

# Phase-transfer synthesis of novel water-soluble gold clusters with tripodal thioether based ligands

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**Tripodal, water-soluble thioethers based on 1,3,5-trimethylbenzene scaffolds are suitable ligands for the Au<sub>55</sub> cluster.**

The so called ‘Schmid-cluster’,<sup>1</sup> Au<sub>55</sub>(PPh<sub>3</sub>)<sub>12</sub>Cl<sub>6</sub>, has stimulated many different areas of chemistry ranging from catalysis research<sup>2</sup> to the concept of nanocrystals<sup>3,4</sup> and quantum electronics.<sup>5</sup> Monofunctionalized water-soluble derivatives of the cluster are commercially available and have found numerous applications as TEM markers for biomolecules.<sup>6</sup> We have recently reported on trisligonucleotidyls,<sup>7</sup> a novel class of branched oligonucleotides that can be used for an informational self assembly of defined nanometer sized objects. TEM imaging of such objects proved to be successful in those cases where heating steps involving oligonucleotide gold conjugates could be avoided. The exploration of general strategies for the non-covalent synthesis of nanoobjects, however, requires sufficient thermal stability of the TEM markers, especially if one conceives a chemical replication of such nanoobjects.

We report here on the synthesis<sup>8</sup> and preliminary characterisation of water-soluble gold clusters bearing tripodal thioether based ligands 1–6 (Fig. 1). The rationale behind these ligands, shown in Fig. 2, relates to the general ideas of symmetry-based host design as outlined by MacGillivray and Atwood.<sup>9</sup> The Au<sub>55</sub> cluster core may be described as a cuboctahedron whose surface

is composed of eight edge-connected triangles (111) and six squares (110). As such, Au<sub>55</sub> is expected to bind four tripodal ligands if the binding mode of the ligands is comparable to the Schmid cluster where the 12 triphenylphosphanes most likely occupy the edges of the cuboctahedron. The affinity of C<sub>3</sub>-symmetrical thioethers towards the (111) gold surface has already been reported in the context of self assembled monolayers.<sup>10</sup> Molecular modelling studies suggested that tris-thioethers derived from 1,3,5-trimethylbenzene scaffolds are suitable candidates for tripodal binding as they seem to match the geometric requirements for covering the (111) triangles of Au<sub>55</sub>. A model of the Au<sub>55</sub> core surrounded by ligand 1 is shown in Fig. 3.

Ligands 1–6 were tested for their ability to extract gold into the aqueous phase from a solution of the triphenylphosphane cluster in methylene chloride, a method used previously by Schmid *et al.*<sup>11</sup> to exchange the ligand into monosulfonated triphenylphosphane. The degree of phase transfer was monitored from the partition of the brown color after stirring the two-phase system for varying periods of time. Complete phase transfer resulting in an decolorization of the organic phase was achieved with ligand 6 after 16 h and with ligands 1 and 4 after 7 days (in buffered<sup>12</sup> solution or when using the sodium salt respectively). Extraction using the other ligands (2, 3 and 5) did not show any phase transfer. The absence of remaining triphenylphosphane ligands was shown by NMR investigation of the precipitated and redissolved clusters with ligands 1, 4 and 6 (in D<sub>2</sub>O). In all cases neither signals of the phosphane aromatics (in <sup>1</sup>H NMR) nor P resonance signals could be detected. The clusters were precipitated from the aqueous phase by addition of propan-2-ol and purified by cycles of dissolution in water and reprecipitation with the alcohol. The solvent was

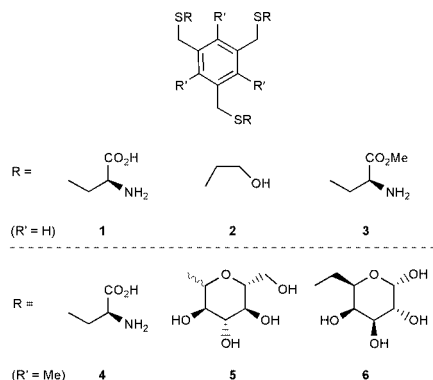


Fig. 1 Structures of examined thioethers.

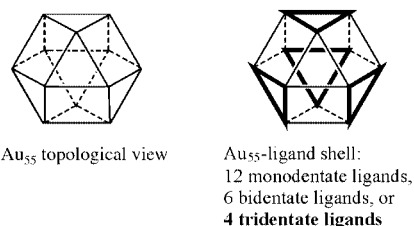


Fig. 2 Proposed cuboctahedron geometry of the Au<sub>55</sub> cluster and some possibilities of coverage with multidentate ligands.

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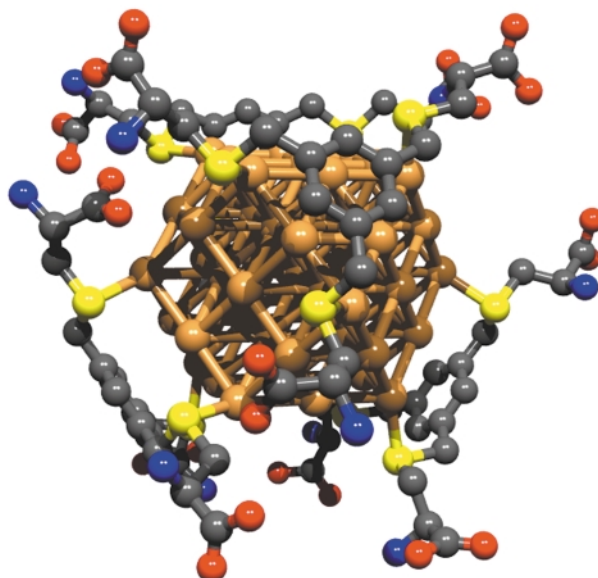
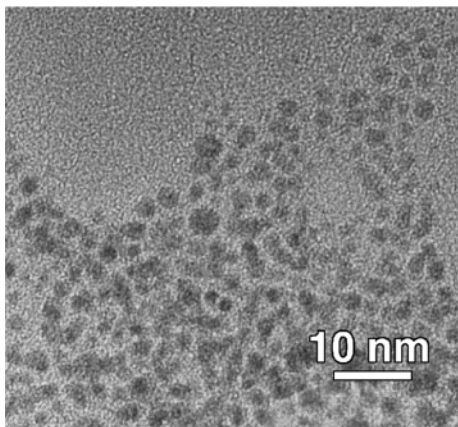


Fig. 3 Computational model structure of the ligand 1 cluster complex.

evaporated *in vacuo* at room temperature, yielding a brownish powder. Elemental analyses were carried out with the cluster bearing ligand **1** as its sodium salt<sup>13a</sup> or with trishydroxymethylaminomethane (TRIS) as counter ion.<sup>13b</sup> The results suggest a ratio of four ligand molecules (with counter ions) per Au<sub>55</sub>Cl<sub>6</sub> core.

Dynamic light scattering/photon correlation spectroscopy (PCS) proved to be a quick and comfortable method for studying the size distribution of the clusters. The mean diameters (and half value widths) were  $2.6 \pm 0.34$  nm for clusters with ligands **1** and **4** and  $2.8 \pm 0.20$  nm for ligand **6**, respectively. These data are not incompatible with the assumption of an Au<sub>55</sub> core if one considers the hydrodynamic radius estimated from PCS is affected by the nature and solvation properties of the ligands. For ligand **1** the distribution of cluster core sizes was further monitored using high resolution TEM (400 kV). A fairly uniform size distribution with a mean diameter of 1.4 nm was found. The cluster preparations were stable in aqueous solution for weeks at ambient temperature, before slow aggregation to larger colloids and precipitation occurs, hinting at their high kinetic stability. A sample that was stored in aqueous solution at room temperature for 70 days still showed a very narrow size distribution (diameter *ca.* 1.4 nm) according to TEM (Fig. 4).



**Fig. 4** HRTEM image of the Au<sub>55</sub> cluster with ligand **1** after storing the sample solution for 70 days.

Gel electrophoresis using 1% agarose gel proved applicable to investigate the charge, uniformity and kinetic stability of the different clusters. The agarose gel of clusters with ligands **1** and **4** reveals a discrete brownish band moving to the anode. Its appearance in terms of broadness is comparable to bromophenyl blue hinting at its uniformity and proving the expected anionic character of the cluster. Under the same conditions, the clusters formed from ligand **6** did not show any mobility, as expected for neutral ligands, if the six chloride ions are tightly bound to the cluster core, with only diffusive broadening at the flanks of the gel pocket being observed. Furthermore, clusters from ligands **1** and **4** show only little smearing of the electrophoresis band so revealing their kinetic stability. All attempts to establish the

molecular weight of the clusters by MALDI-TOF mass spectroscopy have failed so far.

To the best of our knowledge, this work represents the first examples of the utilisation of tripodal ligands and on the use of thioether ligands for the preparation of gold clusters. Future approaches towards the synthesis of stable, water soluble, biocompatible and monofunctionalizable gold clusters may now employ peptide chemistry for further sealing and packaging of Au<sub>55</sub> cores.

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- The synthesis of the ligands was straightforward: *S*-alkylation of sodium cysteinate and potassium 2-hydroxyethylthiolate using 1,3,5-tris(bromomethyl)mesitylene<sup>8a</sup> in H<sub>2</sub>O–methanol (1 : 1) yielded ligands **1** and **2** in 90 and 77% yields, respectively. Ligand **1** was converted into its trimethylester **3** in 91% yield using SOCl<sub>2</sub> in methanol. Treatment of 1,3,5-tris(bromomethyl)benzene<sup>8b</sup> with sodium cysteinate in H<sub>2</sub>O–methanol gave ligand **4** in 94% yield while the analogous conversion of 1-deoxy-1-thioglucose sodium salt<sup>8c</sup> into ligand **5** proceeded with 45% yield under the same conditions. The sugar-based thioether ligand **6** was obtained in an overall yield of 54% from 6-deoxy-6-tosyldiacetonegalactose,<sup>8d</sup> which was converted into the 6-bromo derivative, condensed with 1,3,5-tris(mercaptomethyl)benzene sodium salt<sup>8e</sup> in DMF and deprotected with methanolic HCl. (a) J. Závada, M. Pánková, P. Holý and M. Tichý, *Synthesis*, 1994, 1132; (b) W. Offermann and F. Vögtle, *Synthesis*, 1977, 273; (c) commercially available from ALDRICH Chemicals; (d) B. Iselin and T. Reichstein, *Helv. Chim. Acta*, 1946, 508; (e) A. Ricci, R. Danieli and S. Rossini, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1691.
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- 1 mM TRIS/HCl, pH = 7.90
- (a) Found: C, 5.92; H, 0.81; N, 0.94; S, 3.09; Au, 81.98%(av.) Calc: C, 6.54; H, 0.73; N, 1.27; S, 2.91; Au, 81.26%. (b) Found: C, 10.64; H, 1.40; N, 1.87; S, 4.14; Au, 77.89%(av.). Calc: C, 10.00; H, 1.68; N, 2.33; S, 2.67; Au, 75.18% (calculated for a 1:4 ratio of metal core (with 6 chloride atoms) to ligands).