

# Polymerization of 3,9-Dimethyl-1,5,7,11-tetraoxaspiro[5,5]undecane with Dithiols

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## SYNOPSIS

New polymers containing spiroorthocarbonate units on the main chain were synthesized and characterized. The polymers were prepared by using redox or free-radical catalysts in solution polymerization of 3,9-dimethylene-1,5,7,11-tetraoxaspiro[5,5]undecane [or simply called bimethylenespiroorthocarbonate (BMSOC)] and dithiols at lower temperatures. Their spiroorthocarbonate units could undergo hydrolysis in acidic conditions at room temperature. The structure of polymers was investigated by nuclear magnetic resonance (<sup>1</sup>H- and <sup>13</sup>C-NMR) and Fourier transform infrared (FTIR) spectroscopy. The kind of dithiols had a remarkable effect on properties of the polymers. Block polymers obtained from BMSOC and dithiols could result in a better combination of properties. © 1993 John Wiley & Sons, Inc.

## INTRODUCTION

For some time, we have had an interest in the synthesis of potentially biodegradable polymers that could degrade very fast or very slow by hydrolyzing in moist and acidic conditions at normal temperature, like the conditions in the stomach. We chose to study polymers obtained from BMSOC and dithiols for this purpose.

Marvel and his co-workers<sup>1-7</sup> made a detailed study on the preparation of polymers from diolefins and dithiols, and their pioneering studies led to a number of aliphatic and aromatic polymers by the use of emulsion, solution, or bulk polymerizations. To obtain high molecular weight polymers, it was essential to use high-purity reactants in exactly equivalent amounts since a monofunctional reactant would cause the termination of chains and the oxidation products of dithiols would change the equivalent ratio. They developed a unique technique of emulsion polymerization in which redox systems such as potassium or ammonium persulfate served

as initiators and cupric sulfate with sodium bisulfite served as activators. Polymers were obtained in yields of over 90% with higher inherent viscosities.

Bailey and Endo<sup>8-10</sup> previously prepared BMSOC by treating 2-methylene-1,3-propanediol with dibutyltin oxide followed by carbon disulfide. BMSOC was homopolymerized with di-*t*-butyl peroxide (DTBP) as an initiator in bulk at 130–135°C or in chlorobenzene at 130°C to obtain solid polymers. Its homopolymerization was also initiated with boron trifluoride etherate as a catalyst in bulk at room temperature or in toluene at 110°C, or with stannic chloride in bulk at 82°C. Copolymerization of BMSOC with styrene was carried out with DTBP in chlorobenzene at 120–130°C. In its homo- and copolymerizations, BMSOC always underwent a ring-opening reaction to form polyethercarbonate.<sup>11</sup>

To obtain biodegradable BMSOC–dithiol polymers, it was very important to keep the structure of spiroorthocarbonate intact. It was observed that BMSOC was sensitive to heat and water and tended to undergo ring-opening reaction in these conditions. BMSOC even gradually underwent ring-opening during long-term storage at room temperature. Therefore, we could not use Marvel's technique of emulsion polymerization, which was carried out in water, or the free-radical and cationic polymerizations, which were carried out at higher temperatures.

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Some redox systems were considered effective catalysts for the polymerization of BMSOC and thiols. For example, benzoyl peroxide (BPO)-*N,N*-dimethylaniline (DMA) and DTBP-DMA were a preferable and totally organic redox system used at room temperature. Azobisisobutyronitrile (AIBN) was another suitable catalyst at elevated temperature.<sup>12</sup> BPO-ferrous chloride and BPO-ferrous stearate systems tended to give some cross-linking polymers insoluble in chloroform. The polymerizations were carried out in nonpolar solvents, such as benzene or cyclohexane, to prevent them from chain-transfer reactions.

As shown in Scheme 1, BMSOC can polymerize with dithiols to form polymers (I) of spiroortho-carbonate structures in the presence of the catalysts described above. The acid hydrolysis of (I) will produce tetrahydroxy compounds (tetrols), which results in the degradation of BMSOC-dithiol polymers. The dithiols used for this polymerization are 1,2-ethanedithiol (EDT), 2-mercaptoethyl ether (MEE), 1,6-hexadithiol (HDT), and 2,3-dimercapto-1-propanol (DMP).

The mechanism for the polymerization of BMSOC with dithiols is shown in Scheme 2. This

is similar to Marvel's mechanism for the polymerization of diolefins with dithiols.<sup>7</sup> The first step is the attack of the initiator on a thiol group, forming a thiyl radical that adds to methylene a carbon atom of a double bond of BMSOC, giving a free radical on another carbon. This radical attacks a second thiol to generate a thiyl group. The reaction can be considered a stepwise free-radical polymerization.

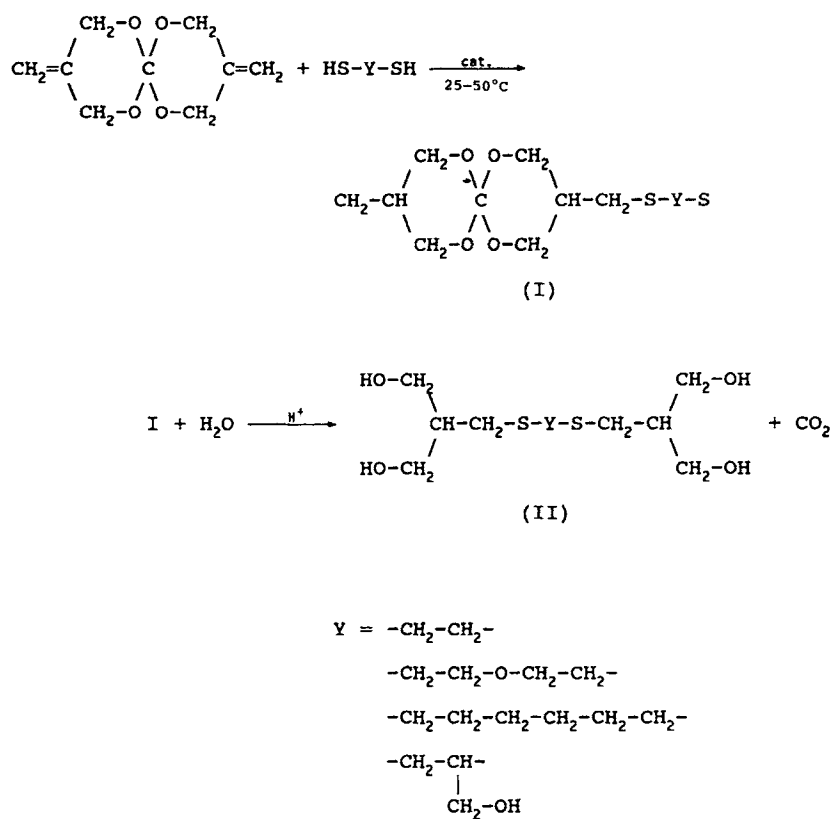
## EXPERIMENTAL

### Materials

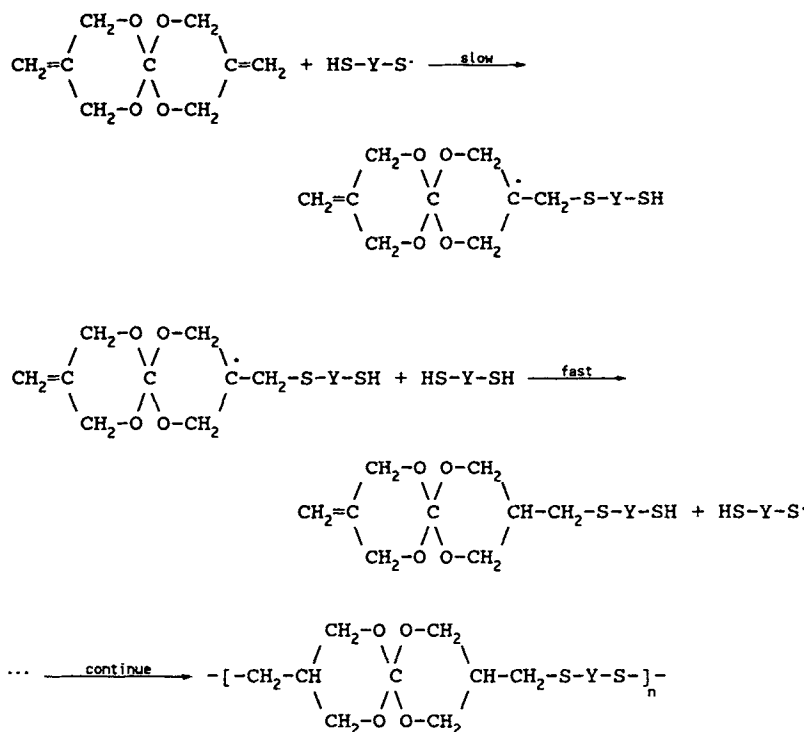
All compounds were obtained from Aldrich Chemical Co. unless otherwise specified. Dithiols were purified by distillation under reduced pressure. BMSOC was supplied by Epolin Inc. (Peterson, NJ 07501) and purified by crystallization from *n*-hexane, mp 78°C. AIBN was obtained from Eastman Kodak Co.

### Measurements

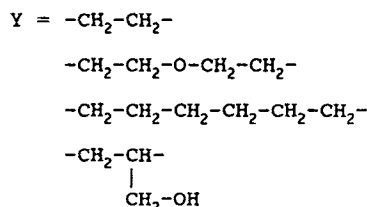
NMR spectra were obtained on a Bruker AF-200 200 MHz NMR spectrometer in CDCl<sub>3</sub> at 25°C with



**Scheme 1** Polymerization of BMSOC with dithiols and hydrolysis of the polymers.



(I)



**Scheme 2** Mechanism for polymerization of BMSOC with dithiols.

TMS as internal reference. IR spectra were taken with a Nicolet 5DXC Fourier transform spectrometer. The viscosity of the polymers were determined with a Ubbelodbe viscosimeter.

### Purification of Dithiols

Dithiols were easily oxidized by air and were freshly distilled under reduced pressure and then stored in nitrogen before use. The dithiols used were 1,2-ethanedithiol (EDT, bp 53°C/18 mmHg), 2-mercaptoethyl ether (MEE, bp 80°C/1.5 mmHg), 1,6-hexanedithiol (HDT, bp 90°C/2.5 mmHg), and 2,3-dimercapto-1-propanol (DMP, bp 105°C/1.5 mmHg).

### BMSOC-EDT Polymers

In a 50 mL flask that flushed with dry nitrogen for several minutes, 0.471 g (0.42 mL, 5 mmol) of freshly distilled EDT, 10 mL of benzene (or cyclohexane), and 0.921 g (5 mmol) of BMSOC were added successively, and then 2.0–10.0 mol % of initiator (based on BMSOC) were added. The mixture was stirred under nitrogen in a bath at 25–50°C. After the polymerization was completed, the mixture was evaporated to remove the solvent, and then the residue was dissolved in chloroform. The resulting solution was filtered, and the filtrate was poured into methanol to precipitate polymer as a white powder. It was filtered, washed twice with methanol, and then dried *in vacuo* overnight at room temperature. The

crude polymer was purified by dissolving it in chloroform and then precipitating it in methanol. The yield and the properties of BMSOC-EDT polymer are given in Table I.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data are shown in Table IV.

### BMSOC-MEE Polymers

In a 50 mL flask that was flushed with dry nitrogen for several minutes, 0.691 g (0.62 mL, 5 mmol) of freshly distilled MEE, 10 mL of solvent, and 0.921 g (5 mmol) of BMSOC were added successively, and then 1.0–5.0 mol % of initiator (based on BMSOC) was added. The polymerization was similarly carried out. The crude polymer was obtained by the procedure described above, but it was separated as a viscous liquid in cyclohexane. The yields and properties of BMSOC-MEE polymers are given in Table II.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data are shown in Table IV.

### BMSOC-HDT and BMSOC-DMP Polymers

The preparation of BMSOC-HDT polymers was similar to that of BMSOC-EDT polymers, and the preparation of BMSOC-DMP polymers was similar to that of BMSOC-MEE polymers. Their yields and properties are given in Table III.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data are shown in Table IV.

## RESULTS AND DISCUSSION

### Polymerizations of BMSOC with Dithiols

The initiators, solvents, reaction conditions, properties of polymers, and yields are given in Tables I–III.

EDT easily polymerized with BMSOC at 25–50°C to form white solid polymers with molecular weight (MW) of 3760–35,200. The best initiating system was BPO-DMA (see Table I, runs 2, 3, and 5). AIBN was used only at elevated temperatures (40–50°C). DTBP-DMA gave polymers but in very low yields. At lower initiator concentration (0.5 mol %), the polymerization started very slowly and gave low yields, whereas at higher initiator concentrations (2% or up), initiating was very fast. However, the polymerization usually proceeded for many hours in order to complete the reaction and eliminate the unpleasant odor of the dithiol. Even low MW polymers could be precipitated from methanol and obtained as white powders. Liquid oligomers were soluble in methanol and then removed. The use of a common redox initiating system BPO- $\text{FeCl}_2$  did not

give linear polymers because the acidity of  $\text{FeCl}_2$  caused the ring-opening of BMSOC, giving a cross-linked solid product insoluble in many common solvents.

HDT also easily polymerized with BMSOC at 25–50°C to form a white solid polymer with high MW. The polymer having the highest MW of 180,000 was obtained by using AIBN as initiator at 50°C (see Table III, run 29). It hydrolyzed very slowly even under acidic conditions (pH 1.2; see Fig. 4).

Although BMSOC-EDT and BMSOC-HDT polymers had good physical properties for processing, they showed low rates of degradation under strongly acidic conditions (pH 1.2). Therefore, we selected more polar dithiols, such as MEE and DMP, to increase the polarity of polymers (I) and the solubility of their hydrolysis products, tetrols (II).

MEE polymerized with BMSOC at 40–50°C to produce viscous liquids or resinous polymers having MW of 5560–30,000. The DTBP-DMA initiating system was preferred because BPO-DMA and AIBN led to polymers with lower MW (see Table II, runs 22 and 23). The reaction was carried out in cyclohexane solution. The polymers were soluble in chloroform and could be precipitated from cyclohexane.

DMP polymerized with BMSOC at 40–50°C and gave viscous liquid polymers with MW of less than 6500 (see Table III, runs 30 and 31). DTBP-DMA and AIBN were used as initiators. Since 2,3-dimercapto-1-propanol employed is an unsymmetrical dithiol, it tends to produce low MW polymers due to the different reactivities of its two mercapto groups. The use of 1,3-dimercapto-2-propanol, a symmetrical dithiol, might lead to polymers of higher MWs.

Although BMSOC-DMP polymers showed higher rates of degradation, they had poorer physical properties. They were liquid polymers, and it proved difficult to prepare solid polymers from these more polar dithiols due to their low  $T_g$  values. A possible approach would be to incorporate a small amount of trithiols, such as 1,2,3-trimercaptopropane in the dithiols, which might increase the MW and  $T_g$  values without causing cross-linking.

### Block Polymerizations of BMSOC with Dithiols

The good physical properties of BMSOC-EDT and BMSOC-HDT polymers can be combined with the higher degradation rates of BMSOC-MEE and BMSOC-DMP polymers by block polymerization. As a result, we would obtain block polymers with higher  $T_g$  and hydrolyzability.

Some block polymers were synthesized in benzene at 25–50°C by using BPO-DMA, DTBP-DMA, or

Table I Polymerization of BMSOC with EDT

Run No.	Monomer Concn (M)		Initiator Concn (mol %) <sup>a</sup>				Solvent	Temp (°C)	Time (h)	Polymer			
	BMSOC	EDT	BPO	DMA	AIBN	DTBP				FeCl <sub>2</sub>	Appearance <sup>b</sup>	$\eta_{inh}$ (dL/g)	M.W. <sup>c</sup>
1	0.50	0.50	2.00	2.00				25	95	w powder	0.102	35,200	36
2	0.50	0.50	5.00	5.00				25	24	w powder	0.095	29,400	79
3	0.50	0.50	5.00	10.0				25	24	w powder	0.072	19,300	81
4	1.00	1.00	0.50	0.50				25	168	w powder	0.025	4,000	5
5	1.00	1.00	2.00	2.00				25	70	w powder	0.073	19,800	55
6	2.50	2.50	2.00	2.00				25	24	w powder	0.034	6,200	27
7	0.50	0.50			2.00			50	24	w powder	0.024	3,800	31
8	0.50	0.50			5.00			50	24	w powder	0.035	6,600	47
9	0.50	0.50			10.0			50	24	w powder	0.027	4,300	37
10	0.50	0.50		2.00		2.00		25	95				0
11	0.50	0.50	5.00				5.00 <sup>d</sup>	25	5	w solid <sup>e</sup>			36
12	0.50	0.50	5.00				5.00 <sup>d</sup>	25	5	w solid <sup>e</sup>			63
13	1.00	1.00	5.00				5.00 <sup>d</sup>	25	5	w solid <sup>e</sup>			63

<sup>a</sup> Based on monomers.<sup>b</sup> w, white.<sup>c</sup> Calculated by the formula:  $\eta_{inh} = KM^\alpha$ , where  $\eta_{inh}$  is inherent viscosity, dL/g, determined in chloroform at 25°C with a Ubbelohde viscometer;  $K$ , a constant,  $10^{-4}$ ;  $\alpha$ , a constant, 2/3; and  $M$ , molecular weight.<sup>d</sup> Dehydrated at 80–100°C under vacuum, brownish.<sup>e</sup> Partly soluble in chloroform: 46.4%, 6.6%, and 9.6%, respectively.

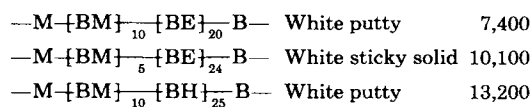
Table II Polymerization of BMSOC with MEE

Run No.	Monomer Concn (M)		Initiator Concn (mol %)*						Ferroous Stearate	Solvent	Temp (°C)	Time (h)	Polymer		
	BMSOC	MEE	BPO	DMA	AIBN	DTBP	FeCl <sub>2</sub>	Appearance <sup>b</sup>					$\eta_{inh}$ (dL/g)	M.W. <sup>c</sup>	Yield (%)
14	0.50	0.50	5.00	5.00					Benzene	40	20	Yel oil <sup>d</sup>		Very low	
15	0.50	0.50	5.00	5.00					THF	40	200	Vis liq	0.052	11,900	
16	0.50	0.50			5.00				Benzene	40	24	Vis liq	0.034	6,400	97
17	0.50	0.50			5.00				Cyclohexane	40	24	Vis liq	0.028	5,600	26
18	0.50	0.50		5.00		5.00			Cyclohexane	40	72	Vis liq	0.035	6,800	47
19	2.50	2.50		5.00		5.00			Benzene	40	96	Vis liq	0.050	11,000	96
20	2.50	2.50		5.00		5.00			Cyclohexane	40	120	Vis liq	0.048	10,500	70
21	5.00	5.00		5.00		5.00			Benzene	40	120	Vis liq	0.084	24,200	80
22	5.00	5.00		5.00		5.00			Benzene	40	144	Resin	0.096	30,000	64
23	5.00	5.00		5.00		5.00			Benzene	50	48	Resin	0.077	21,500	68
24	bulk (B : M = 1)			5.00		5.00					144				0
25	2.50	2.50					1.00		Methanol	40	120	Br oil		Very low	
26	0.50	0.50	5.00					5.00	THF	40	80	Br oil		Very low	

\*— See Table I.

<sup>d</sup> Yel oil = yellow oil; Vis liq = viscous liquid; Br oil = brown oil.

AIBN as initiating systems. The initial monomer concentration were 0.50–0.55 *M*. Their theoretical formulas, appearance, and actual MWs are as follows:



These triblock polymers seem to have better processability than do BMSOC–MEE polymers. The observed MWs are close to the theoretical values calculated by molar ratios of monomers.

### FTNMR and FTIR Determinations

<sup>1</sup>H- and <sup>13</sup>C-NMR (CDCl<sub>3</sub>) data for the BMSOC dithiol polymers are shown in Table IV. The resonances of mercapto groups (EDT δ 1.57, MEE δ 1.62, HDT δ 1.34, and DMP δ 1.70) are absent in our polymers. New resonances for the —CH< linkages (δ 1.92–1.98) are evident. The protons on the —C—CH<sub>2</sub>—O— linkages of the ring appear between δ 3.85–3.88 and δ 4.44–4.19, and the protons on carbons bound to the sulfur atoms, —CH<sub>2</sub>—S—CH<sub>2</sub>—, resonate at chemical shifts around δ 2.7 (BMSOC–EDT δ 2.65–2.72, BMSOC–MEE δ 2.65–2.72, BMSOC–HDT δ 2.50–2.55, and BMSOC–DMP δ 2.67–2.84). These resonances are complexly overlapping multiples. <sup>13</sup>C-NMR spectra show that all the BMSOC–dithiol polymers obtained at 25–50°C retain the spiroorthocarbonate structure since the resonances for carbon atoms on the rings and central atoms of the orthocarbonate appear at almost the same positions as those of BMSOC (BMSOC δ 65.63, δ 116.20; BMSOC–EDT δ 65.58, 114.42; BMSOC–MEE δ 65.56, 114.34; BMSOC–HDT δ 65.70, 114.45; BMSOC–DMP δ 65.46, 114.91). <sup>1</sup>H- and <sup>13</sup>C-NMR spectra of BMSOC, a BMSOC–MEE polymer (see Table II, run 21), and a BMSOC–HDT polymer (see Table III, run 29) are shown in Figures 1, 2, and 3, respectively. The peaks of hydrogen atoms on the BMSOC end group appear at δ 4.96 (CH<sub>2</sub>=C<) and δ 4.43 (=C—CH<sub>2</sub>—O—). The peak is the <sup>1</sup>H spectrum of the BMSOC–HDT polymer. The enlargement between δ 2.2 and 3.0 indicates a typical overlap of the <sup>1</sup>H resonances of the hydrogen atoms on both sides of sulfur atoms [—CH<sub>2</sub>—CH<sub>2</sub>—S—CH<sub>2</sub>—CH<, δ 2.50 (*t*) and 2.55 (*d*)].

IR spectra of BMSOC–dithiol polymers in CHCl<sub>3</sub> at 25°C show that mercapto groups of dithiols (EDT 2575 cm<sup>-1</sup>, MEE 2584 cm<sup>-1</sup>, HDT 2581 cm<sup>-1</sup>, DMP 2571 cm<sup>-1</sup>) were absent in these polymers.

Table III Polymerization of BMSOC with HDT and DMP

Run No.	Monomer Concn ( <i>M</i> )				Initiator Concn (mol %) <sup>a</sup>				Polymer					
	BMSOC	HDT	DMP	BPO	DMA	AIBN	DTBP	Solvent	Temp (°C)	Time (h)	Appearance <sup>b</sup>	η <sub>inh</sub> (dL/g)	M.W. <sup>c</sup>	Yield (%)
27	0.50	0.50		2.00	2.00			Benzene	25	24	w powder	0.130	46,600	42
28	0.50	0.50				2.00		Benzene	50	24	w powder	0.175	73,200	33
29	0.50	0.50				5.00		Cyclohexane	50	24	w powder	0.320	180,000	28
30	2.50		2.50			5.00		Benzene	40	200	Vis liq <sup>d</sup>	0.034	6,100	75
31	0.50		0.50			3.00		Cyclohexane	50	24	Vis liq <sup>d</sup>	0.022	3,300	69

<sup>a-c</sup> See footnotes a–c of Table I.

<sup>d</sup> Vis liq = viscous liquid.





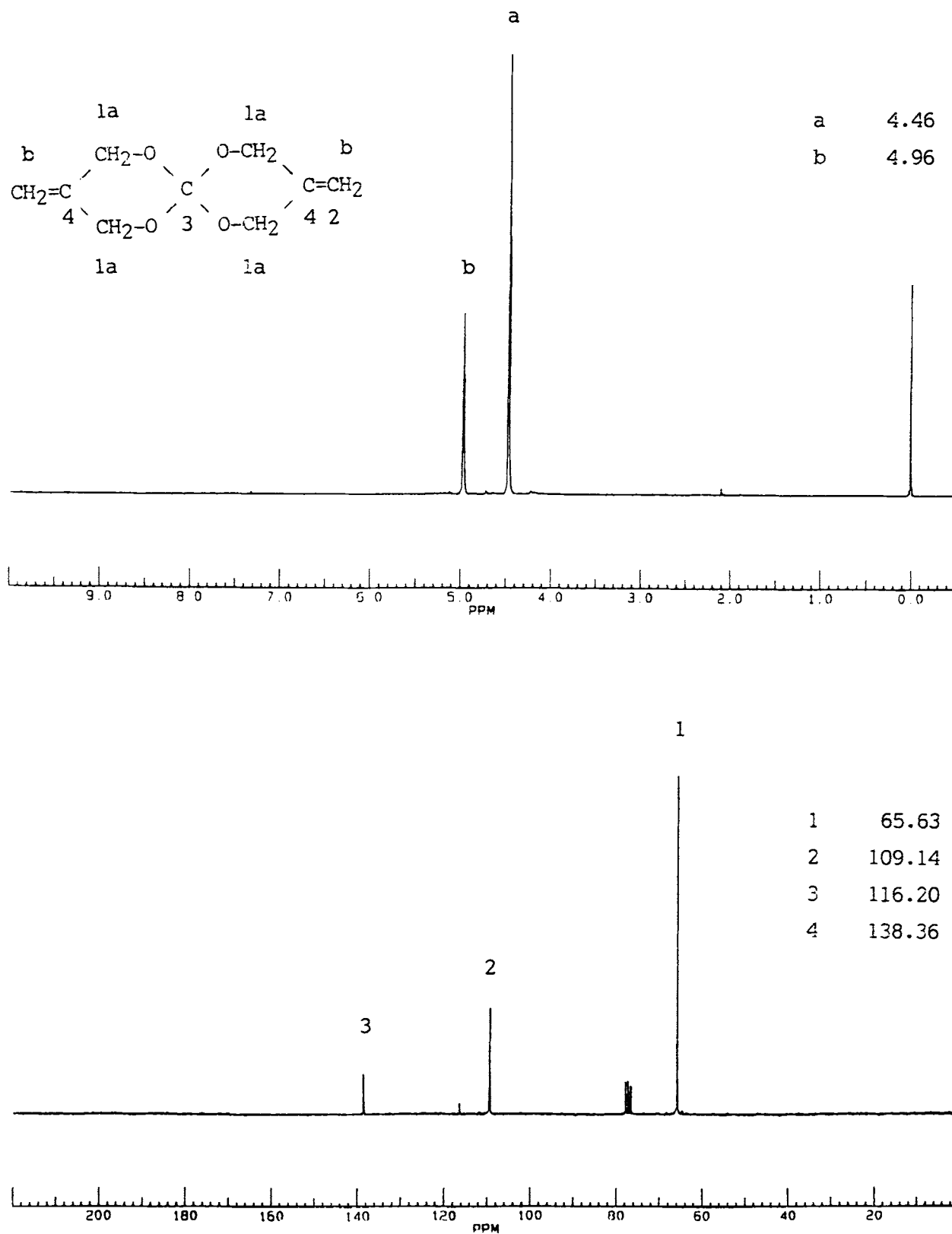
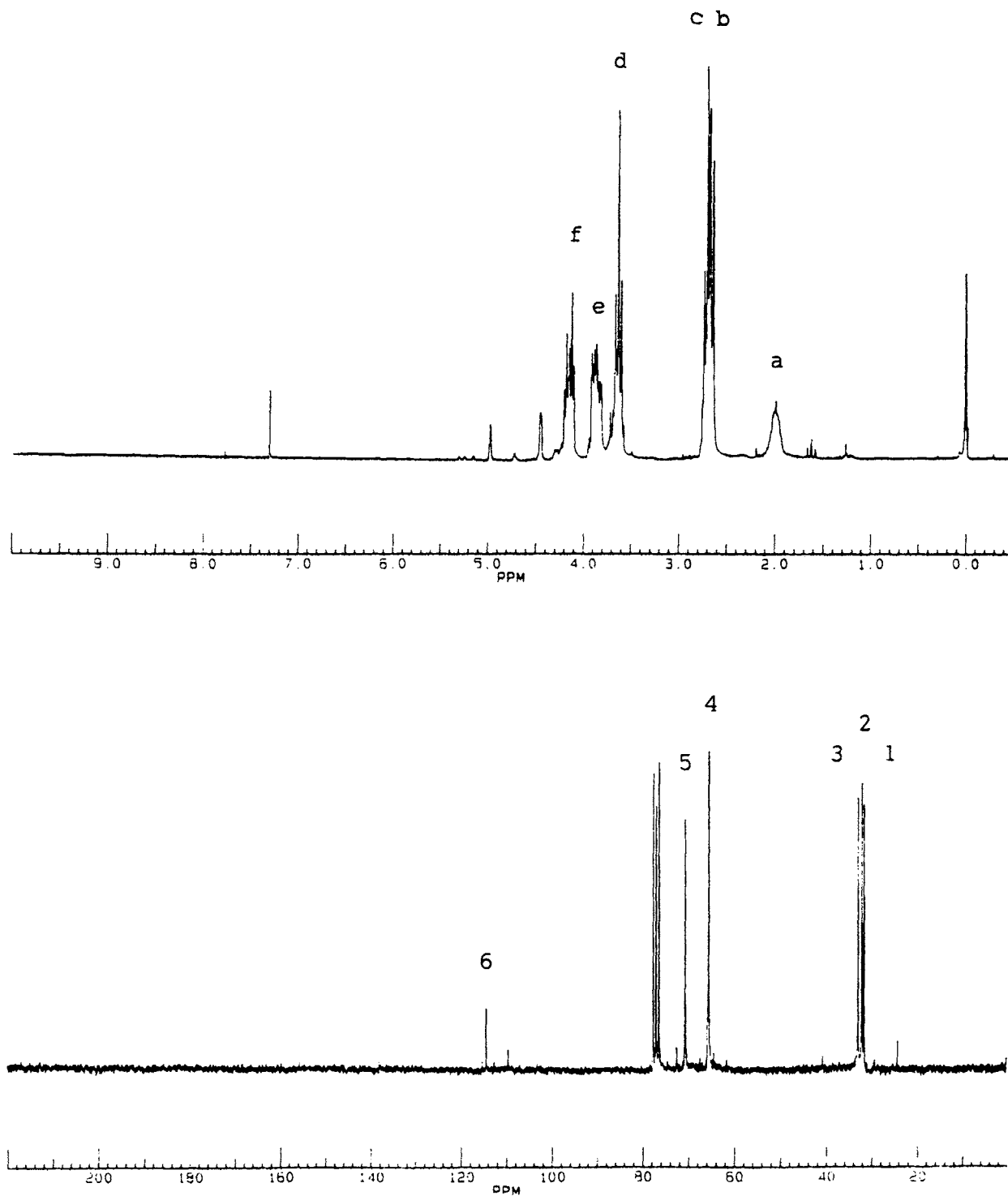
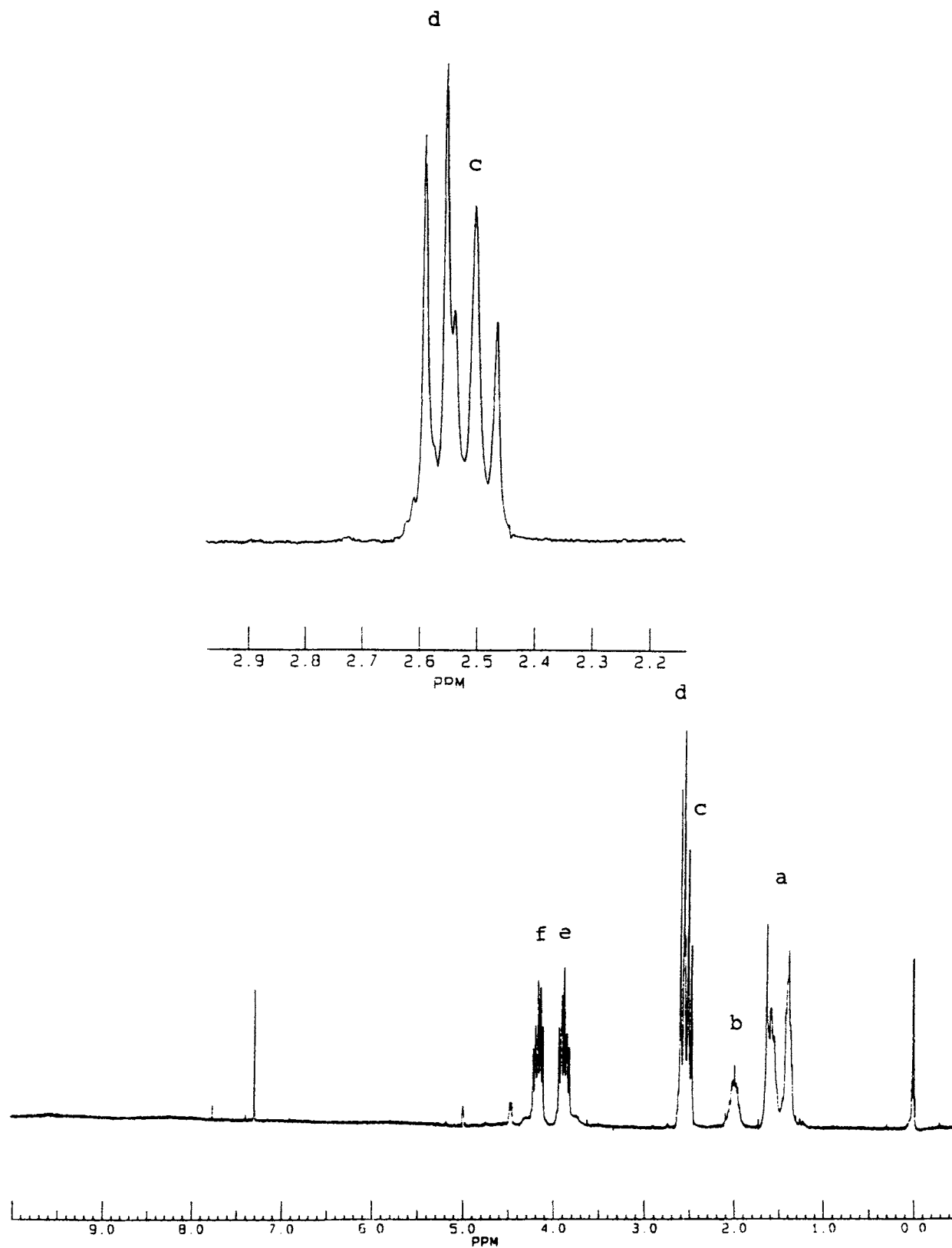


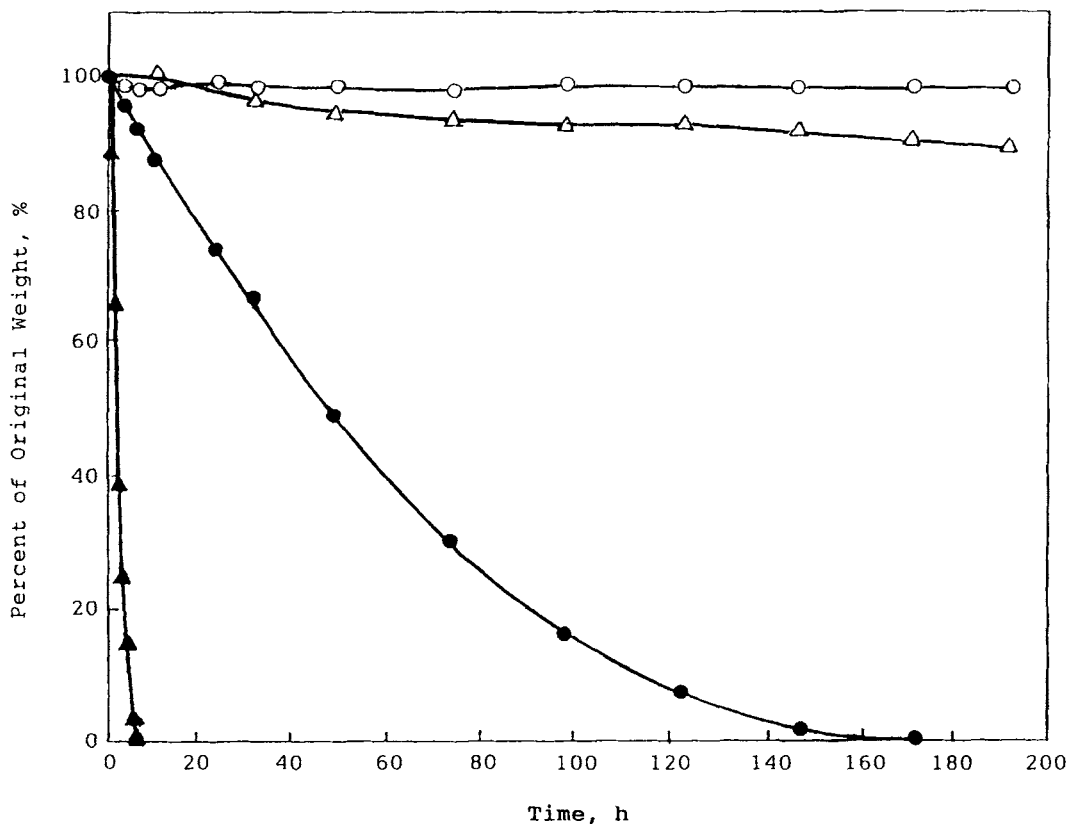
Figure 1 200 MHz <sup>1</sup>H- and 50 MHz <sup>13</sup>C-FTNMR spectra of BMSOC in CDCl<sub>3</sub> at 25°C.



**Figure 2** 200 MHz <sup>1</sup>H- and 50 MHz <sup>13</sup>C-FTNMR spectra of a BMSOC-MEE polymer in CDCl<sub>3</sub> at 25°C.



**Figure 3** 200 MHz <sup>1</sup>H-FTNMR spectrum of BMSOC-HDT polymer in CDCl<sub>3</sub> at 25°C and its enlargement between  $\delta$  2.2 and 2.9.



**Figure 4** The hydrolysis of BMSOC-EDT and BMSOC-HDT polymers in water: (Δ) BMSOC-EDT, pH 7.4; (▲) BMSOC-EDT, pH 1.2; (○) BMSOC-HDT, pH 7.4; (●) BMSOC-HDT, pH 1.2 (by courtesy of Interx Research Corp., Lawrence, KN 66046).

### Hydrolysis of BMSOC-Dithiol Polymers

We have attempted to make novel BMSOC-dithiol polymers for some medical uses, such as for temporary implants, slow- or fast-controlled release of drugs, or carriers for biologically active materials. These polymers easily undergo acid hydrolysis with opening their spiro rings to give low MW tetrols at body temperature. The rate of hydrolysis could be varied by selecting the structure of dithiols and through the use of block polymers.

The hydrolysis of BMSOC-EDT and BMSOC-HDT polymers in water is shown in Figure 4. It is plotted based on data obtained by rotating bottle tests. The polymers hydrolyze very slowly under neutral condition (pH 7.4), but much faster under acid condition (pH 1.2, corresponding to the pH value in the stomach).

### CONCLUSION

The polymerization of 3,9-dimethylene-1,5,7,11-tetraoxaspiro [5,5]undecane (simply, bimethylenes-

piroorthocarbonate [BMSOC]) with dithiols, such as 1,2-ethanedithiol (EDT), 2-mercaptoethyl ether (MEE), 1,6-hexanedithiol (HDT), and 2,3-dimercapto-1-propanol (DMP), were prepared in non-polar solvents by using redox initiating systems, such as BPO-*N,N*-dimethylaniline (DMA) and DTBP-DMA at 25–50°C, or free-radical catalyst AIBN at 40–50°C. The molecular weights varied with monomer and initiator concentrations, temperature, and solvent as well as with the structure of dithiols. BPO-FeCl<sub>2</sub> or BPO-ferrous stearate systems were not efficient in these polymerizations because they caused ring-opening of BMSOC and gave insoluble cross-linking products.

The polymers obtained from more polar dithiols, such as MEE and DMP, were more hydrophilic and easily hydrolyzed, but showed a poorer processing property. This could be improved by preparing their block polymers with EDT and HDT.

The structures of BMSOC-EDT, BMSOC-MEE, BMSOC-HDT, and BMSOC-DMP were confirmed by <sup>1</sup>H- and <sup>13</sup>C-NMR and FTIR determinations. The polymers of BMSOC-dithiols were suggested for some medical applications, such as drug delivery.

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