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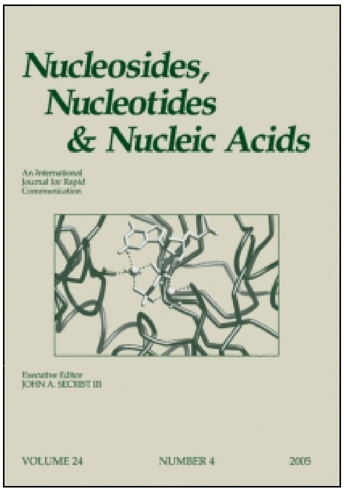

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Synthesis and Preliminary Thermodynamic Investigation of Hypoxanthine-Containing Peptide Nucleic Acids

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SYNTHESIS AND PRELIMINARY THERMODYNAMIC INVESTIGATION OF HYPOXANTHINE-CONTAINING PEPTIDE NUCLEIC ACIDS

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ABSTRACT : A new, hypoxanthine-containing PNA monomer, PNAs and complementary DNAs were designed, produced and investigated by thermal denaturation studies in order to find the analogue of inosine at PNAs [1]. Thermodynamic data were determined with the van't Hoff method [2, 3]. The measured and computational values were correlated.

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RESULTS AND DISCUSSION

PNAs were designed containing the hypoxanthine unit in an intermediate position between adenines (PNA 1) or thymines (PNA 2) (Table 1). Four oligonucleotide probes complementary to PNA 1 or 2 were made, having one base difference at the position opposite the hypoxanthine. The T_m values of the PNA-DNA hybrids in different concentrations were measured. Adenine and cythosine were found to be preferred by hypoxanthine.

TABLE 1. Complementary PNA-ODN sequences. T_m measurement: PNAs 1 or 2 and ODNs 'tx'or 'ax' in a pH 7.1 0.01 M phosphate buffer (0.1 M NaCl, 0.1 mM EDTA) solution at five different concentrations for every heteroduplex from 1 μM to 15 μM. 'h' symbolizes Hyp, 'x' any DNA base.

Name	Sequence	Name	Sequence
PNA 1	H-Gly-ccttahacatc-Lys-NH_2	PNA 2	H-Gly-ccttthtcatc-Lys-NH_2
ODN tx	(3′)-GGAAXATGTAGG-(5′)	ODN ax	(3′)-GGAAXAAGTAGG-(5′)

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The results show that Hyp in PNA has a higher dependence on the neighbourhood than that in native DNA. Hyp binds adenine most intensively when it has thymines as neighbours, and cytosine when the Hyp is between two adenines. There is a significant difference in the binding order, depending on the neighbours of the Hyp.

The nature of the interactions between Hyp and a nucleobase is not well established. Therefore, we performed semiempirical calculations with the pairs of methylated nucleobases as models. From the experimental and calculated data (Table 2 and 3), the following conclusions can be drawn:

TABLE 2. Binding preferences of Hyp containing PNAs to ODNs in terms of decreasing absolute values of experimental thermodynamic parameters. Accuracy: ΔH°, ΔS° ± 15%, ΔG° ± 3%, T_m ± 0.5 °C.

	PNA 1 (...AHypA...)				PNA 2 (...THypT...)			
ΔH° (kJmol^{-1})	A $^{[-494]}$	T $^{[-479]}$	C $^{[-349]}$	G $^{[-172]}$	A $^{[-472]}$	G $^{[-357]}$	C $^{[-240]}$	T $^{[-238]}$
ΔS° (kJmol^{-1}K^{-1})	A $^{[1.49]}$	T $^{[1.45]}$	C $^{[0.99]}$	G $^{[0.45]}$	A $^{[1.35]}$	G $^{[1.03]}$	T $^{[0.66]}$	C $^{[0.65]}$
ΔG^{o}_{25} (kJmol^{-1})	C $^{[-53.2]}$	A $^{[-50.0]}$	T $^{[-45.8]}$	G $^{[-38.1]}$	A $^{[-70.4]}$	G $^{[-49.2]}$	C $^{[-46.6]}$	T $^{[-41.0]}$
T_m (°C)	C $^{[45.3]}$	G $^{[38.0]}$	A $^{[36.9]}$	T $^{[34.5]}$	A $^{[52.2]}$	C $^{[45.7]}$	G $^{[41.0]}$	T $^{[38.2]}$

TABLE 3. Binding preferences of 9-methyl-Hyp to 1-methyl-pirimidines or 9-methyl-purines in terms of decreasing absolute values of semiempirically calculated ΔH data. Calculations were performed by the MSI InsightII version 97.0 molecular modelling software, using a MOPAC module and the PM3 or AM1 MMOK method. The nucleobases were energy and geometry optimized. Indexes in brackets 'a' and 's' refer to the *anti* or *syn* orientation of the bases (see Fig. 2). ΔH values were calculated via Kirchhoff's law.

ΔH_{AM1}(kJmol^{-1})	C $^{[-41.49]}$	G $^{[-36.80]}$	T $^{[-29.52]}$	A (s)$^{[-26.59]}$	A (a)$^{[-24.03]}$
ΔH_{PM3} (kJmol^{-1})	C $^{[-40.36]}$	A (a)$^{[-26.97]}$	A (s)$^{[-26.23]}$	T $^{[-24.31]}$	G $^{[-12.03]}$

1. A or C is preferred in binding to Hyp. 2. G and T are unfavorable binding partners of Hyp. 3. There is a high difference in ΔG and T_m between the highest and the lowest values. 4. The base pairs Hyp(a)-C(a), Hyp(a)-A(s) and Hyp(a)-T(a) are geometrically isomorphous (Table 3 and Fig. 2). However, the geometries of the base pairs Hyp(s)-G(a) and Hyp(a)-A(a) are different. 5. There is no significant enthalpy difference between the *anti-anti* and *anti-syn* interactions of Hyp and adenine.

The outstanding experimental and quantum chemical data for adenine testifies that a Hyp(a):A(s) (Hoogsteen) pair is preferred, because in this case the stacking interaction and the geometry are more favourable than for the Hyp(a):A(a) (Watson-Crick) pair.

We consider that, in future applications, Hyp in PNA can be used as a substitute of G (when A is the neighbour) or T (when T is the neighbour) because of the easier synthesis of either the Hyp monomer or a Hyp containing PNA.

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