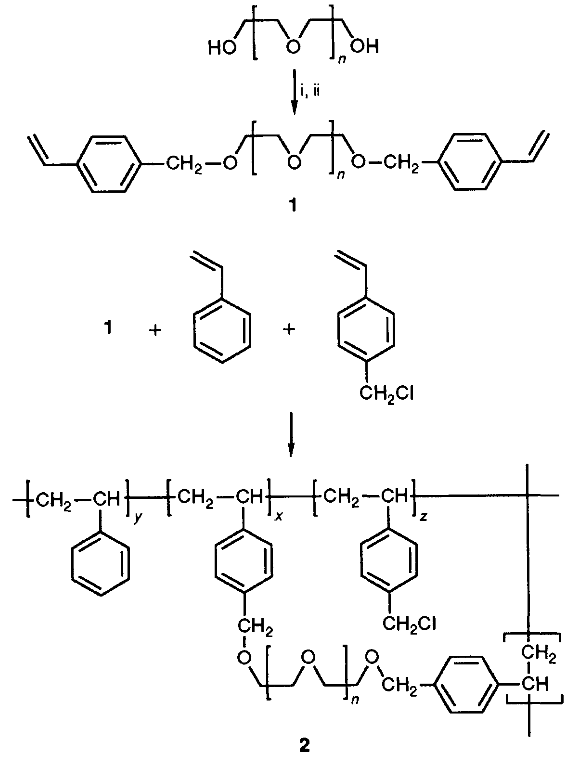
Oxyethylene Networks.[1] Nucleophilic Substitution Reactions of Chloromethylated Polystyrenes in Aqueous Media

Shinichi Itsuno,* Isao Moue and Koichi Ito

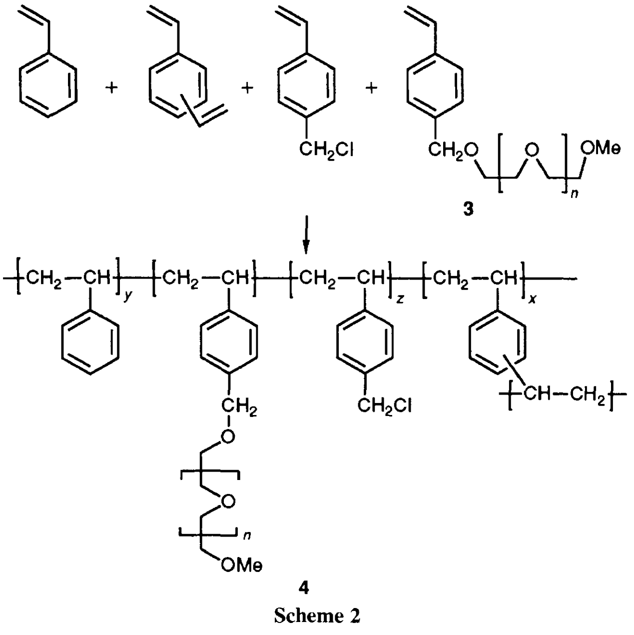
Department of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441, Japan

Some efficient nucleophilic substitution reactions have been achieved on the chloromethyl group of the polystyrene resin crosslinked with an oxyethylene chain in aqueous media.

Divinylbenzene (DVB)–styrene copolymers have been widely used as the starting materials for polymeric catalysts,[2,3] reagents[3] and protecting groups,[4] as well as for solid phase syntheses[3] of peptides and nucleotides. However, DVB crosslinked polystyrenes generally cannot undergo any reactions in aqueous media because of their strong hydrophobicity. Reactions such as the immobilisation of enzymes and their use, without denaturation of the protein, require polymeric materials which are applicable in aqueous media. Moreover, for toxicological, environmental, processing and kinetic



Scheme 1 *Reagents*: i, 2NaH, dimethylformamide (DMF); ii, 4-vinylbenzyl chloride



Scheme 2

Table 1 Preparation of chloromethylated crosslinked polystyrenes

Entry	Chloromethylated resin	Composition[a] [x]	:	[y]	:	[z]	n
1	**5**	2[b]	:	48	:	50	—
2	**2a**	10	:	40	:	50	0
3	**2b**	40	:	10	:	50	0
4	**2c**	5	:	45	:	50	3
5	**2d**	40	:	10	:	50	3
6	**2e**	10	:	40	:	50	7.7[c]
7	**2f**	40	:	10	:	50	7.7[c]
8	**2g**	6	:	44	:	50	21.3[d]
9	**2h**	13	:	37	:	50	21.3[d]
10	**4**	2[b]	:	41	:	50	23.0[e]

[a] Where x = **1**, y = styrene and z = vinylbenzyl chloride. [b] Crosslinking agent is DVB. [c] Calculated from average degree of polymerisation of PEG 400. [d] Calculated from average degree of polymerisation of PEG 1000. [e] Calculated from ^{1}H NMR data of macromonomer **3**.

Table 2 Reaction of chloromethylated crosslinked polystyrene with some nucleophiles in water

Entry	Chloromethylated resin	Nucleophile	Reaction time/h	T[a]/°C	FY[b] (%)
1	**5**	KSCN	24	r.t	0
2[c]	**5**	KSCN	24	r.t	0
3	**5**	KOPh	43	r.t	0
4	**5**	NaN_3	40	r.t	0
5	**5**	Potassium phthalimide	48	r.t	0
6	**5**	Potassium phthalimide	48	70	0
7	**2a**	KSCN	24	r.t.	0
8	**2b**	KSCN	24	r.t.	0
9	**2c**	KSCN	24	r.t.	0
10	**2d**	KSCN	24	r.t.	0
11	**2e**	KSCN	24	r.t.	17
12	**2f**	KSCN	24	r.t.	58
13	**2g**	KSCN	24	r.t.	45
14	**2h**	KSCN	24	r.t.	100
15	**2h**	KOPh	43	r.t.	74
16	**2h**	NaN_3	14	r.t.	55
17	**2h**	NaN_3	40	r.t.	90
18	**2h**	Potassium phthalimide	70	r.t.	12
19	**2h**	Potassium phthalimide	48	70	59
20	**4**	KSCN	24	r.t.	8

[a] r.t. = room temperature. [b] Functional yield (FY) determined by titration and elemental analysis. If all chloromethyl groups were converted into other functionality FY equals 100%. [c] Poly(ethylene glycol) (M_r = 2000) was added.

reasons, it is considered highly desirable to carry out polymer reactions in aqueous solution. Our investigation of crosslinkage in polystyrene resins, consisting of oxyethylene chains, or oxyethylene networks, could solve these problems.

In preliminary experiments, the chemical reactivity of chloromethylated polystyrene resins containing oxyethylene networks was evaluated in aqueous media. Chloromethylated polystyrene resins have been used most frequently as starting materials for functional polymers in organic solvents. This is owing to the ease with which displacement or addition reactions can be carried out on chloromethyl groups. The chloromethylated polystyrene resins **2** were prepared by terpolymerisation of styrene, 4-vinylbenzyl chloride and a crosslinking agent as shown in Scheme 1. Crosslinking agents having the oxyethylene chain **1** were prepared by coupling of 4-vinylbenzyl chloride with the sodium salts of the corresponding oligo(ethylene glycol)s as described previously.[1] The chain length of the crosslinking agent prepared can be varied by the choice of the commercially available oligo(ethylene glycol)s. These resins consist of spherically symmetrical beads. The content of oligo(oxyethylene) chain in the resin can also be readily controlled to balance the hydrophobicity and hydrophilicity of the resin. By the use of this crosslinking agent a flexible structure of crosslinkages was obtained, which gave swellable and mechanically stable resins even when the degree of crosslinking was very high (Table 1). Instead of using oxyethylene networks, a poly(oxyethylene) grafted polystyrene resin crosslinked with DVB, **4**, was also prepared using the macromonomer method in comparison (Scheme 2).

Reactions of various nucleophiles such as potassium thiocyanate (KSCN), potassium phenoxide (KOPh), sodium azide (NaN_3) and potassium phthalimide with the chloromethylated polystyrene resins were tested in aqueous media. The results are summarised in Table 2. Owing to their strong hydrophobicity, the polystyrene resins crosslinked with DVB **5** were floated on the water surface and no reaction occurred with nucleophiles (entries 1–6) even at elevated temperature. Although poly(ethylene glycol)s (PEGs) are known to act as phase transfer catalysts for insoluble polymer reactions,[5] addition of PEG (M_r = 2000) to this aqueous system had no effect on the reactivity of the chloromethylated polymer (entry 2). The crosslinking agent prepared from mono- (n = 0) and tetra-ethylene glycol (n = 3) should have given a more flexible structure than DVB. However, in aqueous media the same results as for those of DVB crosslinked polymers were obtained (entries 7–10). Thus, the short chain length crosslinkages including DVB could not provide enough hydrophilicity in the microenvironment of the crosslinked resins, even for polymers having a high content of oxyethylene chain. In these cases, increasing the quantity of the oxyethylene moiety did not increase the hydrophilicity but resulted in an inflexible highly crosslinked polystyrene. Substitution reactions occurred only when a longer chain of oxyethylene was used for crosslinking. These polymers were suspended entirely in aqueous solution and the long chain oxyethylene networks afforded sufficient hydrophilicity for the microenvironment of the polymer. In the case of **2h** quantitative conversion was attained in the reaction with potassium thiocyanate in aqueous solution at room temperature. Some other nucleophiles also reacted with chloromethyl groups of the polymer. In comparison, grafted oxyethylene chains in **4** were not very effective for these polymeric reactions (entry 20). The oxyethylene chains of **4** may not always exist close to the reactive site of the chloromethyl group in water.

In conclusion oxyethylene networks have been found to control the microenvironment of the crosslinked polymer. These polystyrene resins applicable in aqueous media would be useful for the immobilisation of materials soluble in water and for those sensitive to organic solvent. Functional groups other than the chloromethyl group in the polymer are currently under investigation.

Received, 10th July 1991; Com. 1/03498G

References

1 Part 1, S. Itsuno, I. Moue and K. Ito, *Polym. Bull.*, 1989, **21**, 365.

2 D. C. Bailey and S. H. Langer, *Chem. Rev.*, 1981, **81**, 109.

3 E. C. Blossey and W. T. Ford, in *Comprehensive Polymer Science*, ed. G. Allen, Pergamon Press, Oxford, 1989, vol. 6, p. 81; *Syntheses and Separations Using Functional Polymers*, ed. D. C. Sherrington and P. Hodge, Wiley, Chichester, 1988; *Polymer Supported Reactions in Organic Synthesis*, ed. P. Hodge and D. C. Sherrington, Wiley, Chichester, 1980; N. K. Mathur, C. K. Narang and R. E. Williams, in *Polymers as Aids in Organic Chemistry*, Academic Press, New York, 1980.

4 J. M. J. Fréchet, *Tetrahedron*, 1981, **37**, 663.

5 J. M. J. Fréchet, *Polym. Sci. Technol.*, 1984, **1**; S. Itsuno, K. Yamazaki, F. Arakawa, T. Kitano, K. Ito, E. Yamada and T. Matsumoto, *Kobunshi Ronbunshu*, 1986, **43**, 91; G. E. Totten and N. A. Clinton, *J. Macromol. Sci., Rev. Macromol. Chem.*, 1988, C28.