The swelling characteristics of some hydrogels prepared by ring-opening metathesis polymerization

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Abstract

A series of hydrogels have been prepared by cross-linking polymers formed by the ring-opening metathesis polymerization of *exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride. The polymerization reactions are carried out in various alcoholic solvents which provide ester functionality on the side chain and thereby a means of controlling gel swelling characteristics. These materials swell reversibly in aqueous fluids and their equilibrium water content is sensitive to both the temperature and the pH of the medium. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

One of the factors which has driven the development of polymer chemistry in recent years has been the need to produce new materials for medical and pharmaceutical applications. An important aspect of this development has been the synthesis of materials which will swell isotropically when in contact with aqueous fluids but yet retain significant mechanical strength. A number of these materials respond to environmental parameters such as pH and temperature and small changes in these can lead to dramatic variations in their water content and dimensions. When swollen these hydrogels frequently have equilibrium water contents (EWC) $> 95\%$ which means that they bear a strong resemblance to human tissue and this biocompatibility has led to their exploitation as surgical prosthesis and devices for the site specific delivery of drugs [1].

Although a number of these materials are derived from biopolymers the majority are synthetic and many are the product of the polymerization of α-olefins usually in the presence of small amounts of α,ω-diolefins which act as cross-linking agents and prevent dissolution of the gel [2]. Ring-opening metathesis polymerization (ROMP) of cyclic olefins has only recently been applied to the synthesis of these materials [3,4] and the method has great potential because many potential monomers are syn-

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thetically very accessible via the Diels–Alder reaction and the catalyst systems now available, a number of which can operate in aqueous media, allow wide variations in polymer microstructure [5].

The strategy we have adopted is to prepare precursor polymers from readily available monomers using accessible catalyst systems; these soluble polymers may then be fully characterized prior to cross-linking and gel formation and this allows structure property relationships to be studied.

The repeating units of these polymers have both carboxylic acid and ester functionality: the former allowing the polymer to respond to changes in the pH of the medium whilst the latter permits one to control the hydrophilic–lipophilic balance.

2. Experimental section

2.1. Monomers and catalysts

exo-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **1**, Scheme 1, was prepared from the *endo* isomer (Aldrich) by thermal isomerisation and multiple crystallization [6] and *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, **2**, (Aldrich) was used as received. Half-esters, **3**, were easily prepared by heating solutions of the anhydride in the appropriate alcohol for 72 h at 50°C followed by distillation of the excess solvent under vacuum. The crude product was dissolved in methylene chloride and washed in water several times to remove the last traces of alcohol. This was followed by
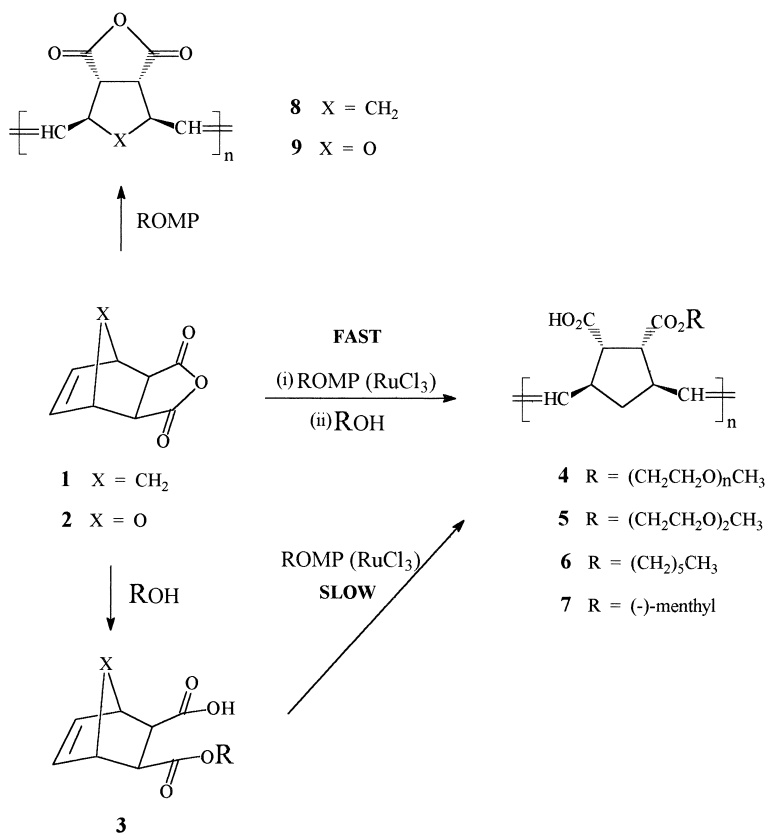
Scheme 1.

drying and removal of the solvent to yield the product as a colourless oil.

The catalysts, $RuCl_3 \cdot nH_2O$ (Aldrich), K_2RuCl_5 (Johnson Matthey), $[(p-cymene)RuCl_2]_2$ (Aldrich), and the Grubb's catalyst $RuCl_2(CHC_6H_5)[P(C_6H_{11})_3]_2$ (Strem), were used as received. Poly(acrylic acid) MW 250 000 (Aldrich) was received as a 35 wt.% aqueous solution and was diluted with the appropriate amount of distilled water before film casting. The solvents diethylene glycol, diethylene glycol monomethylether, hexanol, poly(ethyleneglycol monomethyl ether) MW 350 and (−)-menthol were commercial samples and were used as received, methylene chloride and THF were distilled from CaH_2.

2.2. Polymer synthesis

The various half-ester polymers were prepared by a modification of a previously reported procedure [3]. Typically, 5 g anhydride **1** was suspended in 15 cm^3 chlorobenzene and 15 cm^3 of the respective alcohol followed by flushing with Ar for 15 min. 50 mg of $RuCl_3 \cdot nH_2O$ then added and the reaction mixture heated under Ar at 80°C with stirring for 48 h. The resulting viscous solution was diluted with acetone and the polymeric product precipitated twice in diethyl ether; both solvents were previously flushed with Ar and contained 2,5-di-^{t}butyl-4-methylphenol (Aldrich) as an antioxidant. Typically, yields of 70% were recorded for polymers **5**, **6** and **7**, and 20% for **4**.

The poly(anhydride) **8** was prepared directly from **1** using either the $[(p-cymene)RuCl_2]_2$ [7], or the Grubb's catalyst [8] in dry, Ar-sparged, methylene chloride. **9** was isolated as the diacid after polymerization with K_2RuCl_5 in distilled water under Ar [9]. **1** and **2** were also polymerized in good yield with the Grubb's catalyst using dry THF solutions of these monomers because of their poor solubility, particularly **2**, in methylene chloride; however, methylene chloride solutions of the catalyst were used.

2.3. Gel preparations

Gel formation was accomplished by adding cross-linking agent to 240 mg/cm^3 THF solutions of the respective polymers, followed by film casting on a Teflon substrate. Thus 70 mg diethylene glycol was added to 7 cm^3 of the solutions of **4**, **5**, or **6**, and dry HCl gas bubbled through for 5 min before casting the film. Alternatively 1 cm^3 of a 0.23 M solution of S_2Cl_2 in CH_2Cl_2 was added to 5 cm^3 of the solutions of **5**, or **6**, in THF before film casting. On evaporation of the solvent films were peeled from the substrate and dried under vacuum. S_2Cl_2 cross-linked films were used without further treatment, but diethylene glycol cross-linked materials were heated under vacuum at 80°C for 4 h.

In the case of poly(diacid)s, 600 mg samples of **8** or **9** were added to 6 cm^3 distilled water and, after the polymer had dissolved (overnight for **9**, and approximately one week for **8**), 112 mg diethylene glycol was added and films cast and treated as above.

2.4. Swelling experiments

Swelling experiments were carried out using 1 cm diameter discs cut from the gel films with a steel punch. Swelling isotherms (Fig. 2) were constructed from data obtained from experiments run simultaneously on discs immersed in McIlvaine-type phosphate/citrate buffer solutions of various pH, constant ionic strength of 0.1 M was maintained by addition of solid KCl to each buffer [10]. Fresh aliquots of the buffer solutions were used in succession during each swelling experiment and water uptake was monitored throughout by carefully removing the gel from the solution, drying off excess water on filter paper and immediately weighing. After attainment of maximum water uptake ($Wt._{wet}$) the gels were dried under vacuum to constant weight ($Wt._{dry}$) and the EWC determined according to the equation:

$$\% \ EWC = [Wt._{wet} - Wt._{dry}]/[Wt._{wet}] \cdot 100$$

Variable temperature (Fig. 3), kinetic (Fig. 4) and gel swelling/deswelling experiments (Fig. 5) were each carried out using a similar protocol by changing the appropriate experimental parameters.

3. Polymer synthesis and characterization

The polymers described here are based on the commercially available Diels–Alder adduct of cyclopentadiene and maleic anhydride which is converted to the more reactive *exo* isomer, **1**, by thermal isomerization [6] and polymerized using the RuCl$_3$ catalyst in the presence of various alcohols, which act both as solvent and esterifying agent [3] in a one-pot process (Scheme 1). The *exo* isomer of the 7-oxa analog, **2**, is commercially available but was not used in this direct synthesis of half-ester polymers because of the facile retro-Diels–Alder reaction which occurs at the reaction temperature.

The easily formed half-ester monomers, **3**, were not used in the present study because of their low reactivity with the RuCl$_3$ catalyst although they may be polymerized using preformed metallocarbene complexes such as the Grubbs initiator, and this is the subject of current studies.

In these reactions the RuCl$_3$ catalyst engages in other processes besides ROMP and although it appears to catalyse the esterification reaction it also acts less beneficially as an efficient oxidation catalyst and is responsible, in conjunction with molecular oxygen, for the oxidative degradation of the polymers. We had observed that samples of these polymers prepared under aerobic conditions, even after work-up and redissolving in THF for GPC analysis, underwent a quite dramatic reduction in molecular weight; hydrogels derived from these lower molecular weight polymers were found to be mechanically very weak. Samples prepared identically but with rigorous exclusion of oxygen, were stable in this respect and molecular weights between

6×10^5 and 7×10^5, based on polystyrene standards, were routinely recorded.

The essential nature of this 'one-pot' reaction was determined by investigating the composition of polymers formed at various stages in the reaction in the presence of various alcohols. For example, with relatively unreactive, higher alcohols, the polymers isolated at low monomer conversion, have a much lower degree of esterification than that found at high conversion, so clearly in these cases the rate of metathesis exceeds the rate of esterification; at high monomer conversion half-ester repeating units are formed exclusively. In contrast, when the more reactive methanol was used as the solvent the rate of esterification greatly exceeds the rate of metathesis and only half-ester monomer, which as indicated above is reluctant to polymerize, is recovered.

The fact that mono- and diesterification of the anhydride group is a sequential process, means that the polymers should have a half-ester repeating unit structure and this is confirmed by integration of the side chain and main chain signal groups in the spectra of these polymers (Fig. 1a and b). The ^{13}C NMR spectra of these polymers, typified by the hexyl ester, Fig. 1b, are in fact very simple, primarily because we believe that $> 95\%$ of the double bonds are trans, an assumption based on the traditional behaviour of the RuCl$_3$ catalyst [5]. Minor splitting on the C^{2,3} and C^{1,4} signals is due either to sensitivity to the placement of the ester substituent relative to the double bond (head or tail) or to a tacticity effect; further work using optically active monomers would be required to differentiate the two possibilities [11]. We do not believe that the polymer microstructure is biased towards a head-to-head (tail-to-tail) or head-to-tail orientation since it has been shown that ROMP precedes esterification which would then be expected to occur at random along the polymer chain.

Water-soluble polymers with a diacid repeating unit, which on cross-linking undergo extremely rapid swelling, may be prepared di-
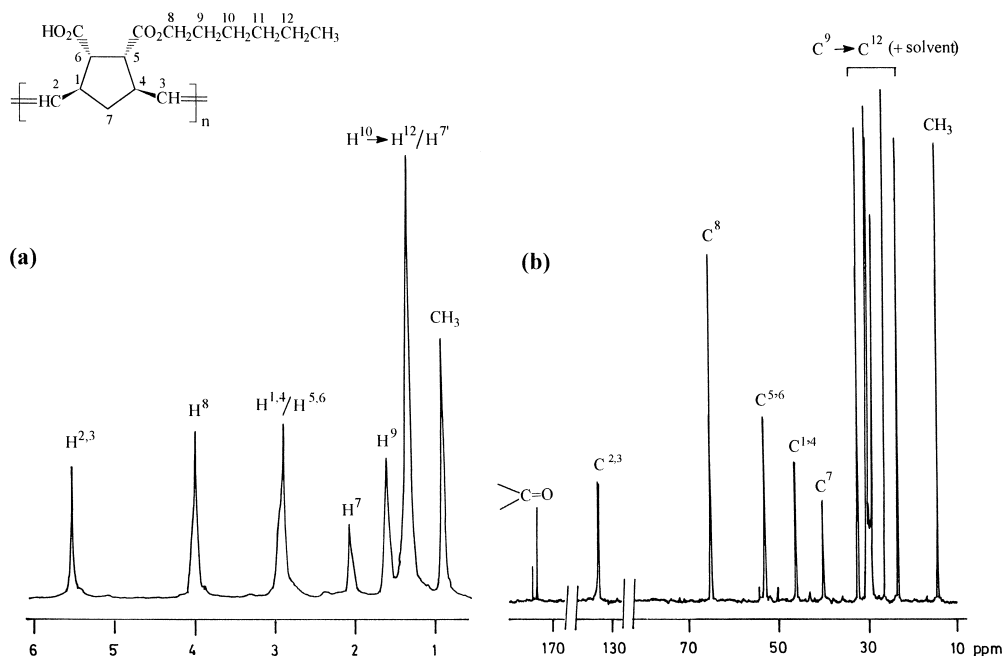
Fig. 1. NMR spectra of acetone-d^6 solutions of high *trans* **6** (a) 300 MHz ^{1}H spectrum and (b) 125 MHz ^{13}C spectrum.

rectly from **1** and its 7-oxa analog, **2**. It is interesting here that although both the K_2RuCl_5/H_2O system [9] and the Grubb's ruthenium benzylidine complex [8] efficiently polymerize **2** the rate of polymerization of **1** is much slower with these catalysts. We have previously commented on the beneficial effect of a proximate oxygen atom on the rate of ROMP [12,13].

4. Preparation of hydrogels

Although the polymers (with the exception of **7**), as prepared in the 'one-pot' process, swell, but are insoluble in distilled water, any attempt to increase the pH, either by addition of alkali or by the use of alkaline buffer solutions, results in rapid dissolution as the carboxylate anion is formed. During preliminary studies [3] gel samples were produced by the simple expedient of adding ∼5% α,ω-diols, such as pentane diol or diethylene glycol, to the one-pot reaction mixture but, although this provided insoluble materials which in the first instance demon-

strated the potential for high water uptake of these polymer gels, films could not be formed and the irregular morphology did not allow any consistent water content measurements to be made.

Subsequently solutions of the isolated polymers, prior to film casting on a Teflon substrate, were treated either with α,ω-diols, to form ester cross-links or cold-vulcanized with sulphur monochloride [14], utilizing the main chain double bonds (Scheme 2).

The first method required the use of dry HCl gas to catalyse the esterification reaction, which was conducted at elevated temperatures, but the use of S_2Cl_2 proved to be more efficient and had the advantage of producing a gel with hydrolytically stable disulphide cross-links, a valuable property if the materials are to be used in potentially aggressive aqueous environments.

In a series of experiments with polymer **5** different ratios of polymer-to-cross-linking agent were employed and this revealed that the minimum mole ratio of diethyleneglycol to polymer repeating unit was approximately 1:9, but that half this ratio, 1:18, was sufficient for S_2Cl_2
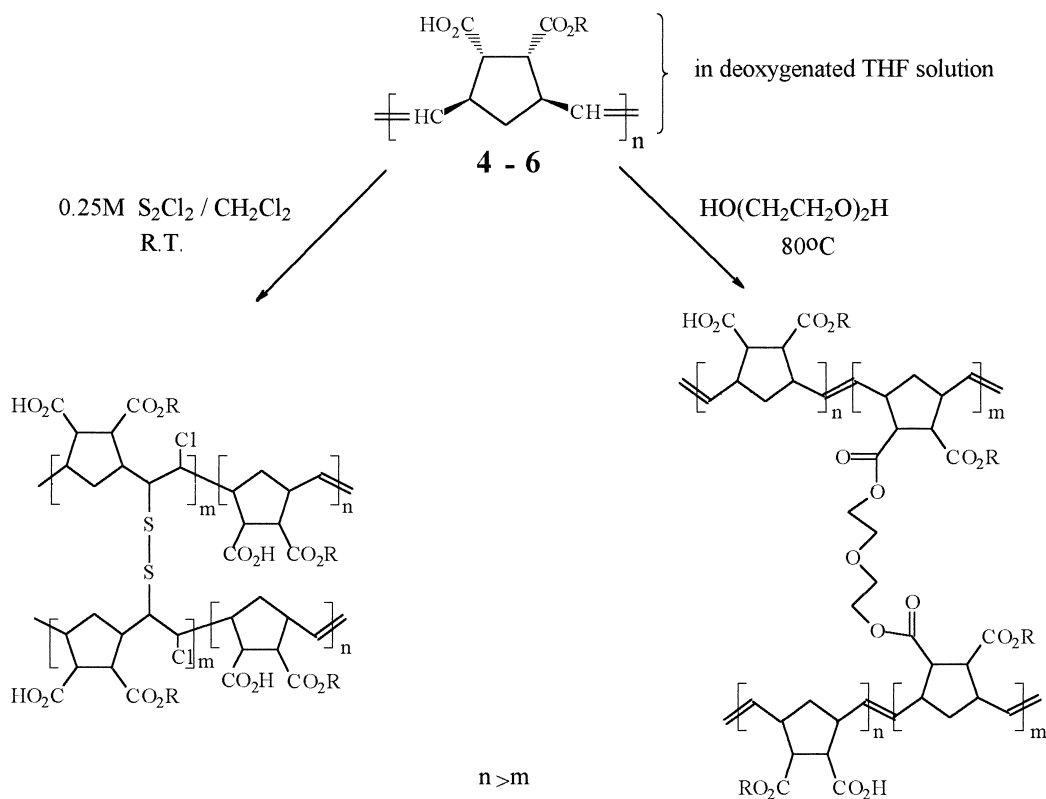
Scheme 2.

cross-linking. This may reflect the greater stability of the S–S cross-links in the gel during the swelling process but more probably is the result of a more efficient cross-linking process with S_2Cl_2 because both gels proved to be stable over several swelling/deswelling cycles. In addition, different preparations of gel using the same S_2Cl_2: polymer ratio gave very consistent swelling results, vide infra, and we therefore conclude that this cross-linking reaction is quantitative and that the cross-link density may thus be determined.

Polymers **8** and **9** with anhydride repeating units, prepared directly from **1** and **2** were soluble only in aqueous solvents (including pure water), where presumably they exist as the respective poly(diacid)s; the hydrophilicity is greatly enhanced when the tetrahydrofuranyl ring is present in the main chain and **9** dissolves much more rapidly than **8**. With these polymers cross-linking methods were therefore restricted

to water soluble agents and again diethylene glycol was used.

5. Swelling characteristics

Polyelectrolyte hydrogels swell because of an uncoiling of the main chain and the resulting expansion of the network structure, caused by the mutual repulsion of the carboxylate anions which are formed as the pH of the medium is increased; this in turn is dependent on the ease with which water molecules and solvated ions can penetrate the polymer network. Gels with only diacid functionality, derived from **8** and **9** or from poly(acrylic acid), swell quickly to a high % EWC and show little sensitivity to changes in the aqueous environment; the swelling behaviour in these cases is dominated by the carboxylate functionality. These properties are modified in polymers formed in the
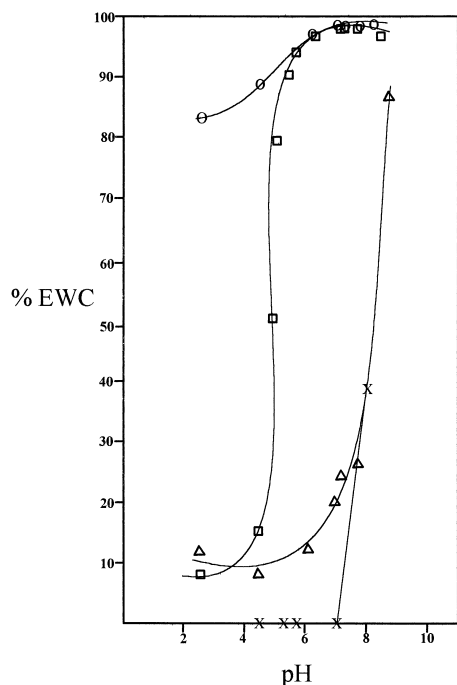
Fig. 2. pH-dependent swelling at 32°C of gels formed from: O, **4** [R = (CH$_2$CH$_2$O)$_n$CH$_3$]; □, **5** [(CH$_2$CH$_2$O)$_2$CH$_2$]; △, **6** [R = (CH$_2$)$_5$CH$_3$] and X, **7** [R = (−)-menthyl]. Gels formed from **4** were cross-linked with diethylene glycol and behaved similarly to those formed from diacid or poly(acrylic acid). Those formed from **5** and **6** were cross-linked with S$_2$Cl$_2$ and those from **7** were used without chemical cross-linking.

one-pot process, which results in essentially alternating ester and carboxylate functionality along the main chain affording the opportunity to control the gel swelling kinetics and response to the environment whilst retaining a high % EWC.

One aspect of this is illustrated in Fig. 2 which shows how ester substituents of different polarity can effect the degree of swelling and the pH range in which they respond: one can discern a gradation of swelling properties, as judged by the form of the swelling isotherms, as the hydrophilic–lipophilic balance is adjusted. Hydrogels bearing the poly(ethylene glycol) side chain, gel **4**, like those formed from the diacid, achieve high EWCs throughout the pH range contrasting the case of the very hydrophobic (−)-methoxy ester, gel **7**, which remains unswollen even at pH values well above the

carboxylic acid's pK_a (approximately 4.6); here the strong hydrophobic interaction of the menthyl groups renders the gel insoluble without the need for chemical cross-linking.

More subtle variations in performance may be induced by using linear side-chains which differ in their oxygen atom content. Thus the diethylene glycol ester, gel **5**, undergoes a transition commencing at ∼ pH 4 while the analogous gel **7**, the hexyl ester, does not start its transition until the former has reached its maximum % EWC at pH ∼ 6: both esters nevertheless achieving similarly high % EWCs.

Another, and perhaps more dramatic, example of how these changes in the side chain structure can effect the gels performance is seen in the variable temperature experiment, Fig. 3. Here each gel was swollen at the optimum pH 8 and the % EWC achieved plotted against temperature in the 0° to 30°C range. The glycol ester, gel **5**, exhibited swelling which was independent of temperature while the hexyl ester, gel **6**, exhibited a distinct, linear, temperature dependence. This reflects the relative ease with which the water molecules can penetrate the different gel networks, the more hydrophobic hexyl ester exhibiting endothermic behaviour
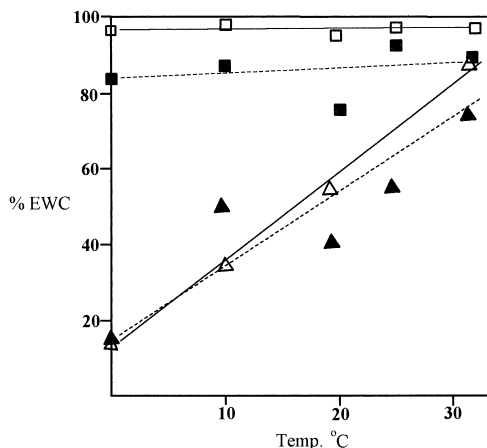

Fig. 3. % EWC as a function of temperature at pH 8 for gels prepared from, **5**, ——— □ ——— [R = (CH$_2$CH$_2$O)$_2$CH$_2$] and **6**, ——— △ ——— [R = (CH$_2$)$_5$CH$_3$] cross-linked with S$_2$Cl$_2$. Polymers cross-linked with diethylene glycol are represented, respectively by --- ■ --- and --- ▲ ---.
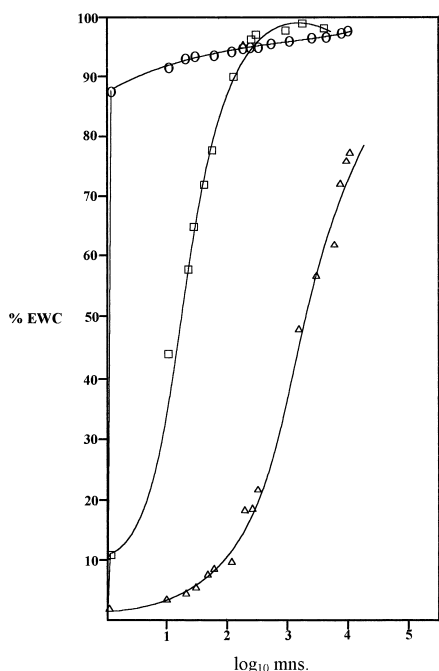
Fig. 4. Swelling kinetics of hydrogels at 32°C and pH 8: O, **4** [R = H] similar behaviour with poly(acrylic acid); □, **5** [R = $(CH_2CH_2O)_2CH_2$] and △, **6** [R = $(CH_2)_5CH_3$].

sorbancy [17], and the results of a series of experiments used to determine this characteristic are presented in Fig. 4. Gels formed from poly(acrylic acid) or the diacid derivatives undergo visible increases in volume as soon as they are placed in the pH 8 buffer solution, attaining more than 90% of their final EWC within 1 min. Ester derivatives are much slower and predictably gel **6** requires approximately seven days to reach equilibrium.

Another important property is the consistency with which a gel sample can recover to a given % EWC on repeated drying out and reswelling. In this experiment gels were allowed to reach their maximum swelling and then were dried to a constant weight before reswelling and repeating the process. The results are presented for gel **5** (Fig. 5) and although optimal are not atypical. The constancy of the dry and wet weight over several cycles shows that gel samples, irrespective of the cross-linking method, are strong enough to resist weight loss by mechanical processes whilst possessing enough chemical stabil-
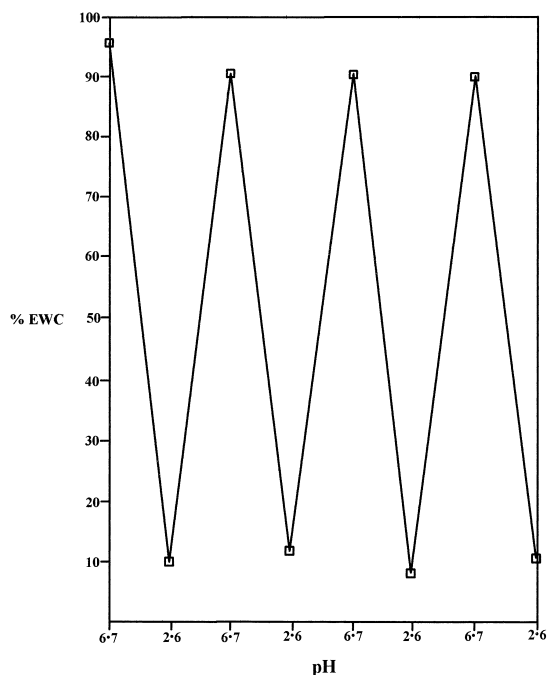
while the glycol ester is thermoneutral. Materials like these which swell differentially in response to temperature have been utilized in the construction of temperature activated switching devices [15,16].

It will be noted from Fig. 3 that although the behaviour is independent of the type of cross-link, the diethylene glycol-cross-linked gels gave a much wider spread of % EWC values than the S_2Cl_2 cross-linked materials which were remarkably consistent. We believe that this is due to the fact that in this particular experiment gel discs were cut from different polymer films, which, although prepared under the same conditions, were prepared at different times; in all other experiments we describe gel discs were cut from the same polymer film. This is further evidence that a much more consistent cross-linking reaction is achieved with the S_2Cl_2 reagent.

The rate of attainment of the maximum % EWC is an important aspect of hydrogel behaviour, especially in the area of superab-

Fig. 5. Reproducibility of % EWC values over several swelling–deswelling cycles of a hydrogel formed by cross-linking **5** with S_2Cl_2.

ity so that further cross-linking, or indeed cross-link breaking, which would result in inconsistent % EWC values, does not occur.

6. Conclusions

Using a metathesis-based synthetic procedure, one can prepare a range of hydrogels with novel main chain architectures which are stable and well-behaved under a variety of swelling conditions. The hydrophilic–lipophilic balance and performance of these materials may be tailored by the simple expedient of altering the side chain functionality.

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