

Combined Effect of Stacking and Solvation on the Spontaneous Mutation in DNA

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Supporting Information Material:

- ONIOM method calibration: p. S2
- Optimized geometries: p. S4

ONIOM method calibration

When the ONIOM approach is employed, the choice of layer borders (e.g. link atoms positions) is a crucial parameter. Consequently, to estimate the introduced error two borders are considered, with either cut N–C or C–C bonds (see Figure S1). Since our goal is to investigate the effect of the border rather than to obtain an accurate relative energies, we use a two-layer ONIOM method instead of the more refined three-layer scheme used in the paper. Several theoretical methods have been combined. The first is a QM/MM scheme, where central GC and surrounding water molecules are fully optimized at M052X/6-311++G(d,p) level and the UFF force field is selected to describe the frozen low level layer. UFF is known to adequately describe the steric effects exert by the sugar units¹. The second method relies on a QM1/QM2 partitioning in which the high level is the same as in the first case, whereas the rest of structure is described by a semiempirical approaches: AM1^{2a} or PM3^{2b}.

According to energies listed in Table S1, when the low layer is described with quantum mechanical approaches the water-assisted DPT presents alike energies: ca. 12 kcal/mol less stable than the canonical base pair. More importantly, this conclusion holds regardless of the borders of the layers. Obviously, with the QM/MM method, the predicted energies for the two paths are more dissimilar; the water-assisted mechanism appearing 3 or 6 kcal/mol less stable than the direct mechanism. The negligible impact of the borders when the low layer is described with QM contrasts with the UFF results. Therefore, the use of the PM3 method for describing to the low layer in the three layer ONIOM scheme is justified by: (i) the consistency of the predictions, that are almost insensitive to the position of the layer border and (ii) the fact that the same PM3 method has been recently applied for the description of the DNA backbone yielding valuable results³.

Table S1: Relative Electronic Energies (E/kcalmol⁻¹) Calculated for the Water-Assisted Proton Transfer

Method	C – N Breaking	C – C Breaking
M052X/6-311++G(d,p)/UFF	15.70	18.03
M052X/6-311++G(d,p)/AM1	12.24	12.19
M052X/6-311++G(d,p)/PM3	11.87	12.39

- (1) N. Sundaresan, C. K. S Pillai and C. H. Suresh, *J. Phys. Chem. A* 2006, **110**, 8826–8831.
- (2) (a) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.* 1985, **107**, 3902–3909 (b) J. J. P. Stewart, *J. Comput. Chem.* 1989, **10**, 209–220
- (3) H.-Y. Chen, C.-L. Kao and S. C. N. Hsu, *J. Am. Chem. Soc.* 2009, **131**, 15930–15938.

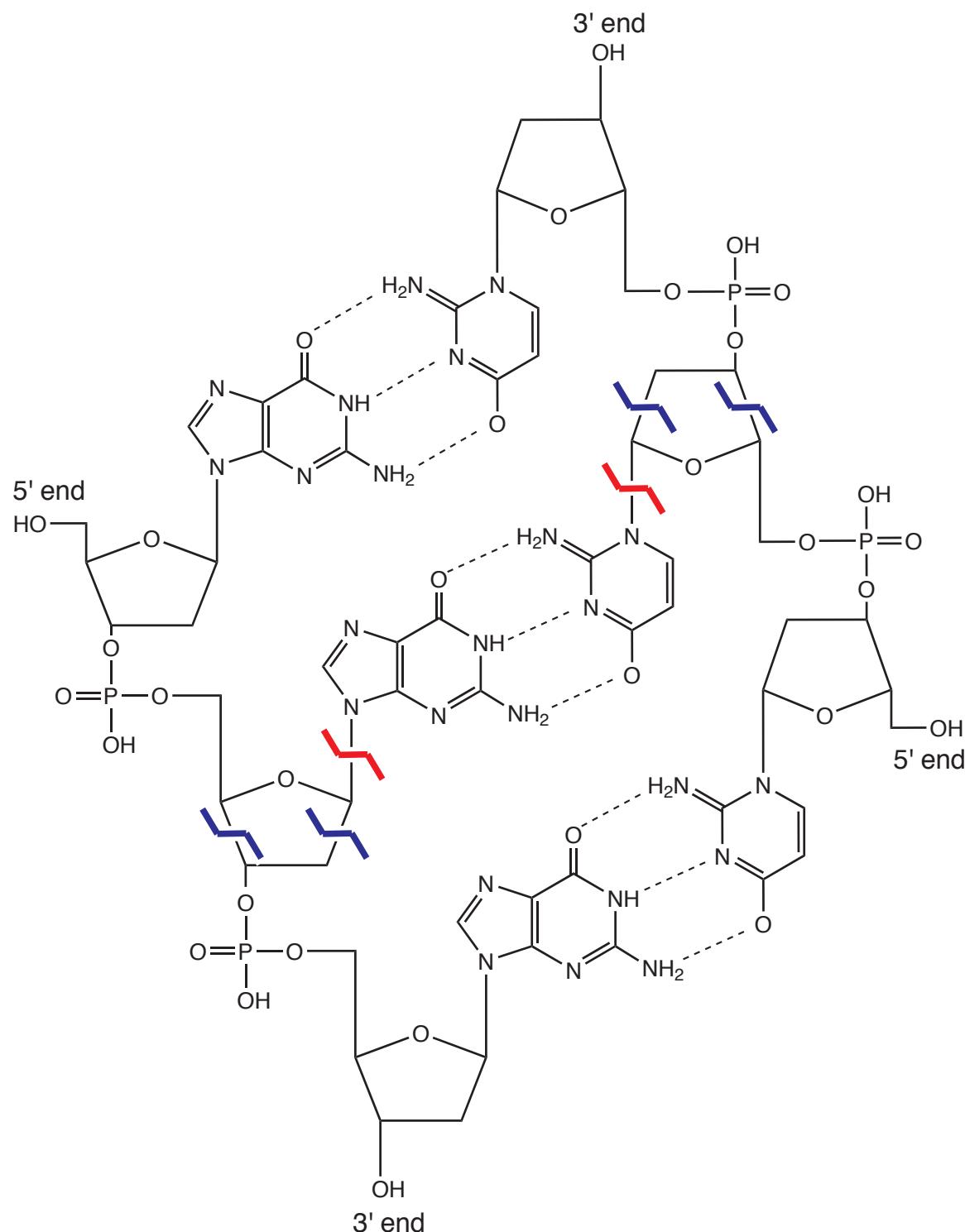


Figure S1. Schematic diagram of the double-stranded trimer, where the frontiers between the ONIOM layers are shown. When only atoms belonging to the base pairs are included in the high level layer, N–C bonds are broken (red lines), and replaced by N–H and C–H bonds as link atoms. An alternative high level layer, in which several atoms of sugar are included, are considered to locate the link atoms in the closest C–C bonds (blue lines). For the sake of clarity, the five-water-molecule hydration shell of the central GC base pair has been omitted, though it is systematically included in the high layer.

Cartesian coordinates (in angstroms) for high-layers optimized geometries

Canonical structure (GC)

N	-4.513880	0.013417	-0.467628
C	-4.837175	-1.309881	-0.712029
N	-3.806826	-2.091644	-0.679884
C	-2.739517	-1.257110	-0.413272
C	-1.355764	-1.532766	-0.293934
O	-0.788721	-2.623316	-0.360639
N	-0.608584	-0.380445	-0.071659
H	0.410777	-0.516241	0.018240
C	-1.118845	0.877104	0.068889
N	-0.248396	1.864436	0.317290
H	0.729498	1.650895	0.476283
H	-0.624999	2.714326	0.708630
N	-2.406361	1.140839	-0.044777
C	-3.156406	0.054321	-0.283621
N	4.441260	-0.026733	0.508640
C	4.916040	-1.296523	0.664980
H	5.976568	-1.391255	0.867745
C	4.108781	-2.366753	0.589685
H	4.489020	-3.369737	0.700228
C	2.723589	-2.115392	0.310634
N	1.874975	-3.114644	0.203770
H	2.087905	-4.069440	0.454244
H	0.887647	-2.913295	0.035007
N	2.264782	-0.871199	0.162440
C	3.068216	0.202009	0.284302
O	2.636201	1.355297	0.236238
O	0.642181	-5.509221	1.081144
H	0.053951	-5.718259	0.340918
H	0.090391	-5.045291	1.719976
O	-0.801072	-5.276468	-1.390411
H	-1.632946	-5.295744	-1.884488
H	-0.794490	-4.355600	-1.092197
O	-2.975421	-4.045471	-2.725520
H	-2.468633	-3.335134	-3.135212
H	-3.391415	-3.606678	-1.969290
O	-2.716170	3.707999	1.057812
H	-2.788496	2.841147	0.615066
H	-2.715685	4.359310	0.355007
O	1.831430	3.882360	-1.124068
H	2.189867	3.121263	-0.652094
H	1.006319	3.555688	-1.495630
H	-5.852727	-1.611888	-0.921011

Intermediate structure (GC1)

N	-4.487688	0.023442	-0.466469
C	-4.767835	-1.310031	-0.704824
H	-5.773311	-1.644527	-0.913190
N	-3.713573	-2.060819	-0.669710

C	-2.666970	-1.192706	-0.405188
C	-1.272809	-1.395638	-0.272939
O	-0.729046	-2.534716	-0.357013
N	-0.512799	-0.291955	-0.037690
H	1.189341	-0.544277	0.015176
C	-1.095515	0.917871	0.083491
N	-0.278157	1.979141	0.331974
H	0.658805	1.763627	0.625984
H	-0.715632	2.755178	0.803293
N	-2.393860	1.189441	-0.038751
C	-3.127389	0.102504	-0.280520
N	4.408921	-0.015553	0.492451
C	4.824115	-1.312846	0.627798
H	5.881225	-1.449224	0.824811
C	3.978214	-2.350567	0.540299
H	4.318634	-3.367870	0.640285
C	2.592537	-2.079469	0.274558
N	1.680719	-2.984471	0.188858
H	1.850328	-3.960087	0.423654
H	0.626066	-2.722943	-0.027417
N	2.233619	-0.774684	0.114195
C	3.068589	0.297920	0.253642
O	2.659332	1.440236	0.201922
O	0.703940	-5.447714	1.083570
H	0.150131	-5.014973	1.744086
H	0.106978	-5.635806	0.341434
O	-0.788552	-5.169398	-1.304595
H	-1.609155	-5.245021	-1.811762
H	-0.839101	-4.240394	-1.026874
O	-2.972404	-4.035404	-2.686234
H	-2.476129	-3.339593	-3.131527
H	-3.347792	-3.568785	-1.922831
O	1.710611	3.992979	-1.259263
H	2.025026	3.275606	-0.700908
H	0.885461	3.646080	-1.616769
O	-2.911265	3.704017	1.087790
H	-2.865389	2.831656	0.644134
H	-2.697883	4.342965	0.406223

Product of direct DPT mechanism (GC2)

N	-4.514555	0.003396	-0.466576
C	-4.813855	-1.334053	-0.652835
H	-5.821889	-1.660436	-0.861968
N	-3.774353	-2.101381	-0.570913
C	-2.720210	-1.237208	-0.327362
C	-1.342372	-1.430360	-0.163243
O	-0.851855	-2.630675	-0.181801
N	-0.561370	-0.361680	0.019474
H	1.233211	-0.570619	0.113631
C	-1.119490	0.868694	0.082573

N	-0.285466	1.914942	0.294645
H	0.660262	1.708172	0.573564
H	-0.703658	2.732318	0.709268
N	-2.413258	1.152682	-0.063900
C	-3.159919	0.072685	-0.265829
N	4.411219	0.016403	0.516355
C	4.847630	-1.287224	0.609146
H	5.909891	-1.408869	0.785983
C	4.022460	-2.336712	0.502607
H	4.395206	-3.346515	0.562981
C	2.610337	-2.107012	0.271872
N	1.691704	-2.979484	0.132791
H	2.005087	-3.945943	0.138267
H	0.173754	-2.694662	-0.044758
N	2.249840	-0.772359	0.216227
C	3.063037	0.305538	0.326444
O	2.630752	1.447658	0.287972
O	1.501228	-5.911132	-0.647821
H	1.627685	-6.789656	-0.289071
H	0.533004	-5.751841	-0.560416
O	-1.161340	-5.531295	-0.386095
H	-1.601696	-5.034575	-1.104365
H	-1.408129	-5.064931	0.418039
O	-2.571586	-4.087416	-2.334072
H	-2.110016	-3.360033	-2.771430
H	-3.160660	-3.627691	-1.716828
O	1.741474	3.914809	-1.238039
H	2.090715	3.207497	-0.685807
H	0.920374	3.546339	-1.580342
O	-2.908909	3.736050	0.960695
H	-2.870110	2.854239	0.541681
H	-2.665158	4.355997	0.271830

Product of water-assisted DPT mechanism (GC21)

N	-4.485775	0.079205	-0.499145
C	-4.813413	-1.231790	-0.769726
N	-3.786356	-2.021830	-0.771968
C	-2.705165	-1.200502	-0.494647
C	-1.322113	-1.408772	-0.410035
O	-0.732696	-2.560294	-0.572469
N	-0.528247	-0.376530	-0.137305
H	1.382106	-0.793154	-0.072090
C	-1.066053	0.845719	0.055118
N	-0.214215	1.849520	0.358019
H	0.741380	1.598770	0.560061
H	-0.600274	2.637117	0.851969
N	-2.361141	1.158677	-0.047390
C	-3.124229	0.110607	-0.319799
N	4.491232	-0.091657	0.489535
C	4.982856	-1.380648	0.619971

H	6.037611	-1.458058	0.854639
C	4.213962	-2.461565	0.481673
H	4.615769	-3.457407	0.574045
C	2.809420	-2.313576	0.153924
N	2.050230	-3.315251	-0.027407
H	1.023790	-4.969888	0.712350
H	1.107605	-3.018123	-0.268487
N	2.386741	-0.980423	0.065849
C	3.144052	0.135421	0.247393
O	2.658915	1.258188	0.221628
O	0.222957	-5.406776	1.032750
H	-1.104732	-5.242242	-0.177286
H	-0.076037	-4.847576	1.766439
O	-1.643976	-4.841053	-0.889478
H	-2.579281	-5.069147	-0.761872
H	-1.296302	-3.407781	-0.757070
O	-4.409704	-4.768142	-0.975838
H	-4.692432	-4.901895	-1.881354
H	-4.206972	-3.812727	-0.905552
O	-2.857393	3.653723	1.179881
H	-2.802316	2.808442	0.693635
H	-2.587384	4.324978	0.551610
O	1.842866	3.928861	-0.934530
H	2.201030	3.143867	-0.506116
H	1.015348	3.615720	-1.314156
H	-5.833241	-1.530287	-0.964536