# Synthesis and Hydrolysis Study of Polyacrylates Containing 2′,5-Dichloro-4′-Nitrosalicylanilide

Y. S. YANG, G. R. QI, J. W. QIAN, S. L. YANG

Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, People's Republic of China

*Received 9 January 1997; accepted 19 February 1997*

**ABSTRACT:** Monomers (meth)acryloyloxy-2′,5-dichloro-4′-nitrosalicylanilide have been synthesized by treating 2′,5-dichloro-4′-nitrosalicylanilide (niclosamide) with acryloyl or methacryloyl chloride, and polymerized by free radical polymerization to give a polymer containing chemically bonded niclosamide. The structure of monomer and polymer were confirmed by IR, UV, and elemental analysis. Hydrolysis data of polymer in different media indicated that the hydrolysis rates of polymer were strongly dependent on the nature of the polymer structure and the hydrolyzing medium. © 1997 John Wiley & Sons, Inc. J Appl Polym Sci **66:** 29–33, 1997

**Key words:** synthesis; hydrolysis; polyacrylates; 2′,5-dichloro-4′-nitrosalicylanilide

## INTRODUCTION

During the past few years, controlled release of drugs has become one of the most heated topics in medical polymer research, because the controlled release systems provide many advantages over conventional drug therapies, such as high efficiency, low toxicity, and localized delivery of the drug.[1–3] Drugs can be combined with polymer materials either by physical combination or chemical combination. In physical combination, drugs are dissolved in or mixed with polymer materials, and in chemical combination, drugs are chemically attached to natural or synthetic polymer materials by an ionic or a covalent linkage.

2′,5-dichloro-4′-nitrosalicylanilide (niclosamide) is a useful drug for combating bilharzia disease through eradication of the schistosomiasis snails. It gives a total kill of *Australorbis glabratus* at 0.3 ppm, but it is expensive.[4] To utilize decreased amount of the drug and eliminate the enivormental and toxicological problems, El-nagar et al.[5] have reported the controlled release formulations of niclosamide by incorporation into plates of ethylene–vinylacetate copolymer. Akelah, Selim, and Rehab[6,7] have synthesized polymer-containing chemically bonded niclosamide with low active groups and polymer-containing niclosamide-diethanol amine salts.

In this article, monomers containing chemically bonded niclosamide were synthesized in cyclohexanone with high yields, and polymerized by free radical polymerization. Monomer and polymer were characterized by IR, UV, elemental analysis, and size exclusion chromatography (SEC) in detail; at the same time, the hydrolysis study of polymer was also reported.

## EXPERIMENTAL

Methacrylic acid, acrylic acid, styrene, and methanol were chemical reagents; cyclohexanone, dioxane, and triethylamine were analytical reagents; 2′,5-dichloro-4′-nitrosalicylanilide (niclosamide) was obtained from the Academy of Medical Science of Zhejiang Province. The molecular weights of polymer were analyzed by SEC with UV detection, using polystyrene as a standard in THF solution at 30°C. Infrared spectra were obtained on a FTIR-5DX spectrophotometer with KBr. Ultraviolet spectra were obtained on a Beckman DU-50

*Correspondence to:* Y. S. Yang.

Journal of Applied Polymer Science, Vol. 66, 29–33 (1997)

spectrophotometer. The compositions of copolymer were analyzed by elemental analysis of N. Acryloyl and methacryloyl chloride were prepared according to the literature.[8]

### Preparation of Acryloyloxy-2′,5-Dichloro-4′-Nitrosalicylanilide (Monomer I)

Freshly distilled acryloyl chloride [4.5 mL (54 mmol)] was dropped to a stirred mixture of 10 g (30.6 mmol) niclosamide and 5.1 mL (36.8 mmol) triethylamine in 150 mL cyclohexanone. Monomer **I** was precipitated from solution, then the precipitate was filtered off and washed with distilled water and absolute ethyl alcohol several times. The raw product was recrystallized from $CH_2Cl_2$/petroleum ether (30–60°C) giving 9.4 g (80.7% yields based on niclosamide) of pure **I,** melting point (mp) 194–195°C.

### Preparation of Methacryloyloxy-2′,5-Dichloro-4′-Nitrosalicylanilide (Monomer II)

Monomer **II** was prepared from methacryloyl chloride and niclosamide. The mixture was stirred for 5 h, then cooled to −10°C. The precipitate was purified as (**I**), giving **II** in 70.5% yields, mp 151–152°C.

### Polymerization of Monomer

A mixture of 1 g monomer **I** or **II** and 0.2 g azobisisobutyronitrile (AIBN) dissolved in 40 mL dioxane was heated at 70°C for 48 h under nitrogen atmosphere. After cooling, the mixture was poured into 250 mL methanol. The precipitate was filtered off, washed with methanol several times, and dried at 50°C under vacuum.

### Preparation of Copolymer

A mixture of 1 g monomer **I,** 0.27 g styrene (mol ratio 1 : 1), and 0.2 g AIBN dissolved in 40 mL dioxane was heated at 70°C for 48 h under nitrogen atmosphere, and the copolymer was purified in the same way as the homopolymer. The copolymer of **I** and acrylic acid were prepared in the same way as the copolymer of **I** and styrene, except that petroleum ether (90–120°C) was used as precipitant for it.

### Hydrolytic Release of Niclosamide

The hydrolytic release of niclosamide was carried out in the mixture of water/dioxane (3 : 1, v/v) of PH 7.0 and PH 10.0. A powder of polymer sample (0.01 g) was placed in a flask containing 100 mL of the medium at 37°C and stirred with a magnetic stirrer. Samples were centrifuged periodically and concentrations of the hydrolyzed niclosamide were measured by UV spectrophotometer at 335 nm. The $A$–$C$ equation of niclosamide ($C < 20$ $\mu$g/mL) in medium was $A = 0.035909C + 0.003653$ [$R = 0.9992$].

**Table I Wavenumber of Monomer**

| Monomer | Wavenumber ($cm^{-1}$) |
|---|---|
| I | 3360(NH), 3100(Ar—H), 1750(C=O of ester), 1680(C=O of amide) |
| II | 3360(NH), 3100(Ar—H), 2920(—CH), 1750(C=O of ester, 1690(C=O of amide) |

## RESULTS AND DISCUSSION

The objective of the present work was to find a way to control niclosamide release for reducing the cost and eliminating environmental problems. Monomers **I** and **II** containing niclosamide were synthesized with high yields by treating niclosamide with acryloyl or methacryloyl chloride in cyclohexanone in the presence of triethylamine. Because the solubility of niclosamide in cyclohexanone (~ 1 g niclosamide versus 15 mL solvent at room temperature) was higher than that in acetone (~ 1 g niclosamide versus 50 mL solvent used by Akelah, Salim, and Rehab),[7] the reaction rate of acryloyl or methacryloyl acid with niclosamide in cyclohexanone was faster than that in acetone; also, **I** was easy to purify for its low solubility in cyclohexanone. Monomers were homopolymerized in dioxane by free radical polymerization with AIBN as initiator; furthermore, **I** was copolymerized with styrene (St) or acrylic acid (AA) to induce a hydrophobic or hydrophilic nature to the polymer. The structures of monomer and polymer were confirmed by IR, UV, elemental analysis, and SEC.

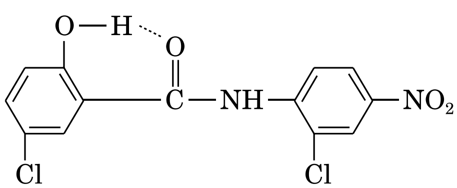
The wavenumber of the monomer and elemental analysis are showed in Tables I and II; their IR and UV spectra in dioxane are shown in Figures 1 and 2, respectively.

In Figure 1(a), the vibration wavenumber of phenolic hydroxyl and N—H in amide were 3580 $cm^{-1}$ and 3500 $cm^{-1}$; however, they were higher than that of phenol and benzanilide, respectively,

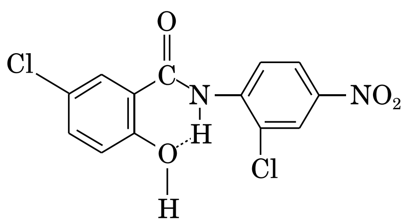
**Table II Elemental Analysis of Monomer and Polymer**

| | Calcd. | | | Found | | | |
|---|---|---|---|---|---|---|---|
| Formula | C (%) | H (%) | N (%) | C (%) | H (%) | N (%) | Weight Percent of **I** in Copolymer |
| $C_{16}H_{10}Cl_2N_2O_5$ | 50.39 | 2.62 | 7.34 | 49.20 | 2.52 | 7.32 | — |
| $C_{17}H_{12}Cl_2N_2O_5$ | 51.65 | 3.04 | 7.09 | 50.06 | 2.99 | 7.08 | — |
| **I**–St | — | — | — | 59.25 | 3.96 | 5.64 | 77.0 |
| **I**–AA | — | — | — | 59.61 | 3.84 | 6.18 | 84.4 |

because there was an intramolecular hydrogen bond between them. Kosheleva, Shumakovich, and Bekhli[9] have demonstrated that niclosamide existed in mixtures of the two conformers **III** and **IV** in solution, but in the solid state, the preformed conformer was **III.**



**III**



**IV**

In Figure 1(b), the intramolecular hydrogen bond disappeared, then the wavenumber of N—H in amide decreased to 3360 $cm^{-1}$. In Figure 2(a), the peak absorption wavelength of niclosamide was 330 nm, but that of **I** shifted to 315 nm for a larger pendant group with larger steric hindrance in **I.**

In the pendant group of monomer, there is functional group nitro-, which may act as retarder or inhibitor in free radical polymerization, so the yields are not quantitative and the molecular weights of polymer are quite low.[10] As a result, the concentration of initiator AIBN was higher than that in polymerization of ordinary acrylate monomer, and the yields were always kept between 5% and 10%, but the yields of copolymerization could be kept between 10% and 20%; furthermore, the number average molecular weights determined by SEC were ~ 3,000. The SEC peak of polymer was single and symmetric without tail; accordingly, we could think it was a copolymer of **I** and styrene or acrylic acid, not a mixture of two homopolymers.

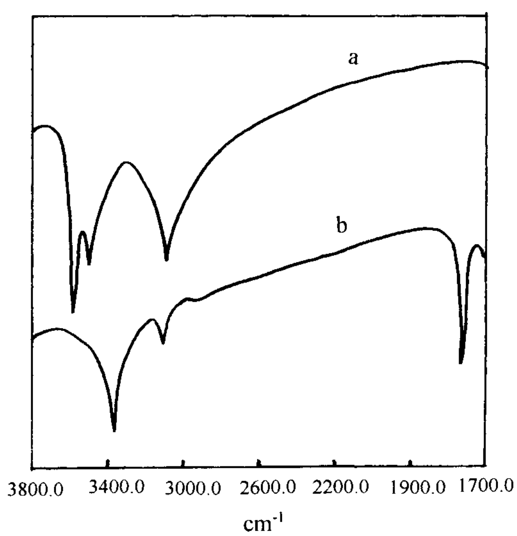



**Figure 1** IR spectra of niclosamide and monomer **I.** (a) Niclosamide, (b) monomer **I.**

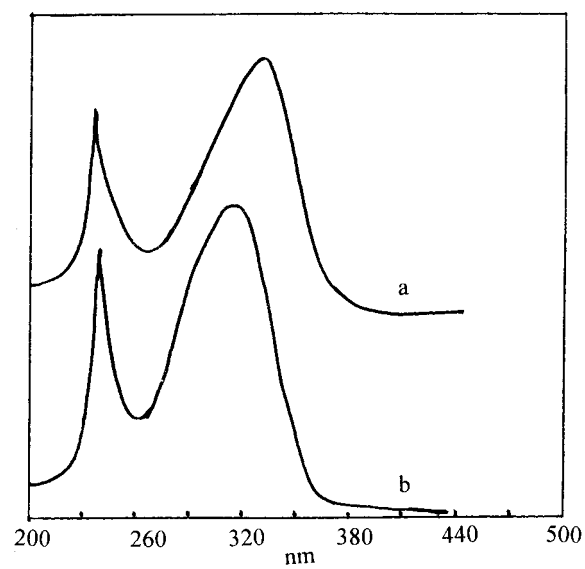



**Figure 2** UV spectra of niclosamide and monomer **I** in dioxane. (a) Niclosamide, (b) monomer **I.**

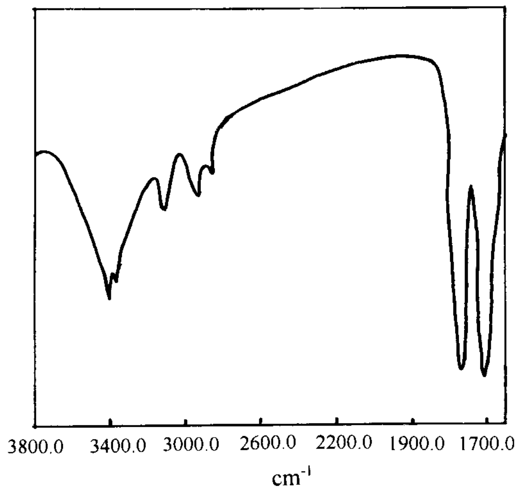



**Figure 3** IR spectra of partial hydrolysis polymer.

IR spectra of the partial hydrolysis product shown in Figure 3 indicated the existence of —COOH with a wavenumber of 1700 $cm^{-1}$ and 3400 $cm^{-1}$, and plots of the hydrolyzed niclosamide versus time of monomer and polymer are shown in Figures 4 and 5.

In Figure 4, hydrolysis of the monomer was a zero-order reaction, and the slopes of **I** and **II** were 0.48%/h and 0.26%/h, respectively, which indicated that the hydrolysis rate of **I** was higher than that of **II.** Comparing Figures 4 and 5, it was obvious that the hydrolysis rates of the polymer were much lower than those of the monomer, so niclosamide could be control-released by being chemically attached to the polymer.

The hydrolysis data of Figure 5 indicated that the release rates were strongly dependent on the nature of the polymer structure and the hydrolyzing medium. Introducing a hydrophilic monomer (acrylic acid) into the polymer could increase the release rate of niclosamide; however, introducing a hydrophobic monomer (styrene) into the polymer could decrease the release rate of niclosamide. Accordingly, the release rate of niclosamide could be controlled by changing the nature of the polymer structure. The nature of the medium appeared to have a great effect on the niclosamide release. The hydrolysis rates of polymer in PH 10.0 were much higher than those in PH 7.0, which might be attributed to the Ingold's BAC2 mechanism[11]:

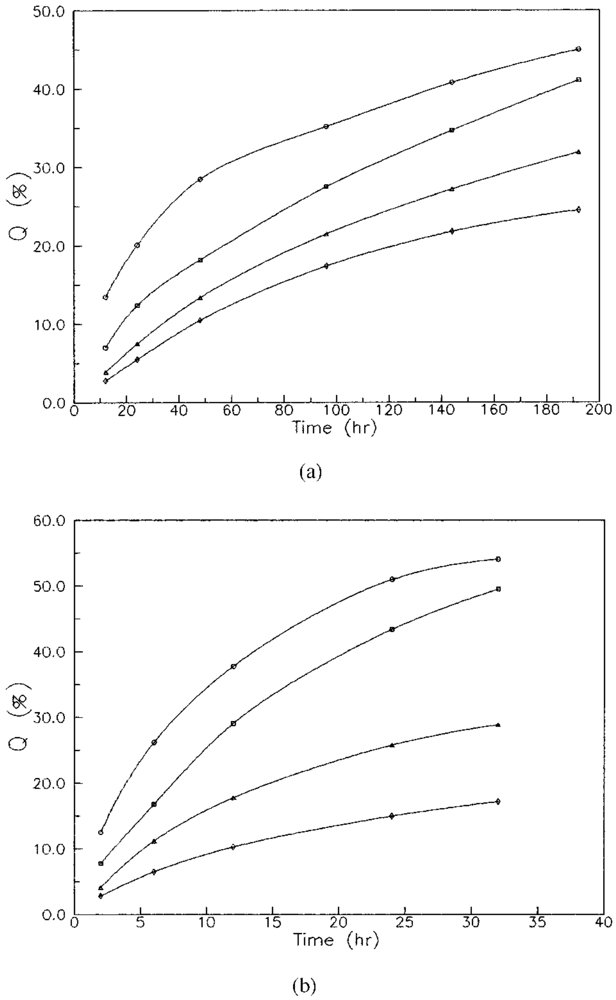



**Figure 5** Accumulative release $Q$ (%) of polymer in dioxane/water (3 : 1, v/v) versus time. (a) pH 7.0, (b) pH 10.0. (○) Co(I-AA) [containing 15.6% AA]; (□) homopolymer of **I;** (◇) homopolymer of **II;** (△) Co(I-St) [containing 23.0% St].

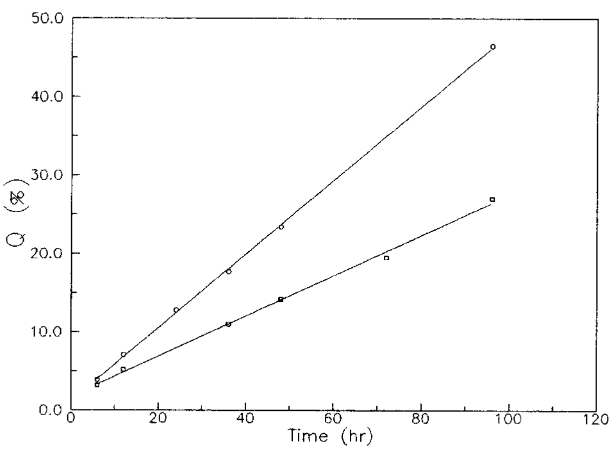
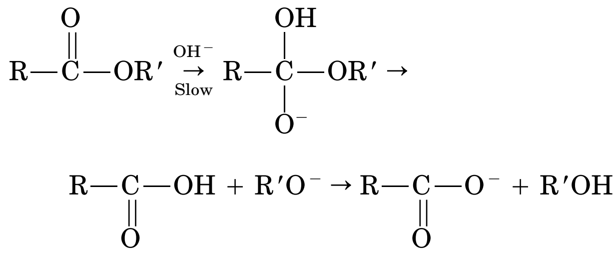
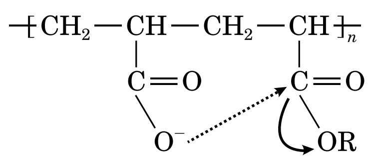



**Figure 4** Accumulative release $Q$ (%) of monomer in dioxane/water (3 : 1, v/v) versus time, pH 7.0. (○) Monomer **I,** (□) monomer **II.**



Furthermore, the carboxylic groups generated during the initial hydrolysis had intramolecular interactions of the neighboring carbonyl,[12] and that also accelerated the hydrolysis of active groups.



Further study of the effect of polymer and morphology as well as the other environmental factors on the release of niclosamide will be described in subsequent articles.

## CONCLUSIONS

Niclosamide could be control-released by being chemically attached to the polymer, and the release rate could be controlled by changing the nature of polymer structure; also, the nature of the medium had a great effect on niclosamide release.

The authors are indebted to the National Natural Science Foundation of China for financial support of this research.

## REFERENCES

1. H. J. Sander, *Chem. Eng. News,* **63,** 1 (1985).
2. L. Robert, *Science,* **249,** 1527 (1990).
3. L. Robert and N. A. Peppas, *Bioeng. Science News,* **16,** 3 (1992).
4. M. S. Mccullough, *Bull. WHO,* **58,** 681 (1980).
5. M. El-nagar, G. Pfister, M. Bahadir, and F. Korte, *Toxicol. Environ. Chem.,* **31–32,** 383 (1991).
6. A. Akelah, A. Selim, and A. Rehab, *J. Polym. Mater,* **3,** 83 (1986).
7. A. Akelah, A. Selim, and A. Rehab, *J. Polym. Mater,* **4,** 117 (1987).
8. Y. X. Qiu, Ph.D. Thesis, Zhejiang University, 1992.
9. L. I. Kosheleva, I. E. Shumakovich, and A. F. Bekhli, *Zh. Obshch. Khim,* **45,** 407 (1975).
10. H. Müller, O. Nuyken, and P. Strohriegl, *Makromol. Chem.,* **13,** 125 (1992).
11. C. K. Ingold, *Structure and Mechanism in Organic Chemistry,* Cornell University Press, Ithaca, New York, 1953.
12. F. M. Li, Z. W. Gu, G. W. Li, and X. D. Feng, *Polymer Communications,* **5,** 393 (1984).