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Solid Phase Synthesis. Evidence for and Quantification of Intra res in Reactions

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Solid Phase Synthesis. Evidence for and Quantification of Intraresin Reactions

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ABSTRACT

Intrareaction occurs between moieties attached to copolystyrene-2% divinylbenzene resin as used in solid phase synthesis even when only 0.5% of the phenyl residues are functionalized. Evidence for this interaction has been obtained from the dimeric products resulting from Dieckmann cyclization of resin bound sebacates and ω-cyanopelargonyl thiol resin esters, from kinetic and product data on radioactivity scrambling during the Dieckmann cyclization of uniquely singly labeled tertiary alkyl pimeloyl resin esters, and from anhydride formation with carboxymethyl resin. The extent to which site-site interactions can occur as a function of the percentage functionalization has been measured quantitatively by radiotracer studies on intraresin anhydride formation from carboxymethyl substituted resin. The synthesis and characterization of the resin bound reactants is described, and the significance of these observations is discussed.

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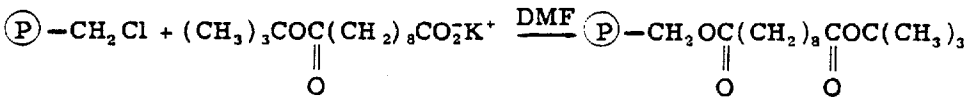
INTRODUCTION

The view is prevalent in solid phase synthesis that copolystyrene-2% divinylbenzene is a rigid polymer in which specific loci maintain their separation during reaction [1-6]. In connection with our investigation of the hyperentropic efficacy of solid phase cyclization [7], we have developed several lines of evidence which establish that intraresin or site-site reactions can occur to the extent of 50-80% of the total functionality with resin functionalized in the range normally employed in solid phase synthesis. Other reports of intraresin reactions have been made. Kraus and Patchornik [8] have observed such reactions using resin with percent substitution considerably higher than that usually employed in solid phase synthesis, and that fact is explicitly emphasized. In two recent reports, Collman et al. [9] and Beyerman et al. [10], in widely different reactions of resin bound moieties, also have reported the intrusion of undesirable intraresin reactions.

RESULTS AND DISCUSSION

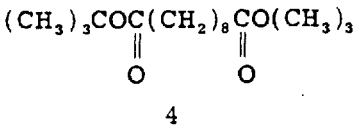
We originally shared the belief that individual sites on the resin would remain separated during reaction. It appeared possible to take advantage of this separation to enhance the rate of cyclization relative to polymerization for moieties covalently bond to the copolystyrene-divinylbenzene resin, provided that the pendant reagent molecules were far enough from each other so that intramolecular reactions could not occur.

The Dieckmann cyclization of alkyl sebacyl resin esters was selected as a useful test of solid phase cyclization because the ineffectiveness of solution Dieckmann conditions, even at high dilution, has been very well documented [11]. For this purpose, t-butyl sebacyl resin ester (3) was prepared from potassium mono-t-butyl sebacate (2) and chloromethylated resin as previously described [7].



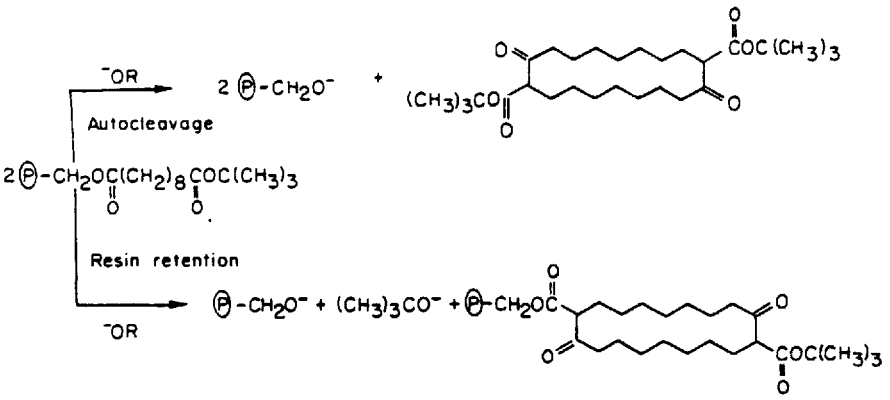
1 2 3

Dieckmann cyclization with potassium tert-butoxide in refluxing xylene yielded chiefly transesterification product 4.

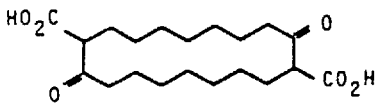


4

However, small yields of cyclic dimeric diketoesters were obtained as both autocleaved and resin retained products:



The cleavage product was isolated as diketodiacid 5, while the resin retained product was identified as diketomonoacid 6, after HBr cleavage in methylene chloride.



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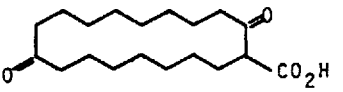
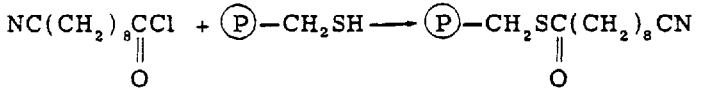


6

We selected ω-cyanopelargonyl thiol resin ester 9 as a sebacyl derivative which would be more reactive toward cyclization and less labile to cleavage under Dieckmann conditions. The thiol resin ester was prepared from ω-cyanopelargonyl chloride 7 [12, 13] and the previously unreported thiolmethyl resin 8, obtained from chloromethyl resin 1 (0.4 meq Cl/g resin) and KHS in DMF (160°, 30 min).



7 8 9

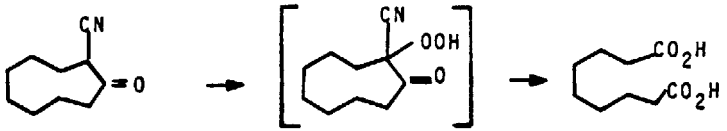
The authenticity of our synthesis was established by IR difference spectra [7] and cleavage of the cyanothiol ester from the resin as N,N-diethyl ω-cyanopelargonamide with silver acetate-diethylamine in dioxane at 120° for 16 hr. The cyanoamide was identified by IR, NMR, mass spectroscopy (MS), and elemental analysis.

$$Ag[NH(C_2H_5)_2]_2OAc \quad + \quad 9 \longrightarrow (C_2H_5)_2NC(=O)(CH_2)_8CN$$

10 11

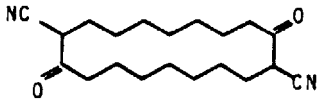
Treatment of this resin thiol ester with lithium diethylamide yielded 40% cyanoamide, 10% dimeric diketodinitrile, and about 5% of 2-cyanocyclononanone, established by MS and by comparison (UV, TLC, GC) of the 2-cyanocyclononanone with authentic material [14].

Our yield of 2-cyanocyclononanone was seriously impaired by rapid conversion (several hours at room temperature) to azelaic acid when stored in ethyl ether, a decomposition which was confirmed with the independently synthesized cyanoketone. The azelaic acid was identified by IR, NMR and MS comparison with authentic material.



12 13 14

When larger bases, e.g., lithium bistriethyl-disilazide [15], were employed, displacement to amide was prevented and the isolated product, 19% yield, was exclusively diketodinitrile; uncyclized cyanothio ester was cleaved from product resin in 75% yield.



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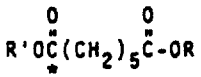
This predominant dimerization undoubtedly occurs because the individual moieties are not effectively separated from each other during reaction.

Further evidence against site isolation during reaction was provided

by the label distribution in resin retained products from the Dieckmann cyclization of uniquely singly labeled alkyl pimeloyl resin esters, 16a*-c*.



16

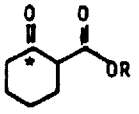
a. R=C_2H_5, R'=Ⓟ-CH_2

b. R=tert-C_4H_9, R'=Ⓟ-CH_2

c. R=$(C_2H_5)_3C$, R'=Ⓟ-CH_2

d. R=Ⓟ-CH_2, R'=Ⓟ-CH_2

e. R,R'=$(C_2H_5)_3C$



17

a. R=C_2H_5

b. R=tert-C_4H_9

c. R=$(C_2H_5)_3C$

d. R=Ⓟ-CH_2, labeled carboxy, not keto

Ⓟ = Polystyrene; 16c**, 16d**, and 16e** signify transesterification reaction products containing pimeloyl residues with the labeled carbon located at the original resin ester carbonyl together with structures in which the label has been scrambled into the nonresin ester carbonyl, or effectively scrambled because both ester groups are the same.

The preparation and analysis of label purity of starting materials has been described [7] together with some data on label distribution in autocleaved products 17a*-c*.

The kinetic relationships required to explain the observed label distribution of ketoester retained on the resin (17d**) prior to HBr/CH_2Cl_2 cleavage support our conclusion that pendant moieties on this type resin do not maintain the separation statistically implied by percent substitution and the well-defined bond lengths in polystyrene.

The pattern of label distribution in Dieckmann products from triethyl carbinyl pimeloyl resin ester are shown in Table 1. To obtain the label distribution in the resin retained ketoester 17d, the ketoacid was cleaved from the support with HBr in methylene chloride and, after concentration, the crude product was decarboxylated in refluxing alcoholic HCl. The CO_2 produced in this reaction was captured as $BaCO_3$ and counted [16].

We interpret the data shown in Table 1 as indicating rapid resin alkoxide participation in the transesterification process through Reactions (1) or (2a) and (2b).

TABLE 1. Mode and Relative Rate of Formation of 2-Carboxycyclohexanone Esters from Triethylcarbinyl Resin Pimelate

Cyclization[a]	% Yield[b]	Distribution[c]	Product[d]	Relative rate[e]
1. Attack at α-ester	46			
Direct		99.4	17c*	163
Transester		0.6	17c**	1.0
2. Attack at ω-ester	10			
Direct		4.0	17d*	1.4
Transester		96.0	17d**	35

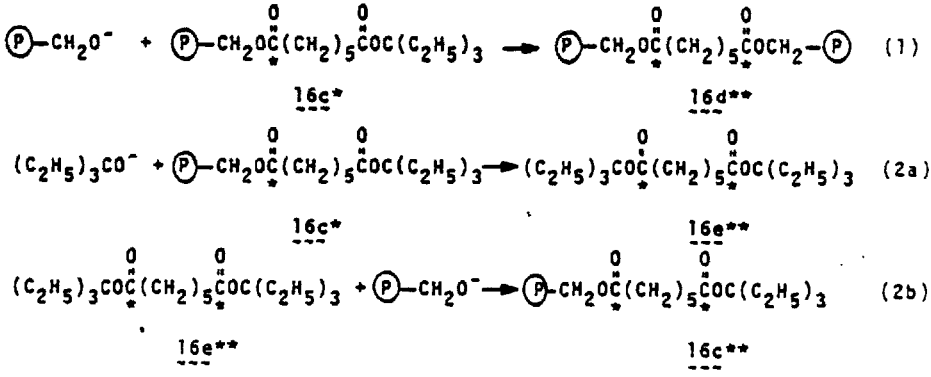
[a]Cyclization direction is described by α for attack on the carbonyl nearest the resin, accompanied by autocleavage, or ω for the alternative direction. The process is further described as direct for cyclizations which do not result in scrambled label, and transester for those following a transesterification.

[b]Percent yield was obtained from the sum of activities of previously reported purified autocleaved ketoester and purified resin-retained activity prior to HBr/CH_2Cl_2 cleavage.

[c]Percent label distributions were obtained by computing twice the % activity observed in the scrambled location as transester and 100% minus transester as direct.

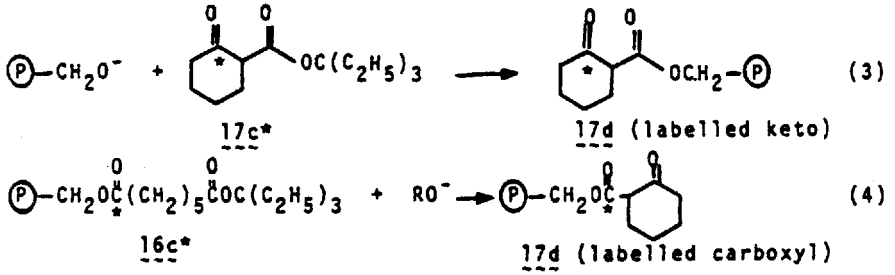
[d]Doubly labeled formulas indicate equimolar mixtures of singly labeled ketoesters.

[e]Relative rates of formation obtained from relative values of % yield times % label distribution.

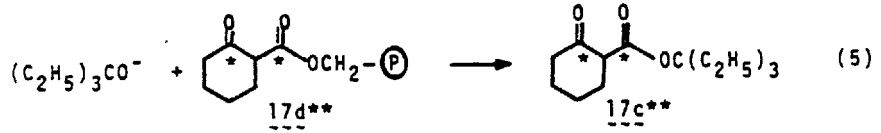


The relative importance of the two reaction sequences can be assessed for the case of triethylcarbinyloxide catalyzed cyclization of triethylcarbinyl resin pimelate (16). The autocleaved ketoester has 99.7% of its activity in the keto group and 0.3% in the carboxyl [7], while the ketoester retained on the resin has 48% in the keto and 52% in the carboxyl. The data establish that the pattern of uniquely located labeling observed for triethylcarbinyl ketoester cleaved from the resin is not observed for ester retained on the resin. If the major source of 17d** is 16c**, then the product ratio 17c**/17d** must equal 17c*/17d*, or 163/1.4. In fact, this ratio is 1/35, requiring the major pathway to scrambled resin-retained ketoester to be through 16d** and not through 16c**.

We rule out independent routes to the components of the scrambled resin retained ketoester 17d** by Reactions (3) and (4).



If Reaction (3) were occurring to a significant extent, we could expect the observed mixture of keto and carboxyl labeled 17d** to yield scrambled 17c** by Reaction (5):



Reactions (3) and (5) should have very similar transition states, and Reaction (5) should be faster in view of the severalfold higher concentration of triethyl carbinyl oxide relative to resin alkoxide. Furthermore, reaction between anionic alkoxide and anionic enolate is not a promising competitor for reaction between alkoxide and neutral ester. We can rule out Reaction (5), and therefore Reaction (3), on the basis

of the very specific labeling pattern observed in the autocleaved 17c*.

For quantitative evaluation of intraresin reactions, carboxymethyl resin was prepared, and its ability to form anhydride was measured. Chloromethyl resin treated with sodium cyanide in DMF (100°, 24 hr) followed by hydrolysis in ethanolic potassium hydroxide [17] gave carboxymethyl resin. Carboxyl groups were converted to either intraresin or mixed trifluoroacetic anhydrides by treating this resin in methylene chloride with trifluoroacetic anhydride and silver trifluoroacetate. Repeated codistillation with methylene chloride then removed trifluoroacetic acid and anhydride, optimizing intraresin anhydride formation [18-20]. Washing this resin with 2% aqueous dioxane hydrolyzed mixed anhydride (IR 1860, 1792 cm^{-1}) without destroying intraresin anhydride (1821, 1748 cm^{-1}). The resin product also showed absorption at 1704 cm^{-1} due to resin acid formed by hydrolysis of the mixed anhydride.

The extent of intraresin anhydride formation was measured by reaction with 1-aminobutane-1-^{14}C (1.26×10^6 dpm/mmole) in methylene chloride, and the resin was counted in dioxane scintillation solution [21]. Ionically bound butylamine was removed by a 10% TFA/CH_2Cl_2 wash; control experiments established complete removal of amine from carboxymethyl resin which had not been treated with anhydride and from anhydrized resin after complete anhydride hydrolysis. The initial resin carboxylic acid content was determined by formation of radioactive butylamide through resin 2,4,5-trichlorophenyl ester. Percent intraresin anhydride formation vs percent carboxymethyl substitution of resin were 78 vs 9.8, 64 vs 4.7, and 53 vs 0.5, respectively. These data are plotted in Fig. 1.

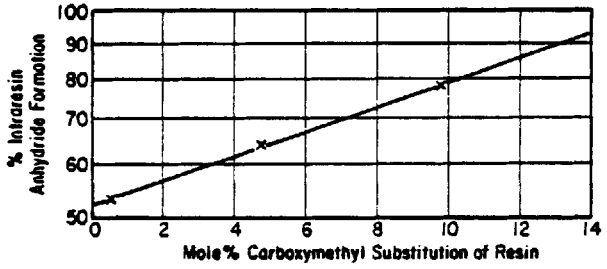


FIG. 1. Intraresin anhydride formation as a function of degree of resin carboxymethyl substitution.

CONCLUSIONS

These results demonstrate that the carboxylic acid groups are not isolated during reaction, and that intraresin reactions occur readily even at 0.5% substitution and even though the functionalized sites are randomly distributed. This inference of random site location was reached [4] on the basis of autoradiography of microtomed sections of peptide-labeled resin peptide ester. We found radioactive resin ester beads sized by screening and by CH_2Cl_2 flotation [22] displayed constant specific activity even though differing in diameter by a factor of 5. Our evidence for resin site interaction suggests that the observed random functionalization may be achieved by translocation of strands of solvent swollen beads and that neither line of evidence may bear on the question of diffuse vs surface reactivity, which was originally inferred from the previous observation [4]. We present this evidence, in agreement with that presented earlier [6], but independent of it, to show that statistically impressive uniformity of the functional distribution in the resin beads exists. This fact can be compatible with all the observations of interactions at high and low levels of functionalization only if the observable distribution and interactins are not related. We find that resin flexibility during chloromethylation and during further reactions is the best explanation for both kinds of data.

With longer molecules attached to the resin, this reactivity should increase due to added flexibility afforded by the increased chain length. Thus molecules attached to copolystyrene-2% divinylbenzene are not isolated to a significant extent during reaction.

Our evidence is directed at establishing that divinyl benzene-copolystyrene is quite flexible, and that those results reported to the present time which imply site separation must be explained on the basis of favorable kinetic relationships between the desired reactions and competitive reactions, the very real purification advantages offered by the solid phase method, and the introduction of steric influences around the substituted site, which cannot be involved in parallel reactions in solution. A further implication of these conclusions is that, as less kinetically favorable reactions are attempted with polymer bound reagents, the extent of site-site interactions will increase.

ACKNOWLEDGMENT

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