A quantum theoretical study of cleavage of the glycosidic bond of 2′-deoxyadenosine: Base excision-repair mechanism of DNA by MutY

Saumya Tiwari[a], Neha Agnihotri and P.C. Mishra*
Department of Physics
Banaras Hindu University
Varanasi – 221005 (India)

NATURE OF THE POTENTIAL ENERGY SURFACE BETWEEN IC1 AND PC

In order to obtain further information about the nature of the potential energy surface between IC1 and PC, the following additional calculations were performed. Six nearly equally spaced points from the point of view of the distances C1′N9, C1′O20, O20H20 and H20O13 between IC1 and PC that would be involved in the reaction under consideration were 'manually' obtained by interpolation (Figs. 2,3). Values of the dihedral angle C4′O4′C1′H1′ were adjusted for each of these distances in order to obviate hindrance to attack of the OH component of the water molecule at C1′. The points thus obtained are denoted by a_1, b_1, c_1, d_1, e_1 and f_1 in Table S1. Single point total energies obtained at the B3LYP/6-31G(d,p) level of theory in gas phase for the points a_1, b_1, c_1, d_1, e_1 and f_1 are plotted in Fig. S1 where these points are connected by the (blue) curve (i). In order to relax the possible undue constraints at the interpolated points to a limited extent, total energy minimization was carried out for 10 cycles at the B3LYP/6-31G(d,p) level of theory in gas phase starting from each of the points a_1, b_1, c_1, d_1, e_1 and f_1, and the energies thus obtained correspond to the points a_2, b_2, c_2, d_2, e_2 and f_2 which are connected by the (red) curve (ii) in Fig. S1. Vibrational frequency calculations at each of the points a_2, b_2, c_2, d_2, e_2 and f_2 yielded more than one imaginary frequencies. The atomic displacements corresponding to one of the imaginary frequencies at each of the points a_2, b_2 and c_2 clearly showed dissociation of the glycosidic bond C1′N9 while in the other three cases (d_2, e_2 and f_2), movements involving bonds of the water molecule and the glutamic acid moiety were prominent. At all the points a_2, b_2, c_2, d_2, e_2 and f_2, the water molecule placed near the C1′ site was formed.

Starting from each of the points a_2, b_2, c_2, d_2 and e_2, dissociating the water molecule into OH and H and placing the oxygen atom of the OH group near C1′ in order to facilitate attack of the OH moiety at this atom (following McCann, J. A. B.; Berti, P. J. *J. Am. Chem. Soc.* **2007**, *129*, 7055), calculations were performed to search the possible transition state. None of these calculations yielded a transition state. The (green colored) points a_3, b_3, c_3, d_3 and e_3 obtained after 20 cycles of optimization for transition state are plotted in the upper part of Fig. S1 while the points a_4, b_4, c_4, d_4 and e_4 obtained after 30 cycles of optimization for transition state are plotted in the lower part of Fig. S1. Curves (iii) and (iv) (green) pass near by the above mentioned two sets of points (a_3, b_3, c_3, d_3, e_3 and a_4, b_4, c_4, d_4, e_4 respectively). An examination of the different interatomic distances given in Table S1 (Fig. S1) shows that as we go from the initial to the fourth set of points (blue curve (i) to green curve (iv)), on the whole, the interatomic distances usually (though not always, as expected from the search procedure), change in the direction from IC1 to PC.

Variation of total energy (graph (i)) and RMS gradient (graph (ii)) on the potential energy surface with respect to optimization cycles during the transition state search started near the point a_2 mentioned above, obtained at the B3LYP/6-31G(d,p) level of theory in gas phase are shown in Fig. S2. It may be remarked that these graphs do not represent physically observable entities. These graphs merely show the nature of a particular track on the potential energy surface obtained by the numerical search procedure for the possible transition state. An examination of the graphs suggests that there may be shallow wiggles between IC1 and PC on the potential energy surface, but no convincing indication supporting the occurrence of a barrier seems to exist (Fig. S2). Thus the potential energy surface in the region of the transition state between IC1 and PC appears to be flat, and the barrier energy appears to be vanishingly small. Thus the reaction step between IC1 and PC appears to be barrierless or nearly barrierless.

Table S1: Values of different distances (Å) obtained by initial interpolation and subsequent optimization at the B3LYP/6-31G(d,p) level of theory in gas phase. For atomic numbering and structures of IC1 and PC, see Figs. 2 and 3. The dihedral angle C4′O4′C1′H1′ corresponding to the first row in each column i.e. corresponding to the points a_1, b_1, c_1 and d_1 was adjusted.

Points	R_1=C1′-N9	R_2= C1′-O20	R_3=O20-H20	R_4=H20-O13
IC1	1.47	4.57	0.99	1.78
a_i, $i=1$-4	1.74[a]	4.12	1.09	1.67
	1.83[b]	3.03	0.95	1.70
	2.32[c]	2.02	1.94	1.00
	2.40[d]	2.07	1.79	1.01
b_i, $i=1$-4	2.01	3.67	1.19	1.55
	2.05	2.84	1.01	1.65
	2.49	1.89	1.19	1.23
	2.79	1.69	1.27	1.18
c_i, $i=1$-4	2.27	3.22	1.29	1.44
	2.35	2.81	0.97	1.80
	3.48	1.47	2.62	0.97
	3.51	1.43	2.55	0.97
d_i, $i=1$-4	2.55	2.77	1.39	1.33
	2.51	2.50	0.98	1.77
	3.17	1.52	2.17	0.98
	3.25	1.47	2.14	0.98
e_i, $i=1$-4	2.82	2.32	1.49	1.22
	3.09	1.67	1.11	1.38
	3.31	1.47	1.63	1.00
	3.41	1.46	1.67	1.00
f_i, $i=1,2$	3.08	1.87	1.58	1.10
	3.30	1.45	1.63	0.99
PC	3.35	1.43	1.68	0.99

[a]Distances given in the first row in each column (corresponding to the points a_1, b_1, c_1, d_1) were obtained by interpolation between IC1 and PC.

[b]Distances given in the second row in each column were obtained after 10 cycles of optimization for minimum energy.

[c]Distances given in the third row in each column were obtained after 20 cycles of optimization for transition state.

[d] Distances given in the fourth row in each column were obtained after 30 cycles of optimization for transition state.
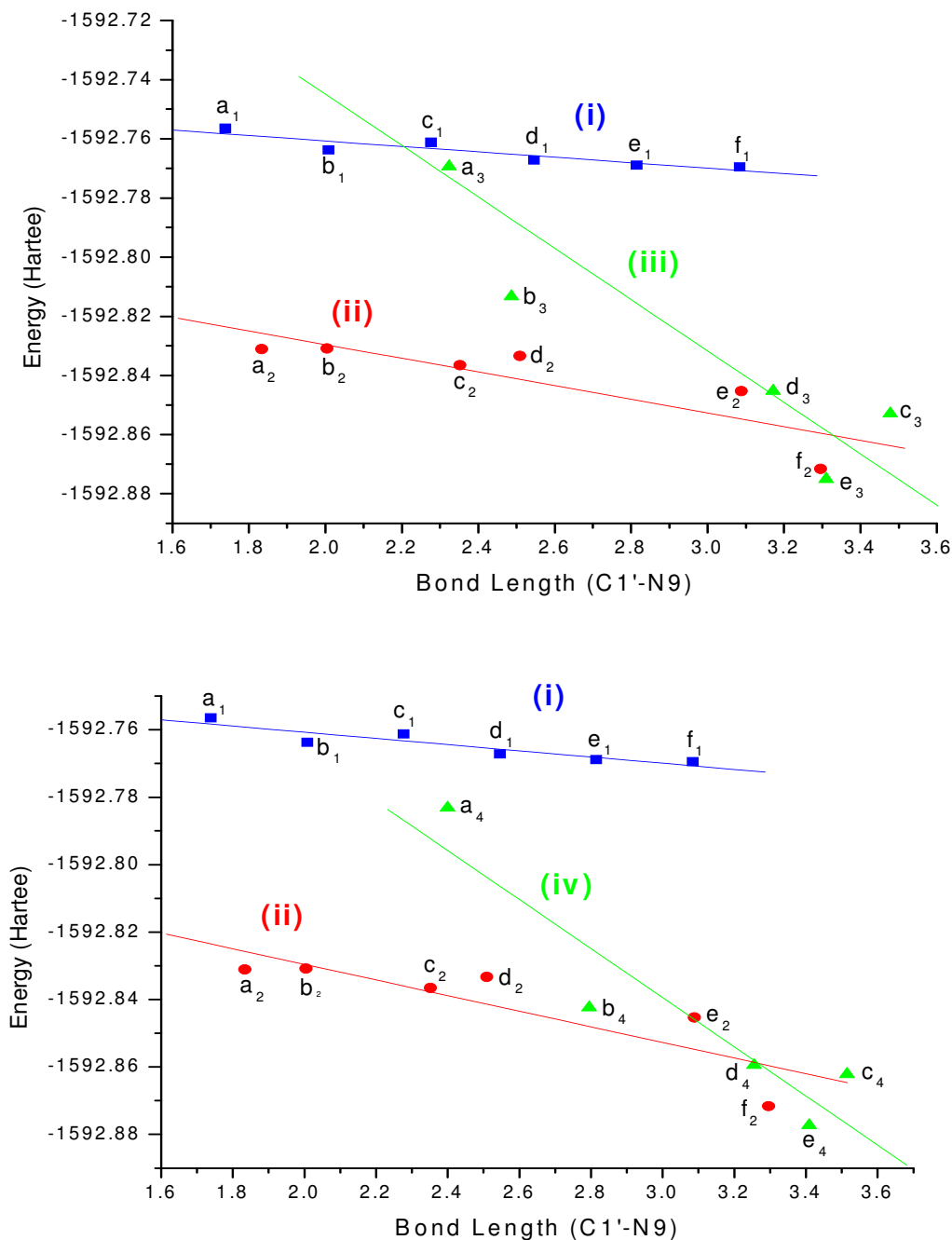
Fig S1: Variation of total energy with respect to glycosidic bond length (C1′-N9) obtained at B3LYP/6-31G(d,p) level of theory in gas phase. Plot (i) shows variation of energy in going from the points a_1 to f_1 through b_1, c_1, d_1 and e_1 where the different bond lengths were obtained by interpolation between IC1 and PC. Plot (ii) shows variation of energy in going from the points a_2 to f_2 through b_2, c_2, d_2 and e_2 where the different bond lengths were obtained by energy minimization for 10 cycles. Plots (i) and (ii) are the same in both the above figures. Plot (iii) shows variation of energy in going from the points a_3 to e_3 through b_3, c_3 and d_3 where the different bond lengths were obtained by optimization for transition state by 20 cycles. Plot (iv) is like plot (iii), but after 30 cycles of optimization for transition state
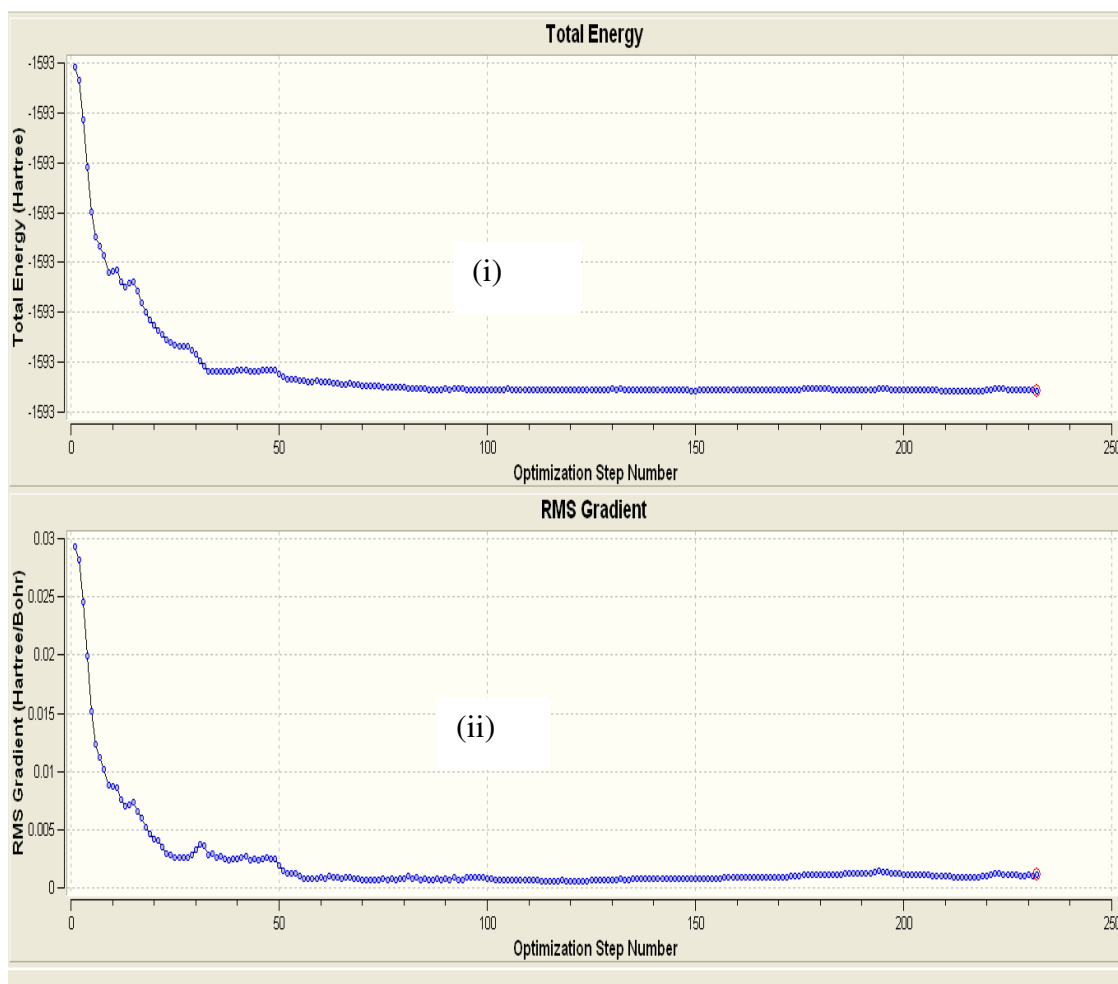
Fig S2: Variation of (i) total energy and (ii) RMS gradient with respect to optimization cycles during the transition state search (see text) obtained at the B3LYP/6-31G(d,p) level of theory in gas phase.