Supporting Information

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Trinuclear cluster parameterization

Table S1: RESP charges used in the parameterization of the tautomeric imidazole ring of histidines in the trinuclear cluster with copper ions.

HIS T3	Charge (ua)	HIS T3	Charge (ua)	HIS T2	Charge (ua)
CB	-0.3384	CB	-0.2365	CB	-0.3243
HB1	0.1649	HB1	0.1179	HB1	0.15760
HB2	0.1649	HB2	0.1179	HB2	0.15760
CG	0.2436	CG	0.2767	CG	0.3549
ND1	-0.3081	ND1	-0.3432	ND1	-0.3691
HD1	0.3658	CD2	-0.3095	HD1	0.3786
CD2	-0.2280	HD2	0.2348	CD2	-0.3345
HD2	0.1892	CE1	0.0378	HD2	0.2223
CE1	0.0378	HE1	0.1712	CE1	0.0285
HE1	0.1712	NE2	-0.2416	HE1	0.2212
NE2	-0.2788	HE2	0.3706	NE2	-0.2021
Cu^+	0.4351	Cu^+	0.4351	Cu^+	0.4351
HIS T3	**Charge (ua)**	**HIS T3**	**Charge (ua)**	**HIS T2**	**Charge (ua)**
CB	-0.3160	CB	-0.3729	CB	-0.3027
HB2	0.1865	HB2	0.1793	HB2	0.1816
HB3	0.1864	HB3	0.1793	HB3	0.1816
CG	0.2981	CG	0.3283	CG	0.3270
ND1	-0.2613	ND1	-0.4219	ND1	-0.2427
HD1	0.3841	CD2	-0.2602	HD1	0.3816
CD2	-0.3023	HD2	0.2646	CD2	-0.3105
HD2	0.2235	CE1	0.0474	HD2	0.2324
CE1	0.0474	HE1	0.1935	CE1	0.0054
HE1	0.1935	NE2	-0.2152	HE1	0.2476
NE2	-0.3192	HE2	0.3988	NE2	-0.2937
Cu^{2+}	1.0377	Cu^{2+}	1.0377	Cu^{2+}	1.1835

Results

Table S2: Pka state of acid residues near the trinuclear cluster. **pK$_a$**: The predicted pK$_a$. **Offset**:The difference between the predicted pK$_a$ and the system pH.

T3"	T3'	T2	Resid	pKa	Offset	T3"	T3'	T2	Resid	pKa	Offset
+	+	+	D105	4.92	-2.27	2+	2+	2+	D105	2.80	-4.39
+	+	+	E109	6.11	-1.09	2+	2+	2+	E109	7.46	0.26
+	+	+	D135	-∞	-∞	2+	2+	2+	D135	-∞	-∞
+	+	+	E275	5.64	-1.55	2+	2+	2+	E275	-∞	-∞
+	+	+	D430	6.66	-0.53	2+	2+	2+	D430	4.65	-2.54
+	+	+	Y453	∞	∞	2+	2+	2+	Y453	∞	∞
+	+	+	E463	10.82	3.62	2+	2+	2+	E463	8.71	1.51
2+	+	2+	D105	3.90	-3.29	2+	2+	+	D105	4.26	-2.93
2+	+	2+	E109	7.34	0.14	2+	2+	+	E109	6.72	-0.48
2+	+	2+	D135	-∞	-∞	2+	2+	+	D135	-∞	-∞
2+	+	2+	E275	-∞	-∞	2+	2+	+	E275	-∞	-∞
2+	+	2+	D430	7.80	0.60	2+	2+	+	D430	2.35	-4.84
2+	+	2+	Y453	∞	∞	2+	2+	+	Y453	∞	∞
2+	+	2+	E463	9.16	1.96	2+	2+	+	E463	9.43	2.23
2+	+	+	D105	6.51	-0.68	+	+	2+	D105	5.08	-2.11
2+	+	+	E109	7.83	0.63	+	+	2+	E109	6.67	-0.52
2+	+	+	D135	-∞	-∞	+	+	2+	D135	-∞	-∞
2+	+	+	E275	-∞	-∞	+	+	2+	E275	-∞	-∞
2+	+	+	D430	-∞	-∞	+	+	2+	D430	-∞	-∞
2+	+	+	Y453	∞	∞	+	+	2+	Y453	∞	∞
2+	+	+	E463	9.62	2.42	+	+	2+	E463	9.81	2.61
+	2+	+	D105	4.47	-2.73	+	2+	2+	D105	-∞	-∞
+	2+	+	E109	6.15	-1.04	+	2+	2+	E109	6.19	-1.00
+	2+	+	D135	-∞	-∞	+	2+	2+	D135	-∞	-∞
+	2+	+	E275	-∞	-∞	+	2+	2+	E275	6.10	-1.09
+	2+	+	D430	4.27	-2.92	+	2+	2+	D430	6.96	-0.23
+	2+	+	Y453	∞	∞	+	2+	2+	Y453	∞	∞
+	2+	+	E463	8.82	1.62	+	2+	2+	E463	9.70	2.50