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Characteristic Structural Effects of Cross-Linked Polymer Supports in Solid-Phase Hypochlorite Oxidations

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ABSTRACT: A series of spacer-modified polystyrene-supported tertiary hypochlorites were prepared starting from 2% divinylbenzene cross-linked polystyrene through multistage analogous polymer reactions. The oxidation efficiencies of these polymer-supported analogues of *tert*-butyl hypochlorites containing spacer arms of varying lengths between the cross-linked matrix and the reactive function were determined. This gives a correlation between the reactivity of the functional groups and the distance of the functional group from the cross-linked macromolecular matrix. The method involved the study of the course of the oxidation reaction of cholesterol to cholestenone by determining (i) the reduction in the capacity of the hypochlorite resin iodometrically, (ii) the uptake of the reactive function for oxidation, and (iii) the amount of the product cholestenone spectrophotometrically. These investigations revealed a sharp increase in reactivity on going from a spacer of one carbon unit to that of two carbon units. Thereafter the reactivity was found to increase gradually with a leveling off at six carbon units. A similar reactivity pattern was also observable in the various analogous polymer reactions employed for the preparation of the polymeric spacer-modified tertiary hypochlorites.

Introduction

In polymer-supported solid-phase organic reactions, it was originally assumed that the polymer matrix acts only as a passive support for binding the active functional groups. But recent studies have revealed that the macromolecular matrix has a profound influence on the nature and course of the reactions. The reactivity of functional groups attached to a polymer network is dependent on the variables of gel preparation.[1] Characteristic features of the polymer support, such as its hydrophobic or hydrophilic nature, linear or cross-linked state, degree of functionalization, and separation of the active function from the matrix, have to be taken into account in the design of an effective reagent. The high local concentration of reagents in a polymer matrix greatly influences the kinetics.[2,3] Here the thermodynamic distribution of a substrate between the support and the bulk reaction medium is a factor that favors interactions between the support phase and the substrate, which in turn enhances the effective concentration of the latter within the support, producing a rate acceleration.[4] The incompatibility of the support and the substrate leads to a diminution of the concentration of the substrate within the support volume. This is very significant with cross-linked insoluble supports.[5]

The topographical nature of the polymer matrix exerts a significant influence on the reactivity of the attached functional groups. The topography of the polymer matrix is determined by the chemical nature of the monomers, the molar percentage of cross-links, and the presence of flexible spacers between the matrix and the reactive function.[6,7]

With a view to understanding the significance of these factors on the reactivity of polymer-bound hypohalite oxidizing reagents,[8] we have prepared a series of spacer-modified polystyrene-supported tertiary hypohalite reagents. In this paper we describe the analogous polymer reactions used for their synthesis and the correlation between the length of the spacer arm and the reactivity of the hypochlorite oxidizing function in these insoluble polymeric reagents.

Results and Discussion

The spacer-modified polymeric reagents were prepared from 2% cross-linked divinylbenzene (DVB)–polystyrene by a seven-step reaction (Scheme I). A ketonic acid function, $CO(CH_2)_{n-1}COOH$, was introduced by Friedel–Crafts reaction of polystyrene (1) with aliphatic dibasic acid anhydrides. The anhydrides used were succinic ($n = 3$) and glutaric ($n = 4$). For the preparation of the ketonic acid with $n = 5$, the diacid chloride was used instead of the anhydride due to the nonavailability of the

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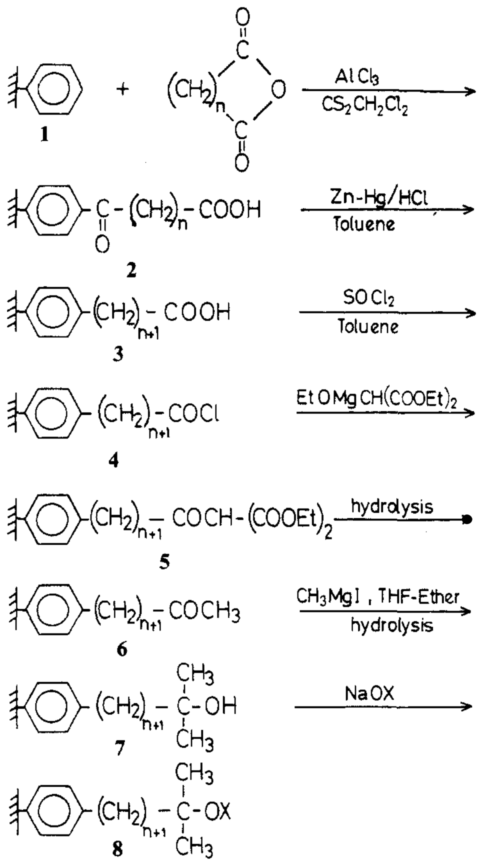
Scheme I
Preparation of Spacer-Modified Polymer-Supported Hypohalites



monomeric anhydride.[9] The product showed the presence of chlorine, indicating that it was a mixture of acid chloride and the acid. The reaction was followed by the IR bands at 1690 cm^{-1} (C=O str) and 1450 cm^{-1} (C—O str). The ketonic group in the product resin was estimated spectrophotometrically by its reaction with the (2,4-dinitrophenyl)hydrazine. The chlorine present in the ketonic acid (chloride) was estimated by the Volhard's method. The ketonic group in resin **2** was reduced by Clemmensen's reduction using Zn–Hg and HCl. The disappearance of the IR band at 1690 cm^{-1} (C=O str) and negative tests with (2,4-dinitrophenyl)hydrazine reagent indicated the complete reduction of the carbonyl group to a methylene group. The carboxyl group capacity in these resins (**2** and **3**) was estimated by titration. The acid resin **3** was converted to the acid chloride **4** by treatment with $SOCl_2$. This polymer showed an intense IR band at 1810 cm^{-1} and the capacity was determined by estimating chlorine. This resin on malonic ester type synthesis with ethoxymagnesium diethyl malonate gave the malonate ester resin **5**, which on hydrolysis with a mixture of H_2SO_4 and HOAc yielded the ketonic resin **6**. The malonic ester resin **5** was characterized by IR bands at 1450 cm^{-1} (C—O str), 1650 cm^{-1} (C=O, ester), and 3300 cm^{-1} (CH str) and the keto resin **6** showed strong IR bands at 1740 cm^{-1}. Grignard reaction of keto resin **6** with CH_3MgI gave the tertiary alcohol resin **7** where the band at 1740 cm^{-1} disappeared completely. Resin **7** on treatment with NaOCl yielded the hypochlorite resin **8**. The available chlorine was estimated by iodometric titration. The capacity of the hypochlorite resin was found to vary with the number of carbon atoms between the polymer matrix and the hypochlorite function. The maximum attainable capacity for the resins were 2.81 mequiv of Cl/g (when $n = 3$), 2.94 mequiv of Cl/g (when $n = 4$), and 3.02 mequiv of Cl/g (when $n = 5$). These were found to be much greater when compared with the earlier resins **9** and **10**, which had a maximum available chlorine content of 1.43 mequiv/g (when $n = 0$) and 2.33 mequiv/g (when $n = 1$).

The different analogous polymer reactions were carried out in appropriate solvents. The dependence of the course of these reactions on the nature of the solvents was prominent in most of the reaction steps. In the Friedel–Crafts reactions of polystyrene, a solvent that could swell the polystyrene and solubilize the anhydride–Lewis acid complex is the most suitable. Solvents like CS_2 and nitrobenzene swell the polystyrene well but could not solubilize the Lewis acid complex. Thus a 4:1 (v/v) mixture of CS_2 and CH_2Cl_2 was chosen as the ideal solvent. A 4-fold increase in the yield of the ketonic acid resin was noted when the solvent was changed from nitrobenzene to a mixture of CS_2 and CH_2Cl_2. Even with this solvent mixture, the solubility of glutaric anhydride–$AlCl_3$ complex was comparatively low and consequently the extent of functionalization was low. The extent of functionalization and hence the capacity could be increased by conducting the reaction four times successively on the resin. With adipoyl chloride, the Lewis acid complex was soluble and the reaction occurred to a much higher extent.

The reduction of the ketonic group by the Clemmensen method was carried out in toluene. Toluene is capable of swelling the resin effectively. Moreover, it serves to create a heterogeneous condition as it is not miscible with the Clemmensen reagent. The mechanism by which this heterogeneous three-phase reaction takes place so effectively is not very clear. The reaction is almost complete as evidenced by the absence of free carbonyl groups in the product resin. It is likely that reaction in the gel phase provides maximum penetration to the heterogeneous reagent. Even though the ketonic group undergoing reduction is adjacent to the cross-linked polystyrene matrix, no particular effect was observable in the rate of the reaction with the increase of the length of the spacer.

The conversion of the acid resin to the acid chloride resin was carried out in toluene. Efficiency of toluene in swelling the resin together with its capability of providing an anhydrous condition makes it a good solvent for the reaction. With the increase in length of the spacer, time required for the acid group to be converted to the acid chloride was reduced as evidenced by the ceasure of the evolution of HCl gas.

The malonic ester type synthesis and hydrolysis of the malonate ester resin were carried out in THF. The Grignard reaction of the ketone resin to form the tertiary alcohol resin and its conversion to the hypochlorite were also carried out in THF. Here also the length of the spacer group was found to influence the extent of conversion. This effect was very prominent in the conversion to the hypochlorite resin. The available chlorine content increased gradually with increase in the number of carbon atoms between the polymer matrix and the tertiary carbon atom. These observations point to the role of good solvents in swelling the hydrophobic polystyrene matrix and the possibility of the reactive function with the spacer groups protruding away from the macromolecular matrix into the solution phase where reactions can take place more effectively. Such effects have been observed earlier in the case of polymer-supported phase-transfer catalysts,[10–12] immobilized enzymes,[13–15] and polymer-supported nucleophilic (dialkylamino)pyridine catalysts.[16]

A drastic increase in hypochlorite capacity was observed with increasing separation from the polymer matrix on going from resin **8a** to **8c**. The dependence of the chlorine

Table I
Relation between Length of the Spacer and Hypochlorite Capacity

resin	structure of the spacer	% Cl	$t_{1/2}$,[a] h	capacity, mequiv/g
9	$C(CH_3)_2OCl$[b]	5.09	49	1.43
10	$CH_2C(CH_3)_2OCl$[b]	8.26	22.5	2.33
8a	$CH_2CH_2CH_2C(CH_3)_2OCl$	9.94	11.5	2.81
8b	$CH_2CH_2CH_2CH_2C(CH_3)_2OCl$	10.35	10.5	2.92
8c	$CH_2CH_2CH_2CH_2CH_2C(CH_3)_2$-OCl	10.69	7.5	3.015

[a] Time taken for half of the alcohol to be oxidized. [b] Preared as described in ref 8.

content in the hypochlorite resins on the length of the spacer is depicted in Table I. It can be seen that there is a drastic increase in chlorine content on going from resin **9**, in which the tertiary carbon is attached directly to the polymer matrix, to resin **10**, which contains one methylene group between the polymer matrix and the tertiary carbon atom. Afterward for resins with three, four, and five methylene groups as spacer between the matrix and the tertiary carbon, there is a gradual increase in the chlorine content. The chlorine content was determined by iodometric titrations and verified by the total halogen analysis.

The separation of the reactive function from the polymer matrix was also found to influence the extent of conversion in the various reaction steps for the synthesis of the different hypochlorite resins. This was observable in the conversion of the acetyl resin and the 2-oxopropyl resin to the corresponding tertiary alcohol resins by the Grignard reaction. Even after 6 h, complete conversion of the acetyl resin could not be achieved. Complete conversion of the ketonic resin to the tertiary alcohol resin could be achieved by repeating the reaction with the same resin for another run. This reaction could be followed by IR spectroscopy and also by (2,4-dinitrophenyl)hydrazone formation reaction. With other ketonic resins where there are three, four, and five methylene groups to separate the carbonyl group from the polymer matrix, the Grignard reaction took place smoothly giving complete conversion to the tertiary alcohol within 6 h. Such a spacer effect was observable in the conversion of the carboxylic acid resin **3** to the acid chloride resin **4**. Here, with the increase in the length of the spacer the time required for conversion was found to be reduced. In the other steps of the reaction sequence the effect was not as easily observed.

Oxidation Reactions Using the Resins. The oxidation of cholesterol to cholestenone was followed spectrophotometrically to investigate the effect of the length of the spacer on the extent of the reaction. Oxidation of cholesterol was carried out at room temperature in chloroform solvent with an alcohol-to-hypochlorite ratio of 1:5. The extent of cholestenone formed was estimated spectrophotometrically by the method of Lappin and Clark.[17] The hypochlorite capacity of the spent resin was also determined at different time intervals. In figure 1, the percentage of cholestenone formed during different time intervals is plotted. From the curves, it can be seen that as the number of carbon atoms in the spacer increases, the time required for the maximum conversion was reduced considerably. In the case of resin with a five-methylene spacer, for a conversion of 98%, only 22 h was necessary, whereas for the resin with no spacer groups the maximum conversion of 86% was achieved only after 96 h. Figure 2 shows the extent of consumption of the hypochlorite reagent as a function of time. In the case of resins which require longer duration for the oxidation reaction, a larger amount of hypochlorite reagent has been found to be consumed than required for the substrate conversion. Probably some amount of the liberated chlorine might have escaped during the prolonged reaction period. The $t_{1/2}$ for oxidation is reduced greatly as the number of carbon atoms separating the hypochlorite function from the polystyrene matrix increased. The time for half-change in the case of the resin having no spacer groups is seven times as great as that for the resin having a five-methylene spacer.

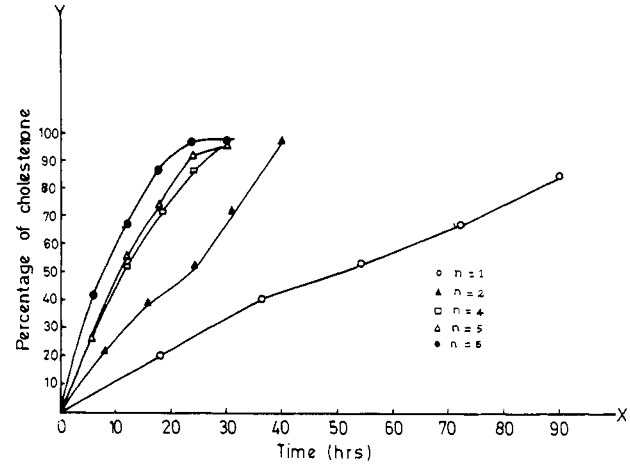


Figure 1. Dependence of reactivity of the hypochlorite resins on the length of the spacer arm.

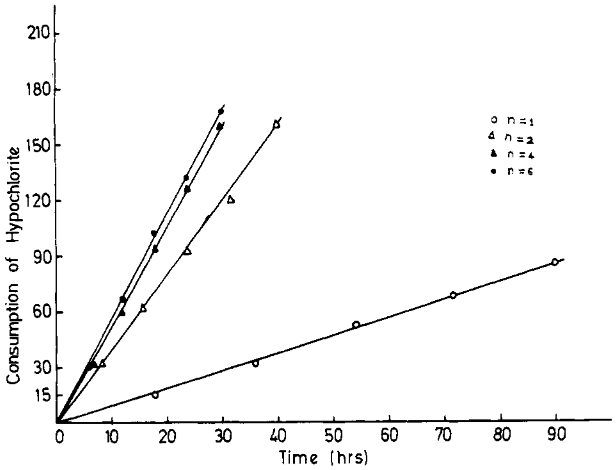


Figure 2. Variation of the consumption of the hypochlorite function on the length of the spacer arm.

Experimental Section

Friedel–Crafts Reaction of Polystyrene (1) with Acid Anhydrides. Preparation of the Ketonic Acid Resin 2. General Procedure. Polystyrene (2% DVB cross-linked, Fluka, 200-400 mesh size 10 g) was suspended in CS_2 (20 mL) and allowed to swell for 20 h. Anhydrous $AlCl_3$ (25 g) was added to a solution of acid anhydride (15 g) (succinic or glutaric)/acid chloride (adipoyl chloride)[18] in a CS_2–CH_2Cl_2 mixture (4:1 v/v) (50 mL), with good stirring and thorough cooling. The preswollen polystyrene (1) was added to the mixture with vigorous stirring and the reaction mixture was heated under reflux for 6 h. Sufficient methanol–water mixture was added to the cooled reaction mixture and the resin was filtered. It was washed with water (30 mL × 10), methanol (10 mL × 5), and acetone (10 mL × 3) and dried in vaccuo to constant weight. Yields of ketonic resin **2a** (n = 3) 14.25 g, capacity in terms of $-CO-(CH_2)_{n-1}-COOH$, 3.57 mequiv/g; yield of resin **2b** (n = 4) 14.7 g, capacity 3.23 mequiv/g; yield of resin **2c** (n = 5) 15.85 g, capacity 2.89 mequiv/g.

Clemmensen's Reduction of Ketonic Acid Resin 2. General Procedure. Zinc amalgam was prepared by shaking zinc granules (35 g) with mercuric chloride (3 g) and concentrated HCl (5 mL). Water (50 mL) was added to the mixture and the supernatant liquid was decanted off. To the amalgamated zinc, the ketonic acid resin **2** (12 g), preswollen in toluene for 20 h was added followed by toluene (30 mL), water (50 mL) and concentrated HCl (75 mL). The reaction mixture was heated under reflux for 30 h and then cooled, filtered, and washed with water (30 mL × 10), methanol (10 mL × 5), and acetone (10 mL × 5) and dried to constant weight. Yield of carboxylic acid resin **3a** ($n = 3$) 9.56 g, capacity 3.45 mequiv/g; yield of resin **3b** ($n = 4$) 10.12 g, capacity 3.42 mequiv/g; yield of resin **3c** ($n = 5$) 10.05 g, capacity 3.93 mequiv/g.

Conversion of the Acid Resin 3 to the Acid Chloride Resin 4. The carboxylic acid resin **3** (8 g) was suspended in toluene (20 mL) for 20 h. Thionyl chloride (20 mL) was added to the resin and the mixture was refluxed for 6 h. The reaction mixture was cooled; filtered; washed with toluene (20 mL × 5), chloroform (10 mL × 5), and acetone (5 mL × 3); and dried in vacuo. Yield of acid chloride resin **4a** ($n = 3$) 8.352 g, capacity 3.5 mequiv of Cl/g; yield of resin **4b** ($n = 4$) 8.274 g, capacity 3.31 mequiv/g; yield of resin **4c** ($n = 5$) 8.193 g, capacity 3.92 mequiv/g.

Reaction of the Acid Chloride Resin 4 with Ethoxymagnesium Diethyl Malonate. General Procedure. (a) Preparation of Ethoxymagnesium Diethyl Malonate. A mixture of magnesium turnings (5.4 g, 0.22 mol), absolute alcohol (5 mL), and CCl_4 (0.5 mL) was taken in a 500-mL round-bottom flask. The reaction mixture was slightly warmed. After 5 min, absolute dry ether was added (50 mL) cautiously with stirring. A solution of diethyl malonate (35.2 g, 0.22 mol), absolute ethanol (20 mL, 0.34 mol), and dry ether (25 mL) was added at such a rate that rapid boiling was maintained. The mixture was refluxed for 3 h on a steam bath when most of the magnesium was dissolved.

(b) Acylation Using Polymeric Acid Chloride Resin 4. A suspension of polymeric acid chloride 4 (7 g) in THF was added to the ethoxy magnesium diethyl malonate with stirring. This was heated under reflux for 6 h, cooled, and shaken with dilute H_2SO_4. The resin was filtered and washed with water (10 mL × 10), methanol (10 mL × 5), and acetone (5 mL × 3). Yield of resin **5a** ($n = 3$) 8.5 g, capacity 3.12 mequiv/g; yield of resin **5b** ($n = 4$) 8.502 g, capacity 2.98 mequiv/g; yield of resin **5c** ($n = 5$) 8.613 g, capacity 3.61 mequiv/g.

(c) Hydrolysis to the 2-Oxoalkyl Resin 6. The malonic ester resin **5** (7 g), preswollen in THF for 20 h, was refluxed with a mixture of concentrated H_2SO_4 (25 mL) and acetic acid (60 mL) for 4 h. The reaction mixture was filtered, washed with water (20 mL × 10), methanol (10 mL × 5), and acetone (5 mL × 3) and dried in vacuo. Yield of resin **6a** ($n = 3$) 6.35 g, capacity 2.97 mequiv/g; yield of resin **6b** ($n = 4$) 6.05 g, capacity 2.94 mequiv/g; yield of resin **6c** ($n = 5$) 6.22 g; capacity 3.31 mequiv/g.

Grignard Reaction of the 2-Oxoalkyl Resins 6. Magnesium turnings (2.4 g) were suspended in dry ether (25 mL). A solution of CH_3I (6 mL) in dry ether (30 mL) was added in portions so that gentle boiling was maintained. When all the magnesium had reacted the mixture was cooled in ice. The 2-oxoalkyl resin **6** (5 g), preswollen in THF for 20 h, was added with vigorous stirring. The reaction mixture was refluxed for 6 h, cooled, and filtered. The resin was washed with ice-cold dilute H_2SO_4, water (20 mL × 5), methanol (10 mL × 5), and acetone (5 mL × 3) and dried in vacuo. Yield of resin **7a** ($n = 3$) 5.1 g, capacity 2.88 mequiv/g; yield of resin **7b** ($n = 4$) 5.02 g, capacity 2.98 mequiv/g; yield of resin **7c** ($n = 5$) 5.103 g, capacity 3.22 mequiv/g.

Conversion of Tertiary Alcohol Resin 7 to the Hypochlorite Resins. The tertiary alcohol resin **5g** was suspended in THF for 20 h. It was stirred with a freshly prepared 2 M solution of NaOCl (50 mL) for 24 h at room temperature. The resin was filtered, washed with water (20 mL × 10), methanol (10 mL × 5), and acetone (5 mL × 3) and dried in vacuo. Yield of resin **8a** ($n = 3$) 5.1 g, capacity 2.81 mequiv/g; yield of resin **8b** ($n = 4$) 5.125 g, capacity 2.92 mequiv/g; resin **8c** ($n = 5$), 5.13 g, capacity 3.02 mequiv/g.

Determination of Hypochlorite Capacity. The hypochlorite resin (200 mg) was suspended in glacial acetic acid (5 mL) for 20 h. H_2SO_4, 1 N, and 10% KI solution (10 mL each) were added and the iodine liberated was titrated against standard thiosulfate solution with starch as the indicator.

Investigation of the Course of the Oxidation Reaction. The oxidation of cholesterol to cholestenone was used as the model system for studying the effect of the length of the spacer group on the rate of the reaction. Cholesterol (100 mg) was shaken with a 5-fold molar excess of the hypochlorite resins (u mequiv of Cl/g) in chloroform solvent (20 mL) at room temperature. Simultaneously five reaction mixtures were set up. Each of these were worked up at definite time intervals. The capacity of the resins and the amount of cholestenone formed were determined. The amount of cholestenone formed was determined by measuring the intensity of the color developed with a methanolic solution of (2,4-dinitrophenyl)hydrazine reagent at 480 nm.

Recyclability of the Spent Resin. The spent hypochlorite resin from the oxidation reaction was washed successively with methylene chloride, chloroform, and acetone (10 mL × 3 each); filtered; and dried in vacuo. The dried resin, preswollen in THF (20 h), was stirred with a freshly prepared 2 M solution of sodium hypochlorite (50 mL) in THF as described earlier. The regenerated resins were found to have capacities almost identical with those of the original resins.

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Registry No. Cholesterol, 57-88-5; cholestenone, 601-54-7.

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