Tetrahedron Vol. 35, pp. 723-731
© Pergamon Press Ltd., 1979. Printed in Great Britain

0040-4020/79/0315-0723/$05.00/0

TETRAHEDRON REPORT NUMBER 60

MECHANISTIC STUDIES USING SOLID SUPPORTS: THE THREE-PHASE TEST

JULIUS REBEK, JR.
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, U.S.A.

(*Received* 21 *August* 1978)

INTRODUCTION

The successful synthesis of peptides on crosslinked polystyrene beads, introduced by Merrifield 15 years ago,[1] focused a good deal of attention on the advantages provided by insoluble, polymer-bound reagents. Before that time, the organic chemist's most frequent contact with such reagents was in the use of ion exchange resins; since then these systems have been applied as vehicles for synthetic, catalytic and mechanistic studies. Parallel development of other solid supports (notably silica, graphite and sepharose) has also resulted, but the present review shall deal only with polystyrene-divinyl benzene copolymers.

These supports are commercially available as beads in a variety of mesh sizes and degrees of crosslinking. Beads with <4% crosslinking are best described as gel phases while those with higher incorporation of divinyl benzene, polymerized in the presence of solvents and emulsifiers, are large clusters of small gel beads with channels or pores. Both swell considerably on contact with typical organic solvents, providing access of solvent-borne reagents to the interior of the beads. The degree of swelling decreases with increased crosslinking.

To a first approximation, the beads resemble toluene in their electrophilic aromatic substitution reactions. With beads of low crosslinking, reaction has been shown to occur homogeneously throughout the bead's volume.[2] Characterization is readily accomplished by IR, combustion analysis and, where appropriate, titration. Several recent reviews[3] describe characterized polymers and many such functionalized polymers may be purchased.

Much of the present interest in these vehicles reflects the ease with which they can be separated from solution phases. For example, in solid phase peptide synthesis (Fig. 1) large excesses of reagents in solution are used to drive the acylation of the polymer-bound (amine) component to completion.

In the complementary sense,[4] excess polymer-bound reagent may be used to force reactions of a substrate in solution. In either case, fractious side products and excess reagents remain in different phases from the desired products and purifications are effected by mere filtration. Additional examples are shown in Fig. 2.

A confusing issue that has emerged during the development of these reagents is the question of matrix isolation or pseudo-dilution. Functional groups attached to the polymer backbone must experience some reduced mobility with the consequence that site-site interactions within the bead are diminished, relative to those in bulk solutions. Attempts to exploit this phenomenon yield results which are frequently difficult to interpret. For example, Grubbs[8] has shown that the polymer-bound (20% crosslinked) titanocene derivative 1 shows catalytic activity, whereas its solution counterpart dimerizes (Fig. 3) to the catalytically inactive 2.

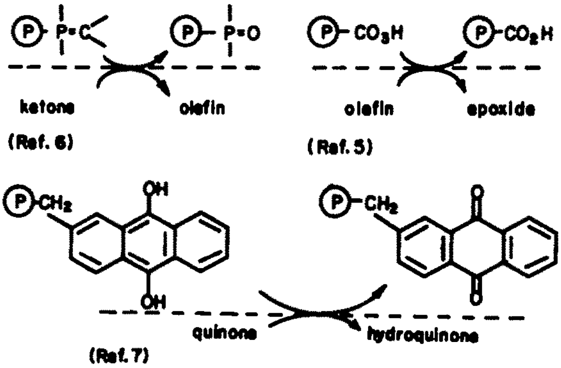


Fig. 2.

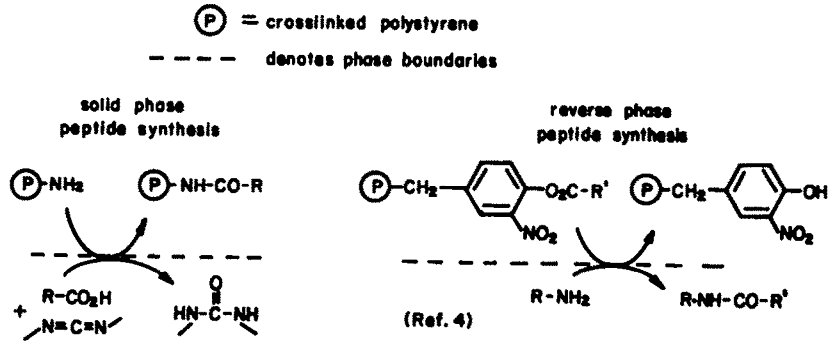


Fig. 1.

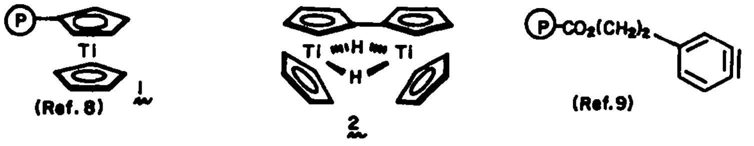


Fig. 3.

Mazur[9] has determined that the polymer-bound benzyne derivative shown has a half-life of about 30 sec, and reports by Leznoff[10] indicate monofunctionalization of symmetrical substrates.

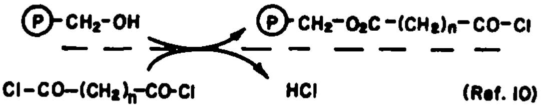


Fig. 4.

Many experiments, however, have provided strong evidence that site–site interactions are quite facile.[11] Rapoport[12] has shown that polymer-bound carboxylic acids on 2% crosslinked polystyrene readily form anhydrides, even at low levels of functionalization (Fig. 5), and our own study[13] of this system using increasingly crosslinked polymers show substantial, through reduced, anhydride formation at even 20% crosslinking.

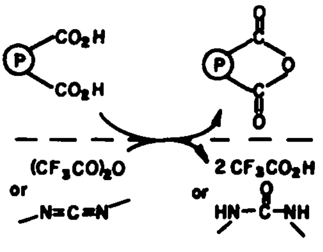


Fig. 5.

Moreover, cross-Claisen condensation products result from polymers on which two esters have been attached,[14] and treatment of the 2% crosslinked phosphine 3 with complex 4 gives the "polymer-chelated" 5 (Fig. 6).

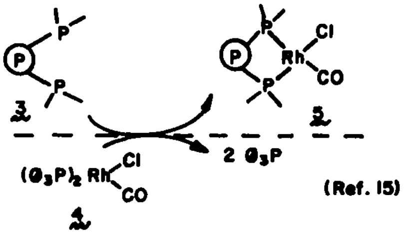


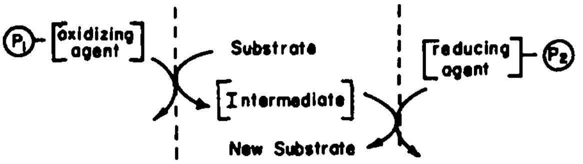
Fig. 6.

An extended X-ray absorption fine structure spectroscopic (EXAFS) study[16] of these polymers at 2% and 20% crosslinking concludes that the site–site interactions in the latter is "substantially reduced".

The reduced mobility of polymer-bound reagents is therefore real, but its successful application appears to be a function of crosslinking, solvent, temperature, method and degree of functionalization and kinetic factors which are incompletely understood. Low levels of functionalization are one of the more likely means by which site isolation can be achieved but such levels are more practical for catalytic than stoichiometric reagents.

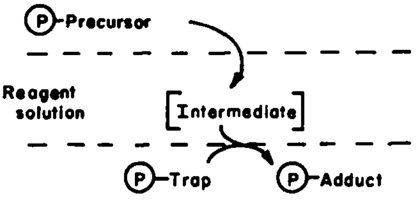
Multiphase systems

Our own research has been concerned with the possibilities afforded by multiphase systems. We reasoned that direct reaction between two reagents, each attached to a different polystyrene bead, must be exceedingly slow, if it occurs at all. Since functionalization of the polystyrene matrix can take place homogeneously throughout the bead, the fraction of functional groups at the surface of the bead is vanishingly small. Moreover, collisions between two beads involve only a small area of the total surface. Consequently a system involving two incompatible reagents suspended in the same medium could be envisioned (Scheme 1).



Scheme 1.

For example, an oxidizing agent on one support would be inaccessible to a reducing agent on a second support, yet a substrate in solution would have access to both species. While such a system might be used to advantage in synthetic chemistry (the first such application appeared in 1977[17]) the mechanistic implication is clear: the overall process *requires* the existence of an intermediate which is polymer-free. In even a simpler form, then, the system can be used for the detection of reactive intermediates (Scheme 2).



Scheme 2.

A precursor for a suspected intermediate is attached to one solid support, and a trap for the intermediate is attached to a second such support, suspended in the same medium. The liberating reagent is added to the solution phase, and the appearance of polymer-bound adduct signals the presence of the intermediate in solution. The system provides an unambiguous method for the detection of intermediates.

Most probably the technique has its origins in electrochemistry but the first explicit three-phase detection of a reactive intermediate was reported nearly 50 years ago.[18] By using two separate surfaces Kautsky was able to demonstrate the existence of free singlet oxygen in 1931, and, had the scientific community accepted his interpretation of the experiment at that time, the technique would surely have been applied to the detection of other reactive intermediates. Unfortunately, some 30 years elapsed before Kautsky's conclusions were confirmed and another decade passed before the technique was resurrected in our hands. Technology, however, moved more rapidly to develop multiphase systems; many water-softeners and de-ionizers consist of a mixed bed of ion exchange resins suspended in the same solution.[19] These systems remove salts by generating acidic and basic intermediates and have been commercially available for some time.

At the outset of our studies it was clear that the types of intermediates amenable to study would be limited by reactivity. Very short-lived species such as free methylene would not be expected to escape the polystyrene matrix without reaction; at the other end of the reactivity scale, intermediates with life-times longer than say, seconds, are probably best examined by isolation or direct observation. The method was expected to complement the kinetic methods used for the former and the spectroscopic methods used for the latter by providing a bridge between these limiting cases.

A second worry was the relevance of reactions occurring inside hydrocarbon matrices to reactions which had previously been studied in aqueous media. Direct comparisons between our results and the conclusions derived from aqueous systems are not warranted; interpretations have been made with caution. However, we were encouraged by the hope, perhaps sanguine, that these matrices resembled enzyme interiors, and our results would be complementary to those found in aqueous media for reactions of biochemical relevance.

Perhaps the most unsatisfactory aspect of the proposed method is concerned with the nature of the intermediates involved. The three-phase method offers unambiguous evidence for the *existence* of an intermediate but only inferences can be drawn concerning its *structure*. Such inferences must always be supported by removal of the adduct from the solid phase (using conditions which minimize undesired structural changes) followed by structure determination of the modified adduct. This uncertainty was regarded as acceptable (since it is present in any kinetic method), nevertheless, direct observations of the intermediates would be desirable and we have made some progress in this direction.

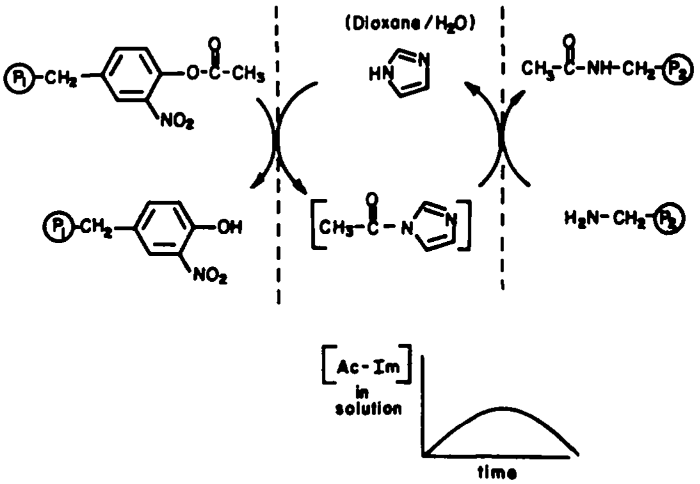
Nucleophilic catalysis. Our initial application of the method involved the detection of nucleophilic catalysis in acyl transfer reactions.[20] Such catalysis is frequently difficult to detect in the presence of general base catalysis, but for imidazole, spectroscopic detection of the intermediate acyl imidazole is possible. Using the polymer bound acylating agents of Patchornik[4] and the polymer-bound amines of Merrifield peptide synthesis, we were able to observe acyl transfer with a number of nucleophiles (Scheme 3).

For the case of imidazole, direct observation of the intermediate was readily accomplished by UV monitoring of the solution phase, or using radio-labels in the acyl group, by scintillation counting of the solution phase. The latter case establishes a unique advantage offered by three phase systems; the intermediate exists in all three phases whereas precursor and trapping agents exist only on the solid phase. The solution phase is therefore a domain unique to the intermediate, and spectroscopic tools applied to this phase become magnified in their scope. The shape of the concentration vs time curves reflect the rate of appearance and disappearance of the intermediate, factors which are easily controlled by the concentration of the catalyst and trap, respectively.

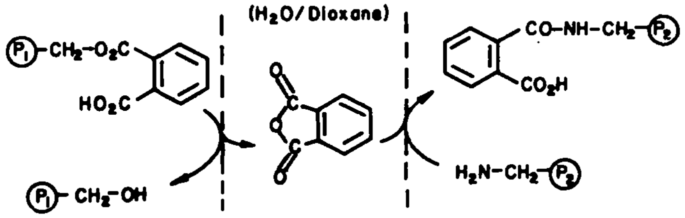
As final controls, we established that grinding the polymer bound acylating agent and polymer bound amine in a mortar, with or without solvent failed to induce direct reaction between the solid phases. Moreover the imidazole-catalyzed acyl transfer occurred smoothly when the two solid phases were suspended in the same medium but were physically separated by a sintered glass frit.

Two additional cases examined involved intramolecular nucleophiles.[20] The polymer-bound half-ester of phthalic acid generated phthalic anhydride, which was cleanly trapped by a second solid phase (Scheme 4).

Now, phthalic anhydride can hardly be called a reac-



Scheme 3.



Scheme 4.

tive intermediate, but *in solution*, Bender[21] has shown that the rate of its hydrolysis is much faster than its rate of formation from its half-esters. Therefore its steady-state concentration is too low for direct observation. The three-phase system does not require a concentration threshold and is well-suited for the detection of intermediates under these conditions.

A much more reactive intermediate is represented in acylated tertiary amine 6 (Scheme 5). Kinetic evidence has implicated its intermediacy in the hydrolysis of substituted phenyl esters 15 years ago,[22] but only recently have these species proved capable of isolation.[23] The detection of 6 by the three-phase method required anhydrous conditions, a base of low nucleophilicity and an electrolyte in the solution phase.

Elimination reactions. Intermediates in elimination reactions are particularly compatible with the method, and we examined several acyl transfers for which elimination-addition mechanisms have been indicated.[24] Bruice had examined the hydrolysis of malonate esters and concluded that carbethoxy ketene 7 (Scheme 6), was an intermediate in this E_1CB reaction. A rate-product discrepancy revealed that the intermediate had been trapped by aniline, but stopped-flow methods failed to yield spectroscopic evidence for the ketene.[25]

Using proton sponge as the base to insure against nucleophilic catalysis, we were able to detect ketene transfer in the three-phase system shown. Also detected were the acyl ketene 8 and isocyanate 9 from their respective polymer-bound nitrophenyl esters.[26] In the latter case, phenyl isocyanate could again be detected in the solution phase (by IR spectroscopy). Subsequently, we observed the transfer of three intermediates through the *gas* phase, on heating the precursor and trapping resins under partial vacuum during attempted drying. It should be possible to exploit this phenomenon in suitably constructed flow systems for synthetic purposes.

Phosphate transfer. As with acyl transfers, phosphate transfers can occur by both addition-elimination and elimination-addition mechanisms. Indeed, the latter mode is one of the first E_1CB reactions described. The phosphorous analogs to the ketenes are the metaphosphates, and evidence for their intermediacy in phosphate transfer reactions had been deduced by Westheimer[27] from kinetic studies, e.g. Fig. 7.

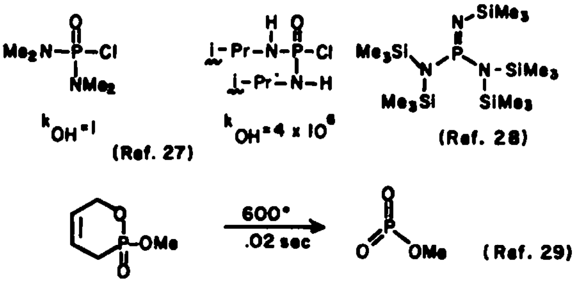
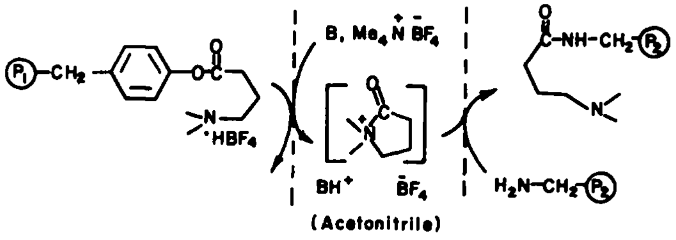
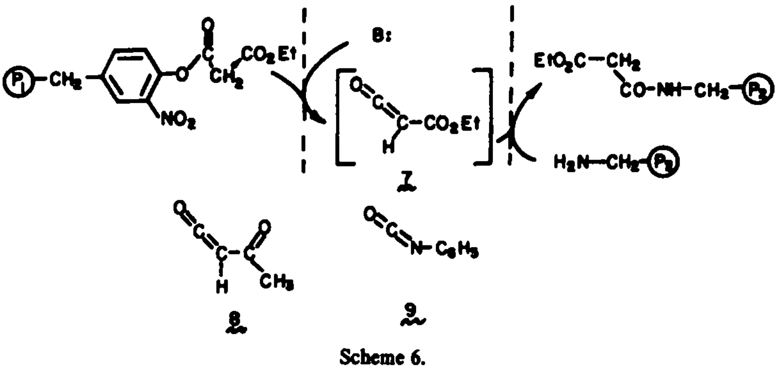


Fig. 7.



Scheme 5.



Scheme 6.

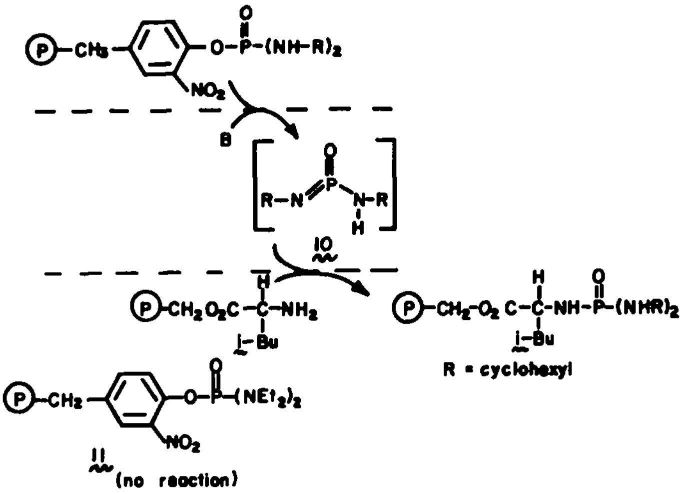
The first monomeric metaphosphate succumbed to full characterization in 1974, and the methyl ester has been generated as shown in the gas phase,[29] but the parent ion and its less hindered derivatives remain unknown. Our initial efforts were directed at the amide 10, Scheme 7 and successful transfer was accomplished to the polymer-bound leucine.[30] Supporting evidence for the elimination mechanism shown was provided by the failure of the fully alkylated 11 to transfer under identical conditions.

Subsequently phosphate transfer from the polymer-bound mixed anhydride was detected.[31] The radioactive phosphorous used in these studies enabled us to establish that 70% of the phosphorous released from the polymer was trapped, and that 90% of the phosphorous trapped appeared as glycine monophosphate in solution after saponification. Recently,[32] we have observed phosphate transfer during the Conant-Swan reaction (Scheme 8).

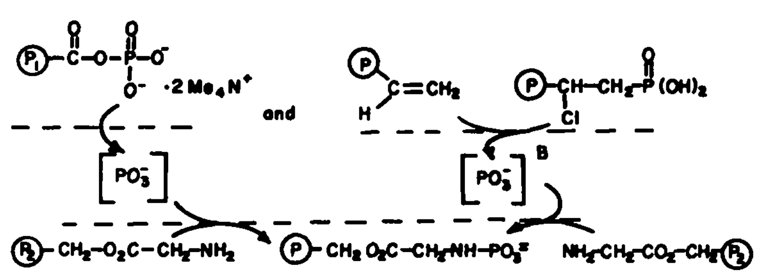
In any of these cases, the actual *structure* of the phosphorylating agent is a matter of uncertainty. Control experiments established that the polymer-bound amines were not phosphorylated with pyrophosphate under these conditions, and higher oligomers of phosphate are seemingly ruled out by the nearly exclusive *mono*-phosphorylation in the observed products. It is probable that the parent ion, PO_3^-, would form a complex with dioxane (as does the isoelectronic SO_3),[33] which could act as the phosphorylating agent, but reactions in which acetonitrile was the solution phase gave results nearly identical to those observed in dioxane. A species as electrophilic as metaphosphate would react with whatever nucleophiles are available and pendant carboxyl groups could provide successive parking places as the ion works its way to the surface. However, we cannot rule out disproportionations within the solid phase precursors that generate polymer-free intermediates say, trimetaphosphates,[34] which could act as carriers in a catalytic sense.

Cyclobutadiene. Evidence for the existence of free cyclobutadiene in inert matrices at low temperatures has been presented[35] and much-discussed.[36] In solution, Grubbs[37] has provided excellent evidence that cyclobudadiene is free of iron when generated by oxidation of its iron tricarbonyl complexes, and we felt such a reactive species would provide a stringent test for the scope of the three-phase method. A polymer-bound precursor and trap for this species were found in the maleimide and phenanthroline complex, respectively, (Scheme 9), and control experiments established that the iron did not escape the savage grasp of the polymer during oxidations. Slow addition of oxidants to the three-phase system in which the trapping agent was present in excess resulted in remarkably efficient (90%) transfer of cyclobutadiene through the solution phase.[38]

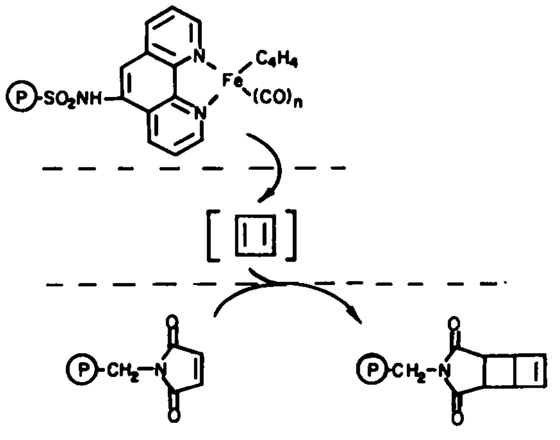
Singlet oxygen. The known lifetime of singlet oxygen, $^1O_2$, in solution[39] and in the gas phase[40] suggested that it might be used to establish the time frame in which the three-phase method operates. Moreover, such an experiment has the historical charm of returning the method to its first successful application. Polymer-bound sensitizers for $^1O_2$ were available through the work of Neckers[41] and, after considerable frustration with a polymer-bound diphenyl anthracene derivative,[42] a suitable trap was ound in the olefin 13 (Fig. 8). Reaction of



Scheme 7.



Scheme 8.



Scheme 9.

13 with known $^1O_2$ sources in solution[43] gave a mixture of hydroperoxide "ene" products which were characterized as the alcohols 14 after removal from the polymer.

We were disappointed to find that no ene products were formed when a suspension of 13 and 15 in solution was exposed to prolonged irradiation; neither did they form when the $^1O_2$ source was the polymer bound cyanate/H_2O_2 system,[44] 16. Successful transfer occurred through the *gas* phase when the irradiation was performed on mixtures of 13 and 15 under partial pressures of oxygen. The observed pressure dependence is also in accord with that expected for $^1O_2$, a species readily deactivated by collisions in the gas phase.

Intra vs intermolecular. Multiphase systems are capable of application to mechanistic problems posed by a number of rearrangement reactions. Does the reaction proceed by way of intramolecular rearrangement, path a, or through dissociation to intermediates, path b?

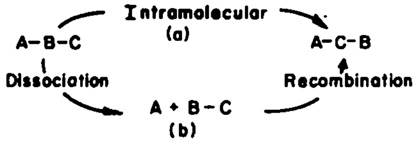
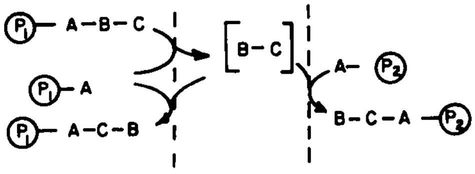


Fig. 10.

The detection of crossover product in appropriately labeled system has been frequently used to answer such questions, and in multiphase systems the polymers themselves can serve as labels. Consider Scheme 10 in which the two solid polymer phases could be distinguished by mesh sizes or by physical separation with a frit as previously described. The dissociation mechanism generates a polymer-free intermediate *which has no history*, and could recombine with either solid phase.



Scheme 10.

A beautiful example of this example of this technique was provided recently by Warshawski.[45] In a mechanistic study of the Fries rearrangement, it was shown that treatment of the ester 17 (Scheme 11) with $AlCl_3$ in the presence of 18, resulted in acylation of the latter. This requires the existence of a polymer-free acylating agent, for which the acylium ion structure was proposed.

In our own application of this method, we examined the reaction of isocyanates with carboxylic acids.[46] The formation of the amide product may arise by intramolecular O→N acyl transfer of the initially formed

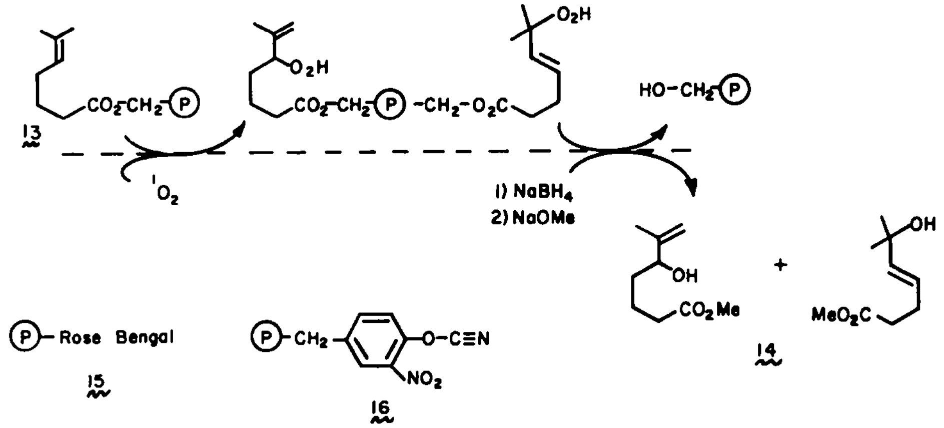


Fig. 8.

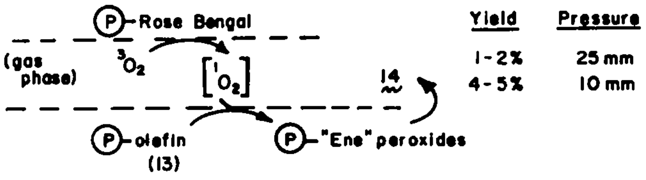
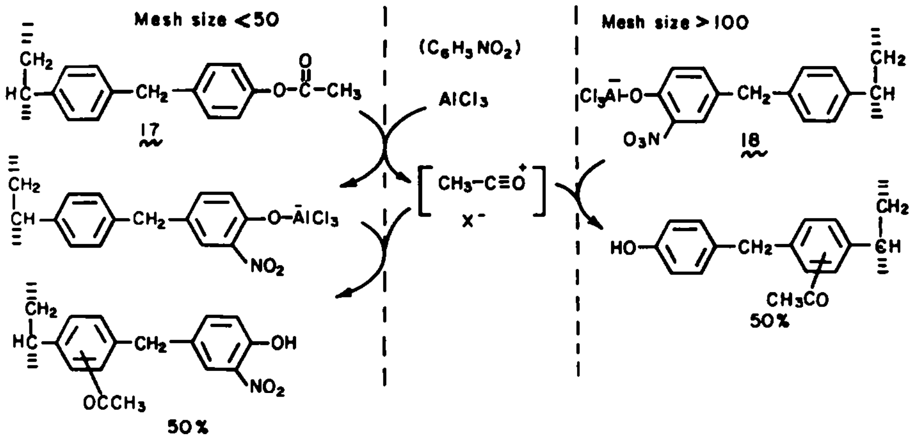


Fig. 9.



Scheme 11.

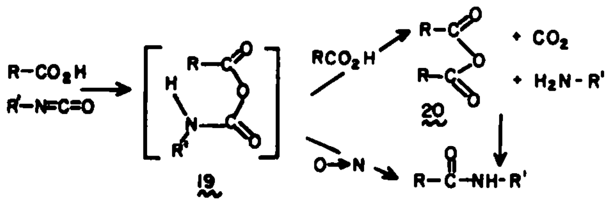


Fig. 11.

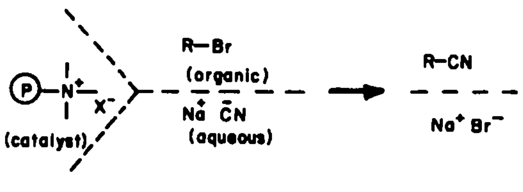
mixed anhydride 19, or by disproportionation to the symmetrical anhydride 20 (Fig. 11).

It would be difficult to imagine a nucleophile which reacts selectively with the symmetrical anhydride in the presence of the mixed anhydride and the isocyanate in solution. However, if the nucleophile were confined to one solid phase and the isocyanate to another, the symmetrical anhydride would be the only acylating agent with access to the nucleophile. In the event,[47] the polymer-bound isocyanate 21 and the polymer-bound amine 22 were suspended in a solution of the carboxylic acid (Scheme 12).

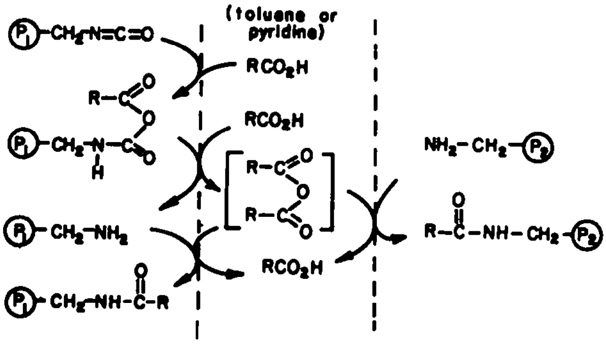
Acylation of both polymers resulted, but 80% of the acylation occurred on 22 as shown. Therefore intramolecular O→N acyl migration of 23 cannot be a rapid process compared to its disproportionation to a polymer-free acylating agent.

Triphase catalysis. A recent development that blends the advantages of insoluble supports with the catalytic effects of phase transfer[48] agents is represented by Regen's[49] "triphase" system. The polymer-bound catalyst and two immiscible liquids provide the three phases involved and the system has been efficacious in substitution reactions (Scheme 13), cyclopropanations with dichlorocarbene and oxidations.

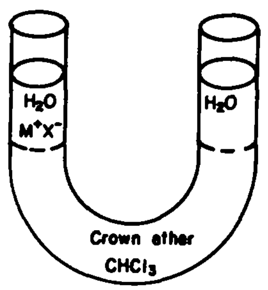
Liquid membranes. For the sake of completeness, we conclude with the use of three liquid phases. Such systems are easily constructed within a U-tube (Fig. 12) and their simplicity accounts for their popularity as models for biological membranes.[50] Recent studies of ion transport by macrocyclic polyethers are particularly elegent[51] and suggest that the application of multiphase systems to problems in chemistry is limited only by the experimenter's imagination.



Scheme 13.



Scheme 12.



Transfer rates (mol/hr x 10^7) with Dibenzo-18-crown-6	
NaCl	0.31
NaBr	1.6
NaI	15
KCl	6.1
KBr	88
KI	620

(Ref. 51)

Fig. 12.

Acknowledgements—Financial support for these investigations was provided by the National Institutes of Health and the Petroleum Research Fund. The success of these studies is derived from the considerable experiments skills of my coworkers, whose names appear on the original publications. For encouragement, timely advice and inspiration, I am deeply indebted to Professors D. A. Evans, C. S. Foote, W. P. Jencks, E. T. Kaiser, A. Patchornik, L. T. Scott and F. H. Westheimer.

REFERENCES

[1] R. B. Merrifield, *J. Am. Chem. Soc.* **85**, 2149 (1963).

[2] R. B. Merrifield and V. Littau, *Peptides*, 1968. (Edited by E. Bricas) p. 170. North Holland, Amsterdam (1968).

[3] M. J. Frechet and M. J. Farral, *Chemistry and Properties of Crosslinked Polymers* p. 59. Academic Press, New York, N.Y. (1977); C. C. Leznoff, *Chem. Soc. Rev.* 3, 65 (1974); C. G. Overgerger and K. N. Sannes, *Angew. Chem.*, Int. Ed. Engl. 13, 159 (1974); D. C. Neckers, *Chem. Technol.* 108 (1978).

[4] L. Kalir, M. Fridkin and Patchornik, *Europ. J. Biochem.* **42**, 151 (1974).

[5] C. R. Harrison and P. Hodge, *J. Chem. Soc.* Perkin I, 605 (1976) and refs therein.

[6] F. Camps, J. Castells, J. Font and F. Vela, *Tetrahedron Letters* 1715 (1971).

[7] D. S. Kemp and J. Reczek, *Ibid.* 1031 (197).

[8] W. D. Bonds, C. H. Brubaker, Jr., E. S. Chandrasekaran, C. Gibbons, R. H. Grubbs and L. Kroll, *J. Am. Chem. Soc.* **97**, 2128 (1975).

[9] P. Jayalekshny and S. Mazur, *Ibid.* **98**, 6710 (1976).

[10] C. C. Leznoff and J. M. Goldwasser, *Tetrahedron Letters* 1875 (1977); T. M. Fyles and C. C. Leznoff, *Can. J. Chem.* **54**, 935 (1976); C. C. Leznoff and S. Greenburg, *Ibid.* **54**, 3824 (1976).

[11] J. I. Crowley and H. Rapoport, *Acc. Chem. Res.* **9**, 135 (1976).

[12] J. I. Crowley, T. B. Harvey and H. Rapoport, *J. Macromol. Sci. Chem.* 7, 1118 (1973).

[13] L. T. Scott, J. Rebek, L. Ovsyanko and C. L. Sims, *J. Am. Chem. Soc.* **99**, 625 (1977).

[14] M. A. Kraus and A. Patchornik, *Ibid.* **93**, 7325 (1971).

[15] J. P. Collman, L. S. Hegedus, M. P. Cooke, J. R. Norton, G. Dolcetti and D. N. Marquardt, *Ibid.* **94**, 1789 (1972).

[16] J. R. Reed, P. Eisenberger, B-K. Teo and B. M. Kincaid, *Ibid.* **100**, 2375 (1978) and **99**, 5217 (1977).

[17] B. J. Cohen, M. A. Kraus and A. Patchornik, *Ibid.* **99**, 4165 (1975). For an earlier catalytic example see C. U. Pittman and L. R. Smith, *Ibid.* **97**, 1749 (1975).

[18] H. Kautsky and H. de Bruijn, *Naturwiss.* **19**, 1043 (1931).

[19] *Organic Chemistry* (Edited by J. Hendrickson, D. J. Cram and G. Hammond), 3rd Edn, p. 985. McGraw-Hill, New York (1970).

[20a] J. Rebek, D. Brown and S. Zimmerman, *J. Am. Chem. Soc.* **97**, 454 (1975); [b] J. Rebek, D. Brown and J. A. Horton, *Isr. J. Chem.* in press.

[21] M. L. Bender, Y-L. Chow and F. Choupek, *J. Am. Chem. Soc.* **80**, 5380 (1958).

[22] T. C. Bruice and S. J. Benkovic, *Ibid.* **85**, 1 (1963).

[23] J. V. Paukstelis and M. Kim, *J. Org. Chem.* **39**, 1499 (1974).

[24] A. Williams and K. T. Douglas, *Chem. Rev.* **75**, 627 (1975).

[25] B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.* **91**, 2185 (1969).

[26] F. M. Menger and L. E. Glass, *J. Org. Chem.* **39**, 2469 (1974).

[27] F. Westheimer, *Chem. Soc. Spec. Publ.* No. 8, 181 (1957); D. F. Heath, *J. Chem. Soc.* 3796, 3804 (1956); P. S. Traylor and F. Westheimer, *J. Am. Chem. Soc.* **87**, 553 (1965).

[28] E. Niecke and W. Flick, *Angew. Chem.* Internat. Ed. 13, 134 (1974); O. J. Scherer and N. Kuhn, *Chem. Ber.* **107**, 2123 (1974).

[29] C. H. Clapp and F. Westheimer, *J. Am. Chem. Soc.* **96**, 6710 (1974); C. H. Clapp, A. Satterthwait and F. Westheimer, *Ibid.* **97**, 6873 (1975).

[30] J. Rebek and F. Gaviña, *Ibid.* **97**, 1591 (1975).

[31] J. Rebek and F. Gaviña, *Ibid.* **97**, 3221 (1975); G. DiSabato and W. P. Jencks, *Ibid.* **83**, 4400 (1961).

[32] J. Rebek, F. Gaviña and C. Navarro, *Tetrahedron Letters* 3021 (1977); A. Satterthwait and F. Westheimer, *J. Am. Chem. Soc.* **100**, 3197 (1978).

[33] W. Truce and C. C. Alfieri, *Ibid.* **72**, 2740 (1950); For a theoretical study see L. M. Loew and W. R. MacArthur, *Ibid.* **99**, 1019 (1977).

[34] G. Weimann and H. G. Khorana, *Ibid.* **84**, 4329 (1962); G. M. Blackburn, M. J. Brown and M. R. Harris, *J. Chem. Soc.* Chem. Comm. 611 (1966).

[35] O. L. Chapman, C. L. McIntosh and J. Pacansky, *J. Am. Chem. Soc.* **95**, 614 (1973); A. Krantz, C. Y. Lin and M. D. Newton, *Ibid.* **95**, 2746 (1973).

[36] S. Masamune, T. Machiguchi and M. Aratani, *Ibid.* **99**, 3524 (1977) and refs cited therein.

[37] R. H. Grubbs and R. A. Grey, *Ibid.* **95**, 5765 (1973).

[38] J. Rebek and F. Gaviña, *Ibid.* **97**, 3453 (1975).

[39] R. B. Merkel and D. K. Kearns, *Ibid.* **94**, 7244 (1972).

[40] T. Frankiewicz and R. S. Barry, *J. Chem. Phys.* **58**, 1787 (1973).

[41] A. P. Schaap, A. L. Thayer, E. C. Blossey and D. C. Neckers, *J. Am. Chem. Soc.* **97**, 3471 (1975).

[42] I. Rosenthal and A. J. Acker, *Isr. J. Chem.* **12**, 897 (1974) describe a trap for $^1O_2$ using a polystyrene in which distyrylanthracene is incorporated.

[43] J. W. Peters, P. J. Bekowies, A. M. Winer and J. N. Pitts, Jr., *J. Am. Chem. Soc.* **97**, 3299 (1975).

[44] J. Rebek, S. Wolf and A. Mossman, *J. Org. Chem.* **43**, 180 (1978).

[45] A. Warshawsky, R. Kalir and A. Patchornik, *J. Am. Chem. Soc.* **100**, 4544 (1978).

[46] S. Goldschmidt and H. Krauss, *Newer Methods of Preparative Organic Chemistry* (Edited by W. Foerst) Vol. II, p. 31. Academic Press, New York (1963); P. N. Satchell and R. S. Satchell, *Chem. Soc. Rev.* 4, 231 (1975).

[47] J. Rebe, D. Brown and S. Zimmerman, *J. Am. Chem. Soc.* **97**, 4407 (1975).

[48] J. Dockx, *Synthesis*, 441 (1973); E. V. Dehmlow, *Angew. Chem.* Int. Ed. Engl. 13, 170 (1974).

[49] S. L. Regen, *J. Org. Chem.* **42**, 875 (1977); S. L. Regen, *J. Am. Chem. Soc.* **98**, 6270 (1976) and **97**, 5956 (1975).

[50] D. E. Fenton, *Chem. Soc. Rev.* 321 (1977) and refs therein.

[51] K. H. Wong, K. Yagi and J. Smid, *J. Membrane Biol.* **18**, 379 (1974); Y. Kobuke, K. Hanji, K. Horiguchi, M. Asada, Y.

Nakayama and J. Furukawa, *J. Am. Chem. Soc.* **98**, 7414 (1976); J. J. Christensen, J. D. Lamb, S. R. Izzat, S. E. Starr, G. C. Weed, M. S. Astin, B. D. Stitt and R. M. Izzat, *Ibid.* **100**, 3219 (1978).

[52] C. S. Foote, J. Rebek and S. F. Wolf, *Ibid.* **100**, 7770 (1978). An experiment in which $^1O_2$ was able to penetrate a 500 Å thick film is described by J. Bourdon and B. Schnuringer, *Photochem. Photobiol.* **8**, 897 (1974).