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Sulfur-containing optically active polymers: 3. Synthesis and chiroptical properties of optically active poly(γ-ketosulfide)s prepared by polyaddition of 1,3-dimercaptobenzene to *trans,trans*-dibenzylidene acetone in the presence of chiral amines

Luigi Angiolini*, Daniele Caretti, Carlo Carlini and Elisabetta Salatelli
Dipartimento di Chimica Industriale e dei Materiali, Università di Bologna, Viale Risorgimento 4, 40136 Bologna, Italy
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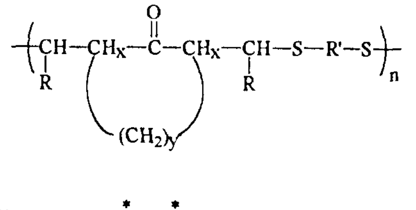
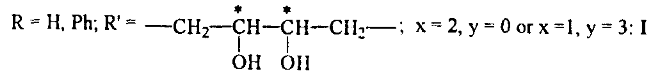
Optically active poly(γ-ketosulfide)s having the asymmetric centres in the main chain have been prepared by polyaddition of 1,3-dimercaptobenzene to *trans,trans*-dibenzylidene acetone in the presence of catalytic amounts of chiral amines. The extent of asymmetric induction on the polymeric product is found to be dependent on the type of amine, *cinchona* and *ephedra* alkaloids giving the highest optical activity in the polymer, due to the presence of the β-hydroxy amine moiety, which favours the formation of tight transition states involving both the reactants. The corresponding low molecular weight analogues have also been synthesized. The stereochemical features have been investigated by n.m.r. and the chiroptical properties studied by circular dichroism measurements. The results indicate that comparable asymmetric induction is found in polymers and model compounds, the former systems not exhibiting appreciable evidence of ordered secondary structures, in agreement with a low degree of stereoregularity along the macromolecular backbone.

(Keywords: optical activity; poly(γ-ketosulfide)s; asymmetric polyaddition)

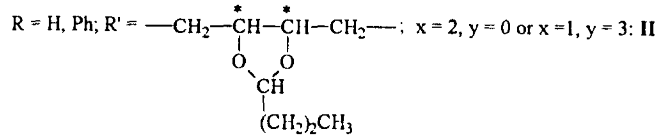
INTRODUCTION

In a previous paper[1] we have described the synthesis and stereochemical features of chiral poly(γ-ketosulfide)s *I*, obtained by reaction of an optically active bis-thiol with $\alpha,\beta,\alpha',\beta'$-unsaturated ketones or bis(β-dialkylamino) ketones. The corresponding derivatives *II*, prepared by acetalization of polymers *I*, were also investigated[2]. It was found that the polymerization reaction proceeds with low stereoselectivity in terms of asymmetric induction on the configuration of the newly formed chiral centres. As a consequence, the macromolecules *I* or *II* are characterized by random sequences of repeating units having different diastereoisomeric configurations, the final result being a rather low stereoregularity degree along the backbone.





$$R = H, Ph;\ R' = -CH_2-\underset{OH}{\overset{*}{C}H}-\underset{OH}{\overset{*}{C}H}-CH_2-;\quad x = 2, y = 0 \text{ or } x = 1, y = 3: \textbf{I}$$



$$R = H, Ph;\ R' = -CH_2-\overset{*}{C}H-\overset{*}{C}H-CH_2-;\quad x = 2, y = 0 \text{ or } x = 1, y = 3: \textbf{II}\quad (\text{the two CH bearing } O\text{—}\underset{(CH_2)_2CH_3}{CH}\text{—}O)$$

Another possible route to optically active poly(γ-ketosulfide)s may be based on the use of chiral catalysts able to induce a prevailing configuration of the asymmetric centres in the main chain during the polymerization reaction. As the polyaddition of thiols to unsaturated ketones is a Michael-type reaction requiring small amounts of amine as promoting agent[3], the presence of a chiral amine in the polyaddition of achiral thiols to prochiral unsaturated ketones should therefore produce poly(γ-ketosulfide)s having sequences of repeating units with a prevailing chirality. Indeed, it is known that the addition of aromatic thiols to prochiral α,β-unsaturated ketones, in the presence of catalytic amounts of *cinchona* and *ephedra* alkaloids[4] as well as of quinine and quinidine[5], leads to the corresponding optically active γ-ketosulfides.

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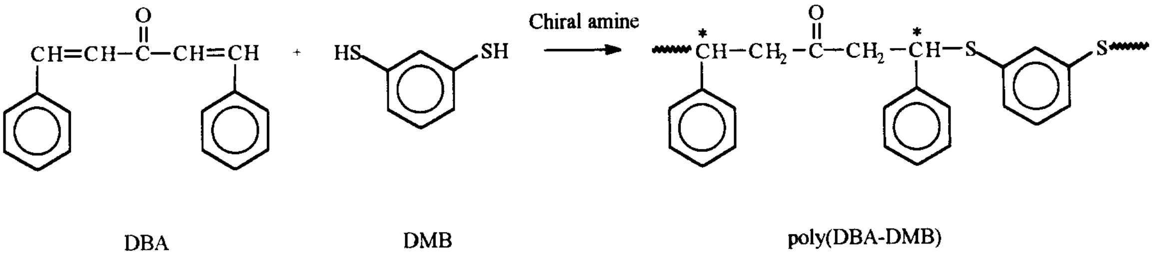
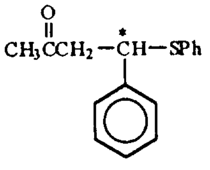
* To whom correspondence should be addressed

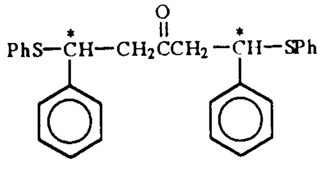


Scheme 1

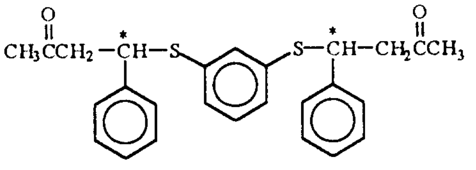
In this context, it appeared interesting to apply the same method to the synthesis of optically active poly(γ-ketosulfide)s by extending to bifunctional reactants the above reaction catalysed by an optically active amine. With this aim, the base-catalysed reaction between prochiral dibenzylidene acetone (DBA) (*trans, trans*-1,5-diphenyl-1,4-pentadien-3-one) with 1,3-dimercaptobenzene (DMB) to give the corresponding polymer [poly(DBA–DMB)] (*Scheme 1*) has been carried out in the presence of different chiral amines, and the chiroptical properties of the obtained product investigated by circular dichroism (c.d.). Moreover, in order to gain a better comprehension of the stereochemical course of the reaction, low molecular weight model compounds (**1–3**), resembling the repeating units of the polymer, have been prepared by reacting monobenzylidene acetone (MBA) (*trans*-4-phenyl-3-buten-2-one) with mercaptobenzene (MB), DBA with MB and MBA with DMB, respectively (see Experimental). In order to select the experimental conditions providing the best performance in terms of induced optical activity in the product, so as to be readily transferred to polymer synthesis, the base-catalysed asymmetric synthesis of **1** has been preliminarily investigated by using different amine concentrations.



1 (MBA-MB)



2 (DBA-MB)



3 (MBA-DMB)

EXPERIMENTAL

Materials

Commercial products were provided by Aldrich Chemicals. Dibenzylidene acetone and monobenzylidene acetone were used after recrystallization from ethyl acetate and petroleum ether, respectively. 1,3-Dimercaptobenzene and mercaptobenzene were distilled just before use. (−)-Brucine dihydrate, $[\alpha]_D^{20} -79.3$ ($c = 1.3$, EtOH) was dehydrated as described in the literature[6], (−)-cinchonidine, $[\alpha]_D^{20} -85$ ($c = 1$, EtOH) was recrystallized from ethyl acetate, (−)-spartein, $[\alpha]_D^{25} -112.5$ ($c = 1.6$, EtOH) was obtained from the corresponding sulfate salt by treatment with aqueous NaOH followed by petroleum ether extraction and drying (Na_2SO_4), $[\alpha]_D^{20} -16.4$ ($c = 1$, EtOH).

(−)-1-Methyl-2-methylol-pyrrolidine, $[\alpha]_D^{20} -49.5$ ($c = 5$, MeOH), (−)-*N*-methyl-ephedrine, $[\alpha]_D^{20} -29.2$ ($c = 5$, MeOH), (−)-*N*-methyl-pseudoephedrine, $[\alpha]_D^{20} -48.0$ ($c = 5$, MeOH), (+)-cinchonine, $[\alpha]_D^{23} +228$ ($c = 0.5$, EtOH) and (−)-ephedrine, $[\alpha]_D^{21} -41$ ($c = 5$, 1N HCl) were used as received.

Physico-chemical measurements

Fourier-transform infra-red (*FT*i.r.) spectra were recorded on a Perkin Elmer model 1750 spectrophotometer equipped with a Perkin Elmer model 7700 data station. The samples were prepared as KBr pellets or liquid films on KBr discs.

^1H and ^{13}C n.m.r. spectra were performed at 200 and 50.3 MHz, respectively, on a Varian FT-NMR Gemini 200 spectrometer on $CDCl_3$ solutions. Chemical shifts are given in δ (ppm) using tetramethylsilane (TMS) as internal standard.

U.v. absorption spectra were recorded on samples in tetrahydrofuran (THF) solution at concentrations between about 5×10^{-5} and $8 \times 10^{-5}\,mol\,l^{-1}$ (in terms of repeating units for the polymers) by using cell path lengths of 1 cm and 0.1 cm for the 350–250 and 250–220 nm spectral regions, respectively, and a Kontron Instruments Uvicon 860 spectrophotometer. C.d. spectra were performed on a Jasco J-500 A dichrograph using the same cell path lengths, solvent and concentrations as for u.v. measurements in the corresponding spectral regions; molar absorption coefficients ε and $\Delta\varepsilon$ are expressed in $l\,mol^{-1}\,cm^{-1}$.

Optical activity measurements were accomplished at 25°C on a Jasco DIP-360 digital polarimeter on $CHCl_3$ solutions ($c = 1\,g\,dl^{-1}$), using a cell path length of 1 dm. Specific rotatory powers $[\alpha]_D$ are expressed as $deg\,dm^{-1}\,g^{-1}\,dl$.

Melting points were determined in glass capillaries with a Büchi 510 apparatus at a heating rate of $1°C\,min^{-1}$.

Average molecular weights of the polymers were determined by size exclusion chromatography (s.e.c.) using an h.p.l.c. Waters Millipore 590 chromatograph equipped with a Waters Styragel 500 Å column, a Waters model U6K injector and a Perkin Elmer LC95 u.v.-visible detector working at 254 nm. Monodisperse polystyrene samples were used for the calibration curve.

Low molecular weight compounds

(+)-*1-Phenyl-1-phenylthio-butane-3-one* (*MBA–MB*) *1.* The synthesis of optically active **1** was carried out following a slightly modified procedure with respect to that reported in the literature[5], starting from mercaptobenzene (7.3 mmol), monobenzylidene acetone (6.6 mmol) and varying catalytic amounts (0.7–68.9 × 10^{-2} mmol) of (−)-cinchonidine in benzene (10 ml). The mixture was heated at 50–80°C for 3–6 h (*Table 1*) under nitrogen atmosphere, then cooled at room temperature and washed with dilute aqueous HCl, water, dilute aqueous NaOH and water again, in that order, until neutrality of the final aqueous washing was obtained. After drying (Na_2SO_4), the benzene solution was evaporated to dryness under reduced pressure and the crude product crystallized from petroleum ether. Reaction yields are reported in *Table 1*. M.p. 59°C (lit.[7] 58°C).

*FT*i.r. (KBr): 3030 (ν_{CH} arom.), 1708 ($\nu_{C=O}$), 1582, 1420 ($\nu_{C=C}$ arom.), 748, 697 (δ_{CH} monosubstituted arom.) cm^{-1}.

^1H n.m.r.: 7.24 (m, 10 H, arom.), 4.69 (t, 1 H, C$\underline{H}$–Ph), 3.04 (d, 2 H, CH_2CO), 2.03 (s, 3 H, CH_3CO).

Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (*III*) [$Eu(hfc)_3$] (Aldrich) dissolved in $CDCl_3$ was used as shift reagent in order to establish the enantiomeric excess (e.e.) in (+)-**1**. Known aliquots of the reagent were progressively added to the $CDCl_3$ solution of the substrate in the n.m.r. tube until the best separation of the signals, along with satisfactory line broadening, was accomplished. A substrate/reagent weight ratio of around 1:0.25 was found to be the most effective.

(−)-*1,5-Diphenyl-1,5-diphenylthio-pentane-3-one* (*DBA–MB*) *2.* A mixture of mercaptobenzene (14.6 mmol), dibenzylidene acetone (6.6 mmol) and (−)-cinchonidine (1.4–5.0 × 10^{-2} mmol, *Table 1*) in benzene (20 ml) was heated at 50–60°C for 28 h under nitrogen atmosphere. After cooling, the reaction mixture was treated as described above. Reaction yields are reported in *Table 1*. The crude material, m.p. 115–123°C, having $[\alpha]_D - 32.8$, was crystallized from EtOH to give a product with $[\alpha]_D - 29.1$. No variation of the optical rotatory power was observed on keeping the compound in boiling EtOH for 1 h.

*FT*i.r. (KBr): 3024 (ν_{CH} arom.), 1708 ($\nu_{C=O}$), 1585, 1438 ($\nu_{C=C}$ arom.), 753, 693 (δ_{CH} monosubstituted arom.) cm^{-1}.

^1H n.m.r.: 7.30–7.10 (m, 20 H, arom. *meso* and DL forms), 4.61 (*meso*) and 4.60 (DL) (two partially overlapped dd, 2 H, C$\underline{H}$–Ph), 2.97, 2.87 (*meso*) and 3.01, 2.85 (DL) (four partially overlapped dd, 4 H, corresponding to A and B protons, respectively, of the CH_AH_BCO spin system).

(+)-*1,3-Bis(3-oxo-1-phenylbutylthio)-benzene* (*MBA–DMB*) *3.* A mixture of 1,3-dimercaptobenzene (3.3 mmol), monobenzylidene acetone (6.6 mmol) and (−)-cinchonidine (0.7–2.5 × 10^{-2} mmol, *Table 1*) in benzene (10 ml) was heated at 50–60°C for 24 h under nitrogen atmosphere. After cooling, the reaction mixture, treated as described above, afforded an oily product (diastereoisomeric mixture) in yields as reported in *Table 1*.

*FT*i.r. (liquid film): 3029 (ν_{CH} arom.), 1715 ($\nu_{C=O}$), 1569, 1453 ($\nu_{C=C}$ arom.), 779 (δ_{CH} 1,3-disubstituted arom.), 759, 699 (δ_{CH} monosubstituted arom.) cm^{-1}.

Table 1 Experimental conditions, optical activity and yield of the product deriving from the addition of thiols to unsaturated ketones in the presence of (−)-cinchonidine (CND) as chiral catalyst[a]

Run	Unsaturated ketone[b]	Thiol	CND conc. (10^{-3} M)	Product	$[\alpha]_D$[c]	Yield (%)
1	MBA	MB	0.7	**1**	+12.7	6
2	MBA	MB	1.1	**1**	+14.5	6
3	MBA	MB	2.5	**1**	+7.4	16
4	MBA	MB	4.6	**1**	+5.5	37
5	MBA	MB	9.3	**1**	+8.0	55
6	MBA	MB	18.0	**1**	+1.6	66
7	MBA	MB	68.9	**1**	−2.7	61
8	MBA	MB	1.1	**1**	+17.2	10
9	DBA	MB	0.7	**2**	−25.8	61
10	DBA	MB	1.1	**2**	−32.8[d]	52
11	DBA	MB	2.5	**2**	−23.4	57
12	MBA	DMB	0.7	**3**	+27.8	49
13	MBA	DMB	1.1	**3**	+18.5	85
14	MBA	DMB	2.5	**3**	+14.4	79
15	DBA	DMB	0.7	poly(DBA–DMB)	−27.0	61
16	DBA	DMB	1.1	poly(DBA–DMB)	−27.5	50
17	DBA	DMB	1.1	poly(DBA–DMB)	−27.3	55
18	DBA	DMB	1.1	poly(DBA–DMB)	−23.5	47

[a] At 50–60°C, except for runs 1–7 (80°C). Reaction duration: 3 h (runs 1–7), 6 h (runs 8, 15, 16), 28 h (runs 9–11), 24 h (runs 12–14), 72 h (run 17) and 192 h (run 18)

[b] MBA conc. 0.66 M, DBA conc. 0.33 M

[c] In $CHCl_3$ at 25°C

[d] $[\alpha]_D - 29.1$ after crystallization of the crude reaction product

Table 2 Optical rotation, molecular weight and conversion yield of poly(DBA–DMB)s prepared in the presence of different chiral amines[a]

Chiral base	*C–N[b]	*C–O[c]	$[\alpha]_D$[d]	$\bar{M}_n$[e]	Yield (%)
(−)-Cinchonidine	*S*	*R*	−27.3	13 600	55
(+)-Cinchonine	*R*	*S*	+47.8	11 100	36
(−)-*N*-Methyl-ephedrine	*S*	*R*	−15.8	9000	12
(−)-*N*-Methyl-ψ-ephedrine	*R*	*R*	+50.4	6100	33
(−)-Ephedrine	*S*	*R*	−22.7	5200	17
(−)-1-Methyl-2-methylol-pyrrolidine	*S*	achiral	−8.2	12 200	10
(−)-Sparteine	*S*, *R*	–	0	14 500	46
(−)-Brucine	*S*	–	0	6100	12

[a] At 50–60°C for 72 h. Amine conc. 1.1×10^{-3} M, reactants conc. 0.33 M
[b] Configuration of the carbon atom linked to the amine nitrogen atom of the catalyst
[c] Configuration of the carbon atom linked to the hydroxy group, when present, of the catalyst
[d] In $CHCl_3$ at 25°C
[e] Determined by s.e.c.

^{1}H n.m.r.: 7.40–7.0 (m, 14 H, arom. *meso* and DL forms), 4.63 (DL) and 4.61 (*meso*) (two partially overlapped dd, 2 H, CH-Ph), 3.03 and 2.92 (two partially overlapped dd, 4 H, corresponding to A and B protons, respectively, of two CH_AH_BCO spin systems given by *meso* and DL isomers), 2.07 (DL) and 2.06 (*meso*) (two s, 6 H, CH_3CO).

The material having $[\alpha]_D + 27.8$ was submitted to reaction with semicarbazide hydrochloride according to the usual procedure[8], thus obtaining the corresponding bis-semicarbazone derivative, $[\alpha]_D + 13.6$, m.p. 98–115°C, which was crystallized from $EtOH/H_2O$ 1:1 (v/v). The precipitated product had $[\alpha]_D + 10.3$ and m.p. 90–110°C.

Polymerization reactions

After preliminary tests performed at 50–60°C with varying concentrations of (−)-cinchonidine or reaction duration (*Table 1*), intended to optimize conversion yield and optical activity of the polymer, the generally adopted polymerization procedure consisted in reacting, under nitrogen atmosphere for 72 h at 50–60°C, a mixture of dibenzylidene acetone (3.3 mmol) and 1,3-dimercaptobenzene (3.3 mmol), in the presence of an optically active amine (1.1×10^{-2} mmol) in benzene (10 ml). After cooling, the polymeric product was precipitated with MeOH and repeatedly dissolved ($CHCl_3$) and reprecipitated (MeOH) up to complete purification from any contaminating low molecular weight material. Conversion yields, optical activity and molecular weight values of the polymers are reported in *Table 2*. The spectroscopic data reported below refer to the product of run 17 of *Table 1*.

*FT*i.r. (KBr): 3028 (ν_{CH} arom.), 1718 ($\nu_{C=O}$), 1569, 1453 ($\nu_{C=C}$ arom.), 780 (δ_{CH} 1,3-disubstituted arom.), 754, 697 (δ_{CH} monosubstituted arom.) cm^{-1}.

^{1}H n.m.r.: 7.4–6.9 (m, 14 H, arom.), 4.6–4.4 (m, 2 H, CH-Ph), 3.0–2.7 (m, 4 H, CH_2CO).

^{13}C n.m.r.: 204.46 (CO), 140.83–127.84 (arom.), 49.29 (CH_2), 47.75 and 47.59 (diastereoisomeric CHPh signals).

U.v.: λ_{max} 293 (sh, $\varepsilon = 1700$), 263 ($\varepsilon = 9000$), 227 (sh, $\varepsilon = 18900$) nm.

RESULTS AND DISCUSSION

As shown in *Table 1*, when monobenzylidene acetone (MBA) and mercaptobenzene (MB) are allowed to react in the presence of catalytic amounts of (−)-cinchonidine (10^{-1} to 10^{-3} molar equivalents with respect to the unsaturated ketone), the optically active addition product **1** is obtained with specific rotatory power depending on the reaction conditions and, in particular, on the concentration of chiral amine, which appears to produce higher asymmetric induction at lower concentration levels. On increasing the relative amount of catalyst, the reaction chemical yield improves, but the optical purity of the product is lowered.

The enantiomeric excess (e.e.) of the sample having the highest rotatory power (run 8 of *Table 1*) has been determined by ^{1}H n.m.r. using the shift reagent (+)-Eu(hfc)$_3$ (see Experimental), which makes it possible to observe in the ^{1}H n.m.r. spectrum of (+)-**1** a splitting of all the signals as a consequence of complexation by the reagent. The anisochroism of the signals, due to the occurrence of diastereotopic protons in the substrate, allows measurement of the ratio between the (+)- and the (−)-isomer and hence the e.e. in the substrate[9,10]. In particular, the non-equivalent resonances of the methyl group (*Figure 1*) prove to be the most useful for the determination of e.e., which is found to be 10%. Similar results were previously obtained[11] for the same product prepared in the presence of (−)-quinine or (+)-quinidine as catalyst, the *R* configuration being assigned to the prevailing dextrorotatory enantiomer. Assuming that the preferred conformation of *trans*-monobenzylidene acetone in the transition state is the *anti* form A depicted in *Figure 2*, the product would therefore be formed by predominant attack by the nucleophilic species from above the plane determined by the unsaturated bonds of substrate.

The synthesis of model compounds **2** and **3**, carried out under the same conditions as those favouring the maximum asymmetric induction in the preparation of **1** (*Table 1*), gives analogous results, the highest optical activity being observed in the product when lower concentrations of chiral amine are employed (runs 10 and 12, *Table 1*). However, since **2** and **3** have two asymmetric centres, the formation of a mixture of *meso* (*RS*/*SR*) and DL (*RR*/*SS*) diastereoisomeric products is expected[12]. As the *meso* stereoisomer is optically inactive due to the presence of an internal plane of symmetry which makes it achiral, the optical activity in (−)-**2** and (+)-**3** must derive from the prevalence of one enantiomer (*RR* or *SS*) over the other one (*SS* or *RR*) in the DL stereoisomer,

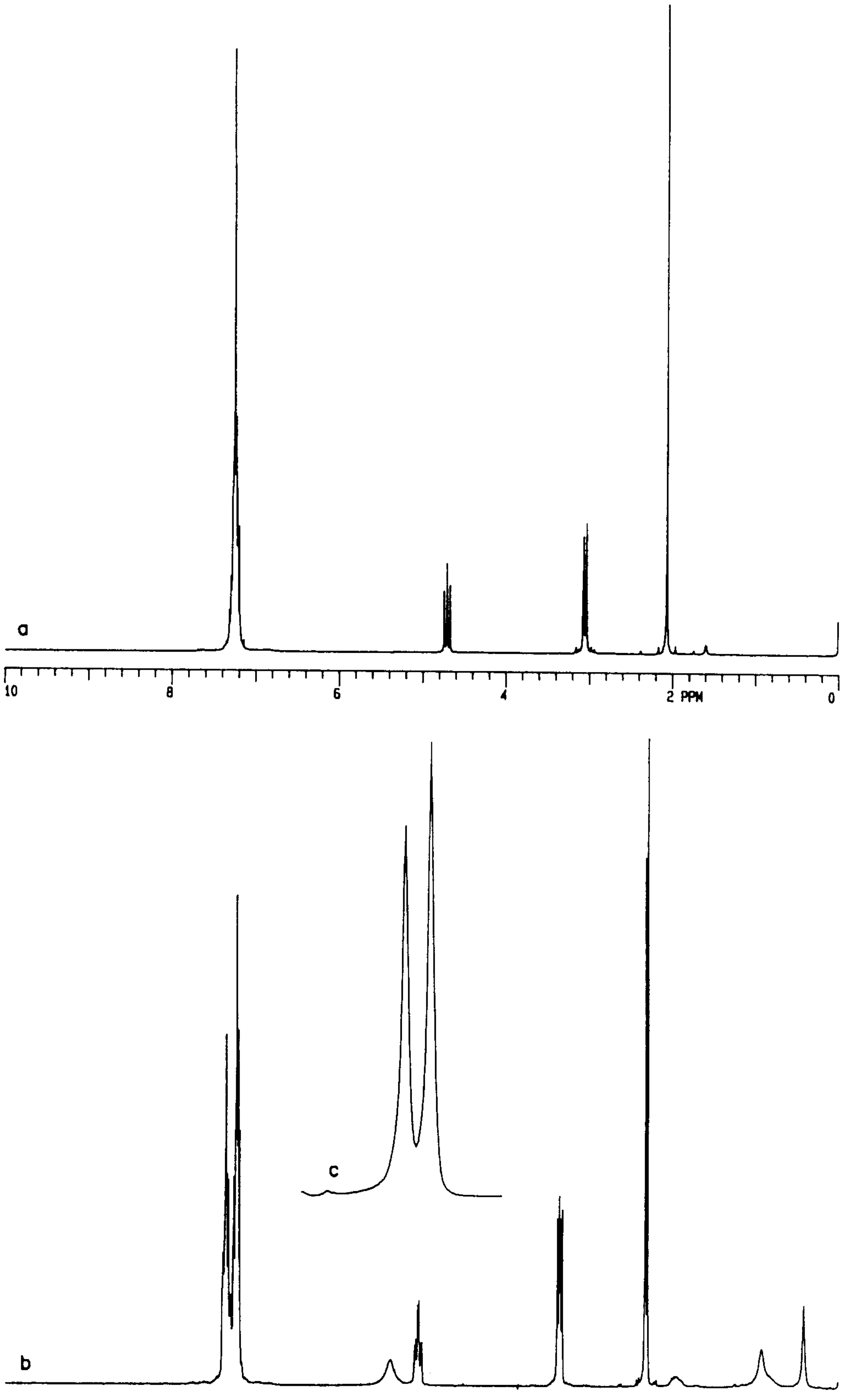


Figure 1 ^{1}H n.m.r. spectra of (+)-**1**: (a) alone; (b) in the presence of (+)-Eu(hfc)$_3$. (c) Enlarged spectrum of the methyl signals at 2.3 ppm

as the consequence of enantioselectivity induced by the presence of (−)-cinchonidine in the reaction mixture. Unfortunately, the determination of e.e. in (−)-**2** and (+)-**3** by the shift reagent technique is not applicable, as it has not been possible to obtain (−)-**2** and (+)-**3** sufficiently free of contamination by the *meso* isomer having overlapping signals in the ^{1}H n.m.r. spectrum (*Figures 3a* and *4a*). Nevertheless, the diastereoisomeric ratios between *meso* and DL forms in (−)-**2** and (+)-**3** have been determined from the ^{1}H n.m.r. spectra by

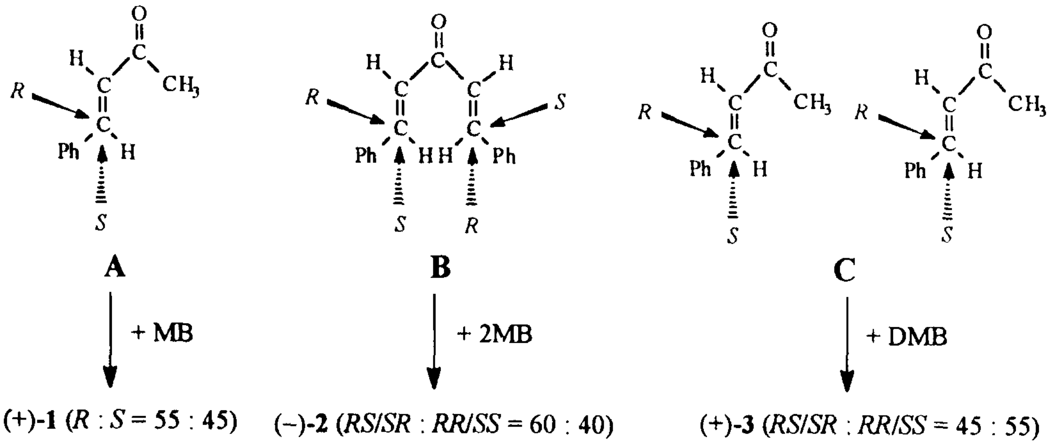


Figure 2 Resulting configuration of the product on addition of the arylmercaptan to the prochiral centre(s) of the unsaturated ketone. Bold and dotted arrows indicate attack from above and below the plane of the sheet, respectively

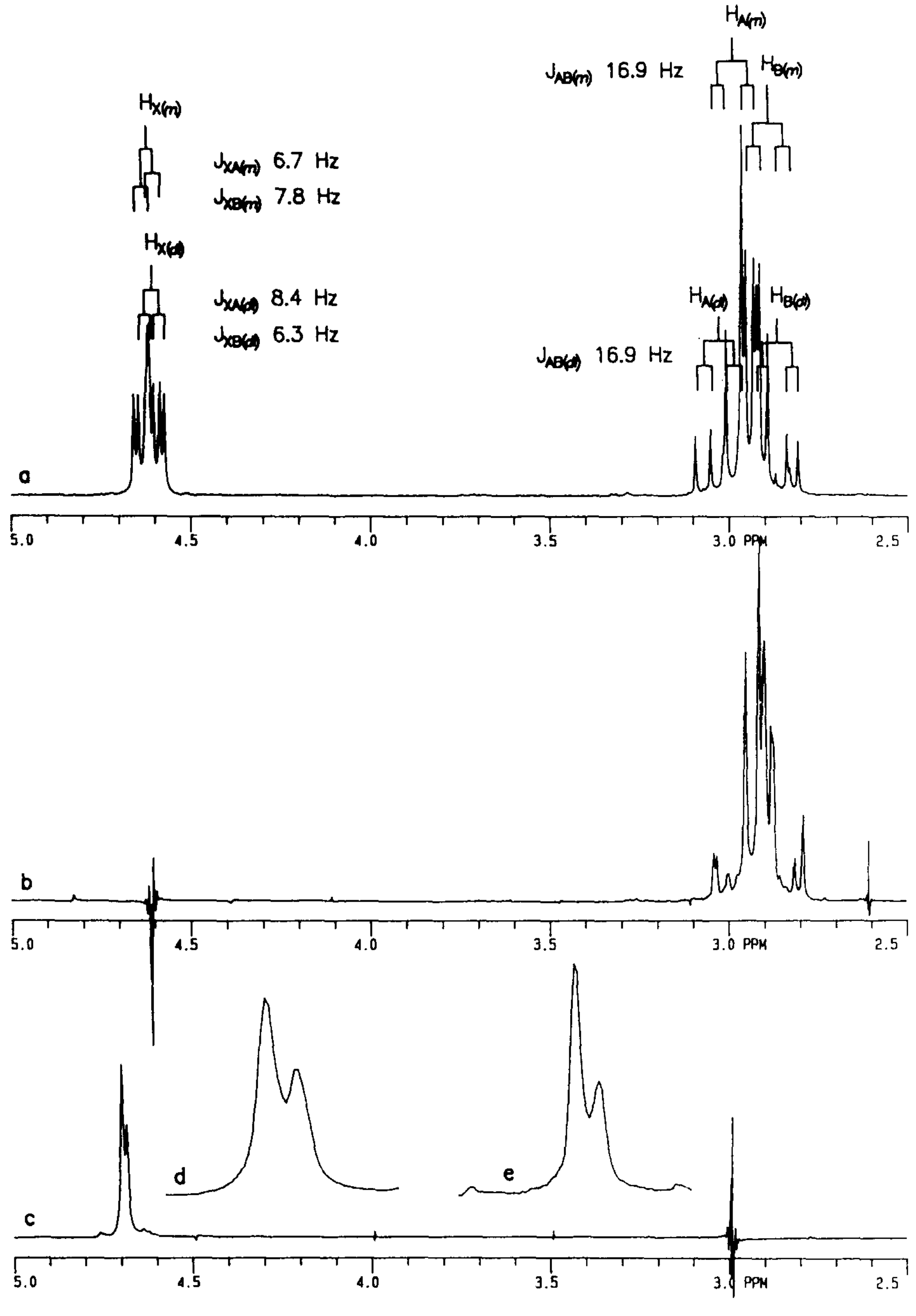


Figure 3 ^{1}H n.m.r. spectra of (−)-**2** (aliphatic region) before (a) and after irradiation at CH (b) and CH$_2$ (c) signals. Inset: CH decoupled signals before (d) and after (e) crystallization

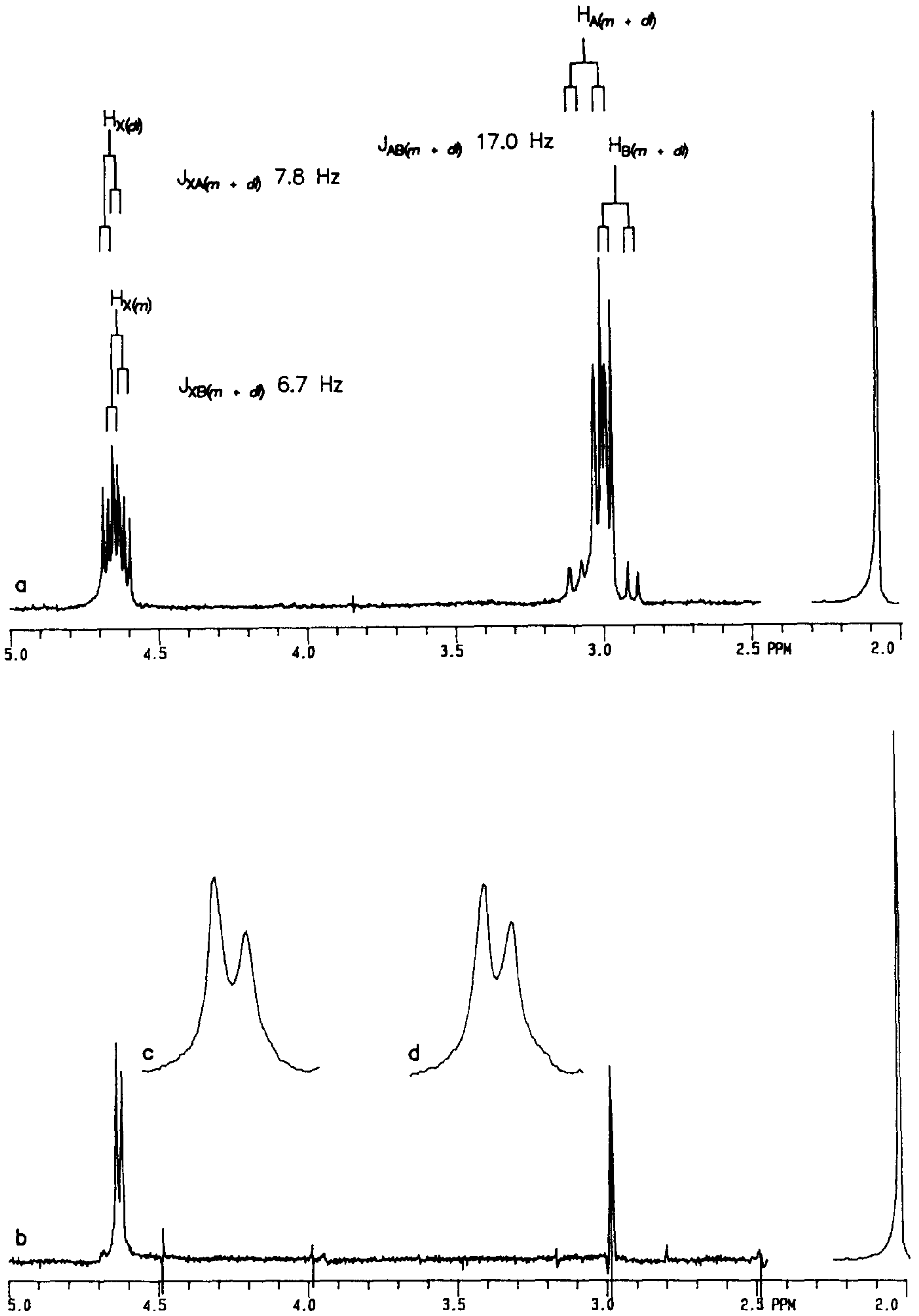


Figure 4 ^{1}H n.m.r. spectra of (+)-3 (aliphatic region) before (a) and after (b) irradiation at CH$_2$ signals. Inset: CH decoupled signals of the bis-semicarbazone derivative before (c) and after (d) enrichment in the less abundant stereoisomer

comparing the integrated areas of the relevant signals given by each stereoisomer after spin decoupling experiments. In particular, the ^{1}H n.m.r. spectrum of (−)-**2** (*Figure 3a*) exhibits in the aliphatic proton region (CH$_2$ and CH resonances at about 2.9 and 4.6 ppm, respectively) two closely overlapped sets of signals having ABX patterns, each of them originated by one diastereoisomer, which do not allow direct determination of the diastereoisomeric ratio. On irradiation at CH$_2$ and CH resonances (*Figures 3b* and *c*, respectively), however, the system is simplified so as to provide evidence of the presence of two singlets for the CH signal, corresponding to the *meso* and DL stereoisomers in the 60/40 ratio (*Figure 3d*). The attribution of the relative configuration to each set of signals has been made possible by repeating the decoupled ^{1}H n.m.r. spectrum of (−)-**2** after enrichment of the diastereoisomeric mixture in the less soluble isomer by fractional crystallization. As the crystallized product has reduced rotatory power (*Table 1*) and enhanced intensity of the predominant n.m.r. signal (66/34, *Figure 3e*), and excluding the possibility of racemization of the optically active component of the diastereoisomeric mixture under the crystallization conditions (see Experimental), the *meso* configuration is thus assigned to the predominant stereoisomer.

The ^{1}H n.m.r. spectrum of (+)-**3** (*Figure 4a*) also exhibits overlapped ABX-type signals indicative of the occurrence of *meso* and DL diastereoisomeric products. Similarly to the model compound (−)-**2**, spin decoupling has allowed determination in this case of a diastereoisomeric ratio of ~55/45 (*Figure 4b*). The subsequent enrichment by crystallization of the bis-semicarbazone derivative (see Experimental) produces a material having lowered specific rotatory power and decreased diastereoisomeric ratio (52/48, *Figures 4c* and *d*), thus allowing the DL configuration to be assigned to the major stereoisomer.

The addition reaction of mercaptobenzene or 1,3-dimercaptobenzene to *trans,trans*-dibenzylidene acetone or *trans*-monobenzylidene acetone, respectively, in the presence of (−)-cinchonidine as chiral promoter appears therefore to afford diastereoisomeric mixtures in which the optically active DL stereoisomer is formed in different amounts with respect to the inactive *meso* (*RS*/*SR*) stereoisomer. This suggests that in model **2** (*Figure 2*, B) the predominant attack by both the nucleophilic molecules acting in the bis-addition would take place by the same side of the plane containing the unsaturated bonds of the carbonyl substrate, if the *anti–anti* coplanar conformation B for DBA is assumed to be the preferred one in the transition state. Thus, the e.e. in the DL stereoisomer would be determined by the difference in free energy of activation between the transition states related to reaction pathways involving bis-attack from opposite faces of the molecular plane and leading, respectively, to the *RR* or the *SS* enantiomer. On similar grounds, the *meso* (*RS*/*SR*) form of model **3** would be produced (*Figure 2*, C) by bis-attack of 1,3-dimercaptobenzene from opposite sides of the plane of the double bond of two MBA reacting molecules, and the DL (*RR*/*SS*) stereoisomer would derive from bis-attack by the same side of the plane. In this case, therefore, the e.e. would depend on the chiral discrimination between either of the enantiofaces of the plane, in an analogous way to what occurs for model **1**. On the basis of the results, it therefore appears that in the reactions giving models **2** and **3** (*Figure 2*, B and C), the nucleophilic reagent has a slightly higher preference for bis-addition from the same side of the plane of the double bonds, independently of the mono- or bifunctional nature of reagent and substrate.

The polycondensation reaction between dibenzylidene acetone and 1,3-dimercaptobenzene in the presence of (−)-cinchonidine also gives an optically active product, (−)-poly(DBA–DMB), when carried out under experimental conditions similar to those producing asymmetric induction in model compounds (*Table 1*, runs 15 and 16). The influence of polymerization duration on optical activity and molecular weight of the product has also been tested. In accordance with results for the models, the maximum optical activity in the polymer is obtained when the concentration of (−)-cinchonidine is 1.1×10^{-3} M (*Table 1*, run 16). Moreover, unsaturated end groups are still present to an appreciable extent in this product, as evidenced by ^{1}H n.m.r. (*Figure 5a*). In particular, the low intensity resonances near 3.2 (CH_2), 4.8 (CH) and 6.6, 7.5 (CH=CH) ppm, originated by styryl ketone moieties, are indicative of the presence in the polymer of end groups to the extent of about 10 mol%. On increasing the reaction duration to 72 h (*Table 1*, run 17), the incidence of the above signals decreases to about 7 mol% but tends to increase again (10 mol%) after 192 h of reaction (*Table 1*, run 18), probably due to thermal depolymerization.

The ^{13}C n.m.r. spectrum of poly(DBA–DMB) (*Figure 5b*) confirms the above results as far as the presence of unsaturated end groups is concerned. In addition, it exhibits (*Figure 5c*) a double signal at 47.75 and 47.59 ppm for the asymmetric benzylic carbon atom of the repeating units. This is indicative of the presence of magnetically non-equivalent diastereomeric structural units disposed along the polymer chain in substantially equal amounts.

The optical activity data (*Table 1*) obtained in the polymerization product with (−)-cinchonidine appear comparable to those given by models **2** and **3**, thus suggesting that a similar stereochemical mechanism could be operative with analogous diastereoselectivity in both the high- and low-molecular-weight systems investigated.

In order to test how the extent of the asymmetric induction in the polymeric product is affected by the nature of the catalyst, several different optically active amines, with or without a hydroxy group in the β position to nitrogen (*Figure 6*), have been employed under the same reaction conditions adopted for run 17 of *Table 1*. The results are reported in *Table 2*, along with the average molecular weights of the polymers obtained.

When (+)-cinchonine, which has opposite configuration at both the *C–N and *C–O carbon atoms with respect to (−)-cinchonidine[13], is employed, a change of sign of the rotatory power in the polymer is observed. The same occurs on passing from (−)-(1*R*,2*S*)-*N*-methyl-ephedrine to its diastereoisomer (−)-(1*R*,2*R*)-*N*-methyl-ψ-ephedrine, having opposite configuration only at the *C–N centre. These results indicate that the configuration of the carbon atom linked to the amine nitrogen is determinant in establishing the sign of optical rotation in the product, as levo- or dextrorotatory poly(DBA–DMB) is obtained when this configuration is *S* or *R*, respectively, regardless of the configuration of the centre bearing the hydroxy group.

Accordingly, (−)-(1*R*,2*S*)-ephedrine, a secondary amine homochiral with (−)-*N*-methyl-ephedrine, as well as (−)-(*S*)-1-methyl-2-methylol-pyrrolidine, having the alcoholic carbon atom achiral, give levorotatory poly(DBA–DMB). In the latter case, however, the absence of chirality at the alcohol moiety has a detrimental effect on enantioselectivity, which is completely cancelled when chiral amines such as (−)-sparteine and (−)-brucine, lacking any hydroxy group, are employed, notwithstanding their remarkable steric bulkiness favouring, in principle, the stereoselectivity of the reaction. Thus, it appears that the presence of both hydroxy and amino groups linked to adjacent chiral centres in the catalyst is essential in order for significant asymmetric induction to take place in the polyaddition reaction. Indeed, an analogous conclusion was drawn[14] in the addition of MB to MBA in the presence of (−)-quinine or (+)-quinidine, structurally related to (−)-cinchonidine and (+)-cinchonine, respectively. The authors proposed the protonation of amine by thiol, followed by intramolecular epoxidation involving the hydroxy group of the catalyst with simultaneous cleavage of *C–N bond of the quinuclidine ring as the first step of the reaction. This intermediate would then evolve towards the products through thiol addition to either of the epoxide ring carbon atoms and subsequent bond formation between sulfur and unsaturated ketone. It is in this step that directional preferences of interaction would be set in, with formation of the optically active ketosulfide and regeneration of the catalyst, accompanied,

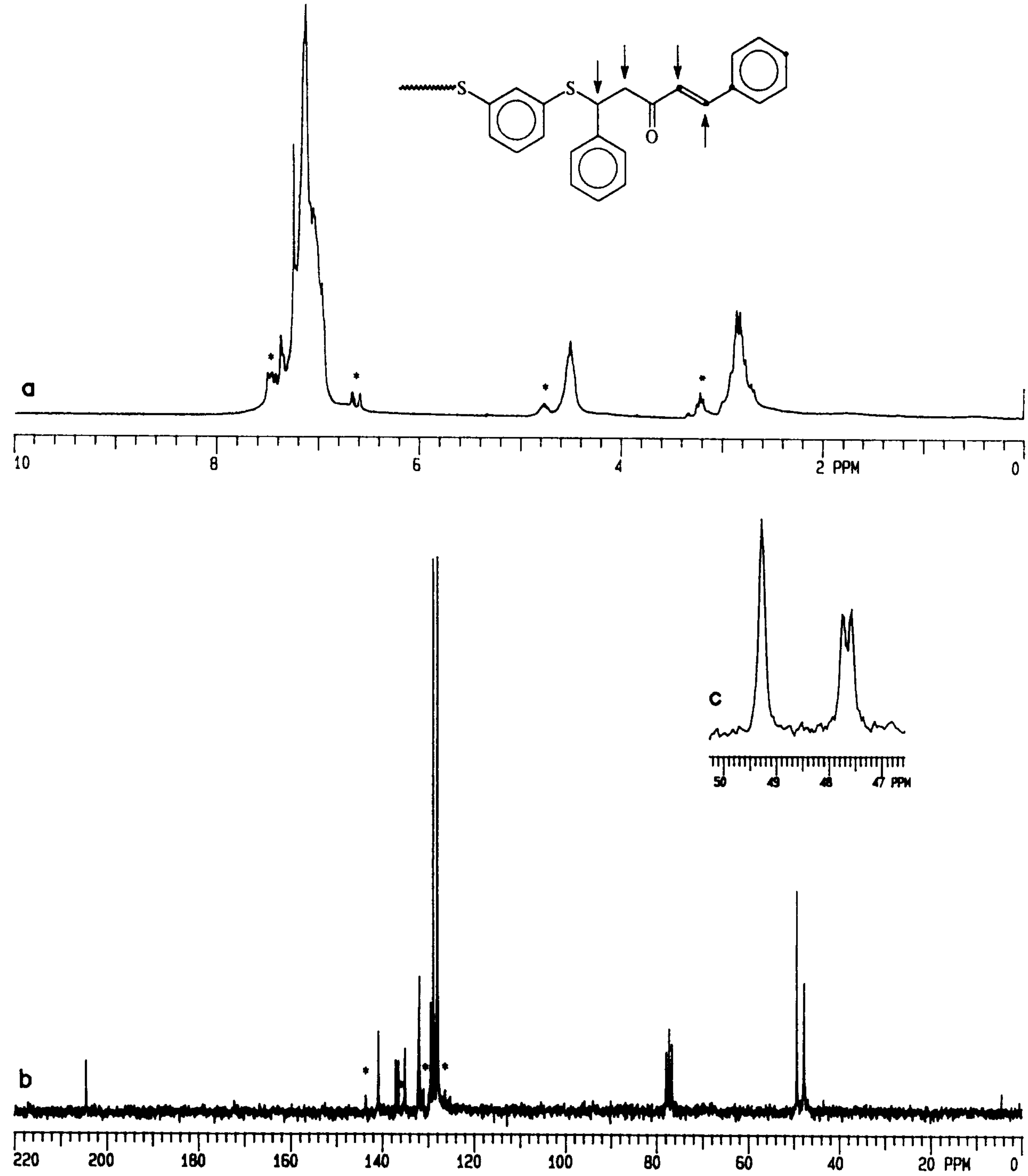
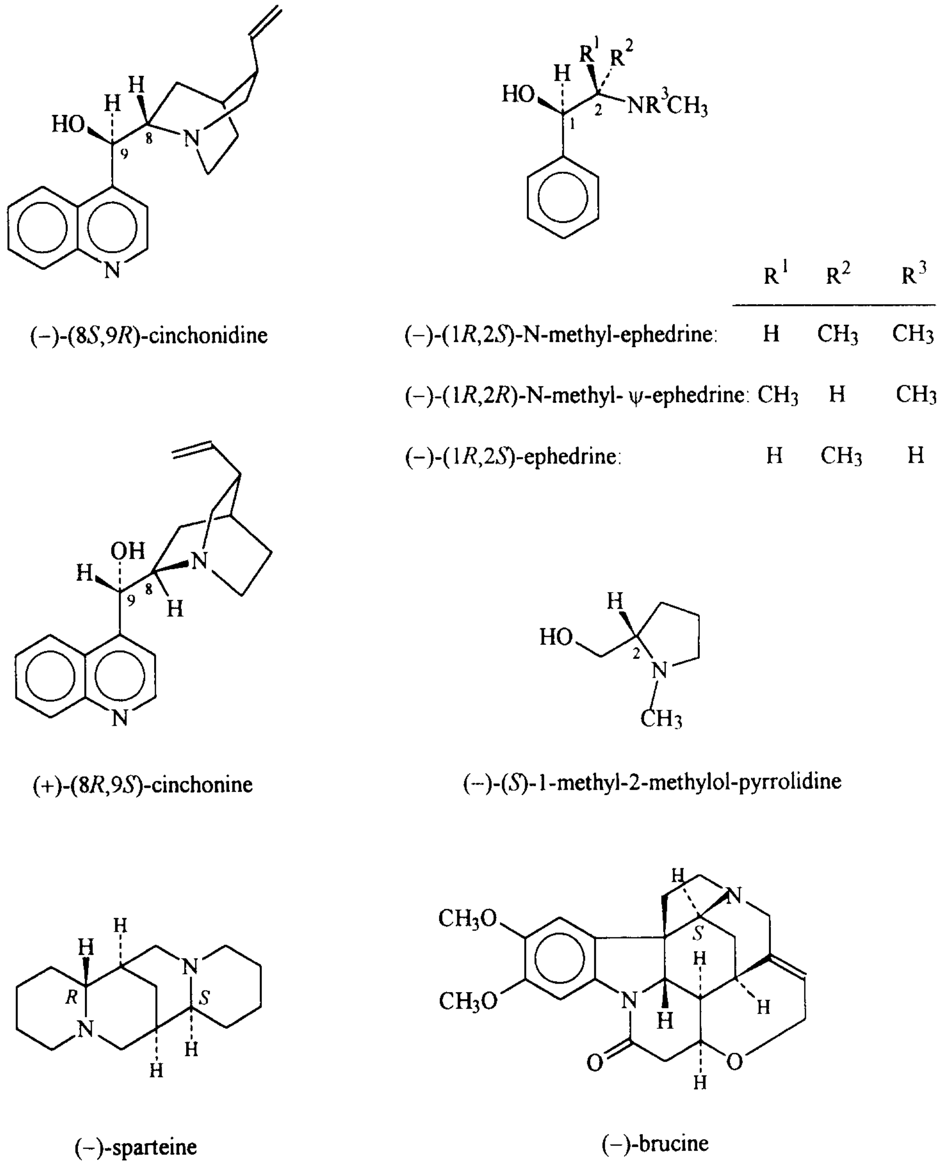


Figure 5 (a) ^{1}H and (b) ^{13}C n.m.r. spectra of poly(DBA–DMB) sample of run 16 obtained in the presence of (−)-cinchonidine. Signals marked by an asterisk refer to hydrogen or to carbon atoms (at the positions indicated by arrows or by dots, respectively, in the formula), belonging to unsaturated end groups. (c) Enlarged region of CH_2 and CHPh resonances

however, by partial epimerization at *C–O which would then favour the formation of the opposite enantiomer. As a consequence, the enantiomeric balance in the product would be affected by the extent of epimerization at *C–O, whereas the configuration of *C–N would determine the sign of the predominant enantiomer.

On the other hand, a tight transition state complex involving thiol and enone has also been suggested[4] for the addition reaction of aryl mercaptans to 2-cycloalkenones in the presence of *cinchona* and *ephedra* alkaloids having relative configuration 'erythro' (*RS* or *SR*) at the β-hydroxy amine moiety. The complex would be stabilized by three concurrent interactions: (i) an electrostatic one between the thiol anion and the ammonium cation deriving from protonation of amine nitrogen; (ii) a hydrogen bond between hydroxy group of the catalyst and carbonyl group of the cyclic ketone; and (iii) a dispersion interaction between the catalyst aromatic ring system and the aromatic thiol anion. Unequal amounts of *R* and *S* product would therefore be formed by different steric conditions at the transition state initiating a free energy difference between two possible orientations of the unsaturated ketone. *Cinchona* alkaloids having relative configuration 'threo' (*RR* or *SS*) of the relevant asymmetric centres, as well as catalysts lacking a hydroxy group, are not able to give at least



(–)-(8*S*,9*R*)-cinchonidine

	R^1	R^2	R^3
(–)-(1*R*,2*S*)-N-methyl-ephedrine:	H	CH_3	CH_3
(–)-(1*R*,2*R*)-N-methyl-ψ-ephedrine:	CH_3	H	CH_3
(–)-(1*R*,2*S*)-ephedrine:	H	CH_3	H

(+)-(8*R*,9*S*)-cinchonine

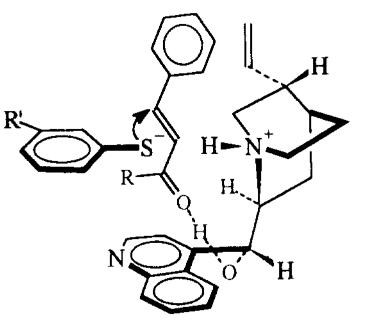
(–)-(*S*)-1-methyl-2-methylol-pyrrolidine

(–)-sparteine

(–)-brucine

Figure 6 Optically active amines employed in the synthesis of poly(DBA–DMB)

one of the above stabilizing interactions, thus producing less structured transition states and consequently lower e.e.'s. Alkaloids having relative configuration 'erythro' at *C–N/*C–O, such as (–)-cinchonidine and (+)-cinchonine, have in fact less tendency than the corresponding 'threo' isomers to give intramolecular hydrogen bonding between hydroxyl group and amine nitrogen in their most stable ground-state conformation when dissolved in an apolar solvent such as benzene[15,16] and could therefore be more readily involved in a transition state of the type *III*[4], where the carbonyl substrate, in the *anti* coplanar conformation, is linked to the catalyst through hydrogen bonding. This could also account for the observed dependence of stereoselectivity on (–)-cinchonidine dilution (*Table 1*), as when the catalyst concentration is increased, the possibility of intermolecular interactions involving alkaloid molecules also increases, with a detrimental effect on the hydrogen bonding with the carbonyl substrate, thus reducing the possibility of tight, i.e. stereoselective, transition states.



III

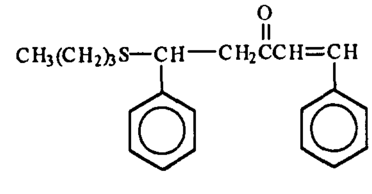
$R = CH_3$, $R' = H$ or SH
R = *trans*-CH=CHPh, R′ = H
R = growing polymeric chain, R′ = SH
R′ = growing polymeric chain, R = *trans*-CH=CHPh
R and R′ = growing polymeric chain

Ephedra alkaloids, although possessing more degrees of conformational freedom than *cinchona* derivatives[17], afford polymeric products with significant optical activity. In particular, (–)-*N*-methyl-ψ-ephedrine (*Table 2*) gives poly(DBA–DMB) with very similar rotatory power to that obtained with (+)-cinchonine, thus indicating that the quinuclidine ring does not play a fundamental role, nor does the quinoline ring as compared to the phenyl ring, in the stereochemistry of polyaddition reaction.

The number average molecular weights, $\bar{M}_n$, of poly(DBA–DMB) samples prepared in the presence of *ephedra* alkaloids are, however, lower than those obtained with *cinchona* alkaloids (*Table 2*). The values for $\bar{M}_n$ appear, in general, in the range of previous results with similar poly(γ-ketosulfide)s[1,18] synthesized using piperidine or dimethylamine as promoting agent of the reaction; however, no systematic investigation concerning the influence of the type of catalyst on the polymerization degree has been reported, to our knowledge. Usually, tertiary aliphatic amines (Et_3N)[19] or hindered secondary amines such as di-isopropylamine[20] or piperidine[3] are employed in the polyaddition reaction between bis-thiols and α,β,α′,β′-unsaturated carbonyl compounds. In the present investigation, the best results appear to be given by cyclic tertiary amines, except for (−)-brucine, whereas acyclic tertiary amines, as well as the secondary amine (−)-ephedrine, afford a product with lower molecular weight. It is known[18] that polymers containing the ketosulfide moiety, when heated in solution in the presence of dimethylamine, exhibit a progressive decrease of intrinsic viscosity, thus evidencing the occurrence of a reverse reaction producing depolymerization. The steric hindrance of the catalyst therefore appears to hamper such a reaction, to the advantage of the $\bar{M}_n$ value of the product.

U.v. and c.d. properties

The u.v. spectra in THF of both model compounds and polymers exhibit an absorption band at around 260 nm and two shoulders at 290 and 230 nm, connected with the $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ electronic transitions of the aromatic ring (^1L_b)[21], carbonyl[22] and sulfide[23,24] groups, respectively (*Figure 7*, inset). Poly(DBA–DMB) samples, however, exhibit ε values for the $n \rightarrow \pi^*$ transition much higher than those expected for saturated aliphatic ketones. In particular, an ε value of 1700 l mol^{-1} cm^{-1} is found for the polymeric product obtained in the presence of (−)-cinchonidine (see Experimental). Taking into account the rather low $\bar{M}_n$ value for the above polymer, this could be attributed to highly absorbing styryl-ketone end groups, as indicated by the ^{1}H and ^{13}C n.m.r. spectra (*Figure 5*). Indeed, the u.v. spectrum in THF of the mono-addition product of *n*-butyl mercaptan to dibenzylidene acetone (**4**)[1], representing a structural model of unsaturated end groups, displays a very intense absorption band at 286 nm with ε = 21 000 l mol^{-1} cm^{-1}.



$$CH_3(CH_2)_3S{-}\underset{C_6H_5}{CH}{-}CH_2\overset{O}{\overset{\|}{C}}CH{=}\underset{C_6H_5}{CH}$$

4

Assuming that ε remains unchanged in the polymer, a content of about 8% of styryl-ketone end groups can be estimated, in good agreement with the n.m.r. data (see above). Consequently, on the basis of the $\bar{M}_n$ value (13 600) found for this polymer (*Table 2*), about two unsaturated end groups per macromolecule can be evaluated; no thiol end group deriving from 1,3-dimercaptobenzene reactant is therefore present in poly(DBA–DMB).

The c.d. spectra in THF of poly(DBA–DMB) samples obtained in the presence of different catalysts exhibit bands related to the above-described electronic transitions, which are indicative of asymmetric perturbation on the chromophoric groups by asymmetric centres having a prevailing chirality located along the main chain (*Figure 7*). In particular, dextro- and levorotatory samples of poly(DBA–DMB) obtained by using (+)-cinchonine and (−)-cinchonidine, respectively (*Table 2*), give substantially specular spectra with corresponding positive and negative dichroic bands. This could be reasonably attributed to an inversion of the prevailing chirality in the macromolecules, i.e. of their handedness, at least for chain sections.

Similar spectra, in terms of maximum wavelengths and Δε values, are given by the low molecular weight models **1**–**3**, obtained in the presence of (−)-cinchonidine (*Figure 8*), thus these molecules can be considered as having substantially comparable stereochemical and conformational features with respect to the polymer. However, the spectrum of **2** has bands of the same sign as (−)-poly(DBA–DMB), obtained with the same catalyst, and hence should more strictly represent the stereochemical nature of the polymer. As **2** is constituted by a 60/40 mixture of *meso* and DL forms, and the polymer exhibits substantially equal amounts of diastereomeric sequences, it can be concluded that no particular enhancement of the chiroptical properties, connected with the presence of a higher conformational rigidity, takes place on passing from the low molecular weight compounds to the polymer, probably due to the low stereoregularity in the main chain. In other words, the macromolecules do not appear to possess a sufficiently high conformational and stereochemical homogeneity for

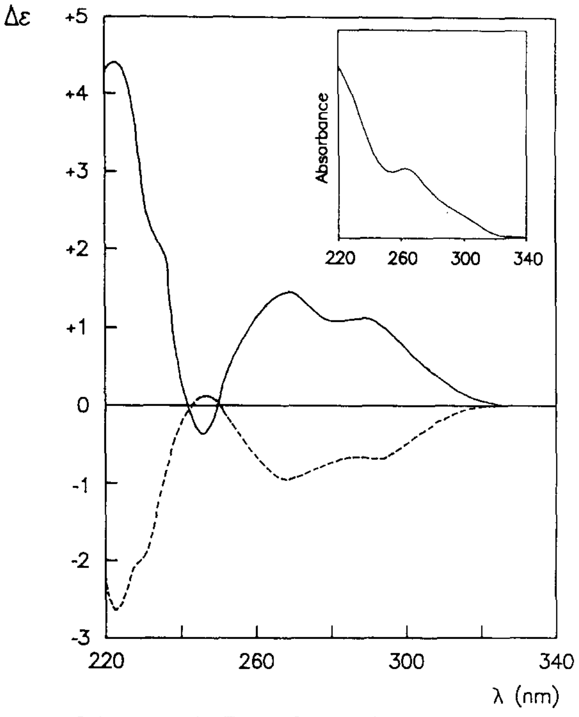


Figure 7 C.d. spectra in THF of (+)-poly(DBA–DMB) (——) and (−)-poly(DBA–DMB) (– – – –) samples obtained in the presence of (+)-cinchonine and (−)-cinchonidine, respectively. Inset: u.v. spectrum in THF

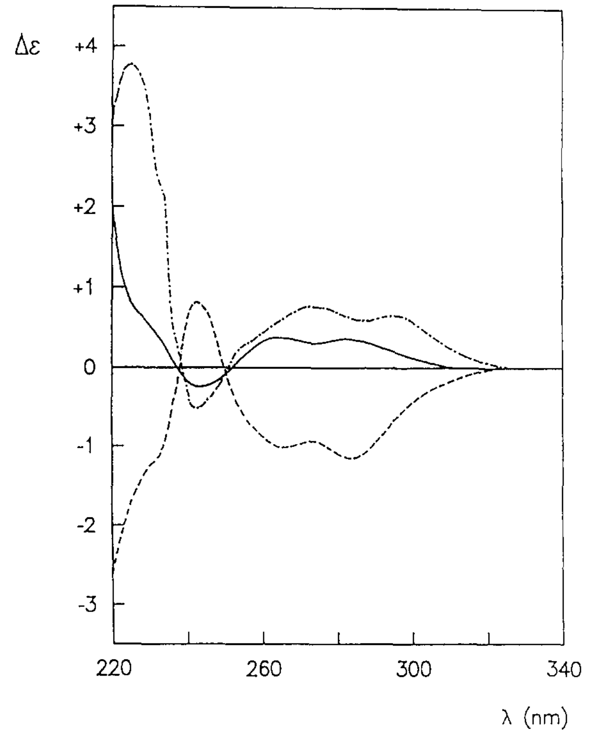


Figure 8 C.d. spectra in THF of (+)-**1** (——), (−)-**2** (– – – –) and (+)-**3** (– · – –) obtained in the presence of (−)-cinchonidine

producing more relevant effects, in terms of dichroic properties and optical activity, with respect to the low molecular weight models.

CONCLUSIONS

The asymmetric induction, promoted by chiral amines, in the polyaddition reaction between di-unsaturated ketone and dithiol, leading to optically active poly(γ-ketosulfide), appears strongly dependent on the type of catalyst. A determinant role is played by the presence in the catalyst of the β-hydroxy amine moiety, as shown by *cinchona* and *ephedra* alkaloids, which is capable of producing chiral discrimination by the thiol reagent between the enantiofaces of the carbonyl substrate through a complex mechanism involving both the amine and hydroxy functions. In particular, the chiral centre linked to amine nitrogen appears to be responsible for the preferred side of addition, and the chiral centre linked to the hydroxy group for the extent of optical activity. This is connected with the possibility of anchorage, through hydrogen bonding with the hydroxy group, of adequate amounts of suitably oriented substrate molecules in the transition state.

Similar results, in terms of chiroptical properties, are given by polymers and low molecular weight models, thus suggesting that the stereochemical course of the reaction is scarcely affected by the steric hindrance of the growing chain on the reacting site, and that conformational effects are not particularly relevant in the polymers.

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