Proline-Based Polymeric Monoliths: Synthesis, Characterization, and Applications as Organocatalysts in Aldol Reaction

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ABSTRACT: Proline-based polymer monoliths were synthesized via green protocol using lipase-catalyzed esterification of methacrylic acid and 4-hydroxyproline. Prolinyl methacrylate thus prepared was polymerized *in situ* as crosslinked monolith. The monolith was characterized by various techniques such as Fourier transform infrared, ^{1}H-NMR, ^{13}C-NMR, scanning electron microscopy (SEM), X-ray diffraction (XRD), and nitrogen analysis and used as catalyst in aldol reactions. The swelling behavior of the monolith was also studied as function of various external parameters like pH and temperature. The monoliths synthesized with 1% crosslinker was selected as candidate monolith for use as catalyst in aldol reaction, which was studied as a function of time, temperature, substrate structure, and amount of water:EtOH. The catalysts exhibited high efficiency in the cross aldol reaction, especially with the aromatic substrates having electron withdrawing substituent, and also good activity retention was observed when recycleability was studied up to five cycles. © 2010 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 48: 1007–1015, 2010

KEYWORDS: aldol reaction; 4-hydroxyproline; lipase; polymer catalyst; polymer monolith

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INTRODUCTION In catalysis, it is often visualized that a catalyst should combine the merits of organocatalyst, biocatalyst, and polymer catalyst. Biocatalysts have comparative advantage over a synthetic catalyst as the former can work at normal operating conditions, and there is no danger of leaching of the toxic ligand/active part of the catalyst. But the applicability of biocatalysts over a wide range of conditions and separation from the reaction medium after the completion of reaction are two major limitations. These limitations can be overcome by their immobilization on solid supports that results in an ease of separation, enhanced recyclability and reusability.[1] The asymmetric catalysts are highly selective and efficient, and despite being very expensive, their research and industrial output far outweigh those of biocatalysts.[2] The polymer-supported or "polymer catalyst" apart from the significant advantage of the ease of separation are effective due to the high concentrations of active groups on the polymer chains.[3] In most of the polymer-supported catalysts, the active part is an inorganic metal or a complex of palladium, titanium, or ruthenium.[4–8] These are cost prohibitive, and the leaching of the active groups of catalyst is a major limitation. It is thus desirable that the monomer/s comprising a polymer catalyst have active groups as part of the monomer itself.

In view of the above, in this communication we report monomer and monolithic hydrogel synthesis with proline as the active part of the monomer. Proline is a model "bifunctional catalyst" and is christened as a "simplest enzyme"[9] and "universal asymmetric catalyst"[10] and it is useful in the synthesis of chiral organic molecules by asymmetric transformation.[11] It is nontoxic, easily available, and cost effective, and it is reactive in water at room temperature. It is bifunctional as the secondary amino group and carboxylic acid impart it the catalytic activity. Proline as catalyst allows the preparation and screening of large libraries of catalysts.[12] It was used since 1970, yet the real thrust to its catalytic potential came after the breakthrough works of List et al.[13] and Sakthivel et al.[14] The use of proline as such is effective in high amount (30 mol%), and its separation from water poses another problem, and at present, the use of non-solvents like chloroform and diethyl ether have been reported to separate it from the solution phase.[15,16] Hence, it is imperative that to realize cost effectiveness and green benefits of proline as catalyst, it was heterogenized by anchoring on different solid supports.[17–23] Consequently, the immobilization of proline has become one of the most explored areas of catalysis, especially in aldol reaction using water as medium.

The support reported for proline range from highly porous and rigid inorganic supports[24–28] to soluble polymers such as polyethylene glycol (PEG).[29,30] More recently, polystyrene (PS) has been used as an efficient polymeric backbone with and without second component to support proline and its

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derivatives in the enantioselective direct aldol reaction.[31–35] To enhance the activity of the hydrophobic backbone, it has been grafted on to TentaGel[36] or PEG-PS aminated resins immobilized with proline tripeptides (D-Pro-Tyr-Phe) for use in aldol reactions in a triphasic solvent media (water/acetone/tetrahydrofuran (THF), 1/1/1)6.[37] Proline-catalyzed asymmetric aldol reaction has also been carried out successfully with supports like ionic liquids,[38–42] polyelectrolyte system[43] with efficient catalyst recovery. Moreover, dendritic polymers catalysts with anchored proline have been reported to affect high yield and enantioselectivity.[44–48] Proline has also been modified to different proline-based polymers for studies and applications other than polymer catalysts. These polymers include poly-(proline),[49] acryloyl-L-proline esters,[50–57] poly(acryloyl-L-proline methyl ester/styrene),[58] proline-substituted acrylamide (AAm),[59] and copolymers as poly(ester-carbonate)[60] or block copolymers and derived from proline derivatives.[61–63]

Most of these studies are related to the copolymerization of proline or its anchoring/immobilization on a inorganic or polymeric backbone support by covalent attachement or derivatization of its carboxylate group, or the grafting onto hydrophobic backbone like PS. Although the former process results in the loss of its natural benefits as catalyst, the latter restricts its applications in water despite offering benefits of easy separation. We have not encountered any report on the synthesis of a monomer with proline or its derivatives to yield a polymer monolith through biocatalytic route and use of the resultant monolith as organocatalyst. In view of the above, in this communication we report synthesis, characterization and use of the new polymeric monoliths for catalysis of aldol reaction in water as reaction medium.

EXPERIMENTAL

Materials

AAm, lipase, *N*,*N*-methylenebisacrylamide (*N*,*N*-MBAAm), *p*-methoxybenzaldehyde and *N*,*N*,*N*,*N*-tetramethylethylene diamine (Sisco, Mumbai, India), acetaldehyde, benzaldehyde, dodecyl methacrylate (DMA; Merck, Mumbai), *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, methacrylic acid (MAAc) and 4-hydroxyproline (HiMedia, Mumbai, India), ammonium persulphate (APS) (Qualigens Fine Chemicals, Mumbai), molecular sieves-4 Å, 1.5 mm (IDP, Hyderabad, India), and tris(hydroxymethyl)-aminomethane (tris-buffer, S.D. Fine, Mumbai, India) were used as received but for *n*-hexane that was distilled before use.

Synthesis of Monomers and Polymer Monoliths

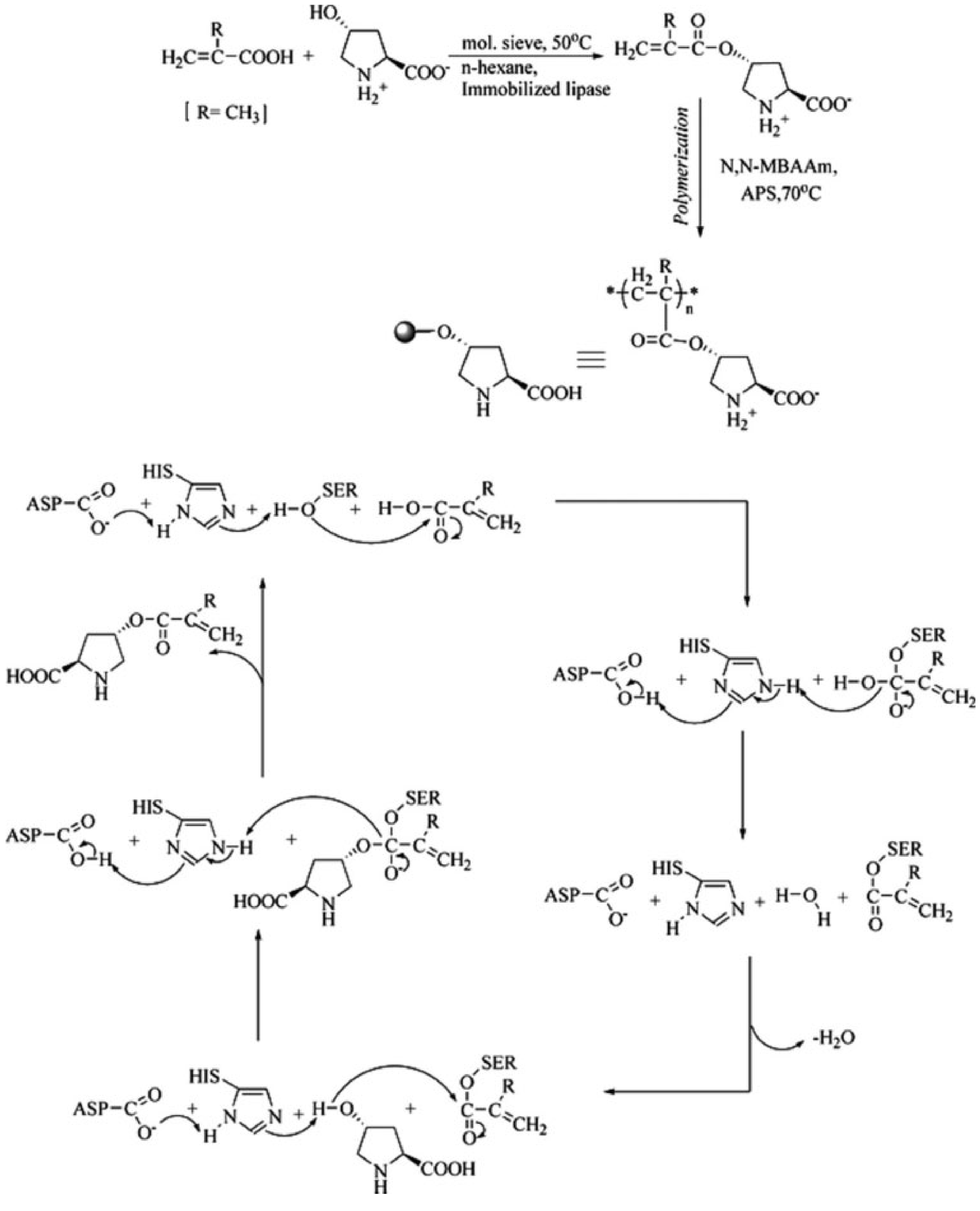
Lipase was immobilized *in situ* on a hydrogel comprising of 28 mM AAm and 3.5 mM DMA that was prepared by an earlier reported procedure.[64] Two hundred milligram of the immobilized lipase was used to catalyze reaction of MAAc with 4-hydroxyproline using a molar ratio of 1: 1.25 in 10.0 mL of *n*-hexane and 300 mg of molecular sieves. The reactions were carried in Mettler b Autochem chemical reactor (Autochem, US) at 50 °C for 12 h with constant stirring. The immobilized lipase was separated by filtration from the reaction mixture and to the resultant filtrate containing prolinyl methacrylate was added 10.0 mL distilled water and *N*,*N*-MBAAm and APS (1% of the initial weight of MAAc). The resultant solution was taken into ampoules of 2′ length with a diameter of 0.5′ under vacuum suction. The ampoules were sealed and placed in chemical reactor at 70 °C for 60 min. The monolith, thus formed, was repeatedly treated with distilled water with stirring, and dried at 40 °C in an air oven. Such repeated stirring and drying cycles were carried till a constant weight was obtained, and there after the resultant monolith was cut in small discs of uniform dimensions. Following the same procedure, poly(MAAc) and poly(PrMA) were also prepared for use as reference.

Characterization of Different Polymers and Monoliths

Fourier transform infrared (FTIR) spectra were recorded in KBr pellets on Nicollet 5700 Spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on INOVA 400 MHz; all the spectra were confirmed by comparing the digitized line spectra with the estimated shifts by computer software, *viz*. ChemNMR Pro (ChemDraw Ultra). SEMs were recorded on Jeol JSM-6100 scanning electron microscope, nitrogen analysis of the monoliths (before and after use) was carried on Carlo Erba EA-1108, and XRD recorded D8 Advance, 120 Bruker AXS using Cu Kα radiation (3 kW). The swelling studies was carried in triplicate by using 0.1 g of the disc cut from the monoliths from 10 to 1440 min, 20–60 °C and at pH 4.0, 7.0, and 9.2 by an earlier reported procedure.[65]

Application in Aldol Reaction

Monolith discs (30 mol%), benzaldehyde (9.42 mM), and acetaldehyde (9.42 mM) were taken in H_2O:EtOH (6:4, 10 mL). The reaction mixture was stirred in chemical reactor for 18 h at 20 °C; thereafter the monolith was filtered, washed thoroughly with water and ethanol, and dried under vacuum for further use. From the filtrate, the solvent and excess of aldehyde/ketone were removed under the reduced pressure at room temperature. The resulting residue was taken in ethyl acetate (30 mL) and stirred with 10% $NaHCO_3$ solution (10 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude oil was extracted from petroleum ether. Each reaction was carried out by setting reaction in triplicate along with a corresponding control reaction. For the optimization of the reaction conditions, the reaction was assayed at different time intervals (6, 12, 18, 24, and 30 h) at different temperatures (20–40 °C). Moreover, the effect of solvent concentration was also determined by varying the concentration of H_2O:EtOH. The reaction mixture was analyzed directly by withdrawing aliquot with from time to time, which was analyzed by high performance liquid chromatography (HPLC), and the percent conversion was calculated on the basis of the benzaldehyde consumed. The reaction was quenched by freezing the reaction mixture. The solid catalyst was filtered, washed thoroughly with water and ethanol, and dried under vacuum to study reusability of the catalyst, which was studied by reusing the used catalyst as such or by stirring with ethyl acetate for 1 h prior to the next reusability cycle. The optimized conditions thus obtained were further used in different cross-aldol reactions.



SCHEME 1 Process and mechanism of the immobilized lipase-catalyzed monomer synthesis.

Quantification and Characterization of Products

All the compounds synthesized using polymer catalysts were quantified by using HPLC (HPLC was performed using Perkin Elmer series 200 Ic pump equipped Inertsil ODS-3, 4.6 × 150 mm, 5 mm in particle size, GL Sciences, Japan, and Applied Biosystems 785 Å programmable absorbance detector). The sample was analyzed using (65% v/v) acetonitrile in water as mobile phase at flow rate of 1.0 mL min^{-1} at ambient temperature. The absorbance was recorded at 210 nm. The injection volume was 0.5 μL. All the standard curves (0.1–1.0 mM) were prepared under similar conditions. The spectra were recorded over the range of 4500–500 cm^{-1} by

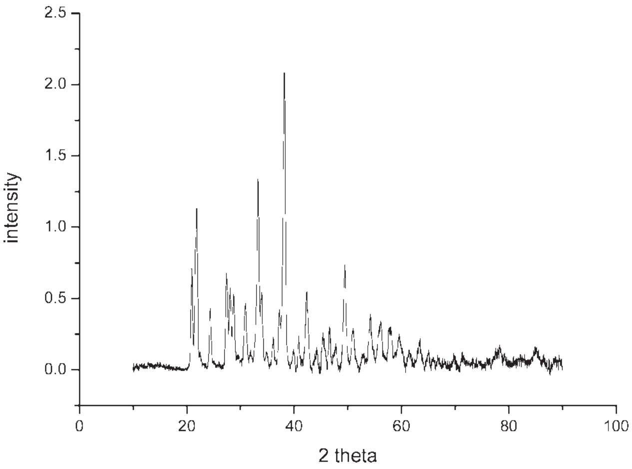


FIGURE 1 XRD of poly(PrMA-*cl-N,N*-MBAAm).

means of OMNIC software. Optical rotations were obtained by research polarimeter (SIPCON, SP-01A) in ethanol. IR spectra of the products were recorded as described earlier.

RESULTS AND DISCUSSION

Monomer Synthesis

Immobilized lipase had a high protein binding efficiency (81%) and exhibited enzyme activity of 5.61 U/mL. It was used to synthesize monomer, PrMA, as illustrated in Scheme 1. The esterification reaction involving acylation and deacylation on the active site of lipase are also illustrated.[66,67] The optical rotation of the proline itself or poly(PrMA) in water was found to be ($[\alpha]_D = -2.01$, $c = 0.1$).

Characterization of Polymers

% N was found in the monomers PrMA, and in its network was found to be 9.95 and 4.26. The monomer formation is supported by the lower amount of N in the monomers than the precursor 4-*trans* hydroxyproline. XRDs exhibit high crystallinity with sharp peaks in the regions of ~20–~40 theta with important peaks at 1.133 at 21.84 and 2.081 at 38.2 theta for poly(PrMA-*cl-N,N*-MBAAm) (Fig. 1). SEMs of the monolith show outgrowths on the surface of the networks that is attributed to the aggregation of the pendant prolinyl groups. Evidently, the surface morphology of the intensely crosslinked polymers exhibits small pore size [Fig. 2(a) and (b)]. Appearance of the characteristic peaks of 4-hydroxyproline in the FTIR spectrum of poly(PrMA) suggests the formation of monomers and their polymers [Fig. 3(a,b)]. The spectrum of the monolith has two characteristic bands, that is, 1641 and 1593 cm^{-1} associated with COO$^-$ absorbance and $^+NH_2$ deformations of proline. Absence of peak at 1730 cm^{-1} rules out the possibility of the presence of the unionized proline.[68] The dipolar nature of the prolinyl moiety is supported by the appearance of two strong bands at 883 and 920 cm^{-1}, due to $^+NH_2$ and $-COO^-$. Distinct changes in the intensity or shifting in the peaks of the characteristic peaks was also observed in the spectra of the monoliths when compared with that of PrMA.

^{1}H-NMR spectrum of poly(MAAc) [Fig. 4(a)] presented as reference shows signals at 1.62 δ and 2.27 δ corresponding to the methylene protons, whereas in ^{1}H-NMR spectrum of poly(PrMA) signals appears at 2.4 δ corresponding to the protons of –NH, and $-CH_2$ positioned adjacent to –COOH groups in the pyrrolidine ring. The signal at 2.45 δ corresponds to methylene proton situated α to –NH, a quartet at 3.4 δ corresponds to –CH group α to polymer chain linkage, and a triplet at 4.3 δ corresponds to –CH placed α to –COOH of the pyrrolidine ring [Fig. 4(b)]. ^{13}C-NMR spectrum of poly (PrMA) has two peaks at 179 ppm and 174 ppm due to the presence of two $-C{=}O$ groups, the peak at 70 ppm relates to the carbon positioned α to $-C{=}O$ and β to –NH, at 60 ppm corresponds to carbon α to –NH and –COOH, at 53 ppm corresponds to carbon placed between –NH and –CO, and the signals at 37 ppm and 34 ppm correspond to carbon β to –COOH and methylene of the polymer chain, respectively (not presented). The contrast of this spectrum with the reference polymer studied provides evidence of the formation of poly(PrMA).

The monoliths behaved as hydrogel and the maximum % swelling was observed in the case of polymers having 1% crosslinker, thus, exhibiting an increase in the degree and intensity of crosslinking at the higher crosslinker concentrations. Under the swelling conditions studied, all the hydrogels exhibited enhanced swelling with an increase in temperature, but these deswell above 50 °C (figures not

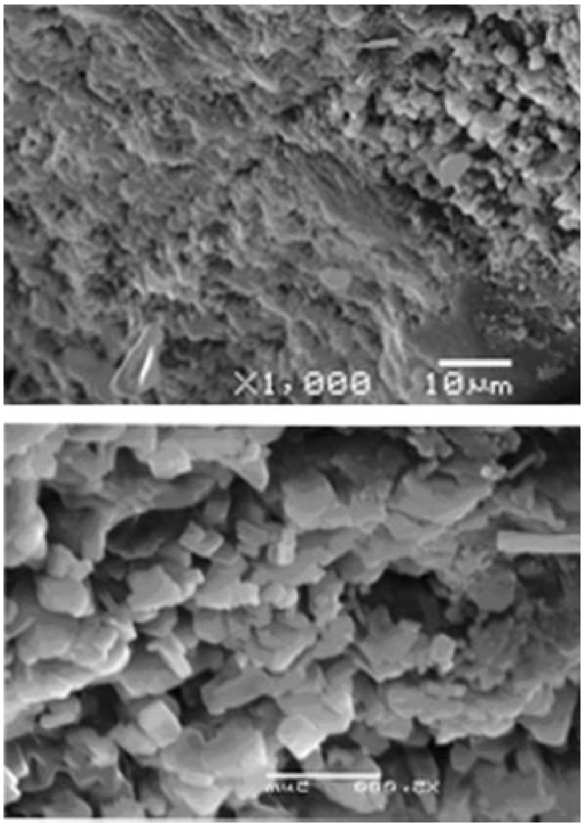


FIGURE 2 SEMs of poly(PrMA-*cl-N,N*-MBAAm) at two different conditions.

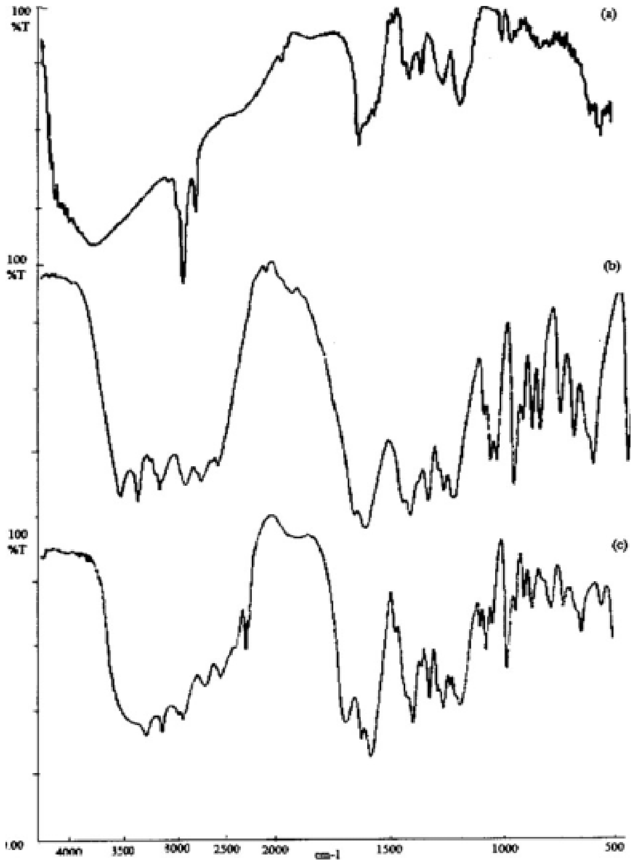


FIGURE 3 FTIR of (a) poly(MAAc) and (b) 4-hydroxyproline and (c) poly(MAAc-*cl*-*N,N*-MBAAm).

presented). On change of pH, higher swelling was observed in the alkaline medium (pH 9.2) than in acidic medium (pH 4.0). The data generated from the swelling studies demonstrated that the swelling capacity of the proline-based polymers was higher than the reference crosslinked poly(MAAc). The increase of the ionic units along the main chain of hydrogel leads to an increase in the repulsive forces among similar ionic groups resulting in the loosening of the network chains, and thus, favouring the higher or increased water uptake.

Applications as Organocatlayst: Effect of Time, Temperature and Solvent Composition in Aldol Reaction, and Selection of Catalyst

On the basis of the swelling behavior, the monoliths synthesized with 1% crosslinker were used as catalysts to examine their catalytic activity in the reaction of benzaldehyde with acetaldehyde. % Conversion was determined from the consumption of benzaldehyde during the advancement of reaction with HPLC. The maximum % conversion (63) was obtained at 18 h, 20 °C, in H_2O: EtOH (6:4) solvent with 30 mol% catalyst loading. The progress of reaction was initially fast up to 18 h, and later it became independent of time (Fig. 5). Thus, from the reaction profile the optimum reaction time of 18 h at 20 °C was obtained. The contact of the catalyst and the substrates increased with time. This is far lower than the reported contact time (48–72 h) for this type of reaction systems.[69] Aldol condensation is a reversible and exothermic reaction; the maximum yields are generally obtained at 5–25 °C.[70] From the histogram, it was inferred that the concentration of solvent had profound effect[71–76] on the reaction kinetics (Fig. 6). The solvent composition at 6:4 (H_2O: EtOH) increased % conversion from 24% to 62%. The high % conversion of catalyst in water is attributed to the good swelling properties of the polymeric monolith in water thereby opening up the catalytic sites and increasing the accessibility and contact of reactants with the catalyst.[77] The total absence of water or EtOH (H_2O:EtOH = 10:0 or 0:10) in both the extremes reduced the extent of reaction, which is in conformity with that reported in literature.[69] The role of water as reaction medium helps in increasing the total catalyst concentration within the catalytic cycle due to suppression of spectator species. In the absence of water, irreversible deactivation due to formation of oxazolidinone derived from proline and aldehyde.[78] These results indicate that acetaldehyde can react with a reactive electrophilic aldehyde even in the presence of a large excess of water, and this can be understood with the hydrogel nature of the catalyst. However, because of the lower polarity of the substrate and reagent, the optimum catalytic activity was observed in the aqueous EtOH. The composition of solvent system (H_2O:EtOH) at 6:4 resulted in the maximum % conversion as at this concentration there is no interaction between constituent molecules as it behaves ideally,[79] whereas with the reverse composition (H_2O:EtOH = 4:6), there was drastic

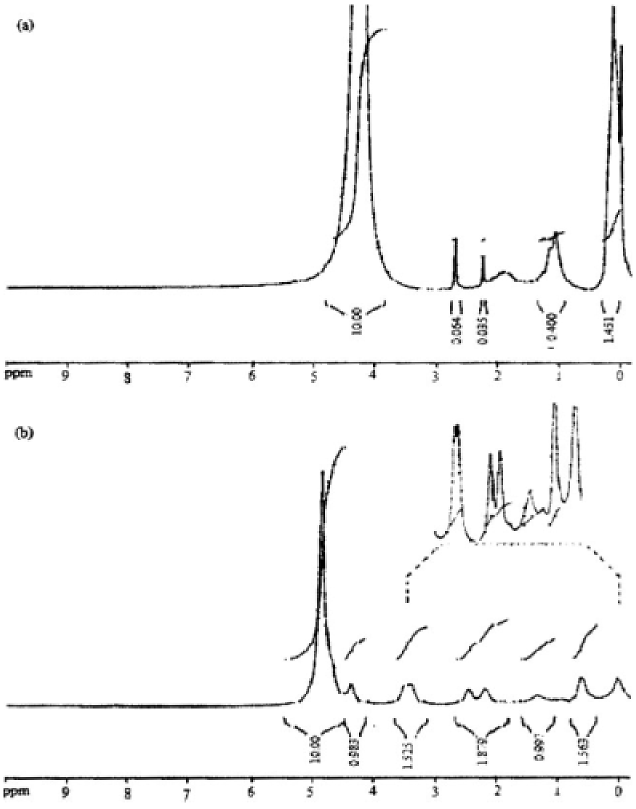


FIGURE 4 ^{1}H-NMR (from top) poly(MAAc) and poly(PrMA).

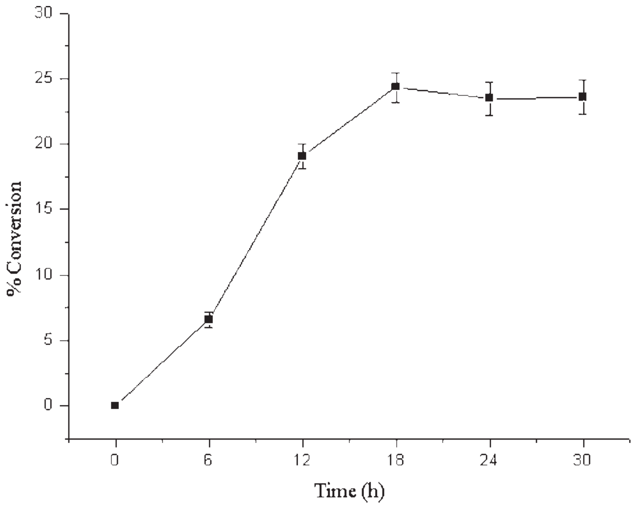


FIGURE 5 Effect of time on the cross-aldol reaction of benzaldehyde with acetaldehyde by proline-based catalysts (temperature = 20 °C, catalyst loading = 30 mol %, without solvent).

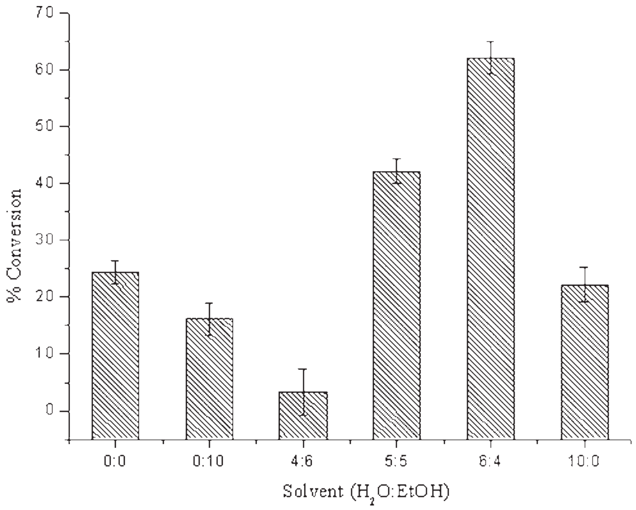
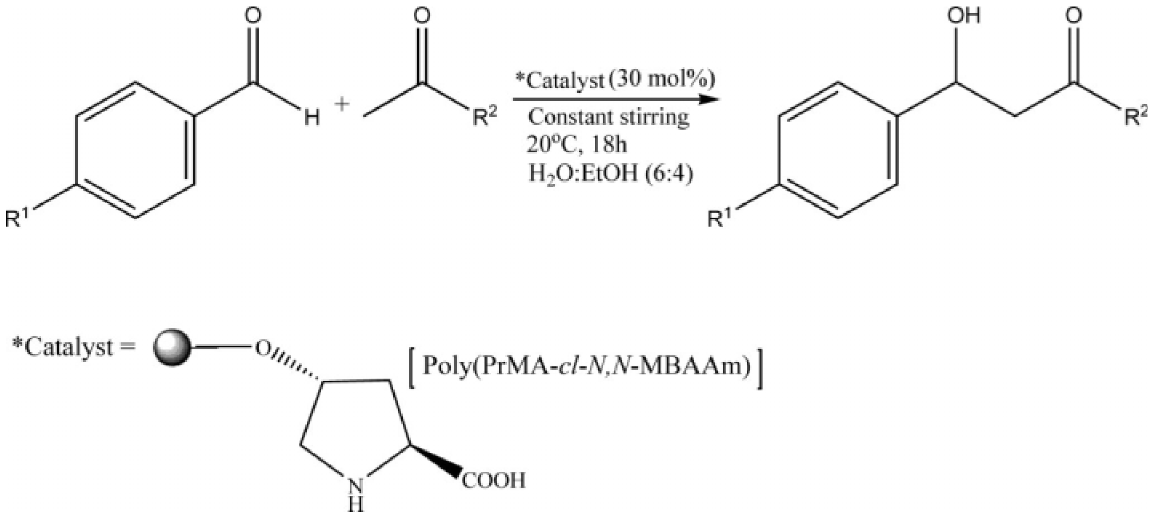


FIGURE 6 Effect of solvent composition on the cross-aldol reaction of benzaldehyde with acetaldehyde (time = 18 h, temperature = 20 °C, catalyst loading = 30 mol %).

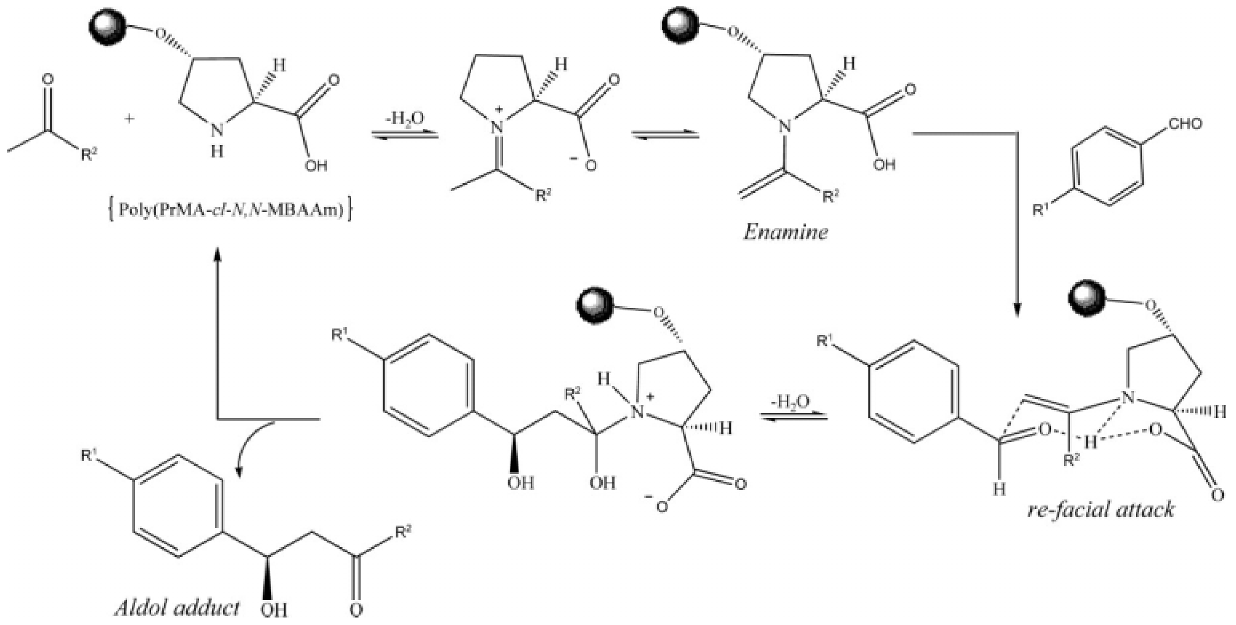
decrease in the % conversion as with an increase in the concentration of EtOH there was a decrease of water-solute interaction energy which leads to an increase in the water-water aggregation or an increase of hydrophobic interactions of ethyl groups of EtOH. This hinders the action of the OH groups of interfacial water molecules which play a key role in catalyzing reactions via the formation of hydrogen bonds.[80]

A generalized aldol reaction is shown in Scheme 2. Benzaldehyde and some portion of the acetaldehyde formed an organic phase. The remaining acetaldehyde was dissolved in the aqueous phase, where it reacted with the hydrophilic polymeric proline, most of which in water is present in the zwitterionic form. As acetaldehyde dissolves in both the aqueous and organic phases, it extracts proline from water to the organic phase. A noteworthy advantage of the present reaction is the realization of an organic solvent-free system.

The key intermediate in the direct intermolecular asymmetric aldol reaction is an enamine formation between proline catalyst and the corresponding donor substrate. In the proposed mechanism, enamine attacks the carbonyl group of the aromatic aldehyde acceptor forming a highly organized tricyclic hydrogen bonded framework resembling a metal-free Zimmermann-Traxler type transition state. Therefore, as reported by Barbas and coworkers,[14] a base and an acidic proton, both are required for the effective catalysis to occur as hydrogen bonding is an essential feature of the transition state. Moreover, it is also speculated that the ester in the polymeric catalysts makes N-H more acidic due to its electron-withdrawing property (Scheme 3). This results in the formation of a stronger hydrogen bond in the transition state.[81] Therefore, the presence of an ester group as in the present case induced a positive effect on the performance of the polymeric catalyst. The reusability of the polymer



SCHEME 2 Model aldol reaction.



SCHEME 3 Proposed mechanism of aldol reaction.

catalysts was studied. The efficacy of the catalysts remained good up to a few cycles and the % conversion decreased in a linear fashion with an increase in the number of cycles. The successive decrease in the catalytic activity could be construed as loss of the active (proline) component from the polymer by hydrolysis. However, the latter was discounted from the nature of the reaction system which is of nonhydrolyzing nature. The nitrogen analysis of the "as prepared" monolith and that used in five repeated cycles did not show an appreciable variation in the % N contents. The other possibility was that some residual product got adsorbed on the polymer monolith surface as the prolinyl part and the network created by crosslinking contribute to such adsorption process. In repeat experiments, the stirring of the used monolith with ethyl acetate was subjected for longer duration (24 h) than studied earlier (1 h) to ensure complete catalyst regeneration. The result was an improvement in the sustainability of the catalytic activity (Fig. 7). The observed retention of the catalytic activity after five cycles is reasonable as also reported elsewhere.[33]

Cross Aldol Reaction

A wide range of aromatic aldehydes was used as substrate in the cross-aldol reaction and for ketone-aldehyde cross-aldol reaction under optimum conditions to give aldol adduct. The % conversion was determined by monitoring the reaction

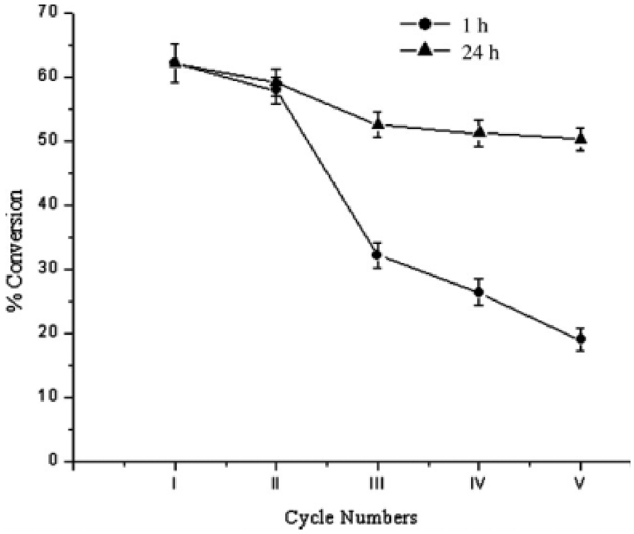


FIGURE 7 Reusability cycles of the polymer catalyst in cross-aldol reaction of *p*-substituted benzaldehyde with acetaldehyde (time = 18 h, temperature = 20 °C, catalyst loading = 30 mol %, H_2O:EtOH = 6:4).

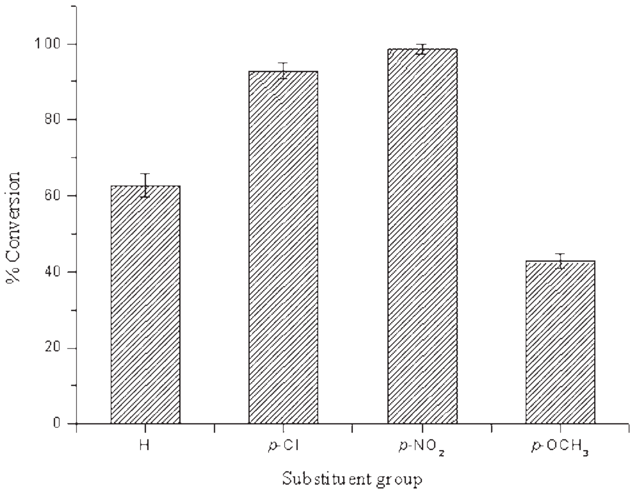


FIGURE 8 Effect of various substituents on aldehyde cross-aldol reaction of *p*-substituted benzaldehyde with acetaldehyde (time = 18 h, temperature = 20 °C, catalyst loading = 30 mol %, H_2O:EtOH = 6:4).

with HPLC. A series of *p*-substituted benzaldehyde reacted with acetaldehyde under optimal conditions to give aldol adduct with high degree of % conversion (Fig. 8). The inductive nature of the substituent strongly affected the conversion rate of the reaction. Significantly, a considerable conversion, that is, 93% was also achieved with *p*-Cl as a substituent. Remarkably higher % conversion, up to 99%, was achieved with *p*-nitrobenzaldehyde. The strong electron withdrawing effect on the electron-deficient aromatic aldehyde, along with the ester group present on the catalysts, further increased the strength of hydrogen bond in the transition state. As discussed in the mechanism, the hydrogen bond formation is the essential feature in the transition state, which improved the performance of the catalyst.

In the ketone-aldehyde aldol reaction, a range of *p*-substituted benzaldehyde was made to react with distilled acetone following the general procedure as cited earlier. Appreciably, a high % conversion was obtained with *p*-chlorobenzaldehyde (89%), *p*-nitrobenzaldehyde (86%), and *p*-methoxybenzaldehyde (85%). Similar electronic effects on the % conversion are also reported in literature for *p*-chlorobenzaldehyde, *p*-cyanobenzaldehyde, and *p*-nitrobenzaldehyde for the modified proline-catalyzed cross aldol reactions though % conversion was low.[81] However, the % conversion with benzaldehyde (as the substrate) was found to be low. Notably, the % conversion between 12 and 55% was achieved with a more complex ketone, 2-acetylfuran. From the last two reactions, it follows that extent and purposes of the reaction are dependent on the structural effects of the substrates.

CONCLUSIONS

Prolinyl methacrylate (monomer) was synthesized by biocatalytic route using esterification reaction for the covalent attachment of 4-hydroxyproline to MAAc using immobilized lipase. The monomer was polymerized to polymer monoliths, and the latter were used as heterogeneous polymer catalysts in the aldol reaction that was studied in three forms viz. simple aldol, cross aldol, and ketone-aldehyde reaction. The high efficiency of the catalysts and selectivity for aromatic aldehydes was observed as high % conversion (even up to 99%), was achieved with *p*-chloro and *p*-nitro substituted benzaldehydes. The results exhibit high reproducibility of results, and the catalyst efficiency was retained at reasonably high levels when studied up to five cycles.

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