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Photoinduced oxo–hydroxo tautomerisation of crystalline 5-fluorouracil

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Photoinduced proton transfer in crystalline 5-fluorouracil results in oxo–hydroxo tautomeric forms.

5-Fluorouracil, a well-known antitumour medicine, is the most important synthetic analogue of uracil and thymine, the structural elements of DNA and RNA. The presence of rare tautomeric forms of nucleic bases can affect DNA replication to give point mutations.[1]

Six tautomers of 5-fluorouracil are theoretically possible (Figure 1).

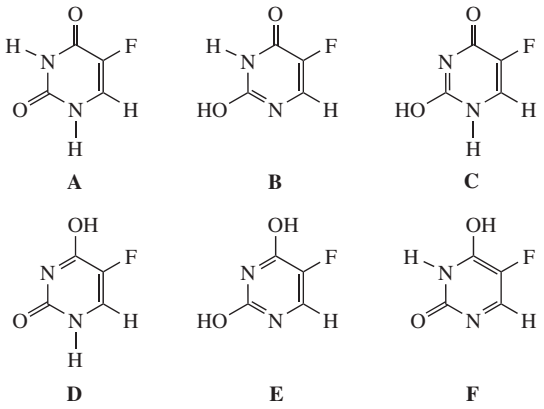
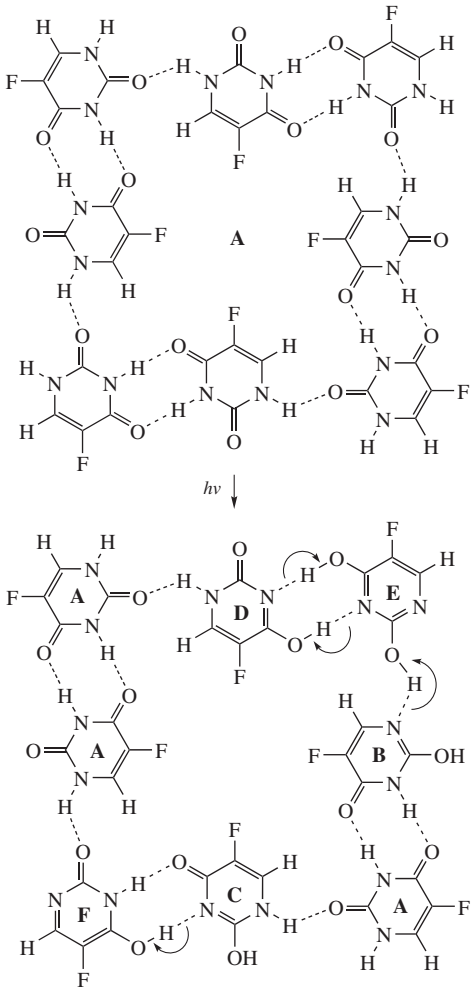


Figure 1

Based on quantum-chemical calculations in tetrahydrate clusters,[2,3] the four most probable 5-fluorouracil tautomers were suggested, namely: 2,4-dioxo (**A**), 2-hydroxy-4-oxo (**B**), 4-hydroxy-2-oxo (**D**) and 2,4-dihydroxy (**E**). The stability of these forms varies in the order **A** > **B** > **D** > **E**. We were able[4,5] to detect experimentally the individual fluorescence spectra of 5-fluorouracil tautomers **A**, **B**, **D**, **E** in neutral aqueous solutions (pH 7) and to determine the emission wavelength maxima (λ_{max}), the fluorescence quantum yields (φ) and the percentages (c %) of the corresponding tautomers as follows: **A**, λ_{max} = 340 nm, $\varphi \approx$ $\approx 1.5\times10^{-4}$, c % = 99.5; **B**, λ_{max} = 380 nm, $\varphi \approx 2.1\times10^{-2}$, c % = = 0.4; **D**, λ_{max} = 410 nm, $\varphi \approx 0.16$, c % = 0.03; **E**, λ_{max} = 440 nm, $\varphi \approx 0.35$, c % = 0.008.

It is believed[2] that, in an H-bound crystal lattice,[6] dehydrated 5-fluorouracil only exists in dioxo form **A** (Scheme 1).

The extremely short lifetime of 5-fluorouracil fluorescence in an electron-excited state in solutions [1.3 ps (H_2O), 0.4 ps (MeCN)[7]] governs its high photochemical stability. On the other hand, it is known that primary photochemical processes such as electron or proton transfer can compete with superfast ($>10^{12}$ s^{-1}) relaxation processes in short-lived (< 1 ps) highly excited singlet S_n-states ($n > 1$).[8–12] It is expected that the fluorescence lifetime of crystalline 5-fluorouracil is much longer than that in solution;



Scheme 1

this allows us to assume that photoinduced proton transfer (PPT) results in hydroxo forms.

In crystalline 5-fluorouracil specimens, we observed a variation in the spectral composition of fluorescence radiation [Figure 2(*a*)][†] upon photoirradiation at the long-wave absorption maximum

[†] Corrected fluorescence spectra were recorded with a CM-2203 spectrofluorimeter. 5-Fluorouracil (Aldrich, 99.5%) was used without preliminary purification. Thin films of crystalline 5-fluorouracil specimens were prepared by the evaporation of aqueous solutions on a side surface of a quartz cell and illuminated with a xenon lamp (λ = 265 nm) directly in a spectrofluorimeter cell compartment.

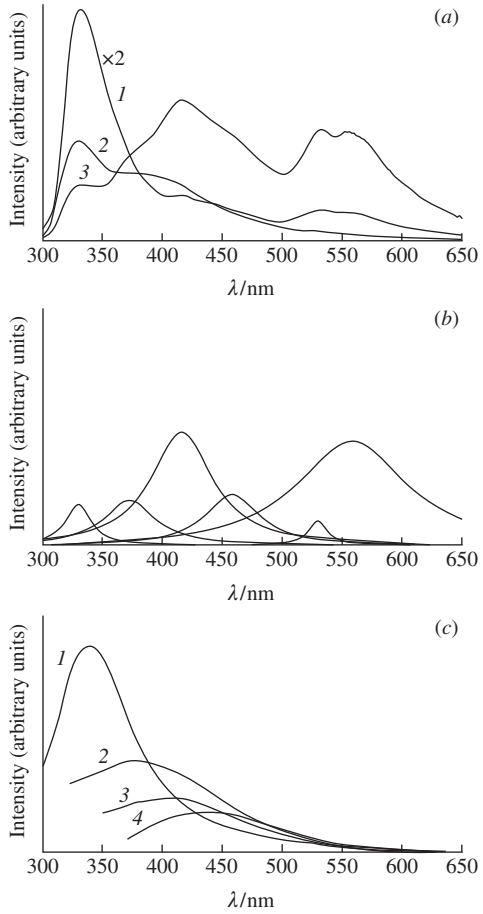


Figure 2 (*a*) Fluorescence spectra of crystalline 5-fluorouracil: (*1*) original specimen; (*2*) photolysis for 2 min; (*3*) photolysis for 20 min (λ_{ex} = 265 nm, 300 K). (*b*) Results of decomposition of spectrum *3* (*a*) into components. (*c*) Fluorescence spectra of 5-fluorouracil tautomers in H_2O: (*1*) **A** (λ_{ex} = = 265 nm); (*2*) **B** (λ_{ex} = 305 nm); (*3*) **D** (λ_{ex} = 320 nm); (*4*) **E** (λ_{ex} = 340 nm), (concentration of 5-fluorouracil, 10^{-4} mol dm^{-3}, pH 7, T = 300 K).

of the $S_1 \leftarrow S_0$ transition (265 nm). With longer exposures, the fluorescence intensity of dioxo tautomer **A** (λ_{max} = 334 nm) decreases and new batochromically shifted fluorescence bands appear [Figure 2(*a*), spectra *2* and *3*]. Figure 2(*b*) shows the results of decomposition of spectrum *3* [Figure 2(*a*)] into components using the Lorentzian method (Origin 8). A comparison of the spectra [Figure 2(*b*) and 2(*c*)] indicates that the fluorescence maxima of crystalline 5-fluorouracil recorded after photolysis in the wavelength range 350–500 nm (λ_{max} = 375, 415 and 455 nm) correlate satisfactorily with those for minor tautomers **B**, **D**, **E** in neutral (pH 7) aqueous solutions (λ_{max} = 380, 410 and 440 nm).[5]

This should undoubtedly be attributed to the processes of photoinduced oxo–hydroxo tautomerisation of crystalline 5-fluorouracil. The luminescence of photolysed crystalline 5-fluorouracil specimens at 530 and 555 nm [Figures 2(*a*) and 2(*b*)] in aqueous solutions was not detected; presumably, it was assigned to the fluorescence of tautomers **C** and **F**. Note that the interpretation of fluorescence in the 'green' region is unclear since we cannot rule out generally known photoionisation processes to give radicals (also observed for pyrimidine bases[13]).

The PPT phenomenon recorded in fluorescence spectra was observed previously in acridine derivatives at low temperatures.[14] The process occurs between molecules that form a strong hydrogen bond under conditions where a 'labile' proton is located in the field of both components.

The above results allow us to assume the intermolecular PPT resulting in rare tautomeric 5-fluorouracil forms in a solid state (Scheme 1); unlike solutions, they are stabilised by the crystalline matrix. This is conclusively supported by the fact that, after dissolution in water and recrystallysation, fluorescence is only observed as dioxo tautomer **A**, whereas the subsequent photoirradiation is accompanied by identical changes in the spectral composition, which are described by kinetic relationships similar to those for the photolysis of the primary specimen. This experiment may be repeated many times. It follows that the PPT process occurs at the expense of the energy absorbed by dioxo form **A** of the 5-fluorouracil molecule, whereas the proton return from the hydroxy group to the heterocycle nitrogen atom occurs upon the release of molecular mobility due to the dissolution of irradiated crystalline specimens. Note that changes in the fluorescence spectra of 5-fluorouracil corresponding to proton transfer in a reverse direction are also observed upon heating (373 K) crystalline specimens exposed to photoirradiation. The PPT resulting in long-lived coloured tautomers that are detected in absorption spectra was previously observed upon the irradiation of crystalline 2-(2′,4′-dinitrobenzyl)pyridine.[15]

Thus, the UV irradiation of crystalline 5-fluorouracil results in intermolecular proton transfer to give oxo–hydroxo tautomeric forms.

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