Chiral polymer materials: a protective group approach to ascertain asymmetric inductions in the backbone of 1,2-disubstituted vinyl type polymers by chiral template mediated polymerization*

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A synthetic methodology is described for unequivocally establishing asymmetric induction in the backbone of copolymers based on 1,2-disubstituted olefins and 1-substituted olefins. For this purpose functional styrene monomers (e.g. 4-vinyl benzaldehyde and 4-vinyl boronic acid) were derivatized with chiral auxiliaries, such as *R*(+)-1-phenyl ethyl amine and diethyl-L-tartrate,which act as protecting groups for the functional groups of the styrene monomers. Copolymerization with maleimide derivatives followed by the removal of the chiral protecting groups produced the appropriate functional copolymers. Spectroscopic techniques were used to confirm quantitative deprotection had occurred and chiroptical techniques were used to ascertain asymmetric inductions in the polymer backbone.

(Keywords: main-chain chirality; asymmetric induction; functional polymers; protecting group chemistry)

INTRODUCTION

The synthesis of optically active polymers possessing main-chain chirality (both configurational and conformational) is of great scientific interest[1-3]. The primary requirements for realizing optical activity based on configurational chirality is to introduce local dissymmetry along the macromolecular chain. To achieve this there are two approaches currently available: the synthesis of copolymers containing 1,2-disubstituted vinylic monomers[4] and vinyl polymer chains consisting of asymmetric triads[5]. The first reported example of optically active polymers based on 1,2-disubstituted vinyl monomers dates back to 1958 with Beredjick and Schuerch[6] reporting the synthesis of optically active maleic anhydride–methacrylic acid copolymers. Since then several reports have appeared on the preparation of such polymers. In all cases, the chirality inducing agents (chiral auxiliaries) were connected through ester, ether or imide linkages[7]. These chemically robust bonds need drastic conditions for their quantitative removal which in certain cases has been reported to be unsuccessful[8]. In the event of incomplete removal of chiral auxiliaries the observed optical activity cannot be unequivocally ascribed to the configurational chirality. This is particularly important, as some recent findings indicate a peculiar role for the side chain substituents (chiral or achiral) on the overall observed optical activity of macromolecules[9].

The principle of protective group chemistry has been successfully used in recent years for the synthesis of functional vinyl polymers with predetermined structures and molecular weights[10]. In order to overcome the problems associated with quantitative removal of the chiral auxiliaries to obtain chiral polymers based on 1,2-disubstituted vinyl monomers, we utilized this concept for temporarily linking the chiral auxiliaries to the monomers. To this end, we designed vinyl monomers carrying chiral auxiliaries where the latter are linked to the polymerizable part through chemical bonds which are stable during polymerization, yet can be cleaved quantitatively when desired under milder conditions. These monomers can be polymerized with 1,2-disubstituted vinyl compounds to yield the desired structures. Our current efforts in this area have been directed towards gaining a detailed insight into the role of the nature of the chiral auxiliaries and monomer structures on asymmetric inductions as well as an evaluation of the relative stability/lability of the protective groups.

This paper deals with the synthesis of two new chiral vinyl monomers (**1** and **2**) and their copolymerization with different 1,2-disubstituted vinyl monomers. The polymers have been deprotected from the chiral templates and have been characterized by different spectroscopic and chiroptical techniques to elucidate their structural and stereochemical features.

EXPERIMENTAL

All the solvents used were reagent grade and were purified by standard procedures prior to use. All the reagents were analytical grade obtained from Fluka AG and were used as received. 2,2'-Azobisisobutyronitrile (AIBN) was recrystallized from ethanol.

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Monomers

Chiral monomers: N-[*(4-vinyl phenyl)methylene*] R(+)-*1-phenyl ethyl amine* (**1**). 4-Vinyl benzaldehyde[11] (10 g, 75.7 mmol), *R*(+)-1-phenyl ethyl amine (9.2 g, 75.7 mmol) and 4-t-butyl catechol (10 mg) were dissolved in dry benzene (150 ml). The reaction mixture was refluxed with azeotropic distillation of the water formed. When no more water was produced, refluxing was discontinued and the solvent was removed under vacuum. The residue was recrystallized from ethanol yielding 12.8 g (72%) of **1**: m.p. 97°C; $[\alpha]^{25}\mathrm{D} = +151°$ ($c = 0.9$; THF); ^{1}H n.m.r. δ 1.4 (d, 3H, CH_3–CH), 4.1 (q, 1H, CH–CH_3), 5.3, 5.6 (two dd, 2H, vinyl CH_2), 6.7 (dd, 1H, vinyl CH); 7.2–7.6 (m, 9H, Ar), 8.3 (s, 1H, N═CH). Analysis: for $C_{17}H_{17}N$: calculated C, 86.77; H, 7.28; N, 5.95; found C, 86.43; H, 7.34; N, 5.82.

*Diethyl-*L*-tartrate-O-*[*(4-vinyl phenyl) boronate*] (**2**). 4-Vinyl phenyl boronic acid[12] (4.8 g, 100 mmol) and diethyl-L-tartrate (20.62 g, 100 mmol) were refluxed with methylene chloride (125 ml) and the water thus formed was removed azeotropically. After removal of the theoretical amount of water, the reaction mixture was cooled and the solvent was removed under reduced pressure. The product was recrystallized from petroleum ether (40–60°C): yield 17.8 g (56%); m.p. 56°C; $[\alpha]^{25}\mathrm{D} = -32°$; ^{1}H n.m.r. δ 1.4 (t, 6H, CH_3); 3.9–4.2 (m, 6H, CH_2–O and -CH–O–B); 5.3, 5.6 (two dd, 2H, vinyl CH_2); 6.8 (dd, 1H, vinyl CH); 7.3, 7.8 (dd, 4H, Ar). Analysis for $C_{16}H_{19}BO_6$: calculated C, 60.41; H, 6.02; found C, 60.05; H, 6.14.

Comonomers. N-phenyl maleimide (**3**)[13] and *p*-nitrophenyl maleimide (**4**)[14] were synthesized following literature procedures. Indene (**5**) was obtained from Fluka AG and was purified by distillation over CaH_2 prior to use.

Polymer synthesis

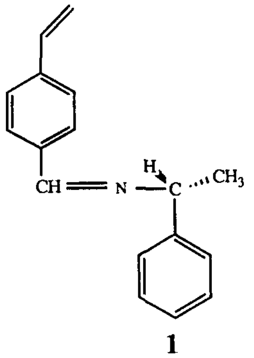
The copolymerization reactions were carried out at 70°C under nitrogen atmosphere by mixing the appropriate amounts of monomers in toluene (15% solution w/v) using AIBN (1% w/w of monomers) as free radical initiator. After achieving the desired conversions, the polymerization reaction mixtures were poured into excess methanol. The polymers were purified by repeated (three cycles) dissolution and reprecipitation from THF and methanol, respectively. The samples were finally dried under vacuum to constant weight.

Removal of R(+)*-1-phenyl ethyl amine from* **1**-*based copolymers.* To copolymer (0.5 g) dissolved in THF (20 ml) 2N HCl (3 ml) was added dropwise with stirring. The cloudy solution was stirred for 24 h at 25°C and subsequently poured into excess water. The operation was repeated twice and finally the precipitated polymer was dissolved in THF, precipitated from petroleum ether and dried to constant weight under vacuum.

*Removal of diethyl-*L*-tartrate from* **2**-*based copolymers.* Copolymer (0.5 g) was dissolved in THF/water (9:1 v/v, 25 ml) and stirred at 25°C for 12 h. The polymer solution was then poured into weakly acidified 50% aqueous methanol (200 ml). The cycle was repeated twice and the polymer was dried under vacuum to constant weight.

Analysis and characterization

The melting points were measured with Buchi 510 melting point apparatus. Elemental analyses were carried out at the National Chemical Laboratory microanalytical facility. ^{1}H and ^{13}C n.m.r. spectra were recorded with a Bruker AM 300 spectrometer using $CDCl_3$/DMSO-d_6 as the solvent and TMS as the internal reference. I.r. spectra were recorded with a Perkin-Elmer 1600 FT IR spectrophotometer with the samples in the form of clean KBr pellets. Optical rotations were measured at 25°C using a Jasco DIP 181 polarimeter. Circular dichroism (CD) spectra were obtained at 25°C with a Jasco J-600 automatic recording spectropolarimeter in dioxane at a sample concentration of $\sim 1\ \mathrm{mg\ ml^{-1}}$. The path length of the cell was 0.1 cm. U.v. spectra were recorded at 25°C in THF using a Hitachi model 220 u.v.-vis. spectrophotometer. The sample concentration was $5\text{–}15\ \mathrm{mg\ ml^{-1}}$ and the path length of the u.v. cell was 0.1 cm.



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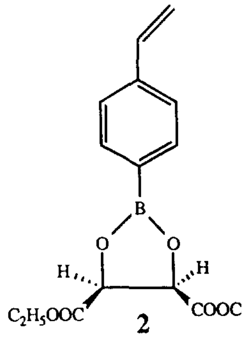

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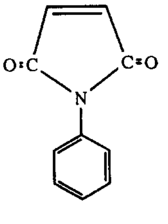

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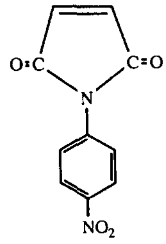

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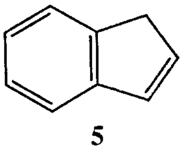

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RESULTS AND DISCUSSION

Monomer synthesis and polymerization

In order to ensure complete removal of the chiral auxiliaries (templates) from the polymers, the monomer design was strategically planned. It has been reported that polymer bound functional groups protected in the form of boronic esters[15], acetals (or ketals)[16] and azomethines[17] can be quantitatively deprotected under mild experimental conditions without adversely affecting the polymer structures. With this in mind we synthesized the appropriate chiral monomers (**1** and **2**). Monomers **1** and **2** were synthesized as described in the Experimental section. Both the monomers were obtained as crystalline solids and their spectral and elemental analysis data testify to their appropriate structures and purity. 1,2-Disubstituted vinyl compounds were chosen as comonomers (**3**–**5**).

The chiral monomers **1** or **2** were copolymerized with the three different comonomers in varying molar concentrations under free radical initiation. All the copolymers thus obtained are soluble in THF, toluene,

Table 1 Chemical compositions and optical activities of copolymers based on **1**

	Comonomer	Mole fraction of **1** in the reaction mixture	Mole fraction of **1** in the copolymer	$[\alpha]^{25}_D$ Before hydrolysis	$[\alpha]^{25}_D$ After hydrolysis	$[\eta]$ (dl g^{-1})^a
1	**3**	0.20	0.41	+48.0	−2.7	0.22
2		0.30	0.45	+45.2	−2.7	0.28
3		0.49	0.52	+80.3	−2.7	0.24
4		0.71	0.53	+83.0	−2.1	0.15
5	**4**	0.22	0.41	+14.0	−2.4	0.062
6		0.41	0.48	+38.0	−1.2	0.064
7		0.51	0.53	+58.0	−1.2	0.098
8		0.60	0.56	+71.0	−1.3	0.096
9	**5**	0.11	0.27	+110.0	+8.0	0.072
10		0.29	0.37	+145.0	+7.0	0.079
11		0.38	0.84	+152.0	+9.0	0.090
12		0.47	0.93	+155.0	+25	0.092

^{a}In THF, 30°C

Table 2 Chemical compositions and optical activities of copolymers based on **2**

	Comonomer	Mole fraction of **2** in the reaction mixture	Mole fraction of **2** in the copolymer	$[\alpha]^{25}_D$ Before hydrolysis	$[\alpha]^{25}_D$ After hydrolysis
1	**3**	0.18	0.38	−17.2	0.0
2		0.34	0.49	−21.0	−0.5
3		0.48	0.53	−22.0	−0.8
4		0.67	0.54	−21.5	−0.6
5	**5**	0.21	0.54	−18.0	0.0
6		0.43	0.85	−24.3	−2.85
7		0.60	0.89	−24.3	−0.0
8		0.58	0.91	−25.5	−0.79

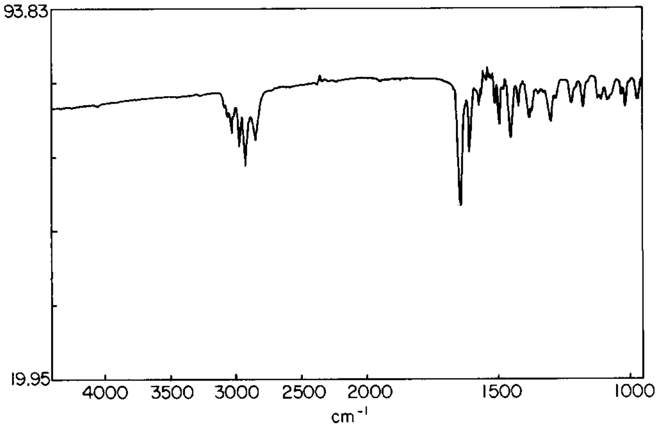
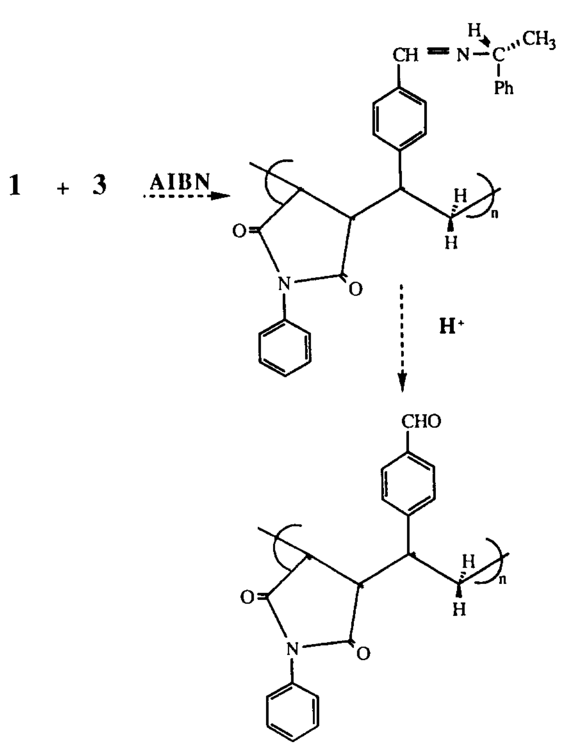


Figure 1 *FT*i.r. spectrum of **1**–**5** (84:16) copolymer before hydrolysis

chloroform, dioxane, etc. The copolymer compositions were estimated from elemental analysis and ^{1}H n.m.r. spectroscopy (*Tables 1* and *2*). Fourier transform i.r. (*FT*i.r.) spectra of the copolymers (*Figure 1*) exhibit the characteristic absorption band at 1644 cm^{-1} corresponding to the C=N (azomethine) linkage and the ^{1}H n.m.r. spectra (*Figure 2*) show the 8.2 ppm singlet resonance due to the azomethine proton. Similarly, the copolymers containing **2** show i.r. bands at 1305 cm^{-1} arising from B–O–C stretching of the boronic ester linkage and at 1730 cm^{-1} due to the carbonyl stretching band of the tartrate moieties as well as the 0.9 and 4.2 ppm peaks in the n.m.r. spectra due to the tartrate units. This evidence suggests that the protected functional groups remained intact during polymerization. The compositions of the copolymers reveal that with the maleimide derivatives **3** and **4** as the comonomers, the polymer obtained has nearly an alternating structure. This is probably due to a donor–acceptor type of polymerization process[18] with chiral monomers acting as the donor and **3** and **4** acting as acceptors. Absence of such a phenomenon with **5**-based copolymers is evident from the fact that incorporation of this comonomer in the polymer chain is somewhat low.

Removal of the chiral template residues

In order to ascertain precisely the extent of asymmetric inductions in the polymer main chain it is necessary to remove the chiral template moieties quantitatively. Furthermore, the deprotection procedures should be mild to prevent any racemization/epimerization of the main chain chiral centres during hydrolysis. For the copolymers based on **1**, removal of *R*(+)-1-phenyl ethyl amine was accomplished by stirring the polymer in



Scheme 1 Synthetic route for obtaining aldehyde group bearing optically active main-chain copolymers

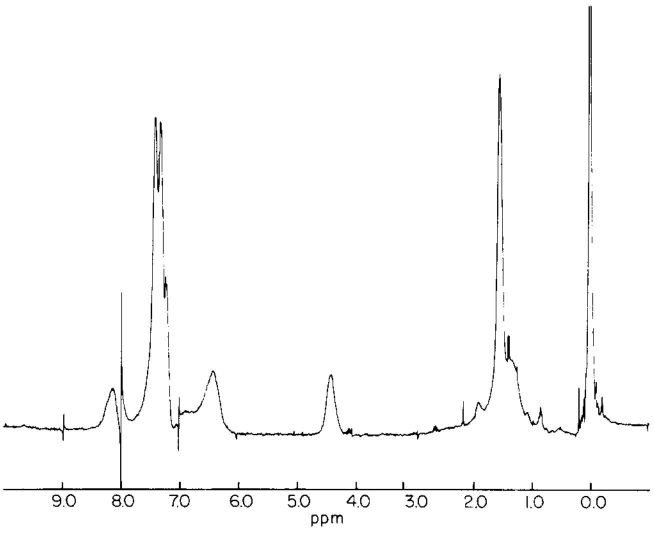


Figure 2 ^{1}H n.m.r. spectrum of **1**–**5** (84:16) copolymer before hydrolysis

weakly acidic THF at room temperature for several hours (*Scheme 1*). Care was taken in adding the dilute acid to the polymer solution and maintaining the temperature below 25°C. With higher acid concentration, reaction exothermicity and crosslinking occurred. The polymers were isolated by precipitating from water. Diethyl tartrate residues were removed from the copolymers based on **2** by dissolving the copolymers in THF:water (9:1 v/v) mixture and stirring for several hours followed by precipitation into weakly acidified methanol:water (1:1 v/v).

Spectroscopic studies of the hydrolysed copolymers reveal complete removal of the template residues. An *FT*i.r. spectrum of a typical copolymer of **1** with **5** after removal of the template is shown in *Figure 3* while that of its precursor is presented in *Figure 1*. While the spectra of the unhydrolysed copolymers show the characteristic C=N stretching of the azomethine linkage at 1644 cm^{-1}, upon hydrolysis this peak disappears and a new peak appears at1698 cm^{-1} corresponding to the aldehyde carbonyl stretching indicating completion of the deprotection procedure. The ^{1}H n.m.r. spectrum of the hydrolysed copolymer is given in *Figure 4*. A comparison of this spectrum with that shown in *Figure 2* reveals that for the unhydrolysed copolymer two characteristic singlets are seen at 4.6 and 8.3 ppm corresponding to the methine protons of the phenyl ethyl amine and the azomethine moieties, respectively. In the hydrolysed copolymers on the other hand, the spectra do not show these peaks but a new peak at 10.0 ppm corresponding to the aldehyde proton appears. Similarly, for the **2**-based copolymers absence of the 1730 cm^{-1} absorption band in the i.r. spectra and the absence of the 0.9 ppm peak in the ^{1}H n.m.r. spectra due to the ester groups are evidence of the complete hydrolysis of these polymers.

Chiroptical behaviour of unhydrolysed copolymers

The copolymers obtained using the chiral template monomers **1** and **2** show appreciable optical rotations. The sign of the optical rotations of these copolymers are the same as those of the respective starting monomers.

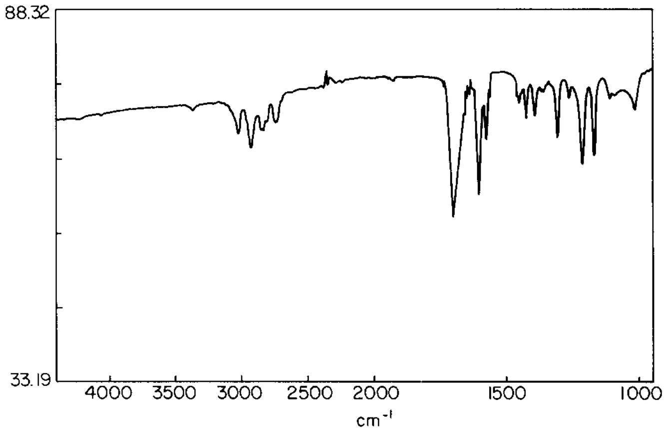


Figure 3 *FT*i.r. spectrum of **1**–**5** (84:16) copolymer after hydrolysis

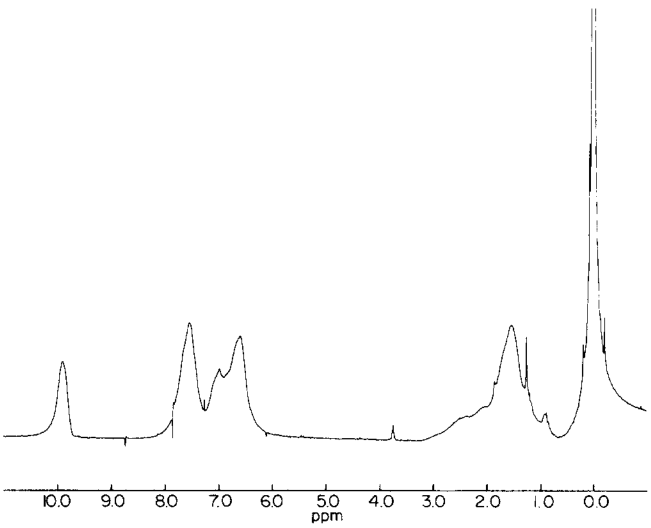


Figure 4 ^{1}H n.m.r. spectrum of **1**–**5** (84:16) copolymer after hydrolysis

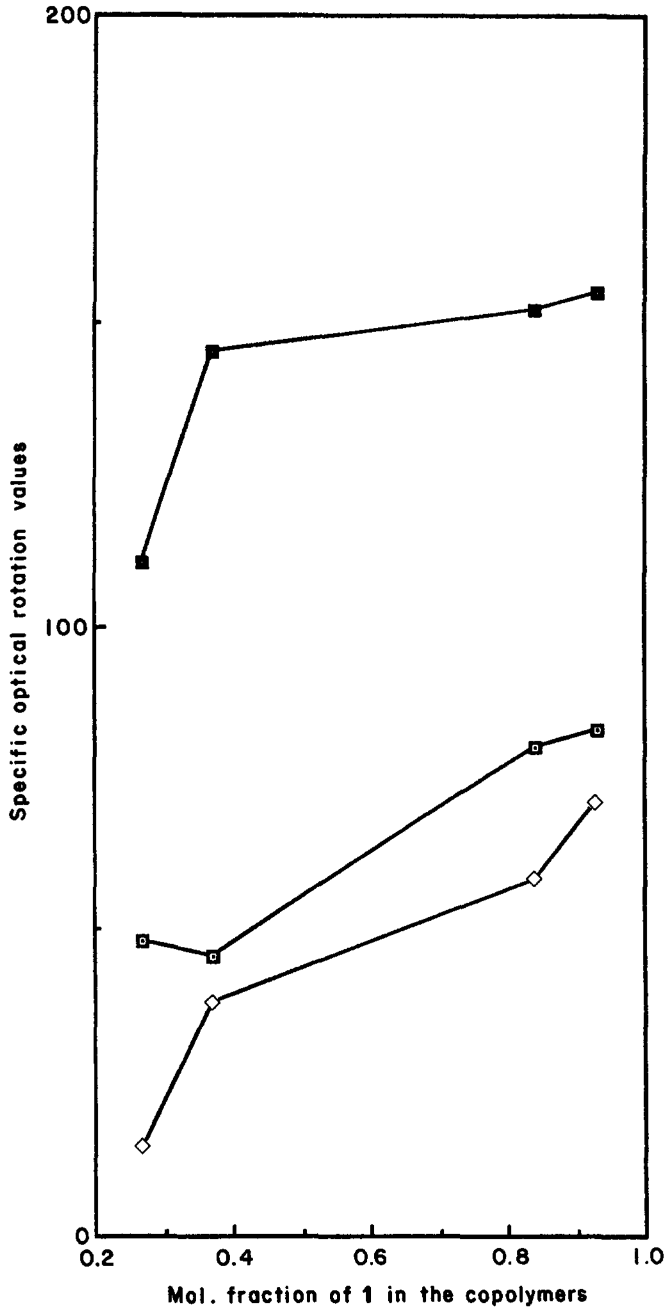


Figure 5 Copolymer composition *versus* specific optical rotations of the copolymers based on **1** before hydrolysis: (□) **3**; (◇) **4**; (■) **5**

The specific optical rotation values of these copolymers for the monomers **1** and **2** are summarized in *Tables 1* and *2*, respectively. The composition-dependent specific rotation values for **1**-based copolymers are presented in *Figure 5*. An examination of the results suggests that the magnitudes of the specific rotations are dependent on the copolymer compositions and the nature of the 1,2-disubstituted vinyl comonomers. Thus, the copolymers containing **3** and **4** show a linear relationship for specific rotations as a function of copolymer composition. However, these values are higher than those expected solely due to the incorporation of the chiral monomers. On the other hand, copolymers containing **5** exhibit a non-linear dependence, the specific rotations being higher than the chiral monomers alone or their homopolymers. These results suggest asymmetric inductions by the chiral groups on the copolymer chains[19]. The existence in solution of a short polymer segment having a helical conformation of a prevailing screw sense cannot be ruled out and it could be responsible for the observed enhancement of the optical rotations. The CD spectra of representative samples of the copolymers based on **1** are shown in *Figure 6*. Typical u.v. spectra of the copolymers are presented in *Figure 7*. The different copolymers with the three different comonomers show similar dichroic band patterns. The polymers show a weak negative band between 300 nm and 270 nm followed by a strong positive couplet with its positive band spreading over 260–220 nm and a negative band with a maximum at 215 nm. All these copolymers are positively rotating. With regard to the interpretation of the CD bands, the higher wavelength weak negative band may be due to the n–π^* transition of the C=N bond. The other bands are the combined outcome of different aromatic π–π^* transi-

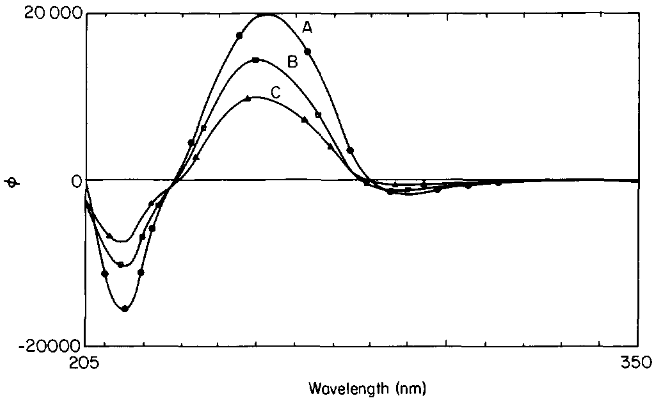


Figure 6 Representative CD spectra of the copolymers of **1** containing (A) **5** (11 in *Table 1*); (B) **3** (3 in *Table 1*) and (c) **4** (7 in *Table 1*) before hydrolysis

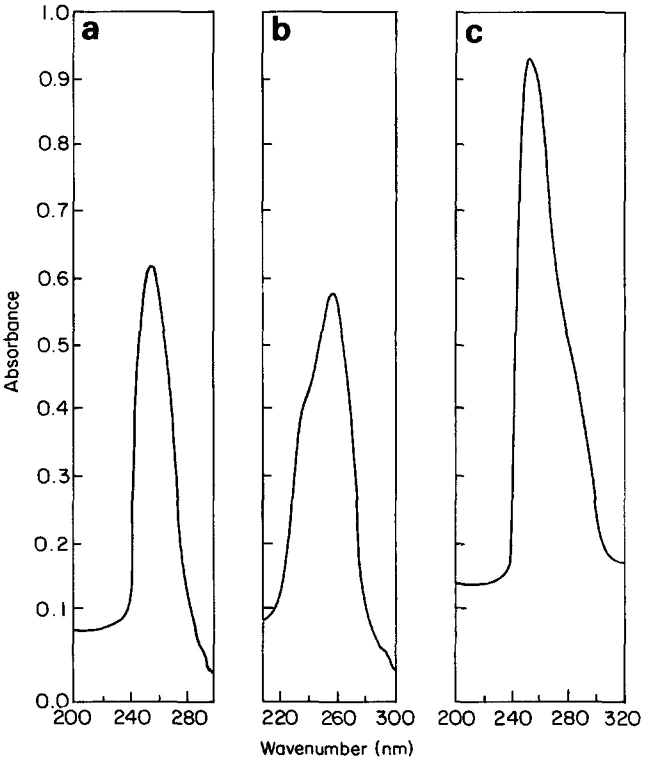


Figure 7 Representative u.v. spectra of the copolymers of **1** containing (a) **5** (11 in *Table 1*); (b) **3** (3 in *Table 1*) and (c) **4** (7 in *Table 1*) before hydrolysis

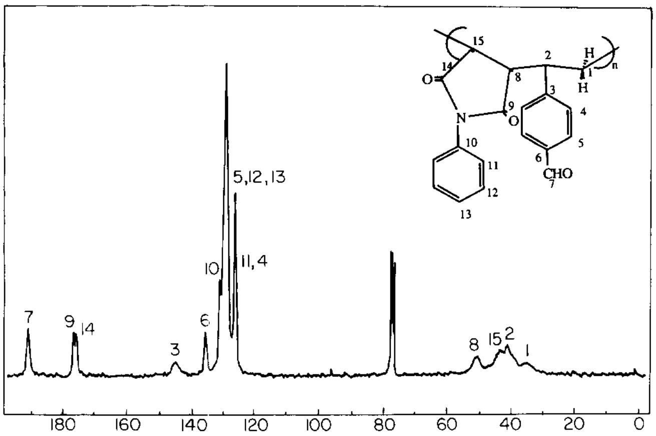


Figure 8 Noise-decoupled ^{13}C n.m.r. spectrum of **1**–**3** (41:59) copolymer after hydrolysis

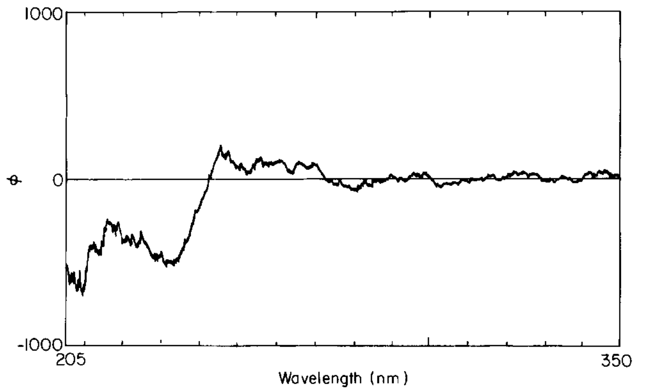


Figure 9 CD spectrum of **1**–**3** (41:59) copolymer after hydrolysis

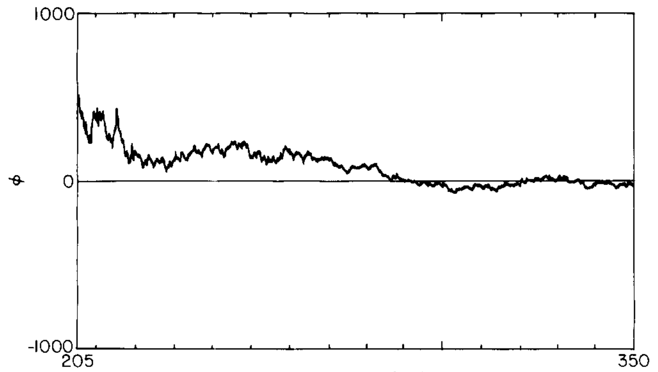


Figure 10 CD spectrum of **1**–**5** (84:16) copolymer after hydrolysis

tions[20]. As both the monomeric units contain aromatic chromophores, it is somewhat difficult to resolve the chiral contributions of the individual comonomers in the overall observed optical activity.

Chiroptical behaviour of template-free copolymers

Examination of the chiroptical properties of the template-free copolymers would provide information on the extent of (if any) asymmetric inductions in the polymer main chain. Furthermore, use of different types of chiral auxiliaries and 1,2-disubstituted vinyl comonomers may prove to be helpful in elucidating the role of these species in inducing optical activity in the polymer main chain in absolute terms.

The specific optical rotation values of these template-cleaved copolymers are presented in *Tables 1* and *2*. The optical rotation values of the **1**-based copolymers (*Table 1*) are discussed first. In general, the specific optical rotation values of these hydrolysed copolymers are lower compared to their template-bearing precursors. The copolymers containing **3** and **4** exhibit negative specific optical rotations contrary to their precursors which are positively rotating. On the other hand, **5**-based copolymers show positive specific rotations and their magnitudes are higher than those based on **3** and **4**. The specific optical rotation values do not appear to depend on copolymer compositions. The ^{13}C n.m.r. analysis of these copolymers show interesting structural patterns. As an illustration, a typical ^{13}C n.m.r. spectrum of hydrolysed **1**–**3** copolymer is shown in *Figure 8*. The chemical shift assignments of different resonance lines to various carbon atoms were carried out on the basis of off-resonance decoupling as well as comparison with the reported ^{13}C chemical shift data for appropriate homopolymers and analogous low molecular weight model compounds. The assignments are also shown in *Figure 8*. The spectrum shows the sensitivity of different chiral carbon atoms to configurational arrangements along the polymer chain[21].

The CD measurements of these hydrolysed copolymers were also carried out. The typical CD spectrum of hydrolysed **1**–**3** copolymer is shown in *Figure 9*, which shows a weak positive band at 270–250 nm followed by a strong negative band over 235–210 nm. These bands largely arise from aromatic π–π^* transitions. In the **1**–**5** copolymer CD spectrum (*Figure 10*), a positive dichroic band over 280–210 nm was observed, which is the combined result of **5** and benzaldehyde aromatic ring π–π^* transitions. Since both the monomeric units constituting the polymer chain possess aromatic rings, it is difficult to establish precisely whether asymmetric inductions occur at the chiral centres of both the monomeric units present in the polymer chain. Design of u.v. transparent monomers might answer this question and merits further investigation.

Contrary to the azomethine-based copolymers, **2**-based copolymers involving diethyl tartrate template show zero or negligible optical activity after removal of the chiral residues. This suggests that although the structural requirements for main chain chirality are met, the choice of the chiral auxiliary can be critical in inducing enantioselectivity on the macromolecular chain. Studies are in progress to elucidate the role of the nature of the chiral templates (flexibility *versus* rigidity) and stereo-electronic relationships between the polymerizable groups and the chiral auxiliary sites on the extent of asymmetric inductions in the polymer chains.

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