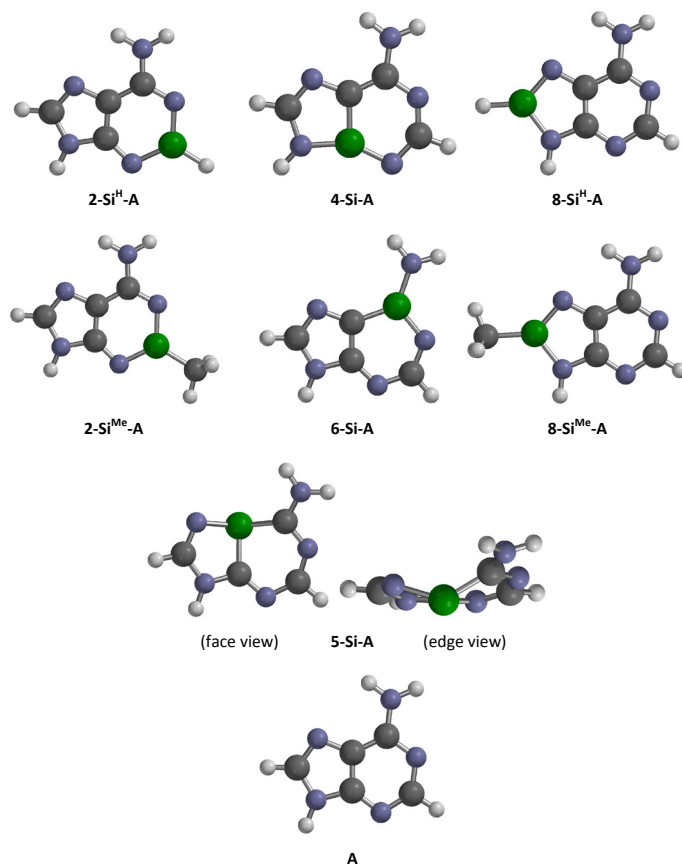


Figure 2. The sila-adenines and adenine. Atom color key: dark gray, C; light gray, H; blue, N; and green, Si.

Table 1. Selected electronic and structural properties of adenine and the sila-adenines

Molecule	Electronic energy (a.u.)	Dipole moment (D)	Heavy atom bond distances (pm) ^a												
			N ¹ -2	2=N ³	N ³ -4	4=5	5-6	6-N ¹	6-NH ₂	5-N ⁷	N ⁷ -8	8-N ⁹	N ⁹ -4	Si-CH ₃	
A	-467.288610	2.50	133.9	132.7	133.4	138.8	140.6	133.6	134.8	138.1	130.2	137.4	137.2		
A⁺			134.4	133.0	133.3	138.8	140.6	133.2	134.8	138.1	130.2	137.4	137.2		
A·HCl⁺			133.	134.	136.	144.	138.	134.	134.	132.	138.	137.	128.		
A·HCl·0.5H₂O⁺			137.4	128.9	135.8	137.7	140.3	136.0	131.1	137.7	132.0	135.1	136.0		
A·2HCl⁺			136.1	130.2	134.8	137.7	140.0	135.8	130.7	137.7	132.0	133.5	137.2		
2-Si^H-A	-718.684008	1.07	166.0	165.1	134.5	140.0	142.6	133.4	134.7	138.2	129.9	137.3	137.5		
4-Si-A	-718.641612	3.40	133.2	135.3	165.3	172.8	140.1	136.1	134.8	139.5	129.4	140.9	171.5		
5-Si-A	-718.612804	1.50	133.7	133.2	133.1	181.0	185.1	134.3	134.5	176.4	128.6	139.9	136.2		
6-Si-A	-718.688403	2.24	133.5	132.6	134.5	141.5	176.4	164.6	167.3	138.8	129.9	136.9	137.3		
8-Si^H-A	-718.669049	4.24	133.5	132.6	133.5	140.1	141.2	133.5	134.9	138.9	163.8	171.0	139.2		
2-Si^{Me}-A	-758.016667	0.90	166.4	165.4	134.4	140.5	142.6	133.3	134.8	138.4	129.9	137.4	137.6	184.4	
8-Si^{Me}-A	-758.002098	6.01	133.4	132.7	133.5	140.0	140.9	133.6	135.5	139.1	163.8	171.3	139.4	184.2	

^a Column heading numbers refer to standard atom numbering as given in Fig. 1. Silicon-carbon bond distances are **bold** and silicon-nitrogen bond distances are **bold italics**. ^b Reference 34. ^c Reference 35. ^d Reference 36. ^e Reference 37.

of 153.3 pm was determined. While the Si-CH₃ bonds in **2-Si^{Me}-A** and **8-Si^{Me}-A** are unremarkable, the Si-C and Si-N bonds in the rings are longer than the experimental bond distances for Si=C and Si=N double bonds, yet shorter than would be expected for single bonds. Thus, some bond delocalization or aromatic character for these silicon-containing heterocycles may exist in these molecules. Adenine itself, along with other purines, is considered to exhibit aromatic character.^{45,46}

The computed electronic and structural properties of guanine, the sila-guanines, and the single methylsila-derivative, are listed in Table 2; the most stable sila-guanine was calculated to be **6-Si-G**. For the parent guanine, an experimental gas-phase electron diffraction structural investigation⁴⁷ has been reported, but this study was of the N⁷-H rather than the N⁹-H tautomer of this study. However, a solid-state x-ray diffraction study has been carried out for the mono-hydrate⁴⁸ of guanine, and these results are reported in Table 2. With the exception of **5-Si-G**, all of the sila-guanines, and guanine itself, optimized as planar molecules, as depicted in Fig. 3, although the exocyclic amino groups in these molecules exhibited some minor amounts of pyramidalization.

As was observed with the sila-adenines, the 5-sila-isomer was strongly distorted, but in the case of **5-Si-G**, the silicon-carbon bond was significantly lengthened and was calculated to be longer

Table 2. Selected electronic and structural properties of guanine and the sila-guanines

Molecule	Electronic energy (a.u.)	Dipole moment (D)	Heavy atom bond distances (pm) ^a												
			N ¹ -2	2=N ³	2-NH ₂	N ³ -4	4=5	5-6	6-N ¹	6=O	5-N ⁷	N ⁷ =8	8-N ⁹	N ⁹ -4	Si-CH ₃
G	-542.528816	6.73	136.7	130.2	137.1	135.6	138.4	143.8	142.8	120.8	137.7	129.9	137.8	136.3	
G (N ⁷ -H) ^b			139.5	131.4	138.8	137.9	140.1	144.3	143.0	123.7	137.5	136.2	131.6	137.5	
G·H ₂ O ^c			137.1	131.5	136.4	139.2	140.5	139.8	133.3	123.9	140.5	131.9	136.9	136.4	
2-Si-G	-793.948367	8.09	168.8	161.8	167.0	136.6	140.1	145.0	144.5	120.7	138.1	129.6	137.7	136.6	
4-Si-G	-793.889678	6.96	137.2	132.2	136.5	166.2	172.2	142.6	148.1	120.7	139.2	129.1	141.7	170.2	
5-Si-G	-793.869566	7.21	136.5	131.6	135.7	134.0	186.5	190.8	146.8	120.2	178.7	127.2	141.5	134.7	
6-Si-G	-793.952046	8.21	137.1	130.0	136.9	135.7	140.0	178.2	174.8	152.1	138.7	129.7	137.3	136.5	
8-Si ^H -G	-793.903946	6.53	136.2	129.8	137.5	136.2	139.6	144.9	142.1	120.9	138.0	163.6	171.9	138.2	
8-Si ^{Me} -G	-833.236011	6.71	136.2	129.7	137.8	136.3	139.3	144.7	142.2	121.1	138.4	163.4	172.0	138.6	184.4

^a Column heading numbers refer to standard atom numbering as given in Fig. 1. Silicon-carbon bond distances are **bold**, silicon-nitrogen bond distances are **bold italics**, and silicon-oxygen bond distances are **bold underlined**. ^b Reference 47. ^c Reference 48.

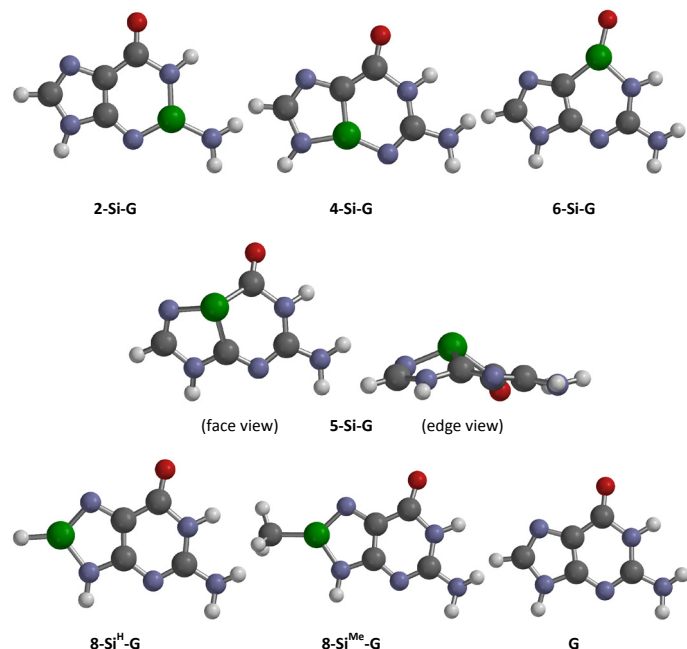


Figure 3. The sila-guanines and guanine. Atom color key: dark gray, C; light gray, H; blue, N; red, O; and green, Si.

than 190 pm. While this length remains shorter than the sum of the covalent radii for silicon and carbon (194.9 pm), the lack of planarity and distortion from planarity may indicate a lack of stability (or enhanced reactivity) for **5-Si-G** (and for **5-Si-A** as well).

The sila-guanines, like the sila-adenines, contain Si-C and Si-N bonds which may exhibit some double bond character, as was noted for the sila-adenines. However, unlike **A** and the sila-adenines, **G** and the sila-guanines contain a carbonyl group and, thus **6-Si-G** contains a silicon-oxygen double bond: a sila-carbonyl group or a silanone. Such molecules are rare; the first reported⁴⁹ silanone exhibited a Si=O bond length of 152.3 pm; the silanone moiety was stabilized with a Si-Cr bond to a tricarbonyl-(pentamethylcyclopentadienyl)chromium complex and a Si-C bond to the “SI-dipp” (1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene) group. The geometry about the silicon atom was trigonal planar in this novel silanone. In **6-Si-G**, the Si=O distance was calculated to be 152.1 pm.

The pyramidalization at the silicon centers in **5-Si-A** and **5-Si-G** may indicate the potential for reactivity in these molecules, such that the silicon atom might attain a tetrahedral-type geometry if a reaction at these sites occurs. Such a reaction would disrupt any aromatic character that these pyrimidines might possess. (A similar pyramidalization was observed in **5-Si^H-C** and **5-Si^{Me}-C**, *vide infra*.)

The sila-pyrimidines

The computed electronic and structural properties of thymine, the sila-thymines, the 6-methylsila-derivative, and the exocyclic 7-trimethylsila-derivative, are listed in Table 3. The most stable sila-thymine was calculated to be **2-Si-T**, in which, as in **6-Si-G**, a silanone moiety was present. Interestingly, the next most stable sila-thymine was **4-Si-T**, which also contained a silanone group. For the parent thymine, an experimental gas-phase electron diffraction structural investigation⁵⁰ (supplemented with MP2/cc-pVTZ computational results) has been reported. In addition, a solid-state x-ray diffraction study has been carried out for the mono-hydrate⁵¹ of thymine, and these results are reported in Table 3. Each of the sila-thymines, and thymine itself, optimized with a planar ring system, as depicted in Fig. 4.

Structurally, the present calculations for thymine compare closely with the gas-phase electron diffraction results, indicating that the results for the sila-thymines are likely to be realistic as well. The sila-thymines contain Si-C, Si-N, and Si-O bonds; the silanone bond distances parallel the distance calculated for **6-Si-G**, and the Si-C and Si-N bonds in the ring are again longer than expected for double bonds and shorter than expected for single bonds. While **7-Si^{H3}-T** was calculated to not be the most stable of the sila-thymines, this derivative, along with **7-Si^{Me3}-T**, may be the most likely of the sila-thymines to be able to be synthesized, as these two derivatives do not contain any unprotected and potentially highly reactive Si-C, Si-N, or Si-O multiple bonds. Neither the exocyclic silyl- or trimethylsilyl-derivative have been reported in the literature to have been synthesized, nor have attempts to synthesize these molecules been reported.

The computed electronic and structural properties of cytosine,

the sila-cytosines, and the two methylsila-derivatives, are listed in Table 4; the molecules are illustrated in Fig. 5. In the gas-phase, apparently, there exist five tautomers (including keto-enol and *cis-trans* systems as well as the two mentioned earlier) of cytosine, making the determination of the gas-phase structure⁵² very complicated. However, a solid-state investigation of the structure of cytosine and cytosine monohydrate has been carried out using x-ray crystallography, and these results are included in the table. Considering that the calculated structure of C herein has no intramolecular contacts and the experimental structure was in the solid-state, the structures are generally similar.

The most stable of the sila-cytosines was 2-Si-C, which, like 2-Si-T and 4-Si-T, contained a silanone moiety. Unlike the

Table 3. Selected electronic and structural properties of thymine and the sila-thymines

Molecule	Electronic energy (a.u.)	Dipole moment (D)	Heavy atom bond distances (pm) ^a																	
			N ¹ -2	2=N ³	2=O	N ³ -4	4-5	4=O	5=6	5-7	6-N ¹	Si-CH ₃								
T	-454.122017	4.52	138.1	138.0	120.9	139.9	146.6	121.1	134.3	149.7	137.7									
T ^b			137.7	137.8	121.0	139.5	146.6	121.5	134.4	148.7	137.2									
T-H ₂ O ^c			135.5	136.1	123.4	139.1	144.7	123.1	134.9	150.3	138.2									
2-Si-T	-705.550748	4.66	170.0	169.6	151.7	140.8	147.7	121.0	134.5	150.2	139.0									
4-Si-T	-705.538235	5.48	139.1	138.3	120.8	172.3	181.2	152.0	135.0	150.9	137.9									
5-Si-T	-705.464453	5.35	137.3	139.7	121.4	139.8	187.3	121.4	172.2	185.4	139.5									
6-Si ^H -T	-705.494187	5.96	139.7	138.1	120.9	142.1	146.1	121.5	170.8	150.6	170.8									
7-Si ^H -T	-705.506077	4.12	138.8	137.8	120.7	140.1	146.4	121.2	134.9	187.0	137.0									
6-Si ^{Me} -T	-744.827930	7.42	139.6	137.9	121.1	142.3	145.6	121.6	171.0	150.7	171.1	184.7								
7-Si ^{Me} -T	-823.494592	4.24	138.4	137.8	120.8	140.1	146.5	121.4	134.8	188.6	137.3	187.6 ^d								

^a Column heading numbers refer to standard atom numbering as given in Fig. 1. Silicon-carbon bond distances are **bold**, silicon-nitrogen bond distances are **bold italics**, and silicon-oxygen bond distances are **bold underlined**. ^b Reference 50. ^c Reference 51. ^d Mean value.

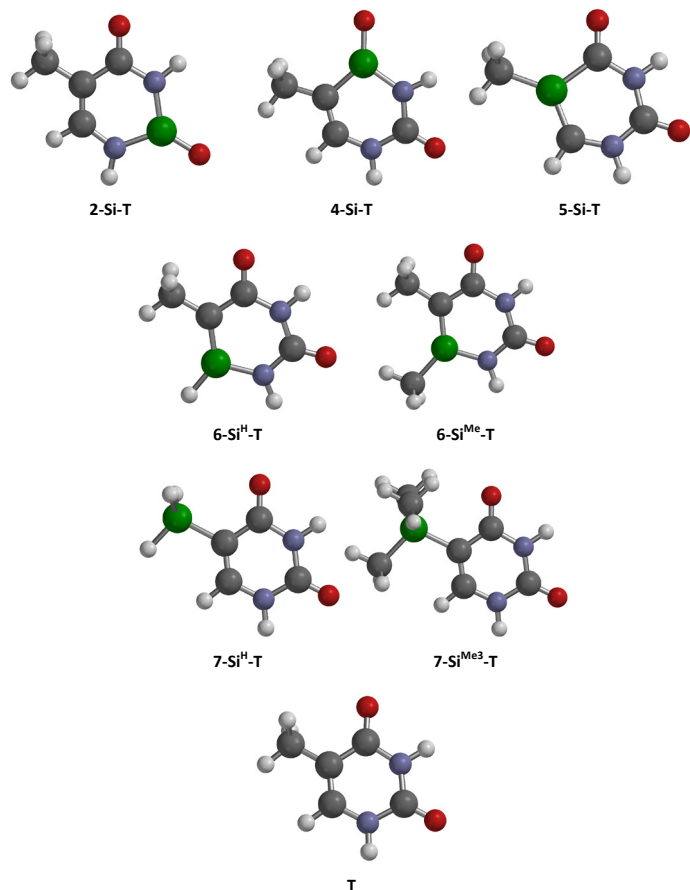


Figure 4. The sila-thymines and thymine. Atom color key: dark gray, C; light gray, H; blue, N; red, O; and green, Si.

sila-thymines, however, wherein all molecules contained planar rings, 5-Si^H-C and 5-Si^{Me}-C optimized as non-planar structures in a similar fashion to 5-Si-A and 5-Si-G. While in 5-Si-A, 5-Si^H-C, and 5-Si^{Me}-C, the silicon substituent was adjacent to a carbon atom with an attached amino group, in 5-Si-G the silicon substituent was adjacent to a carbonyl group; the reasons for the optimization of these molecules as non-planar systems are not clear. However, the geometry about the silicon atom appears to approach pyramidalization rather than remaining trigonal planar in these four molecules.

The hydrogen-bonded dimers

Having established the monomeric structures and relative energies of the sila-derivatives of adenine, guanine, thymine, and cytosine, the ability of these sila-derivatives to form hydrogen bonds in a Watson-Crick fashion with the parent purines and pyrimidines was investigated. However, the energies of the hydrogen bonded

Table 4. Selected electronic and structural properties of cytosine and the sila-cytosines

Molecule	Electronic energy (a.u.)	Dipole moment (D)	Heavy atom bond distances (pm) ^a																	
			N ¹ -2	2=N ³	2=O	N ³ -4	4-5	4-NH ₂	5=6	6-N ¹	Si-CH ₃									
C	-394.915295	6.85	141.9	136.7	121.1	131.2	143.9	135.4	135.1	135.1										
C ^b			138.1	136.4	124.1	133.6	141.0	134.2	134.0	135.3										
C-H ₂ O ^b			137.1	135.0	125.1	134.1	142.5	132.6	133.3	135.3										
2-Si-C	-646.349773	7.99	174.0	166.2	152.0	130.9	145.2	135.4	135.4	136.6										
4-Si-C	-646.322155	7.36	145.6	135.0	121.1	162.1	177.8	167.4	137.0	135.2										
5-Si ^H -C	-646.246324	4.88	144.5	135.9	120.9	131.1	189.5	134.7	180.2	133.0										
6-Si ^H -C	-646.287704	7.04	144.1	136.3	121.1	131.9	144.6	136.0	170.8	168.2										
5-Si ^{Me} -C	-685.571037	6.74	142.2	136.9	121.3	130.7	187.7	135.3	176.6	135.2	188.0									
6-Si ^{Me} -C	-685.621422	8.14	144.0	136.2	121.3	131.9	144.2	136.3	171.2	168.5	184.7									

^a Column heading numbers refer to standard atom numbering as given in Fig. 1. Silicon-carbon bond distances are **bold**, silicon-nitrogen bond distances are **bold italics**, and silicon-oxygen bond distances are **bold underlined**. ^b Reference 53.

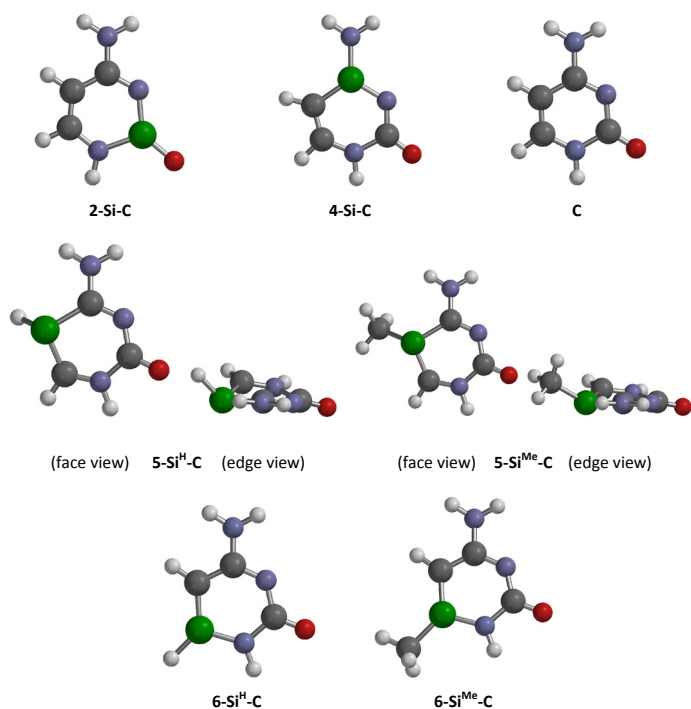


Figure 5. The sila-cytosines and cytosine. Atom color key: dark gray, C; light gray, H; blue, N; red, O; and green, Si.

dimers to be investigated, $A\cdots Si-T$, $Si-A\cdots T$, $G\cdots Si-C$, and $Si-G\cdots C$, and, thus, the hydrogen bond energies, could not simply be calculated by subtracting the energies of the isolated monomers from the energies of the dimers: The energies of the dimers were calculated with additional basis set functions not present in the calculations of the monomers because of the presence of the “other” molecule involved in the dimer structure. Thus, basis set superposition error (BSSE) corrections (*vide supra*) were employed to re-determine the energies of the monomers before the determination of the hydrogen bond energies was made. These BSSE-corrected energies for the monomers are the energies reported in Tables 5 and 6; the BSSE differences ranged from ~ 3 kJ/mol to ~ 6 kJ/mol.

The selected electronic and structural results for the $A\cdots Si-T$ and $Si-A\cdots T$ dimers are listed in Table 5. While the most stable non-methylated sila-adenine was **6-Si-A**, and the most stable non-methylated sila-thymine was **2-Si-T**, the dimers with the greatest total hydrogen bond energies were $A\cdots 4-Si-T$ and $6-Si-A\cdots T$, although the $2-Si^{Me}-A\cdots T$ dimer also was calculated to exhibit a significant hydrogen bond energy and was the most stable of the methylated dimers that could be compared. Fig. 6a and 6b illustrate the structures of the $A\cdots T$, $A\cdots Si-T$ and $Si-A\cdots T$ dimers. With the exception of the $5-Si-A\cdots T$ dimer, all of the $A\cdots T$ dimers optimized as planar systems; **5-Si-A** was the only adenine derivative that did not optimize as a planar molecule and all of the thymine derivatives also optimized as planar molecules.

Table 6 lists selected electronic and structural results for the $G\cdots Si-C$ and $Si-G\cdots C$ dimers; the structures of the dimers are illustrated in Fig. 7a and 7b. With the exceptions of the $G\cdots 5-Si^H-C$, $G\cdots 5-Si^{Me}-C$, and $5-Si-G\cdots C$ dimers, all of the $G\cdots C$ dimers optimized as planar systems; the $5-Si^H-C$, $5-Si^{Me}-C$, and $5-Si-G$ monomers also were calculated to be non-planar after optimization. Of the non-methylated $G\cdots C$ dimers, the most stable were $G\cdots 2-Si-C$ and $2-Si-G\cdots C$; the latter, along with $G\cdots 4-Si-C$, exhibited the greatest hydrogen bond strengths. For the methylated dimers that could be compared, $G\cdots 6-Si^{Me}-C$ was the most stable.

The experimentally-determined hydrogen bond enthalpy for the $A\cdots T$ dimer in the gas phase has been reported⁵⁴ to be 13.0 kcal/mol, while for $G\cdots C$, the same report provides a value of 21.0 kcal/mol. These values convert to 54.4 kJ/mol and 87.9 kJ/mol, respectively. While the current calculations seriously overestimate the hydrogen bond energies of the parent dimers, the exper-

Table 5. Selected electronic and structural properties of the adenine hydrogen-bonded dimers with the sila-thymines and the thymine hydrogen-bonded dimers with the sila-adenines

Dimer	Electronic energy (a.u.) ^a				Bond distance (pm)		Bond angle	
	A monomer	T monomer	A...T dimer	difference ^b	N ^A -O ^T	N ^A -N ^T	$\angle N^AHO^T$	$\angle N^AHN^T$
A...T	-467.288597	-454.121230	-921.436732	0.026905 [70.64]	294.3	283.2	173.2°	179.8°
A...T ^c					294. ^d	284. ^d		
A...2-Si-T	-467.288533	-705.549986	-1172.865741	0.027222 [71.47]	293.0	284.3	173.2°	175.7°
A...4-Si-T	-467.287968	-705.537259	-1172.856485	0.031258 [82.07]	288.2	283.8	179.4°	172.1°
A...5-Si-T	-467.288652	-705.463849	-1172.777736	0.025235 [66.25]	293.9	285.6	172.4°	179.4°
A...6-Si ^H -T	-467.288594	-705.493452	-1172.808023	0.025977 [68.20]	289.6	287.2	172.4°	177.7°
A...7-Si ^{H3} -T	-467.288629	-705.505160	-1172.821288	0.027499 [72.20]	293.0	282.3	173.0°	179.4°
A...6-Si ^{Me} -T	-467.288575	-744.827247	-1212.141636	0.025814 [67.77]	290.7	288.1	172.9°	177.3°
A...7-Si ^{Me3} -T	-467.288560	-823.493823	-1290.809306	0.026923 [70.69]	294.1	283.4	173.5°	179.7°
2-Si ^H -A...T	-718.684162	-454.121194	-1172.832572	0.027216 [71.46]	294.7	283.2	173.8°	178.2°
4-Si-A...T	-718.614542	-454.121029	-1172.790334	0.027763 [72.89]	291.7	283.9	176.6°	178.9°
5-Si-A...T	-718.612652	-454.121185	-1172.761517	0.027680 [72.67]	290.0	284.8	177.8°	178.5°
6-Si-A...T	-718.688298	-454.120906	-1172.838676	0.029472 [77.38]	290.9	282.2	162.6°	179.5°
8-Si ^H -A...T	-718.699027	-454.121109	-1172.816717	0.026581 [69.79]	294.9	282.4	172.3°	179.9°
2-Si ^{Me} -A...T	-758.017066	-454.121136	-1212.167371	0.029169 [76.58]	292.3	286.2	170.7°	177.3°
8-Si ^{Me} -A...T	-758.002035	-454.121019	-1212.149636	0.026582 [69.79]	295.9	282.2	172.3°	179.1°

^a Electronic energies of the monomers have been corrected for BSSE (see text). ^b The difference values are the calculated hydrogen bond energies; difference = $E(A \text{ monomer}) + E(T \text{ monomer}) - E(A\cdots T \text{ dimer})$; the values in square brackets are the differences expressed in kJ/mol. ^c Reference 55. ^d Mean value.

Table 6. Selected electronic and structural properties of the guanine hydrogen-bonded dimers with the sila-cytosines and the cytosine hydrogen-bonded dimers with the sila-guanines

Dimer	Electronic energy (a.u.) ^a				Bond distance (pm)			Bond angle	
	G monomer	C monomer	G...C dimer	difference ^b	N ^G -O ^C	N ^G -N ^C	O ^C -N ^C	$\angle N^GHO^C$	$\angle O^CHN^C$
G...C	-542.526623	-394.913919	-937.492351	0.051809 [136.02]	291.4	291.9	278.0	178.4°	178.5°
G...C ^c					291.	295.	286.		
G...2-Si-C	-542.526725	-646.347716	-1188.923820	0.049379 [129.64]	295.8	294.1	276.1	174.7°	174.9°
G...4-Si-C	-542.526446	-646.320793	-1188.902096	0.054857 [144.03]	292.9	290.8	279.0	178.1°	179.5°
G...5-Si ^H -C	-542.526767	-646.244485	-1188.821038	0.049786 [130.71]	288.4	299.5	276.5	177.0°	175.7°
G...6-Si ^H -C	-542.526566	-646.285972	-1188.864604	0.052066 [136.70]	284.0	301.0	277.2	177.3°	176.0°
G...5-Si ^{Me} -C	-542.526422	-685.568685	-1228.148803	0.053696 [140.98]	283.2	300.7	276.0	177.3°	175.5°
G...6-Si ^{Me} -C	-542.526492	-685.619700	-1228.199055	0.052860 [138.78]	282.7	300.2	278.3	177.4°	176.4°
2-Si-G...C	-793.950579	-394.912937	-1188.920857	0.057341 [150.55]	290.2	294.6	273.4	173.1°	167.8°
4-Si-G...C	-793.887639	-394.913884	-1188.852595	0.051072 [134.09]	286.5	303.9	275.2	174.3°	178.5°
5-Si-G...C	-793.867529	-394.914203	-1188.832271	0.050539 [127.69]	286.1	297.4	280.9	176.5°	178.2°
6-Si-G...C	-793.946190	-394.913789	-1188.912469	0.052490 [137.81]	293.6	288.4	280.5	168.3°	178.0°
8-Si ^H -G...C	-793.900632	-394.913997	-1188.867144	0.052515 [137.88]	290.2	290.9	280.0	177.9°	176.4°
8-Si ^{Me} -G...C	-833.233587	-394.913653	-1228.198311	0.051071 [134.09]	293.4	291.9	276.8	177.9°	176.9°

^a Electronic energies of the monomers have been corrected for BSSE (see text). ^b The difference values are the calculated hydrogen bond energies; difference = $E(G \text{ monomer}) + E(C \text{ monomer}) - E(G\cdots C \text{ dimer})$; the values in square brackets are the differences expressed in kJ/mol. ^c Reference 56.

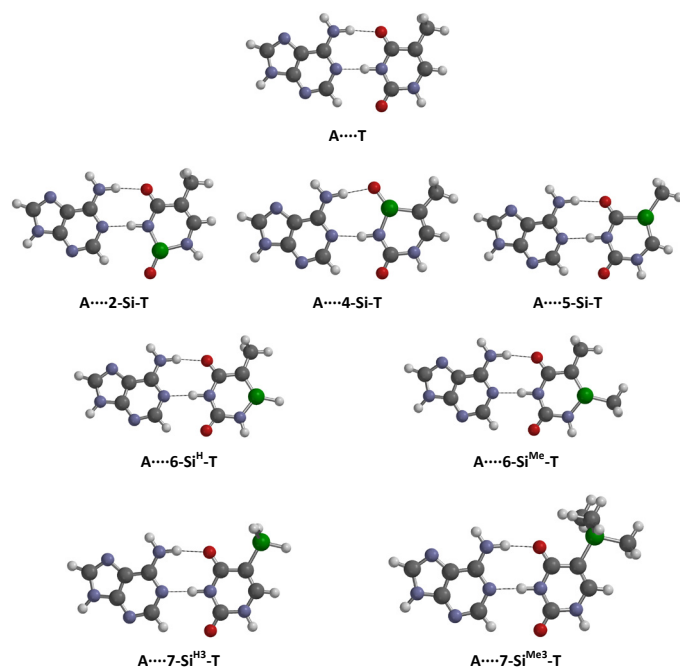


Figure 6a. The adenine dimers with the sila-thymines. Atom color key: dark gray, C; light gray, H; blue, N; red, O; and green, Si.

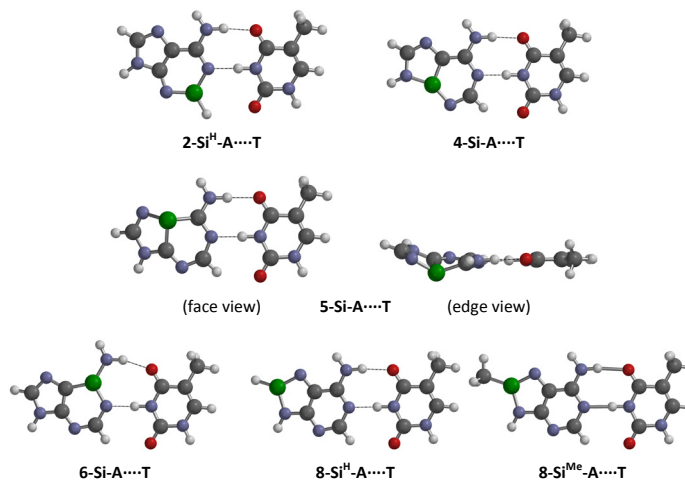


Figure 6b. The sila-adenine dimers with thymine. Atom color key: dark gray, C; light gray, H; blue, N; red, O; and green, Si.

imental hydrogen bond lengths^{55,56} are comparable to experiment for the A····T dimer, but less so for the G····C dimer, as seen in the tables.

Although the hydrogen bond strengths calculated herein are significantly higher than experimental values, the relative values

are internally self-consistent, and do allow comparisons to be made. For the A····Si-T and Si-A····T dimers, silicon substitution does not appear to appreciably alter the hydrogen bond strength, save for A····4-Si-T, which exhibits a significantly stronger hydrogen bond strength than any of the A····T dimers including A····T itself.

Interestingly, A····4-Si-T was the only A····T dimer in which a silicon atom replaced a carbon atom at a carbonyl group to form a silanone and in which the silanone took part in hydrogen bonding. The A····2-Si-T dimer also contained a silanone, but in this case, no direct hydrogen bonding was involved. (There was a small interaction calculated to be present⁵⁷ in the A····T dimer between the C²-H of adenine and the C²=O of thymine.) While the reason for the enhanced hydrogen bond strength in A····4-Si-T is not fully understood, the nature of the silicon-oxygen bond⁵⁸ and the relative strength of the Si-O bond compared to the Si=O double bond may allow for greater hydrogen bonding in the A····4-Si-T dimer.

For the G····C dimers, the systems exhibiting the greatest hydrogen bond energies are G····4-Si-C and 2-Si-G····C, each of which contains a silicon atom that has replaced a carbon atom directly attached to an amino group directly involved in hydrogen bonding. None of the remaining dimers exhibited appreciably different hydrogen bond energies from the G····C dimer itself. (The 6-Si-A····T dimer also contains this moiety, but unlike G····4-Si-C and 2-Si-G····C, the geometry of the hydrogen bond was significantly non-linear.) As was the case with A····4-Si-T, the reasons for this enhanced hydrogen bond strength is not fully understood. However, this may also be related to multiple bonding to silicon. Silicon-nitrogen partial multiple bonding is well-known⁵⁹ and gas-phase electron diffraction studies⁶⁰ indicate that a planar structure is adopted by tris(trimethylsilyl)amine, demonstrating partial Si-N multiple bonding. If partial Si-N multiple bonding occurs here, electron density would be distributed from the nitrogen center to the silicon center, potentially allowing the hydrogen atom involved in hydrogen bonding to exhibit a greater partial positive charge and enhancing the hydrogen bond strength.

Comments on the synthetic potential of the sila-purines and sila-pyrimidines

While the herein-reported calculations at the ω B97X-D/6-311++G** level of density functional theory strongly indicate that the sila-analogs of adenine, guanine, thymine, and cytosine are stable molecules on their respective potential energy surfaces, the calculations do not account for the potential reactivity of these sila-analogs or for the difficulties that may be encountered if the syntheses of these molecules are attempted. With the exception of 7-Si^{H3}-T and 7-Si^{Me3}-T, each of the sila-analogs contains either a silicon-carbon and/or a silicon-nitrogen multiple bond as part of an aromatic ring system and/or contain a silicon-oxygen moiety as a sila-carbonyl. The well-known difficulties⁶¹⁻⁶⁵ in incorporating a silicon atom into an aromatic ring and thus taking part in multiple bonding and the difficulty of preparing a sila-carbonyl, as mentioned earlier, make the synthesis of these molecules unlikely, save for 7-Si^{H3}-T and 7-Si^{Me3}-T. These latter two sila-thymine analogs may, in fact, be the only examples of sila-purines or sila-pyrimidines related to the DNA nucleobases that may be able to be synthesized.

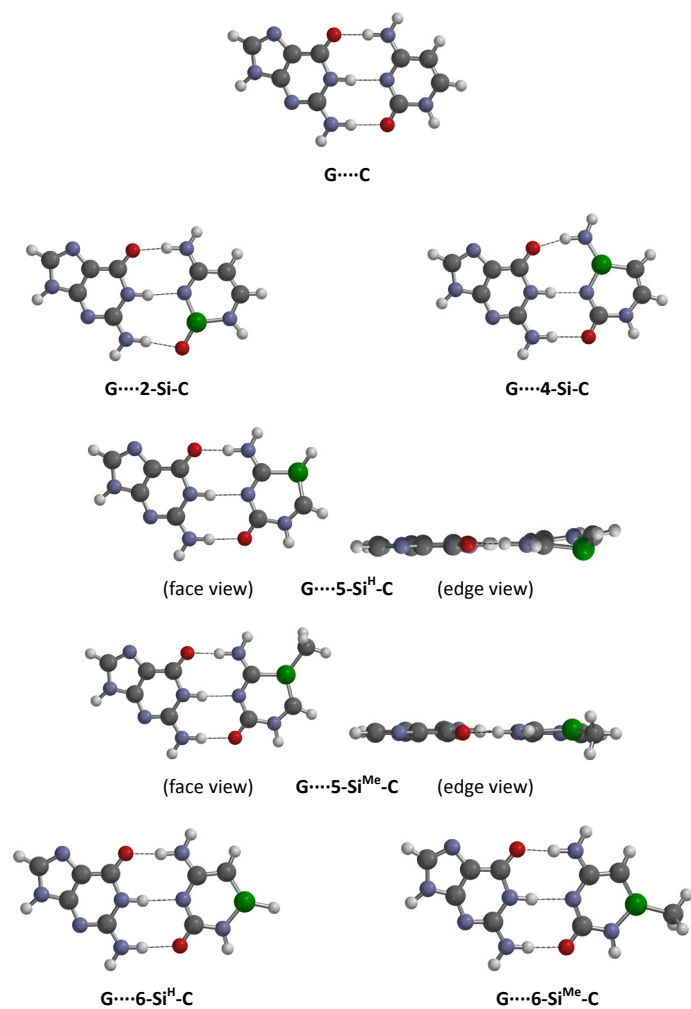


Figure 7a. The guanine dimers with the sila-cytosines. Atom color key: dark gray, C; light gray, H; blue, N; red, O; and green, Si.

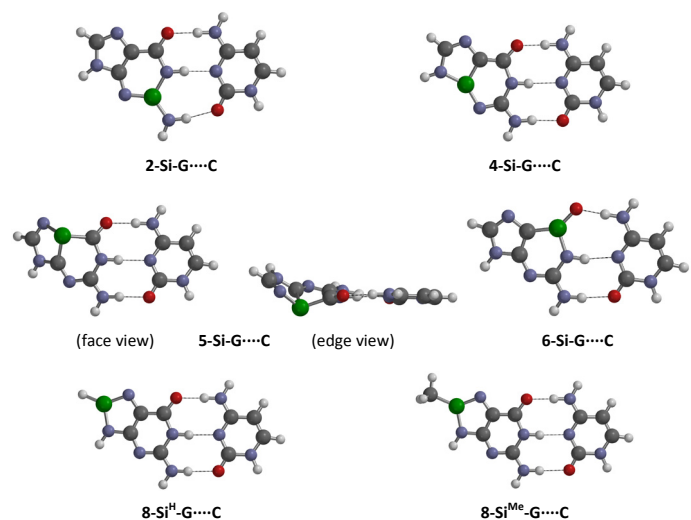


Figure 7b. The sila-guanine dimers with cytosine. Atom color key: dark gray, C; light gray, H; blue, N; red, O; and green, Si.

Conclusions

The mono-sila-analogs of adenine, guanine, thymine, and cytosine have been shown to be stable molecules on their relevant potential energy surfaces. Most optimize as planar systems, and all are predicted to participate in hydrogen bonds with the appropriate parent purine or pyrimidine. However, the sila-analogs do not, in general, exhibit greater hydrogen bond strengths than are calculated to exist in the parent hydrogen-bonded dimers. In addition, in most cases the replacement of an Si–H moiety by an Si–CH₃ group does not significantly change the structures of the molecules, nor does this replacement alter the calculated hydrogen bond strength in the dimers with the parent purines or pyrimidines.

As mentioned earlier, the sole contributor to dsDNA stability is not hydrogen bonding. Other interactions, such as the hydrophobic effect and π - π stacking, also contribute significantly² to the stability of dsDNA. The inclusion of a silicon atom in purines or pyrimidines could affect these additional interactions. Silicon, being less electronegative than carbon, could increase the hydrophobic properties of the nucleobases, perhaps most especially for the exocyclic silyl- or trimethylsilyl-group of 7-Si^{H3}-T and 7-Si^{Me3}-T. However, the incorporation of a silicon atom into a purine or pyrimidine ring system and the effect of this incorporation on π - π stacking is more difficult to predict. The molecular orbitals of the π -systems in the sila-substituted nucleobases might be expected to extend further above and below the plane of the ring system due to the increased size (and *d*-orbital contributions) of the silicon atom, thereby increasing the potential for stronger π - π stacking. On the other hand, if the aromatic character of the ring systems is diminished by the presence of the silicon atom, the result may be a weaker π - π stacking interaction.

Unfortunately, due to the presence of such potentially reactive Si–C, Si–O, and Si–N multiple bonds in these sila-analogs may make these molecules unable to be synthesized or isolates. Despite the calculated stability of the molecules on their relevant potential energy surfaces, the history of failures to incorporate silicon atoms into aromatic systems, may only allow the synthesis of the sila-thymine derivatives 7-Si^{H3}-T and 7-Si^{Me3}-T to be possible.

Supplementary Information

Supplementary information, including all input and output files, is available on request from the corresponding author, <rwz7001@humboldt.edu>.⁶⁶

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