Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting information

Structural and Electronic Analysis of the Octarepeat Region of Prion Protein with Four Cu^{2+} by Polarizable MD and QM/MM Simulations

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August 30, 2021

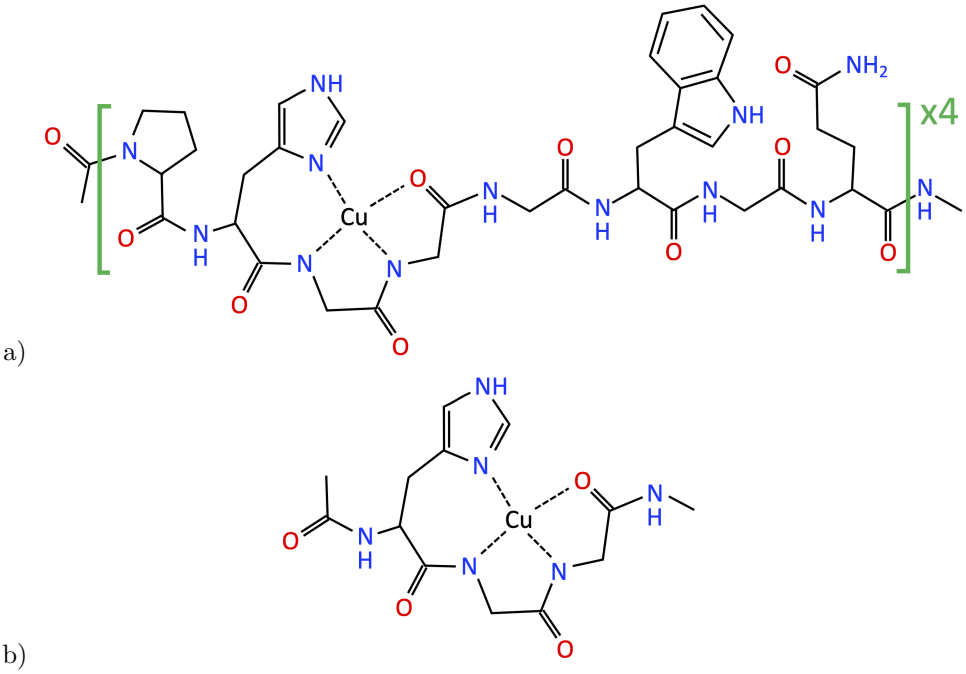

Figure S1: Two-dimensional representation of a) octarepeat region and b) HGG peptide used for the parametrization. Note that the N-terminal and C-terminal regions are capped with acetyl and N-methylacetamide, respectively.

Table S1: Mulliken charges and spin densities for model 1.

No.	Residue	Atom	Mulliken charges	Spin densities	No.	Residue	Atom	Mulliken charges	Spin densities
1	1ACE	C	-0.090405	0.000059	205	18PRO	C	0.245402	0.000024
2	1ACE	C	0.185398	-0.000005	206	18PRO	O	-0.344492	0.000059
3	1ACE	O	-0.430793	0.000017	207	18PRO	H	0.059897	0.000000
4	1ACE	H	0.090082	-0.000001	208	18PRO	C	-0.098483	-0.000037
5	1ACE	H	0.082912	-0.000002	209	18PRO	C	-0.076580	-0.000028
6	1ACE	H	0.072099	0.000011	210	18PRO	C	0.077565	0.000004
7	2PRO	N	-0.338730	0.000012	211	18PRO	H	0.051405	-0.000001
8	2PRO	C	-0.085359	-0.000003	212	18PRO	H	0.135302	0.000010
9	2PRO	C	0.209320	-0.000040	213	18PRO	H	0.092680	-0.000021
10	2PRO	O	-0.355675	0.000059	214	18PRO	H	0.052035	0.000019
11	2PRO	H	0.084538	0.000006	215	18PRO	H	0.104720	-0.000001
12	2PRO	C	0.048804	0.000010	216	18PRO	H	0.011396	-0.000004
13	2PRO	C	-0.125742	-0.000001	217	19HIE	N	-0.205647	0.000119
14	2PRO	C	0.081354	-0.000001	218	19HIE	C	0.050547	0.000712
15	2PRO	H	0.042326	0.000001	219	19HIE	C	0.187422	-0.001985
16	2PRO	H	0.067950	0.000000	220	19HIE	O	-0.402935	0.008316
17	2PRO	H	0.059608	0.000000	221	19HIE	H	0.173466	0.000075
18	2PRO	H	0.043506	-0.000001	222	19HIE	H	0.020192	-0.000193
19	2PRO	H	0.118416	0.000000	223	19HIE	C	0.021327	0.000279
20	2PRO	H	0.107839	0.000001	224	19HIE	C	-0.064037	-0.002492
21	3HIE	N	-0.194527	0.000283	225	19HIE	N	-0.309132	0.039607

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No.	Residue	Atom	Mulliken charges	Spin densities	No.	Residue	Atom	Mulliken charges	Spin densities
22	3HIE	C	0.056505	0.000199	226	19HIE	C	0.019322	0.001403
23	3HIE	C	0.192037	0.001800	227	19HIE	C	0.206039	-0.002379
24	3HIE	O	-0.485847	0.020335	228	19HIE	N	-0.164414	0.001048
25	3HIE	H	0.159593	-0.000008	229	19HIE	H	0.030503	-0.000032
26	3HIE	H	0.063206	-0.000258	230	19HIE	H	0.096575	-0.000225
27	3HIE	C	0.118717	0.000636	231	19HIE	H	0.079871	0.000067
28	3HIE	C	-0.078914	-0.001828	232	19HIE	H	0.077544	0.000749
29	3HIE	N	-0.334711	0.037893	233	19HIE	H	0.221258	0.000565
30	3HIE	C	0.045603	0.001205	234	20GLY	N	-0.400745	0.161738
31	3HIE	C	0.197943	-0.002247	235	20GLY	C	0.170293	-0.002964
32	3HIE	N	-0.195895	0.000795	236	20GLY	C	0.129478	-0.000233
33	3HIE	H	0.038464	-0.000011	237	20GLY	O	-0.342307	0.016256
34	3HIE	H	0.075090	-0.000352	238	20GLY	H	0.029653	0.001005
35	3HIE	H	0.042982	0.000105	239	20GLY	H	0.003441	0.002077
36	3HIE	H	0.084136	0.000780	240	21GLY	N	-0.446985	0.121023
37	3HIE	H	0.271529	0.000553	241	21GLY	C	0.171844	0.001156
38	4GLY	N	-0.420030	0.134757	242	21GLY	C	0.223702	0.003526
39	4GLY	C	0.153078	-0.000698	243	21GLY	O	-0.420272	0.023908
40	4GLY	C	0.175172	-0.004685	244	21GLY	H	0.053872	0.004741
41	4GLY	O	-0.446785	0.004755	245	21GLY	H	0.042780	-0.000164
42	4GLY	H	0.031475	0.000859	246	22GLY	N	-0.205350	0.001372
43	4GLY	H	0.070409	0.000541	247	22GLY	C	0.084025	-0.000339
44	5GLY	N	-0.481573	0.131534	248	22GLY	C	0.168738	0.000121
45	5GLY	C	0.180882	0.001739	249	22GLY	O	-0.329043	0.000358
46	5GLY	C	0.192603	0.001373	250	22GLY	H	0.230466	0.000637
47	5GLY	O	-0.409904	0.020194	251	22GLY	H	0.080693	0.000122
48	5GLY	H	0.081850	0.000920	252	22GLY	H	0.128611	0.000049
49	5GLY	H	0.060097	0.006042	253	23TRP	N	-0.259253	0.000019
50	6GLY	N	-0.235667	-0.000727	254	23TRP	C	0.069173	-0.000008
51	6GLY	C	0.089580	0.000111	255	23TRP	C	0.164026	0.000007
52	6GLY	C	0.163960	-0.000103	256	23TRP	O	-0.429998	0.000002
53	6GLY	O	-0.392488	-0.000003	257	23TRP	H	0.198863	-0.000002
54	6GLY	H	0.199597	0.000602	258	23TRP	H	0.073108	0.000004
55	6GLY	H	0.110517	0.000041	259	23TRP	C	0.043030	-0.000001
56	6GLY	H	0.069251	-0.000003	260	23TRP	C	-0.028876	-0.000001
57	7TRP	N	-0.234328	0.000025	261	23TRP	C	-0.058655	0.000001
58	7TRP	C	0.088386	-0.000004	262	23TRP	C	0.021792	0.000000
59	7TRP	C	0.164887	0.000000	263	23TRP	N	-0.108531	0.000000
60	7TRP	O	-0.435503	0.000002	264	23TRP	C	0.071709	0.000000
61	7TRP	H	0.239492	-0.000003	265	23TRP	C	-0.152307	0.000000
62	7TRP	H	0.039264	0.000001	266	23TRP	C	-0.057840	0.000000
63	7TRP	C	0.009691	0.000010	267	23TRP	C	-0.073056	0.000000
64	7TRP	C	-0.170369	-0.000069	268	23TRP	C	-0.052128	0.000000
65	7TRP	C	0.023918	0.000040	269	23TRP	H	0.078689	0.000000
66	7TRP	C	0.035585	0.000013	270	23TRP	H	0.041575	0.000000
67	7TRP	N	-0.117969	-0.000032	271	23TRP	H	0.071273	0.000000
68	7TRP	C	0.065211	-0.000139	272	23TRP	H	0.169621	0.000000
69	7TRP	C	-0.109024	-0.000006	273	23TRP	H	0.014528	0.000000

Table S1: Mulliken charges and spin densities for model 1.

No.	Residue	Atom	Mulliken charges	Spin densities	No.	Residue	Atom	Mulliken charges	Spin densities
70	7TRP	C	-0.088888	0.000166	274	23TRP	H	0.024613	0.000000
71	7TRP	C	-0.024796	-0.000005	275	23TRP	H	0.057847	0.000000
72	7TRP	C	-0.067769	0.000025	276	23TRP	H	0.065357	0.000000
73	7TRP	H	0.072757	0.000015	277	24GLY	N	-0.234194	0.000002
74	7TRP	H	0.049188	-0.000012	278	24GLY	C	0.102118	0.000000
75	7TRP	H	0.072636	0.000011	279	24GLY	C	0.152735	0.000000
76	7TRP	H	0.168568	-0.000013	280	24GLY	O	-0.420912	0.000000
77	7TRP	H	0.039413	0.000001	281	24GLY	H	0.228736	0.000000
78	7TRP	H	0.013612	0.000009	282	24GLY	H	0.098587	0.000000
79	7TRP	H	0.042592	0.000001	283	24GLY	H	0.097552	0.000000
80	7TRP	H	0.024136	-0.000002	284	25GLN	N	-0.210914	0.000003
81	8GLY	N	-0.160000	-0.000001	285	25GLN	C	-0.012446	0.000001
82	8GLY	C	0.140459	0.000000	286	25GLN	C	0.247201	-0.000012
83	8GLY	C	0.147596	0.000000	287	25GLN	O	-0.335602	0.000036
84	8GLY	O	-0.336123	0.000000	288	25GLN	H	0.165181	0.000000
85	8GLY	H	0.176263	0.000000	289	25GLN	H	0.095011	0.000000
86	8GLY	H	0.075572	0.000000	290	25GLN	C	0.074255	-0.000001
87	8GLY	H	0.095880	0.000000	291	25GLN	C	-0.113207	0.000023
88	9GLN	N	-0.228250	-0.000001	292	25GLN	C	0.058421	-0.000001
89	9GLN	C	0.045109	0.000000	293	25GLN	O	-0.402561	0.000000
90	9GLN	C	0.238046	0.000000	294	25GLN	N	-0.113102	0.000000
91	9GLN	O	-0.333931	0.000001	295	25GLN	H	0.046999	-0.000002
92	9GLN	H	0.184044	0.000001	296	25GLN	H	0.042970	0.000000
93	9GLN	H	0.075873	0.000000	297	25GLN	H	0.075594	-0.000030
94	9GLN	C	-0.003542	-0.000002	298	25GLN	H	0.059084	0.000000
95	9GLN	C	-0.127913	0.000009	299	25GLN	H	0.162053	0.000002
96	9GLN	C	0.106101	-0.000001	300	25GLN	H	0.195619	0.000000
97	9GLN	O	-0.387083	-0.000001	301	26PRO	N	-0.337757	0.000009
98	9GLN	N	-0.152813	0.000019	302	26PRO	C	0.028024	0.000065
99	9GLN	H	0.007090	0.000002	303	26PRO	C	0.153860	-0.000236
100	9GLN	H	0.060085	0.000000	304	26PRO	O	-0.350483	0.000032
101	9GLN	H	0.092519	0.000001	305	26PRO	H	0.077719	-0.000008
102	9GLN	H	0.080500	-0.000005	306	26PRO	C	-0.048094	0.000008
103	9GLN	H	0.205254	0.000003	307	26PRO	C	-0.055454	-0.000003
104	9GLN	H	0.166874	-0.000001	308	26PRO	C	0.097223	-0.000001
105	10PRO	N	-0.381564	0.000000	309	26PRO	H	0.070147	-0.000006
106	10PRO	C	-0.018771	0.000059	310	26PRO	H	0.031403	0.000001
107	10PRO	C	0.185516	-0.000135	311	26PRO	H	0.061617	0.000000
108	10PRO	O	-0.304805	0.000072	312	26PRO	H	0.061663	-0.000035
109	10PRO	H	0.075729	-0.000002	313	26PRO	H	0.060853	0.000001
110	10PRO	C	-0.021843	-0.000009	314	26PRO	H	0.070210	0.000001
111	10PRO	C	-0.047679	-0.000002	315	27HIE	N	-0.133142	0.000658
112	10PRO	C	0.103594	0.000002	316	27HIE	C	0.035514	0.000649
113	10PRO	H	0.052387	0.000000	317	27HIE	C	0.183043	-0.001818
114	10PRO	H	0.092165	0.000001	318	27HIE	O	-0.456965	0.014543
115	10PRO	H	0.071002	0.000000	319	27HIE	H	0.154520	0.000057
116	10PRO	H	0.040725	-0.000001	320	27HIE	H	0.069472	0.000127
117	10PRO	H	0.067930	0.000000	321	27HIE	C	0.069446	-0.000346

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No.	Residue	Atom	Mulliken charges	Spin densities	No.	Residue	Atom	Mulliken charges	Spin densities
118	10PRO	H	0.046892	0.000000	322	27HIE	C	-0.058180	-0.001485
119	11HIE	N	-0.152539	0.000134	323	27HIE	N	-0.322293	0.038404
120	11HIE	C	0.077532	-0.000282	324	27HIE	C	0.017203	0.001009
121	11HIE	C	0.204809	0.003105	325	27HIE	C	0.226399	-0.001145
122	11HIE	O	-0.491847	0.027316	326	27HIE	N	-0.118937	0.001756
123	11HIE	H	0.150934	-0.000023	327	27HIE	H	0.057112	0.000163
124	11HIE	H	0.039380	-0.000146	328	27HIE	H	0.060102	-0.000171
125	11HIE	C	0.027512	0.000883	329	27HIE	H	0.018615	0.000117
126	11HIE	C	-0.019531	-0.000314	330	27HIE	H	0.032978	0.000309
127	11HIE	N	-0.353471	0.034365	331	27HIE	H	0.234229	0.000459
128	11HIE	C	0.029061	-0.000390	332	28GLY	N	-0.419263	0.172076
129	11HIE	C	0.221630	0.000777	333	28GLY	C	0.182602	-0.001677
130	11HIE	N	-0.156119	0.003569	334	28GLY	C	0.226222	-0.003185
131	11HIE	H	0.030166	-0.000135	335	28GLY	O	-0.485253	0.006437
132	11HIE	H	0.059963	-0.000100	336	28GLY	H	0.069569	0.000353
133	11HIE	H	0.031725	0.000169	337	28GLY	H	0.051709	0.002708
134	11HIE	H	0.142740	0.001084	338	29GLY	N	-0.462777	0.146489
135	11HIE	H	0.265296	0.000331	339	29GLY	C	0.154194	0.002552
136	12GLY	N	-0.488121	0.141173	340	29GLY	C	0.232923	0.002971
137	12GLY	C	0.173519	-0.002120	341	29GLY	O	-0.334225	0.026459
138	12GLY	C	0.185143	-0.003463	342	29GLY	H	0.101475	0.002564
139	12GLY	O	-0.377000	0.006590	343	29GLY	H	0.045479	0.003040
140	12GLY	H	0.057038	0.000688	344	30GLY	N	-0.250372	0.000162
141	12GLY	H	0.050757	0.000627	345	30GLY	C	0.106970	-0.000014
142	13GLY	N	-0.503279	0.142749	346	30GLY	C	0.138401	-0.000004
143	13GLY	C	0.115645	-0.000340	347	30GLY	O	-0.309989	0.000187
144	13GLY	C	0.155216	0.002363	348	30GLY	H	0.211047	0.000496
145	13GLY	O	-0.341726	0.019723	349	30GLY	H	0.054447	0.000022
146	13GLY	H	0.082891	0.000058	350	30GLY	H	0.096502	0.000039
147	13GLY	H	0.080439	0.007950	351	31TRP	N	-0.171460	-0.000022
148	14GLY	N	-0.250230	0.001750	352	31TRP	C	0.027053	-0.000032
149	14GLY	C	0.148376	-0.000194	353	31TRP	C	0.139262	0.000003
150	14GLY	C	0.185181	0.000042	354	31TRP	O	-0.358143	0.000001
151	14GLY	O	-0.396708	0.000040	355	31TRP	H	0.142044	-0.000002
152	14GLY	H	0.229853	0.000436	356	31TRP	H	0.045968	0.000028
153	14GLY	H	0.042637	0.000092	357	31TRP	C	0.087655	0.000006
154	14GLY	H	0.100911	0.000138	358	31TRP	C	-0.128416	-0.000029
155	15TRP	N	-0.249763	-0.000006	359	31TRP	C	-0.023071	-0.000024
156	15TRP	C	0.069792	0.000000	360	31TRP	C	0.037233	-0.000066
157	15TRP	C	0.150680	-0.000001	361	31TRP	N	-0.132537	0.000016
158	15TRP	O	-0.364371	0.000000	362	31TRP	C	0.069629	-0.000157
159	15TRP	H	0.192420	0.000013	363	31TRP	C	-0.045362	0.000041
160	15TRP	H	0.066264	0.000000	364	31TRP	C	-0.045591	-0.000101
161	15TRP	C	0.050270	0.000001	365	31TRP	C	-0.043831	0.000151
162	15TRP	C	-0.118254	0.000000	366	31TRP	C	-0.057869	-0.000091
163	15TRP	C	0.013129	0.000000	367	31TRP	H	0.019770	-0.000001
164	15TRP	C	0.016509	-0.000001	368	31TRP	H	0.072032	0.000000
165	15TRP	N	-0.118900	0.000000	369	31TRP	H	0.067849	0.000001

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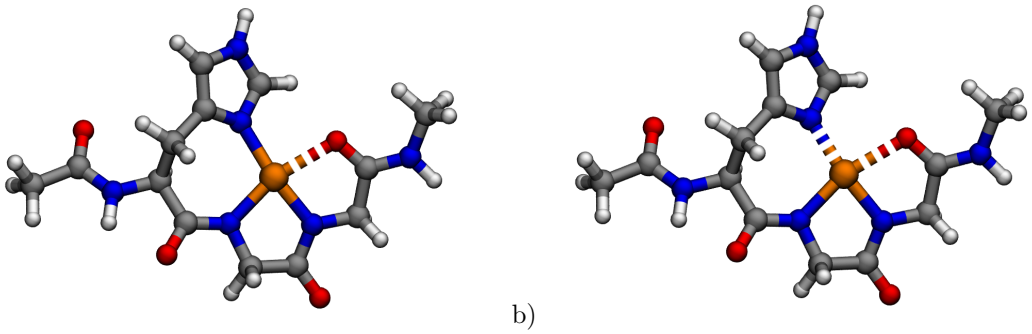
No.	Residue	Atom	Mulliken charges	Spin densities	No.	Residue	Atom	Mulliken charges	Spin densities
166	15TRP	C	0.053931	0.000000	370	31TRP	H	0.188019	-0.000001
167	15TRP	C	-0.132455	0.000007	371	31TRP	H	-0.009480	0.000005
168	15TRP	C	-0.089909	0.000000	372	31TRP	H	0.027326	-0.000004
169	15TRP	C	-0.067127	0.000000	373	31TRP	H	0.018586	-0.000018
170	15TRP	C	-0.023041	0.000000	374	31TRP	H	0.027778	-0.000002
171	15TRP	H	0.034750	0.000000	375	32GLY	N	-0.245057	-0.000001
172	15TRP	H	0.047404	-0.000001	376	32GLY	C	0.096464	0.000000
173	15TRP	H	0.066176	0.000000	377	32GLY	C	0.154802	0.000000
174	15TRP	H	0.161296	0.000000	378	32GLY	O	-0.345839	0.000000
175	15TRP	H	0.048716	0.000007	379	32GLY	H	0.174450	0.000000
176	15TRP	H	0.044294	0.000000	380	32GLY	H	0.110875	0.000000
177	15TRP	H	0.044714	0.000000	381	32GLY	H	0.110888	0.000000
178	15TRP	H	0.042844	0.000000	382	33GLN	N	-0.257748	0.000001
179	16GLY	N	-0.171719	0.000003	383	33GLN	C	-0.021219	-0.000002
180	16GLY	C	0.076653	-0.000002	384	33GLN	C	0.235833	-0.000001
181	16GLY	C	0.193841	-0.000001	385	33GLN	O	-0.420748	0.000001
182	16GLY	O	-0.370295	0.000000	386	33GLN	H	0.185105	-0.000004
183	16GLY	H	0.181416	-0.000008	387	33GLN	H	0.107826	0.000002
184	16GLY	H	0.128808	0.000000	388	33GLN	C	-0.039096	0.000030
185	16GLY	H	0.076163	-0.000003	389	33GLN	C	-0.094488	-0.000023
186	17GLN	N	-0.271328	0.000001	390	33GLN	C	0.113638	-0.000030
187	17GLN	C	0.021222	0.000001	391	33GLN	O	-0.417666	0.000045
188	17GLN	C	0.276823	-0.000006	392	33GLN	N	-0.176901	-0.000021
189	17GLN	O	-0.429240	0.000001	393	33GLN	H	0.078070	-0.000043
190	17GLN	H	0.209642	0.000000	394	33GLN	H	0.057471	-0.000003
191	17GLN	H	0.091848	-0.000002	395	33GLN	H	0.024757	-0.000007
192	17GLN	C	-0.093576	0.000000	396	33GLN	H	0.078856	-0.000515
193	17GLN	C	-0.045267	0.000000	397	33GLN	H	0.171421	-0.000087
194	17GLN	C	0.092827	0.000000	398	33GLN	H	0.204547	0.000002
195	17GLN	O	-0.361612	0.000000	399	34NME	N	-0.268801	-0.000001
196	17GLN	N	-0.127504	0.000000	400	34NME	C	-0.010078	0.000000
197	17GLN	H	0.083585	0.000000	401	34NME	H	0.198036	0.000000
198	17GLN	H	0.085893	0.000000	402	34NME	H	0.056095	0.000000
199	17GLN	H	0.089916	0.000000	403	34NME	H	0.070927	0.000000
200	17GLN	H	-0.006308	0.000000	404	34NME	H	0.071640	0.000000
201	17GLN	H	0.191964	0.000000	405	ION	Cu	0.720523	0.642707
202	17GLN	H	0.185827	0.000000	406	ION	Cu	0.653674	0.611802
203	18PRO	N	-0.300000	-0.000001	407	ION	Cu	0.658903	0.619523
204	18PRO	C	0.007029	0.000002	408	ION	Cu	0.624577	0.586097



a) b)

Figure S2: Models used for parameterization. The dashed bond represents that only non-bonding interactions are taking into account for that interaction. a) Model 1 includes binding interactions between the copper ion and deprotonated nitrogens of glycines as well as the nitrogen atom of the imidazole ring of histidine. b) Model 2 considers only bonding interactions between the copper ion and deprotonated nitrogen atoms.

Table S2: Core (C) and valance (V) basin populations in the fragment defined by His-Gly-Gly (HGG) residues and in the first coordination sphere (FCS).

Basin	HGG	FCS
C(N1)	2.06	2.07
C(N2)	2.05	2.04
C(N3)	2.06	2.04
C(Cu)	26.83	26.76
V(N1,Cu)	3.64	5.68
V(N2,Cu)	3.84	5.94
V(N3,Cu)	3.24	5.08

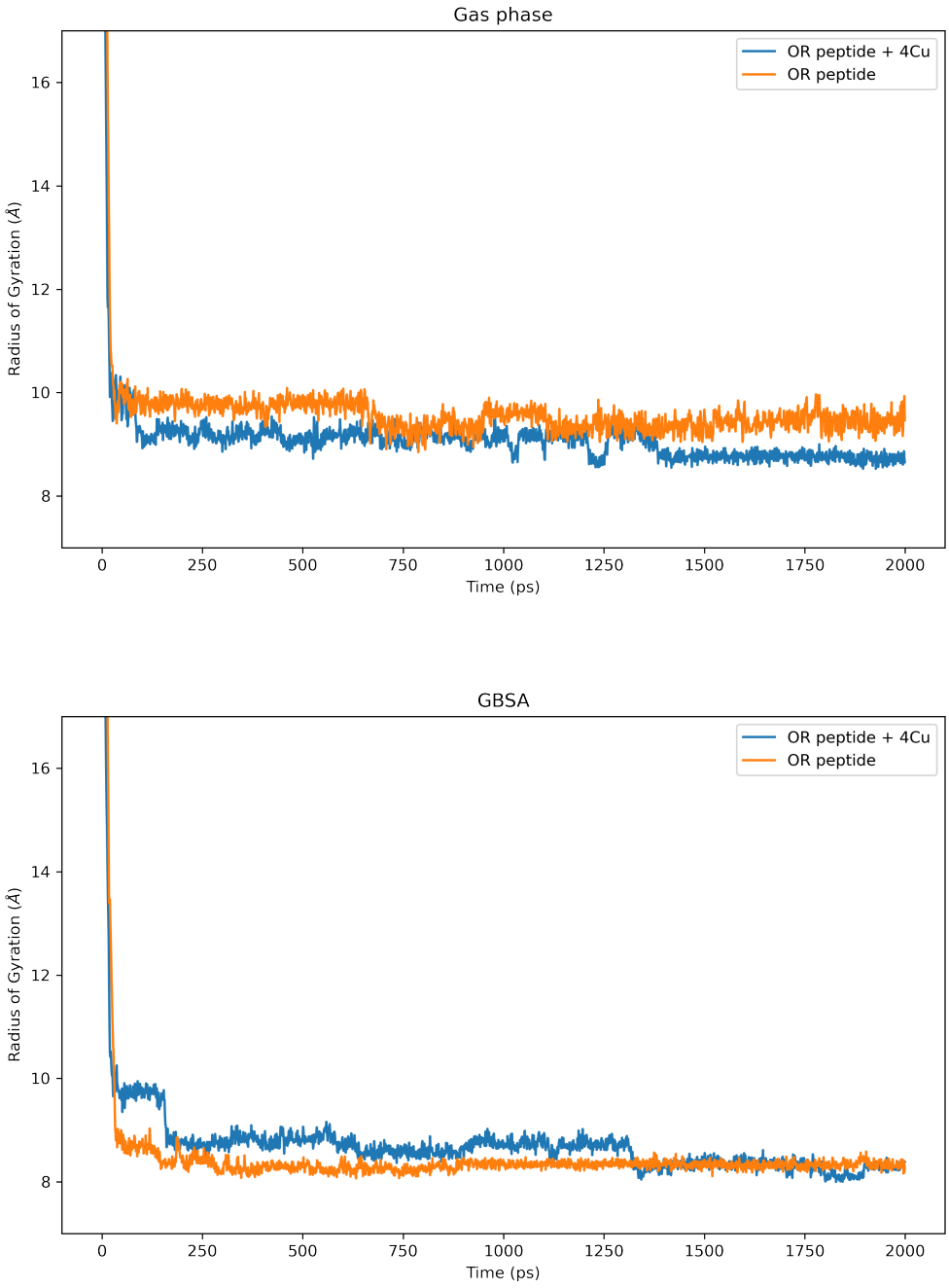


Figure S3: Radius of gyration of the OR region with and without copper ions in gas phase (above) and with solvent implicit (bottom). The graph shows how in the first picoseconds of simulation the peptide changes from an extended structure to a compact structure regardless of whether it contains copper ions or not.

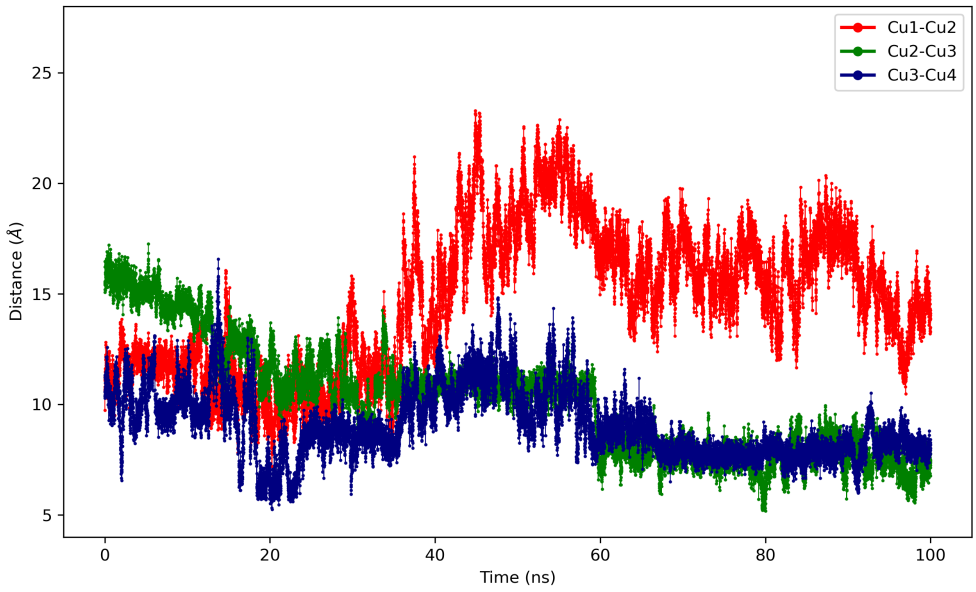


Figure S4: Distances between nearby copper ions in model 1. The distance between the Cu1 and Cu2 ions ranges from 7.2 to 23.3 Å and average of 14.63 Å. The distance between the Cu2 and Cu3 ions ranges from 5.1 to 17.3 and average of 10.18 Å. The distance between the Cu3 and Cu4 ions ranges from 5.2 to 16.6 Å and average of 9.03 Å.

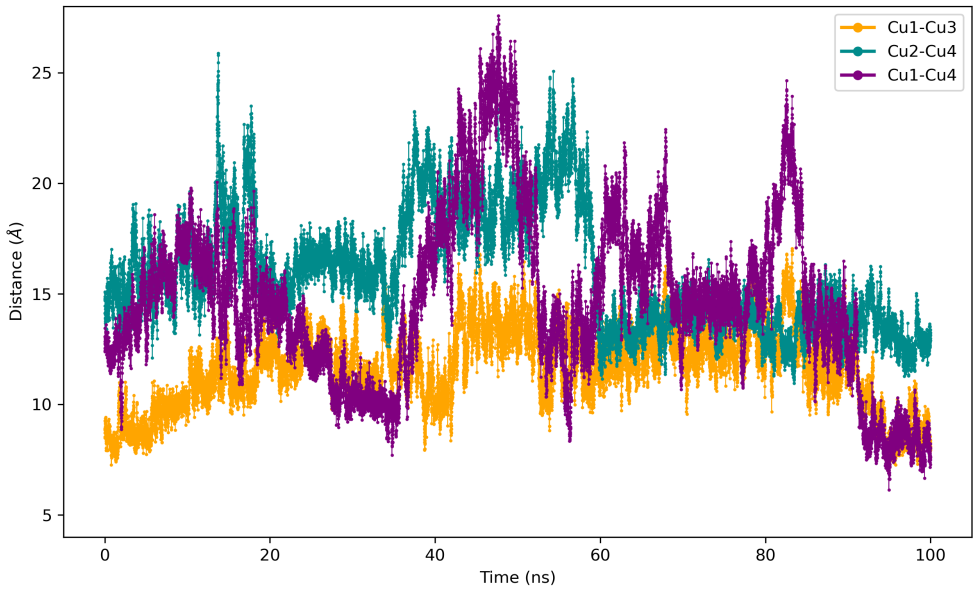


Figure S5: Distances between distant copper ions in model 1. The distance between the Cu1 and Cu3 ions ranges from 6.9 to 17.1 Å and average of 11.64 Å. The distance between the Cu2 and Cu4 ions ranges from 10.9 to 25.9 Å and average of 15.96 Å. The distance between the Cu1 and Cu4 ions ranges from 6.1 to 27.6 Å and average of 14.70 Å.

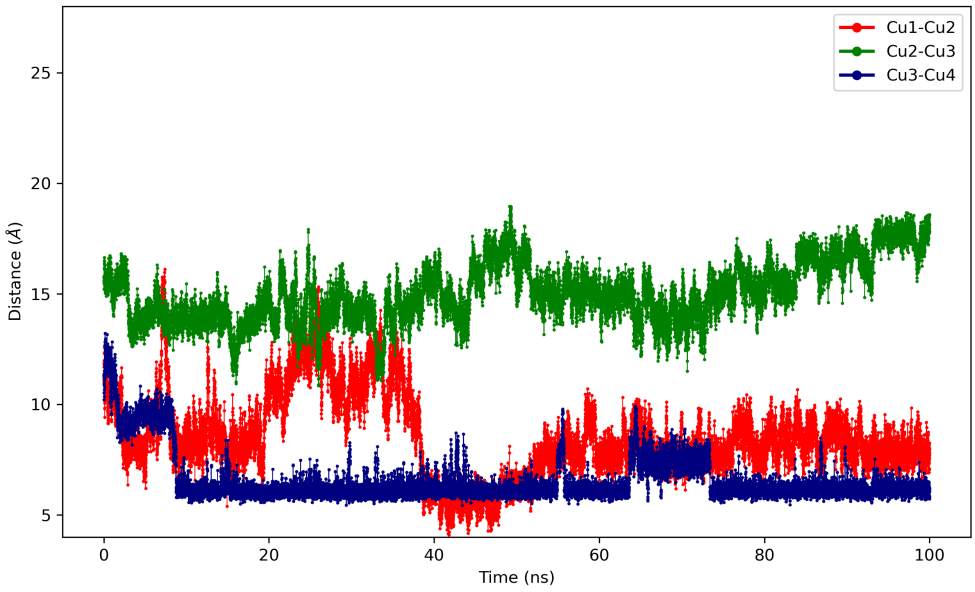


Figure S6: Distances between nearby copper ions in model 2. The distance between the Cu1 and Cu2 ions ranges from 4.1 to 16.1 Å and average of 8.53 Å. The distance between the Cu2 and Cu3 ions ranges from 10.8 to 19.0 and average of 15.05 Å. The distance between the Cu3 and Cu4 ions ranges from 5.4 to 13.2 Å and average of 6.61 Å.

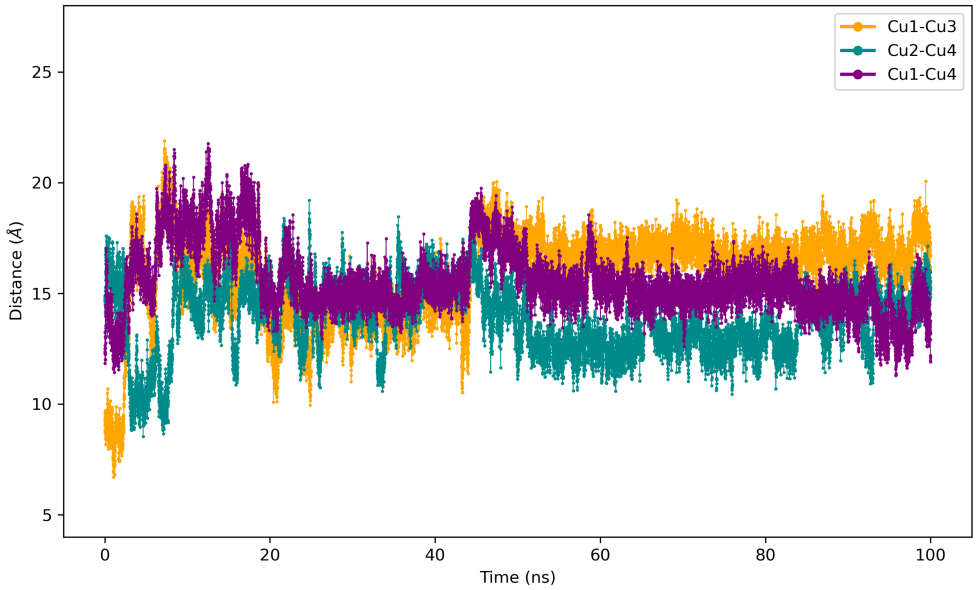


Figure S7: Distances between distant copper ions in model 2. The distance between the Cu1 and Cu3 ions ranges from 6.7 to 21.9 Å and average of 15.93 Å. The distance between the Cu2 and Cu4 ions ranges from 8.5 to 19.2 Å and average of 13.85 Å. The distance between the Cu1 and Cu4 ions ranges from 11.3 to 21.8 Å and average of 15.55 Å.

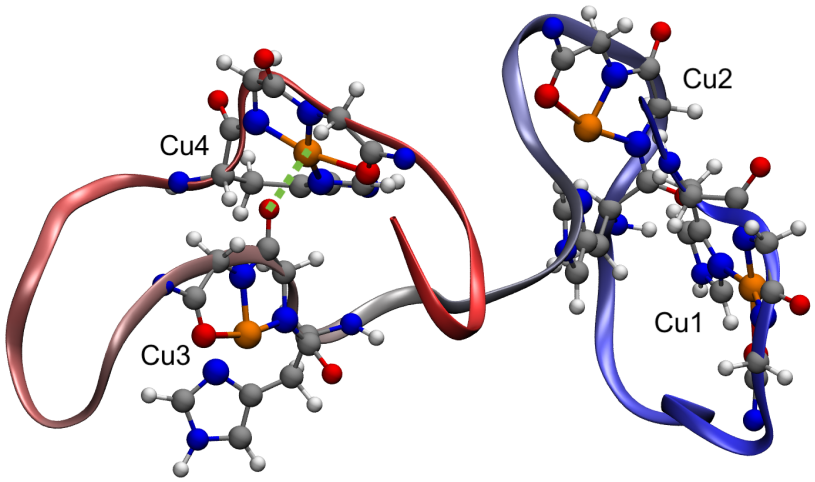


Figure S8: Structure of model 2 at 80 ns simulation where it is shown that the carbonyl oxygen of Cu3 is interacting with Cu4. The dotted green line represents this interaction.

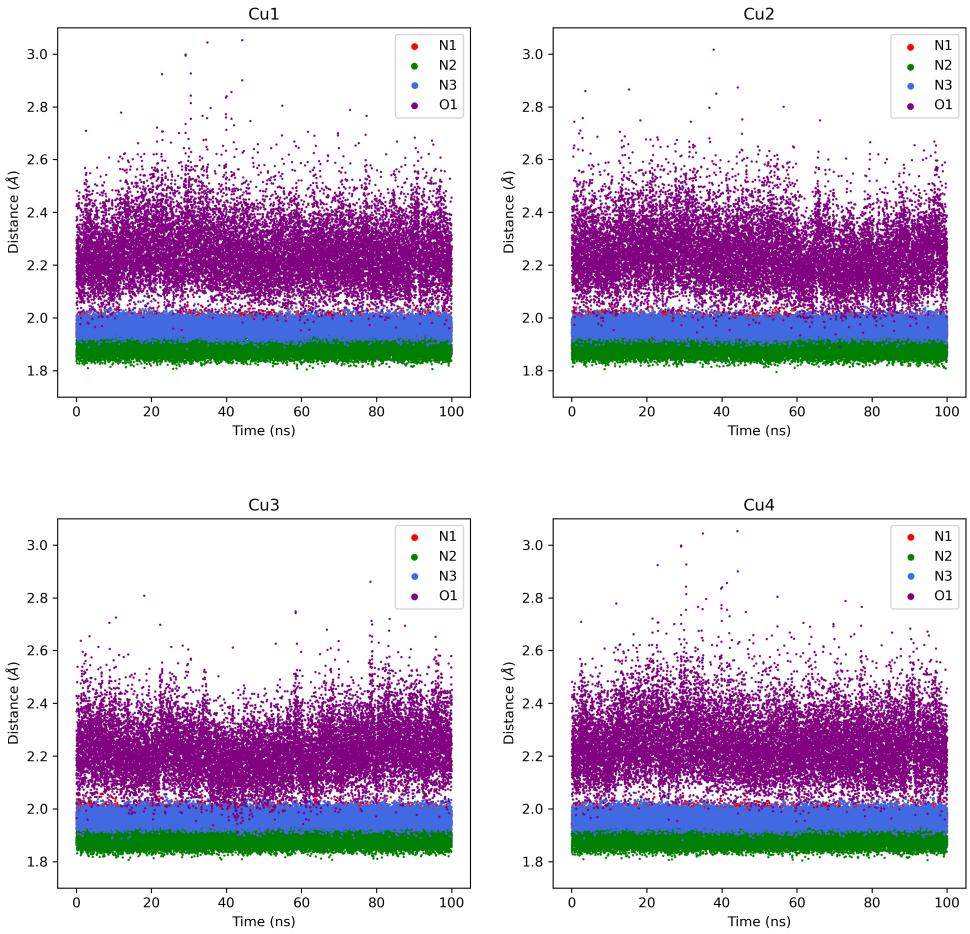


Figure S9: Bond distances of copper ions with their closest atoms in model 1 for each octapeptide. The labeling according to Fig. 4 has been used.

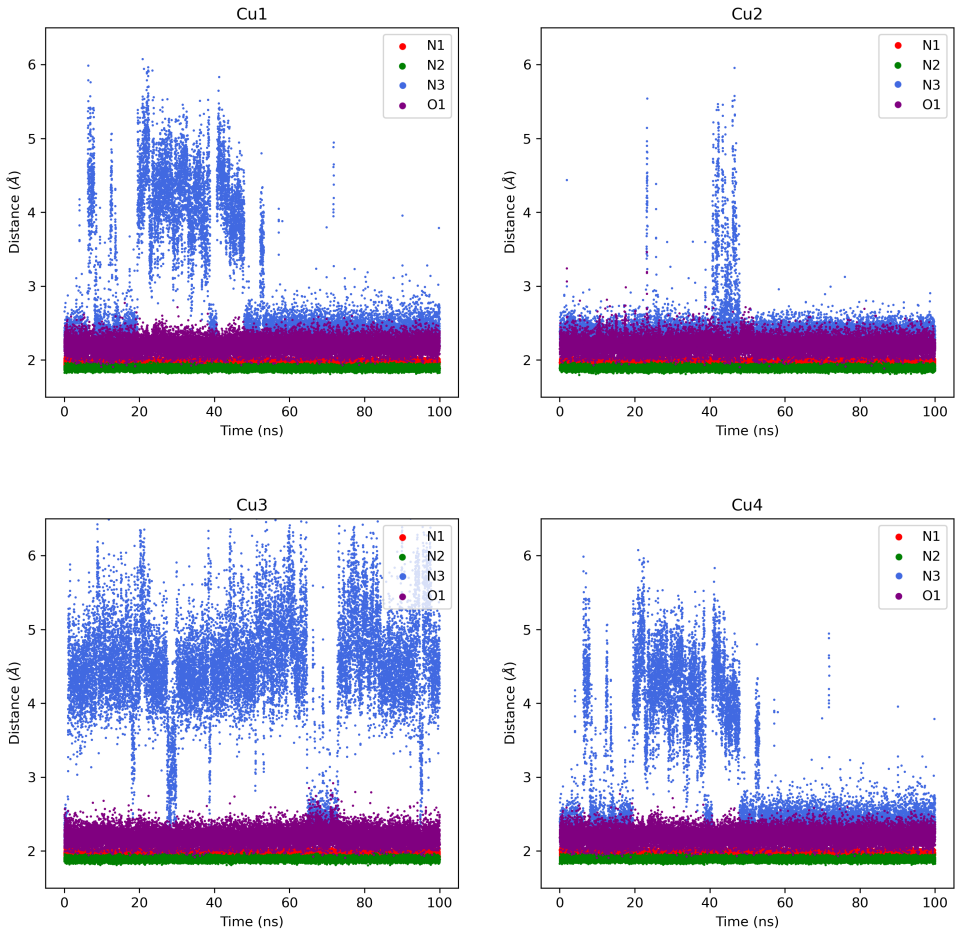


Figure S10: Bond distances of copper ions with their closest atoms in model 2 for each octapeptide. The labeling according to Fig. 4 has been used.

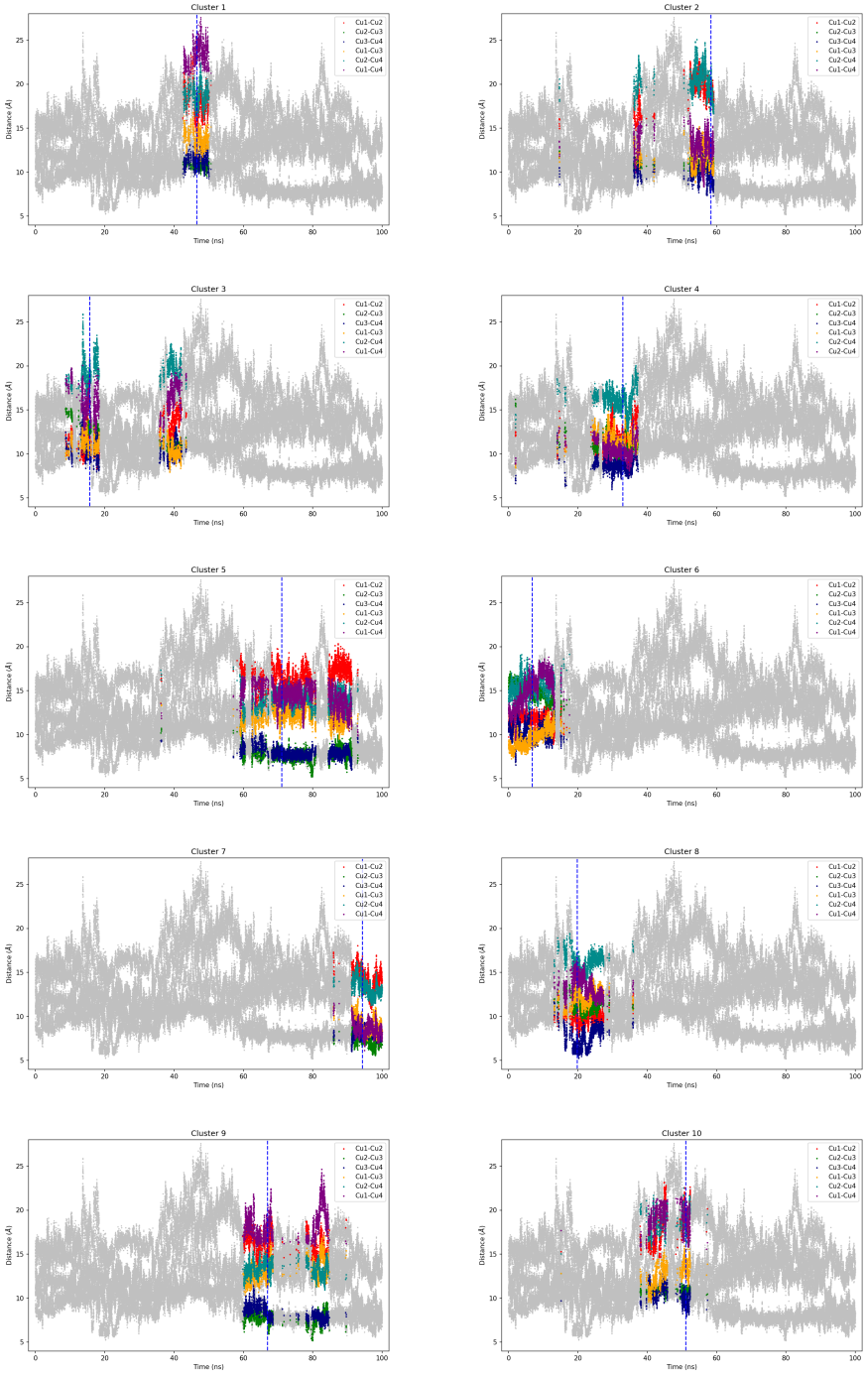


Figure S11: Clusters from the k-means analysis for model 1 (first run).

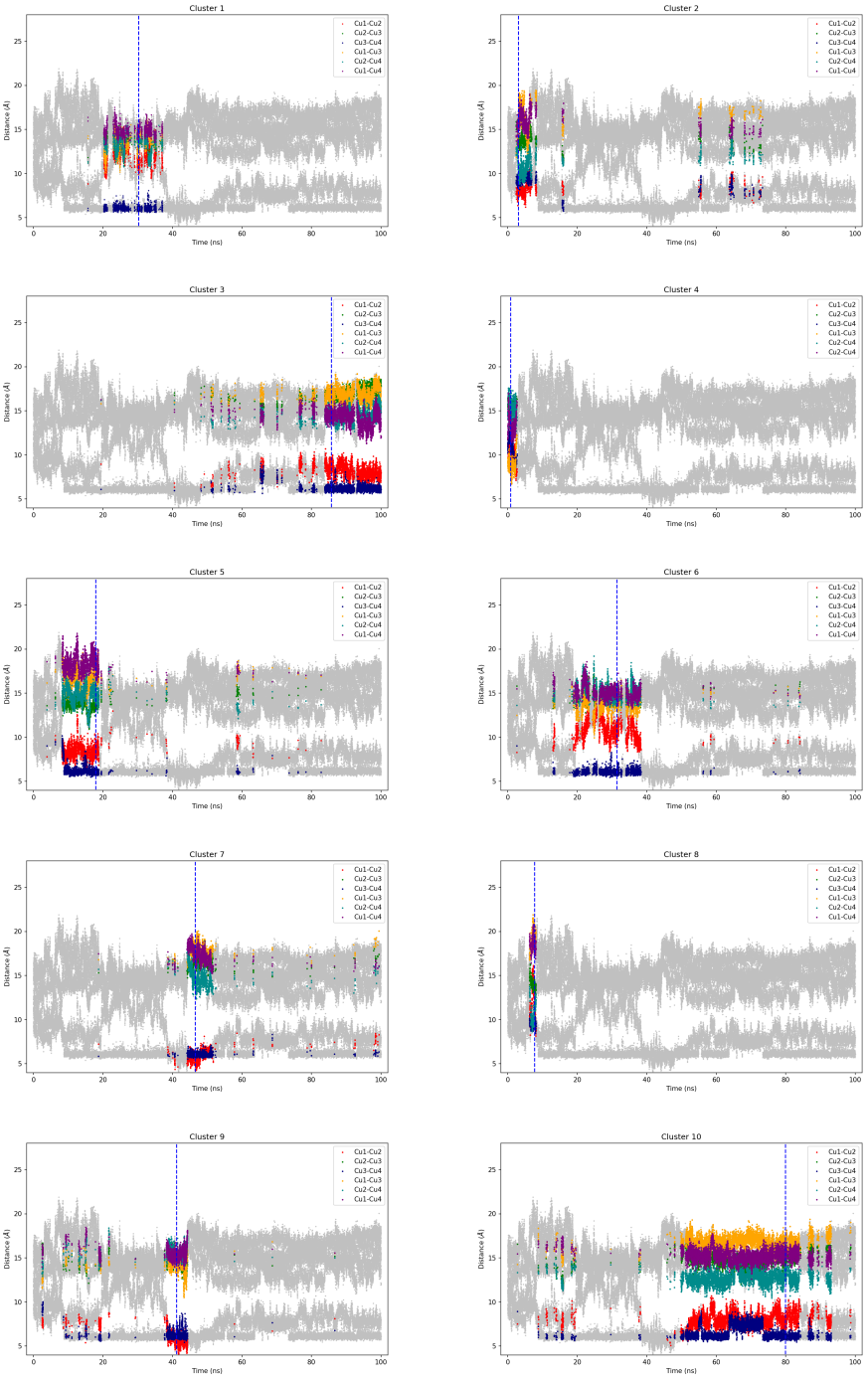


Figure S12: Clusters from the k-means analysis for model 2.

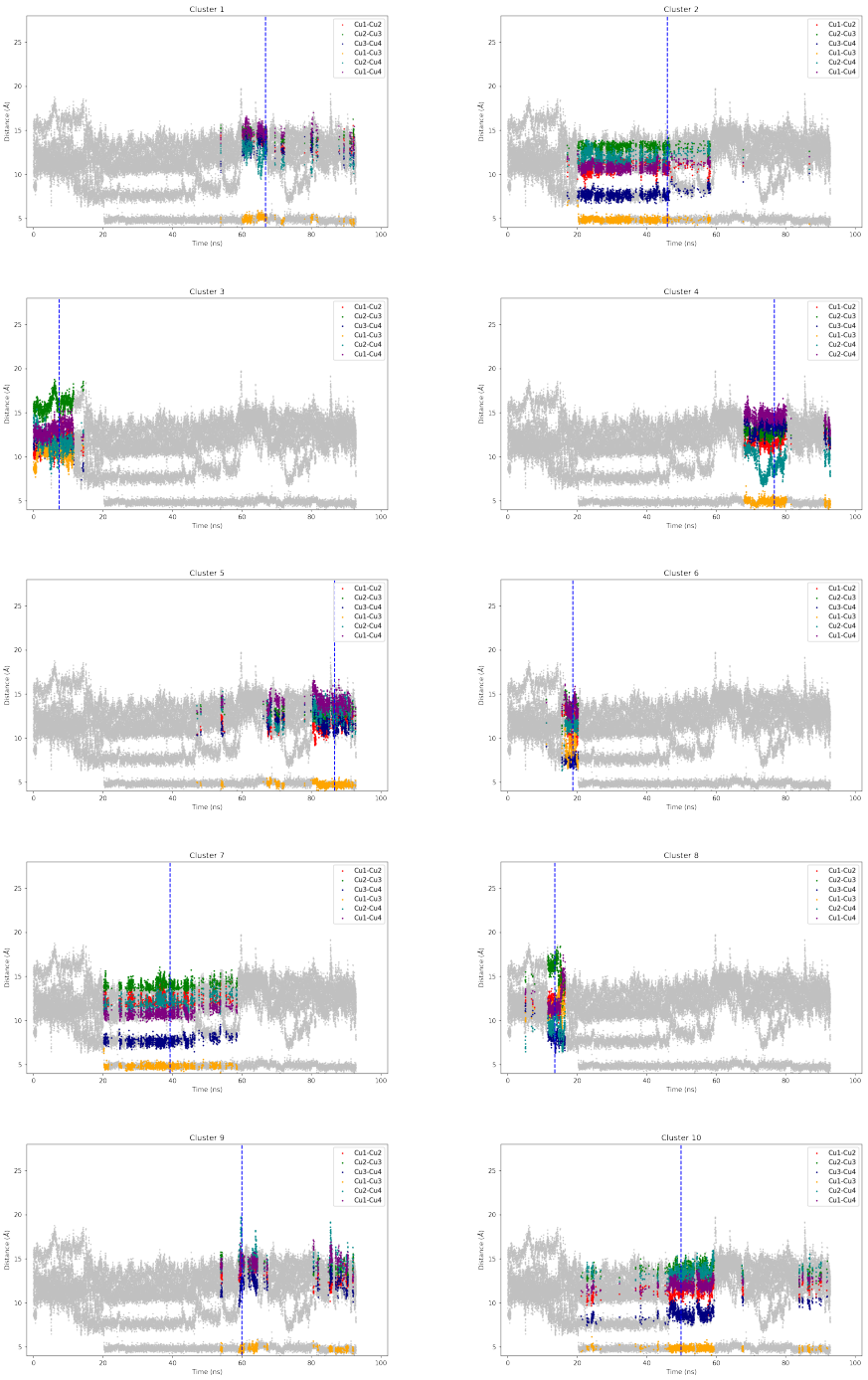


Figure S13: Clusters from the k-means analysis for model 1 (second run).

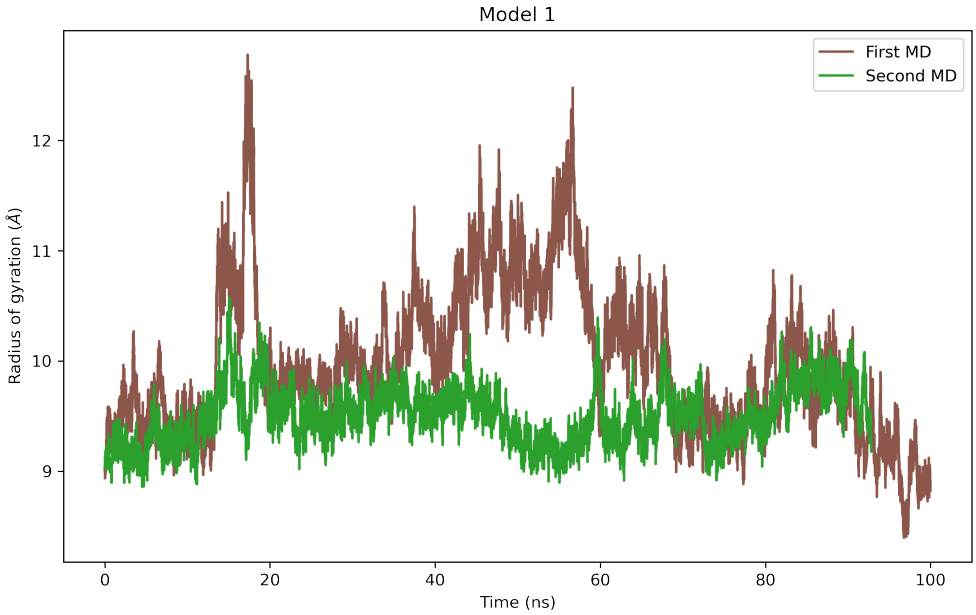


Figure S14: Radius of gyration between two different runs for model 1. In both MD simulations compact structures are obtained.

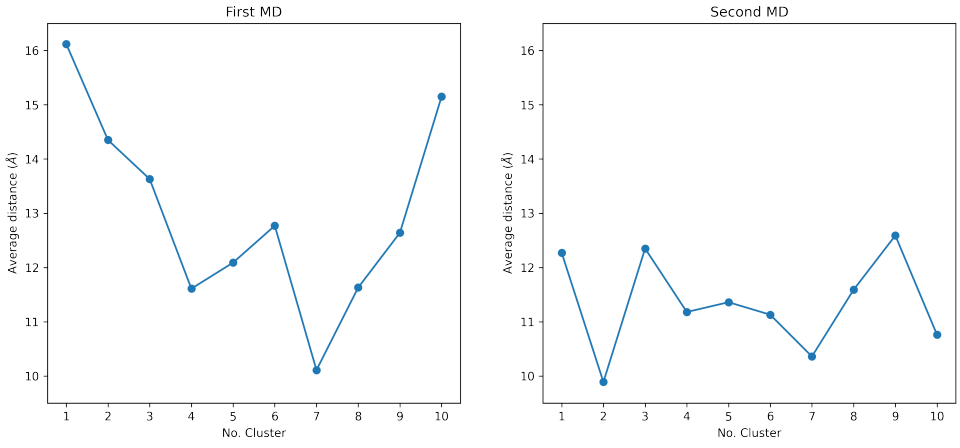


Figure S15: Average distances of the structures corresponding to centroids.

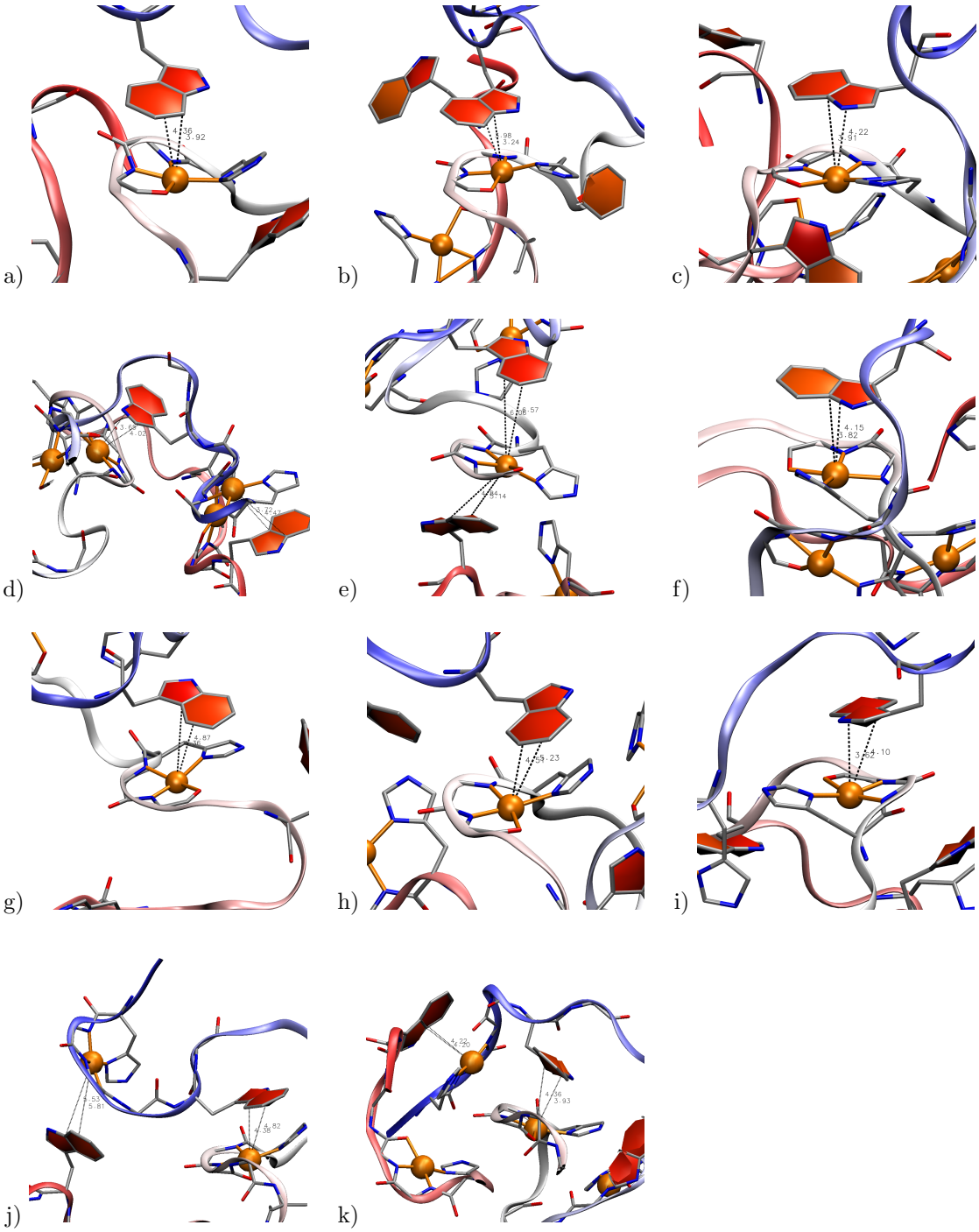


Figure S16: Close-up to show the copper-tryptophan interaction in each representative structure in model 1. The tryptophan has been represented with paper chains and all the hydrogens have been hidden for easy visualization. In all cases there is an interaction between copper 3 and the tryptophan of ORP 1. Note that in figure e) copper 3 also interacts with a tryptophan of ORP 4. In figures d), j) and k) the interaction between copper 1 and tryptophan of ORP 1 is also given.

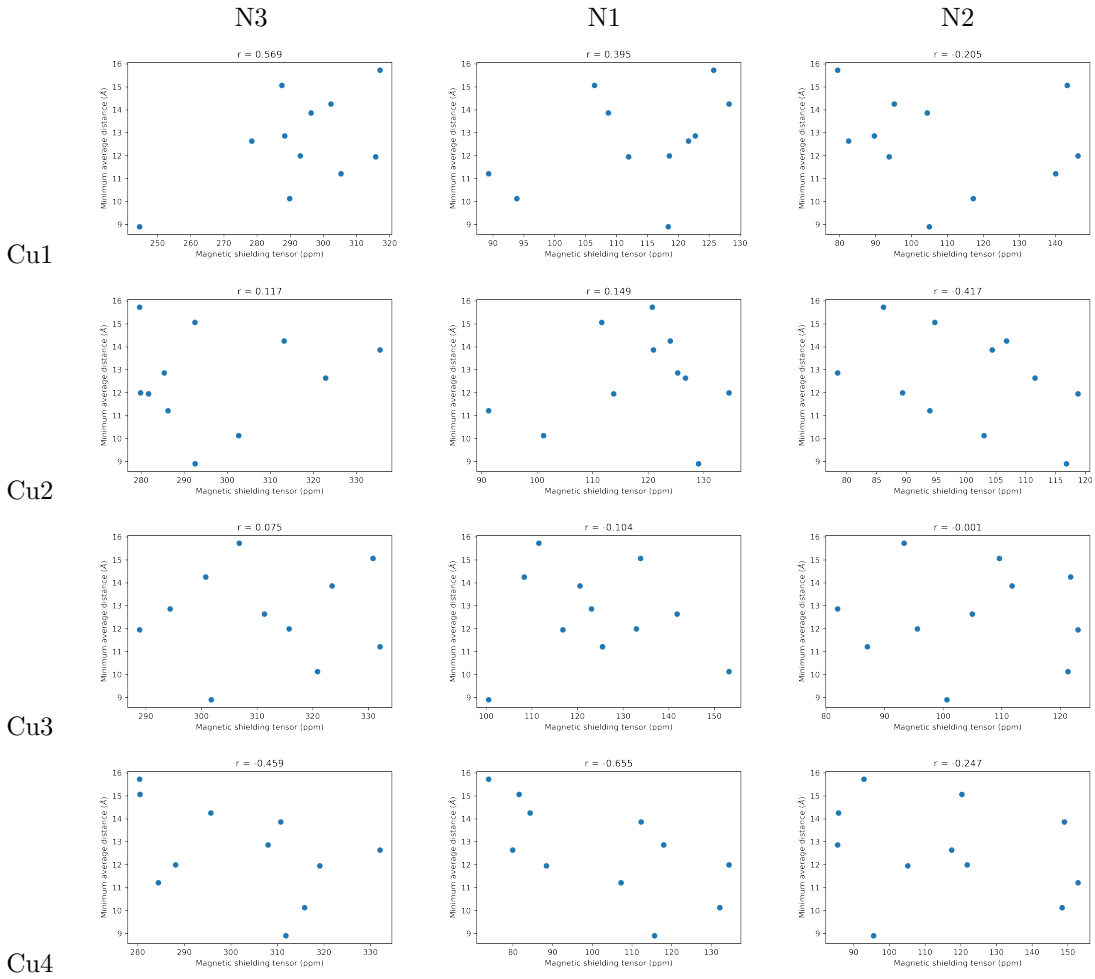


Figure S17: Comparison between chemical shifts and average bond distances for the 11 representative structures. The labeling in figure 6 has been used.

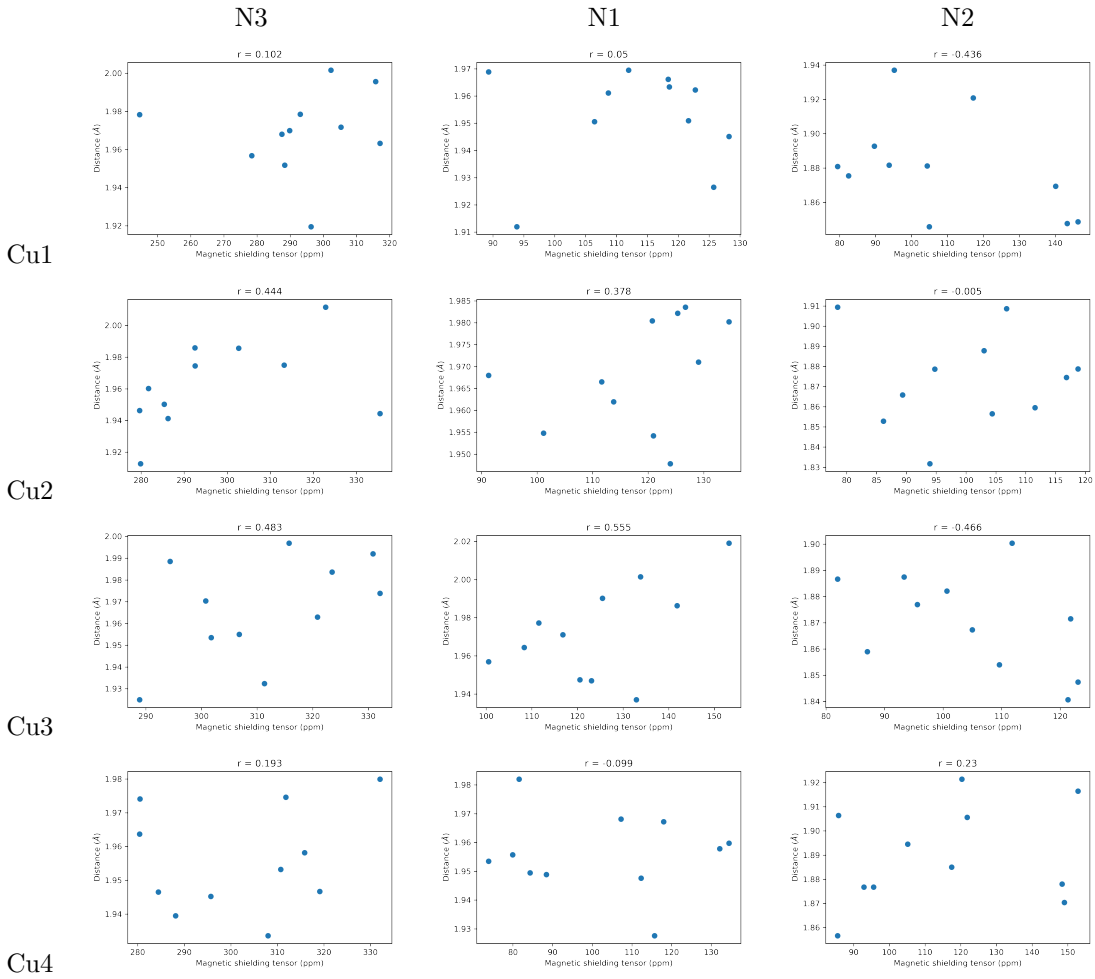


Figure S18: Comparison between chemical shifts and distances of the closest nitrogens to each copper ion for the 11 representative structures. The labeling in figure 6 has been used.

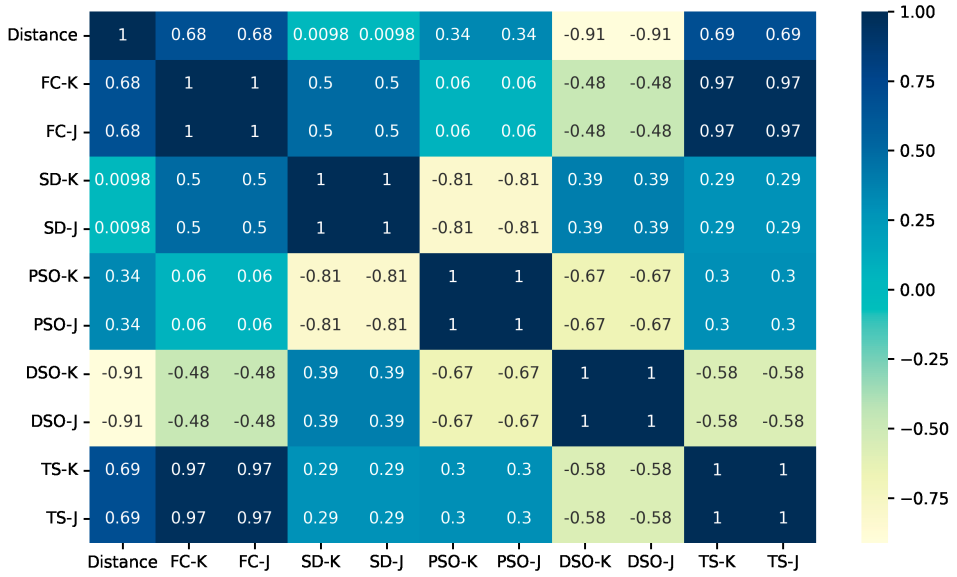


Figure S19: Correlation matrix of the NMR contributions.

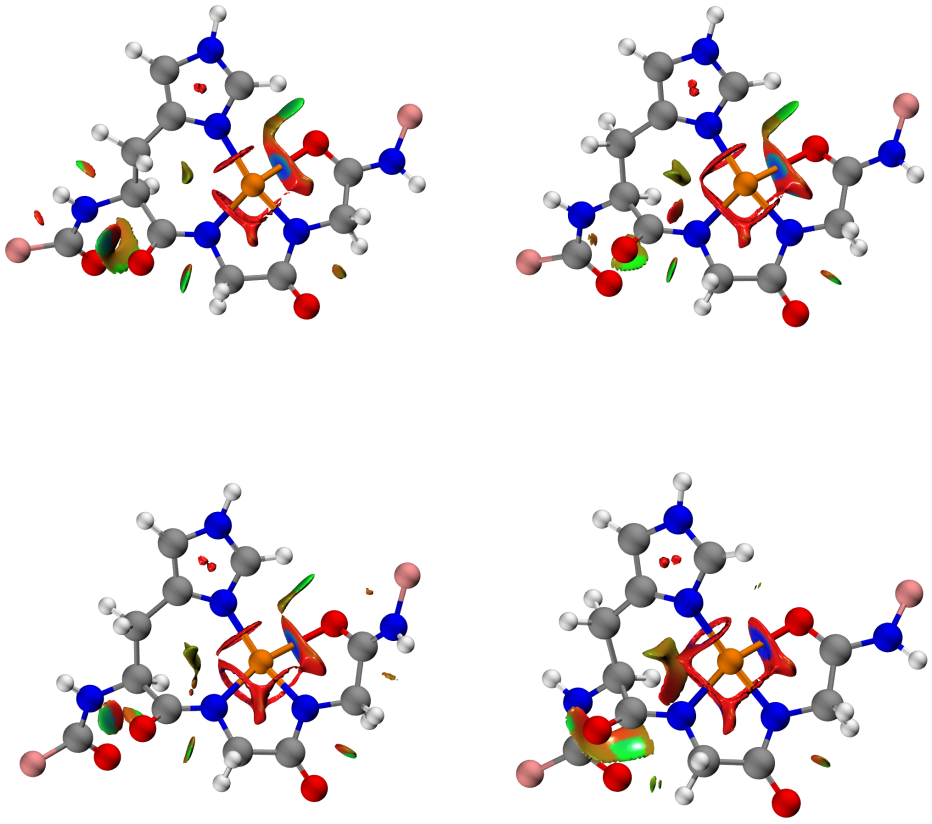


Figure S20: NCI plots for each of the coordination sites in the structure with the minimum average distances between copper ions. The isovalue is 0.6.

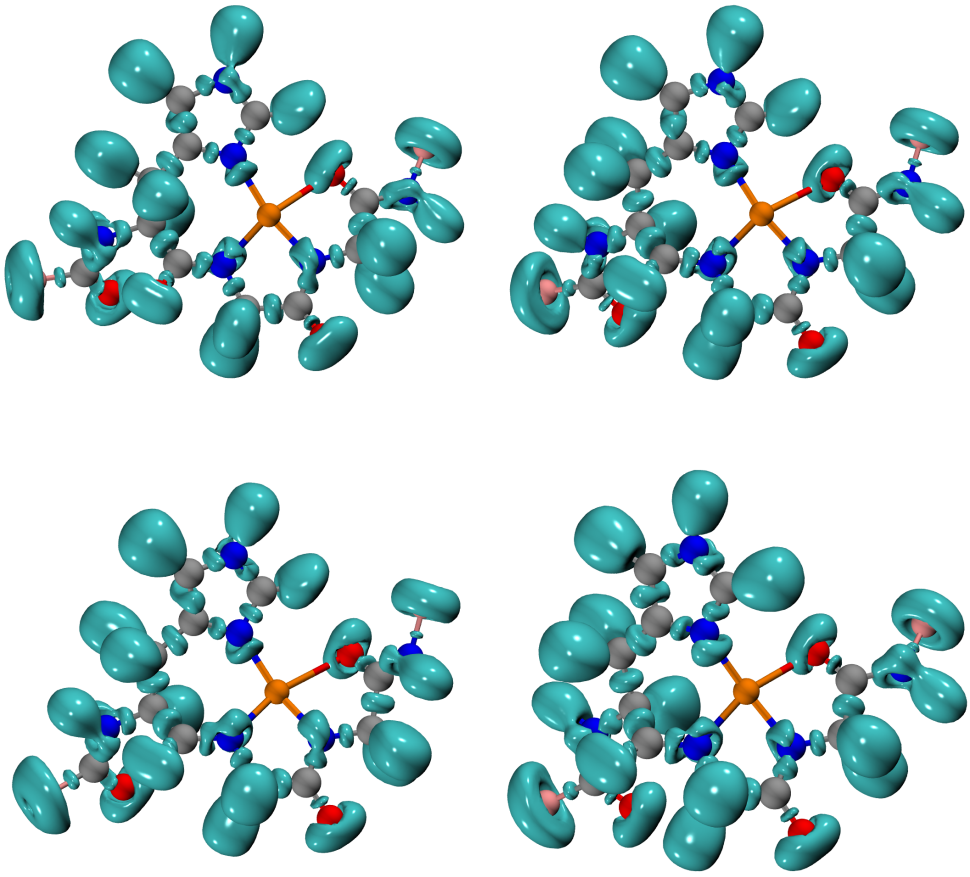


Figure S21: ELF plots for each of the coordination sites in the structure with the minimum average distances between copper ions. The isovalue is 0.82.