

then boiled briefly, cooled to room temperature, and acidified with 20% DCI. The amino anhydride **3** that crystallized was removed by centrifugation. The supernatant was again made basic with NaOD; during the addition, more anhydride crystallized and was removed by centrifugation: NMR (of supernatant) δ 2.50 (3 H, s), 6.89 (1 H, d of d, $J = 2$ Hz, $J = 8$ Hz), 7.17 (1 H, d, $J = 8$ Hz), 7.37 (1 H, d, $J = 2$ Hz). Two singlets, at δ 2.78 and 7.54, were attributed to 4-methylaniline-3,5-disulfonate (about 12 mol %). Two multiplets at δ 7.79–8.00 and 8.59–8.75, attributed to residual naphthalimide impurities, integrated to a total of 0.78 H.

5-Amino-2-toluenesulfonic Acid (Eastman): NMR (D_2O/OD^-) δ 2.49 (3 H, s, CH_3), 6.86 (1 H, d of d, $J = 2.5$ Hz, $J = 8$ Hz, 4-H), 7.14 (1 H, d, $J = 8$ Hz, 3-H), 7.34 (1 H, d, $J = 2.5$ Hz, 6-H).

6-Amino-3-toluenesulfonic Acid (Aldrich): NMR (D_2O/OD^-) δ 2.24 (3 H, s, CH_3), 6.84 (1 H, d, $J = 8$ Hz, 5-H), 7.17 (1 H, d of d, $J = 2$ Hz, $J = 8$ Hz, 4-H), 7.49 (1 H, d, $J = 2$ Hz, 2-H).

Reaction of 5 with Propionaldehyde and Formaldehyde. Equal volumes of 0.2 M propionaldehyde and 0.2 M **5** in D_2O were mixed at room temperature, and the NMR spectrum was recorded as soon as possible. Within 120 s the aldehydic proton ($\delta \approx 9.67$) was greatly reduced; a new triplet (δ 7.52, $J = 5$ Hz) had appeared. A similar experiment with formaldehyde was complicated by the fact that the resonance from the formaldehyde protons at $\delta \approx 4.82$ was too close to the HDO peak for adequate observation. A rapid reaction, however, seemed likely, since the first obtainable spectrum of the naphthalimide region was complex,

indicating a mixture of compounds. Gradually the spectrum of this region became less complex; after 30 min most of the spectrum appeared to be due to a single compound. By then two new doublets (δ 6.68, $J = 12$ Hz; δ 7.12, $J = 11$ Hz) had appeared.

Reaction of 10 with H_2O , Ethanolamine, and Mercaptoethanol. A 60-MHz 1H NMR spectrum of a 10% (w/w) solution of **10** in D_2O was obtained immediately after the compound was dissolved; this spectrum was the same as that subsequently obtained after the solution had stood at room temperature for 6 h, 30 h, 10 days, and 75 days. Compound **10** was distinctly less stable in weak base. The NMR spectrum of a freshly prepared 10% (w/w) solution of **10** in 0.1 M Na^+/D^+ carbonate buffer in D_2O was very similar to the spectrum of **10** in D_2O . After 1 day at room temperature, the pD 9.1 spectrum was not noticeably different, but after 9 days at room temperature the intensity of the vinyl protons was reduced, and a new peak had appeared at $\delta \approx 3.50$. It was estimated that between 20% and 50% of the compound had been converted, presumably to the lithium salt of **7**.

The NMR spectrum of 52 mg of **10** in 0.4 mL of D_2O and 0.1 mL of 0.5 M Na^+/D^+ pD 9.1 carbonate buffer was obtained. To the sample tube was added 14 μ L of ethanolamine, and within 120 s the NMR spectrum of the vinyl region was recorded. No signals were seen, indicating that at least 90% of compound **10** had reacted. The complete spectrum showed the presence of two multiplets at $\delta \approx 3.0$ and $\delta \approx 3.7$.

A similar experiment was performed with 2-mercaptoethanol with virtually identical results.

“Wolf and Lamb” Reactions: Equilibrium and Kinetic Effects in Multipolymer Systems

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Abstract: Two reagents reacting avidly with each other in solution are rendered mutually inactive by attaching each to a separate batch of insoluble polymer. Two-stage reactions in which a soluble reagent reacts first with one polymeric reagent and the product with the second polymeric reagent afford advantages over analogous reactions in solution. In acylation reactions of carbon acids, the simultaneous use of a polymeric strong base and a polymeric acylating reagent proved to be superior to the use of soluble reagents, both for bringing about quantitative acylations and for coping with undesirable side reactions. New polymeric strong bases were prepared: polymeric trityllithium, para-substituted trityllithium polymers, and polymeric lithium diisopropylamide. Active esters of polymeric *o*-nitrophenol and *N*-1-hydroxybenzotriazole were used as acylation reagents. The scope and limitation of these reactions and their application to general multiphase systems are discussed.

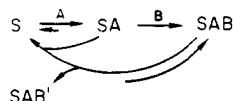
Polymeric reagents—reactive, low molecular weight molecules bound to a polymeric backbone—have been widely used in organic chemistry during the past two decades. The most significant advantages of these reagents over their soluble counterparts are the ease of their separation from the reaction mixture and their possible recycling. Polymeric catalysts, polymers for specific separations, carriers for sequential synthesis, polymeric blocking groups, and polymeric transfer reagents in general organic synthesis, all have utilized these advantages. Use has also been made of the fact that chain fragments within a crosslinked polymeric backbone have restricted mobility. Active species attached to the polymer can thus be effectively isolated from each other at relatively high concentrations, providing the advantages of high dilution and specificity, along with rapid kinetics. In other cases, properties of the backbone itself such as polarity, pore size, and chirality were utilized to achieve unique reactions, the polymer providing a specific microenvironment for the reaction. These aspects of polymeric reagents have been extensively reviewed.¹⁻¹⁴

At present, few examples exist in which more than one polymeric reagent is used in a particular reaction. Pittman and Smith,¹⁵ for instance, described a reaction involving the simultaneous use of two polymeric organometallic catalysts for consecutive isomerization and hydrogenation of olefins. Use of two insoluble polymers or a mixture of a soluble and an insoluble polymeric reagents for peptide synthesis has also been reported.^{16,17}

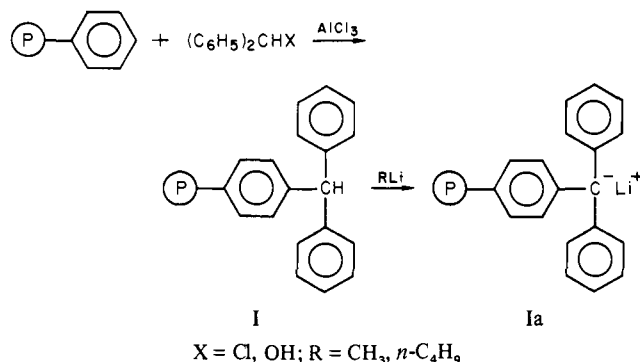
- (1) Pittman, C. U.; Evans, G. O. *CHEMTECH*. 1973, 560-566.
- (2) Leznoff, C. C. *Chem. Soc. Rev.* 1974, 3, 65-85.
- (3) Overberger, C. G.; Sannes, K. N. *Angew. Chem., Int. Ed. Engl.* 1974, 13, 99-104.

- (4) Patchornik, A.; Kraus, M. A. *Pure Appl. Chem.* 1975, 43, 503-526.
- (5) Neckers, D. C. *J. Chem. Educ.* 1975, 52, 695-702.
- (6) Weinschenker, N. M.; Crosby, G. A. *Annu. Rep. Med. Chem.* 1976, 11, 261-270.
- (7) Mathur, N. K.; Williams, R. E. *J. Macromol. Sci., Rev. Macromol. Chem.* 1976, C15, 117-142.
- (8) Crowley, J. I.; Rapoport, H. *Acc. Chem. Res.* 1976, 9, 135-144.
- (9) Heitz, W. *Adv. Polym. Sci.* 1977, 23, 1-23.
- (10) Leznoff, C. C. *Acc. Chem. Res.* 1978, 11, 327-333.
- (11) Kraus, M. A.; Patchornik, A. *CHEMTECH*. 1979, 118-128.
- (12) Kraus, M. A.; Patchornik, A. *Macromol. Rev.* 1980, 15, 55-106.
- (13) Mathur, N. K.; Narang, C. K.; Williams, R. E. "Polymers as Aids in Organic Chemistry"; Academic Press: New York, 1980.
- (14) Hodge, P.; Sherrington, D. C., Eds. "Polymer Supported Reactions in Organic Synthesis"; Wiley: New York, 1980.
- (15) Pittman, C. U.; Smith, L. R. *J. Am. Chem. Soc.* 1975, 97, 1749-1754.

Scheme V



Scheme VI



for example, treating 1 equiv of it (S) with 1 equiv of a strong base such as trityllithium (A) will produce 1 equiv of the anion (SA). The anion will be formed quantitatively due to the large difference between the pK_a values of triphenylmethane and phenylacetonitrile. However, addition of 1 equiv of an acylation reagent such as an active ester of benzoic acid (B) will not lead to the quantitative formation of the acylation product (SAB) because of proton exchange between the product and anion molecules not yet acylated (Scheme IV).

The result is an incomplete reaction and formation of mixtures. The concentrations of the various species at equilibrium depend on the pK_a values of A, SA, and SAB. The increased acidity of the acylation product vs. that of the starting material makes proton interchange a common problem in acylations. It is impossible to add an excess of trityllithium to promote the formation of the product since this excess will react competitively with the acylation reagent.

Various ways to overcome this problem have been proposed: inverse addition of a dilute anion solution to a concentrated solution of the acylation reagent, use of certain base-acylating reagent combinations such as ethoxide-ethyl ester, sodium hydride-ester or use of lithium diisopropylamide as the strong base, at very low temperatures. The results are not always satisfactory. According to our suggested two-polymer approach, a strong polymeric base and a polymeric acylation reagent could be used to obtain the desired product in high yield.

Note that the acylation of carbanions does not exactly follow Scheme II, and a more accurate description is according to Scheme V.

Nevertheless, the use of polymeric reagents for this particular example does not limit the validity of the considerations given above for the use of polymeric reagents in reactions at equilibrium.

To accomplish the "wolf and lamb" acylations we developed a strong polymeric base, polymeric trityllithium Ia (Scheme VI).

Polymer I, carrying triphenylmethane moieties, was prepared by reacting polystyrene with benzhydrol or benzhydryl chloride in a Friedel-Crafts reaction. With benzhydrol, lower loadings (0.7 mmol/g) of trityl groups than with benzhydryl chloride (2.3 mmol/g) were obtained. The latter reaction also required less catalyst. Therefore, polymer I obtained from the chloride was further used as our polymeric reagent.

The blood-red polymeric anion Ia was produced by reacting polymer I with excess methylolithium or *n*-butyllithium in THF or in 1,2-dimethoxyethane. The extent of ionization was determined by washing excess reagents from the polymer, adding ethanol, eluting the resulting ethoxide, and titrating with acid.

A typical loading vs. time graph is shown in Figure 1.

In ordinary use, polymer Ia with a loading of ca. 1.5 mmol/g of trityllithium groups was prepared by applying a 100% excess of *n*-butyllithium in THF for 2 h at 0 °C.

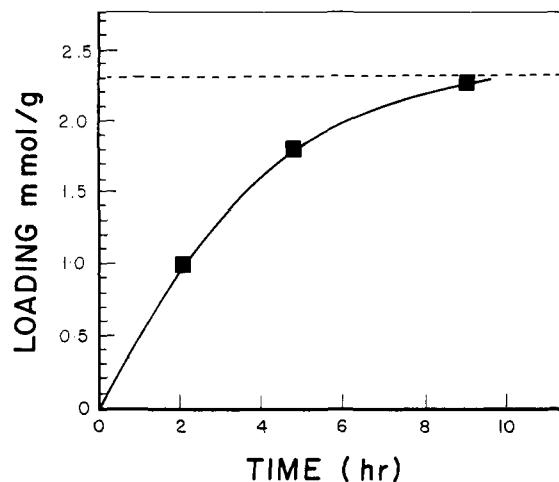
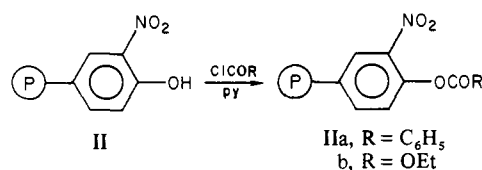


Figure 1. Loading of polymer I with anionic groups as a function of time.

Table I

starting material	alkylation reagent	product	% yield
$(CH_3)_2CHCOC_6H_5$	CH_3I	$(CH_3)_2CCOC_6H_5$	96
$(CH_3)_2CHCOC_6H_5$	$C_6H_5CH_2Br$	$C_6H_5CH_2C(CH_3)_2COC_6H_5$	98
$(CH_3)_2CHCN$	$C_6H_5CH_2Br$	$C_6H_5CH_2C(CH_3)_2CN$	97
$C_6H_5C\equiv CH$	CH_3I	$C_6H_5C\equiv CCH_3$	94
	$ClCH_2CO_2Et$		96
	$C_6H_5CH_2Br$		98

Scheme VII



The structure of polymer I will be discussed later when para-substituted tritylated polystyrenes are described.

Polymer Ia is very sensitive to moisture, oxygen, and carbon dioxide, as is its soluble analogue. Therefore, all manipulations involving this polymer were carried out under an inert atmosphere.

Polymeric trityllithium was shown to abstract acidic protons quantitatively from appropriate compounds. Excess of the polymer was reacted with these compounds, followed by alkylation with an excess of soluble alkylating reagents in the same vessel.

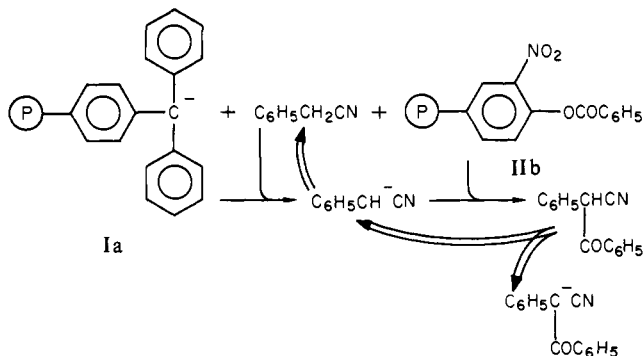
The alkylation products were obtained in excellent yields as Table I shows.

Although the excess of polymer Ia is also alkylated under these conditions, this does not adversely affect the isolation of the desired alkylation product, which is in solution. Workup of the reaction mixture was simple: the polymer was filtered and washed and the excess of alkylating reagent was reacted with pyridine. The salts and excess pyridine were washed with dilute acid, and the organic phase was evaporated to yield the pure product. The advantage of polymeric vs. soluble trityllithium was clearly demonstrated by the fact that with the latter, chromatography was required to separate triphenylmethane from the product.

Using polymeric trityllithium, it was impossible to alkylate esters having α -hydrogens. By the time proton abstraction was complete, side reactions, probably condensations, had already occurred. This will be discussed later.

"Wolf and Lamb" Reactions. A special apparatus, described in the Experimental Section, was designed for these reactions. In

Scheme VIII



this apparatus, the polymeric base Ia was prepared from polymer I by *n*-butyllithium in THF under inert atmosphere, while the acylating polymer—an active ester of polymeric *o*-nitrophenol, IIa or IIb²⁶ (Scheme VII)—was contained in a side arm.

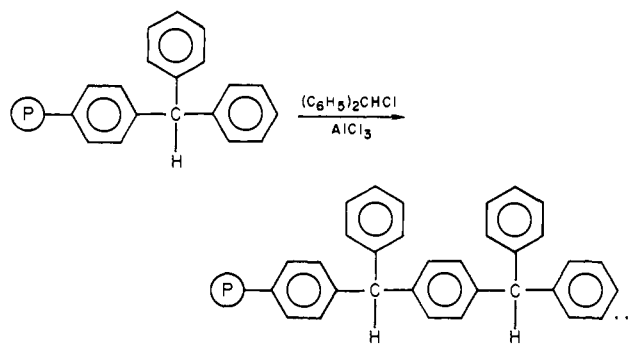
After polymer Ia was prepared, excess *n*-butyllithium was washed out and the side arm turned so as to add the acylating polymer into the reaction chamber. The “wolf and lamb” effect was clearly demonstrated, as the blood-red polymeric trityllithium and the white polymeric active ester did not change their colors upon mixing, whereas their soluble analogues reacted immediately in solution. Color changes did occur, however, when molecules carrying an acidic hydrogen were introduced. The red polymer Ia was converted to its white protonated form I, and the acylation of the carbanion produced the orange polymeric *o*-nitrophenol II as its *o*-nitrophenolate salt (Scheme VIII).

In the benzylation of phenylacetonitrile previously described, the use of the two-polymer system offers a substantial advantage over the reaction in solution. Molecules of phenylacetonitrile, reformed at the acylating polymer as a result of proton interchange between the product and anion molecules, can move back to the polymeric base (present in excess), become deprotonated, acylated, etc., until product formation is complete (Scheme VIII). The stoichiometry of the reaction shows that 2 equiv of base are required per 1 equiv of starting carbon acid (both polymer II and the product will be ionized). We used a 150% excess of polymer Ia over that quantity and a 100% excess of the acylating polymer. Under these conditions, the reactions were complete within less than 15 min.

The mechanism just described implies that molecules of carbon acid may move repeatedly between polymeric reagents. Motion inside a polymer bead is diffusion-controlled and does not depend on stirring. Therefore, in order to shorten the residence time of molecules within the polymer beads, and thereby shorten reaction times, the 20–50 mesh commercial polystyrene (XE-305, Rohm and Haas) used for preparing the polymeric reagents in this work was ground to beads of 100–150 mesh size. Considerable improvement in reaction rates and yields was observed. Thus, with the ground polymers, benzylation of acetophenone was completed in less than 15 minutes, whereas only 72% of the product were obtained in that time with the polymers Ia and IIa prepared from nonground polystyrene beads. All the “wolf and lamb” reactions described in this work were therefore carried out with ground polymers.

Control reactions with analogous soluble reagents were performed in solution. An equivalent of trityllithium was first reacted with 1 equiv of the carbon acid, followed by addition of an excess of the acylating reagent. Without exception, the resulting reaction mixtures had to be separated by chromatography. The work-up of the two-polymer reaction was much simpler: after the reaction mixture was neutralized, the polymers were filtered and washed several times. The inorganic salts were washed with water and the organic phase dried and evaporated to give the product in high yield.

Scheme IX



Scheme X

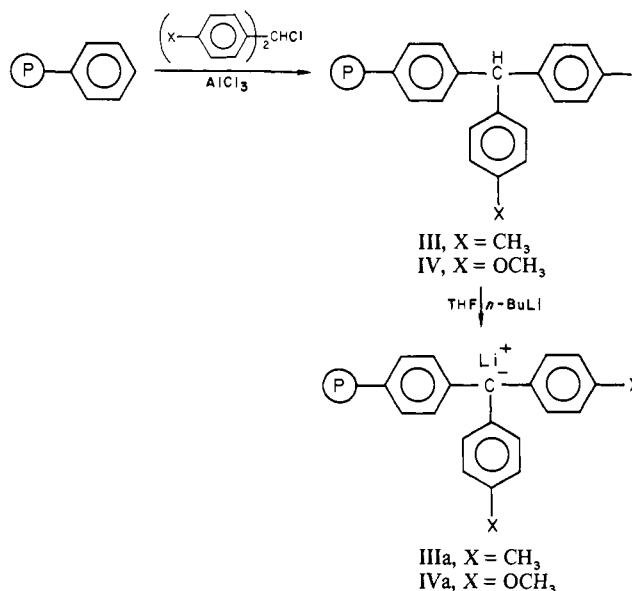


Table II demonstrates the results of the “wolf and lamb” reactions vs. control reactions in solution.

The advantage of using polymers instead of soluble reagents is impressive. The reaction solution has a light color and lacks the highly colored side products typical of many carbanion reactions. The workup is very easy, mainly because of the insolubility of the polymers. The high yields and purity of products are, though, unique to the two-polymer system. They stem from the fact that the two polymers constitute separate, noninteracting phases within the reaction system and the ensuing possibility of using excesses thereof.

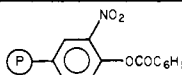
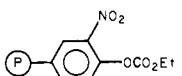
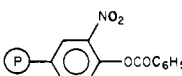
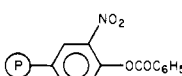
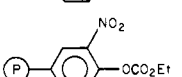
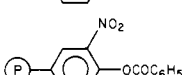
The above described reactions result in an ionized product. No second acylation was evident, although excesses of the basic and acylating polymers were still present. This was further checked with two of the products. They were reacted in a separate experiment with 1 equiv of base and then with an excess of the soluble acylation reagent. No further acylation was detected.

Polymers Carrying para-Substituted Trityl Groups. Polymer I was obtained with loadings of trityl groups as high as 2.3 mmol/g. If the only modification occurring in its preparation is at the phenyl rings of the polystyrene, this would mean that, on the average, one out of every 5.9 phenyl rings is substituted. However, after examining molecular models, it seemed doubtful that such a high loading of the bulky trityl groups could be achieved solely by modification of the phenyl rings of polystyrene. It seems much more likely that benzhydryl substitution also occurs on the trityl groups generated in the initial reaction, the ultimate result being grafting of the polystyrene (Scheme IX).

This bushlike structure explains the low rate of hydrogen abstraction (see Figure 1) even when using the relatively unhindered, highly reactive methyllithium reagent. It is therefore assumed that under the reaction conditions used routinely which lead to

(26) Kalir, R.; Fridkin, M.; Patchornik, A. *Eur. J. Biochem.* **1974**, *42*, 151–156.

Table II

starting material	acylation reagent	product	% yield	% yield of reaction in solution
$C_6H_5CH_2CN$		$C_6H_5CH(CN)COC_6H_5$	94	45
$C_6H_5CH_2CN$		$C_6H_5CH(CN)CO_2Et$	91	37
CH_3CN		$C_6H_5COCH_2CN$	90	27
$C_6H_5COCH_3$		$C_6H_5COCH_2COC_6H_5$	96	48
$C_6H_5COCH_3$		$C_6H_5COCH_2CO_2Et$	92	40
$CH_3CON(CH_3)_2$		$C_6H_5COCH_2CON(CH_3)_2$	92	42

ca. 1.5 mmol/g of trityllithium groups, only the less sterically hindered sites undergo ionization.

Since grafting of this type is likely to occur only at the para position of the phenyl rings, blocking these positions should prevent substitution. In order to test this point we prepared polymers III and IV carrying para-substituted trityl groups (Scheme X).

Loadings of only 1.1 mmol/g for polymer III and 1.0 mmol/g for polymer IV were obtained. These figures were determined both by increase of weight, and by conversion of the trityl polymers to their respective anions, IIIa and IVa, followed by titration, as previously described for polymer Ia.

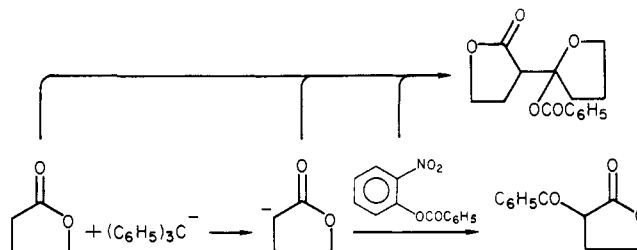
These loadings correspond to an average modification of one out of every 7.5 phenyl rings of the parent polystyrene for polymer III and one out of every 7.4 rings for polymer IV. While these values are almost identical, they differ from the value of 1/5.9 which was calculated for polymer I, assuming no grafting. The differences in molecular sizes of the various polymer-bound trityl groups cannot alone account for these loading values so that grafting probably occurs in the case of polymer I.

The polymeric anions IIIa and IVa are expected to be stronger bases than the polymer Ia.²⁷ No nucleophilic character of the para positions in these anions is to be expected, as observed for trityllithium.²⁸ Because of these features, polymers III and IV may find specific uses in the future.

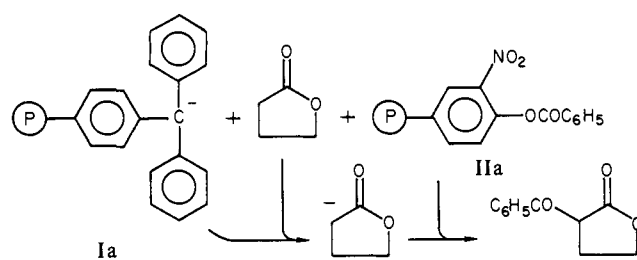
Reactions under Kinetic Control. "Wolf and Lamb" Reactions with Esters. Ester enolates can undergo self-condensation, a reaction which competes with the desired acylation. When acylating an ester in solution using a strong base (such as trityllithium) and an acylation reagent, quantitative enolate formation must be attained (as evidenced by the disappearance of the red color of the base) before the acylation reagent can be introduced, otherwise it will react with the remaining base. During this waiting period, some self-condensation may occur, depending on the reactivity of the enolate, its concentration, etc. For example, when γ -butyrolactone is benzoylated, two products, α -benzoyl- γ -butyrolactone and α -(1-benzoyloxy-1-tetrahydrofuryl)- γ -butyrolactone, are produced, the latter resulting from self-condensation (Scheme XI).²⁹

When the same reaction is carried out as a "wolf and lamb" reaction, using polymeric reagents, no waiting for complete enolate formation is necessary. The acylating polymer, present from the

Scheme XI



Scheme XII



start in excess, can immediately react with enolate molecules formed at the basic polymer, without reaction between the two polymers. Thus, the concentration of enolate molecules can be kept low, and side products are not detected (Scheme XII).

The results of several "wolf and lamb" acylations of esters and yields of the control reactions in solution are shown in Table III.

The solution reactions produced various side products attributed to self-condensation. These impurities were avoided with the polymeric approach. In addition to the kinetic advantages, the "wolf and lamb" reactions also proved to be superior by providing high yields of acylation, a result of overcoming the proton-exchange phenomenon in the particular esters being reacted, which had at least two α -hydrogens.

The rate of enolization and the lifetime of the enolate have an important role in determining the outcome of these reactions. It was already mentioned that no satisfactory alkylations of esters were possible by using polymeric trityllithium and soluble alkylating reagents. The relatively long time (up to a few minutes) needed for complete enolization of the ester when using the polymeric base enabled self-condensation to occur. The comparable reaction with a soluble base is much more rapid and yet may give rise to side products. In a "wolf and lamb" reaction, on the other hand, the electrophilic polymer is present from the start and

(27) Streitwieser, A. *Prepr., Div. Pet. Chem., Am. Chem. Soc.* **1967**, *12*, C-21, C-22 (*Chem. Abstr.* **1967**, *67*, 57703u).

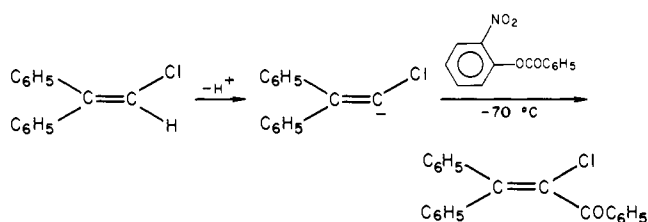
(28) Tomboulian, P.; Stehower, K. *J. Org. Chem.* **1968**, *33*, 1509-1512.

(29) Spencer, E. Y.; Wright, G. F. *J. Am. Chem. Soc.* **1941**, *63*, 1281-1285.

Table III

starting material	polymeric acylating agent	product	% yield	% yield of reaction in solution
CH ₃ CO ₂ Et		C ₆ H ₅ COCH ₂ CO ₂ Et	92	38
CH ₃ CO ₂ Et		CH ₂ (CO ₂ Et) ₂	88	35
C ₆ H ₅ CH ₂ CO ₂ Et			98	47
C ₆ H ₅ CH ₂ CO ₂ Et		C ₆ H ₅ CH(CO ₂ Et) ₂	92	35
C ₆ H ₅ CH ₂ CH ₂ CO ₂ Et			92	40
			95	31

Scheme XIII



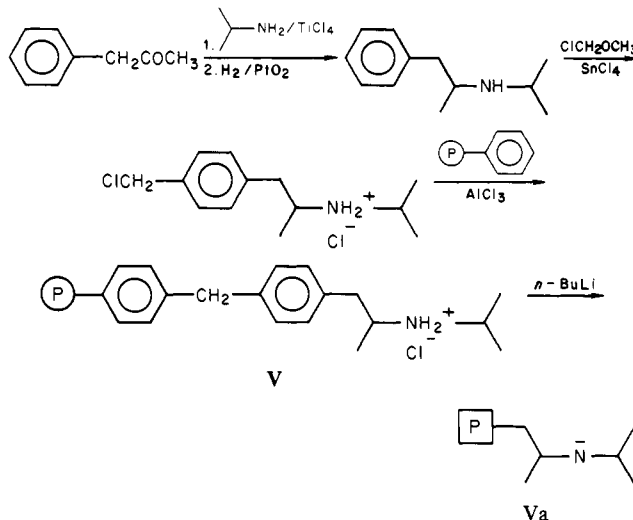
reacts with enolate molecules as soon as they are formed.

“Wolf and Lamb” Reactions with Short-Lived Species. Polymeric Lithium Diisopropylamide. High-yield “wolf and lamb” acylations of esters can be carried out at room temperature, showing that ester enolates are relatively long-lived in the two-polymer system. Because their side reactions are basically second-order reactions, they can be controlled by reducing the effective enolate concentration with an excess of electrophilic polymer. However, anions can also undergo first-order intramolecular changes, which are a function of temperature, but not of concentration. As described above, a two-polymer system may be used for reactions under kinetic control, whereby a short-lived species generated at one polymer is reacted with a second polymer before its decomposition can occur. We chose to study the acylation of 1,1-diphenyl-2-chloroethylene. The carbanion derived from this olefin is stable in solution at $-70\text{ }^{\circ}\text{C}$, and may be acylated at that temperature (Scheme XIII). At higher temperatures it rearranges to diphenylacetylene.³⁰

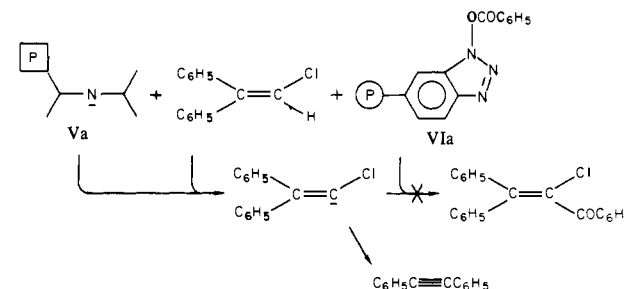
We attempted to acylate this anion at higher temperatures, using a two-polymer reaction. Triyllithium was found to be insufficiently basic to abstract the ethylenic proton from 1,1-diphenyl-2-chloroethylene. Therefore, a stronger polymeric base, polymeric lithium diisopropylamide Va, was prepared according to Scheme XIV.

β -Phenyldiisopropylamine was prepared by modification of a general synthetic route for secondary hindered amines.³¹ Chloromethylation was carried out by using more than 1 equiv of stannic chloride in order to complex the free amine and prevent it from being alkylated by chloromethyl methyl ether. The Friedel-Crafts attachment to the polymer was accomplished by using the hydrochloride of the chloromethylation product. Polymer V was obtained as white beads, with a loading (determined by

Scheme XIV



Scheme XV



increase of weight) of 1.7 mmol of diisopropylamine groups/g of polymer. It was ionized with *n*-butyllithium in THF to give the polymeric anion Va, a dark brown polymer. Titration of the anionic polymer as described for polymeric triyllithium gave a loading value of 1.6 mmol/g.

That polymer Va is a stronger base than polymer Ia was visually verified by reacting the former with triphenylmethane. The blood-red color of triyllithium gradually developed, the reaction being slow because of the bulkiness of the two components.

For the second component of the “wolf and lamb” experiment, the benzoyl derivative of polymeric *N*-1-hydroxybenzotriazole

(30) Kobrich, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473-485.

(31) Stowell, J. C.; Padegimas, S. J. *Synthesis* **1974**, 127-128.

VIa³² was used. This polymer is the fastest known polymeric acylating agent. An improved preparation of this polymer is described in the Experimental Section.

The "wolf and lamb" experiments in this system, however, were not successful. No acylation product was found when the reactions were carried out at temperatures down to -15 °C. Only the rearranged product, diphenylacetylene, could be isolated (Scheme XV).

Apparently, the need to migrate between the polymers limits these reactions to species with relatively longer lifetimes. Although a carbanion molecule has to travel less than 0.1 mm to make this trip (when a thick slurry of finely ground polymers is stirred), the solid beads are surrounded by unstirred layers through which the species must diffuse. Apparently, the diffusion is slow relative to the lifetimes of the species we studied.

While these experiments were being carried out, a paper by Rebek and co-workers was published.²² In that work, singlet oxygen was generated under various conditions at one polymeric reagent and trapped by an olefin supported on another polymer in the same system. The result of Rebek's experiments was that singlet oxygen, with a half-lifetime of about 0.1 s, has little chance of being trapped at the second polymer before decomposition. Singlet oxygen is a small and mobile molecule and Rebek's reaction was carried out in the gaseous state. Changing to organic reactive species in organic solvents will make such reactions even less likely, as our work verifies. Thus, enolates were found to be suitable for "wolf and lamb" experiments whereas very short-lived species are not.

"Wolf and Lamb" Reactions with Sodium Hydride as the Strong Base. So far, only polymeric reagents consisting of soluble reagents attached to insoluble polymers have been described. The general considerations indicating that two noninteracting solid phases and a surrounding liquid phase may bring about distinct synthetic advantages in two-stage reactions are not necessarily limited to polymeric solids. Any insoluble, well-dispersed material capable of carrying out chemical transformations should be suitable. Polymers, however, are unique in that any soluble reagent, in principle, may be attached to them, imparting a general applicability. In addition, porous polymeric beads provide a large surface area enabling easy access to solute components. Solid chemicals are usually reactive only at their surfaces and may be less efficient.

We substituted sodium hydride for polymeric trityllithium Ia in two "wolf and lamb" reactions. Otherwise, these reactions were run under the same conditions as the two-polymer reactions. As an example for an equilibrium-type reaction, the benzoylation of acetophenone was carried out with solid sodium hydride and polymeric *o*-nitrophenyl benzoate IIa. The reaction was completed within 1.5 h due to the slower rate of reaction of the hydride, as compared with the polymeric base Ia. The yield was however, quantitative.

When trying to benzoylate γ -butyrolactone with sodium hydride and the polymeric ester IIa, a mixture of products resulted. Apparently, slow deprotonation with sodium hydride is incompatible with the lifetimes of ester enolates, and side reactions become more pronounced. This implies that the success of the "wolf and lamb" two-polymer reaction is also due to the rapid reaction between polymeric trityllithium and the soluble ester.

Recycling of the Polymeric Reagents. The recycling of polymeric reagents is an important goal, as their preparation is usually longer and more costly than that of their soluble analogs. The ease of separation of the polymeric reagents simplifies their recycling, provided that no irreversible changes occur during their reactions.

The recycling of the polymer I, which was extensively used throughout this work, was studied by subjecting a sample of it to three repetitive ionizations and titrations, as previously described. Loadings of 2.20, 2.15, and 2.25 mmol/g, respectively, were recorded, proving that no changes occur in the polymer with respect

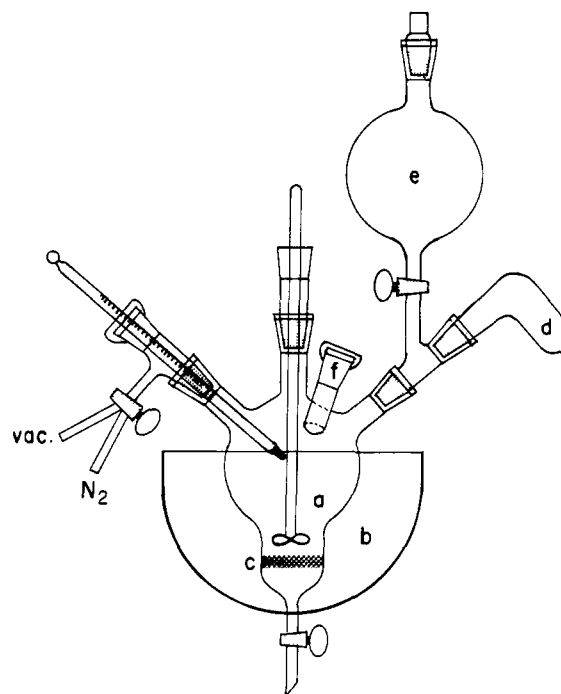


Figure 2. Apparatus for "wolf and lamb" reactions: a, main reaction chamber; b, bath; c, sintered glass disk; d, side arm; e, solvent reservoir; f, injection inlet.

to its basicity. Consequently, samples of this polymer were routinely reused for the "wolf and lamb" reactions. Other polymeric bases described in this work which undergo ionization-protonation cycles are also assumed to be recyclable, although this has not been checked.

At the end of a "wolf and lamb" reaction, the mixture of polymeric reagents may be separated by selective flotation, utilizing differences in their densities. Benzene ($d = 0.88$) and chloroform ($d = 1.5$) can be mixed in such proportions as to cause flotation of one polymeric reagent and precipitation of the other. Each may then be collected and purified.

Experimental Section

General. The polystyrene used throughout this work was XE-305 (Rohm & Haas). The polymer beads were ground for use in "wolf and lamb" reactions as follows: the beads were suspended in the minimum amount of chloroform necessary for complete swelling. The slurry was transferred to a blender operated at maximum speed for a few minutes (the blender blades must be very sharp to prevent the formation of fine dust). The polymer was dried and the 100–150 mesh fraction was collected.

Apparatus for "wolf and lamb" reactions: Figure 2 describes the system used. It enables the preparation and washing of the polymeric base under inert atmosphere in the main reaction chamber a, while the second polymer is stored in the side arm d. By turning it 180°, the second polymer is introduced into chamber a. Thus, all operations can be conducted conveniently in the same apparatus.

Tetrahydrofuran and 1,2-dimethoxyethane were directly distilled into the solvent reservoir e from trityllithium as follows: after a preliminary drying and peroxide removal, half a liter of the solvent was treated with LiAlH₄ until no hydrogen evolution was visible. Then 2–4 g of benzopinacolone was added. The solvent was distilled from the deep red solution under an inert atmosphere. It should be noted that the polymeric strong bases described in this work are washed several times with the solvent prior to reaction. Even the smallest amount of water or oxygen will produce a color change on the surface of the polymer beads. Such a sensitivity to solvent impurities is impossible with the soluble bases.

NMR spectra were recorded on a Bruker 90-MHz NMR spectrometer. Melting points are uncorrected.

Loadings of the polymeric reagents were measured either by increase of weight or by titration of the relevant functional group.

Polymer I Carrying Triphenylmethane Groups. a. Reaction of Polystyrene with Benzhydrol. Benzhydrol (18.4 g) was dissolved in 100 mL of chloroform and impregnated into 10.4 g of polystyrene by evaporation. A solution of 16 g of AlCl₃ in 50 mL of dry nitrobenzene was added. The

(32) Kalir, R.; Warshawsky, A.; Fridkin, M.; Patchornik, A. *Eur. J. Biochem.* 1975, 59, 55–61.

resulting dark mixture was heated at 60 °C for 24 h. Workup was by a mixture of 50 mL of concentrated HCl, 50 mL of DMF, and 100 g of ice. After the beads became light-colored they were washed with warm (60 °C) DMF until the washings were colorless and then with six portions of methylene chloride–methanol (2:1). After being dried, the white polymer weighed 11.8 g (loading 0.7 mmol/g).

b. Reaction of Polystyrene with Benzhydryl Chloride. Distilled benzhydryl chloride (20.2 g) was absorbed into 10.4 g of polystyrene. A solution of 2 g of AlCl₃ in 50 mL of dry nitrobenzene was added. HCl immediately evolved. After being stirred for 24 h at room temperature, the reaction mixture was decomposed as in a. Washing and drying of the polymer afforded 16.9 g of white beads (loading 2.3 mmol/g).

Polymeric Trityllithium Ia. Although polymer I is indefinitely stable, the polymeric anion Ia is very sensitive to moisture, oxygen, and CO₂. It was therefore prepared individually for each experiment. Polymer I (2 g) was introduced into the reaction chamber a (Figure 2). Dry THF was directly distilled into the solvent reservoir e. The system was closed, the walls were heated, and the apparatus was flushed with purified nitrogen several times. Solvent (20 mL) was introduced and an ice–water mixture was placed in bath b. An 8-mmol sample of a solution of *n*-butyllithium in hexane or methylolithium in ether was injected slowly. The polymer turned red, the color deepening with time. After the desired period, the polymer was washed with 20-mL portions of solvent until the washings were free of base. The appropriate reaction (titration, alkylation, “wolf and lamb” reaction, etc.) was then performed.

Titration of Polymer Ia. After preparation, polymer Ia was treated with excess ethanol. The resulting ethoxide was washed into water with THF–ethanol (1:1) solution and then titrated with dilute hydrochloric acid. The dependence of loadings on time is shown in Figure 1, where methylolithium in 1,2-dimethoxyethane was used for ionization of I. Most reactions, however, were done with polymer Ia prepared with a 100% excess of *n*-butyllithium in THF for 2 h at 0 °C. Titration of the resulting polymer showed ca. 1.5 mmol/g of trityllithium groups.

Recycling of Polymer I. Samples of polymer Ia that participated in proton abstraction reactions (not in alkylations) were recycled as follows: the polymer was washed with several portions of warm (60 °C) DMF, then with methylene chloride–methanol (2:1), and dried thoroughly. A sample of the polymer was subjected to three cycles of ionization with a 100% excess of methylolithium in 1,2-dimethoxyethane for 9 h at 0 °C, then titrated, washed, and recycled. The loadings of trityllithium groups were 2.20, 2.15, and 2.25, respectively. Thus, it was demonstrated that polymer I is recyclable. Samples of the polymer were therefore used several times in the various experiments described here.

Alkylation Reactions Using Polymer Ia. The reactions were carried out in the apparatus shown in Figure 2. Polymer I (2 g) was ionized by *n*-butyllithium in THF as previously described. To the resulting polymer Ia (about 3 mmol) was injected 150 mg (1 mmol) of isobutyrophenone. After stirring for a few minutes, 500 mg of benzyl bromide was injected. The reaction mixture was neutralized with hydrochloric acid, and the polymer was washed with 8 portions of 20 mL of methylene chloride. Pyridine was added to the combined washings to react with the excess of benzyl bromide. The salts and excess pyridine were washed with dilute HCl. The organic phase was dried and evaporated to yield 235 mg (98%) of α,α -dimethyl- β -phenylpropionophenone. The results of other similarly performed alkylations are summarized in Table I.

Attempts to Alkylate an Ester with Polymer Ia. A ca. 3-mmol sample of polymer Ia was prepared, as described above. Ethyl isobutyrate (117 mg) was injected, and the mixture was stirred for a few minutes. Benzyl bromide (500 mg) was injected and the workup accomplished as described for the other alkylation reactions. TLC analysis of the reaction mixture revealed several spots, some of which became colored when sprayed with 2,4-dinitrophenylhydrazine solution. These spots, therefore, might be attributed to self-condensation products of the starting ester.

Preparation of the Polymeric *o*-Nitrophenyl Active Esters IIa and IIb. Polymeric *o*-nitrophenol II was prepared from polystyrene and 4-hydroxy-3-nitrobenzyl chloride in a Friedel–Crafts reaction.²⁶ A polymer loaded with 3.5 mmol/g of *o*-nitrophenyl groups was obtained. The polymeric active esters were prepared by reacting the polymer with a twofold excess of either benzoyl chloride and pyridine (to obtain IIa) or ethyl chloroformate and pyridine (to obtain IIb) in dry chloroform at 0 °C for a few hours. The polymeric active ester was washed with dry chloroform until no nonvolatile compounds were detected in the washings (about 6–8 washings) and then dried. The polymers IIa and IIb were obtained in loadings of 2.5 and 2.8 mmol/g, respectively, as evidenced by increase of weight or by titration with benzylamine.

For control reactions in solution, *o*-nitrophenyl benzoate and *o*-nitrophenyl ethyl carbonate were prepared according to the literature.^{33,34}

“Wolf and Lamb” Reactions. These reactions were carried out in the apparatus described in Figure 2. Dry THF was distilled directly into the solvent reservoir before each reaction. The acylating polymer was introduced into the side arm. The system was sealed and flushed several times with pure nitrogen while the walls were heated to remove traces of moisture. The bath was filled with an ice–water mixture, and the polymeric base Ia was prepared and washed as described above. The bath was then filled with water at room temperature, and the acylating polymer was introduced by rotating the side arm. No reaction was apparent between the two polymers. The solvent level was adjusted so as to just cover the polymer mixture. The stirrer was rotated at moderate to high speed, and the substrate to be acylated was injected after being dissolved in a small amount of dry THF. The colors of the polymers changed immediately. The reaction mixture was neutralized with hydrochloric acid, and the polymers were washed 6–8 times with methylene chloride–methanol (2:1) solution. The solvents were evaporated, and the residue was taken up in ether, which after drying and evaporation afforded the desired product. Sometimes, small polymer particles, either formed by the abrasive action of the stirring or present due to imperfect sieving during the grinding of the polystyrene, were present. These fine particles could not be removed by using filter paper, and a short chromatography column was required.

Thus, 120 mg of acetophenone were benzoylated by a mixture of ca. 5 mmol of polymer Ia and 2 mmol of polymer IIa, to yield dibenzoylmethane in 94% yield. Less than 15 min were required for completion of the reaction. The results of other acylations are shown in Table II, along with the results of control reactions in solution.

Control Reactions in Solution. The reactions were carried out under inert atmosphere. A 2-mmol sample of trityllithium in 30 mL of THF was prepared from triphenylmethane and *n*-butyllithium. To the deep-red solution was injected 2 mmol of the same carbon acid used for the corresponding “wolf and lamb” experiment. The red color disappeared within a few seconds, and the soluble acylation reagent was then introduced in 50% excess. The reaction mixture was neutralized and extracted with ether. The organic phase contained triphenylmethane, excess acylation reagent, *o*-nitrophenol, the starting carbon acid, and the product, which was separated by column chromatography.

A “Wolf and Lamb” Reaction with Nonground Polymers. Polymers Ia and IIa were prepared from polystyrene beads of the original, commercial size (20–50 mesh). A “wolf and lamb” benzoylation of acetophenone was carried out in exactly the same way as described for the ground polymers. After 15 min, the reaction mixture still contained some acetophenone. After workup and chromatographic separation, dibenzoylmethane was isolated in 72% yield.

Examination for Possible Second Acylation. The acylation products are obtained at the end of the “wolf and lamb” reactions as their anions. No further acylation was detected. This was separately confirmed in solution. The benzoylation product of acetophenone, dibenzoylmethane, having two hydrogens, and the benzoylation product of phenylacetonitrile, phenylbenzoylacetonitrile, having one α -hydrogen, were both reacted with 1 equivalent of trityllithium, followed by 1.5 equiv of *o*-nitrophenyl benzoate at room temperature. After 15 min, the reaction mixtures were neutralized and worked up, showing no further acylation products.

Separation of the Polymeric Reagents by Flotation. At the end of the “wolf and lamb” reactions, polymeric triphenylmethane I and the polymeric nitrophenol II (partially as its ester IIa or IIb) were mixed together. Their efficient separation for recycling purposes was accomplished by selective flotation in a mixture of 55% benzene and 45% chloroform (v:v). Polymer I floated, the other precipitated.

Preparation of Polymer II, Carrying Triphenylmethane Groups with Methyl Substituents at Para Position. 4,4'-Dimethylbenzhydryl chloride³⁵ (34.5 g) was absorbed into 15.6 g of polystyrene beads. A solution of 3 g of AlCl₃ in 80 mL of dry nitrobenzene was added. The mixture turned black and HCl evolved. After being stirred overnight at 60 °C, the reaction was decomposed with a mixture of 100 mL of DMF, 50 mL of concentrated HCl, and 100 g of ice. The polymer beads became light-colored and were then washed with warm (60 °C) DMF until the washings were colorless. The white polymer was further washed with 6–8 portions of methylene chloride–methanol (2:1) and dried. The yield was 19.8 g (loading of 1.1 mmol/g). A sample of the polymer was converted to the anion IIIa by means of 100% excess of *n*-butyllithium in THF at 0 °C for 2 h. Adding ethanol and titrating the ethoxide formed as described for polymer Ia showed a loading of 1.1 mmol/g.

Preparation of Polymer IV Carrying Triphenylmethane Groups with Methoxy Substituents at Para Positions. Polystyrene (10.4 g) was impregnated with 26.2 g of 4,4-dimethoxybenzhydryl chloride³⁶ by dissolving the chloride in chloroform, adding to the polymer, and evapo-

(33) Hubner, H. *Justus Liebigs Ann. Chem.* **1882**, 210, 328–396.

(34) Bender, G. *Ber. Deutsch. Chem. Ges.* **1886**, 19, 2265–2271.

(35) Norris, J. F.; Banta, C. *J. Am. Chem. Soc.* **1928**, 50, 1804–1808.

(36) Straus, F.; Dutzmann, A. *J. Prakt. Chem.* **1921**, 103, 1–68.

rating to dryness. A solution of 2 g of AlCl_3 in 50 mL of dry nitrobenzene was added, and the reaction was carried out and worked up as described for polymer III. The polymer obtained weighed 13.5 g (loading of 1.0 mmol/g). The loading obtained by titration of the anion IVa was 1.0 mmol/g.

Benzoylation of γ -Butyrolactone in Solution. γ -Butyrolactone (0.17 g) was treated with 2 mmol of trityllithium and then with *o*-nitrophenyl benzoate. Two benzoylation products were obtained and isolated by column chromatography. One (118 mg, 31%) was α -benzoyl- γ -butyrolactone.³⁷ The other (90 mg), according to the ratio of aromatic to aliphatic protons in its NMR spectrum, was suspected to be a product of self-condensation, followed by benzoylation, namely, α -(1-benzoyloxy-1-tetrahydrofuryl)- γ -butyrolactone. Further evidence for this structure was its hydrolysis and water elimination to give dibutyrolactone: 200 mg of the substance was hydrolyzed overnight at room temperature by a mixture of 1 mL of a solution of 40% benzyltrimethylammonium hydroxide (triton B) in water, 1 mL of water, and 2 mL of dioxane. The basic solution was extracted with ethyl acetate to remove unreacted starting material. The aqueous solution was acidified and extracted with ethyl acetate, in which the benzoic acid formed was also taken up. This was eliminated by aqueous sodium bicarbonate. The organic phase was evaporated to yield 105 mg of dibutyrolactone.²⁸

Anal. Calcd for α -(1-benzoyloxy-1-tetrahydrofuryl)- γ -butyrolactone ($\text{C}_{16}\text{H}_{16}\text{O}_5$): C, 65.21; H, 5.84. Found: C, 65.11; H, 6.01. NMR spectrum (CDCl_3): δ 1.96–3.40 (m, 6 H), 3.61–3.79 (m, 1 H), 4.27–4.41 (m, 4 H), 7.30–7.55 (m, 3 H), 7.95–8.06 (m, 2 H).

"Wolf and Lamb" Reactions with Esters. These reactions were carried out under conditions identical with those described above for the reactions at equilibrium. Workup procedures were the same as well. The reactions were carried out at room temperature with fast stirring. Control reactions in solution were carried out as described for the reactions in equilibrium. The reaction mixtures of the control reactions were separated on TLC plates and showed triphenylmethane, *o*-nitrophenol, unreacted nitrophenyl ester, starting material, and product, as well as variable amounts of other products. Some of these gave colored spots when sprayed with 2,4-dinitrophenylhydrazine solution, revealing the existence of carbonyl groups. Acylation products were separated by column chromatography. Their yields are recorded in Table III.

Preparation of the Polymer V Carrying Diisopropylammonium Groups.
a. β -Phenyldiisopropylamine. To a solution of 6.7 g of benzyl methyl ketone, 12.8 mL of isopropylamine, and 100 mL of dry benzene at 0 °C was added dropwise a solution of 3.5 mL TiCl_4 in 15 mL of dry benzene. The mixture was stirred for 15 additional min and then hydrogenated at 60 psi with 25 mg of platinum oxide (Edman catalyst). After hydrogenation was completed (ca. 30 min), 20 mL of 10% aqueous NaOH was added. Two phases formed, with solid titanium dioxide precipitating out. The organic phase was separated, dried, and evaporated. The amine was distilled at 74 °C (1 mmHg). Yield: 8.1 g (91%).

Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{N}$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.10, H, 10.88, N, 7.95. NMR spectrum (CDCl_3): δ 0.93–1.08 (m, 9 H), 1.32 (s, 1 H), 2.4–3.4 (m, 4 H), 7.05–7.52 (m, 5 H).

b. β -(Chloromethylphenyl)diisopropylammonium Hydrochloride. β -Phenyldiisopropylamine (10 g) was dissolved in 50 mL of dry methylene chloride and cooled by an ice-salt bath to 0 °C. SnCl_4 (10 mL) was added dropwise. Chloromethyl methyl ether (20 mL) was added dropwise, maintaining the temperature at 0 °C or below. The solution was kept overnight at 5 °C and then poured over ice. Aqueous NaOH (20%) was added dropwise until the reaction mixture was basic, and the resulting oil was taken up with ether. The organic phase was separated and dried, and dry HCl was bubbled through it. The ether was decanted from the precipitating oil, which solidified upon scratching the vessel walls. The product was triturated with acetone to give a white powder (mp 158–160 °C).

NMR spectrum ($\text{Me}_2\text{SO}-d_6$): δ 1.10–1.38 (m, 9 H), 2.53–3.60 (m, 4 H), 4.75 (s, 2 H), 7.22–7.46 (g, 4 H), 9.24 (s, 2 H).

c. Binding to Polystyrene. Polystyrene (10.4 g) was mixed with 13.0 g of β -(chloromethylphenyl)diisopropylammonium hydrochloride. A solution of 2 g of AlCl_3 in 50 mL of dry nitrobenzene was added, and the mixture was stirred at 60 °C for 24 h. The decomposition of the mixture and washing of the polymer were carried out as for polymer I. Polymer V was obtained as white beads and weighed 17.3 g (loading of 1.7 mmol/g): nitrogen analysis, 2.40% (loading of 1.7 mmol/g); chlorine analysis, 5.65% (loading of 1.6 mmol/g).

Preparation of Polymeric Lithium Diisopropylamide Va. This polymer was prepared according to the procedure adopted for the other polymeric bases described in this work, using a twofold excess of *n*-butyllithium in THF. The loading of the resulting dark brown anion Va was determined

by titration and found to be 1.6 mmol/g.

Improved Synthesis of Polymer VI Carrying *N*-1-Hydroxybenzotriazole Groups.
a. 4-Chloro-3-nitrobenzyl Alcohol. This substance was prepared by *in situ* diborane reduction of 4-chloro-3-nitrobenzoic acid. NaBH_4 (8.5 g) was dissolved in 250 mL of dry diglyme and cooled in an ice bath until the solution became very viscous. 4-Chloro-3-nitrobenzoic acid (50 g) was then added in small portions. Cooling was continued, and 40 mL of distilled boron trifluoride etherate was added dropwise. Stirring was continued for 30 additional minutes. The mixture was poured over 500 g of ice. The solid was filtered and dissolved in ether and the unreacted acid washed with 10% aqueous NaOH. The ether phase was dried and evaporated to give 40 g (yield 85%) of the alcohol.³²

b. Binding to Polystyrene. The original preparation of polymer VI calls for the binding of the alcohol to polystyrene.³² Here, however, the 4-chloro-3-nitrobenzyl chloride, obtained from the alcohol by reaction with thionyl chloride,³⁸ was used, the chloride affording a higher reaction rate and requiring only catalytic amounts of aluminum chloride. Polystyrene (20.8 mg) was impregnated with 17.3 g of the chloride, and a solution of 4 g of AlCl_3 in 100 mL of dry nitrobenzene was added. The mixture was stirred at 60 °C for 24 h. It was hydrolyzed with a mixture of 100 mL of DMF, 100 mL of concentrated HCl, and 200 g of ice. The polymer was washed with warm (60 °C) DMF until the washings were colorless and then with 6–8 portions of methylene chloride-methanol (2:1). The dried polymer weighed 32.1 g (loading of 2.1 mmol/g): nitrogen analysis, 2.97% (2.1 mmol/g); chlorine analysis, 7.46% (2.1 mmol/g).

c. Preparation of Polymer V. The polymer obtained above was reacted with hydrazine and then with hydrochloric acid according to the original preparation.³² The resulting polymer contained 1.7 mmol/g of OH groups.

Preparation of the Polymeric Active Ester VIa. Polymer VI (10 g) was suspended in 60 mL of dry chloroform. Benzoyl chloride (5.8 mL) and 4.0 mL of pyridine were added at 0 °C. After the solution was stirred for 30 min, the polymer was washed with dry chloroform under a nitrogen atmosphere. Drying at high vacuum afforded 11.7 g of polymer VIa (loading of 1.4 mmol/g). Titration with benzylamine gave 1.3 mmol/g. The polymer is sensitive to moisture and was kept in a desiccator.

Benzoylation of 1,1-Diphenyl-2-chloroethylene in Solution. 1,1-Diphenyl-2-chloroethylene³⁹ (430 mg) was dissolved in 20 mL of dry THF. The mixture was cooled to –70 °C, and 2 mmol of *n*-butyllithium was added dropwise, under a purified nitrogen atmosphere. After the solution was stirred for 1 h at that temperature, 2 mmol of *o*-nitrophenyl benzoate was added. Stirring and cooling were continued for 15 additional minutes, and the reaction was then neutralized with hydrochloric acid. The mixture was extracted with ether, dried, and evaporated. The residue was chromatographed to give 402 mg (63% yield) of 1,1-diphenyl-2-chloro-2-benzoyl-ethylene. It was identical with the target compound made according to the literature by a similar route.⁴⁰

"Wolf and Lamb" Reaction with 1,1-Diphenyl-2-chloroethylene and the Polymers Va and VIa. The reaction was carried out in the apparatus described in Figure 2. Dry THF was distilled into the solvent reservoir before the reaction. Polymer VIa (1.5 g, 2.1 mmol) was introduced into the side arm. Polymer V (2 g, 2.6 mmol) was introduced into the main chamber and ionized as described above by a twofold excess of *n*-butyllithium. After excess *n*-butyllithium was washed from the polymer Va, the bath was filled with water or a cooling mixture according to the desired reaction conditions. Polymer VIa was then introduced. No reaction was apparent between the two polymers. The amount of solvent was adjusted to just cover the polymers. With fast stirring 215 mg (1 mmol) of 1,1-diphenyl-2-chloroethylene dissolved in a small amount of dry THF was injected. Polymer Va was immediately bleached. After a few minutes, the reaction mixture was neutralized, filtered, and worked up. Only the rearranged product, diphenylacetylene, was found. Identical results were obtained in reactions carried out at room temperature, 0 °C, and –15 °C.

"Wolf and Lamb" Reactions with Sodium Hydride as the Strong Base. These reactions were carried out exactly as were the "wolf and lamb" experiments with polymeric trityllithium Ia, except that ca. 250 mg of NaH dispersed (50–60%) in oil was substituted for the polymer Ia in the main reaction chamber. The oil was washed off the hydride with solvent, prior to reaction. No reaction between the sodium hydride and polymer

(38) McKay, A. F.; Garmaise, D. L.; Gaudry, R.; Baker, H. A.; Paris, G. Y.; Kay, R. W.; Just, G. E.; Schwartz, R. *J. Am. Chem. Soc.* **1959**, *81*, 4328–4335.

(39) Korshak, V. V.; Samplavskaya, K. K.; Andreeva, M. A. *Zh. Obshch. Khim.* **1949**, *19*, 690–695.

(40) Boehme, H.; Stammberger, W. *Arch. Pharm. Ber. Deutsch. Pharm. Ges.* **1972**, *305*, 392–395.

(37) Ebel, F.; Weissbarth, O. German Patent 801 276, Dec 28, 1950 (*Chem. Abstr.* **1950**, *45*, 2972).

Ila used in these reactions was evident.

When 1 mmol of acetophenone was introduced into the mixture of sodium hydride and polymer Ila, the reaction was slower than with polymeric trityllithium Ia. After 1.5 h, excess hydride was carefully destroyed with water, and after workup 212 mg (yield 95%) of dibenzoylmethane was obtained.

When γ -butyrolactone was introduced into the mixture of the hydride and polymer Ila, TLC analysis of a sample of the reaction mixture revealed several spots. No attempt was made to isolate them.

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The Structure of CC-1065, a Potent Antitumor Agent, and Its Binding to DNA

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Abstract: The crystal and molecular structure of a potent antitumor agent, CC-1065 ($C_{37}H_{33}N_7O_8$), has been determined, and circular dichroism studies have demonstrated a strong interaction between CC-1065 and DNA. The triclinic unit cell, space group $P1$, of dimensions $a = 11.063$ (3) Å, $b = 13.311$ (2) Å, $c = 13.405$ (2) Å, $\alpha = 85.18$ (1)°, $\beta = 99.52$ (1)°, and $\gamma = 103.36$ (2)°, contains two CC-1065 molecules and disordered solvent molecules (two methanols and three waters). Intensity data for 6284 reflections were collected at -155 (2) °C; the final R value was 0.08 for 2411 significant high-angle reflections. NMR spectroscopy was very important in assigning kinds of atoms. The CC-1065 molecule consists of three substituted benzodipyrrole moieties linked by amide bonds. One terminal moiety has a cyclopropyl ring; the only asymmetric carbons in the molecule are at the cyclopropyl ring junctures. The two symmetry-independent molecules have the same configuration, but the absolute configuration is not known. The CC-1065 molecules are curved and somewhat twisted with the outer periphery hydrophilic and the inner surface lipophilic. The interaction between CC-1065 and a number of DNA polymers was studied by circular dichroism. The CD effect requires double-stranded DNA and is strongest with poly(dA-dT):poly(dA-dT).

A number of antitumor agents are known to bind to deoxyribonucleic acid by nonintercalative means.¹⁻⁵ Netropsin is an oligopeptide that binds preferentially to poly(dA):poly(dT) and is thought to interact through hydrogen bonds in the minor groove of DNA.^{1,2} Anthramycin is a pyrrolo[1,4]benzodiazepine that binds covalently to guanine in the minor groove.^{3,4} Braithwaite and Baguley have investigated netropsin, distamycin, and several bisamidine and bisquaternary ammonium heterocyclic drugs by viscometric, spectrophotometric, and fluorometric methods, and propose that they all bind in the minor groove of the DNA double helix.⁵

A new antitumor agent, CC-1065, also binds to DNA without intercalation.⁶ CC-1065 is produced by a soil culture, *Streptomyces zelensis*,⁷ and was isolated in pure form⁸ and found to be significantly more cytotoxic in vitro than actinomycin, vinblastine, or maytansine.⁹ In vivo, CC-1065 is highly active against a variety of mouse tumors,⁸ and, as a result, has been selected by the

Table I. ¹³C NMR Shifts

chemical shift ^a	multi-plicity ^b	tentative assignment ¹⁵	chemical shift	multi-plicity	tentative assignment
9.5	q	C3M	121.3	s	C23
20.9	d	C11	123.5	d	C2
21.6	t	C10	127.2	s	C16
26.6	t	C24	127.5	s	C29
27.6	t	C37	128.9	s	C22
31.5	s	C9	129.1	s	C35
49.4	t	C12	129.5	s	C4
53.3	t	C25	130.4	s	C19
54.8	t	C38	130.7	s	C32
60.0	q	C20M	132.4	s	C21
60.3	q	C33M	133.1	s	C34
105.9	d	C17	138.0	s	C20
106.3	d	C30	138.4	s	C33
110.6	d	C7	157.5	s	C40
113.0	s	C3	157.5	s	C5
117.3	s	C18	160.2	s	C27
117.7	s	C31	160.7	s	C8
118.2	s	C36	161.2	s	C14
			176.4	s	C6

^a Chemical shifts in ppm relative to internal Me₄Si. ^b s = singlet, d = doublet, t = triplet, q = quartet.

National Cancer Institute (as NSC298223) for preclinical toxicology studies.

The structure of a fragment of CC-1065, the base degradation product, was reported previously.¹⁰ A preliminary report of the structure of CC-1065 has also been published.¹¹ We report here

(1) (1) Berman, H. M.; Neidle, S.; Zimmer, C.; Thrum, H. *Biochim. Biophys. Acta* **1979**, *561*, 124-131.

(2) Wartell, R. M.; Larson, J. E.; and Wells, R. D. *J. Biol. Chem.* **1974**, *249*, 6719-6731.

(3) Hurley, L. H.; Gairola, C.; Zmijewski, M. *Biochim. Biophys. Acta* **1977**, *475*, 521-535.

(4) Kohn, K. W.; Glaubiger, D.; Spears, C. L. *Biochim. Biophys. Acta* **1974**, *361*, 288-302.

(5) Braithwaite, A. W.; Baguley, B. C. *Biochemistry* **1980**, *19*, 1101-1106.

(6) Swenson, D. H.; Krueger, W. C.; Lin, A. H.; Schpok, S. L.; Li, L. H. *Proc. Am. Assoc. Cancer Res.* **1981**, *22*, 857.

(7) Hanka, L. J.; Dietz, A.; Gerpheide, S. A.; Kuentzel, S. L.; Martin, D. G. *J. Antibiot.* **1978**, *31*, 1211-1217.

(8) Martin, D. G.; Biles, C.; Gerpheide, S. A.; Hanka, L. J.; Krueger, W. C.; McGovern, J. P.; Mizesak, S. A.; Neil, G. L.; Stewart, J. C.; Visser, J. J. *Antibiot.* **1981**, *34*, 1119-1125.

(9) Martin, D. G.; Hanka, L. J.; Neil, G. L. *Proc. Am. Assoc. Cancer Res.* **1978**, *19*, 99.

(10) Chidester, C. G.; Duchamp, D. J.; Martin, D. G. *Abstr. Am. Cryst. Assoc., Winter Meeting 1979*, 6 (Series 2, No. 2), 67.

(11) Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; and Mizesak, S. A. *J. Antibiot.* **1980**, *33*, 902-903.