1,8-Dimercuri-6-Phenyl-1H-Carbazole as a Monofacial Dinuclear Organometallic Nucleobase

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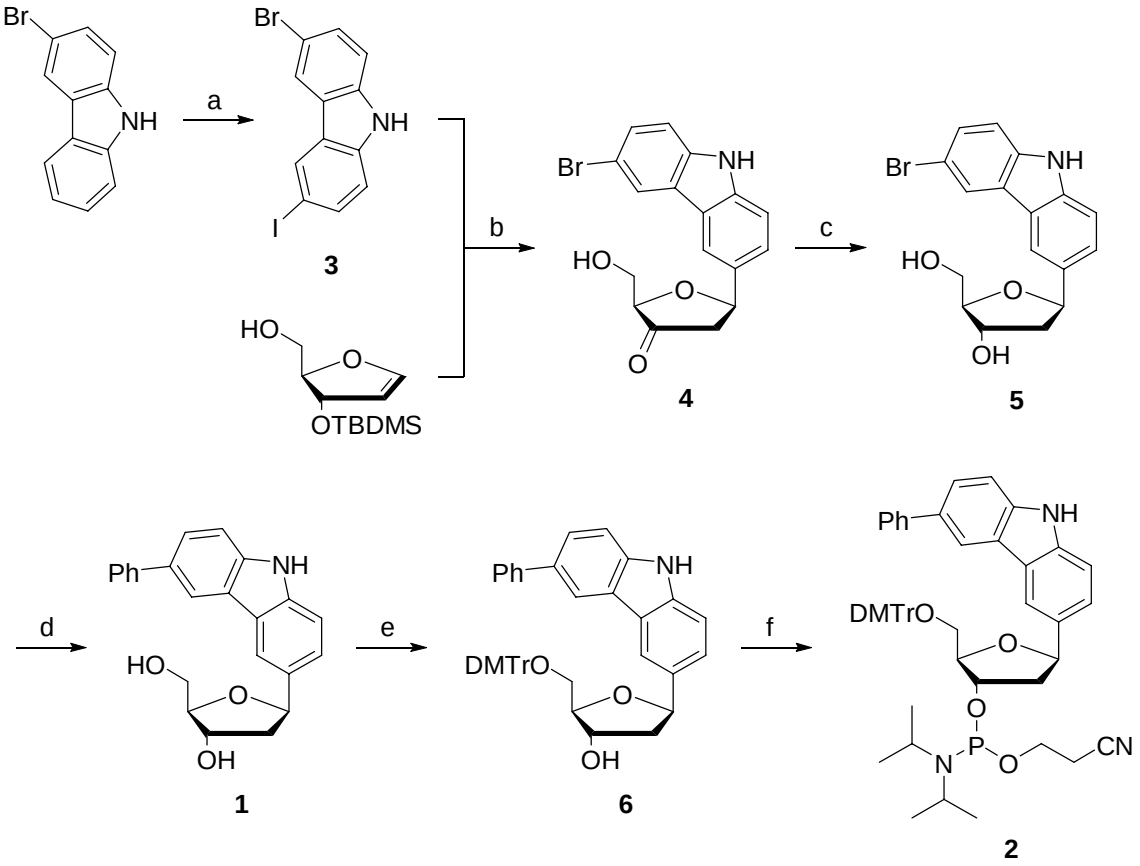
Abstract: A C-nucleoside with 6-phenyl-1H-carbazole as the base moiety has been synthesized and incorporated in the middle of an oligonucleotide. Mercuration of this modified residue at positions 1 and 8 afforded the first example of an oligonucleotide featuring a monofacial dinuclear organometallic nucleobase. The dimercurated oligonucleotide formed stable duplexes with unmodified oligonucleotides placing either cytosine, guanine or thymine opposite to the organometallic nucleobase. A highly stabilizing (ΔT_m = 7.3 °C) Hg(II)-mediated base pair was formed with thymine. According to DFT calculations performed at the PDE0DH level of theory, this base pair is most likely dinuclear, with the two Hg(II) ions coordinated to O2 and O4 of the thymine base.

Metal-mediated base pairing offers an elegant approach to create programmable arrays of transition metal ions within nucleic acid scaffolds for various nanotechnological applications.[1] As many double-helical oligonucleotides incorporating metal-mediated base pairs exhibit higher thermal stability than respective duplexes comprising solely of canonical Watson-Crick base pairs, oligonucleotides functionalized with metal ions could also find use as high-affinity probes for otherwise elusive targets, such as miRNA.[2] Covalently metallated oligonucleotides have the potential to further widen the scope to therapeutic applications.[3]

The greatest duplex stabilizations have been achieved with di- or trinuclear metal-mediated base pairs featuring two or three bridging metal ions between two specifically designed artificial nucleobases.[4] Interestingly, remarkable stabilization by dinuclear metal-mediated hetero base pairs between one canonical and one artificial nucleobase has also been observed.[5] Inspired by these results, we report herein the synthesis and hybridization studies of an oligonucleotide incorporating a 1,8-dimercury-6-phenyl-1H-carbazole residue as the first example of a covalently metallated oligonucleotide with the potential for dinuclear metal-mediated base pairing. Unlike the previously reported 2,6-dimercuriphenol,[6] 1,8-dimercury-6-phenyl-1H-carbazole is monofacial, with the two Hg(II) ions bonded on the same side of the carbazole base. With unsubstituted 1H-carbazole, mercuration should take place exclusively ortho and para to the NH group (a strongly activating ortho/para director) and two of the ortho carbons are bonded two each other, leaving only two ortho and two para carbons available for mercuration. In the C-nucleoside presented herein, the para positions are blocked by

a phenyl substituent and the sugar moiety, making the proposed di-ortho mercuration pattern as the only possible one.

Synthesis of the 6-phenyl-1H-carbazole C-nucleoside 1 and its phosphoramidite building block 2 is outlined in Scheme 1. For formation of the C-glycosidic bond, 3-bromo-1H-carbazole was first iodinated to 6-bromo-3-iodo-1H-carbazole by treatment with $NaIO_4$ and I_2 (3). The product was spectroscopically identical to the material synthesized previously using N-iodosuccinimide as the iodinating agent.[7] Heck coupling between compound 3 and {(2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-2,3-dihydrofuran-2-yl}methanol afforded the ketone intermediate 4 exclusively as the β anomer. Assignment of the absolute configuration at the anomeric carbon was based on comparison of the NMR spectra with those of similar compounds reported previously.[6, 8] The tert-butyldimethylsilyl protection of the secondary hydroxy group of the sugar moiety was also quantitatively removed during the Heck coupling. Reduction of compound 4 gave the 6-bromo-1H-carbazole C-nucleoside 5 and subsequent Suzuki-Miyaura coupling with phenylboronic acid the 6-phenyl-1H-carbazole C-nucleoside 1. Finally, the 5´-hydroxy group of compound 1 was protected as a dimethoxytrityl ether and the 3´-hydroxy group of the resulting intermediate 6 phosphitylated to afford the phosphoramidite building block 2.



Scheme 1. Synthesis of the 6-phenyl-1H-carbazole C-nucleoside 1 and its phosphoramidite building block 2. Reagents and conditions: a) $NaIO_4$, I_2, H_2SO_4, EtOH, 25 °C, 16 h; b) $Pd(OAc)_2$, Ph_3As, Et_3N, MeCN, Ar atmosphere, 70 °C, 15 h; c) $NaBH(OAc)_3$, AcOH, MeCN, Ar atmosphere, 0 °C, 15 min; d) $PhB(OH)_2$, $(Ph_3P)_4Pd$, K_2CO_3, MeOH, H_2O, Ar atmosphere, reflux, 15 h; e) DMTrCl, pyridine, 25 °C, 48 h; f) 2-cyanoethyl-N,N-diisopropylchloro-phosphoramidite, Et_3N, CH_2Cl_2, N_2 atmosphere, 25 °C, 150 min.

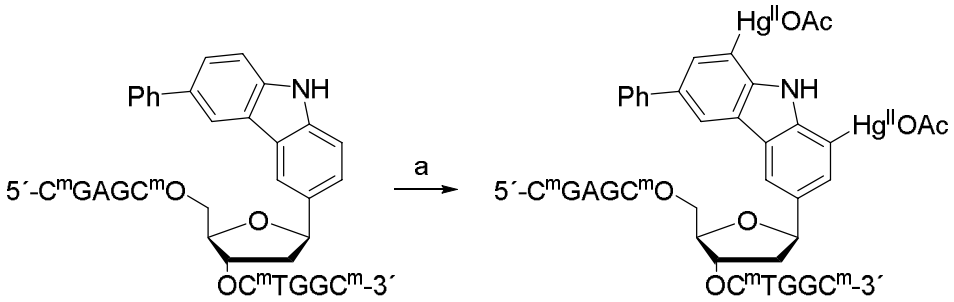
Table 1 summarizes the oligonucleotide sequences used in the present study. In the modified oligonucleotide ON1z, the sequences flanking the central 6-phenyl-1H-carbazole C-nucleoside were identical to those previously used in related studies on 5-mercuricytosine and 2-fluoro-3-mercuri-6-methylaniline,[9, 10] allowing direct comparison of the hybridization properties. 5-Methylcytosine residues were used instead of cytosine residues to prevent off-target mercuration.

Table 1: Oligonucleotides used in the present study

	Sequence[a]
ON1z	5´-d(C^{m}GAGC^{m}ZC^{m}TGGC^{m})-3´
ON1z-Hg_2	5´-d(C^{m}GAGC^{m}Z^{Hg2}C^{m}TGGC^{m})-3´
ON2a	5´-d(GCCAGAGCTCG)-3´
ON2c	5´-d(GCCAGCGCTCG)-3´
ON2g	5´-d(GCCAGGGCTCG)-3´
ON2t	5´-d(GCCAGTGCTCG)-3´
ON2s	5´-d(GCCAGSGCTCG)-3´

[a] C^{m} refers to 5-methylcytosine, Z to 6-phenyl-1H-carbazole, Z^{Hg2} to 1,8-dimercury-6-phenyl-1H-carbazole and S to an abasic site (2-(hydroxymethyl)tetrahydrofuran-3-ol spacer). In each sequence, the residue varied in the hybridization experiments has been underlined.

Oligonucleotide ON1z was assembled on an automated DNA/RNA synthesizer using conventional phosphoramidite strategy. For the 6-phenyl-1H-carbazole C-nucleoside building block 2, the coupling time was extended to 300 s. Dimercuration of ON1z was carried out in aqueous solution of $Hg(OAc)_2$ and NaOAc at 55 °C Scheme 2). A satisfactory conversion was achieved in 16 h, after which the crude product ON1z-Hg_2 was purified by RP-HPLC. The elution buffers contained 1 mM EtSH to suppress non-specific coordination of excess Hg(II). Under these conditions, the starting material ON1z and the product ON1z-Hg_2 eluted as sharp, discrete peaks. The identities of purified ON1z and ON1z-Hg_2 were established by mass spectrometry and the concentrations by UV spectrophotometry. Finally, mass spectrometric analysis of the product mixture on digestion of ON1z-Hg_2 by P1 nuclease confirmed that mercuration was strictly limited to the 6-phenyl-1H-carbazole residue.



Scheme 2. Dimercuration of oligonucleotide ON1z. Reagents and conditions: a) $Hg(OAc)_2$, NaOAc, H_2O, 55 °C, 16 h.

Hybridization affinities of the modified oligonucleotides ON1z and ON1z-Hg^2 for the unmodified counterparts ON2a, ON2c, ON2g, ON2t and ON2s were determined by conventional UV melting experiments at pH 7.4 (20 mM cacodylate buffer) and ionic strength of 0.10 M (adjusted with sodium perchlorate). In each duplex, a modified nucleobase (6-phenyl-1H-carbazole or 1,8-dimercury-6-phenyl-1H-carbazole) was paired with either a canonical nucleobase (adenine, cytosine, guanine or thymine) or an abasic site. Respective studies on unmodified duplexes of otherwise identical sequence but having either cytosine or thymine in place of the modified residue have been reported previously.[9]

UV melting profiles of duplexes ON1z•ON2c, ON1z-Hg_2•ON2c, ON1z•ON2t and ON1z-Hg_2•ON2t are presented in Figure 1 as representative examples (all melting profiles can be found in the Supporting Information). The melting curves of all duplexes formed by the unmetalated oligonucleotide ON1z were sigmoidal and monophasic. The melting temperatures (46 – 50 °C) were considerably higher than with respective unmodified duplexes incorporating a single mismatch in the middle of the chain (30 – 35 °C).[9] The relatively high stability of these duplexes is probably attributable to the large stacking surface of the 6-phenyl-1H-carbazole base. In the case of the dimercurated oligonucleotide ON1z-Hg_2, the duplex melting curves fell into two distinct categories. The curves for ON1z-Hg_2•ON2g, ON1z-Hg_2•ON2t and ON1z-Hg_2•ON2s were monophasic, while those for ON1z-Hg_2•ON2a and ON1z-Hg_2•ON2c were biphasic, featuring an additional low-temperature transition. Duplexes ON1z-Hg_2•ON2c, ON1z-Hg_2•ON2g and ON1z-Hg_2•ON2t were more stable than their unmetalated counterparts, whereas the opposite was true for ON1z-Hg_2•ON2a and ON1z-Hg_2•ON2s (Figure 2). Stabilization upon mercuration suggests Hg(II)-mediated base pairing while destabilization could stem from steric crowding by the bulky Hg(II) ions. The latter effect is easy to understand in the case of ON1z-Hg_2•ON2s, lacking the base pairing partner altogether, but the lower stability of ON1z-Hg_2•ON2a compared to ON1z•ON2a seems enigmatic. Possibly 1,8-dimercury-6-phenyl-1H-carbazole has a lower affinity for adenine than for the other canonical nucleobases or the geometry of the Hg(II)-mediated base pair is incompatible with that of a double helix. The highest melting temperature (53.6 $\pm$ 0.4 °C) as well as the greatest stabilization by mercuration (+7.3 °C) were observed with duplex ON1z-Hg_2•ON2t. For reference, similar melting temperatures have been reported for respective duplexes incorporating a mononuclear Hg(II)-mediated 5-mercuricytosine—thymine or a canonical thymine—adenine base pair in the middle of the chain (56.1 and 56.9 °C, respectively).[9] On the other hand, the stabilization relative to the unmercurated duplex ON1z•ON2t is similar to the value previously reported for parallel-stranded duplexes incorporating a dinuclear Hg(II)-mediated base pair between 1,N^6-ethenoadenine and thymine.[5]

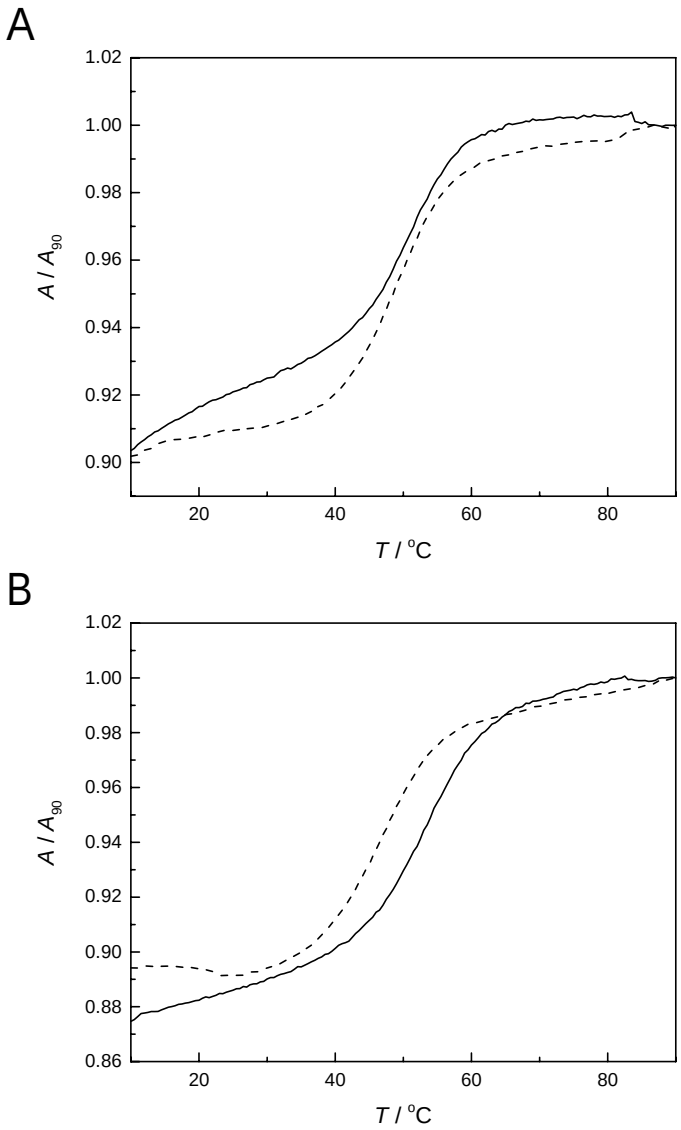


Figure 1. UV melting profiles of A) ON1z•ON2c (dashed line) and ON1z-Hg_2•ON2c (solid line) and B) ON1z•ON2t (dashed line) and ON1z-Hg_2•ON2t (solid line); pH = 7.4 (20 mM cacodylate buffer); [oligonucleotides] = 1.0 μM; I($NaClO_4$) = 0.10 M.

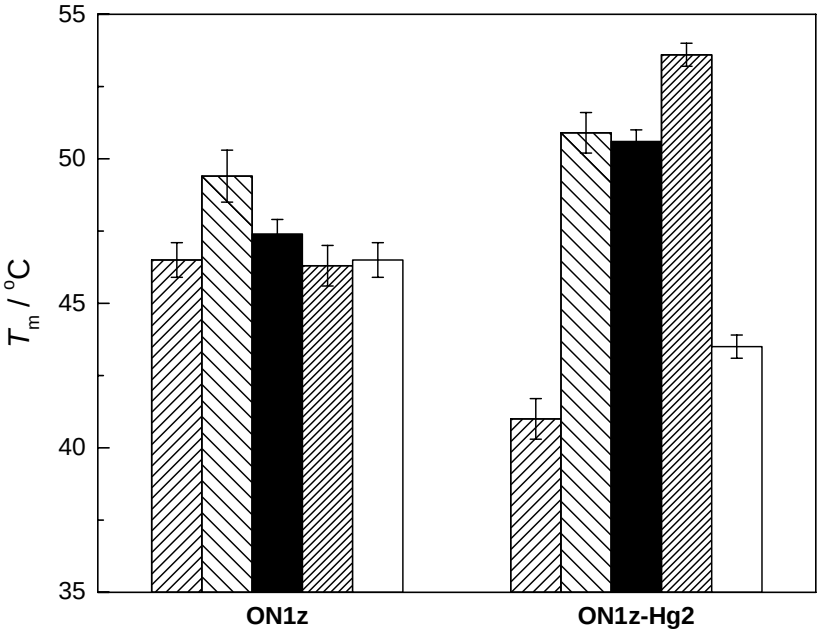


Figure 2. Melting temperatures of duplexes formed by the modified oligonucleotides ON1z and ON1z-Hg_2 with the unmodified counterparts ON2a (medium hash), ON2c (sparse hash), ON2g (black), ON2t (dense hash) and ON2s (white); pH 7.4 (20 mM cacodylate buffer); [oligonucleotides] = 1.0 μM; I($NaClO_4$) = 0.10 M.

Previous studies with oligonucleotides incorporating coordinative or organometallic Hg(II)-mediated base pairs have revealed less negative enthalpies and entropies of hybridization compared to unmodified duplexes, consistent with dehydration of the bridging Hg(II) ion.[9-11] The pattern observed with ON1z and ON1z-Hg_2 was, however, quite different. The enthalpies (Table 2) and entropies (Table 3) of hybridization were highly negative for all of the duplexes studied and in most cases both values were more negative with ON1z-Hg_2 than with ON1z. Only duplexes ON1z•ON2t and ON1z-Hg_2•ON2t exhibited the "normal" pattern of less negative enthalpies and entropies of hybridization for the mercurated duplex and even in that case the difference was small.

Table 2. Enthalpies of hybridization for duplexes formed by the modified oligonucleotides ON1z and ON1z-Hg_2 with the unmodified counterparts ON2a, ON2c, ON2g, ON2t and ON2s; pH 7.4 (20 mM cacodylate buffer); [oligonucleotides] = 1.0 μM; I($NaClO_4$) = 0.10 M.

	$\Delta H°$ / kJ mol^{-1}				
	ON2a	ON2c	ON2g	ON2t	ON2s
ON1z	-315 ± 5	-335 ± 3	-286 ± 2	-355 ± 5	-298 ± 3
ON1z-Hg_2	-383 ± 8	-394 ± 3	-342 ± 2	-322 ± 3	-321 ± 5

Table 3. Entropies of hybridization for duplexes formed by the modified oligonucleotides ON1z and ON1z-Hg_2 with the unmodified counterparts ON2a, ON2c, ON2g, ON2t and ON2s; pH 7.4 (20 mM cacodylate buffer); [oligonucleotides] = 1.0 μM; I($NaClO_4$) = 0.10 M.

	$\Delta S°$ / J mol^{-1} K^{-1}				
	ON2a	ON2c	ON2g	ON2t	ON2s
ON1z	-870 ± 20	-920 ± 10	-772 ± 6	-990 ± 20	-817 ± 9
ON1z-Hg_2	-1090 ± 30	-1090 ± 10	-934 ± 7	-869 ± 8	-890 ± 20

The observed highly negative enthalpies and entropies of hybridization support the idea of stacking interactions of the 6-phenyl-1H-carbazole residue as the main source of stabilization with all duplexes. Restricted rotation of the phenyl substituent upon hybridization would also contribute to the entropic penalty. The relatively high melting temperature of duplex ON1z-Hg_2•ON2t stems from a relatively low entropic penalty of hybridization, a property characteristic of Hg(II)-mediated base pairing. With the other duplexes, the data at hand does not allow a firm conclusion as to whether the differences in the melting temperatures on mercuration are attributable to Hg(II)-mediated base pairing or differences in the stacking properties of 6-phenyl-1H-carbazole and 1,8-dimercury-6-phenyl-1H-carbazole.

The putative Hg(II)-mediated base pair between 1,8-dimercury-6-phenyl-1H-carbazole and thymine could, in principle, be either mono- or dinuclear (Figure 3) and neither alternative can be ruled out based on the results of the hybridization experiments. To help identify the more likely binding mode, DFT calculations were carried out at the PDE0DH level of theory[12] utilizing def-2VSP basis set and pseudopotential for Hg,[13] 6-31+G(d,p) basis set for N and O[14] and 6-31GG(d,p) basis set for C and H atoms.[15] Either of the structures presented in Figure 3 was used as the starting geometry. The sugar moieties of the two nucleosides were

replaced by methyl groups and the phenyl substituent by a hydrogen atom to simplify the system. As coordination of Hg(II) by thymine at neutral pH takes place with concomitant deprotonation of N3, the monoanionic form of thymine was used in the calculations, resulting in an overall charge of +1 for the Hg(II)-mediated base pairs.

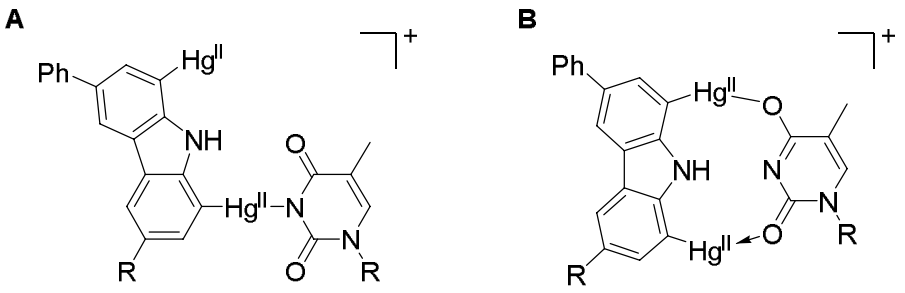


Figure 3. Possible A) mono and B) dinuclear Hg(II)-mediated base pairs between 1,8-dimercury-6-phenyl-1H-carbazole and thymine.

Optimization of the mononuclear Hg(II)-mediated base pair yielded a planar structure having Hg1 coordinated to thymine N3 and the carbazole NH hydrogen bonded to thymine O4 (Figure 4A). The C1-Hg1-N3 angle was reduced to 155.9° and the Hg6-O4 distance to 2.35 Å, suggesting that thymine O4 is also weakly coordinated to Hg6. The distance between the anomeric carbon atoms was 10.8 Å, in good agreement with the canonical value of 10.7 Å.[16] Optimization of the dinuclear Hg(II)-mediated base pair, on the other hand, largely preserved the initial geometry, with Hg1 and Hg6 coordinated to thymine O2 and O4, respectively (Figure 4B). The dinuclear Hg(II)-mediated base pair was also strictly planar and while the distance between the anomeric carbon atoms (10.2 Å) was somewhat shorter than the canonical value, much larger deviations have been observed by X-ray crystallography for both mono- and dinuclear metal-mediated base pairs within A- and B-type double helices.[17] As the latter structure (Figure 4B) was more stable than the former (Figure 4A) by 96 kJ mol^{-1}, we conclude that it represents the most likely binding mode for the Hg(II)-mediated base pair between 1,8-dimercury-6-phenyl-1H-carbazole and thymine in duplex ON1z-Hg_2•ON2t.

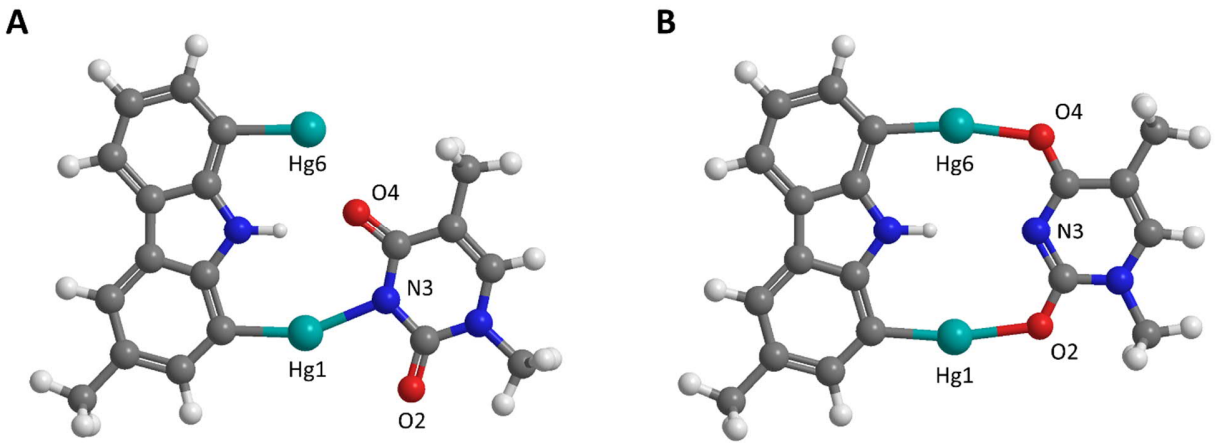


Figure 4. Optimized geometries for a Hg(II)-mediated base pair between 1,8-dimercury-3-methyl-1H-carbazole and 1-methylthymine, with the Hg(II) ions coordinated to A) N3 and O4 or B) O2 and O4 of the thymine base. The latter structure is more stable by 96 kJ mol^{-1}.

Secondary structure of the modified oligonucleotide duplexes was investigated CD spectropolarimetrically. The spectra were acquired at 10 °C intervals over a temperature range of 10 – 90 °C under the same conditions as those used for the UV melting experiments. The spectra of the unmercurated duplexes obtained at 10 °C were typical for B-type double helices, with negative and positive Cotton effects of nearly equal intensity at 240 and 280 nm, respectively (spectra presented in the Supporting Information). With the mercurated duplexes, on the other hand, the positive Cotton effect was stronger than the negative one. Such bias is usually observed with A-type double helices and attributed to tilting of the bases relative to the helical axis.[18]

With all duplexes, the negative Cotton effect at 240 nm gradually diminished on increasing temperature, consistent with denaturation of the duplex. Thermal diminution of the positive Cotton effect at 280 nm, in turn, was much less pronounced with the unmercurated than with the mercurated duplexes. Apparently the single-stranded oligonucleotide ON1z retains a more helical structure than its dimercurated counterpart ON1z-Hg_2. Possible explanations include stronger stacking of unmercurated 6-phenyl-1H-carbazole or kinking caused by intrachain Hg(II)-mediated base pairing of 1,8-dimercuri-6-phenyl-1H-carbazole.

In summary, Hg(II)-mediated base pairing between the dinuclear organometallic nucleobase surrogate 1,8-dimercury-6-phenyl-1H-carbazole and thymine has been demonstrated within a double-helical oligonucleotide. Melting temperature of the duplex was comparable to respective duplexes incorporating either a 5-mercuricytosine—thymine or an adenine—thymine base pair in place of the 1,8-dimercury-6-phenyl-1H-

carbazole—thymine base pair. The increase in melting temperature upon mercuration, on the other hand, was similar to the value previously reported for dinuclear Hg(II)-mediated base pairing between 1,N^6-ethenoadenine and thymine within a parallel-stranded duplex. According to DFT calculations performed at a high level of theory, the most likely binding mode between 1,8-dimercury-6-phenyl-1H-carbazole and thymine is dinuclear Hg(II)-mediated base pairing, with the two Hg(II) ions coordinated to thymine O2 and O4. This binding mode is unprecedented and could, in addition to sequence recognition, be used to synthesize metal arrays of very high density along the axis of a double-helical nucleic acid.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: base pair; hybridization; mercury; nucleobases; oligonucleotides

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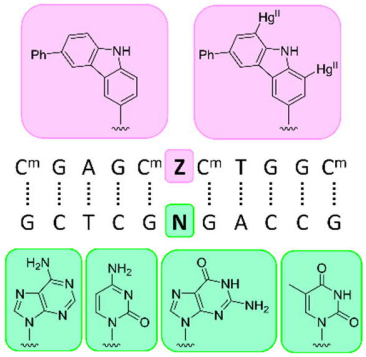

1,8-Dimercuri-6-phenyl-1H-carbazole forms a stable base pair with thymine, an oligonucleotide duplex incorporating this base pair melting at +7.3 °C higher temperature than its unmetallated counterpart. According to DFT calculations performed at a high level of theory, the most likely binding mode is dinuclear Hg(II)-mediated base pairing, with the two Hg(II) ions coordinated to O2 and O4 of the thymine base.

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