Submitted to *J. Am. Chem. Soc.*

Supporting Information

DNA structural distortions induced by ruthenium-arene anticancer compounds

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TABLES:

Table S2. Atom types and RESP charges for the [Ru(η^6-*p*-cymene)(en)]$^{2+}$ moiety. Numbering as in Fig. S9.

Atom name	Atom type	RESP charge
Ru	Ru	0.25962
C2	CT	-0.06675
H3/4/5	HC	0.08739
C6	C4	0.00872
C7/14	CA	-0.05458
H8/15	HA	0.15520
C9/12	C4	-0.06897
H10/13	HA	0.18988
C11	CA	-0.02696
C16	CT	0.02831
H17	HC	0.09874
C18/22	CT	-0.11614
H19/20/21/23/24/25	HC	0.06027
N26/35	N4	-0.03397
H27/28/36/37	H	0.16657
C29/32	CT	-0.20316
H30/31/33/34	H1	0.16793

Table S3. Harmonic force constants (kcal/mol/Å^2) around the equilibrium bond length (Å). Numbering as in Table S2.

Bond	Force constant	Bond length
Ru-C4	1000	2.187
Ru-NB	1000	2.120
Ru-N4	1000	2.133
C4-CA	469	1.400
C4-HA	367	1.080
C4-CT	317	1.510
N4-H	434	0.909
N4-CT	367	1.484

Table S4. Harmonic force constants (kcal/mol*Å^2) around the equilibrium angle (°). Numbering as in Table S2.

Angle	Force constant	Equilibrium angle
Ru-C4-CA	0	0.0
Ru-C4-CT	0	0.0
Ru-C4-HA	0	0.0
Ru-N4-CT	1000	111.15
Ru-N4-H	1000	109.39
Ru-NB-CK	0	0.0
Ru-NB-CB	0	0.0
C4-CA-HA	50	120.0
C4-CA-C4	63	120.0
C4-CT-HC	50	109.5
C4-Ru-C4	0	0.0
C4-Ru-NB	0	0.0
C4-Ru-N4	0	0.0
N4-Ru-N4	1000	78.97
N4-Ru-NB	0	0.0
N4-CT-H1	50	109.5
N4-CT-CT	80	111.2
C4-CA-CT	70	120.0
CA-C4-CA	63	120.0
CA-C4-CT	70	120.0
CA-C4-HA	50	120.0
H-N4-H	35	109.5
CT-N4-H	50	109.5

Table S5. Dihedral angle parameters (kcal/mol). Numbering as in Table S2.

Dihedral	no. of paths	Phase	# barriers	Force constant
Ru-C4-CA-HA	1	0	1	0
Ru-C4-CA-C4	1	0	1	0
Ru-C4-CA-CT	1	0	1	0
CA-C4-CA-HA	1	180	2	100
CA-C4-CA-CT	1	180	2	100
CT-C4-CA-HA	1	180	2	100
CT-C4-CA-C4	1	180	2	100
HA-C4-CA-CT	1	180	2	100
HA-C4-CA-HA	1	180	2	100
HA-C4-CA-C4	1	180	2	100
CA-C4-CA-C4	1	180	2	100
CA-C4-CT-HC	1	0	3	0
Ru-C4-CT-HC	1	0	1	0
CA-C4-Ru-NB	1	0	1	0
HA-C4-Ru-NB	1	0	1	0
CA-C4-Ru-Cl	1	0	1	0
CT-C4-Ru-Cl	1	0	1	0
HA-C4-Ru-Cl	1	0	1	0
CA-C4-Ru-C4	1	0	1	0
HA-C4-Ru-C4	1	0	1	0
CT-C4-Ru-C4	1	0	1	0
CT-C4-Ru-NB	1	0	1	0
CT-C4-Ru-N4	1	0	1	0
CA-C4-Ru-N4	1	0	1	0
HA-C4-Ru-N4	1	0	1	0
NB-Ru-N7-CK	1	0	1	0
C4-Ru-NB-CK	1	0	1	0
C4-Ru-NB-CB	1	0	1	0
N7-Ru-NB-CB	1	0	1	0
NB-Ru-N4-CT	1	0	1	0
C4-Ru-N4-CT	1	0	1	0
C4-Ru-N4-H	1	0	1	0
N4-Ru-N4-CT	1	0	1	0
N4-Ru-N4-H	1	0	1	0
N4-Ru-NB-CK	1	0	1	0
N4-Ru-NB-CB	1	0	1	0
NB-Ru-N4-H	1	0	1	0
C4-Ru-N4-H	1	0	1	0
CT-CT-N4-Ru	9	0	3	0
H1-CT-N4-Ru	9	0	3	0
H1-CT-N4-H	6	0	3	1.8
CT-CT-N4-H	6	0	3	1.8

Table S6. vdWaals parameters R (Å) and ε (kcal/mol). Numbering as in Table S2.

atom	R*	ε
Ru	2.963	0.56
C4	1.908	0.0860
N4	1.824	0.1700

Table S7. Atom types and RESP charges for the [Ru(η^6-*p*-cymene)(en)(N7{G})]$^{2+}$ moiety. Numbering as in Figure S10.

Atom name	Force matching	
	Atom type	charge
Ru1	Ru	1.51841
C2	CX	-0.04765
H3/4/5	HX	0.04121
C6	C6	-0.00400
C7/14	C6	-0.13204
H8/15	H6	0.03541
C9/12	C6	-0.09381
H10/13	H6	0.05848
C11	C6	-0.04773
C16	CI	0.08846
H17	HI	-0.03975
C18/22	CU	-0.07841
H19/20/21/23/24/25	HU	0.02515
N26/35	NE	-0.36211
H27/28/36/37	HE	0.23737
C29/32	CH	0.04087
H30/31/33/34	HH	0.05699
N38	N7	-0.22146
C39	C8	-0.04140
H40	H8	0.08132
N41	N9	-0.48922
Dum42	DU	0.75778
C43	C4	0.07154
C44	C5	0.20064
N45	N8	-0.53469
C46	C7	0.18541
N47	ND	-0.37030
H48/49	HD	0.31579
N50	NF	0.06849
H51	HF	0.27831
C52	CG	0.14171
O53	OG	-0.60927

Table S8. Harmonic force constants (kcal/mol/Å^2) around the equilibrium bond length (Å). Numbering as in Table S7.

Bond	Force Matching	
	Force constant	Bond length
CX-HX	331.2	1.102
C6-H6	361.9	1.083
CI-HI	317.8	1.103
NE-HE	399.1	1.034
CH-HH	327.0	1.099
C8-H8	372.2	1.082
NF-HF	425.0	1.037
ND-HD	462.2	1.024
Ru-NE	64.8	2.326
Ru-C6	32.6	2.264
Ru-N7	47.8	2.255
CX-C6	235.6	1.496
C6-C6	298.4	1.410
C6-CI	172.0	1.484
CI-CU	151.9	1.551
CH-CH	246.2	1.524
NE-CH	168.7	1.526
C7-ND	396.2	1.371
C7-N8	376.2	1.329
C7-NF	277.2	1.378
CG-OG	533.7	1.248
CG-NF	235.6	1.419
CG-C5	305.0	1.417
C4-C5	342.3	1.418
C5-N7	330.5	1.487
C8-N7	397.6	1.349
C8-N9	279.8	1.321
C4-N9	282.0	1.336
DU-N9	128.3	1.464

Table S9. Harmonic force constants (kcal/mol*Å^2) around the equilibrium angle (°). Numbering as in Table S7.

Angle	Force Matching	
	Force constant	Angle
Ru-NE-HE	13.4	125.3
HX-CX-HX	36.4	102.3
HX-CX-C6	42.4	103.0
CI-CU-HU	43.6	105.5
C6-C6-H6	30.1	115.8
C6-CI-HI	38.4	105.0
HE-NE-HE	33.3	110.5
HH-CH-NE	49.2	107.4
HH-CH-HH	33.0	109.0
CH-NE-HE	37.3	111.3
HH-CH-CH	46.3	110.1
H8-C8-N7	18.4	132.9
N9-C8-H8	8.0	149.0
CG-NF-HF	23.5	127.2
HF-NF-C7	25.3	127.3
C7-ND-HD	36.7	120.5
HD-ND-HD	28.8	120.6
Ru-NE-CH	42.0	118.0
Ru-N7-C5	0.0	177.9
Ru-N7-C8	20.9	116.2
CX-C6-C6	47.1	120.6
C6-C6-C6	55.1	116.3
C6-C6-CI	40.0	126.5
C6-CI-CU	35.3	104.2
CU-CI-CU	55.5	108.0
N35-Ru-N7	56.6	84.9
N26-Ru-N7	45.6	85.4
NE-CH-CH	75.9	108.7
NE-Ru-NE	64.2	81.0
ND-C7-N8	1.5	171.6
C7-N8-C4	52.5	118.0
NF-C7-ND	26.4	144.8
NF-C7-N8	20.2	150.9
OG-CG-NF	31.1	141.9
CG-NF-C7	25.7	137.5
CG-C5-C4	6.1	147.0
C5-CG-OG	0.0	179.4
C5-CG-NF	16.4	144.9
C5-C4-N8	3.2	167.5
N7-C5-CG	51.6	135.3
N7-C5-C4	9.3	160.8
C8-N7-C5	17.2	153.1
C8-N9-C4	77.9	111.2
N9-C8-N7	36.2	140.3
N9-C4-N8	19.9	146.0
N9-C4-C5	53.2	131.8
DU-N9-C8	14.6	145.0

DU-N9-C4	12.0	141.1	

Table S10. Dihedral angle parameters (kcal/mol). Numbering as in Table S7.

Dihedral	no. of paths	Phase	# barriers	Force constant
				Force Matching
X-C6-C6-C6	1	180	2	6.3
C8-H8-N9-N7	1	180	2	0.3

Table S11. Atom types and RESP charges for the [Ru(η^6-*p*-cymene)(pta)]$^{2+}$ moiety. Numbering as in Figure S11.

Atom name	Atom type	RESP charge
Ru1	Ru	0.46695
C2	CT	0.04968
H3/4/5	HC	0.05625
C6	C4	-0.02114
C7/14	CA	-0.05314
H8/H15	HA	0.14530
C9/C12	C4	-0.06465
H10/13	HA	0.16040
C11	CA	-0.02606
C16	CT	0.02999
H17	HC	0.06876
C18/22	CT	-0.06829
H19/20/21/23/24/25	HC	0.05152
P26	P3	0.12078
N27/28/29	NT	-0.39820
C30/33/36	CT	-0.00663
H31/32/34/35/37/38	H1	0.10461
C39/42/45	CT	0.01290
H40/41/43/44/46/47	H2	0.19033

Table S12. Harmonic force constants (kcal/mol/Å^2) around the equilibrium bond length (Å). Numbering as in Table S11.

Bond	Force constant	Bond length
Ru-P3	1000	2.30
Ru-C4	1000	2.20
Ru-NB	1000	2.12
P3-CT	500	1.84
C4-CA	469	1.40
C4-HA	367	1.08
C4-CT	317	1.51

Table S13. Harmonic force constants (kcal/mol*Å^2) around the equilibrium angle (°). Numbering as in Table S11.

Angle	Force constant	Equilibrium angle
Ru-P3-CT	0	117.29
Ru-C4-CA	0	71.0
Ru-C4-CT	0	128.75
Ru-C4-HA	0	131.2
Ru-NB-CK	0	120.0
Ru-NB-CB	0	132.0
P3-CT-H1	100	109.07
P3-CT-NT	100	111.6
P3-Ru-C4	0	123.0
P3-Ru-NB	25	78.0
NB-Ru-NB	0	82.0
NT-CT-H2	100	108.65
NT-CT-NT	100	114.25
CT-P3-CT	100	98.42
C4-CA-HA	50	120.0
C4-CA-C4	63	120.0
C4-CT-HC	50	109.5
C4-Ru-C4	0	67.5
C4-Ru-NB	0	0.0
C4-CA-CT	70	120.0
CA-C4-CA	63	120.0
CA-C4-CT	70	120.0
CA-C4-HA	50	120.0

Table S14. Dihedral angle parameters (kcal/mol). Numbering as in Table S11.

Dihedral	no. of paths	Force constant	Phase	# barriers
Ru-P3-CT-NT	1	0	0	1
Ru-P3-CT-H1	1	0	0	1
Ru-C4-CA-HA	1	0	0	1
Ru-C4-CA-C4	1	0	0	1
Ru-C4-CA-CT	1	0	0	1
Ru-C4-CT-HC	1	0	0	1
P3-Ru-C4-CA	1	0	0	1
P3-Ru-C4-CT	1	0	0	1
P3-Ru-C4-HA	1	0	0	1
P3-Ru-NB-CK	1	0	0	1
P3-Ru-NB-CB	1	0	0	1
NT-CT-P3-CT	1	0	0	1
NB-Ru-NB-CK	1	0	0	1
NB-Ru-C4-CT	1	0	0	1
CT-P3-Ru-C4	1	0	0	3
CT-P3-Ru-NB	1	0	0	3
CT-P3-CT-H1	1	0	0	1
C4-Ru-C4-CA	1	0	0	1
C4-Ru-C4-HA	1	0	0	1
C4-Ru-C4-CT	1	0	0	1
C4-Ru-NB-CK	1	0	0	1
C4-Ru-NB-CB	1	0	0	1
C4-CA-C4-HA	1	100	180	2
C4-CA-C4-CA	1	100	180	2
C4-CA-C4-CT	1	100	180	2
CA-C4-CA-HA	1	100	180	2
CA-C4-CA-CT	1	100	180	2
CA-C4-CT-HC	1	0	0	3
CA-C4-Ru-NB	1	0	0	1
CB-NB-Ru-NB	1	0	0	1
HA-CA-C4-CT	1	100	180	2
HA-C4-CA-CT	1	100	180	2
HA-C4-CA-HA	1	100	180	2
HA-C4-Ru-NB	1	0	0	1

Table S15. vdWaals parameters R (Å) and ε (kcal/mol). Numbering as in Table S11.

atom	R*	ε
Ru	2.963	0.56
P3	2.1	0.2
C4	1.908	0.0860

Table S16. Atom types and RESP charges for the $[Ru(\eta^6\text{-benzene})(pta)]^{2+}$ moiety. Numbering as in Figure S12.

Atom name	Atom type	RESP charge
Ru1	Ru	0.51643
H2/5/7/9/11/13	HA	0.15260
C3/6/10	C4	-0.04403
C4/8/12	CA	-0.04403
P14	P3	0.08868
N15/16/17	NT	-0.35533
C18/21/24	CT	-0.01378
H19/20/22/23/25/26	H1	0.12114
C27/30/33	CT	-0.03031
H28/29/31/32/34/35	H2	0.20248

Table S17. Atom types and RESP charges for the $[Ru(\eta^6\text{-benzene})(pta\text{-}H^+)]^{3+}$ moiety. Numbering as in Figure S13.

Atom name	Atom type	RESP charge
Ru1	Ru	0.5758
H2/5/7/9/11/13	HA	0.1813
C4/8/12	CA	-0.0164
C3/6/10	C4	-0.0164
P14	P3	-0.0491
N15/16/17	NT	-0.1030
C18	CT	-0.0813
H19/20	H1	0.1706
C21/24	CT	-0.1704
H22/23/25/26	H1	0.1781
C27/33	CT	-0.1884
H28/29/34/35	H2	0.2397
C30	CT	-0.3817
H31/32	H2	0.2962
H36	H	0.3423

Table S18. Harmonic force constants (kcal/mol*$Å^2$) around the equilibrium angle (Å) in addition to the force field described for $[Ru(\eta^6\text{-benzene})(pta)]^{2+}$. Numbering as in Table S17.

Angle	Force constant	Equilibrium angle
N3-CT-H1	50	109.5
N3-CT-NT	100	114.25
N3-CT-H2	50	109.5
N3-CT-P3	100	111.6

Table S19. Dihedral angle parameters (kcal/mol) in addition to those described for [Ru(η^6-benzene)(pta)]$^{2+}$. Numbering as in Table S17.

Dihedral	no. of paths	Force constant	Phase	# barriers
N3-CT-P3-CT	1	0	0	1
Ru-P3-CT-N3	1	0	0	1

FIGURES:

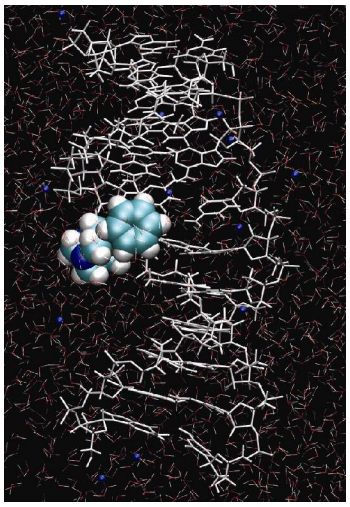

Figure S1. Representative model of the system used in our molecular mechanics (MM) and combined quantum mechanics/molecular mechanics (QM/MM) molecular dynamics (MD) studies. Explicit water molecules are visualized as lines, Na^+ counter-ions as blue balls, the 12-mer DNA-scaffold as silver sticks, and the RA complex coordinated to the N7 atoms of G6* (RA-en) or G6*/G7* (here the benzene RA-pta derivative) in vdW representation.

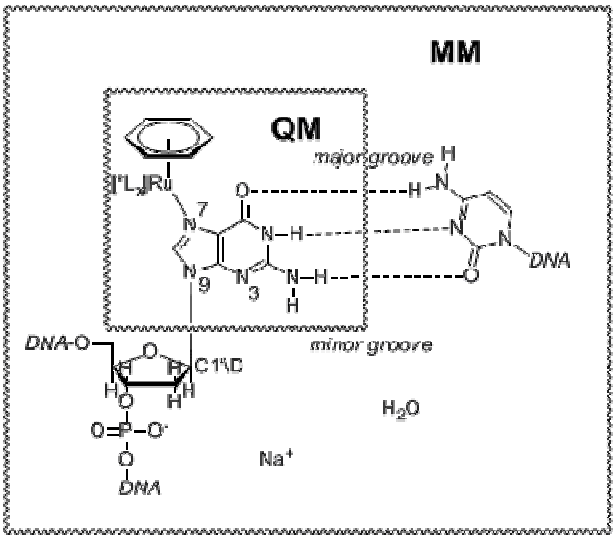

Figure S2. Schematic QM/MM-setup showing the cut at the QM/MM-interface. D is a monovalent carbon dummy atom.

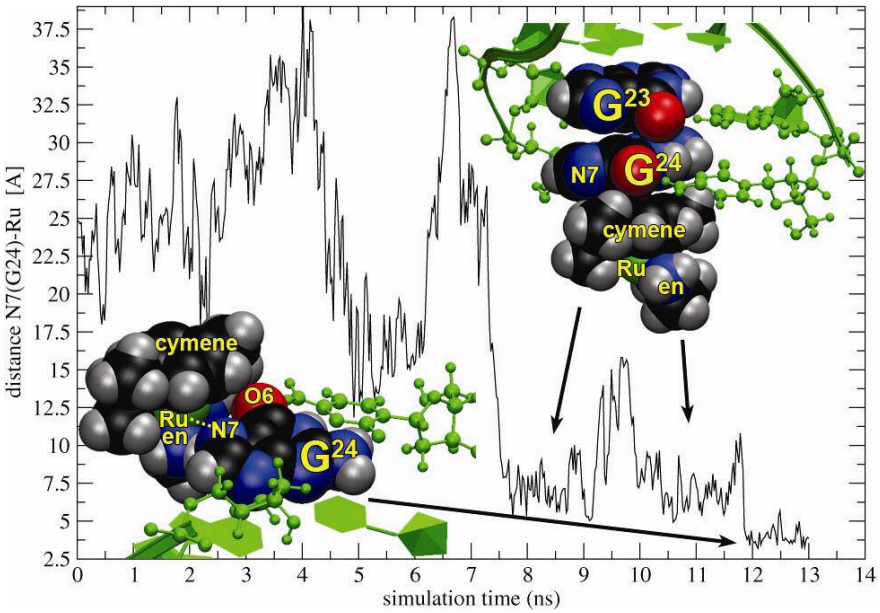

Figure S3. Initially placed at about 20 Å from the central GC pair, RA-en samples the outer major and minor groove regions of the B-DNA. Upon migration to one end (G24/C1) of the 12-mer, the RA-en complex forms a π-π-stacking interaction via the benzene moiety of its *p*-cymene ligand to the (end standing) guanine G24. Finally, the RA-en complex rotates as shown in the figure and docks to G24 via Ru-N7(G) (distance shown in graph) and (en)N*H*-O6(G) interactions.

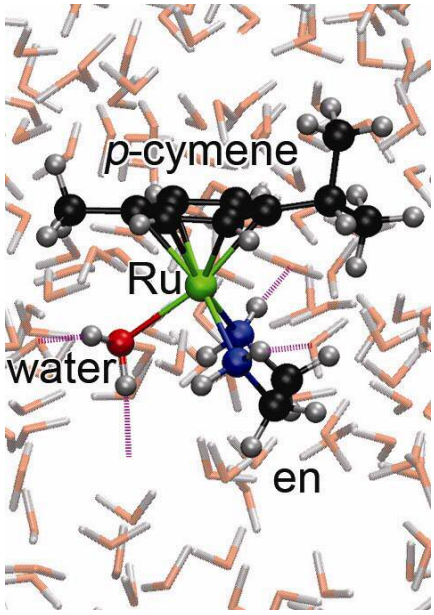

Figure S4. The free aqua complex of RA-en. It corresponds to state *C* in Figure 4.

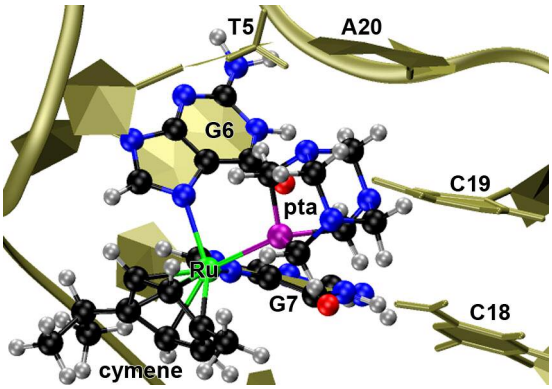

Figure S5. Representative snapshot of a QM/MM MD simulation with an inverted orientation (configuration II) of $[Ru(\eta^6\text{-}p\text{-cymene})(pta)]^{2+}$ relative to the DNA.

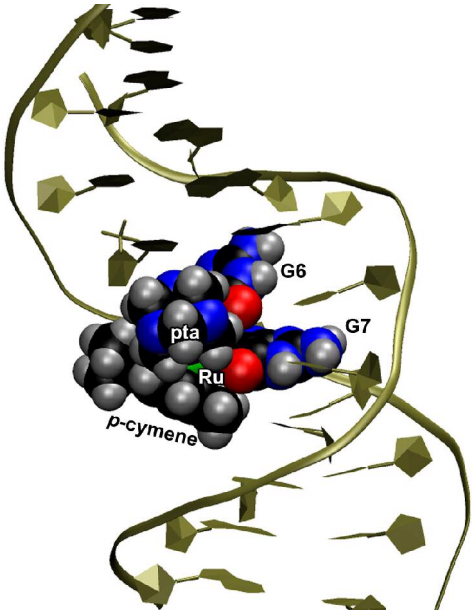

Figure S6. Representative snapshot of the 12-mer DNA geometry upon covalent drug binding; *p*-cymene derivative of RA-pta with pta directed towards complementary strand (configuration II).

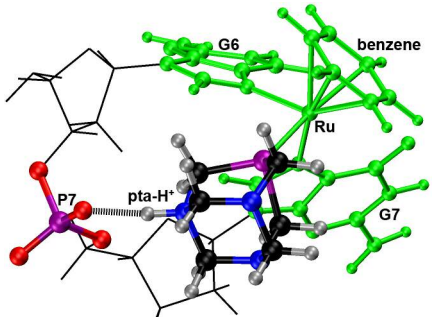

Figure S7. Representative snapshot of a RA-pta MD simulation. If protonated at a nitrogen atom, the pta in $[Ru(\eta^6\text{-benzene})(pta\text{-}H^+)]^{3+}$ forms a stable H-bond to an oxygen atom in phosphate 7 (MM-part). This H-bond increases the observed fluctuations of the DNA molecule (rmsd of the DNA backbone)

compared to the results obtained for the unprotonated RA-pta species. However, the main dynamical properties of the drug-DNA complex remain unchanged.

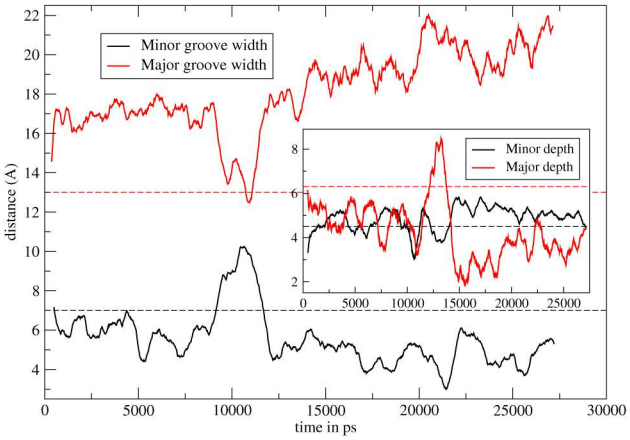

Figure S8. Time evolution of DNA groove width and depth (Å) measured at base step G6/C19 during a classical MD of a RA-en 12-mer adduct. Broken lines indicate the average value measured in a reference MD simulation of B-DNA. The major groove widens immediately to accommodate RA-en. Following the WC-break at 14 ns it widens even further while the depth decreases.

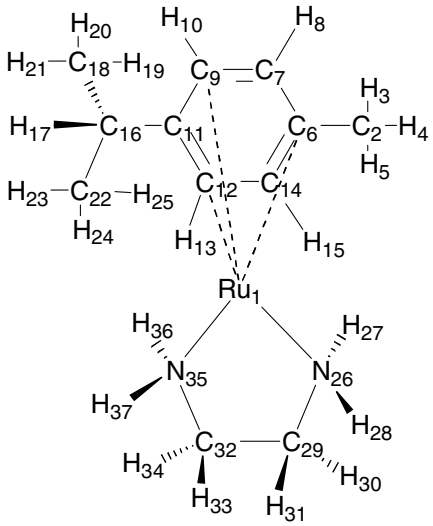

Figure S9. Atom numbering of the [Ru(η^6-*p*-cymene)(en)]$^{2+}$ moiety.

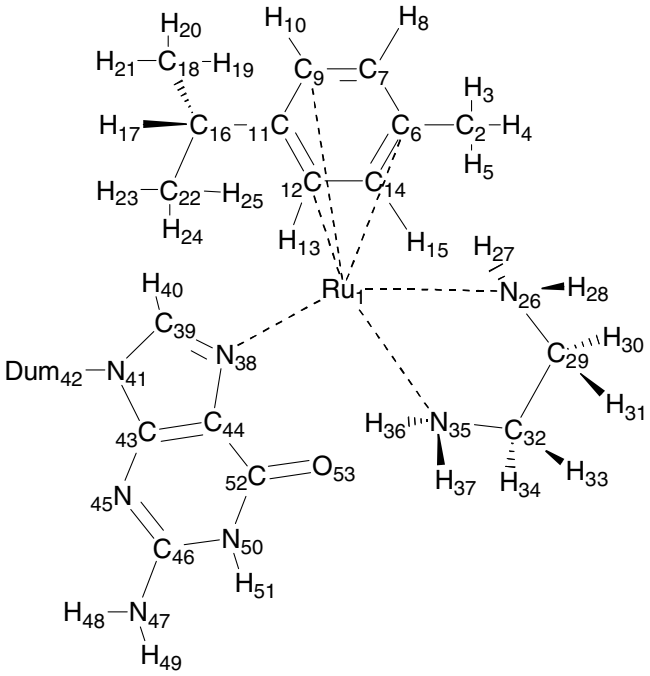

Figure S10. Atom numbering of the [Ru(η^6-*p*-cymene)(en)(N7{G})]$^{2+}$ moiety for force field from force matching.

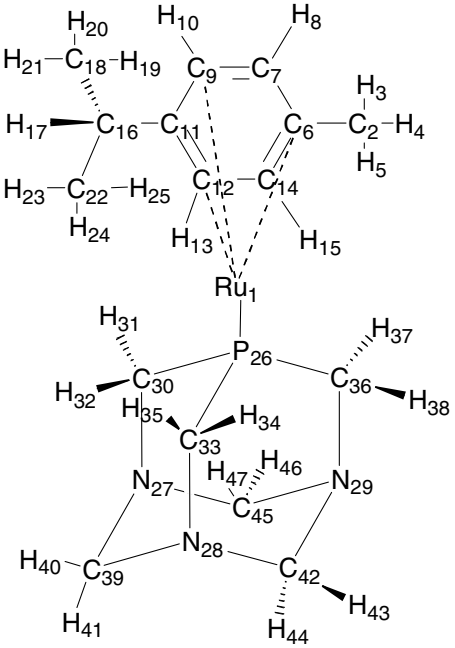

Figure S11. Atom numbering of the [Ru(η^6-*p*-cymene)(pta)]$^{2+}$ moiety.

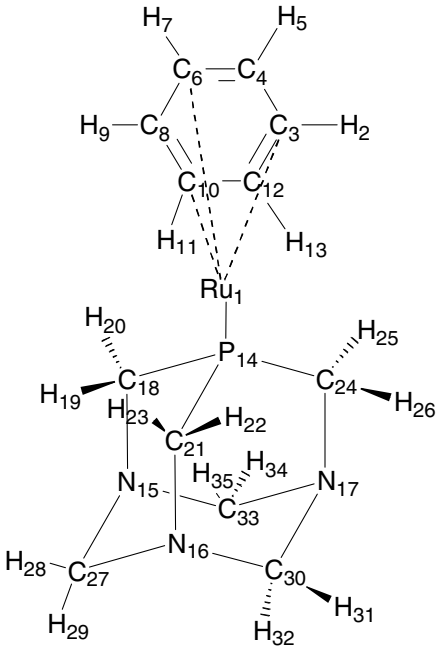

Figure S12. Atom numbering of the [Ru(η^6-benzene)(pta)]$^{2+}$ moiety.

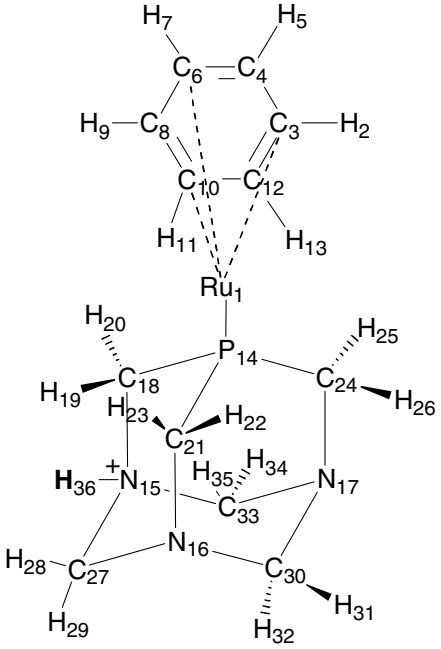

Figure S13. Atom numbering of the [Ru(η^6-benzene)(pta-H$^+$)]$^{3+}$ moiety.