G protein by trypsin treatment, which otherwise leaves the virion intact, also removed the immobilization. This suggested that the immobilization was due to phospholipid–protein interactions involving the G protein.[56] ESR spin label data (Patzer, Wagner, Yeagle, and Grisham, unpublished observations) and fluorescence data[57] indicate that only the headgroups are immobilized, since there are no effects in the hydrocarbon region.

A Red Blood Cell Membrane Protein. Glycophorin, the human erythrocyte MN glycoprotein, was reconstituted in unsonicated egg phosphatidylcholine bilayers. The ^{31}P NMR spectra of this system exhibited chemical shift anisotropy.[55] The magnitude of the effective chemical shift anisotropy is a measure of the motional order of the phosphate group.[58] Two classes of phospholipids were identified in a 1:20 protein to lipid mole ratio sample. One class exhibited a line width so large as to not contribute significantly to the resonance observed. The broad line width indicated immobilization, and it was possible to estimate that about five phospholipid headgroups were immobilized per protein, in an aggregated state. The other class of lipid actually exhibited less motional order in the headgroup than phospholipids in bilayers not containing protein. Since it has been suggested that glycophorin preferentially attracts phosphatidylserine with its carboxyl terminal segment,[59] phospholipid headgroup–protein interactions involving glycophorin may be important in the phospholipid asymmetry of the erythrocyte membrane.

Plasma Lipoproteins. Human low density lipoprotein (LDL) is a much smaller biological assembly consisting of lipids and protein, which gives rise to high-resolution ^{31}P NMR spectra consisting of two distinguishable resonances from the two major phospholipid components, PC and sphingomyelin. Measurement of the absolute resonance intensities revealed that four-fifths of the phospholipids are contributing to the high-resolution intensity, but one-fifth resides in an environment with resonances so broad that they do not contribute to the high-resolution resonance. Trypsin treatment removed that environment, and the conclusion was reached that one-fifth of the phospholipid in native LDL engaged in lipid–protein interactions immobilizing that phospholipid, probably mediated by the phospholipid headgroups.[60]

In these three examples, at least, lipid–protein interactions may be mediated by phospholipid headgroups, resulting in immobilization of those headgroups, analogous to the interaction of hydrocarbon chains of phospholipids with proteins in the boundary layer. Since the major differences between most phospholipids lie in the headgroup region, specificity of interactions of phospholipids with proteins will most likely arise from the interaction of the phospholipid headgroups with the protein, rather than from hydrophobic interactions with the hydrocarbon chains. Preferential interactions between certain phospholipids and membrane proteins might play a role in the lipid composition and asymmetry of natural membranes. They may also be important as effectors in activity of membrane enzymes.

Thus we have progressed from phospholipids in the primeval sea to specific problems of modern membrane biochemistry, via the vehicle of physical chemistry. However, much of the structure and function of the cell membrane remains to be explored.

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The Use of Insoluble Polymer Supports in General Organic Synthesis

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The concept of performing chemical reactions on solid phases in a heterogeneous medium was enunciated by Merrifield[1] and by Letsinger.[2] It was demonstrated that the classical idea that chemical reactions should be performed in a completely homogeneous medium was not necessarily correct and that reactions can be accomplished even if one of the substrates was insoluble in the reaction media. The methodology of some organic synthesis has been revolutionized by this idea in that the normal procedures associated with the workup of a chemical reaction are obviated and replaced by a simple filtration step.[1,2] This general advantage of solid-phase synthesis has been particularly exploited in polypeptide synthesis,[3] where a polypeptide is syn-

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(1) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(2) R. L. Letsinger and M. J. Kornet, *J. Am. Chem. Soc.*, **85**, 3045 (1963).

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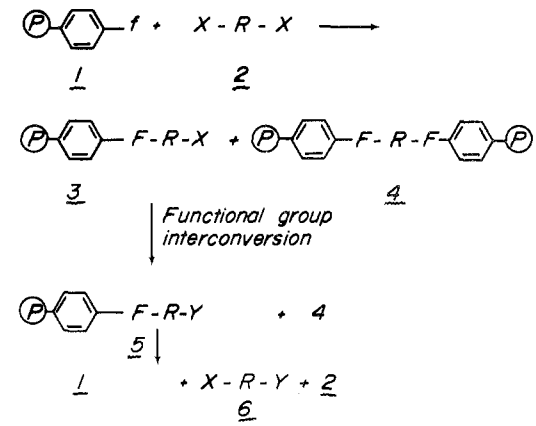
thesized in a repetitive sequential manner on the solid phase and the final products are only liberated from the polymer in a final cleavage reaction. The simplicity of the methodology has led to an automated peptide synthesis.[4] Repetitive-type solid-phase syntheses of polynucleotides[5] and polysaccharides[6] have met with only modest success, and indeed many problems associated with solid-phase peptide synthesis have been reviewed.[7]

Another approach to using polymer supports in organic synthesis was outlined by Fridkin, Patchornik, and Katchalski,[8] who showed that a polymer-bound reagent could be used in a heterogeneous reaction in such a way that excess reagents or by-products remain attached to the insoluble resin. These unwanted materials are then removed by filtration and the pure product is isolated from the filtrate. This general advantage has been widely exploited[9] and reviewed.[10-12] A multistep organic synthesis performed by this approach requires a large array[11] of polymer-bound reagents which can be used in every step of the synthesis. This approach has been recently demonstrated in a two-step reaction using polymer-bound reagents[13] and using a random bifunctional polymer-bound catalyst.[14]

Many specific advantages of using insoluble resins as supports, reagents, or catalysts have been reviewed;[11,15] these include the simulation of high-dilution[16,17] or pseudodilution[18] conditions, the fishhook and concentration principle,[19,20] selective intrapolymeric reactions,[21] bulk and steric effects of the polymer backbone in asymmetric synthesis,[22] the stabilization of reactive substances,[23,24] and the elimination of volatile malodorous reagents.[25]

Scheme I



where f, X, F, and Y are different functional groups and R is an alkyl chain or aromatic ring

The interdisciplinary nature of possible applications of solid phases has led to a number of reviews dealing with biological aspects,[26] the nature of the polymer itself,[27] and most recently a critical evaluation of the question of site isolation (the high-dilution principle) in solid-phase reactions.[28] Crowley and Rapoport[28] have quite rightly emphasized that achieving the conditions of high dilution on an insoluble resin is not straightforward, and indeed intraresin reactions have been shown to quite common.[29-31] The impression may have been given,[28] however, that solid-phase organic synthesis may remain a laboratory curiosity, a viewpoint certainly not held by those working in our laboratory. It is felt that an Account on the real achievements of solid-phase organic synthesis via the Merrifield approach[1] is particularly relevant at this time as considerable practical advances have occurred in the past 2 years, especially in (1) the monoprotection of the most common types of symmetrical difunctional compounds; (2) the gram scale organic synthesis of natural products and general chemicals (outside the fields of repetitive

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synthesis of polypeptides, polynucleotides, and polysaccharides); and (3) the use of bifunctional polymers in organic synthesis.

Monoderivatives of Symmetrical Difunctional Compounds

Solution methods of preparing monoprotected derivatives of symmetrical difunctional compounds give mixtures of diprotected, monoprotected, and unprotected products which, in many cases, are difficult to separate.[32] A common procedure involves the use of a large excess of symmetrical difunctional compound to attacking reagent. This process substantially reduces the amount of diprotected product, but one is then faced with the problem of separating the desired product (a minor component) from the bulk of unreacted symmetrical difunctional compound.[33] This problem can be readily solved using polymer-bound blocking groups. The desired monoprotected product becomes bound to the insoluble polymer and is separated from the large excess of unreacted starting material by filtration. This specific advantage is another application of the "fishhook" principle[19,20] in which a minor component (the monoblocked derivative) is fished out of the large excess of symmetrical substrate used (Scheme I) by the insoluble polymer. Many of the common symmetrical difunctional compounds have been monoblocked in this way. The nature of the polymer-bound blocking agent (1) [prepared from 2% divinylbenzene (DVB)–styrene copolymer] used, the symmetrical difunctional compound (2), the yield of monoprotected compound (6) and recovered 2, and the estimated amount of double-binding represented by 4 are given in Table I. Thus symmetrical dialdehydes[34-36] and diacid chlorides[37] can be completely monoprotected by polymer-bound reagents, while symmetrical diols,[24,38,39] dihydroxy aromatic compounds,[40] and diamines[41] are not solely monoblocked, indicating that these symmetrical difunctional compounds may be doubly bound to the polymer as in 4. At the other extreme, symmetrical diacids appear to be completely doubly bound to the polymer when attached to the polymer through their monosalts,[37] even when large excesses of symmetrical diacids are used. Thus an intraresin reaction can be an important complication in this application but can be circumvented in many cases by various techniques. A candid appraisal of the real usefulness of polymer-bound reagents as mono-

Table I
Monoderivatives of Some Symmetrical Difunctional Compounds from Scheme I

Entry no.	Identity of f in 1	Identity of X–R–Y in 2	Quantity of 2 bound to 3[a] mmol/g	Quantity of 2 recovered from 5[b] mmol/g	Identity of X–R–Y derivatives (6)	Quantity of 6 recovered from 5[b] mmol/g	Relative yield,[c] %	Est. double binding,[d] %	Ref
1	$-CH_2COCl$	1,10-Decanediol	0.042	0	Monoether	0.036	100	0	20a
2	-TrCl	1,10-Decanediol	0.58	0.16	Monoacetate	0.36	69	31	24
3[e]	>TrCl	1,10-Decanediol	0.27	0	Monoacetate	0.24	100	0	24
4	$-CH_2OCH_2CHOHCH_2OH$	Terephthalaldehyde	0.34	0	Chalcone	0.34	100	0	34
5	$-CH_2OCH(CH_2OH)_2$	Terephthalaldehyde	0.38	0	Stilbene deriv	0.36	100	0	35
6	$-CH_2OCH(CH_2OH)_2$	Phthalaldehyde	0.19	0	Stilbene deriv	0.19	100	0	35
7	$-CH_2OCH_2CHOHCH_2OH$	2,7-Dimethyl-2,4,6-octatriene-1,8-dial	0.195	0	Apo-carotenoid	0.195	100	0	36
8	$-CH_2OH$	Sebacyl chloride	0.56	0	Monoanilide	0.55	100	0	37
9	$-CH_2Cl$	Potassium sebacate	0.58	0.58	Monoalcohol	0	0	100	37
10	$-COCl$	Hydroquinone	0.77	0.08	Monomethyl ether	0.57	88	12	40
11	$-CH_2OCO_2Ph\text{-}p\text{-}NO_2$	Octamethylenediamine	0.98	0.18	Monobenzamide	0.80	82	18	41
12	$-COCl$	1,10-Decanediol	0.60	0.36	Monotrityl ether	0.24	40	60	42a

[a] Determined by cleavage of 3. [b] Determined by cleavage of 5. [c] Yield of 6 relative to 2. [d] This value is a maximum value assuming all reactions are complete. [e] For this entry polymer-bound trityl chloride exists at a cross-linked position.

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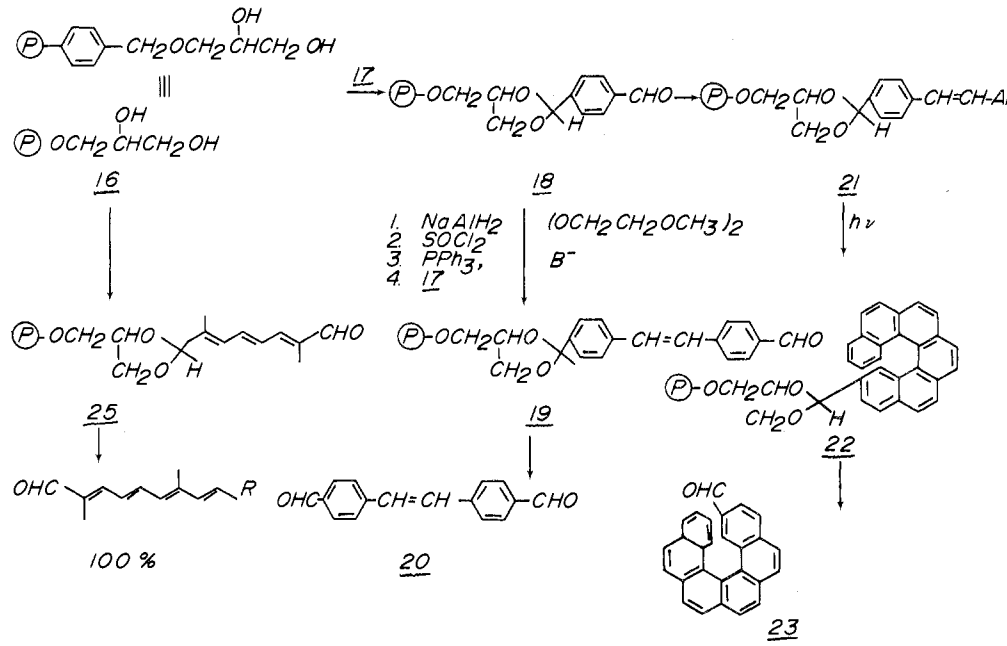
Scheme II



protecting groups is in order. There are at least three criteria unique to polymer-bound monoblocking groups that must be fulfilled to provide useful monoprotection: (1) the extent of double binding must be low; (2) the capacity of the polymer should be high to ensure that useful quantities of product could be made with a minimum amount of polymer; and (3) the polymer-bound monoblocking group should be readily prepared from preformed commercially available polymers. These criteria are all met by the entries listed in Table I except for entry 1 in which the capacity of the polymer is too low and for entries 9 and 12 in which the double binding is too extensive.

Surprisingly, symmetrical aliphatic dialdehydes could not be bound to polymer **16**[35] even though *n*-heptaldehyde was readily bound. Similarly, symmetrical diketones could not be bound to **16** and related polymers under a variety of conditions,[35] presumably due to the increased steric interactions of the bulky polymer with ketones. Alternate solid phase approaches to this problem are being pursued in this laboratory. Symmetrical terminal diacetylenes have been monoblocked in our laboratory[42b] using a polymer-bound silyl chloride [Ⓟ–$PhSi(CH_3)_2Cl$] but unfortunately could not be readily cleaved under the standard conditions.[43]

Multistep Organic Synthesis

In a multistep organic synthesis performed on solid phases, the initial starting material should preferably be bifunctional so that one end of the substrate can be attached to the polymer and the other end be available for synthetic elaboration. In polypeptide, polynucleotide, and polysaccharide synthesis *unsymmetrical* bifunctional or polyfunctional substrates were used in the initial attachment and in the synthetic elaboration. The selective monoprotection of inexpensive *symmetrical* difunctional compounds by solid phase allows the unprotected functional end to be available for synthetic development. Thus, although 4-chloro-1-butanol can be readily made by ring opening of tetrahydrofuran,[44] 9-bromo-[33c] or 9-iodo-1-nonanol[45] cannot be readily made by a similar route and is made from 1,9-nonanediol in inefficient and expensive procedures. Inexpensive long-chain symmetrical diols are logical substrates for the synthesis of insect sex attractants of Lepidoptera[46] and represent particularly good candidates to test the efficacy of solid-phase organic synthesis, since the very first step requires the monoprotection of symmetrical diols. Insect sex attractants have now been prepared on solid phases by at least six different routes,[38,39,42a,47] four of which are outlined in Scheme II. The Wittig route (**7**–**10**) gives 7:3 mixtures of cis/trans sex attractants **10**. As some insect sex attractants[48] consist of cis/trans mixtures near this ratio (which can be moderately varied under different experimental conditions), this synthesis represents a practical synthesis of these attractants, compares favorably to solution methods,[49] can be scaled up, and can possibly be automated. A "reverse" Wittig sequence (**7**–**11**–**10**) gave **10**, having a high cis/trans ratio, equivalent to those Wittig reactions conducted in solution under "salt-free" conditions. Heitz[50,51] had noticed that polymer-bound Wittig reagents upon filtration gave Wittig products of high stereoselectivity, but the conversion of **11**–**10** gave high cis/trans ratios whether the intermediate phosphonium salt was filtered or not.[38b] Perhaps the salt that is liberated does not remain in the pores of the polymer, and an effective

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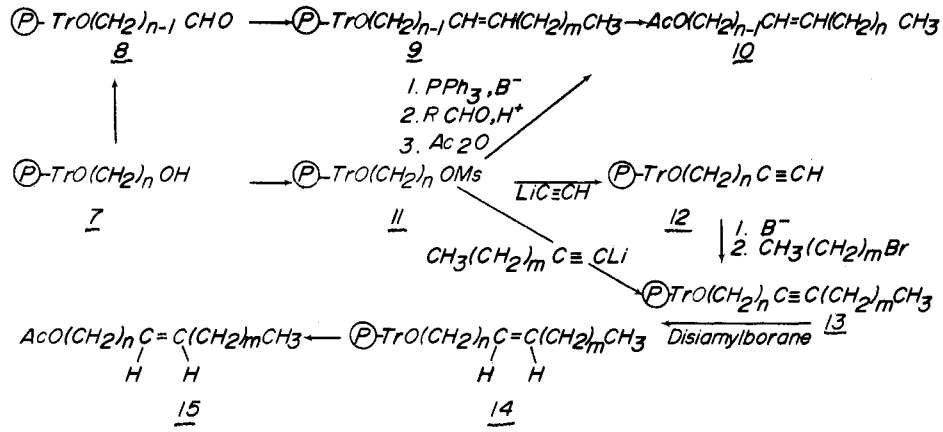
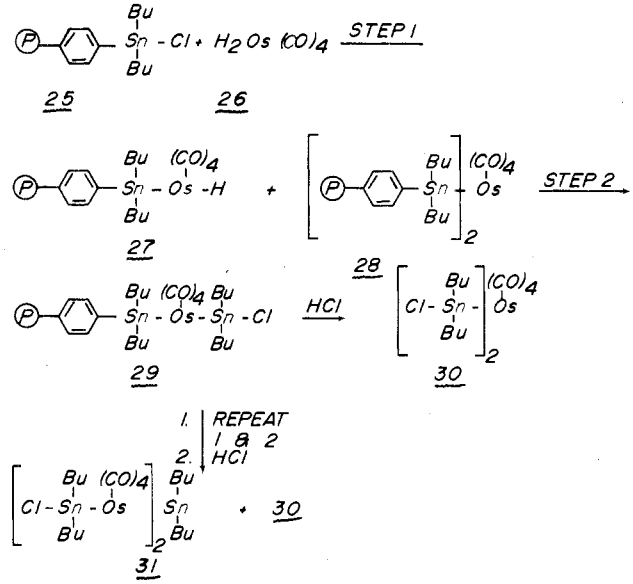
Scheme III



salt-free solution is created. Alternatively, the steric bulk of the polymer backbone has an effect on the cis/trans ratio. Thus, the solid-phase "reverse" Wittig sequence has two specific advantages over solution methods: (1) the monoprotection of the symmetrical diol in the first step and (2) a high stereoselectivity reaction, not to mention the general advantage of simple manipulations of solid-phase reactions which in this example allows one to separate the liberated triphenylphosphine oxide from the polymer by filtration or by extraction of the polymer in a Soxhlet extractor. The two-step alkyne coupling approach (**7**–**11**–**12**–**15**) represents a highly economical approach to pure cis sex attractants, and gram quantities have been routinely prepared in this manner[39,52] for field-testing evaluations.[53] The borane reduction is particularly advantageous on solid phases as the boron-containing impurities do not have to be oxidized to facilitate the isolation of the desired product,[54] and it is believed that elimination of the oxidation step increases the yield of the reaction **13**–**14**.[39] Thus the alkyne coupling route has two specific advantages over solution-phase methods, namely, selective monoprotection of the diol and a facile reduction step. The specific and general advantages outlined above, the capability of preparing gram amounts of attractants on a laboratory scale, and the fact that the polymer can be recycled over 25 times without substantial degradation[39] make solid-phase syntheses of insect sex attractants very attractive to the bench chemist. The major inefficiency in these reactions, namely, the amount of diol initially "doubly bound" to the resin, has most recently been resolved.[42b] In most cases double binding can be circumvented by using large excesses, even as a molten solvent, of the symmetrical difunctional compound.[42b] Alternatively, bifunctional resins and special resins containing functional groups at cross-linking sites can eliminate double binding, but at the cost of decreased capacity.[24,42a]

One of the first multistep organic syntheses on solid phases involved the use of a polymer-bound vicinal diol (**16**) and terephthalaldehyde (**17**) in the preparation of 1,4-diformylstilbene (**20**), as shown in Scheme III.[55]

Scheme IV



One particularly interesting aspect of this synthesis is the fact that a polymer (**16**) can be used to monoprotect a symmetrical dialdehyde (**17**) to give **18**, the free aldehyde end of which can be transformed to react with **17** *again* to give **19**. Obviously, this "*repetitive monoreaction*" *procedure* can be exploited to synthesize a series of oligomers from symmetrical intermediates that would be difficult to synthesize by solution methods, although it should be emphasized that yields are only modest and the possibility for intraresin reaction increases for every repetitive monoreaction. More recently, polymer-bound monoprotected terephthalaldehyde (**18**) was used in the synthesis of helicenes (**18**–**21**–**23**, Scheme III),[56] although the extent of polymer-bound photodimerization was not discussed, and the overall yields were not impressive. Polymer **16** was used to monoprotect (*E,E,E*)-2,7-dimethyl-2,4,6-octatriene-1,8-dial (**24**) to give **25**.[36] Subsequent Wittig reactions gave apocarotenoids in high yield (Scheme III), but the capacity of polymer **16** for **21** was somewhat low for large-scale synthesis (Table I, entry 2).

An interesting example of an organometallic synthesis[57] on solid phases is outlined in Scheme IV. The advantage of using solid phases in this scheme is

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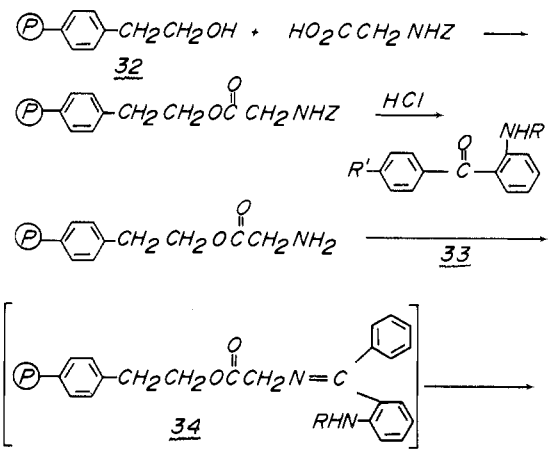
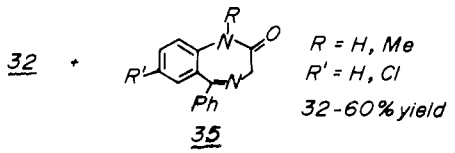
(53) J. Weatherston, A. F. Hedlin, D. S. Ruth, L. M. MacDonald, C. C. Leznoff, and T. M. Fyles, *Experientia*, **33**, 723 (1977).
(54) H. C. Brown, E. F. Knights, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974); G. Holan and D. F. O'Keefe, *Tetrahedron Lett.*, 673 (1973).
(55) J. Y. Wong, C. Manning, and C. C. Leznoff, *Angew. Chem., Int. Ed. Engl.*, **13**, 666 (1974).
(56) J. M. Vanest, M. Gorsane, V. Libert, J. Pecher, and R. H. Martin, *Chimia*, **29**, 343 (1975).
(57) J. M. Burlitch and R. C. Winterton, *J. Am. Chem. Soc.*, **97**, 5605 (1975).

Scheme V



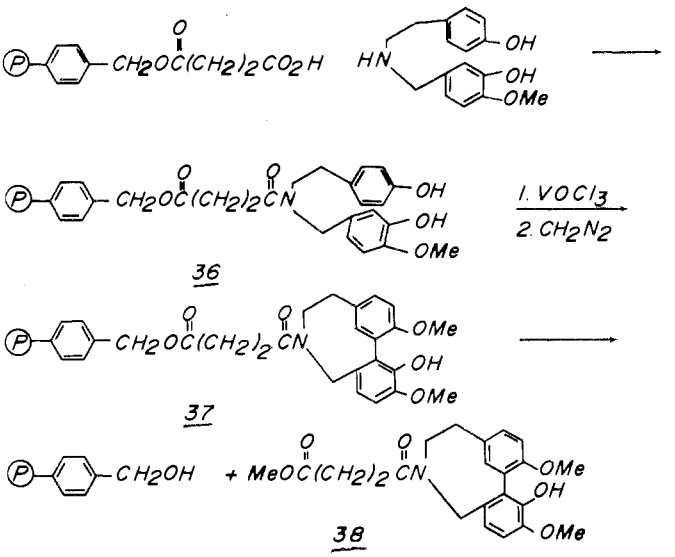


again the fishhook principle,[19,20] as applied to the monoprotection of symmetrical difunctional compounds and repetitive monoreactions,[55] as described above. It is unfortunate that the authors did not treat **27** with a *different* dialkyltin dichloride so that the extent of double binding represented by **28** could be determined. Interestingly, acid cleavage of **28** or **29** would give the *same* product, **30**. As stated by the authors **29** could also be doubly bound, which may account for the eventual low yield of **31**. Since this synthesis does *not* fundamentally depend on site isolation, as suggested by the authors, but rather on the fishhook principle, the choice of a 20% DVB–styrene copolymer was not desirable in that diffusion of excess reagents into the polymer may be limited and may give double binding. The use of a 2% DVB–styrene copolymer and large excesses of reagents [Bu_2SnCl_2,$H_2Os(CO)_4$] in the formation of **25**, **27**, **29**, and **31** should give better results. These and other improvements should increase the low capacities of **25** and **26** and increase the yield of purified **30**.

A synthesis of the benzodiazepinone tranquilizers (**35**) is outlined in Scheme V.[58] This synthesis depends on site isolation for a favorable cyclization step similar to that of Patchornik's synthesis of cyclic peptides,[16] but is particularly favorable due to the unlikely probability of **33** entering into intermolecular dimerizations, especially when attached to the polymer support as in **34**.

In alkaloid synthesis, solid phases have been used in an oxidative coupling reaction to form, for the first time in vitro, the lycoramine-like alkaloid skeleton, as shown in Scheme VI.[59] The most striking aspect of this work is the rare ortho–ortho coupling (**36**–**37**) that appears to occur solely on solid phases. The yield of the coupling to give **37** and hence **38** is good (50–60%). The

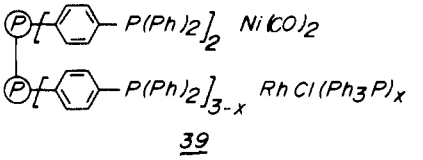
Scheme VI



reasons behind the unusual stereoselectivity are likely a favorable conformation induced by the polymer support, but whether the steric bulk of the polymer and unfavorable solvation of methoxyl groups force the methoxy groups away from the backbone, inducing ortho–ortho coupling, is strictly conjecture at this stage. Intraresin reactions do not appear to be important side reactions, and site isolation has been largely achieved in this case.

Bifunctional Polymers in Organic Synthesis

Soluble bifunctional polymers have been used to mimic enzymatic reactions,[60] but the use of insoluble bifunctional resins in organic synthesis is just beginning to be exploited. Pittman and Smith[14] have prepared resins (e.g., **39**) containing two different catalysts so that a single polymer can effect two sequential reactions. Alternatively, a mixture of two different resins, each containing a single catalytic group, can perform the



same sequence. Patchornik's group[13] has shown how mutually incompatible reagents (**40** and **41**) can be mixed together provided each is attached to a different resin, and this mixture can be used as polymer-bound reagents in a sequential scheme. Rebek's group[61] has used a mixture of two different polymer-bound reagents in mechanistic studies as a means of evaluating the existence of discrete reactive intermediates.

A bifunctional resin has the capability of imparting local order to an otherwise random polymer and has

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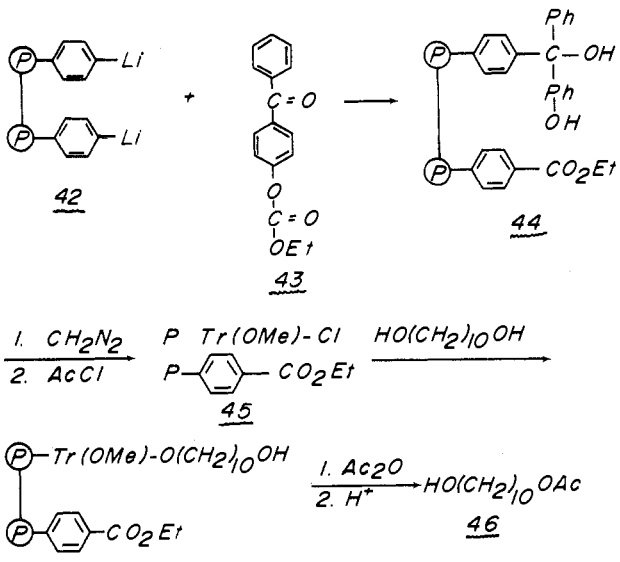
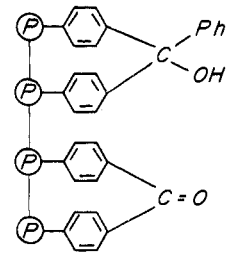
(59) J. W. Apsimon and D. M. Dixit, 59th Conference of the Chemical Institute of Canada, London, Ontario, June 1976; D. M. Dixit, Ph.D. Thesis, Carleton University, Ottawa, Ontario, 1976; D. M. Dixit, *Diss. Abstr. B*, **37**, 6125 (1977).
(60) T. Kunitake and Y. Okahata, *J. Am. Chem. Soc.*, **98**, 7793 (1976).
(61) J. Rebek and F. Gavina, *J. Am. Chem. Soc.*, **96**, 7112 (1974); J. Rebek, D. Brown, and S. Zimmerman, *ibid.*, **97**, 454 (1975); J. Rebek, and F. Gavina, *ibid.*, **97**, 1591, 3221, 3453 (1975); J. Rebek, F. Gavina, and C. Navarro, *Tetrahedron Lett.*, 3021 (1977).

Scheme VII



been used to eliminate intraresin reactions, as shown in Scheme VII.[42a] Thus, a polymer (**42**) having adjacent or conformationally adjacent lithiated sites is quenched by a bifunctional compound (**43**) so that formerly adjacent sites become differentially functionalized, as in **44**. The synthesis of 1,10-decanediol monoacetate (**46**) from **45** proceeded in 100% yield, showing that intraresin reactions were negligible. Although insect sex attractants could be synthesized on both **45** and **45** modified to bind 1,10-decanediol to both functionalities, the capacities of the polymers were somewhat low and the presence of the carboxy functionality inhibited complete reactions at every stage.[42a] The formation of these bifunctional resins, however, has given us insight into the microenvironment of the polymer by suggesting to us that about 40% of the lithiated sites of **42** exist at adjacent or conformationally adjacent sites and allows us to control the relative positions of functional groups on a polymer backbone. Thus, adjacent reactive sites can be selectively quenched; the extent of cross-linking can be controlled; and the functional group(s) can be positioned at a cross-link juncture as in **47**, prepared from a dilute solution of methyl benzoate and **42**.[24]



47

The use of bifunctionalized resins in studying the microenvironment of the polymer[62] and intraresin interactions,[62-64] in performing asymmetric and macrocyclic syntheses, and as models in mimicing enzymatic reactions should become more widespread.

Conclusion

In this Account I have emphasized the very real practical advances made in solid-phase organic synthesis. Insoluble polymer supports can monoprotect symmetrical difunctional compounds which can then be used in multistep organic synthesis to make gram quantities of organic substances, especially insect sex attractants. Macrocyclic formation of alkaloids, tranquilizers, and helicenes on solid phases have been achieved. Although intraresin reactions are common, methods of ameliorating this problem have been described.

To paraphrase Merrifield on the applications of solid phases to organic synthesis, "A gold mine awaits discovery by organic chemists".[65] Many gold nuggets have now been mined. . .and some iron pyrites.

Thanks are due to my co-workers whose names are given in the references and without whom this work would have been impossible. The National Research Council of Canada is gratefully acknowledged for support of our research.

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(65) R. B. Merrifield, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **32**, 221 (1969).