Polymer Bulletin 22, 41–45 (1989)

Polymer Bulletin

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Copolymer of sucrose and naphthoquinone imine derivatives

Synthesis and characterization

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SUMMARY

The purpose of the present work was to prepare a macromolecular prodrug with methacrylic esters of 2-hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine(I) and those of sucrose. The copolymer IV obtained by a bulk copolymerization reaction was purified by GPC and characterized by infrared spectroscopy, differential scanning calorimetry and hydrolysis studies. Its alkaline hydrolysis led to compound I which exhibited trypanocidal activity against T.cruzi.

INTRODUCTION

Most pharmacological agents are low molecular weight compounds which readily penetrate into all cell types and are often rapidly excreted from the body. Large and repeated doses must then be given in order to maintain the therapeutic effect. This often results in damaging side effects and leads to poor control of drug therapy(1).

Attachment of drugs to macromolecular carriers alters their rate of excretion from the body and provides the possibility of a controlled release for prolonged time periods.

One of the procedures which is applied in the preparation of drugs bound to a polymer side chain consists of the reaction of low molecular weight compounds with a polymerizable group(2). The derivative thus formed can subsequently undergo homopolymerization or copolymerization reactions to give macromolecules containing the drug.

In this paper we report the synthesis of a methacryl derivative(II) of the 2-hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine(I,3) which exhibits trypanocidal activity against T.cruzi(4,5,6,7), as well as its copolymerization with sucrose methacrylic esters(III,8).

EXPERIMENTAL

The mass spectrum was recorded on a Finnigan Model 3300 F-100 quadrupole mass spectrometer. Data were collected and processed with an INCOS data System using a NOVA III computer. Ultraviolet spectrophotometric studies were carried out in a Shimadzu UV-260 Spectrophotometer. The ^{1}H-NMR

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*To whom offprint requests should be sent spectrum was recorded on a Bruker 80 FT Spectrophotometer 80.13 MHz. The infrared spectra were run on a Nicolet 5 SXC FT-IR Spectrometer.

2-Hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine(I, 3) and sucrose methacrylic esters(III,8) were obtained and purified by previously reported procedures.

Synthesis of 2-[N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine]methacrylate(II): 5 mL of a chloroform solution containing 0.3 mL (3 x 10^{-3}mole) of methacryloyl chloride was added dropwise to 50 mL of a chloroform solution containing 0.5360 (2 x 10^{-3}mole) of I and 0.1580g (2 x 10^{-3}mole) of pyridine and the mixture was stirred at 0ºC for 2 h. The unreacted compound I was extracted from the reaction mixture with 50 mL of 1 N sodium hydroxide and the chloroform solution was thoroughly washed with water. After drying the chloroform extract with anhydrous sodium sulfate, the solvent was evaporated under reduced pressure yielding a yellow product. m.p. 158-159.5ºC. Yield: 60%. MS: m/z(%) 336($M^{+\cdot}$,4), 267($M^{+\cdot}$ - $C_4H_5O^{+\cdot}$,37), 172(33), 69($CH_3C{=}CH_2CO^{+\cdot}$,100), 55(35), 41(92) and 28(78); ^{1}H-NMR(DMSO-d_6): δ=7.50-8.50(m,5H), δ=5.7-6.3(d,2H), δ=2.27(s,3H), δ=2.16(s,3H) and δ=1.40 ppm(s,3H). The main bands of the IR spectrum in KBr pellets are summarized in Table 1.

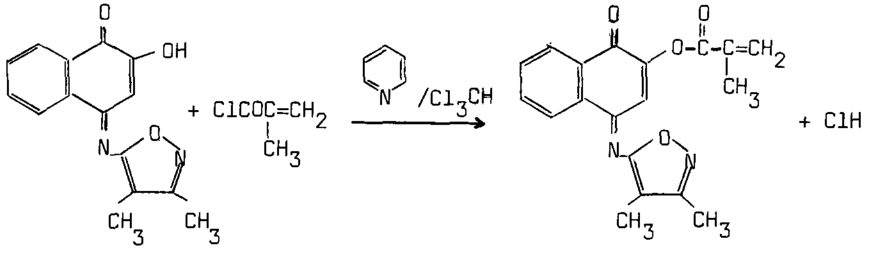
Synthesis of poly-IV: The synthesis of IV was carried out by mixing a DMF solution of both comonomers II and III in 1:2 ratio respectively. After removing the solvent under reduced pressure and by addition of benzoyl peroxide, the mixture was warmed at 80ºC during 24 h yielding a soluble rubbery product which was purified by gel permeation chromatography. The main bands in the IR spectrum are shown in Table 1.

Hydrolytical studies of IV were carried out in aqueous solutions of NaOH. The amount of I released was determined by spectrophotometric analysis using 260 nm light which is the maximum wavelength in the absorption spectrum for I. The absorbance value, which is indicated for each concentration in Table 2, was the average of two separate runs. The solution was continuosly stirred during the experiments and the samples were maintained at the desired temperature by immersing them in a thermostatically controlled bath Haake F 3.

RESULTS AND DISCUSSION

The reaction between I and methacryloyl chloride leads to a polymerizable vinylic comonomer(II), according to the following Scheme:

Scheme 1

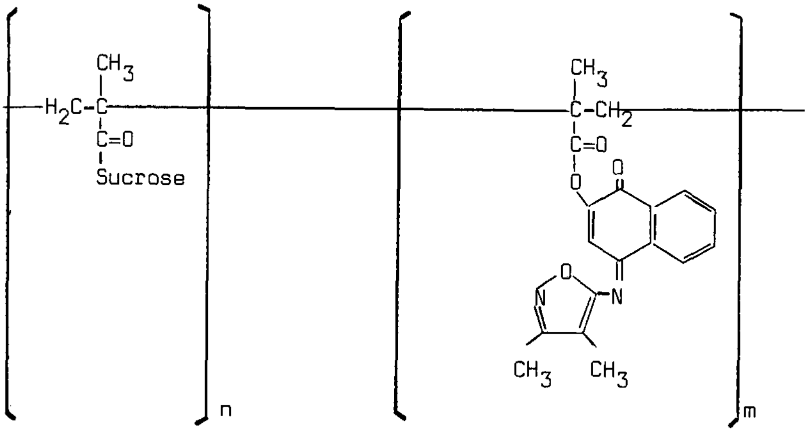


I

II

The vinylic derivative II was converted into a macromolecule(IV) by a bulk copolymerization reaction with sucrose methacrylic esters(III) at 80ºC using benzoyl peroxide as initiator(Scheme 2).

Scheme 2



IV

The copolymer IV is soluble in ethanol, methanol and THF. Its glass transition temperature(T$_g$) is -3ºC as determined by DSC.

In order to discard the possibility that a mixture of homopolymers was obtained, independent homopolymerization reactions were carried out with II and III under the same experimental conditions. The results obtained indicate that the poly-III(Sucrogel H-70) was the only macromolecule formed. It is insoluble in all common solvents as well as in DMF and DMSO. Its T$_g$ value is 52ºC as determined by DSC(8).

Infrared Analysis: Table 1 summarizes the characteristic infrared absorptions of II, III and IV.

Table 1: Infrared absorptions of II, III and IV

Absorption (cm^{-1})	II	III[a]	IV
3550-3450	-	-OH(stretching, association)	-
3400-3200	-	-	-OH(stretching, polymeric association)
3200-2900	>C=CH$_2$(str.)	>C=CH$_2$	-
2900-2800	-CH$_2$-(str.)	-CH$_2$-	-CH$_2$-
1750-1600	>C=O(bending)	>C=O	>C=O
1600	>C=N-C	-	>C=N-C
1096	-	-OH	-OH
700-800	Aromatic	-	Aromatic

[a] See reference 8

The infrared spectrum of II shows an absorption band at 3200-2900 cm^{-1} caused by stretching vibrations of the $>C=CH_2$ group and another one near 1750-1660 cm^{-1} which is attributed to the presence of the $>C=O$ group. The absorption band at 1600 cm^{-1} is characteristic of the $>C=N-C$ group, and a strong peak which is observed near 800 cm^{-1} is indicative of its aromaticity. The infrared spectrum of III shows an absorption band at 3560-3450 cm^{-1} that could be attributed to the hydroxyl group in simple association, a band near 1750-1660 cm^{-1} which is assigned to the presence of $>C=O$ groups and a band near 1096 cm^{-1} caused by bending vibrations of the -OH group. The infrared spectrum of IV shows an absorption band at 3400-3200 cm^{-1} that could be attributed to the hydroxyl group in polymeric association. The absorption band at 3200-2900 cm^{-1} originated by stretching vibrations of the $>C=CH_2$ group present in the spectra of II and III is absent in this spectrum. The two absorption bands near 1750-1600 cm^{-1} are attributed to the presence of both $>C=O$ groups of III.

The results of the hydrolytical studies of IV are in accordance with the physical properties as measured by IR spectroscopy and thermal analysis. Table 2 shows the results obtained under different experimental conditions.

The synthesis of the sucrose monoester also yielded a low amount of diesters which would lead to the formation of branched structures and networks with a helicoidal form. Thus, the great stability of IV towards the alkaline hydrolysis can be accounted for.

Table 2: Hydrolysis studies of IV

Concentration of NaOH, M	Temperature(ºC)	Time(h)	A_{260nm}
0.990	45	24	-
0.990	80	24	-
1.997	45	24	-
1.997	80	24	-
3.990	45	24	-
3.990	80	24	0.348
3.990	80	48	0.450
3.990	80	72	0.450
3.990	80	96	0.450

According to the above results, it can be concluded that a new copolymer was synthesized. The possibility to have a mixture of homopolymers can be eliminated because only one of them, poly-III, was obtained. In addition, the T_g values of poly-IV and III were different from each other. Spectroscopic data and the results of degradation studies also rule out the possibility that poly-III mixed with unreacted II was obtained.

ACKNOWLEDGEMENT

P.Castellano acknowledges receipt of a fellowship granted by the Consejo Nacional de Investigaciones Científicas y Técnicas(CONICET) de la República Argentina.

This research was sponsored by the Secretaría de Estado de Ciencia y Tecnología(SECYT), Consejo de Investigaciones Científicas y Tecnológicas de la Provincia de Córdoba(CONICOR) and the Consejo Nacional de Investigaciones Científicas y Técnicas(CONICET) de la República Argentina.

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Accepted May 30, 1989 K