Polymer 49 (2008) 5233–5240

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Ring opening of epoxides catalysed by poly(amidoamine) dendrimer supported on crosslinked polystyrene

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ARTICLE INFO

Article history:
Received 11 July 2008
Received in revised form
15 September 2008
Accepted 16 September 2008
Available online 1 October 2008

Keywords:
Dendrimers
Polymer supported catalysts
2-Aminoalcohols

ABSTRACT

Three generations of polystyrene supported poly(amidoamine) dendrimer were synthesized and characterized. The supported dendrimers were found to be efficient organocatalysts in the nucleophilic ring opening of epoxides by anilines under mild conditions. Higher generation dendrimer showed increased catalytic activity. The polymer supported catalyst was reusable. The catalytic activity of supported dendrimer was compared with the unsupported one and found that the supported dendrimer was a much more active catalyst. The higher activity of the supported dendrimer is assumed to be due to the better hydrophobic/hydrophilic interaction existing between the polystyrene matrix and the polar dendritic chains.

1. Introduction

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound, which does not contain a metal atom [1]. This area in organic chemistry has achieved remarkable interest during the last decade. It is man's approach to mimic nature in enzyme catalysis. Organocatalysts can be considered as minimalistic versions of enzymes, from which they are conceptually derived and to which are often compared [2]. Even if, only in some cases, they display remarkable selectivity compared to enzymes, organocatalysts are generally more stable, less expensive and enjoy a wider range of applications under a variety of conditions unsustainable by enzymes. Another important feature of organocatalysts is that the same catalyst may be able to catalyze various reactions, which follow entirely different mechanisms and selectivity [3,4]. The disadvantage is that the separation of organic catalysts from the reaction mixture is sometimes tedious. Attaching the catalyst to an insoluble support such as a crosslinked polymer can eliminate this difficulty. In general, organocatalysts are more amenable than both metal based and biocatalysts to anchor on a support [5]. There may be a loss of activity and selectivity when metal complexes and biocatalysts like enzymes are attached to polymer supports, but such an observation is rarely found in the case of organocatalysts.

Dendrimers as the fourth major class of macromolecular architecture have found extensive applications ranging from catalysis to drug delivery [6,7]. In view of the extraordinary structure control and nanoscale dimensions observed for dendrimers, it is not surprising to find extensive interest in their use as globular protein mimics. Based on their systematic, size-scaling properties and electrophoretic and hydrodynamic behavior, they are referred to as artificial proteins. A large number of research publications appear every year describing new catalysts with dendritic architecture and most of them give excellent results under homogeneous conditions [8]. Enzyme like catalytic behavior by suitably functionalized dendrimers in solution was already demonstrated [9]. Examples of dendrimer based organocatalysts attached to polymer supports are very few in the literature [10].

2-Aminoalcohols represent a broad range of β-adrenergic blockers widely used in the management of cardiovascular disorders [11–13] and disorders related to the sympathetic nervous system [14–17]. The common method of preparation of 2-aminoalcohols is the nucleophilic ring opening of epoxides by amines. The flexibility of this transformation is recognized well as it constitutes the key step for the synthesis of a number of biologically important molecules and natural products [18–27]. Catalysts play an important role in both stereo- and enantio-selective synthesis of 2-aminoalcohols [28–42]. Nearly all catalysts used in this synthesis include at least one metal center as an integral part of the catalytic system. There are very few examples of organocatalysts used for

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doi:10.1016/j.polymer.2008.09.038

the synthesis of 2-aminoalcohols. The classical example is the ring opening reaction of epoxides with various nucleophiles catalyzed by tributylphosphine in water [43]. Another example of organocatalysis is reported by Kleiner and Schreiner in which an electron deficient thiourea derivative was used as the catalyst, which gave both excellent yield and selectivity when the reaction was carried out in water [44]. Polymer supported organocatalysts were less explored in the synthesis of 2-aminoalcohols.

In this paper, we describe the application of polystyrene supported poly(amidoamine) (PAMAM) dendrimer as an organocatalyst in the synthesis of 2-aminoalcohols by ring opening of epoxides with amines. The reaction proceeded well under mild reaction conditions compared to many previously reported catalysts [41] and gave good yields. The catalyst was reused at least six times without considerable loss of activity.

2. Experimental

2.1. General methods

All solvents were purified according to standard procedures. Chloromethyl polystyrene (1% DVB crosslinked, 100–200 mesh, 1.1 mmol Cl atoms per gram) was obtained from Thermax India Ltd as a gift sample and was washed with methanol, 1,4-dioxane and acetone (20 mL × 2 times) and dried under vacuum. Methyl acrylate was purified according to literature procedure. FTIR measurements were done on a JASCO FTIR spectrometer as KBr pellets. Solid-state cross-polarized magic angle spinning (CP-MAS) ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument (NMR research centre, IISc. Bangalore) with a spinning rate of 7K. Solution NMR spectra were taken on Bruker 300 MHz or 400 MHz instrument with TMS as internal standard in $CDCl_3$. Gas chromatography/mass spectrometry (GC/MS) was taken on a Varian 1200 L single quadrapole GC/MS with capillary column. Matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI TOF MS) was done using a Schimadzu Kratos compact analytical MALDI TOF MS using an Nd–YAG laser with an operating wave length of 354 nm. The matrix used was α-cyano-4-hydroxy benzoic acid. Angiotensin II and insulin were used as internal standards. Thermogravimetric-TG–DTA analysis was done on Perkin Elmer Diamond model TG/DTA system using platinum as the standard. SEM micrograph was recorded with Jeol JSM 840 microscope.

2.2. General procedure for the solid phase synthesis of PAMAM dendrimers

Nitrated chloromethyl polystyrene and aminomethyl polystyrene were prepared according to literature procedures [45,46]. First-, second- and third-generation PAMAM dendrimers were synthesized on the aminomethyl polystyrene (1% DVB crosslinked, 100–200 mesh, 1 mmol NH_2 per gram), according to previously reported procedure with minor modifications [47–49].

The aminomethyl polystyrene resin (1 g, 1 mmol NH_2 groups) was added in portions at room temperature with stirring to a mixture of methyl acrylate (22 mL, 250 mmol) and methanol (20 mL) in a 100-mL round-bottom flask. The reaction mixture was stirred at room temperature under nitrogen for 5 days. After the reaction, excess reactants and solvent were removed under vacuum. The polymer was washed well with methanol, dichloromethane and acetone (3 × 20 mL). It was dried under vacuum for 24 h. In the second step, the resin obtained as above was subjected to transamination as follows. The resin was added in small fractions with stirring to a mixture of ethylenediamine (16 mL, 250 mmol) and methanol (20 mL) taken in a round-bottom flask and cooled to 0 °C in an ice–salt bath. The reaction mixture was stirred at 0 °C for 1 h, the temperature was allowed to rise to room temperature (30 °C), and the mixture was stirred at room temperature for 4 days to ensure complete reaction. It was filtered under vacuum, was washed well with methanol, acetone and diethyl ether (2 × 20 mL) and was dried under vacuum for 24 h. Repetition of the above steps gave second- and third-generation PAMAM dendrimers attached to the polymer beads.

After the completion of the synthesis, from a portion of the resin bound dendrimer G3 PAMAM dendrimer was cleaved from the support by photolysis as follows. The polystyrene resin (1 g) carrying the dendrimer was suspended in methanol (50 mL) in the reaction chamber of an immersion type photoreactor. The suspension was degassed for 1 h with dry nitrogen and irradiated with Philips HPK 125 W medium pressure mercury lamp at 340–350 nm for 24 h with constant stirring. A solution of $CuSO_4$ was circulated through the outer jacket of the photochemical reactor to filter off light waves below 320 nm. After photolysis the resin was filtered and washed with methanol (20 mL × 3 times). Combined filtrate and washings were evaporated under vacuum. The product obtained was characterized by MALDI TOF MS without further purification.

2.3. General procedure for the synthesis of 2-aminoalcohols

A 10 mL round-bottom flask was charged with epoxide (5 mmol) and amine (5.2 mmol) and polymer supported catalyst (385 mg). The amount of catalyst taken was such that each reaction mixture contains 0.10 mmol of the corresponding dendrimer (2 mol% with respect to the epoxide). Dry 1,4-dioxane (5 mL) was added and the reaction mixture was kept in an oil bath with the temperature preset at 50 °C with constant stirring. The progress of the reaction was monitored by TLC on silica gel plate using hexane and ethyl acetate (25:1) as eluent. After the completion of the reaction, the catalyst was filtered off and washed with ethyl acetate. The filtrate and washings were combined and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (25:1) as eluent. All the products were previously reported compounds [31,32] and were characterized using FTIR, ^1H NMR and GC/MS spectroscopies. The analytical data for representative compounds are given below.

2.3.1. trans-2-(Phenylamino)cyclohexanol

FTIR (KBr, ν_{max} (cm^{-1})) 3590, 3414, 2931, 2858, 1601, 1500, 1448, 1319, 1067; ^{1}HNMR ($CDCl_3$): δ 6.7–7.2 (m, phenyl, 5H), 3.33 (ddd, J = 4.2, 10.4 and 10.5, 1H), 3.13 (ddd, J 3.9, 10.0 and 10.1, 1H), 2.9 (m, 2H), 2.10–2.16 (m, cyclohexyl, 2H), 1.72–1.78 (m, cyclohexyl, 2H) and 1.03–1.42 (m, cyclohexyl, 4H).

2.3.2. trans-2-(2-Methylphenylamino)cyclohexanol

FTIR (KBr, ν_{max} (cm^{-1})) 3597, 3400, 2945, 2865, 1609, 1504, 1450, 1326, 1073; ^{1}H NMR ($CDCl_3$): δ 7.1 (m, 2H), 6.8 (d, J = 7.9 Hz, 1H), 6.7 (m, 1H), 3.4 (ddd, J = 10.5, 9.4, 4.8 Hz, 1H), 3.2 (ddd, J = 10.9, 9.4, 3.8 Hz, 1H), 2.2 (s, 3H), 2.15 (m, 2H), 1.8 (m, 2H), 1.4 (m, 3H), 1.1 (m, 1H).

2.3.3. trans-2-(4-Methoxyphenylamino)cyclohexanol

FTIR (KBr, ν_{max} (cm^{-1})) 3529, 3366, 3013, 2938, 2861, 1612, 1512, 1465, 1450, 1239, 1221, 1067; ^{1}HNMR ($CDCl_3$): δ 6.8 (d, J = 8 Hz, 2H), 6.7 (d, J = 8 Hz, 2H), 3.7 (s, 3H), 3.3 (ddd, J = 9.5, 9.3, 3.9 Hz, 1H), 3.0 (ddd, J = 10.9, 9.3, 3.8 Hz, 1H), 2.1 (m, 2H),1.72 (m, 2H), 1.3 (m, 3H), 1.0 (m, 1H).

2.3.4. trans-2-(4-Nitrophenylamino)cyclohexanol

FTIR (KBr, ν_{max} (cm^{-1})) 3500, 3420, 2987, 2873, 1601, 1592, 1523, 1349, 1073, 890; ^{1}HNMR ($CDCl_3$): δ 7.98 (d, J = 9.3 Hz, 2H) 6.65 (d,

$J = 9.3$ Hz, 2H), 4.84 (s, 2H, N*H* & O*H*), 3.43 (ddd, $J = 10.2$, 10.2, 4.5 Hz, 1H), 3.29 (m, 1H), 2.00 (m, 2H), 1.75 (m, 2H), 1.30(m, 4H).

2.3.5. 2-Phenylamino-2-phenylethanol

FTIR (KBr, ν_{max} (cm^{-1})) 3498, 3354, 2931, 2858, 1601, 1500, 1448, 1319, 1067; ^{1}HNMR ($CDCl_3$): δ 6.6–7.4 (m, 10H), 4.5 (dd, $J = 7.0$, 4.0 Hz, 1H), 3.95 (dd, $J = 11.0$, 4.0 Hz, 1H), 3.75 (dd, $J = 11.0$, 7.0 Hz, 1H).

2.3.6. 2-(2-Methylphenyl)amino-2-phenylethanol

FTIR (KBr, ν_{max} (cm^{-1})) 3500, 3394, 2990, 2888, 1613, 1511, 1446, 1321, 1087; ^{1}HNMR ($CDCl_3$): δ 7.24–7.41 (m, 5H), 7.06 (d, $J = 7.0$ Hz, 1H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.63 (t, $J = 7.4$ Hz, 1H), 6.38(d, $J = 8.1$ Hz, 1H), 4.53–4.57 (m, 1H), 3.96–4.01 (m, 1H), 3.77–3.83 (m, 1H), 2.27 (s, 3H).

2.3.7. 2-(4-Methoxyphenyl)amino-2-phenylethanol

FTIR (KBr, ν_{max} (cm^{-1})) 3533, 3354, 2931, 2858, 1601, 1500, 1448, 1319, 1067; ^{1}H NMR ($CDCl_3$): δ 7.45–6.52 (m, 9 H, ArH), 4.87 (dd, $J = 3.3$, 9.2 Hz, 1H), 3.73 (s, 3H, OCH_3) 3.49 (dd, $J = 14.0$, 3.2 Hz, 1H), 3.30 (dd, $J = 14.0$, 9.2 Hz, 1H).

2.3.8. 2-(4-Nitrophenylamino)-2-phenylethanol

FTIR (KBr, ν_{max} (cm^{-1})) 3500, 3354, 2931, 2858, 1601, 1500, 1448, 1319, 1067; ^{1}HNMR ($CDCl_3$): δ 7.95 (d, $J = 9.2$ Hz, 2H, aryl), 7.38–7.27 (m, 5H, aryl), 6.46 (d, $J = 9.2$ Hz, 2H, aryl), 4.57 (dd, $J = 4.1$, 6.2 Hz, 1H), 4.00 (dd, $J = 11.4$, 4.1 Hz, 1H), 3.81 (dd, $J = 11.4$, 6.2 Hz, 1H).

*2.3.9. 2-*N*-phenylamino-3-butanol*

FTIR (KBr, ν_{max} (cm^{-1})) 3517, 3398, 3053, 2974, 2926, 1922, 1602, 1505, 1439, 1376, 1318, 1254, 1005, 902, 751, 692; ^{1}H NMR ($CDCl_3$): δ 7.15–7.18 (m, 2H), 6.66–6.74 (m, 3H), 3.62 (m, 2H), 3.31 (m, 1H), 2.61 (brs, 1H), 1.25 (d, 3H, $J = 6.8$ Hz), 1.14 (d, 1H, $J = 6.8$ Hz).

2.3.10. 2-(2-Methylphenyl)amino-3-butanol

FTIR (KBr, ν_{max} (cm^{-1})) 3527, 3414, 2972, 2923, 1601, 1511, 1448, 1378, 1313, 1256, 1056, 748, 512; ^{1}HNMR ($CDCl_3$): δ 7.11 (d, 1H), 7.07 (d, 1H), 6.68–6.73 (m, 2H), 3.70 (t, 1H, $J = 6.2$ Hz), 3.40 (t, 1H, $J = 6.2$ Hz), 2.16 (s, 3H), 1.28 (d, 3H, $J = 6.2$ Hz), 1.18 (d, 3H, $J = 6.2$ Hz).

*2.3.11. 2-*N*-(4′-Methoxyphenyl)amino-3-butanol*

FTIR (KBr, ν_{max} (cm^{-1})) 3499, 3394, 2970, 1617, 1512, 1455, 1377, 1236, 1037, 822; ^{1}H NMR ($CDCl_3$): δ 6.83–6.86 (m, 2H), 6.71–6.75 (m, 2H), 3.81 (s, 3H), 3.63 (t, 1H, $J = 6.6$ Hz), 3.23 (t, 1H, $J = 6.9$ Hz), 1.32 (d, 3H, $J = 6.0$ Hz), 1.18 (d, 3H, $J = 6.4$ Hz).

*2.3.12. 2-*N*-(4′-bromophenyl)amino-3-butanol*

FTIR (KBr, ν_{max} (cm^{-1})) 3577, 3400, 2973, 1593, 1492, 1390, 1315, 1080, 1006, 813, 453; ^{1}H NMR ($CDCl_3$): δ 7.23 (m, 2H), 6.53 (m, 2H), 3.65 (t, 1H, $J = 6.2$ Hz), 3.53 (s, 1H), 3.27 (t, 1H, $J = 6.9$ Hz), 2.45 (s, 1H), 1.24 (d, 3H, $J = 6.2$ Hz), 1.14 (dd, 1H, $J = 6.2$ Hz).

2.4. General procedure for the recycling of polymer supported catalyst

After each run, the catalyst was filtered off and was extracted with ethyl acetate in a soxhlet apparatus. It was dried under vacuum for 24 h and reused as above.

2.5. General procedure for the ring opening catalyzed by unsupported dendrimer

A 10 mL round-bottom flask was charged with epoxide (5 mmol) and amine (5.2 mmol) and the dendrimer (0.1 mmol, 2 mol%). Dry 1,4-dioxane (5 mL) was added and the reaction mixture was kept in an oil bath with the temperature preset at 50 °C with constant stirring. The progress of the reaction was monitored by TLC on silica gel plate using hexane and ethyl acetate (25:1) as eluent. After the completion of the reaction the crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (25:1) as eluent. The catalyst was eluted from the column using methanol and reused after the removal of solvent.

3. Results and discussion

3.1. Synthesis and characterization of polymer supported PAMAM dendrimer

Chloromethyl polystyrene was converted to nitrated aminomethyl polystyrene according to previously reported procedures [45,46]. The general scheme of the synthesis is shown in Fig. 1. The number of amino groups on the resin was estimated to be 1 mmol/g of the polymer.

Solid phase synthesis of PAMAM dendrimers proceeded smoothly on aminomethyl polystyrene support. The reaction scheme is given in Fig. 2.

The reaction was monitored by FTIR spectroscopy and estimation of amino groups. FTIR spectra of the polymer after each synthetic step clearly showed the appearance and disappearance of the primary amino groups (at 3390 cm^{-1} and 3344 cm^{-1}), as well as the change in C=O stretching associated with the conversion of a methyl ester into an amide (from 1735 cm^{-1} to 1660 cm^{-1}). Solid-state CP-MAS ^{13}C NMR spectra of the dendronized beads (Fig. 3) showed the appearance of peaks at around 173, 54 and 40 ppm due to the dendrimer parts of the polymer. The prominent peak at 129 ppm arises from the aromatic carbons of the polystyrene support. The intensity of the peak is much higher because of the presence of large number benzene rings compared to the dendrimer moiety.

The structure of the third-generation dendrimer supported on the polystyrene matrix is shown in Fig. 4.

After the completion of the synthesis, a portion of the polystyrene supported PAMAM resin was subjected to photolysis so that the dendrimer was cleaved from the support. The third-generation dendrimer, cleaved from the polystyrene support was analyzed by MALDI TOF MS. The general mechanism of photolysis [50] is given in Fig. 5.

The MALDI spectrum (Fig. 6) of the third-generation dendrimer detached from the polymer support clearly showed a peak at 1615.43 D (M^+ ion), which confirms the formation of G3 PAMAM dendrimer on the polymer. This result showed that the dendrimer obtained was of high purity and without considerable structural defects. From the estimation of amino groups and CHN analysis it was found that the final polymer contained 0.260 mmol G3 PAMAM dendrimer per gram of the resin. That means there are 2.08 mmol primary amino groups, 1.82 mmol of tertiary amino groups and 3.64 mmol amide groups per gram of the resin.

The dendronized polymer showed high thermal stability as observed from thermogravimetric analysis (Fig. 7). The polymer showed first weight loss between 200 °C and 300 °C. This is due to

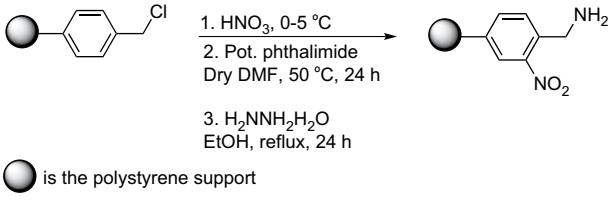

Fig. 1. Chemical modification of the chloromethyl polystyrene support.

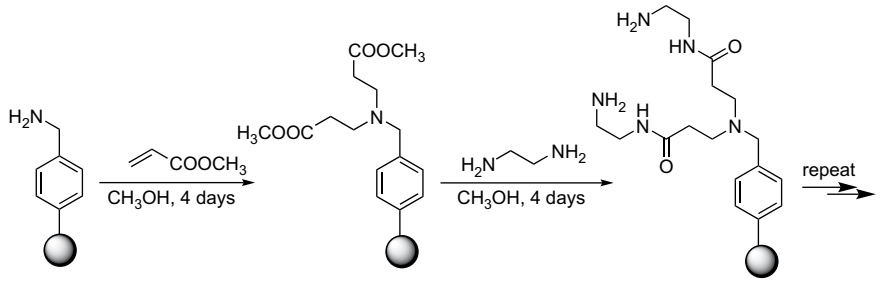

Fig. 2. General scheme of the synthesis of polystyrene supported PAMAM dendrimer.

the decomposition of the dendrimer on the polymer support. Second decomposition occurred between 350 °C and 450 °C. This may be due to the degradation of the polystyrene support and such degradation is observed in the case of aminomethyl polystyrene in the same range of temperature.

SEM images as shown in Fig. 8 revealed that the polystyrene beads retain their spherical shape even after the long synthetic process.

3.2. Organocatalysis by polymer supported PAMAM dendrimer

Various 2-aminoalcohols were synthesized from epoxides and amines using polymer supported PAMAM dendrimer as heterogeneous organic catalysts. The scheme of the reaction is shown in Fig. 9.

Initially cyclohexene oxide and aniline were allowed to react in THF in the presence of various amounts of third-generation PAMAM dendrimer supported on polystyrene. The results are presented in Table 1. It was observed that, only 2 mol% of the catalyst was required for obtaining good yield. The yield of the product was low when lower concentrations of the catalysts were used. An increase in the concentration of the catalyst had virtually no impact on the speed of the reaction and yield of the product. The improved performance of the catalyst under such a low concentration may be due to the dendritic structure, which provides high local concentration of the catalytic groups, which is not possible with ordinary homogeneous or polymer supported catalysts.

In the second step, the influence of solvent on the catalytic activity of the polymer supported dendrimer was studied. The model reaction between cyclohexene oxide and aniline was performed in various solvents under identical conditions and the results are shown in Table 2. The reaction proceeded best in 1,4-dioxane compared to other solvents. In water, the reaction proceeded as if in a triphasic system and this resulted in the reduction of the yield. When water was used along with an organic solvent miscible with water, the yield was increased compared to pure water alone. Solvents like ethanol, methanol etc. were not used because of a possible competition from these nucleophilic solvents with the reactant nucleophile, i.e. the amine. The reaction did not perform well in chloroform because in chloroform it is expected that the dendrimer did not dissolve well.

Temperature of the reaction has significant effect on catalysis in the case of ring opening reaction. The reaction went to completion slowly at room temperature and the yield was low. But increasing the temperature to 50 °C had a remarkable impact on the speed of the reaction and the yield of the product was increased. The model

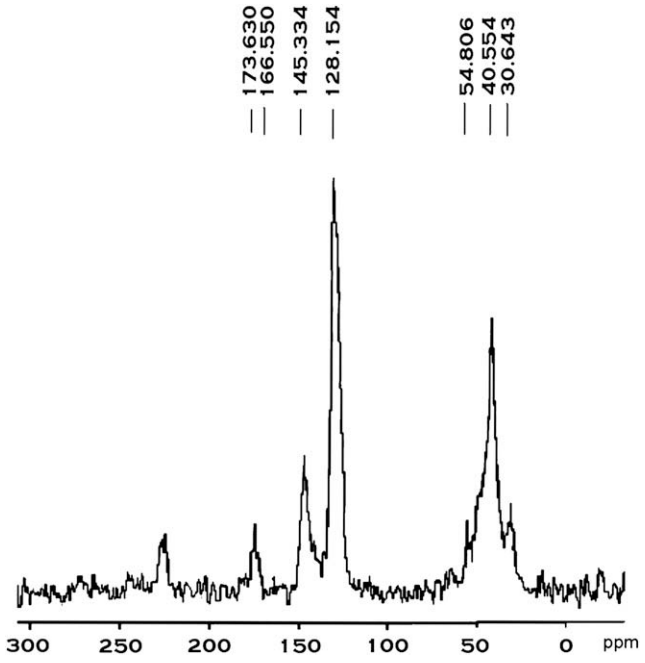

Fig. 3. Solid-state ^{13}C NMR spectra of the dendronized polymer bead.

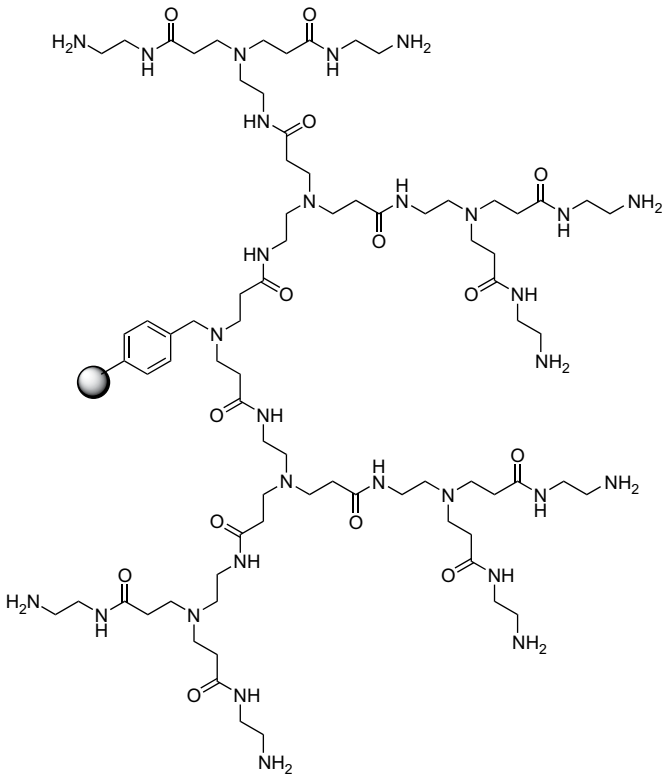

Fig. 4. Polystyrene supported G3 PAMAM dendrimer.

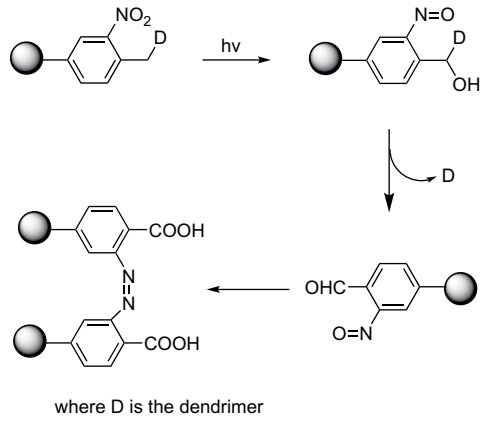

Fig. 5. General mechanism of photolytic removal of dendrimer from the support.

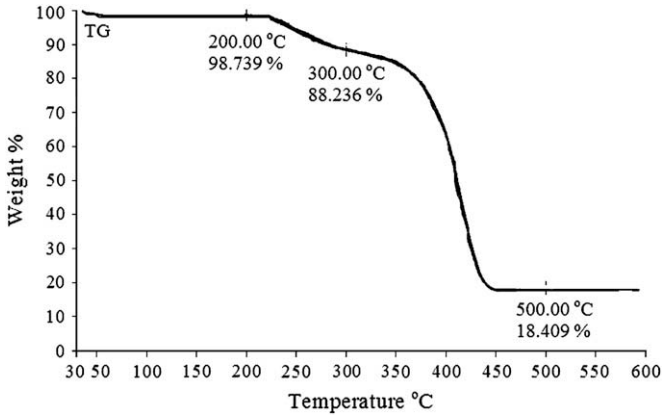

Fig. 7. Thermogravimetric curve of the dendronized polystyrene.

reaction between cyclohexene oxide and aniline went to completion within 12 h at 50 °C with 100% conversion to the product as observed from GC/MS. The yield obtained at room temperature was also good compared to many other catalysts previously reported [41]. Under refluxing condition, the reaction went to completion within 8 h but reaction at such high temperature was avoided considering the possible decomposition of dendritic backbone.

A number of 2-aminoalcohols were synthesized from various epoxides and amines for the generalization of the reaction. The results are summarized in Table 3.

The possible mechanism of the reaction involved activation of the epoxide by hydrogen bond formation with the catalyst followed by attack of the nucleophile. This can be represented as shown in Fig. 10. A similar mechanism was reported earlier for the ring opening reaction catalyzed by hydroxyl compounds by Hine et al. [51,52] and by thiourea derivative reported by Kleiner and Schreiner [44]. The *trans* configuration of the product was confirmed from the determination of the J_{H-H} coupling constants for CH–NH in the corresponding ^{1}H NMR spectrum. This configuration of the products also supports the presented mechanism.

The generation of the dendrimer has shown considerable effect on the catalytic activity. An investigation on the effect of generation of dendrimer on the catalytic activity (Table 4) showed that dendrimer of higher generations were found to be catalytically more active. When the model reaction between aniline and cyclohexene oxide was carried out in the presence of dendrimer of various generations it was observed that a gradual increase in the yield of the product was observed with increase in the generation of the dendrimer and the third-generation dendrimers are the most active catalysts. The variation of easiness of the reaction with the generation of dendrimers is considered to be a dendrimer effect and similar behavior was observed with other dendrimer based catalysts [8]. To prove the effect of generation of dendrimer on catalysis, the model reaction was carried out in the presence of various generations of dendrimers in such a way that the equivalence of amino groups was maintained in all cases. The results are summarized in Table 5. These results proved that higher generation dendrimers are more efficient catalysts and a 'positive dendrimer effect' comes into play in catalysis.

The degree of crosslinking of polystyrene support also has considerable influence on catalysis. The reaction was performed using the catalyst supported on polystyrene beads with higher degrees of crosslinking (Table 6). The speed of the reaction was decreased with increase in the degree of crosslinking of the polymer support. This may be due to the poor swelling of the resin, which prevents diffusion of the reactant molecules to the interior of the polymer where more than 90% catalytic sites are present.

The catalyst described here is reusable. The catalyst used in each run was washed well and reused in the subsequent runs. It was observed that the catalyst could be reused at least six times, but

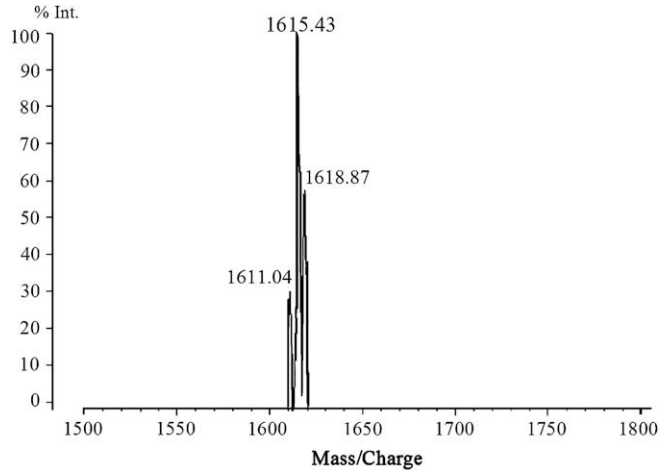

Fig. 6. MALDI TOF MS spectrum of third-generation PAMAM dendrimer.

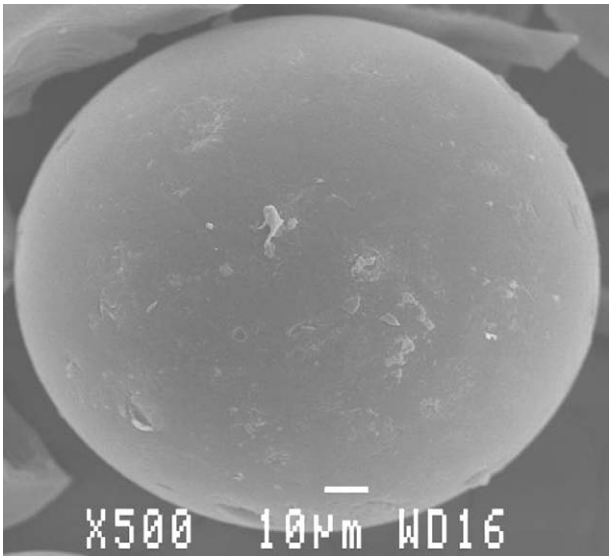

Fig. 8. SEM image of polystyrene beads carrying the dendrimer.

Fig. 9. General scheme of synthesis of 2-amino alcohols.

Table 1
Influence of the catalyst concentration on the reaction

Entry	mol% of the catalyst	%Yield [a,b]
1	0.5	Nil
2	1.0	40
3	1.5	89
4	2.0	100
5	2.5	100

[a] Reaction conditions: 5 mmol cyclohexene oxide, 5.2 mmol aniline, 5 mL 1,4-dioxane, 50 °C, 12 h.
[b] Yield by GC/MS.

Table 2
Solvent effect on the ring opening of epoxides by amines

Entry	Solvent	%Yield[a,b]
1	Water	65
2	1,4-Dioxane	100
3	THF	90
4	Water + 1,4-dioxane (1:1 v/v)	89
5	Water + THF (1:1 v/v)	70
6	$CHCl_3$	60

[a] Reaction conditions: 5 mmol cyclohexene oxide, 5.2 mmol aniline, 2 mol% catalyst, 5 mL solvent, 50 °C, 12 h.
[b] Yield by GC/MS.

Table 3
Ring opening of different epoxides with amines catalyzed by polystyrene supported PAMAM dendrimer

Entry	Epoxide	Amine	Time (h)	%Yield[a,b]
1	Cyclohexene oxide	$C_6H_5NH_2$	12	98
2	Cyclohexene oxide	4-$BrC_6H_4NH_2$	24	95
3	Cyclohexene oxide	4-$CH_3OC_6H_4NH_2$	24	96
4	Cyclohexene oxide	2-$CH_3C_6H_4NH_2$	24	96
5	Cyclohexene oxide	4-$NO_2C_6H_4NH_2$	24	93
6	Cyclohexene oxide	3-$ClC_6H_4NH_2$	24	95
7	Cyclohexene oxide	2-$CH_3$4-$NO_2C_6H_3NH_2$	48	90
8	Styrene oxide	$C_6H_5NH_2$	24	89
9	Styrene oxide	4-$BrC_6H_4NH_2$	24	85
10	Styrene oxide	4-$CH_3OC_6H_4NH_2$	24	90
11	Styrene oxide	2-$CH_3C_6H_4NH_2$	24	93
12	Styrene oxide	4-$NO_2C_6H_4NH_2$	36	95
13	2-Butene oxide	$C_6H_5NH_2$	24	92
14	2-Butene oxide	4-$CH_3OC_6H_4NH_2$	36	94

[a] Reaction conditions: 5 mmol epoxide, 5.2 mmol amine, 2 mol% G3 PAMAM PS, 5 mL 1,4-dioxane, 50 °C.
[b] Isolated yield.

Table 4
Effect of generation of the dendrimer on the reaction

Entry	Generation of dendrimer	mol% of catalyst	Time (h)	% Yield[a,b]
1	0	2	12	51
2	1	2	12	62
3	2	2	12	90
4	2	4	12	94
5	3	2	12	98

[a] Reaction conditions: 5 mmol cyclohexene oxide, 5.2 mmol aniline, 5 mL 1,4-dioxane, 50 °C.
[b] Isolated yield.

there was a gradual loss of activity on going from first to sixth cycle (Table 7).

The FTIR spectra of the catalyst before and after the reaction showed that the peaks due to the primary amino groups at 3390 cm^{-1} and 3344 $cm^{-1}$of the dendrimer remained unaltered. This showed that the primary amino groups of the catalyst were not involved in the reaction under the given set of reaction conditions.

A comparative study was done with unsupported PAMAM dendrimers. Zero and first generations PAMAM dendrimers were prepared according to the standard procedure [53], and were used as homogeneous catalysts. It was observed that unsupported PAMAM dendrimer of both the generations were less efficient catalysts in the ring opening of epoxides (Table 8). The supported dendrimer promoted the reaction efficiently and the yield of the product was high irrespective of the nature of the reactants. But such a constant performance was not observed with unsupported dendrimers. This observation can be explained by assuming that, in the case of supported dendrimer, an enzyme like activity is expected to play a role to enhance the activity of the catalyst. The polar hydrophilic dendrimers situated in a nonpolar hydrophobic polystyrene network are supposed to act as catalysts through an enzyme mimicking mechanism in which the dendrimers playing the role of the enzyme's active site and the polymer that of an oversimplified peptide backbone not directly involved in the catalytic activity. Similar enzyme mimicking properties were shown previously by polymer supported aminoacids in which the amino acid acted as catalytic sites whereas the polymer support acted as the peptide backbone [54,55]. Thus hydrophilic dendrimers attached to a hydrophobic polymer network could mimic an enzyme in activity which enhances the catalysis. This kind of effect which assists catalysis is also not there in the case of unsupported dendrimers.

Moreover it is assumed that the limited freedom of the dendrimer attached to the polymer support compared to the unsupported dendrimer may have some influence on the variation in catalytic performance. When supported dendrimer was used as catalyst, the catalyst and reactants remained in two different phases and this phase separation along with limited freedom of the supported dendrimer prevent it from reacting with the epoxide, even though being a stronger nucleophile. The concentration of the catalyst is also lower compared to the reactants and so there is more chance for the epoxide to meet an

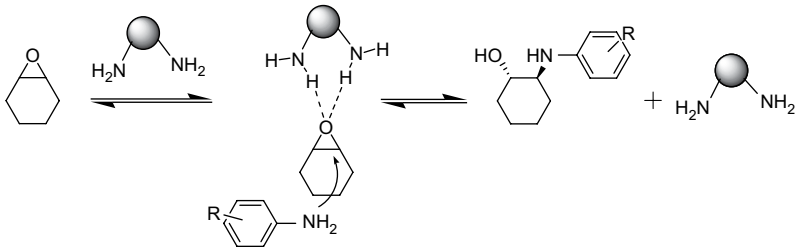

Fig. 10. Proposed mechanism of the reaction.

Table 5
Effect of generation of the dendrimer as a function of the amino group equivalent on catalysis

Entry	Generation of dendrimer	Amino groups [equiv.]	Time (h)	% Yield[a,b]
1	0	2.5	12	56
2	1	2.5	12	67
3	2	2.5	12	92
4	3	2.5	12	98

[a] Reaction conditions: 5 mmol cyclohexene oxide, 5.2 mmol aniline, 5 mL 1,4-dioxane, 50 °C.
[b] Isolated yield.

Table 6
Effect of degree of crosslinking of the support on the reaction

Entry	Degree of crosslinking	Time (h)	%Yield[a,b]
1	1	12	98
2	2	12	96
3	4	12	90
4	6	12	89

[a] Reaction conditions: 5 mmol cyclohexene oxide, 5.2 mmol aniline, 2 mol% supported G3 PAMAM as catalyst, 5 mL 1,4-dioxane, 50 °C.
[b] Isolated yield.

Table 7
Recycling of the catalyst

Entry	No. of recycling steps	% Yield[a,b]
1	1	98
2	2	98
3	5	92
4	6	90

[a] Reaction conditions: 5 mmol cyclohexene oxide, 5.2 mmol aniline, 2 mol% catalyst, 5 mL 1,4-dioxane, 50 °C.
[b] Isolated yield.

Table 8
Ring opening of different epoxides with amines catalyzed by unsupported PAMAM dendrimer

Entry	Epoxide	Amine	Time (h)	% Yield[a,b]
1	Cyclohexene oxide	$C_6H_5NH_2$	24	70
2	Cyclohexene oxide	4-$CH_3OC_6H_4NH_2$	24	63
3	Cyclohexene oxide	2-$CH_3C_6H_4NH_2$	24	65
4	Styrene oxide	$C_6H_5NH_2$	24	60
5	Styrene oxide	4-$CH_3OC_6H_4NH_2$	24	60
6	Styrene oxide	2-$CH_3C_6H_4NH_2$	24	56
13	2-Butene oxide	$C_6H_5NH_2$	24	30
14	2-Butene oxide	4-$CH_3OC_6H_4NH_2$	24	32

[a] Reaction conditions: 5 mmol epoxide, 5.2 mmol amine, 2 mol% G1 unsupported PAMAM, 5 mL 1,4-dioxane, 50 °C.
[b] Isolated yield.

aniline molecule than a supported primary amine remaining in a separate phase. This kind of effect is not operated when unsupported dendrimer was used as the catalyst. So the yield of the product was low and the catalyst became inactive after fewer numbers of cycles compared to the supported system.

The generation of dendrimer has considerable effect on the catalytic properties of unsupported dendrimers also. The reaction was slower in the case of zero generation dendrimer. While considering the ring opening reaction, first generation dendrimer was found to be far better catalyst than the zero generation one. The reaction was extremely slow and gave poor yield when zero generation dendrimer was used as catalyst and the rate and yield increased substantially when zero generation dendrimer was replaced with first generation dendrimer. This is due to the larger number of amino groups present in the first generation dendrimers compared to the zero generation one and the co-operative effect of these sites enhances the catalytic process.

4. Conclusion

Polystyrene supported PAMAM dendrimers were found to be highly efficient organocatalysts for the ring opening of epoxides with amines under mild conditions. The catalyst can be recycled many times without any loss of efficiency. A comparative study between polymer supported PAMAM and unsupported PAMAM was done which showed that polymer supported PAMAM dendrimers were excellent catalysts considering both the ease of separation and high activity.

Acknowledgements

The authors gratefully acknowledge Dipl. Chem. Christian M. Kleiner and Prof. Peter R. Schreiner, Institut für Organische Chemie, Justus-Liebig-Universität, D-35392 Giessen, Germany Heinrich-Buff-Ring 58, for active discussions on the reaction mechanism. The authors also thank DRDO, Govt. of India for financial support, NMR research center, IISc, Bangalore and STIC, CUSAT for various analytical results.

Appendix. Supplementary information

Supplementary information associated with this article can be found in the online version, at doi:10.1016/j.polymer.2008.09.038.

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