

## Supplementary data

### Challenges in chelating positron emitting copper isotopes: tailored synthesis of unsymmetric chelators to form ultra stable complexes

Jon D. Silversides, Rachel Smith and Stephen J. Archibald\*

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Table S1. Bond lengths [Å] and angles [°] for the X-ray crystal structure of **4**.

N(1)-C(1)	1.508(6)	C(3)-N(2)-C(2)	107.7(4)
N(1)-C(10)	1.522(6)	C(20)-N(3)-C(6)	111.8(5)
N(1)-C(11)	1.532(5)	C(20)-N(3)-C(5)	105.9(4)
N(1)-C(13)	1.553(6)	C(6)-N(3)-C(5)	111.2(4)
N(2)-C(12)	1.447(6)	C(20)-N(3)-C(12)	110.4(4)
N(2)-C(3)	1.469(7)	C(6)-N(3)-C(12)	108.5(3)
N(2)-C(2)	1.472(6)	C(5)-N(3)-C(12)	109.0(4)
N(3)-C(20)	1.496(6)	C(11)-N(4)-C(7)	110.5(4)
N(3)-C(6)	1.511(7)	C(11)-N(4)-C(8)	111.4(4)
N(3)-C(5)	1.520(7)	C(7)-N(4)-C(8)	107.4(4)
N(3)-C(12)	1.525(6)	C(2)-C(1)-N(1)	110.8(4)
N(4)-C(11)	1.440(6)	N(2)-C(2)-C(1)	113.4(4)
N(4)-C(7)	1.467(7)	N(2)-C(3)-C(4)	110.5(5)
N(4)-C(8)	1.469(8)	C(5)-C(4)-C(3)	109.6(5)
C(1)-C(2)	1.507(7)	C(4)-C(5)-N(3)	112.8(4)
C(3)-C(4)	1.509(9)	C(7)-C(6)-N(3)	110.8(4)
C(4)-C(5)	1.498(8)	N(4)-C(7)-C(6)	112.4(4)
C(6)-C(7)	1.495(8)	N(4)-C(8)-C(9)	109.7(4)
C(8)-C(9)	1.503(8)	C(8)-C(9)-C(10)	110.0(4)
C(9)-C(10)	1.520(7)	C(9)-C(10)-N(1)	112.6(4)
C(11)-C(12)	1.555(6)	N(4)-C(11)-N(1)	109.8(3)
C(13)-C(14)	1.501(6)	N(4)-C(11)-C(12)	111.6(4)
C(14)-C(19)	1.382(7)	N(1)-C(11)-C(12)	107.3(3)
C(14)-C(15)	1.401(6)	N(2)-C(12)-N(3)	108.8(3)
C(15)-C(16)	1.390(7)	N(2)-C(12)-C(11)	111.8(3)
C(16)-C(17)	1.346(8)	N(3)-C(12)-C(11)	107.9(4)
C(17)-C(18)	1.393(9)	C(14)-C(13)-N(1)	114.2(3)
C(18)-C(19)	1.383(8)	C(19)-C(14)-C(15)	118.7(4)
		C(19)-C(14)-C(13)	122.3(4)
C(1)-N(1)-C(10)	109.7(3)	C(15)-C(14)-C(13)	119.1(4)
C(1)-N(1)-C(11)	109.6(3)	C(16)-C(15)-C(14)	120.3(5)
C(10)-N(1)-C(11)	109.0(4)	C(17)-C(16)-C(15)	120.5(5)
C(1)-N(1)-C(13)	112.4(4)	C(16)-C(17)-C(18)	120.1(5)
C(10)-N(1)-C(13)	108.0(4)	C(19)-C(18)-C(17)	120.3(5)
C(11)-N(1)-C(13)	108.1(3)	C(14)-C(19)-C(18)	120.1(5)
C(12)-N(2)-C(3)	112.1(4)		
C(12)-N(2)-C(2)	110.4(4)		

Table S2. Bond lengths [Å] and angles [°] for the X-ray crystal structure of **6**.

C(1)-N(1)	1.491(5)	N(4)-C(7)-C(6)	114.4(4)
C(1)-C(2)	1.508(6)	N(4)-C(8)-C(9)	112.9(4)
C(2)-N(2)	1.465(6)	C(10)-C(9)-C(8)	113.1(4)
C(3)-N(2)	1.468(5)	C(9)-C(10)-N(1)	111.5(3)
C(3)-C(4)	1.551(8)	N(2)-C(11)-C(12)	117.1(3)
C(4)-C(5)	1.513(8)	N(4)-C(12)-C(11)	116.7(3)
C(5)-N(3)	1.498(6)	C(14)-C(13)-N(1)	114.4(3)
C(6)-N(3)	1.492(6)	C(19)-C(14)-C(15)	118.8(4)
C(6)-C(7)	1.518(6)	C(19)-C(14)-C(13)	120.8(4)
C(7)-N(4)	1.479(6)	C(15)-C(14)-C(13)	120.2(4)
C(8)-N(4)	1.481(5)	C(16)-C(15)-C(14)	120.1(5)
C(8)-C(9)	1.538(6)	C(17)-C(16)-C(15)	120.3(5)
C(9)-C(10)	1.508(6)	C(16)-C(17)-C(18)	120.4(5)
C(10)-N(1)	1.510(5)	C(19)-C(18)-C(17)	119.3(5)
C(11)-N(2)	1.484(5)	C(14)-C(19)-C(18)	121.1(5)
C(11)-C(12)	1.533(6)	C(1)-N(1)-C(10)	112.0(3)
C(12)-N(4)	1.485(5)	C(1)-N(1)-C(13)	114.4(3)
C(13)-C(14)	1.505(5)	C(10)-N(1)-C(13)	113.1(3)
C(13)-N(1)	1.512(5)	C(2)-N(2)-C(3)	107.8(4)
C(14)-C(19)	1.368(6)	C(2)-N(2)-C(11)	113.8(4)
C(14)-C(15)	1.397(6)	C(3)-N(2)-C(11)	110.1(3)
C(15)-C(16)	1.377(6)	C(6)-N(3)-C(5)	112.1(3)
C(16)-C(17)	1.350(8)	C(6)-N(3)-C(20)	111.9(4)
C(17)-C(18)	1.391(8)	C(5)-N(3)-C(20)	111.0(4)
C(18)-C(19)	1.373(7)	C(7)-N(4)-C(8)	107.2(3)
C(20)-N(3)	1.498(6)	C(7)-N(4)-C(12)	112.8(3)
Cl(1)-O(2)	1.383(5)	C(8)-N(4)-C(12)	110.4(3)
Cl(1)-O(1)	1.393(5)	O(2)-Cl(1)-O(1)	107.4(4)
Cl(1)-O(4)	1.404(4)	O(2)-Cl(1)-O(4)	106.4(4)
Cl(1)-O(3)	1.416(4)	O(1)-Cl(1)-O(4)	114.9(3)
Cl(2)-O(8)	1.347(4)	O(2)-Cl(1)-O(3)	113.1(4)
Cl(2)-O(5)	1.359(4)	O(1)-Cl(1)-O(3)	107.3(3)
Cl(2)-O(6)	1.398(5)	O(4)-Cl(1)-O(3)	107.9(3)
Cl(2)-O(7)	1.469(6)	O(8)-Cl(2)-O(5)	114.4(3)
O(9)-C(21)	1.378(12)	O(8)-Cl(2)-O(6)	116.9(4)
		O(5)-Cl(2)-O(6)	114.7(3)
N(1)-C(1)-C(2)	112.3(3)	O(8)-Cl(2)-O(7)	102.9(5)
N(2)-C(2)-C(1)	115.2(4)	O(5)-Cl(2)-O(7)	104.7(4)
N(2)-C(3)-C(4)	112.8(4)	O(6)-Cl(2)-O(7)	100.4(4)
C(5)-C(4)-C(3)	113.3(4)		
N(3)-C(5)-C(4)	111.6(4)		
N(3)-C(6)-C(7)	112.6(3)		

Table S3. Bond lengths [Å] for the X-ray crystal structure of [Cu<sub>6</sub>(OH<sub>2</sub>)](ClO<sub>4</sub>)<sub>2</sub>

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C(1)-N(1)	1.477(5)	C(14)-C(19)	1.410(6)
C(1)-C(2)	1.500(6)	C(15)-C(16)	1.388(6)
C(2)-N(2)	1.491(5)	C(16)-C(17)	1.376(7)
C(3)-N(2)	1.485(5)	C(17)-C(18)	1.376(7)
C(3)-C(4)	1.524(6)	C(18)-C(19)	1.370(7)
C(4)-C(5)	1.498(7)	C(20)-N(4)	1.494(6)
C(5)-N(3)	1.482(6)	Cl(1)-O(2)	1.397(4)
C(6)-C(7)	1.491(7)	Cl(1)-O(3)	1.410(3)
C(6)-N(3)	1.508(6)	Cl(1)-O(4)	1.415(4)
C(7)-N(4)	1.485(6)	Cl(1)-O(5)	1.424(5)
C(8)-N(4)	1.481(6)	Cl(2)-O(7)	1.381(4)
C(8)-C(9)	1.517(6)	Cl(2)-O(9)	1.409(3)
C(9)-C(10)	1.526(7)	Cl(2)-O(8)	1.412(4)
C(10)-N(1)	1.459(6)	Cl(2)-O(6)	1.450(3)
C(11)-N(1)	1.505(5)	Cu(1)-O(1)	2.025(3)
C(11)-C(12)	1.534(6)	Cu(1)-N(3)	2.041(3)
C(12)-N(3)	1.488(5)	Cu(1)-N(4)	2.085(4)
C(13)-C(14)	1.501(6)	Cu(1)-N(2)	2.111(3)
C(13)-N(2)	1.530(4)	Cu(1)-N(1)	2.159(4)
C(14)-C(15)	1.389(6)		

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Table S4. Bond angles [°] for the X-ray crystal structure of [Cu<sub>6</sub>(OH<sub>2</sub>)](ClO<sub>4</sub>)<sub>2</sub>.

N(1)-C(1)-C(2)	112.3(3)	O(1)-Cu(1)-N(4)	85.28(13)
N(2)-C(2)-C(1)	111.4(3)	N(3)-Cu(1)-N(4)	86.30(15)
N(2)-C(3)-C(4)	116.9(4)	O(1)-Cu(1)-N(2)	96.85(12)
C(5)-C(4)-C(3)	115.4(4)	N(3)-Cu(1)-N(2)	91.91(14)
N(3)-C(5)-C(4)	115.0(4)	N(4)-Cu(1)-N(2)	177.34(14)
C(7)-C(6)-N(3)	110.2(4)	O(1)-Cu(1)-N(1)	103.57(13)
N(4)-C(7)-C(6)	108.4(4)	N(3)-Cu(1)-N(1)	87.90(13)
N(4)-C(8)-C(9)	117.6(4)	N(4)-Cu(1)-N(1)	92.56(15)
C(8)-C(9)-C(10)	116.8(4)	N(2)-Cu(1)-N(1)	85.39(14)
N(1)-C(10)-C(9)	115.3(4)	C(10)-N(1)-C(1)	110.8(3)
N(1)-C(11)-C(12)	114.5(3)	C(10)-N(1)-C(11)	111.0(4)
N(3)-C(12)-C(11)	116.9(3)	C(1)-N(1)-C(11)	111.2(3)
C(14)-C(13)-N(2)	115.8(3)	C(10)-N(1)-Cu(1)	114.5(3)
C(15)-C(14)-C(19)	116.8(4)	C(1)-N(1)-Cu(1)	103.2(2)
C(15)-C(14)-C(13)	121.6(4)	C(11)-N(1)-Cu(1)	105.8(2)
C(19)-C(14)-C(13)	121.5(4)	C(3)-N(2)-C(2)	110.8(3)
C(16)-C(15)-C(14)	122.0(4)	C(3)-N(2)-C(13)	108.1(3)
C(17)-C(16)-C(15)	119.3(4)	C(2)-N(2)-C(13)	109.4(3)
C(16)-C(17)-C(18)	120.3(4)	C(3)-N(2)-Cu(1)	113.5(2)
C(19)-C(18)-C(17)	120.4(5)	C(2)-N(2)-Cu(1)	105.9(2)
C(18)-C(19)-C(14)	121.2(4)	C(13)-N(2)-Cu(1)	109.0(2)
O(2)-Cl(1)-O(3)	110.3(3)	C(5)-N(3)-C(12)	111.1(4)
O(2)-Cl(1)-O(4)	110.7(3)	C(5)-N(3)-C(6)	106.4(3)
O(3)-Cl(1)-O(4)	109.0(2)	C(12)-N(3)-C(6)	111.3(3)
O(2)-Cl(1)-O(5)	108.0(3)	C(5)-N(3)-Cu(1)	115.7(2)
O(3)-Cl(1)-O(5)	109.7(3)	C(12)-N(3)-Cu(1)	108.6(2)
O(4)-Cl(1)-O(5)	109.0(3)	C(6)-N(3)-Cu(1)	103.5(3)
O(7)-Cl(2)-O(9)	109.2(2)	C(8)-N(4)-C(7)	112.0(4)
O(7)-Cl(2)-O(8)	110.3(3)	C(8)-N(4)-C(20)	107.1(4)
O(9)-Cl(2)-O(8)	111.2(2)	C(7)-N(4)-C(20)	108.2(4)
O(7)-Cl(2)-O(6)	110.1(2)	C(8)-N(4)-Cu(1)	112.8(3)
O(9)-Cl(2)-O(6)	108.7(2)	C(7)-N(4)-Cu(1)	106.3(3)
O(8)-Cl(2)-O(6)	107.3(2)	C(20)-N(4)-Cu(1)	110.5(3)
O(1)-Cu(1)-N(3)	166.04(14)		

Table S5. Bond lengths [Å] and angles [°] for the X-ray crystal structure of **11**.

C(1)-N(1)	1.485(8)	N(3)-C(6)-C(7)	112.2(7)
C(1)-C(2)	1.534(10)	N(4)-C(7)-C(6)	110.9(6)
C(2)-N(2)	1.494(10)	N(4)-C(8)-C(9)	112.1(6)
C(3)-C(4)	1.392(14)	C(8)-C(9)-C(10)	113.0(6)
C(3)-N(2)	1.419(10)	N(1)-C(10)-C(9)	114.9(5)
C(4)-C(5)	1.450(13)	N(2)-C(11)-C(12)	112.7(5)
C(5)-N(3)	1.576(12)	N(4)-C(12)-C(11)	113.0(5)
C(6)-N(3)	1.458(11)	N(1)-C(13)-C(14)	114.9(5)
C(6)-C(7)	1.533(12)	O(1)-C(14)-O(2)	125.1(6)
C(7)-N(4)	1.462(8)	O(1)-C(14)-C(13)	125.1(6)
C(8)-N(4)	1.456(8)	O(2)-C(14)-C(13)	109.7(5)
C(8)-C(9)	1.483(10)	O(2)-C(15)-C(17)	102.6(5)
C(9)-C(10)	1.514(10)	O(2)-C(15)-C(18)	111.4(5)
C(10)-N(1)	1.457(8)	C(17)-C(15)-C(18)	112.0(7)
C(11)-N(2)	1.460(8)	O(2)-C(15)-C(16)	107.7(6)
C(11)-C(12)	1.530(10)	C(17)-C(15)-C(16)	111.1(8)
C(12)-N(4)	1.452(8)	C(18)-C(15)-C(16)	111.6(7)
C(13)-N(1)	1.451(7)	C(13)-N(1)-C(10)	112.7(5)
C(13)-C(14)	1.522(9)	C(13)-N(1)-C(1)	112.6(5)
C(14)-O(1)	1.205(8)	C(10)-N(1)-C(1)	114.7(5)
C(14)-O(2)	1.339(7)	C(3)-N(2)-C(11)	115.3(6)
C(15)-O(2)	1.486(7)	C(3)-N(2)-C(2)	113.3(7)
C(15)-C(17)	1.487(10)	C(11)-N(2)-C(2)	111.7(5)
C(15)-C(18)	1.490(10)	C(6)-N(3)-C(5)	113.0(6)
C(15)-C(16)	1.526(13)	C(12)-N(4)-C(8)	116.2(5)
C(21)-C(24)	1.316(16)	C(12)-N(4)-C(7)	116.0(6)
C(21)-C(23)#1	1.384(14)	C(8)-N(4)-C(7)	112.3(5)
C(21)-C(22)	1.419(12)	C(14)-O(2)-C(15)	121.1(5)
C(22)-C(23)	1.321(15)	C(24)-C(21)-C(23)#1	118.9(16)
C(23)-C(21)#1	1.384(14)	C(24)-C(21)-C(22)	119.4(17)
C(24)-O(3)	1.376(14)	C(23)#1-C(21)-C(22)	121.5(8)
N(1)-C(1)-C(2)	110.9(6)	C(23)-C(22)-C(21)	118.6(8)
N(2)-C(2)-C(1)	112.7(6)	C(22)-C(23)-C(21)#1	119.9(7)
C(4)-C(3)-N(2)	112.5(8)	C(21)-C(24)-O(3)	107.4(12)
C(3)-C(4)-C(5)	115.1(8)		
C(4)-C(5)-N(3)	115.6(7)		

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y,-z

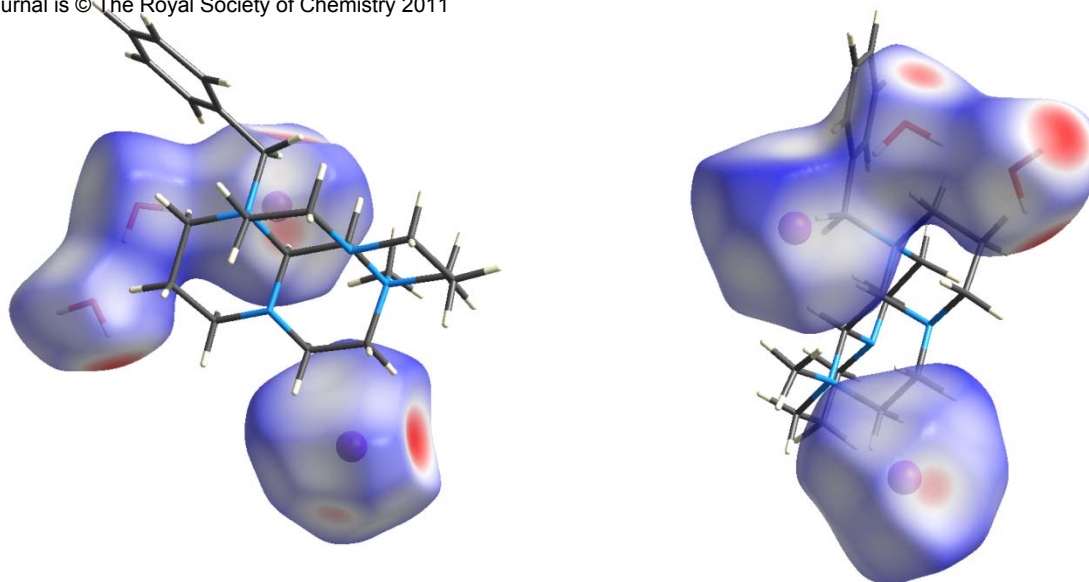


Figure S1. Hirshfeld surface<sup>1</sup> of the two water molecules and two iodide ions in structure **4**, mapped with  $d_{norm}$  which highlights both donor and acceptor equally. (Colour scale set to auto with range -0.43 to 1.10)

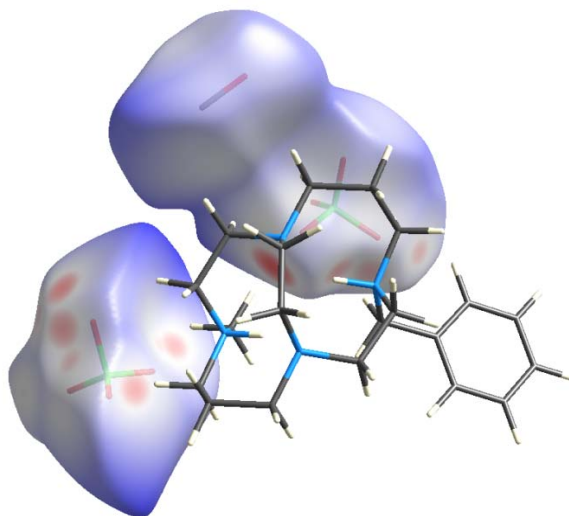


Figure S2. Hirshfeld surface<sup>1</sup> of the two perchlorate anions and the partial occupancy methanol solvent in structure **6**, mapped with  $d_{norm}$  which highlights both donor and acceptor equally. (Colour scale set to auto with range -0.43 to 2.50)

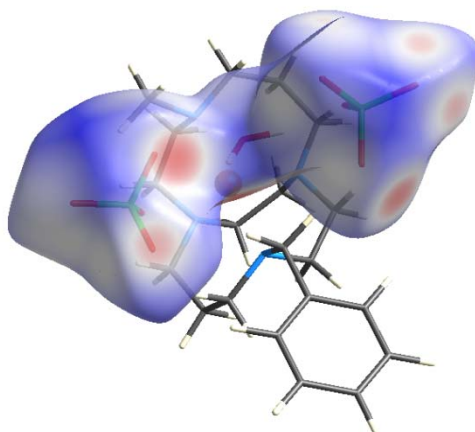


Figure S3. Hirshfeld surface<sup>1</sup> of the perchlorate anions and the bound water molecule in the structure of  $[\text{Cu}(\text{H}_2\text{O})_6][(\text{ClO}_4)_2]$ , mapped with  $d_{norm}$  which highlights both donor and acceptor equally. (Colour scale set to auto with range -0.61 to 1.30)

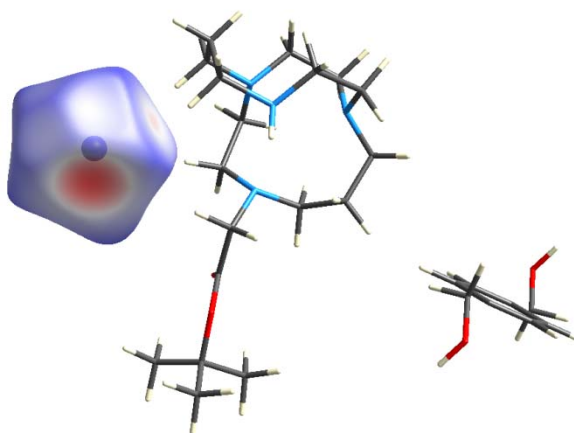


Figure S4. Hirshfeld surface<sup>1</sup> of the bromide ion in structure **11** mapped with  $d_{norm}$  which highlights both donor and acceptor equally. (Colour scale set to auto with range -0.61 to 1.20)



Table S6 Hydrogen bonds with  $H..A < r(A) + 2.000$  Angstroms and DHA angle  $> 110$  deg for **4**.

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D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O1-H21A	0.947	2.584	165.94	3.510	I2 [ -x+1/2, y, z-1/2 ]
O1-H21B	0.958	2.607	160.18	3.524	I1 [ x-1/2, -y+1, z ]
O2-H22A	0.959	2.665	165.52	3.601	I2
O2-H22B	0.957	1.809	172.42	2.760	O1

Table S7 Hydrogen bonds with  $H..A < r(A) + 2.000$  Angstroms and DHA angle  $> 110$  deg for **6**.

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D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H21	0.924	1.881	145.52	2.694	N4
N3-H22	0.949	1.883	147.59	2.732	N2

Table S8 Hydrogen bonds with  $H..A < r(A) + 2.000$  Angstroms and DHA angle  $> 110$  deg for  
**[Cu(H<sub>2</sub>O)<sub>6</sub>][ClO<sub>4</sub>]<sub>2</sub>**

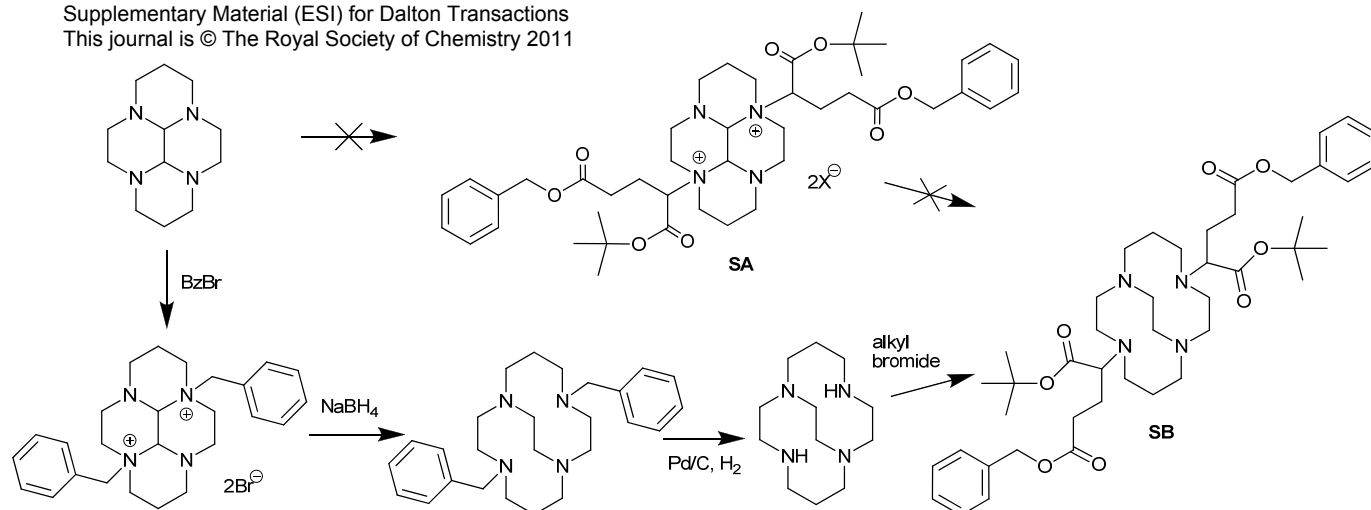
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D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O1-H21A	0.897	1.874	156.88	2.722	O4
O1-H21B	0.912	2.069	128.28	2.730	O8

Table S9 Hydrogen bonds with  $H..A < r(A) + 2.000$  Angstroms and DHA angle  $> 110$  deg for **11**.

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D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N3-H19	0.900	2.289	157.02	3.137	Br1 [ -x+1, -y+1, -z+1 ]
N3-H20	0.902	2.248	116.68	2.773	N2
N3-H20	0.902	2.367	160.72	3.233	N1
O3-H3	0.840	2.214	173.18	3.050	Br1 [ x+1, y-1, z ]



**Scheme S1** Synthetic route to formation of **SB**, a bis-substituted derivative with branched pendant arms. The unsuccessful attempted route via bisaminal reaction is also shown.

#### DISCUSSION OF SCHEME S1

Our initial efforts targeted the direct reaction of the bisaminal followed by borohydride reduction without isolating the cross-bridged cyclam prior to reaction hence reducing the number of steps to the target product from four to two, see Scheme S1. There are two issues that may cause problems with this reaction: the stability of the ester groups to the sodium borohydride reduction step and the substitution of a secondary rather than a primary alkyl halide. It has been shown previously that ethyl ester protected acetate pendent arms may be hydrolysed during the borohydride reduction step. The *tert*-butyl ester provides more robust protection allowing reductive ring cleavage to take place over 7 days at room temperature before ester hydrolysis or reduction is observed. The shortest route to the desired product **SB** is to append the bis-ester arms to the tetracyclic intermediate forming **SA**, as this allows complete synthesis in two steps with subsequent reduction. However, neither bis- nor mono-substitution was observed when this reaction was attempted. The mono-substituted product was also of interest, as a side bridged analogue could be produced. Neither solvent variation, nor the conversion of the bromo- leaving group of branched ester reagent to an iodo- group, resulted in the isolation of either product.

The attachment of the branched ester to the macrocycle requires use of the second synthetic strategy, Scheme S1, in which the ethylene bridge is incorporated to the structure prior to the substitution of the pendent arms. This is the synthetic procedure that was also adopted by Sun and co-workers to produce **SB**.<sup>2</sup> High resolution mass spectrometry confirms the formation of **10** and the subsequent steps of selective deprotection of the benzyl ester followed by reaction with biologically active targeting molecules can be carried out as demonstrated by both Brechbiel and Sun.<sup>2,3</sup>

<sup>3</sup> [ENREF 2](#)

#### 4,11-bis(1-carbo-*tert*-butoxy-3-carbobenzyloxypropyl)-1,4,8,11-tetraazabicyclo [6.6.2]hexadecane (**10**)

To a stirred solution of cross bridged cyclam (100 mg, 442 μmol) in dry acetonitrile (20 mL) was added sequentially anhydrous sodium carbonate (96 mg, 903 μmol) and 1-carbo-*tert*-butoxy-3-carbobenzyloxypropyl bromide (352 mg, 986 μmol). The mixture was heated to 50 °C and stirred for 44 h under N<sub>2</sub>. The solids were removed by filtration, and were washed with dry acetonitrile (2 x 10 mL), before solvent was removed from the filtrate. The residue was taken up into 20 % aqueous sodium hydroxide solution, and extracted with cold chloroform (4 x 50 mL). The combined organic extracts were dried and solvents removed to afford a brown oil (306 mg, 89 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.35 (m, 10H, H-Ar), 5.12 (s, 4H, CH<sub>2</sub>Ar), 4.20-4.20 (m, 1H), 3.60-3.70 (br m, 2H), 2.24-3.31 (br m, 27H), 1.95 (br m, 2H), 1.80 (br m, 2H), 1.46 (s, 18H, t-Bu). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 172.95,

171.89, 135.95, 128.24, 128.33, 82.88, 81.60, 66.55, 62.64, 57.42, 52.51, 51.74, 51.67, 48.83, 46.65, 30.94, 29.71, 28.31, 27.73. MS (ES),  $m/z$ : 779  $[M+H]^+$ , 100%; HRMS: calcd. for  $C_{44}H_{67}O_8N_4$ : 779.4953; found 779.4951.

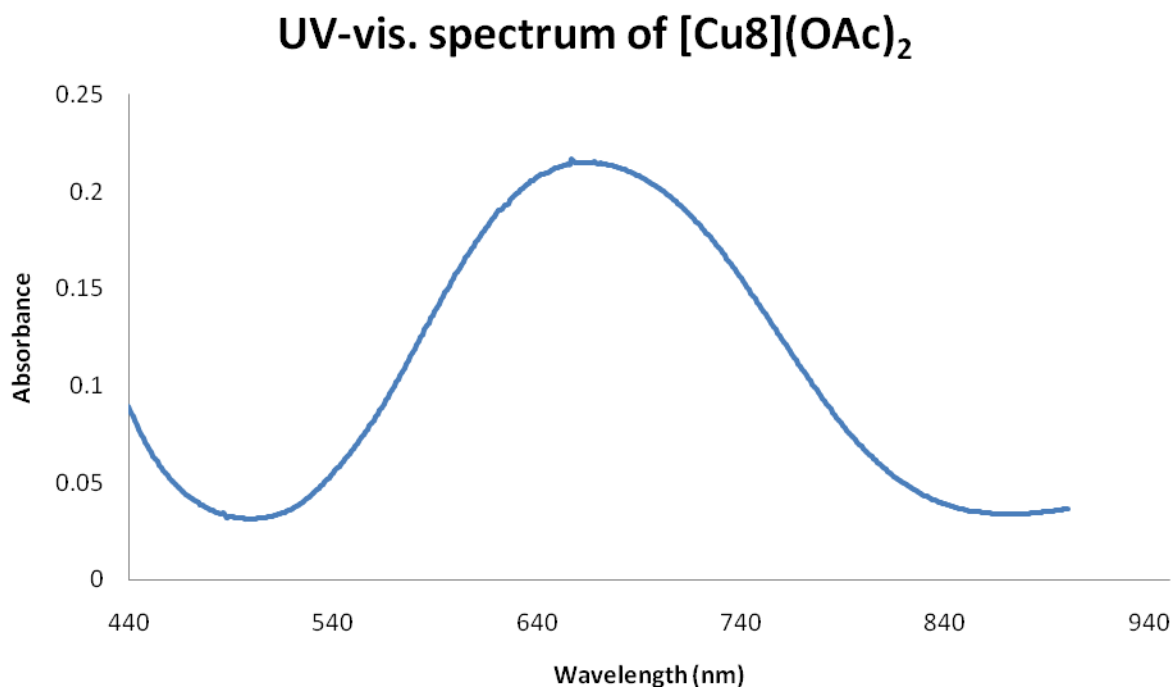


Figure S5: Example of a UV/vis. spectrum for a cross bridged macrocyclic copper(II) complex ( $[Cu_8](OAc)_2$ ) (a single broad peak is observed in the visible region)

#### REFERENCES

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