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Synthesis and Characterization of Polyesters Based on 3,4-Dihydro-2*H*-pyran-2-yl-methanol

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Summary. Diesters of 3,4-dihydro-2*H*-pyran-2-yl-methanol with oxalic and phthalic acid were prepared and polymerized. Boron trifluoride etherate, anhydrous ferric chloride, and *p*-toluene sulfonic acid have been selected as different cationic coinitiators. The resulting polymers can be considered as suitable matrices for controlled drug delivery by *in vivo* biodegradation. They were characterized and their thermal behaviour was investigated.

Keywords. Synthesis; Hydrogel; 3,4-Dihydro-2*H*-pyran.

Synthese und Charakterisierung von Polyestern auf 3,4-Dihydro-2*H*-pyran-2-yl-methanol-Basis

Zusammenfassung. Diester aus 3,4-Dihydro-2*H*-pyran-2-yl-methanol und Oxal- bzw. Phthalsäure wurden hergestellt und unter der Wirkung von Bortrifluorid-Etherat, wasserfreiem Eisentrichlorid und *p*-Toluolsulfonsäure als kationischen Koinitiatoren polymerisiert. Die erhaltenen Polymere können als geeignete Matrizen für kontrollierte Wirkstoffabgabe durch *in-vivo*-Bioabbau fungieren. Sie wurden charakterisiert und ihr thermisches Verhalten wurde untersucht.

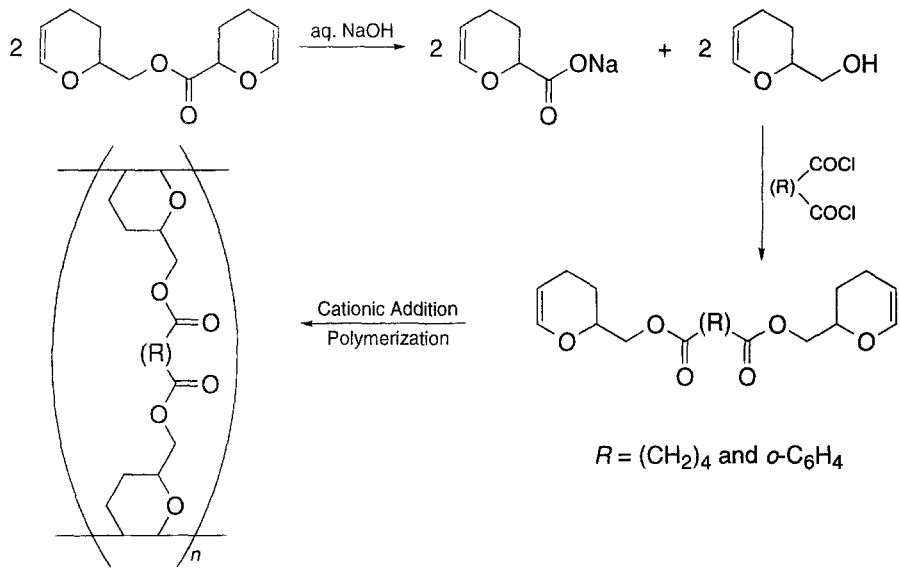
Introduction

It has been reported previously that some polymers synthesized from polyols and molecules containing two or more 3,4-dihydro-2*H*-pyran units can be used for industrial applications to develop a variety of drug delivery devices [1–3]. The present work aims at the synthesis and characterization of further hydrogels derived from 3,4-dihydro-2*H*-pyran. The average molecular weight ($\bar{M}n$) and the polydispersity index ($\bar{M}w/\bar{M}n$), which may reflect the molecular weight distribution of the resulting polymers, have been determined. Besides, the thermal behaviour of the hydrogels has been investigated. The type of crosslinks has, of course, a great effect on their hydrolysis characteristics which affect the ease of their biodegradation. For this purpose, two hydrogels (polydi(3,4-dihydro-2*H*-pyran-2-methyl) oxalate and phthalate) have been synthesized and characterized.

Results and Discussion

Polyethylene glycols have been crosslinked with 3,4-dihydro-2*H*-pyran-2- methyl-(3,4-dihydro-2*H*-pyran-2-yl-carboxylate). Such polymers can biodegrade by hy-

drolysis of the in-chain ester and glycosidic groups, but can also be prepared in hydrolytically stable formulations [4, 5]. The hydrolytic stability of these polymers is determined by the ease of hydrolysis of the ester or acetal groups in the polymer backbone or network and the solubility of water in the polymer [6]. In the present work, di(3,4-dihydro-2*H*-pyran-2-methyl) esters of oxalic and phthalic acids have been synthesized and polymerized in the presence of three different cationic coinitiators: boron trifluoride etherate ($BF_3 \cdot O(C_2H_5)_2$), anhydrous ferric chloride ($FeCl_3$), and *p*-toluene sulfonic acid (*p-TSA*) (Scheme 1). $BF_3 \cdot O(C_2H_5)_2$ and $FeCl_3$ were used as coinitiators in combination with protic impurities as initiators present in polymerization systems providing complex gegen ions, *e.g.* BF_3OH^- or $FeCl_3OH^-$. With *Brønsted* acids (H*A*) such as *p-TSA*, the initiating protons are formed by dissociation leading to A^- gegen ions [7–9]. The polymerization solvent of choice was dichloromethane according to a previously reported kinetic study [10]. The absence of an absorption at $1655\,cm^{-1}$ in the IR spectrum of polymer samples indicates that the two double bonds in the monomer molecule are included in the polymerization process [10].



Scheme 1. Polymerization of diesters of oxalic and phthalic acids with 3,4-dihydro-2*H*-pyran-2-yl-methanol *via* addition polymerization reaction

From the results obtained and listed in Table 1 it was found that the coinitiators affect the molecular weight of the obtained polymers only insignificantly. The coinitiators, however, influence the glass transition temperature (*Tg*). The polymer samples do not melt within the range of the DSC measurements (−150 °C to 150 °C) as shown in Fig. 1. $\bar{M}n$ and $\bar{M}w/\bar{M}n$ determined by GPC as well as *Tg* determined by DSC at a heating rate of $10\,K \cdot min^{-1}$ are also listed in Table 1. It should be noticed that in all cases the polydispersity index $\bar{M}w/\bar{M}n$ is slightly above unity except for phthalate hydrogels prepared in the presence of either $FeCl_3$ or $BF_3 \cdot O(C_2H_5)_2$. This

Table 1. Some characteristic properties of polydi(3,4-dihydro-2*H*-pyran-2-methyl) oxalate, adipate, and phthalate hydrogels

	Oxalate hydrogel			Phthalate hydrogel		
	BF_3·ether	$FeCl_3$	*p-TSA*	BF_3·ether	$FeCl_3$	*p-TSA*
$\bar{M}n$	6308	4349	5007	8014	6890	7880
$\bar{M}w/\bar{M}n$	1.001	1.54	1.16	7.79	3.80	1.50
DP	22	15	18	22	19	22
Tg (K)	165	172	183	193	191	185
$t_{hyd}(h)$*	6	6	6	36	36	36

* Time of complete hydrolysis of the corresponding adipate hydrogel was 24 h [11]

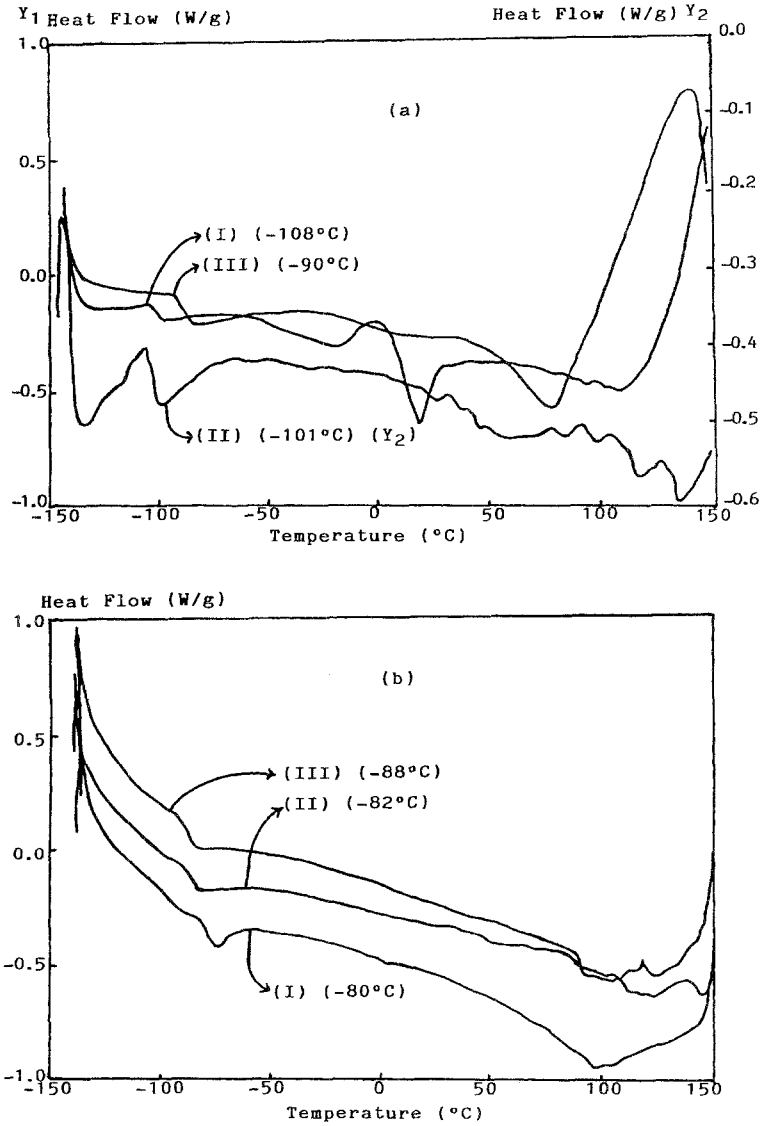


Fig. 1. DSC analysis of a) polydi(3,4-dihydro-2*H*-pyran-2-methyl) oxalate and b) polydi(3,4-dihydro-2*H*-pyran-2-methyl) phthalate synthesized in presence of I) $BF_3 \cdot O(C_2H_5)_2$, II) anhydrous $FeCl_3$, and III) *p*-toluene sulfonic acid as cationic polymerization coinitiators

indicates that oxalate and *p-TSA* initiated phthalate polymers have narrow molecular weight distributions which lead to polymers with precisely defined structures. The polymeric chains are crosslinked together *via* ester groups that hydrolyze easily under basic conditions at 25 °C to the corresponding dicarboxylic acid and the easily soluble linear 3,4-dihydro-2*H*-pyran-2-yl-methanol addition polymer. Ester groups crosslink the polymeric chains either in a form of intramolecular crosslinking or in a ladder-like form or in a mixture of both [11].

The hydrophilicity of the synthesized monomers differs from one to the other due to their different chemical structure. Such changes are reflected in the characteristic properties of hydrogels prepared from these monomers [12]. The time of hydrolysis as a function of the ease of hydrolysis is one of these properties designated as t_{hyd} in Table 1. The slower hydrolysis of phthalate based hydrogels can be attributed to the decreasing hydrophilicity which is in complete agreement with the findings reported for membranes containing carboxylic groups [13]. Later it has been shown that the higher degree of swelling is accompanied by a higher solute absorption [14]. Accordingly, one may conclude that oxalate based hydrogels are expected to possess higher swellability and consequently have higher solution and salt uptakes than the less hydrophilic phthalate based hydrogels. The rigid nature of the crosslinks in the case of phthalate based hydrogels leads to a decreasing sensitivity towards swelling by decreasing the hydrophilicity of the crosslinks. Therefore, higher solution and salt uptake means higher concentration of sodium hydroxide within the matrix , thus accelerating the rate of hydrolysis of the hydrogels under basic conditions. This also is supported by considering the time of complete hydrolysis of the previously synthesized adipate hydrogel [11]. Which lies between those of the oxalate based and phthalate based hydrogels.

Experimental

Materials and Methods

Elemental analyses were carried out at Cairo University, Egypt. IR spectra were recorded on a Perkin-Elmer 257 Grating IR spectrophotometer. UV analyses were achieved using a Cecil CE 5501W double beam spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 60 MHz NMR spectrometer. Thermal analyses were carried out using a DSC V2.2A DuPont 9900 thermal analyzer. Molecular weight measurements were carried out with a 745 GPC Prosram Version 1.0 (Y/N). 3,4-Dihydro-2*H*-pyran-2-yl-methanol was prepared as reported previously [11].

Di(3,4-dihydro-2H-pyran-2-methyl) oxalate

To an ice cold solution of 45.6 g (0.40 mol) of 3,4-dihydro-2*H*-pyran-2-yl-methanol in a mixture of 40 ml pyridine and 200 ml *n*-hexane, a solution of 25.6 g (0.20 mol) of oxalyl chloride in 100 ml *n*-hexane was slowly added with stirring over a period of 2 h. Stirring for another 3 h at room temperature was followed by treatment with sodium bicarbonate solution and subsequent extraction with ether. The organic layer was washed repeatedly with water to get rid of pyridine. Distillation of the ethereal extract afforded 83.5 g (74%) of white crystals of di(3,4-dihydro-2*H*-pyran-2-methyl) oxalate. It melts at 71 °C and is soluble in ether, *n*-hexane, chloroform, and acetone. IR (KBr): $\nu = 3085$, 1740, 1655, 1080 cm^{-1}; UV: $\lambda_{max} = 323.5$ nm; ^{1}H NMR ($CDCl_3$): $\delta = 1.9$–2.4 (aliph. CH_2), 4.0–5.0 (pyran protons), 4.6 and 6.4 (unsat. pyran protons) ppm; $C_{14}H_{18}O_6$ (282.11); calculated: C 59.55, H 6.43; found: C 59.75, H 7.30.

Di(3,4-dihydro-2H-pyran-2-methyl) phthalate

To an ice cold solution of 45.6 g (0.40 mol) of 3,4-dihydro-2*H*-pyran-2-yl-methanol in a mixture of 40 ml pyridine and 60 ml benzene, a solution of 42 g (0.20 mol) of phthaloyl dichloride in 100 ml benzene was slowly added with stirring at such a rate that the reaction temperature was kept at *ca.* 40 °C. Stirring for another 2 h at room temperature was followed by addition of 0.75 ml of water and stirring for further 30 min. The reaction mixture was strongly stirred for 2 h after addition of 40 ml chloroform and 70 ml water. The organic layer was then extracted and treated successively with water and dilute HCl until the solution has no odor of pyridine (3–4 washings are sufficient), sodium bicarbonate solution and water. After the removal of water, the wet solvent (chloroform) is removed up by distillation up to a pot temperature of 120 °C. The remaining solvent is removed under reduced pressure. The product is about 86 g (60%) of a pale yellow, mobile liquid characterized as di(3,4-dihydro-2*H*-pyran-2-methyl) phthalate by elemental and spectroscopic analyses. It is soluble in ether, chloroform, and acetone. IR (KBr): $\nu = 3085$, 1740, 1655, 1080 cm^{-1}; UV: $\lambda_{max} = 244.3$, 276.7 nm; ^1H NMR ($CDCl_3$): $\delta = 1.8$–2.2 (aliphatic CH_2), 4.0–5.0 (pyran protons), 4.6 and 6.4 ppm (unsat. pyran protons), 7.2–7.9 (4-CH aromatic protons) ppm; $C_{20}H_{22}O_6$ (358.14); calculated: C 67.01, H 6.19; found: C 65.99, H 6.36.

Polydi(3,4-dihydro-2H-pyran-2-methyl) oxalate and
polydi(3,4-dihydro-2H-pyran-2-methyl) phthalate

The crosslinked hydrogels were obtained *via* a cationic bulk polymerization process. The cationic coinitiators were: a) 7% boron trifluoride solution in diethyl ether, b) anhydrous ferric chloride, and c) *p*-toluene sulfonic acid. 25 mg of coinitiator were added to 2 g monomer in 18 ml dichloroethane under a nitrogen atmosphere and shaked well at 25 °C for 48 h. The polymerization reaction was stopped by adding 1 ml of a 10% solution of tri-*n*-butylamine in dichloromethane. After evaporation of the solvent and subsequent washing with dilute HCl and distilled water and drying at ambient temperature over P_2O_5 under vacuum, pale brownish materials were obtained. IR (KBr): $\nu = 1740$,1070 cm^{-1} in addition to absorptions at 1500 and 740 cm^{-1} for the phthalate polymer only; UV: $\lambda_{max} = 230$, 263, and 269.5 nm for oxalate based polymer samples and 233.7 and 276.5 nm for phthalate based polymer samples; ^1H NMR ($CDCl_3$): $\delta = 1.8$–2.3 (aliph. CH_2) and 4.0–5.0 (satd. pyran protons) ppm in addition to a peak at 7.3–7.8 ppm (CH-arom. protons) in the case of phthalate based samples only. Average molecular weights ($\bar{M}n$) and polydispersity indices ($\bar{M}w/\bar{M}n$) were determined by GPC; the obtained data are listed in Table 1.

Hydrolysis of polymeric samples

0.25 g of the polymer sample were added to 100 ml of 0.1 *N* sodium hydroxide solution with stirring at room temperature (≈ 25 °C) until complete dissolution. The hydrolysate was extracted with chloroform, dried over magnesium sulfate, and the solvent was evaporated. The times required for complete hydrolysis of the polymeric samples (t_{hyd}) are listed in Table 1. IR (KBr): $\nu = 3300$–3500, 1030 cm^{-1}.

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