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[18] The X-ray diffraction data were collected at 294 K with a Rigaku AFC-5S four-circle diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å). Crystal data for **2**: Formula $C_9H_{27}B_{10}I_2P$, $M_r = 528.18$, crystal size: $0.36 \times 0.34 \times 0.30$ mm, monoclinic, space group $P2_1/a$ (No. 14), $a = 14.087(4)$, $b = 10.358(2)$, $c = 15.230(3)$ Å, $\beta = 110.33(2)^\circ$, $V = 2083.9(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.684$ g cm^{-3}, $\mu = 3.082$ mm^{-1}, $F(000) = 1008$, reflections collected 3835, unique 3673 [$R_{int} = 0.0187$]. An empirical absorption correction with ψ-scan data was applied. The structure was solved using SIR92 and was refined against $|F^2|$ using program SHELXL-97 (230 parameters). R indices were (all data): $R_1 = 0.0524$, $wR_2 = 0.0727$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-144823. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Remote Enantioselection Transmitted by an Achiral Peptide Nucleic Acid Backbone**

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Peptide nucleic acid (PNA; Figure 1b) is an achiral DNA (or RNA) mimic with an amide (pseudopeptide) backbone. PNA oligomers form double helices with complementary DNA or RNA through Watson–Crick base pairing.[1] Complementary strands of PNA form DNA-like double helices but the left-handed and right-handed duplexes have equal stability in the absence of chiral influences.[2]

The RNA-world hypothesis which states that our biological life was preceded by a prebiotic system in which RNA oligomers functioned both as genetic materials and as enzyme-like catalysts is widely accepted.[3] This hypothesis raises the problem of the origin of RNA and, in particular, emphasizes the difficulty of forming and replicating a homochiral nucleic acid in a solution of racemic nucleotides.[4] One possible solution to this problem involves a gradual transition from an achiral genetic material (for example, one resembling PNA) to RNA.

Although there are now claims that PNA could have been a prebiotic molecule,[5] this is highly speculative. We have used PNA extensively as a model for the type of achiral polymer that could have preceded RNA.[6] The influence of chiral substituents on the distribution of left- and right-handed PNA helices has been reported at some length.[2, 7] Here we continue to explore the possibility of a transition from an achiral nucleic acid analogue to RNA, and show that as few as two D-deoxynucleotides incorporated at one end of a decameric PNA double helix can control the handedness of the helix. Furthermore, we show that this can result in enantioselective chemistry both remote from and at residues not covalently connected to the inducing chiral dinucleotide. Remote enantioselection of this kind could overcome the problem of enantiomeric cross-inhibition, and thus greatly simplify a stepwise evolutionary transition from a prebiotic achiral to a biological homochiral genetic material.

We prepared a series of PNA-containing duplexes (Figure 1a): DS is an achiral PNA double helix, while D1 is the corresponding duplex in which the N-terminus cytosine

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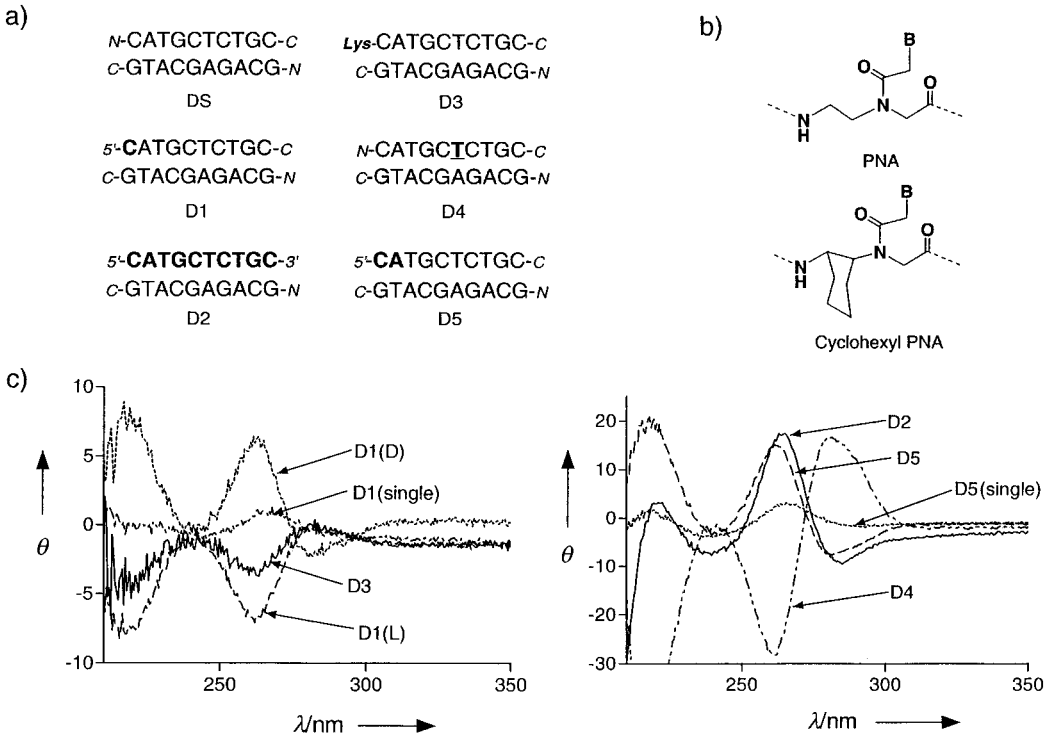

Figure 1. a) Sequences of the basic PNA-PNA duplex DS and the modified duplexes D1-D5. The N and C termini of the PNAs are indicated by -N and -C, respectively. Deoxyribonucleotides are shown in bold. Lys- denotes an N-terminus L-lysinamide, and **T** is a backbone PNA thymine residue modified with an (*R*,*R*)-cyclohexyl group. b) The structures of a PNA residue and a cyclohexyl PNA residue. c) CD spectra of duplexes D1-D5. The D1(D) duplex contains a D-dC residue, and the D1(L) duplex contains an L-dC residue. D1(single) denotes the chimeric strand of D1 (5′-**C**ATGCTCTGC-*C*). D5(single) denotes the chimeric strand of D5 (5′-**CA**TGCTCTGC-C). All spectra were recorded at identical oligomer concentrations ($OD_{260} = 1.0$ (OD = optical density)) in 10 mM sodium phosphate at pH 7.0 containing 100 mM NaCl.

residue has been replaced by a D-deoxynucleotide (D-dC). D2 is a helix formed from one DNA and one PNA strand, D3 is a PNA double helix in which a single L-lysinamide was attached to the N-terminus of one of the strands, and D4 is a PNA double helix with an internal thymine residue replaced by a conformationally constrained PNA residue modified with a chiral cyclohexyl group[8] (Figure 1b).

The CD spectra of these double-helical molecules at equal concentrations are presented in Figure 1c. The results show that the D-dC nucleotide does, indeed, induce a right-handed helicity in the D1 duplex. A comparison of the CD spectra of D1 and D3 suggests that a single D-dC residue is about twice as effective as an attached chiral lysinamide in inducing chirality. A comparison of the spectrum of D1 with those of D2 and D4, which we assume to be locked in right- and left-handed helices, respectively, allows us to estimate that D1 is about 75% right-handed and 25% left-handed, since D1 gives rise to approximately half the CD intensity of the two locked helices. The results also confirm that the N-terminal L-lysine residue induces a left-handed PNA helix,[7] and that about 62% of the helices are left-handed.

Since one chiral deoxyribonucleotide unit at the N-terminus of a 10-*mer* PNA is not sufficient to generate a homochiral population of PNA duplexes, we next prepared a DNA-PNA chimera (5′-**d(CA)**TGCTCTGC-C) in which the two N-terminal nucleobase units were D-deoxyribonucleotides. We then recorded the CD spectrum of a duplex formed between this chimera and the antiparallel oligomer of complementary PNA (Figure 1, D5). Judging from the intensity of the band at 260 nm in the CD spectrum this duplex deviates only slightly from homochirality. Thus the chirality of the N-terminal dinucleotide has been transmitted efficiently through the covalently linked first PNA strand to the hydrogen-bonded and base-stacked second PNA strand.

The above results suggest that the chirality induced by two nucleotides in a template strand could be transmitted through normally achiral PNA and result in a chirally selective template-directed remote elongation of an achiral primer strand. We, therefore, studied ligation in the system illustrated in Figure 2. The structure of the duplex that we used for the ligation experiments resembles the structure of the duplex D5 (Figure 1a). The upper strand (template strand) contains two D-deoxynucleotides at its N terminus, while the primer strand which lacks two residues at its N terminus is made up entirely of PNA monomers. We extended the C terminus of this strand by three thymine residues, solely to simplify the HPLC analysis of the ligation products. The substrate was either the DD or the LL enantiomer of a dinucleotide activated as a phosphorimidazolide (5′-d(GC)pIm-3′). In control experiments we used a duplex in which both the template and primer were composed exclusively of PNA.

In the absence of a template no detectable product was formed (Figure 2a, d). When the template strand was entirely PNA both DD and LL substrates gave product yields of about 15% (Figure 2b, e). However, when the template strand included two D nucleotides the yield of the reaction with the DD dimer doubled to about 30% while the yield of the reaction with the LL isomer decreased to less than 5% (compare Figures 2c and 2f). When we used the racemic dimer as the substrate we found that the presence of the LL isomer did not inhibit the reaction of the DD isomer significantly (compare Figures 2c and 2g). Thus the reaction is more than 90% stereoselective for the DD enantiomer.

Our results can be interpreted as only right-handed helices react with the DD dimer and left-handed helices with the LL dimer. As far as we are aware these experiments demon-

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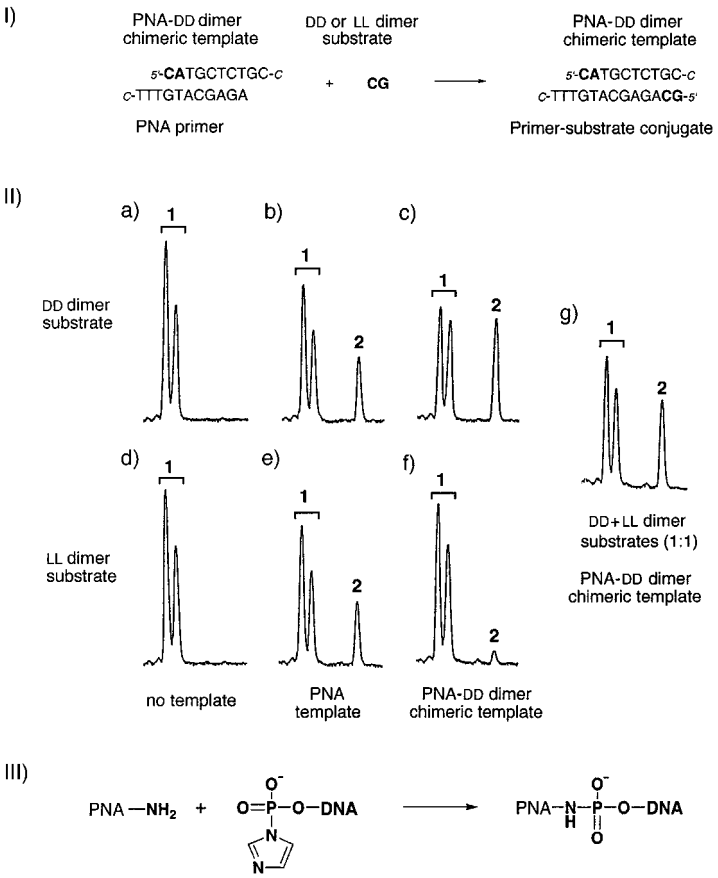

Figure 2. Remote enantioselection in PNA-directed PNA-DNA ligation. The design of the experiment is illustrated in (I) and the nature of the ligation step in (III). Diagrams a – g in (II) present HPLC elution profiles of the products formed by ligation of the PNA primer to the DD and LL enantiomers of 5′-d(GC)pIm-3′. The reaction mixtures contain the DD dimer (a – c), the LL dimer (d – f), or a 1:1 mixture of DD and LL dimers (g). The template is omitted in a and d; the PNA template is present in b and e; and the chimeric PNA-DD-d(CA) template (PNA-DNA chimeric template) is present in c, f, and g. The numbers above the peaks indicate 1: the starting PNA primer, C-TTTGTACGAGA-N, 2: the product, a primer-dimer chimera, C-TTTGTACGAGA**CG**-5′. The double peak representing the starting PNA primer arises from an N-terminal rearrangement of the PNA at pH 12 before and during HPLC.[17] The rearranged product does not undergo template-directed elongation (data not shown).

strate for the first time that chiral influences can be transmitted over long distances through both covalent and noncovalent interactions in nonbiological systems, and result in remote stereoselective chemistry. Previously, Green et al. and others showed that certain synthetic polymers are very sensitive to chiral induction,[9] but these systems cannot carry genetic information and no enantiomeric chemical selection was demonstrated.

The present results also have implications for possible scenarios for the development of homochirality in a prebiotic genetic material. We have previously proposed PNA as a model for an achiral prebiotic genetic material, and have provided evidence that a transition from a "PNA-like" genetic world to an RNA (or DNA) genetic world is in principle possible either through a "one-step" information transfer by PNA-directed RNA oligomerization,[6a,b] or through a multistep process involving PNA-directed PNA-DNA ligation.[6c] However, these experiments do not solve the problem of chirality in the transition from achiral PNA to homochiral DNA (or RNA). On the contrary, it was found that enantiomeric cross-inhibition in PNA-directed RNA polymerization was as profound as seen previously for RNA-directed RNA polymerization.[10]

The results presented here show that the introduction of a short homochiral segment of DNA into a PNA helix could have guaranteed that the next short segment of DNA to be incorporated would have the same handedness as the first. Once two segments of the same handedness were present, the probability that a third segment would have the same handedness would increase, and so on. Evolution could then slowly "dilute out" the PNA part. This scenario would ultimately allow the formation of a chiral oligonucleotide by processes that are largely resistant to enantiomeric cross-inhibition.

It is important to note that the ligation of homochiral dinucleotides on a nucleic acid template would probably be at least as enantiospecific as the reaction that we have studied. The disadvantage of using chiral monomers as components of a replicating system arises from the difficulty of generating a first long homochiral template from a racemic mixture of monomers, although results of experiments designed to overcome this difficulty by employing homochiral tetramers have been reported.[4a] The probability of obtaining a homochiral *n-mer* from achiral substrates is approximately $1/2^{n-1}$ if the nontemplate-directed extension of the primer is not enantioselective. Hence, it would be very hard to get started with a homochiral 40-*mer*, for example. No such difficulty exists in a scenario that originates with an achiral genetic material and in which the incorporation of very few chiral monomers in this achiral background gradually progresses towards homochirality.

It seems possible that some PNA sequences could act as catalysts, analogous to ribozymes, even though PNA lacks clear metal binding sites. Although such catalysts could not be enantioselective, the incorporation of as few as two chiral nucleotides could then impose chiral specificity on the system. Furthermore, such patch chimeras could help to bridge the gap in catalytic potential between PNA and RNA, while guaranteeing enantioselectivity.

Experimental Section

Unless otherwise noted all chemicals were purchased from commercial sources and were used without further purification. L-dCp was synthesised as described.[11] PNA-dC conjugates (D or L) were obtained as described.[12] Unless otherwise stated, the PNA oligomers were prepared as C-terminal carboxamides. The dimers DD-d(CA)p, DD-d(CG)p, and LL-d(CG)p were synthesised on a 10-μM scale on a 391A automatic DNA synthesizer (Applied Biosystems) using appropriate D- or L- phosphoramidites and 3′-phosphate CPG (Chemgenes). DD-d(CA)pIm was synthesized by using the experimental procedure described for mononucleotides.[13, 14] Reactions between PNA and DD-d(CA)pIm and the subsequent purification of the product were performed under conditions previously reported.[12] These procedures led to PNA-DNA chimeras joined by a favorable DNA-3′-phosphoramidate linkage directly to the PNA amino terminus.[6c, 15] The yield of the PNA-dimer conjugate was 60%. The product showed the correct mass as characterized by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (found: 2751, calcd: 2753).

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Ligation reactions were run in total volumes of 10 μL of 0.25 M imidazole (Im) buffer, pH 7.7, for 3 days at 0 °C. The concentration of the PNA primer was 8 μM, of the template 12 μM, and of the activated dimer 0.8 mM. When we used a mixture of DD and LL dimers, the concentration of each enantiomer was 0.8 mM. The duplexes between the primer and templates were preformed by preincubation at 20 °C for 2 h in 5 μL of 10 mM sodium phosphate buffer, pH 7.0, containing 100 mM NaCl and 0.1 mM ethylenediaminetetraacetate (EDTA). The dimers were activated in 0.1 M Im buffer at pH 6.0 containing 0.1 M 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (EDC) by incubating the solution for 3 h at 20 °C and then diluting with an equal volume of 1 M Im buffer at pH 7.7. Aliquots of the resulting solution (5 μL) were added to reaction tubes containing the preformed duplexes. HPLC analyses of the reaction mixtures were performed on an RPC5 column as previously described.[16] Reaction products were eluted with a linear gradient of $NaClO_4$ (pH 12, 0 – 0.06 M over 60 min) and the UV absorption at 254 nm monitored.

Circular dichroism spectra were obtained using equimolar concentrations (10 μM) of the two complementary strands hybridized in 10 mM sodium phosphate at pH 7.0 containing 100 mM NaCl.

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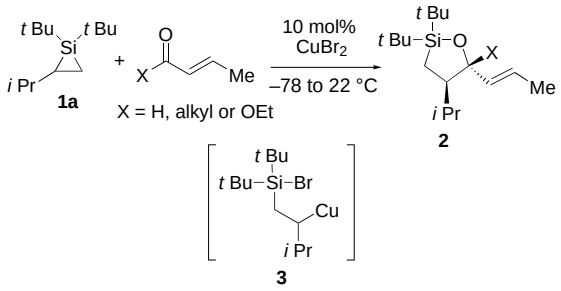
$ZnBr_2$-Catalyzed Insertions of Carbonyl Compounds into Silacyclopropanes: Regiochemical Reversal Dependent on Metal Salt**

Annaliese K. Franz and K. A. Woerpel*

We recently reported that copper salts catalyze the insertion of various carbonyl compounds into the C–Si bond of silacyclopropane **1a** in a stereospecific and highly stereo-, regio-, and chemoselective fashion (see Scheme 1).[1] While formamides, formate esters, and α,β-unsaturated carbonyl compounds inserted under these conditions, saturated aldehydes such as butyraldehyde could not be coaxed to react. Ring-opening of the unsymmetrically substituted silacyclopropane **1a** occurred exclusively with cleavage at the more substituted C–Si bond to afford insertion products such as **2**. The observed regiochemistry and carbonyl reactivity was rationalized by consideration of organometallic species **3** (Scheme 1) which is believed to form upon transmetalation of the more substituted C–Si bond to copper. We have obtained selectively products with this 1,2-regiochemistry for all insertion reactions of silacyclopropanes thus far.[2–4]



Scheme 1. Copper-catalyzed insertions into silacyclopropane **1a** proceed with up to 98:2 diastereoselectivity and > 99:1 regioselectivity.

To complement our previous results, we desired a method to functionalize the less substituted C–Si bond and insert saturated carbonyl compounds. Insertion into the less substituted C–Si bond would provide access to the 1,3-regioisomer **4** which can be oxidized[5] to obtain the 1,3-diol motif **5** (Scheme 2).[6, 7] Herein, we report that metal salts such as $ZnBr_2$ can be employed to access previously unavailable

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