

Supporting Information for

Theoretical Study on the Photo-oxidation and Photoreduction of an Azetidine Derivative as a Model of DNA Repair

Miriam Navarrete-Miguel¹, Antonio Francés-Monerris², Miguel A. Miranda³, Virginie Lhiaubet-Vallet³ and Daniel Roca-Sanjuán^{1,*}

¹ Institut de Ciència Molecular, Universitat de València, València 46071, Spain; Miriam.Navarrete@uv.es

² Departament de Química Física, Universitat de València, 46100 Burjassot, Spain; Antonio.Frances@uv.es

³ Instituto Universitario Mixto de Tecnología Química UPV-CSIC, Universitat Politècnica de València, Consejo Superior de Investigaciones Científicas, Avda de los Naranjos s/n, 46022 Valencia, Spain. e-mail:
mmiranda@qim.upv.es, lvirgini@itq.upv.es

* Correspondence: Daniel.Roca@uv.es

Table of contents

Figure S1. Opening of the azetidine ring of the *cis*-AZT-CH system in the gas phase. The reaction profile corresponds to the neutral system.

Figure S2. Opening of the azetidine ring of the *trans*-AZT-CH system in the gas phase. The reaction profile corresponds to the neutral system.

Table S1. Energy differences between products and reactants (ΔE , ΔE_0 , ΔG) and activation energies (ΔE^\ddagger , ΔE_0^\ddagger , ΔG^\ddagger) for the photocycloreversion of the neutral *cis*- and *trans*-AZT-CH isomers, in the gas phase and in solution. Energies are given in kcal mol⁻¹.

Figure S3. Opening of the azetidine ring of the *cis*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profile corresponds to the reduced system with a net charge of -1 and doublet multiplicity.

Figure S4. Opening of the azetidine ring of the *trans*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profile corresponds to the reduced system with a net charge of -1 and doublet multiplicity.

Figure S5. Opening of the azetidine ring of the *cis*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profiles correspond to the oxidized system with a net charge of +1 and doublet multiplicity, and have been obtained through relaxed scans of the N₃-C₄ and C₁-C₂ bond distances, linear interpolation of internal coordinates (LIIC), and MEP determinations. As indicated by the back arrows, the relaxed scan of the C₁-C₂ bond distance was initiated from the most stable structure that exhibit N₃-C₄ bond cleavage (2.808 Å), and performed freezing the N₃-C₄ bond distance at this value to avoid the return of the system to the reagents region. The pathway that connects the last MEP structure to the products minimum shown in Figure 7 of the main text has not been computed.

Figure S6. Opening of the azetidine ring of the *trans*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profiles correspond to the oxidized system with a net charge of +1 and doublet multiplicity, and have been obtained through relaxed scans of the N₃-C₄ and C₁-C₂ bond distances and linear interpolation of internal coordinates (LIIC) between relevant structures. LIIC point number 14 has been optimized without any constraint. The hydrogen atom that undergoes the 1,2-hydride shift is highlighted with green dashed circles.

Figure S7. Atom labels of the AZT-CH system.

Table S2. Mulliken atomic spin densities for the relevant points on the ring opening reaction of *cis*- and *trans*-AZT-CH isomers of the anionic system. Only the most relevant positive atomic densities are shown, the total spin density is 1.

Table S3. Mulliken atomic spin densities for the relevant points on the ring opening reaction of *cis*- and *trans*-AZT-CH isomers of the cationic system. Only the most relevant positive atomic densities are shown, the total spin density is 1.

Table S4. Mulliken atomic charges for each atom of the *cis*-AZT-CH anion and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene in the reactants, transition states and products.

Table S5. Mulliken atomic charges for each atom of the *trans*-AZT-CH anion and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene in the reactants, transition states and products.

Table S6. Mulliken atomic charges for each atom of the *cis*-AZT-CH cation and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene, in the reactants, transition states and products.

Table S7. Mulliken atomic charges for each atom of the *trans*-AZT-CH cation and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene, in the reactants, transition states and products.

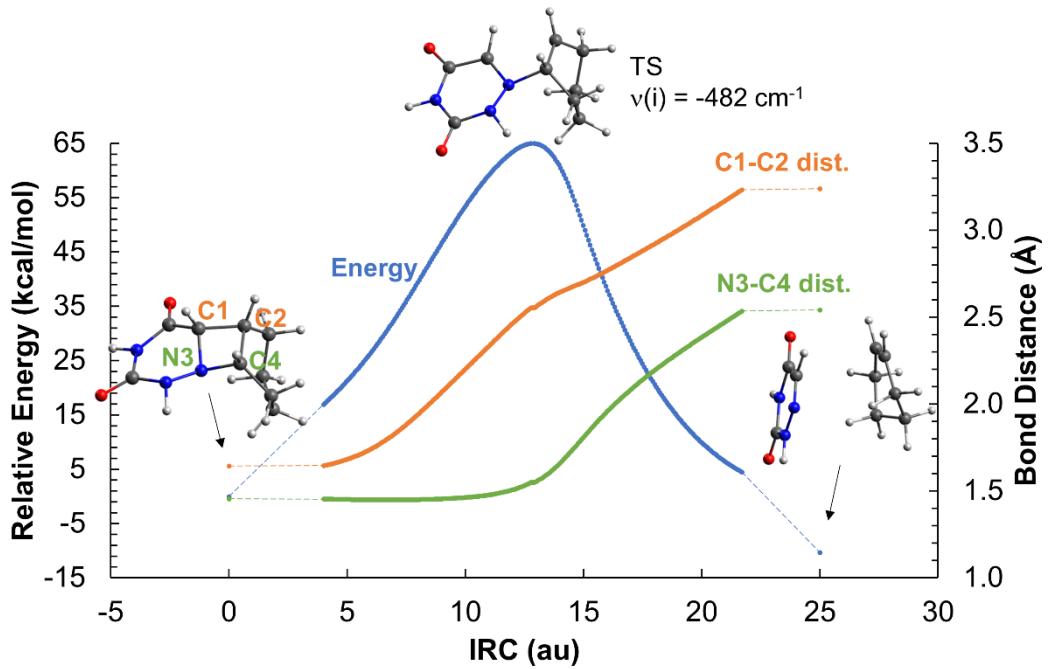


Figure S1. Opening of the azetidine ring of the *cis*-AZT-CH system in the gas phase. The reaction profile corresponds to the neutral system.

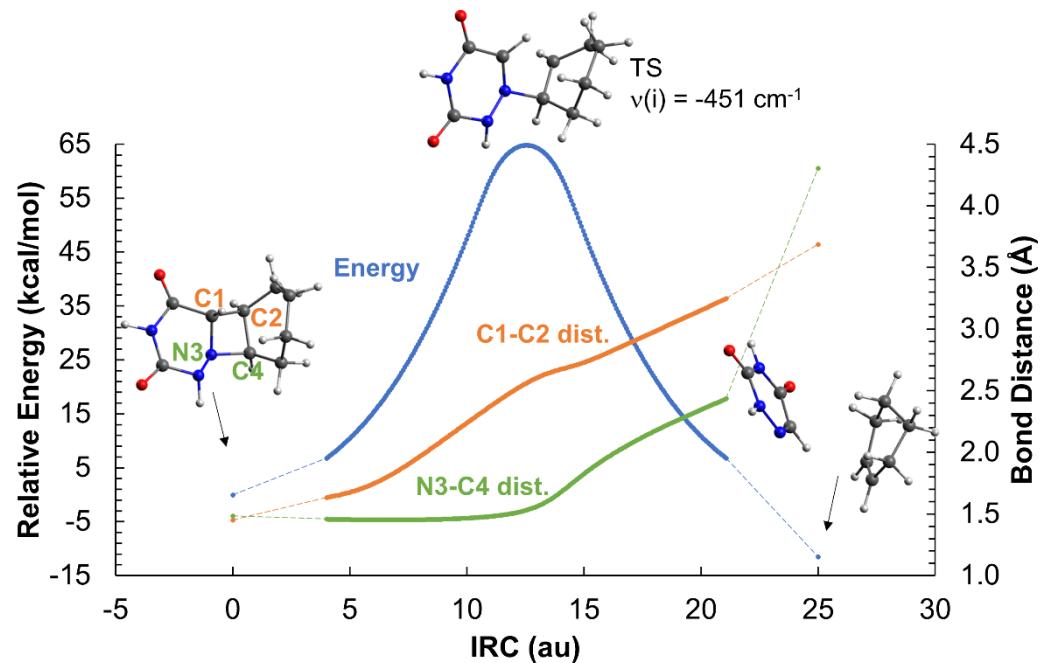


Figure S2. Opening of the azetidine ring of the *trans*-AZT-CH system in the gas phase. The reaction profile corresponds to the neutral system.

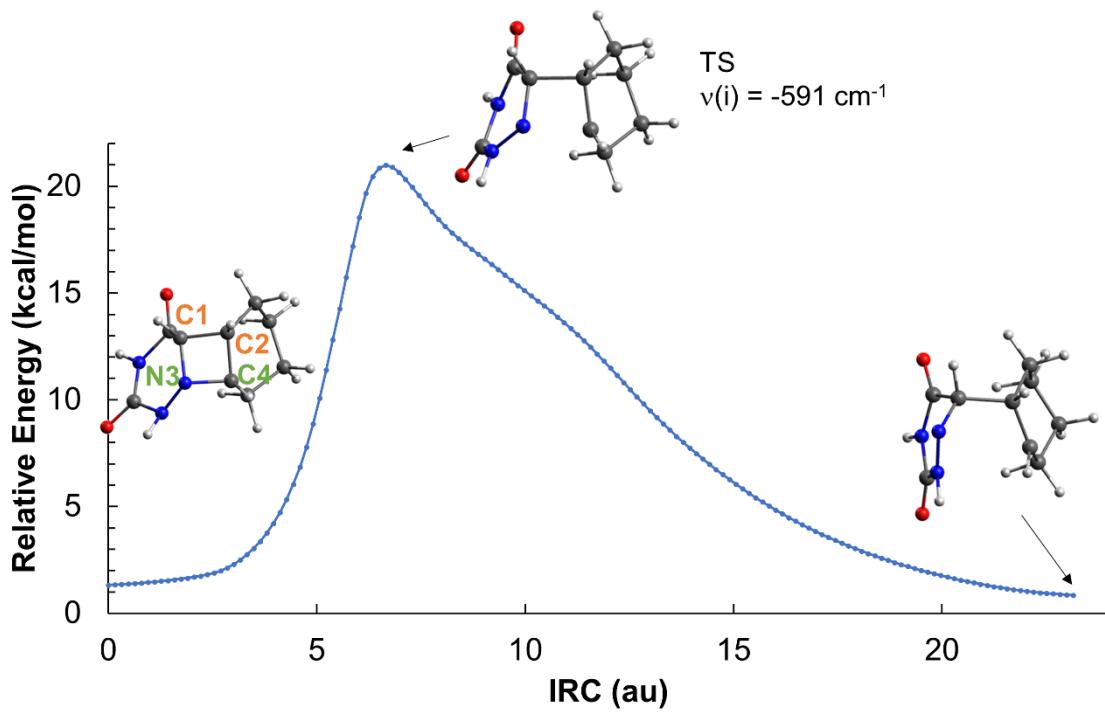


Figure S3. Opening of the azetidine ring of the *cis*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profile corresponds to the reduced system with a net charge of -1 and doublet multiplicity.

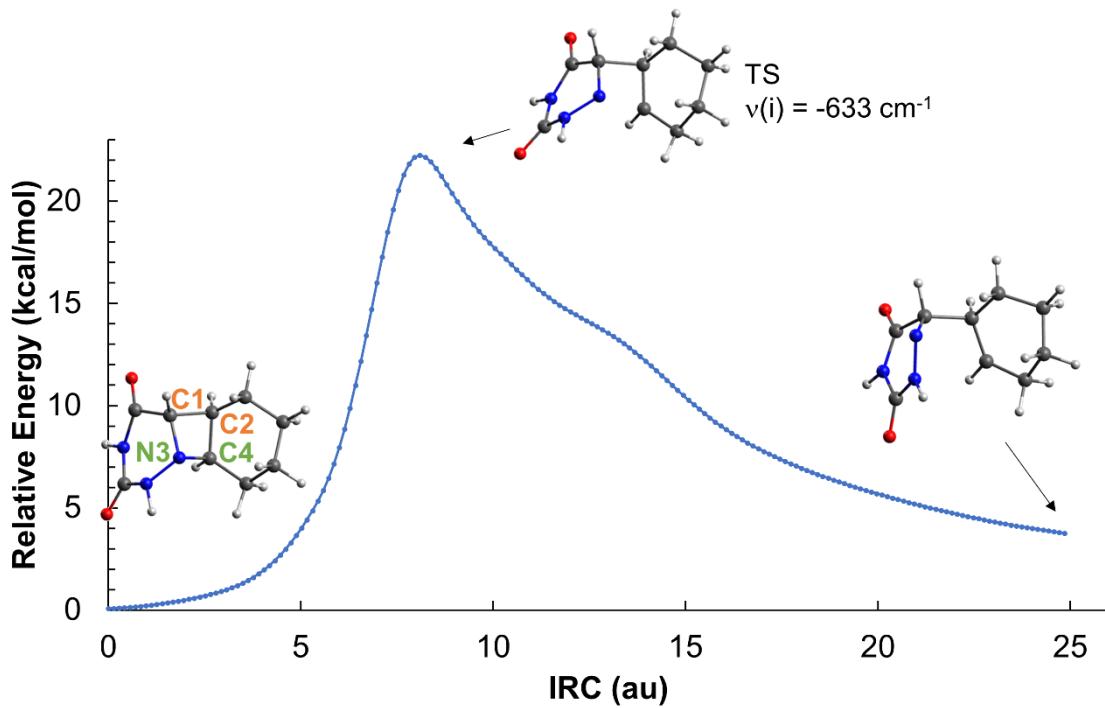


Figure S4. Opening of the azetidine ring of the *trans*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profile corresponds to the reduced system with a net charge of -1 and doublet multiplicity.

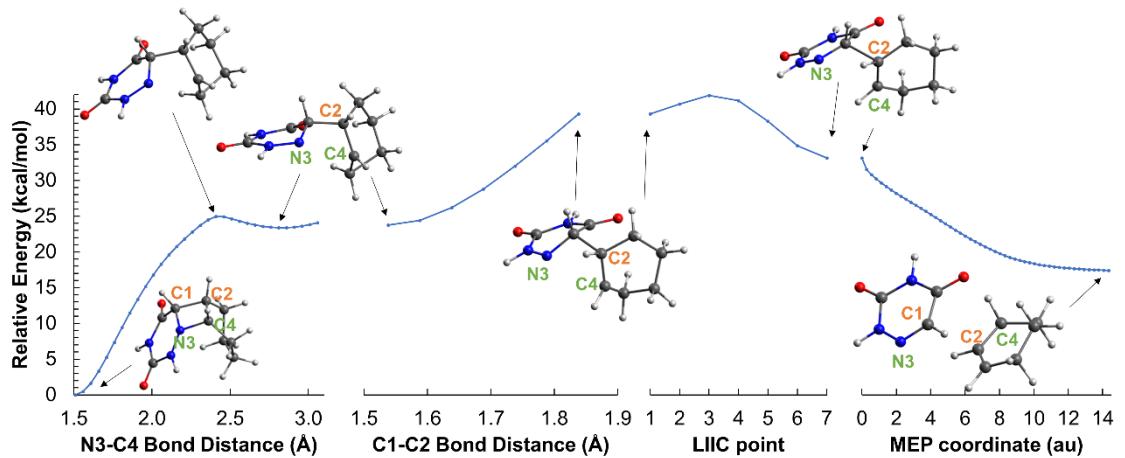


Figure S5. Opening of the azetidine ring of the *cis*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profiles correspond to the oxidized system with a net charge of +1 and doublet multiplicity, and have been obtained through relaxed scans of the N₃-C₄ and C₁-C₂ bond distances, linear interpolation of internal coordinates (LIIC), and MEP determinations. As indicated by the back arrows, the relaxed scan of the C₁-C₂ bond distance was initiated from the most stable structure that exhibit N₃-C₄ bond cleavage (2.808 Å), and performed freezing the N₃-C₄ bond distance at this value to avoid the return of the system to the reagents region. The pathway that connects the last MEP structure to the products minimum shown in Figure 7 of the main text has not been computed.

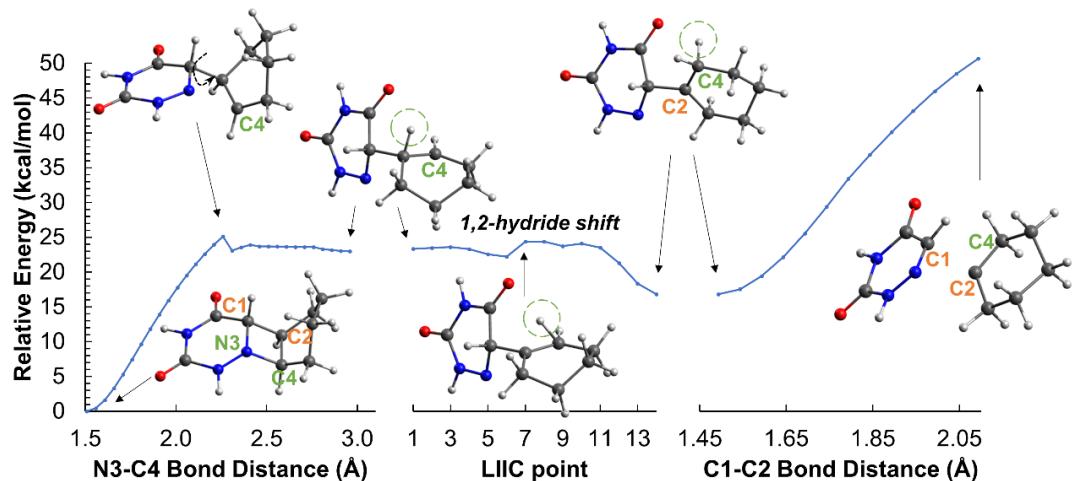


Figure S6. Opening of the azetidine ring of the *trans*-AZT-CH system in the gas phase initiated by the N₃-C₄ bond breaking. The reaction profiles correspond to the oxidized system with a net charge of +1 and doublet multiplicity, and have been obtained through relaxed scans of the N₃-C₄ and C₁-C₂ bond distances and linear interpolation of internal coordinates (LIIC) between relevant structures. LIIC point number 14 has been optimized without any constraint. The hydrogen atom that undergoes the 1,2-hydride shift is highlighted with green dashed circles.

Table S1. Energy differences between products and reactants (ΔE , ΔE_0 , ΔG) and activation energies (ΔE^\ddagger , ΔE_0^\ddagger , ΔG^\ddagger) for the photocycloreversion of the neutral *cis*- and *trans*-AZT-CH isomers, in the gas phase and in solution. Energies are given in kcal mol⁻¹.

Methodology	<i>cis</i> -AZT-CH		<i>trans</i> -AZT-CH	
	ΔE	ΔE^\ddagger	ΔE	ΔE^\ddagger
M06-2X	-10.33	65.01	-11.48	64.83
PCM-M06-2X	-9.94	64.30	-10.29	64.67
	ΔE_0	ΔE_0^\ddagger	ΔE_0	ΔE_0^\ddagger
M06-2X	-13.07	61.34	-14.64	61.01
PCM-M06-2X	-12.68	60.63	-13.45	60.85
	ΔG	ΔG^\ddagger	ΔG	ΔG^\ddagger
M06-2X	-15.88	60.54	-19.62	60.10
PCM-M06-2X	-15.49	59.83	-18.43	59.93

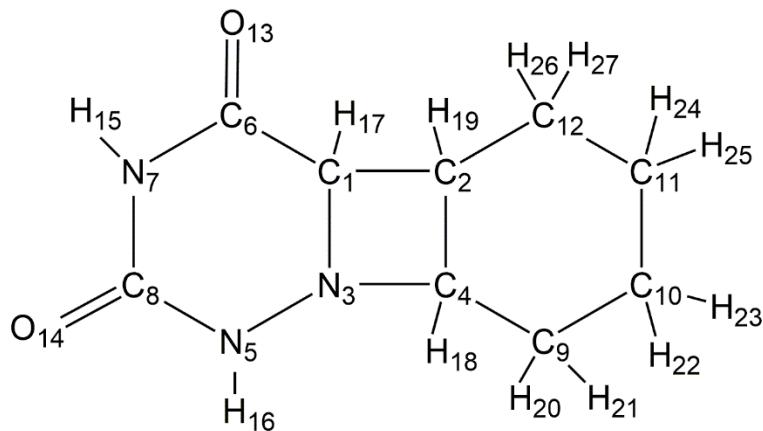


Figure S7. Atom labels of the AZT-CH system.

Table S2. Mulliken atomic spin densities for the relevant points on the ring opening reaction of *cis*- and *trans*-AZT-CH isomers of the anionic system. Only the most relevant positive atomic densities are shown, the total spin density is 1.

	Atom	Mulliken atomic spin density
<i>cis</i> -AZT-CH ⁻		
Reactants	C ₆	1.046
TS1 (C ₁ -C ₂ breaking)	C ₂	0.508
	C ₆	0.311
TS2 (N ₃ -C ₄ breaking)	C ₂	0.932
	N ₃	0.475
Products	C ₆	0.341
<i>trans</i> -AZT-CH ⁻		
Reactants	C ₆	1.045
TS1 (C ₁ -C ₂ breaking)	C ₂	0.503
	C ₆	0.307
TS2 (N ₃ -C ₄ breaking)	C ₂	0.913
	N ₃	0.518
Products	C ₆	0.197

Table S3. Mulliken atomic spin densities for the relevant points on the ring opening reaction of *cis*- and *trans*-AZT-CH isomers of the cationic system. Only the most relevant positive atomic densities are shown, the total spin density is 1.

	Atom	Mulliken atomic spin density
<i>cis</i> -AZT-CH ⁺		
Reactants	N ₃	0.493
TS1 (C ₁ -C ₂ breaking)	N ₅	0.371
	C ₂	0.718
TS2 (N ₃ -C ₄ breaking)	C ₂	0.654
	C ₄	0.261
Products	C ₄	0.504
	C ₂	0.460
<i>trans</i> -AZT-CH ⁺		
Reactants	N ₃	0.477
TS1 (C ₁ -C ₂ breaking)	N ₅	0.394
	C ₂	0.781
TS2 (N ₃ -C ₄ breaking)	C ₂	0.654
	C ₄	0.261
Products	C ₄	0.504
	C ₂	0.460

Table S4. Mulliken atomic charges for each atom of the *cis*-AZT-CH anion and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene in the reactants, transition states and products.

<i>cis</i>-AZT-CH⁻ Mulliken charges				
Atom label	reactants	TS1 (C ₁ -C ₂ breaking)	TS2 (N ₃ -C ₄ breaking)	products
N ₇	-0.40793	-0.426166	-0.519578	-0.4721
C ₈	0.546756	0.532996	0.602183	0.570944
N ₅	-0.53812	-0.61287	-0.799852	-0.678128
N ₃	0.092886	0.195189	0.014692	0.059472
C ₁	-0.002999	-0.623092	-0.441099	-0.23582
C ₆	-0.558744	0.21513	0.461627	0.264927
C ₄	-0.957931	-0.53682	-0.209638	-0.694023
C ₂	0.599589	0.321088	0.224291	0.599045
C ₉	0.265884	-0.004313	-0.52008	0.064922
C ₁₀	-0.486388	-0.371836	-0.259374	-0.628249
C ₁₁	-0.174072	-0.316049	-0.275613	-0.366059
C ₁₂	-0.48177	-0.504056	-0.43204	-0.609291
O ₁₃	-0.696397	-0.700947	-0.766047	-0.759239
O ₁₄	-0.659975	-0.620639	-0.6275	-0.622852
H ₁₅	0.33682	0.37397	0.37155	0.368069
H ₁₆	0.382534	0.379746	0.371771	0.37285
H ₁₇	0.052766	0.115808	0.113073	0.132041
H ₁₈	0.114568	0.104325	0.18175	0.130577
H ₁₉	0.184619	0.150013	0.166036	0.171298
H ₂₀	0.158891	0.169344	0.191663	0.177921
H ₂₁	0.212108	0.1973	0.168017	0.183504
H ₂₂	0.156221	0.16208	0.156123	0.16793
H ₂₃	0.149978	0.151373	0.152195	0.151866
H ₂₄	0.153434	0.155956	0.163935	0.152183
H ₂₅	0.229187	0.191668	0.174509	0.163968
H ₂₆	0.17721	0.152679	0.164848	0.166449
H ₂₇	0.150875	0.148122	0.17256	0.167794
Sum of charges				
6-azauracil	-1.452403	-1.170875	-1.21918	-0.999836
cyclohexene	0.452403	0.170874	0.219182	-0.000165

Table S5. Mulliken atomic charges for each atom of the *trans*-AZT-CH anion and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene in the reactants, transition states and products.

<i>trans</i>-AZT-CH · Mulliken charges				
Atom label	reactants	TS1 (C ₁ -C ₂ breaking)	TS2 (N ₃ -C ₄ breaking)	products
N ₇	-0.442959	-0.496374	-0.510062	-0.504573
C ₈	0.606781	0.584966	0.622982	0.627613
N ₅	-0.575865	-0.611735	-0.754204	-0.706638
N ₃	-0.071587	-0.019181	0.009340	-0.030008
C ₁	-0.174724	-0.60303	-0.491493	-0.427598
C ₆	-0.265601	0.415713	0.501541	0.427817
C ₄	-0.053859	-0.211234	-0.435325	-0.480414
C ₂	0.107837	0.157514	0.285642	0.161306
C ₉	-0.35767	-0.359429	-0.309589	-0.263457
C ₁₀	-0.287305	-0.266068	-0.260421	-0.227971
C ₁₁	-0.371624	-0.396714	-0.405521	-0.444022
C ₁₂	-0.259765	-0.253305	-0.359241	-0.253722
O ₁₃	-0.701366	-0.722613	-0.767682	-0.777474
O ₁₄	-0.648686	-0.631765	-0.638811	-0.622323
H ₁₅	0.361485	0.370664	0.371818	0.367892
H ₁₆	0.366445	0.366716	0.374301	0.37041
H ₁₇	0.151495	0.139762	0.117509	0.125901
H ₁₈	0.160609	0.143606	0.179917	0.152798
H ₁₉	0.183802	0.171576	0.168120	0.171727
H ₂₀	0.160796	0.151601	0.135683	0.179798
H ₂₁	0.160748	0.160022	0.177178	0.170584
H ₂₂	0.161639	0.159583	0.160057	0.155552
H ₂₃	0.159946	0.162146	0.176904	0.173089
H ₂₄	0.162563	0.14331	0.155306	0.155575
H ₂₅	0.151053	0.147947	0.159641	0.159334
H ₂₆	0.15902	0.147313	0.159079	0.155225
H ₂₇	0.156792	0.14901	0.177331	0.183579
Sum of charges				
6-azauracil	-1.394582	-1.206877	-1.164761	-1.148981
cyclohexene	0.394582	0.206878	0.164761	0.148981

Table S6. Mulliken atomic charges for each atom of the *cis*-AZT-CH cation and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene, in the reactants, transition states and products.

<i>cis</i>-AZT-CH⁺ Mulliken charges				
Atom label	reactants	TS1 (C ₁ -C ₂ breaking)	TS2 (N ₃ -C ₄ breaking)	products
N ₇	-0.345335	-0.436147	-0.537438	-0.499371
C ₈	0.511443	0.510817	0.557336	0.646715
N ₅	-0.622271	-0.754911	-0.565795	-0.445706
N ₃	0.46334	0.496111	0.173842	0.165842
C ₁	-0.162679	-0.059295	-0.096237	-0.115995
C ₆	0.030099	0.206077	0.434451	0.280444
C ₄	-0.143504	0.050584	0.338267	0.297866
C ₂	0.160071	-0.05393	0.003559	0.038879
C ₉	-0.450184	-0.47045	-0.553115	-0.492401
C ₁₀	-0.229649	-0.25486	-0.322484	-0.402875
C ₁₁	-0.227108	-0.265786	-0.290608	-0.322435
C ₁₂	-0.543785	-0.47937	-0.504429	-0.432112
O ₁₃	-0.344887	-0.4292	-0.490373	-0.61496
O ₁₄	-0.398531	-0.43777	-0.447874	-0.401583
H ₁₅	0.428189	0.432837	0.423104	0.405814
H ₁₆	0.472858	0.470263	0.456847	0.422899
H ₁₇	0.307746	0.272282	0.195611	0.247315
H ₁₈	0.255304	0.280832	0.283057	0.236254
H ₁₉	0.245465	0.259356	0.249048	0.213298
H ₂₀	0.215654	0.226297	0.168426	0.250438
H ₂₁	0.205847	0.18913	0.262763	0.228799
H ₂₂	0.188421	0.181125	0.189225	0.19653
H ₂₃	0.199197	0.203372	0.194821	0.201241
H ₂₄	0.199048	0.205729	0.209912	0.21168
H ₂₅	0.18549	0.215367	0.209635	0.204944
H ₂₆	0.203815	0.213835	0.238730	0.247293
H ₂₇	0.195947	0.227704	0.219720	0.231186
Sum of charges				
6-azauracil	0.339972	0.271064	0.103474	0.091414
cyclohexene	0.660029	0.728935	0.896527	0.908585

Table S7. Mulliken atomic charges for each atom of the *trans*-AZT-CH cation and sum of the charges for both fragments, *i.e.* 6-azauracil and cyclohexene, in the reactants, transition states and products.

<i>trans</i>-AZT-CH⁺ Mulliken charges				
Atom label	reactants	TS1 (C ₁ -C ₂ breaking)	TS2 (N ₃ -C ₄ breaking)	products
N ₇	-0.449123	-0.500129	-0.537438	-0.499371
C ₈	0.621811	0.638032	0.557336	0.646715
N ₅	-0.45979	-0.62183	-0.565795	-0.445706
N ₃	0.409407	0.602685	0.173842	0.165842
C ₁	-0.663745	-0.32088	-0.096237	-0.115995
C ₆	0.334284	0.445491	0.434451	0.280444
C ₄	-0.251633	-0.517712	0.338267	0.297866
C ₂	0.309313	0.293601	0.003559	0.038879
C ₉	-0.359083	-0.265778	-0.553115	-0.492401
C ₁₀	-0.232261	-0.227637	-0.322484	-0.402875
C ₁₁	-0.352939	-0.34769	-0.290608	-0.322435
C ₁₂	-0.388526	-0.527174	-0.504429	-0.432112
O ₁₃	-0.390211	-0.434667	-0.490373	-0.61496
O ₁₄	-0.410015	-0.455963	-0.447874	-0.401583
H ₁₅	0.44212	0.44212	0.423104	0.405814
H ₁₆	0.461716	0.447238	0.456847	0.422899
H ₁₇	0.317764	0.211997	0.195611	0.247315
H ₁₈	0.257593	0.231948	0.283057	0.236254
H ₁₉	0.249419	0.261657	0.249048	0.213298
H ₂₀	0.197987	0.200163	0.168426	0.250438
H ₂₁	0.202443	0.212426	0.262763	0.228799
H ₂₂	0.198352	0.210444	0.189225	0.19653
H ₂₃	0.198661	0.193621	0.194821	0.201241
H ₂₄	0.178058	0.191654	0.209912	0.21168
H ₂₅	0.187292	0.198464	0.209635	0.204944
H ₂₆	0.198202	0.22722	0.238730	0.247293
H ₂₇	0.192906	0.210699	0.219720	0.231186
Sum of charges				
6-azauracil	0.214218	0.454094	0.103474	0.091414
cyclohexene	0.785784	0.545906	0.896527	0.908585