ON THE CHANGE OF THE ORDER OF STABILITY OF DNA BASE PAIRS AS A RESULT OF THE METHYLATION OF GUANINE

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Dedicated to Dr R. Zahradnik on the occasion of his 60th birthday.

The interaction of the 6-O methylguanine cation with cytosine and thymine was studied using the *ab initio* SCF method in combination with a London type expression for dispersion energy. The structure of the complex formed with cytosine differs from that found previously with guanine itself.

In one of our previous papers[1] the nonempirical *ab initio* SCF method, employing Huzinaga's minimal MINI-1 basis set[2] in combination with a London-type expression for the dispersion energy[3], has been applied to all the 29 possible DNA base pairs. The most stable pair was found[1] to be the guanine(G)···cytosine(C) pair in the Watson–Crick structure, folowed by the homopairs G···G and C···C. This result confirms the known fact that guanine normally bounds to cytosine. The question arises, however, whether chemically modified guanine will do the same or will bound preferentially with an other base. There are reasons to take such a process into acount. It is known that chemical carcinogens like benzo[*a*]pyrene modify the DNA bases. The ultimate carcinogen of benzo[*a*]pyrene is known[4] to be the carbocation, which preferentially bounds to oxygen 6 or nitrogen 7 of guanine. In the present paper we investigate the changes in the structure of DNA pairs induced by the methylation of guanine.

CALCULATIONS AND RESULTS

The same computational strategy was applied as in our previous paper[1], in order to make the results comparable. First, the geometry of the 6-O methylguanine cation was optimized at the STO-3G level. We have started from the fully optimized guanine[5] and optimized step-by-step in two cycles the geometry of the O—CH_3 group; the respective geometry is given in Table I. The resulting structure of the 6-O methylguanine cation···cytosine pairs was optimized with Huzinaga's[2] MINI-1 basis set.

The optimized structures of the complexes are depicted in Fig. 1. The first complex (*a*) corresponds to the Watson–Crick (WC) structure, the second one (*b*) to the structure assigned in our previous paper[1] to GC (II). The geometrical characteristics of both complexes, as well as those complexes containing guanine, are given in Table II. The stabilization energy is constructed (as in ref.[1]) as the sum of SCF interaction energy, basis set superposition error and dispersion energy. As expected complexes containing the methylguanine cation are more stable than those containing guanine. For the 6-O metG$^+$···C (WC) and 6-O metG$^+$···C (II) pairs the stabilization energies amount to 145·0 and 164·2 kJ mol^{-1}. The stability of parent complexes is reversed; for G···C (WC) and G···C (II) the stabilization energy of 110·6

TABLE I

Geometry of the —OCH_3 group in the 6-O methylguanine cation

Bond	*r*, pm	Angle	α, deg
C—H	109·1	N(1)—C(6)—O(6)	116·8
O(6)—C	145·7	C(6)—O(6)—C	121·2
C(6)—O(6)	128·8	O(6)—C—H	109·5[a]

[a] Assumed.

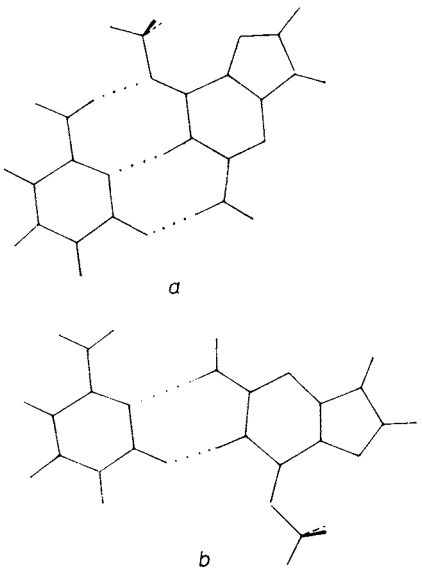

FIG. 1

The optimized structures of the 6-O methylguanine cation···cytosine (WC) (*a*) and 6-O methylguanine cation···cytosine (II) (*b*) complex

TABLE II

Geometrical characteristics of 6-O methylguanine cation ··· cytosine (WC) and 6-O methylguanine cation ··· cytosine (II). For comparison, the geometrical characteristics of complexes containing guanine are given in parentheses

H-bond[a]	R(X···Y), pm	α(X—H···Y), deg
	6-O metG$^+$ C (WC)	
C(6)···H—N(4)	301 (296)	166[b] (166)
N(1)—H···N(3)	291 (294)	170 (164)
N(2)—H···O(2)	270 (291)	177 (171)
	6-O metG$^+$ C (II)	
N(1)—H···O(2)	273 (285)	177 (180)
N(2)—H···N(3)	297 (303)	172 (169)

[a] Cf. Fig. 1; [b] taken from G···C (WC).

and 82·1 kJ mol^{-1} was found[1]. Clearly, the methylation of guanine reverses the stability of these pairs.

Besides the complexes mentioned we have investigated the complex between the 6-O metG$^+$ and thymine (T). We have expected with this complex formation of the third H-bond between oxygen of thymine and hydrogen of methyl group of the guanine cation. The stability of 6-O metG$^+$···T (I) was found to be larger than that of G···T (I) but still far smaller than the stability of the 6-O metG$^+$···C (WC) and 6-O metG$^+$···C (II) pairs.

In conclusion we can state that chemical modification of guanine to the 6-O methylguanine cation leads to the change of order of preference of the DNA base pairs. Whereas guanine prefers to bind with cytosine to form the Watson–Crick structure, the methylguanine cation also prefers to bind to cytosine but with different geometrical structure containing only two H-bonds. Formation of this pair during DNA replication could have serious consequences in the replication or transcription processes.

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