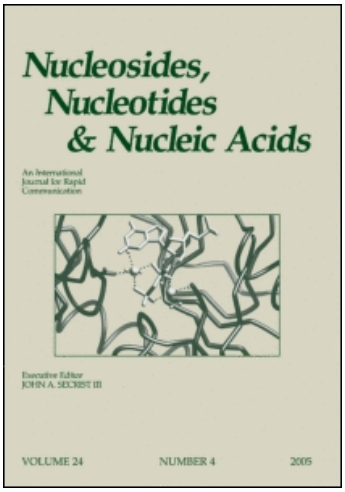

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Gautschi, Daniel and Leumann, Christian J.(2003) 'Olefinic Peptide Nucleic Acid (OPA)', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1211 — 1213
To link to this Article: DOI: 10.1081/NCN-120022838
URL: http://dx.doi.org/10.1081/NCN-120022838

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1211–1213, 2003

Olefinic Peptide Nucleic Acid (OPA)

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ABSTRACT

The olefinic peptide nucleic acid analogues (OPA) monomers containing the bases thymine and adenine were synthesised in 11 steps. Fully modified oligomers containing these units were prepared and their pairing properties assessed by means of UV-melting experiments.

Polyamide or peptide nucleic acids (PNAs), first described in 1991,[1] are DNA analogues based entirely on an achiral polyamide backbone. A key structural feature of PNA monomers **1** is the central amide linker between the base and the backbone. This tertiary amide functionality is conformationally labile and occurs in both the *E*- and *Z*-rotameric forms in uncomplexed PNA. In PNA/PNA, PNA/DNA and PNA/RNA duplexes, the carbonyl oxygen of the amide linker unit points uniformly to the carboxy terminus of the strand. OPA[2] was designed to remove this ambiguity. The central amide functionality is replaced by an isostructural, configurationally stable C = C double bond in either the *E* (**2**) or the *Z* (**3**) configuration.

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DOI: 10.1081/NCN-120022838
1525-7770 (Print); 1532-2335 (Online)

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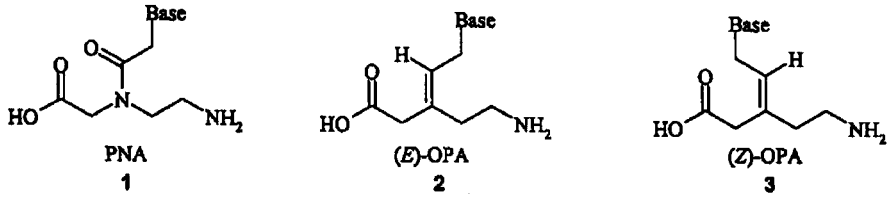
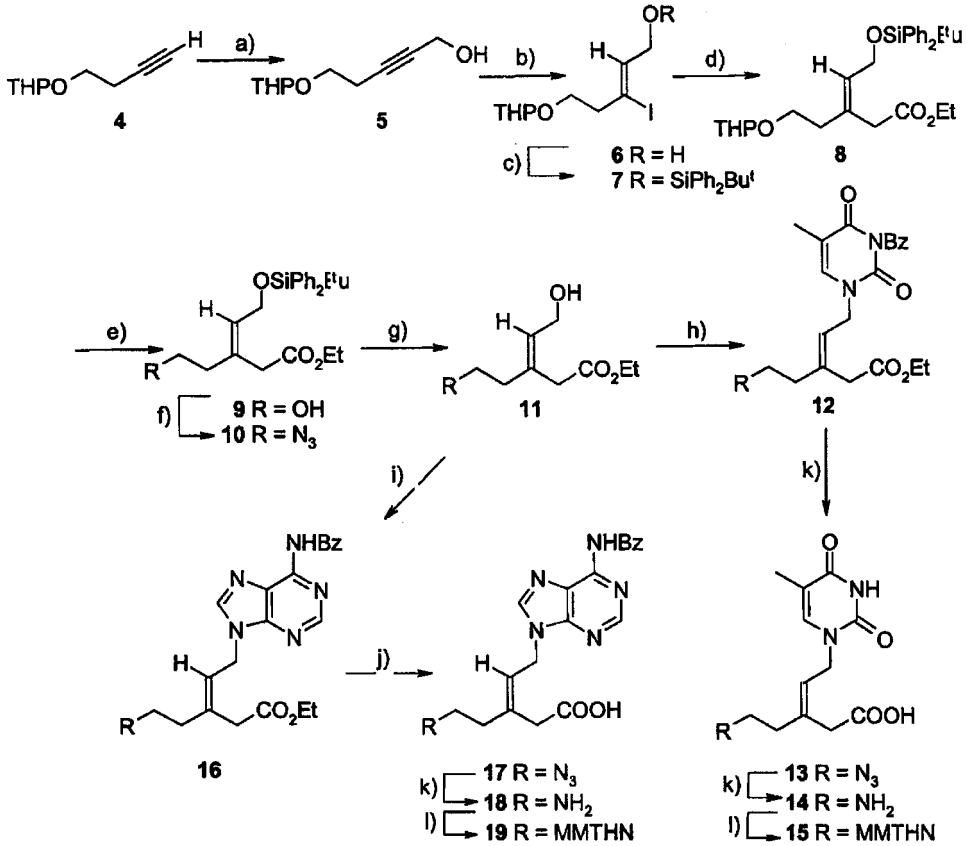


Figure 1. Chemical structure of the monomeric units of the different peptide nucleic acid analogues.



Scheme 1. a) *n*-BuLi, THF, −78°C, 10 min, then $(CHO)_n$, r.t., 1.5 h (83%); b) Red-Al, THF, addition 0°C-r.t., then NIS, −78°C, 10 min (90%); c) *t*$BuPh_2SiCl$, imidazole, THF, r.t., 16 h (97%); d) Reformatsky reagent: $BrCH_2$ CO_2Et, Zn, $CH_2(OCH_3)_2$, reflux, 30 min; coupling: $Pd(PPh_3)_4$, DMPU, 65°C, 2 h (88%); e) PPTSA, EtOH, 45°C, 2.5 h (80%); f) PPh_3, LiN_3, CBr_4, DMF, 0°C, 16 h (68%); g) HF·Py/Py 1:9, CH_3CN, r.t., 2.5 h; h) DIAD, PPh_3, N^3-benzoylthymine, THF, r.t., 2 h, (74% over two steps); i) DIAD, PPh_3, N^6-benzoyladenine, DMF, 0°C, 16 h, (50% over two steps); j) $LiOH_{(aq)}$ 1 M, Dioxane, 0°C, 16 h, (74%); k) Lindlar-catalyst, H_2, MeOH, r.t., 16 h; l) MMt-Cl, Et_3N, DMSO, 16 h, (65%).

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Table 1. Mass spectrometry data and T_m values [°C] (UV-melting-curves, 260 nm) of PNA, All-*E*-OPA and All-*Z*-OPA with parallel and antiparallel DNA (c = 4 μM in 100 mM NaCl, 10 mM, Na_2HPO_4, pH 7.0).

	Sequence	m/z calcd	m/z found (ESI^+TOF)	T_m (antiparallel DNA)[a]	T_m (parallel DNA)[b]
20	dC(ttttaatata)-Gly-NH_2[c]	3060.9	3060.9	29.4	13.1
21	dC($t^Et^Et^Et^Ea^Ea^Et^Ea^Et^Ea^E$)-Gly-$NH_2$[c]	2891.0	2891.3	< 0	16.0
22	Lys-$t^Zt^Zt^Zt^Za^Za^Zt^Za^Zt^Za^Z$-Gly-NH2	2731.03	2730.75	not detected	21.5

[a]d(TATATTAAAA).
[b]d(AAAATTATAT).
[c]Data from 2.

The MMT-*Z*- OPA monomer **15** and **19**, containing the bases thymine and adenine, were now synthesised in 11 steps, starting from THP-protected-3-Butyn-1-ol. The synthesis is outlined in Sch. 1.

In order to study the pairing properties, oligomers **20**–**22** were prepared using the MMT-/Acyl-strategy,[3] and the stability of the duplexes formed with anti-parallel and parallel DNA was assessed by means of UV-melting curves (Table 1). All-*Z*-OPA binds preferentially to parallel DNA ($T_m = 21°C$) rather than antiparallel (no pairing detected). Thus it shows opposite strand alignment behavior compared to PNA. This might be a consequence of the structural preorganisation of the monomeric unit, which mimics the rotameric form of PNA that is not observed in complexes. The overall lower affinity to DNA compared to PNA seems to be a consequence of differential solvation or dipole moment, rather than being of conformational origin.

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