Although insoluble polymer supports were beginning to be well established by 1974 in the synthesis of polypeptides and nucleotides, their applications to organic synthesis in general were in their infancy. This review introduced the topic to the main body of organic chemists and biotechnologists. [The SCI® indicates that this paper has been cited in over 135 publications.]

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The concept of deliberately performing chemical reactions in heterogeneous rather than homogeneous media was suggested by R.B. Merrifield for use in polypeptide synthesis, and by R.L. Letsinger for polynucleotide synthesis. They reasoned that these repetitive types of preparations could be advantageously performed on an insoluble matrix, whereby the individual steps of the inordinate number of reactions could be facilitated by using solid phases. In this way, the normal workup of reactions was simplified and automated using common filtration procedures.

During a postdoctoral fellowship with Letsinger in 1964–1965, I became aware of insoluble polymer supports and also experienced the difficulties of performing oligonucleotide synthesis by the classical diester route. Although I was discouraged by oligonucleotide syntheses, I was intrigued by the idea of applying insoluble polymer supports to organic synthesis outside the specialized confines of polypeptide and polynucleotide chemistry.

The difficulty of polypeptide synthesis stemmed from the large number of reactions required, and this problem was solved by using solid phases to facilitate workup procedures. Although this difficulty does not pertain to a typical organic synthesis requiring fewer reaction steps, it was perceived that some specific advantages of insoluble supports could be applied to organic synthesis.

During a subsequent postdoctoral sojourn at Franz Sondheimer's laboratory at Cambridge University, we had to prepare an annulene precursor, trans-1-chloro-2-hexen-5-yne, from trans-1,4-dichloro-2-butene and ethynylmagnesium bromide. The reaction yielded an inseparable mixture of starting material, the desired monoreacted product, and the unwanted bis-reacted product trans-4-octen-1,7-diyne.

Although this particular problem was ultimately solved in another way, the concept of using insoluble polymer supports as a specifically advantageous method of performing reactions selectively at one terminus of completely symmetrical difunctional compounds was born. Amino acids and nucleosides are unsymmetrical polyfunctional compounds and attachment of these unsymmetrical moieties to the solid phase followed normal blocking group procedures. However, the use of insoluble polymer supports provided a general method to monoblock completely symmetrical, difunctional compounds for the first time and the free end could be available for synthetic elaboration.

Most common, symmetrical, difunctional compounds have now been monoprotected by this method. Other specific applications of insoluble polymer supports by some early pioneers in the field include their use to simulate "high dilution" conditions, to simulate "hyperenantiomeric" conditions, to remove an unwanted by-product from a reaction mixture, to synthesize a threaded macrocycle, to eliminate odorous or toxic by-products from reaction media, to alter the regioselective course of a chemical reaction, to study reaction mechanisms, to synthesize new classes of compounds, and to conduct asymmetric synthesis.

The publication in Chemical Society Reviews, consisting of less than 50 references devoted to the title topic, established a new field of endeavour. Subsequently, publications on the use of insoluble polymer supports in organic synthesis, as polymeric reagents, as phase transfer catalysts, as extraction agents, and as chromatography supports mushroomed exponentially so that six years later, two books were published on the topic, along with another review of my own.

2. Letsinger R L & Mahadevan V. Oligonucleotide synthesis on a polymer support. J. Amer. Chem. Soc. 87:3526-7, 1965. (Cited 100 times.)