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Reactive Monomers and Polymers Containing Chiral Groups
Synthesis and Copolymerization of N-p-Methylstyryl-(1R,2S)-Ephedrine

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Abstract

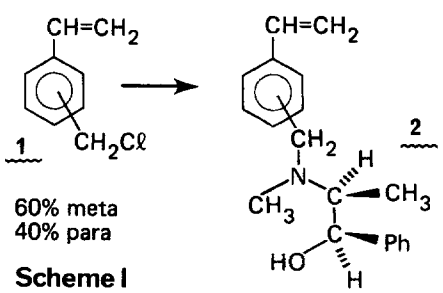
N-(p-methylstyryl)-(1R,2S)-ephedrine is prepared by alkylation of p-chloromethylstyrene under conditions which do not favor quaternization. A series of copolymerization reactions confirm that the new chiral monomer and styrene copolymerize in random fashion with $r_1 = 1.09$ and $r_2 = 0.98$. The optical rotation of the copolymers does not vary linearly with composition. Applications of the copolymer include its use as chiral ligand for asymmetric synthesis or as a separation medium.

Introduction

Over the past few years, polymers containing reactive chiral groups have been sought for applications such as the preparation of separation media [1,3] capable of resolving racemic compounds with complementary functionalities or as regenerable chiral auxiliaries in asymmetric syntheses [4-8]. While in many instances it is possible to obtain reactive polymers containing chiral groups by chemical modification of functionalized resins such as chloromethylated polystyrene, monomers containing optically active moieties have added potential due to their versatility which allows their use in various compositions from homopolymers to highly crosslinked resin beads. These may contain varying amounts of functional groups and may be produced with tightly controlled particle sizes and porosities as is suitable for HPLC applications.

Results and Discussion

The target molecule for this study was a styrenic monomer containing pendant chiral (1R,2S)-α-(1-methylaminoethyl) benzyl alcohol also known as 1-(-)-ephedrine units. The synthesis of such a monomer can be most easily visualized as proceeding via chemical modification of commercially available chloromethyl styrene 1 (scheme I). Indeed N-alkylation of 1-(-)-ephedrine with 1 is easily accomplished under conditions which do not favor quaternization and monomer 2 can be isolated in good yield by preparative HPLC or distillation. The obvious drawback of



Scheme I

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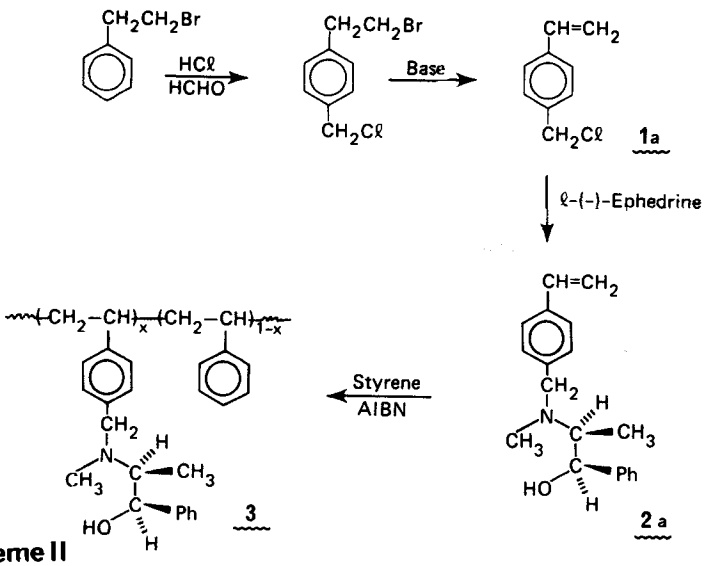
this procedure is that starting monomer 1 being a mixture of meta and para isomers, the final product will also be impure. It is likely however that this mixture of isomers should be suitable for most applications since the structural variations in the two possible isomeric structures are located at a point far removed from the chiral center; they are therefore unlikely to affect its ability to participate in subsequent applications involving chiral recognition. Nevertheless, to avoid any ambiguity, or the multiplication of plausible pathways in the interpretation of results involving polymers derived from 2, it was desirable to prepare a single isomer such as the p-isomer 2a.

Preparation of 2a is best carried out as shown in scheme II whereby p-chloromethyl styrene is prepared by successive chloromethylation and dehydrohalogenation of 2-bromoethylbenzene as described by Kondo et al. [9]. After purification, p-chloromethylstyrene 1a is alkylated using excess 1-(-)-ephedrine in pyridine to afford 2a which can be purified by preparative HPLC.



Scheme II

Copolymerization of 2a with styrene is expected to afford a random copolymer 3 in view of the similarity of structures. Nevertheless, a copolymerization study was carried out to determine the reactivity ratios of the two monomers as it is useful to ensure that random placement will indeed be obtained in the various copolymers. The results of this study, in which varying amounts of the comonomers were used in low conversion copolymerizations, were used to calculate reactivity ratios according to the classical expressions [10]. The reactivity ratios calculated from analysis of the copolymers were $r_1 = 1.09$ and $r_2 = 0.98$ for monomer 2a and styrene respectively. This data confirms that for these two monomers the composition of the copolymer is essentially a reflection of the monomer feed.

Monitoring of the optical rotations of the copolymers as a function of composition affords the results shown in Figure 1. It is interesting to

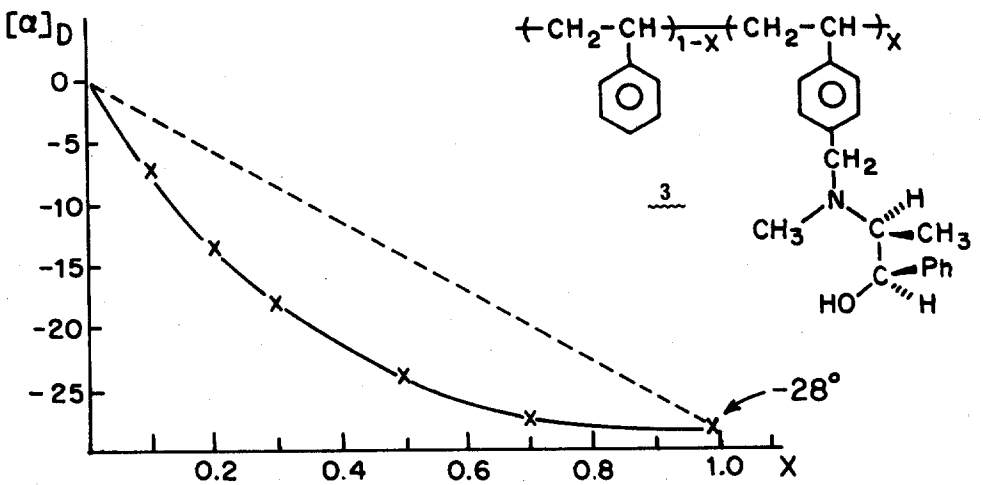


FIGURE 1. OPTICAL ROTATION vs. COMPOSITION FOR 3

note a certain deviation from a direct relationship which results in maximum optical rotation being obtained for a composition incorporating only 70% of 2a. This abnormal behavior may be caused by some induced effect due to the creation of additional asymmetry along the main chain of the polymer during polymerization.

The chemical reactivity of polymers 3 is typical of that expected for a supported ephedrine moiety. For example, the polymer can be used as a chiral ligand in asymmetric reductions with polymer-supported lithium aluminium hydride complexes using techniques similar to those described in a previous paper [5]. In a typical application, using a 1:2:1 complex of chiral polymer 3, 3,5-dimethylphenol and lithium aluminium hydride for the reduction of acetophenone, the enantioselectivity of the reaction was found to depend on the degree of functionalization of the chiral polymer 3. The degree of functionalization of the polymer is shown by x in structure 3, scheme II. While the homopolymer (x = 1) typically affords 20% ee in the reduction of acetophenone, higher values of 32% and 45% ee respectively are obtained with polymers having degrees of functionalization of x = 0.52 and 0.11. Once the reductions were complete polymer 3 could be recovered essentially quantitatively and used again in further reductions. Though somewhat disappointing, these results confirm the potential usefulness of chiral polymers such as 3; the relatively low optical yields which were observed were likely due to severe site-site interactions whereby several ephedrine sites can cooperate in the complexing of lithium aluminium hydride. Such interactions inevitably lead to crosslinking through multiple binding via aluminium alkoxide linkages, and indeed the chiral complex precipitates during its formation. This undesired crosslinking which leads to precipitation of the polymer probably also prevents full participation of all available ephedrine sites in the complexation of lithium aluminium hydride. Irregular complexation through several chiral sites is probably also responsible for a decrease in optical yield. We are exploring now the application of polymer 3 and its highly crosslinked macroporous analog in chromatographic resolutions.

Experimental

Optical rotations were measured on a Perkin-Elmer Model 241 digital polarimeter using the D line of a sodium lamp. NMR spectra were measured on CFT 80 or XL-300 spectrometers in $CDCl_3$ solutions; data is reported in PPM from TMS. Infrared spectra were recorded on a Nicolet 10-DX Fourier transform spectrometer. Preparative HPLC separations were carried out on a Waters 500 LC fitted with 500 g silica gel columns. The l-(-)ephedrine obtained from Sigma Chemicals was used without purification.

Preparation of p-chloromethylstyrene:

This monomer was prepared following the procedure of Kondo et al. [9] starting from 2-bromoethylbenzene by chloromethylation, followed by separation of o- and p-isomers and dehydrohalogenation.

Preparation of monomer 2a

5.46 g (33.0 mmol) of l-ephedrine is mixed with 5.03 g (33.0 mmol) of p-chloromethylstyrene in 18.5 mL of dry pyridine. The mixture is stirred at RT for 7 days. After addition of 20.0 mL of water the mixture is extracted three times with ethyl acetate. The combined organic phases are backwashed with water twice, dried over $MgSO_4$ and evaporated to yield 7.59 g of a crude mixture. Separation by column chromatography using a 9:1 mixture of hexane and ethyl acetate give 4.39 g of the pure ephedrine derivative. Additional fractions contained 1.43 g of 2a for a total yield of 63%. $[\alpha]_D$ = -41.8 (C = 2.35, $CHCl_3$).

^{1}H-NMR: S = 0.97 (d,3H), 2.13 (s,3H), 2.80 (m,1H), 3.43 (s,b,1H alcohol), 3.53 (s,2H), 4.77 (d,1H), 5.15 (ABX,1H, Jcis = 10Hz), 5.65 (ABX,1H), 5.65 (ABX,1H, Jtrans = 16 Hz), 6.67 (ABX,1H) 7.20 (m,9H).
^{13}C-NMR: 9.515(q), 38.455(q), 58.713(t), 63.346(d), 73.414(d), 113.494(t, = CH2), 136.403 (d, = CH), 126.088 - 142.422 (aromatic C).
IR (cm^{-1}): 3370 (OH), 1620 (C = C stretch), 1039 (C-o stretch)
MS: m/e 282 (M+1, chemical ionization, ether); 174 (M^+ - C_7H_7O) 117 ($C_9H_9^+$), 91 ($C_7H_7^+$)
Analysis (C,H,N); calc. 81.10, 8.24, 4.98; found: 80.97, 8.33, 5.12.

Preparation of monomer 2

The synthesis of 2 from m,p-chloromethylstyrene is carried out exactly as described above for 2a. The final product has spectral characteristics similar to those of 2a with minor variations due to the presence of both meta and para isomers.

Preparation of the homopolymer of 2a

1.4552 g (5.17 mmole) of 2a is dissolved in 1.5 mL toluene and 0.038g AIBN is added. The solution is stirred and heated at 75° for 24 h. The viscous mass is then dissolved in a small amount of dichloromethane and the polymer is precipitated in petroleum ehter. The polymer (1.3362 g, 92%) has Mn = 22,200 (osmometry) and $[\alpha]_D$ = -27.5° (C = 2.3, $CHCl_3$).

^{1}H-NMR: 80.90 (broad, 3H), 2.05 (b,3H), 3.10(m,4H), 4.80(b,1H), 6.90(m,b,9H).

^{13}C-NMR: 9.70 (CH_3), 14.06 and 22.30 (backbone) 38.64 (CH_3), 58.67 (CH_2), 63.61 (CH), 73.64 (CH), 125.51 - 144.03 (aromatic).
IR(cm^{-1}): 3388 (OH), 1040 (C-O stretch).
Analysis (C,H,N): calculated: 81.10, 8.24, 4.98; found: 81.03, 8.42, 5.03.

Preparation of copolymers of 2a and styrene

The copolymers were prepared as for 2a using varying amounts of the two comonomers (see figure 1) and stopping the polymerization at low conversion after a few minutes at 75°. Elemental analysis provides an indication of the composition of the copolymers. For example, a monomer feed of 49% 2a and 51% styrene affords a copolymer with 51% 2a repeating units. Analysis; found (C,H,N): 83.95, 8.39, 3.67.
$[\alpha]_D$ = -25.1 (C = 2.4, $CHCl_3$). Mn = 19,900 (osmometry).

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