

# Reactions of polymer-supported $\omega$ -bromoalkylcarboxylates: formation of lactones *versus* oligomerization

Philip Hodge\*, Jiang Ji-Long and Glynn J. Owen

Chemistry Department, University of Manchester, Oxford Road, Manchester M13 9PL, UK

and Mark P. Houghton

Chemistry Department, University of Lancaster, Bailrigg, Lancaster LA1 4YA, UK

(Received 2 November 1995)

The reactions of 4-bromobutyric acid, 5-bromopentanoic acid, 6-bromohexanoic acid, 8-bromo-octanoic acid, 11-bromoundecanoic acid and 12-methanesulfonyloxydodecanoic acid with the bicarbonate forms of various anion-exchange resins were investigated. Both macroporous resins and 2% crosslinked gel-type resins were used. The macroporous resins and some of the gel-type resins had quaternary ammonium sites; other gel-type resins had quaternary phosphonium sites. Various loadings of these sites were used. Ester formation could take place intramolecularly or intermolecularly and the ester products were analysed for lactone, diolide and oligoesters. 4-Bromobutyric acid and 5-bromopentanoic acid reacted with the macroporous polymer-supported bicarbonate to give the lactones in high yield. The remaining acids gave mainly oligomers with the macroporous resins and with the highly loaded gel-type resins. In the case of 11-bromoundecanoic acid it was shown that the oligomers had average degrees of polymerization of up to 27 and later work has shown that a substantial number of these are cyclic. As the loading of the bicarbonate on gel-type resins fell (<33% of the phenyl residues bearing 'onium ion sites) site isolation became important and lactones and diolides were formed in significant yields. In all but one case, 8-bromo-octanoic acid, the yields were, however, consistent with the concentrations of the bicarbonate in the beads compared with the 'effective molarities' for such reactions. With 8-bromo-octanoic acid the yield of lactone obtained with a lightly loaded gel-type resin suggests considerable site isolation was achieved. There is evidence that as the chain lengths of the  $\omega$ -bromo acids increases site isolation decreases due to 'bridging', i.e. the ability of the bromo end groups to reach over to the carboxylate groups on neighbouring sites. Substantial site isolation was achieved when 11-bromoundecanoic acid was reacted with a gel-type resin on which most of the 'onium salt sites were in the chloride form and only a small fraction were in the bicarbonate form. The reason why site isolation occurred in this case is unclear at present. Copyright © 1996 Elsevier Science Ltd.

(Keywords: lactones; polymer-supported; site isolation)

## INTRODUCTION

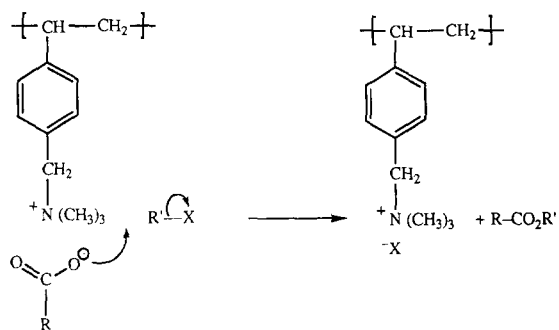
Several research groups have described the synthesis of esters by the reaction of solutions of alkyl halides in organic solvents with the carboxylate forms of anion-exchange resins<sup>1–5</sup>. Both ammonium<sup>1–4</sup> and phosphonium<sup>5</sup> types of resin have been used. In most cases these polymer-supported (PS) ester syntheses are examples of Reaction 1. This paper is concerned with the same type of reaction but where the bromide and carboxylate groups are in the same molecule. Such reactions are of interest because they may follow two courses. Thus, the ester-forming reactions may take place *intramolecularly* to give simple lactones, or they may take place *intermolecularly* to give oligo-esters. The *intramolecular* reaction is of particular interest when the lactones formed contain eight to 12 ring atoms because such

'medium sized rings' are usually difficult to form on account of the numerous unfavourable non-bonded interactions present in rings of these sizes<sup>6</sup>. The *intermolecular* reactions are of interest because such reactions might form the basis of convenient syntheses of certain oligo-esters. It is already known that polyesters can be synthesized by the step-growth reactions of non-polymeric quaternary ammonium salts, usually formed in phase transfer catalysed reactions, of  $\omega$ -halogeno carboxylic acids<sup>7</sup>.

The main objective of the present work was to determine how, in the present PS reactions, the balance between lactone formation and oligomerization is a function of (i) the ease of cyclization of the particular  $\omega$ -bromoalkanoic acids used<sup>8,9</sup>, and (ii) the extent of 'site isolation' (SI) provided by the various polymer supports used<sup>10–12</sup>. Whilst there have been earlier studies of this general type which were aimed at achieving the efficient synthesis of 'medium sized ring' lactones<sup>13–16</sup>, the attraction of the present reaction

\* To whom correspondence should be addressed. Work on this topic began whilst PH was at the University of Lancaster

Reaction 1



Where X<sup>-</sup> = Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup> or *p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-SO<sub>3</sub><sup>-</sup>.

system is the ready availability of anion-exchange resins, the ease with which PS carboxylates can be prepared from them, and, potentially, the ease with which the resins can be re-used. Of previous studies, the most relevant are those of Mohanraj and Ford<sup>12</sup>, and of Tomoi *et al.*<sup>14</sup>. The former studied the cyclization of 12-hydroxydodecanoic acid bound *covalently* to various polymer supports, both macroporous and gel-type, via reactive thiol ester linkages involving the carboxylic acid group of the substrate. They were interested in the amounts of mono- and di-lactones formed and they concluded that the yields of these esters obtained under certain conditions from the supported reactions on gel-type polymers were significantly larger than those obtained from the analogous non-supported reactions. That is, the results they obtained support the idea of SI<sup>10-12</sup>. Tomoi *et al.* studied the cyclization of  $\omega$ -bromoalkanoic acids to lactones in the presence of PS 1,8-diazabicyclo[5.4.0]undec-7-ene (PS-DBU)<sup>14</sup>. Their results will be discussed together with ours later in this paper.

In the reactions of  $\omega$ -bromoalkanoic acids two types of SI need to be considered. The first is 'permanent SI'<sup>11</sup>. This is where the active sites in the beads are unable to react together under any reaction conditions. This is only likely to be the case with extremely lightly loaded highly crosslinked rigid matrices. Even then only a fraction of the groups are likely to be isolated. Resins of this description have not been used in the present work. The second type of SI, 'kinetic SI'<sup>11</sup>, is where active sites on the beads can react together but, because of relatively low loadings and the relatively low mobility of the polymer chains, the site-site interactions occur with reduced rates compared with the analogous reactions in non-polymeric systems. This means that the PS species have a greater chance to react intramolecularly or with low-molecular-weight species in solution. The extent of SI achieved then depends on the relative rates of the reactions involved and it becomes meaningful to refer to the extent of SI in a particular reaction under particular reaction conditions.

EXPERIMENTAL

12-Hydroxydodecanoic acid, the  $\omega$ -bromoalkanoic acids, and the Amberlyst A26 beads were purchased from the Aldrich Chemical Company. Chloromethylated

Biobeads SX2, 2% crosslinked polystyrene beads with diameters 50–200  $\mu$ , were purchased from Biorad Ltd. Organic solutions were dried using magnesium sulfate monohydrate. Melting points were determined using a microscope equipped with a Kofler hotstage. Fourier transform infrared (FTi.r.) spectra were measured using a Nicolet FX100 instrument. The combined gas liquid chromatography-mass spectrometer (g.l.c.-m.s.) was a Hewlett-Packard HP 5995 instrument. Gel permeation chromatography (g.p.c.) was carried out using a Waters  $\mu$ -Styragel 4-column set with chloroform as the eluant and a refractive index detector. Molecular weight values quoted are relative to polystyrene standards.

Bicarbonate form of Amberlyst A26

Before use the commercial Amberlyst A26 beads were packed into a column and washed extensively with deionized water (>10 bed vols), methanol (>3 bed vols), acetone (>3 bed vols) and then dried in a vacuum oven (2 mm of Hg; 70°C) for 120 h.

A column of Amberlyst A26 beads was washed with 1.6 molar aqueous sodium bicarbonate (10 bed vols) over 6–7 h, then with deionized water until the washings were neutral to litmus. To remove most of the water from the beads they were washed successively with methanol (2 bed vols), acetone (1 bed vol.) and diethyl ether (2 bed vols) then dried in a vacuum oven (2 mm of Hg; 20°C) for 72 h. The water content was estimated by Karl-Fisher titration and the bicarbonate anion content by titration against standard hydrochloric acid. The resin used in the present work had a water content of 5.3% by weight and a bicarbonate anion content of 3.81 mmol g<sup>-1</sup>. After being stored at 20°C for 6 months the bicarbonate anion content fell by less than 1%.

Bicarbonate anion forms of 2% crosslinked polystyrene beads functionalized with quarternary ammonium and phosphonium residues

Samples of chloromethylated 2% crosslinked polystyrene beads containing, by elemental analysis, 4.96, 3.90, 0.84 and 0.19 mmol g<sup>-1</sup> of chlorine, available either commercially or from previous studies in our laboratories, were separately treated with a large excess of trimethylamine in *N,N*-dimethylformamide at 90°C for 1 week. The products were then filtered off, washed and dried. This gave, respectively, the chloride forms of resins VII, VIII, IX and XII. Similarly reactions of chloromethylated polystyrenes containing 2.75, 0.92 and 0.28 mmol g<sup>-1</sup> of chlorine with tributylphosphine gave the chloride forms of resins XIV, XV and XVI. The FTi.r. spectra of the various products no longer displayed a band at 1263 cm<sup>-1</sup> (due to CH<sub>2</sub>Cl) and chloride analyses gave the results shown in Table 1. The bicarbonate forms of the various resins were prepared using the procedure described above. Loadings were estimated by back titrations using aqueous hydrochloric acid. The loadings achieved are given in Table 1.

Determination of suitable conditions for polymer-supported ester synthesis

*Neutralization.* A sample of resin (I) (20 mmol), the chosen solvent (40 ml) and a magnetic stirrer bar were placed in a flask and the stirred mixture heated in a thermostatically controlled oil bath at 50°C. When the

**Table 1** Properties of various ion exchange resins

| Designation of the bicarbonate form of the resin | Polymer type <sup>a</sup> | 'Onium cation residues <sup>b</sup> | Chloride form   |   | Bicarbonate form                             |  | Approximate concentration of 'onium bicarbonate in THF <sup>e</sup> (mol l <sup>-1</sup> ) |
|--|---------------------------|-------------------------------------|---|---|--|--|--|
|  |                           |                                     | Loading of residues <b>1a</b> or <b>2a</b> <sup>c</sup> (mmol/g <sup>-1</sup> ) | Rings functionalised by sites <b>1a</b> or <b>2a</b> <sup>c</sup> (%) | Loading <sup>d</sup> (mmol g <sup>-1</sup> ) | Rings functionalised by sites <b>1b</b> or <b>2b</b> (%) |  |
| I  | M                         | A                                   | 4.22  | 81  | 3.81   | 81   | 3.8  |
| II   | M                         | A                                   | —   | —   | 3.19 <sup>f</sup>                            | 65 <sup>g</sup>  | 3.2  |
| III  | M                         | A                                   | —   | —   | 0.96 <sup>h</sup>                            | 19 <sup>g</sup>  | 0.97   |
| IV   | M                         | A                                   | —   | —   | 0.80 <sup>i</sup>                            | 17 <sup>g</sup>  | 0.81   |
| V  | M                         | A                                   | —   | —   | 0.22 <sup>h</sup>                            | 5 <sup>g</sup>   | 0.22   |
| VI   | M                         | A                                   | —   | —   | 0.15 <sup>h</sup>                            | 3 <sup>g</sup>   | 0.15   |
| VII  | G                         | A                                   | 3.82  | 68  | 3.48   | 68   | 1.0  |
| VIII   | G                         | A                                   | 3.16  | 50  | 2.93   | 50   | 0.9  |
| IX   | G                         | A                                   | 0.81  | 9   | 0.79   | 9  | 2.4 × 10 <sup>-1</sup>   |
| X  | G                         | A                                   | —   | —   | 0.74 <sup>j</sup>                            | 13 <sup>g</sup>  | 2.2 × 10 <sup>-1</sup>   |
| XI   | G                         | A                                   | —   | —   | 0.19 <sup>j</sup>                            | 3 <sup>g</sup>   | 5.7 × 10 <sup>-2</sup>   |
| XII  | G                         | A                                   | 0.17  | 2   | 0.17   | 2  | 5.1 × 10 <sup>-2</sup>   |
| XIII   | G                         | P                                   | 1.90  | 33  | 1.81   | 33   | 5.4 × 10 <sup>-1</sup>   |
| XIV  | G                         | P                                   | 0.78  | 10  | 0.76   | 10   | 2.3 × 10 <sup>-1</sup>   |
| XIV  | G                         | P                                   | 0.24  | 3   | 0.24   | 3  | 7.0 × 10 <sup>-2</sup>   |

<sup>a</sup> G = Gel-type polystyrene beads, 2% crosslinked. M = Amberlyst A26 macroporous beads supplied in chloride anion form

<sup>b</sup> A = Quaternary ammonium cation residues as in **1**. P = Quaternary phosphonium residues as in **2**

<sup>c</sup> Reaction of chloromethylated beads with trimethylamine or tributylphosphine afforded directly ion exchange beads in the chloride form. Calculations of the percentage of phenyl residues functionalized by residues **1a** or **2a** is based on the chloride ion content of beads (determined by titrations using silver nitrate) after allowance for the water present (up to 5%, by Karl-Fisher titration). Calculation assumes the beads consist entirely of styryl residues

<sup>d</sup> By titration against 2 N hydrochloric acid assuming beads contain 5% water

<sup>e</sup> Calculated from loading in mmol g<sup>-1</sup>, assuming density of dry beads is 0.9, that macroporous beads swell in THF at 60°C by a factor of 1.1 and that gel-type beads swell in THF at 60°C by a factor of 3.7

<sup>f</sup> Prepared by partial ion exchange of Amberlyst A26 with NaHCO<sub>3</sub> solution

<sup>g</sup> The remaining 'onium ion sites available (see appropriate entry in column 5) are in the chloride form

<sup>h</sup> Prepared from resin II by partial neutralization with 2 N hydrochloric acid

<sup>i</sup> As footnote *h*, but prepared from resin I

<sup>j</sup> As footnote *h*, but prepared from resin VIII

mixture had attained 50°C, the acid (40 mmol) under investigation was added. After 15 and 90 min small samples of resin were removed, washed and dried. The amount of unreacted bicarbonate in a known weight of resin was estimated by titration using 2 N hydrochloric acid. The results obtained are summarized in *Table 2*.

*O-Alkylation.* A sample of resin I (50 mmol) and benzoic acid (100 mmol) in methanol (75 ml) were heated together under reflux for 24 h. The reaction mixture was then cooled and the beads filtered off. They were washed extensively with methanol and then ether and dried. The beads contained 3.10 mmol of benzene per g.

A sample of the above PS benzoate (1.5 g, 4.65 mmol of benzoate) was placed in the solvent (40 ml) under

investigation. A magnetic stirrer bar was added and the mixture was stirred and heated at 50°C using a thermostatically controlled oil bath. When the mixture had attained 50°C n-butyl bromide (828 mg, 6.0 mmol) was added. Samples were removed after 1 and 4 h and analysed by gas chromatography using an authentic sample of n-butyl benzoate. Nitrobenzene was used as an internal standard. The results are summarized in *Table 2*.

*Combined neutralization and O-alkylation.* A mixture of the resin I (5.00 g, 19.1 mmol), benzoic acid (2.11 g, 17.3 mmol), n-butyl bromide (2.39 g, 17.3 mmol) in THF (100 ml) was vigorously stirred and heated at 60°C using a thermostatically controlled oil bath. Samples were removed hourly and analysed as above. The yields after 1, 2, 3 and 4 h were, respectively, 38, 58, 69 and 77%.

#### *Methanesulfonyloxidodecanoic acid*

This compound, prepared from 12-hydroxydodecanoic acid using the general procedure given by Vogel<sup>22</sup>, had mp 73°C.

#### *Source of authentic samples of lactones*

Samples of butyrolactone, valerolactone, caprolactone, undecanolactone and dodecanolactone were purchased from Aldrich Chemical Company or Fluka Chemicals.

**Table 2** Yields from neutralizations and O-alkylations carried out in various solvents at 50°C<sup>a</sup>

| Solvent    | Neutralization                               |  | O-Alkylation |                         |
|------------|--|--|--------------|-------------------------|
|            | Using acetic acid % neutralized after 15 min | Using benzoic acid % neutralized after |              | % Yields of ester after |
|            |  | 15 min                                 | 90 min       |                         |
| Methanol   | 100  | 82                                     | 100          | 5 10                    |
| THF        | 100  | 65                                     | 85           | 40 80                   |
| Chloroform | 100  | 70                                     | 100          | 18 60                   |
| Toluene    | 100  | 60                                     | 78           | 23 50                   |

<sup>a</sup> See Experimental section for details of reaction procedures

A sample of octanolactone was prepared by Baeyer–Villiger oxidations of cyclo-octanone using trifluoroperoxyacetic acid in dichloromethane at 0°C according to the procedure of Sauers and Ubersax<sup>23</sup>. The product had bp 75°C at 10 mm of Hg (ref. 24 72–73°C at 11 mm).

#### Source of authentic samples of diolides

Small samples of diolides were prepared by separately treating samples (2 g) of 6-bromohexanoic acid, 8-bromooctanoic acid, 11-bromoundecanoic acid and 12-methanesulfonyldodecanoic acid with equivalent amounts of resin XI in THF (25 ml) at reflux temperature for 24 h. At the end of the reaction period the beads were filtered off and the filtrate evaporated. The residue was extracted with hexane and the extract purified using a Chromatotron equipped with a Kieselguhr-coated (4 mm) plate and hexane as the eluant. The hexanolactone dimer had mp 110–113°C (ref. 25, 112°C); the octanolactone dimer had mp 91°C (ref. 25, 93°C); the undecanolactone dimer had mp 71°C (ref. 25, 72°C) and the dodecanolactone dimer had mp 95°C (ref. 25, 101°C).

#### Reaction of $\omega$ -bromoalkanoic acids with various polymer-supported bicarbonates

In each experiment a mixture of the resin (1.10 mmol), the bromo acid (1.00 mol) in THF (25 ml) was vigorously stirred and heated at 60°C using a thermostatically controlled oil bath. After 18 h the mixture was allowed to cool to ambient temperature and the resin was filtered off. The solvent was evaporated off and the residue weighed to determine the yield of ester products. The residue was then analysed by gas chromatography–mass spectrometry calibrated using authentic samples of lactone and diolide. Nitrobenzene was added as an internal standard.

## RESULTS AND DISCUSSION

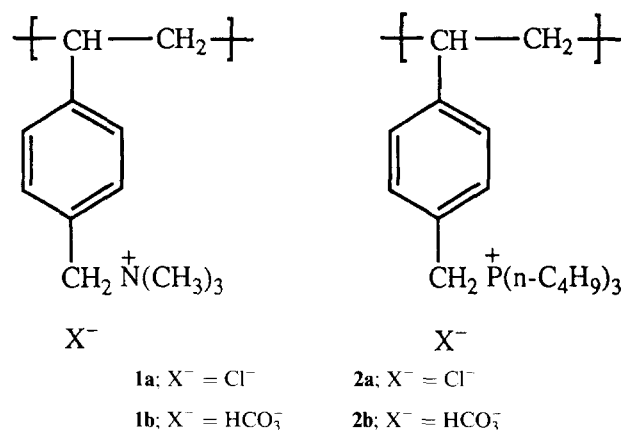
The present studies can be considered conveniently in four parts: the preparation of a range of anion-exchange resins; determination of suitable reaction conditions for ester formation using the anion-exchange resins; the carrying out of the PS ester syntheses together with a discussion of the results obtained, and, finally, a brief consideration of the nature of the oligomeric products.

#### Preparation of various anion-exchange resins

Amberlyst A26, a macroporous anion-exchange resin containing quaternary ammonium salt moieties (**1a**), was obtained commercially. Several samples of chloromethylated 2% crosslinked polystyrene beads with a range in the extents of chloromethylation were available either from previous studies in our laboratories or from commercial sources. Samples of these beads in *N,N*-dimethylformamide at 90°C were treated for one week either with trimethylamine or with tributylphosphine. This gave *gel-type* anion-exchange resins containing quaternary ammonium salt moieties (**1a**) or quaternary phosphonium salt moieties (**2a**), respectively. The loadings of the onium salt sites on all the resins were estimated by chloride analyses. The results are summarized in Table 1.

Anion exchange with sodium bicarbonate (column technique) gave the anion-exchange resins in the

bicarbonate forms, i.e. containing moieties **1b** or **2b**. In all except one case exchange was essentially quantitative. In some cases resins with sites **1b** were partially neutralized with hydrochloric acid in order to obtain resins with lower loadings of sites **1b**, yet with the same total loading of ionic sites. These results are also summarized in Table 1.



#### Determination of suitable conditions for polymer-supported ester synthesis

Two reactions are involved in the ester syntheses discussed in the present work: first the formation of the PS carboxylate, then the reactions of the latter with an alkyl bromide.

The formation of the PS carboxylate could be achieved in two ways: by anion exchange or by neutralization. The former is unattractive in the present work because it needs relatively large amounts of water-soluble salts of the carboxylic acids. Furthermore, the carboxylate residues, once formed, would be likely to react with the bromide groups present to give esters both during the anion exchange process and during drying prior to use in the second reaction in organic solvents. For these reasons the PS carboxylates were prepared by neutralization, i.e. by reacting the carboxylic acids with the bicarbonate forms of the anion exchange resins. PS hydroxides were not used here because such resins tend to lose activity on storage (the hydroxide form of Amberlyst A26 was found to lose 12% of its activity when stored at 20°C for 6 months<sup>17</sup> whereas the bicarbonate form loses <1%) and during the loading process they are likely to react with the alkyl halides to give some elimination.

To identify suitable conditions for the neutralization reaction, the bicarbonate form of Amberlyst A26 was reacted separately with acetic acid and with benzoic acid in a range of solvents. The reactions were monitored by filtering off the resin beads and titrating the unreacted bicarbonate with hydrochloric acid. The results, summarized in Table 2, show that in all the solvents used acetic acid reacts more rapidly than benzoic acid. This suggests that the neutralization reaction is diffusion controlled and in agreement with this it was found that in the reactions with benzoic acid if the stirring speed was less than *ca* 500 rpm the extents of neutralization decreased. The results in Table 2 also show that with

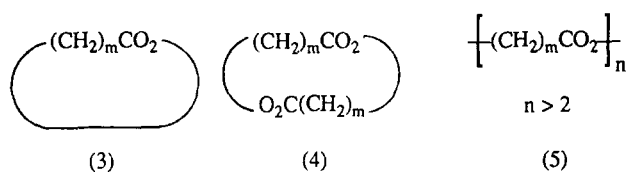
benzoic acid the yields decreased in the order methanol > chloroform > tetrahydrofuran (THF) > toluene, though all these solvents were satisfactory.

The benzoate form of Amberlyst A26 was prepared and the O-alkylation reaction with n-butyl bromide studied in the same solvents used for the neutralization reactions. The reactions were carried out at 50°C and the formation of n-butyl benzoate was monitored by gas chromatography. It is evident from the results, summarized in Table 2, that THF was the best solvent of those studied. Again yields decreased if stirring speeds of less than ca 500 rpm were used.

Since ester formation will commence once a PS carboxylate salt is formed from an  $\omega$ -bromoalkanoic acid, it was decided that in the studies with these substrates it would be best to carry out the neutralization and the subsequent O-alkylation in one practical step. On the basis of the results presented above THF was selected as the most suitable of the solvents investigated. As a trial an equimolar mixture of benzoic acid and n-butyl bromide in THF was heated at 60°C with a 10% excess of the bicarbonate form of Amberlyst A26. The mixture was stirred at 900 rpm and the formation of n-butyl benzoate was monitored by gas chromatography. It was found that the yields of the ester were 38, 58, 69 and 77% after 1, 2, 3 and 4 h, respectively. These reaction conditions were, therefore, adopted as standard for the reactions of the  $\omega$ -bromoalkanoic acids discussed below except that the reaction time was extended to 18 h. Although these conditions were established using Amberlyst A26, a macroporous resin, in the subsequent studies it was found that reactions using gel-type resins also proceeded in excellent yields under these conditions.

*Polymer-supported ester syntheses using various  $\omega$ -bromoalkanoic acids*

Using the reaction conditions given in the preceding paragraph, 4-bromobutyric acid, 4-bromopentanoic acid, 6-bromohexanoic acid, 8-bromo-octanoic acid, 11-bromoundecanoic acid and 12-methanesulfonyloxydodecanoic acid were separately treated with one or more of the PS bicarbonate resins. In general both intra- and intermolecular ester-forming reactions took place in combined yields of 74–95%. The ester products were analysed by gas chromatography or by gel permeation chromatography (g.p.c.) to determine the yields of the lactone (3), the diolide (4), and the oligomers (5). The results are given in Tables 3 and 4.



In analysing the results it is helpful to note the reported effective molarities (EM) for the lactonization of  $\omega$ -bromoalkanoates<sup>9</sup>. Selected values are given in Table 5. Although these were determined using 99% aqueous dimethyl sulfoxide (DMSO) as the solvent and not THF, it is generally found that the EM for cyclizations of this general type closely follow the same pattern<sup>8</sup>. The EM is, theoretically, the concentration at

which the intra- and intermolecular reactions proceed at the same rate. At concentrations below EM lactonization is the more rapid. At concentrations above EM intermolecular reactions are the faster process. For comparisons, approximate values of the initial concentrations of the PS<sup>+</sup>onium bicarbonates in the beads swollen in THF at 60°C are given in Table 1. These were estimated from the loadings of the bicarbonate in mmol per g (given in Table 1), with the assumptions that the densities of the dry beads are 0.9 and the macroporous beads swell in THF at 60° by a factor of 1.1 whilst the gel-type beads swell by a factor of 3.7. These swelling factors were those measured experimentally for resins II and VIII, respectively. The concentrations calculated in this way are probably accurate to within a factor of 3. The concentrations of the carboxylate salts present at any one time will, of course, be significantly lower than the initial concentrations of bicarbonate because both the neutralization and O-alkylation reactions take place over a period of hours. Thus, some molecules of  $\omega$ -bromoalkanoic acid will be neutralized and be taking a full part in ester synthesis before other molecules of the acid have even been neutralized. A further variable is that the swelling properties of the beads will vary throughout the reaction as PS bicarbonate gives way to PS carboxylate and then, finally, PS bromide. Thus, the reaction concentration values given in Table 1 must be used with care but will generally represent maximum possible concentrations of the carboxylates.

The  $\omega$ -bromoalkanoic acids studied in the present work fall into two groups. 4-Bromobutyric acid and 5-bromopentanoic acid constitute the first group. With these acids cyclization to give, respectively, the 5- and 6-ring lactones is so easy (see Table 5) that chain growth has very little chance to make a significant contribution. Consistent with this, these acids reacted with resin (I) (see Table 3, entries 1 and 2) to give high yields of the lactones (3), though the C<sub>5</sub> acid did afford a relatively small amount of the diolide (4). It is estimated that in resin (I) the concentrations of the  $\omega$ -bromoalkanoates are approximately 3 molar. These two experiments serve mainly to demonstrate that the neutralization and O-alkylation reactions proceed very efficiently.

The second group is more interesting. These are those acids which lactonize to give 'medium sized rings', and the lactonizations are, therefore, expected to be relatively slow: see Table 5. This makes it possible to obtain an estimate of the extent of SI in various circumstances. Thus, three situations may arise.

- (1) The lactone 3 is obtained in high yield because there is substantial SI<sup>11</sup>.
- (2) Oligomers 5 are obtained in high yield because there is little or no SI. The converse is that a low yield of oligomers is a clear indication that there is substantial SI.
- (3) Diolide 4 is formed in good yield. This will arise when there is significant SI and lactonization is slow. In these circumstances, because SI is not complete, there will be a reaction between two  $\omega$ -bromoalkanoates to afford linear dimer. The latter will then cyclize relatively rapidly to the diolide because a 'medium sized ring' is no longer being formed. Note

**Table 3** Distribution of the products of ester formation from various  $\omega$ -bromo- or -methanesulfonyloxy-alkanoic acids obtained by using polymer-supported bicarbonates in THF at 60°C for 18 h

| Entry number                             | PS bicarbonate used <sup>a</sup> | Type and loading of PS bicarbonate <sup>b</sup> | Total yield <sup>c</sup> (%) | Composition of ester products <sup>d</sup> |               |               |
|--|----------------------------------|---|------------------------------|--|---------------|---------------|
|  |                                  |   |                              | % Lactone (3)                              | % Diolide (4) | % Polymer (5) |
| (a) 4-Bromobutyric acid                  |                                  |   |                              |  |               |               |
| 1  | I                                | M; A; 81  | 93 <sup>e</sup>              | 100  | 0             | 0             |
| (b) 5-Bromopentanoic acid                |                                  |   |                              |  |               |               |
| 2  | I                                | M; A; 81  | 94 <sup>e</sup>              | 94   | 6             | 0             |
| (c) 6-Bromohexanoic acid                 |                                  |   |                              |  |               |               |
| 3  | I                                | M; A; 81  | 90                           | 2  | 15            | 83            |
| 4  | VII                              | G; A; 68  | 84                           | 3  | 16            | 81            |
| 5  | IX                               | G; A; 9   | 76                           | 28   | 67            | 5             |
| 6  | XII                              | G; A; 2   | 83                           | 81   | 29            | 0             |
| 7  | XIII                             | G; P; 33  | 91                           | 46   | 50            | 4             |
| 8  | XIV                              | G; P; 10  | 88                           | 54   | 44            | 2             |
| 9  | XV                               | G; P; 3   | 76                           | 59   | 40            | 1             |
| (d) 8-Bromo-octanoic acid                |                                  |   |                              |  |               |               |
| 10                                       | VII                              | G; A; 68  | 89                           | 4  | 14            | 80            |
| 11                                       | IX                               | G; A; 9   | 92                           | 23   | 63            | 14            |
| 12                                       | XII                              | G; A; 2   | 81                           | 59   | 37            | 4             |
| 13                                       | XIII                             | P; A; 33  | 79                           | 8  | 80            | 12            |
| 14                                       | XIV                              | P; A; 10  | 82                           | 14   | 76            | 10            |
| 15                                       | XV                               | P; A; 3   | 77                           | 34   | 65            | 1             |
| (e) 12-Methanesulfonyloxydodecanoic acid |                                  |   |                              |  |               |               |
| 16                                       | I                                | M; A; 81  | 80                           | 0  | 0             | 100           |
| 17                                       | IV                               | M; A; 19 <sup>f</sup>                           | 75                           | 0  | 0             | 100           |
| 18                                       | VI                               | M; A; 3 <sup>f</sup>                            | 77                           | 0  | 0             | 100           |
| 19                                       | VII                              | G; A; 68  | 88                           | 0  | 1             | 99            |
| 20                                       | IX                               | G; A; 9   | 85                           | 3  | 27            | 70            |
| 21                                       | XII                              | G; A; 2   | 91                           | 9  | 89            | 2             |
| 22                                       | XIII                             | G; P; 33  | 74                           | 0  | 7             | 93            |
| 23                                       | XIV                              | G; P; 10  | 83                           | 1  | 15            | 84            |
| 24                                       | XV                               | G; P; 3   | 91                           | 7  | 85            | 8             |

<sup>a</sup> See Table 1 for details of these resins

<sup>b</sup> M = macroporous resin; G = gel-type resin; A = quaternary ammonium salts (1b); P = quaternary phosphonium sites (2b); number is the percentage of phenyl residues functionalized to give sites 1b or 2b as appropriate

<sup>c</sup> Total yield of soluble material as a percentage of that expected for 100% ester formation

<sup>d</sup> Lactone (3) and diolide (4) were estimated by gas chromatography using internal standards. Remainder was assumed to be oligomers (5)

<sup>e</sup> Isolated by distillation: see Experimental section

<sup>f</sup> Remaining 'onium ion sites present in chloride from: see Table 1

that if oligomers are formed in good yield, then a *small* yield of diolide is to be expected because the oligomer fraction will normally contain molecules with a range of sizes.

Bearing these three situations in mind several conclusions can be drawn.

In all the reactions involving 6-bromohexanoic acid, 11-bromoundecanoic acid and 12-methanesulfonyloxydodecanoic acid and the macroporous polymer, Amberlyst A26, oligomers are obtained in high yield: see, for example, Table 3, entries 3 and 16 and Table 4, entry 1. There is, therefore, little or no SI in these systems. This is even true when only a small proportion of the 'onium salt sites are occupied by carboxylate groups: see Table 4, entries 3 and 4. This suggests that there is a rapid internal anion exchange process and/or that the bound molecules have chain lengths that are sufficiently long that the terminal bromo groups can reach to the carboxylate

groups on nearby sites, an effect that can be termed 'bridging'.

The situation with the gel-type resins is much more complex. When the percentage of the phenyl groups bearing quaternary ammonium bicarbonate moieties (1b) is  $\geq 50\%$ , i.e. approximate concentrations of carboxylate *ca* 1 molar, the resins behave like the macroporous ones discussed above and the reactions give high yields of oligomers: see Table 3, entries 4, 10 and 19 and Table 4, entries 5 and 6. However, as the percentage of rings bearing these groups, or the corresponding phosphonium groups, falls SI begins to appear. Thus, the 'ammonium' resin (IX) and 'phosphonium' resins (XIII) and (XIV), which have carboxylate concentrations of approximately  $2 \times 10^{-1} \text{ mol l}^{-1}$ , give significant yields (44–80%) of the diolides with the C<sub>6</sub> and C<sub>8</sub> acids: see Table 3, entries 5, 7, 8, 11, 13 and 14. Surprisingly, in view of the EM values given in Table 5, the C<sub>11</sub> acid still gives mainly or entirely oligomers with these resins: see

**Table 4** Distribution of the products of ester formation from 11-bromoundecanoic acid obtained by using polymer-supported bicarbonates in THF at 60°C for 18 h

| Entry number | PS bicarbonate used <sup>a</sup> | Type and loading of PS bicarbonate <sup>b</sup> | Total yield <sup>c</sup> (%) | Composition of ester products <sup>d</sup> |                 |                 |
|--------------|----------------------------------|---|------------------------------|--|-----------------|-----------------|
|              |                                  |   |                              | % Lactone (3)                              | % Diolide (4)   | % Polymer (5)   |
| 1            | I                                | M; A; 81  | 88                           | 0  | 2               | 98              |
| 2            | II                               | M; A; 65 <sup>e</sup>                           | 88                           | 0 <sup>f</sup>                             | 11 <sup>f</sup> | 89 <sup>f</sup> |
| 3            | III                              | M; A; 19 <sup>e</sup>                           | 79                           | 0 <sup>f</sup>                             | 9 <sup>f</sup>  | 91 <sup>f</sup> |
| 4            | V                                | M; A; 5 <sup>e</sup>                            | 68                           | 0 <sup>f</sup>                             | 8 <sup>f</sup>  | 92 <sup>f</sup> |
| 5            | VII                              | G; A; 68  | 84                           | 0  | 2               | 98              |
| 6            | VIII                             | G; A; 50 <sup>e</sup>                           | 95                           | 0 <sup>f</sup>                             | 7 <sup>f</sup>  | 93 <sup>f</sup> |
| 7            | X                                | G; A; 10 <sup>e</sup>                           | 76                           | 50 <sup>f</sup>                            | 12 <sup>f</sup> | 38 <sup>f</sup> |
| 8            | IX                               | G; A; 9   | 81                           | 0  | 17              | 83              |
| 9            | XI                               | G; A; 3 <sup>f</sup>                            | 80                           | 81 <sup>f</sup>                            | 6 <sup>f</sup>  | 13 <sup>f</sup> |
| 10           | XII                              | G; A; 2   | 78                           | 1  | 64              | 35              |
| 11           | XIII                             | G; P; 33  | 90                           | 0  | 0               | 100             |
| 12           | XIV                              | G; P; 10  | 79                           | 0  | 0               | 100             |
| 13           | XV                               | G; P; 3   | 81                           | 1  | 68              | 31              |

<sup>a</sup> See Table 1 for details of these resins

<sup>b</sup> M = macroporous resin; G = gel-type resin; A = quaternary ammonium salts (1b); P = quaternary phosphonium sites (2b); number in the percentage of phenyl residues functionalised to give sites 1b or 2b as appropriate

<sup>c</sup> Total yield of soluble material as a percentage of that expected for 100% ester formation

<sup>d</sup> Lactone (3) and diolide (4) were estimated by gas chromatography using internal standards. Remainder was assumed to be oligomers (5)

<sup>e</sup> Remaining 'onium ion sites present in chloride form: see Table 1

<sup>f</sup> Determined by gel permeation chromatography: see Experimental section for method

**Table 5** Effective molarities for the lactonisation of selected  $\omega$ -bromoalkanoates<sup>a</sup>

| Ring size | Effective molarity    | Temperature (°C) |
|-----------|-----------------------|------------------|
| 5         | $1.60 \times 10^3$    | 50               |
| 6         | $1.45 \times 10$      | 50               |
| 7         | $5.51 \times 10^{-2}$ | 20               |
| 9         | $6.33 \times 10^{-4}$ | 40               |
| 12        | $6.02 \times 10^{-3}$ | 20               |
| 13        | $1.82 \times 10^{-2}$ | 20               |
| 14        | $2.37 \times 10^{-2}$ | 20               |
| 18        | $2.90 \times 10^{-2}$ | 20               |

<sup>a</sup> Lactonization in 99% aqueous DMSO. Data taken from ref. 9

Table 4, entries 8, 11 and 12. So too does the C<sub>12</sub> acid: see Table 3, entries 20, 22 and 23. This suggests that the 'bridging' effect may be reducing the effective SI with these longer chain acids.

Significant yields (59–81%) of lactones are obtained in some cases with the 'ammonium' resin (XII) and 'phosphonium' resins (XV). These have carboxylate concentrations of approximately  $5 \times 10^{-2} \text{ mol l}^{-1}$ . This applies with the C<sub>6</sub> acid and C<sub>8</sub> acid, see Table 3, entries 6, 9, 12 and 15. Given the EM values for these acids the results with the C<sub>6</sub> acid are not surprising but that with the C<sub>8</sub> acid suggests the polymer (XII) has achieved considerable SI.

With the same two resins, the C<sub>11</sub> and C<sub>12</sub> acids give mainly the diolides: see Table 3, entries 21 and 24 and Table 4, entries 10 and 13. Again it is surprising that the C<sub>8</sub> acid gives lactone when the C<sub>11</sub> does not and again this may be due, at least in part, to 'bridging'.

In the above discussion of gel-type resins the loadings of 'onium sites and bicarbonate sites were essentially the same. It was of interest to see if the SI could be reduced by using gel-type resins with a high concentration of quaternary ammonium sites only a fraction of which

were in the bicarbonate form (1b), the rest being in the chloride form (1a). Internal anion exchange might then reduce SI. This prompted the preparation of resins (VIII), (X) and (XI) and these were reacted with the C<sub>11</sub> acid under the same conditions as before. With the more heavily loaded resin (VIII) oligomer formation was again dominant (Table 4, entry 6), but surprisingly the results obtained with resins (X) and (XI) indicated (see Table 4, entries 7 and 9) that SI was substantially greater than before. Thus, the C<sub>11</sub> lactone constituted 50 and 81%, respectively, of the ester products. This corresponds to a carboxylate concentration in the beads of  $ca 10^{-3}$  molar compared to the values of  $ca 2 \times 10^{-1}$  and  $5 \times 10^{-2}$  given in Table 1. The reason(s) for this is not clear, but evidently internal anion exchange is not rapid. Perhaps the presence in the gel-type beads of so many charged sites greatly reduces the mobility of the polymer chains. Also the 'onium salt sites occupied by chloride anions may in some way cluster to produce a highly 'cross-linked' structure throughout which the carboxylate sites are well distributed. This is clearly an important effect and it will be the subject of further study.

#### The nature of the oligomeric products

In a few cases the oligomers derived from 11-bromoundecanoic acid were analysed by g.p.c. to estimate the molecular weights. The results are summarized in Table 6. High molecular weights would not be expected from these syntheses because of the difficulty long polyester chains would have diffusing through the polystyrene matrix. In the event the number average molecular weights ( $M_n$ ; relative to polystyrene standards) obtained corresponded to average degree of polymerisation ( $\overline{DP}$ ) of up to 27. Polydispersities were up to 2.4. In general the higher  $\overline{DP}$ 's were obtained with the more heavily loaded resins and as the loadings fell, not surprisingly, the  $\overline{DP}$ 's and yields tended to fall.

**Table 6** Yields and molecular weights of the oligomers from 11-bromoundecanoic acid

| Entry number in Table 4 | PS bicarbonate used <sup>a</sup> | Type and loading of PS bicarbonate <sup>b</sup> | Overall yield of oligomers (%) <sup>c</sup> | $\bar{M}_n$ <sup>d</sup> | $\bar{M}_w$ <sup>d</sup> | $\overline{DP}$ <sup>e</sup> |
|-------------------------|----------------------------------|---|---|--------------------------|--------------------------|------------------------------|
| 1                       | I                                | M; A; 81  | 86  | 5000                     | 10400                    | 27                           |
| 1 <sup>f</sup>          | I                                | M; A; 81  | 79  | 2400                     | 4200                     | 13                           |
| 2                       | II                               | M; A; 65  | 78  | 2300                     | 2900                     | 13                           |
| 3                       | III                              | M; A; 19  | 72  | 900                      | 1200                     | 5                            |
| 4                       | V                                | M; A; 5   | 63  | 700                      | 1000                     | 4                            |
| 6                       | VIII                             | G; A; 50  | 88  | 1500                     | 3600                     | 8                            |
| 7                       | X                                | G; A; 10  | 29  | 400                      | 450                      | 2                            |
| 9                       | XI                               | G; A; 3   | 10  | 370                      | 390                      | 2                            |

<sup>a</sup> See Table 1 for details of these resins

<sup>b</sup> See Table 4, footnote b

<sup>c</sup> (Yield of ester products)  $\times$  (percentage of oligomers in ester products)

<sup>d</sup> By g.p.c. (see Experimental section) relative to polystyrene standards

<sup>e</sup>  $\bar{M}_n$  divided by the molecular weight of the repeat unit (184)

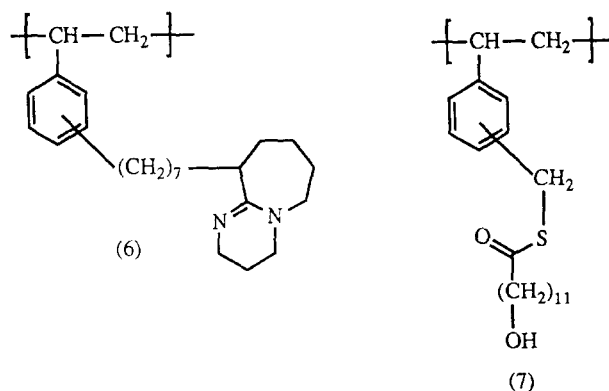
<sup>f</sup> A duplicate of the preceding experiment

Of particular interest with the oligomer fraction is the extent to which the oligomers are cyclic, i.e. the extent to which the linear oligomers underwent *intramolecular* cyclization. Oligomers produced in this way will be the subject of future papers, but in preliminary studies we have shown that 30–70% of the oligomeric molecules are rings<sup>18</sup>. Using a g.p.c. specifically set up to analyse oligomers, the present oligomers can be resolved for molecules with  $\overline{DP}$ 's of up to *ca* 10 (ref. 19). Cyclic oligomers are of interest as starting materials for ring-opening polymerizations to give linear polymers<sup>20</sup>.

## CONCLUSIONS

In the present studies on the reactions of 6-bromohexanoic acid and of 8-bromo-octanoic acid with gel-type anion-exchange resins containing initially only residues **1b** or **2b**, SI first becomes significant when resins IX, XIII or XIV are used. These give carboxylate concentrations of *ca*  $2 \times 10^{-1} \text{ mol l}^{-1}$ . Thus, the diolides (**4**) were obtained in yields of 44–80%. With lower carboxylate concentrations (*ca*  $5 \times 10^{-2} \text{ mol l}^{-1}$ ), i.e. with resins XII or XV, lactone formation becomes important and the lactones are obtained in yields of 59–81%. Bearing in mind the EM values for these acids (see Table 5), the results with the C<sub>6</sub> acid are not surprising, but the formation of the C<sub>8</sub> lactone in good yield suggests considerable SI. A major contribution to the SI may be that, as noted above, the neutralization and O-alkylation reactions are both slow reactions and this may result in the concentration of 'active' carboxylates being significantly lower than the simple calculations used above suggest.

Surprisingly when the above resins were reacted with 11-bromoundecanoic acid and 12-methanesulfonyloxy-dodecanoic acid less SI was obtained than with the C<sub>6</sub> and C<sub>8</sub> acids. Thus, the first three resins (IX, XIII and XIV) gave mainly oligomers and the last two resins (XII and XV) gave mainly the diolides. We attribute this to 'bridging', i.e. despite the inherent SI provided by the support matrix, the bound molecules have chain lengths that are sufficiently long that the terminal bromo or mesylate groups can reach to carboxylate groups on neighbouring sites.



It is of interest to compare these results with those of others seeking SI to assist in lactone synthesis. The most relevant work is that of Tomoi *et al.*<sup>14</sup>. They studied lactone formation from the salts formed from 14-bromotetradecanoic acid and gel-type PS-DBU (**6**). With the percentage of phenyl residues functionalized only 1.3% they obtained up to 57% yields of the lactone. However, as they noted, this was not surprising as the EM<sup>9</sup> for this acid is  $2.6 \times 10^{-2}$  and the concentration of salt in the beads under the reaction conditions was *ca*  $1.8 \times 10^{-2} \text{ mol l}^{-1}$ . The latter is not low enough to get good yields of the lactone from 11-bromoundecanoic acid and the lactone was obtained in  $\leq 21\%$  yield. Mohanraj and Ford have pointed out<sup>13</sup> that in some other cases in the literature<sup>15,21</sup> where SI was sought to assist lactone synthesis and where lactones were obtained in significant yields, the concentrations of the active species present were below the respective EM and, hence the results obtained do not indicate that the support *itself* brings about any SI<sup>13</sup>.

Mohanraj and Ford have studied the formation of lactone and diolide in crosslinked polystyrenes containing residues (**7**)<sup>13</sup>. Cyclization yields achieved using mercuric trifluoroacetate in dichloromethane were significantly higher using 2% crosslinked beads than they were in similar reactions in non-polymeric systems. In the PS reactions the concentrations of residues **7** were  $3 \times 10^{-2}$  to  $8 \times 10^{-2} \text{ mol l}^{-1}$ , whereas the EM for the non-polymeric systems as  $1.2 \times 10^{-3}$ . Hence the polymeric



reaction systems provides some SI, although in these systems the yields of lactone were  $\leq 13\%$  and of diolide  $\leq 19\%$ .

In the present work substantial SI was obtained in the reaction of 11-bromoundecanoic acid using gel type resins with a low loading of bicarbonate residues (**1b**) and a high loading of chloride residues (**1a**). Thus, undecanolactone was obtained in an overall yield of 65%. The reasons for this effect are obscure and it will be the subject of further studies. In this connection it is of interest to note that Tomoi *et al.*<sup>14</sup> obtained surprisingly high yields of tetradecanolide by using a 10-fold excess of a relatively heavily loaded (DS 5.1%) PS-DBU. No explanation was offered.

We find that in the present systems with gel polymers that have at least 50% of the phenyl residues modified into residue **1b** and with all the macroporous resins, there is no significant SI in the reactions with the C<sub>6</sub>, C<sub>11</sub> and C<sub>12</sub> acids. Thus, oligomers are obtained in high yields. In the case of the oligomers from the C<sub>11</sub> acid we have shown they have  $\overline{DP}$ 's up to 27 and, in subsequent work, that 30–70% of the molecules are cyclic<sup>18</sup>.

#### ACKNOWLEDGEMENT

We thank the SERC/EPSRC for the award of PhD Studentships to MPH and GO.

#### REFERENCES

- Cainelli, G. and Manescalchi, F. *Synthesis* 1975, 723
- Cainelli, G., Contento, M., Manescalchi, F. and Plessi, L. *J. Chem. Soc., Chem. Commun.* 1982, 725
- More, G. G., Foglia, T. A. and McGahan, T. J. *J. Org. Chem.* 1979, **44**, 2425
- Bandgar, B. P., Jagdale, M. H., Mare, R. B. and Salunkhe, M. M. *Indian J. Chem.* 1986, **25B**, 421
- Hassanein, M., Akelah, A. and Abdel-Galil, F. *Eur. Polym. J.* 1985, **21**, 475
- March, J. 'Advanced Organic Chemistry', 4th Edn, John Wiley, New York, 1992, pp. 155–157
- Hodge, P., O'Dell, R., Lee, M. S. K., and Ebdon, J. R. *Polymer* 1996, **37**, 1267 and refs cited therein
- Illuminati, G. and Mandolini, L. *Acc. Chem. Res.* 1981, **14**, 95
- Galli, C., Illuminati, G., Mandolini, L. and Tamborra, P. *J. Am. Chem. Soc.* 1977, **99**, 2591
- Ford, W. T. in 'Polymeric Reagents and Catalysts' (Ed. W. T. Ford), ACS Symposium Series 308, American Chemical Society, Washington, 1986, Chap. 11
- Hodge, P. in 'Encyclopaedia of Polymer Science and Engineering' (Eds H. Mark, N. Bikales, C. Overberger and J. Menges), 2nd Edn, Vol. 12, John Wiley, New York, 1988, pp. 627–633
- Hodge, P. in 'Syntheses and Separations Using Functional Polymers' (Eds D. C. Sherrington and P. Hodge), John Wiley, Chichester, 1988, pp. 60–65
- Mohanraj, S. and Ford, W. T. *J. Org. Chem.* 1985, **50**, 1616
- Tomoi, M., Watanabe, T., Suzuki, T. and Kakiuchi, H. *Makromol. Chem.* 1985, **186**, 2473
- Regan, S. L. and Kimura, Y. *J. Am. Chem. Soc.* 1982, **104**, 2064
- Amos, R. A., Emblidge, R. W. and Havens, N. *J. Org. Chem.* 1983, **48**, 3598
- Houghton, M. P., Ph.D. Thesis, University of Lancaster, 1989
- Hodge, P., Houghton, M. P. and Lee, M. S. K. *J. Chem. Soc., Chem. Commun.* 1993, 581
- Wood, B. R., Hodge, P. and Semlyen, J. A. *Polymer* 1993, **34**, 3052
- Brunnelle, D. J. and Shannon, T. G. *Macromolecules* 1991, **24**, 3035
- Scott, L. T. and Naples, J. O. *Synthesis* 1976, 738
- Furniss, B. S., Hannaford, A. J. Smith, P. W. G. and Tatchell, A. R. 'Vogel's Practical Organic Chemistry', 5th Edn, Longman Scientific and Technical, London, 1989, p. 572
- Sauers, R. R. and Ubersax, R. W. *J. Org. Chem.* 1965, **30**, 3939
- Huisgen, R. and Ott, H. *Tetrahedron* 1959, **6**, 253
- Stoll, M. and Rouvé, A. *Helv. Chim. Acta* 1935, **18**, 1087