Supplementary Information

The Chemical Nature of the 2'-substituent in the Pentose-Sugar Dictates the Pseudoaromatic Character of the Nucleobase (pK_a) in DNA/RNA

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Figure S1. The stack plots of the pH-dependent ^{1}H NMR chemical shifts of aromatic protons for compounds **2a–2i**, **4a–4j, 5c-5j and 6c-6i** at 298 K [only 10-11 pHs points (including two plateaus at two extreme pHs) are shown out of total ~20 – 33 pHs used for the titration plots, see Experimental section for details].

Figure S2. Sigmoidal plots of the pH-dependent chemical shifts of aromatic protons for compounds **2a–2i**, **4a–4j, 5c-5j** and **6c-6i** to calculate the pKa of N1/N3/N7 of the nucleobase as well as the protonation pK_a of N-azetidine as well as N-amine.

Figure S3. Hill plot analysis of the pH-dependent chemical shifts of aromatic protons for compounds **2a–2i**, **4a–4j, 5c-5j and 6c-6i** to calculate the pK_a of the corresponding nucleobases as well as nitrogen protonation in amine and in azetidine modified nucleotides.

Figure S4. Sigmoidal plots of the pH-dependent **^{31}P** chemical shifts of 3'and 5' phosphorus of the 3',5'-bis-ethyl and 3´mono ethyl phosphates *i.e.*, **5c-j , 6c-i** to calculate the protonation pKa of N-azetidine as well as N-amine.

Figure S5. Hill plot analysis of sigmoidal curves in **Figure S4.**

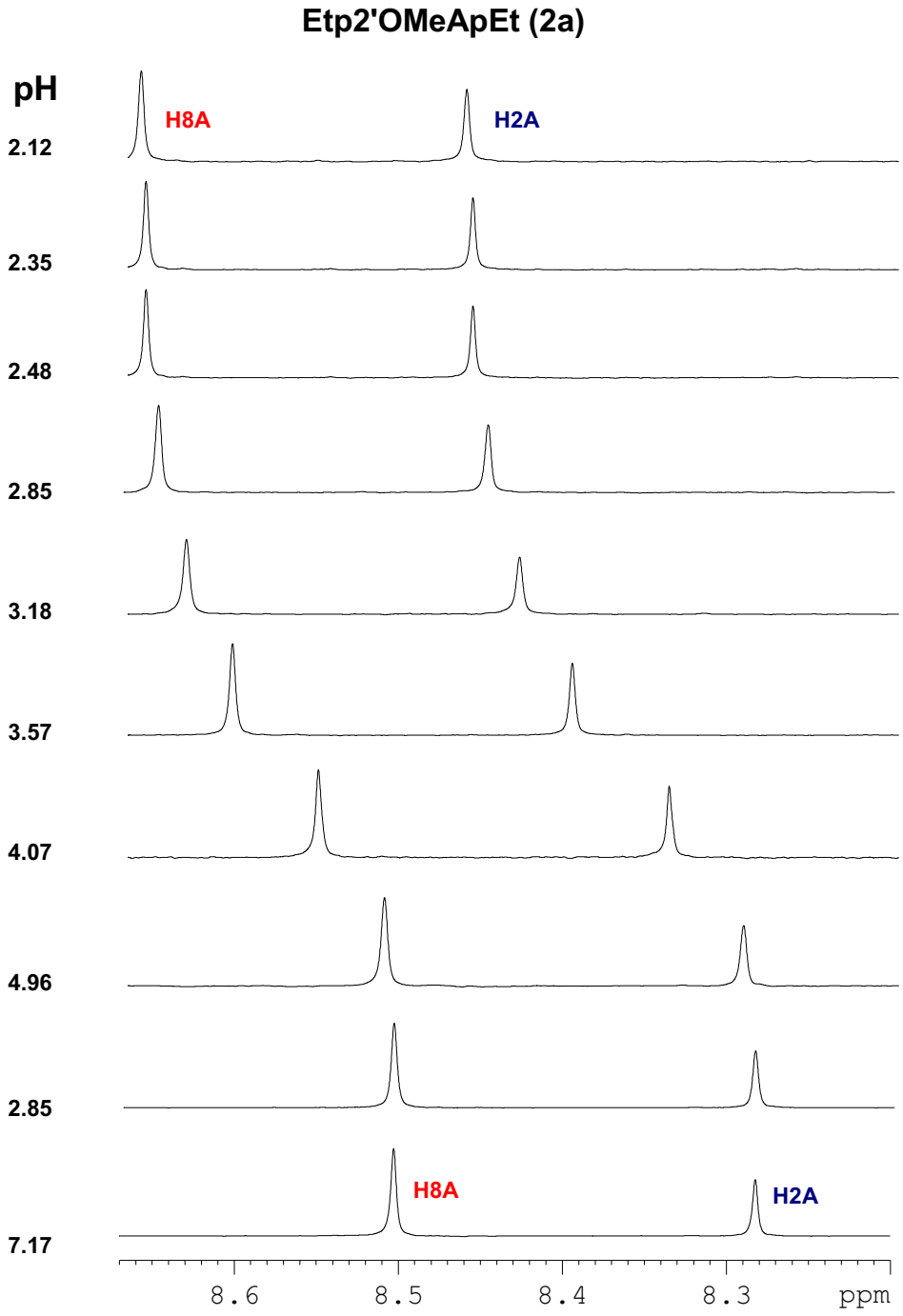
Table S1. Theoretical proton affinities (PA), thermodynamic circle's components enthalpies Gibbs free energies (gas phase and solvation), and the theoretical pK_a values of the nucleobases, 2'-ribo-, 2'-deoxy-, 2'-amino-, 2'-methoxy-, oxetane and azetidine nucleosides as well as the experimental pK_a values for the corresponding bis-ethylphosphate nucleotides.

Table S2. Frontier orbitals of the 2'-ribo, 2'-deoxy, 2'-amino-, 2'-methoxy-, oxetane- and azetidine- nucleosides.

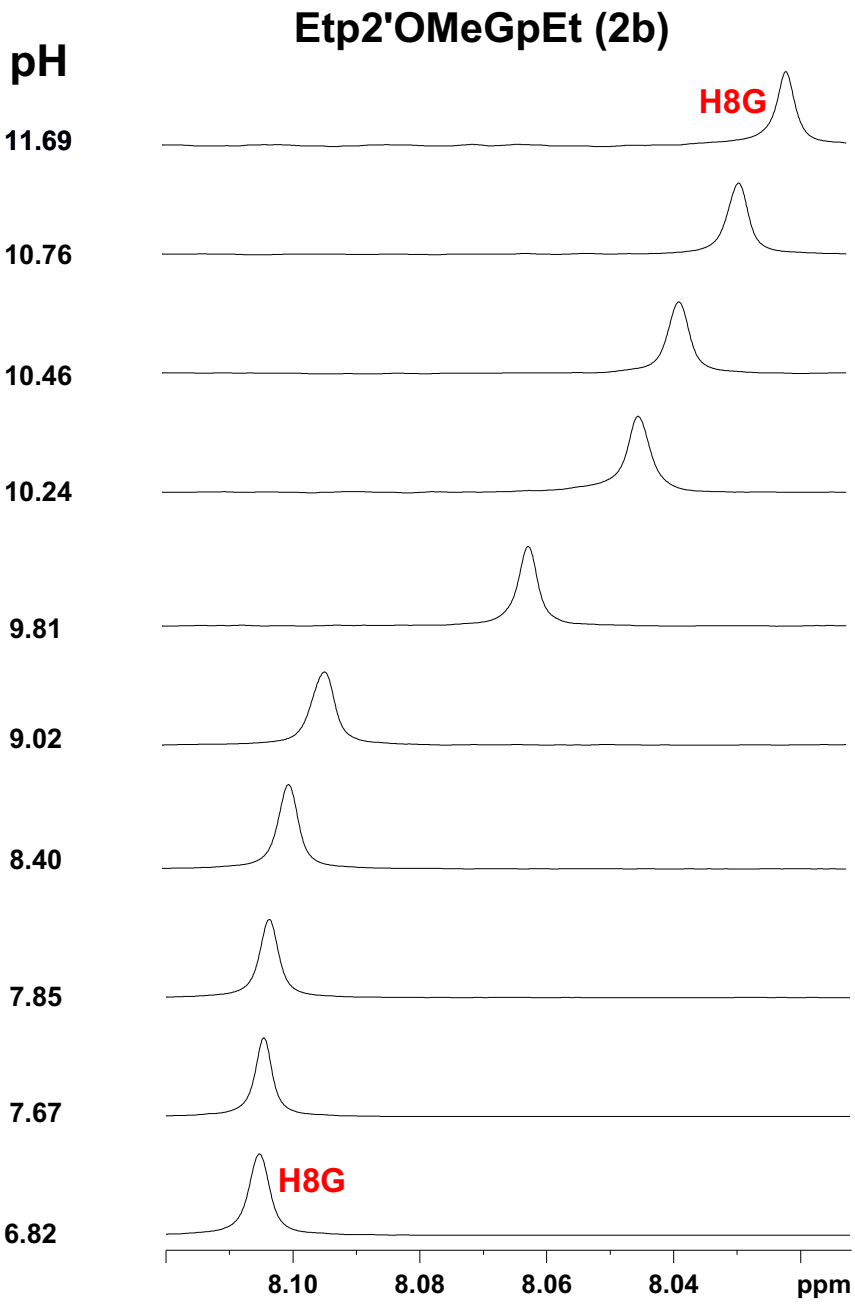
Table S3. Calculated acid-base dipole moments differences (Δdipole moments) of the nucleobases, 2'-deoxy-, 2'-ribo-, 2'-OMe-, oxetane-, and azetidine- nucleosides as well as the experimental pK_a values of the respective bis-ethylphosphate nucleotides.

Figure S1. The stack plots of the pH-dependent ^{1}H NMR chemical shifts of aromatic protons for compounds **2a–2i**, **4a–4j, 5c-5j and 6c-6i** at 298 K [only 10-11 pHs points (including two plateaus at two extreme pHs) are shown out of total ~20 – 33 pHs used for the titration plots, see Experimental section for details].

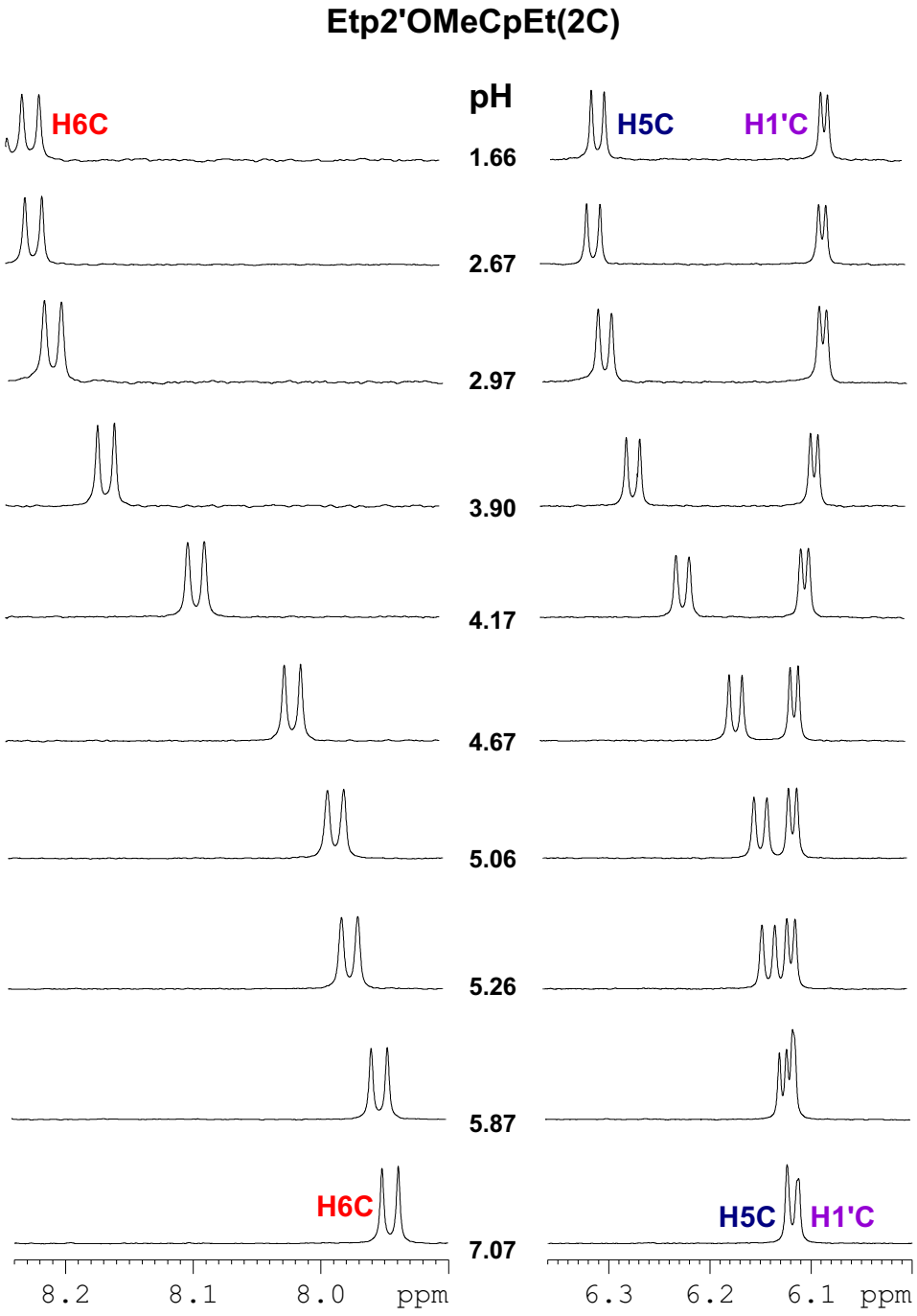
(1) pH dependent ^{1}H chemical shift (in D_2O) of Etp-2′OMe-ApEt (2a) at 298 K



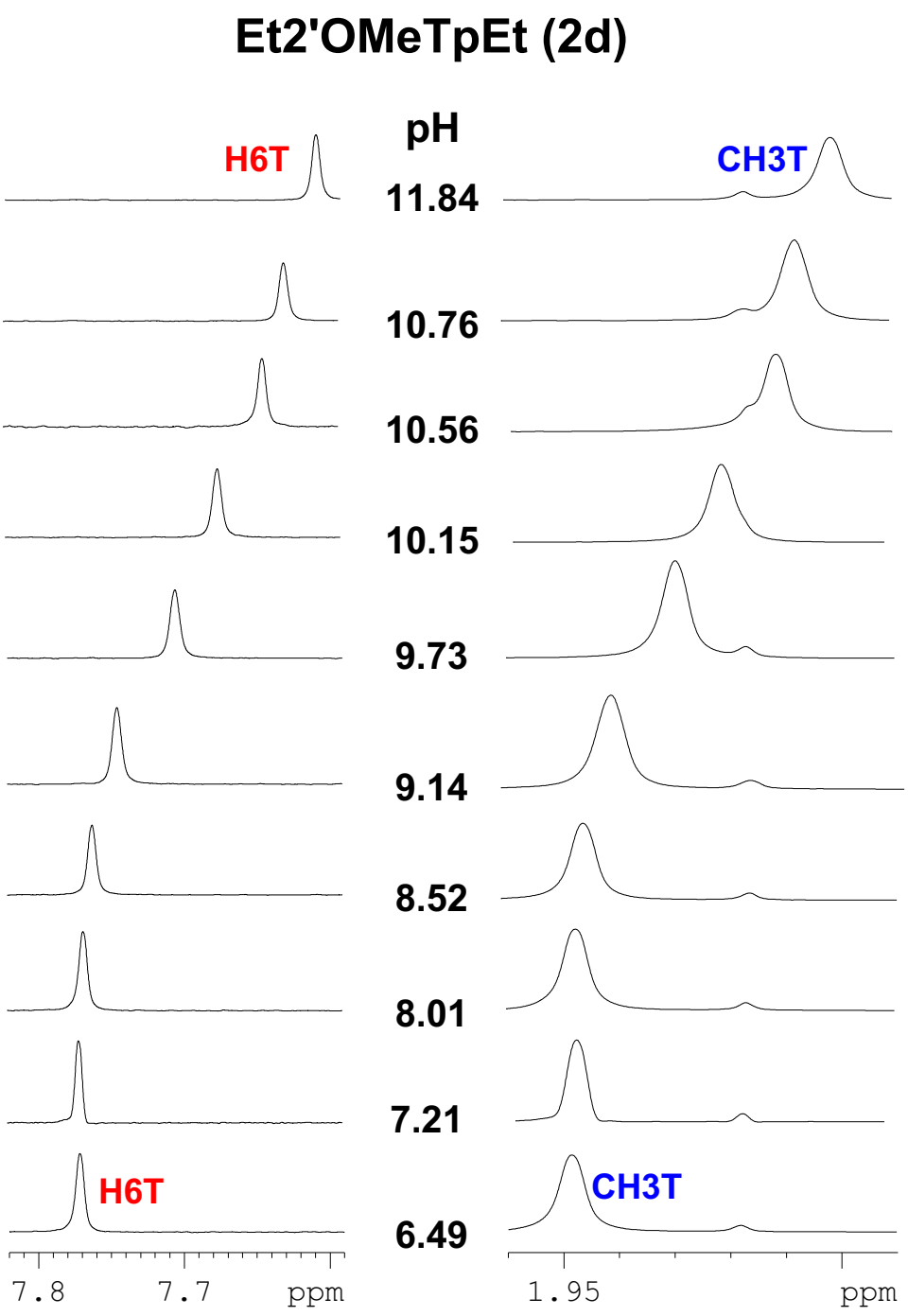
(2) pH dependent ^{1}H chemical shift (in D_2O) of Etp-2′OMe-GpEt (2b) at 298 K



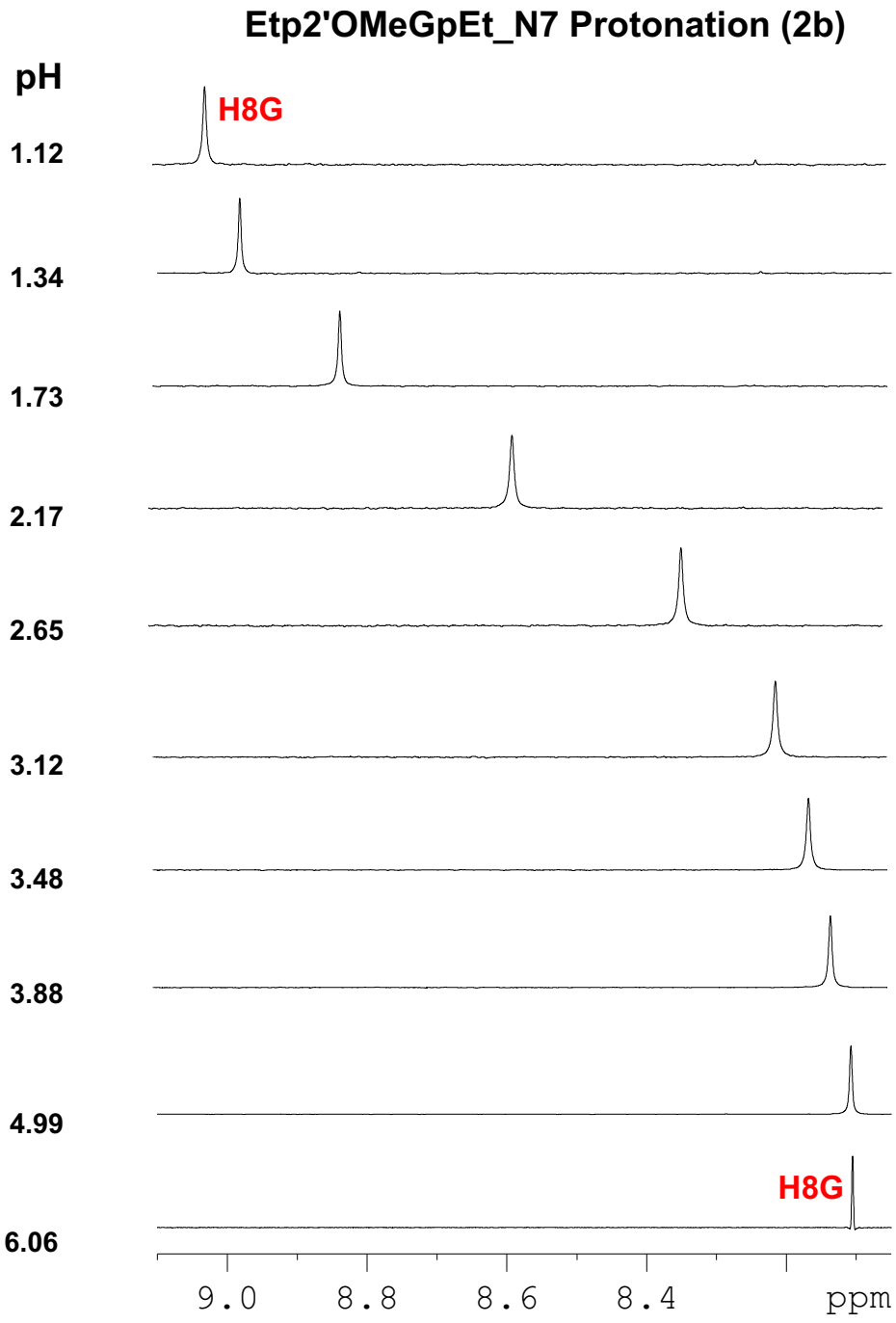
(3) pH dependent ^{1}H chemical shift (in D_2O) of Etp-2′OMe-CpEt (2c) at 298 K



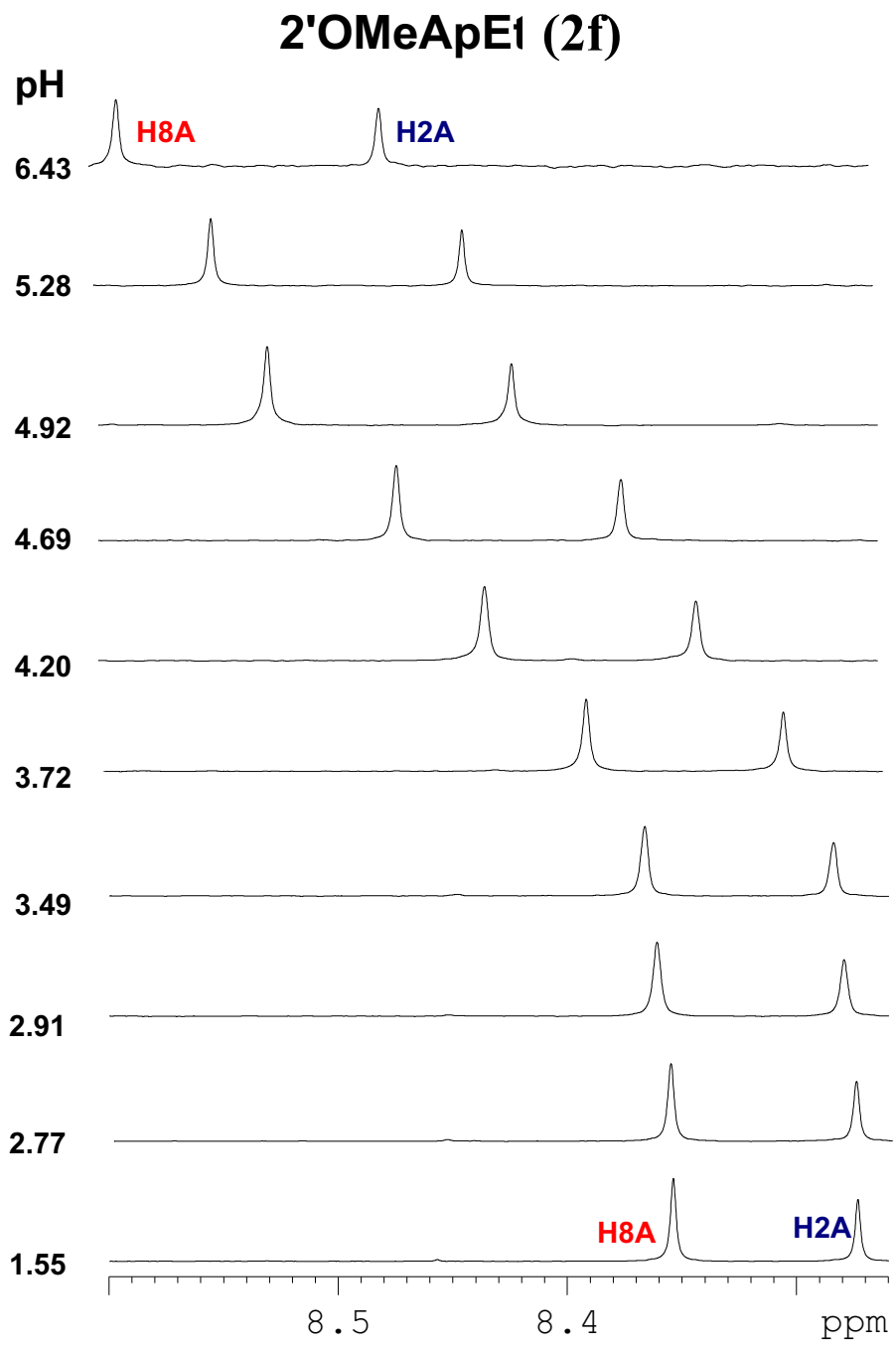
(4) pH dependent ^{1}H chemical shift (in D_2O) of Etp-2′OMe-TpEt (2d) at 298 K



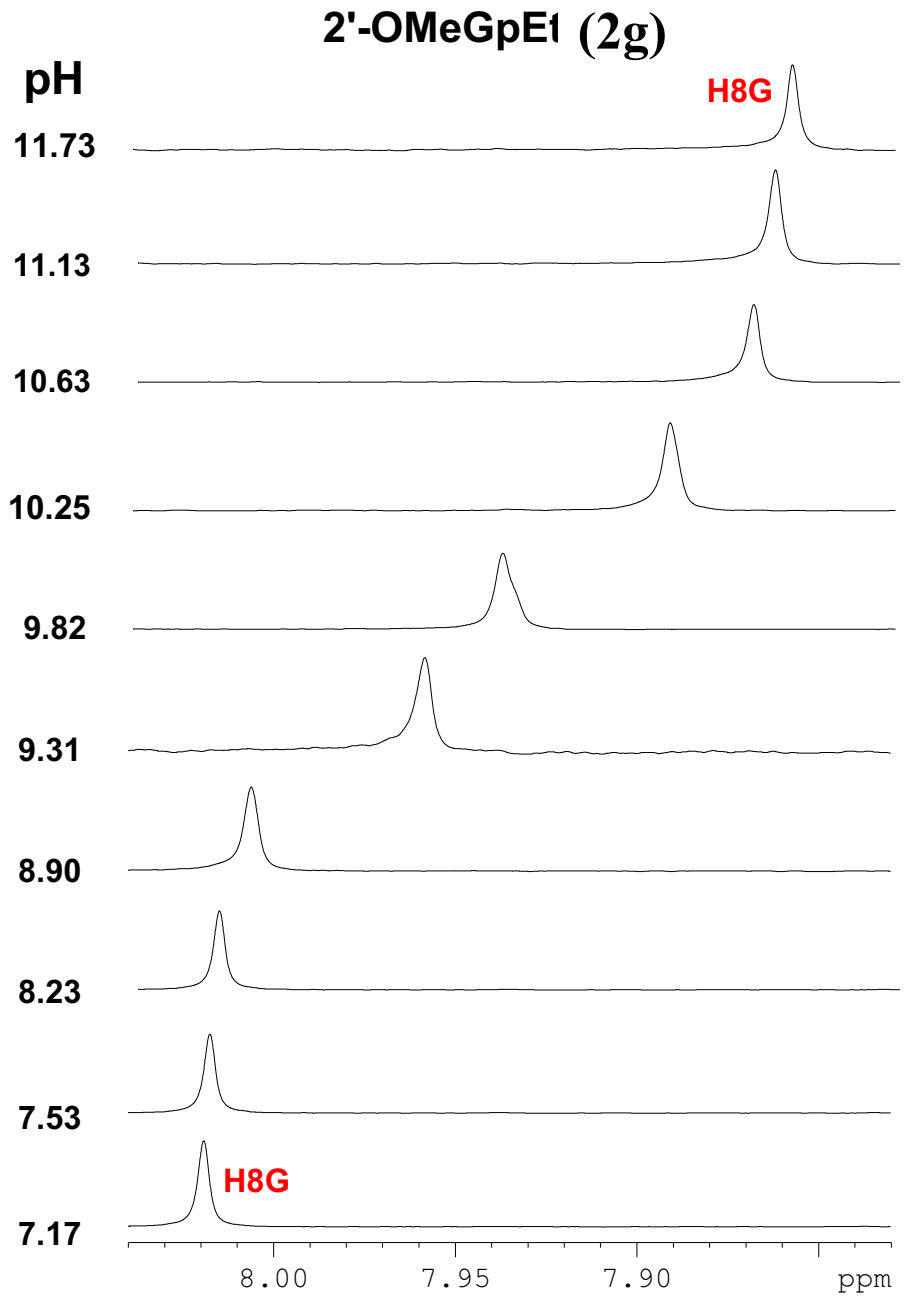
(5) pH dependent ^{1}H chemical shift (in D_2O) of Etp-2′OMe-GpEt for *N7* protonation (2b) at 298K



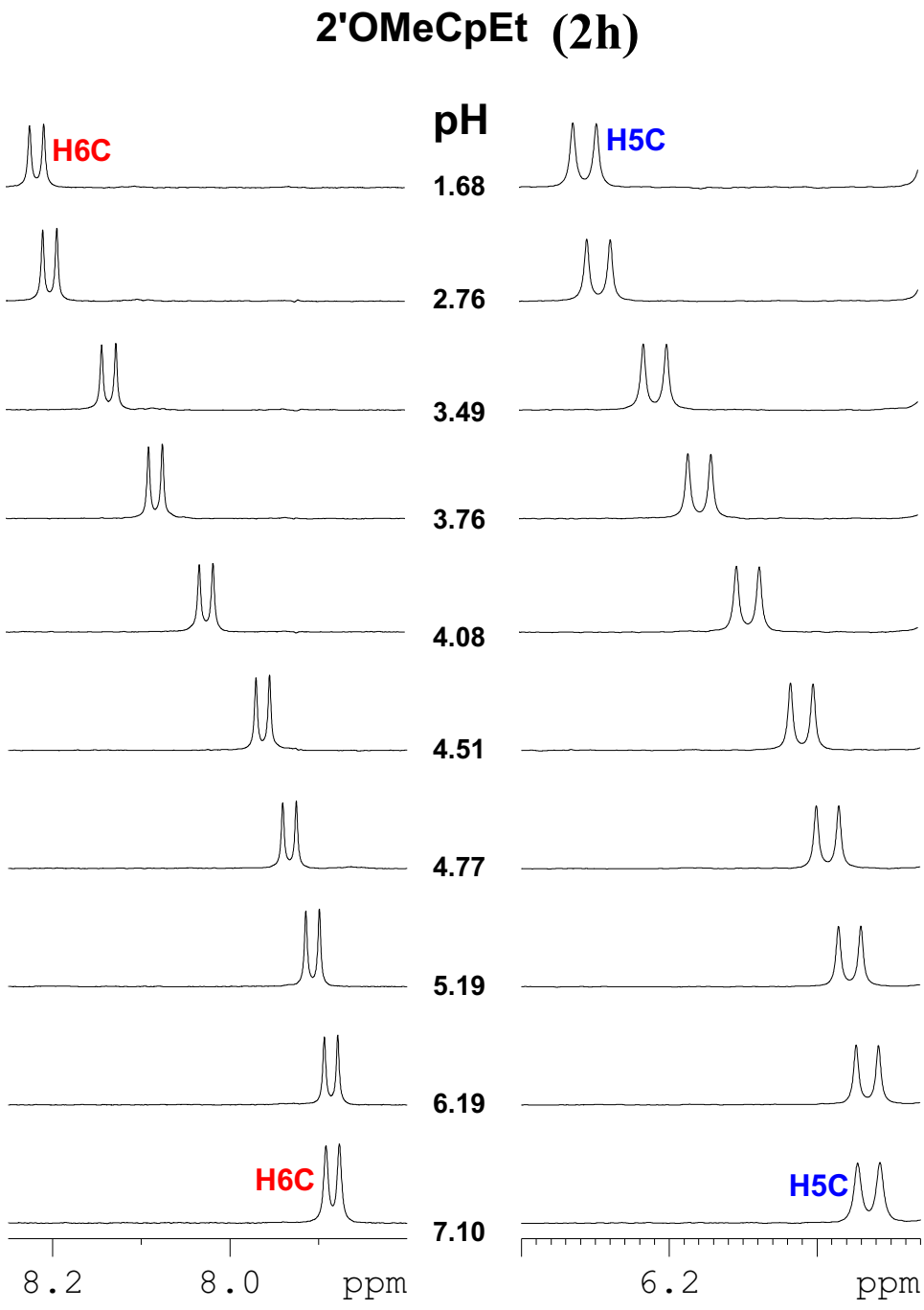
(6) pH dependent ^{1}H chemical shift (in D_2O) of 2′OMe-ApEt (2f) at 298 K



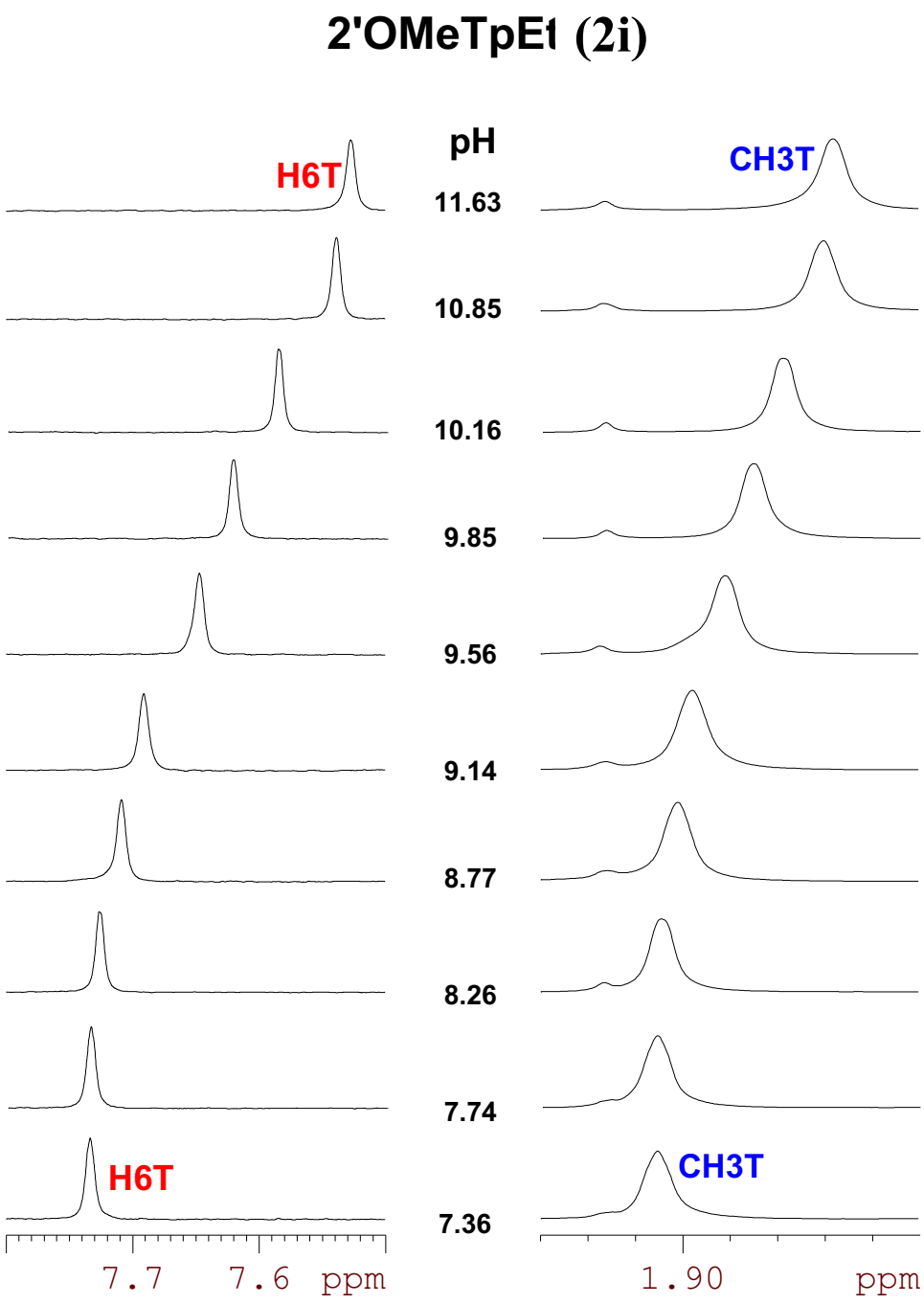
(7) pH dependent ^{1}H chemical shift (in D_2O) of 2′OMe-GpEt (2g) at 298 K



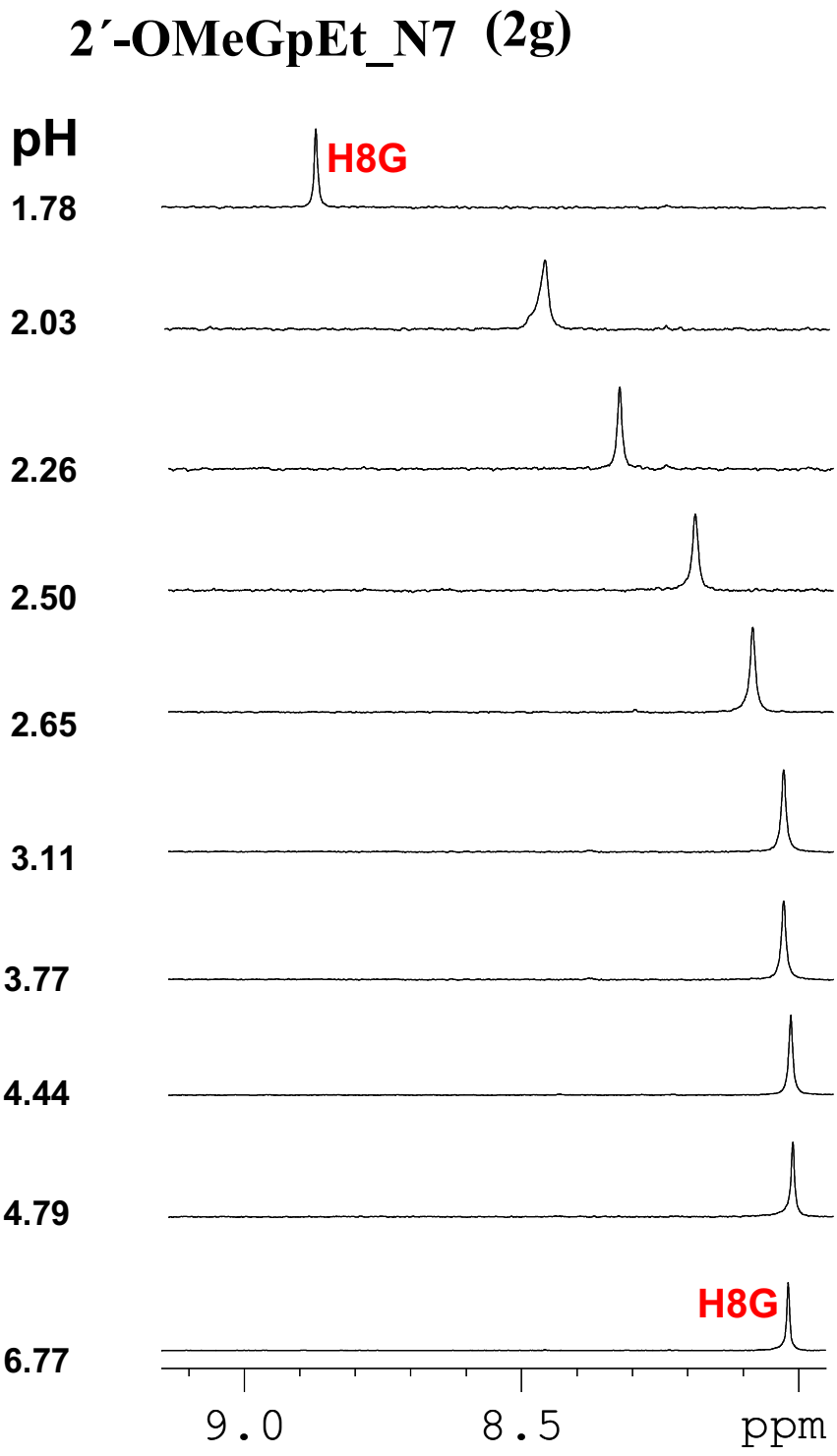
(8) pH dependent ^{1}H chemical shift (in D_2O) of 2′OMe-CpEt (2h) at 298 K



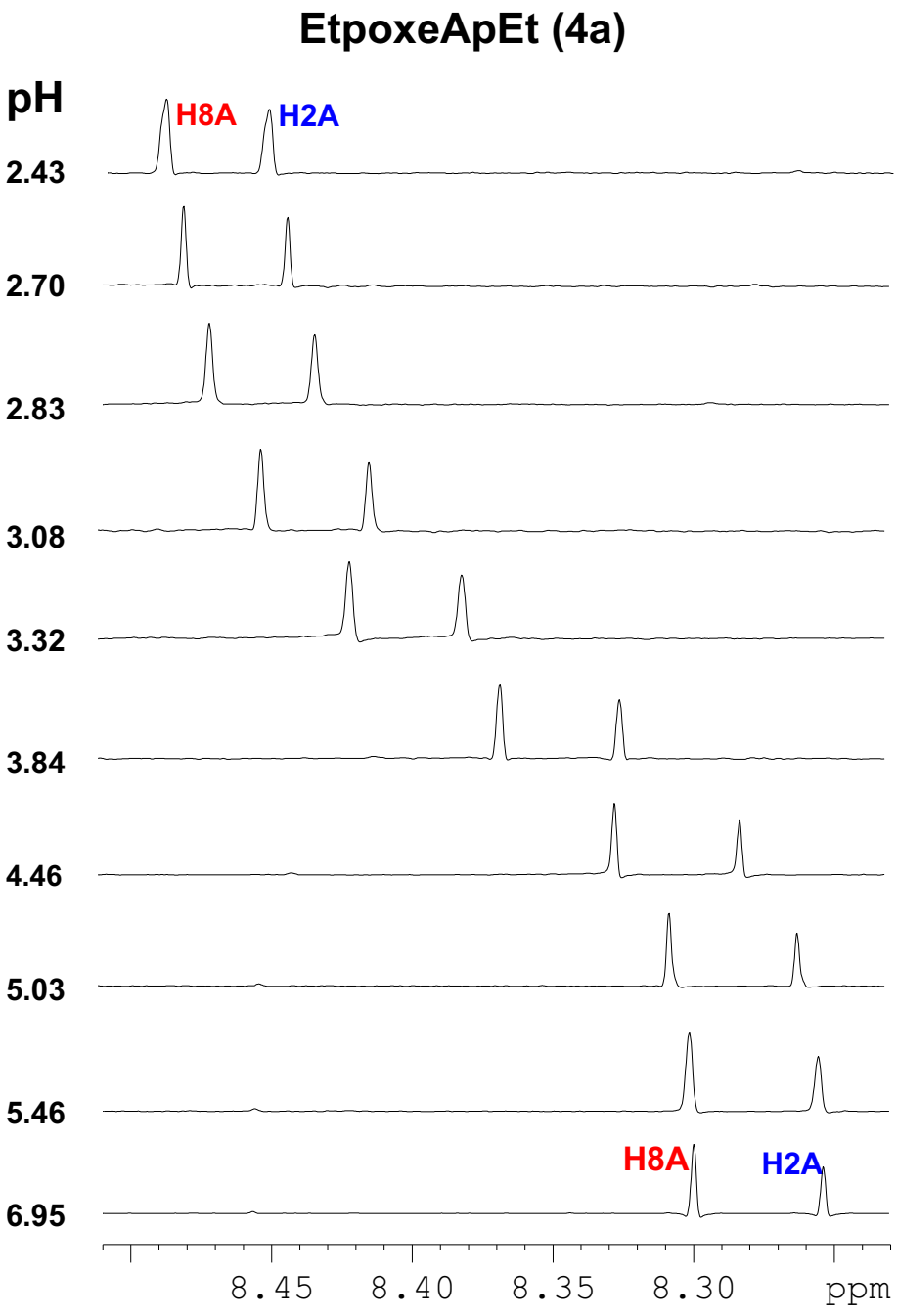
(9) pH dependent ^{1}H chemical shift (in D_2O) of 2′OMe-TpEt (2i) at 298 K



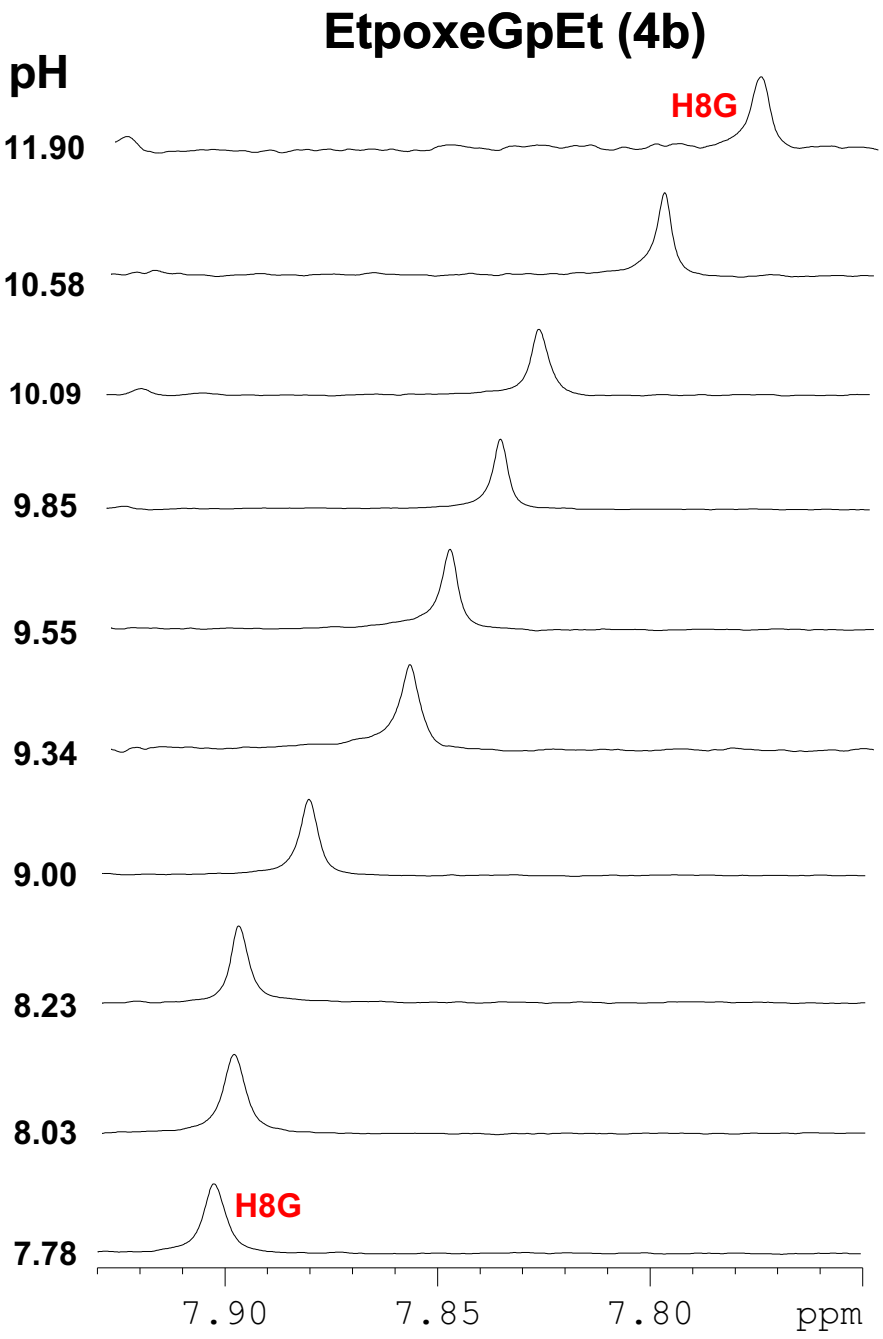
(10) pH dependent ^{1}H chemical shift (in D_2O) of 2′OMe-GpEt_N7 (2g) at 298 K



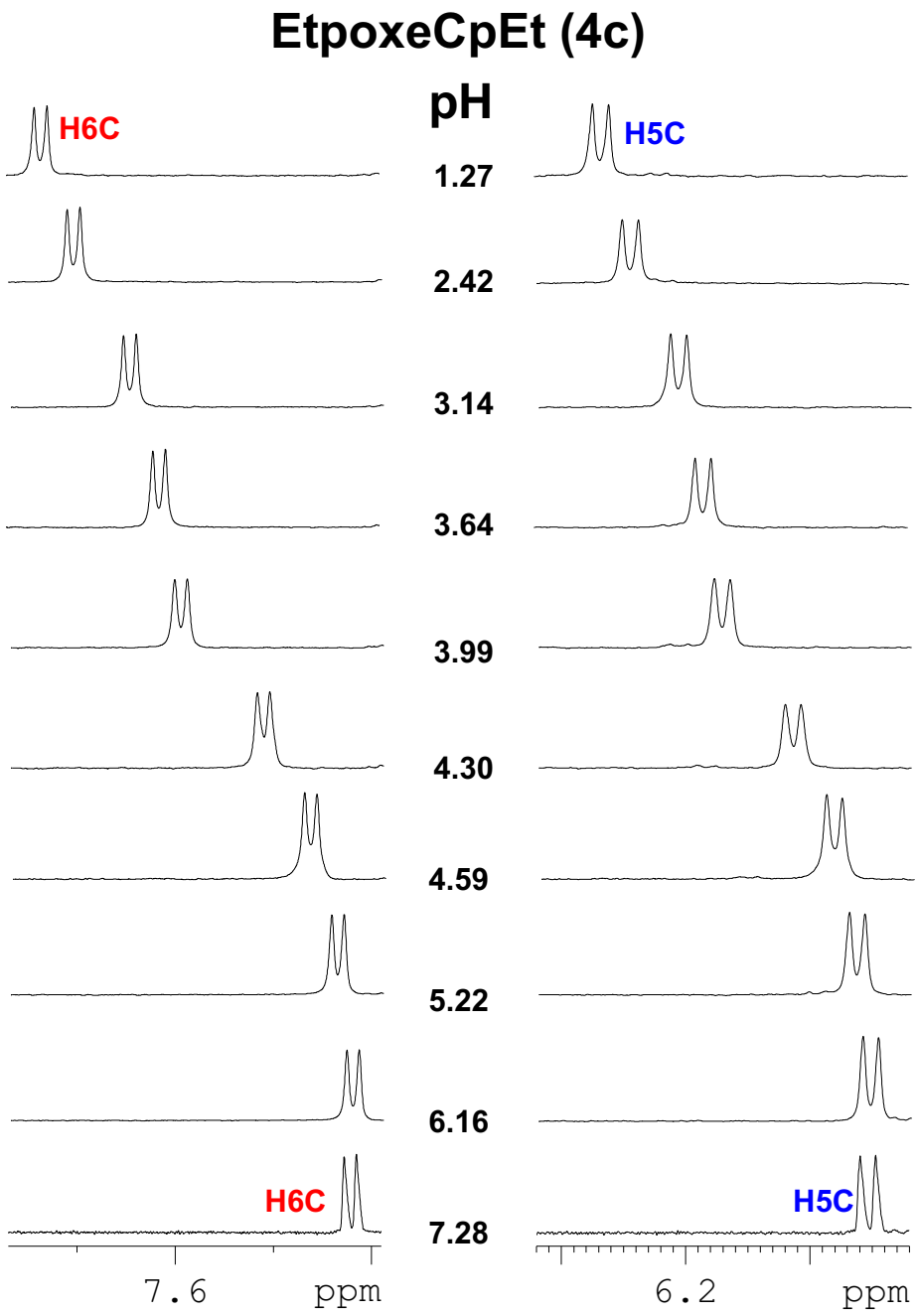
(11) pH dependent ^{1}H chemical shift (in D_2O) of EtpOxeApEt (4a) at 298 K



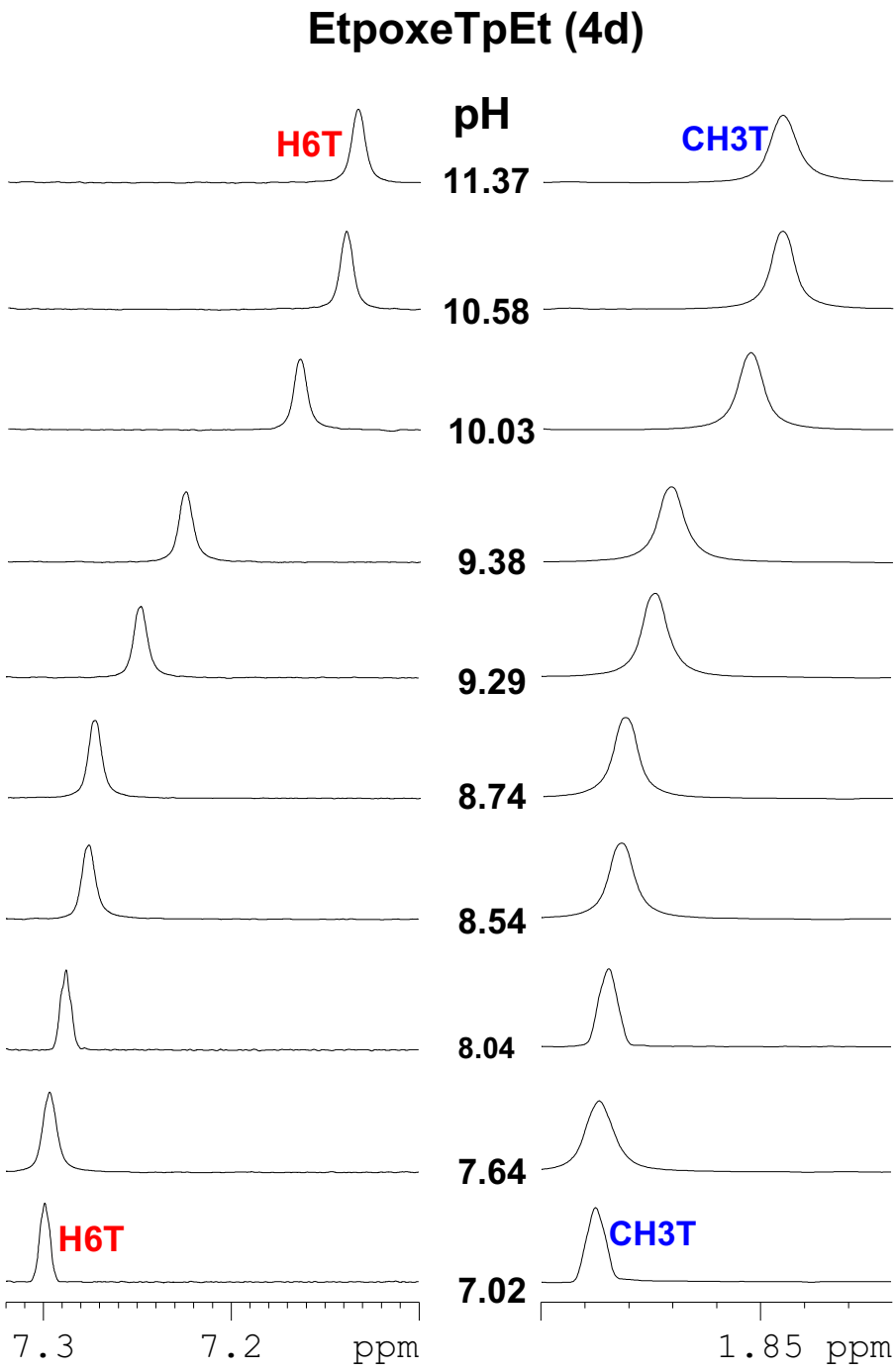
(12) pH dependent ^{1}H chemical shift (in D_2O) of EtpOxeGpEt (4b) at 298 K



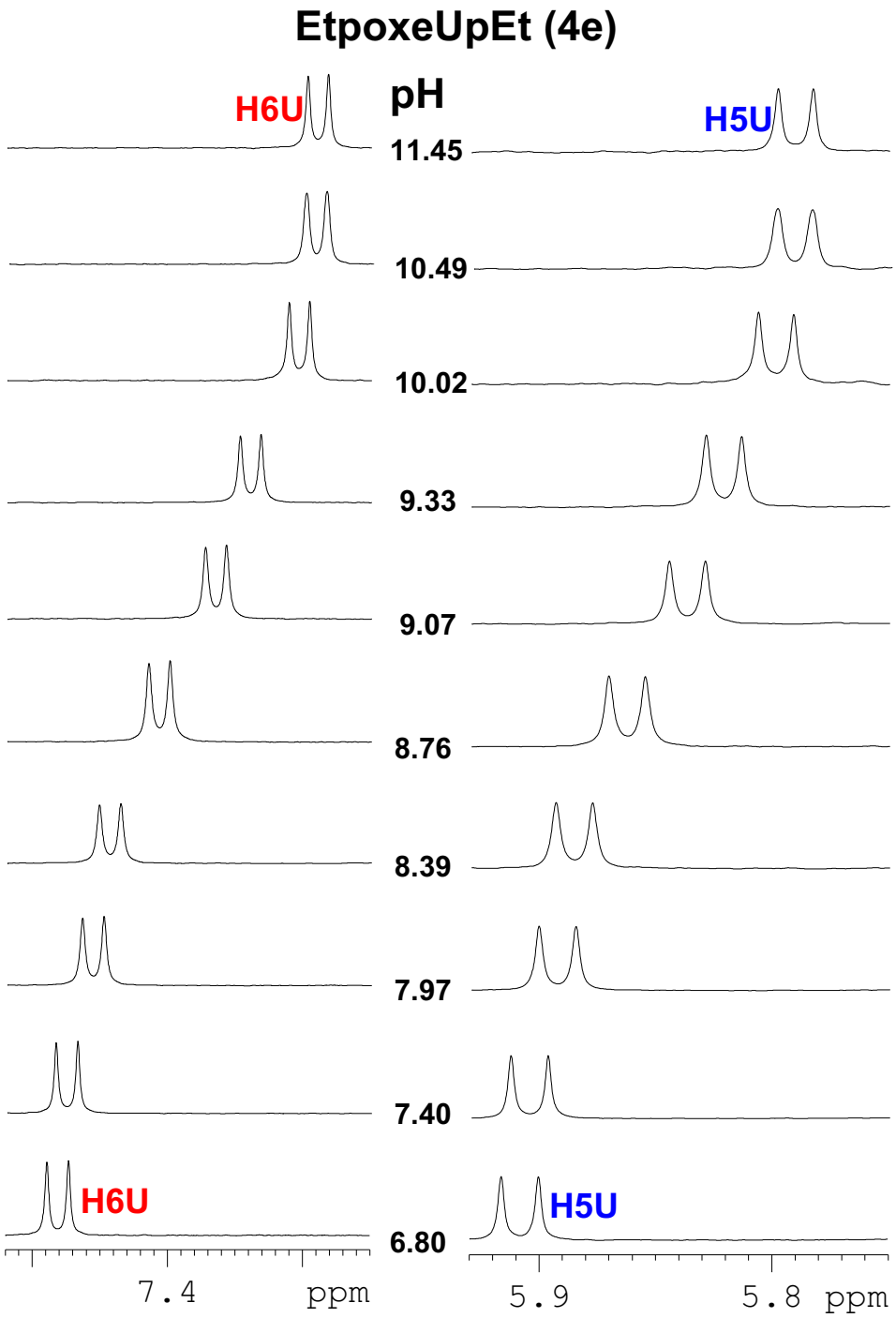
(13) pH dependent ^{1}H chemical shift (in D_2O) of EtpOxeCpEt (4c) at 298 K



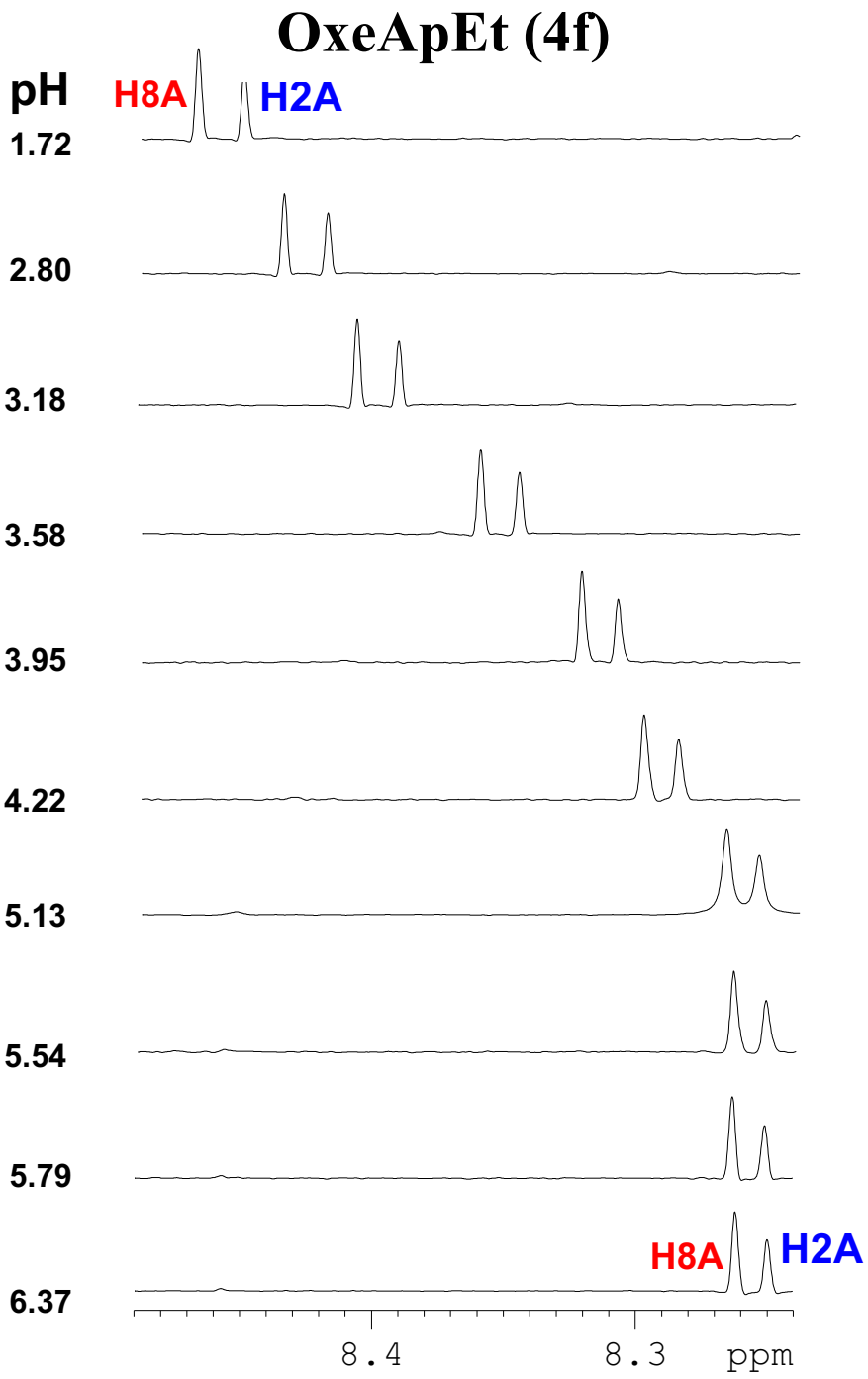
(14) pH dependent ^{1}H chemical shift (in D_2O) of EtpOxeTpEt (4d) at 298 K



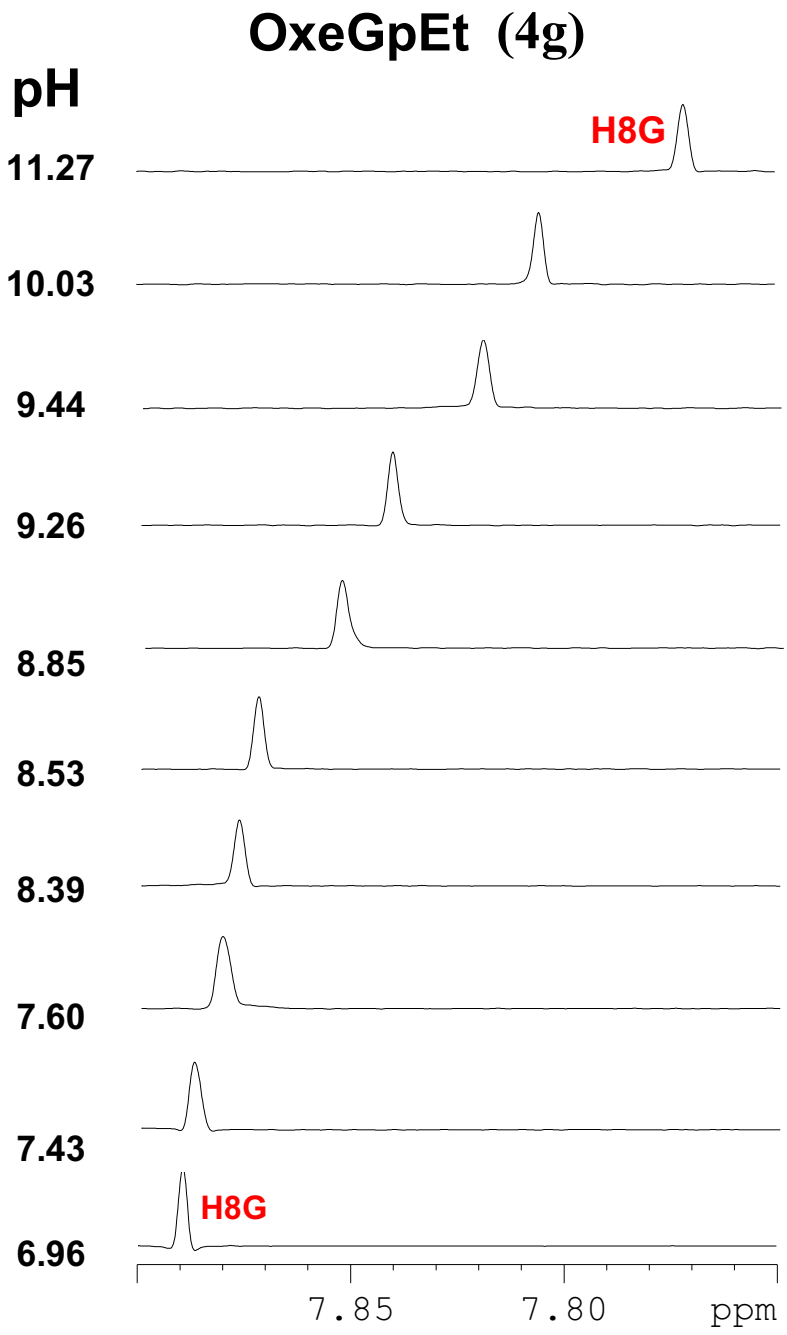
(15) pH dependent ^{1}H chemical shift (in D_2O) of EtpOxeUpEt (4e) at 298 K



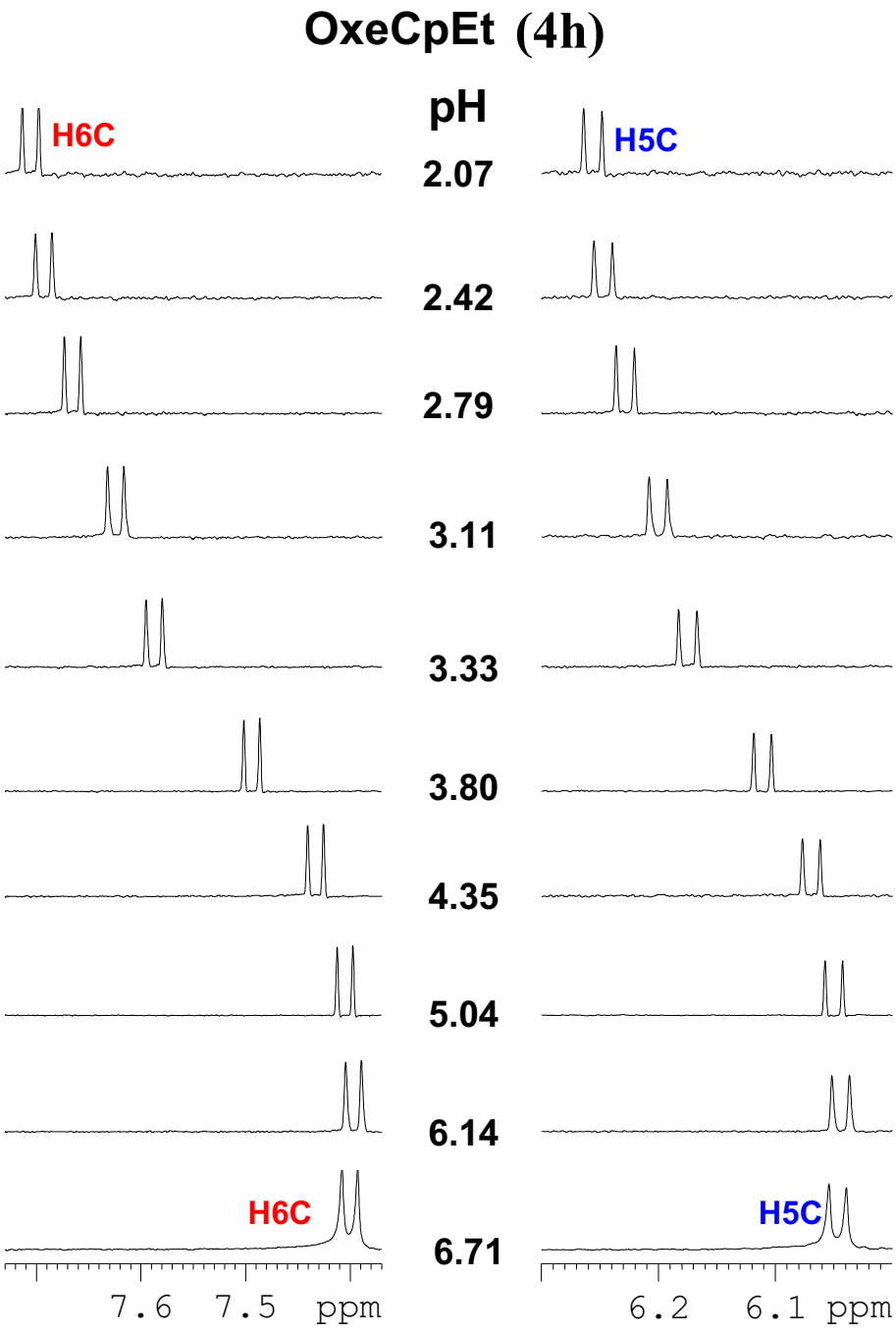
(16) pH dependent ^{1}H chemical shift (in D_2O) of OxeApEt (4f) at 298 K



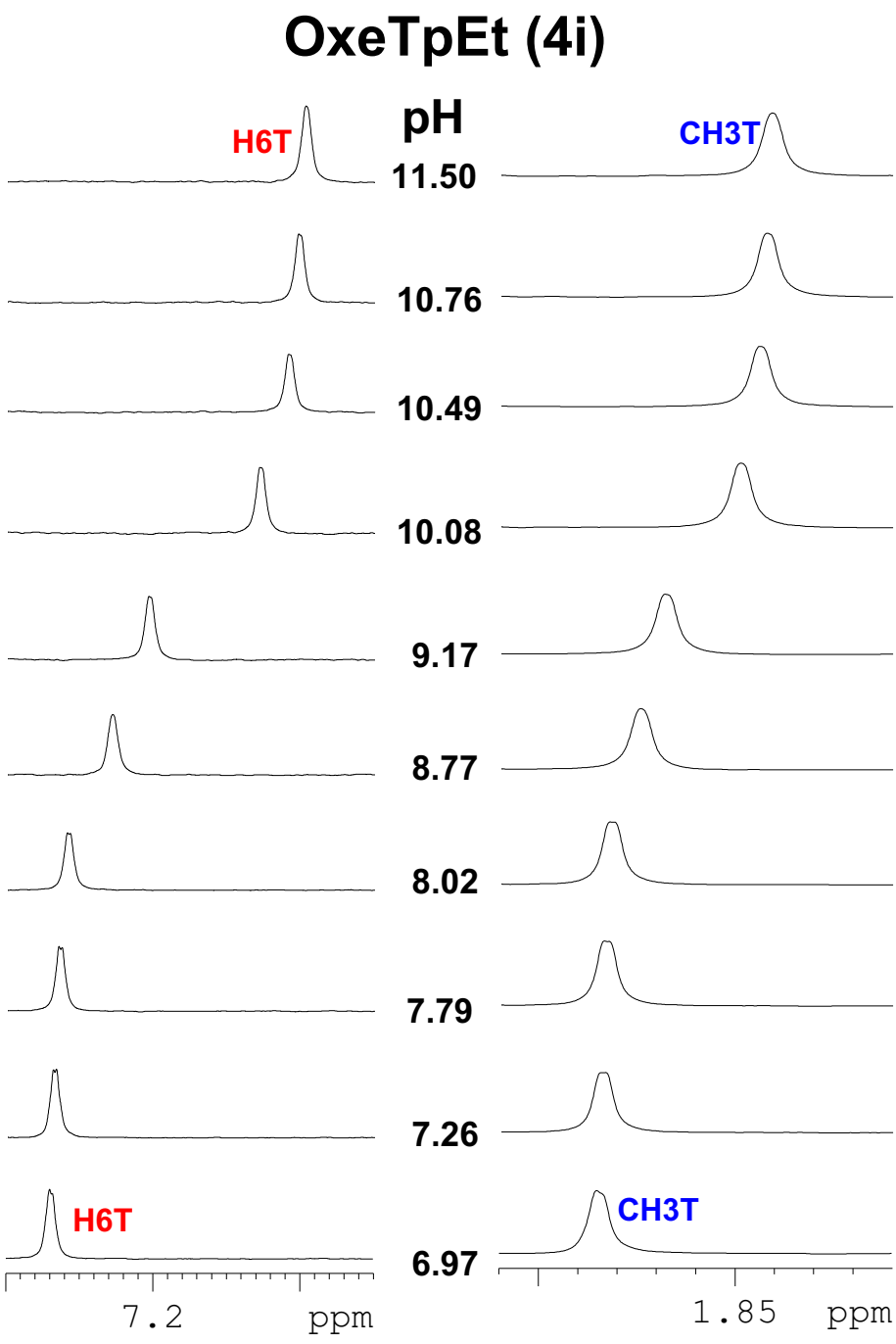
(17) pH dependent ^{1}H chemical shift (in D_2O) of OxeGpEt (4g) at 298 K



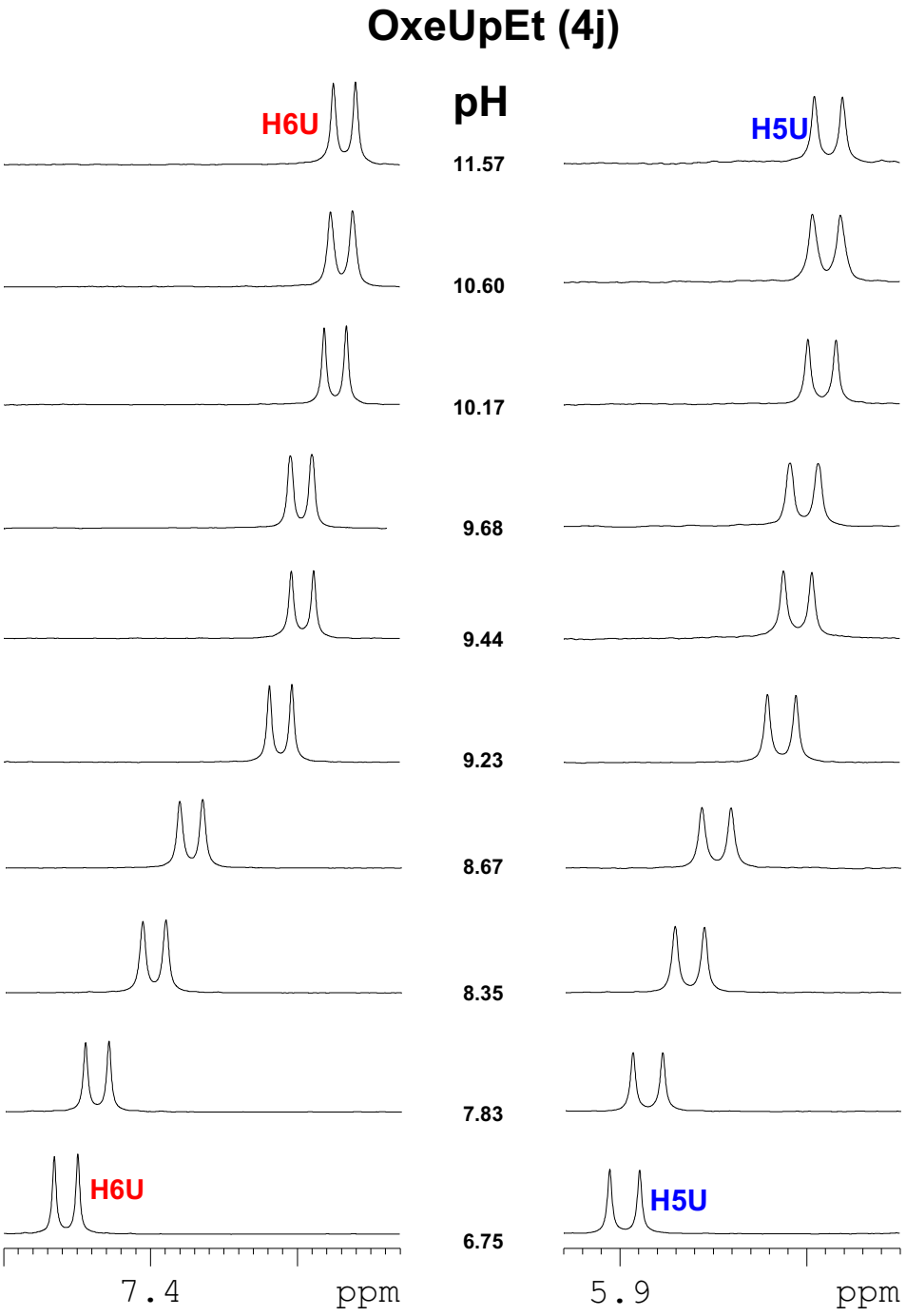
(18) pH dependent ^{1}H chemical shift (in D_2O) of OxeCpEt (4h) at 298 K



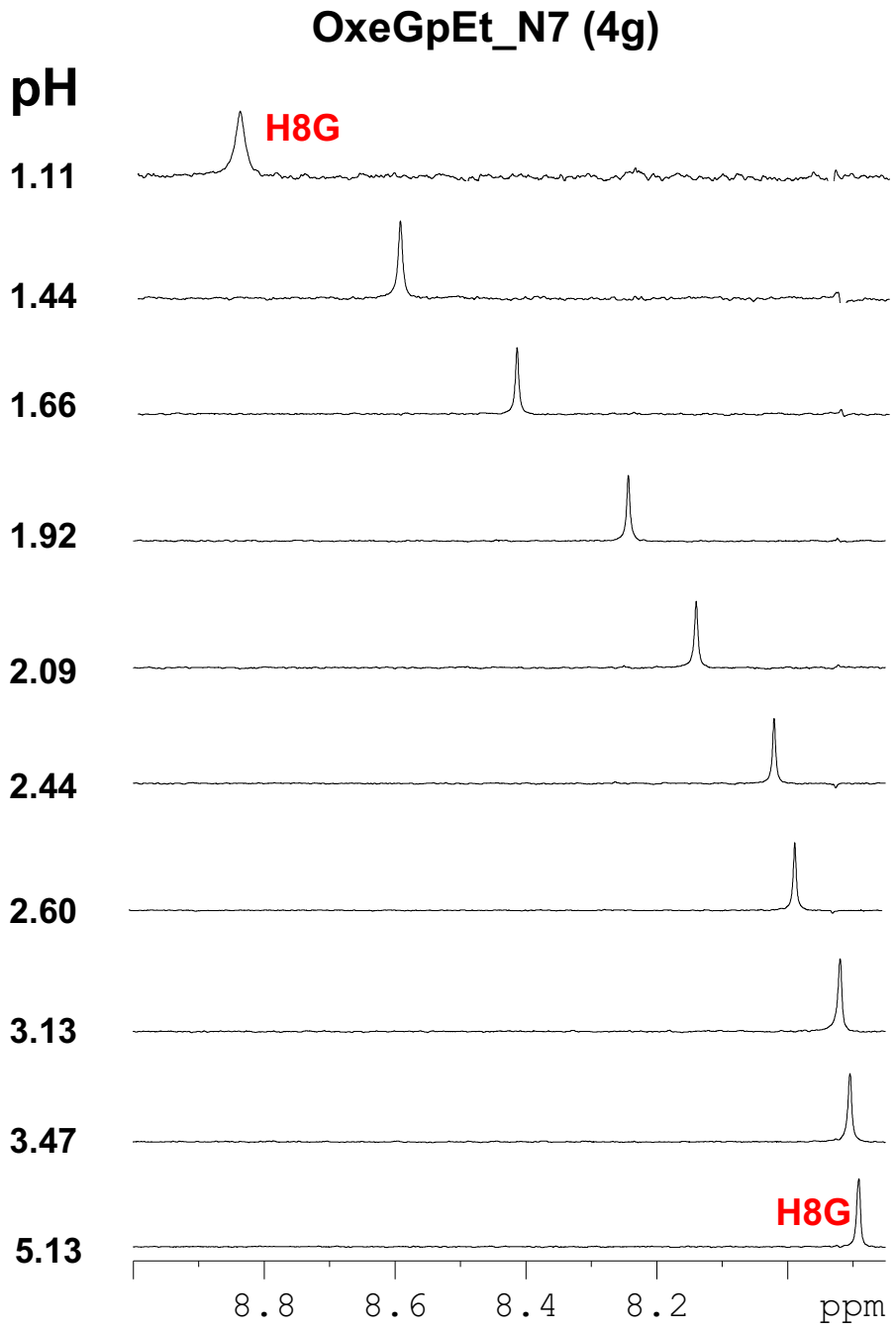
(19) pH dependent ^{1}H chemical shift (in D_2O) of OxeTpEt (4i) at 298 K



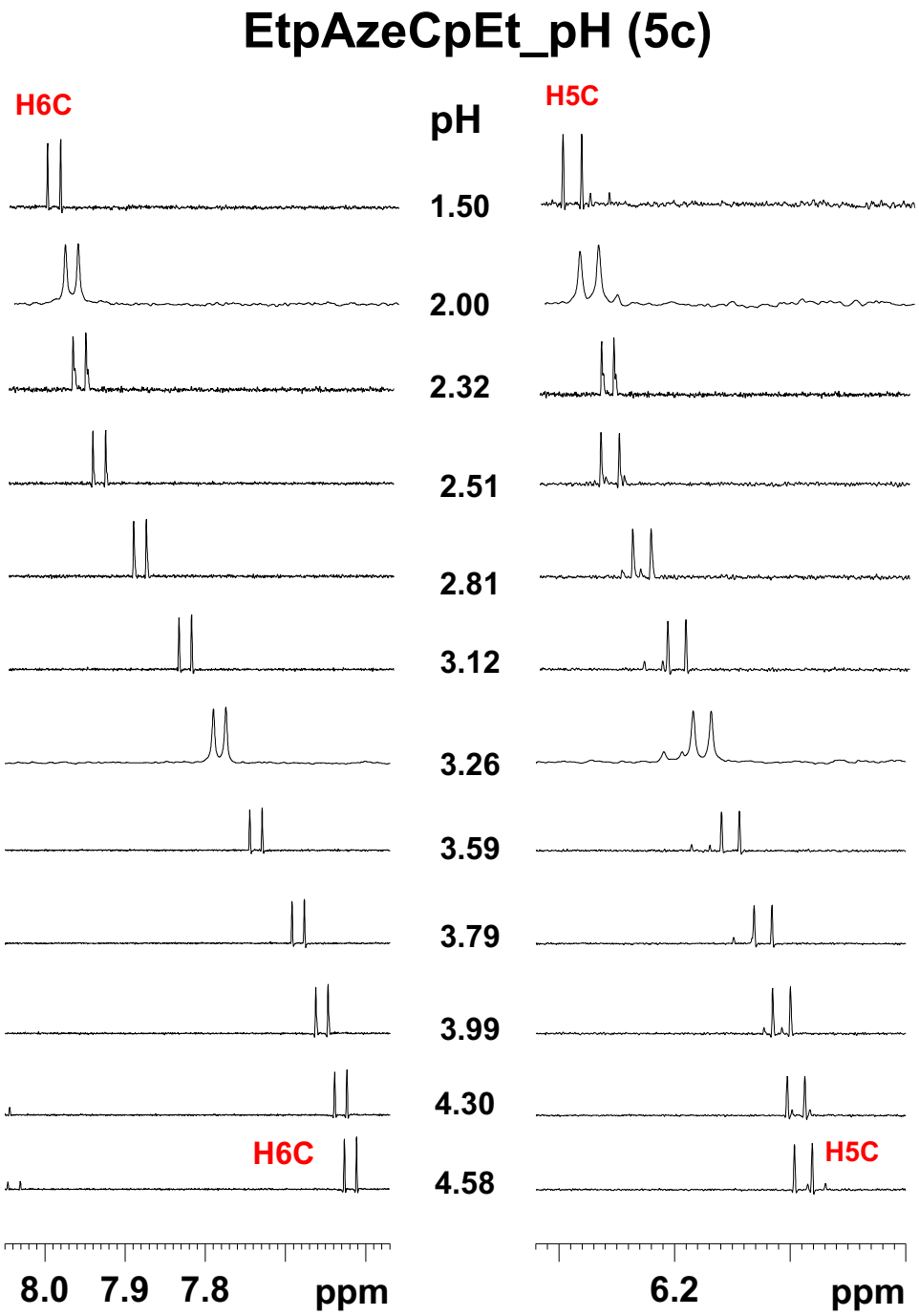
(20) pH dependent ^{1}H chemical shift (in D_2O) of OxeUpEt (4j) at 298 K



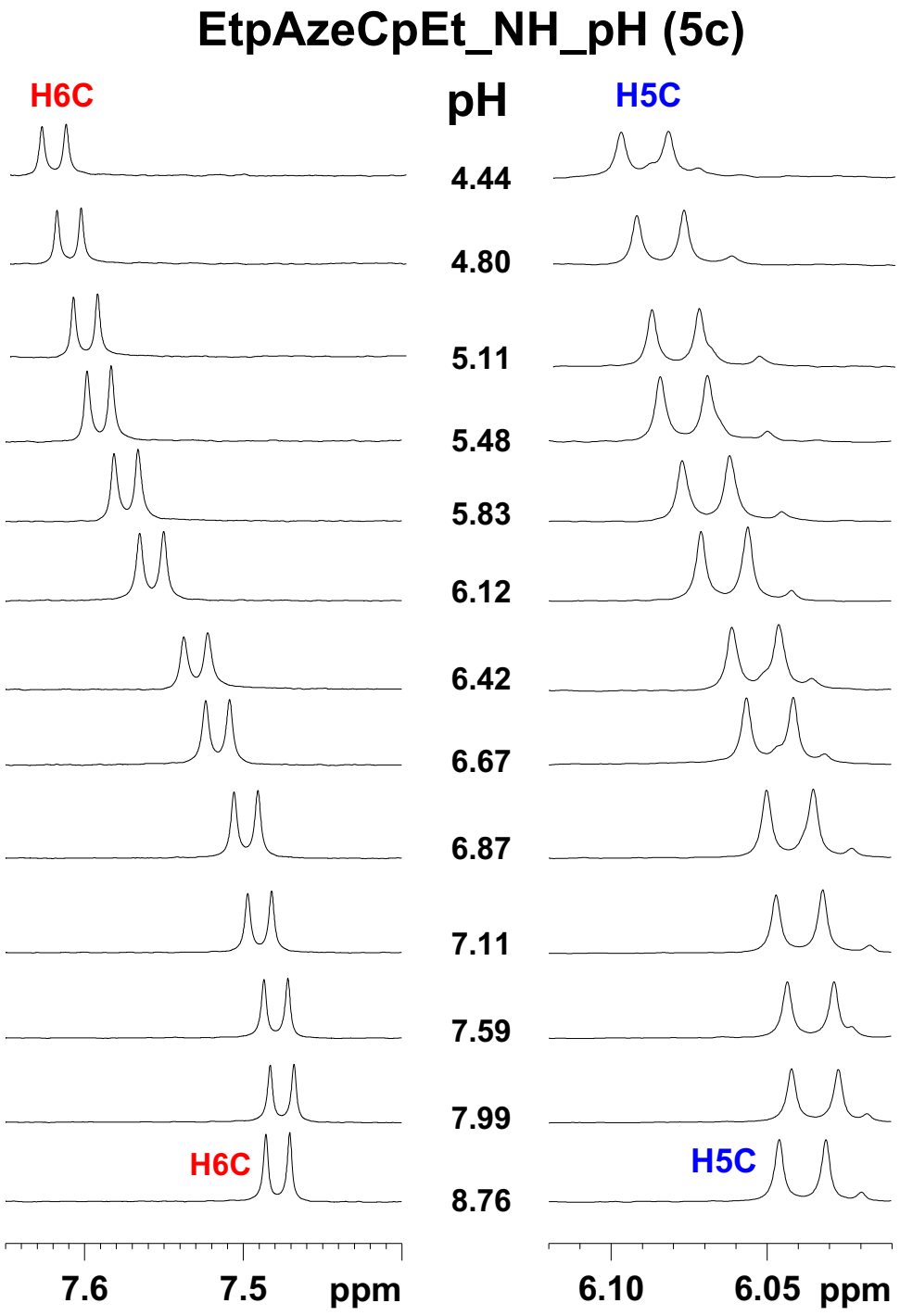
(21) pH dependent ^{1}H chemical shift (in D_2O) of OxeGpEt (4g) at 298 K



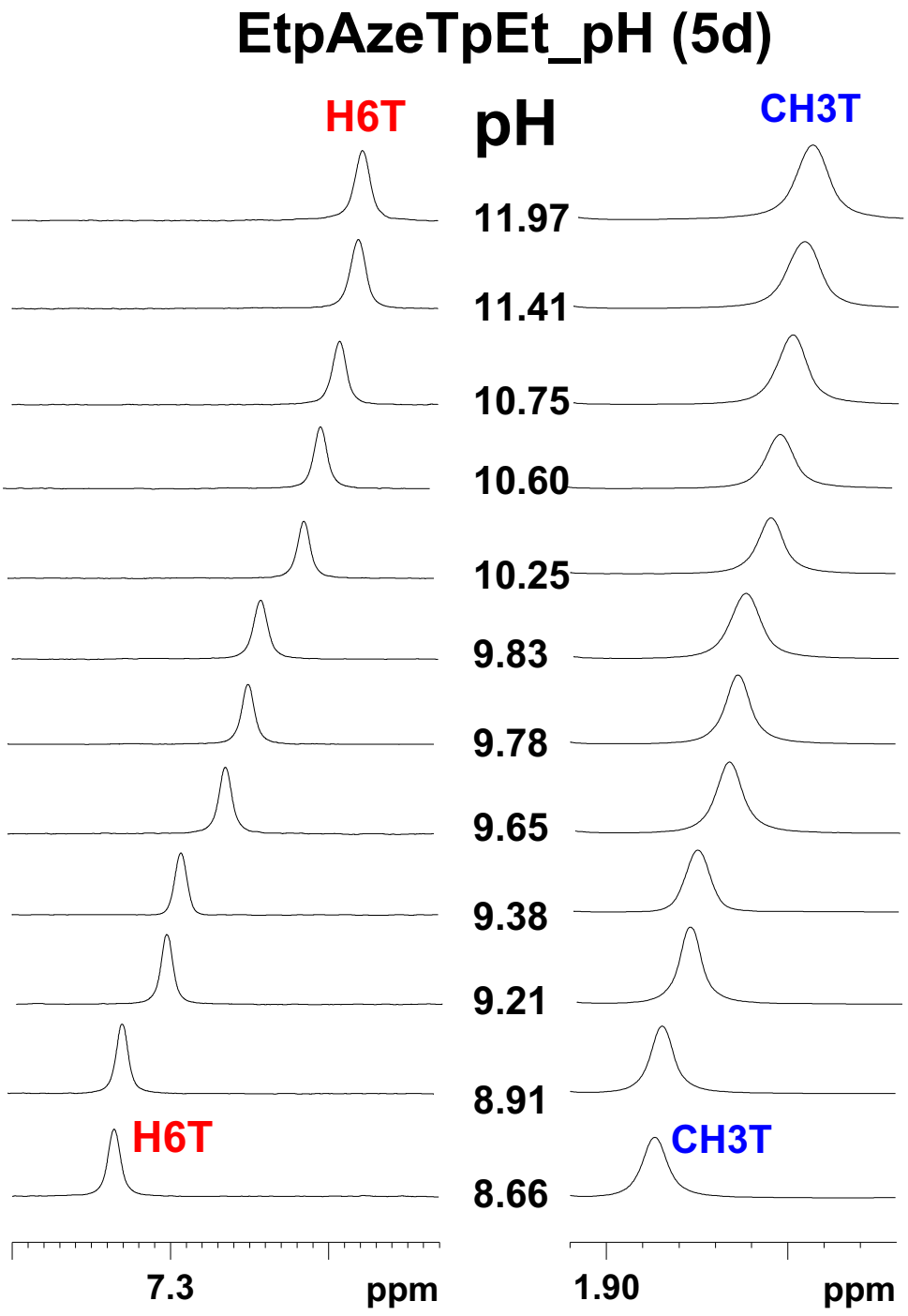
(22) pH dependent ^{1}H chemical shift (in D_2O) of EtpAzeCpEt (5c) at 298 K



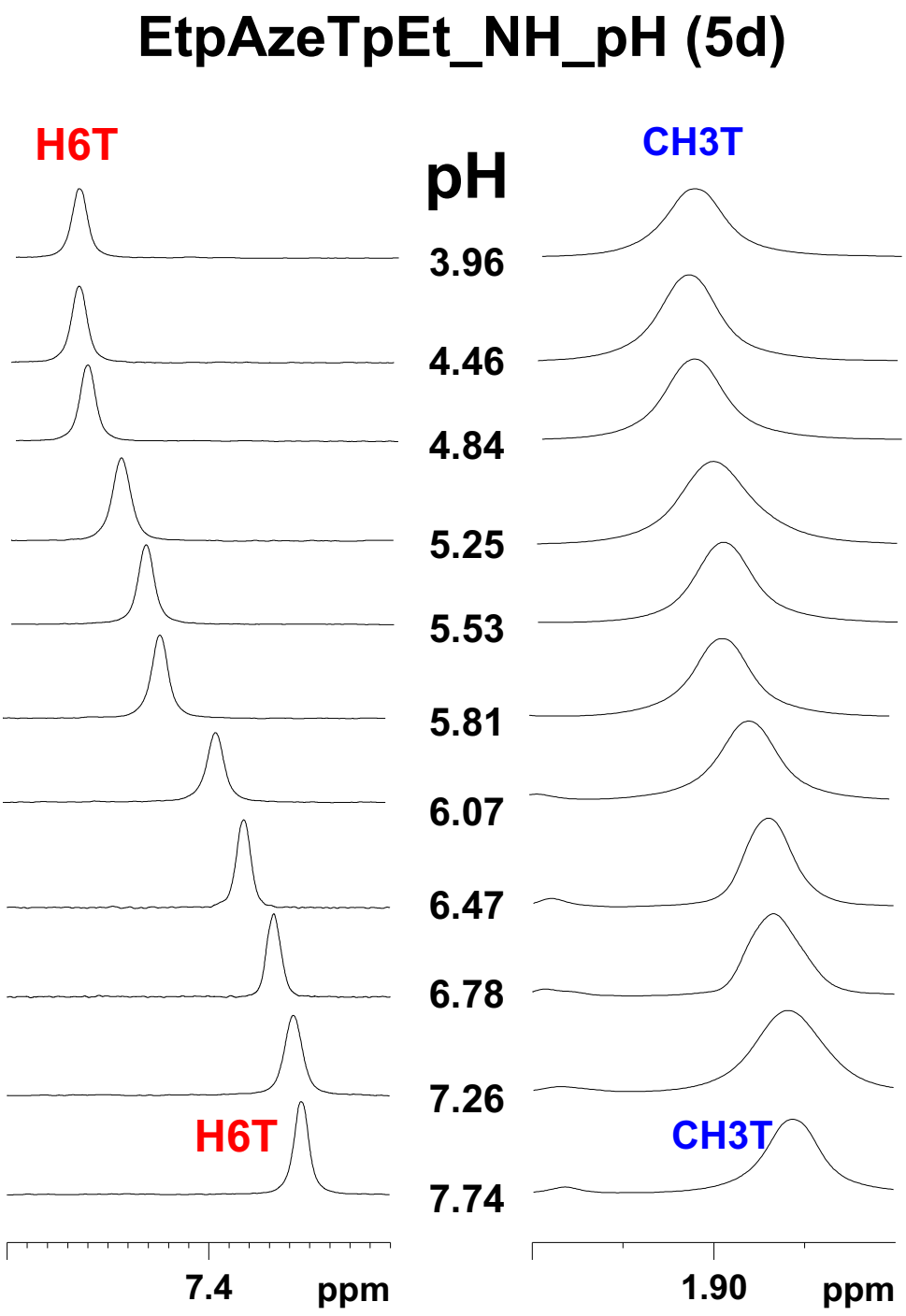
(23) pH dependent ^{1}H chemical shift (in D_2O) of EtpAzeCpEt azetidine protonation (5c) at 298 K



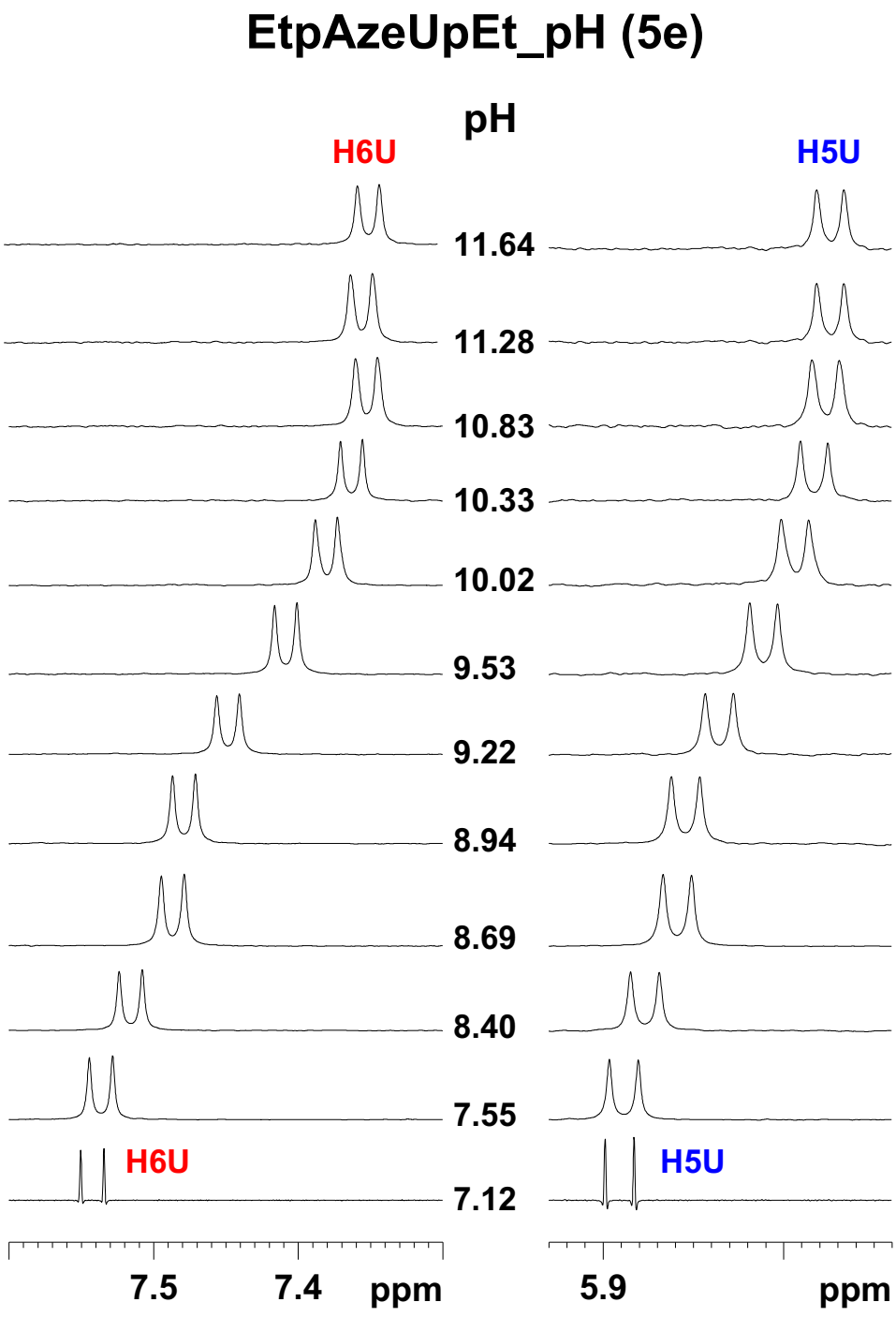
(24) pH dependent ^{1}H chemical shift (in D_2O) of EtpAzeTpEt (5d) at 298 K



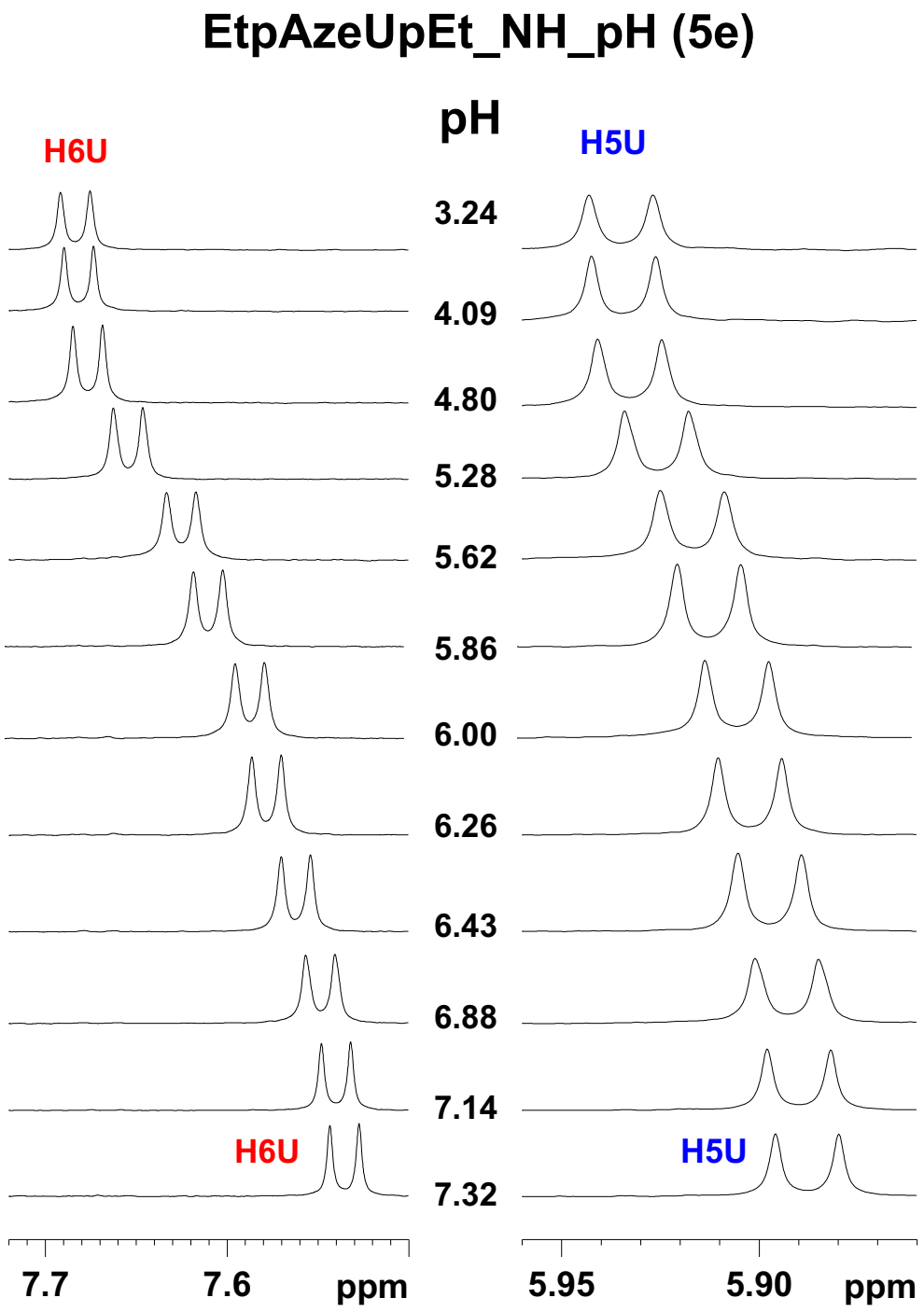
(25) pH dependent ^{1}H chemical shift (in D_2O) of EtpAzeTpEt azetidine protonation (5d) at 298 K



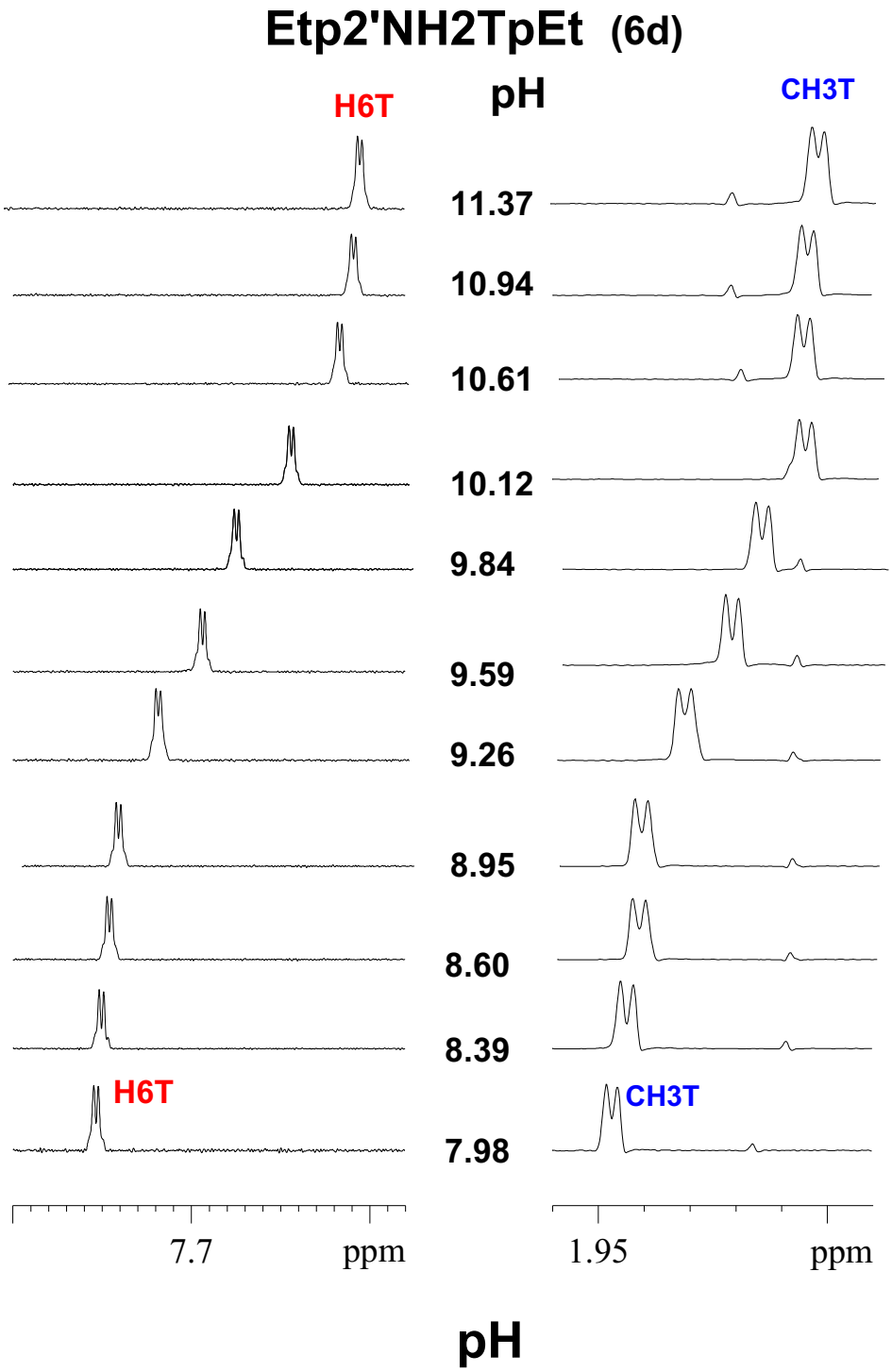
(26) pH dependent ^{1}H chemical shift (in D_2O) of EtpAzeUpEt (5e) at 298 K



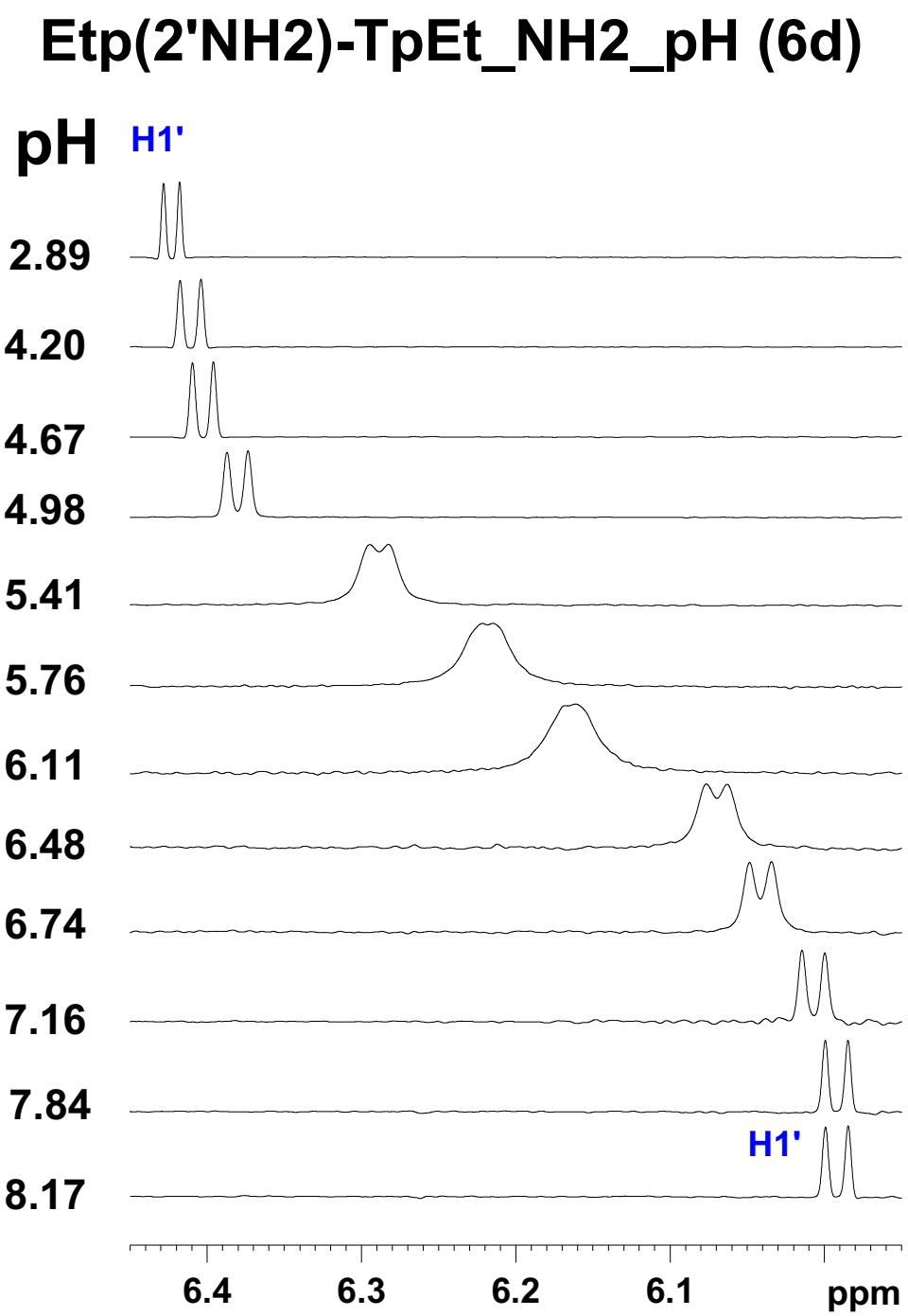
(27) pH dependent ^{1}H chemical shift (in D_2O) of EtpAzeUpEt azetidine protonation (5e) at 298 K



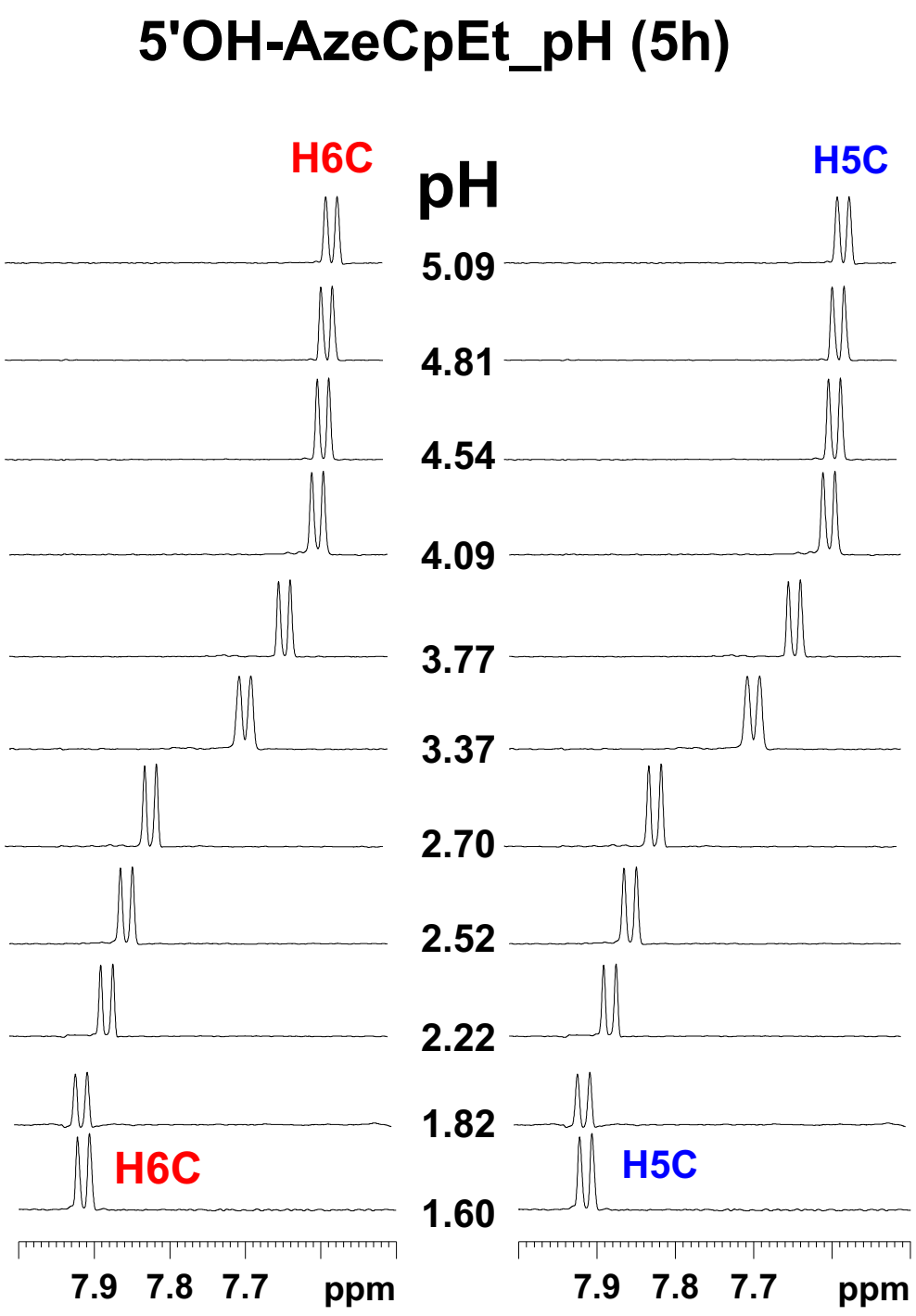
(28) pH dependent ^{1}H chemical shift (in D_2O) of Etp2′-aminoTpEt (6d) at 298 K



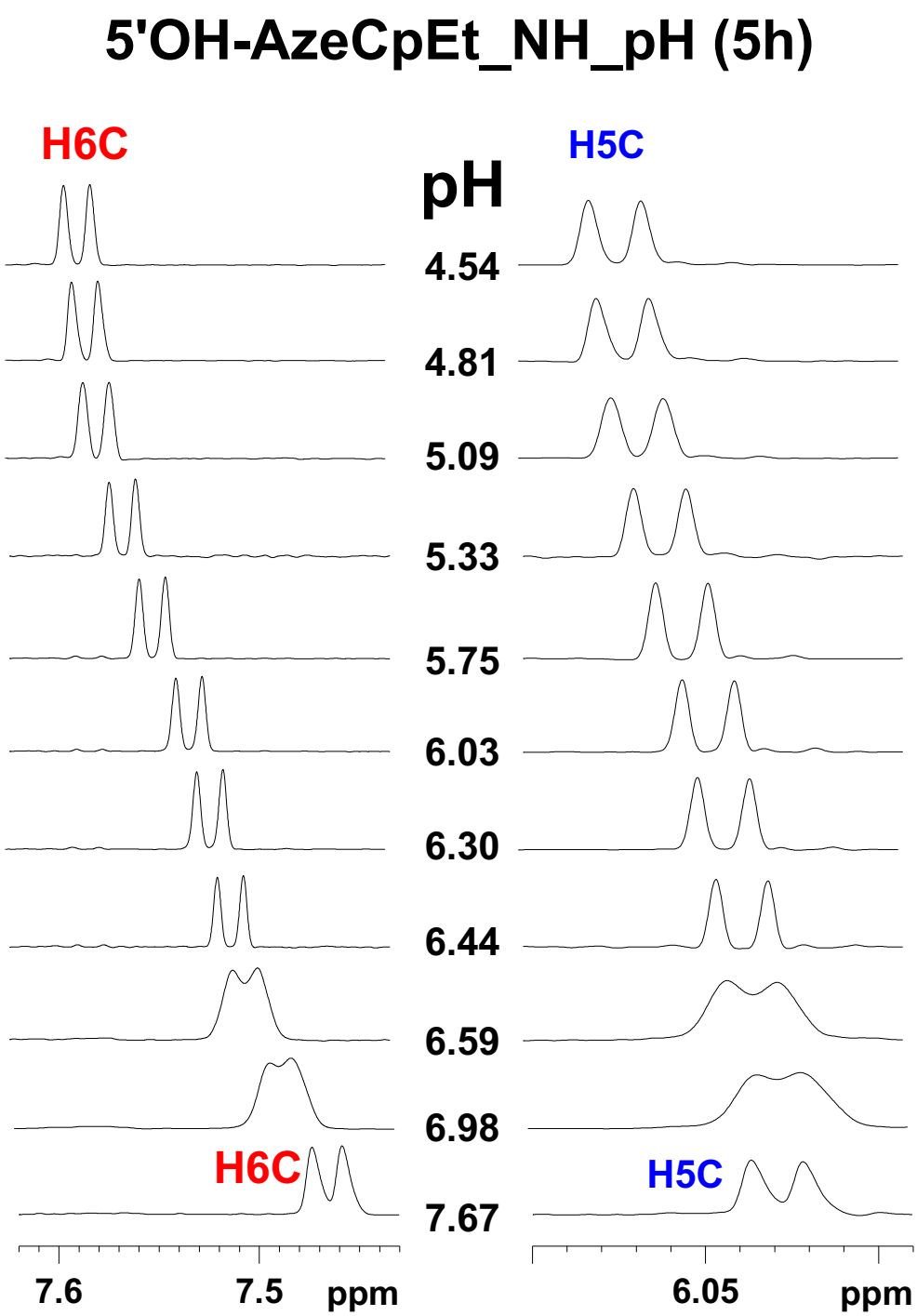
(29) pH dependent ^{1}H chemical shift (in D_2O) of Etp2´AminoTpEt amino protonation (6d) at 298 K



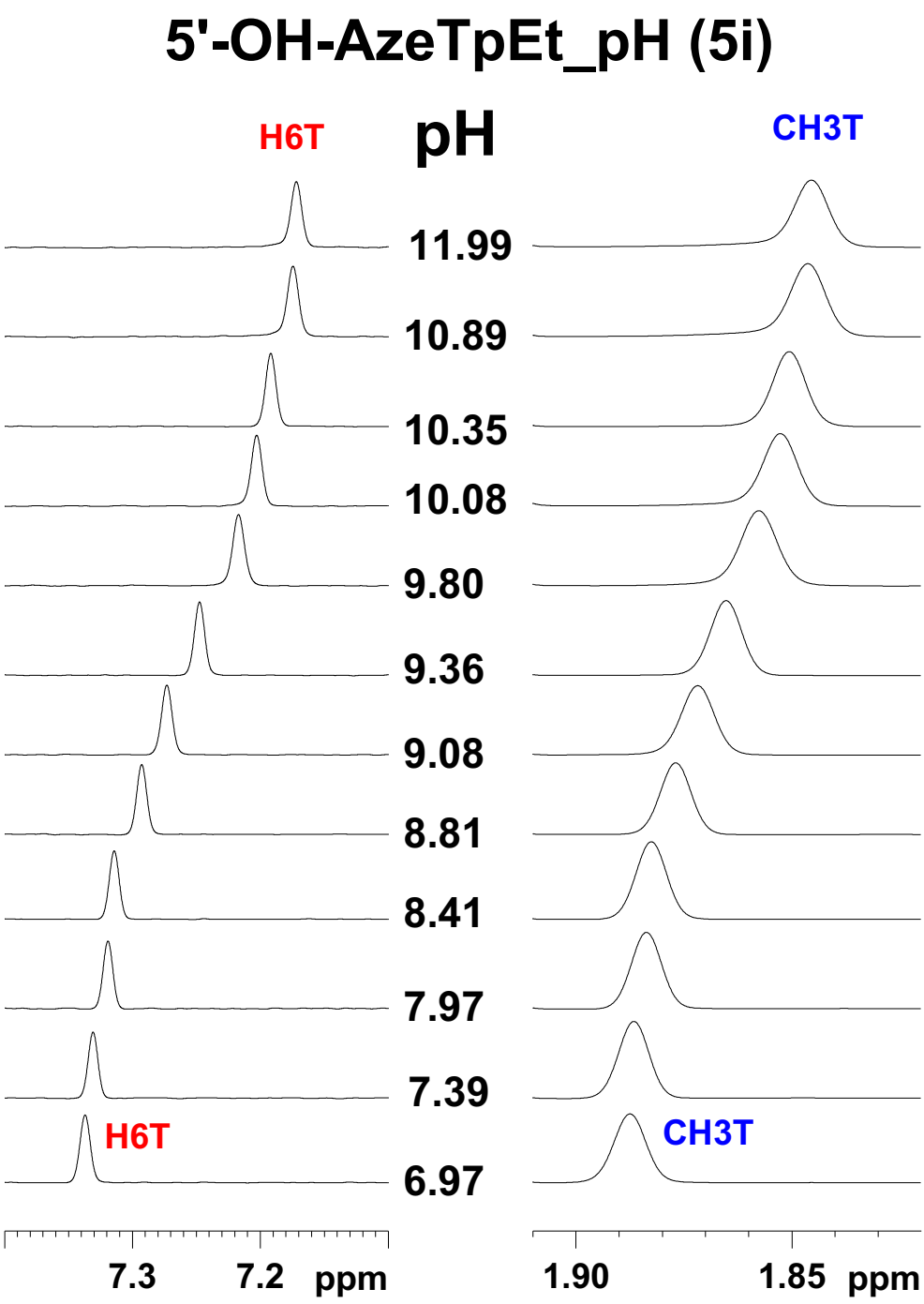
(30) pH dependent ^{1}H chemical shift (in D_2O) of AzeCpEt (5h) at 298 K



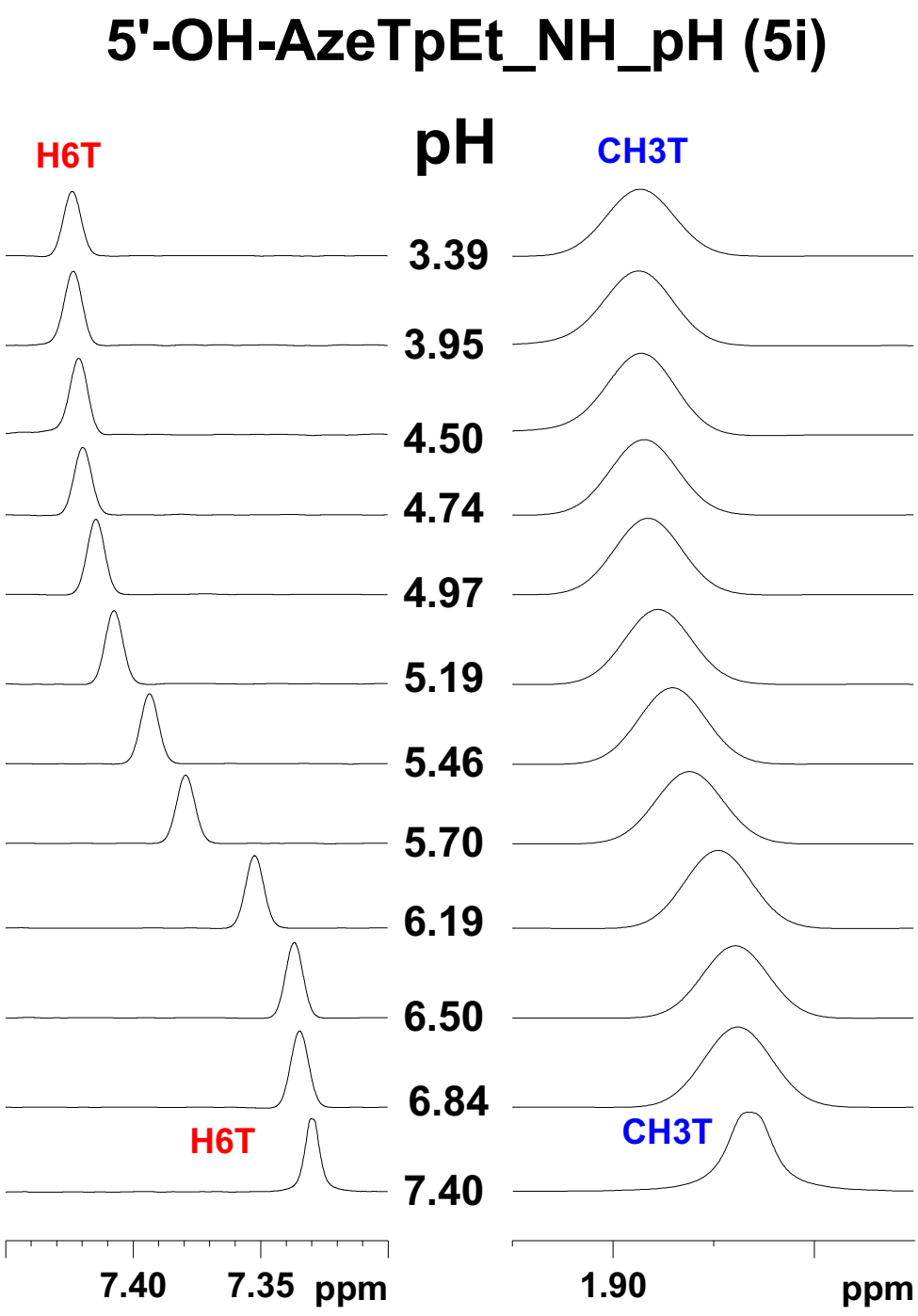
(31) pH dependent ^{1}H chemical shift (in D_2O) of AzeCpEt azetidine protonation (5h) at 298 K



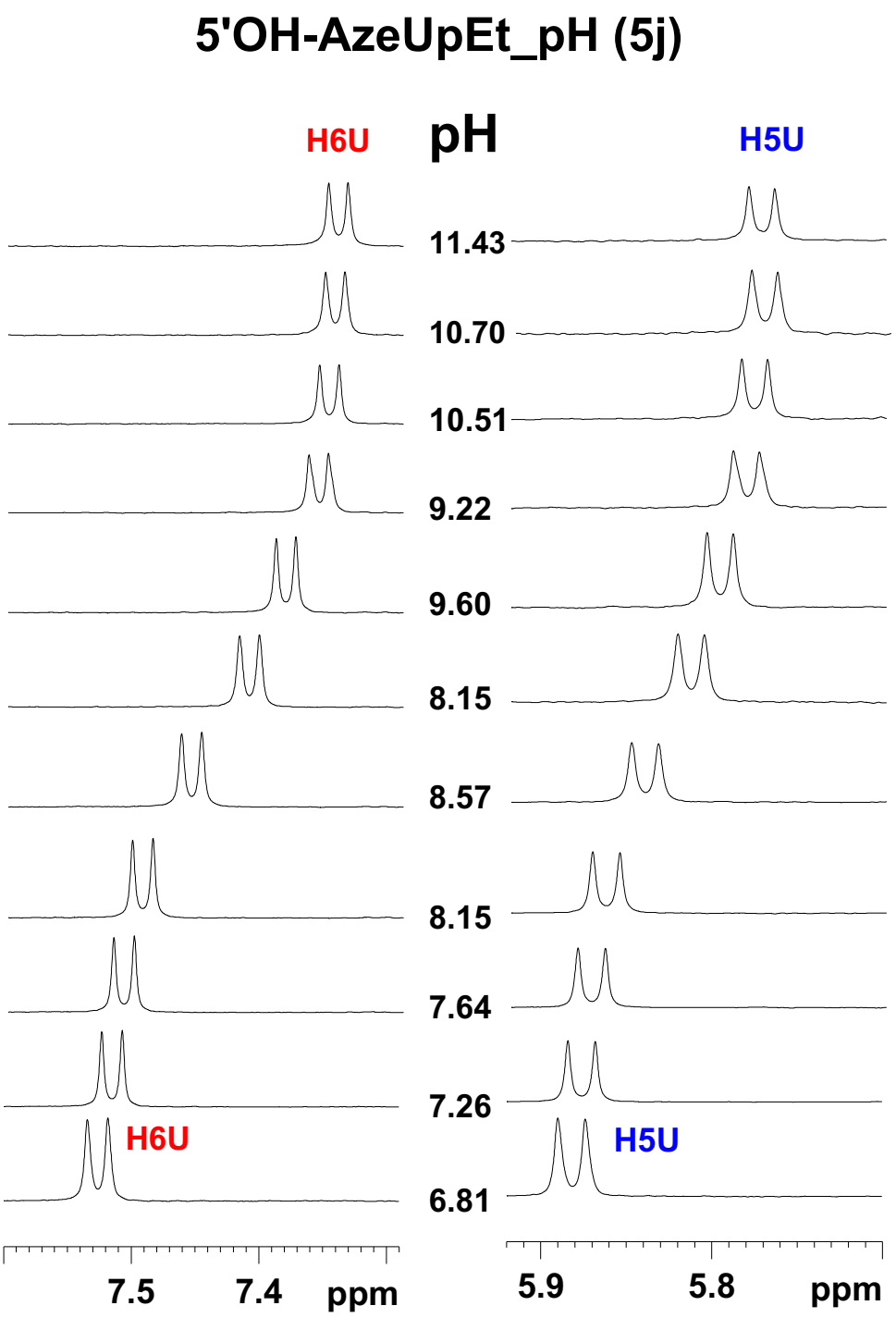
(32) pH dependent ^{1}H chemical shift (in D_2O) of AzeTpEt (5i) at 298 K



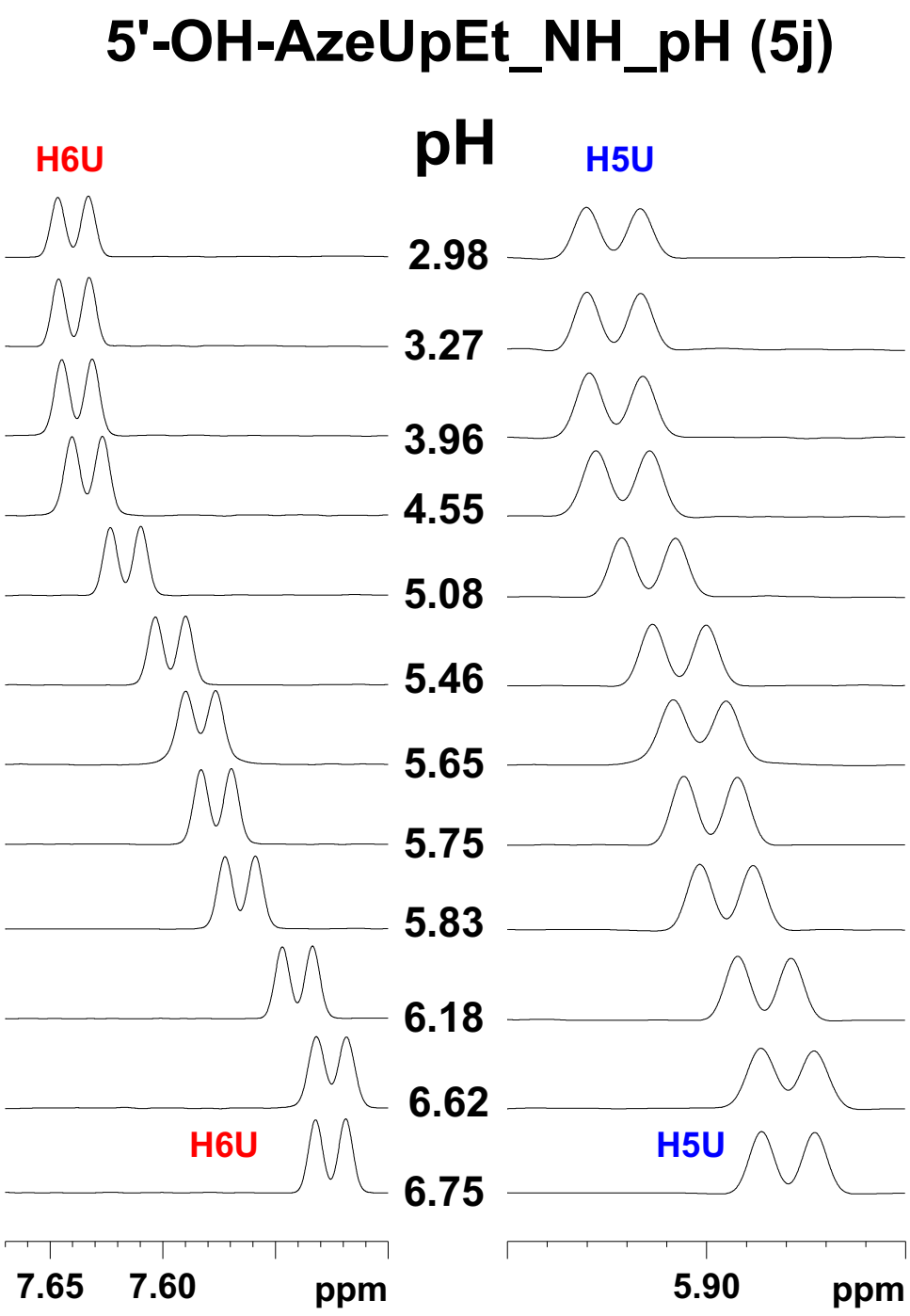
(33) pH dependent ^{1}H chemical shift (in D_2O) of AzeTpEt azetidine protonation (5i) at 298 K



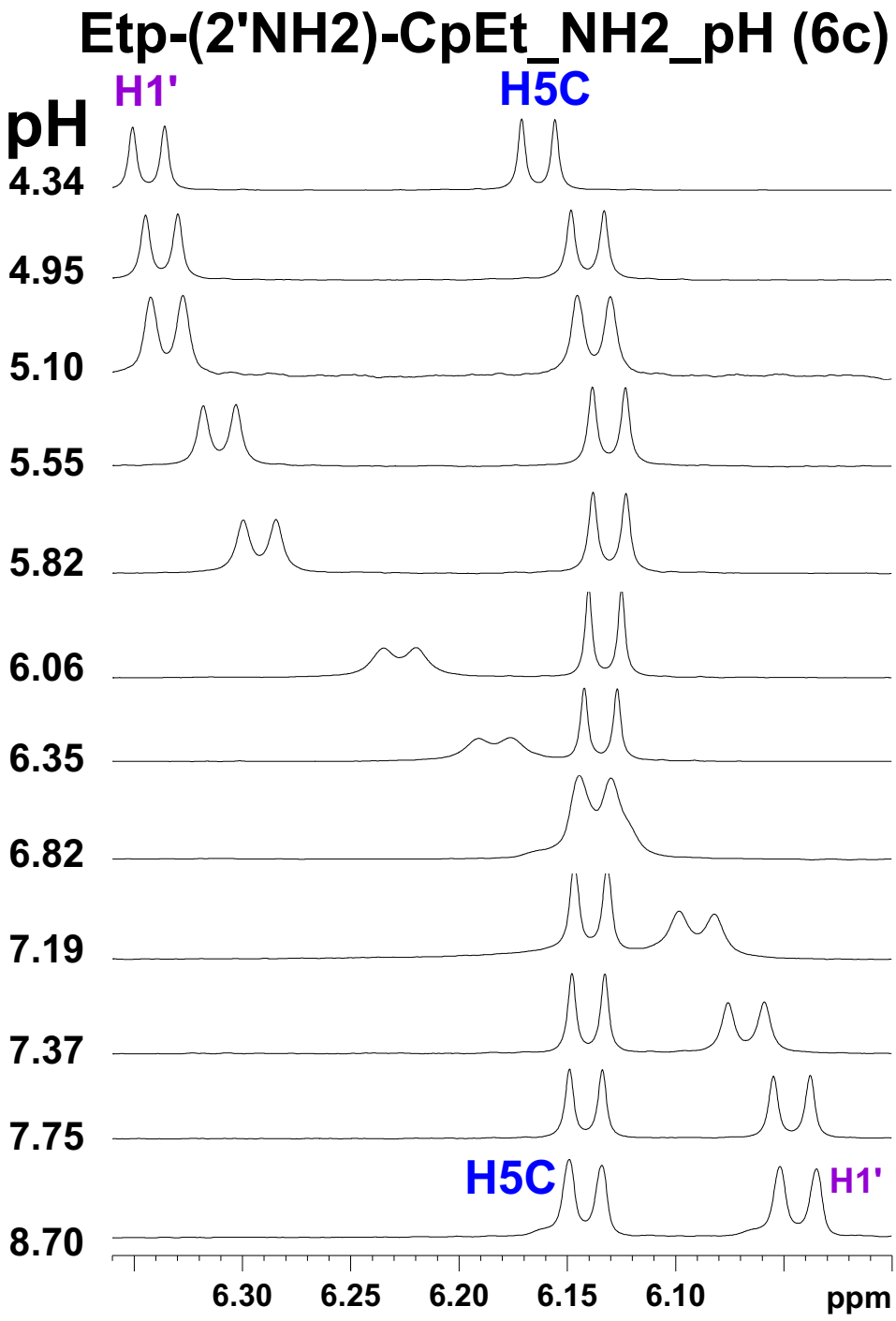
(34) pH dependent ^{1}H chemical shift (in D_2O) of AzeUpEt (5j) at 298 K



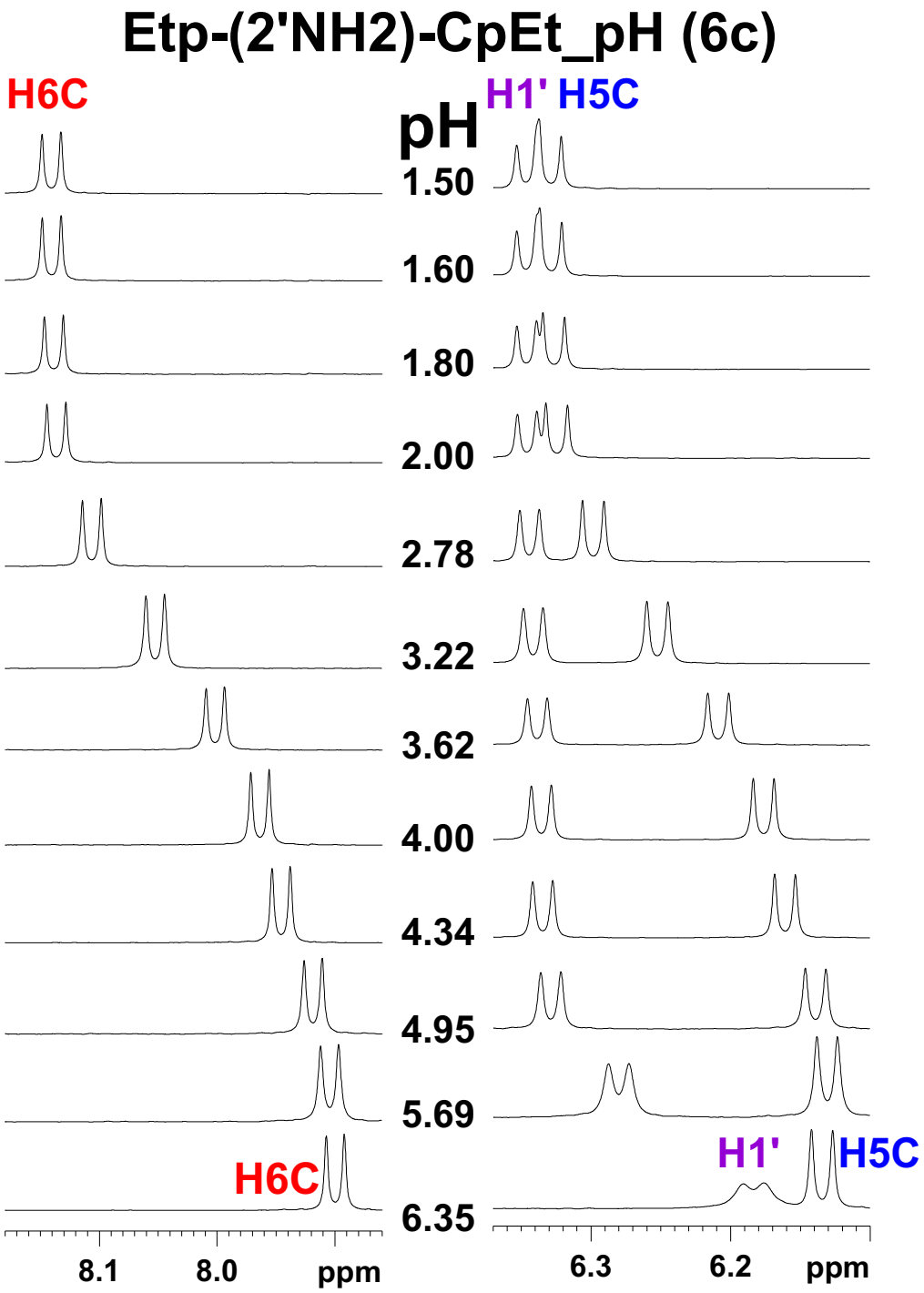
(35) pH dependent ^{1}H chemical shift (in D_2O) of AzeTpEt azetidine protonation (5j) at 298 K



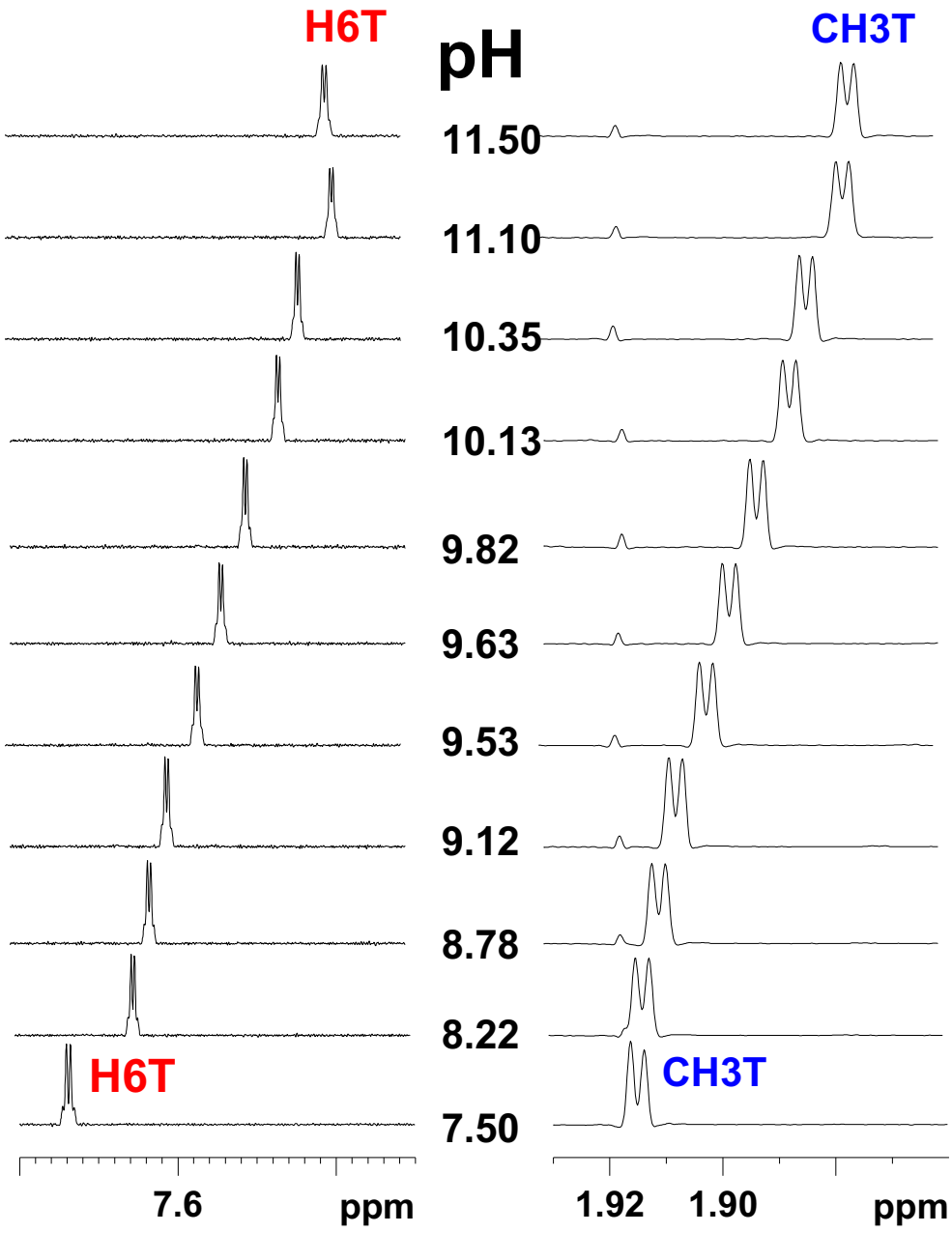
(36) pH dependent ^{1}H chemical shift (in D_2O) of Etp2´NH_2CpEt azetidine protonation (6c) at 298K



(37) pH dependent ^{1}H chemical shift (in D_2O) of Etp2´NH_2CpEt (6c) at 298 K



(38) pH dependent ^{1}H chemical shift (in D_2O) of 2′-NH_2TpEt (6i) at 298 K



(39) pH dependent ^{1}H chemical shift (in D_2O) of 2′NH_2TpEt amino protonation (6i) at 298 K

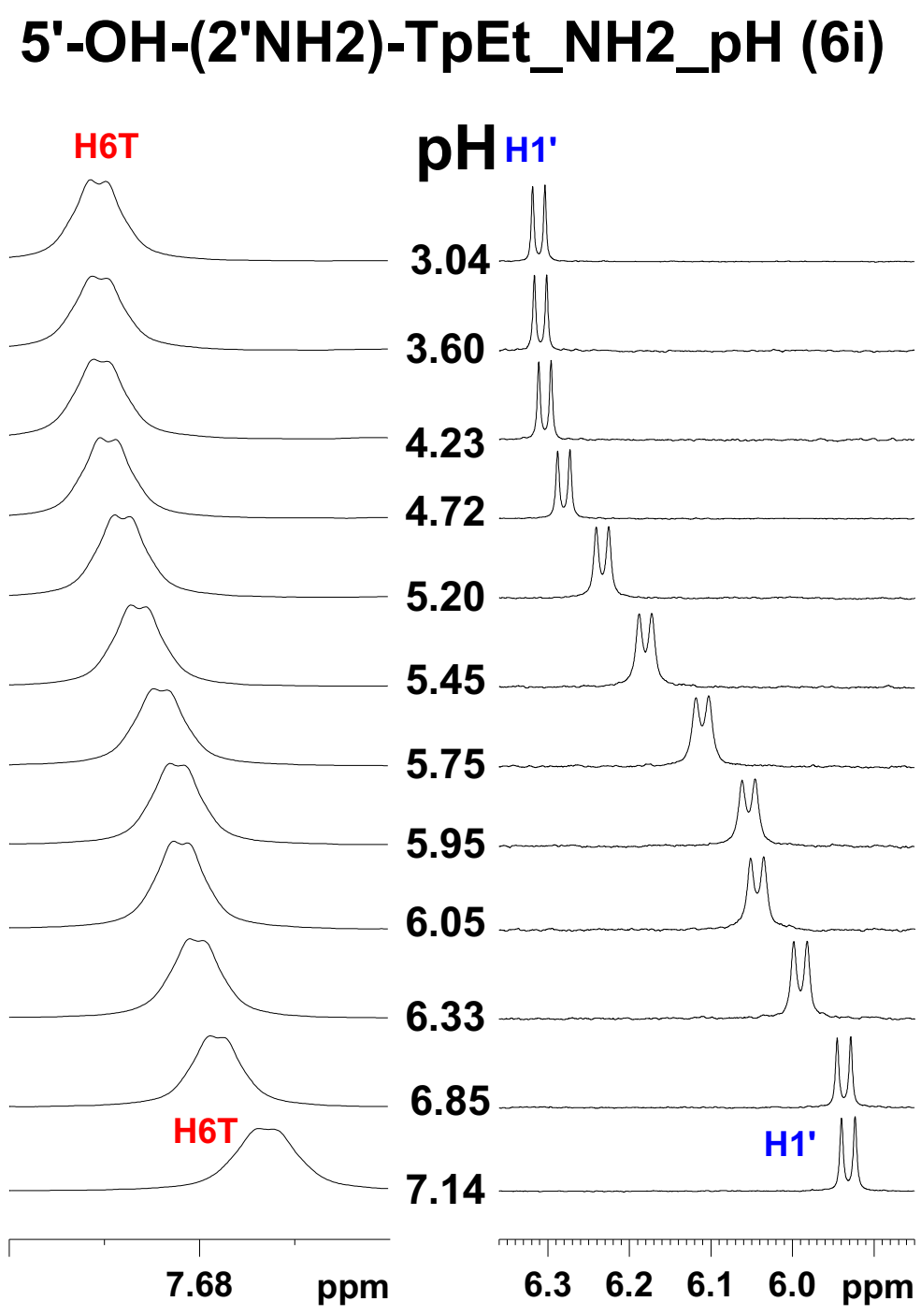
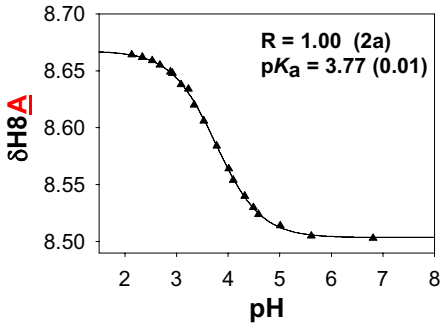
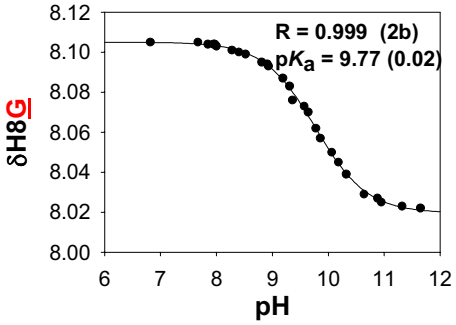
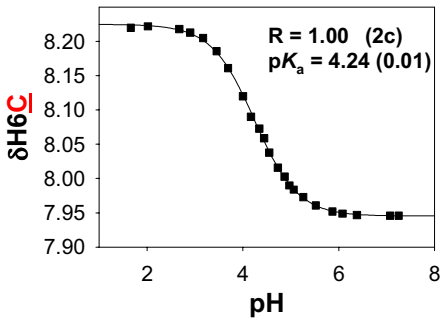
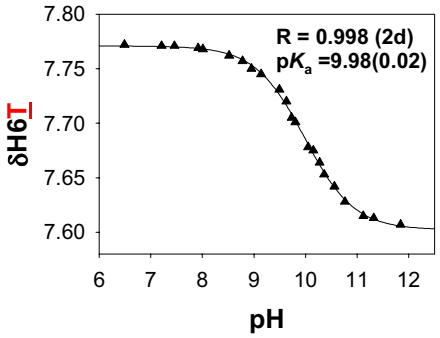


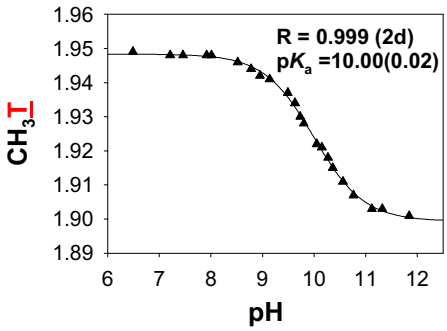
Figure S2. Sigmoidal curves of pH metric titrations of the 2′-OMe analogs (2a – 2i)

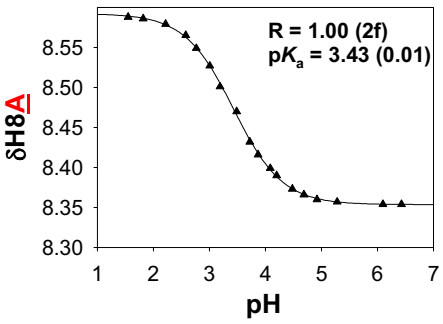


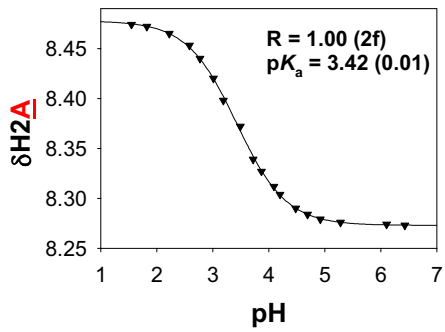


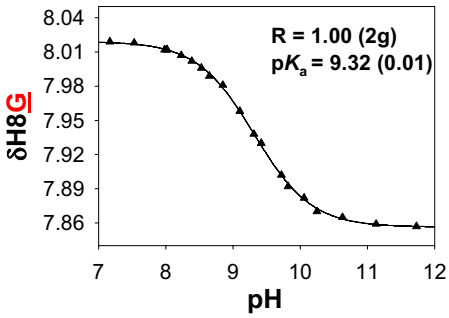


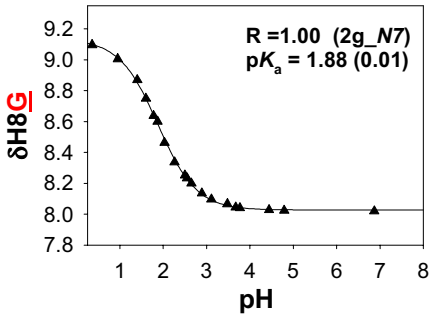


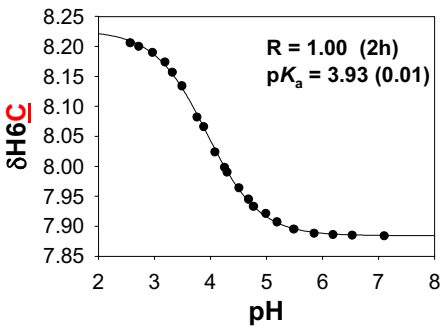


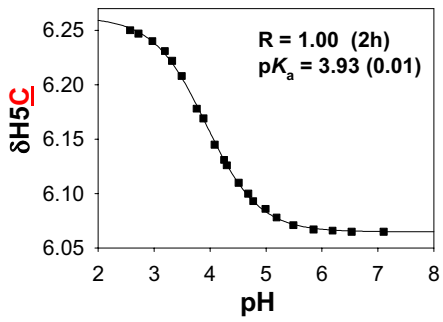


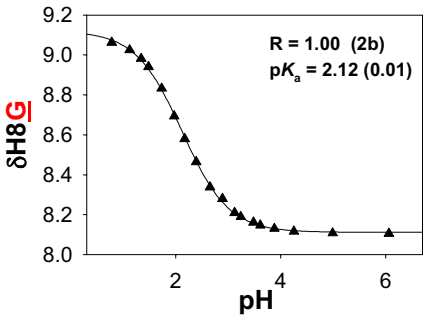


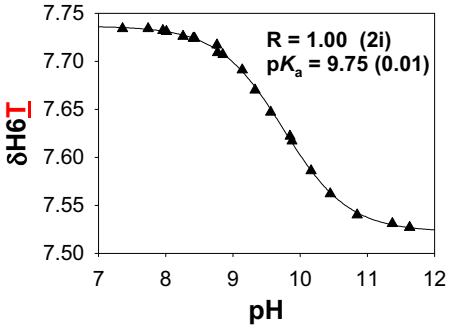


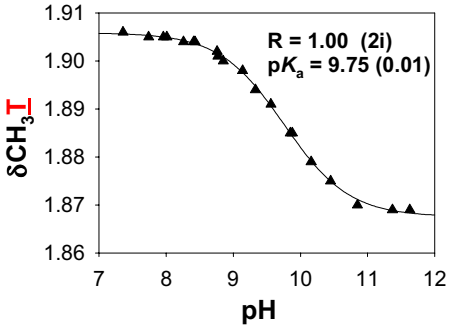




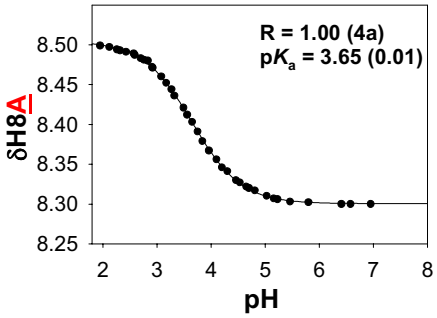


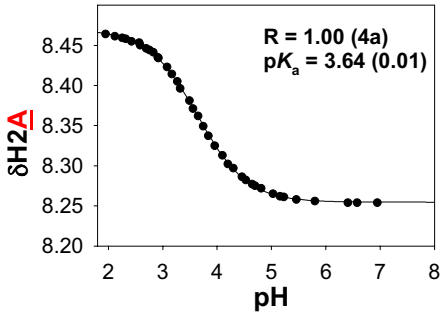


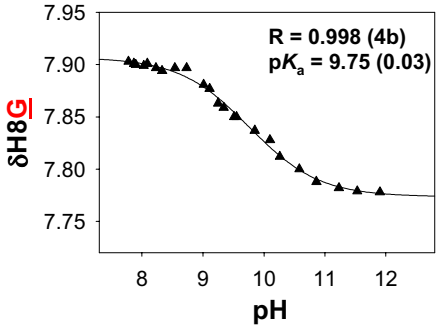


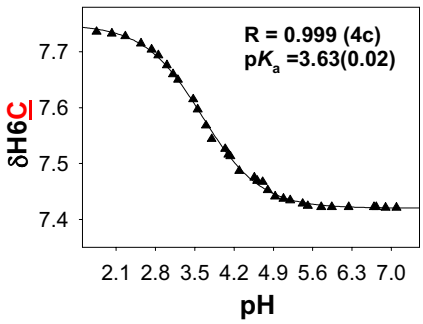


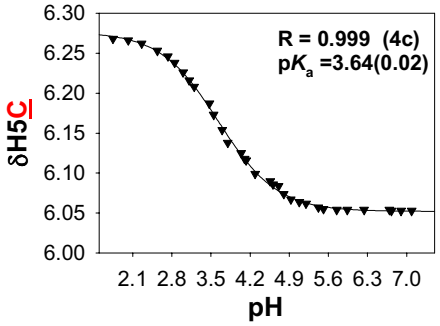
Sigmoidal curves of pH metric titrations of the oxetane analogs (4a – 4j)

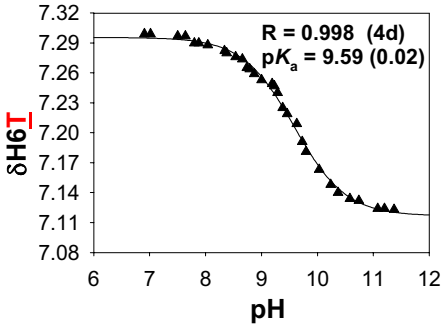


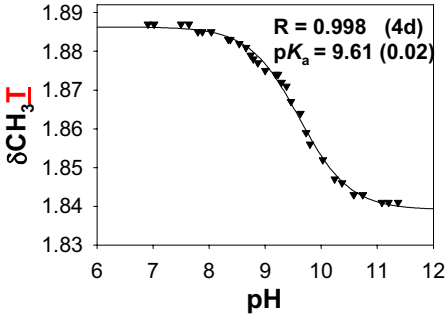


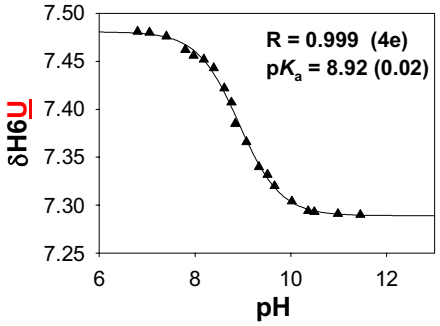


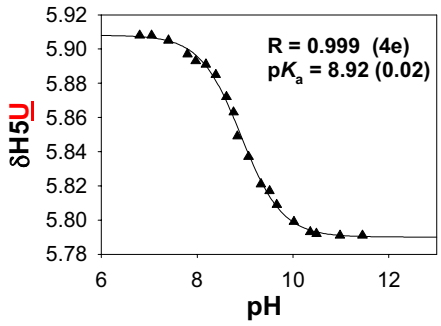


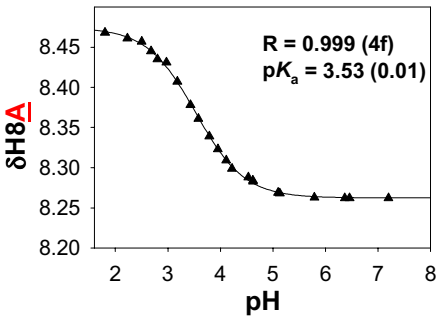


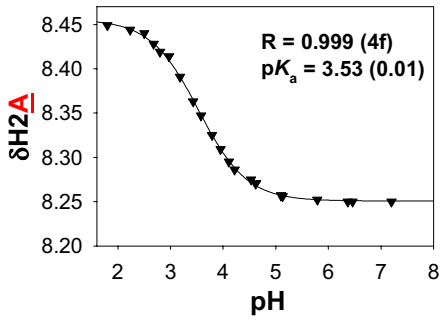


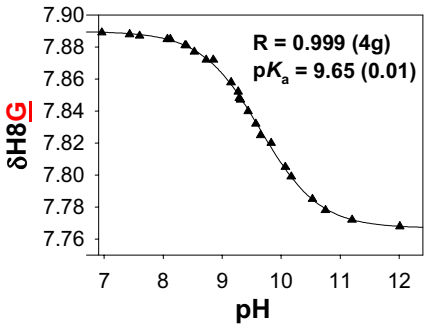


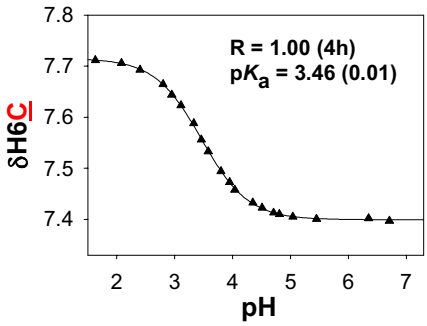


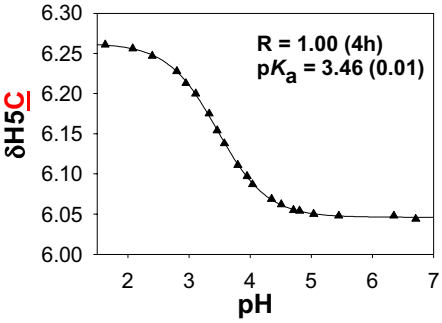


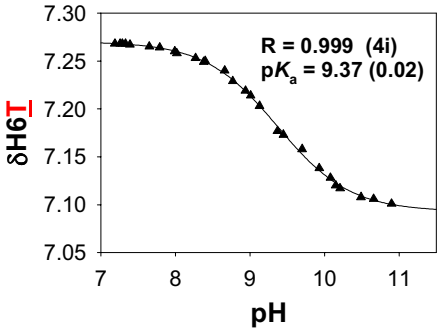

δH8A
R = 0.999 (4f)
pKa = 3.53 (0.01)
pH

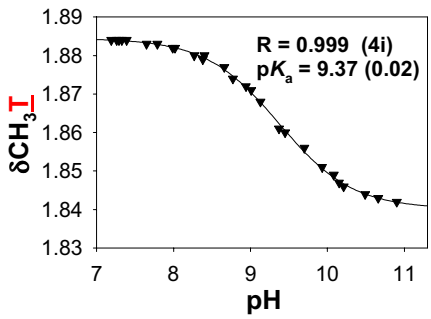

δH2A
R = 0.999 (4f)
pKa = 3.53 (0.01)
pH

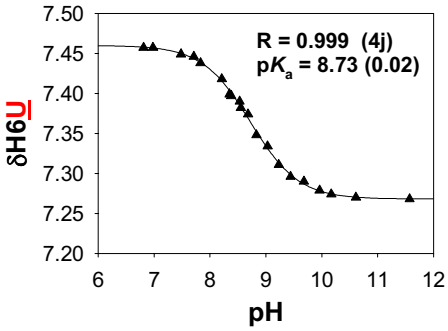

δH8G
R = 0.999 (4g)
pKa = 9.65 (0.01)
pH

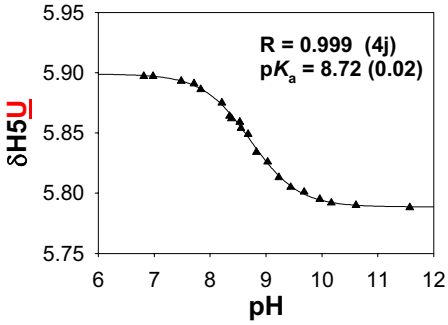

δH6C
R = 1.00 (4h)
pKa = 3.46 (0.01)
pH


δH5C
R = 1.00 (4h)
pKa = 3.46 (0.01)
pH

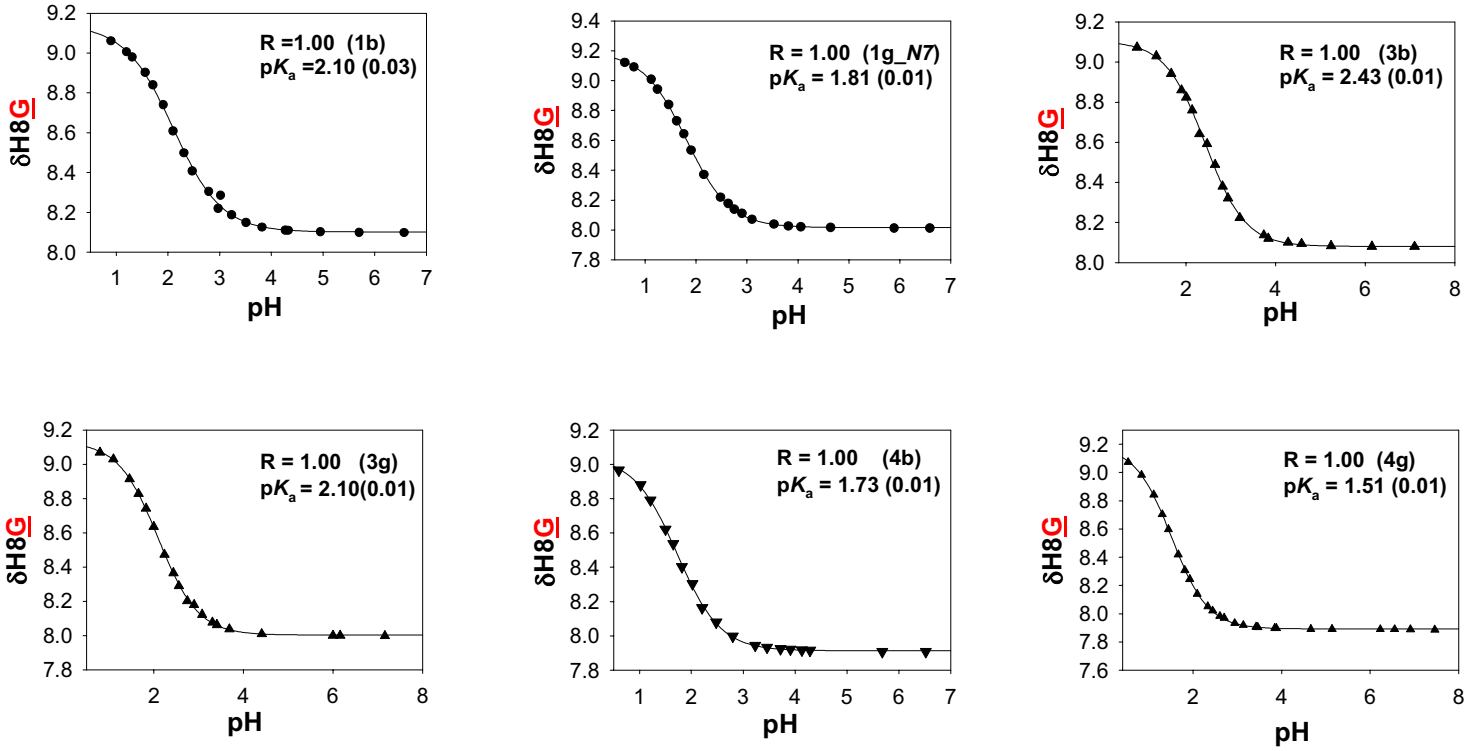

δH6T
R = 0.999 (4i)
pKa = 9.37 (0.02)
pH


δCH3T
R = 0.999 (4i)
pKa = 9.37 (0.02)
pH

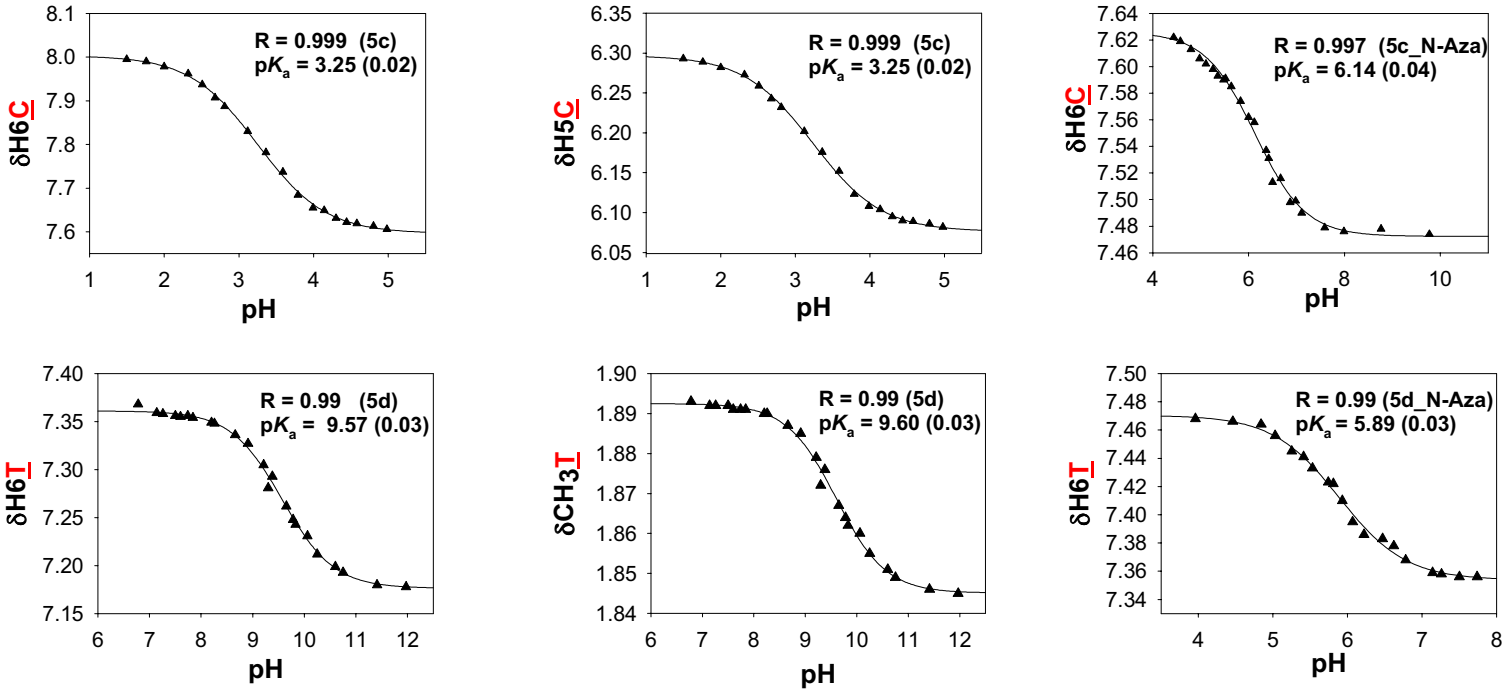

δH6U
R = 0.999 (4j)
pKa = 8.73 (0.02)
pH

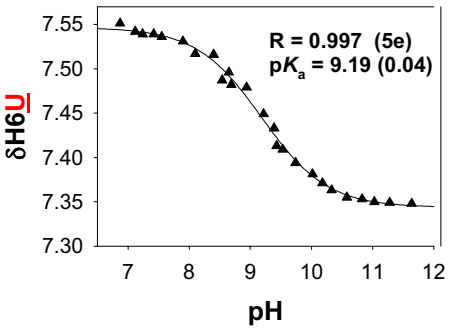

δH5U
R = 0.999 (4j)
pKa = 8.72 (0.02)
pH

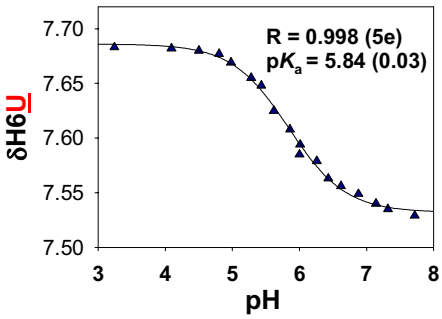
Sigmoidal curves of pH metric titrations of the deoxy-, ribo- and oxetane G analogs (N7 pK_a)

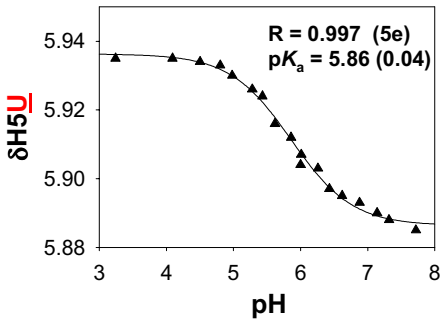


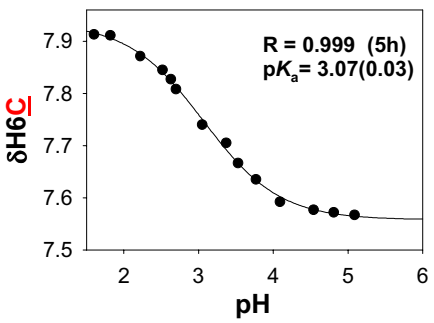
Sigmoidal curves of pH metric titrations of the (N3/N-azetidine/N-amino) of the azetidine and 2′-amino analogs

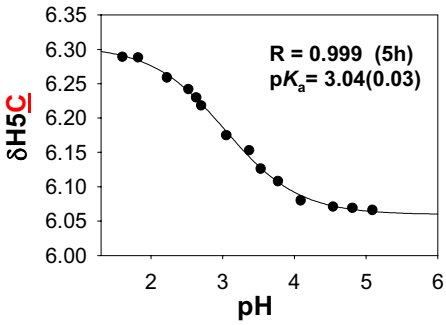


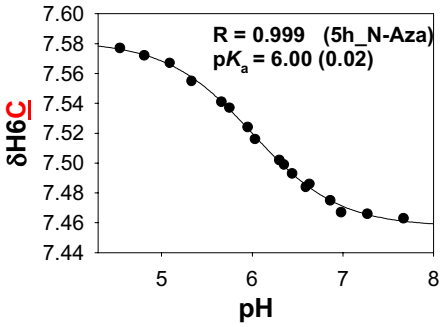

R = 0.997 (5e)
pKa = 9.19 (0.04)
δH6U
pH

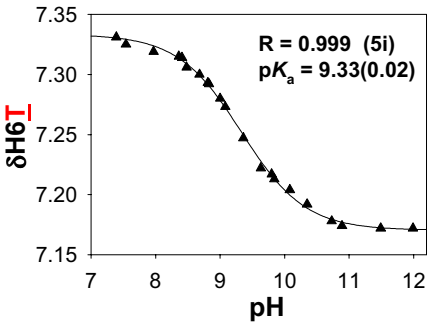

R = 0.998 (5e)
pKa = 5.84 (0.03)
δH6U
pH

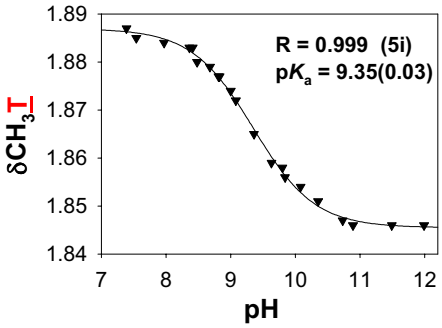

R = 0.997 (5e)
pKa = 5.86 (0.04)
δH5U
pH

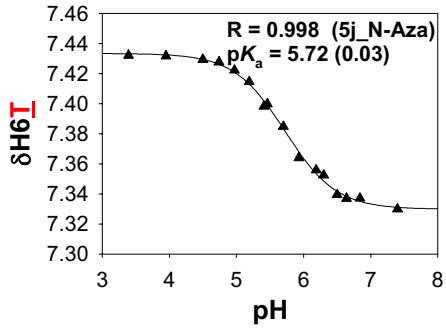

R = 0.999 (5h)
pKa= 3.07(0.03)
δH6C
pH

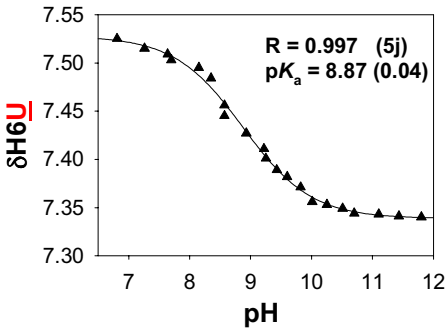

R = 0.999 (5h)
pKa= 3.04(0.03)
δH5C
pH

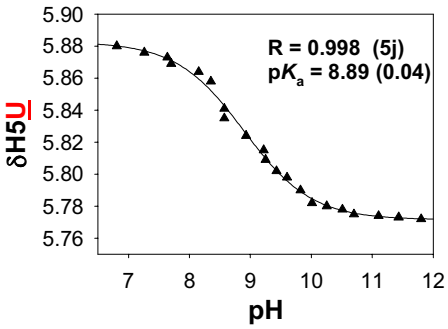

R = 0.999 (5h_N-Aza)
pKa = 6.00 (0.02)
δH6C
pH

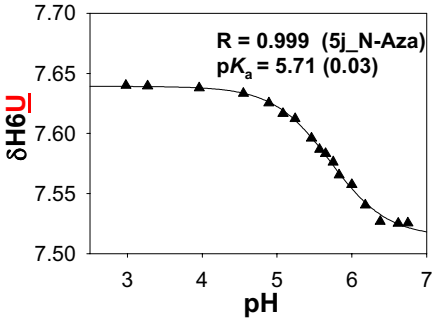

R = 0.999 (5i)
pKa = 9.33(0.02)
δH6T
pH

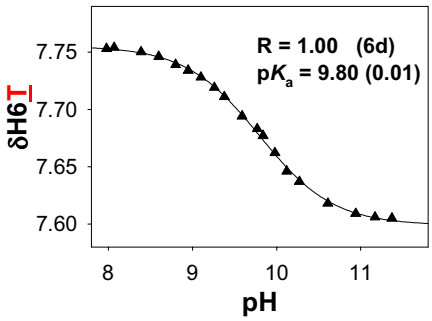

R = 0.999 (5i)
pKa = 9.35(0.03)
δCH3T
pH

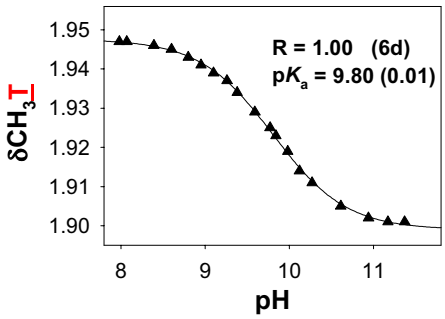

R = 0.998 (5j_N-Aza)
pKa = 5.72 (0.03)
δH6T
pH

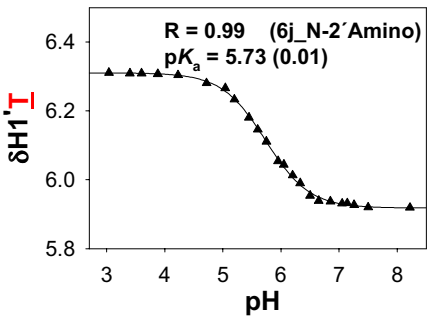

R = 0.997 (5j)
pKa = 8.87 (0.04)
δH6U
pH

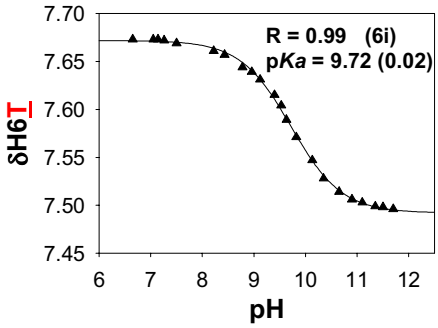

R = 0.998 (5j)
pKa = 8.89 (0.04)
δH5U
pH

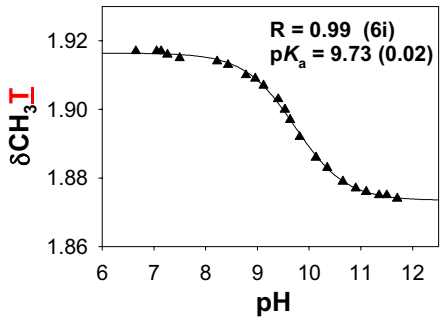

R = 0.999 (5j_N-Aza)
pKa = 5.71 (0.03)
δH6U
pH

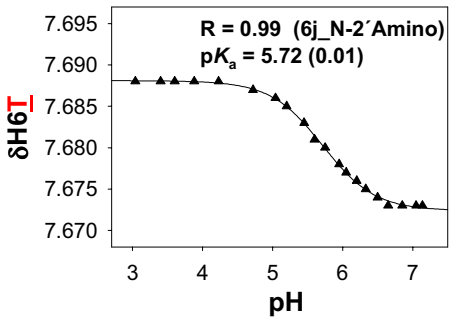

R = 1.00 (6d)
pKa = 9.80 (0.01)
δH6T
pH

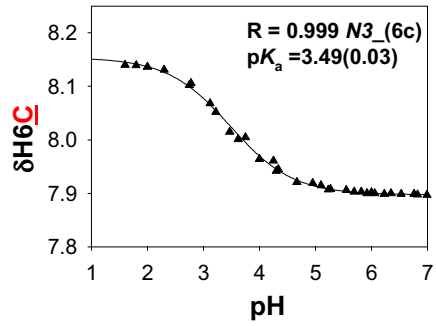

R = 1.00 (6d)
pKa = 9.80 (0.01)
δCH3T
pH

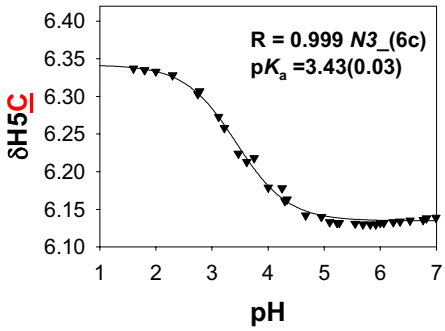

R = 0.99 (6j_N-2´Amino)
pKa = 5.73 (0.01)
δH1'T
pH


R = 0.99 (6i)
pKa = 9.72 (0.02)
δH6T
pH


R = 0.99 (6i)
pKa = 9.73 (0.02)
δCH3T
pH


R = 0.99 (6j_N-2´Amino)
pKa = 5.72 (0.01)
δH6T
pH


R = 0.999 N3_(6c)
pKa =3.49(0.03)
δH6C
pH


R = 0.999 N3_(6c)
pKa =3.43(0.03)
δH5C
pH

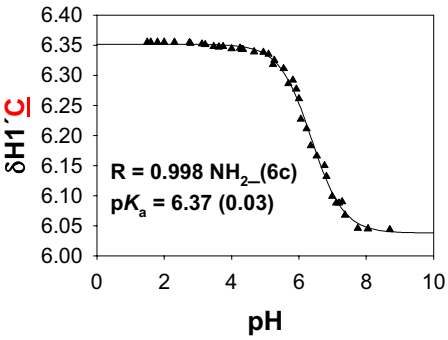
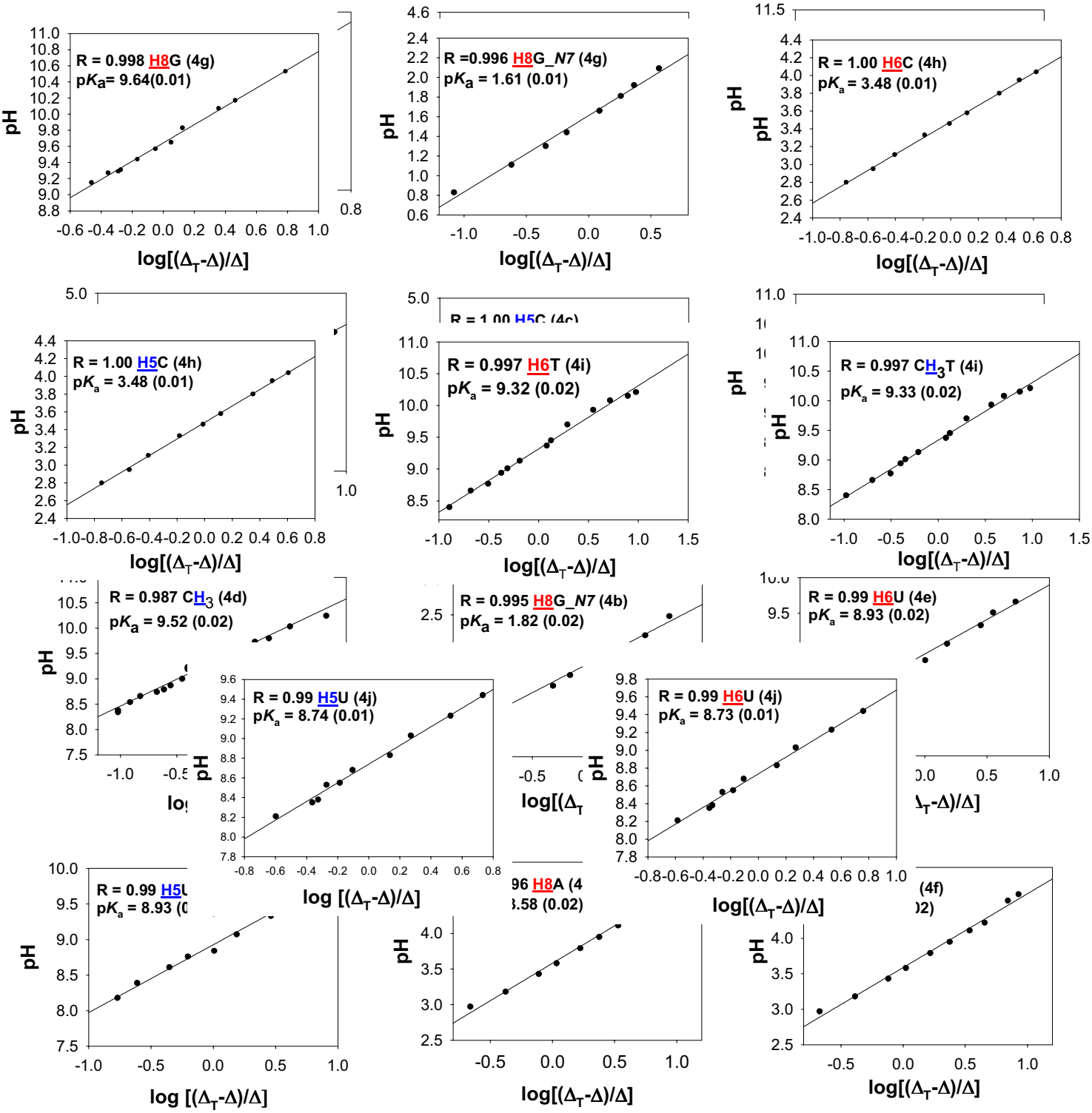
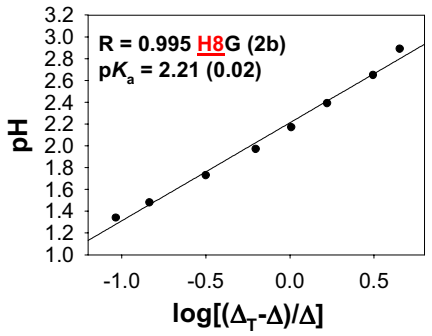
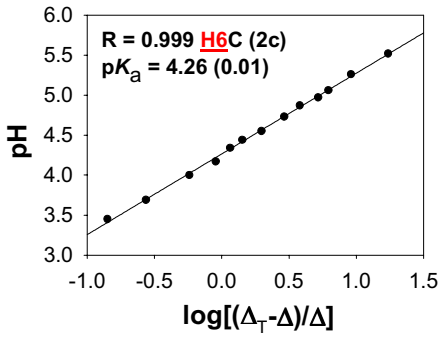

R = 0.998 NH2_(6c)
pKa = 6.37 (0.03)
δH1´C
pH

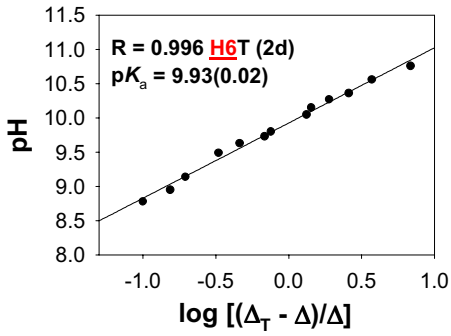
Figure S3. Hill plots: oxetane analogs [4a – 4j] (series 4 in Table 1)

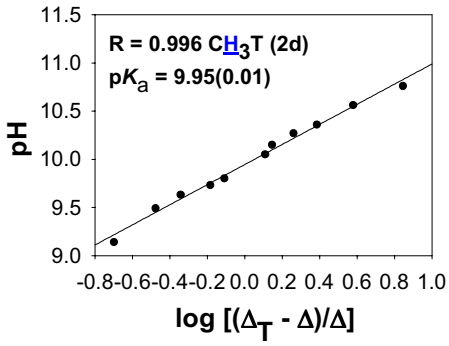


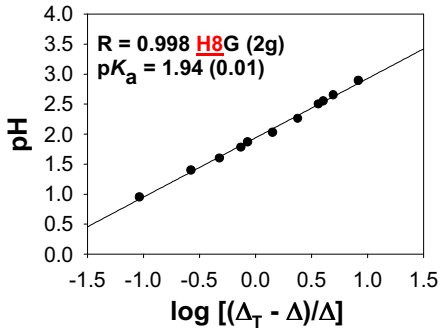
Hill plots: 2′-OMe analogs [2a–2i] (series 2 in Table 1)

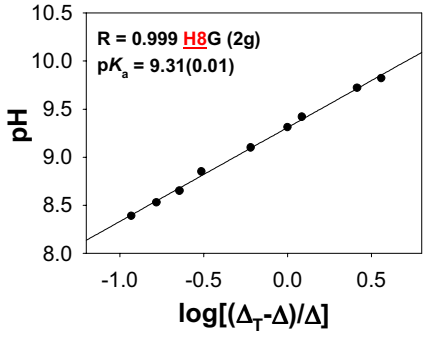


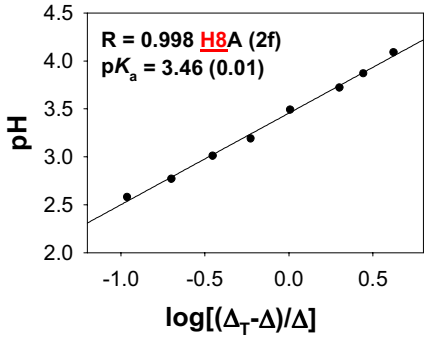


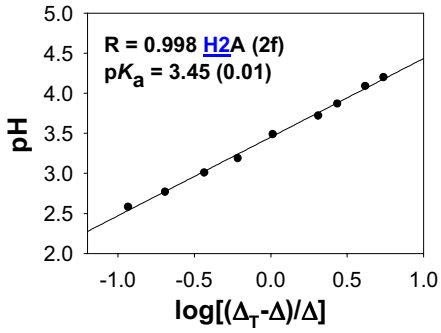


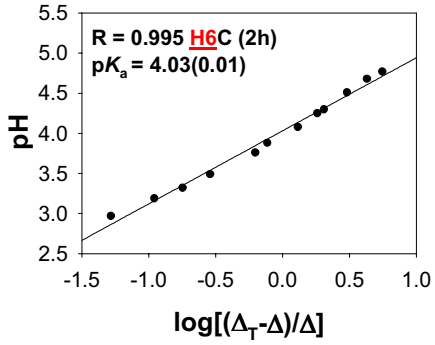


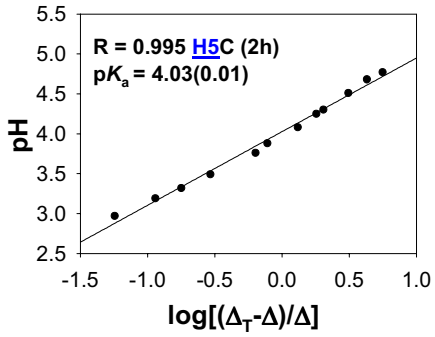


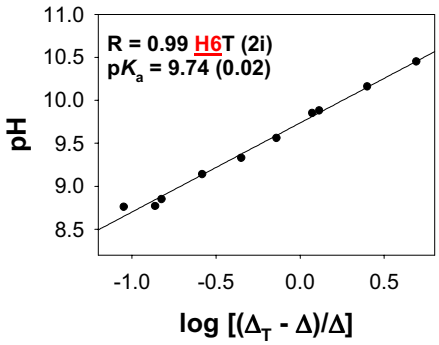


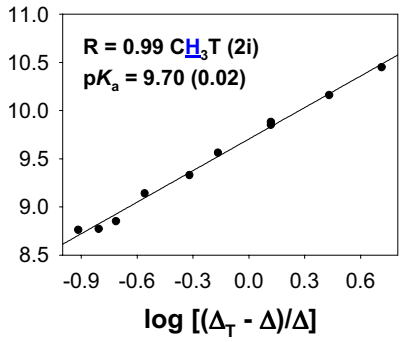


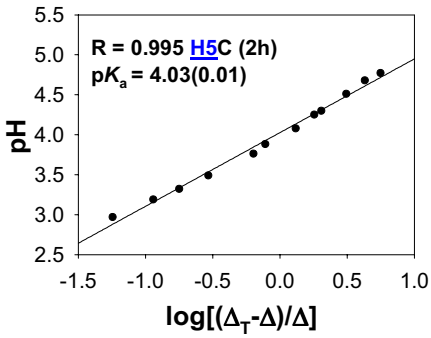


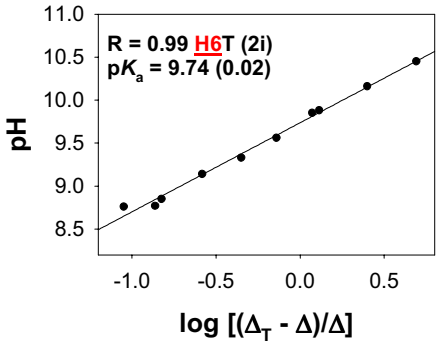


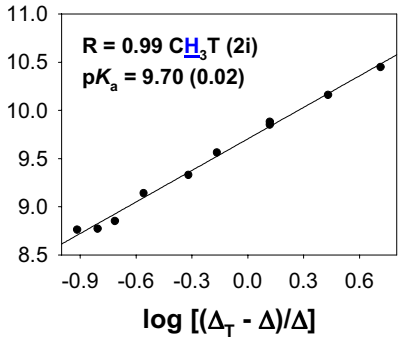




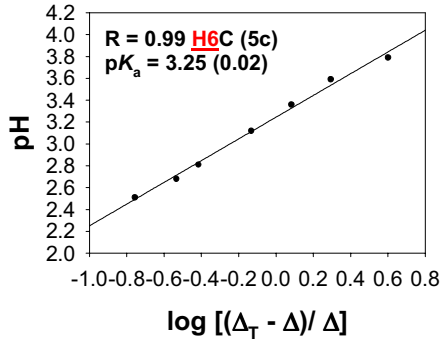


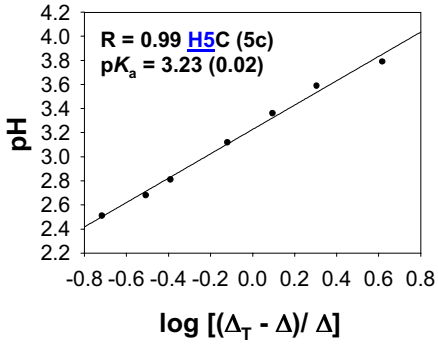


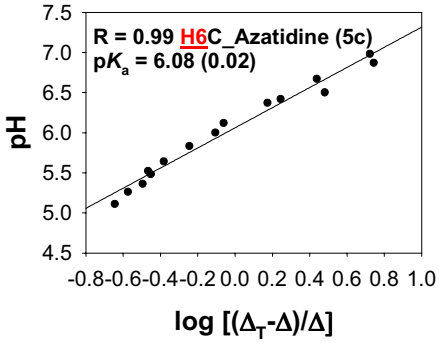


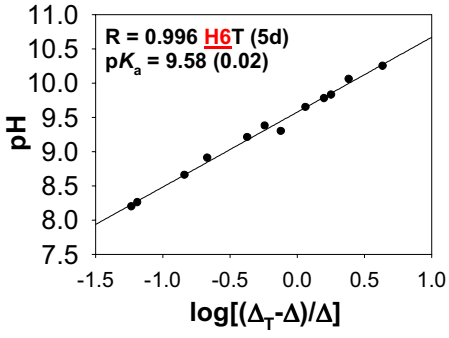


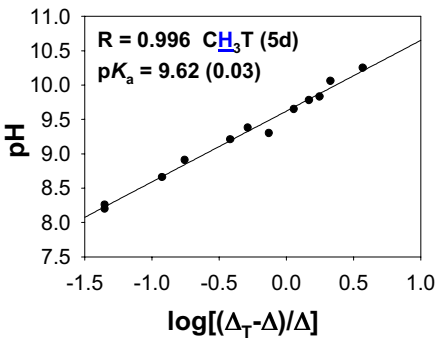
Hill Plots: azetidine and 2′-amino analogs [5c – 6i] (series 5 of Table 1)

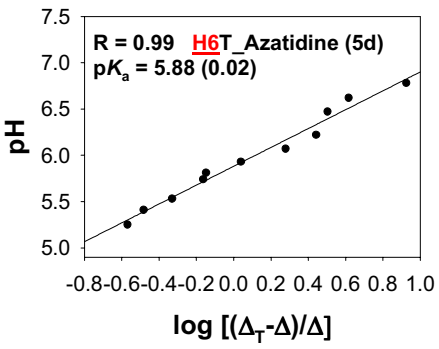


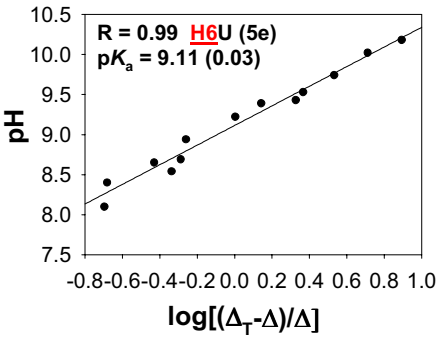


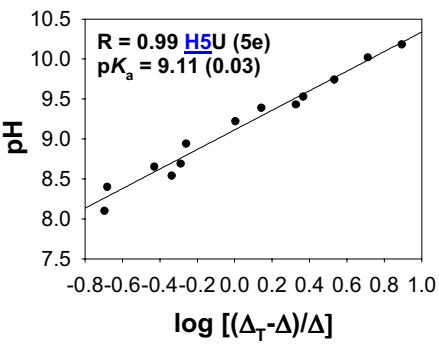


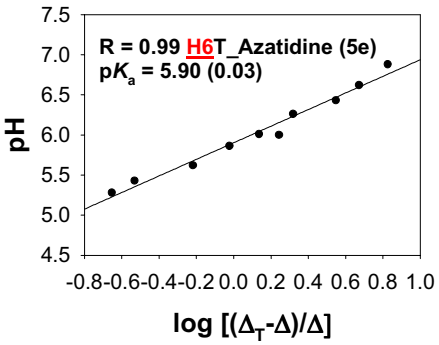


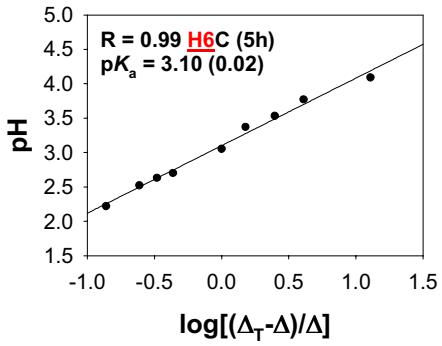


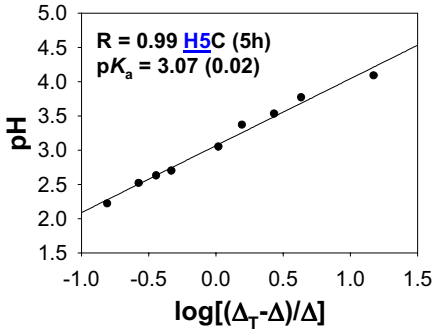


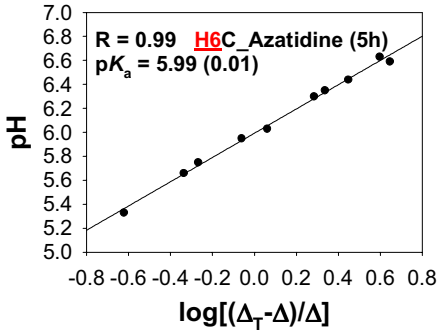


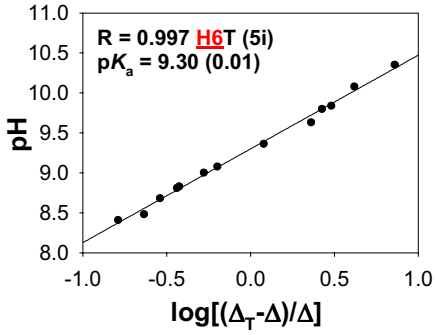


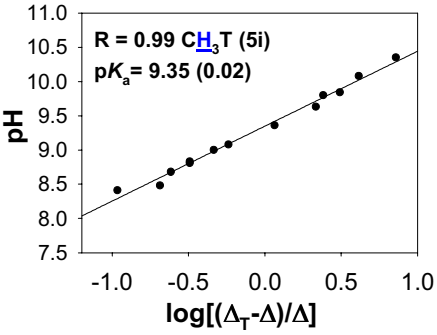


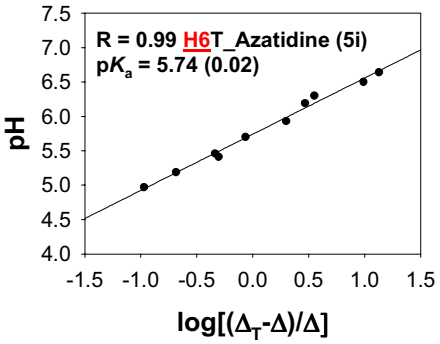

R = 0.99 H6C (5h)
pKa = 3.10 (0.02)
pH
log[(ΔT-Δ)/Δ]

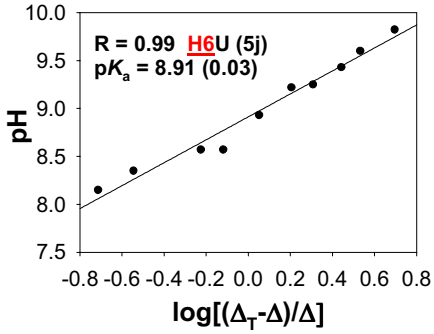

R = 0.99 H5C (5h)
pKa = 3.07 (0.02)
pH
log[(ΔT-Δ)/Δ]

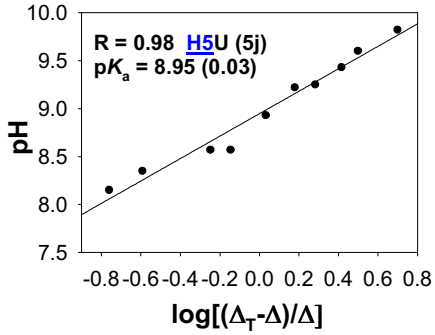

R = 0.99 H6C_Azatidine (5h)
pKa = 5.99 (0.01)
pH
log[(ΔT-Δ)/Δ]

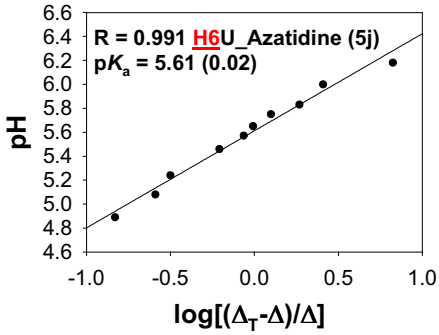

R = 0.997 H6T (5i)
pKa = 9.30 (0.01)
pH
log[(ΔT-Δ)/Δ]

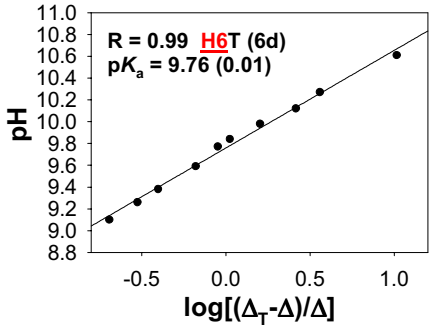

R = 0.99 CH3T (5i)
pKa = 9.35 (0.02)
pH
log[(ΔT-Δ)/Δ]

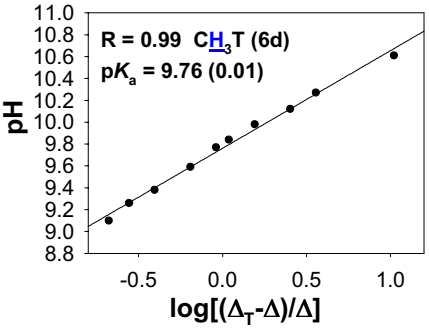

R = 0.99 H6T_Azatidine (5i)
pKa = 5.74 (0.02)
pH
log[(ΔT-Δ)/Δ]

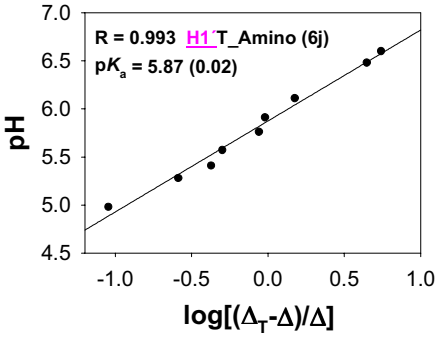

R = 0.99 H6U (5j)
pKa = 8.91 (0.03)
pH
log[(ΔT-Δ)/Δ]


R = 0.98 H5U (5j)
pKa = 8.95 (0.03)
pH
log[(ΔT-Δ)/Δ]


R = 0.991 H6U_Azatidine (5j)
pKa = 5.61 (0.02)
pH
log[(ΔT-Δ)/Δ]


R = 0.99 H6T (6d)
pKa = 9.76 (0.01)
pH
log[(ΔT-Δ)/Δ]


R = 0.99 CH3T (6d)
pKa = 9.76 (0.01)
pH
log[(ΔT-Δ)/Δ]


R = 0.993 H1'T_Amino (6j)
pKa = 5.87 (0.02)
pH
log[(ΔT-Δ)/Δ]

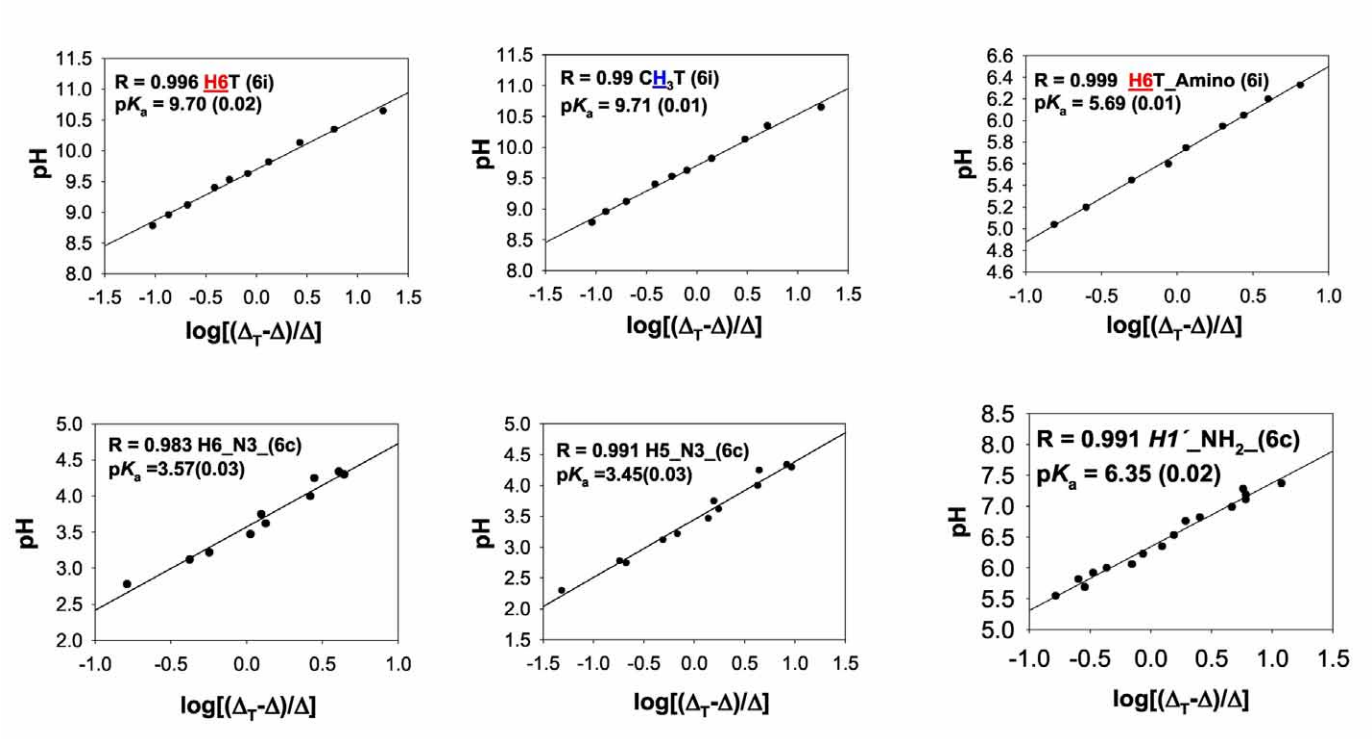
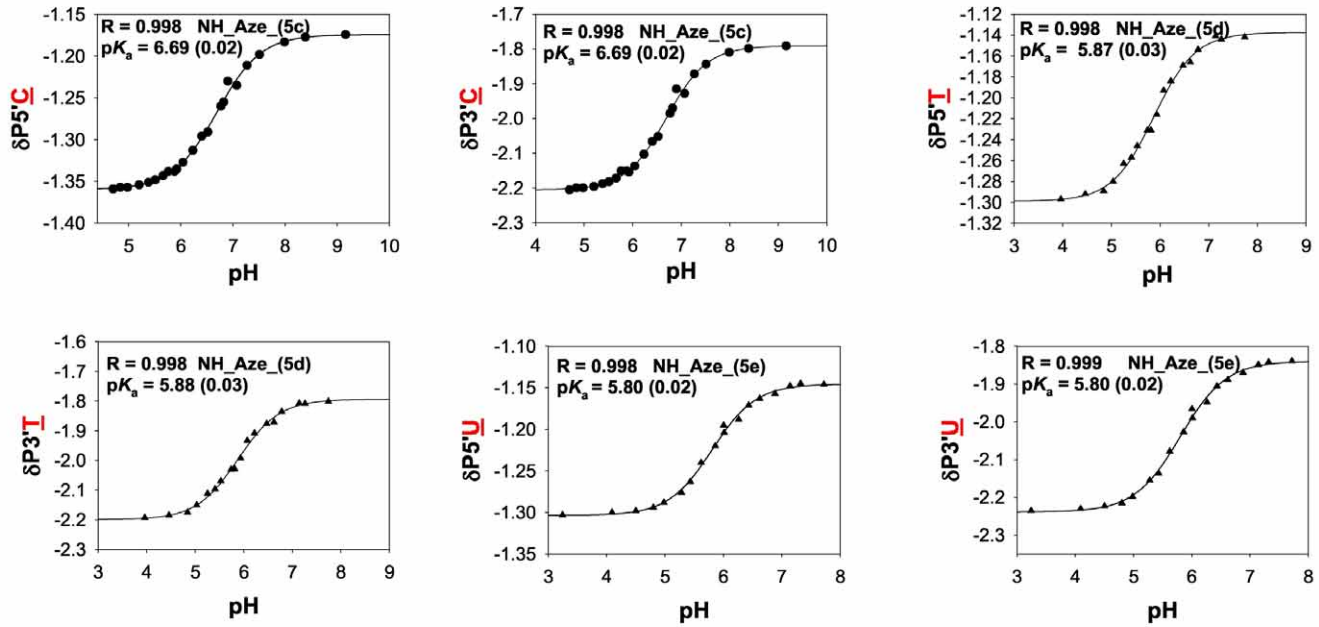
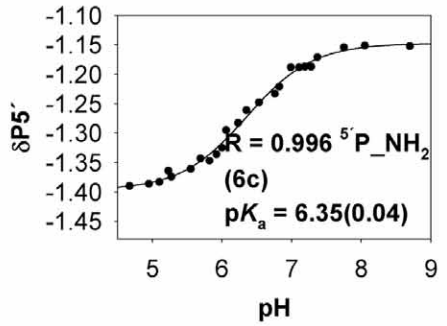
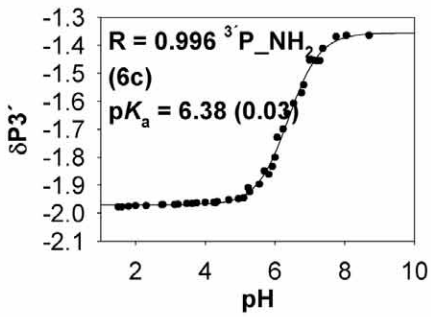
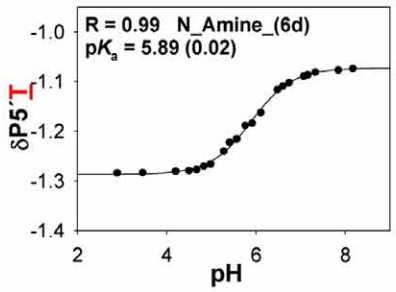


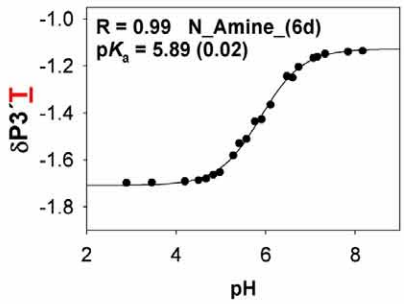
Figure S4. Sigmoidal plot of the pH-dependent **^{31}P** chemical shifts of 3´and 5´phosphorus of the 3´5´bis-ethyl and 3´mono ethyl phosphates i.e., **5c-j , 6c-i.** to calculate the protonation pK_a of N-azetidine as well as N-amine.

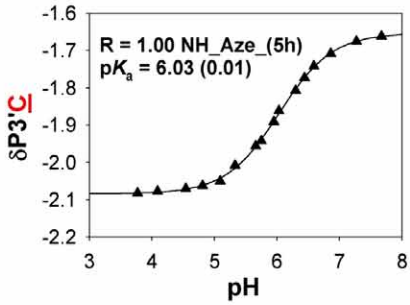


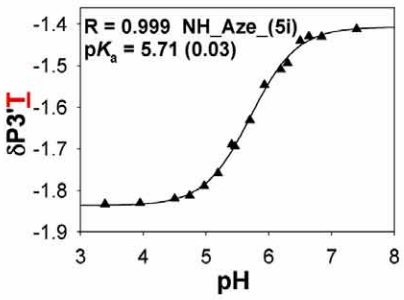

δP5´
R = 0.996 5´P_NH2
(6c)
pKa = 6.35(0.04)
pH

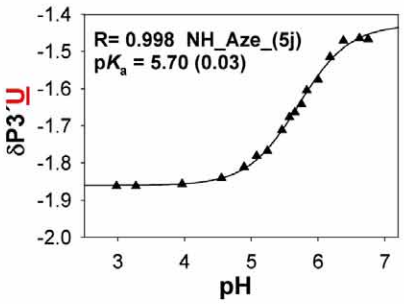

δP3´
R = 0.996 3´P_NH2
(6c)
pKa = 6.38 (0.03)
pH


δP5´T
R = 0.99 N_Amine_(6d)
pKa = 5.89 (0.02)
pH


δP3´T
R = 0.99 N_Amine_(6d)
pKa = 5.89 (0.02)
pH


δP3'C
R = 1.00 NH_Aze_(5h)
pKa = 6.03 (0.01)
pH


δP3'T
R = 0.999 NH_Aze_(5i)
pKa = 5.71 (0.03)
pH


δP3´U
R= 0.998 NH_Aze_(5j)
pKa = 5.70 (0.03)
pH

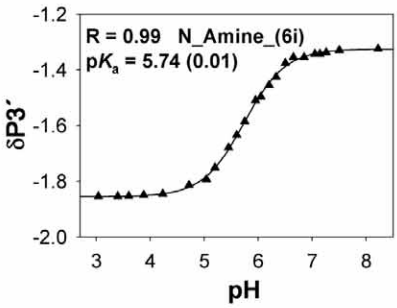
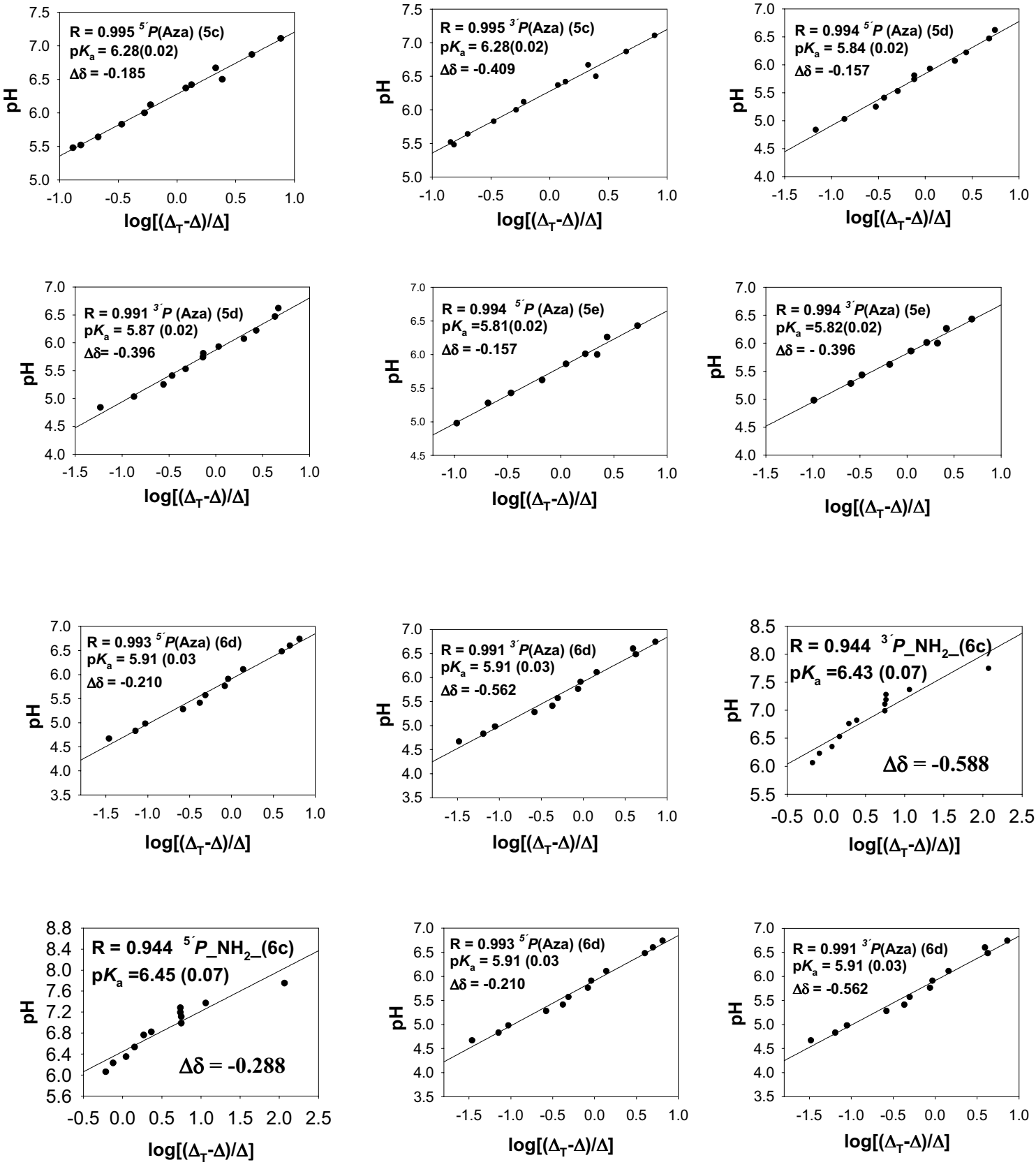
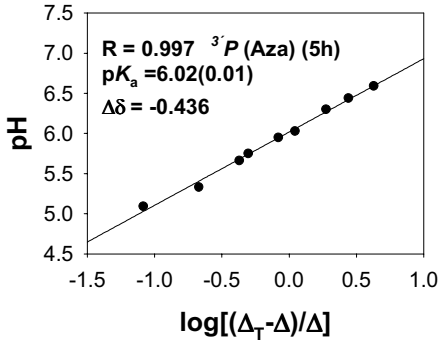
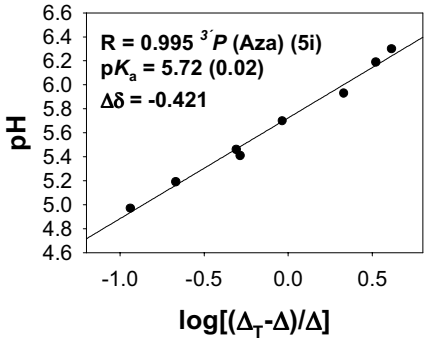
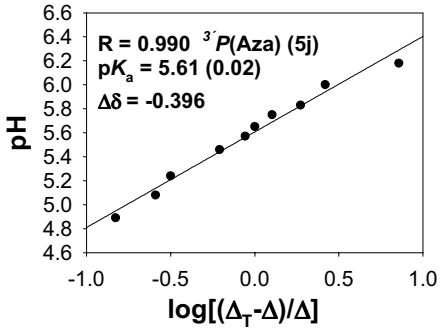

δP3´
R = 0.99 N_Amine_(6i)
pKa = 5.74 (0.01)
pH

Figure S5. Hill plot analysis of sigmoidal curves in **Figure S4.**




R = 0.997 3´P (Aza) (5h)
pKa =6.02(0.01)
Δδ = -0.436
pH
log[(ΔT-Δ)/Δ]


R = 0.995 3´P (Aza) (5i)
pKa = 5.72 (0.02)
Δδ = -0.421
pH
log[(ΔT-Δ)/Δ]


R = 0.990 3´P(Aza) (5j)
pKa = 5.61 (0.02)
Δδ = -0.396
pH
log[(ΔT-Δ)/Δ]

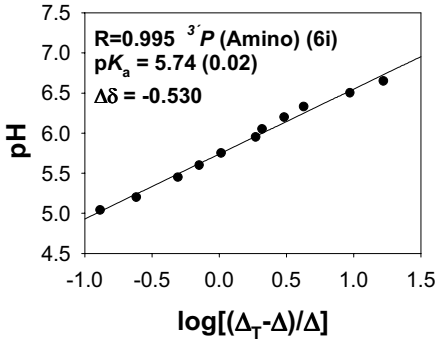

R=0.995 3´P (Amino) (6i)
pKa = 5.74 (0.02)
Δδ = -0.530
pH
log[(ΔT-Δ)/Δ]

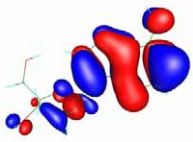
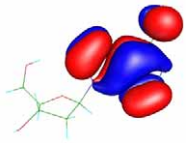
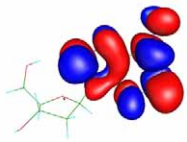
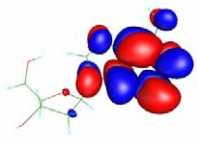
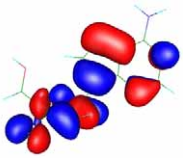
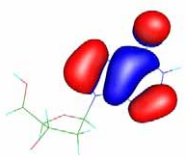
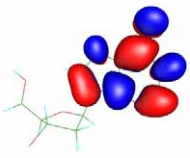
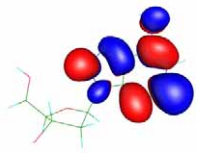
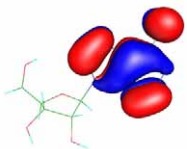
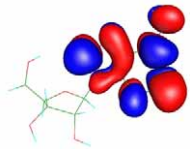
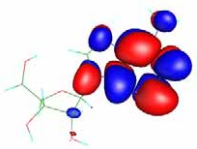
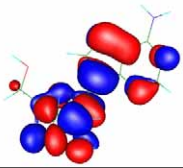
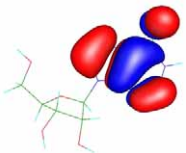
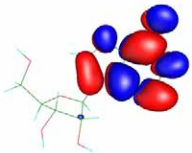
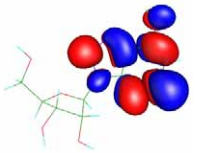
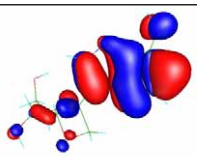
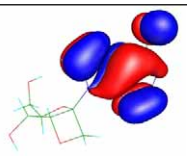
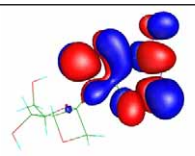
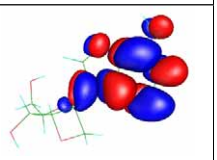
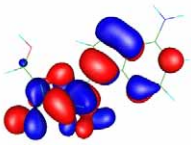
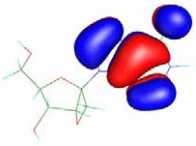
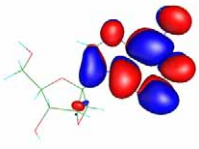
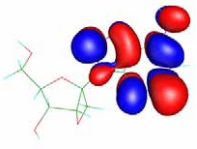
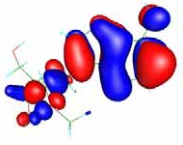
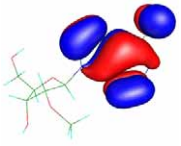
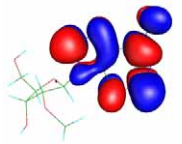
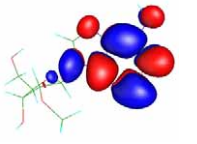
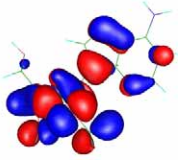
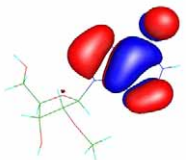
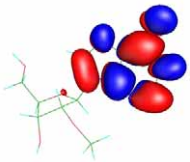
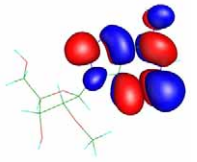
Table S1. Theoretical proton affinities (PA), thermodynamic circle's components enthalpies Gibbs free energies (gas phase and solvation), and the theoretical pK_a values of the nucleobases, 2′ ribo-, 2′-deoxy-, 2′-amino-, 2′-methoxy-, oxetane and azetidine nucleosides as well as the experimental pK_a values for the corresponding bis-ethylphosphate nucleotides.

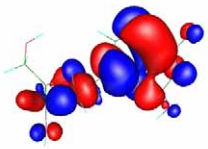
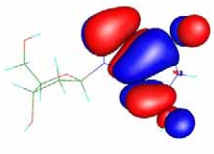
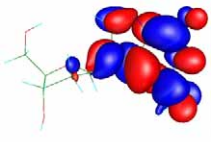
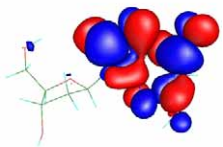
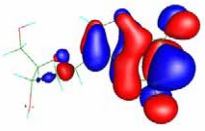
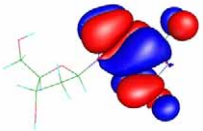
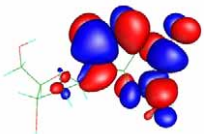
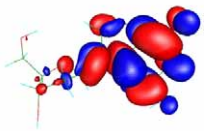
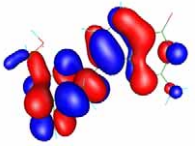
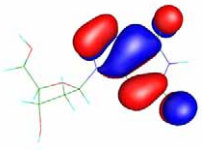
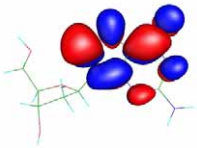
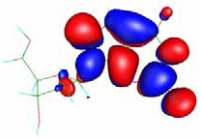
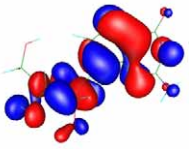
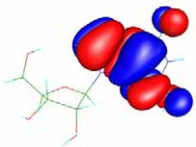
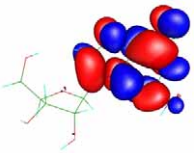
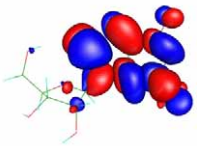
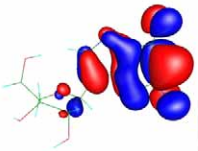
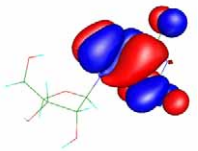
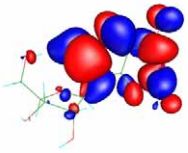
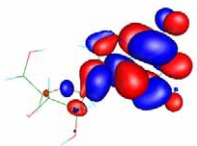
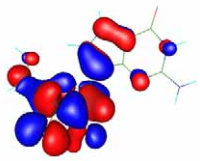
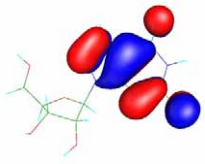
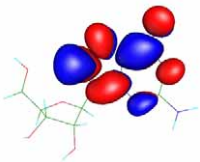
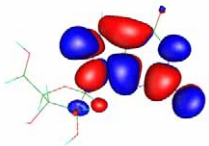
Nucleobase/ nucleoside/ nucleotide	dH, BH (gas), a.u.	ΔG, BH (gas), a.u.	ΔG_s, BH (aq), kcal/mol.	dH, B (gas), a.u.	ΔG, B (gas), a.u.	ΔG_s, B (aq), kcal/mol	PA (gas) kcal/ mol	$\Delta\Delta G_{gas+}$ $\Delta\Delta G_s$ kcal/ mol	$\Delta\Delta G_s$ kcal/mol	pKa (calc)	pKa (exp)
Adenine N1	-464.789510	-464.829581	-69.14	**-464.420414**	**-464.459749**	**-15.68**	231.61	285.53	53.46	12.12	3.88
Guanine N1	**-539.289880**	**-539.332412**	**-29.77**	-538.728519	-538.770575	-80.02	352.26	301.54	-51.02	23.85	10.00
Thymine N3	**-451.404438**	**-451.446003**	**-15.47**	-450.826522	-450.868080	-73.80	362.65	304.32	-58.33	25.89	10.47
Cytosine N3	-392.906651	-392.944908	-73.62	**-392.529170**	**-392.566883**	**-24.82**	236.87	286.01	48.80	12.47	4.56
Uracil N3	**-412.390199**	**-412.427943**	**-19.39**	-411.812207	-411.850009	-77.97	362.70	304.08	-58.58	25.71	10.06
Deoxy-A N1	-883.245706	-883.306857	-67.20	**-882.866148**	**-882.928008**	**-17.28**	238.18	287.65	49.92	13.67	3.83
Deoxy-G N1	**-957.735180**	**-957.799469**	**-31.95**	-957.178066	-957.241982	-79.73	349.59	302.05	-47.78	24.22	9.59
Deoxy-C N3	-811.367637	-811.426481	-67.19	**-810.973000**	**-811.032912**	**-25.98**	247.64	288.18	41.21	14.06	4.35
Deoxy-T N3	**-869.847982**	**-869.910817**	**-15.98**	-869.275890	-869.338478	-71.51	358.99	303.62	-55.53	25.37	10.12
Ribo-A N1	-958.095392	-958.158419	-72.48	**-957.718794**	**-957.783107**	**-19.86**	236.32	288.13	52.62	14.02	3.69
Ribo-G N1	**-1032.587474**	**-1032.653389**	**-34.66**	-1032.029893	-1032.095091	-83.07	349.89	301.93	-48.41	24.13	9.27
Ribo-C N3	-886.219071	-886.279279	-70.55	**-885.831939**	**-885.893140**	**-21.86**	242.93	291.00	48.69	16.12	4.24
Ribo-U N3	**-905.688515**	**-905.748859**	**-18.92**	-905.130677	-905.190191	-64.95	350.05	304.54	-46.03	26.05	9.26
Oxe-**A** N1	-995.918488	-995.982344	-68.21	**-995.547148**	**-995.611323**	**-15.90**	233.02	285.13	52.31	11.82	3.68
Oxe-**G** N1	**-1070.416758**	**-1070.482548**	**-30.34**	-1069.867982	-1069.932855	-73.05	344.36	302.23	-42.71	24.35	9.74
Oxe-**C** N3	-924.034273	-924.095727	-70.46	**-923.654259**	**-923.715889**	**-25.48**	238.46	283.33	44.98	10.50	3.54
Oxe-**T** N3	**-982.528975**	**-982.593174**	**-15.38**	-981.967389	-982.030678	-65.63	352.40	302.72	-50.25	24.72	9.51
3-Etp-Oxe-**T** N3	**-1551.646976**	**-1551.729075**	**-21.17**	-1551.085009	-1551.166023	-72.69	352.64	301.80	-51.52	24.04	-
5-Etp-Oxe-**T** N3	**-1626.520543**	**-1626.605358**	**-18.15**	-1625.959836	-1626.043581	-69.16	351.85	301.51	-51.01	23.83	9.36
Oxe-**U** N3	**-943.514404**	**-943.574828**	**-19.90**	-942.952908	-943.012507	-70.08	352.34	302.68	-50.18	24.69	8.93

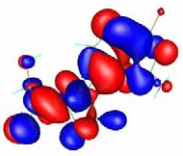
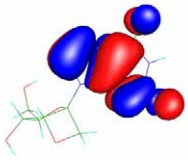
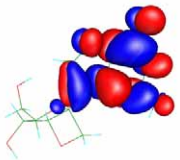
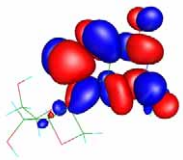
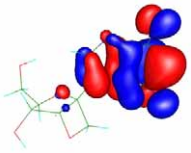
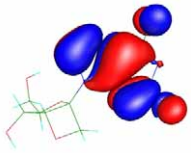
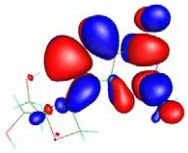
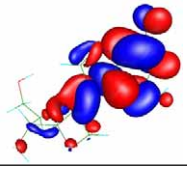
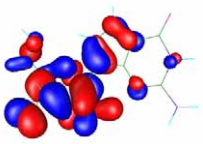
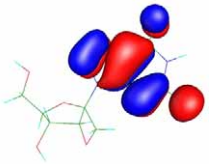
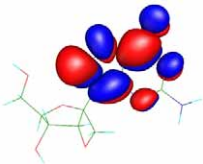
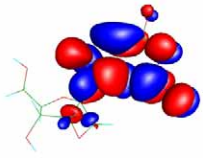
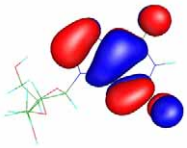
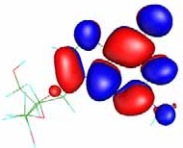
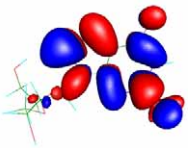
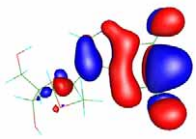
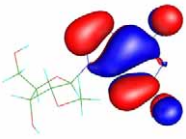
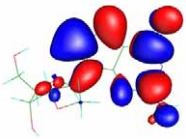
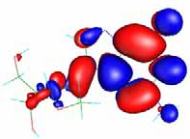
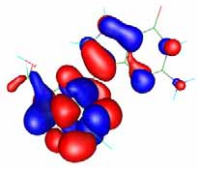
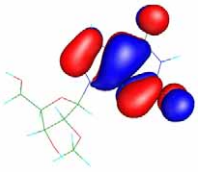
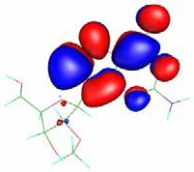
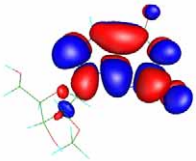
Table S1 (continue).

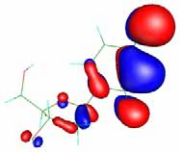
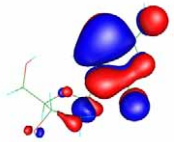
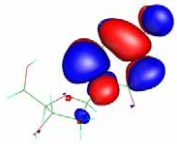
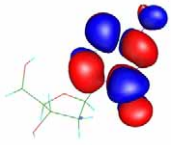
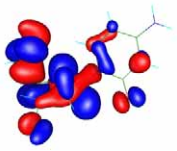
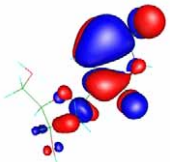
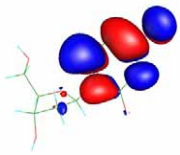
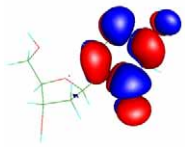
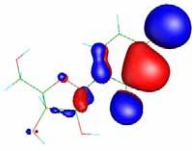
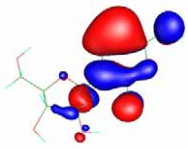
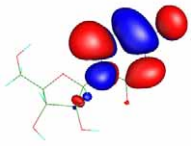
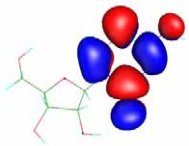
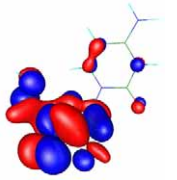
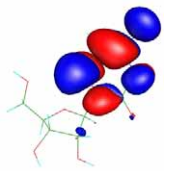
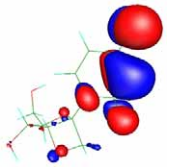
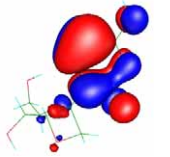
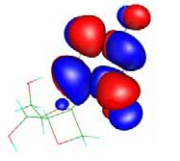
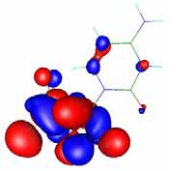
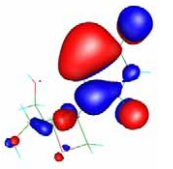
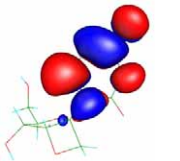
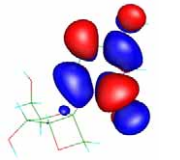
nucleoside	dH, BH (gas), a.u.	ΔG, BH (gas), a.u.	ΔG_s, BH (aq), kcal/mol.	dH, B (gas), a.u.	ΔG, B (gas), a.u.	ΔG_s, B (aq), kcal/mol	PA (gas) kcal/mol	$\Delta\Delta G_{gas+}$ $\Delta\Delta G_s$ kcal/mol	$\Delta\Delta G_s$ kcal/mol	pKa (calc)	pKa (exp)
Aze-**A** N1	-976.070333	-976.135228	-75.15	**-975.699122**	**-975.764621**	**-22.17**	232.94	285.54	52.98	12.12	-
Naze	-976.094284	-976.156380	-62.33	**-975.699122**	**-975.764621**	**-22.17**	247.97	285.99	40.16	12.45	-
Aze-**G** N1	**-1050.574037**	**-1050.640265**	**-33.59**	-1050.019017	-1050.084485	-81.10	348.28	301.25	-47.51	23.63	-
Naze	-1050.943030	-1051.011125	-90.87	**-1050.574037**	**-1050.640265**	**-33.59**	231.55	290.00	57.28	15.39	-
Aze-**C** N3	-904.199795	-904.261293	-62.36	**-903.814699**	**-903.876459**	**-26.94**	241.65	276.91	35.42	5.80	3.24
Naze	-904.185948	-904.248465	-80.68	**-903.814699**	**-903.876459**	**-26.94**	232.96	287.18	53.74	13.32	6.08
Aze-**Me-C** N3	-943.208385	-943.274726	-65.20	**-942.820181**	**-942.886762**	**-25.35**	243.60	283.30	39.85	10.48	-
Naze	-943.198987	-943.263703	-74.64	**-942.820181**	**-942.886762**	**-25.35**	237.70	285.82	49.29	12.33	-
Aze-**T** N3	**-962.690147**	**-962.754509**	**-16.82**	-962.124209	-962.187689	-69.14	355.13	303.37	-52.32	25.19	9.60
Naze	-963.052553	-963.118856	-76.23	**-962.690147**	**-962.754509**	**-16.82**	227.41	288.04	59.41	13.96	5.88
3-Etp-Aze (H down) –**T** N3	**-1531.808617**	**-1531.889260**	**-17.02**	-1531.233404	-1531.315301	-81.17	360.95	296.02	-64.15	19.80	-
Naze	-1532.178989	-1532.260287	-71.63	**-1531.808617**	**-1531.889260**	**-17.02**	232.41	287.43	54.61	13.51	-
3-Etp-Aze (H up) –**T** N3	**-1531.810806**	**-1531.891363**	**-16.04**	-1531.241960	-1531.323162	-76.10	356.96	296.49	-60.06	20.15	-
Naze	-1532.178991	-1532.260284	-71.66	**-1531.810806**	**-1531.891363**	**-16.04**	231.04	287.12	55.62	13.28	-
5-Etp-Aze (H down) –**T** N3	**-1606.677256**	**-1606.762644**	**-20.84**	-1606.110853	-1606.195675	-74.69	355.42	301.93	-53.85	24.13	9.34
Naze	-1607.054795	-1607.140208	-69.15	**-1606.677256**	**-1606.762644**	**-20.84**	236.91	285.24	48.31	11.90	5.71
5-Etp-Aze (H up) –**T** N3	**-1606.681254**	**-1606.766686**	**-19.29**	-1606.115150	-1606.199671	-72.96	355.24	302.14	-53.67	24.29	9.34
Naze	-1607.054795	-1607.140212	-69.17	**-1606.681254**	**-1606.766686**	**-19.29**	234.40	284.27	49.88	11.19	5.71
Aze-**U** N3	**-923.670689**	**-923.731642**	**-23.67**	-923.101294	-923.161586	-78.83	357.30	302.56	-55.16	24.59	9.11
Naze	-924.037934	-924.099509	-79.57	**-923.670689**	**-923.731642**	**-23.67**	230.45	286.74	55.90	13.00	5.90
Me-O-A N1	-997.084214	-997.150884	-64.18	**-996.704971**	**-996.773393**	**-13.45**	237.98	287.61	50.73	13.64	3.77
Me-O-G N1	**-1071.582056**	**-1071.652937**	**-26.09**	-1071.029785	-1071.098757	-69.79	346.56	304.05	-43.700	25.69	9.73
Me-O-C N3	-925.213389	-925.278075	-62.90	**-924.815932**	**-924.883015**	**-23.06**	249.41	287.74	39.84	13.74	4.26
Me-O-T N3	**-983.686985**	**-983.755475**	**-12.30**	-983.120383	-983.187677	-63.28	355.55	305.32	-50.98	26.62	9.94

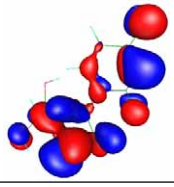
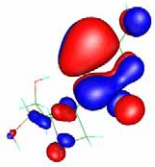
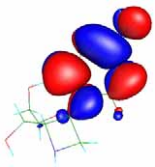
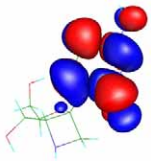
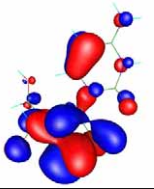
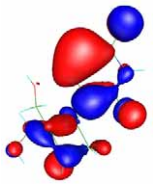
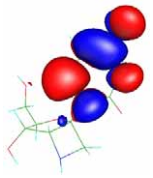
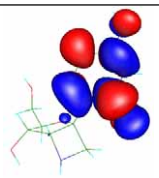
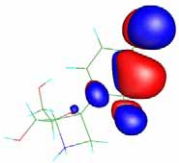
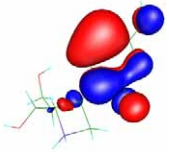
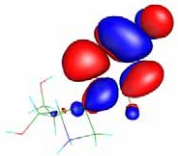
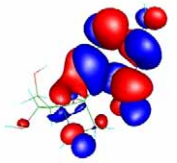
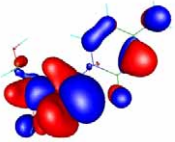
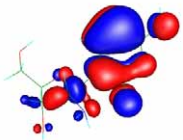
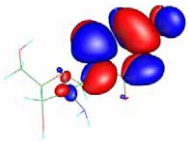
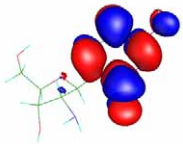
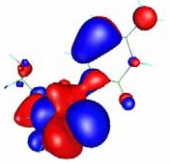
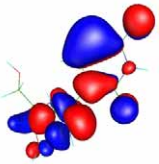
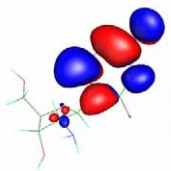
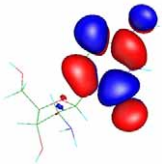
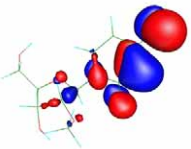
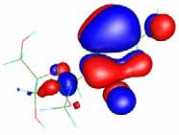
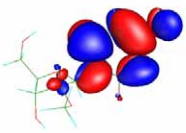
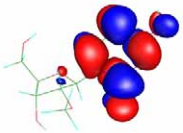
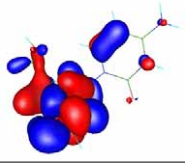
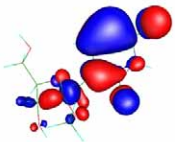
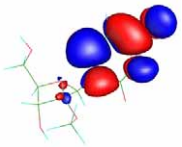
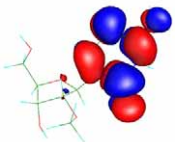
Table S2: Frontier orbitals of the 2′-ribo, 2′-deoxy, 2′-amino-, 2′-methoxy-, oxetane- and azetidine-nucleosides.

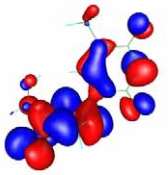
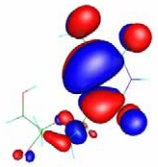
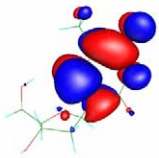
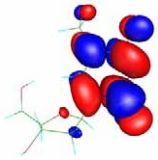
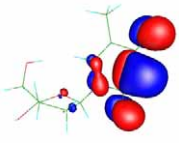
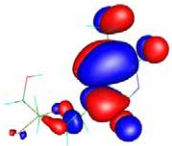
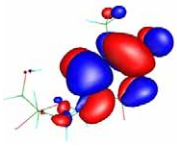
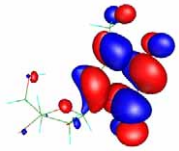
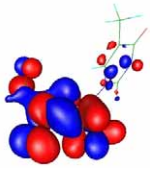
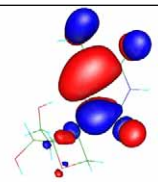
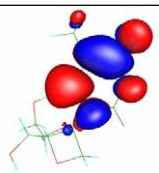
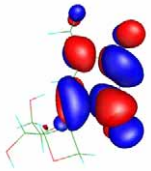
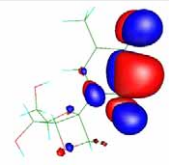
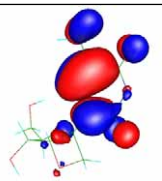
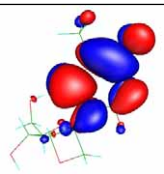
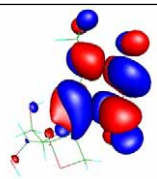
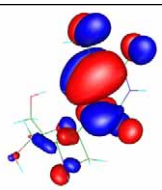
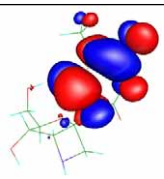
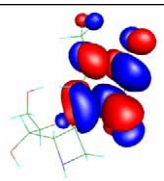
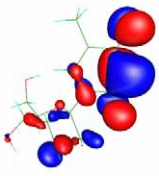
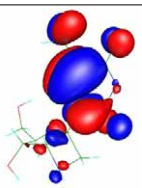
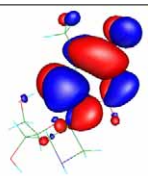
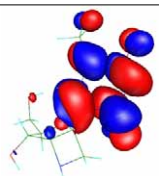
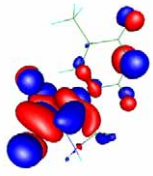
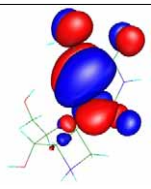
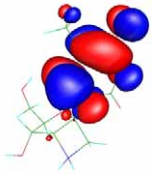
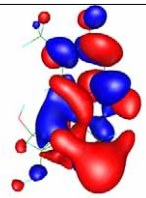
	HOMO-1	**HOMO**	**LUMO**	**LUMO+1**
dA ground				
MO energy (a.u.)	-0.36188 (-0.37104)	-0.30677 (-0.31318)	0.13445 (0.12857)	0.16432 (0.15528)
N1 protonated				
MO energy (a.u.)	-0.51492 (-0.40391)	-0.46701 (-0.34055)	-0.04077 (0.09709)	-0.02470 (0.10780)
rA ground				
MO energy (a.u.)	-0.36673 (-0.37117)	-0.31054 (-0.31311)	0.13094 (0.12867)	0.15831 (0.15395)
N1 protonated				
MO energy (a.u.)	-0.50948 (-0.40203)	-0.47095 (-0.34122)	-0.04540 (0.09640)	-0.02990 (0.10684)
Oxe-**A** ground				
MO energy (a.u.)	-0.37505 (-0.37779)	-0.31733 (-0.31579)	0.12446 (0.12637)	0.15302 (0.15120)
N1 protonated				
MO energy (a.u.)	-0.50492 (-0.40200)	-0.47569 (-0.34433)	-0.04934 (0.09339)	-0.03281 (0.10448)
A-OMe ground				
MO energy (a.u.)	-0.36694 (-0.37360)	-0.31100 (-0.31440)	0.13145 (0.12827)	0.16033 (0.15373)
N1 protonated				
MO energy (a.u.)	-0.49051 (-0.39346)	-0.46799 (-0.34271)	-0.03927 (0.09705)	-0.02502 (0.10609)

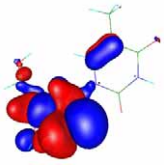
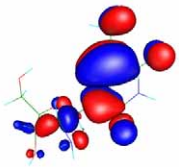
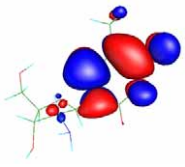
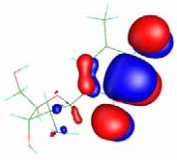
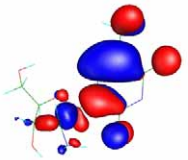
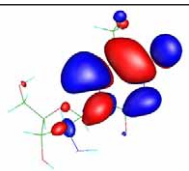
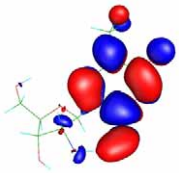
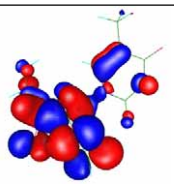
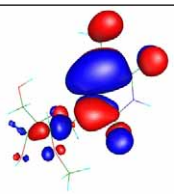
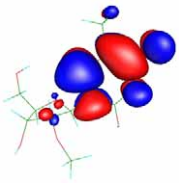
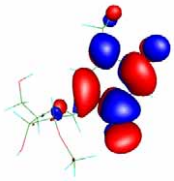
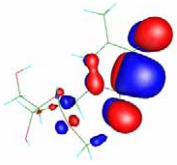
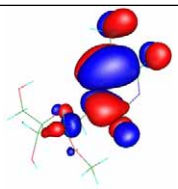
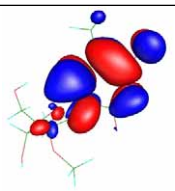
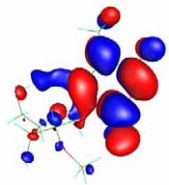
	HOMO-1	HOMO	LUMO	LUMO+1
dG ground				
MO energy (a.u.)	-0.38989 (-0.39480)	-0.29724 (-0.30490)	0.14929 (0.14697)	0.16615 (0.15953)
N1 de-protonated				
MO energy (a.u.)	-0.19183 (-0.34728)	-0.12450 (-0.27368)	0.28839 (0.17518)	0.30231 (0.19678)
N7 protonated				
MO energy (a.u.)	-0.53972 (-0.42191)	-0.45327 (-0.33023)	-0.02054 (0.10587)	0.01621 (0.14245)
rG ground				
MO energy (a.u.)	-0.38620 (-0.39109)	-0.29642 (-0.30469)	0.15006 (0.14631)	0.16435 (0.15848)
N1 de-protonated				
MO energy (a.u.)	-0.19171 (-0.34728)	-0.12482 (-0.27369)	0.26965 (0.17091)	0.30011 (0.19732)
N7 protonated				
MO energy (a.u.)	-0.54010 (-0.42296)	-0.45414 (-0.33030)	-0.02050 (0.10633)	0.01371 (0.14110)

Oxe-**G** ground				
MO energy (a.u.)	-0.40174 (-0.39934)	-0.3072 (-0.30664)	0.13806 (0.14420)	0.15633 (0.15576)
N1 de-protonated				
MO energy (a.u.)	-0.20158 (-0.34952)	-0.13476 (-0.27515)	0.29150 (0.17088)	0.30292 (0.19203)
N7 protonated				
MO energy (a.u.)	-0.52403 (-0.41502)	-0.46227 (-0.33231)	-0.02708 (0.10486)	0.00328 (0.13533)
G-OMe ground				
MO energy (a.u.)	-0.38816 (-0.39384)	-0.29701 (-0.30589)	0.14981 (0.14591)	0.16502 (0.15738)
N1 de-protonated				
MO energy (a.u.)	-0.19864 (-0.34759)	-0.13170 (-0.27387)	0.29024 (0.17317)	0.30144 (0.19559)
N7 protonated				
MO energy (a.u.)	-0.52090 (-0.41233)	-0.45162 (-0.33068)	-0.02151 (0.10418)	0.01663 (0.14007)

	HOMO-1	**HOMO**	**LUMO**	**LUMO+1**
dC ground				
MO energy (a.u.)	-0.37048 (-0.37725)	-0.32956 (-0.33362)	0.12346 (0.12421)	0.19234 (0.18366)
N3 protonated				
MO energy (a.u.)	-0.49830 (-0.43517)	-0.05996 (-0.36364)	0.02430 (0.08135)	0.04809 (0.15654)
rC ground				
MO energy (a.u.)	-0.38275 (-0.37966)	-0.34550 (-0.33678)	0.11162 (0.12342)	0.17628 (0.17970)
N3 protonated				
MO energy (a.u.)	-0.52632 (-0.42058)	-0.50246 (-0.36287)	-0.06313 (0.08242)	0.01579 (0.15444)
Oxe-**C** ground				
MO energy (a.u.)	-0.38477 (-0.38124)	-0.34897 (-0.34529)	0.10518 (0.11624)	0.18029 (0.18002)
N3 protonated				
MO energy (a.u.)	-0.52360 (-0.41807)	-0.51178 (-0.37358)	-0.07376 (0.07475)	0.01318 (0.15226)

Aze-**C** ground				
MO energy (a.u.)	-0.37633 (-0.37336)	-0.34314 (-0.34145)	0.10982 (0.11842)	0.18506 (0.18253)
N3 protonated				
MO energy (a.u.)	-0.51142 (-0.38678)	-0.49082 (-0.36871)	-0.06764 (0.07794)	0.01899 (0.15480)
N_{aze} protonated				
MO energy (a.u.)	-0.48393 (-0.38646)	-0.46122 (-0.35381)	-0.00327 (0.10996)	0.01511 (0.17496)
Amino-C ground				
MO energy (a.u.)	-0.36905 (-0.37220)	-0.32937 (-0.33561)	0.12243 (0.12213)	0.18858 (0.18539)
N3 protonated				
MO energy (a.u.)	-0.50203 (-0.38182)	-0.48148 (-0.36093)	-0.05646 (0.08075)	0.03123 (0.15798)
C-OMe ground				
MO energy (a.u.)	-0.37430 (-0.38021)	-0.33397 (-0.34002)	0.11740 (0.11890)	0.18970 (0.18326)
N3 protonated				
MO energy (a.u.)	-0.52539 (-0.42067)	-0.49665 (-0.36641)	-0.06098 (0.07875)	0.02663 (0.15596)

	HOMO-1	HOMO	LUMO	LUMO+1
dT ground				
MO energy (a.u.)	-0.42556 (-0.42012)	-0.34313 (-0.34003)	0.11524 (0.11881)	0.18814 (0.18585)
N3 de-protonated				
MO energy (a.u.)	-0.17866 (-0.35020)	-0.17533 (-0.30774)	0.28690 (0.15558)	0.29572 (0.21448)
Oxe-**T** ground				
MO energy (a.u.)	-0.42095 (-0.40921)	-0.35882 (-0.34845)	0.10438 (0.11562)	0.17515 (0.18015)
N3 de-protonated				
MO energy (a.u.)	-0.19077 (-0.35266)	-0.18852 (-0.31482)	0.27845 (0.15281)	0.31035 (0.21049)
Aze-**T** ground				
MO energy (a.u.)	-0.39742 (-0.38009)	-0.35304 (-0.34471)	0.10881 (0.11753)	0.18036 (0.18296)
N3 de-protonated				
MO energy (a.u.)	-0.18614 (-0.34910)	-0.18375 (-0.31130)	0.28199 (0.15505)	0.30260 (0.21296)
N_{aze} protonated				
MO energy (a.u.)	-0.53817 (-0.43656)	-0.46713 (-0.35646)	0.00150 (0.11145)	0.00542 (0.17202)

Amino-T ground				
MO energy (a.u.)	-0.39362 (-0.37584)	-0.33942 (-0.33943)	0.12066 (0.12040)	0.18590 (0.18644)
N3 de-protonated				
MO energy (a.u.)	-0.19053 (-0.35210)	-0.17870 (-0.30523)	0.28242 (0.15760)	0.30298 (0.20933)
T-OMe ground				
MO energy (a.u.)	-0.41162 (-0.40227)	-0.34798 (-0.34310)	0.11269 (0.11782)	0.18225 (0.18293)
N3 de-protonated				
MO energy (a.u.)	-0.18638 (-0.35083)	-0.18218 (-0.30998)	0.28435 (0.15507)	0.30334 (0.21168)

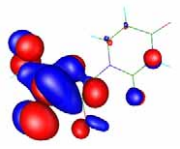
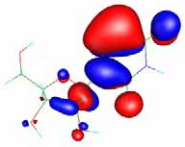
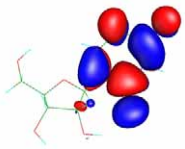
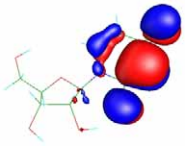
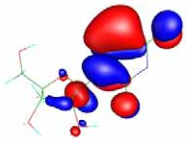
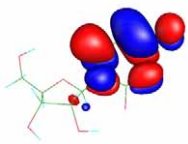
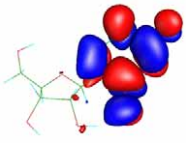
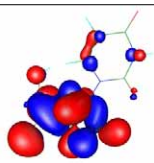
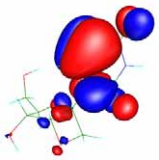
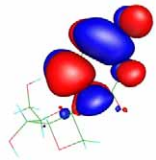
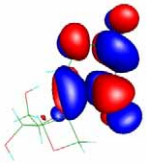
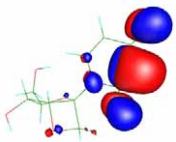
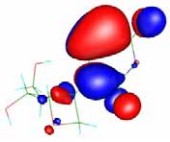
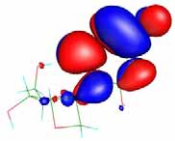
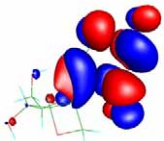
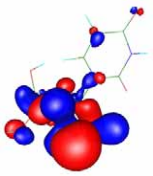
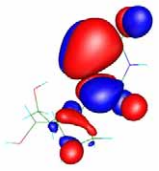
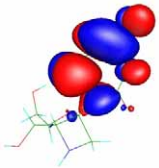
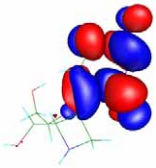
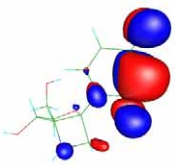
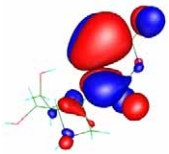
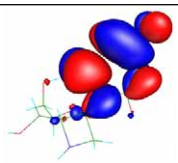
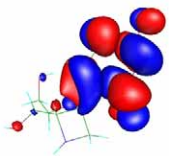
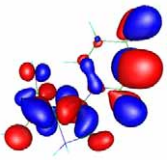
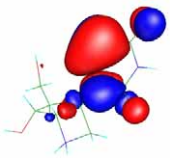
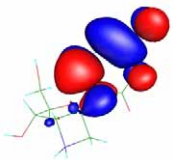
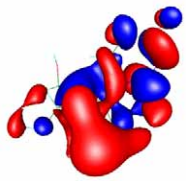
	HOMO-1	HOMO	LUMO	LUMO+1
rU ground				
MO energy (a.u.)	-0.42612 (-0.41494)	-0.36243 (-0.34880)	0.10560 (0.11912)	0.16963 (0.18040)
N3 de-protonated				
MO energy (a.u.)	-0.19997 (-0.35654)	-0.18637 (-0.31726)	0.28485 (0.15633)	0.30898 (0.20640)
Oxe-**U** ground				
MO energy (a.u.)	-0.42338 (-0.40989)	-0.37221 (-0.35969)	0.09897 (0.11252)	0.17251 (0.17894)
N3 de-protonated				
MO energy (a.u.)	-0.19750 (-0.35417)	-0.18807 (-0.32616)	0.27610 (0.14895)	0.30926 (0.20837)
Aze-**U** ground				
MO energy (a.u.)	-0.38314 (-0.37304)	-0.36304 (-0.35562)	0.10712 (0.11568)	0.18036 (0.18137)
N3 de-protonated				
MO energy (a.u.)	-0.18907 (-0.35138)	-0.17969 (-0.32219)	0.28298 (0.15212)	0.28697 (0.21094)
N_{aze} protonated				
MO energy (a.u.)	-0.53454 (-0.43944)	-0.47463 (-0.36651)	0.00124 (0.10949)	0.00511 (0.17178)

Table S3. Calculated acid-base dipole moments differences (Δdipole moments) of the nucleobases, 2'-deoxy-, 2'-ribo-, 2'-OMe, oxetane-, and azetidine- nucleosides as well as the experimental pK_a values of the respective bis-ethylphosphate nucleotides.

Nucleobase/ nucleoside	**Δdipole moment (gas phase)**	**Δdipole moment (in H_2O)**	**pK_a (exp)**[†]
cytosine	-1.3377	-2.3516	4.56
adenine	1.4630	1.9510	3.88
guanine	-1.3479	-2.4596	10.00
thymine	-4.2695	-5.7786	10.47
uracil	-3.5033	-4.8393	10.06
deoxy-C	4.9102	5.3112	4.35 (**3c**)
deoxy-A	9.4177	11.8638	3.83 (**3a**)
deoxy-G	-9.5262	-11.5763	9.59 (**3b**)
deoxy-T	-10.6595	-13.3928	10.12 (**3d**)
ribo-C	4.6386	5.0668	4.24 (**1c**)
ribo-A	11.4977	14.3498	3.69 (**1a**)
ribo-G	-11.0964	-13.4892	9.27 (**1b**)
ribo-U	-10.1665	-12.6251	9.26 (**1e**)
oxetane-**C**	8.0784	8.8815	3.54 (**4c**)
oxetane-**A**	12.1316	15.2689	3.68 (**4a**)
oxetane-**G**	-7.1178	-9.0084	9.74 (**4b**)
oxetane-**T**	-11.1152	-13.8222	9.51 (**4d**)
oxetane-**U**	-11.6434	-14.3914	8.93 (**4e**)
2'-OMe-**C**	4.6904	4.7199	4.26 (**2c**)
2'-OMe-**A**	10.4398	12.4241	3.77 (**2a**)
2'-OMe-**G**	-8.9266	-11.2460	9.73 (**2b**)
2'-OMe-**T**	-10.2846	-12.8102	9.94 (**2d**)
azetidine-**C**	7.2827	7.8803	3.24 (**5c**)
azetidine-**T**	-9.9700	-12.4144	9.60 (**5d**)
azetidine-**U**	-11.4124	-14.1284	9.11 (**5e**)

[†] Compound numbers (Figure 1) of the 3′,5′-bis-ethyl-phosphate nucleotides are shown in parenthesis