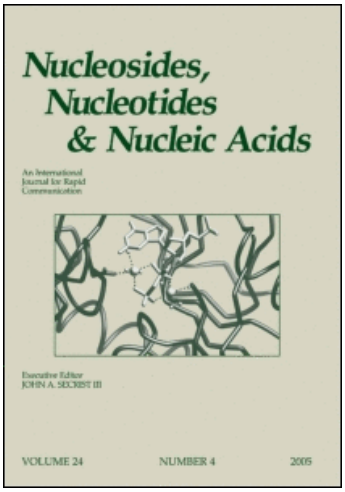

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A Study of H-Bonding of 3- and 5-Substituted 6-Aminouracils in Duplex and Triplex Structures

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A STUDY OF H-BONDING OF 3- AND 5-SUBSTITUTED 6-AMINOURACILS IN DUPLEX AND TRIPLEX STRUCTURES

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▫ *All possible dimers of the title modified bases with native nucleobases [10 dimers from 3-methylated 6-aminouracils (**3sau**) and 20 from 5-methyled 6-aminouracils (**5sau**), respectively have been calculated by ab initio method (Hartree-Fock method, 3 21G basis set). We have found two potential duplexes of **5sau** and three possible duplexes of **3sau**. Altogether seven dimers containing one or two bifurcating H-bonds have been found. Later on, five triplexes from ten possible calculated dimers have been found. In two of them the amino group of 6-aminouracil moiety takes part in H-bonding and there are H-bonds, too, between the first and third base of the triplexes causing an extra stabilization.*

COMPUTATIONAL METHOD

Duplexes of native nucleobases with 3- (**3sau**) and 5-substituted 6-aminouracil (**5sau**) and triplex structures of nucleobase pairs with the above modified uracil derivatives have been examined. Oligonucleotides or peptide nucleic acids (PNAs) derived from these modified bases can be considered as potential inhibitors of gene expression.

All possible duplexes of modified bases with native nucleobases [10 duplexes from 3-methylated 6-aminouracils (**3sau**) and 20 from 5-methylated 6-aminouracils (**5sau**)] have been calculated by ab initio method, (Hartree-Fock method, 3–21G

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basis set; bond length, bonding energy and distance of methyl groups substituting the C-1′ atoms). First, geometrical optimization was performed. After these calculations the interaction energies were calculated taking into account the BSSE (basis set superposition error) in all cases. The largest part of this energy is originating from H-bonding. The results obtained were compared with the calculated values of the native duplexes to evaluate potential duplex structures. After the above calculations the triplex structures of 3/5-substituted 6-aminouracils were studied applying an ab initio method (gas phase in all cases). Gaussian03 program package was used in geometrical optimizations and Gaussian98 was applied in calculations of the interaction energies (Hartree-Fock method, 3–21G and 6–311G** basis sets).

RESULTS AND DISCUSSION

Two potential duplexes of **5sau** and three possible duplexes of **3sau** have been found. In these cases the calculated interaction energies were comparable with those of native DNA nucleobase duplexes. There are two H-bonds in these duplexes, yet their interaction energy is comparable with the native G:C base pair with three H-bonds. This fact can be explained by assuming bifurcating hydrogen bonds between the $NH_2\cdots O = C$ groups of a nucleobase and the above uracils, respectively (other factors, of course, cannot be ruled out). Altogether, seven duplexes containing one or two bifurcating H-bonds have been found. The existence of bifurcating H-bonding has been supported by indirect proofs from calculations in which the amino groups participating in the supposed interaction have been replaced by hydrogen (thymine: 9-methylhypoxanthine base pair) and these calculations led to lower stabilization (Figure 1).

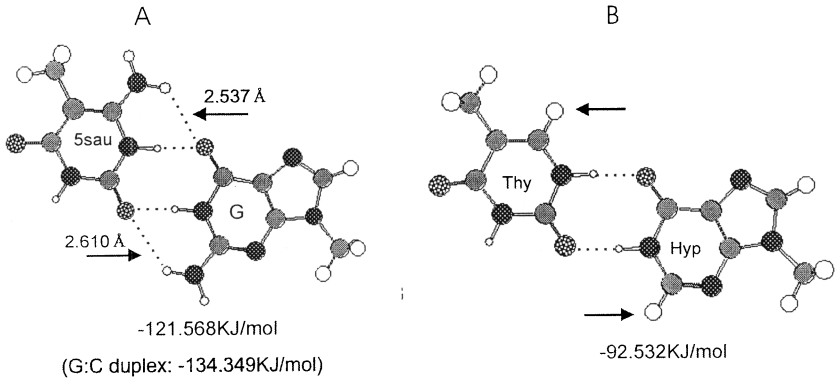

FIGURE 1 An indirect computational proof of the existence of bifurcating hydrogen bonds (Hartree Fock method and 3–21G bases set). Panel A: geometry of 5sau: G duplex, arrows denote the bifurcating H-bonds; panel B: geometry of thymine: 9-methylhypoxanthyne duplex, arrows show the hydrogen atoms replacing the amino groups.

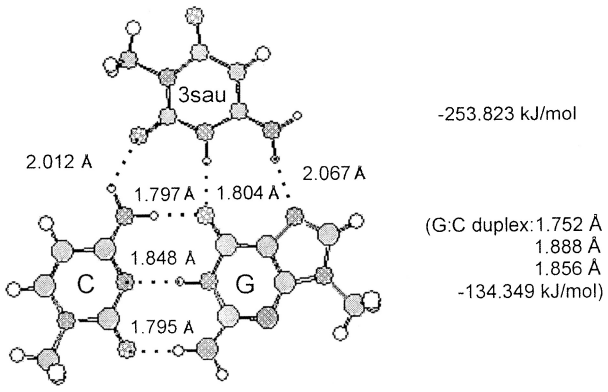

FIGURE 2 One of the triplex structures of 3-methyl 6-aminouracil (3sau) with the native G:C base pair (Hartree-Fock method and 3–21G basis set).

Five triplexes from 10 possible calculated duplexes have been found. In two of them the amino group of the 6-aminouracil moiety takes part in H-bonding and there are H-bonds, too, between the first and third base of the triplexes causing an extra stabilization (Figure 2). Selectivity has also been found in duplex and triplex formation (Figures 3–5, Hartree-Fock method and 3–21G basis set). The main advantage of using 3sau and 5sau is the fact that they are alternatives of the C:G × C^+ triplex unit without the need to protonate them to form two or three H-bonds with native base pairs. It is noteworthy, however, that the interaction energies manifesting in the C:G × 5sau or C:G × 3sau triplexes are significantly lower than that in the native C:G × C^+ triplex underlying the importance of a protonated species (Figure 5). With the 6–311G** basis set, lower energy values have been obtained.

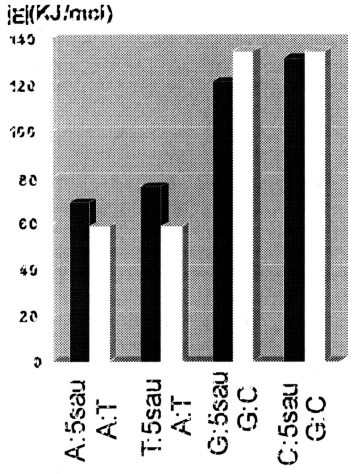

FIGURE 3 Comparison of the highest interaction energies of duplexes from 5sau and native base pairs.

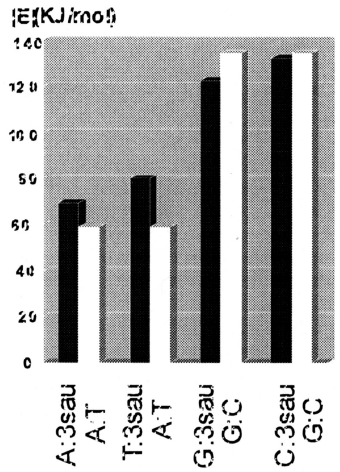

FIGURE 4 Comparison of the highest interaction energies of duplexes from 3sau and native base pairs.

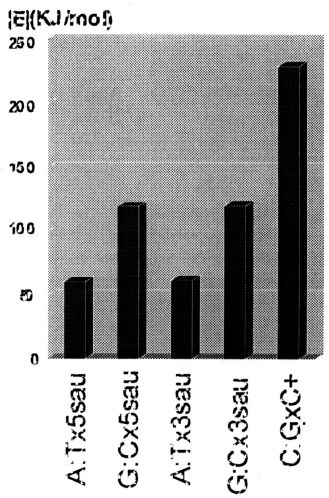

FIGURE 5 The highest interaction energies in the triplexes formation of 5sau or 3sau or c + with native base pairs.