Direct functionalization of self-assembled nanotubes overcomes unfavorable self-assembling processes[†]

Thi-Thanh-Tam Nguyen, François-Xavier Simon, Marc Schmutz and Philippe J. Mésini*

Received (in Cambridge, UK) 23rd February 2009, Accepted 8th April 2009 First published as an Advance Article on the web 7th May 2009 DOI: 10.1039/b903797g

Diamides containing alkyne and azido were self-assembled into nanotubes and were reacted under their self-assembled state with small molecules by "click chemistry"; the resulting compounds remain self-assembled into new nanotubes that cannot be formed by simple self-assembly of the constituting molecules.

The recent development of carbon nanotubes¹⁻³ shows that many of their applications result not only from their unique shape and electronic properties but also from chemical functionalization of their surface.⁴⁻⁶ This step requires elaborate chemistry due to the difficulty to solubilize or to purify them.⁷ These drawbacks have aroused interest in nanotubes resulting from the self-assembly of small molecules.⁸ These nano-objects are attractive owing to their high purity, ease of formation and high processability. They are formed through non-covalent interactions, such as van der Waals interactions or H-bonds between specific groups.⁹⁻¹³ But the assembling molecules can bear side groups, yielding new functions for applications such as support for 2D crystallization of proteins,^{14,15} for cell growth^{16,17} or chiral recognition.¹⁸ In principle, the possibility of tuning their properties by adding functional groups in the constituting compounds can be easily addressed by synthesis. But very often, the mere introduction of a functional group results in the loss of their self-assembling pattern. For this reason, direct modification of the self-assembled nanotubes remains very rare. The recent development of copper catalyzed cycloaddition of alkyne and azides¹⁹⁻²¹ (CuAAC) allows one to tackle such derivatization. Indeed, this highly specific reaction does not interfere with groups responsible for the self-assembly; then, the introduction of a small group like azide or alkyne in a molecule can be done without changing its self-assembling properties. It has been shown that this reaction can be carried out with supramolecular assemblies like gelator fibrils, and moreover in heterogeneous conditions or in high viscosity media such as gels.²²

We have shown²³ that diamide **1** (Scheme 1) self-assembles in alkanes through H-bonds between the amide groups and π - π stacking between the aromatic parts to form nanotubes with outer diameters of 29 nm and lengths of several micrometres (Fig. 1a). The formation of these tubes results, at the macroscopic level, in the gelification of the solvent for concentrations greater than 0.4 wt%. Usually, introduction of

a bulky or polar group in this compound yields compounds unable to form nanotubes. We have surmised that the small and non-polar alkyne and azide groups would preserve the self-assembling pattern. Therefore, the analogues 2 and 3 bearing, respectively, an alkyne and an azide function, were prepared with good yield at the scale of the gram (see electronic supplementary information[†]) according to methods developed for other analogues.^{24–26} The compounds 2 and 3form gels in cyclohexane for a concentration of 1 wt%. Examination of the gels was performed by TEM after cryofracture of the gels. This technique, first developed in aqueous systems, has been implemented successfully to study self-assembled systems in organic solvents.23,25-27 The micrographs show that 2 and 3 self-assemble into nanotubes (Fig. 1b and c) with diameters of 25.3 \pm 3.6 nm and 27.2 ± 5.0 nm, respectively, and polydisperse lengths of the order of the micrometer.

The new nanotubes of 2 and 3 form in alkanes, thus we were lead to use (PPh₃)₃CuBr as the catalyst,^{28,29} since it is soluble (although only slightly) in those solvents. Nanotubes of 2 were formed in cyclohexane at a concentration of 2 wt%, which resulted in the formation of a gel. A solution containing azidodecane or azidodecanol in excess and the catalyst was layered on top of the gel and allowed to diffuse (Fig. 2A). The diffusion of the catalyst through the gel resulted in staining of the gel into a dark brown color. The reacting solution was removed when the color frontline had reached the bottom of the gel. The top solution was removed and replaced by cyclohexane to remove the excess reagents. The rinsing solution contained the unreacted reagent and small amounts of compounds 2. Acetylacetone (acac) was also added in the rinsing solution in order to extract all remaining copper-containing products of the reaction.

The diffusion of the rinsing solution resulted in the progressive bleaching of the lower phase. After the reaction, the resulting nanotubes could be dissociated in CHCl₃ and analyzed by NMR and HPLC. Compounds **4**, **5** and **6** were synthesized independently in solution (ESI \dagger), and were used as references to measure the yields of each species by HPLC (ESI \dagger). These analyses showed that the CuAAC reaction



Scheme 1 Structure of the self-assembling compounds.

Institut Charles Sadron, CNRS, 23 rue du Loess, BP 84047, 67034 Strasbourg Cedex 2, France. E-mail: mesini@ics.u-strasbg.fr; Fax: 33 (0)388 41 40 99; Tel: 33 (0)388 41 40 70

[†] Electronic supplementary information (ESI) available: Experimental, electron micrograph of gels not treated with acac. See DOI: 10.1039/b903797g



Fig. 1 Freeze fracture TEM of gels of 1 (a), 2 (b) and 3 (c) in cyclohexane (2 wt%).



Fig. 2 (A) Schematic set-up of the reaction. (B) Structure of the compounds formed during the reaction with nanotubes.

between the nanotubes of **2** and azidodecane yielded compound **4** according to Fig. 2, and unreacted **2** in a proportion 4/2 of 67/33 (yield of 4 + 2: 91%). Only small amounts of catalysts phosphines and azidodecane were detected. Similar results were obtained when the nanotubes of **2** were reacted with azidodecanol or when nanotubes of **3** were reacted with undecynol. (5/2: 82/18; 6/3: 72/28). Cryofracture of the gels showed that the tubular shape of the self-assemblies was preserved after the reaction (Fig. 3).

The diameters of the tubes in the gels containing 4, 5 and 6 are the same as those of the starting nanotubes within the uncertainty of the measurements (resp. 24.6 ± 4.1 , 23.6 ± 3.6 , 27.9 ± 4.4 nm). The density of the tubes is the same as in the initial one, which shows that the final compounds 4, 5 or 6



Fig. 3 Freeze fracture-TEM of the gels of nanotubes after reaction; (a) 2 and N_3 - $C_{10}H_{21}$; (b) 2 and N_3 - $C_{10}H_{20}$ -OH; (c) 3 and \equiv - C_9H_{18} -OH.

do not dissolve or segregate from the tubes formed from 2 or 3. When acac is omitted in the rinsing step, the reactions have similar yields, but examination of the resulting suspensions by electron microscopy shows nanoparticles scattered throughout the samples along with the tubes (ESI, Fig. S1 \dagger). Their angular edges and layered structure suggests they are nanocrystallites that are probably particles of copper side-products. The diffusion of the catalyst and the reagent limits the reaction rate therefore we checked if it induces heterogeneities in the resulting gel. The gels were analyzed at different distances from the top. Chromatography measurements showed similar yields close to the top or close to the bottom. Electron microscopy also showed no significant differences between the different spots.

The conversions of the functional groups in solution is between 70 and 89% (ESI \dagger). The same conversion rates in the gels are lower, between 55% and 61%. These lower yields may be explained by the heterogeneous conditions of the reaction or by the possible orientation of part of the reactive groups toward the inner cavity of the tubes where the catalyst diffusion is expected to be reduced.

Pure 4 forms gels for concentrations greater than 0.8 wt%, and the micrographs of these gels show they are composed of nanotubes like in the reacted gel, but with a larger diameter $(31.6 \pm 4.3 \text{ nm})$. There is a gap between the objects resulting from the reaction of tubes of 2 and the ones resulting from the spontaneous self-assembly of 4. The difference is even stronger for compound 5, since it does not form tubes at all. When pure 5 is mixed in cyclohexane and heated, it does not dissolve but melts in a separate phase, and recrystallizes upon cooling. We also checked whether mixtures of 5 and 2 in the same proportions as in the nanotubes after reaction (82/18) can reform the same nanotubes: one observes precipitation of 5, and gelation upon cooling of the supernatant containing 2. The same result was also obtained when the product mixture from the reaction with gel was dissolved in CHCl₃ and tentatively re-assembled in cyclohexane. These observations are summarized on Scheme 2. They indicate that the nanotubes resulting from reactions of tubes by click chemistry, when they



Scheme 2 Summary of the reactions and spontaneous self-assemblies involving compounds 2, 4 and 5. (a) Composition of the tubes: 4/2 67/33. (b) Composition of the tubes 5/2 : 81/18. Nanotubes containing 4 or 5 can be formed only from the reaction with nanotubes.

are disassembled, cannot be re-assembled from the same constituting molecules, and thus are metastable although they are kinetically stable (for several weeks). This behavior can be explained by the fact that the nanotubes have a crystalline array as has been shown by WAXS.²¹

The molecules react by their end groups, but the structure is too rigid to allow the reorganization in different phases or larger nanotubes. When a hydroxyl group is introduced instead of the alkyne, the resulting compound, forms precipitates instead of nanotubes, as **5** does, which suggests that polar groups at the end of the ester chain prevent the formation of the nanotubes.

In conclusion, we have shown that the introduction of azido and alkyne groups into compounds able to self-assemble into nanotubes does not perturb the molecular packing: these analogues form nanotubes that have dimensions comparable to those formed from the parent compounds and that are now functional. They react with azides or alkynes to yield nanotubes with dimensions similar to the starting tubes. This illustrates the high efficiency of the CuAAC even in heterogeneous sol-gel conditions and in an alkane, where the catalyst is sparingly soluble. It is to the best of our knowledge the only example of click reaction in cyclohexane. These new self-assemblies are metastable, but the mild reaction conditions prevent their reorganization toward more stable shapes or mixtures. This approach allows one to obtain highly functionalized nanotubes and opens new avenues to synthesize new functional nanomaterials.

This work was supported by a PhD fellowship from the Ministère de l'Education (F.-X. S.) and by a fellowship from

the Région Alsace (T.-T.-T. N). We thank Dr P. Baxter for fruitful discussions, A. Rameau and C. Foussat for the chromatography experiments, and Dr P. Schultz, IGBMC, Illkirch, for the use of the cryofracturing apparatus.

Notes and references

- 1 S. Iijima, Nature, 1991, 354, 56-58.
- 2 S. Iijima and T. Ichihashi, Nature, 1993, 363, 603-605.
- 3 D. S. Bethune, C. H. Klang, M. S. de Vries, G. Gorman, R. Savoy, J. Vazquez and R. Beyers, *Nature*, 1993, 363, 605–607.
- 4 R. H. Baughman, A. A. Zakhidov and W. A. de Heer, *Science*, 2002, **297**, 787–792.
- 5 I. W. Eugenii Katz, ChemPhysChem, 2004, 5, 1084–1104.
- 6 M. Moniruzzaman and K. I. Winey, *Macromolecules*, 2006, **39**, 5194–5205.
- 7 D. Tasis, N. Tagmatarchis, A. Bianco and M. Prato, *Chem. Rev.*, 2006, **106**, 1105–1136.
- 8 T. Shimizu, M. Masuda and H. Minamikawa, *Chem. Rev.*, 2005, 105, 1401–1443.
- 9 J. P. Hill, W. Jin, A. Kosaka, T. Fukushima, H. Ichihara, T. Shimomura, K. Ito, T. Hashizume, N. Ishii and T. Aida, *Science*, 2004, **304**, 1481–1483.
- 10 P. Terech, A. De Geyer, B. Struth and Y. Talmon, Adv. Mater., 2002, 14, 495–498.
- 11 A. Singh, E. M. Wong and J. M. Schnur, *Langmuir*, 2003, 19, 1888–1898.
- 12 M. Reches and E. Gazit, Science, 2003, 300, 625-627.
- 13 C. Valery, M. Paternostre, B. Robert, T. Gulik-Krzywicki, T. Narayanan, J. C. Dedieu, G. Keller, M. L. Torres, R. Cherif-Cheikh, P. Calvo and F. Artzner, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 10258–10262.
- 14 E. M. Wilson-Kubalek, R. E. Brown, H. Celia and R. A. Milligan, Proc. Natl. Acad. Sci. U. S. A., 1998, 95, 8040–8045.
- 15 P. Ringler, W. Muller, H. Ringsdorf and A. Brisson, *Chem.-Eur.* J., 1997, 3, 620–625.
- 16 J. D. Hartgerink, E. Beniash and S. I. Stupp, Science, 2001, 294, 1684–1688.
- 17 S. Vauthey, S. Santoso, H. Gong, N. Watson and S. Zhang, Proc. Natl. Acad. Sci. U. S. A., 2002, 99, 5355–5360.
- 18 H. Fenniri, B.-L. Deng and A. E. Ribbe, J. Am. Chem. Soc., 2002, 124, 11064–11072.
- 19 H. C. Kolb, M. G. Finn and K. B. Sharpless, Angew. Chem., Int. Ed., 2001, 40, 2004–2021.
- 20 R. Huisgen, in 1,3-Dipolar Cycloaddition Chemistry, ed. A. Padwa, Wiley-Interscience, New York, 1984, vol. 1, pp. 1–176.
- 21 J. F. Lutz, Angew. Chem., Int. Ed., 2007, 46, 1018-1025.
- 22 D. D. Diaz, K. Rajagopal, E. Strable, J. Schneider and M. G. Finn, J. Am. Chem. Soc., 2006, **128**, 6056–6057.
- 23 N. Diaz, F. X. Simon, M. Schmutz, M. Rawiso, G. Decher, J. Jestin and P. J. Mésini, *Angew. Chem.*, *Int. Ed.*, 2005, 44, 3260–3264.
- 24 R. Schmidt, F. B. Adam, M. Michel, M. Schmutz, G. Decher and P. J. Mésini, *Tetrahedron Lett.*, 2003, 44, 3171–3174.
- 25 R. Schmidt, G. Decher and P. J. Mésini, *Tetrahedron Lett.*, 1999, 40, 1677–1680.
- 26 R. Schmidt, M. Schmutz, M. Michel, G. Decher and P. J. Mésini, *Langmuir*, 2002, 18, 5668–5672.
- 27 M. Schmutz and P. J. Mésini, in *Handbook of Cryopreparation Methods for Electron Microscopy*, ed. A. Cavalier, D. Spehner and B. M. Humbel, Francis and Taylor CRC press, New York, 2008.
- 28 P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless and V. V. Fokin, *Angew. Chem.*, *Int. Ed.*, 2004, **43**, 3863.
- 29 S. Binauld, D. Damiron, T. Hamaide, J.-P. Pascault, E. Fleury and E. Drockenmuller, *Chem. Commun.*, 2008, 4138–4140.