Exchange Reactions of Poly-2-(*N*-phthalimido)ethyl Acrylate with Hydroxy and Amino Compounds

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ABSTRACT: 2-(*N*-Phthalimido)ethyl acrylate was prepared by the reaction of *N*-(2-hydroxyethyl)phthalimide with acrylic acid in the presence of *N*,*N*-dicyclohexylcarbodiimide. The exchange reactions of the resulting polymer with hydroxy and amino compounds have been studied. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 99: 2258–2262, 2006

Key words: polymer; exchange reactions; acrylic acid; phthalimide; hydroxy; amino compounds

INTRODUCTION

One promising approach for targetable drug delivery is the use of polymers. Recently, several activated polymers, containing phthalimido moiety, have been used as macromolecular drugs.[1–4] One of the most interesting topics in the field of pharmacologically active polymers is the preparation of polymeric drugs, in which drugs are attached to the polymeric backbone via covalent bonds with limited stability to biological environments.[5,6] Activated esters of acrylic and methacrylic acids may be used as precursors of some classes of multifunctional polymers.[5] This is due to the ability of many of them to react selectively with compounds bearing hydroxy or amino groups, giving esters or amidic bond, respectively, even in the presence of other chemical functions. For this reason, they provide a very convenient means for the preparation of some classes of macromolecular drugs.[6] Several activated esters and amides of acrylic and methacrylic acid and their polymers have been described.[7–10] In our previous work, we described the synthesis, polymerization, copolymerization, and exchange reactions of the acrylic and methacrylic esters of *N*-hydroxyphthalimide and *N*-hydroxy-tetrabromophthalimide.[11–16] The aim of the present work is to report the synthesis and polymerization of 2-(*N*-phthalimido)-ethyl acrylate (NPEA) as well as the exchange reactions of the resulting polymer with aminated and hydroxylated compounds. This has been done to obtain macromolecular chains, in which the drug residues could be attached at some distance from the main backbone.

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EXPERIMENTAL

Materials

Ethyl amine, pipridine, *p*-anisidine, *p*-aminobenzoic acid, *tert*-butanol, cyclohexanol, phenol, *o*-hydroxybenzoic acid, and *p*-hydroxybenzoic acid were BDH (England) products. Potassium phthalimide, 2-bromoethanol, triethylamine, and *N*,*N*-dicyclohexylcarbodiimide (DCCI) were from Aldrich. Acrylic acid and the free radical initiator, azobisisobutyronitril (AIBN), were from E. Merck, Darmstadt. All the solvents were of reagent grade and were purified by distillation before use.

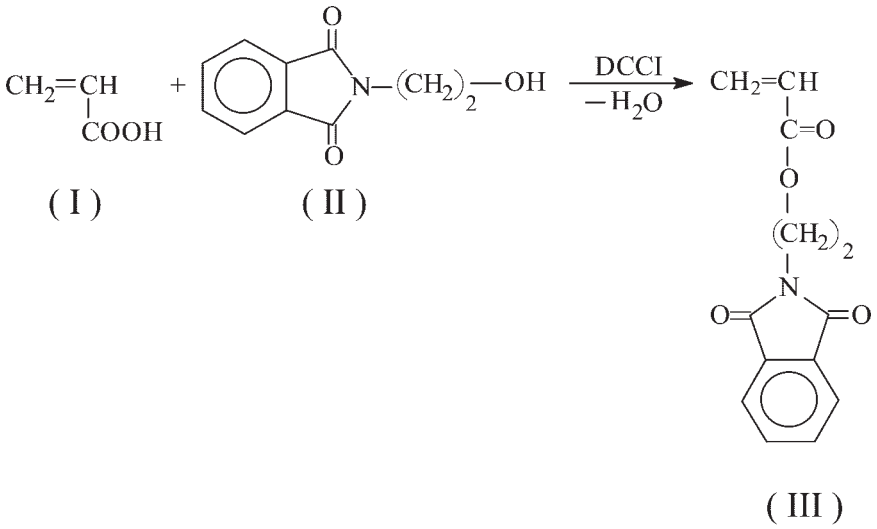
Synthesis

Preparation of *N*-(2-hydroxyethyl)phthalimide

To 0.1 mol of potassium phthalimide in DMF, 0.1 mol of 2-bromoethanol was added dropwise, with stirring. A white precipitate was formed, and stirring was continued for another 6 h. The solvent was evaporated, and the residue was washed with water and recrystallized from benzene. The product (65%) showed a m.p. of 212–213°C (literature value: 212°C[17]).

Preparation of NPEA

NPEA was prepared by the reaction of *N*-(2-hydroxyethyl)phthalimide (NHEP) with acrylic acid in the presence of DCCI. To a cold solution (0–5°C) of 19.1 g (0.1 mol) of NHEP and 7.2 g (0.1 mol) of acrylic acid in methylene chloride (100 mL) was added 20.6 g of DCCI, with stirring. After stirring for 6 h at room temperature, the precipitated dicyclohexyl urea was removed by filtration and the filtrate was evaporated to dryness in vacuum. The residue was then recrystallized from benzene–petroleum ether (20/80).



Scheme 1

The yield was 70% and m.p. was 103–104°C (literature value: 102°C[17]. Anal. calcd for ($C_{13}H_{11}NO_4$): C, 63.67%; H, 4.49%; N, 5.71%. Found: C, 63.98; H, 4.39; N, 5.75.

Polymerization

Solution (10%) of the monomer in DMF was treated with AIBN (1 mol %). After purging with deoxygenated nitrogen, the reaction mixture was allowed to stand at 60°C for 6 h. The polymer was obtained by reprecipitation in methanol, forming a viscous sticky yellowish precipitate, which was isolated and purified by dissolving in acetone and reprecipitation with petroleum ether. The yield was 70%, and the polymer was a soft, sticky, transparent material.

Exchange reactions

To a 10% solution of polymer in DMF, two equivalents of amine were added. The reaction mixture was allowed to stand at 60°C for 6 h. Similarly, the exchange reactions with hydroxylated compounds were carried out, except that triethylamine (two equivalents) was also added to the reaction mixture. In all cases, the products were isolated by pouring into an excess of diethyl ether, filtering, dissolving in DMF, reprecipitating with diethyl ether, and drying.

Characterization

IR spectra were run on a Unicam SP-1200 spectrophotometer. ^{1}H NMR spectra were measured on a 90 MHz Varian EM-390 spectrometer in DMSO-d_6, with tetramethylsilane as the internal standard. The elemental analysis was carried out at the Microanalytical Center, Cairo University.

RESULTS AND DISCUSSION

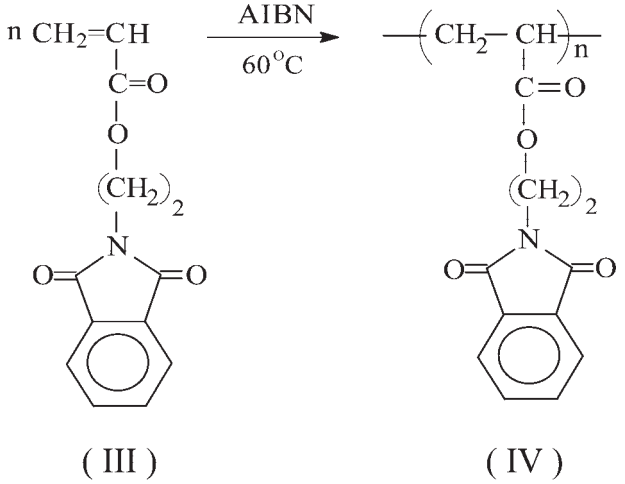
In the present investigation, NPEA was prepared by the reaction of NHEP with acrylic acid in the presence of DCCI, according to the following scheme (Scheme 1):

The monomer was a crystalline solid, easily soluble in most organic solvents, but sparingly soluble in aliphatic hydrocarbons, such as *n*-hexane and petroleum ether. The monomer was readily polymerized in solution, with AIBN as a free radical initiator. The polymer was soluble in DMF, DMSO, chloroform, acetone, and dioxane and insoluble in water, benzene, and ether (Scheme 2).

The structure of the monomer and polymer was established from IR and ^{1}H NMR spectra (Table I).

Reactions of the polymer (IV) with amines

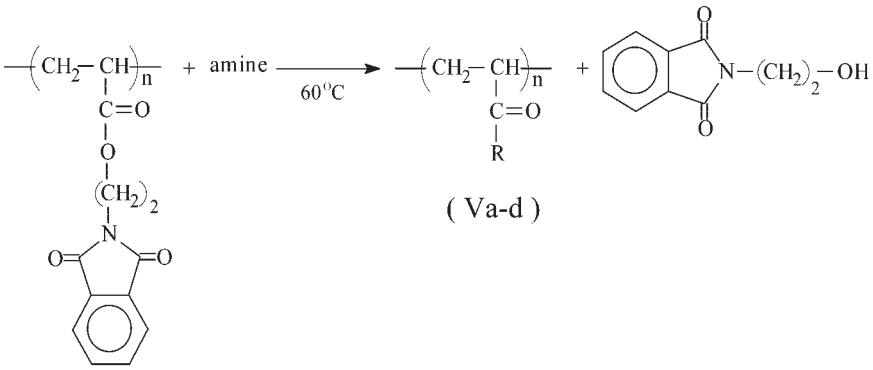
The ability of poly-NPEA to enter into an exchange reaction with amines was tested with ethylamine, pi-



Scheme 2

TABLE I
IR and ^{1}H NMR Spectra of Monomer (III) and Its Polymer (IV)

Compound	IR spectra: $\nu_{C=O}$ (ester) cm^{-1}	IR spectra: $\nu_{C=O}$ (cyclicimide) cm^{-1}	IR spectra: $\nu_{C=C}$ cm^{-1}	^{1}H NMR: Segment	^{1}H NMR: Chemical shift (ppm)
III	1738	1840, 1790	1620	CH_2═CH—	6.1–6.4
				CH_2—N	2.90
				CH_2—O	3.20
				C_6H_5—	7.90
IV	1740	1810, 1785		—CH_2—CH	1.82
				—CH—CO	2.65
				—CH_2—N	3.00
				—CH_2—O	3.50
				—C_6H_5	7.85



Va, R = C_2H_5NH
b, = $C_5H_{10}N$
c, = CH_3O-C_6H_4-NH(P-)
d, = HOOC-C_6H_4-NH(P-)

Scheme 3

peridine, *p*-anisidine, and *p*-aminobenzoic acid. In a typical experiment, a 10% solution of polymer (IV) in DMF was treated with two equivalents of amine, and the reaction mixture was allowed to stand at 60°C for 10 h (Scheme 3):

The yield of the exchange reaction was calculated from nitrogen analysis (Table II). In all cases, the exchange reaction was almost practically quantitative. This was confirmed by IR spectroscopy. In the spectra of compounds (Va–c), the bands at about 1740 and 1785, 1810 cm^{-1} present in the spectrum of polymer (IV), which are attributed to $\nu_{C=O}$ of ester and cyclic imides, respectively, entirely disappeared after the exchange reaction. At the same time, new strong bands at about 1630–1640 and 1510–1530 cm^{-1} assigned to $\nu_{C=O}$ (amides I and II), respectively, appeared. This was also confirmed by ^{1}H NMR spectroscopy (Table III). From Tables II and III, it is clear that the yields of the exchange reactions calculated from nitrogen analysis are in agreement with those obtained from ^{1}H NMR spectroscopy.

Reaction of the polymer (IV) with hydroxy compounds

The ability of the poly-NPEA for exchange reactions with hydroxy compounds was tested with *tert*-butanol, cyclohexanol, phenol, and *o*- and *p*-hydroxybenzoic acids (Scheme 4):

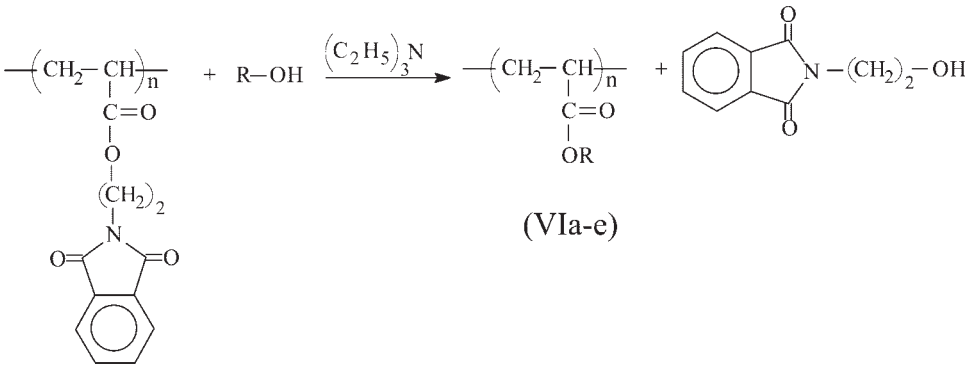
All the aforementioned exchange reactions take place easily when a 10% solution of poly-NPEA (IV) was treated with two equivalents of a hydroxy compound and two equivalents of triethylamine, and al-

TABLE II
Analytical Data for the Exchange Reactions of Poly-NPEA (IV) with Amines

Co-reactant	Calcd. for 100% Exchange	N (%)	Exchange (%)	Time (h)
Ethylamine	14.14	14.19	100	10
Piperidine	10.07	10.10	100	10
p-Anisidine	7.95	7.95	100	10
p-Aminobenzoic acid	7.33	7.30	100	10

TABLE III
^{1}H NMR Spectral Data for the Exchange Reactions of Poly-NPEA with Amines

Exchange products	Segments	Chemical shift (ppm)	Exchange (%)
Va	CH_3—	1.2	100
	—CH_2—CH—	1.5–2.0	
	—CH_2N—	3.0	
	—NH	5.4	
Vb	—$(CH_2)_3$—, —CH_2—CH—	1.2–1.8	100
	—CH_2—N—CH_2—	3.4	
Vc	—CH_2—CH—	1.5	100
	—OCH_3	3.6	
	—NH	5.8	
	C_6H_4—	6.6–7.6	
Vd	—CH_2—CH—	1.5 (broad)	100
	—NH	6.0	
	—C_6H_4—	6.6–7.4	



VI a, R = C_4H_{10} –
b, = C_6H_{11} –
c, = C_6H_5 –
d, = C_6H_4-COOH (o-)
e, = C_6H_4-COOH (p-)

Scheme 4

TABLE IV
Analytical Data for the Exchange Reactions of Poly-NPEA (IV) with Hydroxy Compounds

Co-reactant	N (%)	Exchange (%)	Time (h)
tert-Butanol	0.61	94	10
Cyclohexanol	0.85	90	10
Phenol	0.00	100	10
o-Hydroxybenzoic acid	0.63	91	10
p-Hydroxybenzoic acid	0.00	100	10

TABLE V
Analytical Data for the Exchange Reactions of Poly-NPEA (IV) with Cyclohexanol at 20°C in the Presence of Triethylamine

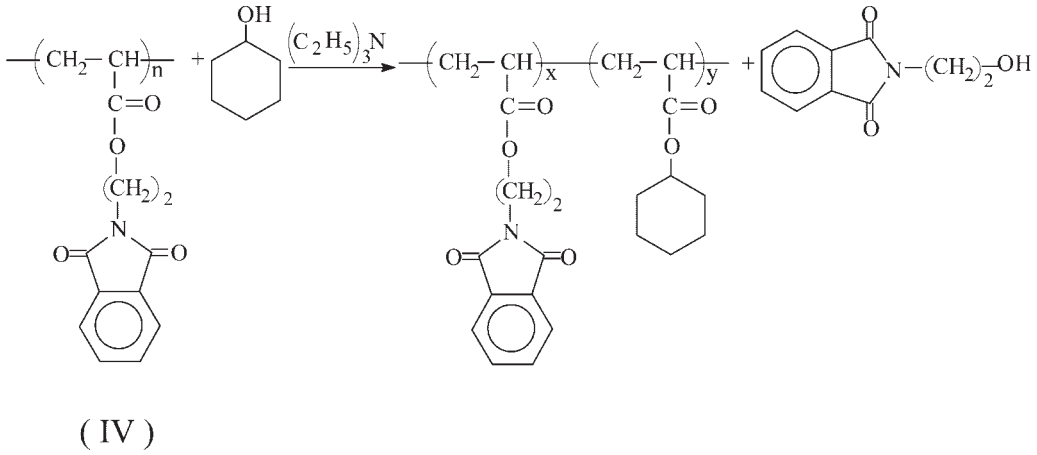
Reaction time (days)	N (%)	Exchange (%)
1	5.11	16
2	4.55	29
4	3.81	44
8	2.93	60
12	2.1	73
16	1.54	81

TABLE VI
Analytical Data for the Exchange Reactions of Poly-NPEA (IV) with Cyclohexanol at 60°C in the Presence of Triethylamine

Reaction time (min)	N (%)	Exchange (%)
15	5.40	8
30	5.06	17
60	4.80	23
120	3.85	43
240	3.24	55
480	2.36	69

lowed to stand at 60°C for 10 h. The results are summarized in Table IV.

The exchange reactions of poly-NPEA with cyclohexanol in DMF solution was further investigated. We were especially interested in cyclohexanol, because it is a model for studying polymeric adducts of steroid hormones and prostaglandins.[18]



(IV)

Scheme 5

For equivalent quantities of polymer, cyclohexanol, and triethylamine, the progress of the reaction[5] (percent exchange) was recorded against the reaction time (*t*) at 20 and 60°C. The results are reported in Tables V and VI. From Tables V and VI, it is clear that poly-NPEA showed a good behavior as a model compound for a long-active polymeric drug (Scheme 5).

From the earlier data, it may be concluded that the new monomer described in this article may be useful for preparation of polymeric-drug adducts. Furthermore, similar monomeric phthalimides may be synthesized starting from a number of other hydroxy or amino acids, thus, providing a wider possibility for the synthesis of pharmacologically active polymers.

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