Supplementary Material for PCCP

Adenine deactivation in DNA resolved at the CASPT2//CASSCF/AMBER level

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Supporting Information

S1. The QM/MM method

We have developed a new code based on an hybrid Quantum Mechanical/Molecular Mechanical potential (QM/MM)[1] to study the chemical and photo-chemical reactivity of large systems. The method (called COBRAMM) has been presented in detail elsewhere[2] and it is briefly described here.

Following our approach we divide the system into three layers (*high*, *medium* and *low*) as depicted in Figure S1 by adopting a hydrogen *atom-link* scheme[3] (i.e. free valences of the *high* (QM) layer are saturated with hydrogen atoms to give *model-H*, see Figure S1). Energies and forces of the *high* layer are computed at the QM level with an electrostatic embedding scheme to account for the electrostatic influence of the surrounding MM region on the QM (*high*) layer. That is, QM computation are performed on *model-H* surrounded by the atomic point charges of the MM layers (i.e. the *emb* charges). In our notation *pod* and *emb* are two subsets of atomic point charges of the MM region, see Figure S1. The *medium* and *low* layers are treated at the MM level and, analogously, the effect of charge changes occurring during the (photo)chemical process in the *high* (QM) layer is accounted for by using in the MM calculations the QM atomic point charges coming from QM computations. The energy values for the QM and MM region are added together to compute the correct QM/MM energy, and a subtractive scheme similar to ONIOM[4] is used for this purpose:

$$E^{tot} = E_{QM}^{model-H} + E_{MM}^{real} + E_{QM}^{el._{model-H/emb}} - E_{MM}^{el._{model/pod}} - E_{MM}^{model-H}$$

The cartesian forces of the two regions are merged, then the total QM/MM energy and forces are transferred to an accurate optimization algorithm. In our code the *high-medium* layers are simultaneously optimized using the BFGS algorithm,[4] while the *low* region may be kept frozen or be fully optimized at each optimization step with a fast and rough algorithm, e.g. steepest descent (this feature nearly resembles the so called "micro-iteration" technique of ONIOM)[4]. The capability of handling coupled together the *high-medium* region allows the explicit treatment of large molecular motions around the reactive region without increasing the computational cost, because energy and forces of non-reacting (MM) atoms included in the *medium* region are computed at the MM level. The hydrogen atom-link approach is adopted to handle the boundary region between the QM and MM sub-systems.

In summary, all the energy components of the *high* layer (QM region) are obtained from QM calculations, including the electrostatic term (that is accounted for by an Electrostatic Embedding scheme). The bonded (stretching, bending, torsions) and non-bonded (electrostatic and van der Waals) interactions within the *medium* and *low* layers (MM region) are handled at the MM level. The bonding and van der Waals cross terms are treated at the MM level, while the electrostatic interaction term between the QM and the MM region is computed classically for MM atoms.

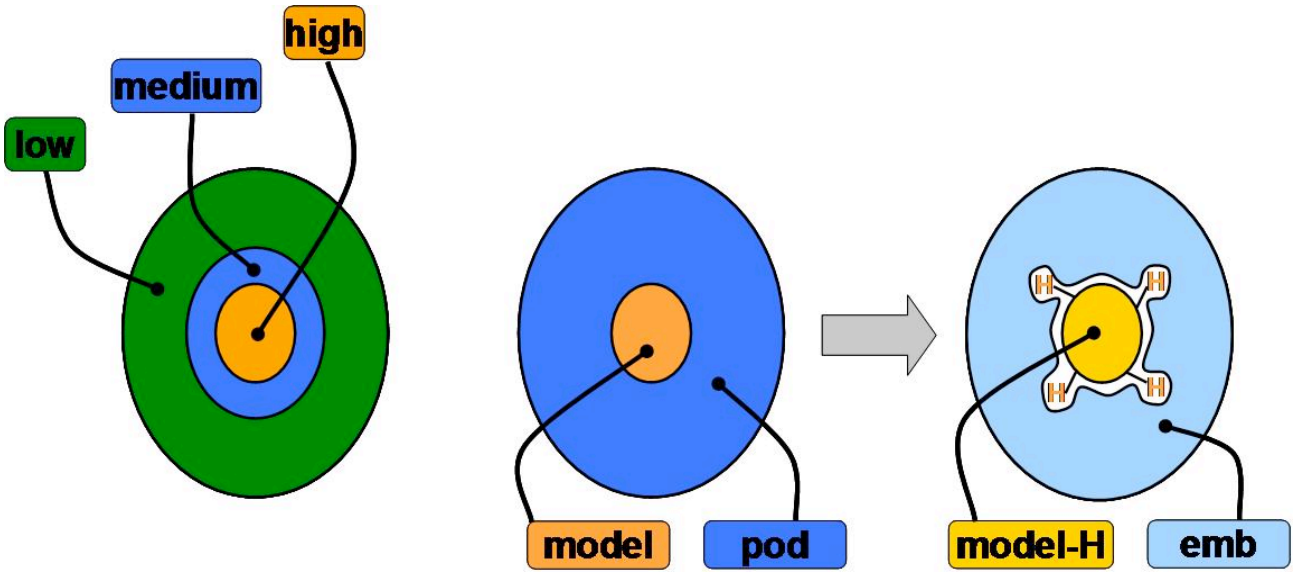

Figure S1. Partitioning scheme of the whole system.

S2. DNA QM/MM set-up

Ground state molecular dynamics. To generate a good starting point for QM/MM optimizations we performed a classical molecular dynamics simulation, of the double strand $d(A)_{10}\cdot d(T)_{10}$ DNA fragment (Figure S2.a), including explicit solvent (water) and counterions (sodium), with the periodic boundary conditions. The starting crystallographic B'-DNA structure[5] (code 1PLY) is available in the protein data bank archive.

Dynamics calculations were carried out in a solvent box of explicit TIP3P water molecules with the right number of Na+ ions, using AMBER-8[6] program and Parm99[7] parameter set. Molecular dynamics simulations were performed at constant temperature (300 K) and pressure (1 atm) using the Berendsen algorithm[8]. An integration time step of 2 fs was used, and all bond lengths involving hydrogens were constrained using SHAKE[9]. Long-range electrostatic interactions were treated using the particle mesh Ewald (PME) approach[10], with a 11 Å direct space cut-off. Initially, the water molecules and ions were relaxed by energy minimization. The entire system was then heated from 0 to 300 K for 1 ns at constant volume; the simulation continued at constant pressure, and an unrestrained simulation followed for over 4 ns. Coordinates were saved every 200 fs. The choice of the best starting structure amongst the achieved snapshots has been made through a cluster analysis. The chosen structure was further refined via MM (*ff03*)[11] optimizations.

QM/MM calculations. A three layers approach was used for QM/MM computations: the fourth adenine (starting from the 5-position of dA_{10} chain) in the first system (Figure S2.b) and both the fourth and the fifth adjacent adenines pair (called Ade(1) and Ade(2)) in the second system was assigned the *high* QM layer. The sugar-phosphate backbone, the two adenines confining to the *high* part, and the thymine bases paired with all of them and finally the water molecules connected with the *high* part through hydrogen bonds were assigned to the *medium* layer (free to move), as shown in Figure S2.c. The rest of the bases, water molecules and counter-ions belong to the *low* (kept frozen) part (Figure S2.d). For both *medium* and *low* layers the AMBER MM level (*ff03*)[11] was applied. The CASSCF(6-31G*) QM level, used for

QM/MM geometry optimizations, has been refined to account for correlation effects using single point CASPT2 (MSPT2)[12] computations. Both the Gaussian-03[13] and AMBER-8[6] packages were employed during QM/MM computations with the COBRAMM[14] interface. MOLCAS-6[15] was finally used for CASPT2 (MSPT2)[12] computations.

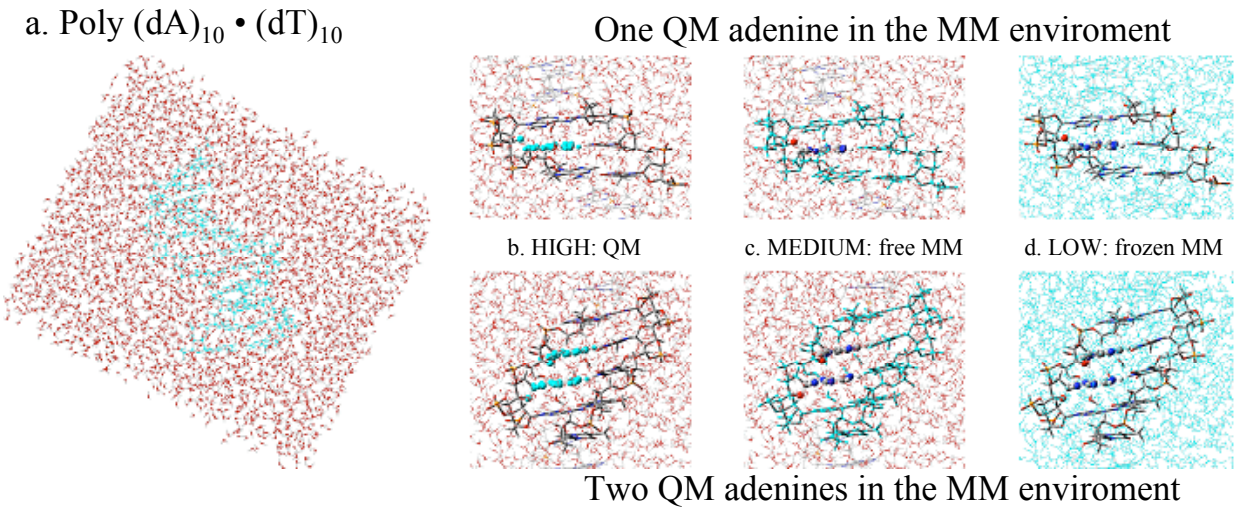

Figure S2. a) $d(A)_{10}$· $d(T)_{10}$ B-DNA fragment (teal blue part) inside the water box, including 18 Na^+ counterions. b) teal blue atoms represent the 'high' part of the three layers approach adopted in the QM/MM calculations; in the upper side the system is constituted by just a single 'high' adenine (the fourth in the chain), in the lower side by two (the fourth and the fifth);' high' part calculation are made at the CASSCF/6-31g* level. c) Teal blue atoms are the 'medium' layer: it includes the sugar-phosphate backbone, the two adenines confining to the high part, and the thymine bases paired with all of them and finally the water molecules connected with the high part through hydrogen bonds. d) The rest of the bases, water molecules and counter-ions belong to the' low part' (teal blue colour) and are kept frozen throughout the optimizations. For both' medium' and 'low' layers the MM level was always applied.

We have assumed that the deactivation path on the L_a state remains essentially the same in DNA as in the gas phase:[16, 17] thus the gas phase reaction path was taken as the basis for determining the optimized scan for the deactivation of the L_a excited molecule in DNA. Specifically, this path is computed by optimizing on the L_a state the adenine molecular geometry at fixed values of the $C_6N_1C_2N_3$ dihedral that, jointly to the $N_1C_2N_3C_4$ twisting, originate the ring puckering on the C_2 atom. This approach has been coherently applied both *in vacuo* and DNA (monomer approach), thus allowing a direct and homogeneous comparison between the paths computed in the two environments. Very notably, the L_a deactivation path (relaxed scan) computed here for the isolated adenine (see below), matches the fully unconstrained minimum energy path (MEP) previously computed in gas phase,[16] showing that the employed procedure is accurate enough.

Single base calculations have been made usually by CASSCF(8,7)/6-31g* (one n, 3 π and 3 π* orbitals), except for the S_0 and L_b minima where a fourth π* orbital was added and an (8,8) active space was used. On top of each CASSCF optimized geometry, energies were re-evaluated at the CASPT2 (MSPT2) level by averaging over the lowest 6 states (SA-6) and employing a CASSCF(12,10)/ANO-l(C,N,O[4s3p2d]/H[3s2p]) zero*th* order wavefunction, where 2 n, 4 π and 4 π* orbitals were included. QM/MM geometry optimizations of a single adenine within the double chain were made exactly as for the isolated molecule, that is with the same active space and orbital basis set.

QM/MM geometry optimizations of the adenines pair within the DNA double chain were made at the CASSCF(8,8)/6-31g* level (4 π and 4 π* orbitals). A state-averaging over the lowest 8 roots at the CASPT2/CASSCF(12,10)/6-31g* level, where one n, 5 π and 4 π* orbitals are included in the active space, was used to calculate correlation effects (when we attempted to include two n orbitals (one for each base) in

the active space, we found that the CASSCF calculation always excludes the n orbital of base (1), and substitutes it with one π orbital). Note that the electrostatic effect of DNA is accounted for already at the CASPT2(MSPT2) QM level by modeling the environment with AMBER point charges.[18]

S3. Cartesian coordinates (x, y and z in Å) of all the structures discussed in the paper

Single QM adenine *in vacuo*

Min S_0

N	1.928586	0.524519	0.004800
C	1.281268	1.698623	0.006474
N	-0.025408	1.904985	0.000317
C	-0.709060	0.765811	-0.003636
C	-0.174444	-0.507654	-0.008182
C	1.225903	-0.596842	-0.009170
N	-1.180410	-1.462801	0.001540
C	-2.261482	-0.776708	0.004094
N	-2.069743	0.573958	0.002168
H	-2.767815	1.281199	0.002823
H	-3.248216	-1.194417	0.009055
H	1.904073	2.572799	0.014415
N	1.880713	-1.796129	-0.066871
H	1.366795	-2.596253	0.228909
H	2.835877	-1.774440	0.213644

24°

C	1.171306	0.062226	-0.682415
N	0.062771	-0.067362	0.085317
C	0.283688	0.102784	1.471432
N	1.488656	-0.078170	2.133935
C	2.494842	-0.030002	1.356191
C	2.465420	0.131567	-0.074020
N	3.715829	0.173187	-0.585898
C	4.517389	0.044394	0.458243
N	3.832185	-0.102961	1.644747
H	4.220644	-0.172497	2.556884
H	5.584632	0.042875	0.414165
H	-0.589227	0.086979	2.076055
N	1.005214	0.061426	-2.014547
H	1.777238	0.227909	-2.626619
H	0.071955	0.104667	-2.372894

32°

C	1.165498	0.050395	-0.679365
N	0.064706	-0.113934	0.087305
C	0.288192	0.131149	1.459384
N	1.486236	-0.100765	2.135006
C	2.492782	-0.038766	1.359631
C	2.458952	0.161868	-0.066796
N	3.709564	0.212433	-0.580553
C	4.511986	0.053869	0.455825

N	3.830348	-0.131072	1.640589
H	4.221467	-0.215105	2.550430
H	5.579543	0.054414	0.410046
H	0.586563	0.141030	2.063239
N	1.005863	0.035344	-2.009560
H	1.777641	0.197400	-2.623709
H	0.073420	0.027390	-2.373971

40°

N	1.912846	0.567753	0.272953
C	1.286856	1.754828	0.046372
N	-0.080485	1.906212	0.431627
C	-0.674917	0.843120	0.047320
C	-0.070821	-0.423127	-0.325779
C	1.295953	-0.560522	0.081922
N	-1.038058	-1.413931	-0.325611
C	-2.141394	-0.809401	-0.112961
N	-2.016644	0.553658	0.071392
H	-2.715415	1.167311	0.426728
H	-3.103781	-1.280562	-0.082252
H	1.566427	2.249768	-0.875950
N	1.844519	-1.771057	0.363920
H	1.373383	-2.569953	0.001962
H	2.835640	-1.830895	0.424325

48°

N	1.858113	0.588827	0.366488
C	1.260852	1.765425	0.040540
N	-0.108988	1.935397	0.397485
C	-0.691105	0.859714	0.039423
C	-0.071002	-0.405371	-0.343389
C	1.268980	-0.548814	0.094042
N	-1.041769	-1.407313	-0.334162
C	-2.141201	-0.809645	-0.108075
N	-2.028943	0.557640	0.071757
H	-2.726585	1.159895	0.448420
H	-3.099899	-1.287563	-0.055537
H	1.534666	2.180557	-0.922905
N	1.838862	-1.759565	0.369122
H	1.370533	-2.547297	-0.021649
H	2.832577	-1.804280	0.336208

54°

N	1.890136	0.613992	0.390762
C	1.228555	1.729444	-0.015217
N	-0.105634	1.945742	0.412546
C	-0.709490	0.876958	0.071601
C	-0.069910	-0.384638	-0.297459
C	1.286372	-0.513690	0.157676
N	-1.026760	-1.388106	-0.334160
C	-2.156123	-0.796407	-0.125405

N	-2.038698	0.576660	0.085529
H	-2.752211	1.189370	0.407768
H	-3.112265	-1.278008	-0.116417
H	1.454180	2.066767	-1.021400
N	1.833614	-1.729034	0.452893
H	1.388076	-2.519566	0.042613
H	2.827105	-1.773390	0.492216

62°

N	0.054612	0.255774	0.147945
C	0.293669	-0.016558	1.437976
N	1.396369	0.600340	2.081937
C	2.370433	0.122796	1.397868
C	2.251769	-0.463547	0.069035
C	1.044830	-0.115667	-0.623109
N	3.529478	-0.594037	-0.481546
C	4.330629	-0.224349	0.436343
N	3.733003	0.199127	1.599615
H	4.180929	0.600043	2.390340
H	5.399833	-0.227676	0.347666
H	0.079196	-1.032086	1.767735
N	0.957808	-0.141398	-1.985618
H	1.827650	-0.105145	-2.471413
H	0.225961	0.403516	-2.386069

Single QM adenine in DNA

Min S_0

O	25.995241	20.916736	20.858602
C	26.198602	21.703523	22.006891
H	25.954319	22.740018	21.830127
N	25.361682	21.216569	23.048612
C	25.436655	19.972427	23.641839
H	26.085613	19.213284	23.258405
N	24.676897	19.851065	24.676320
C	24.033635	21.077792	24.793942
C	23.099438	21.589322	25.719115
N	22.634155	20.906881	26.763523
H	21.881418	21.301832	27.288512
H	22.802104	19.918519	26.850351
N	22.685981	22.848441	25.525761
C	23.146023	23.549798	24.493014
H	22.757483	24.547167	24.402469
N	24.009577	23.163589	23.571152
C	24.441310	21.920306	23.780486
H	26.930884	20.907299	20.299511
H	27.256865	21.610154	22.250737

24° (L_a Min at CAS level)

O	25.979960	20.896413	20.880753

C	26.171504	21.723164	22.000549
H	25.916518	22.752133	21.795172
N	25.335480	21.262902	23.055886
C	25.447762	20.021457	23.716428
H	26.094335	19.251198	23.353834
N	24.696094	19.950465	24.774818
C	24.036582	21.136330	24.855932
C	23.005193	21.660204	25.764131
N	22.512314	20.905791	26.740980
H	21.764017	21.276183	27.288240
H	22.713795	19.924266	26.808508
N	22.638720	22.879195	25.552810
C	23.248563	23.645507	24.568904
H	22.984102	24.679817	24.576590
N	23.916606	23.183261	23.414381
C	24.413308	21.985574	23.729875
H	26.911766	20.902607	20.315244
H	27.228841	21.640937	22.252298

32°

O	26.013045	20.891850	20.831677
C	26.198164	21.711520	21.960301
H	25.964672	22.743862	21.747580
N	25.335706	21.269447	22.995040
C	25.417951	20.049876	23.665711
H	26.037013	19.257146	23.299578
N	24.704736	20.004492	24.748239
C	24.131201	21.244385	24.871126
C	22.986266	21.677594	25.628639
N	22.424769	20.913073	26.513640
H	21.631670	21.276717	27.023707
H	22.725424	19.953804	26.678723
N	22.499864	22.912305	25.444532
C	23.235291	23.699734	24.617027
H	22.945549	24.725864	24.550140
N	24.016224	23.219502	23.472359
C	24.484198	22.066362	23.728749
H	26.952910	20.893896	20.279634
H	27.251188	21.618763	22.226077

40°

O	25.975418	20.872136	20.822919
C	26.120169	21.719055	21.935305
H	25.852949	22.739520	21.706261
N	25.258328	21.259222	22.969652
C	25.382897	20.046620	23.647575
H	26.009276	19.263105	23.274626
N	24.694322	20.003620	24.747848
C	24.086158	21.226922	24.847827
C	23.016810	21.713205	25.672022
N	22.478862	20.936666	26.601474

H	21.708211	21.307600	27.145832
H	22.765347	19.965458	26.738985
N	22.517597	22.927931	25.475660
C	23.316664	23.722963	24.636478
H	22.998944	24.740323	24.558577
N	23.964685	23.211501	23.477086
C	24.419696	22.041714	23.713095
H	26.921269	20.891012	20.281523
H	27.171646	21.663450	22.217091

48°

O	26.008755	20.881041	20.862179
C	26.199264	21.714773	21.979305
H	25.966490	22.744611	21.753041
N	25.342633	21.293344	23.028512
C	25.448546	20.099780	23.750307
H	26.069687	19.298359	23.404590
N	24.752724	20.089572	24.842719
C	24.163690	21.329537	24.927730
C	22.935441	21.713372	25.616538
N	22.355327	20.908585	26.452641
H	21.524572	21.227745	26.924269
H	22.687752	19.964809	26.626168
N	22.453096	22.933059	25.400259
C	23.319883	23.690668	24.684250
H	23.248109	24.754376	24.780033
N	23.983927	23.236394	23.455126
C	24.492243	22.106078	23.739670
H	26.942293	20.890216	20.299576
H	27.253971	21.623872	22.238977

55°

O	26.010105	20.879329	20.865353
C	26.199327	21.715268	21.980911
H	25.965543	22.744445	21.752161
N	25.342819	21.295694	23.031089
C	25.458635	20.109823	23.765707
H	26.083684	19.309120	23.424019
N	24.767072	20.103322	24.859183
C	24.161745	21.340319	24.933410
C	22.908564	21.704657	25.603488
N	22.325224	20.887518	26.427212
H	21.486351	21.194607	26.889024
H	22.664772	19.948574	26.604506
N	22.428942	22.918164	25.374340
C	23.353516	23.657723	24.711758
H	23.385668	24.713579	24.890876
N	23.964611	23.233435	23.449739
C	24.485349	22.106371	23.733813
H	26.943236	20.889764	20.302096
H	27.254209	21.626065	22.240462

62°

O	26.008673	20.875027	20.885134
C	26.203829	21.715269	21.996661
H	25.970733	22.743752	21.763221
N	25.351386	21.305197	23.054363
C	25.486404	20.138918	23.820381
H	26.121187	19.338760	23.494506
N	24.798224	20.146457	24.914119
C	24.160334	21.371847	24.953562
C	22.882948	21.710313	25.602517
N	22.303504	20.877663	26.417286
H	21.448907	21.160972	26.861510
H	22.658223	19.945492	26.590667
N	22.397404	22.909999	25.346571
C	23.375234	23.626833	24.729846
H	23.508951	24.658639	24.987031
N	23.936566	23.233123	23.443094
C	24.476827	22.114948	23.735417
H	26.937476	20.887639	20.314812
H	27.260230	21.625842	22.249880

70°

O	26.006006	20.868298	20.906236
C	26.203581	21.715053	22.012610
H	25.968517	22.741698	21.771942
N	25.356917	21.315006	23.078556
C	25.522440	20.181931	23.890269
H	26.173726	19.384451	23.588938
N	24.839935	20.209430	24.985060
C	24.153111	21.412385	24.973859
C	22.852017	21.716340	25.603469
N	22.284040	20.871634	26.419667
H	21.418586	21.134830	26.851276
H	22.654076	19.946378	26.591996
N	22.353454	22.895142	25.309286
C	23.389460	23.585072	24.743978
H	23.633012	24.569478	25.085223
N	23.897734	23.230671	23.431359
C	24.459520	22.122643	23.730794
H	26.930041	20.887329	20.328397
H	27.261773	21.629464	22.259601

75°

O	25.999391	20.861056	20.947295
C	26.205715	21.722593	22.041757
H	25.976155	22.746716	21.784061
N	25.363207	21.349915	23.121319
C	25.559688	20.265726	23.997486
H	26.223614	19.465023	23.732498
N	24.884538	20.333899	25.092983

C	24.158118	21.509962	25.015764
C	22.832725	21.773858	25.618959
N	22.282980	20.913243	26.435645
H	21.399851	21.142963	26.847365
H	22.671799	19.995816	26.599554
N	22.307797	22.924514	25.281107
C	23.374942	23.605509	24.744866
H	23.646056	24.574091	25.103459
N	23.853205	23.255548	23.419619
C	24.452163	22.170723	23.741116
H	26.914828	20.883794	20.356059
H	27.265882	21.633809	22.278955

QM adenines pair in DNA

Min S_0

O	0.496396	-7.748810	-7.449306	-0.574990
C	0.911119	-6.545339	-6.871652	0.370334
H	0.950789	-5.732542	-7.581845	0.219822
N	-0.014145	-6.155941	-5.854482	-0.574525
C	-0.351878	-6.811857	-4.708895	0.535299
H	0.088421	-7.753134	-4.449473	0.338635
N	-1.218276	-6.181719	-3.996315	-0.606351
C	-1.483307	-5.018575	-4.707337	0.238225
C	-2.274888	-3.881486	-4.446142	0.865773
N	-3.035064	-3.724674	-3.368966	-0.800592
H	-3.623794	-2.917444	-3.318565	0.471418
H	-3.187547	-4.457967	-2.699949	0.507273
N	-2.222612	-2.876873	-5.333703	-0.676965
C	-1.476230	-3.008404	-6.426428	0.442537
H	-1.484769	-2.168776	-7.095748	0.245668
N	-0.730475	-4.033554	-6.785306	-0.646986
C	-0.746811	-5.004843	-5.860914	0.876136
O	3.020615	-2.146126	-7.605098	-0.618053
C	3.270793	-1.345325	-6.476390	0.374728
H	3.038834	-0.306783	-6.656257	0.226057
N	2.466235	-1.800232	-5.393501	-0.579489
C	2.571398	-3.003925	-4.754870	0.447253
H	3.237848	-3.761622	-5.112295	0.305620
N	1.818383	-3.113885	-3.728248	-0.547828
C	1.134440	-1.910188	-3.661821	0.188958
C	0.162719	-1.390279	-2.760940	0.835125
N	-0.293231	-2.061322	-1.715130	-0.819163
H	-1.065704	-1.671258	-1.213876	0.435589
H	-0.152951	-3.056918	-1.643621	0.497696
N	-0.266180	-0.156311	-2.991886	-0.697612
C	0.185693	0.527391	-4.047904	0.381243
H	-0.231275	1.509982	-4.170299	0.183587
N	1.055663	0.143416	-4.947147	-0.673757
C	1.519582	-1.093950	-4.689624	0.834405
H	1.354808	-8.064506	-8.042234	0.433829

H	1.918827	-6.756343	-6.513740	0.205351
H	3.932354	-2.151998	-8.202423	0.413472
H	4.334574	-1.457422	-6.266860	0.177820

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Supplementary Material for PCCP