

USING MICROENVIRONMENTAL EFFECTS TO INCREASE LOADING AND STEREOSELECTIVITY FOR POLYMER BOUND NaBH₄ REAGENTS

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ABSTRACT

Past studies have illustrated that the microenvironment of the functional groups attached to polymer-bound reagents and catalysts plays a major role in their reactivity. This study investigated the effect that concentrating stereogenic centers within a polymer matrix had on the reduction of acetophenone. Both crosslinked polystyrenes and crosslinked polyurethanes were functionalized using chiral appendages derived from δ -gluconolactone and used as supports for sodium borohydride. The results of the reduction reactions indicated that as the number of stereogenic centers increased at the linking point on the polymer, the % enantiomeric excess of the alcohols produced during the reaction also increased from 13 % enantiomeric excess to 54 % enantiomeric excess. Overall, the results of this study suggest that asymmetric pockets were formed within the polymer matrix when polar functional groups containing chiral appendages were concentrated within a non-polar polymer.

INTRODUCTION

Previously, it had been established that the microenvironment surrounding the functional group in a crosslinked polymer could affect that group's reactivity. The microenvironment includes the nature of the groups on the polymer near the functional group in question; and, to some extent, the type of solvent that is used to swell the polymer. (Alexandratos and Miller, 1996; Pillai and Mathew, 1993) More recently, it has also been shown that the microenvironment within the polymer matrix in the vicinity of the functional group may be tailored to optimize the effect that group has on the reaction. (Alexandrotos and Miller, 2000) It has been demonstrated that the chemical environment of the polymer matrix can be modified to be more compatible with the reaction. For instance, a more polar polymer can be used to interact more favorably with a growing polypeptide by increased solvation of all the reactive sites. Conversely, by this approach, more nonpolar polymers have been prepared to increase the concentrations of the nonpolar reactants in the polymer matrix. (Krishnakumar and Mathew, 2002) While these previous studies focused on optimizing the kinetics and product yields for the reaction, it may also be possible to introduce more stereochemical control as well. In particular, examples using polymer or dendrimer supported chiral auxiliaries have begun to appear in the literature that yield high degrees of chiral induction in reduction and alkylation reactions. (Van Heerbeek, et al., 2002; Sato, et al., 2002; Hutchison, et al., 2004; Sashiwa and Shigemasa, 2002; Schmitzer, et al., 2001) In both instances, the high degree of chiral induction appears to be related to the microenvironment of the reactive groups on the polymer or dendrimer. While it is not as apparent in the alkylations

reported by Hutchison using polymer supported ephedrines, the reduction reactions reported by Schmitzer using a dendrimer support illustrates that the microenvironment does play an important role. Because it was shown that a critical concentration of chiral groups was required before significant chiral induction occurred, the high degree of chiral induction appears to be related to the microenvironment of the reactive groups on the polymer or dendrimer.

In this report, we extend this idea that the microenvironment of a polymer or dendrimer may be manipulated to prepare reagents capable of reducing prochiral ketones to secondary alcohols with moderate to high stereoselectivities. In order to accomplish this goal, polymers with pockets of polar, asymmetric environments within a relatively nonpolar polymer matrix were prepared. Furthermore, these polymers were prepared from readily available starting materials to circumvent the time and expense associated with obtaining dendrimers. Two different polymer matrices were utilized in this study: polystyrene that was either chloromethylated (Merrifield resin) or aminomethylated; and polyurethanes that utilized differing degrees of crosslinking or crosslinks with different chemical characteristics. In all cases, the asymmetric region of the polymer was prepared by using δ -gluconolactone or derivatives using δ -gluconolactone as a starting material.

METHODS AND MATERIALS

All starting materials and solvents were obtained from the Aldrich Chemical Company and used without further purification. The FT-IR spectra were obtained using a Nicolet 550 Magna IR spectrometer. The polymer loadings and %ee data for the products were obtained from gas chromatographic data using a Hewlett-Packard 5890 gas chromatograph equipped with a 3390A integrator and a Supelco Beta Dex 120 column (30 m x 0.25 mm x 0.25 μ m film). The % enantiomeric excess was determined by comparing the areas of the R and S isomers relative to the area of a hydrocarbon reference. The signals of the R and S isomers were identified using samples of the actual compounds. All NMR spectra were obtained using an Anasazi Eft, 60 MHz spectrometer.

Preparation of (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamidomethylated-polystyrene, 1. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. To the round-bottom flask were added 15 mL of dry methanol and 2.9 g of aminomethylated polystyrene (0.9 meq of N/g of polymer) and the polymer was allowed to swell. The round-bottom flask was then heated to 60-62°C and allowed to equilibrate at this temperature. In a separate flask that was equipped with a septum and purged with nitrogen, 1.0 g (0.0056 mols) of δ -gluconolactone was dissolved in a mixture of 25 mL of dry methanol and 5 mL of dry DMSO with gentle heating. The resulting solution was transferred via cannula to the reaction vessel. The mixture was allowed to stir for 72 h at 60-62°C. The reaction was terminated by filtering the polymer and washing it successively with 3 x 15 mL portions of the following solvents: THF, 1:1 (v:v) water:THF, water, 1:1 (v:v) water:THF, and THF. The polymer was dried to yield 3.23 g of an off-white colored solid (70% of theoretical weight). FT-IR analysis: 3500-3300, 1660, 1300-1000 cm^{-1} .

Preparation of (2R,3S,4R,5R)-N-(2-{bis[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)ethyl]amino}ethyl)-2,3,4,5,6-pentahydroxyhexanamide, 2. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. The round-bottom flask was then heated to 60-62 °C and allowed to equilibrate at this temperature. To the round-bottom flask were added 20 mL of dry methanol and 3.01 g (0.0206 mols) of tris-(2-aminoethyl)amine. In a separate flask that was equipped with a septum and purged with nitrogen, 11.1 g (.062 mols) of δ -gluconolactone was dissolved in a mixture of 50 mL of dry methanol and 18 mL of dry DMSO with gentle heating. In the event any solid remained, additional DMSO was added drop-wise until a homogeneous solution formed. The resulting solution was transferred via cannula to the reaction vessel. The reaction was allowed to proceed for 72 h with stirring at 59-61°C. A solid cake of white precipitate had formed. The solid was broken up and filtered to yield a very tacky white residue. The solid was washed with isopropyl alcohol until it was no longer tacky. The solid was then allowed to dry under a nitrogen flow to yield a white powder. FT-IR: 3500, 1660, 1200-1000 cm^{-1} . ^{13}C NMR (D_2O): 174.1, 73.3, 72.1, 71.0, 70.2, 64.1, 62.6, 33.7 ppm.

Preparation of Polystyrene-bound (2R,3S,4R,5R)-N-(2-{bis[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)ethyl]amino}ethyl)-2,3,4,5,6-pentahydroxyhexanamide, 3. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. To the round-bottom flask were added 55 mL of dry DMF and 2.9 g of Merrifield Resin (1.0 meq of Cl/g of polymer) and the polymer was allowed to swell. The round-bottom flask was then heated to 63-65°C and allowed to equilibrate at this temperature. In a separate vessel, 1.35 g (1.99 mmol) of **2** were added to *ca.* 20 mL of dry DMF and gentle heating was applied until the solid dissolved. The resulting homogeneous solution was added to the polymer suspension in the round-bottom flask. Additionally, 0.5 g of K_2CO_3 and 0.05 g of 18-crown-6 were added to assist in the substitution reaction and removing the HCl as it formed. The mixture was allowed to stir for 96 h at 63-65 °C. The polymer was then isolated by filtration and washed successively with 3 x 20 mL portions of THF, 1:1 (v:v) water:THF, water, 1:1 (v:v) water:THF, and THF. The polymer was dried to yield 3.61 g of an off-white colored solid (45% of theoretical weight). FT-IR analysis: 3500-3300, 1300-1000 cm^{-1} ; the signal at 1261 cm^{-1} for the chloromethyl group had disappeared.

Preparation of Polyurethane-bound (2R,3S,4R,5R)-N-(2-{bis[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)ethyl]amino}ethyl)-2,3,4,5,6-pentahydroxyhexanamide, General Procedure. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. To the round-bottom flask were added 55 mL of dry DMF and 3.00 g (0.0044 mol) of **2**. The solid was dissolved by heating the mixture to 78-80°C with stirring. The appropriate diisocyanate was dissolved in hot, dry DMF and added to the reaction vessel. The temperature was allowed to equilibrate at 78-80°C and the reaction was allowed to proceed for a total of 72 h. After 24 h, the mixture began to take on the appearance of gelatin. The polymer, was separated by filtration and washed with 3 x 20 mL portions of water, acetone, ether, and acetone in that order. The polymer was dried *in vacuo* to yield an off-white, translucent solid.

Preparation of 4. The reaction was conducted using 3.00 g (0.0044 mol) of **2** and 8.80 g (0.0088 mol) of the polypropylene glycol, tolylene, 2,4-diisocyanate terminated (M.W. =1000). All other amounts were as listed in the general procedure. FT-IR data: 3500, 3100, 1730, 1680, 1600, 1520, 1150-1050 cm^{-1} .

Preparation of 5. The reaction was conducted using 3.00 g (0.0044 mol) of **2** and 1.45 mL (0.0088 mol) of 1,6-diisocyanatohexane. All other amounts were as listed in the general procedure. FT-IR data: 3500, 1730, 1680, 1520, 1150-1050 cm^{-1} .

Preparation of 6. The reaction was conducted using 3.00 g (0.0044 mol) of **2** and 2.90 mL (0.0176 mol) of 1,6-diisocyanatohexane to yield a less pliable, hard solid. All other amounts were as listed in the general procedure. FT-IR data: 3500, 1730, 1680, 1520, 1150-1050 cm^{-1} .

Polymer-bond NaBH_4 Derivatives, General Procedure. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. A 1.0-1.5 g sample of polymer was added to the reaction vessel and allowed to swell in 20-25 mL of dry diglyme. The theoretical maximum meq of alcohol per g of polymer was estimated and a two-fold molar excess of 0.5 M NaBH_4 (in diglyme) was added to the reaction vessel. The reaction mixture was allowed to stir for 4 h at 68-70°C. A slow evolution of H_2 was noted during the process. At the end of the reaction time, no gas evolution was noted. The polymer was separated via filtration and washed 3 x 25 mL portions of dry diglyme. The polymer was used immediately in the ensuing reduction reaction.

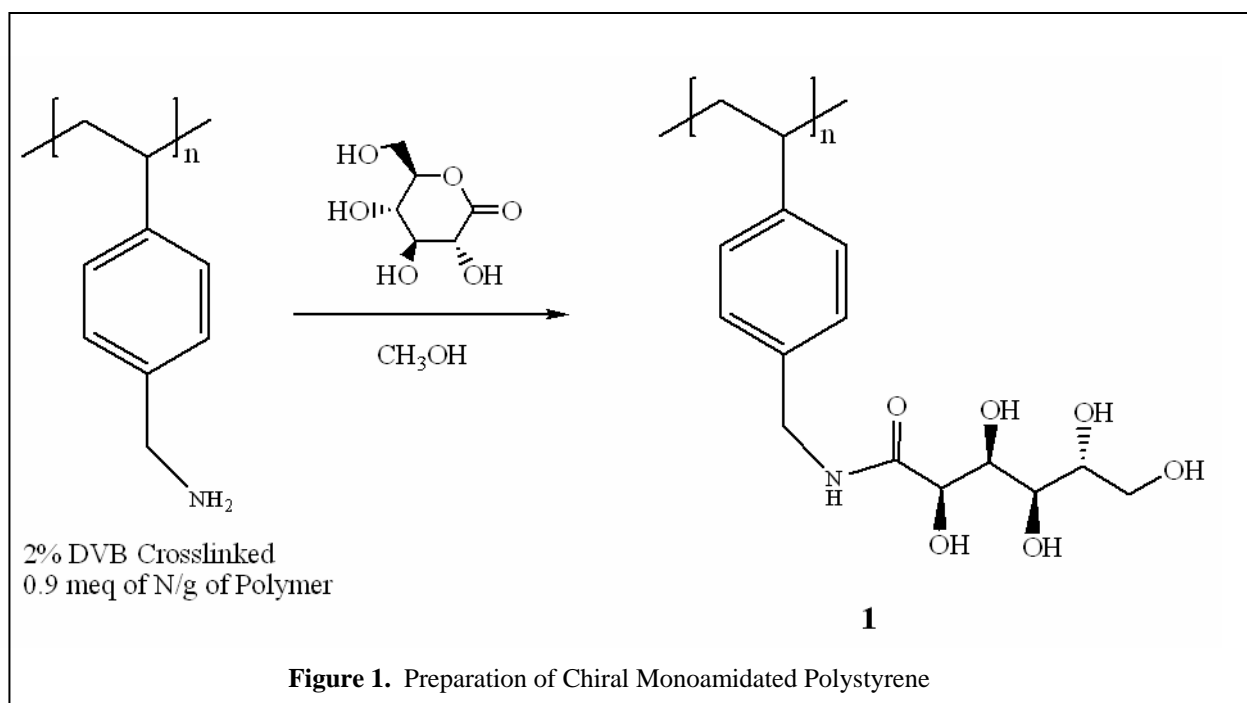
Ketone Reduction, General Procedure. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. The NaBH_4 derivatized polymer was swollen in 20 mL of dry toluene for 30 min at 22-24°C. The theoretical maximum meq of hydride per g of polymer was estimated and a five-fold molar excess of acetophenone and 0.10 mL of dodecane dissolved in 5 mL of toluene was added to the reaction vessel. The reaction was sampled after 2 h and allowed to continue reacting for a total of 24 h before the reaction was terminated. The mixture was washed with water and the organic layer dried over MgSO_4 before subjecting it to GC analysis.

Swelling Determination. To a dry, tared sample vial was added a 0.3-0.5 g sample of the crosslinked polymer. The bottle was sealed with a septum and the polymer was allowed to swell with an excess amount of toluene for 6 h at room temperature. The excess solvent was carefully removed and the swollen polymer was weighed. The difference in weight represented the amount of solvent that was trapped within the polymer network. This volume represented by this difference was determined using the density of the solvent. The swelling factor was determined by dividing the volume by the mass (mL/g).

RESULTS

Initially, it was determined that polymers with relatively nonpolar characteristics might prove useful as support matrices in this study. Any polar region within this non-polar polymer matrix would be more receptive to polar reactions such as the ones used in this study to form the chiral borohydrides. The chiral borohydrides were formed by allowing the polymer to react with NaBH_4 in diglyme, and the polymer was washed and swollen in toluene to conduct the reduction reaction. Toluene was chosen because its relatively nonpolar nature should further assist in concentrating the more polar reactants near the polar, reagent bearing sites of the polymer. Because the reduction reactions were also polar, these concentrated chiral pockets would facilitate asymmetric reductions of prochiral ketones.

The first polymer, **1**, was prepared by allowing 2% divinylbenzene crosslinked aminomethylated polystyrene to react with δ -gluconolactone as illustrated in Figure 1. While this polymer did not have a high number of chiral groups within the polymer, it



was felt that some degree of chiral induction was possible due to the chiral groups being concentrated within the polar microenvironment where the reduction would take place. As illustrated by the data in Table 1, a synthetically useful degree of loading of 8.35 meq of hydride per gram of polymer was obtained. However, the degree of chiral induction

Table 1. Polystyrene Based Polymers

Polymer	Polymer Matrix	Crosslinking	Loading(meq H/g)	Swelling (mL/g)	%ee ^a
2	polystyrene	2%	8.35	6.1	13
3	polystyrene	2%	9.45	6.6	54

a. The uncertainty based on standard deviations is +/- 2% enantiomeric excess. The major stereoisomer in each case was the S isomer.

was rather low at 13 % enantiomeric excess. Apparently, the microenvironment around the reactive sites did not possess the concentrations of chiral groups that were necessary to effect the higher enantiomeric excesses that have been reported in other studies.

As a means of increasing the number of the chiral hydroxyl sites, a triamide that possessed a total of 12 chiral hydroxyl groups was prepared. As shown in Figure 2, δ -gluconolactone was allowed to react with tris-(2-aminoethyl)amine to form (2R,3S,4R,5R)-N-(2-{bis[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)-ethyl]amino}ethyl)-2,3,4,5,6-pentahydroxyhexanamide, **2**. In order to attach this

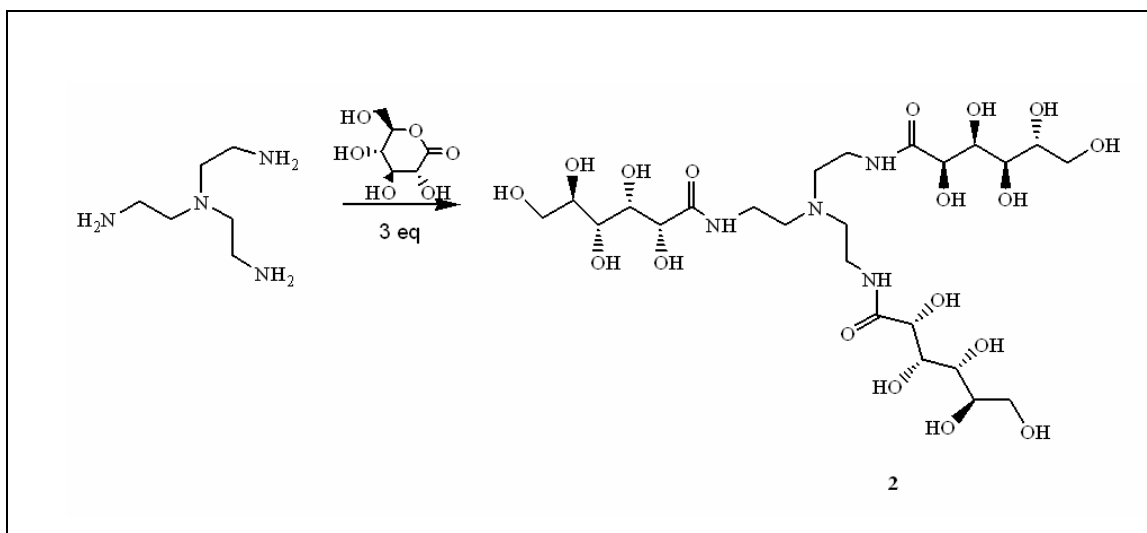


Figure 2. Preparation of Chiral Triamide

triamide to a polymer backbone, a different linking site had to be used. As illustrated in Figure 3, 2% divinylbenzene crosslinked Merrifield resin was allowed to react with **2** under S_N2 conditions to form **3**. Because it has been found that DVB crosslinked polymers are not rigid or static in their structure, multiple substitutions should have occurred due to the number of hydroxy groups present on **2** and the flexibility of the polymer matrix. (Yan and Sun, 1998; Crosby and Kato, 1976; Blanton and Salley, 1989; Alexandrotos and Miller, 2000) Also, due to the inherent reactivity of the primary alcohol versus the secondary alcohol, it was predicted those sites will react first. This seems to be substantiated by the loss of the primary alcohol stretch in the FT-IR spectra. Based on the weight gain of the polymer, only 45% of **2** was found to react with the polymer; but FT-IR analysis indicated that all the linking sites on the polymer were no longer present. Additionally, as illustrated in Table 1, the loading was 9.45 meq of hydride per gram of polymer, which was considerably lower than the theoretical maximum of 42 meq of hydride per gram of polymer. These observations certainly support the idea that each equivalent of **2** underwent multiple substitutions with the linking sites on the polymer.

However, as shown in Table 1, this further concentration of the chiral sites within the polymer matrix had a favorable effect on the stereochemical control of the acetophenone reduction. The degree of chiral induction increased to 54 % enantiomeric excess. Based on the results obtained using the polystyrene based polymers, it was felt that further concentration of the chiral groups could be obtained using hyperbranched polymers as the

polymer matrix. The polymers were polyurethanes that were prepared using **2** as the alcohol substrate and commercially available diisocyanates as linking agents. Diisocyanates with different chemical properties were used to study the effect this had on the stereochemical control of the reduction reaction.

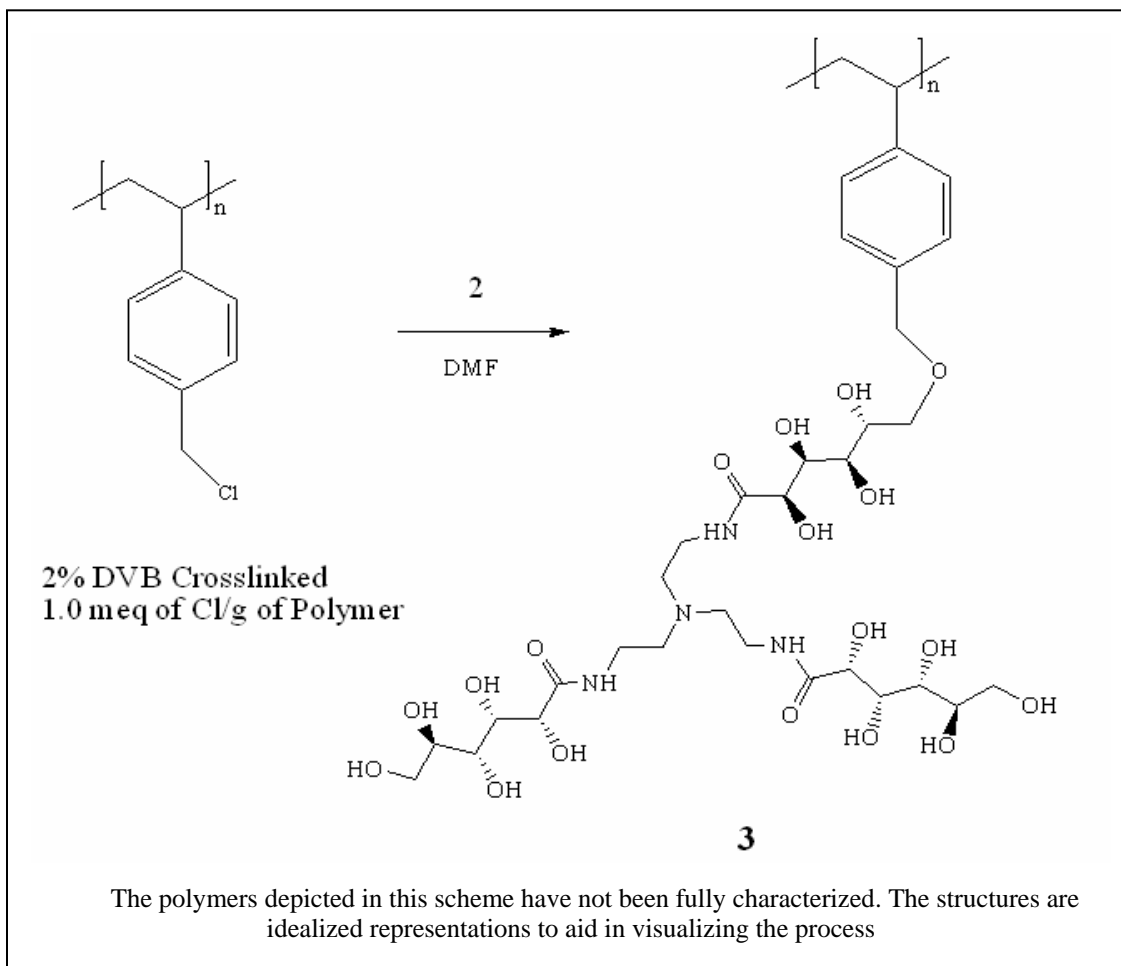


Figure 3. Preparation of Triamidated Polystyrene

Table 2. Polyurethane Based Polymers

Polymer	Polymer Matrix	Crosslinking ^a	Loading(meq H ⁺ /g)	Swelling (mL/g)	%ee ^b
4	polyurethane	1:2	6.8	10.3	26
5	polyurethane	1:2	7.8	6.6	33
6	polyurethane	1:4	1.3	1.3	44

- For the polyurethanes, the molar ratio of the chiral agent:diisocyanate (mol:mol) is provided.
- The uncertainty based on standard deviations is +/- 2% enantiomeric excess. The major stereoisomer in each case was the S isomer.

As illustrated in Figure 4, a hyperbranched polymer was prepared using **2** and a polypropylene glycol whose chain was functionalized on each end by an isocyanato group as the starting materials. Because of the inherent reactivity of the primary alcohol versus the secondary alcohol, it was predicted those sites will react first. This seems to be substantiated by the loss of the primary alcohol stretch in the FT-IR spectrum. The formation of the carbamate group of the polyurethane was also present in the FT-IR spectrum. This particular diisocyanate was chosen because it yielded a polyurethane with a more polar backbone with longer linking chains. As shown in Table 2, when the

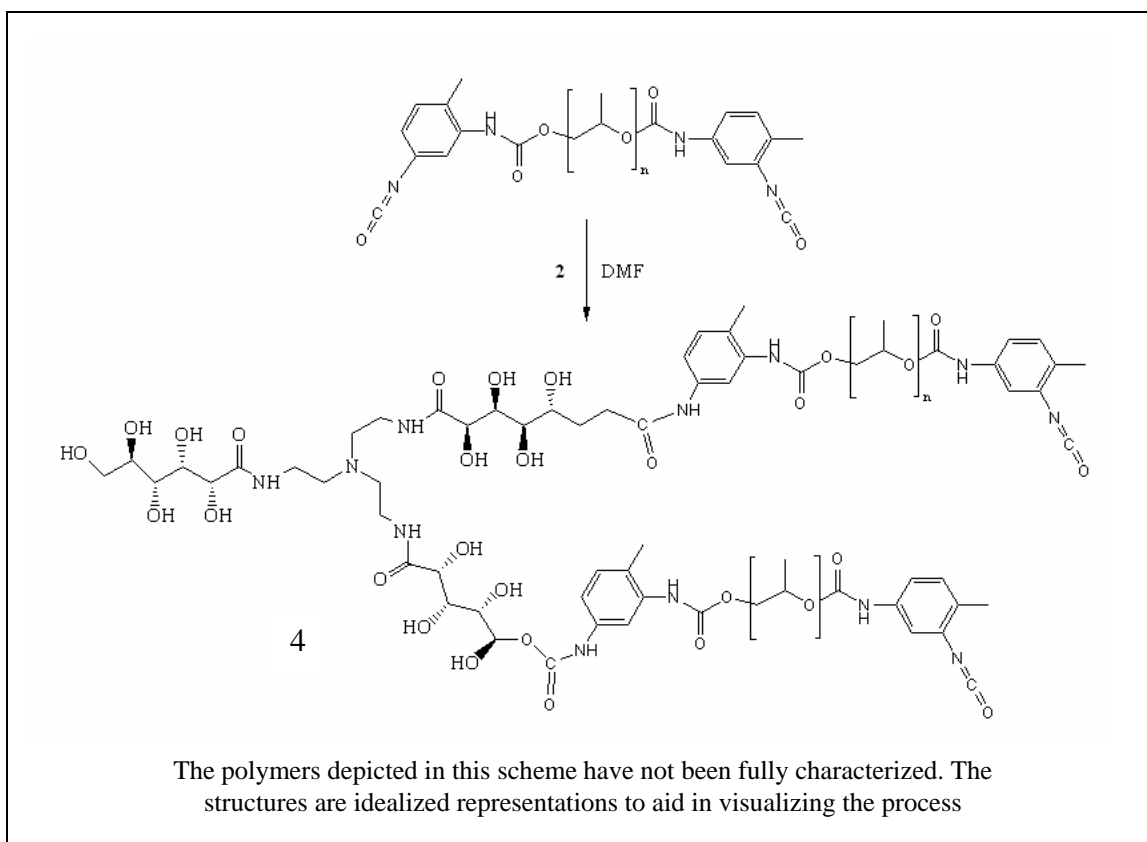


Figure 4. Preparation of Chiral Polyurethanes Using Polyether Linkages

reduction reaction was carried out using polymer **4** it was found that the loading was 6.8 meq of hydride per gram of polymer, which was comparable to the polystyrene based systems. In addition to the loading, the product mixture was found to yield only a moderate degree of chiral induction at 26 % enantiomeric excess. This observation could be explained by the nature of the chains linking the chiral sites. The longer links in the polymer matrix allowed for a polymer swelling of 10.3 mL/g, which exceeded those of the crosslinked polystyrenes. While the increased swelling allowed for better solvation of sites within the polymer matrix, the chiral pockets within the polymer were not as concentrated. Additionally, polyethers such as polymeric glycols have been shown to be reasonable phase transfer catalysts. This could have also affected the stereochemical distribution of the products because any phase transfer component to the reduction would have taken place in a more achiral environment. By increasing the number of

coordinating sites on the polymer chain, such a process would have affected the loading of the functional groups as well.

Because of the data obtained from polymer **4**, hyperbranched polymers with shorter linking groups were prepared. The reaction scheme described in Figure 5 utilizes **2** as the chiral alcohol component and 1,6-diisocyanatohexane as the linking agent. Two different

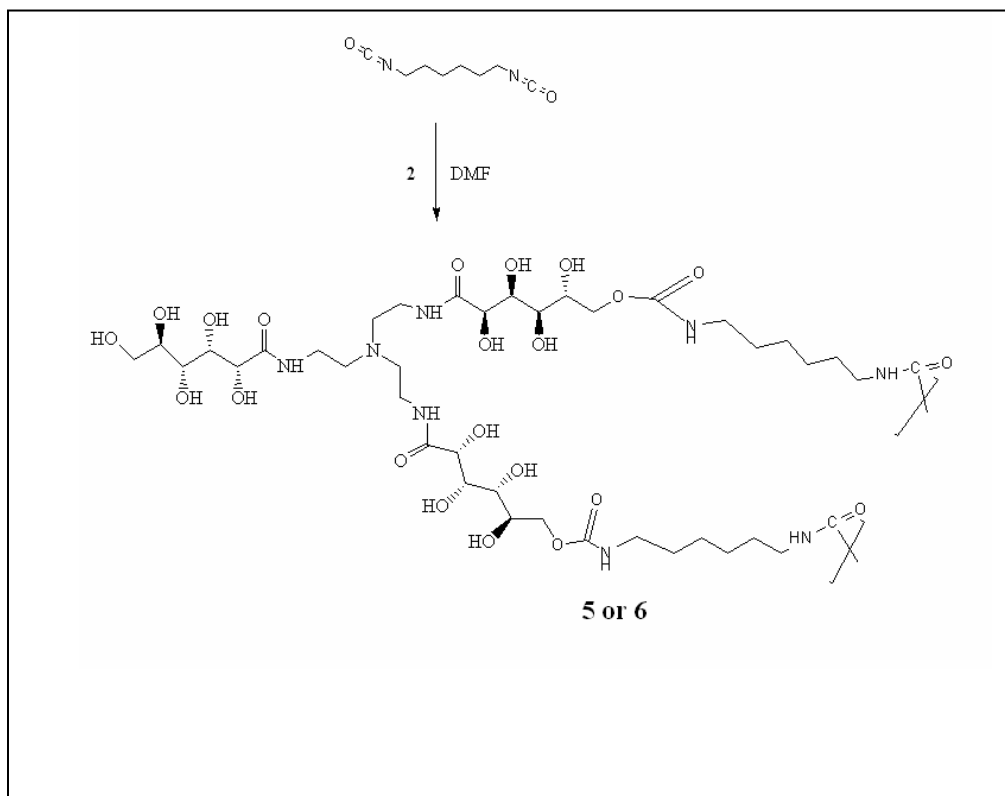


Figure 5. Preparation of Chiral Polyurethanes Using Alkane Linkages

hyperbranched polymers were synthesized in this manner: polymer **5** was prepared using 2 equivalents of diisocyanate; and, polymer **6** was prepared using 4 equivalents of diisocyanate. The two polymers were physically different in that **5** was soft and elastic while **6** was very hard and almost rock-like in appearance. When both **5** and **6** were further derivatized with NaBH_4 , it was noted that **6** exhibited less gas evolution than **5**; and **6** did not swell as much. The information in Table 2 shows that **5** swelled as much as a typical Merrifield-type resin at 6.6 mL/g; but **6** did not swell to any extent at 1.3 mL/g. This difference in swelling also had an effect on the loading of the NaBH_4 on the polymer matrix. Polymer **5** had an appreciable swelling which resulted in better accessibility to the reactive sites and yielded a loading of 7.8 meq of hydride per gram of polymer; but, polymer **6** which did not swell, had a loading of 1.3 meq of hydride per gram of polymer. While the swelling ability had a detrimental affect on the loading of **6**, it also seemed to better concentrate the chiral pockets with the polymer. This made it more effective than polymer **5** in reducing acetophenone to yield a more enantiomerically enriched product mixture. The 33 % enantiomeric excess and 44 % enantiomeric excess obtained for the reduction reactions **5** and **6**, respectively, were significantly higher than the 26%

enantiomeric excess obtained when **4** was used as the polymer matrix. Furthermore, the 44 % enantiomeric excess that was obtained using **6** as the polymer was similar to that of the polystyrene based polymer **3**, which also incorporated **2** in its polymer matrix. This increased effectiveness corresponded to using the shorter six carbon chain linking groups.

DISCUSSION

Based on the data obtained during the course of this study, it was found that significant changes in the reactivity of a polymeric reagent might be accomplished by altering the microenvironment of the polymer support. Previous studies involving polymeric reagents focused more on how reaction rates could be affected by altering the microenvironment in the vicinity of the functional groups; or, how error sequences were reduced in peptide syntheses by improving the compatibility of the growing peptide with the microenvironment of the solid-phase support. In this study, we extended the idea of manipulating the microenvironment to include concentrating chiral linkages to exert more stereochemical control in reducing a prochiral ketone. In all cases, we were able to use readily available starting materials to prepare the functionalized polymers. Regardless of the type of polymer, we found certain similarities between the systems: reasonable loadings could be obtained provided the polymer swelled in the solvent; and increased chiral induction occurred in the instances the chiral pockets were more concentrated.

With the exception of polymer **6**, all the polymers had swelling capabilities that were in line with Merrifield type resins. In fact, the backbones for **1** and **3** were derived from 2% DVB crosslinked Merrifield resin. The swelling for polymers **1** and **3-5** varied between 6.1-10.3 mL/g, with unmodified Merrifield resin being 6.6 mL/g. The more highly crosslinked polymer **6** had a much lower swelling capability of 1.3 mL/g. The loadings of the NaBH₄ derivatized polymers were consistent with the swelling factors in that loadings of 6.8 to 9.4 meq of hydride per gram of polymer were obtained with polymers **1** and **3-5**. Loadings of this level have been shown to be synthetically useful. However, the loading for polymer **6** was 1.3 meq of hydride per gram of polymer, which mirrored its swelling capability. While the polymers with higher swellings did result in higher loadings, factors other than site accessibility were important to improve the degree of chiral induction of the reduction products.

A comparison of **1** and **3** indicate their loadings and solvent accessibility are very similar. The major difference is that **3** utilized a chiral side group that contained 12 stereogenic centers that underwent multiple substitution reactions as it was being prepared. Furthermore, the stereogenic centers were concentrated due to the multiple reactions of **2** with the linking sites on the polymer during the preparation of **3**. In the case of **1**, the chiral group only had 4 stereogenic centers and multiple reactions with the polymer were not possible. The net result was that **3** had a more effective asymmetric microenvironment that was the result of the higher concentration of stereogenic centers within the polar pocket in the bead. This finding was further highlighted when the data from the polyurethanes were compared to those of the polystyrenes. In the case of **4**, when a longer more polar link was used to prepare the chiral polymer, the 26 % enantiomeric excess of the major product was the lowest of the ones utilizing **2** as the chiral group. There were two possibilities for this decreased degree of asymmetric induction in the products: the polypropylene glycol (PPG) was serving as a phase transfer catalyst, or the chiral groups were not concentrated due to the size of the PPG links. Because polypropylene glycols have not been shown to be as effective polyethylene

glycols as phase transfer catalysts, this possibility was assumed to have a minimal effect on the process. The higher loading of **5** relative to **4** supported this position. Had there been a significant phase transfer effect, the loading data would have shown a higher loading for **4**. The greater distance between asymmetric regions was the more likely explanation for the lower enantiomeric excesses obtained using reagents derived from this polymer. This explanation was further supported by the data obtained from polymers **5** and **6**. Polymers **5** and **6** were prepared from diisocyanates containing nonpolar linking chains that were only six carbons in length to form the polyurethanes. The data for **5** showed a small but significant increase in the percentage of the major enantiomer in the product mixture when compared to **4**. Considering that the loading of this polymer increased slightly and the swelling decreased significantly, the more probable explanation for the increased asymmetric induction was a more concentrated chiral microenvironment. It was interesting to note that in spite of the lower loading for **6**, it was the most effective of the polyurethanes as a chiral matrix for the reduction reactions. This further supported the idea regarding a microenvironmental effect because the degree of crosslinking was increased in **6**, which seems to have further concentrated the asymmetric regions of the polymer matrix. Overall, the enantiomeric excess of the major product obtained from the reduction increased for the reducing agents derived from **5** and **6** because the shorter six carbon chains concentrated the asymmetric pockets in the polymers.

Prior to this report, it had been shown that solvents, porosity, polarity of the groups or polymer, and proximity of synergistic groups play an important part in the nature of the polymeric reagents microenvironment. The results of this study extend these parameters to include the concentration of the groups that are attached to the polymer. By increasing the concentration of the asymmetric appendages within the polymer matrix, the microenvironment in the vicinity of the polymeric reagent played a significant role in the stereochemistry of the alcohols formed during the reduction reaction. While this sort of concentration have been shown to lead to improved reaction rates or better group/polymer compatibility, we have found that the formation of a concentrated asymmetric microenvironment leads to increased stereochemical control of the products.

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