

USING MICROENVIRONMENTAL EFFECTS: LOADING, ACTIVITY, AND STEREOSELECTIVITY RELATIVE TO POLYMER BOUND NABH₄ REAGENTS

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ABSTRACT

The microenvironment of a polymer support plays an active role during the course of a reaction. This study investigated how reduction reactions of a prochiral ketone were affected by concentrating stereogenic centers within a polymer matrix. A 1% divinylbenzene crosslinked polystyrene polymer functionalized with isocyanato groups as the linkers was used as the original polymer support. A variety of chiral polyols were synthesized from δ -gluconolactone and attached to the polymer support by means of a carbamate bond. The chiral reducing agents were then prepared by allowing the alcohol groups to react with a solution of 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 6.8 % enantiomeric excess to 34.2 % enantiomeric excess. The rate constants also experienced an effective two-fold increase in magnitude when the polyol with the largest number of stereocenters was used. However, it was interesting to note that the effective loading of the polymers remained effectively constant at 4.0-5.0 meq of hydride per gram of polymer for all the polymers that used polyols as the linking points. Overall, the results of this study suggest that polar, asymmetric pockets were formed within the polymer matrix when polar functional groups containing chiral appendages were concentrated within a non-polar polymer. While this change in microenvironment had a positive effect on the activity and chiral induction of the reaction, it also appeared to increase the interaction between the linking sites on the polymer and the polyol sites of the chiral groups as the polymers were being prepared.

INTRODUCTION

Within the past decade it has been established that the microenvironment surrounding the functional group in a crosslinked polymer could affect that group's reactivity, selectivity, or even the loading of the polymer. The microenvironment includes the nature and the concentrations 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. (Choi, et al., 2004; Alexandratos and Miller, 1996; Pillai and Mathew, 1993) Specifically, 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 on optimizing the kinetics or product yields for specific reactions. (Alexandrotos and Miller, 2000) For instance, it has been demonstrated that the chemical environment of the polymer matrix can be modified to be more compatible with the reactions dealing with peptide

synthesis. (Krishnakumar and Mathew, 2002) The techniques reported during these studies involved using either polar or nonpolar polymers to increase compatibility of the growing chains with the solvents or other reagents. More recently, studies related to loading levels and microenvironmental effects have been reported. In particular, the flexibility of the polymer matrix in conjunction with the level of reactive site loading affects the efficiency of the catalyst or reagent. (Zhao, et al., 2004)

Additionally, it has been shown that it is possible to use microenvironmental effects to introduce more stereochemical control as well. Examples of reduction and alkylation reactions that yield high degrees of chiral induction using polymers or dendrimers as supports have been reported in that literature. (Blanton, J., 2005; Van Heerbeek, et al., 2002; Sato, et al., 2002; Hutchison, et al., 2004; Sashiwa and Shigemasa, 2002; Schmitzer, et al., 2001) In all instances, the higher degrees of chiral induction appear to be related to the microenvironment surround the reactive groups on the polymers or dendrimers. The data relative to dendrimers reported by Schmitzer illustrated that a critical concentration of chiral groups was required before significant chiral induction occurred during the reduction of prochiral, aryl ketones. It was interesting to note that high functional group concentrations were required for substantial chiral inductions when dendrimers were used as the reagent support; but a lesser concentration of the groups were necessary when crosslinked polymers were used as supports. This may be a function of dendrimer having all its active sites external to the dendrimer matrix versus the reactive sites on the crosslinked polymers being internal where swelling and concentrations may be more sensitive. However, this critical concentration of chiral groups was in itself an example of how the microenvironment of the dendrimer affects the reaction. While the systems using crosslinked polymers reported by both Blanton and Hutchinson didn't provide chiral inductions to the magnitude of the dendrimer supported studies, they did illustrate that altering the nature of the support did have a microenvironmental effect on the ensuing reactions. It should also be noted that in the latter studies the number of chiral groups were considerably less than the number of groups on the dendrimers used by Schmitzer.

In this report, we further extend this idea that the microenvironment of a polymer may be manipulated to prepare reagents capable of reducing prochiral ketones to secondary alcohols with moderate to high stereoselectivities with higher overall activities. This goal was realized by preparing polymers with pockets of polar, asymmetric environments within a relatively nonpolar polymer matrix. The polymers were prepared utilizing 2% divinylbenzene crosslinked polystyrene that contained isocyanato groups (1 meq of N per gram of polymer) as the polymer support. In all cases, the asymmetric region of the polymer was prepared by using norephedrine or derivatives using δ -gluconolactone as a starting material. Because each of these chiral groups contain either active amino or hydroxy groups, it was relatively easy to prepare the derivatized polymers.

METHODS AND MATERIALS

All starting materials and solvents were obtained from the Aldrich Chemical Company and used without further purification. The isocyanated polystyrene, 2% divinylbenzene crosslinked polystyrene containing (2.0 meq of N/g of polymer), was also obtained from the Aldrich Chemical Company under the StratospheresTM, trade name. 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 :m film). All NMR spectra were obtained using an Anasazi Eft, 60 MHz spectrometer.

Preparation of Polystyrene-bound (1S,2R)-norephedrine, 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 was added 30 mL of dry DMF and 1.0 g of isocyanated polystyrene (2.0 meq of N/g of polymer), and the polymer was allowed to swell. The round-bottom flask was then heated to 75-77EC and allowed to equilibrate at this temperature. In a separate flask that was equipped with a septum and purged with nitrogen, 0.4 g (0.0026mols) of (1S,2R)-(+)-norephedrine was dissolved in a mixture of 10 mL of dry DMF with gentle heating. The resulting solution was transferred via cannula to the reaction vessel. The mixture was allowed to stir for 48 h at 75-77EC. 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 1.20 g of an off-white colored solid (70% of theoretical weight). FT-IR analysis: the isocyanato signal at 2200-2300 cm^{-1} disappeared and new signals appeared at 1680, 1660 cm^{-1} and the OH stretches at 3500 cm^{-1} increased.

Preparation of (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxy--((1S,2R)-1-hydroxy-1-phenylpropan-2-yl)hexanamide, 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 60-62EC and allowed to equilibrate at this temperature. In a separate flask that was equipped with a septum and purged with nitrogen, 1.18 g (6.62 mmols) of δ -gluconolactone was dissolved in a mixture of 20 mL of dry methanol and dry DMF (ca. 1 mL) was added via syringe until the solid dissolved with gentle heating. In a second flask that was equipped with a septum and purged with nitrogen, 1.00 g (6.60 mmols) of (1S,2R)-(+)-norephedrine was dissolved in 20 mL of dry methanol with gentle heating. The contents of both flasks were transferred to the reaction pot via cannula. The reaction was allowed to proceed with stirring for 24 h at 60-62EC. A small sample of the solution was taken and precipitated using diethyl ether to yield a white solid. The solid was recrystallized from isopropyl alcohol and subjected to FT-IR analysis. The lactone signal at 1730 cm^{-1} had disappeared and new signal at 1645 cm^{-1} which corresponds to an amide bond had appeared. The methanol was removed to yield a tacky solid. This solid was washed further with diethyl ether to yield a white powder that was recrystallized from isopropyl alcohol. FT-IR: 3500, 1645, 1200-1000 cm^{-1} . ^{13}C NMR (D_2O): 172, 140, 131, 129, 126, 77, 73, 72, 71, 65, 62, 52, 50, 12 ppm. ^1H NMR (D_2O): 7.4 (5H), 5.0 (1H), 4.1 (3H), 3.6 (5H), 1.1 (3H) ppm.

Preparation of Polystyrene-bound (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxy--((1S,2R)-1-hydroxy-1-phenylpropan-2-yl)hexanamide, 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 was added 20 mL of dry DMF and 1.0 g of isocyanated polystyrene (2.0 meq of N/g of polymer), and the polymer was allowed to swell. The round-bottom flask was then heated to 75-77EC and allowed to equilibrate at this temperature. In a separate vessel, 0.67 g (2.0 mmol) of **2** was added to ca. 15 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. The mixture was allowed to stir for 48 h at 75-77EC. 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 an off-white colored solid. FT-IR analysis: 3500-3300, 1300-1000 cm^{-1} ; the signal at 2200-2300 cm^{-1} for the isocyanato group had disappeared.

Preparation of (2R,3S,4R,5R)-N-[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)ethyl]-2,3,4,5,6-pentahydroxyhexanamide, 4. 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 60-62EC and allowed to equilibrate at this temperature. To the round-bottom was added 20 mL of dry methanol and 1.00 g (16.6 mmols) of 1,2-diaminoethane. In a separate flask that was equipped with a septum and purged with nitrogen, 6.0 g (34 mmols) of δ -gluconolactone was dissolved in a mixture of 30 mL of dry methanol and 10 mL of dry DMF with gentle heating. In the event any solid remained, additional DMF was added drop-wise until a homogeneous solution formed. The resulting solution was transferred via cannula to the reaction vessel. After 5 min a white solid began to form as the mixtures was stirred. The reaction was allowed to proceed for 24 h with stirring at 59-61EC. 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, 73, 72, 71, 70, 62, 38 ppm. ^1H NMR (D_2O): 8.2 (1H), 4.3, 4.2, 4.0, 3.7, 3.4 (the signals were too close for individual integration) ppm.

Preparation of Polystyrene-bound (2R,3S,4R,5R)-N-[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)ethyl]-2,3,4,5,6-pentahydroxyhexanamide, 5. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. To the round-bottom was added 20 mL of dry DMF and 1.0 g of isocyanated polystyrene (2.0 meq of N/g of polymer), and the polymer was allowed to swell. The round-bottom flask was then heated to 75-77EC and allowed to equilibrate at this temperature. In a separate vessel, 0.83 g (2.0 mmol) of **4** was added to *ca.* 15 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. The mixture was allowed to stir for 48 h at 75-77EC. 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 1.1 g of an off-white colored solid. FT-IR analysis: 3500-3300, 1300-1000 cm^{-1} ; the signal at 2200-2300 cm^{-1} for the isocyanato group had disappeared.

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, 6. 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 60-62EC and allowed to equilibrate at this temperature. To the round-bottom was 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 (0.062 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 59-61EC. 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, 7. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. To the round-bottom was added 20 mL of dry DMF and 1.0 g of isocyanated polystyrene (2.0 meq of N/g of polymer), and the polymer was allowed to swell. The round-bottom flask was then heated to 61-63EC and allowed to equilibrate at this temperature. In a separate vessel, 0.70 g (1.0 mmol) of **6** was added to *ca.* 15 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. The mixture was allowed to stir for 72 h at 61-63EC. 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 1.2 g of an off-white colored solid. FT-IR analysis: 3500-3300, 1300-1000 cm^{-1} ; the signal at 2200-2300 cm^{-1} for the isocyanato group had disappeared.

Polymer-bound 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 68-70EC. 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.

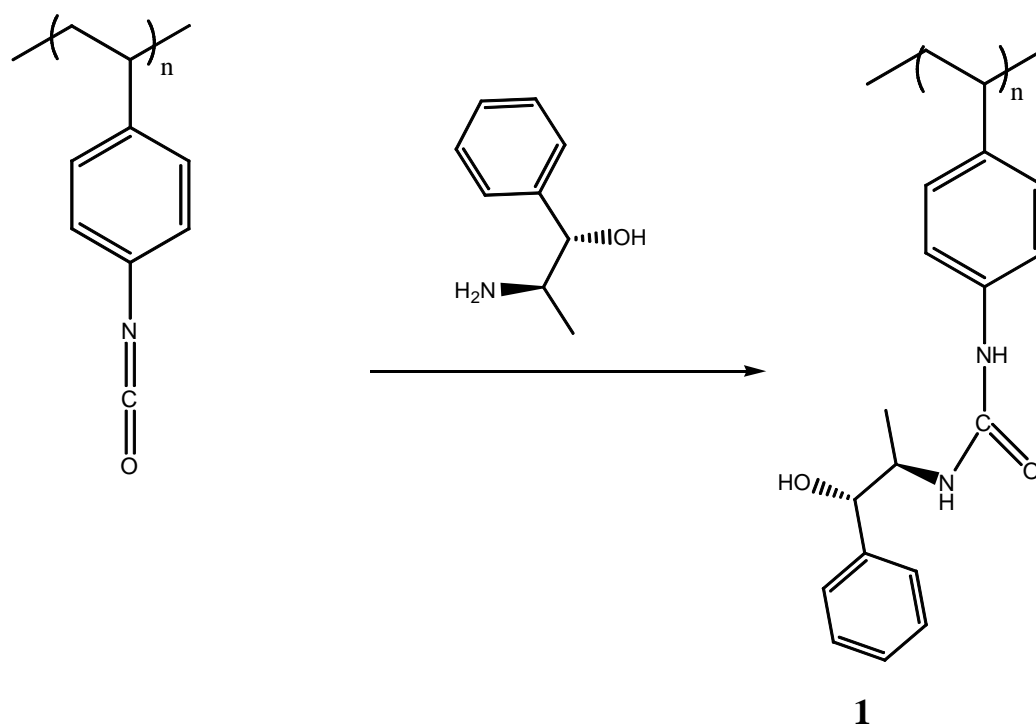
Ketone Reduction, General Procedure. A dry 250 mL round-bottom flask equipped with reflux condenser, magnetic stirrer bar, and septa was purged with nitrogen. The NaBH_4 derivatized polymer was swollen in 20 mL of dry toluene for 30 min at 22-24EC. The theoretical maximum meq of hydride per g of polymer was estimated and a five-fold molar excess of acetophenone and 0.10 mL of dodecane was dissolved in 5 mL of toluene 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.

RESULTS

Based on the results of our previous study, a polymer with relatively nonpolar characteristics was used as the support matrice in this study. (Blanton, 2005) In this case a more polar isocyanate linking site was employed within a relatively non-polar polystyrene matrix. It was perceived this linking site 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 of its favorable swelling capabilities with crosslinked polystyrene; and, 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 isocyanated polystyrene to react with (1*S*,2*R*)-norephedrine as illustrated in Figure 1. While this polymer did



The polymer depicted in this scheme has not been fully characterized. The structure is an idealized representation to aid in visualizing the process.

Figure 1.

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 2.6 meq of hydride per gram of polymer was obtained. The potential loading for this polymer was 3.0 meq of hydride per gram of polymer. Subsequent derivatization of **1** with sodium borohydride yielded a low 10% enantiomeric excess when this chiral reducing agent was allowed to react with acetophenone. The rate constant, normalized with respect to the loading of hydride, indicated this reagent was reasonably active for synthetic

applications as well. These findings were consistent with previous findings in our group and further support the idea that the microenvironment around the reactive sites does have an effect on reaction rates, as well as, the degree of asymmetric induction. However, this particular polymer 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 altering the microenvironment of the polymer in a controlled fashion, a series of chiral amides with an increasing number of the chiral hydroxyl sites was prepared. As shown in Figure 2, δ -gluconolactone was allowed to react with (1S,2R)-norephedrine to form

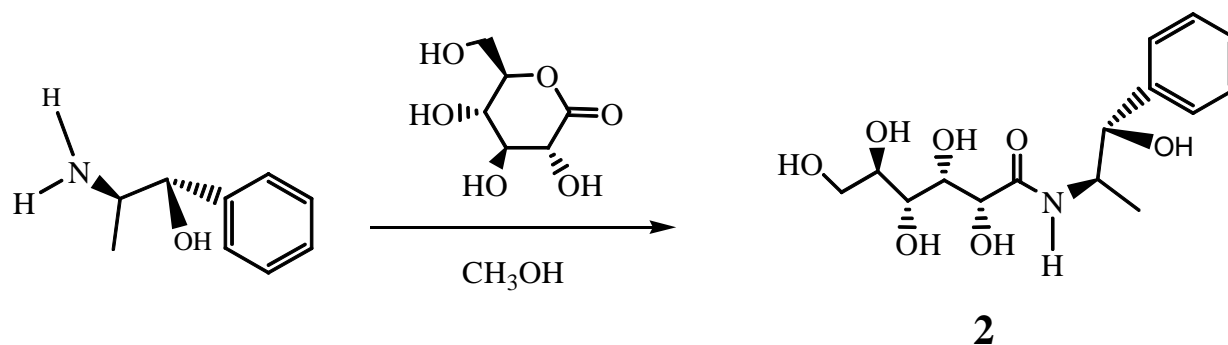
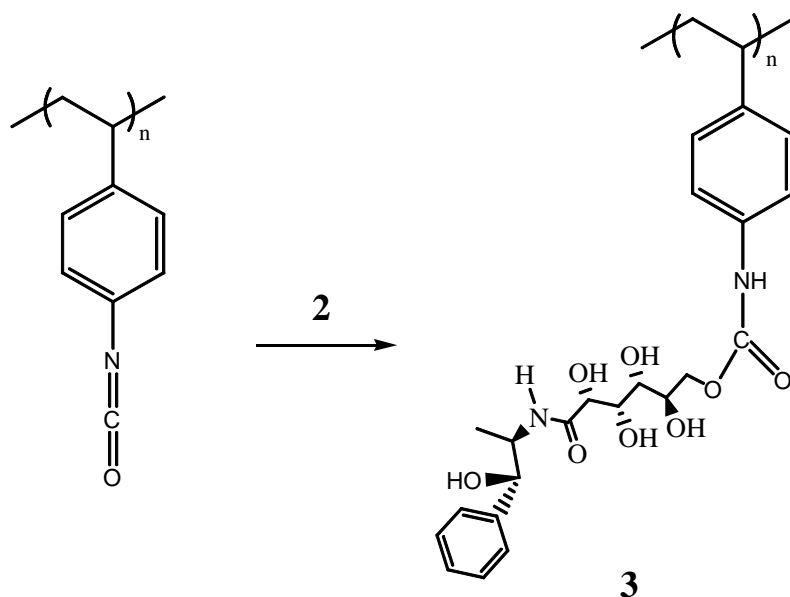


Figure 2

(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxy--((1S,2R)-1-hydroxy-1-phenylpropan-2-yl)hexanamide, **2**. A polymer containing **2** as a reactive site was prepared by allowing **2** to react with 2% divinylbenzene crosslinked isocyanated polystyrene as depicted in Figure 3 to form **3**. The FT-IR



The polymer depicted in this scheme has not been fully characterized. The structure is an idealized representation to aid in visualizing the process.

Figure 3

data confirmed the presence of carbamate links with a corresponding lack of signals for the isocyanate group.

As a means of increasing the number of chiral hydroxy units, the strategy was to use starting materials that contained multiple primary amino groups. As illustrated in Figure 4, 1,2-

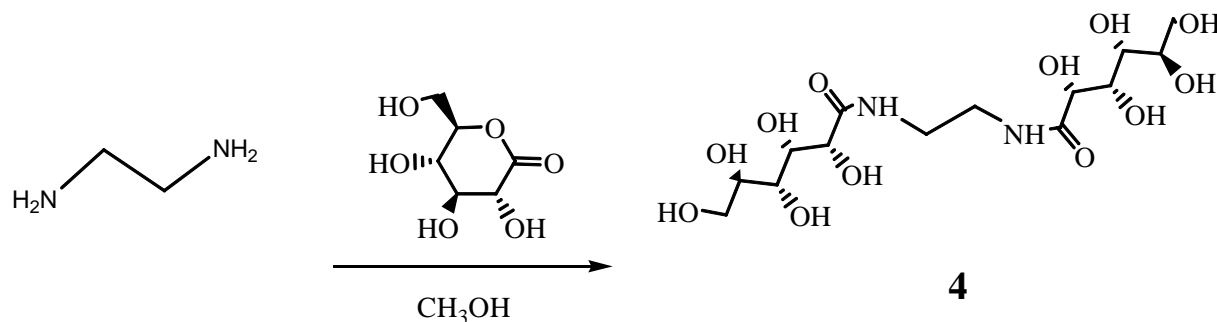
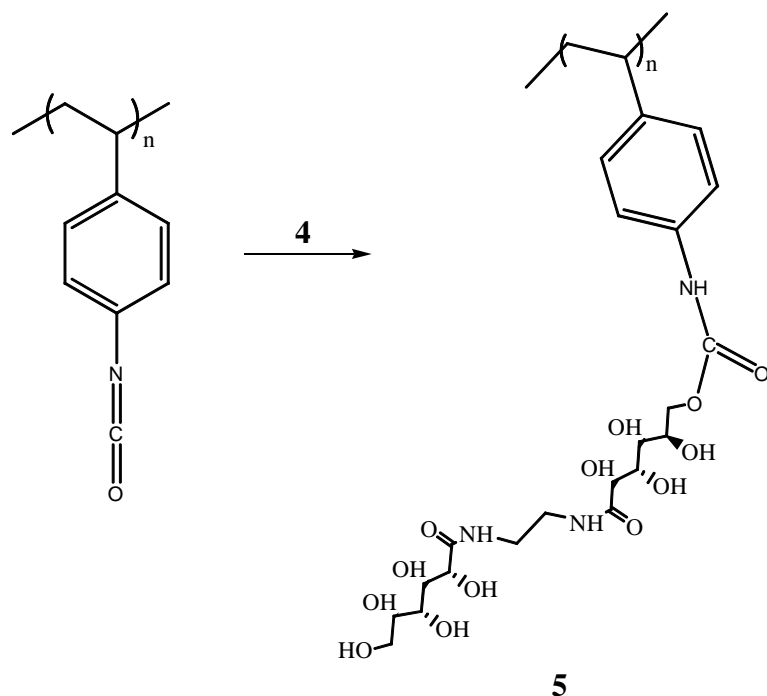


Figure 4

diaminoethane was allowed to react with 2 equivalents of δ -gluconolactone to form (2R,3S,4R,5R)-N-[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)ethyl]-

2,3,4,5,6-pentahydroxyhexanamide, **4**. This product was also allowed to react with 2% divinylbenzene crosslinked isocyanated polystyrene to form **5**, as illustrated in Figure 5. While



The polymer depicted in this scheme has not been fully characterized. The structure is an idealized representation to aid in visualizing the process.

Figure 5

the isocyanate signals in the FT-IR had disappeared and signals for the carbamate were present, the polymer did not increase in weight to an appreciable degree. This observations was similar to that reported in the previous study and lends credibility that multiple reactions per chain was taking place. (Blanton, 2005).

To further increase the number of stereogenic centers, a triamide, (2R,3S,4R,5R)-N-{bis[2-((2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoylamino)ethyl]amino}ethyl)-2,3,4,5,6-pentahydroxyhexanamide, **6**, was prepared as depicted in Figure 6, and used to prepare the polymer as illustrated in Figure 7. The progress of the reaction was followed by FT-IR and the formation of carbamate signals was accompanied by the loss of the isocyanate signal.

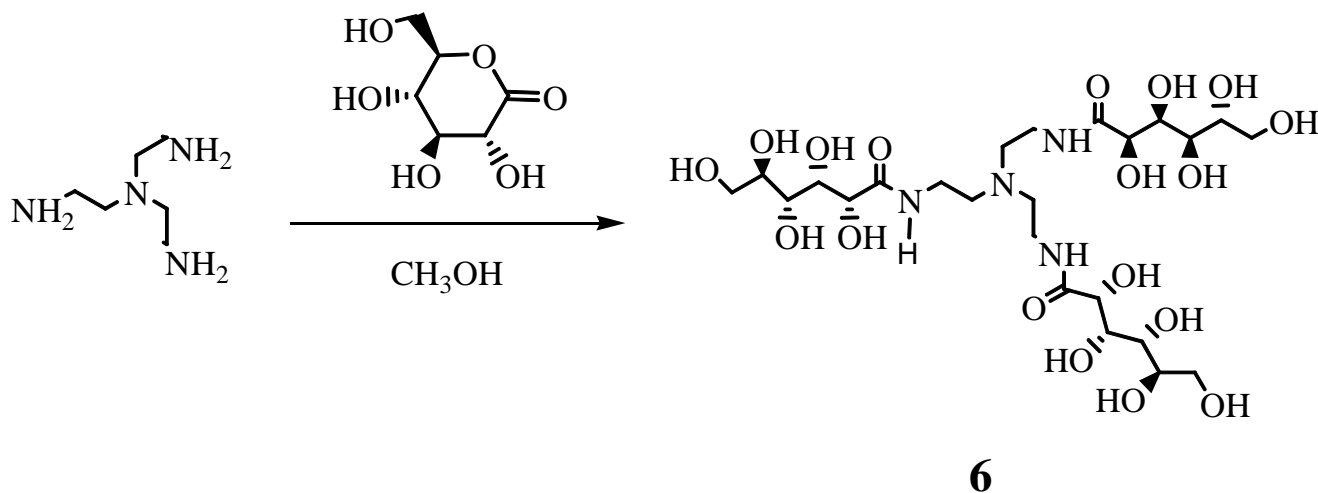
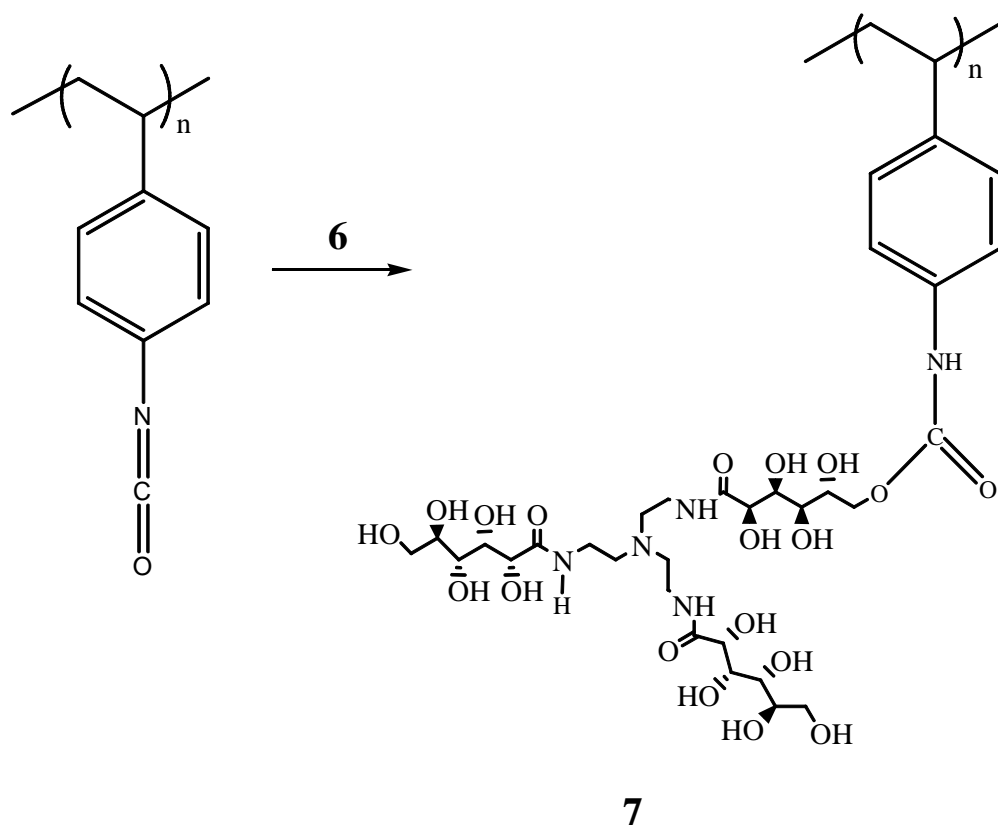


Figure 6

Once polymers **1**, **3**, **5**, **7** were prepared, they were further derivatized by allowing them to react with sodium borohydride dissolved in diglyme to yield the chiral reducing agents. The reagents were evaluated by the reduction of acetophenone, as illustrated in Figure 8. A five-fold excess of acetophenone with a known amount of dodecane as an internal standard was added to the polymers and the progress of the reduction followed by gas chromatographic analysis using a cyclodextrin column. The reductions were conducted using four different samples of each polymer with rates, chiral induction, and loadings determined from the gc data. The uncertainties for each category were the standard deviations calculated for the four reactions, see Table 1. As illustrated in Table 1, an interesting trend was apparent. The loadings of the polymers were effectively constant in spite of the increased number of chiral hydroxy groups. However, while the loadings for essentially flat, the asymmetric inductions and activities observed for the reduction reactions increased as the chains with larger numbers of hydroxy groups were attached to the polymers.



The polymer depicted in this scheme has not been fully characterized. The structure is an idealized representation to aid in visualizing the process.

Figure 7

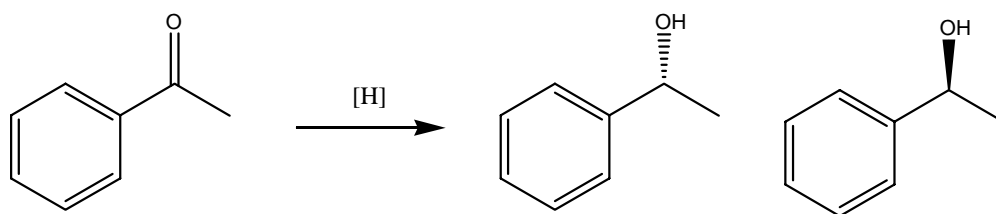


Figure 8

Table 1. Reduction Results^a

Polymer	Loading^b (meq H⁺/g)	Rate (10⁴k/meq H⁺)s⁻¹	Swelling (mL/g)	% Enantiomeric Excess
1	2.6 ∓ 0.3 (3)	8.0 ∓ 0.8	6.6	10.4 ∓ 1.4 (R)
3	4.8 ∓ 0.3 (15)	7.3 ∓ 0.7	6.6	6.8 ∓ 1.1 (S)
5	4.3 ∓ 0.5 (27)	9.7 ∓ 0.2	6.5	22.0 ∓ 1.5 (S)
7	4.1 ∓ 0.3 (42)	14.7 ∓ 1.8	6.5	34.2 ∓ 3.0 (S)

a. All uncertainties listed are the standard deviations for each set of experiments.

b. The numbers in the parentheses represent the potential loadings of hydride per gram of polymer.

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, the concentration of these groups increased activity of the reagent, and the microenvironment affected the loadings of the polymers.

When the loadings of active hydride per gram of polymer were considered, an interesting trend was noted. As illustrated in Table 1, the loadings of polymers **3**, **5**, and **7** were effectively the same. However, the potential loadings were significantly different. For instance, polymer **3** had a potential loading of 15 meq of hydride per gram of polymer; polymer **5** had a potential loading of 27 meq of hydride per gram of polymer; and polymer **7** had a potential loading of 42 meq of hydride per gram of polymer. Because the actual loadings were consistently between 4.1 and 4.8 meq of hydride per gram of polymer, this further suggests that the polymers linking sites are not sufficiently isolated as to preclude multiple linking reactions with the same polyalcohol. Since the loadings were so constant, the reaction of the alcohol groups with the isocyanate groups on the polymer must have been faster than the diffusion of the polyalcohols into the crosslinked polymer matrix. The most probable cause of this phenomenon must be the relatively nonpolar nature of the polystyrene being somewhat incompatible with the very polar polyalcohols that were used as reactants. Unlike the S_N2 reactions utilized in the previous study, the addition reactions in this study were more active; and, as the chiral chains were attached to the polymer, the proximity

of the additional hydroxy groups to the isocyanate groups on the polymer resulted in multiple reactions per chiral chain. (Blanton, 2005) Because of the similar chemical properties of the isocyanate groups and the resulting urethane groups, the microenvironment of the reactive region of the polymer may have become more conducive for the addition reaction. As the reaction proceeds, the overall activity increases. This phenomenon has been reported for the production of polypeptides and it is reasonable to conclude that it happened in this instance. Furthermore, this increased number of reactions between the linking sites on the polymer and the alcohol groups on the polyalcohols resulted in fewer alcohol units being available as linking sites to react with the sodium borohydride in the next step of the process.

While there was a definite decrease in the number of available sites for the reducing agent, the net result was a very polar region within the nonpolar polymer matrix that contained a high concentration of stereogenic centers. This concentration increased as the larger polyalcohols were used. Such a microenvironment should be conducive to chiral inductions such as those observed during the reduction reactions involving acetophenone. With respect to this reaction, we found the degree of chiral induction observed during this study was lower than what was reported previously. It was found previously that parameters such as loading and swelling of the polymer affect the concentration of the chiral groups. In this study, the same batch of polymer matrix was used which should ensure a consistent bead size and group distribution throughout the bead. The only thing that is appreciably different is the number of stereogenic sites within the reactive sites of the polymer. As suggested by Rico-Lattes, there is a critical concentration of chiral sites that is necessary to effectively impart chiral induction in these reduction reactions. This critical concentration appeared to have begun to occur when polymer 7 was used as the support for the borohydride. Using this polymer as the support for the reduction reaction, it was found that a moderate 34% enantiomeric excess of alcohol was obtained. With polymers 1, 3, and 5, while the loadings were similar to that of polymer 7, the concentrations of the stereogenic centers and the reducing agents within the polymer were lower due to the smaller chiral molecules that were attached to the polymers. This observation was also noted in our previous study. Even though the loadings of hydride were higher, the chiral induction was considerably lower when the smaller chiral molecules were supported on the polymers. Because there were a greater number of reduction sites within similar polymer matrices, there appeared to be a reasonable correlation between concentration of the groups and the chiral induction of the product. It was interesting to note it was when the three branched amido compound, **6**, was attached to the polymer matrix during this study and the study conducted previously, that a significant increase in chiral induction occurred. This is in contrast to the dendrimers reported by Rico-Lattes which required 32 to 64 chiral amido chains containing a significant number of hydroxyl groups to effect a critical concentration. This could be a significant finding relative to using microenvironments within a polymer to concentrate the groups.

In addition to the increased degree of stereochemical induction, the activities increased as the number of branches per amide increased. While this increase in activity, as illustrated in Table 1, is not as dramatic as those reported in other studies, it is significant with respect each additional amide branch. For instance, as illustrated by Table 1, there was effectively no difference in activity between polymers **1** and **3**. However, a slight increase in activity resulted when polymer **5** was used as the support for the reducing agent. This amide possessed a second branch that

contained five additional hydroxyl groups. With this increase in polarity near the reaction site, the microenvironment began to assist in the reaction. The increase in activity became more significant when polymer **7** was used. Polymer **7** was functionalized by the triamide, **6**, which possessed a total of 15 hydroxyl groups. This precursor allowed for the formation of even more highly polar pockets within the polymer matrix. As has been shown with other systems, a change in polarity of microenvironments within a polymer can lead to increased activity for the reaction if that microenvironment is more compatible with the reaction than the original polymer matrix. In this instance, the reduction is a polar reaction and the microenvironment containing the chiral groups is considerably more polar than that of the polystyrene matrix. In fact, the polar precursors, **2**, **4**, and **6** are very soluble in water. Because of the multiple chain to polymer reactions that were discussed as a result of the rather constant loading levels, the polarity of the microenvironment near the reducing sites increased as the larger polyamides were used. The higher concentrations of the polar groups within a nonpolar polymer matrix led to the increased activities for the borohydrides attached to the larger polyamides.

Overall, it has been established 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 degree of stereochemical induction, and the rate of reactions relative to how the polyalcohols would bind to the polymer matrix and the activity of the borohydrides during the reduction reactions

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LITERATURE CITED

- Alexandratos, SD; Miller, DH. 1996. Microenvironmental Effects in Polymer-Supported Reagents. 1. Influence of Copolymer Architecture on the Mitsunobu Reaction. *Macromolecules* 25: 8025-8029.
- Alexandratos, SD; Miller, DH. 2000. Microenvironmental Effects in Polymer-Supported Reagents. 2. The Prins Reaction and the Influence of the Neighboring Group Content on Catalytic Efficiency. *Macromolecules* 33: 2011-2015.
- Blanton, J.R., Salley, J.M. 1991. Reducing Alkyl Halides Using a Polymer-Bound Crown Ether/Tin Hydride Catalyst. *Journal of Organic Chemistry* 56: 490-491.
- Blanton, J.R. 2005. Using Microenvironmental Effects to Increase Loading and Stereoselectivity for Polymer Bound NaBH₄ Reagents. *Journal of the South Carolina Academy of Science* 2: 30-41.
- Choi, M.K.W.; He, H.S., Toy, P.H. 2003. *Journal of Organic Chemistry* 68: 9831-9834.
- Crosby, G.A., Kato, M. 1976. The Utilization of a Polymeric Phenylthiomethylithium Reagent for the Homologation of Alkyl Iodides and Its Application for the Study of Intramolecular Reactions of Polymer-Bound Functional Groups. *Journal of the American Chemical Society*

99: 278-280.

- Hutchison, PC; Heightman, TD; Procter, DJ. 2004. Application of a Recyclable Pseudoephedrine Resin in Asymmetric Alkylations on Solid Phase. *Journal of Organic Chemistry* 69: 790-801.
- Krishnakumar, I.M.; Mathew, B. 2002. A comparison of Rigid and Flexible Crosslinked Polymer-Supported Peptide Synthesis. *European Polymer Journal* 38: 1745-1752.
- Okhapkin, I.M; Bronstein, L.M.; Makhaeva, E.E.; Matveeva, V.G.; Sulman, E.M.; Sulman, M.G.; Khoklov, A.R. 2004. Thermosensitive Imidazole-Containing Polymers as Catalysts in Hydrolytic Decomposition of p-Nitrophenyl Acetate 37: 7879-7883.
- Pillai, VNR; Mathew B. 1993. Functionalised Polymers: Chemistry and Applications. *Indian Journal of Technology* 31: 302-316.
- Sashiwa, H.; Shigemasa, R.R. 2002. Chemical Modification of Chitosan 8: Preparation of Chitosan-Dendrimer Hybrids via Short Spacer. *Carbohydrate Polymers* 47: 191-199.
- Sato, I.S.; Kodaka, R.; Hosoi, K.; Soai, K. 2002. Highly Enantioselective Addition of Dialkylzincs to Aldseyhdes Using Dendritic Chiral Catalysts with Flexible Carbosilane Backbones. *Tetrahedron: Asymmetry* 13: 805-808.
- Schmitzer, A.R.; Franceshi, S.; Perez, E.; Rico-Lattes, I.; Lattes, A.; Thion, L. 2001. Reactivity at the Interface of Chiral Amphiphilic Dendrimers. High Asymmetric Reduction by NaBH₄ of Various Prochiral Ketones. *Journal of the American Chemical Society* 123: 5956-5961.
- van Heerbeek, R; Kamer, PCJ; van Leeuwen, PWNM; Reek, JNH. 2002. Dendrimers as Support for recoverable Catalysts and Reagents. *Chemical Reviews* 102: 3717-3756.
- Yan, B.; Sun, Q. 1998. Crucial Factors Regulating Site Interactions in Resin Supports Determined by Single Bead IR. *Journal of Organic Chemistry* 63: 55-58.
- Zhao, L-J.; He, H.S.; Shi, M.; Toy, P.H. 2004. Polystyrene-Supported Phosphine-Catalyzed aza-Baylis-Hillman Reactions and the Relationship between Resin Loading Level and Catalyst Efficiency. *Journal of Combinational Chemistry* 6: 680-683.