Table S1. Distribution of Cu^+-MeCN complexes at various concentrations of acetonitrile, based on stability constants reported by Kamau and Jordan.[1]

	10 mM	25 mM	500 mM	1000 mM
		% of Total Copper		
Cu^I	16	4	0	0
$Cu^I(MeCN)$	68	43	2	1
$Cu^I(MeCN)_2$	16	51	56	40
$Cu^I(MeCN)_3$	0	2	42	59
Average CN‡	1.0	1.5	2.4	2.6

‡CN = coordination number

Table S2. Average best fits of the experimental ITC data for BCA/ Cu^+ titrations in 25 mM Tris pH 8.0 and 25 mM MeCN to a one-site model.

[NaCl] (mM)	[$NaNO_3$] (mM)	n	ΔH (kJ mol^{-1})	K (x 10^6)
100	0	2.02 ± 0.01	-27.0 ± 0.2	2.0 ± 0.3
75	25	1.91 ± 0.04	-27.9 ± 0.7	4.9 ± 0.9
50	50	2.14 ± 0.06	-27.4 ± 0.5	3.6 ± 0.3
25	75	1.91 ± 0.04	-27.9 ± 0.7	4.9 ± 0.9
0‡	100	1.98 ± 0.03	-28.0 ± 0.4	3 ± 1

‡Although care was taken to eliminate all chloride sources, residual chloride (equimolar to Cu^+ ≈ 100 μM, but diluted during the titration) is present from the $CuCl_2$ salt used in the comproportionation reaction.

Table S3. Sequential and overall thermodynamic parameters for ligands binding to Cu^+ in 25 mM MeCN, 100 mM NaCl and 25 mM Tris at pH 8.0 and 25 °C. Values are in kJ mol^{-1}.

	Site 1 $Cu^I + L \rightleftharpoons Cu^IL$			Site 2 $Cu^IL + L \rightleftharpoons Cu^IL_2$			Overall $Cu^I + 2L \rightleftharpoons Cu^IL_2$		
	ΔG	ΔH	-TΔS	ΔG	ΔH	-TΔS	ΔG	ΔH	-TΔS
BCA	-36.0 ± 0.2	-27.0 ± 0.2	-9.0 ± 0.3	-36.0 ± 0.2	-27.0 ± 0.2	-2.19 ± 0.04	-71.9 ± 0.4	-54.0 ± 0.3	-17.9 ± 0.4
BCS	-47 ± 1	-33 ± 1	-14 ± 1	-43.39 ± 0.06	-42 ± 2	-1 ± 2	-90 ± 1	-75 ± 1	-15 ± 2
GSH*	-34.90 ± 0.01	-79.9 ± 0.7‡	45.0 ± 0.7		-	-	-	-	-

*GSH data in Tris at pH 8.0 showed no evidence of a 2nd binding event.
‡The heat of Tris protonation is subtracted from the enthalpy term.

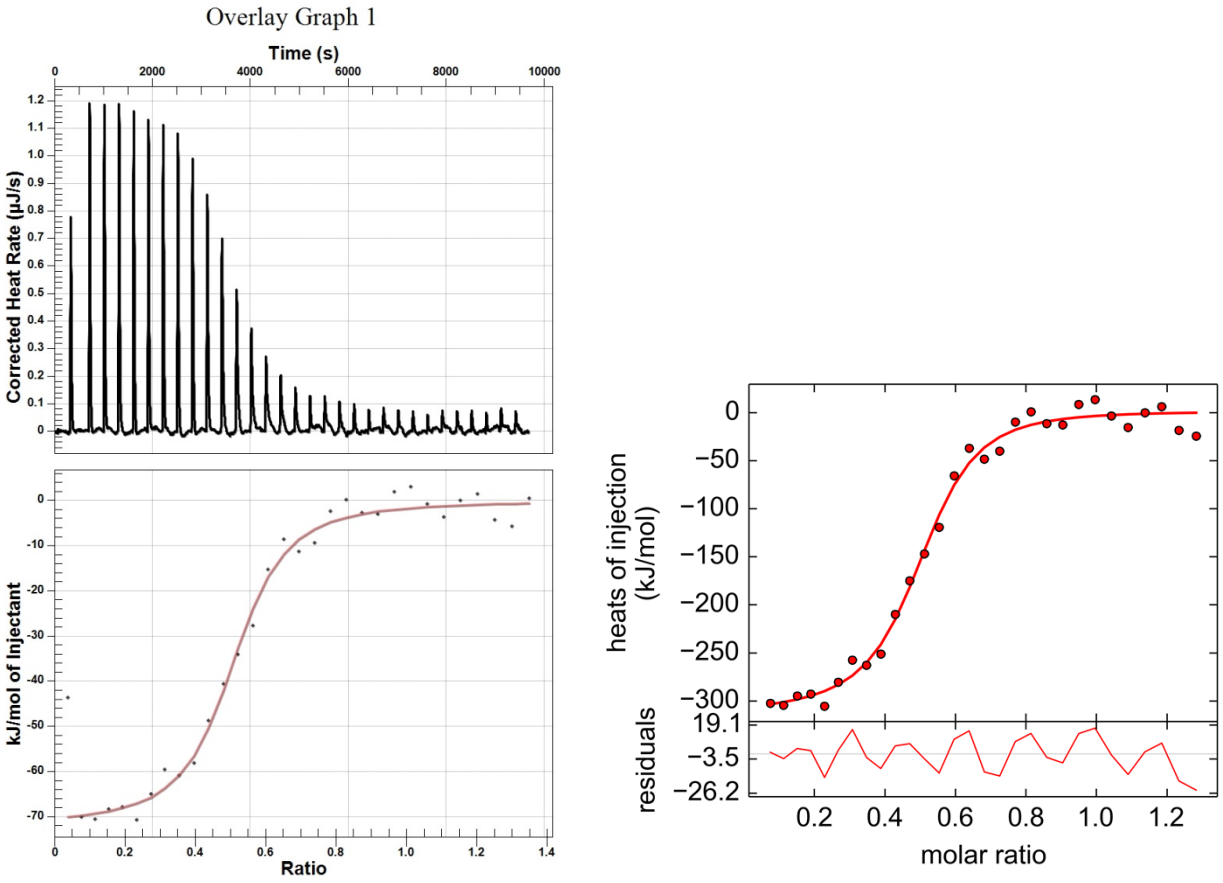

Figure S1. Representative ITC titration of 250 µM Cu^{+} into 60 µM BCA in 25 mM HEPES, 100 mM NaCl and 25 mM MeCN at pH 7.0 and 25 °C on a TA Instruments Nano ITC. The red line indicates the best fit using a one-site binding model (n = 0.51 ± 0.01, K = 1.5 ± 0.4 x 10^6, ΔH = -72 ± 2 kJ mol^{-1}. The right panel shows the data fit using the 2 symmetric sites model (A + B + B < -- > AB + B < -- > ABB) in SEDPHAT[2] with the direction set to A into B. K_1 = 1.45 x10^6, ΔH_1 = -35.3 kJ mol^{-1}, K_2 = 6.08 x10^5, ΔH_2 = -35.8 kJ mol^{-1}.

Sample Equilibrium Calculation: BCS → $Cu^{I}(Me_6Trien)^{+}$

Relevant Conditions:

pH 7.4 $[H^+] = 3.98x10^{-8}$ M

$[Me_6Trien]_{total}$ = 5 mM = 0.005 M

$pKa_1 = 9.19$ $K_1 = 10^{9.19} = 1.55x10^9$ (K_1 = acid Association, not dissociation $H + L \rightleftharpoons HL$)

$pKa_2 = 8.38$ $K_2 = 10^{8.38} = 2.40x10^8$ (K_2 = acid Association, not dissociation $H + HL \rightleftharpoons H_2L$)

$\beta_2 = K_1K_2 = 3.715x10^{17}$ ($2H + L \rightleftharpoons H_2L$)

$K'_{ITC} = 1.53 \times 10^5$ (From data in Figure 7A) – this is for each binding event. K_{ITC} for the overall process = K'^2_{ITC} $K_{ITC} = (1.53x10^5)^2 = 2.89 \times 10^{10}$

$K_{Cu\text{-}BCA} = 3.16 \times 10^{17}$ (Literature Value[3])

Calculating proton competition (α):

$$\alpha = \sum_{n=0}^{i} \left(\beta_n [X]^n\right)$$

$$\alpha = 1 + 1.55x10^9\left[3.98x10^{-8}\right] + 3.715x10^{17}\left[3.98x10^{-8}\right]^2$$

$$\alpha = 1 + 61.66 + 588.84 = 651.5$$

Calculating $[Me_6Trien]$ (this is the fully deprotonated form that binds to Cu^+) – this approach can be used for any ligand (e.g. the pH-dependent calculation for GSH)

$$[Me_6Trien]_{total} = [Me_6Trien] + [H_1Me_6Trien] + [H_2Me_6Trien]$$

$$[Me_6Trien]_{total} = [Me_6Trien]\left(1 + K_1[H^+] + \beta_2[H^+]^2\right) = [Me_6Trien]\, x\, \alpha$$

$$[Me_6Trien] = \frac{[Me_6Trien]_{total}}{\alpha} = \frac{0.005}{651.5} = 7.67x10^{-6}M$$

$$K_{Cu-BCA} = K_{ITC}\left(1 + \frac{[Me_6Trien]_{total}}{\alpha} K_{CuMe_6Trien}\right)$$

$$3.16x10^{17} = 2.89x10^{10}\left(1 + \frac{0.005}{651.5}K_{CuMe_6Trien}\right)$$

$$1.09x10^{7} = 1 + \frac{0.005}{651.5}K_{CuMe_6Trien}$$

$$K_{CuMe_6Trien} = 1.43x10^{12}$$

The condition-dependent K can be calculated from this:

$$K_{pH\ 7.4} = \frac{K_{CuMe_6Trien}}{\alpha_{pH\ 7.4}} = \frac{1.43x10^{12}}{651.5} = 2.19x10^{9}$$

When Considering the MeCN/Cl- competition determined in this study (Q = 65000), the apparent K_{ITC} for Cu^{+} → Me_6Trien in 25 mM MeCN and 100 mM Cl^{-} would be:

$$K_{expected} = \frac{K_{pH\ 7.4}}{Q_{MeCN/Cl}} = \frac{2.19x10^{9}}{65000} = 3.4x10^{4}$$

This value is at the very bottom of the measurable window for ITC (and well below the recommended range).[4] This is consistent with our observation of no clear evidence for binding in the Cu→ Me_6Trien titration data.

$c = nK[Macromolecule] = 1\ x\ 3.4x10^{4}\ x\ 5\ x\ 10^{-5} = 1.6$

Calculating ΔH for $Cu^{I}(MeCN)_x$ → Me_6Trien from $Cu^{I}Me_6$Trien → BCA

Thermodynamic Cycle:

	Reaction (contribution to measured heat)	n	ΔH (kJ mol^{-1})	nΔH (kJ mol^{-1})
1	**Cu^{I}Me6Trien + xMeCN ⇌ $Cu^{I}(MeCN)_x$ + Me_6Trien**	1	X	X
2	Me_6Trien + H^{+} ⇌ Me_6Trien-H (pKa 9.19)	0.984	-28.03	-27.584
3	Me_6Trien-H + H^{+} ⇌ Me_6Trien-2H (pKa 8.38)	0.805	-30.125	-27.2629
4	HEPES-H ⇌ HEPES + H^{+}	1.889	21.422	+40.467
5	$Cu^{I}(MeCN)_x$ + 2 BCA ⇌ $Cu(BCA)_2$ + xMeCN	2	-27	-54
Net	Net Reaction (ΔH_{ITC} from Table 4)	1.92	-30	-57.6

X = -57.6-(-54+40.467-27.263-27.584) = 10.78

$\Delta H_{CuIMe6Trien}$ = -X = -10.78 kJ mol^{-1}

From BCS data – only line 5 and Net change:

	Reaction (contribution to measured heat)	n	ΔH (kJ mol^{-1})	nΔH (kJ mol^{-1})
1	**Cu^{I}Me6Trien + xMeCN ⇌ $Cu^{I}(MeCN)_x$ + Me_6Trien**	1	X	X
2	**Me_6Trien + H^+ ⇌ Me_6Trien-H (pKa 9.19)**	0.984	-28.03	-27.584
3	Me_6Trien-H + H^+ ⇌ Me_6Trien-2H (pKa 8.38)	0.805	-30.125	-27.2629
4	HEPES-H ⇌ HEPES + H^+	1.889	21.422	+40.467
5	$Cu^{I}(MeCN)_x$ + 2 BCS ⇌ $Cu(BCS)_2$ + xMeCN	2	-37	-74
Net	Net Reaction (ΔH_{ITC} from Table 4)	2.12	-31	-65.72

X = -65.72-(-74+40.467-27.263-27.584) = 22.66

$\Delta H_{CuIMe6Trien}$ = -X = -22.66 kJ mol^{-1}

(1) Kamau, P.; Jordan, R. B. *Inorganic Chemistry* **2001**, *40*, 3879.

(2) Zhao, H.; Piszczek, G.; Schuck, P. *Methods* **2015**, *76*, 137.

(3) Bagchi, P.; Morgan, M. T.; Bacsa, J.; Fahrni, C. J. *Journal of the American Chemical Society* **2013**, *135*, 18549.

(4) Hansen, L. D.; Fellingham, G. W.; Russell, D. J. *Analytical Biochemistry* **2011**, *409*, 220.