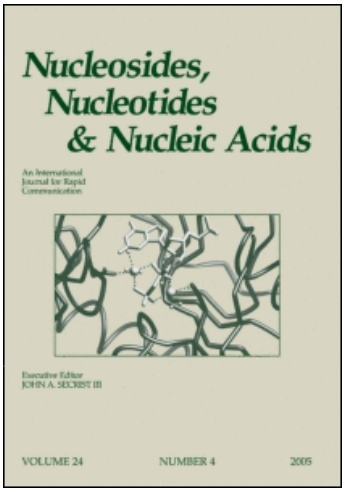

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Transition Metal Ligands as Novel DNA-Base Substitutes

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ABSTRACT

The base modified nucleoside dBP, carrying a non-hydrogen-bonding non-shape complementary base was incorporated into oligonucleotides (Brotschi, C.; Häberli, A.; Leumann C.J. Angew. Chem. Int. Ed. **2001**, *40*, 3012–3014). This base was designed to coordinate transition metal ions into well defined positions within a DNA double helix. Melting experiments revealed that the stability of a dBP: dBP base couple in a DNA duplex is similar to a dG: dC base pair even in the absence of transition metal ions. In the presence of transition metal ions, melting experiments revealed a decrease in duplex stability which is on a similar order for all metal ions (Mn^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}) tested.

In the last decade the interest to replace natural bases by other molecular entities has grown. Among others,[2–5] our laboratory follows the strategy to design a DNA base which acts as a ligand for transition metals. The generation of such unnatural bases could not only lead to a third orthogonal DNA base-pair, useful for the extension of the genetic code, but also to novel DNA structures with functional properties

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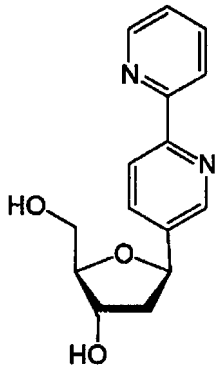


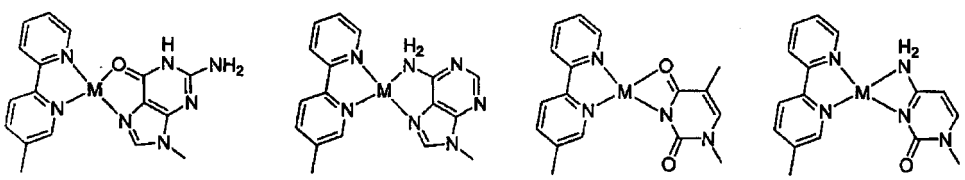
dBP

Figure 1.

of interest in molecular electronics and nanochemistry. We wished first to explore, whether 'ligandoside' **dBP** (Fig. 1), can act as a universal nucleoside analogue, recognizing all four natural bases via coordinative bonds (Sch. 1).

The synthesis of the *C*-nucleoside **dBP**, the corresponding phosphoramidite building block as well as the synthesis of the oligonucleotides followed standard routes in *C*-nucleoside- and DNA- chemistry and will be described in detail elsewhere. Thermal denaturation experiments were performed on duplex **1** in the presence and absence of transition metal ions (see Table 1).

In the absence of transition metal ions, melting experiments revealed that the stability of a dBP: dBP base pair in a DNA duplex is similar to a dG: dC base pair.[1] The T_m values of a dBP: natural base pair under the same conditions are lower by 2–6.1 K compared to that of a natural dA: dT base pair in the given sequence context (T_m of a dA: dT base pair is 64.0°C). In the presence of transition metal ions the T_m's are even slightly more depressed. The destabilization is very alike for all transition metal ions tested (see Table 1) and follows the order G > A > C > T. This order corresponds to the order of preferential stacking of the bases. A spacial case revealed to be Mn^{2+}, in the presence of which we observed in all cases a second, less hypochromic transition at ca. 70°C for yet unknown reasons. Whether the transition metal ions tested do coordinate to the dBP or to the backbone or both is currently



Scheme 1. Proposed models for natural base recognition with **dBP** via transition metal ion coordination.

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Table 1. Sequence of the 19-mer duplex **1** and T_m data in the absence and presence of various metal ions, as extracted from UV melting curves (260 nm, 1.2 μM, in 10 mM NaH_2PO_4, 150 mM NaCl, pH 7.0).

	5′-GAT GAC -BP-GC TAG CTA GGA C 3′-CTA CTG - Y -CG ATC GAT CCT G			**1**	
Y	No metal	0.1 mM $MnCl_2$	6 μM $CuCl_2$	0.2 mM $ZnCl_2$	0.2 mM $NiCl_2$
T	57.9	58.7, 70.1	56.9	57.2	57.3
C	59.7	59.2, 70.7	57.5	57.6	58.1
A	61.4	60.6, 72.2	58.4	58.6	58.9
G	62.0	61.4, 70.9	59.5	60.0	59.9

not known. Possible reason for the decrease in duplex stability might be an unfavourable geometry of the corresponding base-pair, leading to backbone distortion or to loss of base stacking interactions, or to the absence of metal-base complex formation. The currently available data do not yet conclusively support the existence of metal mediated recognition of natural bases by dBP.

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