The toxic and volatile nature of many organic solvents that are widely used in organic synthesis have posed a serious threat to the environment. One of the recently developed methods is to use water as solvent. However, its use is limited by the low solubility of organic compounds. One of the most important strategies to overcome this limitation of water is the utilization of organic cosolvents. Thus, as new polymeric cosolvents poly (vinyl amine) (PVA) and poly (allylamine) (PAA) were prepared and used as cosolvent/catalyst systems in the regioselective ring opening of epoxide by azide ion in water at room temperature to give azidohydrine in excellent yield under mild reaction conditions. These polymeric catalysts can be used several times without any loss in their activity.

**ABSTRACT**

The toxic and volatile nature of many organic solvents that are widely used in organic synthesis have posed a serious threat to the environment. One of the recently developed methods is to use water as solvent. However, its use is limited by the low solubility of organic compounds. One of the most important strategies to overcome this limitation of water is the utilization of organic cosolvents. Thus, as new polymeric cosolvents poly (vinyl amine) (PVA) and poly (allylamine) (PAA) were prepared and used as cosolvent/catalyst systems in the regioselective ring opening of epoxide by azide ion in water at room temperature to give azidohydrine in excellent yield under mild reaction conditions. These polymeric catalysts can be used several times without any loss in their activity.

**INTRODUCTION**

Until recently the use of water as a solvent for organic reactions was mainly restricted to simple hydrolysis reactions. However, because of cost, safety, and environmental concerns, utilization of water as a solvent has increased significantly in recent years, and chemists have begun investigating the possibility of using water as solvent for organic reactions with sometimes surprising and unforeseen results [1]. Unfortunately the use of water is limited by low solubility of organic
compounds in water. A variety of strategies have been developed in order to expand the scope of water-based organic synthesis to embrace also highly hydrophobic reactants, the most important of these being the use of organic cosolvents [1,2].

It is well known that low molecular weight solvents such as hexamethylphosphoric triamide (HMPT), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) have been used as effective polar cosolvents for promoting nucleophilic displacement reactions [3-5]. Moreover, much research has been done on preparation of polymeric analogous of such solvents with a view to their use as solid phase cosolvents and catalysts in organic reactions [3-11]. By virtue of their insolubility, such materials would be particularly attractive since they can be recovered by filtration and be used again. β-azidoalcohols are an important class of organic compounds and they serve as precursors in the syntheses of vicinal aminoalcohols, carbohydrates, nucleosides [10-16], lactames [17], and oxazolines [18]. They are usually prepared through ring opening of epoxides by using different kinds of azides in suitable solvents. The reactions are often carried out under either alkaline or acidic conditions and several different methods have been devised in order to obtain the direct azidolysis of epoxides in the presence of sodium azide [12,14,19-21]. Under these conditions, azidolyses are usually carried out over a long reaction times and high temperatures, and so side reactions such as isomerization, epimerization and rearrangements may be induced by the alkaline condition in these systems [12,14]. The rate of reaction is not significantly improved by using NaN₃ in anhydrous acetonitrile in the presence of catalysts such as LiOTf [22], or Mg(ClO₄)₂ [22]or by using Me₃SiN₃ with Yb(Oi-Pr)₃ [23], Ti(Oi-Pr)₄[24,25], V(Oi-Pr)₃ [26] and imidochromium complexes [27] in organic solvents. Other reported reagents are Bu₃SnN₃ without solvent and promoter [28], titanium [29], aluminum[30], and tin [31] azides in organic solvents, triethylaluminium/hydrogen azide as a mild and efficient reagent for medium to large ring cyclic epoxides [32], diethylaluminium azide for the regio and stereoselective ring opening of 2,3-epoxy alcohols [33], trimethylsilylazide [34] and sodium azide [35] in the presence of Lewis acid, and quaternary ammonium salts [36]. In most of the above cases, the presence of a cation or a Lewis acid seems to be necessary to facilitate the cleavage of epoxides.

Azidolyses of epoxides have also been done by polymer-supported azide anion [37], and by using polymeric phase-transfer catalyst/sodium azide system [38]. NaN₃ supported on porous solid acids (zeolite, alumina, and silica gel) has also been reported [39].

There are only few reports in the literature on azidolysis of epoxides carried out in water [13,19]. On the other hand, performing organic reactions in water is environmentally friendly and offer economical advantages over the use of organic solvents and has attracted much attention in recent years. Therefore, in continuation of our studies on preparations and applications of new solid resins that behave as phase transfer catalysts in organic reactions under aqueous or non-aqueous conditions [38,40,41], we now report the regioselective azidolysis of epoxides in water using new polymeric cosolvents.

**EXPERIMENTAL**

**General**

Substrates were purchased from Fluka AG and Merck Companies. All products were characterized by comparison of their IR and NMR spectra and physical data with those reported in the literature. Progress of reactions were followed by TLC on silica-gel Polygram SIL/UV 254 plates or by GLC on Shimadzu GC 14-A with hydrogen flame ionization detector. Separation of the products was conducted on silica gel column. FTIR Spectra were run on a Shimadzu FTIR-8300 spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance DPX instrument (250MHz).

**Preparation of Polyacrylamide**

Polyacrylamide of 1,2,4 and 8 percent cross-linking with divinylbenzene (DVB) were prepared by previous reported method [40].

**Preparation of PVA [42]**

In a typical procedure, the corresponding cross-linked polyacrylamide (1.5g) was swelled in NaOH(25mL, 8%) for 10 min. Then upon cooling in an ice bath, NaOCl (21mL, 1M) was added and the mixture was stirred for 10 h. It was then filtered, washed with water, acetone and finally dried at 60°C overnight under vacuum. The weight of yellow product was 1.1g. FTIR:
Preparation of PAA
To THF (20 mL) in a round bottom flask (50 mL) was added cross-linked polyacrylamide 2% (1 g). LiAlH₄ (1.6 g) was slowly added to this suspension and the mixture was stirred for 12 h at 50°C under N₂. The excess LiAlH₄ was destroyed with slightly wet ethylacetate and the mixture was then acidified with HCl solution. The solid was filtered and washed with water, sodium bicarbonate, and finally with water, methanol and THF. It was then dried at 60°C overnight under vacuum to gain 0.87 g of grey powder. FTIR: (cm⁻¹) 3100-3400(broad), 1664, 1560.3, 1114.8, 831.2 (weak), 760.

Determination of the Content of Amino Group of PVA and PAA
In a typical procedure HCl(30 mL, 0.1 M) was added to PVA (0.200 g) and the mixture was stirred at room temperature for 4 h. Then it was filtered and washed several times with water. The filtrate was titrated with NaOH (0.1 M) in the presence of phenolphthalein as indicator. NaOH (8.2 mL) was used. The capacity of polymer was determined as 10.9 mmol NH₂ per gram of PVA.

Reaction of Epoxides with Sodium Azide
To a mixture of epoxide (1.0 mmol) and sodium azide (5 mmol) in water (20 mL), polymer (0.05 g) was added. The suspension was stirred at room temperature for the lengths of time shown in Table 3. The progress of reaction was monitored by TLC, using hexane-ethylacetate (5:1) as eluent, and/or GC. On completion of the reaction, the product was obtained upon extraction with CH₂Cl₂. The organic solvent was dried with anhydrous Na₂SO₄ and filtered. The pure product was obtained by evaporation of the solvent. The solid polymer was filtered, washed with water and methanol and dried overnight at 60°C under vacuum. This polymer could be used again without any loss in its efficiency as a cosolvent catalyst.

RESULTS AND DISCUSSION

Cross-linked polyacrylamide was prepared by free radical solution polymerization of acrylamide/DVB mixture in ethanol using potassium persulphate as an initiator. PVA was prepared by Hofmann rearrangement of polyacrylamide using NaOCl, and PAA was prepared by reduction of polyacrylamide using LiAlH₄ (Scheme I). The degree of amino content of these polymers were determined by titration method and were found to be 10.9 and 10.2 meq/g of PVA and PAA, respectively.

The effects of solvent and molar ratio of the polymeric cosolvent on the ring opening reaction of styrene oxide with sodium azide were investigated. With wet solvents and specially water the reaction proceeded more rapidly (Table 1). This is probably due to better swellability of polymeric cosolvent in hydroxylated solvents. Therefore, water was chosen as the solvent of choice for the azidolysis reactions. It is interesting to notice that the reaction of styrene oxide/NaN₃ in water undergoes with very high regioselectivity. The optimum molar ratio of both polymeric catalysts to epoxides was found to be 0.1:1.

The effect of degree of cross-linking of PVA on the reaction of epoxides with sodium azide in water was investigated. Table 1 shows the effect of solvent on the reaction of styrene oxide with NaN₃ using PVA.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H₂O</td>
<td>1</td>
<td>I</td>
<td>97</td>
</tr>
<tr>
<td>1</td>
<td>MeOH (dry)</td>
<td>10</td>
<td>I, II(84,16)</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>MeOH/H₂O (10:1)</td>
<td>10</td>
<td>I, II(95,15)</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>EtOH (95%)</td>
<td>10</td>
<td>I, II(89,11)</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>EtOH/H₂O (10:1)</td>
<td>4</td>
<td>I, II(91,9)</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂ (dry)</td>
<td>10</td>
<td>I</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂/H₂O (10:1)</td>
<td>10</td>
<td>I</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>CH₃CN (dry)</td>
<td>10</td>
<td>I</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>CH₃CN/H₂O (10:1)</td>
<td>10</td>
<td>I, II(91,9)</td>
<td>56</td>
</tr>
</tbody>
</table>

(a) All reactions were carried out at room temperature. The molar ratio of catalyst to epoxide was 0.1:1.
(b) Structures and ratios of regioisomers determined by ¹H NMR.
(c) GC yield.
(e) Yields refer to isolated yield.
The rate of azidolysis was investigated. As shown in Table 2 the best result was obtained when 1% cross-linked PVA was used. However, because of handling problems (being gelatinous and difficult to filter), 2% cross-linked polymer was chosen for further studies. This observation supports the general fact that increased cross-linking decreases the ability of the polymer matrix to swell in solvents [43].

The reactions of different epoxides with sodium azide using PVA and PAA as polymeric cosolvents were performed effectively and in high yields in water at room temperature (Scheme II, Table 3). Except for the reaction of 1,2-butene oxide (entry 7), which produces a minor percentage of the other regioisomer, the reaction of other epoxides were found to be highly regioselective and only one isomer was obtained. Also, in the case of epichlorohydrin (entry 3), the diazidoalcohol product, and in the case of cyclic epoxides (entry 4) trans-product were obtained. Obviously, in these reactions, the attack appears to be largely, if not entirely, on the less substituted carbon. The direction of ring opening is that characteristically observed for reactions of monoalkyl-substituted epoxides under SN2 conditions and is probably dictated by steric and electronic factors. In the reaction with styrene oxide, the azide ion attacks exclusively at the more substituted benzylic carbon atom of the epoxide ring.

In order to compare these polymeric cosolvent catalysts’ efficiencies with those of other phase transfer catalysts and cosolvents in the azidolysis of epoxides, a series of reactions were performed on styrene oxide with NaN$_3$ in the presence of these catalysts (Table 4). As shown in this table in the absence of any catalyst no reaction occurs. In the presence of monomeric and polymeric phase transfer catalysts (entries 3, 4, and 5) and cosolvent catalysts (entries 2 and 6) and PVA and PAA reactions occur with very high yields but different efficiencies. Among these, the new polymeric cosolvent catalysts PVA and PAA show the best efficiencies compared to others. It is believed that these polymeric amines species can catalyze the azidolysis of epoxides in aqueous phase in two ways. First by swelling in the aqueous media they can act as cosolvents for the organic substrates, namely epoxides, and therefore, can provide the necessary microenvironment for the water-soluble nucleophile, i.e. N$_3^-$, to be in the vicinity of the epoxide molecules for the reactions to occur. Secondly, and more important is that amino functionalities on these polymeric cosolvents can interact through H-bonding with the oxygens of epoxide molecules to facilitate the attack of azide anion as the nucleophile. This kind of interactions has been suggested for other nucleophilic ring opening reactions of epoxides using polymeric phase transfer catalysts [38, 40, 41].

To compare the catalytic effect of these polymeric species as cosolvents with those of ordinary aprotic cosolvents such as DMF, DMAc, DMSO, NMP, and

<table>
<thead>
<tr>
<th>Degree of cross-linking</th>
<th>Time(h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>0.45</td>
<td>94</td>
</tr>
<tr>
<td>2%</td>
<td>1.00</td>
<td>97</td>
</tr>
<tr>
<td>4%</td>
<td>1.45</td>
<td>95</td>
</tr>
<tr>
<td>8%</td>
<td>2.15</td>
<td>91</td>
</tr>
</tbody>
</table>

Scheme I. Synthesis of monomer 6.

Scheme II. Preparation of model compound 7.
HMPA, the azidolysis reactions of styrene oxide with azide anion in the presence of such solvent were performed. As shown in Table 5 the efficiencies of these monomeric cosolvents are much less than the polymeric cosolvents PVA and PAA. Probably, these cosolvents act only as solvents in bringing the epoxide molecules and azide anions to the vicinity of each other in the water phase, however, they can not act as a catalyst the way the polymers did through their amino functional groups, to make the epoxides more susceptible for the nucleophilic attack. Actually this study strengthened our belief that these amino polymers catalyze such reactions through their amino functionalities in addition to act as cosolvents. In addition as seen in Table 3 the efficiency of PAA is appreciably more than PVA in the azidolysis reactions. This is probably due to better availability of the amino groups for interaction with oxygens of the epoxides in the case of PAA, as the amino functionality is further from the chain and sterically less hindered.

### Table 3. Reaction of different epoxides with NaN₃ using PVA and PAA as cosolvent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>Time(h)</th>
<th>Product</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Ph]O</td>
<td>0.75(I)</td>
<td>![Ph]OH</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1(I)</td>
<td>![N₃]OH</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>![Ph]O</td>
<td>4(I)</td>
<td>![Ph]OH</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5(I)</td>
<td>![N₃]OH</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>![Cl]O</td>
<td>1.4(I)</td>
<td>![N₃]OH</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5(I)</td>
<td>![N₃]OH</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>![cyclo]O</td>
<td>2(I)</td>
<td>![N₃]OH</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3(I)</td>
<td>![N₃]OH</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>![COCl]O</td>
<td>1.5(I)</td>
<td>![N₃]OH</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2(I)</td>
<td>![N₃]OH</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>![Cl]O</td>
<td>3(I)</td>
<td>![N₃]OH</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4(I)</td>
<td>![N₃]OH</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>![Cl]O</td>
<td>1.5(I)</td>
<td>![N₃]OH</td>
<td>91(88,12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2(I)</td>
<td>![N₃]OH</td>
<td>88(92,8)</td>
</tr>
<tr>
<td>8</td>
<td>![OH]O</td>
<td>3(I)</td>
<td>![N₃]OH</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4(I)</td>
<td>![N₃]OH</td>
<td>87</td>
</tr>
</tbody>
</table>

(a) All reactions were carried out in H₂O at room temperature. (b) I = PVA, II = PAA (c) Products were identified by comparison of their IR and NMR spectra and/or physical data with those reported in the literatures [22,39,44]. The ¹H NMR of products d and e as representative examples are: (d) ¹H NMR (CDCl₃): δ (ppm) 7.30-7.43 (m, 5H), 4.68 (dd, 1H), 3.77 (d, 1H), 2.74 (s, 1H). (e) ¹H NMR (CDCl₃): δ (ppm) 6.8-7.25 (m, 5H), 3.93 (d, 2H), 3.43 (m, 3H), 2.68 (s, 1H). (f) Regiochemical ratios determined by ¹H-NMR. (g) Yields refer to isolate yield.
CONCLUSION

In conclusion, PVA and PAA proved to be highly efficient polymeric cosolvent for regioselective ring opening of epoxides to azidohyrins by azide anion in aqueous solution. They played a special role as an electrophilic catalyst, as well, for such reaction. In comparison with most of the reported azidolysis reactions of epoxides no addition of Lewis acid, or basic catalysts are needed. The reaction is green and is performed in water. The polymeric cosolvents have the inherent advantages of a solid-phase catalyst, including operational simplicity, filterability and reuse.

ACKNOWLEDGEMENTS

We are thankful of Shiraz University Council for partial support of this work.

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