**8**: $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 17.0$; $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 147.8$ (d, $^1J(P,C) = 113.2$ Hz, P–CH=N); $^1H$ NMR ($CDCl_3$): $\delta = 7.23$ (d, 1H, $^2J(P,H) = 40.0$ Hz, CH=N).

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# A Convergent Strategy for the Modification of Peptide Nucleic Acids: Novel Mismatch-Specific PNA-Hybridization Probes**

Oliver Seitz,* Frank Bergmann, and Dieter Heindl

Medicinal applications such as gene therapy as well as gene diagnostics greatly benefit from synthetic compounds that sequence-specifically recognize and bind nucleic acids.[1] Peptide nucleic acids (PNAs) represent a promising class of DNA analogues in which the entire sugar – phosphate backbone is replaced by a pseudopeptide backbone.[2] Their successful use as hybridization probes fuels research that is aimed at the development of new polyamide-based DNA binders.[2d] However, little attention is directed towards the elaboration of techniques to site-specifically modify PNA oligomers, although the feasibility to serve as hybridization probe relies on the selective introduction of reporter groups. In all studies to date, nonstandard nucleobases were incorporated by coupling of the corresponding monomeric building blocks.[2d, 3] A strategy in which the modified nucleobases are coupled to an orthogonally protected backbone on solid phase would omit the need to synthesize an entire monomer in solution.[4] Thus, the rapid synthesis and the efficient screening of modified PNA conjugates would be greatly facilitated. This work presents a convergent strategy to selectively functionalize and label PNA at terminal as well as internal positions.

The central building block for the "on-resin synthesis" of nonstandard PNA monomers is the orthogonally protected aminoethylglycine **1** (Scheme 1).[5] For validation, the building block **1** was conjugated to the allylic HYCRON linker, which provides orthogonal stability in combination with commonly used protecting-group strategies.[6] The aminoethylglycine – HYCRON conjugate **3** was synthesized by allowing the Boc/Fmoc-protected PNA backbone **1** to react with the allylic bromide **2** followed by the reductive removal of the phenacyl ester moiety. The Boc/Fmoc-protected conjugate **3** was attached to the resin using HBTU and HOBt. Treatment of **4** with DMF/morpholine liberated a compound with a secondary amino group, which subsequently was subjected to a coupling reaction with **5**. In the presence of the allyl scavenger morpholine, resin **6** was treated with catalytic amounts of the $Pd^0$ catalyst $[Pd(PPh_3)_4]$. The Boc/Z-protected guanosine analogue **7** was obtained in a yield of 61 % based on the initial load of resin **4** with Fmoc groups. A comparison with the 70 – 80 % yield of the corresponding solution synthesis illustrates the efficiency of this on-resin synthesis of the protected PNA-monomer **7**.[7, 8]

As part of our research on new assays for the real-time detection of oligonucleotide hybridization of an oligomer, we

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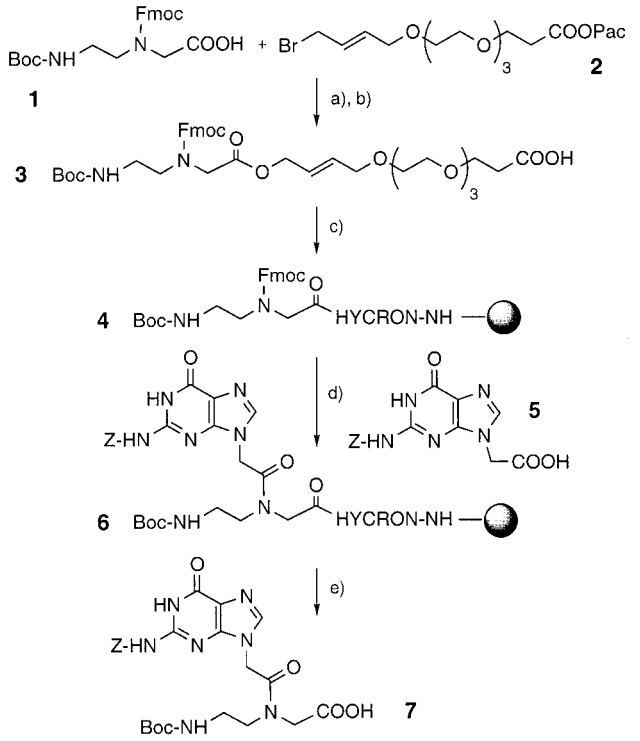
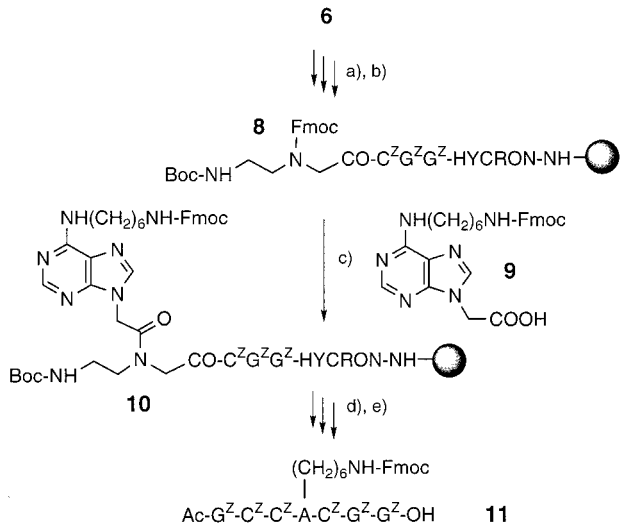


Scheme 1. Synthesis of the protected PNA monomer **7**. a) Sat. $NaHCO_3$, $Bu_4NBr$, $CH_2Cl_2$, 92%; b) Zn, AcOH, 94%; c) 1. aminomethylpolystyrene, HBTU, $iPr_2NEt$, HOBt, DMF; 2. $Ac_2O$, pyridine; d) 1. DMF/morpholine (1/1); 2. HATU, $iPr_2NEt$, pyridine, DMF; 3. $Ac_2O$, pyridine, DMF; e) $[Pd(PPh_3)_4]$, morpholine, DMSO, DMF, 61%. Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate, HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HOBT = 1-hydroxy-1*H*-benzotriazole, HYCRON = hydroxycrotyloligoethylene glycol-*n*-alkanoyl, Pac = $CH_2COPh$, Z = benzyloxycarbonyl.

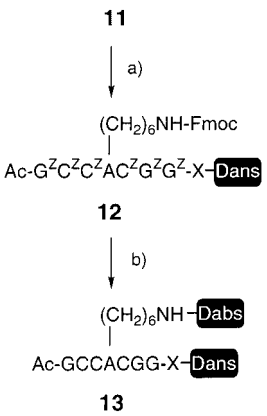
needed to introduce a conjugation site at an internal position. To direct the attachment of reporter groups to the major groove of a DNA duplex, we employed the Fmoc-protected $N^6$-aminoalkyladenine **9** (Scheme 2).[9, 10] Starting from **6** the linear solid-phase synthesis was performed according to standard PNA synthesis protocols.[11] The Boc/Fmoc-protected building block **1** was incorporated at position 4. After removal of the Fmoc group, the liberated compopund was acylated at the secondary amino group with **9** to give the polymer-bound tetramer **10**. Photometric analysis of the Fmoc load revealed a near quantitative yield for the coupling. The elongation of **10** was performed as described in Scheme 2. Finally, the $Pd^0$-catalyzed cleavage reaction and subsequent purification by HPLC furnished the analytically pure protected PNA heptamer **11** in 47% overall yield (based on the Fmoc load of **4**).[12]

Fully protected PNA-conjugates such as **11** enable selective reactions at the C terminus as well as at the primary alkylamino group. The selective coupling of **11** to dansylethylenediamine yielded conjugate **12**, which is labeled at the C terminus, demonstrating that protected PNA oligomers can serve as acyl donors in peptide couplings (Scheme 3). Successive treatment with DMF/morpholine and trifluoromethanesulfonic acid/TFA resulted in removal of the Fmoc group and the Z groups, respectively. The liberated primary alkylamino



Scheme 2. Synthesis of PNA conjugate **11**. a) 1. TFA/*m*-cresol (95/5); 2. Boc-$B^Z$-OH, HATU, $iPr_2NEt$, pyridine, DMF; 3) $Ac_2O$, pyridine, DMF; b) 1. TFA/*m*-cresol (95/5); 2. **1**, HATU, NMM, DMF; 3. $Ac_2O$, pyridine, DMF; c) 1. DMF/morpholine (1/1); 2. HATU, NMM, pyridine, DMF; 3. $Ac_2O$, pyridine, DMF; d) 1. TFA/*m*-cresol (95/5); 2. Boc-$B^Z$-OH, HATU, NMM, DMF; 3. $Ac_2O$, pyridine, DMF; e) $[Pd(PPh_3)_4]$, MeNHPh, DMSO, DMF, 47% (based on **4**). $B^Z$ = a PNA monomer with an exocyclic amino protecting group, NMM = *N*-methylmorpholine, TFA = trifluoroacetic acid.

group was used to selectively attach a second reporter group. Reaction with the fluorescence-quenching dabsyl chloride yielded the doubly labeled PNA conjugate **13**. The HPLC analysis showed no side products and only traces of starting material, confirming the high selectivity of the dabsyl introduction. Doubly labeled oligomers of type **13** might be useful for monitoring the conformational change that PNA experiences upon hybridization to complementary DNA.[13]



Scheme 3. Synthesis of doubly labeled PNA conjugate **13**. a) EDC, HOAt, Dans-X-H, DMF, $CH_2Cl_2$; b) 1. DMF/morpholine (1/1); 2. *m*-cresol/MeSMe/TFMSA/TFA (1/1/1/10), 66% % (based on **11**); c) Dabs-Cl (4 equiv), sat. $NaHCO_3$, DMF, 50%. Dabs = 4-dimethylaminoazobenzene-4′-sulfonyl, Dans = 5-dimethylaminonaphthaline-1-sulfonyl, EDC = $Me_2N(CH_2)_3$-N=C=NEt · HCl, HOAt = 1-hydroxy-7-azabenzotriazole, TFMSA = trifluoromethanesulfonic acid, X = $NHCH_2$-$CH_2NH$.

The on-resin synthesis of nonstandard nucleobases provides access to conjugates which are difficult to obtain by standard routes. For instance, we were interested in incorporating the environmentally sensitive thiazolorange fluorophore into PNA.[14] However, in our hands the synthesis of the corresponding PNA building block could not be accomplished. Therefore, we made use of the orthogonally protected backbone **1**. The PNA 21-mer **17** containing the intercalating thiazolorange was synthesized from Boc-protected glycine–MBHA resin (Scheme 4). The first ten monomers were

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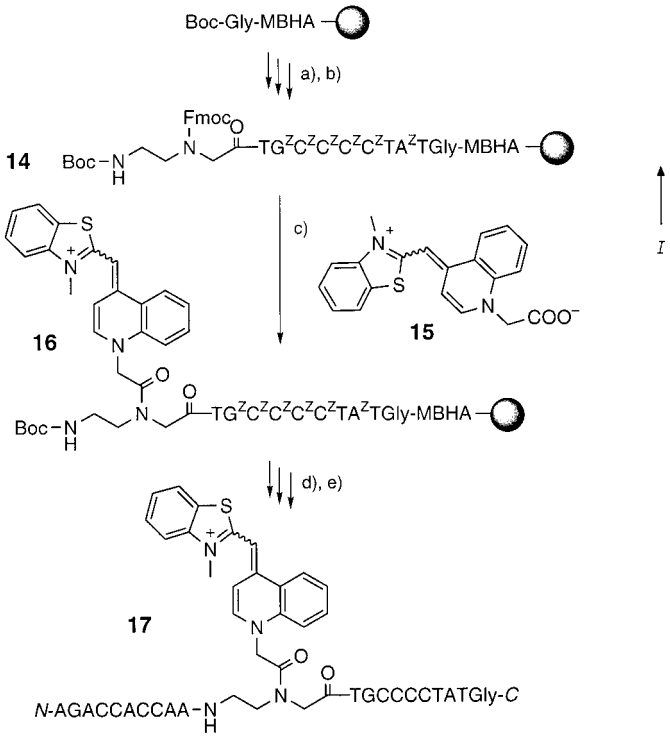


Scheme 4. Synthesis of PNA 21-mer **17**. a) 1. TFA/*m*-cresol (95/5); 2. Boc-B$^Z$-OH, HATU, *i*Pr$_2$NEt, pyridine, NMP; 3. Ac$_2$O, pyridine, NMP; b) 1. TFA/*m*-cresol (95/5); 2. **1**, HATU, *i*Pr$_2$NEt, pyridine, NMP; 3. Ac$_2$O, pyridine, NMP; c) 1. DMF/piperidine (8/2); 2. HATU, iPr$_2$NEt, NMP; 3. Ac$_2$O, pyridine, DMF; d) 1. TFA/*m*-cresol (95/5); 2. Boc-B$^Z$-OH, HATU, *i*Pr$_2$NEt, NMP; 3. Ac$_2$O, pyridine, NMP; e) trifluoromethanesulfonic acid/TFA/*m*-cresol (2/8/1), 1.5 h. MBHA = 4-methylbenzhydrylamine, NMP = *N*-methylpyrrolidine.

assembled as described.[11] Building block **1** was incorporated at position 11. The Fmoc group of **14** was removed prior to the coupling of the carboxylthiazolorange **15**. After capping, the linear solid-phase synthesis was continued, and standard acidolysis liberated the unprotected PNA conjugate **17**, which subsequently was purified by reverse-phase HPLC. UV/Vis spectrometry and MALDI-TOF-MS confirmed the identity of **17**.[15]

Upon hybridization, the environmentally sensitive thiazolorange moiety of **17** will be located in the interior of the PNA – DNA duplex, and should thus be able to sense changes in the immediate vicinity. Hybridization experiments with partial sequences of the hepatitis B virus were carried out. Figure 1 shows the fluorescence spectra of the PNA probe **17** as it was measured before and after addition of an equimolar amount of the target DNAs **18** and **19.** As expected, upon formation of duplex **17**·**18** the fluorescence intensity increased from 17.8 (**17**) to 40.3 (**17**·**18**), and the emission maximum shifted from 538 to 530 nm. In contrast, duplex **17**·**19**, which contains one mismatched base pair (A – A) adjacent to the fluorophore **O**, exhibited a slight fluorescence decrease from 24.8 to 21.1. The emission maximum was shifted from 538 to 534 nm.

It was reported that the fluorescence of nonconjugated thiazolorange increases dramatically upon binding to double-stranded DNA; this explains the increase in fluorescence for **17**·**18**.[16] The slight, but significant, decrease in fluorescence

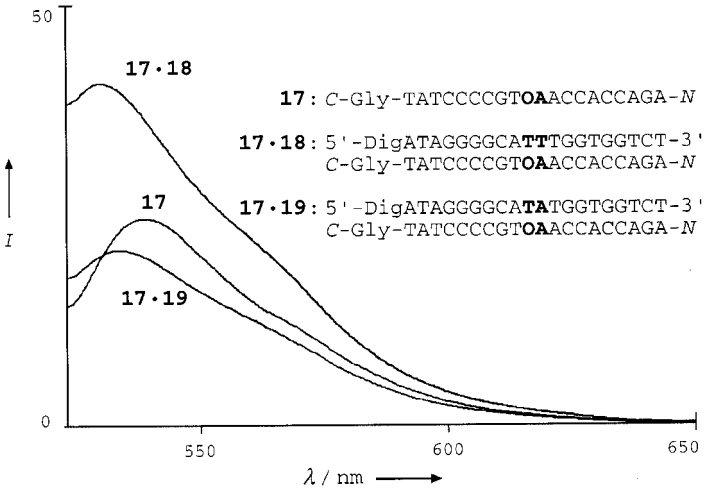


Figure 1. Fluorescence spectra (arbitrary intensity units) of the PNA probe **17**, the PNA – DNA duplex **17**·**18**, and the PNA – DNA duplex **17**·**19**, which contains one base-pair mismatch adjacent to the thiazolorange dye **O**. For **17** only the fluorescence spectrum before addition of **19** is shown (**17** ($I_{max}$ = 24.8) → **17**·**19** ($I_{max}$ = 21.1)). For clarity one representation of the orginal spectrum of the second experiment has been omitted (**17** ($I_{max}$ = 17.8) → **17**·**18** ($I_{max}$ = 40.3)). Measurement conditions: 100 mM NaCl, 10 mM sodium phosphate buffer, pH 7, 0.1 mM EDTA, 298 K, 0.5 optical density (OD) at 260 nm of **17**, **18**, and **19**, excitation at 513 nm. Dig = digoxigenin.

that accompanied the formation of duplex **17**·**19** is less readily explained. However, it can be concluded that the exeperiments clearly distinguished between the hybridization to the perfectly complementary strand **18** and the hybridization to the complementary strand **19** containing one adjacent mismatched base pair.

The methodology elaborated in these studies should be applicable to the site-selective modification of PNA in general, and adds new opportunities for the development of medicinally relevant PNA conjugates. It provided access to PNA – fluorophore conjugates such as **17**, which might serve as new tool for the real-time sequence analysis of DNA, particularly for the detection of single-base mutations. In future work we will investigate whether the remarkable phenomenon illustrated in Figure 1 can be generalized to any type of base mismatch in the presence of unrelated sequences.

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# Activation of a Carbon–Oxygen Bond of Benzofuran by Precoordination of Manganese to the Carbocyclic Ring: A Model for Hydrodeoxygenation**

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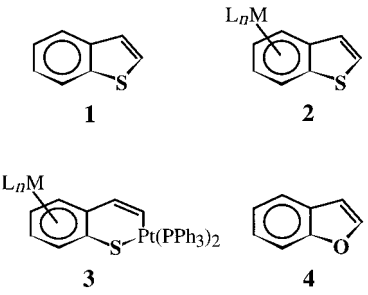
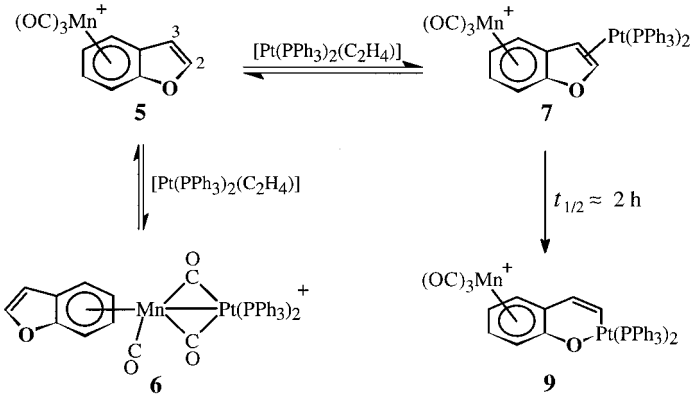
The use of hydrogen in the presence of a catalyst to remove the heteroatoms S, N, and O from petroleum is practiced on a massive scale and is known as hydrodesulfurization (HDS), hydrodenitrogenation (HDN), and hydrodeoxygenation (HDO).[1] Generally, the most difficult molecules to treat by hydroprocessing contain highly stable unsaturated heterocyclic ring systems, for example, those based on thiophene, pyrrole, pyridine, and furan. In the case of sulfur and nitrogen, this results in significant contamination of fossil fuels. Problems associated with the presence of oxygen compounds are less severe but nevertheless significant.[2] For these reasons, there has been substantial interest in developing homogeneous model systems for C–X bond cleavage (X = S, N, O) and subsequent removal of the X atom in unsaturated heterocycles.[3, 4]

We have shown[5] that precoordination of a metal center to the carbocyclic ring of benzothiophene (BT, **1**) and dibenzothiophene activates a C–S bond towards cleavage by reducing agents and by metal nucleophiles. For example, the weak nucleophiles $[Pt(PPh_3)_3]$ and $[Pt(PPh_3)_2(C_2H_4)]$ do not react with free BT, but react rapidly with $[(\eta^6\text{-BT})ML_n]$ (**2**, $ML_n$ = $Mn(CO)_3^+$, $FeCp^+$, $RuCp^+$, etc.) to afford the metallathiacycles **3**. Similar activation of a C–O bond in benzofuran (BF, **4**) is expected to be more difficult due to the much greater strength of C–O bonds compared to C–S bonds and because most late transition metal centers prefer S to O ligands. Nevertheless, we report here that insertion of a metal center into the C(2)–O bond of $[(\eta^6\text{-BF})Mn(CO)_3]^+$ (**5**) is readily achieved. Addition of free **4** to $[Pt(PPh_3)_2(C_2H_4)]$ produces no reaction, but **5** ($\tilde{\nu}_{CO}$ = 2079, 2020 $cm^{-1}$) reacts rapidly at room temperature to produce initially two products, both of which rapidly revert to **5** upon addition of CO or $PPh_3$. Scheme 1 summarizes the chemistry proposed to be occurring. Although the minor initial product could not be isolated, IR ($\tilde{\nu}_{CO}$ = 1775, ca. 1980 $cm^{-1}$), $^1H$ NMR, and $^{31}P$ NMR spectroscopic data strongly suggest that it has structure **6**. Similar species are formed with a wide variety of $[(arene)Mn(CO)_3]^+$ complexes on treatment with $[Pt(PPh_3)_2(C_2H_4)]$.[6] Furthermore, analogous bonding to that proposed for **6** is found in the related complexes $[(CO)_4Re(\mu\text{-H})(\mu\text{-CO})Pt(PPh_3)_2]$ and $[(CO)_4Mn(\mu\text{-H})(\mu\text{-CO})Pt(PEt_3)_2]$.[7]




Scheme 1. Insertion of $Pt(PPh_3)_2$ into activated benzofuran.

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