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Noteworthy Chemistry

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- Consider all factors and interactions when you optimize with DoE
- Make polyacetylene liquid-crystalline and light-emitting
- Actuation behavior: It's all in the direction
- Enhanced optical properties of regioregular poly(*p*-phenylenevinylene)s
- This tubular carbon has superior electrochemical capacitive activity
- Copper promotes meta-selective arylation
- Optimize a three-solvent crystallization system to avoid oiling out

Consider all factors and interactions when you optimize with DoE. R. Hanselman and coauthors at Rib-X Pharmaceuticals (New Haven, CT) and ScinoPharm Taiwan (Shan-Hua) identified a new dimeric impurity in early scale-up batches of delafloxicin, a 6-fluoroquinolone antibiotic that is undergoing phase II clinical trials. They undertook a design of experiments (DoE) study of the effect of several parameters in a chlorination step on the level of the impurity. They initially studied seven parameters, but reaction time was not one of them.

Higher amounts of chlorinating agent (*N*-chlorosuccinimide, NCS), lower temperature, faster addition rate of NCS, and dry solvents had the most beneficial effects on suppressing the amount of the impurity. Longer reaction times also led to larger quantities of the impurity under "standard" conditions, and this caused concerns about the turnaround time for in-process checks. Reaction time, however, has a minimal effect on impurity levels when another variable, H_2SO_4 charge, is lowered from 3.5 to 1%. (*Org. Process Res. Dev.* **2009,** *13,* 54–59; **Will Watson**)

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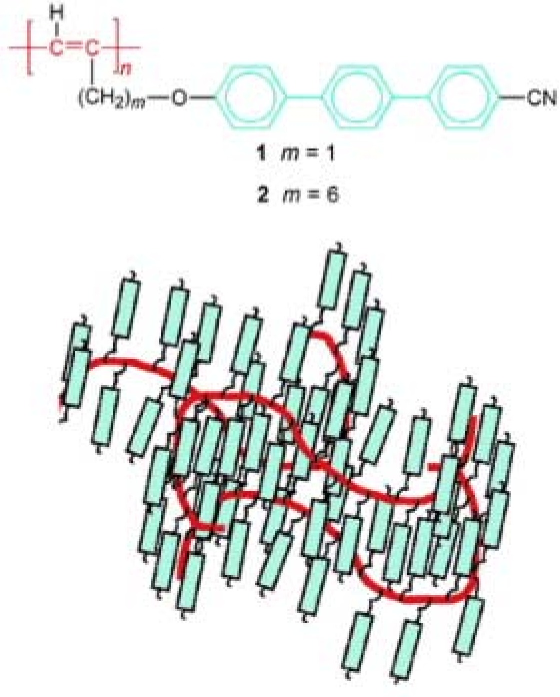

Use molecular engineering to make polyacetylene liquid-crystalline and light-emitting. Polyacetylene is an archetypal conjugated polymer that exhibits metallic conductivity when doped. The polymer is neither mesomorphic nor luminescent. Through judicious structural design, Y. Chen, L. Chen, and co-workers at Nanchang University (China) gave this polymer liquid crystallinity and light emissivity.

The researchers synthesized two terphenyl-containing poly(1-alkyne)s with different lengths of alkyl spacers ($m = 1$ or 6). Whereas polymer **1** with a short spacer is nonmesomorphic and weakly luminescent, polymer **2** with a long spacer shows nematic mesomorphism and emits strong deep-blue light. The long, flexible spacer helps the terphenyl pendants decouple from the polyene backbone, allowing them to act as mesogens and luminophores without interference from the backbone. (*Macromolecules* **2009,** *42,* **1454–1461**; **Ben Zhong Tang**)

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Actuation behavior: It's all in the direction. J. K. Park and R. B. Moore* at Virginia Polytechnic Institute and State University (Blacksburg) probed the nanostructured morphology and actuation phenomena of oriented ionic polymer–metal composites (IMPCs). They uniaxially stretched Nafion membranes (neutralized by ion exchange with Bu_4NOH) to a draw ratio of 2:1. Compared with the isotropic scattering of the as-extruded Nafion membrane, the Bu_4N^+-form oriented membranes exhibit a highly anisotropic scattering pattern along the equator with streaking indicative of fibrillar morphology resulting from chain alignment in the stretch direction.

Investigation of the actuation behavior of IMPCs (made with platinum nanoparticles) of the oriented Nafion membranes showed an anisotropic bending actuation compared with the unoriented IMPCs. Whereas higher bending amplitudes have been reported in the direction perpendicular to orientation, the authors observed a resistance to bending actuation parallel to the stretch direction. This actuation anisotropy is a function of field strength and is well resolved at a strength of 15 V/mm.

The authors note that the actuation response at 45° to the stretch direction is a twisting mode. They explored the mechanism for actuation and report that the actuation driving force must exceed the intrinsic stiffness of the material. They determined the role of orientation by measuring the bending modulus of the oriented, ionic material in the dry (Bu_4N^+–Nafion membrane) and hydrated (H^+–IMPC) states. Because of plasticization by water, the bending modulus of the hydrated IMPC is lower than that of the dry membrane.

Additional studies indicated anisotropy in bending stiffness and swelling, confirming that orientation and microstructure are primary factors in the observed actuation phenomena. The authors show that the platinum nanoparticles within the electrode layer are not affected by uniaxial orientation and are therefore not relevant to the anisotropic actuation. (*ACS Applied Materials & Interfaces* **2009,** *1,* **697–702**; **LaShanda Korley**)

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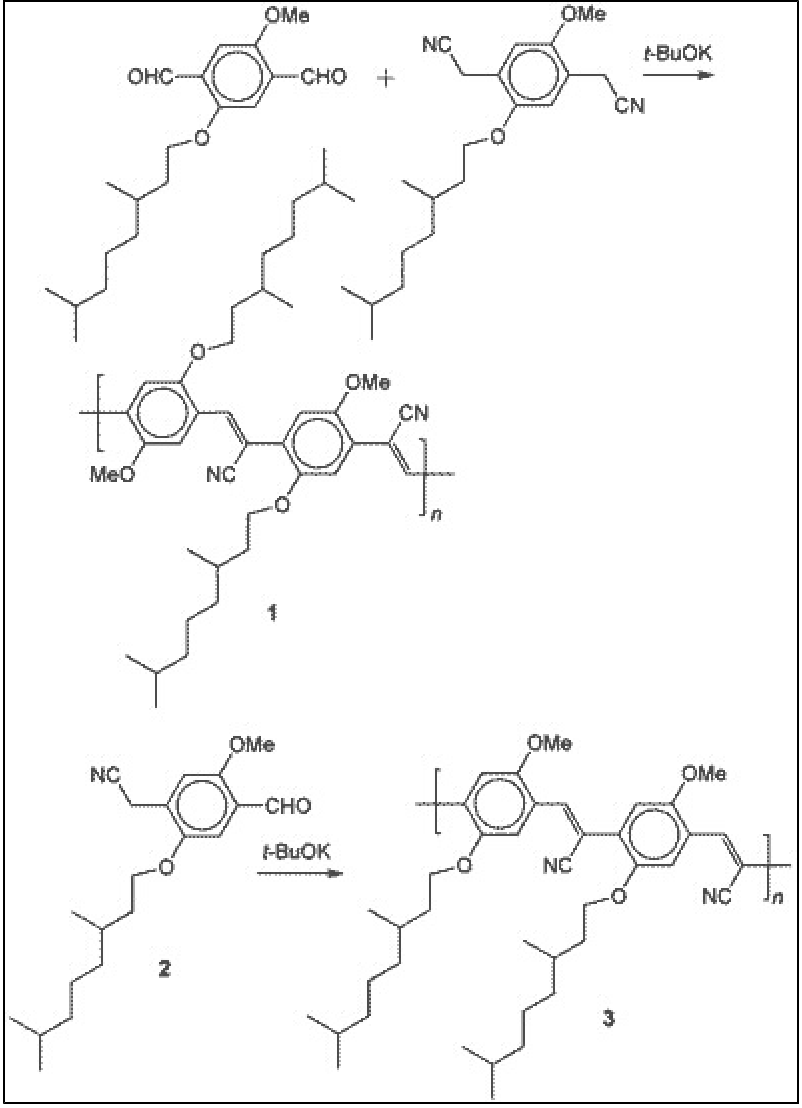
Regioregular poly(*p*-phenylenevinylene)s show enhanced optical properties. Dialkoxy-substituted poly(*p*-phenylenevinylene) (PPV) derivatives with cyano groups on the vinylene units have been studied for use in organic electronic devices. The electron-withdrawing cyano groups enhance the ability of these polymers to accept and transport electrons.

S. Sato, K. Tajima*, and K. Hashimoto* at the University of Tokyo and the Japan Science and Technology Agency (Tokyo) reasoned that the regioregularity of these conjugated polymers should be important in improving intra- and intermolecular ordering and should significantly affect the charge mobility in the resulting polymer films. Conventional regiorandom cyano-modified PPVs (**1**) are typically prepared by alternating polycondensation of dialdehyde and dinitrile monomers. The lack of selectivity in this coupling technique results in a regiorandom configuration of the alkoxy group substitution. This method also creates two nonequivalent phenylene units, making the configuration even more structurally complex.



The authors developed a synthesis of a single monomer (**2**) that contains aldehyde and nitrile groups. This process forces the resulting polycondensation to proceed only in a head-to-tail manner to form completely regioregular CN-PPVs (**3**).

Monomer **2** is produced in a six-step synthesis that begins with readily available *p*-methoxyphenol. Polymer **3** is then prepared by the Knoevenagel polycondensation of **2**. Its regioregularity was confirmed by its ^{1}H NMR spectrum, which showed only a single peak for **3** for the methoxy group, indicating a highly uniform environment.

The authors prepared test films of polymers **1** and **3** by spin-coating from hot chlorobenzene and compared the films' optical properties. Films of **3** showed a more drastically red-shifted absorption than those of **1**, which suggests an elongated conjugated path or enhanced π–π stacking of chains of **3** because of higher structural order. Test devices built from **1** and **3** showed that electron mobility of **3** in the film state was improved by ~30-fold compared with that of **1.**

The effect of regioregularity on electron mobility should lead to the design of new n-type polymer semiconductors. Additional features, including the high electron acceptability and lower band gap of polymer **3**, suggest its potential for device applications. (*Macromolecules* **2009,** *42*, 1785–1788; **W. Jerry Patterson**)

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This tubular carbon has superior electrochemical capacitive activity. Supercapacitors are energy storage devices that function by storing and releasing charges at the interface of electrode and electrolyte. The electrode plays a vital role in supercapacitors. Researchers at Max Planck Institute for Polymer Research and Johannes Gutenberg University (Mainz, Germany); Nanjing University of Aeronautics and Astronautics (China); and the National Center for Nanoscience and Technology of China (Beijing) report an advance in electrode materials.

L. Zhi, K. Müllen, and coauthors show that 1-D mesoporous nanocarbons prepared by the thermolysis of alkylsubstituted hyperbranched polyphenylene impregnated into the channels of an anodic aluminum oxide (AAO) template display superior electrochemical capacitive activity. Depending on thermolysis temperature, carbons with bicontinuous porous structures can be obtained with Brunauer–Emmett–Teller surface area as high as 1140 m^2/g. The cleavage of alkyl chains forms nanoporous walls.

The rectangular shape of cyclic voltammogram curves at different scan rates show the reversible capacitive characteristic of the mesoporous carbons. The specific capacitance C_g can be estimated by the equation $C_g = i/m\ dt/dV$, where i is the applied current and m is the electrode mass. The specific capacitances of the as-prepared carbons are estimated to be 304, 285, 270, 267, and 243 F/g at sweep rates of 5, 10, 25, 50, and 100 mV/s, respectively. The authors believe that the key to the capacitive activity is the tubular structure with bicontinuous porous walls. (*Chem. Commun.* **2009,** 809–811; George Xiu Song Zhao)

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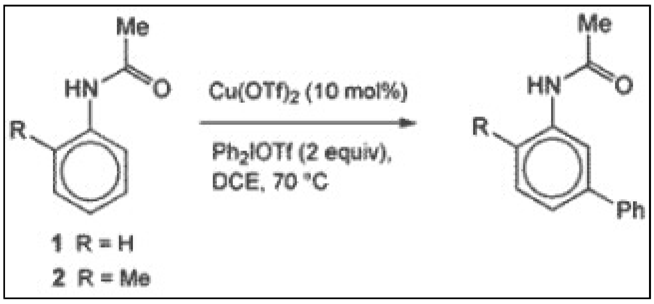
Copper promotes meta-selective arylation. Electron-donating substituents on a benzene ring direct electrophiles to the ortho and para positions, whereas electron-withdrawing groups direct then to the meta position. This pattern affects synthesis strategies; access to the isomer that is “forbidden” by the rules often requires several functional group manipulations.

R. J. Phipps and M. J. Gaunt* at the University of Cambridge (UK) developed a new reactivity concept that selectively places phenyl electrophiles meta to electron-donating substituents in the arylation of indoles and anilides. They used a Cu(II) catalyst to reverse the reactivity of conventional Pd(II) catalysts.

For example, treating acetanilide (**1**) with Ph$_2$IOTf in presence of Cu(OTf)$_2$ produces the meta isomer with no detectable ortho or para arylation. (Tf is trifluoromethanesulfonyl; DCE is 1,2-dichloroethane.) The yield from this reaction is a low 14%, but placing a methyl group ortho to the anilide (**2**) increases the yield to 43%, again with 100% meta selectivity. The authors note that no ring arylation occurs if an amide group is not present.



The authors propose a mechanistic pathway for the reaction that involves highly electrophilic Cu(III)–aryl species that activate the aromatic ring to permit an anti-oxycupration of the carbonyl group of the acetamide across the 2- and 3-positions on the benzene ring. The de-aromatizing process places the Cu(III)–aryl species at the meta position, and a rearomatizing deprotonation is followed by reductive elimination to give the meta product.

The method was expanded to several anilides, and the authors showed that benzamides and pivanilides give especially good yields. Halogen groups are tolerated, indicating that this Cu(II)-catalyzed method can complement Pd(II) catalysis. The process is experimentally simple, proceeds under mild conditions, uses readily available copper catalysts, and gives arylated products that are difficult to obtain by other protocols. (*Science* **2009,** *323,* 1593–1597; José C. Barros)

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Optimize a three-solvent crystallization system to avoid oiling out. G. A. Weisenberger and co-workers at Pfizer (Groton, CT, and Chesterfield, MO) found that crystallizing an $\alpha_v\beta_3$ integrin antagonist by adding heptane to an ethyl acetate solution is unreliable and that the compound occasionally oils out. Using hexane in place of heptane avoids the oiling-out problem, but the authors prefer heptane to hexane on a large scale for safety reasons.

The authors added a third solvent to the system to provide a bridge from high solubility in ethyl acetate to very low solubility in heptane. They added toluene to the ethyl acetate solution and then distilled it to remove water.

Ethyl acetate was added back to give a 1:1 mixture of toluene and ethyl acetate. Heptane was then added slowly in three portions. After the first addition, which gave ~20% supersaturation, the mixture was seeded. (It is known that oiling occurs at ~40% supersaturation.) This was followed by two more heptane additions and cooling to –5 °C to give ~85% yield of >98.7% pure product. (*Org. Process Res. Dev.* **2009,** *13,* 60–63; **Will Watson**)

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