

Catalysis of nifuroxazide formation by crosslinked poly(vinylpyridine)-supported acids

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Abstract

The condensation reaction of either 5-nitrofur-2-aldehyde (NFA) or 5-nitrofur-2-aldehyde diacetate (NFAD) with *p*-hydroxybenzaldehyde (PHBH) gave nifuroxazide (NF), a drug used for the treatment of acute bacterial diarrhea, by catalysis with crosslinked poly(vinylpyridine)-supported acids (PVPHX). The product NF was obtained with high yield and purity. The effects of the counteranion, X⁻, in polymer catalyst (PVPHX) on the rate of the reaction were studied. It was found that the catalytic activity is increasing in order: I⁻ > ClO₄⁻, Cl⁻ = Br⁻ > TsO⁻. The effects of temperature and amount of catalyst on the reaction rate were discussed. © 1999 Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Nifuroxazide (NF), *p*-hydroxybenzoic acid [(5-nitrofuryl)methylene] hydrazide, is the active principle of Ercefuryl which is used for the treatment of acute bacterial diarrhea. The synthesis of nifuroxazide was performed on laboratory and industrial scale by H₂SO₄ acid-catalyzed condensation of *p*-hydroxybenzhydrazide (PHBH) with 5-nitrofur-2-aldehyde diacetate (NFAD) [1] or by the reaction of PHBH with 5-nitrofur-2-aldehyde [2]. The industrial process is accompanied by a tedious follow-up

purification process due to the presence of undesired byproducts in amounts generally 0.5–1.0% in the crude NF product.

We have developed a simple and versatile electrochemical synthesis of new polymeric reagents through the ion exchange–electrochemical oxidation reaction of the released iodide from crosslinked poly[styrene-4-vinyl *N*-methylpyridinium iodide] and poly(styrene-4-vinylpyridinium hydroiodide) [3].

This procedure was recently applied for the transformation of grafted copolymers of cellulose with 4-vinylpyridine, 1-vinylimidazole, 1-vinyl-2-pyrrolidine, and 9-vinylcarbazole [4].

The polymeric reagents or catalysts have been used as reagents in a variety of reactions [5,6] because of the main expected advantages:

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(i) they can be easily removed from the reaction mixture, (ii) when used as a catalysts they may be recycled many times, (iii) they may give the unexpected reaction products, and (iv) they may give products of high purity. This paper describes the synthesis of nifuroxazide by using crosslinked poly(vinylpyridine)-supported acids (PVPHX) in high yield and without formation of byproducts. The influence of several polymer-supported acids on the kinetics of nifuroxazide formation was discussed.

2. Experimental

2.1. Materials and apparatus

5-Nitrofurane-2-aldehyde (NFA), 5-nitrofurane-2-aldehyde diacetate (NFAD), *p*-hydroxybenzhydrazide (PHBH), DMF, CH₃CN, and H₂O (HPLC-grade solvents) supplied by Fluka were used as received. Crosslinked poly(styrene-4-vinylpyridine) PVP, poly[styrene-4-vinyl(pyridiniumhydroiodide)] PVPHI were prepared according to the published procedure [7]. The crosslinked poly(vinylpyridine)-supported acids, PVPHX, with the capacity of 2.5 meq/g of fully loaded resin, were prepared by electrochemical synthesis from PVPHI described earlier [3]. The ion exchange–electrochemical oxidation reaction is more convenient than simple exchange reaction since the equilibrium can be shifted towards product formation by electrochemical oxidation of released anion giving the quantitative yields of products. Notably, the equilibrium of reaction studied [3] showed that the products were formed in 20–50% yield, depending on exchanged anion, without electrochemical oxidation step.

IR spectra were run on a Perkin-Elmer 1724 FTIR instrument. HPLC analyses were performed using Varian Vista 5500 equipment with a UV-200 detector and Varian 440 integrator using a MCH-5N CAP micro column (15 cm × 4 mm).

2.2. Preparation of NF from 5-nitrofurane-2-aldehyde diacetate (NFAD) using polymer catalysts (PVPHX)

Into a round-bottomed flask filled with ethanol (100 ml), PHBH (300 mg, 2.17 mmol) was added. The mixture was heated to the reflux temperature, at which point NFAD (620 mg, 2.55 mmol) and 300 mg of PVPHCl or H₂SO₄ as a catalyst were added. The reaction mixture was heated under reflux for 3 h and during the reaction the product NF precipitated. After cooling the mixture at the room temperature the precipitate was filtered and dissolved in DMF (25 ml) and the insoluble PVPHCl catalyst was separated by filtration. The crude NF precipitated by adding water (50 ml) was filtered, washed with water, ethanol and ether then dried under vacuum.

2.3. Preparation of NF from 5-nitrofurane-2-aldehyde (NFA) using polymer catalysts (PVPHX)

Into a round-bottomed flask filled with DMF (25 ml), PHBH (300 mg, 2.17 mmol), NFA (360 mg, 2.55 mmol) and PVPHX (300 mg) were added. The mixture was heated to 110°C for 1 h and left to cool at room temperature. The insoluble polymer catalyst was separated by filtration. Water (50 ml) was added to the filtrate, and the mixture was left in a refrigerator for 1 h. The precipitated NF was filtered, washed with water, ethanol, ether and dried.

2.4. Kinetic experiments

A three-necked round-bottomed flask, equipped with condenser and stirrer, was charged with DMF (25 ml), NFA (7.8 mg, 0.055 mmol), and PHBH (200 mg, 1.45 mmol). The flask was placed in a thermostat and the temperature was maintained within ±0.5°C. Into stirred solution, 50 mg of polymeric catalyst (PVPHX) was added and 10-μl samples

were collected at regular time intervals and analyzed by HPLC technique using a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (65:35%) mixture for chromatographic separation at a flow rate of 0.7 ml/min. The concentration of the product NF formed during the reaction was measured at 374 nm. The obtained ϵ_{max} values vs. time were used for calculating the apparent pseudo-first-order rate constant by iterative nonlinear regression using the least-squares method.

3. Results and discussion

3.1. Synthesis

The synthesis of NF was performed by polymer-supported catalyzed reaction of *p*-hydroxybenzhydrazide (PHBH) with 5-nitrofur-2-aldehyde diacetate (NFAD) or 5-nitrofur-2-aldehyde (NFA). The reaction with NFAD (Eq. (1) in Scheme 1) by PVPHCl catalyst required a longer time (3 h) than the reaction with NFA (Eq. (2)) which was accomplished after 1 h. The

yield of the reaction shown in Eq. (1) was 70% by using PVPHCl or 75% by using H_2SO_4 as a catalyst. The structure of the product NF was proved by comparison of FTIR spectra and m.p. of the product with that of authentic sample.

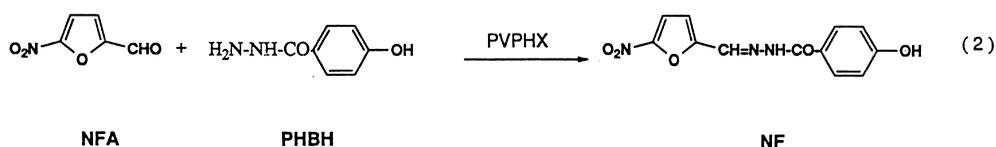
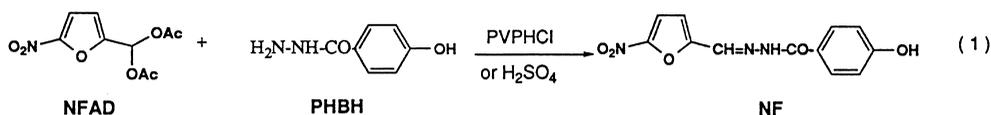
The effect of the counter anion of the polymer-supported acids was evaluated under the same reaction conditions (Eq. (2)). As summarized in Table 1, the product NF was formed in high yields ranging from 83 to 93% as an

Table 1

Results of condensation reaction of NFA with PHBH using polymer-supported catalysts PVPHX^a

Catalyst (X^-)	Yield of NF (%)	Recycled number
I^-	90	1
ClO_4^-	85	1
Br^-	88	1
TsO^-	83	1
Cl^-	91	1
Cl^-	93	2
Cl^-	89	3
Cl^-	90	4

^aThe reaction was carried out with NFA (2.55 mmol) and PHBH (2.17 mmol) in DMF (25 ml) using 300 mg of PVPHX catalyst at 110°C.



Scheme 1.

average value obtained from three experiments. The catalytic activity of reused PVPHCl catalyst was examined and the results showed that there was no apparent activity loss after four cycles of use of the PVPHCl catalyst.

The purity of the crude NF was examined by HPLC chromatography. Two types of chromatograms, i.e. A and B in Fig. 1, were obtained.

Type A chromatogram, exemplified by that of PVPHCl is shown in Fig. 1A. Similar chromatograms were obtained by using PVPHI and PVPHBr catalysts and showed only one peak ($R_t = 1.41$ min) of the pure NF. Type B chromatogram (Fig. 1B), as found for PVPHTsO, showed the major peak at $R_t = 1.41$ min, and the second peak at $R_t = 2.12$ min, which can be presumably attributed to the 5-nitrofurfural-diazene formed as a byproduct. The same type

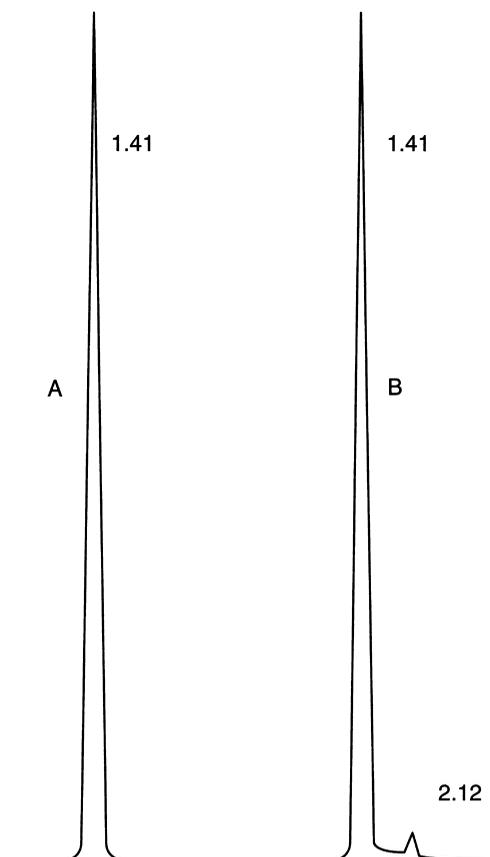


Fig. 1. HPLC chromatograms of NF obtained by PVPHX catalysts: (A) PVPHCl; (B) PVPHTsO.

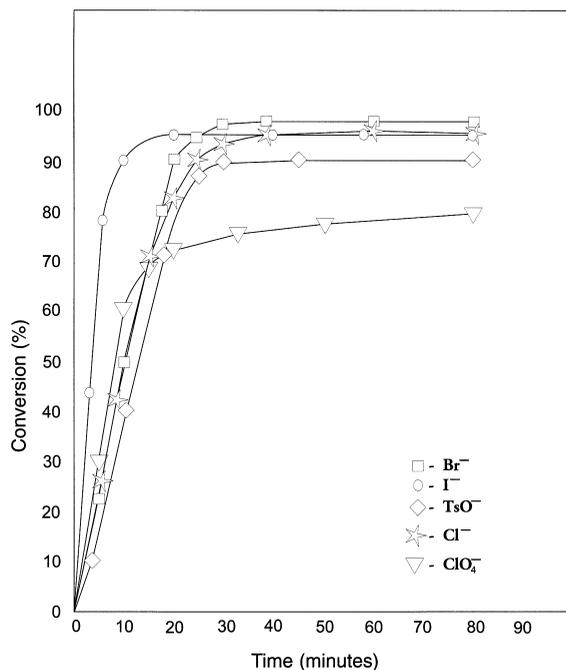


Fig. 2. Influence of several polymer-supported acids, PVPHX, on the reaction kinetics: NFA (2.21 mM), PHBH (57.97 mM), PVPHX (50 mg) in DMF at 300.5 K.

B chromatogram was also observed when PVPHClO₄ was used as a catalyst. Notably, when the reaction (Eq. (1)) was run in the presence of H₂SO₄ the crude product showed the peak at $R_t = 2.12$ min, due to the byproduct formed, with about three times larger area than in other type B chromatograms.

3.2. Kinetic studies

The acid-catalyzed reaction of aldehydes with a variety of nitrogen bases have been reported to occur generally in two steps, in which the first step leading to the corresponding carbinolamine is rate-determining at acidic pH, and the following dehydration step is rate-determining at neutral and alkaline pH [8,9]. We anticipated that the polymer-supported acid catalysts, PVPHX, differing in the counterion would influence the rate-determining step.

All kinetic experiments were carried out at the same concentration of PVPHX catalyst at

300.5 K and under the same stirring conditions. The molar ratio of reacting components, i.e. NFA/PHBH, was 1:26 in order to provide reaction conditions characteristic for pseudo-first-order reaction. The increase of NF concentration as a function of reaction time was measured by HPLC and results were plotted in Fig. 2.

The analysis of the curves in Fig. 2 showed that most of the NF product was formed in the first 20 min of the reaction time, and at longer reaction times the curves are reaching plateau. In the region where the concentration of the formed product NF were increasing proportionally to the reaction time, the curves exhibited different slopes. This means that the reaction rates are dependent on the counter anion of the used PVPHX catalysts. Therefore, the catalytic activity could be qualitatively estimated by means of apparent pseudo-first-order rate constant, k_{obs} , values and the results are shown in Table 2.

The above results suggest that the rate of the reaction is related to the $\text{p}K_{\text{a}}$ value of the polymer-supported acids, PVPHX. The strong acidity of PVPHI immediately results in the formation of the corresponding conjugated acid of NFA, while PVPHTsO, which is expected to have a higher $\text{p}K_{\text{a}}$ value by a few orders of magnitude, is a less-effective protonating agent. The results shown in Fig. 2 demonstrate that the PVPHCl catalyst has a higher activity than PVPHClO₄ from the viewpoint of the yield of product NF, although the observed pseudo-first-order rate constant is higher for PVPHClO₄. These conflicting results can be explained after detailed examination of the experimental results. The lower yield of NF by using PVPHClO₄ compared to PVPHCl, and the higher value of k_{obs} for PVPHClO₄, indicates that the

PVPHClO₄ catalyst is inactivated by the formed byproduct during the reaction. This conclusion is supported by HPLC analysis of the crude product after reaction with PVPHClO₄ in which the byproduct was found, while the catalysis using PVPHCl gave pure NF.

The condensation reaction of NFA with PHBH using PVPHCl as a catalyst was studied at various temperatures ranging from 300.5 to 316.5 K. As shown in Fig. 3 the rate of the reaction is increasing with temperature, as expected. From the Arrhenius plot, $\ln k_{\text{obs}}$ vs. $1/T$, the activation energy of the reaction was estimated to be 75.5 kJ/mol.

The rate of the reaction (Eq. (2)) was examined by varying the amounts of catalyst PVPHCl and the results are shown in Fig. 4. The rate of reaction is generally increasing with the enhanced amount of catalyst and gradually tends to the saturation value. These results can be rationalized by adsorption of a progressively greater fraction of the protonated NFA in the polymer phase leaving it less susceptible to

Table 2
Catalytic activity of PVPHX

Catalyst (PVPHX)					
X^-	I^-	ClO_4^-	Cl^-	Br^-	TsO^-
$k_{\text{obs}} \times 10^3 \text{ (s}^{-1}\text{)}$	5.8	1.6	1.1	1.1	0.75

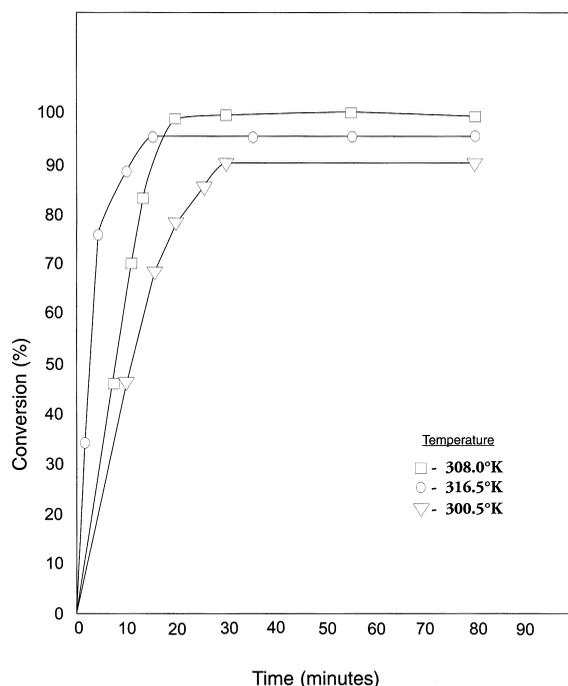


Fig. 3. Influence of temperature on the reaction kinetics; NFA (2.21 mM), PHBH (57.97 mM), PVPHCl (50 mg) in DMF.

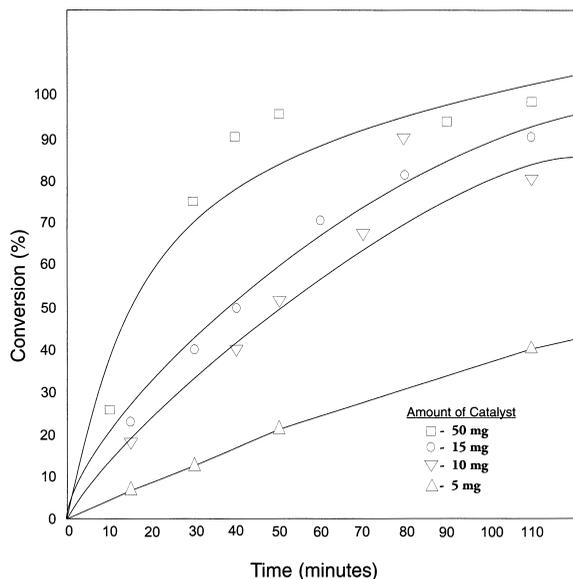


Fig. 4. Influence of the amount of PVPHCl catalyst on the reaction kinetics; NFA (2.21 mM), PHBH (57.97 mM).

nucleophilic attack by PHBH, which results in a lower rate of the overall reaction.

4. Conclusions

We have demonstrated that the condensation reaction of NFA with PHBH, leading to NF, can be successfully carried out in the presence of crosslinked poly(vinylpyridine)-supported acids,

PVPHX. The product NF was obtained with high yield and the catalyst can be reused several times. The key result obtained in this work is an analytical purity of the crude product NF by using the following catalysts: PVPHI, PVPHCl, and PVPHBr.

We were able to show that the rate of the reaction is dependent on the pK_a values of the polymer-supported acids. The effects of temperature and the amount of catalyst on the reaction rate were also studied and discussed.

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