General procedure (alkylation): Benzyl bromide (0.1 mL, 0.85 mmol) was added to a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**11**; 50 mg, 0.17 mmol) and the chiral catalyst **9** (1.7 mg, 0.0017 mmol) in toluene/chloroform (7:3, 0.75 mL). The reaction mixture was then cooled (0 °C), aqueous KOH (50 %, 0.25 mL) was added, and the reaction mixture was stirred at 0 °C until the starting material had been consumed (10 h). The suspension was diluted with diethyl ether (20 mL), washed with water (2×5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc 50:1) afforded the desired product **12g** (62 mg, 95 % yield) as a colorless oil. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD, hexane/2-propanol (500:2.5), flow rate 1.0 mL min^{-1}, 23 °C, λ 254 nm, retention times: *R* (minor) 12.2 min, *S* (major) 22.5 min, 97 % *ee*) The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the reported procedure.[4–7]

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Facile Syntheses of Copper(I) Alkynyl Clusters Stabilized by Hexafluoroacetylacetonate (hfac) Ligands: The Structure of [$Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}$]**

Timothy C. Higgs,* Phillip J. Bailey, Simon Parsons, and Peter A. Tasker*

Whilst the copper(I) alkynyl complexes have been widely studied, for their potential as synthetic reagents,[1] their photophysical (luminescent) properties,[2–18] and the extraordinary variety of binding modes exhibited by alkynyl ligands,[14,18–24] only a few homometallic and homovalent Cu^I clusters with low nuclearities of 2,3,4, or 6 have been structurally characterized.[1,3–15,18–27] One of the problems in preparing and isolating high-nuclearity copper(I) complexes containing terminal alkynyl ligands is the propensity of such systems to aggregate indiscriminately to yield highly insoluble polymers or oligomers. One approach to overcoming this problem is to employ suitable "capping ligands" to protect the periphery of the cluster. If such ligands were available they could, in principle, be used to control the size and shape of clusters by varying the relative concentrations of capping and interstitial (alkynyl) ligands. To date, this synthetic strategy has been employed using predominantly neutral ligands, mostly phosphane-based (for example, PPh_3 and $Ph_2PCH_2PPh_2$),[2,3,5–10,12–15,18–22,24] and in a few cases monoanionic ligands (for example, $2\text{-}Me_2NCH_2C_6H_4S^-$).[1,25]

Herein, we report a very convenient method for the synthesis of homovalent Cu^I clusters of the type [$Cu_{x+y}(hfac)_x(RC{\equiv}C)_y$] (hfac = hexafluoroacetylacetonate) and the structural characterization of the largest Cu^I cluster obtained to date, [$Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}$]. When hfacH is added dropwise to a suspension of Cu_2O and anhydrous $MgSO_4$ in excess alkyne ($RC{\equiv}CH$, R = $n\text{-}C_3H_7$, $n\text{-}C_4H_9$, $n\text{-}C_5H_{11}$, $n\text{-}C_6H_{13}$) an exothermic reaction is observed. After addition of *n*-hexane, filtration and washing, a lime-green solution is obtained which is presumed to contain mononuclear [$Cu(hfac)(\eta^2_\pi\text{-}RC{\equiv}CH)$] or similar species containing more than one neutral 1-alkyne ligand (Scheme 1).

Evaporation and subsequent heating (65 °C) in vacuo gives viscous red or orange oils or, more frequently, crystalline solids containing discrete organometallic complexes of the type [$Cu_{x+y}(hfac)_x(RC{\equiv}C)_y$], with yields in the range 20–50 %. In certain cases, partial aerial oxidation of such systems has generated new [$Cu_{x+y}(hfac)_x(RC{\equiv}C)_y$]-type clusters with higher nuclearities. Thus, when 1-pentyne was used as the reagent, [$Cu_{18}(hfac)_{10}(pentynyl)_8$] (orange solid) was isolated which, in

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[*] Dr. T. C. Higgs, Prof. P. A. Tasker, Dr. P. J. Bailey, Dr. S. Parsons
The Department of Chemistry
The King's Buildings, The University of Edinburgh
West Mains Road, Edinburgh, Lothian, Scotland, EH9 3JJ (UK)
Fax: (+44) 131-650-6452
E-mail: pat01@holyrood.ed.ac.uk, pat05@holyrood.ed.ac.uk

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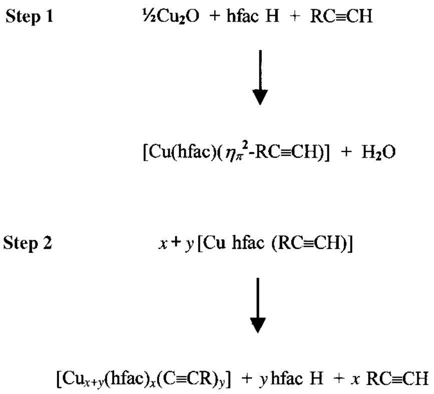

Scheme 1.

turn, was oxidatively converted into $[Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}]$ (red solid), of which crystals of X-ray crystallographic quality were grown from an *n*-hexane solution.[28]

A discrete cluster molecule $[Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}]$ defines the asymmetric unit. The disc-shaped cluster is neutral, with all 26 ligands present as monoanions; 25 copper atoms are located within four concentric annuli, as shown in Figure 1. The cross-section of the disc (Figure 2) reveals two layers of Cu atoms which are spaced by a linear two-coordinate $Cu(\eta^1_\sigma\text{-C}{\equiv}CR)_2$ unit containing Cu(1) (see also Figure 1). Each of the $(\eta^1_\sigma\text{-C}{\equiv}CR)$ alkynyl ligands of this central unit coordinates in a $\mu_3\text{-}(\eta^1_\pi)_3$ fashion through long bonds (2.181(5)–2.366(4) Å) to three of the Cu atoms in the second ring. The triangles defined by these Cu atoms in the upper and lower layers, Cu(2), Cu(4), Cu(6) and Cu(3), Cu(5), Cu(7), respectively, are nearly eclipsed when viewed along the $RC{\equiv}C\text{-}Cu(1)\text{-}C{\equiv}CR$ axis (Figure 1), thus forming a distorted trigonal prismatic arrangement.

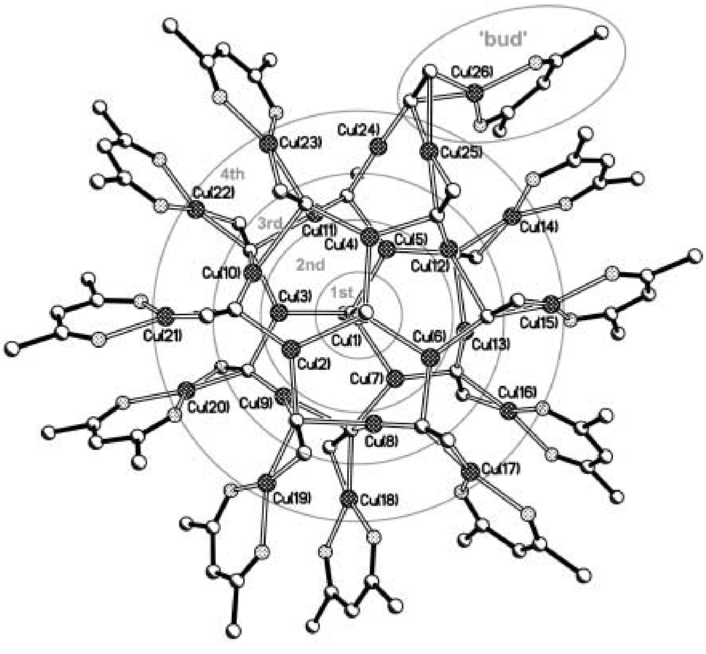

Figure 1. Representation of the disc-shaped cluster $[Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}]$ showing the radial distribution of the Cu atoms in four concentric annuli and in a "bud" on the rim of the disc. Possible Cu···Cu interactions, H and F atoms, and the C_3H_7 groups of the 1-pentyne ligands are omitted for clarity.

The six Cu atoms in the second annulus in Figure 1 all have trigonal planar geometry. In addition to the η^1_π bond to the central $Cu(RC{\equiv}C)_2$ unit, each of these atoms is linked to alkynyl ligands in the third annulus of the cluster through η^1_σ and η^1_π bonds. The third annulus also contains six Cu atoms, Cu(8–13). These are linked to the inner alkynyl ligands predominately through η^1_σ bonds.

The fourth annulus contains 12 Cu atoms linked through η^2_π bonds to inner pentynyl ligands. Ten of these Cu atoms are capped by hfac ligands which radiate outwards to define the edge of the disc (see Figure 2). The two other Cu atoms, Cu(24) and Cu(25), are linked to Cu(26). The latter center has a unique environment, in which it forms a "bud" on the exterior of the cluster that breaks down the otherwise symmetrical radial distribution of Cu–hfac units on the rim of the disc.

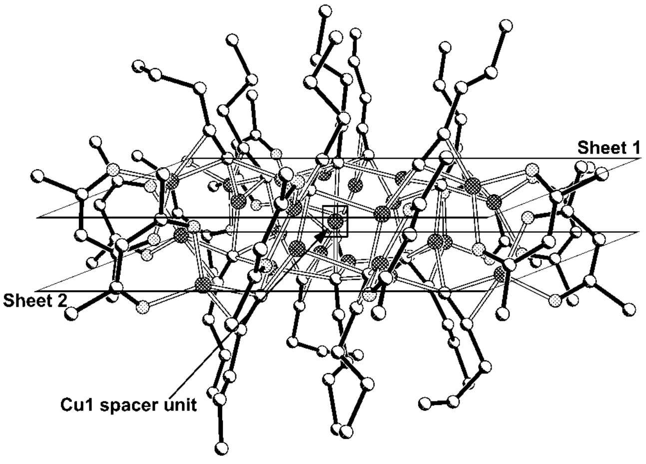

Figure 2. Lateral view of the $[Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}]$ molecule. For the purposes of clarity all possible Cu···Cu interactions, H, and F atoms are omitted, and the disorder within one of the C_3H_7 groups is simplified.

The distribution of the pentynyl and hfac ligands is strikingly anisotropic. All of the pentynyl groups are involved in bridging between Cu atoms in the various annuli or the bud, and are thus distributed across the faces of the disc, with their associated propyl groups lying approximately parallel to the axis perpendicular to the plane of the disc. In contrast, the "terminal" anionic hfac ligands are associated exclusively with the rim of the disc (see above).

The linear $Cu(\eta^1_\sigma\text{-C}{\equiv}CR)_2$ arrangement at the central Cu(1) atom is also observed for Cu(24), which provides a link to the bud. These are the first crystallographically characterized examples of this mode of complexation. Another unusual copper coordination environment is displayed by Cu(25), which forms two linearly disposed η^2_π bonds to alkynyl ligands. Such an arrangement has also been observed in the mixed Cu^I/Pt^{II} cluster, $[Pt_2Cu_4(C{\equiv}CPh)_8]_2$[29] and the mixed-metal Cu^I/Re^I alkynyl complex, $[\{\eta^2\text{-Re(CO)}_3(bpy)(C{\equiv}CPh)\}_2\text{-}Cu][PF_6]$.[30] The prevalence of low coordination numbers for these copper ions raises the question of the nature and strength of $Cu^I\cdots Cu^I$ (d^{10}–d^{10}) closed-shell interactions in the cluster.[31–34] Numerous pairs of Cu atoms are in proximity; 28 Cu···Cu contacts are shorter than the sum of the van der

Waals radii for two Cu^I atoms (2.8 Å).[35] The 12 closest contacts (2.520(1)–2.601(1) Å) exist between Cu atoms in the second annulus approaching two Cu atoms in the third annulus.[36] Weak $Cu^I\cdots Cu^I$ interactions have been used to rationalize the excited states of several luminescent Cu^I–alkynyl complexes.[3,31] Recent theoretical studies[33] have indicated that $Cu^I(d^{10}–d^{10})$ attractive interactions can have energies of up to 4 kcal mol^{-1}, which is comparable to the strength of hydrogen bonds. Therefore, these closed shell interactions in the $[Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}]$ cluster make only a minor contribution to defining its primary structure.[37] The hfac-capped Cu atoms all have near-planar O_2C_2 donor-sets with hfac chelate ring dimensions similar to those in other Cu^I complexes.[38,39]

The simplicity of the preparation of these clusters and the range of nuclearities obtained is remarkable. Work is in hand to establish the nature of the intermediate arising from the reaction of Cu_2O and hfacH in excess 1-alkyne. Control experiments indicate that Cu_2O does not react directly with aliphatic 1-alkynes in the presence of $MgSO_4$, probably as a result of their low acidity (1-hexyne, $pK_a = 25$),[40] whereas more acidic 1-alkynes such as 1-phenylethyne ($pK_a = 18.5$)[41] react quickly to form bright-yellow voluminous solids, which are presumed to contain $[\{Cu(\mu_x\text{-}\eta^y_{\sigma/\pi}\text{-}C\equiv CPh)\}_n]$.

If, as postulated in Scheme 1, the intermediate contains only neutral 1-alkynes, it can be envisaged that cluster formation involves deprotonation of 1-alkyne ligands to form Cu-bridged units, with the protons transferring to hfac moieties, which are then readily removed from the system in vacuo as the volatile hfacH (b.p. 70–71 °C). This reaction has similarities to those reported by Vicente and Chicote[42] where protic acids were treated with metal complexes containing acetylacetonate (acac) ligands (M(acac) + BH→MB + (acac)H). The cluster size increases as the ratio of alkynyl to hfac in the complex increases. Oxidation provides another mechanism for increasing the alkynyl to hfac ratio by the loss of $\{Cu(hfac)_2\}$ units from the periphery of the cluster. Under these circumstances the nature of the cluster isolated will depend on a subtle balance of the relative volatilities and pK_a values of the 1-alkyne and hfacH.

Experimental Section

All chemicals were purchased from Aldrich. *n*-Hexane was distilled over sodium/benzophenone/tetraglyme (trace) under nitrogen. All reactions and manipulations were carried out under nitrogen (dried 4-Å molecular sieves, deoxygenated with BTS-catalyst) by using standard Schlenk-line techniques. 1-Pentyne and hfacH were degassed by three freeze–vacuum–thaw cycles.

$[Cu_{18}(hfac)_{10}(1\text{-pentynyl})_8]$: Cu_2O (2.53 g, 17.66 mmol) and anhydrous $MgSO_4$ (2.0 g, 16.6 mmol) were added to 1-pentyne (7.0 mL), to yield a red suspension into which hfacH (2.50 mL, 17.66 mmol) was then added dropwise. The reaction mixture, which refluxed under the heat of reaction during addition of hfacH, was then stirred at room temperature for 66 h. *n*-Hexane (10 mL) was then added to mobilize the reaction mixture, a viscous orange suspension, before it was cannula-filtered and the residual solid washed three times with *n*-hexane (10 mL aliquots). The combined filtrate and washings, which were pale-green in color, were evaporated to dryness in vacuo yielding an orange-brown oil. This was then dried at 65 °C (water bath) in vacuo for a further 30 min. During this time the oil thickened, turned opaque, and ultimately solidified. This solid was suspended in *n*-hexane (20 mL), a process that required ultrasonic agitation, to give a green solution containing a microcrystalline orange solid. The solution was removed by cannula filtration leaving behind a bright-orange solid, which was washed twice with *n*-hexane (5 mL aliquots) and dried in vacuo. Yield 2.87 g (43.3 %). IR (KBr disk): $\tilde{\nu} = 3499$, 2964, 1672, 1642, 1554, 1528, 1513, 1463, 1255, 1209, 1146, 1100, 795, 743, 662, 580, 526 cm^{-1}; elemental analysis calcd for $C_{90}H_{66}Cu_{18}F_{60}O_{20}$: C 28.82, H 1.77; found: C 28.93, H 1.83%.

$[Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}]$: Crystals of $[Cu_{18}(hfac)_{10}(1\text{-pentynyl})_8]$ were obtained by dissolving the orange solid, described above (2.50 g, 0.667 mmol), in the minimum volume of refluxing Et_2O. The resultant orange solution was allowed to cool to room temperature and was exposed to the air for several minutes (max. 5 min). The solution was then placed back under a nitrogen atmosphere and then cooled to 4 °C for several days, during which time a mixture of deep-red and green block crystals deposited from the solution. The mother liquor was removed with a cannula and the crystals washed with *n*-hexane (3 mL) and dried in vacuo. The crystals were then recrystallized twice from a minimum volume of refluxing *n*-hexane to yield solely deep-red block crystals, which were collected, washed with *n*-hexane, and dried in vacuo. Yield 0.26 g (15.8 %). IR (KBr disk): $\tilde{\nu} = 2966$, 2927, 2879, 1892, 1641, 1555, 1529, 1468, 1343, 1257, 1207, 1147, 1099, 796, 743, 671, 587, 528 cm^{-1}; elemental analysis calcd for $C_{130}H_{116}Cu_{26}F_{66}O_{22}$: C 31.62, H 2.35; found: C 31.50, H 2.27%.

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[28] a) Crystal structure analysis for [$Cu_{26}(hfac)_{11}(1\text{-pentynyl})_{15}$]: Crystals were grown by slow cooling of a supersaturated solution of the complex in hot *n*-hexane and were analyzed with a Bruker smart APEX CCD area detector equipped with an Oxford Cryosystems LT device operating at 150 K. $C_{133}H_{115}Cu_{26}F_{66}O_{22}$, $\lambda = 0.71073$ Å, crystal size $= 0.44 \times 0.38 \times 0.29$ mm, cell determination: range $4° < 2\theta < 58°$, no. reflections: 4764, monoclinic, space group *Cc* (checked with MISSYM[28b-d]), $Z = 4$, $a = 26.009(3)$, $b = 21.114(2)$, $c = 31.078(4)$ Å, $\beta = 94.214(2)°$, $V = 17021(3)$ Å^3, $\rho_{calcd} = 1.943$ g cm^{-3}, $\mu = 3.300$ mm^{-1}. 75941 reflections were collected in the range $1.31° < \theta < 28.94°$, of which 38578 were unique and 33027 had $F_o > 4\sigma(F_o)$. A multiscan absorption correction was applied using Sadabs[28e] ($T_{max} = 0.862$; $T_{min} = 0.679$). The structure was solved by direct methods (SHELXS-97),[28f] and refined by block-matrix least-squares against F^2 (SHELXTL97).[28f] All non-hydrogen atoms were modeled with anisotropic displacement parameters, except for one half-occupancy hexane solvate molecule, and H atoms were included in ideal positions. Numerous CF_3 groups were disordered, a combination of similarity and ADP equalization restraints were used to model this. The conventional R_1 factor ($F_o > 4\sigma(F_o)$) was 0.0409 and wR_2 was 0.0913. ($w = 1/[\sigma^2(F_o^2) + (0.0490P)^2]$ where $P = (F_o^2 + 2_c^2)/3$). Largest max/min residual electron density: $+1.094/-0.917$ e Å^3;b) Y. LePage, *J. Appl. Crystallogr.* **1999**, *20*, 264; c) A. L. Spek, *J. Appl. Cryst.* **1987**, *21*, 578; d) L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837; e) G. M. Sheldrick, SADABS, Program for Empirical Correction of Area Detector Data, University of Göttingen, Göttingen (Germany), **1998**; f) G. M. Sheldrick, SHELXTL97, Program for the refinement of crystal structures, University of Göttingen, Göttingen (Germany), **1997**. CCDC-186669 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[36] Pairs of atoms in the second annulus defining the parallel sides of the pseudotrigonal prism make contact with the same pair of atoms in the third annulus, namely Cu(2) and Cu(3) with Cu(9) and Cu(10); Cu(4) and Cu(5) with Cu(11) and Cu(12); and Cu(6) and Cu(7) with Cu(8) and Cu(13).

[37] The closest Cu···Cu contacts formed by atoms in the "bud unit" (Figure 1) are either longer than the sum of van der Waals radii of two Cu^I atoms or, for Cu(24)···Cu(11) and Cu(24)···Cu(25), close to this value (2.7401(9) Å and 2.7057(10) Å respectively).

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Synthesis and Evaluation of Transition-State Analogue Inhibitors of α-1,3-Fucosyltransferase[**]

Michael L. Mitchell, Feng Tian, Lac V. Lee, and Chi-Huey Wong[*]

Glycosidases and glycosyltransferases involved in the biosynthesis of glycoconjugates associated with intercellular recognition, metastasis, and immune response represent viable therapeutic targets.[1–7] Of particular interest are the fucosyltransferases (FucTs), which play a key role in the biosynthesis of many important fucose-containing oligosaccharides such as sialyl Lewis x (sLe^x), a determinant in numerous cell–cell interactions, for example, in inflammation[8,9] and tumor metastasis.[10,11] The terminal step in the biosynthetic pathway of these fucose-containing saccharides is the transfer of L-fucose from guanosine diphosphate β-L-fucose (GDP–Fuc) to the corresponding glycoconjugate acceptors,[12,13] which is catalyzed by α-1,3-fucosyltransferase (α-1,3-FucT).[14,15] Since inhibitors of fucosyltransferase may disrupt the biosynthesis of these saccharides, they have potential medicinal applications as anti-inflammatory or antitumor agents.

In the proposed transition state of α-1,3-FucT V,[16] the pyrophosphate chelates a divalent manganese and the fucose ring adopts a flattened half-chair conformation with substantial oxocarbenium ion character (Scheme 1). Recognition of these salient features of the transition state guided our design of potential inhibitors **1**–**3** for fucosyltransferase.

In the present study, analogues of fucose, which incorporate the geometry or charge of the fucose moiety in the transition state, were linked to GDP, thereby retaining the contribution of GDP to binding. The cyclohexene ring of **1** was designed to mimic the flattened half-chair conformation of the fucose moiety. In addition, the carbocyclic ring is chemically more stable than its pyranose counterpart and may be more stable in vivo.

Triazoles also resemble the flattened conformation of the fucose moiety in the transition state.[17] Previous work based on fucose-derived triazoles lacking the negative charge normally present in the GDP-fucose substrate only weakly inhibited fucosyltransferase.[18] Therefore, a triazole was attached to GDP providing **2**, which allowed us to exploit the electrostatic interactions of the pyrophosphate and residues in the active s9ite.

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[*] Prof. C.-H. Wong, Dr. M. L. Mitchell, Dr. F. Tian, Dr. L. V. Lee
Department of Chemistry and the Skaggs Institute
for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2409
E-mail: wong@scripps.edu

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