The computation of lipophilicities of ^{64}Cu PET systems based on a novel approach for fluctuating charges

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Experimental determination of the log *D* values reported in this study

Information about the lipophilicity of the ^{64}Cu-labeled bispidine ligands was obtained using water/1-octanol mixtures. The experiments were performed with 100 µM solutions of the bispidine ligands dissolved in 1-octanol. Aqueous phases consisted of 440 µL of a 0.05 M 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES)-NaOH buffer (pH = 7.4), 10 µL of a $^{64}CuCl_2$ solution (500 kBq) and 50 µL of a 100 µM solution of $Cu(NO_3)_2$. For the highly hydrophilic tetraazacyclotetradecane ligands CMPA, CDPA and CTrPA, the distributuion experiments were performed with 100 µM buffered solutions of the ligands (0.05 M 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES)-NaOH buffer, pH = 7.4). The aqueous solutions contained 10 µM $Cu(NO_3)_2$ and were spiked with 500 kBq $^{64}CuCl_2$.

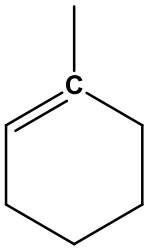
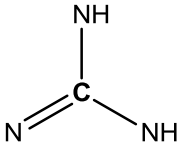
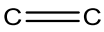
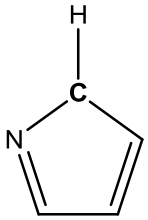
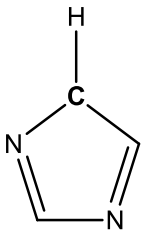
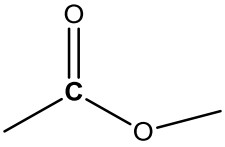
The distribution experiments were carried out at 25 ± 1°C in microcentrifuge tubes (2 cm^3) with mechanical shaking for 30 min. The phase ratio $V_{(1\text{-}octanol)}$:$V_{(aq)}$ was 1:1 (0.5 mL each). Full complexation was checked by radio-HPLC, which gave no evidence of free copper(II) in the aqueous phase. All samples were centrifuged and the phases then separated. The copper complex concentration in both phases was determined radiometrically using γ-radiation [^{64}Cu, NaI(Tl) scintillation counter automatic gamma counter 1480, Wizard 3″, Perkin Elmer] for log *D* values in the range of -3 to +3. γ-Radiation measurements lead to inaccurate values due to the counting statistics, if log *D* values were lower than -3 or higher than +3. In this case, β-liquid-scintillation counting was applied to allow for exact determination of counts in the organic and aqueous phases. The results are the average values of three independent experiments (see manuscript, Tables 2 and 3 for the experimental data).

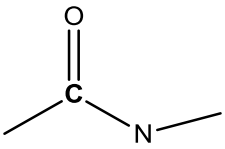
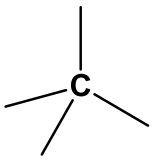
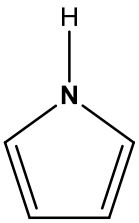
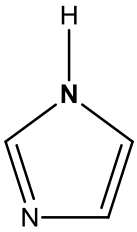
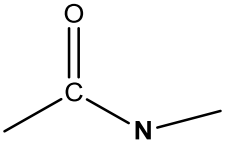
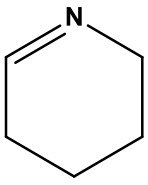
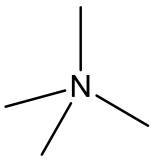
Table SI1. New parameters added to the Momec force field (see references 36-38 in the main manuscript for the original Momec force field parameters)[a)]

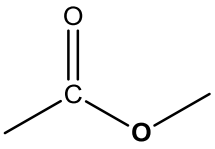
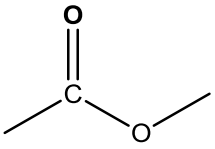
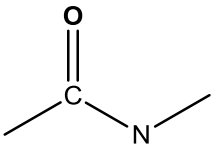
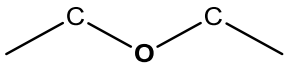
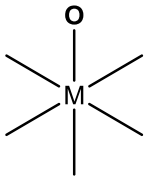
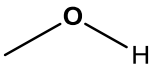
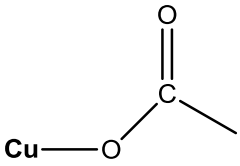
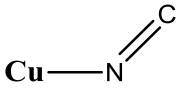
Interaction Type	Interaction	Force constant (dynes/mA)	Reference value (Å/radians)	Multiplicity
Stretch	OC - CT	1.000	1.430	-
Stretch	OC - H	1.019	1.037	-
Stretch	ND - H	1.000	0.896	-
Stretch	CA - OR	1.000	1.380	-
Bend	CCO - OC - CT	0.145	2.283	-
Bend	CCO - CT - CA	0.144	2.005	-
Bend	CA - OR - CT	0.101	2.086	-
Bend	CON - ND - H	0.118	1.905	-
Bend	CCO - OC - H	0.100	1.905	-
Bend	CT - ND - H	0.100	2.126	-
Torsion	** - CT - OR - **	0.0100	1.571	2.000
Torsion	** - CA – OR - **	0.0100	0.100	2.000

a) Functional form of the Momec force field: $E_{strain} = E_b + E_\theta + E_\varphi + E_{vdW} + E_{oop}$, where bond stretch deformation energy $E_b = \frac{1}{2}k_b(r - r_0)^2$, valence angle deformation energy $E_\theta = \frac{1}{2}k_\theta(\theta - \theta_0)^2$, torsional angle deformation energy $E_\varphi = \frac{1}{2}k_\varphi(1 + \cos m(\varphi + \varphi_0))$, non-bonded interaction energy $E_{vdW} = Ae^{-Br_{ij}} + Cr_{ij}^{-6}$ and out of plane deformation energy $E_\delta = \frac{1}{2}k_\delta\delta^2$. k_b, k_θ, k_φ, k_δ are the respective force constants, r_0, θ_0, φ_0 are the respective reference values, m is the torsion multiplicity and A, B, C are the van der Waals' interaction parameters

Table SI2: Description of the Momec3 atom types used in this study [a)]

Atom type	Structure	Description
CA		Aromatic Carbon, Guanidine, sp^2 Carbon
		
		
CAH		Pyrrole, Imidazole
		
CCO		Carboxylate

CON		Amide
CT		sp^3 Carbon
NAH		Pyrrole, Imidazole
		
ND		Amide
NP		Pyridine
NT		sp^3 Nitrogen

OC		Carboxylate
OCO		Carboxylate, Amide
		
OR		Ether
OW		Oxygen attached to 6-coordinate metal, Alcohol, Water
		
H	**H**	Hydrogen
CU2	**Cu**	Copper(II)
CU2C		Copper(II) coordinated to carboxylate
CU2P		Copper(II) coordinated to sp^2 N

[a)] Note that these atom types were used only during geometry optimization with the modified Momec force field Atom type assignments for the fluctuating charge computations were done according to the list provided in reference [39] of the main manuscript.

Table SI2. van der Waals radii used in the generation of solvent-accessible surfaces in Momec3 [reference 56-58 in the main manuscript]

Element	Atomic no.	vdW radius (Å)	Element	Atomic no.	vdW radius (Å)
H	1	1.09	Ge	32	2.05
He	2	1.40	As	33	2.08
Li	3	2.14	Se	34	1.90
Be	4	1.69	Br	35	1.85
B	5	1.68	Kr	36	2.02
C	6	1.75	Ru	37	2.13
N	7	1.61	Sr	38	2.42
O	8	1.56	Y	39	2.32
F	9	1.44	Zr	40	2.23
Ne	10	1.54	Nb	41	2.18
Na	11	2.38	Mo	42	2.17
Mg	12	2.00	Tc	43	2.16
Al	13	1.92	Ru	44	2.13
Si	14	1.93	Rh	45	2.10
P	15	1.80	Pd	46	2.10
S	16	1.79	Ag	47	2.11
Cl	17	1.74	Cd	48	2.18
Ar	18	1.88	In	49	2.21
K	19	2.52	Sn	50	2.23
Ca	20	2.27	Sb	51	2.24
Sc	21	2.15	Te	52	2.06
Ti	22	2.11	I	53	2.00
V	23	2.07	Xe	54	2.16
Cr	24	2.06	Cs	55	2.75
Mn	25	2.05	Ba	56	2.59
Fe	26	2.04	La	57	2.43
Co	27	2.00	Ce	58	2.42
Ni	28	1.97	Pr	59	2.40
Cu	29	1.96	Nd	60	2.39
Zn	30	2.01	Pm	61	2.38
Ga	31	2.03	Sm	62	2.36

Element	Atomic no.	vdW radius (Å)
Eu	63	2.35
Gd	64	2.34
Tb	65	2.33
Dy	66	2.31
Ho	67	2.30
Er	68	2.29
Tm	69	2.27
Yb	70	2.26
Lu	71	2.24
Hf	72	2.23
Ta	73	2.22
W	74	2.18
Re	75	2.16
Os	76	2.16
Ir	77	2.13
Pt	78	2.13
Au	79	2.14
Hg	80	2.23
Tl	81	2.27
Pb	82	2.37
Bi	83	2.38
Po	84	2.49
Ac	89	2.47
Th	90	2.45
Pa	91	2.43
U	92	2.41
Np	93	2.39
Pu	94	2.37
Am	95	2.35

Table SI3: Computed descriptor and log *D* values for the entire set of 24 Cu^{II} complexes

Complex	log $D_{7.4}$ (expt)	Total formal charge	A (Å^2)	V (Å^3)	Π	Π * A	σ_-^2	σ_+^2	σ_{tot}^2	A_{pol}	O_v	log $D_{7.4}$ (eqn. 7)	log $D_{7.4}$ (eqn. 8)
Cu-L1	-2.45	2	718.18	1597.02	13.01	9343.71	0	251.09	251.09	0.1128	2.53	-	-3.24
Cu-L3	-2.05	2	806.41	1830.10	14.94	12050.50	0	196.70	196.70	0.1166	2.59	-	-1.49
													-1.11
Cu-L3OH	-2.11	2	808.04	1849.48	13.72	11091.66	0	138.93	138.93	0.0952	2.58	-	
Cu-L6	-2.68	2	773.54	1766.52	12.59	9737.15	0	237.07	237.07	0.1212	2.54	-	-3.85
Cu-L7OH	-2.44	2	852.74	1987.29	9.85	8399.49	0	121.66	121.66	0.0966	2.59	-	-2.59
Cu-L8	-2.77	2	857.20	1942.63	10.78	9238.80	0	182.21	182.21	0.0886	2.65	-	-1.83
Cu-L8OH	-2.88	2	863.44	1952.91	10.52	9087.22	0	173.12	173.12	0.0697	2.66	-	-1.58
Cu-L10	-2.76	2	812.08	1844.93	12.20	9904.08	0	231.76	231.76	0.0877	2.60	-	-2.89
Cu-L13	-3.28	2	854.93	1972.16	10.07	8611.14	0	164.39	164.39	0.0531	2.61	-	-2.82
Cu-L14	-3.58	2	811.86	1864.09	13.09	10630.73	0	271.52	271.52	0.0857	2.58	-	-3.92
Cu-L15	-3.01	2	1061.06	2527.77	12.63	13399.06	0	218.95	218.95	0.1428	2.75	-	-2.85
Cu-L16	-1.45	2	729.16	1600.31	9.01	6569.25	0	95.45	95.45	0.0274	2.56	-	-0.94
Cu-L17	-1.94	2	819.32	1918.55	7.69	6302.20	0	79.98	79.98	0.0259	2.55	-	-3.04
Cu-Y1	2.36	2	1329.48	3015.92	9.86	13112.36	0	48.04	48.04	0	3.06	3.12	3.30
Cu-Y2	3.19	2	889.65	1931.62	10.43	9280.85	0	61.36	61.36	0	2.76	3.73	2.87
Cu-Y4	2.73	2	1103.27	2457.44	8.43	9301.57	0	56.71	56.71	0	2.91	2.62	2.60
Cu-Y5	1.27	0	811.72	1829.38	11.37	9228.14	30.66	21.00	51.65	0.1829	2.61	1.30	0.60

Cu-Y6	2.28	0	968.02	2175.17	9.16	8867.08	46.55	4.38	50.93	0.1053	2.77	1.79	1.51
Cu-Y7	1.77	0	953.04	2163.87	9.37	8930.37	46.42	6.45	52.87	0.1128	2.74	1.07	0.97
Cu-Y8	2.73	1	1141.00	2595.23	10.20	11632.59	0	58.37	58.37	0.0491	2.90	2.23	2.18
Cu-dota	-3.24	0	662.3	1491.92	7.06	4675.89	10.66	20.79	31.45	0.3119	2.44	-2.78	-2.46
Cu-cbte2a	-2.29	0	560.03	1239.13	13.90	7781.70	67.59	16.66	84.35	0.1900	2.33	-2.30	-2.48
Cu-cmpa	-4	1	534.92	1150.80	10.22	5466.93	0	105.58	105.58	0.1035	2.34	-4.03	-3.36
Cu-ctrpa	-4.5	1	716.27	1650.91	14.89	10667.89	0	272.44	272.44	0.2041	2.47	-4.44	-4.67