Supporting Information

Table S1. All pK_a values calculated from CPHMD for the holo and apo states

Residue	pK_a^{holo}	pK_a^{apo}	ΔpK_a
Asp9	4.17	3.51	0.66
Glu12	5.29	4.30	1.00
Glu17	4.94	6.15	-1.20
Asp20	5.54	4.48	1.06
Lys31	10.73	10.59	0.14
Asp34	3.56	2.41	1.15
Glu35	5.97	5.20	0.77
Glu41	4.75	4.24	0.51
Asp47	4.23	4.20	0.03
Glu48	5.23	4.99	0.24
Asp54	4.28	4.12	0.15
Lys60	11.11	8.94	2.17
Glu61	3.42	3.55	-0.13
Lys67	11.43	10.26	1.18
Lys71	12.00	9.93	2.06
Asp77	3.75	3.57	0.18
Glu80	3.96	4.00	-0.04
His84	7.14	7.31	-0.17
Asp93	3.31	3.50	-0.19
Cys110	11.88	11.45	0.43
His132	5.76	6.39	-0.63
Cys134	10.93	10.05	0.88
Glu135	4.67	4.28	0.39
Lys141	12.02	11.73	0.29
Glu143	5.36	5.03	0.33
Glu151	5.15	4.59	0.56

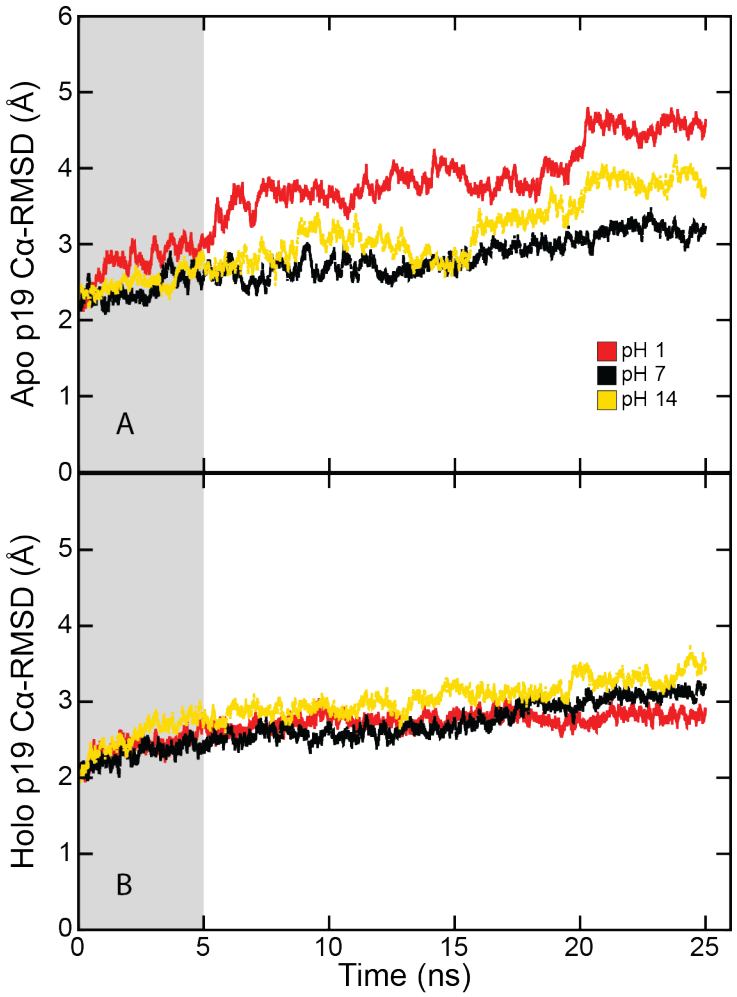

Figure S1. C_α root mean square deviation (RMSD) of apo and holo p19 at low, medium, and high pH. The grey box denotes the first 5 ns of simulation time that are excluded from subsequent analyses. (A) Apo p19 C_α-RMSD. (B) Holo p19 C_α-RMSD.

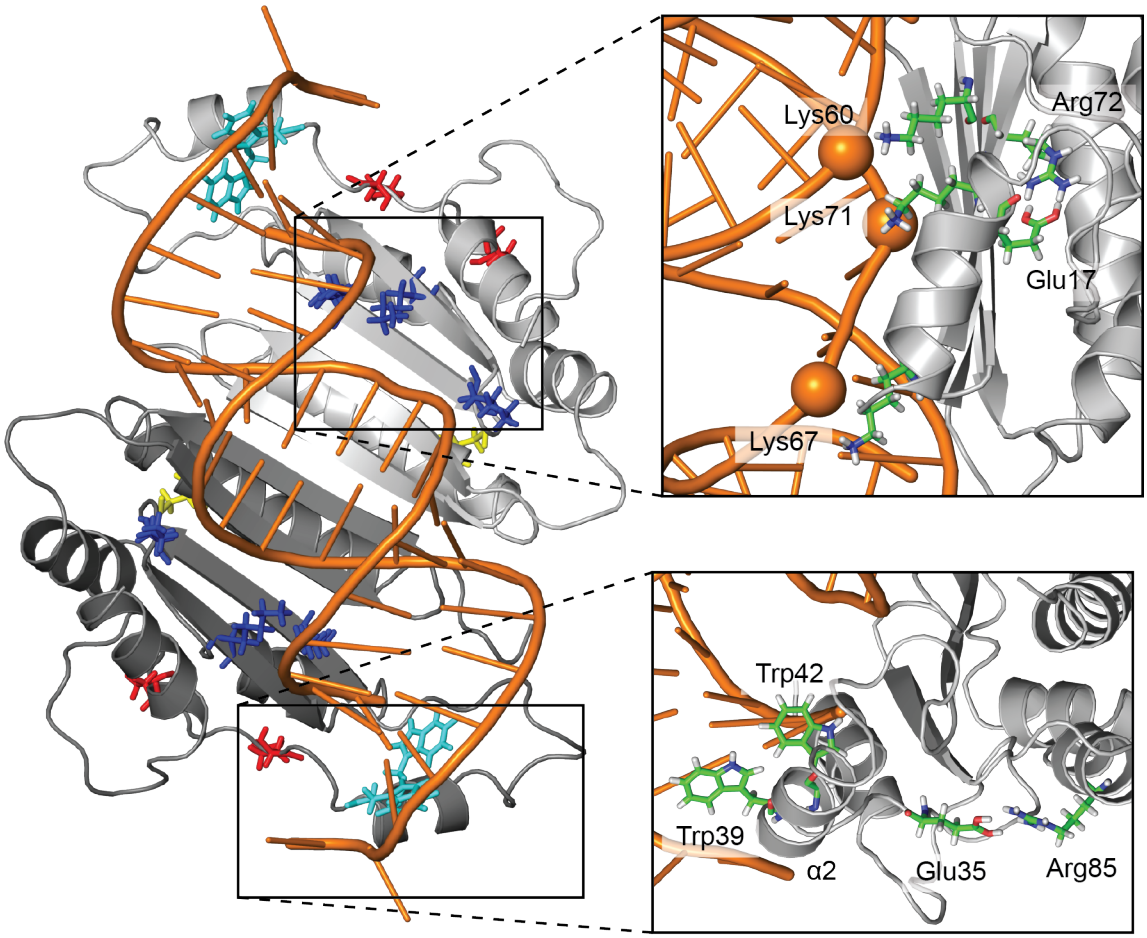

Figure S2. Enlarged views of the Lys-RNA, Glu17-Arg72, Glu35-Arg85, and Trp-RNA interactions. The image on the left is provided as a reference and is identical to Figure 1. The two images on the right show the relative positions and interactions of key amino acid residues (stick representation) and are rotated to allow for the best vantage point. Carbon is green, nitrogen is blue, oxygen is red, and hydrogen is white. Orange spheres correspond to siRNA backbone phosphorous atoms. For clarity, only one monomer is shown.

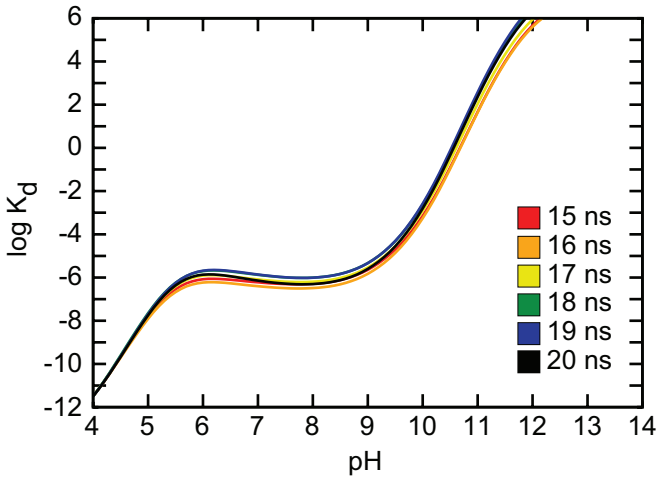

Figure S3. Dissociation constant profiles generated using 15 – 20 ns of production simulation.