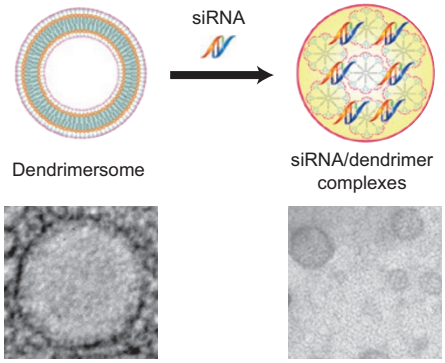
NUCLEIC ACIDS

An interfering delivery

Angew. Chem. Int. Ed. http://dx.doi.org/10.1002/anie.201406764 (2014)



Short interfering RNAs (siRNAs) are double-stranded pieces of RNA that can act as antiviral agents or can be used to reduce the expression of specific genes via RNA interference pathways. The potential for altering complex biological systems makes them interesting therapeutic candidates. However, siRNA is not easily taken up by cells, therefore therapies based on exogenous siRNA require a mechanism to transfer siRNA across the cell membrane. Although a variety of viral, lipid and polymer vectors have been developed, delivery efficiency is often low and can vary depending on the type of cell being targeted.

Ling Peng from Aix-Marseille University, France, and co-workers have developed a nanocarrier for delivering siRNA into cells that is based on an amphiphilic dendrimer. In water the dendrimer self-assembles into vesicle-like dendrimersomes; however, on addition of siRNA the dendrimersomes rearrange into smaller micelle structures. This rearrangement increases the positively charged surface area of the micelle and thereby increases the potential for stabilizing interactions between the dendrimer and negatively charged siRNA. These interactions induce the micelles and siRNA to condense and form colloidal nanoparticles. Computational studies confirm the adaptive rearrangement and assembly mechanism, and initial experiments established that the nanoparticles could protect the siRNA from degradation and were rapidly taken up by cells.

Next, the team tested the efficacy of the nanoparticles for releasing siRNA inside the cell. Experiments with cancer cell lines showed that siRNA could be effectively delivered, and that the production of both messenger RNA and protein targets could be reduced. Further experiments showed that siRNA could also be delivered into both stem cells and primary cells. In a final demonstration, the team showed that the siRNA/dendrimer nanoparticles could reduce messenger RNA and protein expression levels in a prostate cancer mouse model. This led to the effective inhibition of tumour growth without discernible toxicity. *RJ*

ASYMMETRIC CATALYSIS

Not so boring boron

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Multicomponent synthesis — the coupling of multiple reagents in one pot — is an attractive option for synthetic chemists when the creation of structurally complex target compounds in meaningful quantities is difficult via typical linear chemical transformations. Although there have

CLICK CHEMISTRY

Two-faced copper

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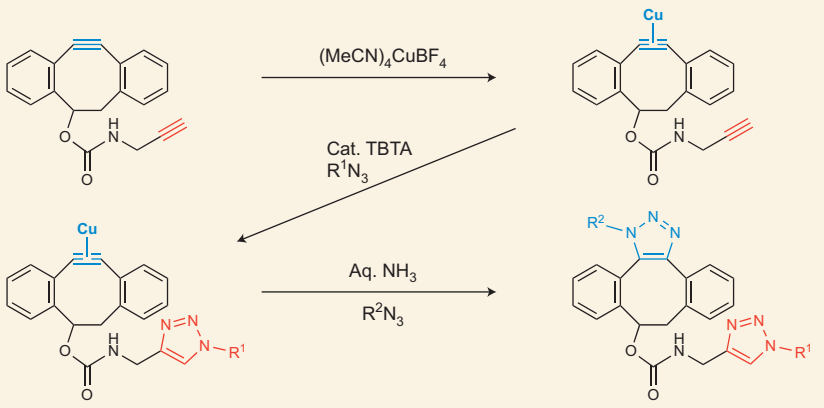
The very high conversions reached by 'click' reactions under mild conditions make them very popular for modular syntheses — and none more so than the copper-catalysed azide–alkyne cycloaddition (CuAAC). To avoid the use of a copper catalyst, it has also been shown that cyclooctyn substrates can be used in a strain-promoted azide–alkyne cycloaddition (SPAAC) reaction that is often exploited for bioorthogonal labelling. However, if a molecule contains both a cyclooctyne and a terminal alkyne, any azide added for a cycloaddition will be swiftly mopped up by the cyclooctyne — and protecting groups for cyclooctynes are scarce.

Now, Suguru Yoshida and Takamitsu Hosoya, leading a team from Tokyo Medical and Dental University and the Tokyo Institute of Technology, have exploited a copper salt to both protect a cyclooctyne, and then catalyse the CuAAC reaction on a terminal alkyne in the same molecule. Yoshida, Hosoya and co-workers screened a variety of coinage metal salts, and found that addition of a slight excess of $(MeCN)_4CuBF_4$ quantitatively formed an isolable octyne–Cu complex



that was unreactive towards free azides. The Cu–alkyne complex could be disrupted by the addition of aqueous ammonia, regenerating the cyclooctyne and making it available for strain-promoted azide–alkyne cycloaddition.

Using copper as both a protecting group and catalyst, a CuAAC reaction followed by a SPAAC reaction were carried out on a single molecule in a one-pot, three-step process. An excess of copper salt was used — one equivalent for protection and the remaining pre-dissolved for the CuAAC step — after which a copper-binding ligand suitable for CuAAC catalysis was added with an excess of azide in order to react with a terminal alkyne on the same molecule. Addition of aqueous ammonia unmasked the cyclooctyne, which reacted immediately with the remaining azide. It was also shown that two different azides could be used in the CuAAC and SPAAC reaction steps. The combined protection–reaction strategy opens the door for modular click syntheses of cyclooctyne-containing compounds. *CH*