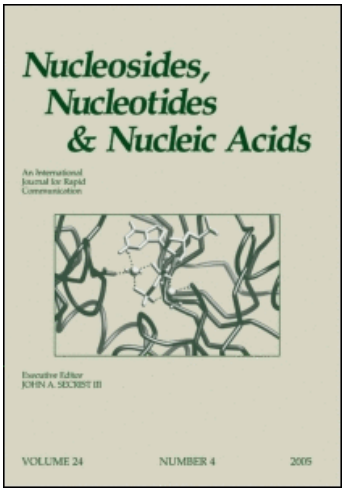

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POLYAZA CROWN ETHER AS NON-NUCLEOSIDIC BUILDING BLOCKS IN DNA-CONJUGATES

Ulla Jakobsen, Katja Rohr, Rasmus K. Madsen, and Stefan Vogel □ *Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M, Denmark*

□ *The synthesis of amphiphilic polyaza crown ether monomers X (palmityl-substituted), Y (cholesteryl-substituted) and Z (dipalmityl-subtituted) and their incorporation into oligonucleotides are described. Their effects on thermal duplex stability were investigated by UV melting curve analysis. Thermal denaturation experiments showed remarkable stabilization of dsDNA by polyaza crown ether monomers when incorporated in opposite positions. The series of polyaza crown ether monomers (X, Y, and Z) with different lipophilicity showed a trend of increased stability of the corresponding dsDNA with increasing lipophilicity of the polyaza crown ether monomer.*

Keywords Polyaza crown ether; amphiphilic DNA; DNA-conjugates

INTRODUCTION

Based on the unique properties of DNA as a building block useful materials will likely be hybrid materials that utilize DNA as a scaffold for arranging synthetically more accessible organic and inorganic building blocks.[1–7] Non-nucleosidic building blocks with terminal lipophilic groups have been reported to decrease or have only minor effects on stability of oligonucleotide duplexes.[9–11] In the present study a number of macrocyclic building blocks with highly lipophilic substituents has been incorporated in DNA-conjugates (Figure 1).[12]

RESULTS AND DISCUSSION

The desired non-nucleosidic building blocks (monomers **X, Y,** and **Z,** Scheme 1) have been synthesized in a highly convergent synthetic approach. The synthetic route can be easily adapted for a larger series of amphiphilic macrocyclic building blocks for automated DNA synthesis.[8,12]

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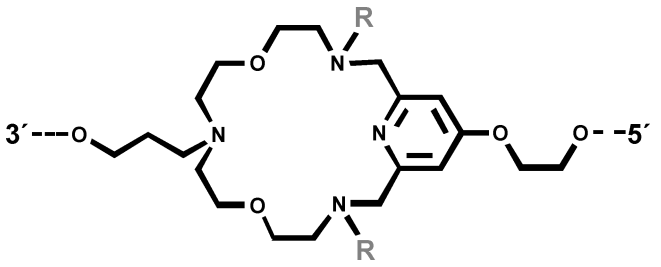
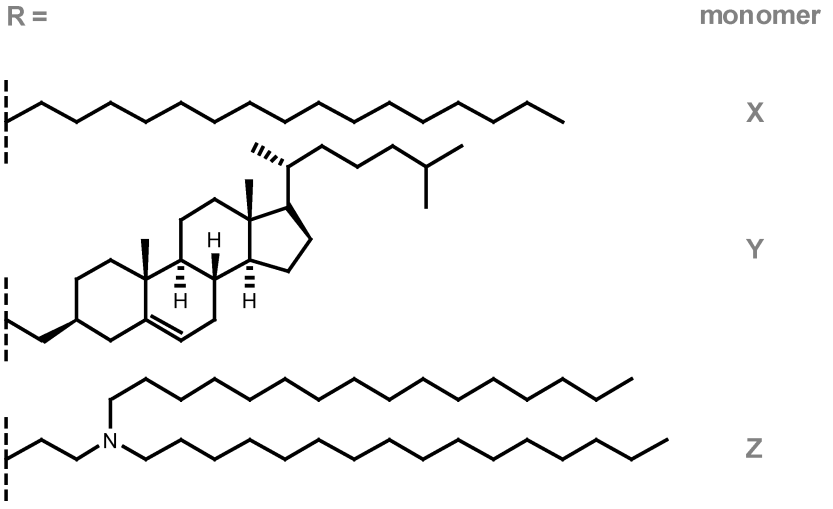


FIGURE 1 Polyaza crown ether building block (R = lipophilic substituents).



SCHEME 1 Substitution pattern for the building block monomers **X, Y**, and **Z**.

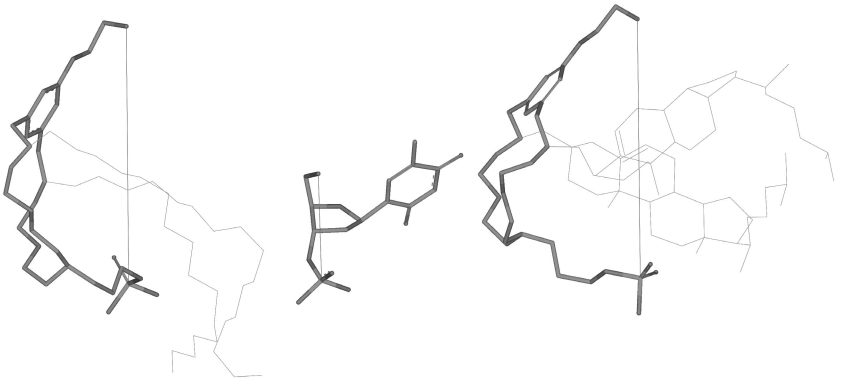


FIGURE 2 Putative structure of monomer **X** (left), monomer **Y** (right) and a T-nucleotide. Substituents are in gray and hydrogens have been omitted for clarity.

TABLE 1 Influence of monomer X and Y on thermal DNA duplex stability

Entry	Sequence	Tm [°C][a]
1	5′-TTT- TGT-GGA-AGA-AGT-TGG-TG -TTT 3′-TTT- ACA-CCT-TCT-TCA-ACC-AC -TTT	58
2	5′-TTT-X-TGT-GGA-AGA-AGT-TGG-TG-X-TTT 3′-TTT-X- ACA-CCT-TCT-TCA-ACC-AC-X-TTT	77
3	5′-TTT-X-TGT-GGA-AGA-AGT-TGG-TG-X-TTT 3′-TTT-Y-ACA-CCT-TCT-TCA-ACC-AC-Y-TTT	77
4	5′-TTT-Y-TGT-GGA-AGA-AGT-TGG-TG-Y-TTT 3′-TTT-Y-ACA-CCT-TCT-TCA-ACC-AC-Y-TTT	>85

[a]10 mM sodium phosphate, 100 mM NaCl, 0.1 mM EDTA, adjusted to pH 7.0, concentration of 1 μM for each DNA strand.

A modeling study has been performed to estimate the steric demand of monomer **X** and **Y**, the relative spatial arrangement of the lipophilic substituents as well as the conformational flexibility of the macrocyclic core structure (Figure 2).

Two juxtapositioned monomers in each DNA strand as dangling ends stabilize the duplex considerably ($\geq$20°C, Table 1, entries 2–4). This is most likely caused by hydrophobic forces which induce dense packing of the dangling lipids. Incorporation of two juxtapositioned monomers in the middle of a DNA duplex resulted in very efficient hybridization and strongly increased thermal stability which correlates to the relative lipophilicity of the substituents (Table 2, entries 5–8).

The results are remarkable considering the steric demand (compared to a natural T-nucleotide) and the structure of the "abasic" non-nucleosidic building blocks.

A flexible synthetic strategy towards amphiphilic polyaza crown ether amidites as well as an efficient incorporation of the respective building

TABLE 2 Influence of monomer X, Y, and Z on thermal DNA duplex stability

Entry	Sequence	Tm [°C][a]
5	5′-TGT-GGA-AGA-AGT-TGG-TG 3′-ACA-CCT-TCT-TCA-ACC-AC	56
6	5′-TGT-GGA-AGX-AGT-TGG-TG 3′-ACA-CCT-TCX-TCA-ACC-AC	64
7	5′-TGT-GGA-AGY-AGT-TGG-TG 3′-ACA-CCT-TCY-TCA-ACC-AC	78
8	5′-TGT-GGA-AGZ-AGT-TGG-TG 3′-ACA-CCT-TCZ-TCA-ACC-AC	74

[a]10 mM sodium phosphate, 100 mM NaCl, 0.1 mM EDTA, adjusted to pH 7.0, concentration of 1 μM for each DNA strand.

blocks into DNA sequences has been achieved. The strongly increased thermal stability of the corresponding duplexes depends mainly on the relative lipophilicity of the polyaza crown ether substituents. Future work is directed towards biophysical studies on the interactions of such DNA-conjugates with biological and artificial membranes.

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