Supporting Information

Detecting DNA mismatches with metalloinsertors. A molecular simulation study.

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Table S1. List of the systems studied with the number of atoms and the length of the simulation performed.

System	Atoms	Time (ns)
2/DNA_AC	24000	35
3/DNA_AC	23800	30
1/DNA_AC	21600	70
1/DNA_AA	22600	48
1/DNA_AC'	18800	30
1/DNA_CC	18800	70
DNA	17300	16
DNA_AA	16900	16
DNA_AC	15300	16
DNA_CC	17100	16
1/DNA	17300	30
2/DNA	20400	30
3/DNA	20500	45

(a)

QM/MM MD			
System	QM atoms	MM atoms	Time (ps)
1/DNA_AC	73	21600	3
2/DNA_AC	73	24000	3
3/DNA_AC	81	23800	3
1/DNA	73	17300	3
2/DNA	73	20400	3
3/DNA	81	20500	3

(b)

Table S2. Intra-base pair (bp) DNA structural parameters (buckle (deg), propeller (deg), opening (Å)) relative to insertion for the bp levels formed by C9-A16 (MM) and C10-G15 (Flk2$_{ins}$). Standard deviations are reported in parenthesis.

	MM			**Flk2 $_{ins}$**		
System	**Buckle**	**Propeller**	**Opening**	**Buckle**	**Propeller**	**Opening**
2/DNA_AC	-52.90 (10.70)	32.70 (38.70)	-103.20 (21.50)	-6.90 (7.70)	-4.00 (8.5)	0.00 (3.2)
3/DNA_AC	-78.50 (23.10)	88.30 (25.20)	-38.30 (31.60)	-1.30 (8.90)	-15.50 (8.30)	3.50 (4.80)
1/DNA_ACI	-32.70 (27.90)	-76.40 (81.30)	-127.50 (52.90)	1.00 (9.70)	-9.40 (7.80)	0.30 (3.40)
1/DNA_ACII	-32.80 (28.20)	-104.50 (66.50)	-119.60 (50.40)	1.50 (9.40)	-6.90 (8.00)	1.30 (3.50)
1/DNA_AA	-86.30 (22.10)	34.60 (29.20)	-24.20 (25.00)	-1.30 (8.80)	1.50 (7.20)	0.60 (2.90)
1/DNA_AC'	-47 .00(45)	139.00 (40)	11.20 (64.90)	4.40 (8.60)	-13.60 (7.90)	1.00 (3.60)
1/DNA_CC	-31.20 (30.50)	128.00 (35.40)	82.70 (59.60)	8.10 (7.80)	-15.70 (6.90)	8.10 (7.80)
DNA	-0.30 (13.10)	-10.50 (9.30)	1.60 (3.30)	-4.70 (11.50)	-6.40 (9.40)	0.80 (3.20)
DNA_AA	-2.30 (13.70)	-22.80 (13.80)	25.20 (28.00)	-2.60 (14.00)	-17.20 (11.00)	2.10 (6.50)
DNA_AC	4.50 (12)	-18 .00(10)	-4.00 (12)	-3.20 (12.00)	-14.50 (9.60)	1.30 (3.90)
DNA_CC	2.30 (17.80)	-19.20 (9.80)	-8.60 (13.80)	2.90 (14.40)	-17.60 (13.50)	-17.60 (13.50)
X-ray	-47.70	130.50	-37.00	-17.70 (0.00)	-5.40 (0.00)	0.70 (0.00)

Table S3. Inter-bps parameters relative to insertion (shift (Å), slide (Å), rise (Å), tilt (deg), roll (deg) and twist (deg)) of A7-T18/T8-A17 (Flk1-1$_{ins}$/Flk1$_{ins}$) (a) and of C10-G15/C11-G14 (Flk2$_{ins}$/Flk2+1$_{ins}$)(b). Standard deviations are reported in parenthesis.

	Flk-1$_{ins}$/Flk1$_{ins}$					
System	**Shift**	**Slide**	**Rise**	**Tilt**	**Roll**	**Twist**
2/DNA_AC	0.83 (0.44)	0.36 (0.40))	3.43 (0.28)	4.40 (3.70)	-4.40 (5.80)	41.40 (3.80)
3/DNA_AC	1.20 (0.57)	0.63 (0.45)	3.45 (0.32)	3.40 (3.70)	4.80 (5.50)	37.10 (3.30)
1/DNA_ACI	0.64 (0.65)	0.23 (0.50)	3.22 (0.29)	3.60 (4.00)	6.70 (6.40)	33.40 (5.40)
1/DNA_ACII	0.68 (0.60)	0.28 (0.47)	3.26 (0.29)	3.90 (3.90)	4.10 (7.40)	34.80 (5.20)
DNA	0.13 (0.54)	-0.71 (0.58)	3.29 (0.33)	2.10 (4.20)	1.40 (5.50)	32.90 (4.70)
DNA_AA	0.15 (0.55)	-0.46 (0.56)	3.25 (0.30)	2.60 (4.30)	2.80 (5.80)	34.80 (4.60)
DNA_AC	0.13 (0.57)	-0.64 (0.57)	3.26 (0.31)	2.10 (4.30)	1.70 (5.60)	33.20 (4.70)
DNA_CC	0.07 (0.58)	-0.71 (0.55)	3.32 (0.31)	2.90 (4.20)	1.20 (5.20)	32.20 (5.40)
1/DNA_AA	0.96 (0.59)	0.20 (0.48)	3.32 (0.28)	4.20 (3.90)	4.90 (5.10)	36.90 (3.80)
1/DNA_AC'	1.37 (0.44)	0.73 (0.38)	3.17 (0.29)	5.10 (3.90)	6.70 (4.80)	32.30 (3.00)
1/DNA_CC	1.34 (0.46)	0.71 (0.41)	3.16 (0.29)	5.30 (3.90)	7.60 (5.10)	31.90 (3.30)

(a)

	Flk2$_{ins}$/Flk2+1$_{ins}$					
System	**Shift**	**Slide**	**Rise**	**Tilt**	**Roll**	**Twist**
2/DNA_AC	0.23 (0.63)	0.02 (0.60)	3.22 (0.27)	2.20 (3.60)	3.60 (5.60)	30.90 (5.40)
3/DNA_AC	-0.14 (0.67)	0.11 (0.80)	3.27 (0.36)	3.10 (4.60)	4.70 (7.10)	31.10 (8.30)
1/DNA_ACI	-0.15 (0.62)	0.62 (0.87)	3.12 (0.34)	2.90 (4.70)	9.40 (5.50)	21.00 (13.20)
1/DNA_ACII	0.28 (0.74)	1.37 (1.03)	3.16 (0.33)	0.40 (5.40)	8.30 (5.60)	-2.70 (26.50)
DNA	-0.42 (0.74)	-0.49 (0.85)	3.37 (0.35)	1.20 (5.00)	4.20 (6.60)	28.90 (6.90)
DNA_AA	-0.28 (0.78)	0.07 (1.02)	3.54 (0.41)	0.30 (4.80)	4.30 (7.50)	33.40 (7.80)
DNA_AC	-0.02 (0.77)	-0.45 (0.89)	3.40 (0.37)	1.10 (4.50)	6.20 (5.80)	31.40 (6.60)
DNA_CC	-0.65 (0.86)	-0.37 (0.83)	3.68 (0.41)	-1.50 (4.90)	4.70 (8.10)	31.10 (5.30)
1/DNA_AA	0.43 (0.42)	2.62 (0.42)	3.17 (0.34)	0.10 (4.60)	2.40 (5.50)	-22.10 (4.00)
1/DNA_AC'	0.12 (0.91)	-0.07 (0.99)	3.48 (0.36)	3.80 (4.50)	4.90 (5.80)	33.60 (6.40)
1/DNACC	0.12 (0.50)	-1.32 (0.84)	3.77 (0.36)	0.30 (4.50)	7.30 (4.80)	32.70 (4.40)

(b)

Table S4. Overall axis bending (deg) for all systems investigated. Standard deviations are given in parenthesis.

System	Global Axis Bending
2/DNA_AC	33(19)
3/DNA_AC	36 (13)
1/DNA_ACI	23 (12)
1/DNA_ACII	40 (22)
1/DNA_AA	56 (16)
1/DNA_AC'	34 (16)
1/DNA_CC	36 (14)
DNA	31 (12)
DNA_AA	37 (15)
DNA_AC	28 (13)
DNA_CC	32 (13)
1/DNA	26 (13)
2/DNA	32 (12)
3/DNA	21 (9)

Table S5. H-Bond contacts found along the trajectories of the simulated systems. Occupancy and donor acceptor length (Å) are reported, with standard deviations in parenthesis. Only H-bonds with occupancy higher that 20% are listed.

	donor	acceptor	Occupancy	Length
1/DNA_ACI	16@N1	14@N2	62	3.1 (0.2)
	12@O3'	16@N6	31	3.0 (0.2)
	12@O4'	16@N6	21	3.0 (0.2)
	8@O2P	9@N4	83	2.9 (0.1)
	9@O2	10@N4	21	3.1 (0.2)
1/DNA_ACII	16@N1	15@N2	81	3.1 (0.1)
	8@O2P	9@N4	66	2.9 (0.2)
	9@O2	10@N4	27	3.0 (0.2)
3/DNA_AC	16@N7	15@N2	94	3.1 (0.2)
	11@O2	16@N6	83	2.9 (0.2)
	12@O4'	16@N6	75	3.0 (0.2)
	8@O2P	9@N4	76	2.9(0.2)
2/DNA_AC	16@N7	15@N2	95	3.0 (0.1)
	11@O2	16@N6	56	2.9 (0.2)
	12@O4'	16@N6	52	3.0 (0.2)
	16@N1	14@N2	30	3.1 (0.2)
	8@O2P	9@N4	40	2.9 (0.2)
	9@O2	10@N4	56	3.0 (0.2)
1/DNA_AA	16@N7	5@N2	89	3.1(0.1)
1/DNA_AC'	8@O2P	9@N4	92	2.9 (0.1)
	16@N3	15@N2	36	3.1 (0.2)
1/DNA_CC	16@O2	5@N2	77	3.0(0.2)
	11@O2	16@N4	56	3.0 (0.2)
	12@O4'	16@N4	43	3.1 (0.2)
	8@O2P	9@N4	91	2.9 (0.1)
	16@N3	15@N2	36	3.3(0.2)
	17@O5'	27@N1	36	3.2 (0.2)
	16@O3'	27@N1	49	3.2 0.2)
DNA_AA	9@N1	16@N6	52	3.1 (0.2)
DNA_AC	16@N1	9@N4	92	3.0 (0.1)
DNA_CC	16@N3	9@N4	47	3.0 (0.2)
	9@N3	16@N4	33	3.0 (0.2)

Table S6. Intra-bp DNA structural parameters (buckle (deg), propeller (deg), opening (Å)) relative to intercalation for bp level A5-T20 (Flk1-1_{int}) and T8-A17 (Flk2+1_{int}) and inter-bps (rise (Å), tilt (deg), roll (deg) and twist (deg)) for A5-T20 and A6-T19 (Flk1-1_{int} and Flk1_{int}) (a). Intra-bp parameters (buckle (deg), propeller (deg), opening (Å)) of T7-A18 (Flk2_{int}) and inter-bps (rise (Å), tilt (deg), roll (deg) and twist (deg)) for T7-A18/T8-A17 (Flk2_{int} and Flk2+1_{int}). Standard deviations are reported in parenthesis.

	Flk-1_{int}			**Flk-1_{int}/Flk1_{int}**			
System	**Buckle**	**Propeller**	**Opening**	**Rise**	**Tilt**	**Roll**	**Twist**
2/DNA	9.70 (10.20)	-8.60 (8.20)	3.80 (6.00)	2.99 (0.26)	0.00 (4.50)	3.90 (5.60)	29.00 (4.60)
3/DNA	2.30 (9.30)	-8.40 (8.10)	2.00 (5.10)	3.20 (0.28)	0.80 (4.30)	0.20 (5.60)	32.60 (5.50)
1/DNA	-8.50 (10.60)	-10.10 (8.10)	3.40 (5.20)	3.19 (0.28)	-0.40 (4.00)	1.20 (6.20)	29.00 (6.00)
DNA	2.00 (11.00)	-15.30 (7.90)	3.40 (5.50)	3.28 (0.30)	-1.80 (4.20)	1.10 (5.60)	32.60 (5.00)

(a)

	Flk2+1_{int}			**Flk2_{int}/Flk2+1_{int}**			
System	**Buckle**	**Propeller**	**Opening**	**Rise**	**Tilt**	**Roll**	**Twist**
2/DNA	9.80 (8.50)	-2.40 (7.20)	9.80 (8.50)	2.94 (0.26)	3.60 (4.40)	-1.30 (5.00)	26.70 (3.90)
3/DNA	9.50 (9.70)	-11.30 (7.80)	2.30 (5.50)	3.15 (0.28)	1.60 (4.20)	-0.30 (5.70)	27.90 (7.00)
1/DNA	-0.70 (11.00)	-11.80 (7.60)	4.40 (5.60)	3.15 (0.29)	0.40 (4.20)	1.40 (5.60)	30.00 (5.30)
DNA	1.00 (12.30)	-15.60 (8.00)	3.40 (5.30)	3.29 (0.33)	2.10 (4.20)	1.40 (5.50)	32.90 (4.70)

(b)

Table S7. Inter-bps parameters (shift (Å), slide (Å), rise (Å), tilt (deg), roll (deg) and twist (deg)) relative to the free DNA sequences of T8-A17 (Flk2_{ins}) and nucleobases 9-16 (MM), and the MM and C10-G15 (Flk2_{ins}). Standard deviations are reported in parenthesis.

	Flk1_{ins}/MM					
System	**Shift**	**Slide**	**Rise**	**Tilt**	**Roll**	**Twist**
DNA	0.10 (0.65)	-0.57 (0.73)	3.39 (0.34)	-0.10 (4.20)	2.90 (6.00)	33.50 (5.40)
DNA_AA	0.67 (1.24)	0.69 (1.14)	3.50 (0.41)	6.20 (5.90)	5.20 (6.70)	44.10 (15.00)
DNA_AC	-0.71 (0.75)	-0.67 (0.56)	3.11 (0.32)	2.10 (4.80)	7.40 (7.10)	23.30 (8.30)
DNA_CC	-0.97 (0.85)	-0.26 (0.51)	3.27 (0.59)	-3.00 (6.60)	5.60 (8.30)	33.60 (12.30)
	MM/Flk2_{ins}					
DNA	0.07 (0.75)	-0.78 (0.87)	3.48 (0.37)	-0.70 (4.60)	5.80 (5.60)	31.10 (6.10)
DNA_AA	-0.79 (1.28)	0.49 (0.88)	3.12 (0.38)	-2.60 (5.70)	10.70 (8.30)	15.50 (16.10)
DNA_AC	0.91 (0.85)	-0.29 (0.66)	3.65 (0.38)	-5.30 (4.60)	4.60 (6.40)	39.30 (7.80)
DNA_CC	1.12 (0.78)	-0.35 (0.59)	3.33 (0.50)	2.80 (7.00)	3.00 (7.30)	35.80 (11.90)

Table S8. Configurational and interaction energies (kcal/mol) labeled with subscripts c and i, respectively. The inorganic compound, the mismatched and flanking bases are labeled as IC, MM and Flk$_{ins}$, respectively. El, vdw and tot refer to electrostatic, van der Waals and total interaction energies, respectively. Standard deviations are reported in parenthesis.

	DNA$_c$	**IC$_c$**	**MM$_c$**	**Flk*ins*$_c$**	**MM+Flk$_c$**	**IC/ Flk*ins*$_i$**	**IC/ MM$_i$**	**IC/ MM+Flk*ins*$_i$**	**IC/ DNA$_i$ El**	**IC/ DNA$_i$ vdW**	**IC/ DNA$_i$ Tot**
1/DNA_AA	1120 (21)	83(6)	95 (6)	190 (9)	284 (11)	-468 (11)	-186 (10)	-660 (16)	-1458 (23)	-64 (3)	-1523 (25)
1/DNA_AC'	1123 (21)	83 (7)	96 (7)	192 (8)	289 (11)	-468 (13)	-222 (11)	-691 (21)	-1499 (26)	-66 (3)	-1565 (28)
1/DNA_CC	1123 (21)	83 (7)	96 (6)	192 (9)	288 (11)	-466 (19)	-233 (16)	-699 (32)	-1508 (34)	-64 (4)	-1572 (36)
	DNA$_c$		**MM$_c$**	**Flk*ins*$_c$**	**MM+Flk*ins*$_c$**	**MM/ Flk*ins*$_i$ El**	**MM/ Flk*ins*$_i$ Vdw**	**MM/ Flk*ins*$_i$ Tot**	**MM/ DNA El**	**MM/ DNA vdW**	**MM/ DNA Tot**
DNA	1120 (20)	-	93 (6)	189 (8)	282 (11)						
DNA_AA	1119 (22)	-	94 (7)	190 (8)	283 (10)	59 (6)	-47 (3)	12 (7)	581 (15)	-52 (3)	530 (14)
DNA_AC	1120 (22)	-	92 (6)	191 (9)	283 (11)	61 (5)	-46 (3)	14 (6)	585 (13)	-51 (3)	534 (13)
DNA_CC	1119 (21)	-	93 (6)	189 (7)	282 (10)	71 (9)	-44 (3)	27 (8)	596 (19)	-49 (3)	547 (19)

Table S9. Sugar puckers for the binding region of all systems simulated

System	C/A9	A/C16
2/DNA_AC	C2'-endo	O1'-endo
3/DNA_AC	C2'-exo	C1'-exo
1/DNA_ACI	C2'-endo	C2'-exo
1/DNA_ACII	C2'-endo	C1'-exo
1/DNA_AA	C3'-exo	C1'-exo
1/DNA_AC'	C2'-endo	C2'-endo
1/DNA_CC	O1'-exo	O1'-exo
DNA_AA	C3'-exo	C2'-endo
DNA_AC	C2'-endo	C2'-endo
DNA_CC	C2'-endo	C2'-endo

System	A6	T7	T19	A18
2/DNA	C2'-endo	C2'-endo	C1'-exo	C2'-endo
3/DNA	C3'-endo	C1'-exo	C1'-exo	C1'-exo
1/DNA	C1'-exo	C1'-exo	C1'-exo	C3'-endo
DNA	C1'-exo	C1'-exo	C1'-exo	C1'-exo

Table S10. BI/BII transitions given as % BI conformation along the trajectory.

System	C/A9	A/C16
2/DNA_AC	84	5
3/DNA_AC	77	47
1/DNA_ACI	76	53
1/DNA_ACII	82	74
1/DNA_AA	22	81
1/DNA_AC'	72	30
1/DNA_CC	56	58
DNA_AA	95	94
DNA_AC	100	97
DNA_CC	100	100

System	A6	T7	T19	A18
2/DNA	88	99	99	100
3/DNA	98	84	74	98
1/DNA	93	94	85	97
DNA	97	100	100	100

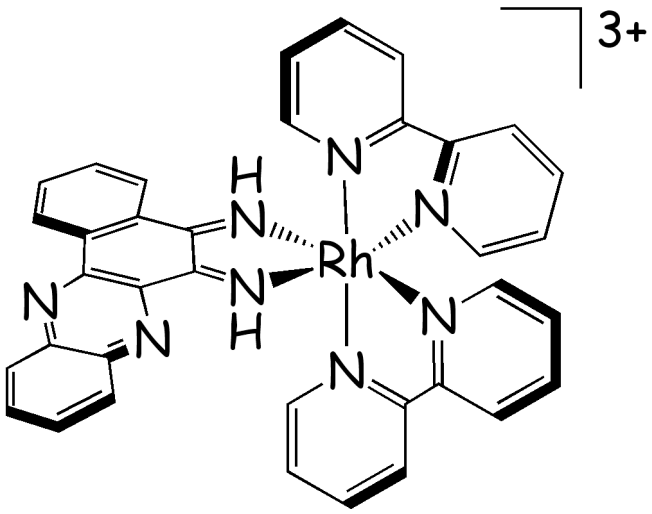

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Figure S1. Scheme of complex **4**.

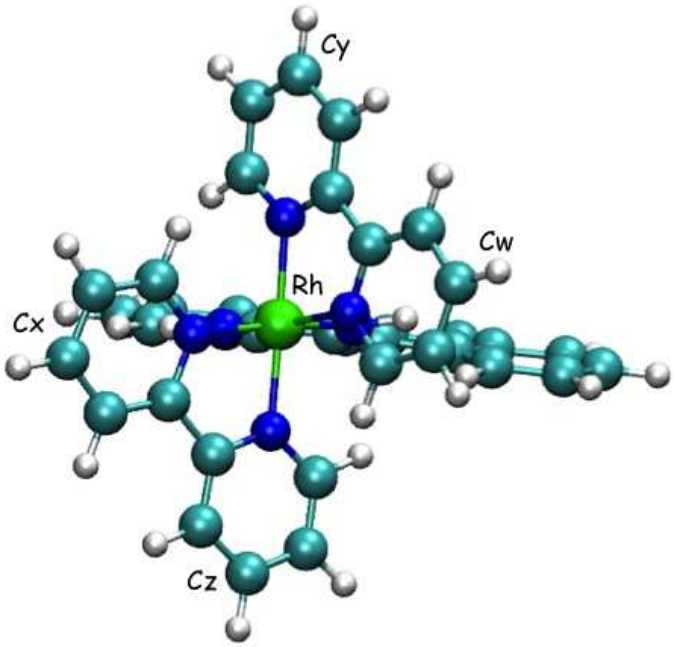
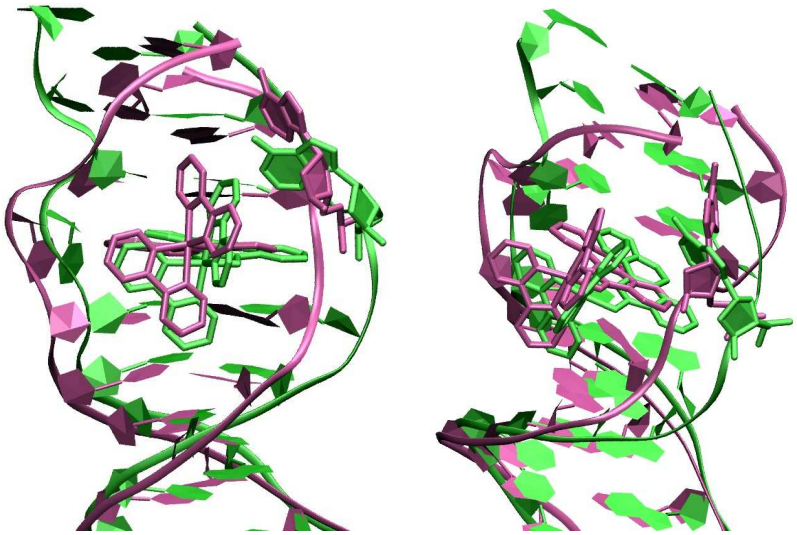


Figure S2. Atom labeling scheme of para carbon atoms of the bpy ligands.



(a) (b)

Figure S3. Front and side view of the two main representative clusters of **1/DNA_ACI** and **1/DNA_ACII** in (a) and (b), respectively. 1**/DNA_ACI** and **1/DNA_ACII** are represented in green and in pink, respectively. Base A16 is represented in licorice.

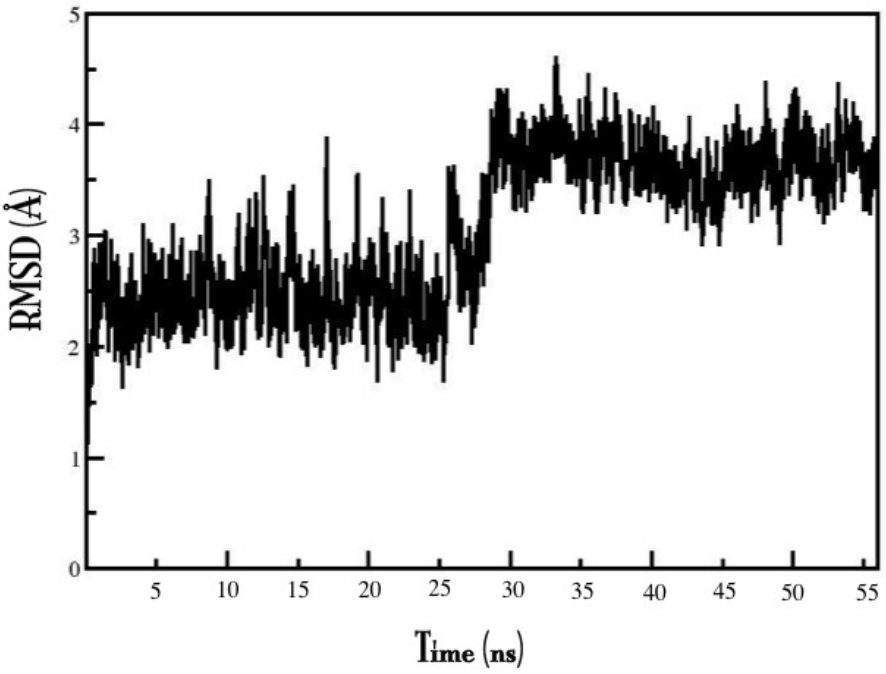


Figure S4. RMSD of **1/DNA_AC** vs simulation time(along the final 55 ns of simulation).

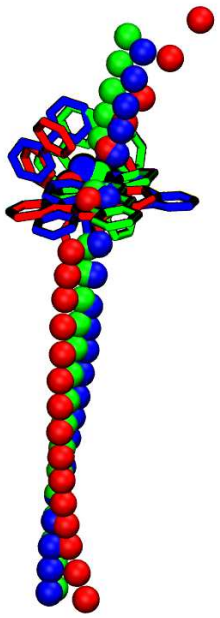


Figure S5. Simplified view of the overall axis bending for **1/DNA_AC** (red), **2/DNA_AC** (green) and **3/DNA_AC** (blue).

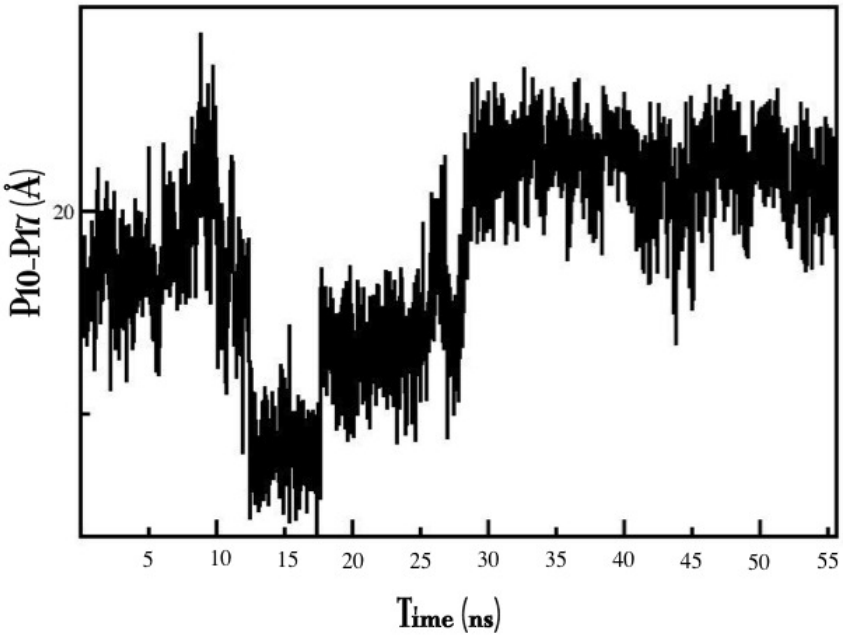


Figure S6. P@C10-P@A17 distance (Å) vs simulation time (along the final 55 ns of simulation) of **1/DNA_AC**.

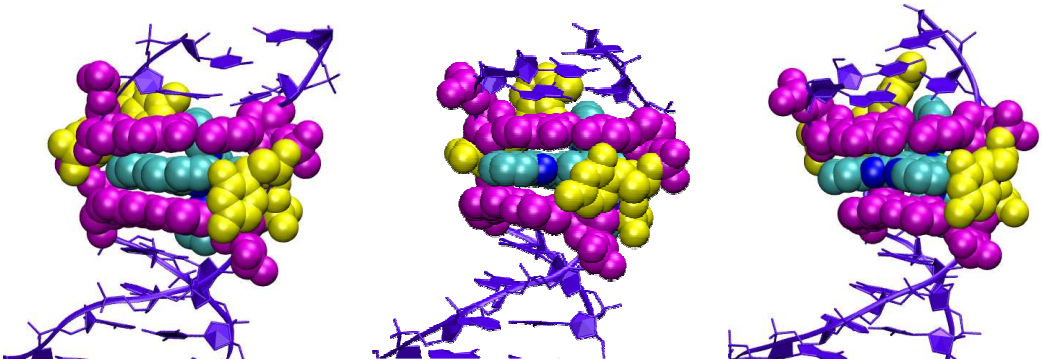
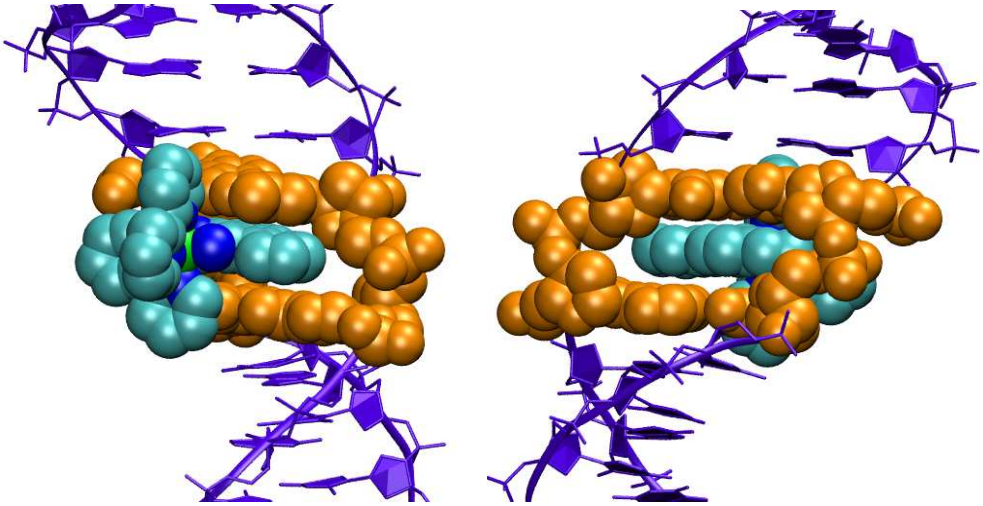
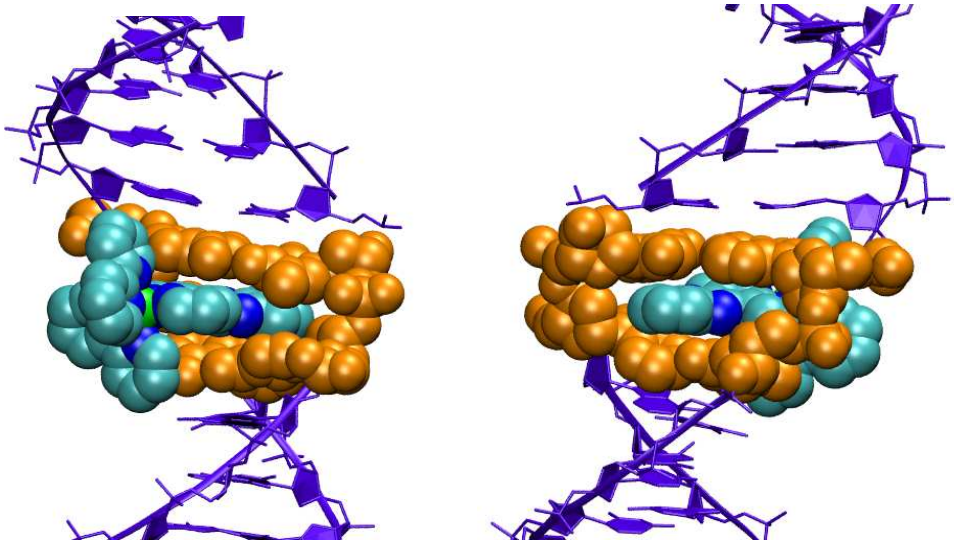


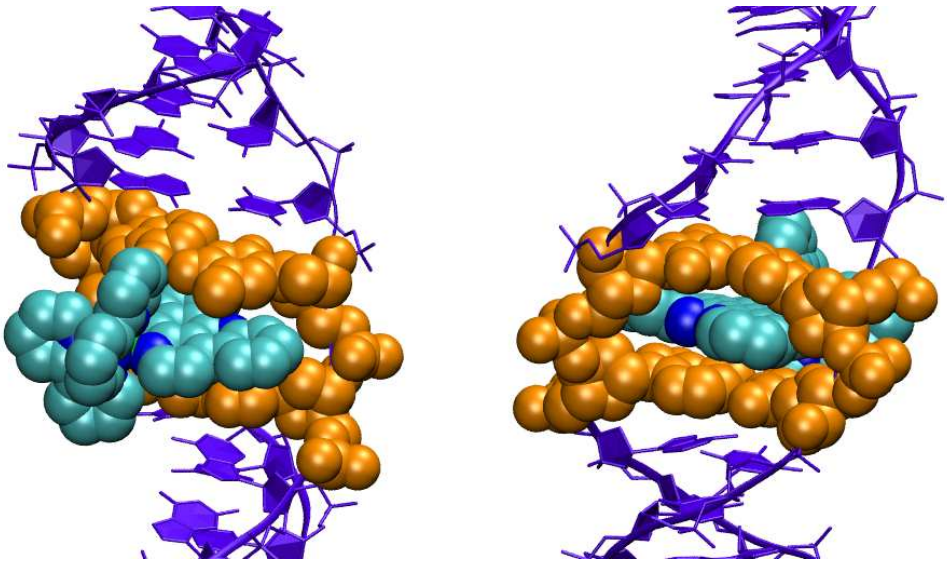
Figure S7. Close view from the major groove side for the insertion of **1**, **2** and **3** in (a), (b) and (c), respectively. **1**,**2** and **3** are represented as van der Waals (vdw) spheres and colored by atom names. The mismatch (MM) and the bases flanking the MM are in vdw spheres and are yellow and magenta colored, respectively. The rest of the DNA filament is represented in ribbons and is colored in violet.



(a) (b)



(c) (d)



(e) (f)

Figure S8. Close view from the major groove and the minor groove sides for the intercalation into the DNA of **1**, **2**, **3** in a and b, c and d, and e and f, respectively. **1**,**2** and **3** are represented as van der Waals (vdw) spheres and colored by atom names. The bases flanking the intercalation site are in vdw spheres and are orange colored. The rest of the DNA filament is represented in ribbons and is colored in violet.

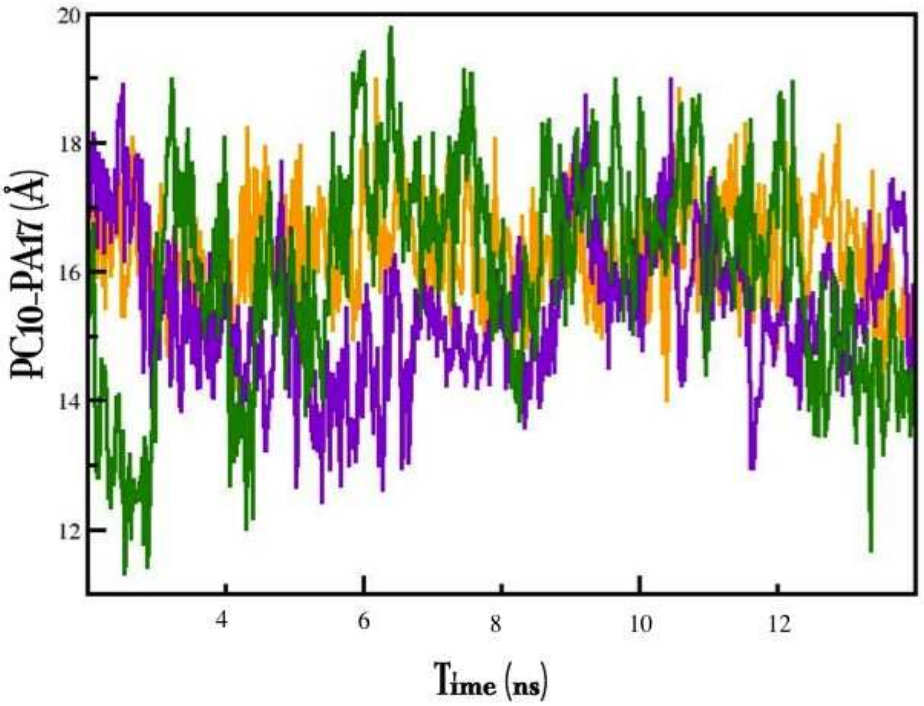


Figure S9. Distance of P@C10-P@A17 for **DNA_AA** (violet), **DNA_AC'** (orange), **DNA_CC** (green) versus simulation time.

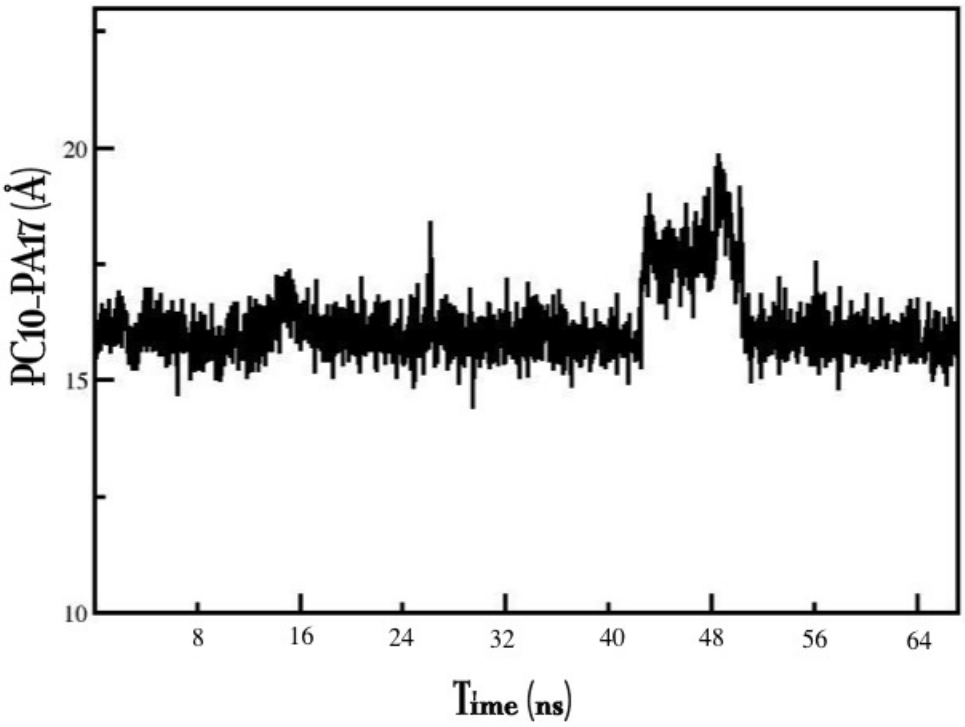


Figure S10. Distance of P@C10-P@A17 for **1/DNA_CC** versus simulation time (along the final 65 ns of the trajectory).