Facile synthesis of novel hybrid POSS biomolecules via “Click” reactions

How to cite:

For guidance on citations see FAQs.

© 2017 The Royal Society of Chemistry

Version: Version of Record

Link(s) to article on publisher’s website:
http://dx.doi.org/doi:10.1039/C7RA07915J

Copyright and Moral Rights for the articles on this site are retained by the individual authors and/or other copyright owners. For more information on Open Research Online’s data policy on reuse of materials please consult the policies page.

oro.open.ac.uk
Facile synthesis of novel hybrid POSS biomolecules via “Click” reactions†

Youssef El Aziz,*a Nazia Mehrban,b Peter G. Taylor, Martin A. Birchall,b James Bowen, Alan R. Bassindale,a Mateusz B. Pitakc and Simon J. Colesd,c

A novel alkyne-terminated cubic-octamer POSS was synthesised in high yield (82–90%). The X-ray crystal structure revealed intra- and intermolecular hydrogen bonding between the amide groups of the arms. Hybrid biomaterials were synthesised in nearly quantitative yields via a click reaction with (i) azido-\(N\text{-Fmoc}\)-norleucine and (ii) 3’-azido-3’-deoxythymidine.

The synthesis and click reaction of mono alkynepentaisobutyl POSS were first reported by Müller et al. Müller et al. have used aminopropylpentaisobutyl polyhedral oligomeric silsesquioxane (POSS) to produce mono-alkyne-POSS in three steps and the click coupling occurred between the azido-terminated polystyrenes and alkynepolystyrene to afford mono-, di-, and pentafunctional POSS-containing hybrid polystyrenes as star-shaped telechelic POSS-containing hybrid polymers. Wu et al. have prepared alkynepolymerized-POSS in three steps from allyl-pentaisobutyl substituted-POSS and the product was linked to an azido-functionalized elastomer of polystyrene-\(b\text{-}(\text{ethylene-co-butylene})\text{-}(\text{ styrene})\) (SEB-\(\text{CH}_2\text{N}_3\)) via a click coupling reaction to form a novel hybrid copolymer. These approaches focused mostly on the preparation of a hybrid copolymer based on mono-alkynepentaisobutyl and azido-polystyrene. However, the preparation of octa-alkyne-terminated POSS and their click coupling reactions with azido-biomolecules to produce hybrid biomaterials has not been investigated yet. We believe that this approach will open a wide range of biomedical applications that were not accessible in the past.

Herein we report a novel synthetic approach to hybrid biomaterials based on octa-alkyne-terminated POSS and their reaction with (i) azido-N-Fmoc-norleucine and (ii) 3’-azido-3’-deoxythymidine, using the CuAAC reaction. Our approach

![Octa(3-azidopropyl)POSS](Image)

Fig. 1 Octa(3-azidopropyl)POSS.

Among the most commonly studied scaffolds for developing hybrid biomaterials is polyhedral oligomeric silsesquioxane (POSS). POSS units are symmetrical, three-dimensional cubic molecules, which are unique nanometer-sized hybrid inorganic–organic materials with the formula \((\text{RSiO}_3/2)_8\), known as \(T_8\). POSS contains an inorganic inner siloxane nanocore, with the possibility of chemical functionalisation at each of the eight corners of the cubic unit. POSS units have been used extensively as scaffolds for the development of liquid crystals, biocompatible materials, catalysts and dendrimers and can also be used in cross-linking polymers. Functionalisation of \(T_8\) with different substituents has usually been achieved by hydroxylation, Heck and cross-metathesis reactions.

Copper-catalyzed Azide–Alkyne Cycloaddition (CuAAC), which is a simple method for coupling organic molecules containing azide and alkyne functional groups in high yields and its use in the fields of peptide and protein biomedical and material sciences is accelerating. The click reaction has been used to synthesise POSS biomaterials such as hybrid POSS–PEG hydrogels that support chondrocyte attachment and proliferation. Only one synthetic approach towards peptidyl silsesquioxanes using click chemistry has been reported to date. Focusing on the synthesis of octa(3-azidopropyl)polyhedral oligomeric silsesquioxane POSS-(\(N_3\))$_8$ (Fig. 1) and its reaction with a variety of alkynes.

† The Open University, Faculty of Science, Technology, Engineering & Mathematics, Walton Hall, Milton Keynes, MK7 6AA, UK. E-mail: youssef.elaziz@open.ac.uk; Fax: +44 (0)1908 858 327

‡ University College London, Ear Institute, Brain Sciences, 332 Gray’s Inn Rd, London WC1X 8EE, UK

§ UK National Crystallography Service, Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK

Electronic supplementary information (ESI) available: Detailed experimental procedures, $^1$H, $^{13}$C, $^{29}$Si NMR, IR, MALDI-TOF MS, elemental analysis, and analytical data for all new compounds. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra07915j
presents a particularly versatile route which provides a facile and convenient way to functionalise a cubic silsesquioxane core with biomolecules that are more readily available as their azido derivative than their alkyne derivative.

Compound 2 was prepared in one step from commercially available materials; octa(3-aminopropyl)octasilsesquioxane (1) and 5-hexynoic acid (Scheme 1), in 82–90% yield. Product 2 was isolated and purified by column chromatography, followed by characterisation using standard techniques (see ESI†). The crystal structure determined by X-ray crystallography (Fig. 2) suggests that intra- and inter-molecular hydrogen bonding between the arms were a fundamental driving force for the formation of a well-defined crystal structure.‡

The length of intramolecular nitrogen–hydrogen (N–H) bonds varies between 2.09(3) and 2.12(3) Å, whereas for an intermolecular bond the distance is 1.87(3) Å.

The completion of the cycloaddition reaction was confirmed by MALDI-TOF and the reaction progress was monitored by observing the disappearance of the azide asymmetric stretch at 2093 cm⁻¹ and the triple bond C=C asymmetric stretch of T₈-[propylhex-5ynamide]₈ (2) at 2100 cm⁻¹ by FT-IR spectroscopy together with monitoring the disappearance in the ¹³C-NMR spectrum of the two peaks (89.20 and 76.56 ppm) representing the triple bond of 2.

Compounds 3 and 4 have been analysed and characterised using NMR (¹H, ¹³C and ²⁹Si) spectroscopy, infrared and MALDI-TOF mass spectrometry in positive ion mode with a DHB matrix.

Trastoy et al. have reported an efficient preparation of highly functionalised cubic-octameric POSS frameworks by click chemistry and the highest yield (96%) was obtained with the CuSO₄·H₂O/sodium ascorbate precatalyst system using a biphasic organic solvent/water mixture at room temperature for 24 hours. We have used these reaction conditions for the functionalisation of the octa-alkyne-terminated POSS with azido-N-Fmoc-norleucine and 3₀-azido-3₀-deoxythymidine (Scheme 2).

The MALDI-TOF MS of compound 3 and 4 revealed that the octa-alkyne-terminated POSS has been fully functionalised with azido-N-Fmoc-norleucine for 3 and 3₀-azido-3₀-deoxythymidine for 4. The molecular ion peak of 3 observed at found 4787 Da is attributed to [M + H]+ and 4 observed at 3835.3 Da is attributed to [M + Cu]+.

‡ Crystal data of compound 2: C₇₂H₁₁₂N₈O₂₀Si₈ (M = 1634.41 g mol⁻¹); triclinic, space group P1 (no. 2), a = 9.6202(3) Å, b = 14.1254(3) Å, c = 17.6565(6) Å, α = 71.392(2)°, β = 74.675(3)°, γ = 70.560(2)°, V = 2110.47(12) Å³, Z = 1, T = 100.15 K, μ(Mo Kα) = 0.198 mm⁻¹, Dcalc = 1.286 g cm⁻³, 28211 reflections measured (6.088 ≤ 2θ ≤ 50.054°), 7434 unique (Rint = 0.0375, Rsigma = 0.0368) which were used in all calculations. The final R₁ was 0.0459 (I > 2σ(I)) and wR₂ was 0.1280 (all data).
Conclusions

In this study we have described a novel, efficient method for the synthesis of 3D radially symmetrical biomolecule-POSS hybrids. We have developed a one-step synthesis of 2 from commercially available octakis(3-aminopropyl)octa-silsesquioxane (1) with high yield (82–90%). The X-ray crystal structure shows that compound 2 exhibits plane-to-plane stacking with an intra- and inter-molecular hydrogen bond network. The octa-alkyne-terminated POSS was efficiently and regioselectively octa-functionalised with two azido-R species (where R are Fmoc-Leu and thymidine) by copper(I)-catalysed 1,3-dipolar azide cycloaddition (CuAAC) under biphasic conditions. This led to the synthesis of 3D radially symmetrical biomolecule-POSS hybrids.

Acknowledgements

We thank the EPSRC National Mass Spectrometry Service Centre (NMSSC) at Swansea and MEDAC Ltd. of Brunel University for elemental analysis. We thank the EPSRC National Crystallography Service at the University of Southampton for the collection of the crystallographic data.

Notes and references