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Two Watson–Crick-Like Metallo Base-Pairs

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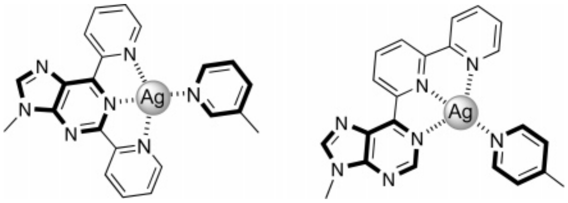
ABSTRACT



Two Watson–Crick-like metallo base-pairs are described with mutually independent geometries that have similar dimensions and stabilities to their natural, hydrogen-bonded counterparts.

Among biomolecules, nucleic acids have unique physical properties that render them highly adapted to their role of information storage and transfer. Nevertheless, etiological deconstruction of nucleic acids has shown that considerable latitude exists for replacement of component features, including both the backbone and nucleobases.[1] Natural nucleobases encode genetic information by presenting complementary arrays of hydrogen-bond donors and acceptors, leading to Watson−Crick base-pairs incorporating (large) purine and (small) pyrimidine components. A goal of synthetic biology is to generalize the function of biomolecules in a way that extends their behaviors to new molecular systems. Efforts to extend the information-encoding capabilities of nucleobases have utilized altered hydrogen-bonding patterns,[1b] hydrophobic interactions,[2] and metal coordination.[3] However, the construction of metallo base-pairs that closely resemble natural Watson−Crick base-pairs—and mirror their properties in all respects—remains a challenge. Toward thisend, we report the synthesis and characterization of two Watson−Crick-like metallo pairs, Pur$^{2,6-\mathrm{py}}$•Ag(I)•3-Py and Pur$^{6-\mathrm{bipy}}$•Ag(I)•4-Py (Figure 1).

The metallo base-pairs Pur$^{2,6-\mathrm{py}}$•Ag(I)•3-Py and Pur$^{6-\mathrm{bipy}}$•Ag(I)•4-Py shown in Figure 1 incorporate large and small heterocyclic components (purine and pyridine cores, respectively) that resemble natural Watson−Crick pairs. Differentiation of the core purine•pyridine motif was accomplished geometrically by appending pyridyl groups to the purine component symmetrically and asymmetrically, yielding Pur$^{2,6-\mathrm{py}}$ and Pur$^{6-\mathrm{bipy}}$. The resultant di-pyridyl purines are complemented with a cognate 3-pyridyl or 4-pyridyl base. Density functional calculations were used to initially validate metallo pair design. The resulting geometries, displayed at the bottom of Figure 1, show that the closest correspondence

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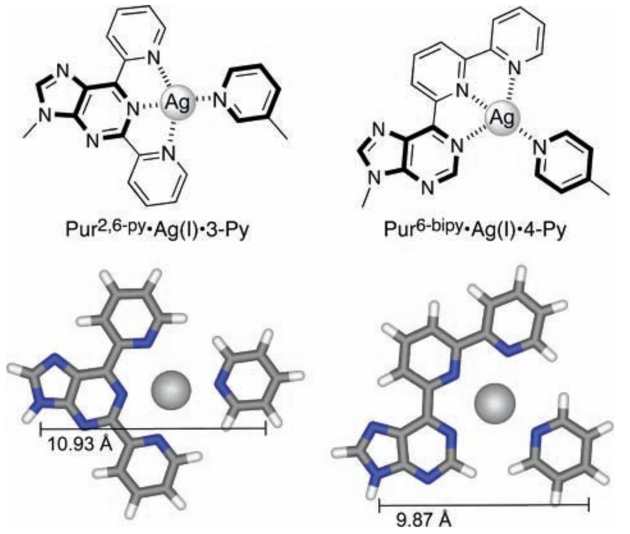


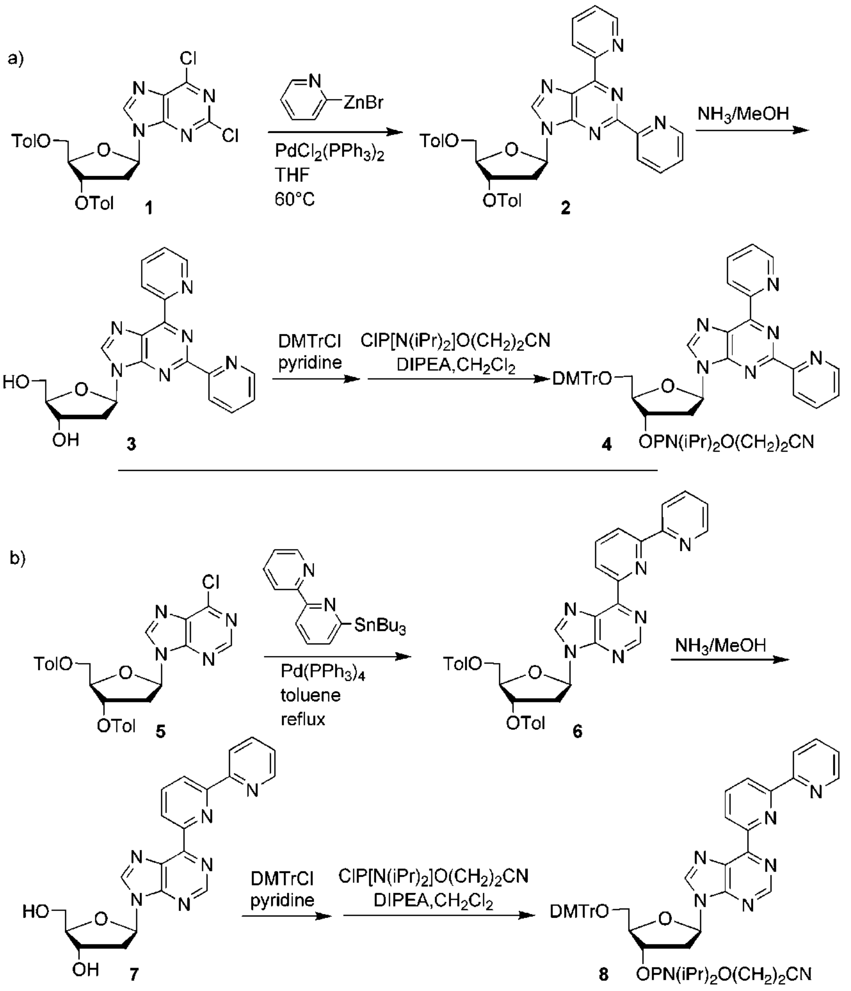
Figure 1. (Upper) Metallo base-pairs characterized in this work; (Lower) BP86/def-SV(P) geometries of the same (Turbomole, version 5.9).

with natural base-pairs results from the combination of Pur$^{2,6-\text{py}}$•Ag(I) with 3-Py, and Pur$^{6-\text{bipy}}$•Ag(I) with 4-Py, and not the converse. Correspondence was judged by superposing Pur$^{2,6-\text{py}}$•Ag(I)•3-Py and Pur$^{6-\text{bipy}}$•Ag(I)•4-Py on A•T (data not shown).

The synthesis of nucleoside phosphoramidites incorporating Pur$^{2,6-\text{py}}$ and Pur$^{6-\text{bipy}}$ are shown in Scheme 1. Beginning from the chloropurinyl deoxyribosides **1** and **5**, palladium-catalyzed cross-coupling with an appropriate pyridyl reagent yielded dipyridyl-purine nucleosides **2** and **6**.[3i,j,4] Remarkably, **1** was found to undergo substitution at the 2- as well as the 6-position. Generally, substitution at the 2-position of purines is slow and occurs under more vigorous conditions.[4b] Deprotection followed by tritylation and phosphitylation gave the phosphoramidites **4** and **8** required for oligonucleotide synthesis. The 3-pyridyl and 4-pyridyl deoxyriboside phosphoramidites needed to make complements of Pur$^{2,6-\text{py}}$ and Pur$^{6-\text{bipy}}$ were prepared as previously described.[3j] DNA oligomers bearing the nonstandard bases were synthesized according to standard protocols, purified by PAGE, and analyzed by MALDI-TOF mass spectrometry.

The results from UV-monitored thermal denaturation of DNA duplexes bearing Pur$^{2,6-\text{py}}$, Pur$^{6-\text{bipy}}$, 3-Py, and 4-Py

Scheme 1



in the presence and absence of Ag(I) are shown in Table 1.

Table 1. Results from UV-Monitored Thermal Denaturation of DNA Double Helices[a]

5′-d-CTTTCT**Y**TCCCT
3′-d-GAAAGA**X**AGGGA

X/Y	2,6-py Pur	6-bipy Pur	3-Py	4-Py	A	G	C	T
3-Py		29.6	<10					
		24.5[b]	*15.0*[b]					
4-Py		**39.1**	<10	13.4				
		26.6[b]	*<10*[b]	*12.8*[b]				
2,6-py	49.9	39.1	**40.2**	32.0	28.7	36.8	32.4	24.1
Pur	*37.9*[b]	*42.0*[b]	***23.7***[b]	*24.0*[b]	*25.2*[b]	*24.8*[b]	*28.6*[b]	*29.1*[b]
6-bipy		42.1	31.6	**39.0**	28.5	32.1	32.7	31.0
Pur		*35.4*[b]	*29.0*[b]	***27.9***[b]	*25.2*[b]	*26.6*[b]	*31.6*[b]	*29.3*[b]
T		24.2	20.0	21.1				
		25.4[b]	*17.3*[b]	*19.7*[b]				
C		29.8	26.9	28.3				
		26.9[b]	*14.4*[b]	*16.3*[b]				
G		24.8	25.0	17.5			**41.0**	
		24.5[b]	*18.7*[b]	*14.0*[b]			***38.0***[b]	
A		22.1	18.2	18.2				**38.7**
		22.5[b]	*15.0*[b]	*14.6*[b]				***34.1***[b]

[a] Samples contained 2.5 μM of each oligonucleotide strand, 50 mM $NaNO_3$, 10 mM HEPES at pH 7.0, and 5 μM $AgNO_3$ except where indicated otherwise. [b] No Ag(I).

Pur$^{2,6-\mathrm{py}}$•Ag(I)•3-Py and Pur$^{6-\mathrm{bipy}}$•Ag(I)•4-Py base-pairs yield duplexes with stabilities comparable to natural A/T and G/C pairs: T_m's 40.2 and 39.0 °C vs 38.7 and 41.0 °C. Further, the metallo pairs are stabilized by 16.5 and 11.1 °C in the presence Ag(I) in comparison to its absence. Reversing the context of the Pur$^{6-\mathrm{bipy}}$•Ag(I)•4-Py from X/Y to Y/X (resulting in the Pur$^{6-\mathrm{bipy}}$ embedded between pyrimidines rather than purines and vice versa for 4-Py) gave a T_m of 39.1 °C and an Ag(I) stabilization of 12.5 °C. Pur$^{2,6-\mathrm{py}}$•Ag(I)•3-Py has one of the highest Ag(I) induced stabilities observed to date for a base-pair incorporating a monodentate component (i.e., 16.5 °C vs 12.9 °C,[3j] 11.5 °C,[3e] and 3.8−6.8 °C).[3c] It is notable in this context that Ag(I) may contribute to duplex stabilization by pi-coordination to nearest-neighbor bases in addition to coordination to ligand nitrogens.[5]

With the Pur$^{2,6-\mathrm{py}}$•Ag(I)•3-Py and Pur$^{6-\mathrm{bipy}}$•Ag(I)•4-Py matched pairs validated, three categories of mismatches were investigated. In the first, the result of crossing each dipyridyl-purine with its noncognate pyridyl nucleoside was investigated. The mismatches Pur$^{2,6-\mathrm{py}}$•Ag(I)•4-Py and Pur$^{6-\mathrm{bipy}}$•Ag(I)•3-Py yielded T_m's of 32.0 and 31.6 °C, a decrease in stability of 8.2 and 7.4 °C relative to the cognate pairs. In the second category, mispairs between Pur$^{2,6-\mathrm{py}}$, Pur$^{6-\mathrm{bipy}}$, 3-Py, 4-Py, and the four natural bases were examined. As a rule, these mismatches show strong destabilization. Here, the main body of the values in the presence of Ag(I) range from a minimum of 17.5 °C for G/4-Py to 32.7 °C for Pur$^{6-\mathrm{bipy}}$/C, with the average value for all mispairs with natural bases of 26 °C. The Pur$^{2,6-\mathrm{py}}$/G mismatch with a T_m of 36.8 °C led to the most stable mispair of the series. The third and final category of mispairs investigated was self-pairs. The subcategory of pyridyl self-pairs (i.e., 3-Py/3-Py, 4-Py/4-Py, 4-Py/3-Py) are highly destabilized in comparison to the matched metallo pairs in the presence of Ag(I), with average T_m values of <10 °C. In marked contrast, however, dipyridyl-purine self-pairs (i.e., Pur$^{2,6-\mathrm{py}}$/Pur$^{2,6-\mathrm{py}}$, Pur$^{6-\mathrm{bipy}}$/Pur$^{6-\mathrm{bipy}}$, Pur$^{2,6-\mathrm{py}}$/Pur$^{6-\mathrm{bipy}}$) are stable both in the presence and absence of Ag(I), with an average T_m of 43.7 °C in the presence of Ag(I) and 38.4 °C in its absence.

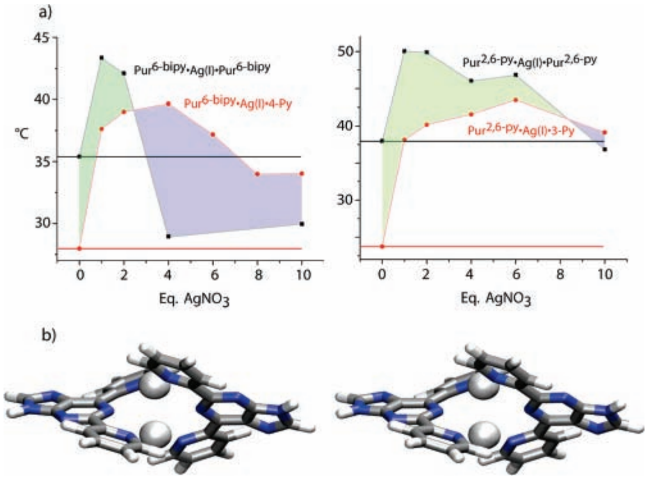


Figure 2. (a) Comparison of dipyridyl-purine•pyridine (match) and dipyridyl-purine•dipyridyl-purine (mismatch) base-pair stability in duplexes (sequences and conditions from Table 1) while varying Ag(I) equivs per metallo base-pair; (b) stereo structure of the BP86/def-SV(P) geometry of {[Pur$^{2,6-\mathrm{py}}$]$_2$•[Ag(I)]$_2$}.

Given the above findings, dipyridyl-purine self-pairing was investigated further. Figure 2a shows matched versus mismatched duplex stabilities for Pur$^{6-\mathrm{bipy}}$ and Pur$^{2,6-\mathrm{py}}$ in the presence of 0−10 equiv of Ag(I). Critical points where the self-pair and cross-pair stabilities invert are apparent between 2 and 3 equiv of Ag(I) for Pur$^{6-\mathrm{bipy}}$ and 8−9 equiv Ag(I) for Pur$^{2,6-\mathrm{py}}$. Preferred geometries of Ag(I) are linear (CN = 2) and tetrahedral (CN = 4), but trigonal, pentagonal, and octahedral geometries are also known.[6] In the context of Pur$^{2,6-\mathrm{py}}$ and Pur$^{6-\mathrm{bipy}}$ self-pairing in the presence of Ag(I), it is notable that terpyridyl ligands may be mono- or bidentate, in addition to tridentate.[7] As a result, numerous options are available to Pur$^{2,6-\mathrm{py}}$ and Pur$^{6-\mathrm{bipy}}$ to avoid an octahedral geometry and the distortion it might confer to a

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double helix, upon self-pairing with Ag(I). Among the multiple geometries available to the Pur$^{2,6-\text{py}}$ self-pair with Ag(I), one attractive possibility invokes coordination of terminal pyridyl groups on opposing bases to two Ag(I) ions, resulting in a linear geometry for each silver atom with an effective coordination number of two, as shown in Figure 2b.[8] It follows that dipyridylpurine self-pairs may be distinguished from dipyridylpurine·pyridine cross-pairs thermodynamically in the presence of more than eight Ag(I) equivalents/base-pair (Figure 2a), and geometrically, if they adopt less planar configurations.

In summary, Pur$^{2,6-\text{py}}$·Ag(I)·3-Py and Pur$^{6-\text{bipy}}$·Ag(I)·4-Py are Watson−Crick-like, base-pairs with similar stabilities, dimensions, and geometries to their natural counterparts. The results reported here provide a framework for considering these metallo base-pairs as components of a genetic alphabet in the context of replication or translation.

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Supporting Information Available: Spectra of all synthetic compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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