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Density functional calculations on dissociation reactions of radical anions of 5-fluorouracil derivatives

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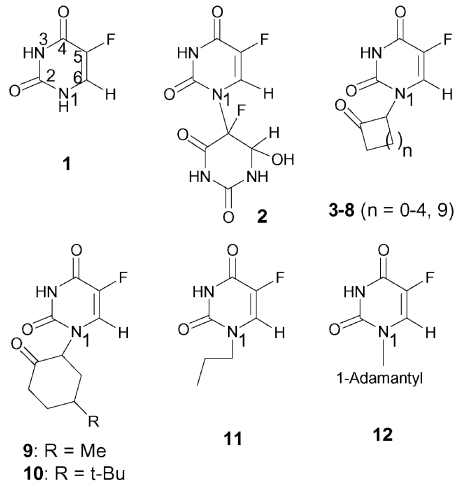
Fragmentation reactions upon electron attachment to 5-fluorouracil with CH_2R substituents at N_1 have been evaluated by means of density functional calculations. The present results show that electron attachment to R = F, HC=O or CN derivatives follows a stepwise pathway with radical anions as intermediates. For these compounds, the most stable species formed is the π radical anion which bears an unpaired spin density at the $C_6{=}C_5{-}C_4{=}O$ π-conjugated system of the uracil ring. Cleavage of the $N_1{-}CH_2R$ or $N_1CH_2{-}R$ bond of these intermediates proceeds through the mixing of the π and σ states by means of proper geometrical fluctuations along the reaction coordinate. No σ radical anion could be characterised on any of these σ basal potential surfaces. A noticeable decrease in the activation energy for the $N_1{-}CH_2R$ bond dissociation was observed for R = H–C=O or CN. Therefore, such derivatives with unsaturated groups positioned vicinal to the $N_1{-}C_1'$ bond are identified as targets for the development of novel radiation-activated antitumour drugs. On the other hand, the electron transfer to the compounds with R = Cl, Br is dissociative, *i.e.* it occurs without the mediation of radical anions. For compounds with R = halides or R = NO_2, the fragmentation of the $N_1CH_2{-}R$ bond is the preferred dissociation pathway.

Introduction

Exposure of DNA and RNA to ionising radiation induces chemical processes that lead to damage of the genetic material.[1] Radical anions of pyrimidine bases are intermediates in these reactions.[2] The replacement of uracil and thymine with 5-halouracil enhances the radiosensitivity of these biomolecules and has therefore been employed as a sensitizer in radiation therapy by eventually halting DNA or RNA replication in tumour cells.[3] The 5-halouracil radical anions formed by irradiation dissociate to give halide anions plus the very reactive uracil-5-yl radical,[4] which produces the ultimate damage in the nucleic acids, including dimerization, cross-linking, and subsequent DNA strand breaking.

Alternatively, the antitumour drug 5-fluorouracil (**1**) has been observed to be released, upon γ-radiation in anoxic aqueous solutions, by radical anions of 5-fluorouracil derivatives such as its $N_1{-}C_5'$-linked dimer (**2**),[5] and a series of 5-fluoro-1-(2′-oxocycloalkyl)uracils (**3–10**).[6] In the latter case, the presence of the 2′-oxo substituent was crucial for efficient $N_1{-}C_1'$ bond cleavage, as compounds without this substituent (**11**, **12**) proved unreactive toward the one-electron reductive dissociation path. Structures are shown in Scheme 1, where the atom numbering on the uracil ring is shown.

Even though a large amount of experimental work has been reported on the radiolytic activity of halouracils, only a few theoretical studies have been carried out. Recently, Wetmore *et al.*[7] and Li *et al.*[8] reported the calculation of DFT B3LYP values for both gas and solution phase electron affinities, the ionisation potentials of uracil, thymine and a series of 5-halouracils (5XU, X=F, Cl, Br), and the calculated barriers for the dissociation of the corresponding radical anions to X^- plus the uracil-5-yl centred radical. As regards the $N_1{-}C_1'$ cleavage of radical anions of 5-fluorouracils, semiempirical AM1 calculations have been performed for some derivatives.[9] However, these computations did not properly describe the release of halide anions from this type of intermediate, as semiempirical methods overestimate the heat of formation of halides in comparison with those of the larger and more delocalized anions.[10] On the other hand, the ease of the fragmentation of 5-fluoro-1-(2′-oxocycloalkyl)uracil radical anions was qualitatively rationalised by electron transfer to their LUMO + 1 MO, which, according to AM1, delocalizes between the 2′-oxo substituent and the adjacent $N_1{-}C_1'$ moieties.[6]



Scheme 1 5-Fluorouracil and some N_1-derivatives.

Considering the biological importance of this type of compound, the aim of this work was to perform a density functional study on the fragmentation of 5-fluorouracil derivatives. Our ultimate goal is to make a contribution to the design of compounds that could potentially be novel radiation-activated prodrugs. We selected two types of N_1-substituted structures: molecules substituted by a halomethyl group, to evaluate the feasibility of halide release; and structures with substituents that possess a π system, in order to analyse their contribution to the general mechanism and to the ease of dissociation.

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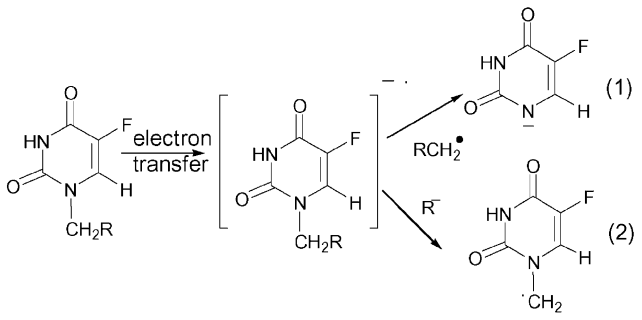
Computational methods

Density functional calculations at the UB3LYP[11] level were performed by employing the Gaussian 98 program package,[12] using the diffuse and polarisation function augmented 6-31+G* split-valence shell basis set.[13] The 3–21G* basis set[14] was employed for the iodine atom, as this element is not defined within the 6-31+G* basis set in Gaussian 98. Geometries were fully optimised and stationary points were characterised as minima (*i.e.* with no imaginary frequencies) or transition states (*i.e.* with only one imaginary frequency) by calculation of the harmonic vibrational frequencies. The solvent effect was estimated by means of the polarized continuum model (PCM)[15] without geometry optimisation.

The calculated compounds have positive gas phase electron affinity (EAs computed as $E_{\text{neutralmolecule}}$–$E_{\text{radicalanion}}$), *i.e.* the anionic surfaces lie at lower energy than the neutral surfaces.

Results and discussion

We focused our study on the inspection of the anionic potential surface of 5-fluorouracils with CH_2R substituents at N_1 (R = F, Cl, Br, I, H–C=O, CN and NO_2) in order to investigate the role of the substituent in determining the existence of radical anions as intermediates and the preferred dissociation pathway followed upon electron attachment. The two alternative dissociation reactions considered refer to the fragmentation of either the N_1–CH_2R or the N_1CH_2–R bond, eqn. (1) and (2), respectively.Energies of reaction (ΔE_r) are presented in Table 1 while activation energies ($\Delta E^{\neq}$) are displayed in Table 2. Semiempirical AM1 values are included for comparison.



Scheme 2

Halomethyl substituents

For R = F, a π radical anion was characterised on the anionic ground state potential surface. This species possess a slightly nonplanar structure with the unpaired spin density delocalized on the C_6=C_5–C_4=O conjugated system of the uracil ring and mainly located at C_6. The C_6–H bond is strongly deviated from the ring plane, *i.e.*, C_6 exhibits piramidalization. The N_1–CH_2F bond is also slightly deviated from the plane.

The intramolecular electron transfer (*intra*-ET) from the π system to the σ* N_1–CH_2F or σ* H_2C–F MOs is necessary for dissociation of the π intermediate in the sense of eqn. (1) or (2), respectively. We have determined that as the π and σ* states approach in energy they become coupled and the *intra*-ET becomes feasible by bending of the N_1–CH_2F bond (away from the uracil-ring plane for the N_1–CH_2F bond cleavage, and towards that plane for the CH_2–F break). The σ surfaces which arise as a consequence of these intra-ETs to the N_1–CH_2F or CH_2–F bonds are dissociative, meaning that no σ ground state minimum exists on any of these surfaces with the exception of a shallow minimum corresponding to the electrostatic complex formed between the dissociated fragments.[16] From these two σ surfaces, that of lowest energy corresponds to dissociation according to eqn. (2) and leads to the most stable fragments, which are the halide anion plus the 5-fluorouracilmethyl radical (Table 1).

In addition, the fragmentation path at the C_5–F bond leading to formation of the 1-fluoromethylura-5-yl radical plus fluoride anion was calculated for R = F. This cleavage reaction involves bending of the C_5–F bond from the uracil-ring plane, in order for the extra electron to be transferred from the uracil π system to the C_5–F breaking bond. As this path was less favourable than those described in reactions (1) and (2) (Table 1), it was not considered for the other 5-fluorouracil derivatives.

The energy profiles for the preferred reactions (1) and (2) (N_1–CH_2F and CH_2–F bond cleavage, respectively) are shown in Fig. 1 and the more relevant intermediates are depicted in Fig. 2. Activation energies for the three reactions pathways are shown in Table 2.

Dissociation in the sense of eqn. (2) is also the preferred pathway for R = Cl, Br and I (Table 1). As opposed to the behaviour shown by the fluoride derivative, for R = Cl and Br neither π nor σ radical anions could be located on the anionic ground state potential surface. For this reason, the electron transfer reaction to these compounds is proposed as dissociative,

Table 1 ΔE_r for reactions (1) and (2)

		ΔE_r/kcal mol^{-1} [a]			
		UB3LYP/6-31+G*		AM1-UHF[b]	
R	Reaction type	Gas phase	Aqueous phase	Gas phase	Aqueous phase[c]
F	1	(−31.79) 8.88	15.00	1.1	2.6
	2	(−40.66) <0.01	−11.63	111.5	—
	[d]	(−28.37) 12.30	4.73	—	—
Cl	1	(−30.62)	—	—	—
	2	(−54.97)	—	—	—
Br	1	(−41.71)	—	—	—
	2	(−67.90)	—	—	—
I[e]	1	(−31.44) 21.72	20.02	12.0	10.1
	2	(−57.68) −4.52	−2.18	44.7	—
CN	1	(−50.98) −12.94	−2.81	6.9	5.0
	2	(−25.44) 12.60	11.13	72.2	—
HC=O	1[f]	(−47.34) −6.16	−0.64	2.7[g]	—
	1[h]	−9.54	−4.21	−7.0[g]	—
NO_2	1	(−48.01) 11.29	25.90	10.4	15.8
	2	(−53.28) 6.03	15.62	3.9	—

[a] Energy of reaction for dissociation of the radical anion. Energy of reaction for dissociation from the neutral compound (within parentheses). [b] From ref. 9. [c] AM1-SM2.1. [d] Fluorine anion cleavage at C_5. [e] 3-21G* basis set for I. [f] From the π uracil radical anion (see text). [g] This work. [h] From the π carbonyl radical anion (see text).

Table 2 Activation energy for dissociation of π radical anions (kcal mol^{-1})

R	Leaving group	UB3LYP/6-31+G*		AM1-UHF	
		Gas phase	Aqueous phase	Gas phase	Aqueous phase[a]
F	$^{\bullet}CH_2F$	27.44	29.45	20.20	27.7
	F^-	14.08	0.26	—	—
	F^- (at C_5)	27.56	4.73	—	—
H–C=O	$^{\bullet}CH_2CHO$	1.16	0.28	8.73	—
CN	$^{\bullet}CH_2CN$	9.75	15.85	17.40	27.0
NO_2	NO_2^-	15.99	23.50	6.38	—

[a] AM1-SM2.1.

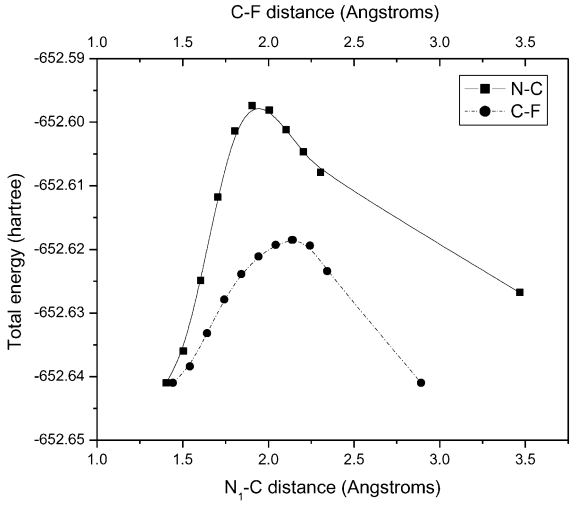


Fig. 1 Energy profiles for reactions (1) and (2) with R = F; B3LYP/6-31+G* results. Reaction coordinates are the N_1–C distance for reaction 1, and the C–F distance for reaction (2).

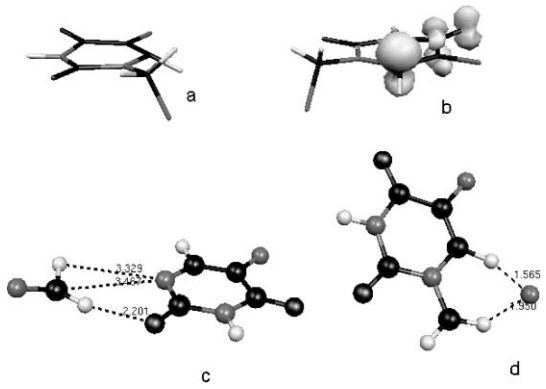
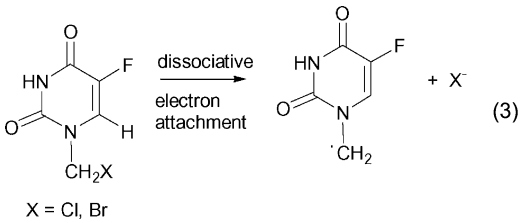


Fig. 2 Minima on the basal PES for R = F; (a) uracil π radical anion; (b) spin density for the π radical anion; (c) products for reaction (1); (d) products for reaction (2). Bond distances are in Å (B3LYP/6-31+G* values).

in other words, the C-halogen bond fragments as the electron is being received, as shown in eqn. (3).[17]



X = Cl, Br (3)

A slightly bounded σ radical anion was found for R = I (C–I = 2.969 Å). This intermediate, separated by a low barrier (0.03 kcal mol^{-1}) from the electrostatic complex of the dissociated fragments, could result from the more contracted 3–21G* basis used for iodine. Therefore, we conclude that this compound could be following a dissociative mechanism similar to the one found for R = Cl, Br.

A summary of the UB3LYP results obtained for the R = halogen family is schematically presented in Fig. 3.

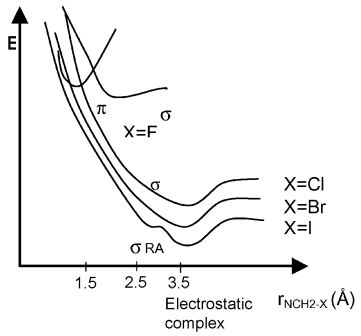


Fig. 3 π and σ anionic profiles for the derivatives with R = halogen and their dissociation in the sense of eqn. (2).

This theoretical study shows an anionic profile for the uracil system similar to the one found for the halobenzene family.[18] For the latter compounds we have shown that the σ surface lies at higher energy than the π surface only for PhF, which is consistent with our results for the R = F uracil derivative and with the existence of a π intermediate on its anionic potential energy surface. The σ surface decreases in energy with respect to the π surface (the dissociation being exothermic) for PhCl and PhBr, while for PhI no π intermediate could be found. A similar σ energy profile is observed for the corresponding uracil derivatives for which no π intermediate is located. The energy of the σ surface can also be roughly rationalised by comparing the energy of the σ* CH_2–R MO of the neutral uracils along the family. This MO, the first unoccupied orbital with adequate symmetry for dissociation in the sense of eqn. (2), is the LUMO + 2 for R = Cl, the LUMO + 1 for R = Br while it is the LUMO for R = I.

The calculations here presented provide an adequate description of halide ion release from this type of uracil derivatives, at variance with the profile predicted on the basis of AM1 evaluations.

Substituents with a π system: structures with R = H–C=O, CN and NO_2

Two π intermediates were characterised on the ground state surface for the derivative with R = H–C=O. One of these species has the extra electron delocalized over the π-conjugated system of the uracil ring, its geometrical features being similar to those of the π intermediate obtained for R = F. In this radical anion the CH_2–CHO bond is perpendicular to the ring. The main radical centre is located at C_6, despite some amount of unpaired spin also being found at the carbonyl group of R.

In the other π intermediate the unpaired spin mainly locates at the carbonyl group of R, with some amount at C_5 and N_1. In

this intermediate the CH_2–CHO bond lies on the ring plane. The N_1–CH_2CHO and C=O bond lengths increase from 1.448 and 1.236 Å in the former π species to 1.514 and 1.273 Å, respectively, in this π C=O intermediate. Unpaired spin distributions for both π species are displayed in Fig. 4. From these two species, the most stable is that bearing the unpaired spin at the uracil ring.

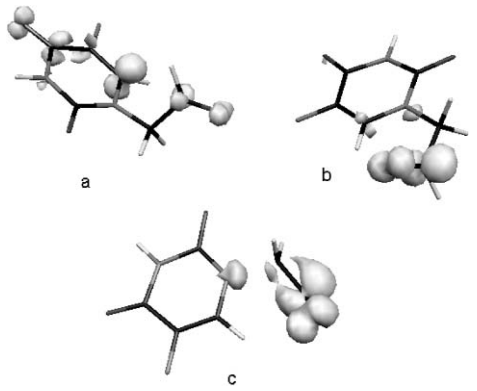


Fig. 4 Unpaired spin density for stationary points of R = H–C=O; (a) uracil π radical anion; (b) carbonyl π radical anion; (c) transition state for N_1–C bond dissociation.

The concerted rotations along the N_1–CH_2R and N_1CH_2–CHO bonds, coupled with the N_1–CH_2R bond elongation, result in the electron transfer from the uracil to the less stable π carbonyl state. The latter π system mixes with the σ surface by further lengthening of the N_1–CH_2R bond leading to cleavage in the sense of reaction (1) through a small energy barrier. No radical anion intermediate was isolated on the σ surface.

As can be seen, the electron attachment to this type of compound is mediated by a π radical anion (uracil system) the surface of which merges, on the ground state, with another π state (C=O) which is close in energy; the latter species corresponding to an excited state at the equilibrium geometry of the most stable π radical anion. This assistance is responsible for a gradual and adiabatic π–σ intra-ET by adequate geometrical modifications along the dissociation path. A similar type of π* assistance has been recently demonstrated for the PhX family.[18] The reaction profile for the R = H–C=O derivative is shown in Fig. 5. The transition point from the carbonyl π state to the σ state takes place at a N_1–C bond distance of 1.699 Å. This stationary point is also shown in Fig. 4.

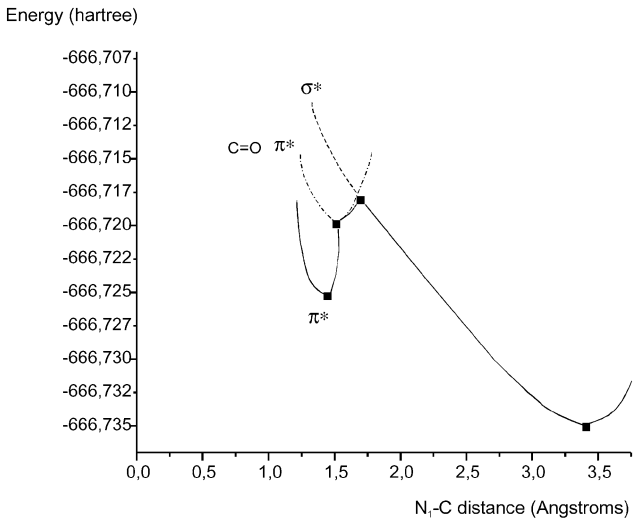


Fig. 5 B3LYP/6-31+G* energy profile for reaction (1) with R = H–C=O.

The noticeable decrease in the activation energy for the dissociation of R = H–C=O with respect to the R = F (Table 2) is in very good agreement with the experimental results of Mori *et al.*[6] In that work, a 2′-oxo group yielded an efficient N_1–C_1' bond cleavage, while compounds with saturated substituents did not dissociate.

For R = CN the only radical anion characterised on the anionic ground state surface is of the π type with the extra electron in the uracil moiety. This intermediate shares similar features to the π species previously described for other substituents. The CN group affords a relatively low barrier for the N_1–CH_2CN bond fragmentation (Table 2), suggesting that reaction (1) could take place at room temperature. In this way, it can be concluded that a vicinal π system assists the N_1–CH_2R bond dissociation by lowering the energy barrier required to shift the unpaired electron to this bond.

At variance with the behaviour shown by the H–C=O and CN substituents, the radical anion characterised for R = NO_2 bears the unpaired spin density at the NO_2 group. This radical anion which is the only one isolated, undoubtedly owes this spin localisation to the high electronegativity of the nitro group. The uracil ring presents a planar structure with the N_1–CH_2R bond laying on the ring plane. The most favoured path for dissociation of this derivative corresponds to the CH_2–NO_2 cleavage in the sense of reaction (2),[19] reaction (1) being more endothermic. It should be noted, consequently, that substitution with an R group that presents a very high electron affinity is unfavourable for the N_1–CH_2R bond cleavage.

Aqueous phase calculations were performed in order to estimate chemical behaviour within living organisms (Tables 1 and 2). In general, reaction (1) was disfavoured and reaction (2) was assisted by the solvent effect. Nevertheless, the solvent did not modify the gas phase pattern previously described, as these computations afforded the same reactivity order for both reactions, as well as the same preferred path for each substituent. In this way, the present gas phase results appear to be a good indication of the reactivity expected in biological systems. We note the remarkably greater exothermicity and the important reduction in the activation energy for the fluoride ion release in water. Therefore, it should be noted that, according to the calculations for the R = F derivative, C_5–F bond cleavage would be feasible in the aqueous phase, which is consistent with the known occurrence of this process in 5-fluorouracil radical anions.[4] In contrast, nitrite anion loss was less favoured in water than in the gas phase.

Another possibility to take into consideration in a polar solvent, is dissociation *via* dianions instead of radical anions. However, as radical anions are proposed as the most plausible intermediates in biological media, this possibility was not considered in the present study.

Conclusions

One-electron attachment to 5-fluorouracil derivatives substituted at N_1 with a group containing a π system generates the most stable π isomer, generally the species with unpaired spin on the C_6=C_5–C_4=O system of the uracil ring, primarily at C_6. In addition, other π intermediates have been characterised: one which bears the extra electron at the carbonyl group of the –CH_2CHO substituent, and the radical anion with the electron at the nitro group. In this way, both reactions (1) and (2) proceed by merging of the π and σ* electronic surfaces through appropriate geometrical fluctuations that result in the shift of the unpaired spin density to the bond that will dissociate.

With R = halogen, the release of halide ion (reaction (2)) was the preferred path. A π radical anion was isolated only for R = F. With the other halogens, the halide loss was a barrierless process. In this manner, the present calculations propose the liberation of halide ions as the preferred dissociation pathway for this type of compound, and significantly improve on earlier computations.

The presence of a π system at R, such as a carbonyl or cyano group, produces an important diminution in the activation energy of the N_1–CH_2R bond cleavage [reaction (1)]. These results agree with experimental observations of the crucial effect of a 2′-oxo substituent for efficient N_1–C_1' bond fragmentation. Therefore, inclusion of an unsaturated group vicinal to the N_1–C_1' bond is strongly recommended for the development of novel radiation-activated antitumour prodrugs derived from 5-fluorouracil.

Accounting for the solvent effect, by means of aqueous phase calculations, did not modify the general conclusions brought about by the gas phase results. However, the halide release was more favourable in water, indicating that the theoretical computations agree with the known experimental reactivity of these compounds.

Acknowledgements

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