

Preparation and properties of stereoregular poly(hydroxyethyl methacrylate) polymers and hydrogels

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Linear poly(hydroxyethyl methacrylate) (HEMA) has been synthesized in highly syndiotactic and highly isotactic configurations. The high syndiotactic PHEMA prepared by u.v. photolysis at -40°C was found by ^{13}C n.m.r. to have a tactic triad content of 84% syndio, 16% hetero and 0% iso. High isotactic PHEMA was prepared by anionic polymerization of benzoxyethyl methacrylate in toluene followed by selective hydrolysis of the benzoate ester, and was observed by ^{13}C n.m.r. to have a 5% syndio, 15% hetero and 80% isotactic triad content. A linear PHEMA polymer formed by radical polymerization at 60°C in ethanol solvent was found to have a tactic triad content of 58% syndio, 42% hetero and 0% iso. These polymers have been crosslinked with hexamethylene diisocyanate and their water swelling properties determined as functions of temperature and crosslinker concentration. Isotactic PHEMA exhibited greater aqueous swelling below 30°C than the syndiotactic PHEMA samples. The stereochemistry of the polymer chain is shown to be a factor in determining the swelling behaviour of hydrophilic methacrylate gels.

INTRODUCTION

Hydrophilic polymers have been investigated as potential biocompatible materials¹. The most widely studied polymer in this class is poly(hydroxyethyl methacrylate) (HEMA)^{2,3}. We have been intrigued by the possibility of synthesizing this polymer in various tactic configurations and in learning how the tacticity would affect bulk swelling and interfacial properties.

The synthesis of methyl and other alkyl methacrylates of high stereoregularity is well known. Highly syndiotactic poly(methyl methacrylates) can be prepared by either of two methods; (1) radical polymerization at low temperature⁴, or (2) anionic polymerization in an ether solvent⁵. Isotactic poly(methyl methacrylate) was synthesized by anionic polymerization in non-polar solvents⁵⁻⁷. The low temperature radical initiation method is suitable for obtaining highly syndiotactic PHEMA, but to prepare highly isotactic polymer by means of anionic initiation, some method must be used to block the hydroxyl group on HEMA. The blocking group must also be readily removable after polymerization without interfering with the methacrylate ester linkage. The benzoate ester was found suitable for this purpose.

Finally the syntheses described here produce essentially uncrosslinked polymers. To study the swelling behaviour, a method had to be devised to post-crosslink the polymers. Hexamethylene diisocyanate was used for this purpose to obtain the desired hydrophilic gels.

RESULTS AND DISCUSSION

Polymer synthesis

In the normal preparation of hydroxyethyl methacrylate polymers, thermal decomposition of a radical source is used to initiate polymerization⁸. Although different initiators are used for this purpose, the thermolysis is commonly run between 50° to 70°C . If little or no solvent is used in this procedure, an insoluble gel or crosslinked polymer is produced due to radical chain transfer mechanisms. From experience, the initiator and solvent have little or no effect on tacticity, but polymerization temperature produces moderate changes in tacticity⁴. Soluble polymer is obtained only above a dilution of greater than 60% solvent, and these soluble polymers are routinely obtained by us by polymerizing at 9:1 v/v solvent to monomer concentration at 60°C using azobis(methyl isobutyrate)⁸ as the initiator.

Highly syndiotactic PHEMA was synthesized by radical polymerization at low temperature. Utilizing a reactor design as shown in *Figure 1*, polymer in a yield of 28% resulted after only 4 h of u.v. photolysis at -40°C .

The production of isotactic PHEMA required the use of a suitable blocking group on the free hydroxyl of HEMA. Previous preparations of isotactic poly(alkyl methacrylates) have utilized organometallic bases in non-polar solvents. These, of course, would abstract the free hydroxyl proton and the initiator would be quenched. An ester group containing no α protons should be suitable as a blocking group

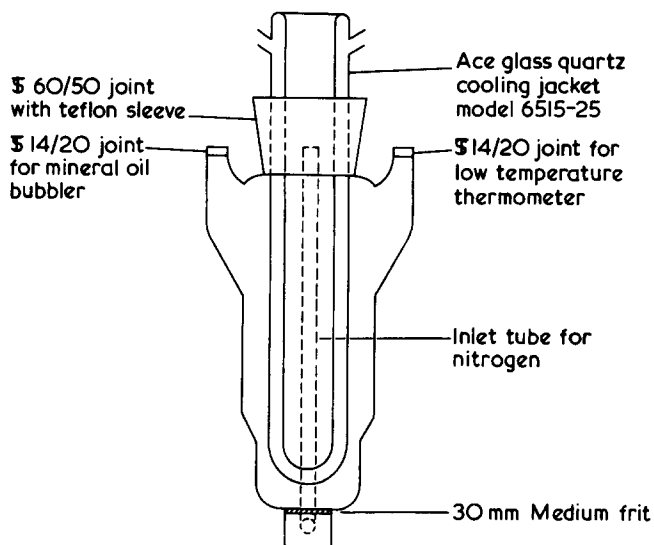


Figure 1 Photolysis vessel for low temperature ultra-violet polymerization of monomers

during polymerization, providing that it could be selectively removed after polymerization. This proved to be the case with the benzoate ester of hydroxyethyl methacrylate (Figure 2a). A standard anionic initiator for alkyl methacrylate polymerization is *n*-butyllithium. However, when this initiator was used with benzoxyethyl methacrylate in toluene at -10°C , only a low yield of high polymer was produced. The infra-red spectrum of the product showed a large absorption in the hydroxyl region, indicating ester hydrolysis had occurred during the reaction. This is not surprising since *n*-butyllithium is known to react readily with unhindered esters. Recently, dialkyl copper lithium reagents⁹ have found popular use in chemical synthesis for selective addition to α , β -unsaturated ester and ketone double bonds. Essentially no reaction at the carbonyl is noted with this reagent. This reagent probably exists as a $\text{Li}^+(\text{R}_2\text{Cu})^-$ complex¹⁰. Using this reagent as initiator, a good yield of isotactic poly(benzoxyethyl methacrylate) was produced (Figure 2b). The infra-red spectrum shows that negligible ester hydrolysis occurred with this initiator. To our knowledge, this is the first reported use of the dialkyl copper lithium complex as a polymerization initiator for vinyl monomers.

Selective hydrolysis of the benzoate ester occurred using aqueous KOH. Recently, it has been shown that base hydrolysis of poly(acetoxyethyl methacrylate) also occurs selectively at the acetate ester¹¹. This result is expected since the methacrylate ester is α to a quaternary carbon and therefore sterically hindered to nucleophilic attack as compared to the acetoxy and benzoxy groups.

¹³C n.m.r. spectra of polymers

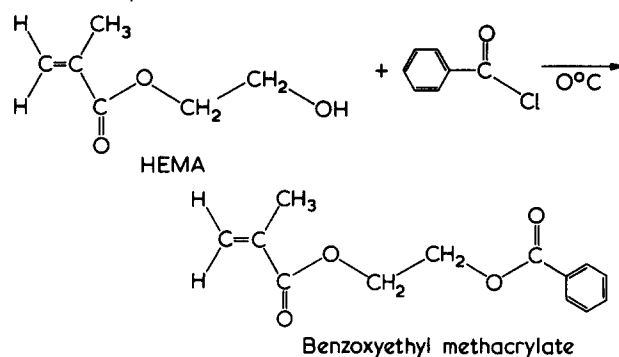
Poly(methyl methacrylate) was one of the first polymers to be characterized by high resolution ¹H n.m.r.¹². Since this first publication, a large number of studies have been made, especially as each succeeding generation of n.m.r. spectrometers has been introduced. Bovey cited over twenty such studies of both ¹H and ¹³C n.m.r. in one review¹³. The ¹³C n.m.r. spectra of predominately syndiotactic and of isotactic poly(methyl methacrylate) obtained using Fourier transform techniques has recently been published by us¹⁴. As a result of these studies, we can now routinely determine the tacticity of the methacrylate polymer from its ¹³C n.m.r. spectrum. The spectrum

of PHEMA produced by photolysis at -40°C using u.v. irradiation is shown in Figure 3a. The spectrum of PHEMA radically initiated at 60°C is shown in Figure 3b. In Figure 3c is shown the spectrum of isotactic PHEMA produced by polymerizing benzoxyethyl methacrylate at -10°C using (*n*Bu) LiCu and hydrolysing the resulting poly(benzoxyethyl methacrylate) with aqueous potassium hydroxide. As we can see, the α -methyl carbon splits into a triplet at 45.1 ppm, 48.1 ppm and 50 ppm upfield from dioxane due to the presence of isotactic, heterotactic and syndiotactic triads, respectively. The Fourier transform n.m.r. spectra were obtained by dissolving 200 mg/ml of polymer in methanol. The n.m.r. probe was heated to 50°C to increase chain mobility so as to obtain narrow linewidths. The spectra were plotted after accumulation of 2000–4000 free induction decays (FIDs), and are typical of those used for determination of tacticity of all polymers in this study (Table 1).

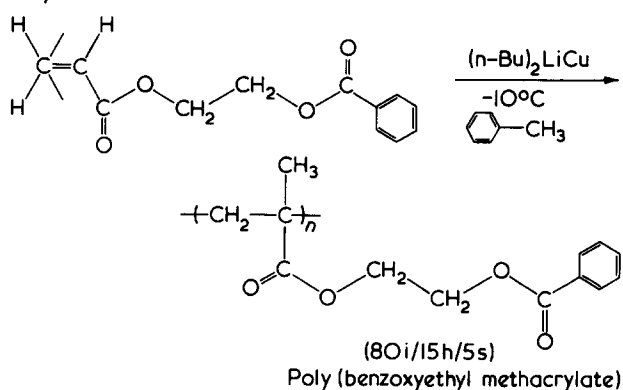
Crosslinking of polymers and aqueous swelling studies

Several different polymerization techniques were used to produce polymers for crosslinking studies. Consequently,

a Monomer synthesis



b Polymerization



c Conversion to PHEMA

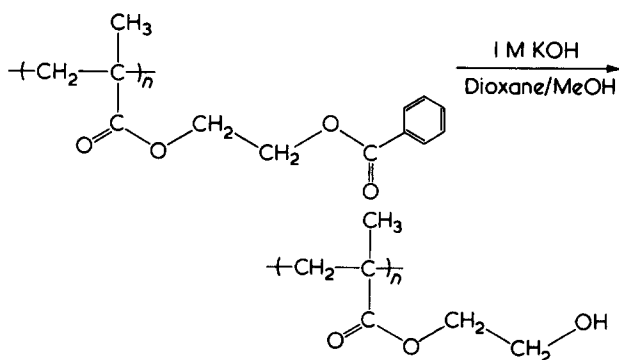


Figure 2 Synthesis of isotactic PHEMA from benzoxyethyl methacrylate

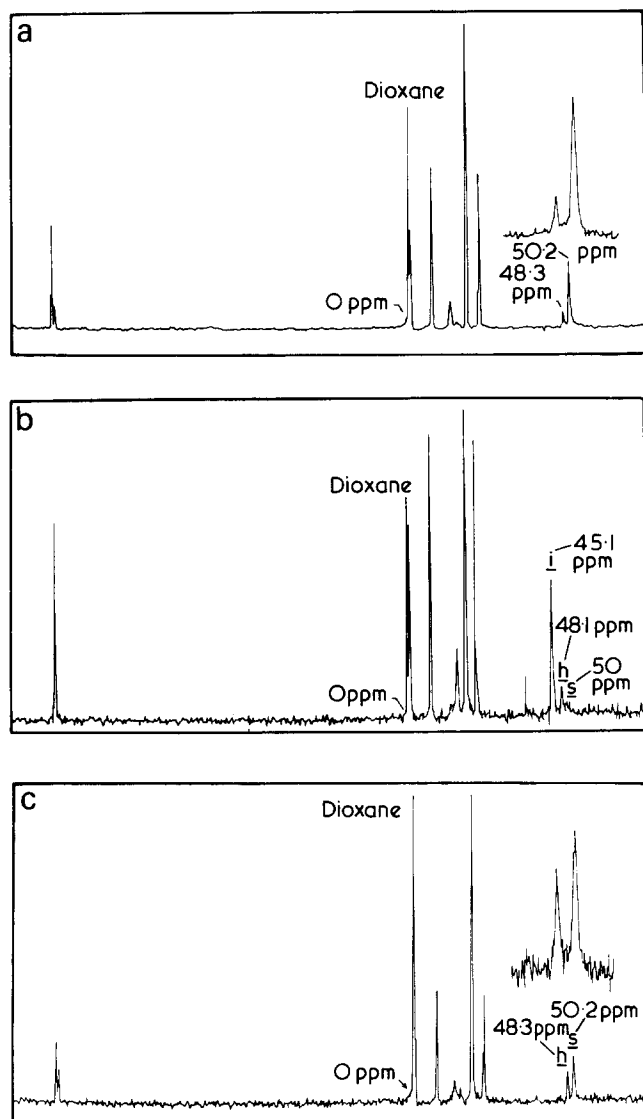


Figure 3 25.2 MHz ^{13}C n.m.r. spectra. A, Syndiotactic PHEMA produced by u.v. photolysis at -40°C ; B, isotactic PHEMA produced by alkaline hydrolysis of isotactic poly(benzoxethyl methacrylate) and C, PHEMA produced by thermal decomposition of a radical initiator at 60°C from 10% HEMA in ethanol, v/v

we wished to compare the molecular weight distributions of the various polymers, since molecular weight distribution could influence the degree of crosslinking, and hence the swelling properties. To increase the solubility of PHEMA in non-polar eluents such as tetrahydrofuran (THF), the side chain hydroxyl groups were esterified with propionic anhydride. To ensure complete esterification, treatment with propionic anhydride was continued until no hydroxyl absorption remained in the i.r. spectra of the samples. The esterified polymers were chromatographed using μ Styragel columns (Waters Associates) with nominal pore sizes of 5×10^2 , 3×10^4 , and 10^5 Å. Tetrahydrofuran (Burdick & Jackson) was used as eluent. A Waters Associates Model 401 differential refractometer was used as a detector. The column set was calibrated using narrow MWD polystyrene standards (Pressure Chemical). The resulting g.p.c. chromatograms are shown in Figure 4. The abscissa is calibrated in polystyrene equivalent molecular weight units rather than in absolute molecular weight units. The u.v. initiated polymer exhibits a bimodal molecular weight distribution, probably as a result of two simultaneous mechanisms for chain initia-

tion: (1) photolysis of AMIB to form two isobutyrate radicals, and hence two growing chains, and (2) direct photolysis of the vinyl double bond of HEMA monomer to form a di-radical, resulting in a chain growing at both ends. The effect of the two growth processes on tacticity is not known.

Crosslinking of the polymers was effected by hexamethylene diisocyanate. Care was used to maintain anhydrous conditions during crosslinking. The polymers were dried to constant weight in a vacuum of 10^{-3} mmHg, and then dissolved in anhydrous dimethyl formamide (DMF). The desired amount of hexamethylene diisocyanate was added to a known amount of polymer solution, mixed well and the crosslinking carried out at 60°C for 24 h under a blanket of argon in a closed oven. After this time, the oven was evacuated under reduced pressure to remove the DMF solvent. The gels were placed in distilled water in glass vials, equilibrated for 2 days, removed and dried. This was done until both the wet weight and dry weight equilibrated. A temperature range of 10° to 90°C was covered. Figure 5 shows the equilibrium swelling of each of the tactic polymers at 5% crosslinker concentration. Table 2 shows the effect of swelling with temperature for each of the polymers. The aqueous swelling of PHEMA gels crosslinked during polymerization has been reported previously^{15,16}. The tacticity of

Table 1 Polymerization conditions and triad tacticities for PHEMA polymers

Initiator	Solvent	Reaction temperature ($^\circ\text{C}$)	Triad content ^a		
			i	h	s
AMIB ^b	Ethanol	60	<1	42	58
AMIB	Methanol	-40	<1	16	84
$(n\text{-Bu})_2\text{LiCu}^c$	Toluene	-10	80	15	51

^a Determined by height times width at half-height method unless otherwise noted;

^b AMIB = azobis(methyl isobutyrate);

^c monomer used is benzoate ester of hydroxyethyl methacrylate. After polymerization the poly(benzoxethyl methacrylate) is hydrolyzed to PHEMA;

^d Integrated using compensating polar planimeter (5 passes)

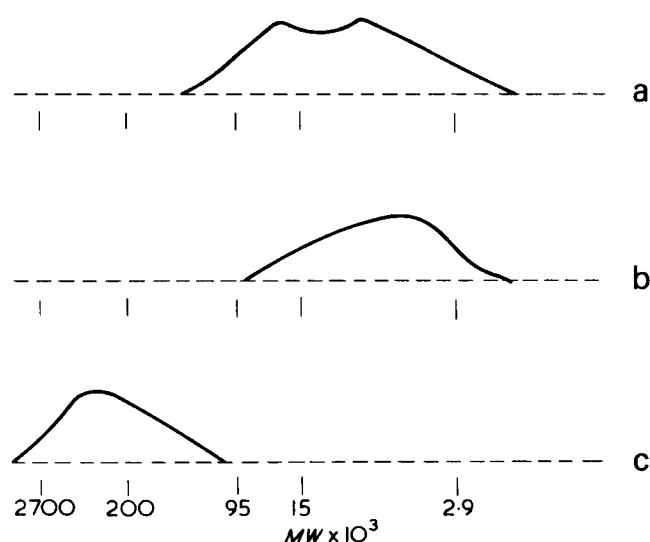


Figure 4 Gel permeation chromatograms of propionic esters of the tactic HEMA polymers calibrated against narrow molecular weight distribution polystyrene standards. A, syndiotactic PHEMA; B, isotactic PHEMA and C, PHEMA produced by thermal decomposition of a radical initiator at 60°C from 10% HEMA in ethanol, v/v

the PHEMA in refs 15 and 16 would correspond closely to the tacticity of our 60°C polymerized PHEMA, i.e. about 60% syndiotactic triads. The results show a slight swelling minimum at about 70°C. The effect of temperature on the swelling of other hydrophilic methacrylates (and acrylates) has been reported for poly(propylene glycol monoacrylate)¹⁵, poly(glycerol methacrylate)^{16,17} and poly(2-hydroxypropyl methacrylamide)¹⁶. Poly(glycerol methacrylate) shows an increase in swelling with temperature, an endothermic process. The poly(propylene glycol monoacrylate) and poly(2-hydroxypropyl methacrylamide) show a decrease in swelling with temperature, an exothermic process. [We have also noted exothermic swelling with poly(methoxyethoxyethyl methacrylate) and poly(methoxyethoxyethyl methacrylate)]. The PHEMA with a tactic content of ~58 h, 42 S, 0 i has a swelling minimum at ~60°C. There does not seem to be a noticeable effect in aqueous swelling between the syndiotactic PHEMA and the 60°C polymerized PHEMA. This is not unexpected since there is only a slight difference

in tacticity between the two polymers. The isotactic PHEMA shows a noticeable swelling increase at low temperatures even though a swelling minimum is still noted at between 50° to 70°C.

Highly syndiotactic PHEMA shows abnormally high swelling in the uncrosslinked polymer and gels with 1% crosslinker added. These gels seem to overswell in water and take on an opaque appearance. In addition the same gel exhibits non-reproducible swelling when measured several times for equilibrium water content and swells to a higher value than would be predicted from the higher crosslinked syndiotactic PHEMA. The uncrosslinked or lightly crosslinked PHEMA no longer retains its shape when equilibrated with water but starts to show viscous flow indicating that the polymer contains minimal effective crosslinks. The lower molecular weight of these materials could affect its effective crosslink density and, therefore, allow it to absorb a greater amount of water than expected. All the other gels are homogeneous and clear at equilibrium water content. The increased swelling of isotactic PHEMA is also pronounced in the uncrosslinked case where it tends to dissolve in water, especially at low temperatures. Isotactic PHEMA gels prepared with 0.5 and 1% crosslinker microphase separate when equilibrated at 10°C and rapidly warmed to room temperature. This seems to be characteristic of gels which show a marked change in swelling with temperature.

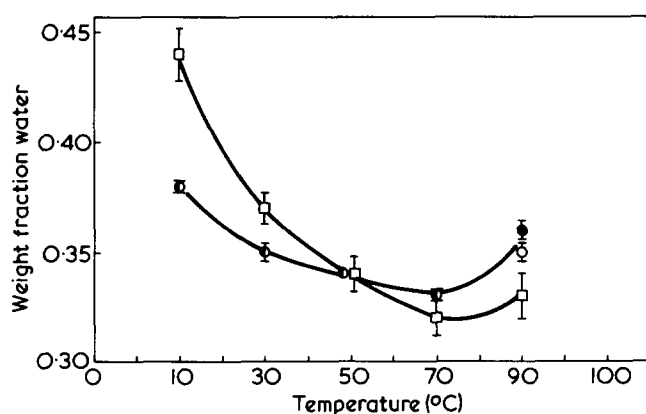


Figure 5 Equilibrium water content of tactic HEMA polymers as a function of temperature. 5% crosslinker concentration was used for gelation of polymers. □, Isotactic PHEMA; ●, 60°C initiated PHEMA; ○, syndiotactic PHEMA

EXPERIMENTAL

All hydroxyethyl methacrylate (HEMA) used in this work was highly pure (Hydron Laboratories Inc.). Typically, this HEMA contains 0.4% methacrylic acid, 0.02% ethylene dimethacrylate, 0.15% diethylene glycol monomethacrylate and 0.11% water. The initiator, azobis(methyl isobutyrate) was prepared from azobisisobutyronitrile by the method of Mortimer¹⁸. Infra-red (i.r.) spectra were obtained on a Beckman Acculab 1 Instrument and nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian XLFT-100

Table 2 Water fraction of tactic HEMA polymers in distilled water as a function of temperature and crosslinker concentration. These equilibrium values represent an average of four determinations with a range of ± 1 standard deviation

	Temperature (°C)	Syndiotactic PHEMA 84% <i>s</i> , 16% <i>h</i> , 0%	60°C Polymerized 58% <i>s</i> , 42% <i>h</i> , 0%	Isotactic PHEMA 5% <i>s</i> , 15% <i>h</i> , 80%
No crosslinker	10	0.51 ± 0.034	0.44 ± 0.004	0.54 ± 0.002
	30	0.51 ± 0.019	0.40 ± 0.010	0.44 ± 0.004
	50	0.41 ± 0.012	0.38 ± 0.015	0.39 ± 0.010
	70	0.43 ± 0.024	0.37 ± 0.007	0.39 ± 0.004
	90	0.57 ± 0.033	0.40 ± 0.005	0.41 ± 0.012
1% Crosslinker	10	0.46 ± 0.028	0.43 ± 0.002	0.51 ± 0.001
	30	0.42 ± 0.018	0.39 ± 0.004	0.43 ± 0.002
	50	0.43 ± 0.022	0.37 ± 0.002	0.38 ± 0.003
	70	0.40 ± 0.024	0.36 ± 0.004	0.36 ± 0.002
	90	0.43 ± 0.024	0.39 ± 0.001	0.37 ± 0.002
5% Crosslinker	10	0.38 ± 0.002	0.38 ± 0.001	0.44 ± 0.012
	30	0.35 ± 0.004	0.35 ± 0.002	0.37 ± 0.007
	50	0.34 ± 0.001	0.34 ± 0.001	0.34 ± 0.008
	70	0.33 ± 0.002	0.33 ± 0.001	0.32 ± 0.008
	90	0.37 ± 0.004	0.36 ± 0.004	0.33 ± 0.010
10% Crosslinker	10	0.33 ± 0.001	0.33 ± 0.004	0.37 ± 0.009
	30	0.31 ± 0.004	0.30 ± 0.004	0.33 ± 0.006
	50	0.30 ± 0.003	0.30 ± 0.003	0.30 ± 0.006
	70	0.30 ± 0.003	0.29 ± 0.006	0.30 ± 0.004
	90	0.33 ± 0.002	0.32 ± 0.002	0.30 ± 0.004

† Phase separated; ‡ 0.5% crosslinker

instrument. Elemental analyses were obtained from Galbraith Laboratories Inc., Tennessee. Molecular weights were determined by g.p.c. (Water Associates, μ -Styragel columns) on the propionate esters of the PHEMA polymers using tetrahydrofuran as eluent.

Preparation of syndiotactic poly(hydroxyethyl methacrylate)

Into a specially prepared reaction vessel (Figure 1), containing a low temperature thermometer and a nitrogen bleed was added a solution containing 100 ml hydroxyethyl methacrylate, 100 ml methanol and 0.35 g of azobis (methyl isobutyrate). A Hanovia u.v. source fitted with quartz cooling jacket was fitted into the reaction vessel and the reaction vessel was cooled with a dry ice-acetone bath. The reaction was photolysed at -40°C during which the progress of the reaction was monitored by pipetting a small amount of the reaction solution into anhydrous diethyl ether and observing the amount of polymer precipitated. After 3 h the reaction was stopped. The polymer was isolated by precipitation from anhydrous diethyl ether (750 ml) and dried in vacuum to yield 30 g of a white, brittle, amorphous solid. I.r.: 4320, 2960, 1730, 1155 cm^{-1} . Elemental analysis: calculated for $\text{C}_5\text{H}_{10}\text{O}_3$: C, 55.37; H, 7.75; found: C, 54.05; H, 7.92.

Preparation of benzoxyethyl methacrylate

To a 100 ml, 3 neck, round bottom flask containing a thermometer, pressure equalizing dropping funnel and magnetic stirrer was added a solution containing 100 ml (107 g 0.82 mol) hydroxyethyl methacrylate, 73 ml (65 g, 0.90 mol) pyridine, 300 ml anhydrous benzene and 300 ml 30° – 60° petroleum ether. Benzoyl chloride (10.5 ml, 127 g, 0.90 mol) was added slowly to the stirred solution, and the reaction temperature kept between 10° and 20°C with an ice bath. After 12 h, the reaction was filtered to remove the pyridine hydrochloride salts. The filtrate was exhaustively washed with 5% HCl then washed twice with 5% NaOH and twice with distilled water. After drying (MgSO_4), the solvent was removed under reduced pressure and the product was vacuum distilled to yield 158 ml (177 g) of a colourless oil, b.p. 125°C , 0.8 mmHg.

Preparation of isotactic poly(benzoxyethyl methacrylate)

To a 250 ml, 3 neck, round bottom flask containing a thermometer, nitrogen bleed, pressure equalizing dropping funnel and magnetic stirring bar was added 100 ml dry toluene, 0.3 g cuprous iodide, and 2 ml of 1.6 M n-butyllithium in hexane. Upon the addition of the n-butyllithium, a fine black precipitate formed in the flask. The temperature was kept at -10°C with an ice-salt bath and a blanket of nitrogen was maintained over the reaction. 20 ml benzoxyethyl methacrylate was added and after 4 h the reaction was stopped by the addition of 10 ml of methanol. The insoluble catalyst was removed by centrifugation and the polymer was isolated by pouring the solution into 500 ml 30° – 60° petroleum ether. The polymer was dried in vacuum to yield 13.9 g of a pale yellow solid. I.r.: 2950, 1720, 1265, 1100, 700 cm^{-1} . Elemental analysis: calculated for $\text{C}_{13}\text{H}_{14}\text{O}_4$: C, 66.66; H, 6.02; found: C, 66.64; H, 6.02.

Preparation of isotactic poly(hydroxyethyl methacrylate)

A solution containing 0.5 g poly(benzoxyethyl methacrylate), 30 ml dioxane and 20 ml methanol was heated to 60°C . To this was slowly added a solution of 0.3 g KOH in 5 ml water. A precipitate formed initially, but at the end of the reaction the solution was homogeneous. After reacting for

10 min, the reaction was cooled to room temperature and poured into 250 ml water. The water was acidified to pH 5 with 5% HCl and then saturated with sodium chloride. The polymer was isolated and redissolved in 5 ml ethanol. Reprecipitation in 50 ml of diethyl ether and vacuum drying yielded 0.26 g white, amorphous isotactic poly(hydroxyethyl methacrylate). I.r. 3420, 2960, 1730, 1160 cm^{-1} . Elemental analysis: calculated for $\text{C}_5\text{H}_{10}\text{O}_3$: C, 55.37; H, 7.75; found: C, 54.22; H, 8.07.

Preparation of poly(propionyloxyethyl methacrylate)

Poly(hydroxyethyl methacrylate), 0.50 g, was dissolved in 5 ml anhydrous pyridine. 5 ml of propionic anhydride was added to the solution and reacted at 60°C for 12 h. The polymer was isolated by pouring into 50 ml water. After extensive washing with water the polymer was redissolved in 10 ml methylene chloride, and reprecipitated in 40 ml 30° – 60° petroleum ether. The reaction was quantitative as judged by the disappearance of the hydroxyl absorption in the infra-red. I.r. 2980, 2940, 1730, 1450, 1170 cm^{-1} .

Crosslinking poly(hydroxyethyl methacrylate) with hexamethylene diisocyanate

Into a polyethylene mould (Scientific Products, Illinois) was placed a solution 0.100 g poly(hydroxyethyl methacrylate) dissolved in 1 ml of anhydrous dimethyl formamide. Hexamethylene diisocyanate in the required molar amount was added and the solution was mixed thoroughly. The crosslinking was carried out in a closed oven at 60°C for 24 h after which the gels were placed under vacuum for 12 h to remove the solvent. The last traces of DMF were removed by equilibrating the polymer in water and drying in vacuum until the dry weight remained constant. The equilibrium water fraction was determined by placing the gels into 20 ml distilled water for two days in a thermostatically controlled water bath, the excess water was removed from the gel by lightly tamping between filter paper and they were weighed. The gels were dried at 60°C for 18 h in vacuum for constant weight. Four gels were used for each swelling determination.

$$\text{Water fraction} = \frac{\text{Wt hydrated gel} - \text{Wt dry gel}}{\text{Wt hydrated gel}}$$

CONCLUSIONS

The aqueous swelling of hydrogel is due primarily to water interactions with hydrophilic groups of the polymer. In non-charged polymers, these interactions are primarily due to hydrogen bonding between water and the hydrophilic groups. It appears that these polymers are separated into microdomains of hydrophilic and hydrophobic regions. In poly(hydroxyethyl methacrylate) the hydrophilic region is probably dominated by the free hydroxyl group, and the hydrophobic region is composed of the polymer backbone.

The aqueous swelling behaviour of isotactic and syndiotactic poly(hydroxyethyl methacrylate) is interesting as the chemical structures are identical but the stereochemistry is different. As demonstrated in Table 2 the stereochemistry does influence the swelling behaviour of PHEMA. The exact conformation of the PHEMA chains has not yet been determined. Stereoregular poly(methyl methacrylate) PMMA has been well studied^{5,6,19}. Isotactic and syndiotactic PMMA has been shown to crystallize in different molecular

arrangements^{4,20}. Recently it has been proposed that isotactic PMMA exists as double helix²¹. It is reasoned that tactic PHEMA has similar conformational changes. Undoubtedly, the stereochemistry of tactic PHEMA is a factor in determining swelling behaviour of the hydrophilic gels.

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