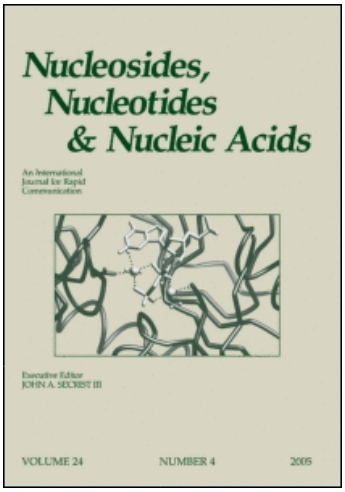

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Florobenzene as Artificial Nucleobases-Base Pairing and Stacking Interactions

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FLOROBENZENE AS ARTIFICIAL NUCLEOBASES-BASE PAIRING AND STACKING INTERACTIONS

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□ *Base stacking is a complicated and not completely understood phenomenon that is influenced by contributions of electrostatic (dipole-dipole and dipole-induced dipole) interactions, dispersion (permanent dipole–induced dipole) effects and solvation effects. The plots of those factors did not show qualitative correlation (Guckian et al., J. Am. Chem. Soc. 1996, 118, 8182–8183). We tried to correlate the stacking and solvation contributions with lipophilicity, extent of fluorine substitution and dipole moment.*

Keywords RNA; fluorine; fluorine interactions; duplex stability; molecular modeling

INTRODUCTION

The stability of the secondary structures of nucleic acids is a complex issue and there are three predominant forces responsible for it. These forces are hydrogen bonds, base stacking and solvation.[1−3] Since the natural RNA is limited to four predominant structures A, C, G, and U for those studies it is necessary to synthesize and investigate a series of modified nucleosides. To address this problem we synthesized novel nucleic acid analogues in which nucleobases are replaced by fluorobenzenes. We prepared eight protected phosphoramidites, seven of them with base modifications and one abasic site (Figure 1).

The synthesis of the compounds is published elsewhere.[4,5]

RESULTS AND DISCUSSION

The modified nucleosides were tested in a defined RNA sequence. In the 12mer oligoribonucleotides (5′-CUU UUC XUU CUU paired with

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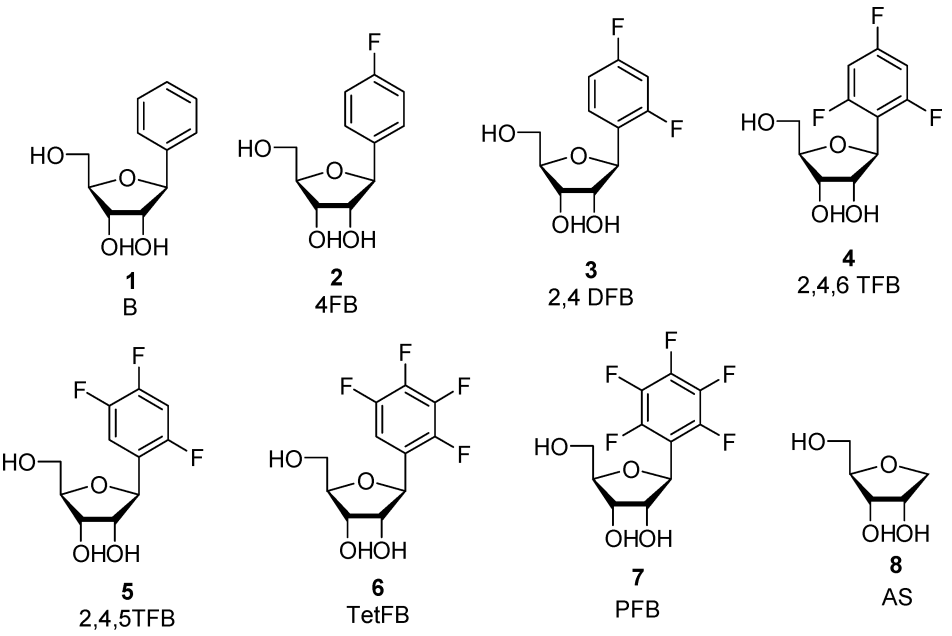

FIGURE 1 Synthesized modified nucleosides and one letter abbreviations of the nucleoside "bases."

3′-GAA AAG YAA GAA) only one position was modified, marked as X and Y, respectively. All measurements were done in phosphate buffer containing 140 mM NaCl, 10 mM Na_2 HPO_4, 10 mM NaH_2 PO_4.

We measured RNA duplexes where fluorinated benzenes were paired with natural bases, AS and the same fluorinated benzene in the pairing helix. The individual contributions of base stacking and solvation were calculated from those measurements and are shown in the Table 1.

The stacking free energies of 2, 4, 6 TFB and PFB modifications is more destabilizing than it would be expected. Therefore we assume that *bis-ortho* substitution is very poor in stabilizing and there are big differences when fluorine is moved from ortho to meta position. This could be due to

TABLE 1 Contributions of base-stacking and solvation of modified nucleosides[a]

Nucleoside	Gain of stability through better stacking	Loss of stability through solvation
B	1.3°C; 0.2 kcal/mol	−8.3°C; −2.2 kcal/mol
4FB	2.7°C; 0.5 kcal/mol	−7.2°C; −1.8 kcal/mol
2,4 DFB	4.4°C; 1.1 kcal/mol	−6.6°C; −1.7 kcal/mol
2,4,6 TFB	1.6°C; 0.2 kcal/mol	−8.8°C; −2.1 kcal/mol
2,4,5 TFB	8.2°C; 2.9 kcal/mol	−10.8°C; −3.7 kcal/mol
TetFB	10.9°C; 3.9 kcal/mol	−14.2°C; −5.1 kcal/mol
PFB	1.4°C; 0.2 kcal/mol	−8.4°C; −2.2 kcal/mol

[a]Modification is incorporated as X and complementary base for analogues is uridine.[3]

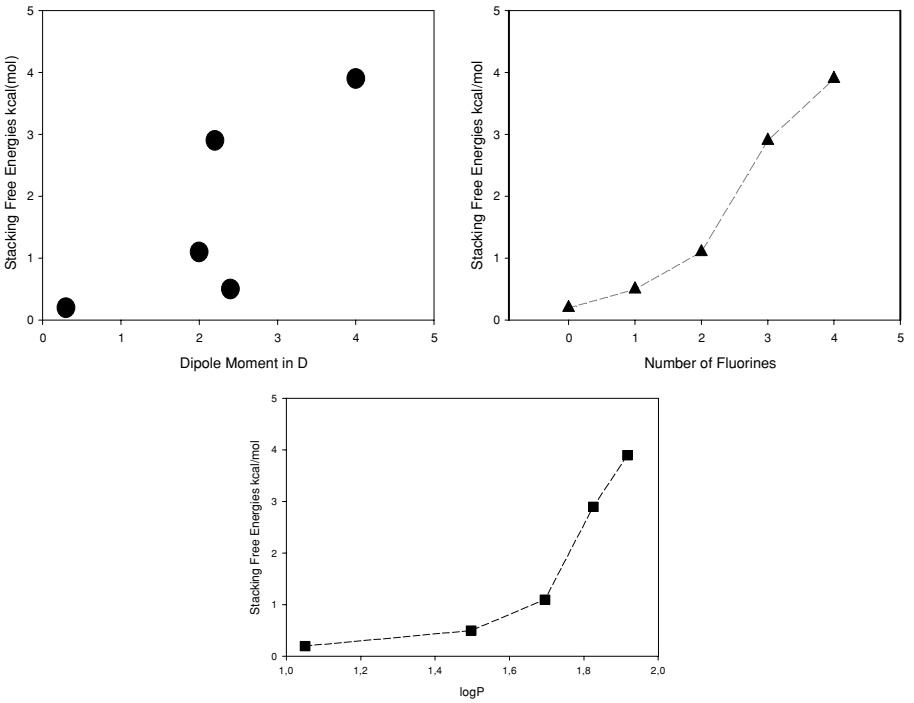

FIGURE 2 Correlation of base stacking free energies with dipole-moments, number of fluorines, and logP.

sterically induced twist in the glycosidic bond and/or in the sugar and would correspond to *bis-ortho* effect already found in DNA.[6]

If we try to make a qualitative correlation, where we omit bis-ortho substituted analogues, with dipole moments,[6] partition coefficient,[4] and number of fluorine atoms one can conclude that on the one hand with dipole moment there is no correlation (Figure 2) and on the other the stacking free energies are increasing with increasing of fluorine substitution and measured lipophilicity of nucleosides (Figure 2).

Further investigations of fluorinated artificial fluorobases are under the way to gain a deeper insight into the interaction properties of fluorobenzenes. Potentials of mean force of constrained paired and stacked base configurations are calculated by the weighted histogram analysis method from biased distribution functions obtained by molecular dynamic simulations.[5,7]

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