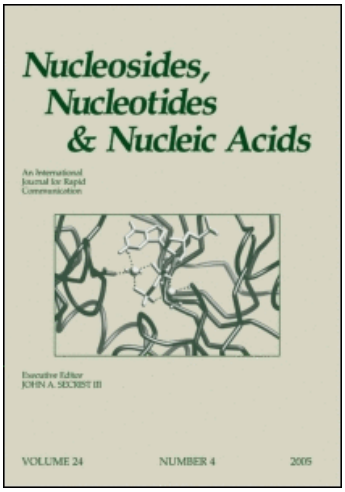

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A New Type of Acyclic, Achiral Nucleoside Analogue. How Does It Simulate Nucleosides?

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ABSTRACT

The new monomer **1** seems to be an excellent mimic of nucleosides with different sugar conformations (north, south, and envelope), because of the relatively free rotation around γ, δ, and χ. The rotation around χ is primarily controlled by the repulsion between H6 and the two hydrogen atoms on C4′ and not pi conjugation between the double bond and the nucleobase. A viable synthesis of the guanine monomer **8** is described.

DFT calculations on **1** without OH groups by Steen Hammerum (Department of Chemistry, University of Copenhagen) showed that pi conjugation between the nucleobase and the double bond is insignificant compared to a repulsion between H6 and the two hydrogen atoms on C4′. The energy minimum for rotation around χ was found for $\chi = 56°$ (13 kJ/mol lower than the energy for $\chi = 0°$).

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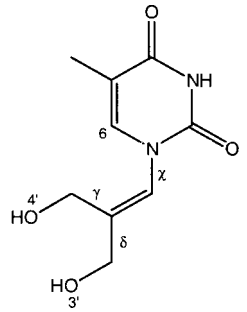


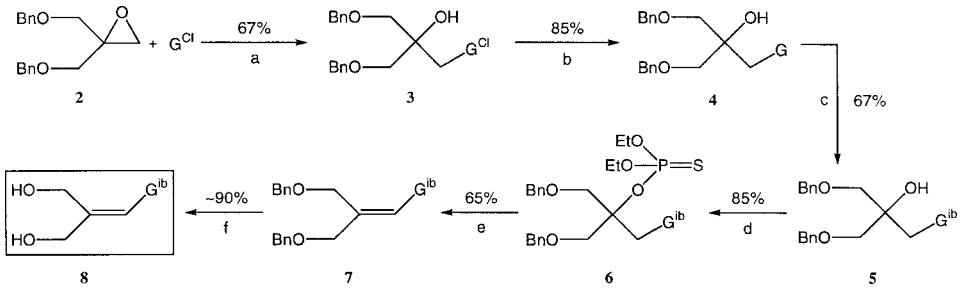
Using a minimized structure of **1** ($\chi = 30°$) with uracil, Thomas Boesen[1] calculated that a 360° rotation around δ gave structures that differed less than 1 kJ/mol in energy, while rotation around γ was hindered only by repulsion between HO4′ and H6 (max. 12 kJ/mol).

SYNTHESIS OF THE GUANINE MONOMER 8

The opening of the epoxide **2** was tried with different guanine derivatives without succes. These included N2-isobutyrylated guanine and NaH, fully silylated guanine and fluoride, guanine on Al_2O_3, and N2-acetylated-O6-diphenylcarbamylated guanine with NaH, which gave either no opening or mixtures of N7/N9 alkylated guanine derivatives. However, 2-amino-6-chloropurine (G^{Cl}) with K_2CO_3 as the deprotonating agent (NaH led to degradation of the chloro guanine) gave solely the N9 alkylated product **3**.

Elimination of the tertiary alcohol **5** with $SOCl_2$,[5] gave a mixture of several different elimination products (less than 10% **7**) and substitution of the alcohol with chloride. Elimination via thiophosphate **6** with sodium t-amylate under anhydrous conditions gave **7** as the sole elimination product.

The synthesis described in Sch. 1 was achived in 19% overall yield and needed only purification by column chromatography of compound 3, the remaining compounds were purified by recrystallizations.



Scheme 1. a) K_2CO_3 (cat.), DMF, 110 °C, 6h; b) $NaOCH_2CH_2CN$, THF, rt, 3h; c) i) TMSCl, py, rt, 5 h, ii) isobutyric anhydride, rt, 18 h, iii) $Et_3N{\cdot}3HF$, rt, 12 h; d) i) $(EtO)_2PCl$, py, 20 min, ii) S_8, rt, 1 h; e) t-amylONa, THF, rt, 24 h; f) BCl_3, DCM, −78 °C, 4 h.

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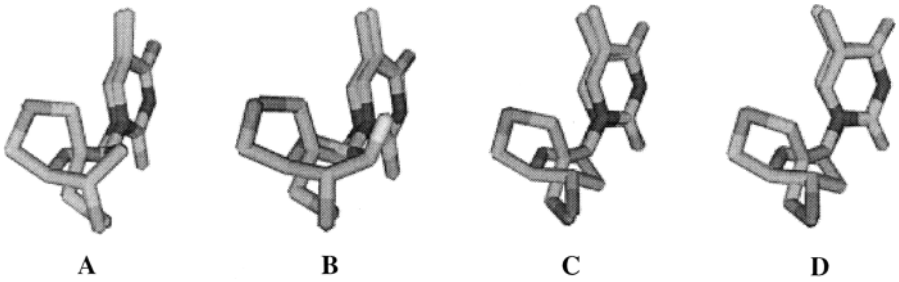

Figure 1. Overlayed Structures* **A)** **1** + B-helix thymidine (from a DNA/DNA B-helix); **B)** **1** + 2′F-*ara*-thymidine (from a DNA/DNA modified B-helix); **C)** **1** + DNA A-helix thymidine (from a RNA/DNA A-helix); **D)** **1** + DNA A-helix thymidine (from a RNA/DNA A-helix, **1** minimized). **1** in **A**, **B**, and **C** have $\chi = 7°$, 2°, and 12° while **1** in **D** (**1** minimized) has $\chi = 27°$. (*The new monomer was drawn with ChemDraw and PM3 minimized with Hyperchem 7 (except **1** and **D**), the nucleoside structures were taken from the crystal structures. The crystal structures were downloaded from NDB (The Nuclei Acid Database): Ref.[2] (**BD0023**); **B**: Ref.[3] (**BD0007**); **C** & **D**: Ref.[4] (**AH0005**). The overlay comparisons was made in Macromodel with the help from Per-Ola Norrby (DTU, Lyngby, Denmark): **A**, **B** & **C**: Compared by distance minimization between N1, O2, N3, and O4 in the nucleobases and pairwise distance minimization between O3′ and O5′ in the sugar and O3′ and O4′ in the new monomer by rotation around γ, δ, and χ in **1**. **D**: Compared by distance minimization between N1, O2, N3, and O4 in the nucleobases and pairwise distance minimization between O3′ and O5′ in the sugar and O3′ and O4′ in the new monomer by energy minimization of **1** in Macromodel.)

Synthesis of the monomer **8** without the isobutyryl group has been described in a Japanese patent,[5] using a route similar to ours, but in much lower yield.

CONCLUSION

Our new analogue seems to be an excellent mimic of nucleosides with different sugar conformations (Fig. 1). However, a reduced binding of oligonucleotides modified with **1** to DNA and RNA has been observed. The reason for this is under investigation.

A viable synthesis of the guanine monomer **8** has also been made.

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