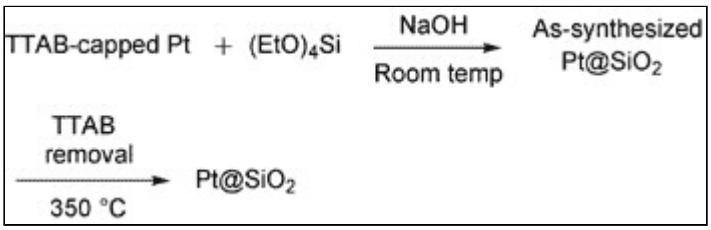
Noteworthy Chemistry

March 2, 2009

Thermally stable platinum core–mesoporous silica shell nanocatalysts can be used for high-temperature reactions. Colloidal nanoparticles show high catalytic activity and selectivity, but they often aggregate and deactivate easily. Organic capping agents, such as polymers and surfactants, can prevent the aggregation of nanoparticles in solution; but organic-agent–capped nanoparticles cannot be used in high-temperature catalytic reactions.



G. A. Samorjai and co-workers at the University of California, Berkeley, and Lawrence Berkeley National Laboratory report a new method for synthesizing platinum core–mesoporous silica shell ($Pt@mSiO_2$) nanocatalysts that are stable at high temperatures. The $Pt@mSiO_2$ nanoparticles are prepared in three steps: synthesis of platinum nanoparticles using a tetradecyltrimethylammonum bromide (TTAB) capping agent; polymerizing $(EtO)_4Si$ around the TTAB-capped platinum cores; and removing TTAB by calcination.

The $Pt@mSiO_2$ particles consist of 14-nm-diam platinum cores and 17-nm-thick mesoporous silica shells. The $Pt@mSiO_2$ nanoparticle catalysts exhibit catalytic activity similar to TTAB-capped platinum nanoparticles for ethylene hydrogenation and CO oxidation. (*Nat. Mater.* **2009,** *8,* 126–131; George Xiu Song Zhao)

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Control drug release through supramolecular grafting in copolymers. J. Qian and F. Wu* at the Chinese Academy of Sciences (Beijing) probed vesicle formation of pH-sensitive supramolecular graft copolymers (SGPs) and their potential as drug delivery vehicles. They developed two families of SGPs based on ionic associations: hydrophobic main-chain poly(4-vinylpyridine) (PVPy) with hydrophilic carboxylic acid–capped graft poly(*N*-vinylpyrrolidone) (PNVP-CO_2H) and hydrophobic main-chain poly(acrylamidobenzoic acid) (PABA) with hydrophilic PNVP.

Stable vesicles (250–300 nm diam) of PVPy–PNVP-CO_2H (4:1 mass ratio) in DMF are formed when deionized water (65.1 vol%) is added. PABA–PNVP (3:1 mass ratio) vesicular aggregates (~300 nm) are obtained in DMSO–deionized water (33.3 vol%). In both systems, adding salt (0.025 M NaCl) prevents the assembly of stable vesicles as a result of shielding of ionic interactions in the SGP precursor.

The authors note that the vesicular size of both SGPs can be controlled via the mass ratio (i.e., tuning the

grafting density). For example, increasing the mass ratio from 2:1 to 5:1 results in diameter increase from 180 to 480 nm in the PVPy–PNVP-CO_2H SGP system. The reversibility of vesicle formation and the deformation of the vesicular structure were explored by varying pH. As an example, the PABA–PNVP vesicles are deformed under basic conditions (pH >7.8).

The authors show that reversibility of the SGP-based vesicle systems is not achieved by adjusting pH because of the ionic character and specific pathway of vesicle assembly. By exploiting the pH sensitivity of the SGP-based vesicle, variations in drug-release profiles can be obtained. In the PVPy–PNVP-CO_2H vesicle, complete release of sunset yellow is achieved within 8 min at pH 4.0, compared with only a 5% release in >24 h at pH 5.0. Similar results are observed with increasing basicity for the PABA–PNVP vesicles. This supramolecular approach offers structural control and release tunability through variations in pH and grafting ratio. (*Chem. Mater.* **2009,** *21,* **758–762**; **LaShanda Korley**)

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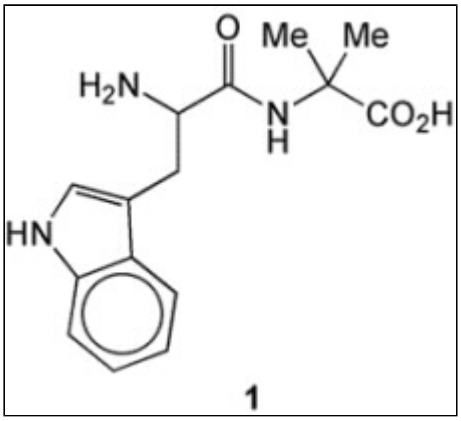
Alzheimer's disease responds to small-molecule therapy in mouse models. Early investigations into the mechanism of this devastating disease involved the accumulation of β-amyloid polypeptide (Aβ) plaques, but more recent research implicates soluble Aβ oligomers as the major toxic species. E. Gazit and coauthors at Tel Aviv University (Israel) and Hebrew University of Jerusalem developed a strategy that blocks the oligomerization of these soluble peptides. Specifically, their approach is based on targeting aromatic recognition modules together with a unique C^{α}-methylation β-breakage strategy.

In the authors' experimental method, 40 small molecules that target aromatic recognition interfaces and contain β-breaker elements were analyzed. This initial screening verified that the desired peptide inhibitors must contain the β-breaker in the C-terminus and must contain metabolically stable D-amino acids. Screening also identified a preference for α-aminoisobutyric acid to optimize β-breaking potential. The results of this initial phase identified a small dipeptide (**1**) that combines an indole (a potent aromatic Aβ binder) and α-aminoisobutyric acid.



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Compound **1** is expected to overcome several limitations of earlier peptide-based amyloid inhibitors by combining the molecular weight of an ideal small-molecule drug with high serum stability, oral bioavailability, low toxicity, high solubility, and stability in solution. The authors used a variety of diagnostic tests to validate these properties, followed by in vivo studies in transgenic mice (mice modified by introducing foreign DNA at the fertilized oocyte or embryonic stage). The transgenic mice—designed to overexpress human amyloid precursor protein—were treated with **1** for 120 days and carefully observed for changes in plaque load and learning abilities.

The results indicate significant differences between treated and control groups; the behavior of treated mice improved markedly. More importantly, treatment with **1** led to a notable decrease in Aβ concentration compared with control animals. Also, the average size of plaque cores in the cortex of the treated animals was significantly smaller than in the control group.

The ability of **1** to restore cognitive performance in the transgenic mice suggests that targeting early oligomers may be a useful method for treating of Alzheimer's disease. (*Angew. Chem., Int. Ed*. **2009,** *48*, **1981–1986**; **W. Jerry Patterson**)

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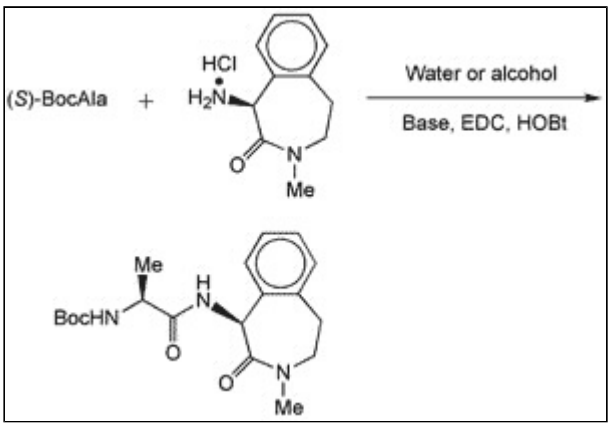
Here's a practical way to couple peptides in water or ethanol. The peptide coupling reaction is well established in organic chemistry for preparing natural products and pharmaceutically active compounds. Several methods have been developed; in one, the activating agent *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC) and the catalyst 1-hydroxybenzotriazole (HOBt) usually give high yields, conserve the optical purity of the reagents, and permit easy workup without detectable amounts of water-insoluble byproducts. However, this coupling reaction usually requires a hazardous low–dielectric constant solvent such as $CHCl_3$ or CH_2Cl_2 to stabilize the reactive species.

During the development of a process that requires two peptide couplings, Y. J. Pu and co-workers at Eli Lilly (Indianapolis) explored several factors that affect EDC–HOBt–mediated coupling in aqueous or ethanolic media. Their model reaction was the coupling of (*S*)-BocAla and an amine (see figure); Boc is *tert*-butoxycarbonyl.



The researchers found the following:

- The addition order had no influence on reaction yield.
- Peptide coupling was slower in water than in EtOH, mostly because the reaction mixture becomes heterogeneous in water.
- The products from reactions conducted in EtOH can be crystallized when water is added.
- Excellent yields were obtained with 5 mol% HOBt, and no residual HOBt was found after workup.
- Other optimal conditions were *N*-methylmorpholine as base, EtOH as solvent, and 1.2 equiv EDC.
- EtOH- and water-mediated processes are both suitable for scale-up.

This method was expanded to several amines and carboxylic acids, including some possessing aliphatic or aromatic hydroxyl groups. (*Org. Process Res. Dev.* **2009,** *13,* Article ASAP DOI: **10.1021/op800240d**; **José C. Barros**)

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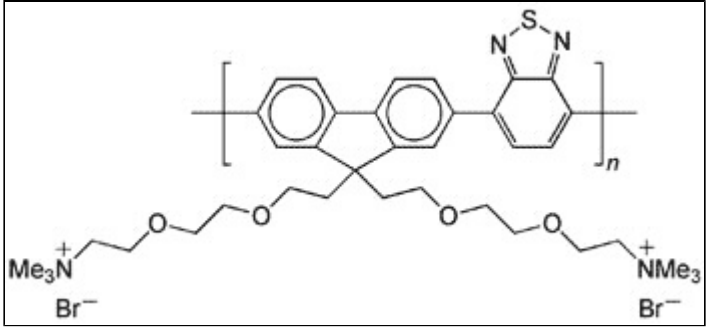
Aggregation-enhanced emission enables conjugated polyelectrolytes to work as turn-on biosensors. Many fluorescent biosensors based on conjugated polyelectrolytes (CPEs) have been developed; most of them work by a fluorescence-quenching or turn-off mechanism. However, there are few examples of CPE-based fluorescent turn-on biosensors. Because a turn-on biosensor has the advantage of reduced false–positive signals compared with its turn-off counterpart, it is highly desirable to develop new CPEs that allow direct fluorescence turn-on biosensing.

K.-Y. Pu and B. Liu* at the National University of Singapore developed such a light-up biosensor system. They designed and synthesized cationic poly(fluorene-*alt*-benzothiadiazole)s with various pendant groups; an example (**1**) is shown in the figure. The polymer emits weakly in the aqueous solution because of charge transfer in its excited state. The polymer chain carries numerous cationic pendant groups and readily forms a complex with heparin, which has the highest negative charge density among known biomolecules. The bioconjugation induces the polymer chain to aggregate in the aqueous buffer and the aggregation dramatically enhances the polymer's emission.



Aqueous solutions of **1** are beneficial to the sensitivity and contrast of the heparin turn-on sensor because of its low background emission. The strong complex of **1** with heparin provides a substantially larger fluorescence increase in the presence of heparin relative to that in the presence of hyaluronic acid, making it possible to discriminate between the two biomolecules. The biosensor permits heparin quantitation with a calibration range that covers all therapeutic dosing levels (0.2–8 units/mL). (*Adv. Funct. Mater.* **2009,** *19,* **277–284**; **Ben Zhong Tang**)

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Controlled synthesis produces thermoresponsive electrospun fibers. G. D. Fu and coauthors at Southeast University (Jiangsu, China), Donghua University (Shanghai), and Suzhou Institute of Sichuan University (Jiangsu) designed responsive, stable electrospun fibers for a range of biotechnology applications. They used reversible addition–fragmentation chain-transfer polymerization to generate poly(4-vinylbenzyl chloride)-*b*-poly(glycidyl methacrylate) (PVBC-*b*-PGMA).

Solutions of PVBC-*b*-PGMA in tetrahydrofuran were electrospun into uniform nanofibers with diameters between 400 nm and 1.5 μm, depending upon the concentration of the spinning solution and block copolymer molecular weight. A reduction in solution concentration resulted in smaller diameter fibers at a given molecular weight. By reacting the PVBC-*b*-PGMA electrospun fibers with NaN_3 in a DMF–H_2O mixture, the nanofibers were stabilized (i.e., cross-linked) and surface-functionalized with azido groups for subsequent "click chemistry".

Alkyne-terminated poly(*N*-isopropylacrylamide) ($PNIPAM_{AT}$) (8.3 kDa) was synthesized by using atom-transfer radical polymerization and grafted to the PVBC-*b*-PGMA nanofibers via the azido units. The thermoresponsiveness of the PVBC-*b*-PGMA-*g*-PNIPAM is regulated by the critical solution temperature (CST, 32 °C), which is dominated by the hydrogen-bonding character of the PNIPAM brushes. Using water contact angle measurements, the authors determined that the $PVBC_{74}$-*b*-$PGMA_{46}$-*g*-$PNIPAM_{73}$ nanofiber was hydrophobic above CST (45 °C) and hydrophilic below CST (20 °C). The reversibility of the surface responsiveness between 20 and 45 °C was also demonstrated for two cycles. (*ACS Appl. Mater. Interfaces* **2009,** *1,* **239–243**; **LaShanda Korley**)

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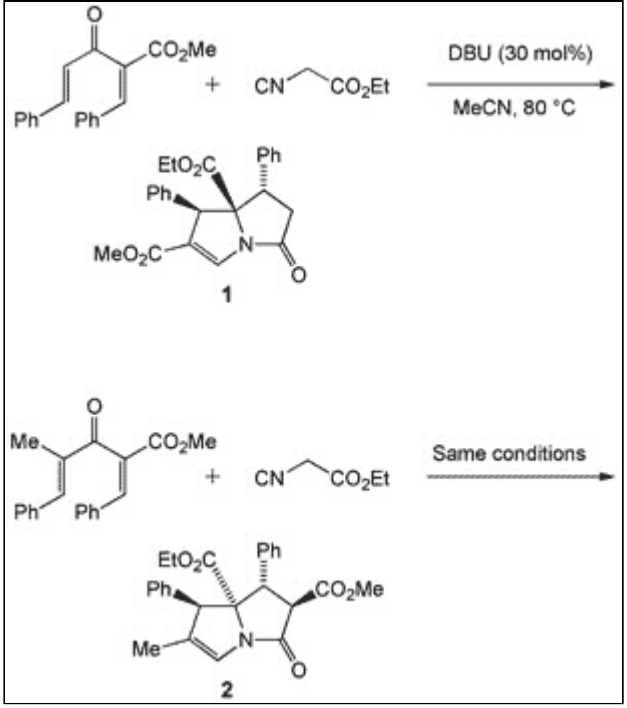
Stereoselectively synthesize pyrrolizidines in one step. Bioactive pyrrolizidine alkaloids are widely observed in plants and insects and serve important functions in biological transformations. Earlier syntheses of the pyrrolizidine skeleton typically involved adding a second five-membered ring to a preformed pyrrolidine to create the desired azabicyclic scaffold. Adding to the complexity of these compounds is the presence of as many as four adjacent stereocenters.



X. Xu, Q. Liu, and co-workers at Northeast Normal University (Changchun, China) developed a remarkable one-pot synthesis of the pyrrolizidine framework in which the multiple stereocenters are created simultaneously. The reactants for this procedure are acyclic 1,4-dien-3-ones and ethyl isocyanoacetate; the reaction is promoted by the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Depending on the substituents on the dienones, the resulting pyrrolizidines contain three or four adjacent stereocenters, as illustrated by structures **1** and **2**, respectively.

Pyrrolizidines such as **1** are produced in high yields and, surprisingly, no diastereomers are formed. More highly substituted dienone reactants result in products such as **2**, with four adjacent stereocenters. In this case, one C–N bond and three C–C bonds are formed in a regio- and diastereoselective manner. The authors summarize the mechanism of this synthetic process as a tandem double-Michael addition–cyclization–1,3-acyl migration. (*Angew. Chem., Int. Ed*. **2009,** *48,* Early View DOI: **10.1002/anie.200805703**; **W. Jerry Patterson**)

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