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Synthesis and characterization of poly (2-acetoxymethyl-3,4-dihydro-2H-pyran)

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Summary

2-acetoxymethyl-3,4-dihydro-2H-pyran was synthesized and polymerized using different cationic coinitiators, namely boron trifluoride/diethyl ether complex system; anhydrous ferric chloride and p-toluene sulphonic acid. The obtained polymers have been found to be both low molecular weight and water soluble. The thermal as well as hydrolytic behaviour of the polymeric samples was investigated.

Introduction

Many industrial applications developing a variety of drug delivery devices are using some polymers made from polyols and molecules containing two or more 3,4-dihydro-2H-pyran groups (1-3). In a preceeding study, polydi(3,4-dihydro-2H-pyran-2-methyl) adipate was synthesized in presence of different cationic coinitiators (4). The possibility to use such polymers as controlled drug delivery hydrogels was predicted. This prediction was made on the basis of their thermal and hydrolytic behaviour. Accordingly, the title polymer was synthesized; characterized and investigated towards hydrolysis.

Results and discussion

In a preceeding study, polydi(3,4-dihydro-2H-pyran-2-methyl) adipate was synthesized in presence of different cationic coinitiators, namely, complex system of boron trifluoride and diethyl ether ($BF_3.O(C_2H_5)_2$); anhydrous ferric chloride ($FeCl_3$) and p-toluene sulphonic acid (p-TSA) (4). $BF_3.O(C_2H_5)_2$ 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 Bronsted acid (HA) such as p-TSA, the initiating protons are formed by dissociation leading to A^- gegen ions (5-7).

The present work aims at synthesis of a polymer containing biodegradable 3,4-dihydro-2H-pyran units that needs shorter hydrolysis time and consequently shorter biodegradation time. This was achieved through polymerization of 2-acetoxymethyl-3,4-dihydro-2H-pyran to make its cationic polymerization possible. The title polymer may be considered more advantageous than that of the adipate diester due to its linearity in nature.

From GPC determination of the molecular weight, differences in $\overline{Mn}$ are not significant to make reliable conclusion either on the effect of acids on polymerization or molecular weight on T_g and crystallization. It is noticed also that the polydispersity indices ($\overline{Mw}/\overline{Mn}$) are slightly higher than unity indicating that the obtained polymers have a narrow molecular weight distribution (Exp. part). Such polymers with narrow molecular weight distribution are suitable to produce precisely defined networks. It is interesting to mention that the number average molecular weight of the obtained polymeric samples in case of using anhydrous ferric chloride and p-toluene sulphonic acid are nearly close to each other. In a separate experiment, 2-acetoxymethyl-3,4-dihydro-2H-pyran was polymerized in presence of $BF_3.O(C_2H_5)_2$ at 0°C in stead of 25°C. It leads to formation of similar product to great extent but with slightly higher number average molecular weight and polydispersity index. This means that the polymer sample formed at 25°C has narrower molecular weight distribution than that obtained at 0°C. This may be attributed to the inhomogeneity of the reaction mixture resulted from different mobilities of the reacting molecules when the reaction was carried out at lower temperature.

On the other hand, the glass transition temperature (T_g) is an important factor affecting the diffusion process. The free volume increases significantly with increasing temperature above Tg (8). Tg and the crystalline melting points determined by DSC for polymer samples **IIIa,b,c** as well as that obtained at 0°C with $BF_3.O(C_2H_5)_2$ as coinitiator were listed in Table 1. From Tg values (Figure 1: 186, 248 & 205 K for samples **IIIa,b,c**. respectively) one can conclude that polymer obtained in case of anhydrous $FeCl_3$ changes into the rubbery state easier than that obtained either in case of $BF_3.O(C_2H_5)_2$ or p-TSA. This means that the higher crystallinity e.g. in case of **IIIb**, the less mobile the polymer chains. As a result, the time of diffusion of an incorporated substrate such as a drug to be released, through the polymer matrix increased and consequently long release time of it is expected. Also the crystalline melting point of the polymers obtained with boron triflouride/ether complex coinitiator system was lower than that obtained with p-TSA. This would reflect the lower crystallinity of such polymer type i.e. **IIIc** and **IIIc***.

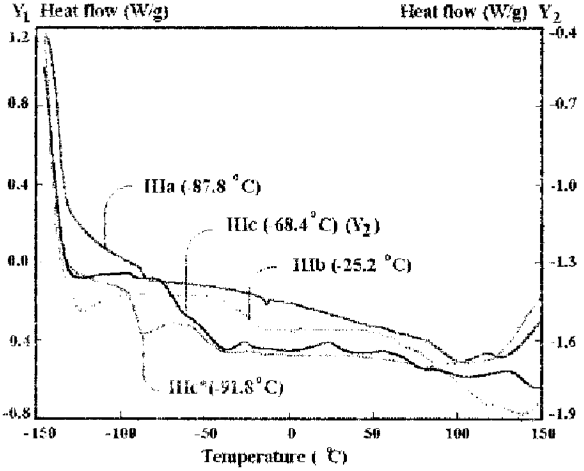
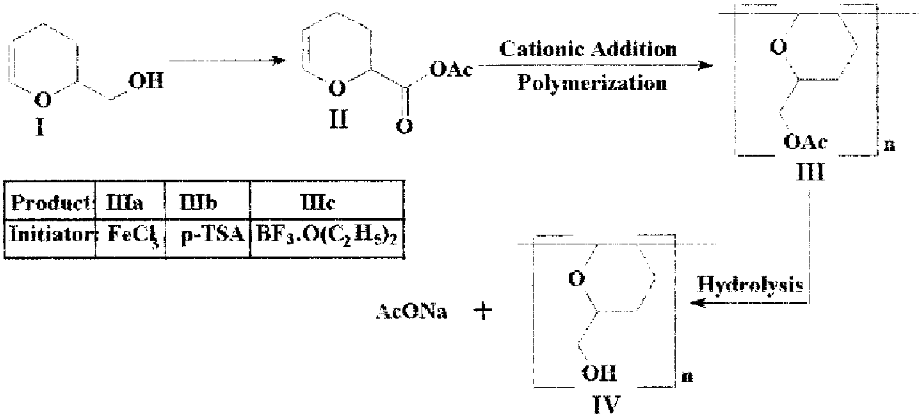


Figure 1: DSC analysis of poly-(2-acetoxymethyl-3,4-dihydro-2H-pyran) synthesized using the following cationic initiators: a) Anhyd $FeCl_3$, b) p-Toluene sulphonic acid (p-TSA); and c) $BF_3.O(C_2H_5)_2$ at 25°C. c*) $BF_3.O(C_2H_5)_2$ at 0°C.

In the present work, the reaction was occured through addition polymerization mechanism leading to backbone composed exclusively of C-C bonds (2,3) (Scheme 1). They are normally resistant to hydrolysis and enzyme attack causing main chain degradation. This is in contrast to the hydrogels composed of polyethylene oxide, a compatible triol or polyol and either diisocyanates (9-11) or the pyran monomer (8,12,13). This has been expected to overcome the storage instability problem and it was the case as the polymeric samples are still stable even after more than nine months. Also synthetic water-soluble polymers can have biological activity (14,15) and it is possible to polymerize certain types of drugs such as steroid (16). In a separate experiment, a synthesized polymeric sample at 0°C in presence of $BF_3.O(C_2H_5)_2$ initiator was hydrolyzed in mild alkaline medium (0.1N NaOH) at room temperature (≈25°C). It is important to mention that the polymeric sample is completely hydrolyzed into soluble polymer IV after 16h. Thus, it is promising to study its utilization as drug carrier for providing prolonged action formulations.



Product	IIIa	IIIb	IIIc
Initiator	$FeCl_3$	p-TSA	$BF_3.O(C_2H_5)_2$

Scheme 1: Cationic polymerization of poly(2-acetoxymethyl-3,4-dihydro-2H-pyran) and its alkaline hydrolysis product.

Experimental

Materials and methods

Elemental microanalysis was carried out at Cairo University, Egypt. IR was recorded on Perkin-Elmer 257 Grating IR-spectrophotometer. UV analysis was achieved using Cecil CE 5501 W double beam spectrophotometer. ^{1}H-NMR was recorded on Varian 60 MHz and thermal analysis was carried out using DSC V2.2A DuPont 9900. Molecular weight measurements were carried out on 745 GPC Prosram Version 1.0 (Y/N).

Synthesis

1. Preparation of 2-acetoxymethyl-3,4-dihydro-2H-pyran (II):

To an ice cold solution of 57 g (0.5 mole) of 3,4-dihydro-2H-pyran-2-methanol in 40 ml pyridine, 45 ml (0.52 mole) of acetic anhydride was slowly added with stirring over a 2 h period. After additional stirring for 3h at room temperature was followed by treatment with sodium bicarbonate solution and subsequent extraction with ether. The product was worked up in the usual manner and fractionated three times. 2% of a polymeric form of diphenylmethane diisocyanate was added to the final distillation step to remove completely the hydroxylic impurities. A colorless liquid (55 g) of boiling point 86.5-87°C was obtained in ≈70% yield. It has been stored over calcium hydride and distilled immediately prior to use. IR(KBr) ν=3080, 1740, 1655, 1100 cm^{-1}; UV λ_{max}= 240.8 nm;^{1}H-NMR($CDCl_3$): δ=1.8-2.2 ppm (aliph.CH_2); 4-5 ppm (pyran protons); 4.6 & 6.4 ppm (pyran unsat. protons); Elemental analysis: $C_8H_{12}O_3$ (156.18): Calculated: C, 61.53; H, 7.69; Found: C,60.58; H, 7.96.

2. Synthesis of poly (2-acetoxymethyl-3,4-dihydro-2H-pyran) (III a-c):

The polymeric product was batch synthesized by a cationic bulk polymerization process. Three different cationic initiators were used in 1.0 wt % of total weight of the reactants. They are: a) anhydrous ferric chloride; b) p-toluene sulphonic acid (p-TSA) and c) solution of 7 % boron trifluoride in diethyl ether. The initiator (50 mg) was added to 2 ml monomer (II) in 18 ml dichloroethane under nitrogen atmosphere and shaked well at 25°C for 6h. The polymerization reaction was stopped by adding 1ml of 10 % solution of tri-n-butyl amine. After evaporation of solvent and subsequent washing with dilute HCl and distilled water and finally drying at ambient temperature over P_2O_5 in vacuum, pale yellow thick liquid was obtained and spectroscopically characterized. IR(KBr) $\nu = 1740$, 1040 cm^{-1} and no absorption at 3080 and 1655 cm^{-1} confirming the polymerization process; UV $\lambda_{max} =$ 232 nm for all samples and 315.5 nm for IIIa only; ^1H-NMR($CDCl_3$): $\delta = 1.9$-2.2 ppm (aliph. CH_2); 4-4.8 ppm (pyran sat. protons) and no bands at 4.6 and 6.4 ppm reflecting the disappearence of the pyran double bonds due to polymerization. Number average molecular weight ($\overline{Mn}$) and polydispersity index ($\overline{Mw}/\overline{Mn}$) were determined by GPC and the data obtained are listed in table 1. In a separat experiment, the monomer was polymerized in presence of boron trifluoride in diethyl ether at 0°C. It led to formation of practically similar product as that obtained at 25°C with slight differences in some characteristic parameters such as $\overline{Mn}$ and I_{disp}. Also it has Tg of 182K i.e. lower than that of the corresponding polymer obtained at 25°C. The polymerization yields with respect to monomer conversion as well as the average degree of polymerization ($\overline{DP}$) are not significantly different from each other to conclude an effect of acids on the molecular weight. DP were ranged between 23 and 25.

Acid	Yield (%)	$\overline{Mn}$	$\overline{Mw}/\overline{Mn}$	Tg (K)	T_c (K)
Anhyd $FeCl_3$	93	3860	1.08	186	266
p-TSA	94	3850	1.07	248	276
$BF_3.O(C_2H_5)_2$	92	3590	1.04	205	236
$BF_3.O(C_2H_5)_2$*	95	3660	1.05	182	235

Table 1: Polymerization yield %; number average molecular weight ($\overline{Mn}$); polydispersity index ($\overline{Mw}/\overline{Mn}$); glass transition temperature and crystalline melting points (T_g & T_c, respectively) of poly(2-acetoxymethyl-3,4-dihydro-2H-pyran) determined by GPC.

(*) The reaction carried out at 0°C.

Characterization

Differential scanning calorimetry

Crystalline melting points were obtained using a DuPont 9900 thermal analyzer. Small samples (10-13 mg) of polymers were sealed in aluminum pans and melting endotherms were obtained by DSC at heating rate 10 $K.min^{-1}$ under nitrogen atmosphere (Figure 1).

Hydrolysis of III into poly (2-hydroxymethyl-3,4-dihydro-2H-pyran) (IV):

0.25 g of IIIa was added to 100 ml of 0.1 N sodium hydroxide solution with stirring at 37°C until it completely soluble (≈24 h). The hydrolysate was extracted with chloroform, dried over magnesium sulphate and the solvent was then evaporated.

IR (KBr) $\nu = 3300$ - 3500, 1030 cm^{-1}.

Acknowledgment

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