

The use of novel cyclic monomers in hydrogel synthesis

C. B. St. Pourcain,* A. W. P. Jarvie and B. J. Tighe

Department of Chemical Engineering and Applied Chemistry, Aston University, Aston Triangle, Birmingham, UK B4 7ET

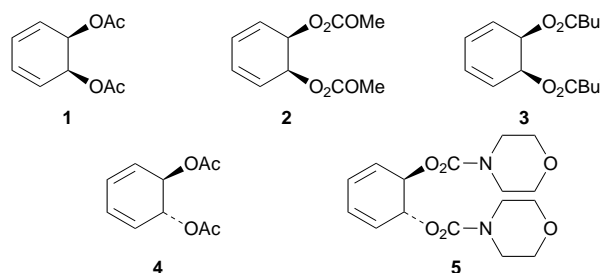
A range of hydrogels was prepared by the copolymerisation of 2-hydroxyethyl methacrylate (HEMA) with various cyclic monomers (CM) derived from *cis*- and *trans*-1,2-dihydroxycyclohexa-3,5-diene (DHCD). The specific systems investigated were the *cis*-diacetate, -dimethyl carbonate and -dipivalate, and the *trans*-diacetate and -dimorpholinocarboxy. It was observed that the *cis*-derivatives polymerised more readily than the *trans*-derivatives. The poly(HEMA-CM) hydrogels prepared from *cis*-derivatives showed superior mechanical properties compared with the corresponding systems containing styrene or methyl methacrylate.

The hydrogels are a class of materials which have been used widely in biomedical applications. They have the particular property that they absorb and contain water but do not dissolve in it. The absorbed water affects such characteristics as mechanical and surface properties,^{1,2} permeability and biocompatibility. The effect of the contained water is mainly beneficial in that it acts as a plasticiser, a transport medium for dissolved species and as a link between the body fluids and the synthetic polymer. Its main disadvantage is that it is generally observed that the mechanical strength decreases as the water content increases.³

A number of strategies have been developed for the preparation of hydrogel type materials which are mechanically strong and have high water contents. Included amongst these is the grafting of the hydrogel onto a polymer with superior mechanical properties so that the surface of the support exhibits greatly improved biocompatibility whilst the composite as a whole retains the mechanical strength. These materials are limited in use in particular applications, where permeability is an important factor.^{4,5} A more generally useful approach has been the development of a new family of hydrogels based on interpenetrating polymer networks (IPNs). It is found that IPN formation produces materials with dramatically increased mechanical strength compared with hydrogel copolymers of similar water content.^{6,7}

We describe here exploratory studies directed towards an alternative approach to the synthesis of hydrogel materials with high water content and good mechanical properties. If conventional monomers such as styrene and methyl methacrylate are added to hydrogels, *e.g.* HEMA-*N*-vinylpyrrolidone (NVP)-crosslinker systems, in order to stiffen the polymer backbone they tend to reduce the hydrophilicity of the material and lower the water content of the swollen state.^{2,8} The monomer 1,2-dihydroxycyclohexa-3,5-diene (DHCD) and its derivatives could be an exception to this rule.^{9,10} These dienes can be polymerised with acrylic monomers to produce in-chain cyclohexene rings. These rings would be expected to enhance the mechanical strength of the acrylic material. The in-chain ring structure which is absent in conventional syn-

thetic hydrogels could also have a marked influence on water binding. The copolymerisation of DHCD derivatives with hydrophilic monomers offers a potential route to high strength, high water content materials. The diacetate **1**, dimethyl carbonate **2** and dipivalate **3** systems derived from *cis*-DHCD and the diacetate **4** and dimorpholinocarboxy **5** from *trans*-DHCD were copolymerised with HEMA to form a new group of hydrogels. Various properties of these materials were measured and the results of these investigations are discussed. HEMA was selected as the comonomer because of the predominance of poly(HEMA) hydrogels in many applications.



Experimental

Materials

All solvents were dried and distilled prior to use. The *cis*-1,2-dimethoxycarboxy- **2** and *cis*-1,2-dipivaloyloxy-cyclohexa-3,5-diene **3** were gifts from ICI (courtesy of D. G. H. Ballard) and the 2-hydroxyethyl methacrylate was supplied by Ubichem. The *cis*-1,2-diacetoxycyclohexa-3,5-diene **1** was synthesised by the method of Ballard and co-workers⁹ and the *trans*-1,2-diacetoxycyclohexa-3,5-diene **4** according to the procedure of Platt and Oesch.¹¹ The IR and NMR spectra of these products were in accord with those observed previously.

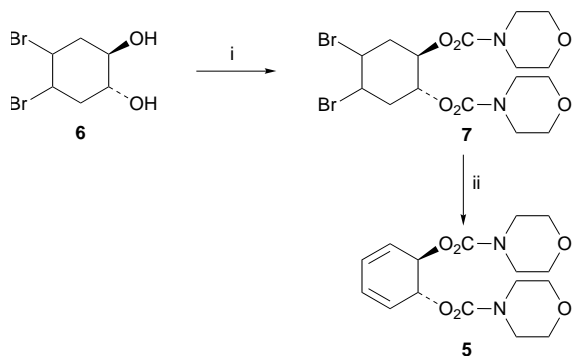
The *trans*-1,2-bis(morpholinocarboxy)cyclohexa-3,5-diene **5** was synthesised as outlined in Scheme 1.

trans-1,2-Bis(morpholinocarboxy)-4,5-dibromocyclohexane **7**.

The *trans*-1,2-dihydroxy-4,5-dibromocyclohexane¹¹ **6** (13.7 g, 50 mmol) triethylamine (17.4 cm³, 0.125 mol), morpholinocarbonyl chloride (14.6 cm³, 0.125 mol) and 4-dimethylaminopyridine (DMAP) (0.09 g, 0.74 mmol) were refluxed for 3 days in dry THF (150 cm³). The THF was removed and dichloromethane (150 cm³) added. The solution was washed with water (150 cm³), a saturated aqueous solution of sodium hydrogen carbonate (3 × 50 cm³) and water (2 × 50 cm³), then dried over magnesium sulfate. Solvent removal yielded a crude solid

Table 1 Composition of hydrogels

monomer	monomer content of hydrogels, mol%
1	9, 17, 24
2	9, 17, 24
3	9, 17, 24
4	10, 20, 30
5	5, 10, 15



Scheme 1 Reagents and conditions: i, morpholinocarbonyl chloride, DMAP, THF; ii, Li_2CO_3 , LiCl, HMPA

product. Washing with diethyl ether gave 16.2 g (32 mmol, 65%) of the desired material 7, as a pale beige amorphous solid, mp 129–130 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 1697 (C=O); δ_{H} (CDCl_3) 2.35 (d, br, 2H), 2.57 (s, br, 2H), 3.40 (s, br, 8H), 3.59 (s, br, 8H), 4.47 (s, br, 2H), 5.18 (s, br, 2H); δ_{C} (CDCl_3) 34.42, 44.00, 44.31, 50.04, 66.53, 71.24, 154.2 (Found: C, 38.25; H, 5.03; N, 5.42. $\text{C}_{14}\text{H}_{24}\text{Br}_2\text{N}_2\text{O}_6$ requires C, 38.42; H, 4.84; N, 5.60%).

trans-1,2-Bis(morpholinocarbony)cyclohexa-3,5-diene 5. The *trans* compound 7 (5.0 g, 30 mmol) LiCl (3.6 g, 85 mmol) and Li_2CO_3 (5.6 g, 76 mmol) in HMPA (100 cm^3) were heated, under nitrogen, for 2.5 h at 90–100 °C. After cooling to room temperature dichloromethane (120 cm^3) was added followed by the dropwise addition of a 7% v/v aqueous solution of HCl (100 cm^3). The aqueous layer was then extracted with dichloromethane (3 × 60 cm^3). The combined organic extracts were washed with water (120 cm^3) and a saturated aqueous solution of sodium hydrogen carbonate (100 cm^3). The organic phase was dried over magnesium sulfate and the solvent removed. Purification of the crude material by dry flash chromatography (silica gel; ethyl acetate) gave 3.2 g (9.5 mmol, 32%) of the monomer 5 as a viscous yellow liquid, $\nu_{\text{max}}/\text{cm}^{-1}$ (neat liquid) 1708 (C=O); δ_{H} (CDCl_3) 3.27 (m, br, 8H), 3.45 (s, br, 8H), 5.44 (s, 2H), 5.67–5.69 (m, 2H), 5.81–5.85 (m, 2H); δ_{C} (CDCl_3) 43.74, 66.04, 73.17, 124.65, 125.76, 154.0 (Found: C, 56.40; H, 6.63; N, 7.94. $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_6$ requires C, 56.78; H, 6.55; N, 8.28%).

Hydrogel synthesis¹²

A mixture of HEMA, the comonomer, and 1% w/w ethylene glycol dimethacrylate were degassed by bubbling nitrogen through the solution for 15 minutes. Azoisobutyronitrile (0.5% w/w) was added and the solution injected into a mould, the needle was removed and the mould was placed in an oven at 60 °C for 3 days followed by 2 h postcure at 90 °C. The mould was then separated and the xerogel placed in 175 cm^3 of distilled water to equilibrate for at least two weeks, the water being changed daily. The mould consisted of two polyethylene gaskets (10 cm × 6 cm external; 6 cm × 2.5 cm internal) sandwiched between two Melinex (polyethylene terephthalate) sheets which had been attached to two glass plates by spray mount adhesive (manufactured by 3M and purchased from BDH). The compositions mentioned in the discussion refer to the composition of the feed mixture.

Analyses

IR spectra were recorded on either a Nicolet 510 Fourier Transform Infrared Spectrometer or a Perkin Elmer 1710 Fourier Transform Infrared Spectrometer. Solid samples were prepared as KBr discs and liquids as thin films between sodium chloride plates. NMR spectra were recorded on a Bruker AC 300 spectrometer. The ^{13}C spectra were recorded as either

APT (attached proton test) or DEPT (distortionless enhanced polarisation transfer) spectra. Elemental microanalyses were performed by Medac Ltd, Department of Chemistry, Brunel University, Uxbridge, Middlesex. Melting points were determined in capillary tubes with a Gallenkamp Melting Point Apparatus, Model No. ME-370, and are uncorrected.

Measurement of the physical properties of hydrogels

Determination of equilibrium water content (EWC). EWC determinations were carried out on five separate pieces of gel and the average value calculated. A No. 4 cork borer was used to cut out small discs of gel, which were then placed in a sample bottle of distilled water. For each determination the disc was blotted lightly with filter paper, to remove surface water, and weighed. Dehydration of the gel was achieved by placing it in a microwave oven for 12 min, after which time the gel was re-weighed. The EWC was then calculated using eqn. (1)

$$\text{EWC} = \frac{\text{mass of water in the gel}}{\text{mass of the swollen gel}} \times 100 \quad (1)$$

Agreement between samples was at worst $\pm 1\%$ and typically $\pm 0.5\%$. The hydrogels were dried to constant mass in the microwave oven. Identical values were obtained for poly(HEMA) dehydrated by the microwave method and dried in a vacuum oven at 60 °C.

Measurement of mechanical properties. All mechanical tests were performed with a Hounsfield Tensometer (Model: HK 10KN) fitted with a 10 N load cell, jaws specially designed for use with hydrogel samples and a test speed of 8 mm min^{-1} . Five samples were tested for each gel and a minimum of three consistent values used for further calculations. Dumbbell shaped samples were used for the *cis*-1,2-diacetate, -dimethyl carbonate and -dipivalate containing hydrogels. The samples for the other gels were parallel sided. A gauge length of 10 mm and a width of 3 mm were used for both sets of samples.² The thickness of each sample was measured with a micrometer in five different places on the gel. An average value was then calculated. The average values were in the range 0.2–0.5 mm.

Results and Discussion

The effect of CM concentration on EWC for the poly(HEMA-CM) hydrogels is shown in Fig. 1.

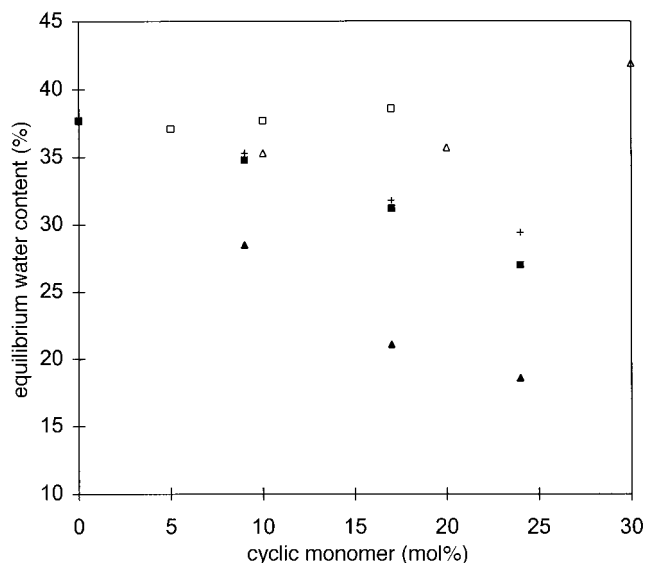


Fig. 1 Effect of CM concentration on EWC: (+) 1; (■) 2; (▲) 3; (△) 4; (□) 5

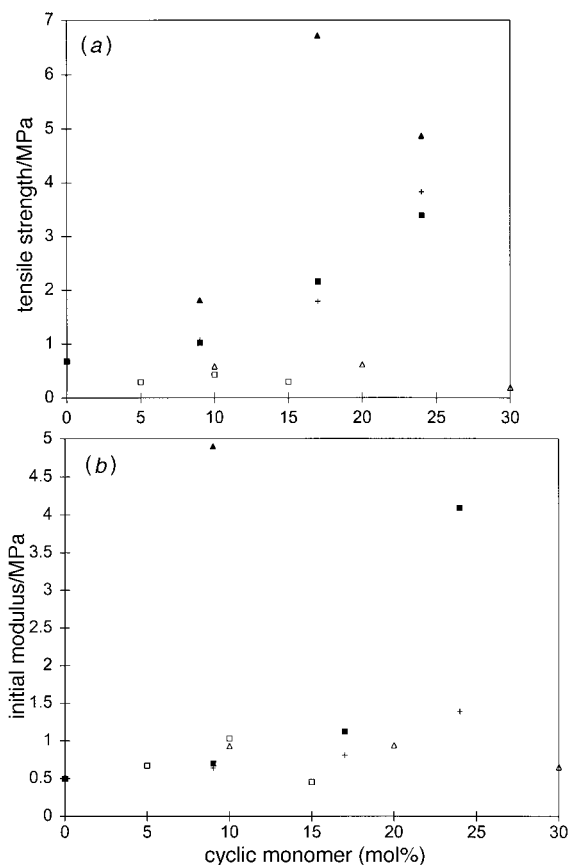


Fig. 2 Effect of CM concentration on the mechanical properties of poly(HEMA-CM) hydrogels: (+) 1; (■) 2; (▲) 3; (△) 4; (□) 5

The hydrogels containing the pure *cis*-derivatives showed the expected decrease in EWC with decrease in HEMA content. The decrease in EWC with decreasing HEMA content is substantially less for the *cis*-diacetate 1 and -dimethyl carbonate 2 derivatives than for the bulky dipivalate. The HEMA copolymers of the *cis*-diacetate and dimethyl carbonate monomers produced clear hydrogels, when hydrated, in all proportions studied, whereas the *cis*-dipivalate 3 gels were heterogeneous due to the limited miscibility of this monomer with HEMA. Hydrogels derived from the *trans*-diacetate 4 or the *trans*-dimorpholinocarboxy 5 derivatives showed a slight increase in EWC with decrease in HEMA content. Whilst this behaviour might be expected for the hydrogels containing the hydrophilic *trans*-dimorpholinocarboxy derivative, the reverse would be expected for the hydrophobic *trans*-diacetate derivative. The xerogels of the HEMA-CM hydrogels which contained derivatives of *trans*-DHCD were homogeneous; when swollen they became heterogeneous and increased in fragility with decrease in HEMA content. These observations are consistent with a poor network structure and increased oligomer formation resulting in a higher EWC for the hydrogel. It was observed previously¹⁰ that the *trans*-diacetate derivative homopolymerised poorly, giving low conversion of monomer to polymer and low molecular weight polymer. No explanation has yet been advanced to explain the difference in the polymerisation behaviour of *cis*- and *trans*-DHCD derivatives. The availability of the π -electrons could be an important factor in determining the polymerisation properties of the *cis*- and *trans*-monomers. It seems probable that the pendant groups shield both faces of the *trans*-DHCD derivative whereas for the *cis*-DHCD derivatives only one face of the ring is shielded. In consequence the *cis*-compounds undergo polymerisation more readily.

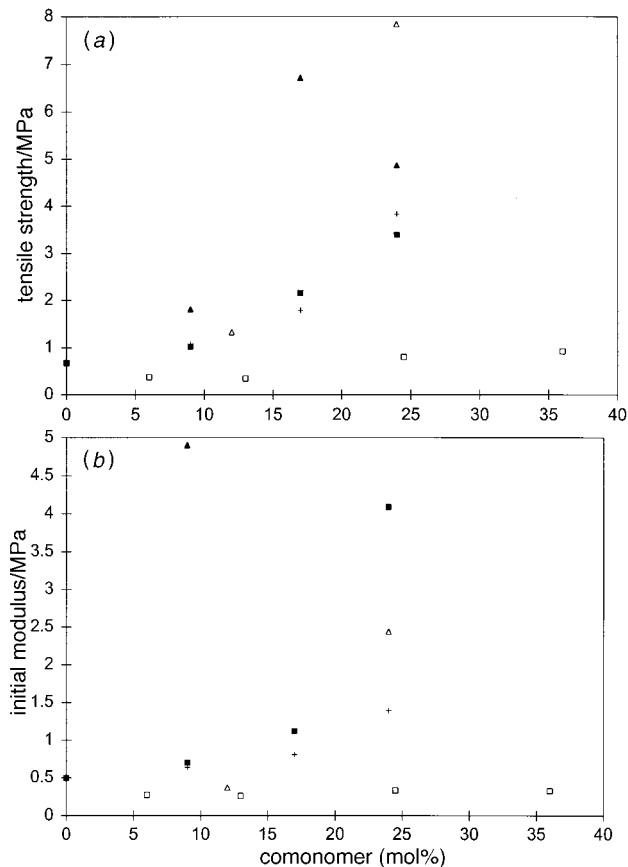


Fig. 3 Comparison of the mechanical properties of poly(HEMA-CM) hydrogels with those of poly(methyl methacrylate) and polystyrene at equivalent composition: (+) 1; (■) 2; (▲) 3; (△) styrene; (□) methyl methacrylate

Mechanical properties

The initial tensile strengths and initial moduli of the poly(HEMA-CM) hydrogels are shown in Fig. 2. The hydrogels obtained from the *trans*-derivatives exhibited comparable or lower values of tensile strength than poly(HEMA) itself, and variable values for initial modulus due to poor network structure. Hydrogels containing the *cis*-cyclic monomers all had significantly higher tensile strengths and Young's moduli than poly(HEMA). The gel containing the highest concentration of dipivalate derivative was highly rigid and tended to fracture when cut. It was practically impossible to obtain an intact sample of this material. The relatively low tensile strength of this sample was probably due to fracturing prior to testing.

The tensile strengths and initial moduli of the poly(HEMA-CM) hydrogels containing *cis*-DHCD derivatives were compared with those reported for the corresponding HEMA-styrene and HEMA-methacrylate hydrogels.³ The dipivalate systems with the two highest dipivalate contents have been omitted from the comparisons of initial moduli for clarity.

For a given composition the poly(HEMA-CM) systems had higher values of tensile strength and initial moduli than did the comparable methyl methacrylate systems, (Fig. 3). This was also true for the styrene analogues at higher concentrations of HEMA, but the situation was reversed as the concentration of HEMA decreased. This abrupt change in the properties of the styrene system can be accounted for by the loss of plasticising freezing water, at higher concentrations of styrene.¹ Comparison of tensile strength and initial moduli with EWC show that the poly(HEMA-CM) systems possessed superior mechanical properties to their styrene and methyl methacrylate analogues (Fig. 4). It appears that the *cis*-DHCD derivatives are better comonomers for poly(HEMA) hydrogels than

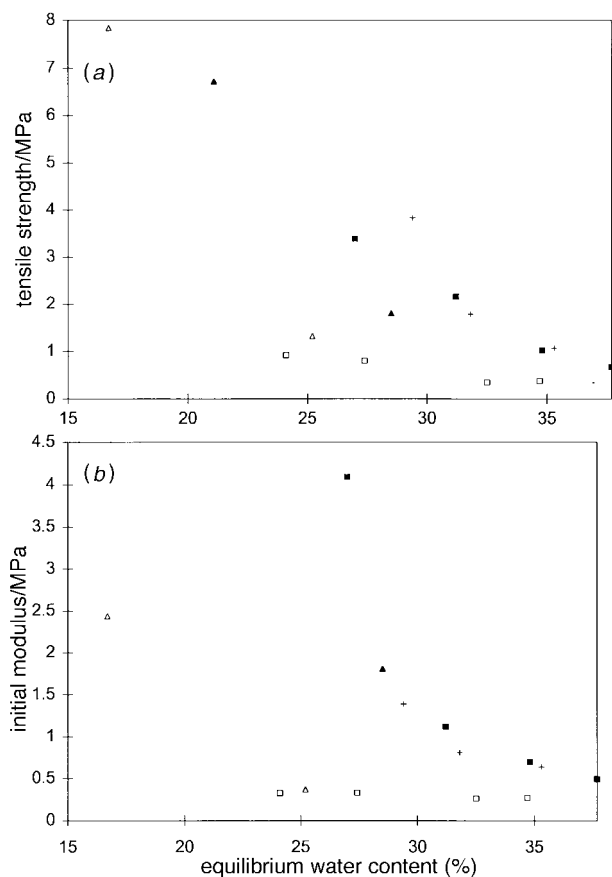


Fig. 4 Comparison of the mechanical properties of poly(HEMA-CM) hydrogels with those of poly(methyl methacrylate) and polystyrene at equivalent EWC: (+) 1; (■) 2; (▲) 3; (△) styrene; (□) methyl methacrylate

styrene or methyl methacrylate as they strengthen the polymer but degrade the hydrophilicity to a lesser extent.

It would be expected that the poly(HEMA-DHCD) systems would show enhanced main chain stiffness due to the presence both of the cyclohexene rings and interactions of the pendant groups on these rings. This decrease in the mobility of the

polymer chains is probably responsible for the greater tensile strengths and initial moduli exhibited by these HEMA-CM hydrogels compared with their HEMA-methyl methacrylate and HEMA-styrene analogues.

Conclusions

Poly(HEMA-*cis*-DHCD) hydrogel copolymers showed higher tensile strengths and initial moduli than their styrene and methyl methacrylate analogues, at similar EWC and in most cases at similar composition. Thus *cis*-DHCD derivatives appear to be superior to styrene and methacrylate as comonomers in poly(HEMA) hydrogel systems. It was found that the *trans*-derivatives of DHCD polymerise with difficulty, giving poly(HEMA-*trans*-DHCD) copolymers with a poor network structure and lower values of tensile strength and initial modulus than poly(HEMA) itself.

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Paper 7/03806B; Received 2nd June, 1997