"Wolf and Lamb" Chemistry

Many useful reactions difficult to perform by conventional means can be carried out easily with polymeric reagents

Polymeric reagents—reactive, low molecular weight molecules bound to a polymeric backbone—have been widely used in organic chemistry during the past two decades. Some rather unusual new types of reactions involving more than one polymeric reagent were described last month at the 28th Macromolecular Symposium of the International Union of Pure and Applied Chemistry* by Abraham Patchornik of the Weizmann Institute of Science in Rehovot, Israel. The new reactions can give much higher yields than conventional reactions in most cases while simplifying the procedures.

The most important feature of polymeric reagents is that they are insoluble, but the reactive species remains exposed to the solvent. Once the reaction is complete, the polymeric reagent is removed by filtration, often leaving a virtually pure product. Because chain fragments within a cross-linked polymeric backbone have restricted mobility, active species that would ordinarily be used only in dilute solutions can be effectively isolated from each other at relatively high concentrations. The polymers frequently also solve problems of lability, volatility, toxicity, and odor associated with many standard reagents.

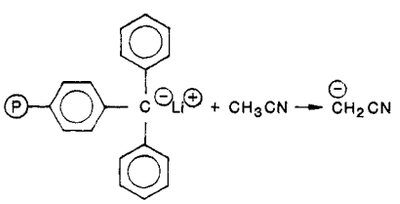
In most cases studied to date, only one polymeric reagent has been used. Patchornik told the symposium that many types of reactions can be performed more easily with multiple polymers. Patchornik has been a pioneer in this field, although some valuable work has also been performed by Julius Rebek and his colleagues at the University of California, Los Angeles.

"Consider," Patchornik says, "the case of a two-step reaction in which a substrate S reacts with reagent A to form an intermediate SA, which then reacts with reagent B to form product SAB. If SA is short-lived, it would be desirable or necessary to have A and B in the same reaction medium; in many cases, however, they will interact to form an undesired by-product AB."

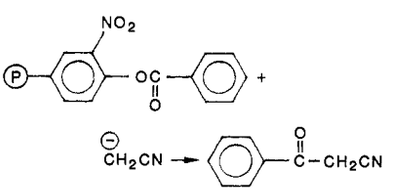
Patchornik has found that the undesired reactions can be avoided by attaching the reagents to separate insoluble polymers. The polymer-bound reagents can then coexist in the same reaction vessel "like the proverbial wolf and lamb" [Isaiah 11:6].

In one example of this "wolf and lamb" chemistry, Patchornik, Barry J. Cohen, and M. A. Kraus attached a triphenylmethane (trityl) group to one polystyrene macromer and *o*-nitrophenol to a second. The trityl groups can then be treated with butyllithium or similar reagents to form the strong base trityllithium. The *o*-nitrophenol can be readily acylated with an acyl chloride, such as benzoyl chloride. In solution, the base would attack the ester, but the polymers keep them apart.

If a molecule with an acidic hydrogen, such as acetonitrile, is added to the solution, the hydrogen is abstracted to form a short-lived carbanion:

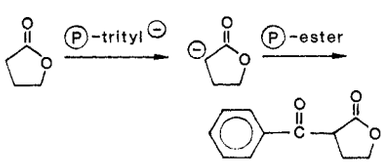


The carbanion then reacts with the ester:



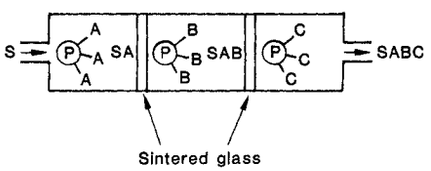
With the two polymeric reagents, the reaction proceeds in a 90 percent yield, as compared to 27 percent for monomeric reagents in solution.

When acylating an ester in solution, the ester enolate must be completely formed before the acylating agent is introduced so that the latter does not react with the base. During this period, however, the ester enolate can undergo a self-condensation. With wolf and lamb chemistry, however, γ-butyrolactone, for example, can be benzoylated in 95 percent yield:



In solution, the yield is only 31 percent. A large number of related reactions can be performed using these and other polymeric reagents Patchornik has developed.

Another potential way to use polymeric regents, Patchornik says, is called cascade or "on-line" synthesis. This re-



action makes use of a glass tube divided into compartments by sintered glass filters, with a different polymeric reagent trapped in each compartment. When a substrate in solution is passed through the tube, it will react sequentially with each reagent. If the reagent is present in excess and there are no side reactions, each step will go to completion. Patchornik has so far carried out reactions involving three different reagents and is confident that longer sequences will be possible. He speculates that this could be a useful technique for production of such materials as pyrazoles, polymeric active esters, and hydroxybenztriazole esters of carboxylic acids, among other things.

But Patchornik holds the greatest hope for a technique he calls "shadchen" chemistry from the Hebrew word for "matchmaker." In this case, an active molecule, or matchmaker, is used to carry a reactive species from one insoluble polymer to another to carry out each step in a synthesis. In the application of shadchen chemistry to oligopeptide synthesis, for example, an amine-blocked amino acid is attached to an activated nitrophenol to form an ester that is about 40 times more reactive than the *o*-nitrophenyl ester discussed previously. The growing peptide chain is attached by a benzyl ester linkage to a second polymer in a separate reaction vessel.

A dilute solution of a shadchen molecule, such as imidazole, is then pumped between the two vessels in a closed loop. It picks up the acyl group from polymer I and transfers it to the free amine of the amino acid attached to polymer II. The

*Held at the University of Massachusetts, Amherst, 12 to 16 July 1982.

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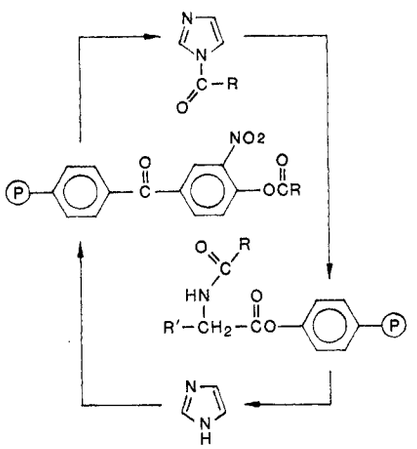
free imidazole is then recycled through the loop until the process is virtually 100 percent complete. The blocking agent of the amine group is then removed quantitatively with trifluoroacetic acid and the process repeated with the next amino



acid desired. Using the shadchen techniques, Patchornik and Yechiel Shai synthesized the blocked form of the pentapeptide Leu-enkephalin with a purity of 99 percent. "With this synthesis," he says, "we proved two things: that it worked, and that it worked beautifully."

Shadchen chemistry can also be used to recharge the system. Polysulfonyl chloride, for example, can be used as polymer II to make anhydrides of the appropriate amino acids; the anhydrides then acylate polymer I. (The polysulfonyl chloride can be regenerated with chlorosulfonic acid.) Polysulfonyl chloride can be used in a similar fashion to convert phosphoric acid derivatives to phosphoric anhydrides for the synthesis of oligonucleotides. It can also be used to convert nitrates to their anhydrides, producing a useful nitrating agent.

The great potential utility of shadchen chemistry, Patchornik says, lies in the fact that more than 40 percent of all organic chemistry reactions can be written in the form

$$B + A{-}\alpha \rightarrow B{-}A + \alpha$$

which is the form of the shadchen reaction with α as the matchmaker molecule. Patchornik has patented the process and is now attempting to license it. The great specificity and high yields associated with each of the techniques he describes should make them very useful not only in industrial processes but also for the laboratory chemist.—THOMAS H. MAUGH II

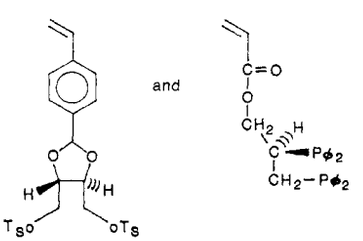
Additional Reading

1. B. J. Cohen, M. A. Kraus, A. Patchornik, *J. Am. Chem. Soc.* **103**, 7620 (1981).
2. A. Patchornik and B. J. Cohen, in *Perspectives in Peptide Chemistry*, A. Eberle, R. Geiger, T. Weiland, Eds. (Karger, Basel, 1981), pp. 118–128.

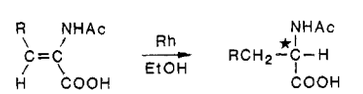
Stereoselective Synthesis of Amino Acids

New chiral monomers that can be used in the stereoselective synthesis of amino acids were described at the 28th Macromolecular Symposium of the International Union of Pure and Applied Chemistry* by John K. Stille of Colorado State University. L-Amino acids are very difficult to synthesize now and have generally been obtained from natural products or by cloning techniques. Stille's work could establish an industrial synthetic route to some that are in short supply.

Stille first synthesized monomers such as†:



These can be copolymerized with hydroxyethyl methacrylate and ethylene methacrylate to give polymers that swell in ethanol and that contain ligand sites onto which rhodium can be exchanged. With the use of the polymer-bound rhodium, amino acids of more than 90 percent optical purity can be synthesized by the hydrogenation of *Z*-acylaminocinnamic acid derivatives:



The polymeric catalyst can be recovered and used again. A polymer carrying the enantiomeric compounds can be used to produce D-amino acids in similar high yields.

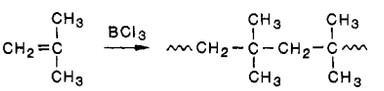
The same polymers with rhodium replaced by platinum can also be used to perform chiral hydroformylations, a process that is useful in drug synthesis, among other things. In this case, the polymers produce an optical purity of 70 to 90 percent, compared to the 20 to 40 percent obtained by conventional techniques.

*Held at the University of Massachusetts, Amherst, 12 to 16 July 1982.
†Ts = tosylate; ø = phenyl; Ac = acyl; EtOH = ethanol; PVP = polyvinylpyrrolidone.

Novel Materials from Telechelic Prepolymers

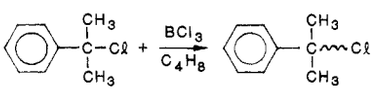
Interesting new materials can be obtained by copolymerizing conventional monomers with telechelic prepolymers prepared by the inifer method, reported Joseph P. Kennedy of the University of Akron. Telechelic prepolymers (from the Greek for "far claws") are soluble polymers, with a mass of 500 to 20,000 daltons, that carry one or more functional end groups; they can be linear or branched. The term inifer (from *ini*tiator-trans*fer* agent) was coined by Kennedy to denote compounds capable both of initiating polymerization and terminating a growing polymer chain by transferring the active species to start a second chain.

Most of Kennedy's studies have been performed with polyisobutylene (PIB), an inexpensive polymer that generally does not undergo side reactions during polymerization and that has good physical properties. It is readily formed by a carbocationic process with boron trichloride as a catalyst:

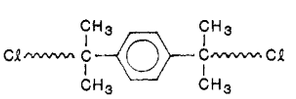


A short (or long) polymer formed in this manner has no reactive end groups.

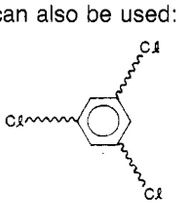
When cumyl chloride is used as a monofunctional inifer (minifer), however, it is possible to prepare PIB of controlled size with a functional end group:



With the corresponding binifer, it is possible to obtain two functional end groups:



Trinifers can also be used:



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