

## Supporting Information

**Table S1:  $pK_a$  values, Hill coefficients, shifts from the residues reference  $pK_a$  values ( $\Delta pK_a$ ) and shift of the theoretical from the experimental  $pK_a$  values ( $\Delta\Delta pK_a$ ) of the four pentapeptides estimated via NMR (using the chemical shifts of  $C_\beta$  and  $H_{\delta_2}$  atoms for Glu and His, respectively) and constant pH MD.**

		Amber99sb			NMR			$\Delta\Delta pK_a$
		$pK_a$	$\Delta pK_a$	Hill coefficient	$pK_a$	$\Delta pK_a$	Hill coefficient	
GHAHG	N-term His	$6.07 \pm 0.05$	-0.47	0.91 +0.07 -0.06	$6.27 \pm 0.02$	-0.27	$0.95 \pm 0.03$	-0.20
	C-term His	$6.58 \pm 0.05$	+0.04	1.02 +0.09 -0.07	$6.69 \pm 0.02$	+0.15	$1.00 \pm 0.03$	-0.11
GEAEG	N-term Glu	$3.81 \pm 0.05$	-0.27	1.08 +0.1 -0.09	$4.06 \pm 0.02$	-0.03	$0.79 \pm 0.02$	-0.25
	C-term Glu	$4.09 \pm 0.05$	-0.04	+0.01 1.04 +0.09 -0.08	$4.05 \pm 0.02$	-0.04	$0.91 \pm 0.03$	+0.04
GEAHG	N-term Glu	$3.60 \pm 0.05$	-0.48	1.05 +0.1 -0.08	$3.70 \pm 0.04$	-0.39	$1.09 \pm 0.09$	-0.10
	C-term His	$6.77 \pm 0.05$	+0.23	0.97 +0.08 -0.07	$6.61 \pm 0.02$	+0.07	$0.96 \pm 0.03$	+0.16
GHAEG	N-term His	$6.24 \pm 0.04$	-0.30	0.92 +0.06 -0.05	$6.15 \pm 0.01$	-0.39	$0.92 \pm 0.02$	+0.09
	C-term Glu	$3.92 \pm 0.04$	-0.16	1.12 +0.08 -0.07	$3.82 \pm 0.02$	-0.27	$0.89 \pm 0.04$	+0.10

The reference  $pK_a$  values used in constant pH MD simulations were 4.081 and 6.54 for Glu and His, respectively which were calculated as average from all atoms in the residue. The reference  $pK_a$  value for the  $C_\beta$  is 4.086 which differs slightly from the one used in constant pH MD. Although the differences are too small to have any effect on the conclusions, in the Table the  $\Delta pK_a$  values are calculated using the former values for constant pH MD and the latter value for Glu for experiment.