Solid-Phase Organic Synthesis: Novelty or Fundamental Concept?

John I. Crowley and Henry Rapoport*

Materials Science Department, General Products Division, IBM, San Jose, California, and Department of Chemistry, University of California, Berkeley, California 94720

Received May 6, 1975

Since the introduction of "solid-phase" synthesis[1] in 1963, this new synthetic method has been successfully applied to peptides of increasing size. These developments have been crowned by the solid-phase preparation of ribonuclease[2] and human growth hormone,[3] both with a significant degree of enzymic activity. As more demanding synthetic goals have been essayed by solid-phase practitioners, a lengthening list of experimental difficulties has been charted.[4] The methodology has matured to its first critical plateau. Further progress will depend upon major advances in experimental technique which solve problems such as failure sequences,[4l] incomplete coupling,[4a,f] product molecular weight restrictions,[4e] an inadequate catalog of protecting groups, and incomplete cleavage from the solid phase.

After the original successes of the solid-phase method were reported, parallel activity developed in the application of resin attachment to nonpeptide organic synthetic objectives. It was reasoned that polymer-bound reactants could be converted to products with two major advantages over solution chemistry. One of these is the ease of purification afforded by the method, the dominant thrust behind its widespread utilization in peptide synthesis. The other objective rested on the concept that resin linkage would confer hyperentropic utility[5] on the solid-phase method. Reactant moieties could be isolated from each other by polymer attachment and converted to product with a minimum of intermolecular side reactions. Solid-phase synthesis was to be an alternative to high dilution and provide isolated molecules with no near neighbors. The possibilities of resin-bound chemistry were amplified to include reagents such as catalysts, dehydrating agents, and analytical aids as conceptually distinct from reactants on their way to products.

Both peptide and nonpeptide methodology have been the subject of many recent reviews.[6] We do not intend to add a further catalog of the experimental ensemble already constructed. Instead, we will critically evaluate four experimentally ambiguous limitations of nonpeptide solid-phase chemistry whose resolution is required if the process is to mature from publishable novelty to fundamental methodology. Our topics are (1) the degree of separation of resin-bound functional sites provided by solid-phase techniques; (2) the foreshortened range of experimentally established analytical methods applicable to solid-phase intermediates and resin-bound products; (3) the inadequate attention which has been paid to the nature and kinetics of competing side reactions during solid-phase reactions; (4) the need to design experimental objectives which can distinguish any unique advantages of the solid-phase method.

Hyperentropic Efficacy (the High Dilution Principle). It has been suggested that separation of the loci of polypeptide growth provided an advantage for the new procedure over classical techniques.[7] Many recent reports have followed on such an advantage for the solid-phase method in organic synthesis. The view has prevailed until recently that co-(polystyrene–2% divinylbenzene) is a rigid polymer in which specific loci maintain their separation during reaction; however, others have presented convincing evidence that intraresin site separation is not achieved.

Support for hyperentropic efficacy in solid-phase reactions rests on a number of observations and conceptions. Using infrared spectroscopy, both hydrogen-bonded and non-hydrogen-bonded carboxyls were seen on popcorn poly(styrene–divinylbenzene) with pendant carboxyl groups.[8a] This is in contrast to the hydrogen bonding which is usually so extensive in

John I. Crowley is the manager of Printing and Polymer Chemistry, Materials Science Department, GP Division, IBM. He received his B.S. degree from UCLA, his M.S. from CSU Long Beach, and the Ph.D. from UC Berkeley in 1971. From 1949 to 1966 he was employed in the paint and chemical cleaning industries in Southern California, and has been at IBM since 1971. His research interests include polymer bound reagents, spectroscopic and radioanalytic characterization of industrially important polymers, and synthesis of materials for printing technology.

Henry Rapoport was born in 1918 in New York and grew up in Atlantic City. He obtained both S.B. and Ph.D. degrees at Massachusetts Institute of Technology. After 2 years in industry on the collaborative penicillin program, he spent a year as National Research Fellow with Lyndon Small at National Institutes of Health. Presently he is Professor of Chemistry at University of California, Berkeley, where he has been since 1946. His research interests are natural products, bioorganic chemistry, and synthesis.

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

(2) (a) B. Gutte and R. B. Merrifield, *J. Am. Chem. Soc.*, **91**, 501 (1969); (b) B. Merrifield, *Harvey Lect.*, 143 (1971).

(3) C. H. Li and D. Yamashiro, *J. Am. Chem. Soc.*, **92**, 7608 (1970).

(4) (a) O. Grahl-Nielsen and G. L. Tritsch, *Biochemistry*, **8**, 187 (1969); (b) E. Bayer, H. Eckstein, K. Hagele, W. A. Konig, W. Bruning, H. Hagenmaier, and W. Parr, *J. Am. Chem. Soc.*, **92**, 1735 (1970); (c) H. Hagenmaier, *Tetrahedron Lett.*, 283 (1970); (d) J. Meienhofer, P. M. Jacobs, H. A. Godwin, and I. H. Rosenberg, *J. Org. Chem.*, **35**, 4137 (1970); (e) E. Wunsch, *Angew. Chem., Int. Ed. Engl.*, **10**, 786 (1971); (f) G. Losse and R. Ulbrich, *Tetrahedron*, **28**, 5823 (1972); (g) W. S. Hancock, D. J. Prescott, P. R. Vagelos, and G. R. Marshall, *J. Org. Chem.*, **38**, 774 (1973); (h) G. Losse and R. Ulbrich, *Pept., Proc. Europ. Pept. Symp., 12th, 1972*, 153 (1972); (i) H. C. Beyerman, J. Hirt, E. W. B. de Leer, W. van Vossen, and H. A. Billiet, *ibid.*, 170 (1972); (j) P. Fankhauser, B. Schilling, and M. Brenner, *ibid.*, 162 (1972); (k) M. Rothe and J. Mazenek, *Justus Liebigs Ann. Chem.*, 439 (1974); (l) E. Bayer, M. Mutter, R. Uhmann, J. Polster, and H. Mauser, *J. Am. Chem. Soc.*, **96**, 7333 (1974).

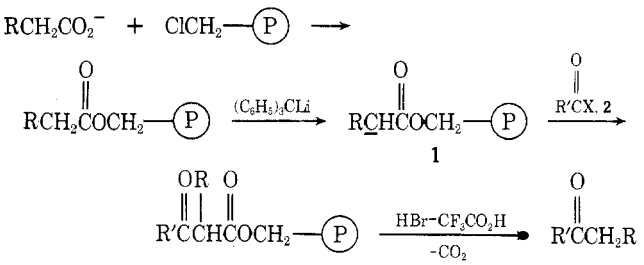
(5) J. I. Crowley and H. Rapoport, *J. Am. Chem. Soc.*, **92**, 6363 (1970).

(6) (a) G. R. Marshall and R. B. Merrifield in "Biochemical Aspects of Reactions on Solid Supports", G. R. Stark, Ed., Academic Press, New York, N.Y., 1971, p 111; (b) R. C. Sheppard, *Pept., Proc. Europ. Pept. Symp., 11th, 1971*, 111 (1971); (c) C. C. Leznoff, *Chem. Soc. Rev.*, **3**, 65 (1974); (d) C. U. Pittman, Jr., and G. O. Evans, *Chem. Technol.*, 560 (1973); (e) C. G. Overberger and K. N. Sannes, *Angew. Chem., Int. Ed. Engl.*, **13**, 159 (1974).

(7) (a) R. B. Merrifield, *Adv. Enzymol.*, **32**, 221 (1969); (b) S. L. Regen and D. P. Lee, *J. Am. Chem. Soc.*, **96**, 294 (1974).

acid spectra that the free carboxyls at 5.79 μm are rarely observed. Similarly,[8b] both free and hydrogen-bonded OH have been observed in poly(4-(2-hydroxyethyl)styrene). The conception of a penetrable polymer network is supported by autoradiographic data[9] which showed the distribution of radiolabeled dipeptides in a microtomed resin bead section to be quite uniform.

Specific allusion has been made[10,11] to the enhanced preference for cyclization over open-chain coupling of peptides bound to high molecular weight poly(nitrophenol) resins. Using co(polystyrene–2% divinylbenzene)[1] higher yields have been achieved[12] in the acylation of resin phenylacetic and acetic esters (1) with *p*-nitro- and *p*-bromobenzoyl chlorides and α-naphthylacetic anhydride (2) relative to solution chemistry. Specifically it is claimed that intraresin reactions are avoided by immobilizing the bound esters, providing an analog of infinite dilution.

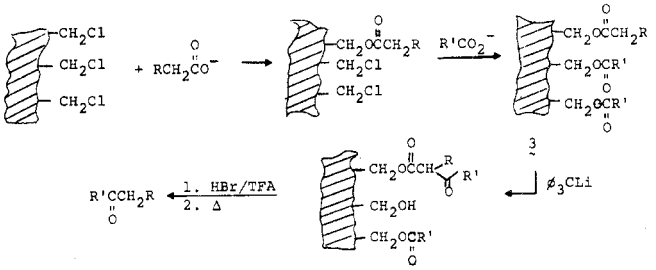


X = Cl, OCOR′; R = C_6H_5,H; R′ = C_6H_4-*p*-NO_2, C_6H_4-*p*-Cl, $CH_2C_{10}H_7$-1 (naphthyl)

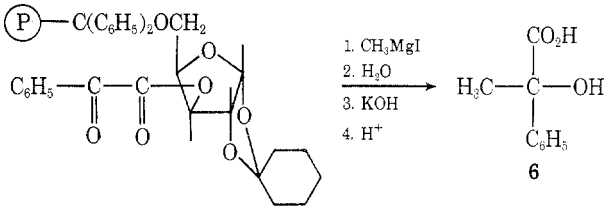
Subsequently the intraresin condensations of phenylacetic, β-phenylpropionic, hexanoic, and octanoic resin esters with benzoate and *p*-chlorobenzoate ester sites bound to the same resins (3) have been reported.[13,14a] High concentrations relative to the previous experimental example are cited as the driving force for the intersite reactions. Analogous solution chemistry provided lower yields and more complex product mixtures. Soluble aliphatic esters could not be induced to react satisfactorily with the enolizable resin esters, and interresin reactions did not occur between different resin particles. On reexamination,[14b] up to 40% self-condensation was observed, with 10–15% generally being found in the absence of competing electrophiles. Solution conditions provided 67% self-condensation, and the authors concluded that short times between addition of base and electrophile are required to minimize self-condensation.

The literature on the physical nature of ion-exchange resins prepared from polymerized co(polystyrene–divinylbenzene) has been reviewed.[15] Concepts such as bead surface, impurity gradients, pore size, and transport channels are used to explain the observation of variations in penetration temperature encountered during sulfonation of the resin. A sharp exothermic inflection in the temperature vs. time curve of sulfonation is observed as reaction temperature is slowly raised. The inflection is interpreted as occurring at the temperature which permits penetration of the bead by sulfuric acid and results in increased sulfonation rates.

Stereochemical selectivity in the asymmetric synthesis of atrolactic acid (6)[16] was assumed to be slightly enhanced by the conformational rigidity of the resin-bound starting material.



R = *n*-C_4H_9, C_6H_5, $C_6H_5CH_2$, *n*-C_6H_{13}; R′ = C_6H_5, C_6H_4-*p*-Cl



Monofunctionalization of diols and dialdehydes has been treated as an example of site separation[17d,e] because the yields of reaction product with a single function were high. It appears that the purification advantages of the resin method were significant; however, monofunctionalization also could be achieved with benzyl chloride and excess diol, or analogous reactants in the aldehyde case. In fact, the oxidation of diols to hydroxy aldehydes via a resin-supported sulfoxonium intermediate was found[17f] not to be competitive with the solution procedure due to significant intrusion of difunctionalization.

Resin-bound analogs of transition-metal catalysts are currently being vigorously investigated with the hope that: (1) resin binding will provide typical homogeneous catalytic chemistry plus the convenience and economy of heterogeneous catalysts; (2) resin binding can change the steric environment and consequently the substrate specificity found in homogeneous systems; and (3) rigid resin binding should provide catalytic sites containing a single metal atom, avoiding the formation of ligand-bridged species (4) which are inactive in analogous solution cases.[18a]

(8) (a) R. L. Letsinger, M. J. Kornet, V. Mahadevan, and D. M. Jerina, *J. Am. Chem. Soc.*, **86**, 5163 (1964); (b) F. Camps, J. Castells, M. J. Ferrando, and J. Font, *Tetrahedron Lett.*, 1713 (1971).

(9) R. B. Merrifield and V. Littau, *Pept., Proc. Eur. Pept. Symp., 9th, 1968*, 179 (1968).

(10) M. Fridkin, A. Patchornik, and E. Katchalski, *Israel J. Chem.*, **3**, 69 (1965).

(11) M. Fridkin, A. Patchornik, and E. Katchalski, *J. Am. Chem. Soc.*, **87**, 4646 (1965).

(12) A. Patchornik and M. A. Kraus, *J. Am. Chem. Soc.*, **92**, 7587 (1970).

(13) M. A. Kraus and A. Patchornik, *Israel J. Chem.*, **9**, 269 (1971).

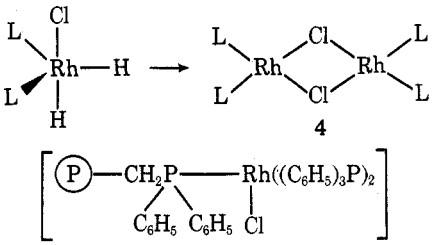
(14) (a) M. A. Kraus and A. Patchornik, *J. Am. Chem. Soc.*, **93**, 7325 (1971); (b) M. A. Kraus and A. Patchornik, *J. Polym. Sci., Polym. Symp.*, **47**, 11 (1974).

(15) J. A. Patterson in ref 6a, p 189.

(16) M. Kawana and S. Emoto, *Tetrahedron Lett.*, 4855 (1972).

(17) (a) E. H. Jardine, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. A*, 1574 (1967); (b) R. H. Grubbs and L. C. Kroll, *J. Am. Chem. Soc.*, **93**, 3062 (1971); (c) R. H. Grubbs, L. C. Kroll, and E. M. Sweet, *J. Macromol. Sci., Chem.*, **7**, 1047 (1973); (d) C. C. Leznoff and J. Y. Wong, *Can. J. Chem.*, **50**, 2892 (1972); (e) J. Y. Wong and C. C. Leznoff, *ibid.*, **51**, 2452 3756 (1973); (f) G. A. Crosby, N. M. Weinshenker, and H. S. Uh, *J. Am. Chem. Soc.*, **97**, 2232 (1975); (g) N. M. Weinshenker, G. A. Crosby, and J. Y. Wong, *ibid.*, **97**, 1966 (1975).

(18) (a) J. P. Collman, *Acc. Chem. Res.*, **1**, 136 (1968); (b) W. O. Haag and D. D. Whitehurst, *Int. Congr. Catal., 5th, Abstr.*, 30 (1972); (c) K. G. Allum, R. D. Hancock, S. McKensie, and R. C. Pitkethly, *ibid.*, 29 (1972); (d) G. Strathdee and R. Given, *Can. J. Chem.*, **52**, 3000 (1974).



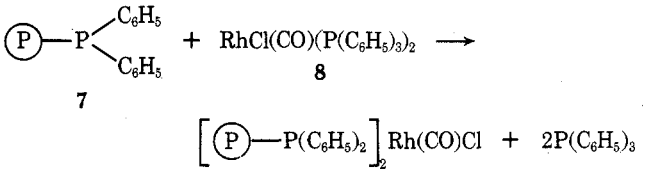
4

5

A resin analog (**5**) of tris(triphenylphosphine)chlororhodium[17a] has been employed[17b,c] as a hydrogenation catalyst. This polymer-bound catalyst was considerably less active than the unbound material, and a significantly more rapid decline in activity occurred when the bulk of the olefin substrate was increased. The size selectivity was interpreted as proof of solvent channels into the catalytic cleft or cavity in a semiordered polymer. While no direct spectroscopic evidence for actual bonding of the phosphinatorhodium to the polymeric phosphine was presented, such evidence has been developed by others.[18b-d] Although originally,[17b,c] and subsequently in several reviews,[6c-e] a single bond was assumed to be involved in the attachment of the polymer to each rhodium, subsequent data[19] established that two ligands of the catalyst are exchanged for polymeric phosphine bonds. Hydroformylation,[18b] olefin hydrogenation and cyclotrimerization,[18c] and deuterium exchange with alcohols[18d] have been reported. Multiple binding described in these reports is believed to occur from nearest and next-nearest neighboring groups and neighboring fixed chains.

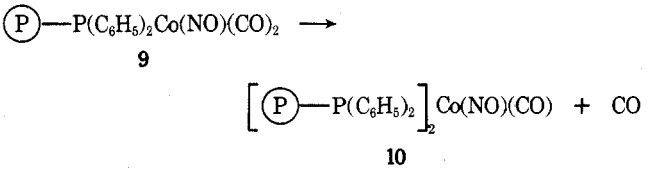
Influenced by these reports, three recent reviews[6c-e] of nonpeptide solid-phase chemistry have all adopted the view that site separation is easily attainable. Exceptions are considered to result from poor choices of reaction conditions.

Contradicting these conclusions are the findings of other experimenters in solid-phase organic chemistry. In an effort to prepare catalysts more active for hydrogenation than the homogeneous material, the resin-bound triphenylphosphine (**7**) was treated with rhodium (**8**) and iridium complexes.[19] In the rhodium case, analysis of the solvent from the polymer reaction showed that at least two triphenylphosphines were always released for each metal atom incorporated.



7 8

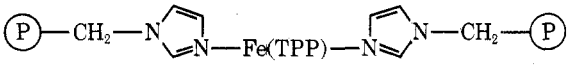
In cases where monosubstitution is kinetically favored and triphenylphosphines are not replaced, 1:1 metal polymer complexes could be prepared. For example 1 equiv of $Co(NO)(CO)_3$ reacted with 2 equiv of resin phosphine to yield 1:1 metal polymer complex (**9**) under mild conditions. However, the complex in which two polymeric ligands were attached to a single cobalt (**10**) resulted from further heating. It was concluded that this situation arises because of



9 10

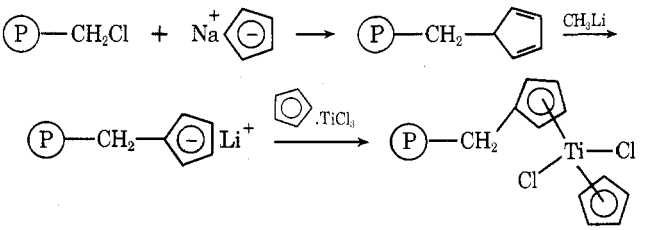
the flexibility of the co(polystyrene–2% divinylbenzene) and can be expected in all cases where bispolymeric reactions are kinetically competitive with the desired reaction with a single resin function. Reduced levels of substitution and more highly cross-linked resins were tested, but provided no advantage.

Subsequently another failure to achieve isolation was reported;[20a] in this instance, of resin-bound imidazole treated with (*meso*-tetraphenylporphyrin)-iron. The product was apparently the six-coordinate diamagnetic complex with two resin-bound imidazoles (**11**). Later[20b] a pentacoordinate Co^{II}(TPP) was successfully bound to resin by a single imidazole.



11

The extent of bispolymeric binding could be substantially reduced by using 20% divinylbenzene polymer.[21a,b] In this experiment, 1.4 mol of cyclooctadiene was released per mol of metalloorganic complex absorbed. This experimental approach was successful in producing a polymer-bound titanocene catalyst (**12**) which was 25–120 times as active as its nonsolid-phase analog. The conclusion was reached that



12

2% cross-linked resin is not sufficiently rigid to prevent dimerization. Further understanding of the generality of multiple binding of bound catalysts has appeared[21c-e] in which some of the multiply bound metal atoms are identified as new cross-links formed during the cyclic processing of the resin-catalyst. Decreased catalytic activity and difficulty of regeneration are no doubt related to multiple metal bonding to resin.

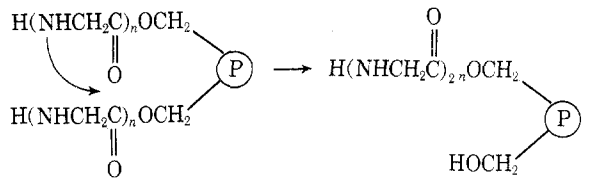
Interchain aminolysis of resin peptide esters by deprotected amino groups (**13**)[22a] has been reported. The hazards which this side reaction poses for high-purity oligomer synthesis have been signalled, as well

(19) J. P. Collman, L. S. Hegedus, M. P. Cooke, J. R. Norton, G. Dolcetti, and D. N. Marquardt, *J. Am. Chem. Soc.*, **94**, 1789 (1972).

(20) (a) J. P. Collman and C. A. Reed, *J. Am. Chem. Soc.*, **95**, 2048 (1973); (b) J. P. Collman, R. R. Gagne, J. Kouba, and H. Ljustberg-Wahren, *ibid.*, **96**, 6800 (1974).

(21) R. H. Grubbs, C. Gibbons, L. C. Kroll, W. D. Bonds, Jr., and C. H. Brubaker, Jr., *J. Am. Chem. Soc.*, **95**, 2373 (1973); (b) W. D. Bonds, Jr., C. H. Brubaker, Jr., E. S. Chandrasekaran, C. Gibbons, R. H. Grubbs, and L. C. Kroll, *ibid.*, **97**, 2128 (1975); (c) C. U. Pittman, Jr., and R. M. Hanes, *Ann. N.Y. Acad. Sci.*, **239**, 76 (1974); (d) C. U. Pittman, Jr., L. R. Smith, and R. M. Hanes, *J. Am. Chem. Soc.*, **97**, 1742 (1975); (e) C. U. Pittman, Jr., and L. R. Smith, *ibid.*, **97**, 1749 (1975); (f) L. D. Rollman, *ibid.*, **97**, 2132 (1975).

(22) (a) H. C. Beyerman, E. W. B. de Leer, and W. van Vossen, *J. Chem. Soc., Chem. Commun.*, 929 (1972); (b) G. C. Windridge and E. C. Jorgensen, *J. Am. Chem. Soc.*, **93**, 6318 (1971); *Intra-Sci. Chem. Rep.*, **5**, 375 (1971).

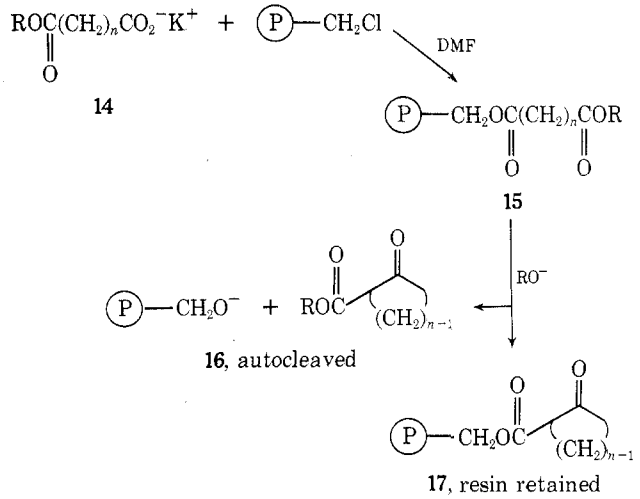


13

as its possible relation to observations of failure sequences in solid-phase peptide synthesis. Solid-phase coupling of histidine residues to resin-bonded polypeptides is accompanied by significant racemization,[22b] and this side reaction has been minimized by using ω-imidazole basicity-reducing reagents. The participation of resin-bound pendant imidazoles in the racemization of other chiral groups may be implicated.

It is interesting that our report[5] of Dieckmann closure of adipate and pimelate resin esters to cycloalkanonecarboxylates has frequently been treated as an example of successful utilization of hyperentropic efficacy in the solid-phase method.[6c,e] Indeed, in common with many other practitioners of solid-phase organic synthesis, we anticipated that functionalized sites would remain separated during reaction. However, we have reported both the successful cyclization of those dioate esters for which cyclization is entropically favored and our failure in the more significant test with sebacic acid derivatives.[23]

Resin esters (**15**) were prepared from potassium salts of alkanedioic monoesters (**14**) and chloromethylated co(polystyrene–2% divinylbenzene). Cyclization using potassium alkoxide occurred in both directions, yielding autocleaved alkyl 2-alkanonecarboxylate (**16**) and resin-retained keto ester (**17**). All resin esters were obtained with total conversion of the chloromethyl groups to ester functions. None of these results are confounded by the intervention of alkylation from polymeric benzyl chloride or by interference from quaternized centers which always accompanies ester formation from triethylammonium carboxylates.[7]



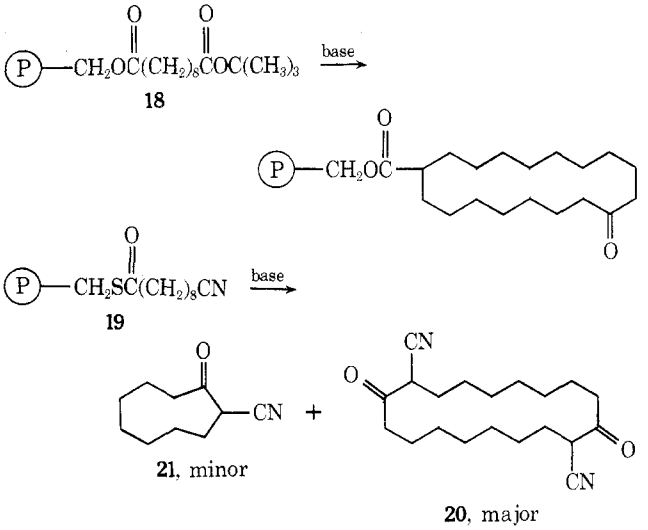
14 **15** **16**, autocleaved **17**, resin retained

In connection with the failure to achieve significant yields of cyclononanone products, we have presented three lines of evidence which seem unequivocably to establish that intraresin site–site reactions are rapid compared with the desired cyclization.[23,24]

Table I
Radioactivity Distribution in Keto Esters

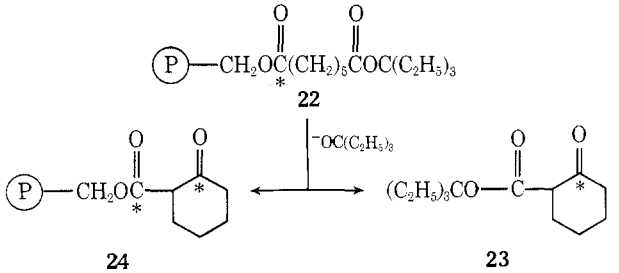
	Keto label, %	Ester label, %
Autocleaved keto ester, **23**	99.7	0.3
Resin retained keto ester, **24**	48	52

Dimeric diketo esters were identified from attempted cyclization of *tert*-butyl sebacyl resin ester (**18**). Diketodinitrile **20** was isolated from the attempted cyclization of ω-cyanopelargonyl thiol resin ester (**19**). Much smaller quantities of 2-cyanocyclononanone (**21**) were obtained from the reaction, and the monoketone was not converted to dimer under these conditions. These product observations point toward site–site condensations as the most straightforward mechanism.



18 **19** **21**, minor **20**, major

A kinetic analysis of the cyclization of triethylcarbinyl pimeloyl resin ester (**22**) with potassium triethylcarbinylate was possible because we had prepared the resin ester with a radiolabel uniquely located at the resin ester carbonyl. The very hindered base was used in order to minimize competitive transesterification which scrambles the label (double asterisk) and removes ester from the resin prior to cyclization.



22 **24** **23**

The distribution of label resulting from cyclization in the two directions is shown in Table I. Other data unequivocally established the intervention of transesterification with all bases less hindered than triethylcarbinylate.[24,25] We have interpreted these results as proving that resin benzylic alkoxide participated

(23) (a) J. I. Crowley, T. B. Harvey, III, and H. Rapoport, *Polym. Prepr., Am. Chem. Soc., Div. Polym. Chem.*, 13 (2), 958 (1972); (b) J. I. Crowley, T. B. Harvey, III, and H. Rapoport, *J. Macromol. Sci., Chem.*, 7, 1118 (1973).

(24) J. I. Crowley and H. Rapoport, manuscript in preparation.

(25) H. C. Beyerman, H. Hendriks, and E. W. B. de Leer, *Chem. Commun.*, 1668 (1968).

Table II
Relative Rates of Keto Ester Formation

	Yield	% label	Relative rate
Autocleaved, **23**	46		
Direct		99.4	163
Transesterified, path 2		0.6	1
Resin Retained, **24**	10		
Direct		4	1.4
Transesterified, path 1		96	35

rapidly in the formation of bisresin pimelate (**25**).

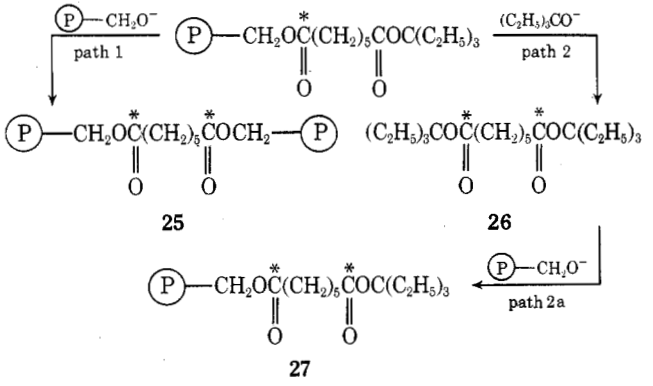


Table II lists the relative rates of the four processes taking place. Relative rates are obtained as the relative values of yield times percent label distribution. The pattern of unique labeling in the product from direct autocleavage is not observed in the case of resin-retained keto ester. The scrambling observed for resin-retained keto ester can occur either by path 1, transesterification to bisresin ester, or by path 2a, serial transesterification to bis(triethylcarbinyl) pimelate (**26**) and retransesterification to scrambled resin ester.

If the major source of scrambled keto ester detected after acid hydrolysis is resin ester **27**, then the product ratio between scrambled triethylcarbinyl keto ester and scrambled resin keto ester must be the same as the product ratio for nonscrambled products. However, these ratios are 1:35 and 163:1.4, respectively. The major pathway to scrambled resin keto ester must be path 1, through the bisresin ester (**25**). Independent routes to the two resin keto esters were ruled out by evidence analyzed in the original reference.

The extent of intraresin reactions[23] was quantified by a third approach. Resin carboxylates were converted to intraresin anhydrides and analyzed by further conversion to radiolabeled amide. The variation in intraresin anhydride with degree of resin substitution is shown in Figure 1. These data establish that carboxylic acid groups, directly attached to the pendant phenyl groups of polystyrene, are not isolated during reaction. Intraresin reactions occur readily even at 0.5% resin substitution (0.05 mmol/g of resin).

One of the samples of radiolabeled resin ester was subjected to sizing by flotation[26] and by sieving. We found samples varying in diameter by a factor of five to possess constant specific activity. Thus there may not be a specific set of polymeric sections or sites

(26) J. W. M. Baxter, M. Manning, and W. H. Sawyer, *Biochemistry*, 8, 3592 (1969).

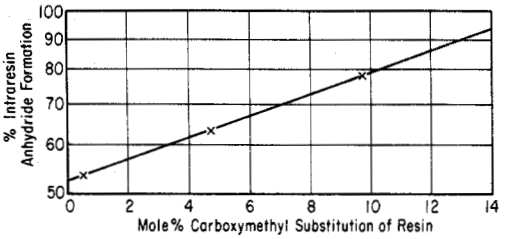


Figure 1. Intraresin anhydride formation as a function of degree of resin carboxymethyl substitution.

which can properly be considered as surface sites. Polymer swelling is so extensive that solvent-swollen beads are rather like very concentrated dissolved polymer.[27] Much of the total length of the polymer strands is translocated to and from the bead surface during the period of reaction, 1.5 to 5 min.

The contradiction between the two interpretations of site isolation is striking. Any explanation must eliminate the contradiction, and account in a rational, testable manner for the graduation of effects observed between the extremes of apparent substantial site isolation and as much as 80% site–site interactions. The following criteria should be employed in any analysis.

(1) Careful distinction must be made between purification effects and hyperentropic efficacy in solid-phase synthesis.

(2) Immobilization of moieties bound to the resin can be tested only in the case of reactions involving real entropic and/or enthalpic barriers. These reaction types, in turn, must be distinguished because immobilization on the resin will subject them to different competitive side reactions.

(3) Controls should be employed to identify and quantify gross surface and/or catalytic effects occasioned by the presence of huge extents of surface in any resin reactions.

(4) The same degree of attention should be paid to the characterization of resin reactants and resin products as that applied in solution chemistry. The nature and extent of side reactions are also crucial in assessing solid-phase organic reactions.

(5) Results from appropriately modeled non-resin-bonded chemistry must be compared to the solid-phase results.

(6) Close attention must always be devoted to the intervention of special effects whose origin is the polymeric nature of solid-phase reactants. We are specifically referring to the enhanced likelihood that competing side reactions will effectively increase the degree of cross-linking during the reaction, or that kinetically anomalous effects of solvent changes will be seen.

The purification advantages of the solid-phase method are clearly substantiated.[5,17e,28,29] This advantage has been frequently erroneously interpreted as resulting from site isolation.

(27) H. W. Relles and R. W. Schluenz, *J. Am. Chem. Soc.*, **96**, 6469 (1974).

(28) (a) F. Camps, J. Castells, J. Font, and F. Vela, *Tetrahedron Lett.*, 1715 (1971); (b) W. Heitz and R. Michels, *Angew. Chem., Int. Ed. Engl.*, **11**, 298 (1972); (c) S. V. McKinley and J. W. Rakshys, Jr., *J. Chem. Soc., Chem. Commun.*, 134 (1972); (d) J. M. Frechet and C. Schuerch, *J. Am. Chem. Soc.*, **93**, 492 (1971).

(29) N. M. Weinshenker and C. M. Shen, *Tetrahedron Lett.*, 3281, 3285 (1972).

A reaction which is normally rapid, and which effectively competes with side reactions at reasonably high concentration, cannot be used to test for the ability of the resin to isolate attached moieties. Reactions whose velocity is reduced by unfavorable enthalpic changes will suffer from the intrusion of ambiguous or undesirable side reactions in solid-phase chemistry. A proper probe of hyperentropic utility must use reactions which do not succeed under solution conditions.

Those reactions whose products appear to support the case for hyperentropic efficacy have usually been carried out at room temperature, or lower, and in solvents which are less effective in swelling the resin beads. Thus, in our hands, the only reaction conditions which yielded cyclononanone derivative were conducted at room temperature in ether, a relatively poor resin-swelling solvent. Temperature has been identified as a parameter of significance in achieving conditions equivalent to high dilution,[12] and its role in catalytic reactions has been considered.[21c-e]

A rather fundamental deficiency in using the ester acylation results to support site immobilization is the kinetic facility of these reactions. Intersite reaction products from the Claisen condensation of two esters would not be expected to compete successfully with acid chloride or anhydride acylation. In fact, subsequent work[14] established that the Claisen condensation does occur in similar resins. Here the desired products were favored by manipulation of the relative concentrations of the two esters and steric perturbation of the enolizable ester loci. They were also found in the absence of kinetic competition from stronger electrophiles.

The solution controls were treated in a manner which does not permit the high dilution effects and the purification effects of the resin to be separated. Any undesired reaction products from the nonenolizable acid chlorides and anhydrides in the resin case were removed from the desired reaction products in a step preliminary to cleavage. This step has no analog in the nonresin control example. Comparison of the filtrate from this preliminary step with the product mixture from solution chemistry would have been of interest.

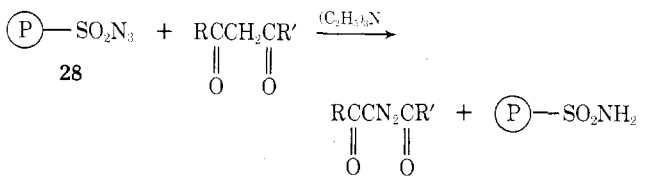
The earlier work[10,11] on cyclic peptides does not satisfy the criterion of reactions displaying entropic deficits in solution chemistry. Dieckmann cyclization of adipates and pimelates similarly fails this criterion. Five- and six-membered cyclic products are kinetically favored because of a favorable balance of entropic and enthalpic relationships.

An important class of evidence presented on behalf of site separation has been obtained by examination of dry, solvent-free, resin products. These data appear to be improperly used in this argument. Molecular events which have previously occurred during solution chemistry on solvent-swollen mobile resin cannot be monitored by examination of the dry resin. Extension of the polymer strands in solvent will have disappeared.

Other instances of solvent-free resin-bound reagents include reports of resin-isolated $AlCl_3$.[30] No evidence is presented which defines the binding of the $AlCl_3$ to the resin. The authors suggest that the catalyst is freed by solvent during the reaction. On the other hand, the resin-bound Lewis catalyst is sufficiently isolated in the dry, solvent-free resin that it is stable to atmospheric moisture and even to slurrying in water.

An interesting claim is made that the polymer-bound material has its activity sufficiently modified that the yield of ether from acid-labile dicyclopropylcarbinol is greatly increased relative to the nonresin $AlCl_3$. One cannot conclude from the data presented how carefully the nonresin model was designed. A possible conclusion is that higher yields of ether would be obtained from lower concentrations of nonresin-bound $AlCl_3$; these lower concentrations may correspond to the actual concentrations realized in the resin catalyst reactions.

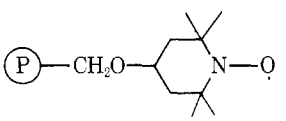
The suggestion[30a] was made that hazardous and unstable reagents can be prepared with useful activity and much greater storage stability. This has been experimentally supported[31] in work involving the preparation of polymer-bound tosyl azide (**28**), and its use in diazo transfer reactions with β-diketones.



Our own studies required a carefully characterized resin benzyloxycarbonyl chloride. When this was prepared on co(polystyrene–2% divinylbenzene), we also observed that it was more stable to storage than the neat liquid, and that it could be manipulated in water without reacting. These data serve to characterize the dry solvent-free resin, but they do not describe the nature or extent of intraresin interactions when slurried in swelling solvent.

The relatively complete oxidation of cysteine resin derivatives to cystine derivatives was demonstrated[32] while the amino acid moieties were attached to the resin. This result has special significance for attempts to prepare cyclic peptides.[6b,33]

The spin-label technique[34] used ESR to assess the mobility of the resin sites labeled by attachment of 2,2,6,6-tetramethyl-4-piperidinyl-1-oxy (**29**). The



29

data are interpreted to prove that those solvents which swell the polystyrene matrix the most will allow for the greatest mobility of resin-bound substances. Increased cross-link density in the polystyrene also led to increased correlation times for the

(30) (a) D. C. Neckers, D. A. Kooistra, and G. W. Green, *J. Am. Chem. Soc.*, **94**, 9284 (1972); (b) E. C. Blossey, L. M. Turner, and D. C. Neckers, *Tetrahedron Lett.*, 1823 (1973).

(31) W. R. Roush, D. Feitler, and J. Rebek, *Tetrahedron Lett.*, 1391 (1974).

(32) W. Lunkerheimer and H. Zahn, *Justus Liebigs Ann. Chem.*, **740**, 1 (1970).

(33) E. Flanigan and G. R. Marshall, *Tetrahedron Lett.*, 2403 (1970).

(34) (a) S. L. Regen, *J. Am. Chem. Soc.*, **96**, 5275 (1974); (b) C. L. Hamilton and H. McConnell, "Structural Chemistry and Molecular Biology", A. Rich and N. Davidson, Ed., W. H. Freeman, San Francisco, Calif., 1968, p 115.

label and to the expected diminution in polymer swelling.

Cross-linking may be increased significantly during a resin reaction. For example, the formation of anionic exchange resin from chloromethylated resin and amines has been studied.[7b] Decreasing the percentage of chloromethylation or the length of the methylene chain between the amino functions results in less chloride displacement. Two explanations were considered: either neutral backbone rigidity or charge clustering during the formation of the ammonium centers, with a preference for the latter. This effect can certainly be operating, to an as yet undetermined extent, in all resin esters prepared from triethylammonium carboxylates because of the concurrent quaternization. A number of peptide reports[35] have concluded that the extent of swelling and other physical properties of the resin peptides may change as the peptide chain is lengthened.

The weight of existing evidence points to the failure of co(polystyrene–2% divinylbenzene) to provide significant hyperentropic efficacy. Contrary interpretations are based upon reactions which are not entropically disfavored or subject to kinetically significant enthalpic deficits. Insufficient care has been exercised in distinguishing between site isolation and purification effects. Data obtained on dry solvent-free beads have been improperly adduced in drawing conclusions about the solvent-swollen state of the resin reactants and products.

Some data have been presented which suggest a small advantage for cyclization over oligomerization and for modest site separation. In these cases, decreased resin mobility appears to have been achieved by lowering reaction temperatures, decreasing the swelling ability of the solvents, and greatly increasing the degree of resin cross-linking. Data in several other cases may also be reasonably explained by assuming that cross-linking has been significantly increased during the reaction.

Analytical Problems in Solid-Phase Synthesis. Analysis of resin-bound reactants and products is severely restricted. The most informative direct method presently employed is infrared spectroscopy. The advantages of infrared are associated with the possibility of making unambiguous transmission mode measurements on insoluble polymers with approximately the same sensitivity as that attained with low molecular weight compounds. However, the complex spectrum of the resin tends to obscure the spectral features of the attached moiety.

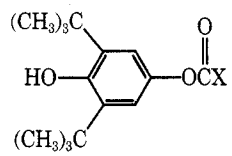
We have found that difference spectra,[24] using purified unreacted co(polystyrene–2% divinylbenzene) in the reference beam, dramatically simplify the spectra of many solid-phase compounds. We have routinely quantified the extent of chloromethylation by such a procedure, employing a standard curve prepared from resins of known percentages of chlorine.

The analytical inadequacies of solid-phase synthesis have been most strongly felt in peptide applications. Most of the analytical developments have been reported in this literature.[36] Automation of the peptide-synthesizing process should not be considered complete until automatic analytical data can be provided in a feedback mode during the synthesis.[37]

Analysis of the solution in which the solid-phase reaction is conducted may prove very useful.[37b] Nonaqueous potentiometric titration has been used to monitor free amino groups at each solid-phase coupling step, even though the analysis may not exactly reflect the stoichiometry within the resin. 2-Hydroxy-1-naphthaldehyde has been used[37c] to measure residual free amino groups of the resin. The aldehyde is converted to Schiff base, excess aldehyde washed out, and the reacted aldehyde displaced with a soluble amine. The resulting solution can be analyzed spectrophotometrically. A serious disadvantage of the reported procedure is that more than 12 h is required for analysis per coupling step.

Proton NMR integration of the supernatant solution in a resin reaction has been used[27] to monitor the formation of phosphine dichlorides. Atomic absorption was used to measure residual metallic impurities in the resin. Particularly informative data have been obtained with radiolabeled resins of various kinds.[38] It is especially convenient that labeled resin could be counted directly with the use of a suspending agent such as Cab-o-Sil.[39]

ESR has been used to analyze the mobility of a spin-labeled resin[34] and to evaluate the paramagnetism of the resin titanocene catalyst.[21] The line broadening of paramagnetically marked half-esters (**30**) and analogous resin esters has been analyzed.[40a]



30

X = $(CH_2)_2CO_2H$, $(CH_2)_3CO_2H$, $(CH_2)_4CO_2H$, $(CH_2)_3CO_2(CH_2)_3OH$

The results suggest much greater dependence of the line width on resin loading than on the length of the dioate link between the resin and the 2,6-di-*tert*-butyl-4-hydroquinonyl marker.

X-ray backscattering from an ion microprobe beam has been used to scan sections of rhodium-phosphinated polystyrene.[40b] Metal concentration was uniformly distributed throughout the beads where stoichiometric or excess metal reactant had been employed in the synthesis. Under metal-deficient conditions, the metal was confined to an annular shell about one-third the bead radius in thickness. Resuspension of these beads in a strongly swelling solvent would be of interest, since a more uniform distribution should result.

There are three techniques which appear to be at,

(35) G. R. Marshall, W. S. Hancock, D. J. Prescott, W. L. Nulty, J. Weintraub, and P. R. Vagelos, *Pept., Proc. Eur. Pept. Symp., 11th, 1971,* 185 (1971).

(36) A. Marglin and R. B. Merrifield, *Annu. Rev. Biochem.,* 860 (1970).

(37) K. Brunfeldt, *Pept., Eur. Pept. Symp., 12th, 1972,* 141 (1972); (b) K. Brunfeldt, T. Christensen, and P. Villemoes, *FEBS Lett.,* **22,** 238 (1972); (c) K. Esko, S. Karlsson, and J. Porath, *Acta Chem. Scand.,* **22,** 3342 (1968).

(38) (a) H. C. Beyerman, P. R. M. van der Kamp, E. W. B. de Leer, W. Maassen van den Brink, J. H. Parmentier, and J. Westerling, *Pept., Proc. Eur. Pept. Symp., 11th, 1971,* 138 (1971); (b) W. Geising and S. Hornle, *ibid.,* 146 (1971).

(39) (a) C. L. Krumdieck and C. M. Baugh, *Biochemistry,* **8,** 1568 (1969); (b) T. B. Harvey, III, Thesis, University of California, Berkeley, Calif., 1972.

(40) (a) H. B. Stegmann, H. Breuninger, and K. Scheffler, *Tetrahedron Lett.,* 3793 (1972); (b) R. H. Grubbs and E. M. Sweet, *Macromolecules,* **8,** 241 (1975).

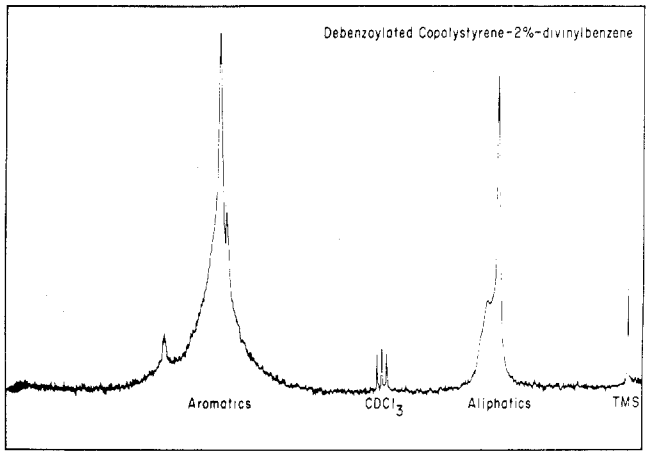


Figure 2. Natural abundance ^{13}C NMR of debenzoylated co-(polystyrene–2% divinylbenzene).

or nearing, the level of development sufficient to encourage attempts at resin analysis. These are ^{13}C NMR,[41] Raman,[42] and ENDOR spectroscopy.[43] We have determined that the alkyl and aromatic carbons of the co(polystyrene–2% divinylbenzene) can be easily identified by natural abundance ^{13}C NMR, as shown in Figure 2.[44] Use of specific enriched ^{13}C functionality on the resin could permit observation of concentrations of the magnitude now being used in solid-phase reactions. It is possible the resin functionality can be observed in natural abundance with an instrument capable of using the Allerhand probe.[45]

Of these three, the ENDOR (electron–nuclear double resonance) technique is least familiar to organic chemists. As developed by Feher,[43] it involves the observation of NMR transitions via ESR and possesses the high sensitivity of ESR while retaining the advantages in resolution associated with NMR. Although ENDOR has mainly been used by solid-state physicists, it has been applied to several chemically interesting problems. ENDOR has been used as an analytical tool to evaluate radiation damage mechanisms in proteins,[46] to study hydrogen bonding in solids,[47] and to study the dynamics of the rather unusual C–H··O type hydrogen bonds thought to be important for determining the conformation of some polypeptide units.[47]

A most impressive application of ENDOR is the observation[48,49] of ENDOR signals from ^{13}C in natural abundance in 1% deuterated malonic acid crystals. The sensitivity of this technique is several orders of magnitude higher than that of conventional NMR. Since it depends upon the presence of a paramagnetic probe in the neighborhood of moieties of interest, one can anticipate that such probes could be diffused into the polymer, or bound covalently. Irradiative approaches like those used in ESR may also be applicable.

Side Reactions in Solid-Phase Organic Synthesis. The side reactions occurring in solid-phase synthesis of polypeptides have been described only as the specific difficulties presented by them have been identified in peptide products. With the exception of failure sequences and interchain aminolysis, little quantitative work has been done. These side reactions, especially as they inhibit complete coupling to the growing peptide chain, place an upper limit on the length of pure polypeptide capable of synthesis. This problem has received major strategic attention in the past 2 years.

Very little of this type of work has been reported in the nonpeptide applications of the procedure. Resin-bound diester-containing quaternary ammonium carboxylates failed to cyclize under Dieckmann conditions to cyclopentanone- and cyclohexanonecarboxylates. Hoffmann degradation of the quaternary salts was probably the competitive process. Transesterification results have already been described. Resin benzylate will displace triethylcarbinylate at a rate competitive with Dieckmann closure of hindered pimelates to autocleaved or resin-bound keto ester.

During mass spectrometric and chromatographic characterization of several products from resin reactions, we identified benzoates or benzoic acid as a contaminating species. Consideration of the possible sources suggested that we were observing benzoate groups originally present in the resin because benzoyl peroxide had been used as a catalyst for the polymerization of the styrene–divinylbenzene mix. Treatment of unfunctionalized beads with *tert*-butoxide in refluxing toluene resulted in isolation of benzoic acid and disappearance of the ester carbonyl from the resin.

We have cited these examples of a significant but essentially unexplored aspect of resin chemistry. Increased attention to side reactions in solid-phase organic synthesis will permit increased efficiencies in resin utilization and will greatly contribute to defining the limits of utility of any specific solid-phase procedure. The rapidly growing interest in recycling and reusing solid-phase reagents[17f,21c,f] will necessitate such study.

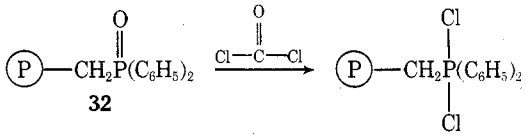
Few solid-phase reactions are conducted with pure resin esters because the triethylamine esterification methods do not go to completion. Several procedures, using potassium[4c,24,50] and cesium carboxylates[51] and dimethylformamide have been described for which complete conversion to ester has been verified. A relative decrease in side reactions should result from the substitution of these newer methods of esterification.

The Design of Experimental Objectives in Solid-Phase Organic Synthesis. Chemical reactions which take place reasonably successfully under solution conditions cannot be employed to test for site isolation in analogous resin cases. However, such resin chemical processes can possess great merit; in

(41) (a) M. W. Duch and D. M. Grant, *Macromolecules*, **3**, 165 (1970); (b) G. C. Levy, *Acc. Chem. Res.*, **6**, 161 (1973).
(42) P. J. Hendra, *Adv. Polym. Sci.*, **6**, 151 (1969).
(43) G. Feher, *Phys. Rev.*, 500 (1956).
(44) We have employed a Varian CFT-20 instrument.
(45) (a) A. Allerhand, R. F. Childers, and E. Oldfield, *J. Magn. Reson.*, **11**, 272 (1973); (b) E. Oldfield and A. Allerhand, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 3531 (1973).
(46) H. C. Box, E. E. Budzinski, and W. R. Potter, *J. Chem. Phys.*, **61**, 1136 (1974).
(47) (a) N. S. Dalal, C. A. McDowell, and R. Srinivasan, *Chem. Phys. Lett.*, **4**, 97 (1969); (b) N. S. Dalal and C. A. McDowell, *Phys. Rev.* [*Sect.*] *B*, **5**, 1074 (1972); (c) N. S. Dalal, J. A. Hebden, and C. A. McDowell, *J. Magn. Reson.*, **16**, 312 (1974).
(48) R. C. McCalley and A. L. Kwiram, *Phys. Rev. Lett.*, **24**, 1729 (1970).
(49) L. R. Dalton and A. L. Kwiram, *J. Am. Chem. Soc.*, **94**, 6930 (1972).
(50) B. Green and L. R. Garson, *J. Chem. Soc. C*, 401 (1969).
(51) B. F. Gisin, *Helv. Chim. Acta*, **56**, 1476 (1973).

general these advantages will be related to enhanced purification.

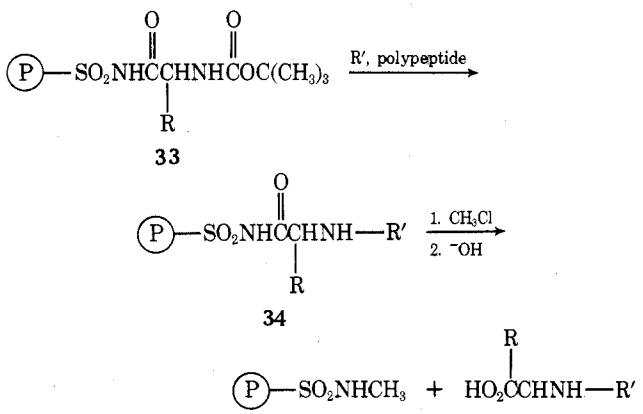
An aspect of resin-bound chemistry recently receiving considerable attention is the reuse of specifically functionalized resin. For example, bromo- or iodomethylated polymer obtained from HI or HBr cleavage of resin esters[52] may serve as a reusable reagent. Only slightly impaired effectiveness was reported[16] for the polymer-bound sugar when it was reused in a straightforward asymmetric synthesis. In the use of resin-bound trisubstituted phosphine dichlorides (**31**) as easily removable reagents for the synthesis of acid chlorides, imidoyl chlorides, and nitriles, the product resin phosphine oxide (**32**) was quite successfully reconverted to starting reactant with phosgene.[27]



32 **31**

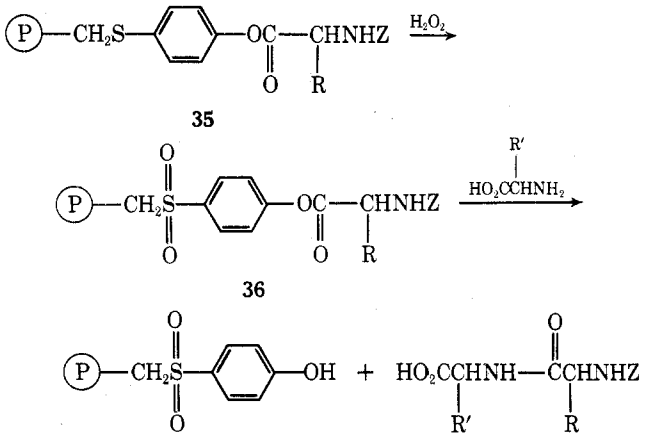
Several reports on polymer bound catalysts have included data on reusability, including the recently reported[53] polymer-bound nickel dibromophosphinato complex which catalyzes butadiene dimerization to (*E,E*)-1,3,6-octatriene in high yield.

There are several examples in the peptide literature utilizing what has been called the safety catch principle.[54] In this case, polystyrene sulfonylamides were allowed to react with 2,4,5-trichlorophenyl esters of protected amino acids. These resin bound amino acids (**33**) could be deprotected and coupled



33 **34**

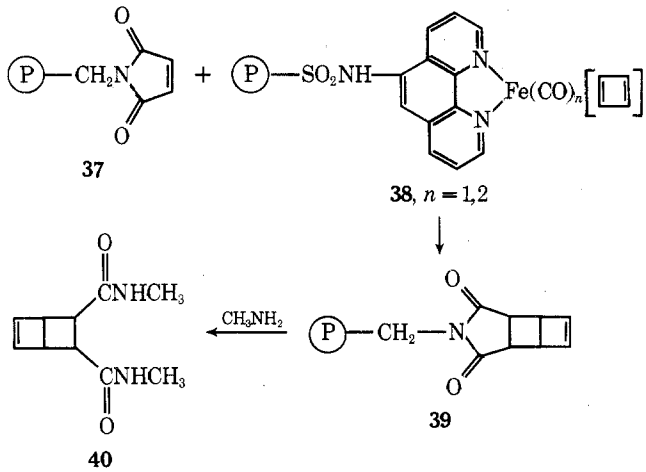
and the cyclic process continued until the desired peptide had been obtained. Lability to cleavage was obtained by alkaline hydrolysis of the N-methylated sulfonamide (**34**). In the work cited there are numerous facets requiring improvement, including incomplete reactions and side reactions. However, the principle has merit in maintaining bonds to the resin under a variety of reaction conditions. Analogous processes had earlier employed the conversion of thiol ether **35** to sulfone **36** as a labilization procedure.[55]



35 **36**

There are two applications which take advantage of the heterogeneous nature of the solid-phase reactants and which suggest themselves for further experimental exploitation. An inverse addition of chlorodiphenylphosphine to a bis-heterogeneous mixture of lithium metal and chloromethylated beads worked out smoothly and avoided alternative techniques which seemed likely to trap large quantities of air and water.[27]

In the second experiment two physically distinct and separable resins have been combined to devise an interesting trap for reactive intermediates.[56] In one resin, co(polystyrene–2% divinylbenzene), the trapping moiety, maleimide, was bound (**37**). Chlorosulfonated macroreticular resin was converted to cyclobutadiene precursor with 5-amino-*o*-phenanthroline and tricarbonylcyclobutadieneiron (**38**). The two resins were suspended in solvent and the mixture oxidized with ceric ion or pyridine 1-oxide. The resins were separated by flotation[39a] or screening, and the adduct resin (**39**) treated with methylamine to yield a mixture of *N,N'*-dimethylmaleamide and cyclobutadiene adduct (**40**). This approach is related to a proposal made earlier[57] for resin isolation of cyclobutadiene derivatives.



37 **38**, $n = 1,2$ **39** **40**

A mixture of two differently functionalized resin catalysts has been used to perform sequential reactions within the same vessel.[21e] The goal of this work, not yet achieved, is the realization of simultaneous,

(52) M. A. Tilak, *Tetrahedron Lett.*, 6323 (1968).
(53) C. U. Pittman, Jr., and L. R. Smith, *J. Am. Chem. Soc.*, **97**, 341 (1975).
(54) G. W. Kenner, J. R. McDermott, and R. C. Sheppard, *Chem. Commun.*, 636 (1971).
(55) D. L. Marshall and I. E. Liener, *J. Org. Chem.*, **35**, 807 (1970).
(56) (a) J. Rebek and F. Gavina, *J. Am. Chem. Soc.*, **96**, 7112 (1974); (b) J. Rebek, D. Brown, and S. Zimmerman, *ibid.*, **97**, 454 (1975); (c) J. Rebek and F. Gavina, *ibid.*, **97**, 1591, 3221, 3453 (1975).
(57) "Bio Beads for Organic Synthesis:, Bio-Rad Laboratories, Richmond, Calif., Feb, Aug, 1973.

multistep reactions via low intermediate concentrations. The resin bonding, though not essential in the experiments reported, would minimize disadvantageous interactions between the catalysts.

This review is largely the result of extended consideration of the reasons for earlier failure to maintain site separation and our efforts to construct an experimental probe of the parameters influencing site isolation in resin chemistry. The Dieckmann closure still appears to be a superior chemical probe of site isolation. The mechanistic parameters are well understood, in terms of a defined transition state whose energy is the finely balanced resultant of entropy and enthalpy, and the chemistry may be carried out under a range of conditions of alkali and temperature.

Most important, under solution conditions, the facility of closure to unstrained five- and six-membered rings, the virtual absence of closure to medium rings, and the modest but reproducible yield of large rings in competition with polymerization and dimerization are well established. Our earlier work has established that unstrained and medium-ring closure in resin reactions will occur with strictly analogous results, and many elements of a superior chemical recipe have been defined.

Thus closure of resin-bound analogs of dioate esters to large-ring ketones is a promising probe of site isolation in solid-phase synthesis. Site isolation cannot be studied via closure to five- and six-membered rings, and the yield of medium rings is so low that material improvements cannot be monitored as a sensitive function of changes in reaction conditions. But closure to large rings, which occurs in 15–45% yields under solution condition, provides a range of isolable products in which improvements can be unambiguously observed with techniques already validated for this same resin chemistry. When optimal reaction conditions have been established in closure to large-ring Dieckmann product, these conditions can be applied to the presently difficultly accessible medium-size cyclic keto derivatives. Prior optimization in the large-ring cases should provide yields large enough for subsequent sensitive analysis and improvement in the medium-ring cases.

Some of the prime optimization parameters can already be identified. Increased cross-linking to 20% or even to 40%, using high surface area resin such as microporous[58] or macroreticular resin,[59] seems promising on the basis of limited improvements in more facile chemistry already reported. Pellicularized resins,[4b,60] i.e., glass beads coated with thin layers of cross-linked polystyrene, will probably not be successful. Our own efforts in this direction failed because water accompanying the glass, either trapped or chemisorbed on the glass, could never be completely removed. It always led to alkaline hydrolysis instead of condensation. Furthermore, these beads were not susceptible to analysis by infrared methods which were successful in other cases.

Lower reaction temperatures should assist in site isolation. However, our earlier results suggest that transesterification reactions will compete most successfully at the lowest temperatures. Alkyl dioates are not the substrates of choice, in any event, because of their lability to transesterification. Sufficient displacement took place in the thiol ester nitrile of the C_{10} example to suggest that a less labile bond to the resin should be established. It may be best to employ a doubly bound heterocyclic analog of the resin ester linkage. Certainly, the greatest generality in such a resin synthesis will be obtained if the carbocyclic product can be constrained to close 100% of the time with maintenance of the bond to the resin.

The understanding of solid-phase synthesis achieved thus far suggests that a major objective should be development of a specific resin with hyperentropic efficacy as its chief characteristic.

(58) J. R. Millar, D. G. Smith, W. E. Marr, and T. R. E. Kressman, *J. Chem. Soc.*, 85 (1963).

(59) R. Kunin, E. Meitzner, and N. Bortnick, *J. Am. Chem. Soc.*, **84**, 305 (1962).

(60) C. G. Horvath, B. A. Preiss, and S. R. Lipsky, *Anal. Chem.*, **39**, 1422 (1967).