Allowance for a Different Pairing of 5-Fluorouracil

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A different pairing of 5-fluorouracil with adenine and guanine is proposed; this pairing may contribute to explain its mutagenic effect. IEHT charges and bond indices support the assumption.

The effect of 5-fluorouracil (5FU) incorporation into RNA has since long been pondered on [1]. There exists plentiful theoretical and experimental literature about its structure [2]. The problem of its mutagenic effect has been approached by considering base pairs involving 5FU as supermolecules in a CNDO/2 treatment [3]. Since 5FU is always supposed to pair like U, the mutagenic effect has been ascribed to the greater probability of finding 5FU under enol form compared to U, due to its lower pK_a [3].

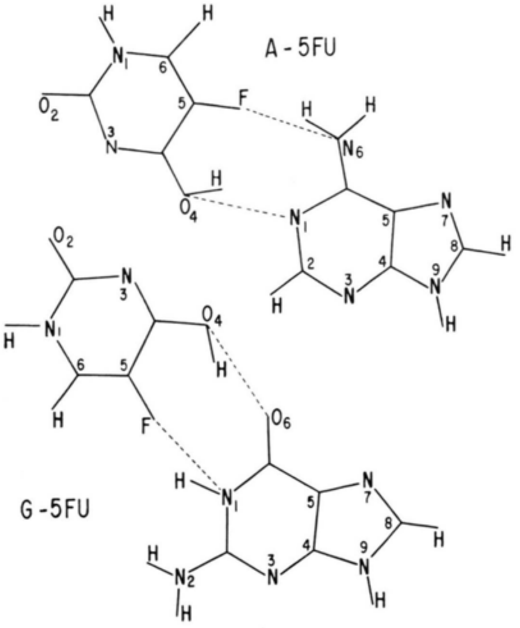

Fig. 1. Proposed pairing for 5FU with A and G.

Now, in the enol form 5FU allows a kind of H-bond pairing (both with adenine A and guanine G) which is impossible for U, namely that of Fig. 1, where the F atom takes part in the H-bond. This is a Hoogsteen-type pairing in the sense that it is 7-sided instead of the 6-sided Watson-Crick pairing. We find no "a priori" reasons for discarding this conformation, hitherto apparently overlooked, on the same grounds as other pairings between the nucleic acid bases [4]. Recently, attention has been drawn to unusually strong H-bonds involving F^-, and to its possible biochemical implications [5]. Our IEHT calculation (Table 1) predicts for fluorine a net charge close to that of the carbonyl oxygens, so that it should have a similar ability to give rise to usual H-bonds.

Hoogsteen [6] mentions the feasibility of a departure from linearity up to 25° in H-bonds. This tolerance is commonly applied to one of the bonds, keeping the other linear. In Figure 1 we have conjectured, in order to build our model, that both bonds distort from linearity as shown in Table 2. Aside from this assumption, geometry is irrelevant as regards the results we are interested in [7]; therefore, geometry optimization is not required. Ours is more a topological than a geometrical question.

In the IEHT calculation carried out, we obtained bond indices I_{XY} for the H-bonds XH … Y. The bond index formula [8] (which we shall not repeat here) reduces to the known Wiberg formula [9] for orthogonal basis, and measures the electronic density along the bond. This physical interpretation has proved suitable for describing H-bond proper-

Table 1. Net IEHT charges (for separate bases and pairs) for fluorine and the carbonyl oxygens. Geometry is taken from [12]. For IEHT, see P. Dibout, program No. 256, QCPE, supplement for 1975–1978 to vol. X (1974), Indiana University, Chemistry Department; we have added a subroutine for bond indices. (I) Watson-Crick type pairing (see [3] for diagrams). (II) Hoogsteen type pairing (Figure 1).

	F	O_2	O_4	O_6
5FU	– 0.30	– 0.28	– 0.27	
G				– 0.30
A-5FU (I)	– 0.29	– 0.28	– 0.27	
A-5FU (II)	– 0.26	– 0.31		
G-5FU (I)	– 0.29	– 0.30		– 0.29
G-5FU (II)	– 0.27	– 0.31		– 0.29

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Table 2. I_{XY}, bond index between atoms X and Y. (I) Watson-Crick type pairing (see [3] for the diagrams). (II) Hoogsteen type pairing (Figure 1).

Pair		H-bond (XH ... Y)	I_{XY}	Deviations from linearity
A-5FU	(I)	NH ... O	0.026	—
		N ... HN	0.054	—
	(II)	NH ... F	0.050	9.75°
		N ... HO	0.046	24.56°
G-5FU	(I)	O ... HO	0.065	—
		NH ... N	0.054	—
		NH ... O	0.044	—
	(II)	O ... HO	0.064	22.86°
		NH ... F	0.040	20°

ties in the three classical Watson-Crick pairings A-T, A-U and G-C [7]. The effectiveness of semiempirical methods in dealing with this and other related problems [10] needs hardly be emphasized. The purpose of this note is to verify whether or not the application of the bond index formula yields sensible results for the pairing we propose. Table 2 shows that, from this viewpoint, the pairings make sense. Indeed, the I_{XY} values for both kinds of pairings are comparable, and for A-5FU configuration II appears even favoured in relation to configuration I.

Figure 2 shows the contour density diagram for the G-5FU (II) pair in the H-bond region. In other pairs [7, 11], the electron density contours corresponding to the conjugation curves are roughly proportional to the I_{XY} values. Curiously, in the present case not only this is not so, but the lowest I_{XY} corresponds to a slightly higher conjugation value, and viceversa.

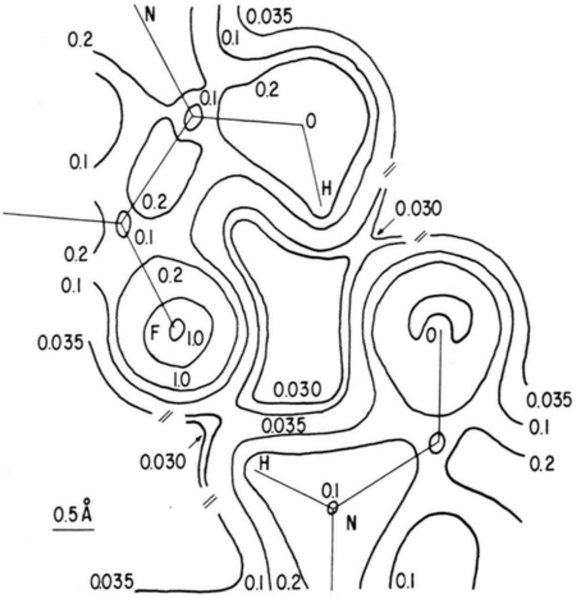

Fig. 2. Contour density diagram of the H-bond region in G-5FU, in the molecular plane (units are e/au³).

One may wonder whether, in a non linear XH ... Y bond, the bridge will tend to be on the HY line or on the XY line. The answer is not straightforward. In the upper bridge it is nearer the HY line, while in the lower one it is midway from both HY and XY lines.

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