Supramolecular self-assembly on a solid support: metal-directed complementarity

Edwin C. Constable,*[a] Catherine E. Housecroft,[a] John N. Lambert*[bc] and Dan A. Malarek[ac]

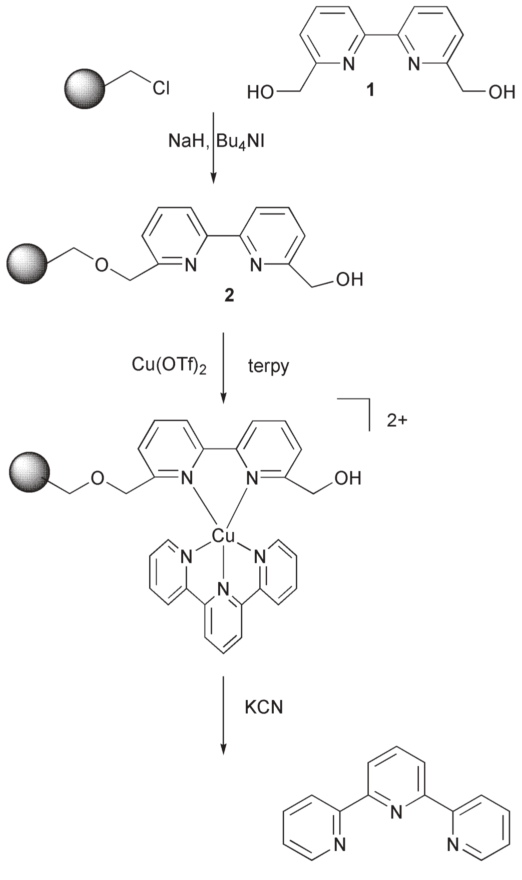
Received (in Cambridge, UK) 28th April 2005, Accepted 25th May 2005
First published as an Advance Article on the web 10th June 2005
DOI: 10.1039/b505968b

Resin immobilised (poly)-2,2′-bipyridines have been prepared and used as templates for the copper(II)-mediated assembly of alkene-functionalised 2,2′:6′,2″-terpyridines which undergo subsequent templated metathesis to form complementary poly-2,2′:6′,2″-terpyridine strands.

A common strategy for the construction of supramolecular systems takes advantage of metal ion coordination, whereby metal ions control the self-assembly of ligands to form thermodynamically favoured assemblies.[1] There have been a number of approaches to the design of self-replicating systems in the past 15 years.[2–4] However, there are limited examples of artificial self-replicating systems based upon multisite complementarity,[5–7] similar to that in duplex DNA, although this is potentially a powerful method for information storage and transmission. In this paper, we describe the design, modification, and self-assembly of supramolecular structures to create an artificial complementary replicating system based upon metal–ligand interactions.

Lehn[8] and Sauvage[9] have shown that the coordination preferences of copper in different oxidation states (tetrahedral, copper(I); five- or six-coordinate, copper(II)) may be used to drive supramolecular systems. Conveniently, a four-coordinate environment is provided by two 2,2′-bipy (B) residues and a five-coordinate by a B and a terpy (T) ligand. Our strategy is to covalently attach an oligomeric ligand, for example with a B•T•B sequence, to a solid support. Future work will include a coupling reaction coupled with copper(I)–copper(II) redox chemistry to give genuinely self-replicating systems. Treatment with copper(II), B and T, could lead to a library of trinuclear complexes, but the thermodynamically favoured species will be $[Cu_3(B{\bullet}T{\bullet}B)(T)(B)(T)]^{6+}$ with one B and one T per metal centre. Subsequent covalent linking of the B and T residues will give a complementary T•B•T strand in the complex $[Cu_3(B{\bullet}T{\bullet}B)(T{\bullet}B{\bullet}T)]^{6+}$.

Initial studies were carried out using standard Merrifield polystyrene resin[10] which allows for a diverse range of relatively extreme reaction conditions without danger of resin cleavage. Reactions on the solid phase were performed with reagents in large excess followed by filtration of the resin and repeated washing with swelling solvents in which both reagents and non-resin-bound species were soluble. Deprotonation of 6,6′-di(hydroxymethyl)-2,2′-bipyridine[11] **1** (NaH, DMF) followed by reaction with chloromethyl-form Merrifield resin gave a B-functionalised bead **2**. This was characterised using magic angle spinning nano-probe ^1H NMR which revealed the expected B aromatic signals (δ 7.27 (7.17), 7.22 (7.41), 7.57 (7.69), 7.73 (7.79), 8.14 (8.18), 8.35 (8.32) ppm, 6-hydroxymethyl-6′-methyl-2,2′-bipyridine in CD_3OD solution in parentheses).[11] Reaction of the functionalised resin **2** with $Cu(OTf)_2$ (OTf = O_3SCF_3) and terpy followed by repeated washing, resulted in the formation of olive green beads, consistent with known $\{Cu(bipy)(terpy)\}^{2+}$ solution species.[8] Treatment of the beads with KCN resulted in decolorisation and a solution phase that contained terpy as the only organic species (Scheme 1).



Scheme 1 Synthesis of the Merrifield resin bound $\{CuBT\}^{2+}$ complex followed by KCN cleavage and isolation of the complementary (terpy) ligand. The Merrifield resin is represented by the shaded sphere. The inset LC ESI mass spectrum of the solution obtained after treatment with KCN shows only the presence of $\{terpy + H\}^+$ (*m*/*z* 234) and $\{terpy + Na\}^+$ (*m*/*z* 256).

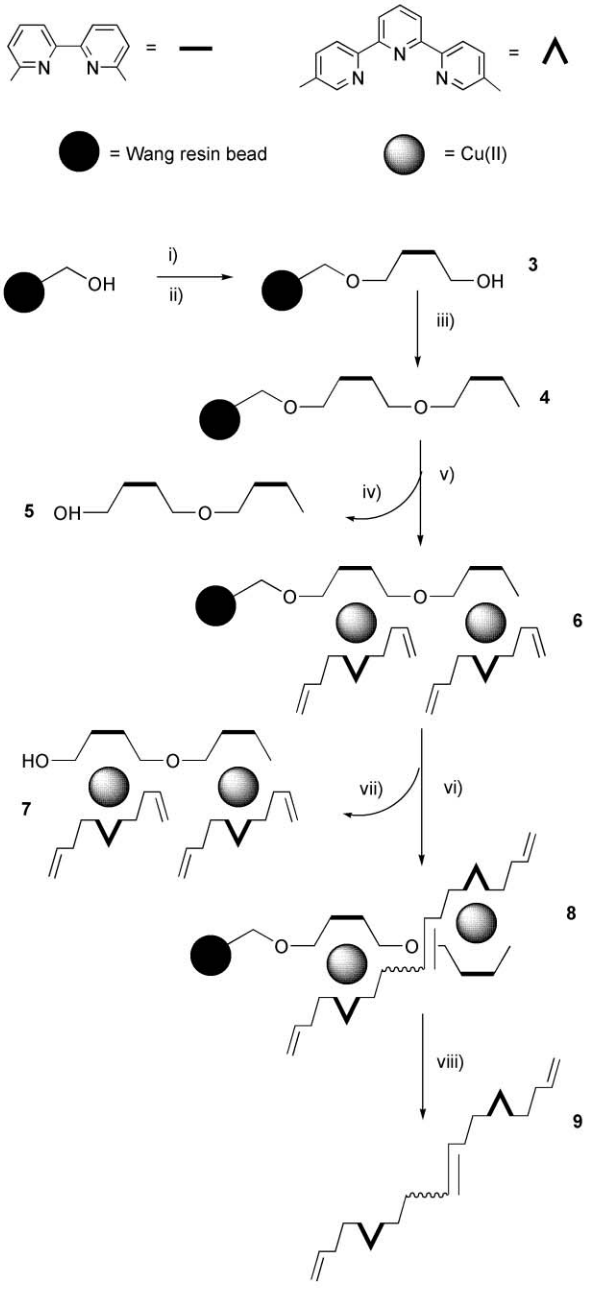
---

[a] *Department of Chemistry, Spitalstrasse 51, CH-4056, Basel, Switzerland. E-mail: edwin.constable@unibas.ch; Fax: 41 61 267 1005; Tel: 41 61 267 1001*
[b] *Biota Holdings Limited, 10/585 Blackburn Rd., Notting Hill, Victoria, 3168, Australia. E-mail: j.lambert@biota.com.au; Fax: 61 3 9915 3701; Tel: 61 3 9915 3725*
[c] *School of Chemistry, The University of Melbourne, Parkville, Victoria, 3010, Australia*

In a competition experiment, **2** was reacted with $Cu(OTf)_2$ and excess but equimolar amounts of terpy and bipy in 1 : 1 $CHCl_3$–MeCN. The resultant olive green beads could contain $\{CuB_2\}^{2+}$ or $\{CuBT\}^{2+}$ centres or a mixture of both motifs. After thorough washing and cleavage with potassium cyanide, LC ESI-MS revealed only one organic product in solution, terpy (*m*/*z* 234, MH^+), indicating the selectivity is very high for the formation of the five-coordinate $\{CuBT\}^{2+}$ centres.

At this stage, we changed from the standard Merrifield resin to the *p*-benzyloxybenzyl alcohol substituted (Wang) resin (1 mmol g^{-1} loading, 200–400 pmol $bead^{-1}$),[12,13] to allow facile cleavage of the resin bound products under mildly acidic conditions.[16] We also found concurrently, that MALDI-TOF MS can be used for the direct characterisation of picomole quantities of products bound to a single bead, avoiding the tedious task of cleavage and extraction. The laser is focused on a single resin bead in α-cyano-4-hydroxycinnamic acid matrix, whereupon the benzyl ether is cleaved and the attached functionality is detected directly in the mass spectrometer.

We now planned to use Grubbs' catalyst[14,15] under standard olefin metathesis conditions to link two suitably alkene-functionalised complementary ligands into a new strand whilst still bound to the modified solid support as the copper(II) complex. The Wang resin was activated by reaction with Cl_3CCN and DBU[17] to form the trichloroacetimidate functionalised resin,



Scheme 2 Synthesis of the modified Wang resin and complementary strand: i) Cl_3CCN, DBU; ii) $BF_3 \cdot Et_2O$, **1**; iii) NaH, 6-bromomethyl-6′-methyl-2,2′-bipyridine; iv) 1% TFA–CH_2Cl_2; v) $Cu(OTf)_2$, 5,5″-bis(but-3-enyl)-2,2′:6′,2″-terpyridine; vi) Grubbs' second generation ruthenium catalyst; vii) MALDI-TOF, α-cyano-4-hydroxycinnamic acid; viii) KCN.

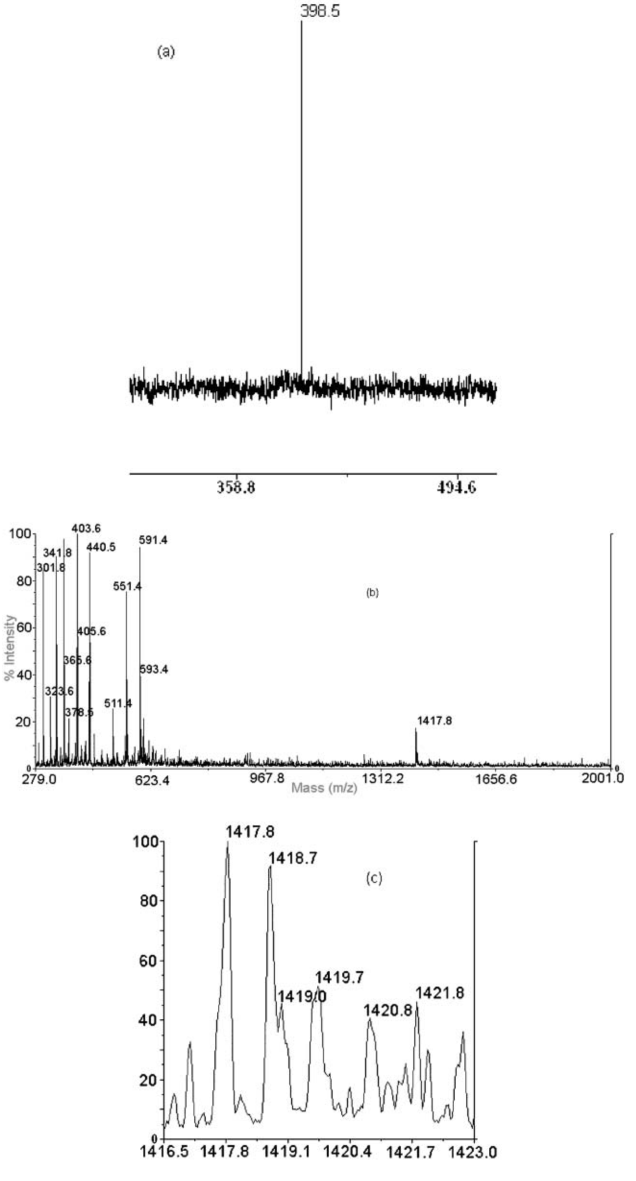


Fig. 1 a) MALDI-TOF MS of B•B strand **5** after cleavage of **4** with TFA; b) MALDI-TOF MS of **7** cleaved *in situ* from a single resin bead in α-cyano-4-hydroxycinnamic acid matrix and c) expansion of the *m*/*z* 1418 envelope corresponding to $\{\mathbf{7} + Na + matrix\}^+$.

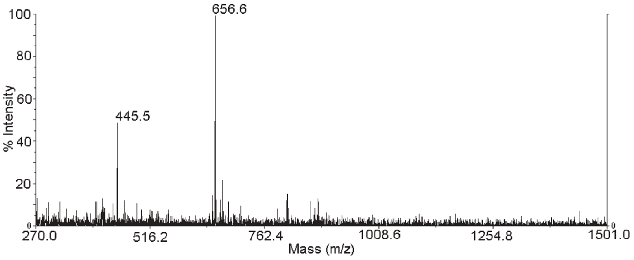


Fig. 2 MALDI-TOF MS of T•T strand **9** after cleavage from the bead with TFA.

which was then reacted with **1** and $BF_3 \cdot Et_2O$ to give the B-functionalised resin **3**. Deprotonation (NaH–DMF) followed by reaction with 6-bromomethyl-6′-methyl-2,2′-bipyridine[11] yielded the resin functionalised with a bis-bipy B•B strand **4** (Scheme 2), confirmed by MALDI-TOF MS of the organic material cleaved from the bead by reaction with TFA (Fig. 1a).

Subsequent reaction of **4** with excess $Cu(OTf)_2$ and 5,5″-bis(but-3-enyl)-2,2′:6′,2″-terpyridine† yielded the dinuclear single-stranded functionalised resin **6** as a dark green solid. The MALDI-TOF mass spectrum of a single bead exhibited a highest mass peak at *m*/*z* 1417.8, corresponding to $\{\mathbf{7} + Na + \text{matrix}\}^+$.

Reaction of the resin bound dicopper(II) complex **6** with Grubbs' second generation catalyst (5 mol %) in CH_2Cl_2 gave olive-green beads. The resin was then filtered off and thoroughly washed with CH_2Cl_2, DMF and methanol to remove all excess reagents and by-products; cleavage of the complementary strand with KCN (Scheme 2) yielded the expected bis-terpyridine **9** in solution, confirmed by MALDI-TOF MS, with the molecular ion peak being observed at *m*/*z* 656 ($[M + H]^+$) (Fig. 2). We were originally concerned that multiple coupling reactions might occur, but the conversion of **6** (all alkene groups equivaent) to double-helical **8** results in a large spatial separation of the terminal alkenes. Accordingly no cyclic metathesis products are obtained and no interstrand coupling occurs.

We have shown that complexes containing complementary strands of bipy and terpy ligands may be prepared on solid supports through olefin metathesis reactions using the preference of copper(II) for five-coordinate (bipy)(terpy) environments to provide interstrand recognition. Characterisation of the ligands and complexes alike can be undertaken from a single resin bead using laser-induced cleavage by MALDI-TOF MS.

In conclusion, we have demonstrated the templated formation of complementary ligand strands using solid phase synthetic methods. In particular, MALDI-TOF provides a powerful method for characterising picomolar quantities of products from a single bead. We are currently extending these studies toward genuinely self-replicating systems.

We would like to thank the Universities of Basel and Melbourne for financial support and Lukas Scherer for measuring the MALDI-TOF spectra.

Notes and references

† Freshly prepared lithium diisopropylamide (2.98 mmol) in THF (10 mL) was cooled to −78 °C and transferred by cannula to a solution of 5,5″-dimethyl-2,2′:6′,2″-terpyridine (709 mg, 2.72 mmol) in dry THF (20 mL) at −78 °C. This solution was allowed to warm to room temperature for 30 min and then cooled to 0 °C and a solution of allyl bromide (655 mg, 0.47 mL, 5.43 mmol) in dry THF (10 mL) added and the solution stirred at 0 °C for 1 h, then at room temperature for 2 h. Water was added and the solution extracted with diethyl ether. The organic layers were combined and dried with Na_2SO_4 and evaporated. ^{1}H NMR revealed successful mono-allylation. The above procedure was repeated for the addition of the second allyl group. After the second addition of LDA and allyl bromide, the product was purified *via* alumina chromatography over alumina (1 : 1 dichloromethane–petroleum spirit 40–60 °C). An overall yield of 27% (205 mg) was obtained. $R_f = 0.35$.^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.42$ (m, 4H, H-8, 8″), 2.77 (t, 4H, $J = 6.6$ Hz, H-7, 7″), 5.02 (m, 4H, H-10, 10″), 5.83 (m, 2H, H-9, 9″), 7.64 (dd, 2H, $J = 8.4$ Hz, $J = 2.1$ Hz, H-4, 4″), 7.91 (t, 1H, $J = 8.0$ Hz, H-4′), 8.38 (d, 2H, $J = 7.8$ Hz, H-3′, 5′), 8.40 (d, 2H, $J = 7.8$ Hz, H-3, 3″), 8.51 (s, 2H, H-6, 6″). ESI-MS *m*/*z*: 302, 342 ($[M + H]^+$).

1 Z. Dinev and J. N. Lambert, *Aust. J. Chem.*, 2001, **54**, 625.
2 E. A. Wintner and J. J. Rebek, *Acta Chim. Scand.*, 1996, **50**, 469.
3 A. Terfort and G. von Kiedrowski, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 654.
4 D. H. Lee, J. R. Granja, J. A. Martinez, K. Severin and M. R. Ghadiri, *Nature*, 1996, **382**, 525.
5 G. von Kiedrowski, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 932.
6 D. H. Lee, K. Severin and M. R. Ghadiri, *Curr. Opin. Chem. Biol.*, 1997, **1**, 491.
7 B. G. Bag and G. von Kiedrowski, *Pure Appl. Chem.*, 1996, **68**, 2145.
8 B. Hasenknopf, J. M. Lehn, G. Baum and D. Fenske, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 1397.
9 J. P. Collin, C. Dietrich-Buchecker, P. Gavina, M. C. Jimenez-Molero and J. P. Sauvage, *Acc. Chem. Res.*, 2001, **34**, 477.
10 R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149.
11 U. S. Schubert, G. R. Newkome, A. Goldel, A. Pemp, J. L. Kersten and C. D. Eisenbach, *Heterocycles*, 1998, **48**, 2141.
12 S. S. Wang, *J. Am. Chem. Soc.*, 1973, **95**, 1328.
13 V. Swali and M. Bradley, *Anal. Commun.*, 1997, **34**, 15.
14 G. C. Fu, S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9856.
15 T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.
16 P. Sieber, *Tetrahedron Lett.*, 1987, **28**, 6147.
17 S. Hanessian and F. Xie, *Tetrahedron Lett.*, 1998, **39**, 733.