Electronic Supplementary Information to the paper:

Lone pair–π vs π–π interactions in 5-fluoro-1-hexyluracil and 1-hexyluracil: a combined crystallographic and computational study

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1. EXPERIMENTAL DETAILS

Analysis and physical measurements:

Elemental microanalyses were carried out using a Carlo Erba model 1108 microanalyzer. ^{1}H-NMR spectra were recorded on a Brucker AMX 300 spectrophotometer at room temperature. ^{1}H and ^{13}C chemical shifts in deuterated dimethylsulfoxide (DMSO-d$_6$) were referenced to DMSO-d$_6$ [(^{1}H-RMN, δ(DMSO) = 2.47 ppm; ^{13}C-RMN, δ(DMSO) = 39.88 ppm)]. To confirm the peak assignations bi-dimensional spectra (^{1}H^{13}C-HMQC and ^{1}H^{13}C-HMBC) were used. High Resolution Mass Spectroscopy with Electro Spray Ionization (ESI-HRMS) was focused on an AUTOSPEC 3000 with PEG-600 as standards for exact mass determination (2 mg/10 ml MeOH). IR spectra in the solid state (KBr pellets) were measured on a Brucker IFS 66 spectrometer. The reagents were used as received from Sigma-Aldrich.

Synthesis of N^1-hexyl-5-fluorouracil (1) and N^1-hexyluracil (2):

100 mmol of 5-X-uracil (X = F, H) in hexamethyldisilazane (HMDS) (400 mmol for fluorouracil; 950 mmol and some mg of ammonium sulfate anhydrous for uracil) are heated under reflux, in nitrogen atmosphere, during 4 hours. Subsequent distillation of non-reacted HMDS and its more volatile byproducts yield the corresponding O,O'-bis-trimethylsilyloxy derivative with NMR purity. These products are used without any further purification.

A suspension of O,O'-bis-trimethylsilyloxy-5-X-uracil (X = F, H) (15 mmol) and 1-bromohexane (15 mmol) in 30 ml dry acetonitrile, under nitrogen, are heated at 130 ºC in PARR® bomb during 36 hours. The resulting mixture is boiled with 50 ml methanol for 30 minutes and stirred overnight at room temperature. The corresponding N^1-hexyl-5-X-uracil appears from the methanol solution after a first precipitation of non-reacted 5-X-uracil and white crystals, suitable for X-ray diffraction studies, were obtained after recrystallisation in water.

N^1-hexyl-5-fluorouracil (1): (40% yield). *Anal. Found*: C, 56.41; H, 7.01; N, 12.97 %. Calc. for $C_{10}H_{15}FN_2O_2$: C, 56.06; H, 7.06; N, 13.08%. *^{1}H-RMN (DMSO-d$_6$)*: δ (ppm) 11.72 [bd, 1H, N(3)-H], 8.06 [d, 1H, H(6), $J_{F\text{-}H(6)}$ = 6.9 Hz], 3.57 [t, 2H, H(7), J = 6.9 Hz], 1.53 [t, 2H, H(8), J = 6.9 Hz], 1.23 [s, 6H, H(9,10,11)], 0.86 [t, 3H, H(12), J = 6.9 Hz]. *^{13}C-RMN (DMSO-d$_6$)*: δ (ppm) 157.9 [d, C(4)=O, $J_{F\text{-}C(4)}$ = 26.4 Hz], 150.0 [C(2)=O], 140.0 [d, C(5)-F, $J_{F\text{-}H(5)}$ = 228.7 Hz], 130.5 [d, C(6), $J_{F\text{-}C(6)}$ = 30.2 Hz], 48.1 [C(7)], 31.3 [C(10)], 28.6 [C(8)], 25.8 [C(9)], 22.4 [C(11)], 14.3 [C(12)]. *IR (cm^{-1})*: 420w, 564w, 709vw, 751vw, 869vw, 938vw, 1103w, 1147w, 1237m, 1253w, 1365w(br), 1481w, 1664s, 1704vs, 2847w, 2931m, 2960w, 3061m(br), 3174 w(br), 3432 w(br). *ESI-HRMS*: [M+1]: exact mass, 215.1198; calc. 215.1196.

N^1-hexyluracil (2): (20% yield) *Anal. Found*: C, 61.17; H, 8.21; N, 14.11 %. Calc. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27%. *^{1}H-RMN (DMSO-d$_6$)*: δ (ppm) 11.16 [s, 1H, N(3)-H], 7.61 [d, 1H, H(6), J = 8.1 Hz], 5.51 [d, 1H, H(5), J = 8.1 Hz], 3.60 [t, 2H, H(7), J = 6.9 Hz], 1.52 [t, 2H, H(8), J = 6.9 Hz], 1.22 [s, 6H, H(9,10,11)], 0.82 [t, 3H, H(12), J = 6.9 Hz]. *^{13}C-RMN (DMSO-d$_6$)*: δ (ppm) 164.2 [C(4)=O], 151.4 [C(2)=O], 146.2 [C(6)], 101.2 [C(5)], 47.9 [C(7)], 31.3 [C(10)], 28.8 [C(8)], 25.9 [C(9)], 22.4 [C(11)], 14.3 [C(12)]. *IR (cm^{-1})*: 421m, 442w, 465vw, 494vw, 543w, 558m, 619vw, 725w, 760w, 816m, 886m, 987w, 1154m, 1178m, 1231m, 1251m, 1307w, 1368s, 1420s, 1466s, 1649vs, 1693vs, 2819m, 2862m, 2931s(br), 3044m(br), 3097m, 3154m.

Crystallographic studies:

Suitable crystals of **1** and **2** were selected for X-ray single crystal diffraction experiments and mounted at the tip of glass fibres on an Enraf-Nonius CAD4 diffractometer producing graphite monochromated MoKα radiation (λ = 0.71073Å). In each case, after the random search of 25 reflections, the indexation procedure gave rise to the cell parameters (see Table 1 for a summary of the crystal data). Intensity data were collected in the ω-2θ scan mode and corrected for Lorenz and polarization effects. The absorption correction was performed following the DIFABS method.[1] The structural resolution procedure was made using the WinGX package.[2] Solving for structure factor phases was performed by SIR2004 [3], and the full matrix refinement by SHELXL97 [4] for the two crystals. Non-H atoms were refined anisotropically and H-atoms were introduced in calculated positions and refined riding on their parents atoms. A summary of refinement parameters can also be seen in Table 1. In compound 1, the lateral chain of 5-fluorouracil is spitted into four different position where atoms from C(11) to C(16) and C(21) to C(26) have fractional occupancy (30%), while theirs corresponding relatives from C(31) to C(36) and C(41) to C(46) present 20% occupancy.

Description of the restrains:

36: The restrains are DFIX and DANG to properly describe the alkyl chain.

211: The restrains are DFIX and DANG as before. In addition four EXYZ and EADP have been used to split the alkyl chain having the first carbon atom in common. Finally, ISOR and DELU have been applied to maintain the anisotropy.

Table S1. Crystal data and structure refinement for compounds **1** and **2**.

		1	2
Empirical formula		$C_{10}H_{15}FN_2O_2$	$C_{10}H_{16}N_2O_2$
Formula weight		214.24	196.25
Temperature (K)		294(2)	294(2)
Crystal system		Monoclínic	Triclínic
Space group		$P2_1/c$	P-1
Unit cell dimensions	a (Å)	12.369(5)	13.111(4)
	b (Å)	8.867(2)	13.285(8)
	c (Å)	11.904(7)	13.332(6)
	α (º)	90	90.66(7)
	β (º)	117.17(4)	102.36(5)
	γ (º)	90	94.35(4)
Volume (Å^3)		1161.5(10)	2260.9(18)
Z		4	8
Density (calculated)) (Mg/m^3)		1.225	1.153
Absorption correction		DIFABS	DIFABS
Absorption coefficient (mm^{-1})		0.096	0.081
F(000)		456	848
Crystal size (mm^3)		0.46 x 0.21 x 0.09	0.38 x 0.11 x 0.04
Theta range for data collection (º)		1.85 a 25	1.54 a 24.97
Index ranges		-14<=h<=13	-15<=h<=15
		0<=k<=10	-15<=k<=15
		0<=l<=14	0<=l<=15
Reflections collected		2021	7328
Independent reflections		2021 [R(int) = 0]	7328 [R(int) = 0]
Completeness to theta max. (%)		98.5	92.2
Max. and min. transmission		0.9914 i 0.957	0.9968 i 0.9698

Data / restraints / parameters		2021/211/275	7328/36/509
Goodness-of-fit on F^2		1.124	0.932
Final R indices [I>2sigma(I)]	R1	0.1015	0.1006
	wR2	0.3588	0.2299
R índices (all data)	R1	0.2321	0.3275
	wR2	0.4153	0.2914
Largest diff. peak and hole (e·Å^{-3})		0.194 i -0.256	0.225 i -0.206

Crystallographic data for compounds **1** and **2** have been deposited in the Cambridge Structural Database. CCDC 730817 and 730816 contain the supplementary crystallographic data for **1** and **2**, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

2. COMPUTATIONAL DETAILS

All calculations were carried out using the Gaussian03 suite of programs [5] using the MP2 method, which has been widely used to study noncovalent interactions. In this study, a combination of Pople's [6] basis sets were used (truncated basis set), varying levels of polarisation and diffuse functions as in 6-31G*, 6-31+G* and 6-31++G** depending on the implication of the different atoms in noncovalent interactions. See Figure S1 for a schematic representation of the basis set used for each atom. To reduce the size of the model, the hexyl chain of one uracil molecule has been replaced by a methyl group. To analyze the inter-molecular interactions, the Atoms-In-Molecules (AIM) theory was employed.[7,8] AIM is based upon those critical points where the gradient of the density,$\nabla\rho$, vanishes. Such points are classified by the curvature of the electron density, for example bond critical points represented as red balls in Figure 5 have one positive curvature (in the internuclear direction) and two negative ones (perpendicular to the bond). Two bonded atoms are then connected with a bond path through the bond critical point. The properties evaluated at such bond critical points characterise the bonding interactions present, and have been previously used to study molecular interactions.[7,8]

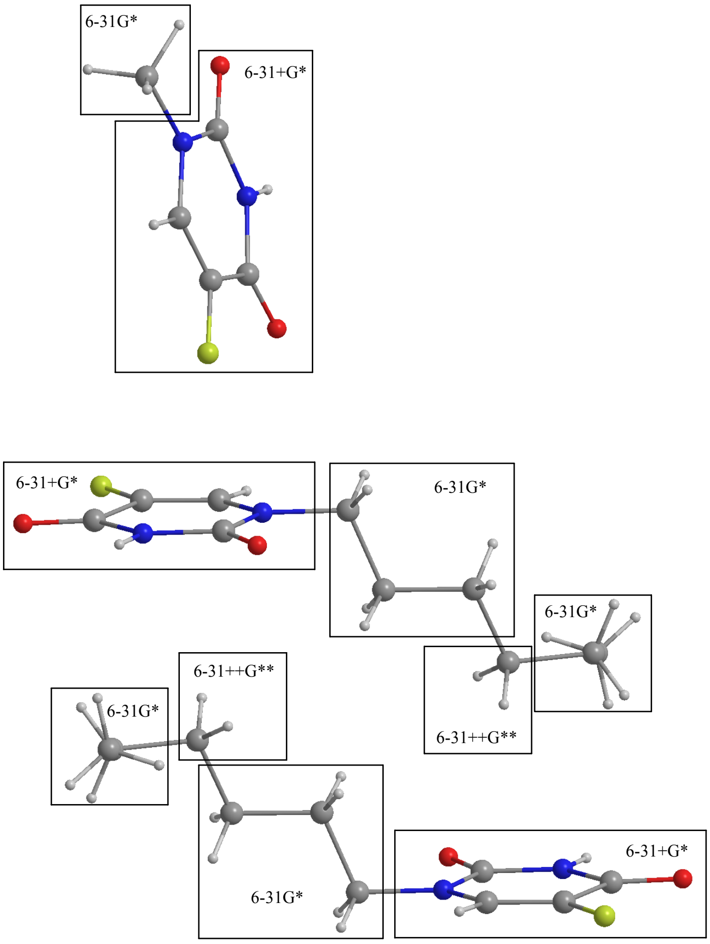

Figure S1. Schematic representation of fragment of the crystal structure with indication of the basis set employed.

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