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ALLOWANCE FOR A DIFFERENT PAIRING  
OF 5-FLUOROURACIL  
by

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The effect of 5-fluorouracil (5FU) incorporation into RNA is pondered since long time ago (Horowitz & Chargaff, 1959; Johnson, Kaiser & Horowitz, 1980). There exists plentiful theoretical and experimental literature about its structure (see for example Berthod, Giessner-Prettre & Pullman, 1967; Srivastava & Mishra, 1979; Egert, Lindner, Hillen & Bökm, 1980). Abdulnur (1976) analyzed particularly the base pairs involving 5FU, considering them as supermolecules through a CNDO/2 treatment, in order to approach the problem of its mutagenic effect. This effect seems to be related with the enhanced probability of 5FU being in enol form compared to U, due to its lower  $pK_a$ .

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 Figure 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.

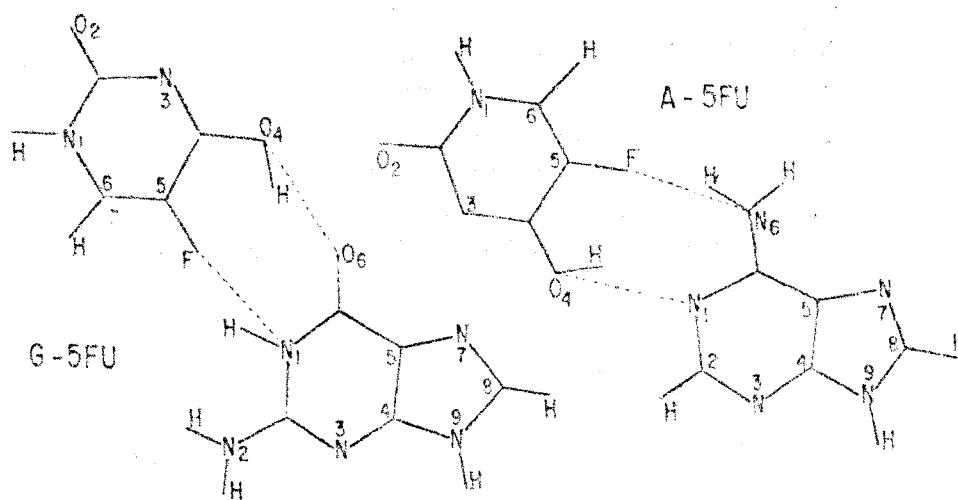


Fig. 1 - Proposed pairing for 5FU with G and A.

We find no "a priori" reasons for discarding this conformation, on the same geometrical grounds as other acceptable possible pairings between the nucleic acid bases (Donohue, 1956; Donohue & Trueblood, 1960; Sudaralingham, 1977). Recently, attention has been drawn to unusually strong H-bonds involving F<sup>-</sup>, and to its possible biochemical implications (Emsley, Jones, Miller, Overill & Waddilove, 1981). An IEHT calculation (Table I) predicts for fluorine a net charge quite close to that of the carbonyl oxygens, so that it should have a similar ability to give rise to usual H-bonds.

	F	O <sub>2</sub>	O <sub>4</sub>	O <sub>6</sub>
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

Table I - Net IEHT charges (for separate bases and pairs) for fluorine and the carbonyl oxygens. Geometry is taken from Pauling (1960). (I) Watson-Crick type pairing. (II) Hoogsteen-type pairing (Fig.1). IEHT program is QCPE's N<sup>o</sup> 256, to which we have added a subroutine for bond indices.

Hoogsteen (1963) 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. Besides this assumption, geometry is irrelevant as regards the results we are interested in (Giambiagi, Giambiagi & Barroso Filho, 1981); therefore, geometry optimization is not required. Ours is more a topological than a geometrical question.

Pair	H-bond (X...HY)	$I_{XY}$	Derivations from linearity
G-5FU	(I)	OH...O	-
		N...HN	-
		O...HN	-
	(II)	OH...O	22.86°
		F...HN	20°
A-5FU	(I)	O...HN	-
		NH...N	-
	(II)	F...HN	9.75°
		OH...N	24.56°

Table 2 -  $I_{XY}$ , bond between atoms X and Y. (I) Watson-Crick type pairing. (II) Hoogsteen type pairing (Fig. 1).

We have thus explored whether the application of the bond index formula (Giambiagi, Giambiagi, Gempel & Heymann, 1975) which yielded satisfactory results in a IEHT calculation of the Watson-Crick case (Giambiagi et al., 1981), leads or not to acceptable values now. Table 2 shows that, from the bond index

viewpoint, the proposed pairing makes sense.

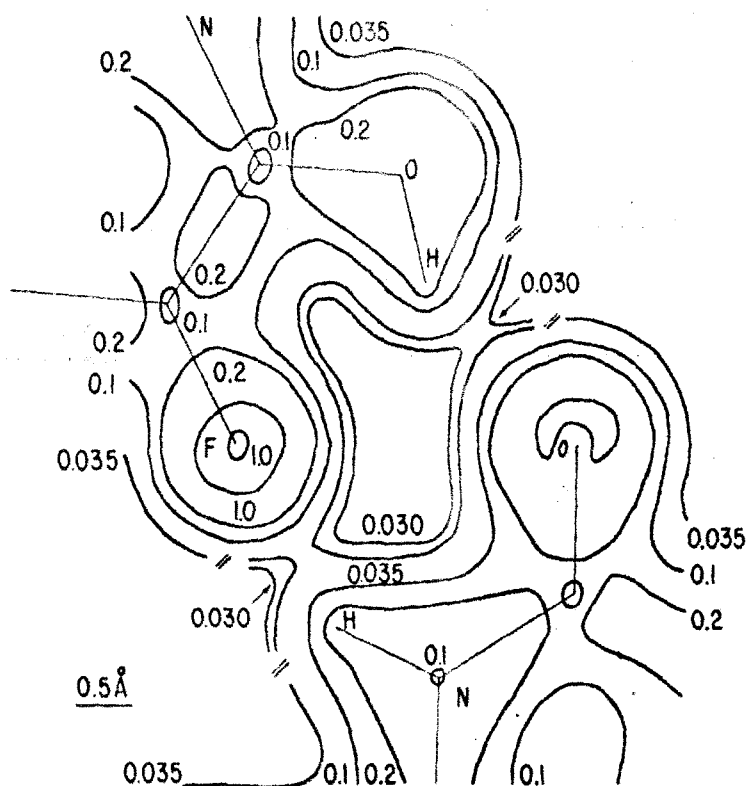


Fig. 2 - Contour density diagram of the H-bond region in G-5FU, in the molecular plane. (Units are  $e/au^3$ ).

Figure 2 shows the contour density diagram for the G-5FU(II) pair in the H-bond region. In other pairs (Giambiagi et al., 1981), 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.

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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