

Effect of Polymer Architecture on the Efficiency of Acyl Transfer Reactions

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SYNOPSIS

A series of spacer-modified polystyrene-supported hydroxamic esters and hydroxamic dithiocarbonic anhydrides were prepared starting from divinyl benzene and ethyleneglycol dimethacrylate crosslinked polystyrene resins through multistage polymer-analogous reactions. Acyl transfer reactions using these polymer-supported hydroxamic acylating agents containing spacer arms of various lengths were carried out. The investigation revealed a sharp increase in reactivity as the length of the spacer arm was increased from zero methylene spacer to five methylene spacers. Investigations were also carried out to correlate the extent of acyl transfer with the nature and degree of crosslinking and the relative polarity of the polymer network. It was found that the extent of functionalization in each of the polymer analogous reactions and the extent of acylation reaction decreased with an increase in the degree of crosslinking. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

Polymer-supported solid-phase organic synthesis utilizes reactive residues attached to insoluble crosslinked polymeric supports as reagents for effecting functional group conversions.¹⁻³ It has been established that the facilitation of reactions using polymeric reagents and the reactivity of functional groups attached to the polymeric network were influenced by a number of characteristic features of the polymer matrix.⁴ The polarity of the support material is one of the most important features influencing the reactivity of the bound species with the substrate.^{5,6} It has also been established that the degree of crosslinking and the topographical nature of the gel network affect the chemical reactivity of the attached functional groups.⁷ The feasibility of a polymer-supported reaction involving a crosslinked polymer support depends on the accessibility of the reactive groups in the polymer matrix, which in turn depends on the proximity of the macromolecular backbone. For a given polymeric reagent, the mobility of the bound functionality depends on whether

the group is attached directly to the polymer or whether the group is attached through a spacer handle. The increase in reactivity by the introduction of a flexible spacer grouping has been observed in many cases.^{8,9,10}

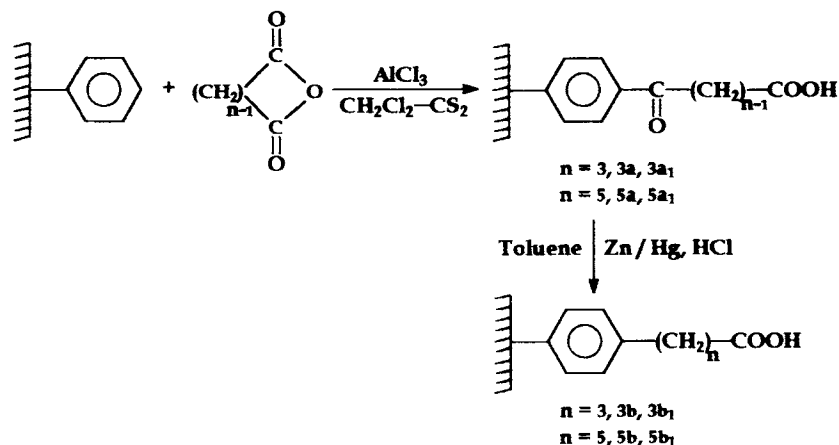
This article describes the effect of spacer methylene groups and the nature and extent of crosslinking on the extent of functionalization reaction and on the reactivity of hydroxamic esters and hydroxamic dithiocarbonic anhydrides as reagents in polymer-supported solid-phase acylation reactions. In the present study, acyl transfer reagents containing five, three, one, and zero methylene groups in the spacer arm were synthesized and used for the acylation of amines. The crosslinking agents divinyl benzene (DVB) and ethylene glycol dimethacrylate (EGDMA) were used in various molar proportions.

EXPERIMENTAL

Materials and Methods

The monomers, styrene, DVB, and EGDMA (Aldrich), were purified by low pressure distillation. Styrene-DVB and styrene-EGDMA copolymer supports were prepared by adopting procedures reported for parallel cases.¹¹ Chloromethyl polysty-

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Scheme 1

rene,¹² carboxylic acid^{18,9,13,14} and carbethoxy¹⁵ polystyrene were prepared as per the literature procedure. Solvents were of reagent grade and were distilled and purified by standard procedures.

Preparation of Hydroxamic Acid Resin

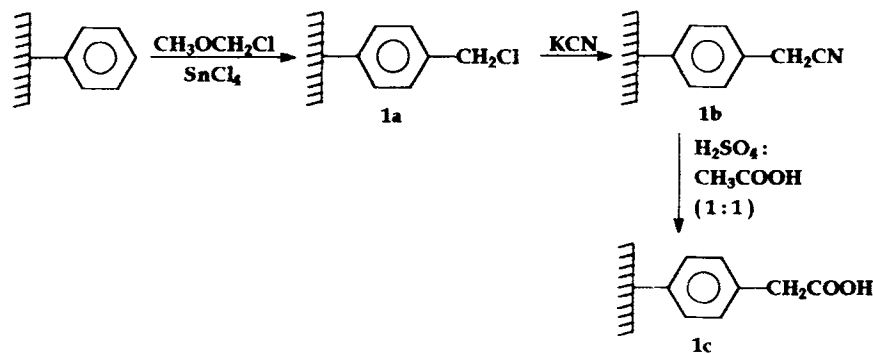
Hydroxylamine hydrochloride (9.2 g) in methanol (15 mL) was neutralized with methanolic potassium hydroxide (10.2 g). The mixture was cooled to 0°C, and potassium chloride precipitated was filtered off. Carbethoxy polystyrene resin (10 g) preswollen in dichloromethane (20 mL) was then added to the filtrate and stirred for 6 h. The polymeric potassium hydroxamate was heated at 80°C with acetic acid (2*N*, 50 mL) for 10 h to get the hydroxamic acid resin. It was filtered at the pump and washed successively with water (20 mL × 5 times), ethanol, methanol, and acetone (20 mL × 5 times each). The resin was then dried in vacuum.

Preparation of Dithiocarbonate Resins

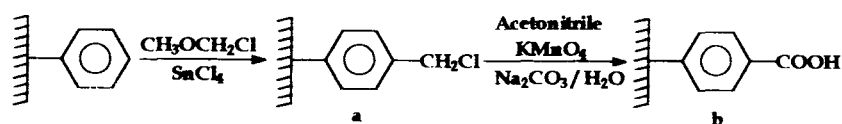
The hydroxamic acid resin (10 g) was mixed with five fold molar excess of an equimolar mixture of carbon disulphide and sodium hydroxide and was shaken for 10 h. The sodium dithiocarbonate resin obtained was washed successively with water (20 mL × 5 times), ethanol, and methanol (20 mL × 5 times each). The resin was dried in vacuum.

Acylation of Polymeric Hydroxamic Acids and Polymeric Dithiocarbonates

The hydroxamic acid resin or dithiocarbonate resin (10 g) was suspended in an acetonitrile : chloroform mixture (1 : 1, v/v, 50 mL), and a three-fold molar excess of benzoyl chloride was added to the suspension. Pyridine (5 mL) was added, and the mixture was stirred for 8 h. The reaction mixture was filtered at the pump to collect the resin particles, washed with acetonitrile, hot water, ethanol, and methanol



Scheme 2



Scheme 3

(20 mL \times 2 min \times 3 times each), and dried in vacuum.

Acyl Transfer Reactions Using Polymeric Hydroxamicbenzoate and Polymeric Hydroxamic Dithiocarbonic Anhydride Resins

The polymeric hydroxamicbenzoate or hydroxamic dithiobenzoic anhydride resin (1 mmol) was suspended in chloroform (20 mL), and the amine (0.5 mmol) was added to it. The mixture was stirred at room temperature for a definite period when maximum conversion was obtained, as indicated by TLC. The mixture was then filtered and washed with chloroform. To the filtrate, dilute HCl (25 mL) was added and shaken well to remove the excess amine. The organic layer was collected, and chloroform was evaporated off to obtain the amide.

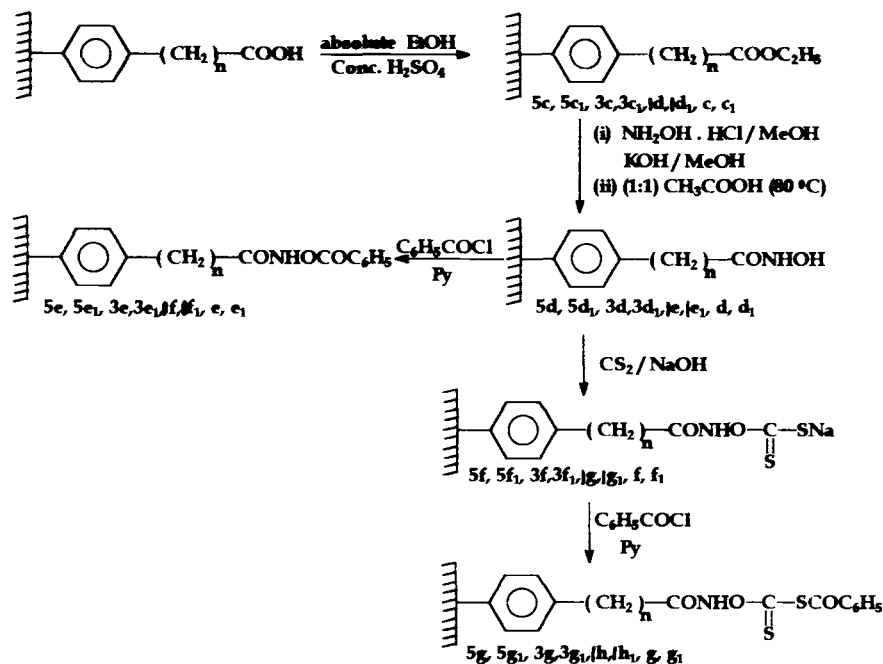
Estimation of Acyl Group Capacity

The acylated resin (either polymeric hydroxamicbenzoate or polymeric hydroxamic dithiobenzoic

anhydride resins) (1 mmol) was suspended in chloroform (20 mL). Aniline (0.05 mL, 0.5 mmol) was accurately measured and added to the suspension. The mixture was stirred for 4 h, filtered, and washed several times with chloroform. The excess aniline present in the filtrate was extracted with 1 : 1 HCl, made up to 250 mL, and estimated by the iodometric method. The amount of excess or unreacted aniline in each case was estimated, from which the amount of aniline reacted was calculated. The acyl group capacity of resins is thus obtained.

RESULTS AND DISCUSSION

Polystyrene-supported acylating reagents containing five, three, one, and zero methylene groups in the spacer arm were synthesized. The difunctional crosslinking agents used were DVB and EGDMA. The extent of crosslinking varied from 2 to 20% (2, 5, 10, 15, and 20%).



Scheme 4

Table I Effect of Length of the Spacer Arm on the Functional Group Capacity of Polystyrene-bound Acylating Agents

Resin	Functional Group Capacity (meq/g) PS-DVB (PS-EGDMA)			
	<i>n</i> = 0	<i>n</i> = 1	<i>n</i> = 3	<i>n</i> = 5
Carboxylic acid resin ^a	3.7 (4.2)	4.0 (4.3)	4.2 (4.6)	4.8 (5.0)
Carbetoxy resin ^b	3.4 (3.9)	3.7 (4.0)	4.0 (4.3)	4.3 (4.7)
Hydroxamic acid resin ^c	3.1 (3.4)	3.5 (3.8)	3.8 (4.0)	4.0 (4.4)
Hydroxamic benzoate resin ^d	2.3 (2.9)	2.5 (3.1)	2.9 (3.4)	3.2 (3.9)
Hydroxamic dithiobenzoic anhydride resin ^d	1.3 (2.4)	1.6 (2.7)	1.9 (3.0)	2.2 (3.8)

^a Determined by volumetric method.^b Determined by saponification method.^c Determined by acetylation method.^d Determined by titrimetric method.

Spacer-modified Polystyrene-supported Acyl Transfer Reagents

The synthesis of carboxylic acid resin containing five and three methylene spacer groups between the polymer backbone and the reagent function was accomplished by a series of polymer analogous reactions. The reaction sequence is presented in Scheme 1.

The starting material used was 2% DVB (EGDMA) crosslinked polystyrene beads. The first step in the reaction sequence was the incorporation of a ketonic acid function $-\text{CO}(\text{CH}_2)_{n-1}\text{COOH}$ by Friedel-Crafts reaction of polystyrene with aliphatic acid anhydrides or acid chlorides using Lewis acid catalysts. Succinic anhydride was used for the synthesis of ketonic acid resins with $n = 3$. Ketonic acid chloride resin with $n = 5$ was obtained when adipoyl chloride was used in the Friedel-Crafts reaction step. The ketonic acid resins indicated the presence of keto and carboxyl group when treated

with 2,4-dinitrophenyl hydrazine reagent and sodium bicarbonate solution, respectively. When the resin was heated with a freshly prepared methanolic solution of 2,4-dinitrophenyl hydrazine reagent, a yellow colored product was obtained. The presence of ketonic group was thus confirmed. Presence of these two groups was confirmed further by the appearance of strong absorption bands at 1690 cm^{-1} ($\text{C}=\text{O}$ str), 1450 cm^{-1} ($\text{C}-\text{O}$ str) of carboxyl group and a strong band at 1710 cm^{-1} due to carbonyl absorption in the infrared (IR) spectrum.

The ketonic acid resin (5a, 5a₁, 3a, 3a₁) was reduced with Zn/Hg and HCl to afford the carboxylic acid resin (5b, 5b₁, 3b, 3b₁). The ketonic group was reduced by Clemensen's method of reduction to methylene group. The resin still gave effervescence with bicarbonate solution, but the test with 2,4-dinitrophenyl hydrazine reagent was negative. The IR absorption band at 1710 cm^{-1} disappeared, and that at 1690 ($\text{C}=\text{O}$ str) and 1450 cm^{-1} still persisted. The carboxyl group capacity was determined by volumetric method.

Polystyrene-supported carboxylic acid resin with one methylene spacer group was prepared from chloromethylated polystyrene (Scheme 2). The chloromethylated polystyrene (1a) was converted to cyanomethyl resin (1b) by reaction with potassium cyanide. Hydrolysis of cyanomethyl polystyrene using acetic acid-sulphuric acid mixture (1 : 1 v/v) afforded the polystyrene-supported carboxylic acid resin with one methylene spacer. The resin gave effervescence with bicarbonate solution, indicating the presence of carboxyl group. The IR spectrum showed bands at 1700 ($\text{C}=\text{O}$ str) and at 1470 cm^{-1} ($\text{C}-\text{O}$ str). The carboxyl group capacity was determined by volumetric method.

Polystyrene-supported carboxylic acid with zero methylene spacer was also prepared from chloro-

Table II Effect of Length of the Spacer Arm on the Extent of Acyl Transfer Reactions Using Polystyrene-supported Acyl Transfer Reagents

Resin Number	Percentage of Anilide Formed	Resin Number	Percentage of Anilide Formed
e	54	e ₁	60
1f	59	1f ₁	67
3e	64	3e ₁	74
5e	74	5e ₁	82
g	50	g ₁	55
1h	54	1h ₁	60
3g	59	3g ₁	65
5g	63	5g ₁	70

Molar ratio, 1 : 2; time, 4 h; temperature, 30°C; solvent, chloroform.

Table III Effect of Crosslink Density on the Benzoyl Group Capacity of Polystyrene-bound Acyl Transfer Reagents

Resin Number	Benzoyl Group Capacity (meq/g) Degree of Crosslinking					Resin Number	Benzoyl Group Capacity (meq/g) Degree of Crosslinking				
	2%	5%	10%	15%	20%		2%	5%	10%	15%	20%
e	2.3	2.0	1.6	1.3	1.0	e ₁	2.9	2.4	2.0	1.7	1.4
1f	2.5	2.3	2.0	1.6	1.1	1f ₁	3.1	2.8	2.5	2.0	1.7
3e	2.9	2.7	2.4	2.0	1.5	3e ₁	3.4	3.1	2.7	2.3	1.8
5e	3.2	2.9	2.5	2.3	1.8	5e ₁	3.9	3.6	3.3	2.8	2.3
g	1.3	1.0	0.9	0.7	0.5	g ₁	2.4	2.1	1.7	1.3	1.0
1h	1.6	1.3	1.0	0.8	0.6	1h ₁	2.7	2.4	2.1	1.7	1.4
3g	1.9	1.6	1.3	1.0	0.8	3g ₁	3.0	2.7	2.4	2.1	1.5
5g	2.2	2.0	1.7	1.4	1.2	5g ₁	3.3	3.0	2.7	2.4	2.0

Molar ratio, 1 : 2; temperature, 30°C; time, 4 h; solvent, chloroform.

methylated polystyrene by oxidation using alkaline KMnO_4 (Scheme 3).

Polystyrene-supported acyl transfer reagents with varying lengths of spacer arm was prepared from carboxylic acid resin by a series of polymer analogous reactions (Scheme 4). Polystyrene-bearing carboxylic acid function was converted to the ester function by reaction with absolute ethanol in the presence of few drops of concentrated H_2SO_4 . The ester resin (5c, 5c₁, 3c, 3c₁, 1d, 1d₁, c, c₁) was characterized by the appearance of strong absorption bands in the IR spectrum at 1420 (C—O str) and 1730 cm^{-1} (C=O ester). The ester group capacity was determined by the saponification method. The ester function on reaction with hydroxylamine, followed by acetic acid, afforded the hydroxamic acid resin (5d, 5d₁, 3d, 3d₁, 1e, 1e₁, d, d₁).¹⁶ The absorption band due to ester function disappeared completely,

and a new band corresponding to NH—OH [3500 cm^{-1} (O—H str), 3400 cm^{-1} (N—H str)] was found to occur. The hydroxyl group capacity of the hydroxamic acid resin was determined by acetylation method.¹⁷ The polymeric hydroxamic acid resin was then reacted with benzoyl chloride in presence of pyridine to obtain the hydroxamicbenzoate resin (5e, 5e₁, 3e, 3e₁, 1f, 1f₁, e, e₁). The hydroxamic dithiocarbonic anhydrides (5g, 5g₁, 3g, 3g₁, 1h, 1h₁, g, g₁) were obtained from hydroxamic acid resin by reaction with an equimolar mixture of CS_2 -NaOH, followed by reaction with benzoyl chloride. The hydroxamicbenzoates were characterized by IR bands at 1710 (C=O str), 3400 (N—H str), and 1700 cm^{-1} (C=O) ester). The quantitative estimation of nitrogen and sulphur was done by C—H—N analysis and the gravimetric method, respectively. The benzoyl group capacity of the resins was determined by

Table IV Effect of Crosslink Density on the Efficiency of Acyl Transfer Reactions Using Polystyrene-bound Acylating Agents

Resin Number	Percentage Yield of Anilide Degree of Crosslinking					Resin Number	Percentage Yield of Anilide Degree of Crosslinking				
	2%	5%	10%	15%	20%		2%	5%	10%	15%	20%
e	54	50	43	35	28	e ₁	60	54	50	45	40
1f	59	55	50	44	38	1f ₁	67	63	58	53	48
3e	64	61	57	53	44	3e ₁	74	70	66	50	56
5e	68	65	61	57	48	5e ₁	82	78	74	70	65
g	50	43	37	30	23	g ₁	55	51	47	43	38
1h	54	50	44	40	33	1h ₁	60	55	51	46	40
3g	59	56	53	48	44	3g ₁	65	60	55	50	46
5g	63	60	57	53	49	5g ₁	70	66	60	55	50

Molar ratio, 1 : 2; time, 4 h; temperature, 30°C; solvent, chloroform.

transferring the acyl group to a standard solution of aniline, and the unreacted aniline was determined titrimetrically.

From the capacity of the resins obtained in each step of the reaction sequence, the effect of separation of functional groups from the polymer matrix was observed to be significant. The results are given in Table I. The effect was very much pronounced in all the conversion steps, indicating an increase in capacity of the resins with an increase in spacer chain length. The separation of functional groups from the polymer backbone gave the facility of these groups being attacked more efficiently by low molecular weight reagents such that greater extent of functional group conversion was achieved.

The acyl transfer reagents having different methylene spacer groups between the reagent function and the polymer matrix prepared were used for the acylation of amines. The results are given in Table II. The effect of separation of the active functional group from the polymer backbone was found to influence the reactivity of the acyl transfer reagent profoundly. Thus, the reagent containing the five methylene spacer arm exhibited the greatest reactivity in terms of product yield, and the reagent in which the reactive function was attached directly to the polymer backbone presented the least reactivity. For the other resins, the reactivity decreased in the descending order of the length of the spacer arm. Acylation of aniline was chosen as a model reaction to study this effect. The acylation was carried out in chloroform at room temperature, and the percentage of anilide formed after a fixed time interval was noted. These studies indicated that the reagent having a five methylene spacer arm was the most reactive.

Effect of the Nature and Degree of Crosslinking

Polystyrene-supported acyl transfer reagents were prepared starting with 2, 5, 10, 15, and 20% crosslinked styrene-DVB and styrene-EGDMA copolymer beads. Acyl transfer reagents containing five, three, one, and zero methylene groups between the polymer backbone and the reagent function were prepared and used for acylating amines. The extent of functionalization of polystyrene resins has been found to be highly dependent on the degree of crosslinking. This was most conspicuous in the case of acyl transfer reagents in which the reagent function was attached directly to the polymer backbone. As the number of spacer methylene groups between the polymer backbone and the reagent function was increased, the effect of increasing crosslinks in re-

tarding the extent of functional group conversions diminished gradually. However, even with the acyl transfer reagent containing five methylene spacer group, the reactivity of the functional group was very much less for the highly crosslinked resins than for the lightly crosslinked resins. This effect was noticed in the acyl group capacity of the acyl transfer resin. The results are given in Table III.

Polystyrene-supported acyl transfer reagents having varying crosslink densities were used for the acylation of amines. It was observed that the reagents prepared from 2% crosslinked polystyrene were more efficient in terms of product yield. Acylation of aniline was taken as the model reaction. The amount of anilide formed after a fixed time interval was measured. The results are presented in Table IV.

From the foregoing observations, it is clear that, compared to DVB crosslinked polystyrene, EGDMA crosslinked copolymers showed significant increase in the reactivity of the bound functionality. The acyl group capacity of the DVB crosslinked polystyrene-bound acyl transfer reagents for 20% crosslinked resin was very low compared to that of 20% EGDMA crosslinked resins. The EGDMA crosslinked polystyrene resins can be more flexible due to the long and flexible EGDMA crosslinks. The enhanced reactivity of the styrene-EGDMA resin can be attributed to the flexibility and also to the increased compatibility with the substrate and solvent.

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