

Biomedical

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OBOC Libraries screened with cDNA phage libraries

Kit Lam is probably the main intellectual driving force behind the application of one-bead-one-compound (OBOC) libraries (prepared via split syntheses). Over the years, his work has evolved from using antibodies to directly screen OBOC libraries, to cells that tend to grow around beads that bear a high affinity ligand. Even more recently, he attempted to screen beads using cell lysates, but found identification of proteins that bind to be problematic.

Working with a team of people mostly from UC Davis, US, he has demonstrated a modification that could be transformative: screening OBOC libraries with cDNA phage libraries (*ACS Combinatorial Sci.*, doi: acscombsci.5b00194) (Figure 1).

Their work featured a cDNA expression proteome library that had been 'size-fractionated and normalised' to exclude highly abundant DNA. Basically, they selected beads that strongly bound members of this phage library, and found 91 different supported compounds that bound strongly. Randomly, 19 of the 91 compounds were selected, and resynthesised.

Lam is an oncologist interested in cytotoxic compounds, so he performed MTT assays and found 4 of the 19 were cytotoxic. Phage that bound these particular compounds were enriched, sequenced to identify the protein the phage expressed, and a series of experiments were undertaken to confirm the identity of the binding protein (eg pull-down assays).

Ultimately, they found a mildly cytotoxic compound (IC₅₀ ~30 μM) that binds eukaryotic initiation factor 5B, and is cytotoxic to liver cancer cells with some selectivity over normal fetal hepatocytes.

Fluorescent reporter for ATP binding receptor kinases

Wilson and others from the University of Miami, US, have reported on a fluorescent probe that is turned on

in the ATP binding site of ERBB2 kinase (*Biorg. Med. Chem. Lett.*, 2012, 22, 5532).

Their design (**1**) is based on a fragment (shown in red) known to bind members of the ERBB family, and approved inhibitors like Gefitinib. Thus, the benzpyrimidine core was used as an electron withdrawing group in a push-pull styrene chromophore, which is significantly (23x) less fluorescent outside the ATP binding site of ERBB2 than in it. This probe-inhibitor hybrid suppressed autophosphorylation with a K_i of 3.1 μM. The compound was selective insofar as it was not active on Akt and Src.

A genetic study and multiple sclerosis (MS)

Groups from UBC, Vancouver, Canada, have reported a correlation between a particular form of MS and mutations in a gene that encodes liver X receptor alpha (LXRA) (*Neuron*, doi: b.j.neuron.2016.04.039).

This protein forms dimers with the retinoid X receptors (RXRs) but the mutation negates this association. LXRA forms a subfamily of nuclear receptors that control transcriptional regulation of genes associated with lipid homeostasis, inflammation and innate immunity. These receptors effect cholesterol and this plays key roles in the CNS related to myelination and remyelination; this is significant because MS involves damage to the myelin sheath around axons.

The mutation that the UBC group observed is only found in a small fraction of MS patients, but the authors of this study suggest that

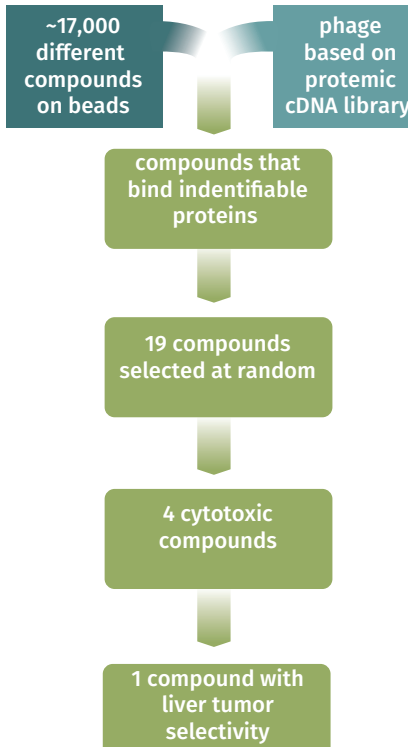
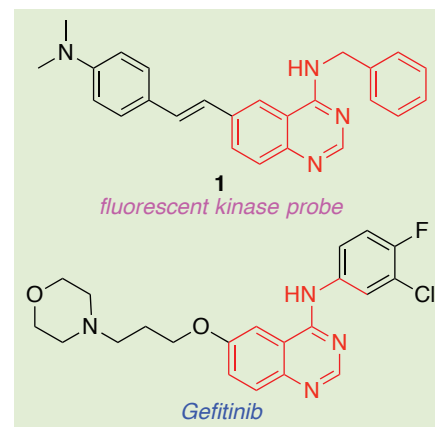


Figure 1 Lam's approach to screening libraries with libraries

decreased levels of mRNA expression associated with LXR signalling in other persons who suffer from the disease, suggests a wider impact.



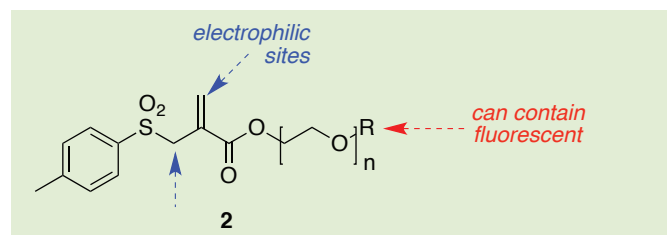
LXR's and RXR's are currently under investigation in the context of other diseases, some of which are neurological, hence it seems that interest in agonists that positively impact the LXR-RXR interactions will increase.

New agent for disulfide rebridging

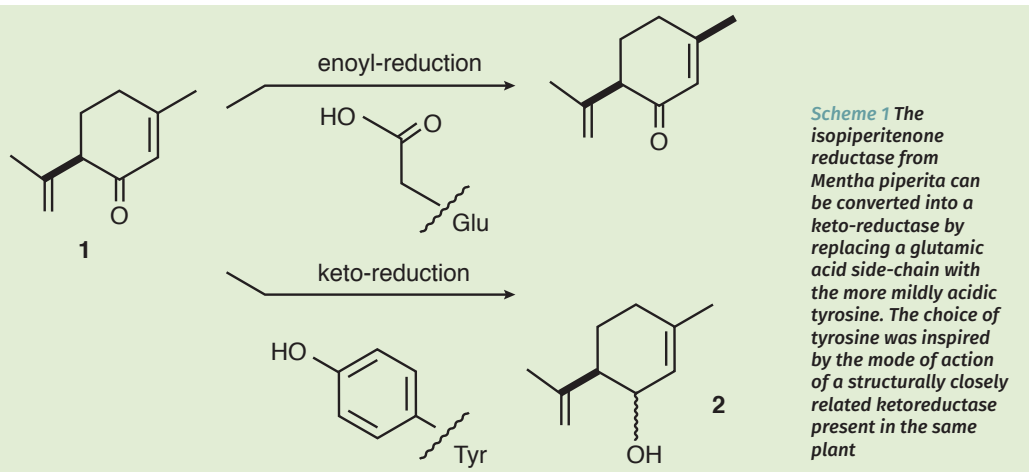
In disulfide rebridging, a reduction liberates two reactive thiolate groups that add to proximal electrophiles on the bridging agent. This process may give a peptide or protein derivative that is more biologically robust, and allow functionalisation by introduction of a peptide on the bridging group.

A new rebridging agent (**2**) has been introduced (Weil *et al.*, *Chem. Sci.* doi: c6sc00005c). This acts via conjugate addition of a thiolate, expulsion of sulfinate by the enolate formed in this process, then a second conjugate addition. Being more hydrophilic than the most commonly used reagent, **2** can be more efficient as the authors proved in a direct comparison.

The authors tested their agent on somatostatin and bovine albumin, and used the method to introduce GFP and lysozyme in aqueous solution.



Organic chemistry



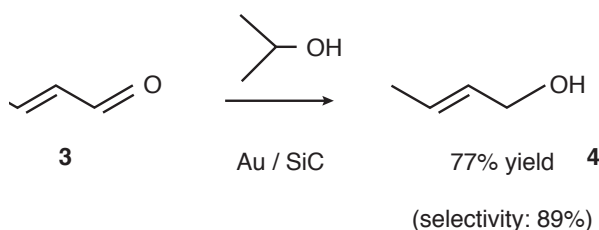
Scheme 1 The isopiperitenone reductase from *Mentha piperita* can be converted into a keto-reductase by replacing a glutamic acid side-chain with the more mildly acidic tyrosine. The choice of tyrosine was inspired by the mode of action of a structurally closely related ketoreductase present in the same plant

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Switch amino acid – switch catalysis

Catalytic activity in enzymes often depends on the chemistry of individual amino acid side-chain functional groups within the complex sequence of peptide bond-linked amino acids that fold up to form the tertiary structure of the protein. Despite the power of genetics to swap one amino acid for another by re-writing the gene sequence, cases where this is used to switch chemical reactivity are rare.

A recent example may prove to be particularly significant if it can be replicated with other ketoreductases



Scheme 2 A Xenon lamp (400 – 800nm) at 1Wcm⁻² promotes the reduction of aldehydes by propan-2-ol/KOH

(A. Lygidakis, V. Karuppiah, R. Hoeven, A. N. Cheallaigh, D. Leys, J. M. Gardiner, H. S. Toogood, N. S. Scrutton; *Angew. Chem. Int. Ed.*, 2016, **55**, 9596).

Replacing tyrosine by glutamate differentiates keto-reduction and enoyl-reduction in two very similar enzymes (menthone:menthol reduc-

tase and isopiperitenone reductase from *Mentha piperita*). For example, the enone of isopiperitenone (1) is reduced to an alcohol (2) if the phenolic side-chain of Tyr244 is replaced by a carboxylic acid (Scheme 1).

Using visible light to drive reactions

Nature is an expert at harvesting energy from visible light, and using it to drive chemical reactions and processes, but does this in an indirect way. By contrast, photochemists conventionally rely in the high energy photons of UV light to do the work.

There are, however, advantages in chemistry as well as biology, in using visible light directly, and photocatalysts that are capable of achieving this offer prospects of environmental benefits. Using light to drive reactions is a clean process with few bi-products, and moving away from the need for high-power UV lamps saves energy.

An example which continues the theme of enone reduction uses SiC-supported gold nanoparticles (Au/SiC NPs), which absorb strongly visible light strongly due to localised surface plasmon resonance effects (C.-H. Hao, X.-N. Guo, Y.-T. Pan, S. Chen, Z.-F. Jiao, H. Yang, X.-Y. Guo; *J. Am. Chem. Soc.*, 2016, **138**, 9361).

A typical example is the reduction of the butenal (3) to produce the allylic alcohol (4) as the main product (saturated aldehydes and alcohols are also formed), but in the case of cinnamaldehyde, 100% conversion and 100% selectivity for ketone reduction is reported.

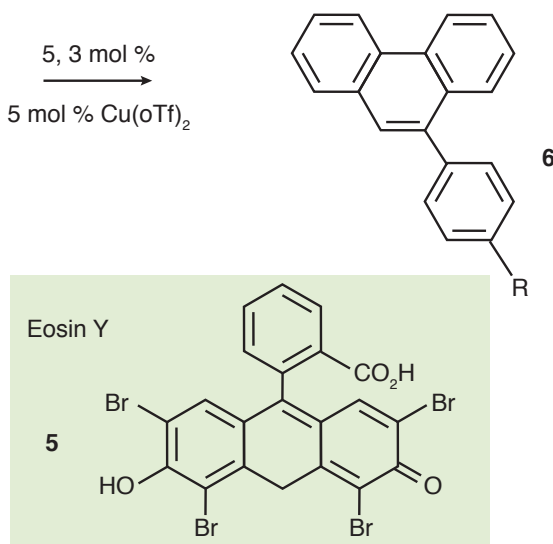
Dual catalysis

Dual catalysis is an increasingly popular topic. Guo's group at Fudan University have now reported an example that combines the photocatalysis of eosin Y (5) with the Lewis acid catalysis of copper(II) triflate (R. Jin, Y. Chen, W. Liu, D. Xu, Y. Li, A. Ding, H. Guo; *Chem. Commun.*, 2016, **52**, 9909).

The result is the capability to effect a rather unusual cyclisation in which an alkyne reacts with an ortho biaryl unit to form a phenanthrene (eg 6, Scheme 3).

In this work, too, with the high-energy alkyne being consumed, and a low-energy aromatic structure being produced, visible light (from a standard 23W light bulb) is again enough to drive the chemistry.

Scheme 3 A range of substituted arylalkynes (R = Me, Et, OMe, OEt, OAc, Cl) have been cyclised in 90–100% yield by the combined action of two different catalysts (box: photoredox catalyst, eosin Y)



Applied chemistry

NIGEL P FREESTONE

University of Northampton, UK

Synthetic leaf

An artificial leaf has been developed that beats photosynthesis at its own game. The device, which is 10 times more efficient than a plant, converts carbon dioxide into a series of liquid fuels (C. Liu, B. C. Colón, M. Ziesack, P. A. Silver, D. G. Nocera; *Science*, 2016, **352**, 1210) (Scheme 1).

Although it's a driving force behind the world's ecosystems, photosynthesis is an inefficient process. Most plants can only convert around 1% of incoming energy into sugars. Artificial photosynthetic cells have tried to exceed this low threshold with limited success, often splitting water with a catalyst, but falling short of creating a viable energy source or fuel.

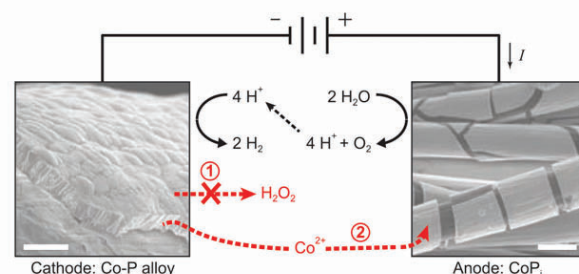
Scientists at Harvard University have created an electrochemical cell that can convert solar energy into isopropanol, isobutanol or isopentanol. Immersing cobalt-phosphorous alloy electrodes in water, the team combined this catalyst with a Gram-negative soil bacterium – *Ralstonia eutropha*. The alloy catalyst drives water-splitting and the bacteria absorb the evolving hydrogen. Once absorbed, carbon dioxide reduction takes place and an alcohol forms.

The researchers found this process was more efficient than plant photosynthesis, with the catalyst-bacteria system capable of efficiencies of up to 10%. They also contend the leaf will usher in an era of chemical production using solar energy.

Light and heat phase flip

Japanese chemists have synthesised a ruthenium-containing ionic liquid, which transforms into a yellow solid coordination polymer when irradiated with UV light. Applying heat reverses the process (Y. Funasako, S. Mori, T. Mochida; *Chem. Commun.*, 2016, **52**, 6277) (Scheme 2).

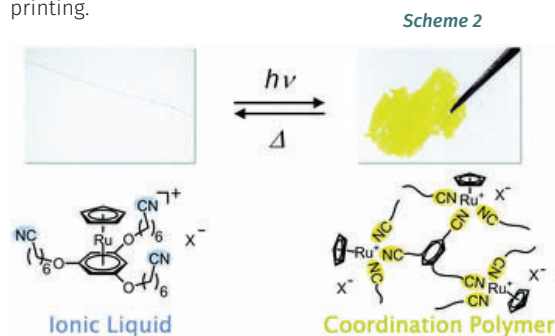
The material's structure changes as the ruthenium coordination bonds break and form with the different external stimuli. Careful design and



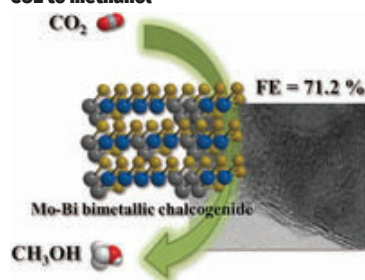
choice of the ligand system means that the system can switch reversibly between the kinetic product – the coordination polymer – and the thermodynamic product – the ionic liquid.

Most photocured materials in industrial processes exploit irreversible transformations. Several other materials reversibly transform upon heat or light stimuli, but often rely on photoisomerisation. In contrast, making and breaking coordination bonds changes this new system's structure, which has potential applications in printed circuit boards, adhesives and 3D printing.

Scheme 1 The water splitting reaction (black) provides bacteria with hydrogen that they convert into alcohols



CO2 to methanol



Methanol is a very useful platform molecule and liquid fuel. Electrocatalytic reduction of CO₂ to methanol is a promising route, which currently suffers from low efficiency

and poor selectivity. Mo-Bi BMC/CP with a Mo:Bi molar ratio of 1:1 is a very efficient and stable electrode for the electrochemical reduction of CO₂ to methanol (X. Sun, Q. Zhu, X. Kang, H. Liu, Q. Qian, Z. Zhang, B. Han; *Angew. Chem. Int. Ed. Engl.*, 2016, **55**, 6771).

When 0.5 M [Bmim]BF₄ in MeCN is used as the electrolyte, the Faradaic efficiency for CO₂ electrochemical reduction to methanol can be as high as 71.2% with a current density of 12.1 mA cm⁻², which is much higher than the values reported up to now (Scheme 3).

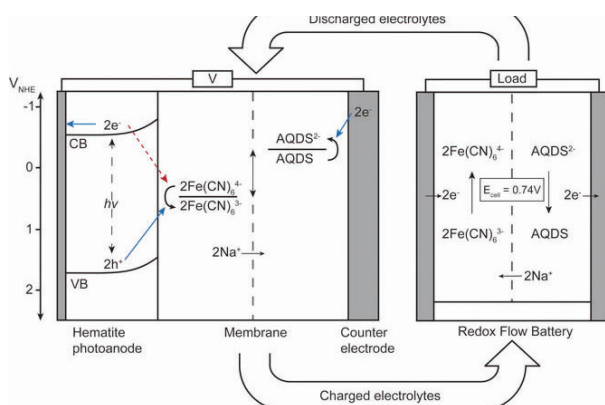
The high electrocatalytic selectivity of the Mo-Bi BMC/CP electrode can be attributed to the synergistic effect between Mo and Bi for producing methanol. The Bi enhances the transformation of CO₂ to CO, and the Mo favours the generation of H₂ and can bind CO. Thus, the CO is bound and can be further hydrogenated to obtain methanol. It is thought that the reaction proceeds with the pathway of CO₂ → CO₂⁻ → CO_{ads} → CHO_{ads} → CH₃O_{ads} → methanol.

Solar battery charging

The intermittent nature of the sunlight and its increasing contribution to electricity generation is fostering energy storage research. Direct solar charging of an auspicious type of redox flow battery could make solar energy directly and efficiently dispatchable. The first solar aqueous alkaline redox flow battery using low cost and environmentally safe materials has been demonstrated (K. Wedege, J. Azevedo, A. Khataee, A. Bentine, A. Mendes; *Angew. Chem. Int. Ed. Engl.*, 2016, **55**, 7132) (Scheme 4).

The photoelectrochemical/redox flow (PEC/RF) cell, with a standard potential of 0.74 V, is built from a hematite photoanode immersed in an aqueous solution of ferrocyanide and NaOH and a graphite felt counter electrode immersed in an aqueous anthraquinone-2,7-disulphonate (AQDS) and NaOH solution separated by a cation conductive Nafion-117 membrane.

Upon illumination of the photoanode, electron-hole pair generation takes place in the hematite and holes move to the hematite surface oxidising ferrocyanide. In the photo-induced redox reactions, the photon energy



Scheme 4 Energy diagram of the PEC/RF cell for solar charging of electrolytes connected to a RF cell for discharge. Desired electron-hole pathways under light exposure are shown with full blue arrows. Undesirable back-electron transfer is shown with red dotted arrow

is converted and stored directly as electrochemical energy. The process produces ferricyanide ($\text{Fe}(\text{CN})_6^{3-}$) and AQDS^{2-} that correspond to charged species in the redox flow battery (RFB) and, when needed, can be converted into electricity in an RF cell.

Electro-chocolate treatment for lower fat

Chocolate is one of the most popular food types and flavours in the world. Unfortunately, at present, chocolate products contain too much fat, leading to obesity. Each mouthful typically contains 40% fat by volume due to the presence of cocoa butter, which gives chocolate its characteristic melt-in-the-mouth quality and texture. Lower-fat alternatives do exist, but many countries do not allow these products to be labelled as chocolate because the cocoa butter is replaced with substitutes.

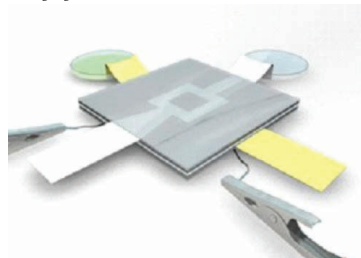
A true reduced-fat chocolate would still contain cocoa butter, but less of it. However, manufacturers have struggled with this because reducing chocolate's fat content increases the viscosity of melted chocolate, clogging up production pipelines. Now, it turns out that applying a small electric field is all that's required to keep it flowing (R. Tao, H. Tang, K. Tawhid-Al-Islam, E. Du, J. Kim; *Proc. Natl. Acad. Sci. USA*, 2016, **113**, 7399).

The fat content of chocolate is related to the basic science of soft matter, especially to the viscosity of liquid suspension and maximally random jammed (MRJ) density. When the concentration of cocoa solid is high, close to the MRJ density, removing a small amount of fat jams the chocolate flow. However, applying unconventional electrorheology to

liquid chocolate with applied field in the flow direction, aggregates the cocoa particles into prolate spheroids in micrometers. This microstructure change breaks the rotational symmetry, reducing liquid chocolate's viscosity along the flow direction, and increases its MRJ density significantly, allowing a 20% reduction in the fat content of chocolate, without impairing its taste.

Scheme 5 Microbial fuel cell. The device allows flow of the streams of *Shewanella Oneidensis* MR-1 (yellow) and the Potassium Ferricyanide (white) into the chambers. Proton exchange membrane is placed between the two chambers to separate the two liquids as well as allow the positively charged ions released in the biocatalytic breakdown of the anolyte to flow from the anode to the cathode

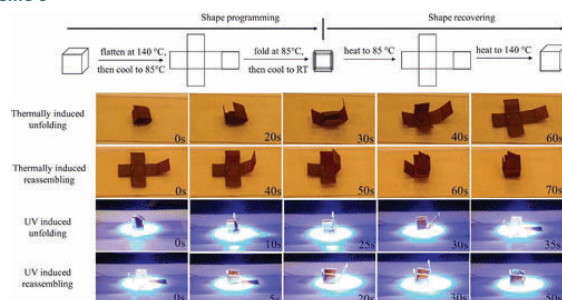
3-D paper-based microbial fuel cell



Microbial fuel cells have gained popularity as a viable, environmentally friendly alternative for the production of energy. However, the challenges in miniaturising the system for application in smaller devices as well as the short duration of operation have limited the application of these devices.

A team of researchers from the Iowa State University, US, have employed capillary motion

Scheme 6



to design a self-pumped paper-based microbial fuel cell operating under continuous flow condition (N. Hashemi, J. M. Lackore, F. Sharifi, P. J. Goodrich, M. L. Winchell; *Technology*, 2016, 4, <http://www.technologythejournal.com/inside-technology/NANOENGINEERING-04.pdf>) (Scheme 5).

A proof-of-concept experiment ran approximately 5 days with no outside power or human interference required for the duration of operation. *Shewanella oneidensis* MR-1 was used to create a maximum current of 52.25 μA in a 52.5 μL paper-based microfluidic device. SEM images of the anode following the experiment showed biofilm formation on the carbon cloth electrode.

The results showed a power density of approximately 25 W/m^2 and proved unique capabilities of the paper-based microbial fuel cells to produce energy for an extended period of time.

Multifunctional smart material

In the US, Washington State University researchers have developed a unique, multifunctional smart material that can change shape from heat or light and assemble and disassemble itself (Y. Li, O. Rios, J. K. Keum, J. Chen, M. R. Kessler; *ACS Appl. Mater. Interfaces*, 2016, **8**, 15750) (Scheme 6).

This is the first time researchers have been able to combine several smart abilities, including shape memory behaviour, light-activated movement and self-healing behaviour, into one material.

This novel material incorporates three functional building blocks (azobenzene chromophores, liquid crystals, and dynamic covalent bonds) into an epoxy-based liquid crystalline network (LCN), in which an azobenzene-based epoxy monomer is polymerised with an aliphatic dicarboxylic acid to create exchangeable ester bonds that can be thermally activated.

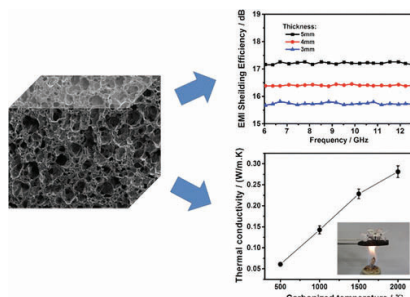
Liquid crystalline networks (LCNs) are versatile functional materials because of the unique properties of the liquid crystalline (LC) molecules, eg, self-organisation, reversible phase transition, and macroscopic orientation under external fields. The coupling between LC molecules and polymer networks allows these remarkable properties to be transferred to the bulk material,

which results in a number of functional LCNs that are thermally responsive and are able to change their shape reversibly upon temperature cycling.

The incorporation of the photoresponsive chromophores, azobenzene, into LCNs allows the material to convert light energy into mechanical work because of the transformation between two geometrically different azobenzene isomers upon light irradiation.

The degree of this transformation can be controlled by selecting an appropriate irradiation wavelength (between the ultraviolet and the blue region), which in turn will induce bending or reorientation of the azobenzene molecules and subsequently result in a macroscopic shape change of the bulk LCN materials, including bending, twisting, and oscillating.

The presence of dynamic ester bonds improves reprocessability of



Scheme 7

the material.

Bread-based foam

Lightweight and stiff carbon foam (CF) with adjustable pore structure are available from flour via a simple fermentation and carbonisation process (Y. Yuan, Y. Ding, C. Wang, F. Xu, Z. Lin, Y. Qin, Y. Li, M. Yang, X. He, Q. Peng, Y. Li; *ACS Applied Materials & Interfaces*, 2016, **8**, 16852) (Scheme 7).

The synthetic approach is based a bread recipe. Flour, yeast and water are mixed, kneaded and the

resulting dough is baked before being carbonised into a hard foam using a tube furnace under argon gas conditions.

The foam's inner pore structure can be tuned by changing the amounts of yeast and water, allowing it to be used for a variety of different applications.

The compressive strength of CF exhibits a high value of 3.6MPa whereas its density is 0.29g/cm³ (compressive modulus can be 121MPa).

The electromagnetic interference (EMI) shielding effectiveness measurements (specific EMI shielding effectiveness can be 78.18 dB·cm³·g⁻¹) indicate that CF can be used as lightweight, effective shielding material.

Unlike ordinary foam structure materials, the low thermal conductivity (lowest is 0.06W/m·K) with high resistance to fire makes CF a good candidate for commercial thermal insulation material.

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