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A new support for anchorage of 1,4-dihydronicotinamide

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SUMMARY

The synthesis of dihydronicotinamide anchored to acrylic polymers is achieved. It is shown that the reduction of p-nitrobenzaldehyde is clean at 60° and the yield is quantitative. A comparison is done between these reagents and the MERRIFIELD based system published earlier.

INTRODUCTION

The reactions of 1-benzyl-1,4 dihydronicotinamide (BNAH) as a model for the reduced nicotinamide-adenine dinucleotide (NADH) have been widely investigated in respect to the biomimetic organic reactions.

However, reductions with BNAH are not easy to carry out and it is very difficult to isolate the products from the reaction mixture. Consequently, it is of great interest to use NADH models grafted onto a polymer (1). The most significant advantage in using a grafted reagent is the simplification of the workup. In two previous papers (2)(3), we reported the first truly reactive NADH bounded model on a MERRIFIELD type resin. Quantitative yields were obtained in the reduction of various products. Recently we obtained new samples of resins from the same suppliers but we were surprised to find that the new batches of polymers behaved differently. CARPINO et al. (4) have reported similar drawbacks with MERRIFIELD resins. These facts have prompted us to find out new polymers making the grafting anchorage of the 1,4-dihydronicotinamide moiety possible. The synthesis of iodinated polymers was published by BROWN et al. (5), a few years ago. We shall now describe the use of these acrylic polymers in the synthesis of immobilized 1,4-dihydronicotinamide and study the efficiency of this new reagent.

EXPERIMENTAL

Copoliodals (2-1-1) and (4-1-1) were obtained according to the procedure of BROWN et al. (5) (scheme 1). The physical constants of the products were similar to those published.

Quaternization of nicotinamide (scheme 2)

Copoliodal (100 g of 2-1-1 or 4-1-1) and nicotinamide (50 g) were added to freshly distilled acetonitrile (500 ml). The mixture was refluxed for 48 h. The yellow product was filtered and thoroughly washed with acetonitrile, before being dried overnight in a vacuum oven at 40°C, to give 100 g of functionnalized polymer <u>2a</u> or <u>3a</u>.

IR: C=O (ester) at 1732 cm^{-1}, C=O (amide) at 1685 cm^{-1};
^1H NMR: 0.7 (m), 1.7 (m), 3.5 (s), 3.9 (m), 4.7 (m), 8.3 (m), 8.9 (d), 9.3 (d), 9.6 (s) ppm in D_2O/TMS.

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Reduction by sodium dithionite

The polymer synthesized above (26 g) was dissolved in 1000 ml of water. An aqueous solution of sodium dithionite (44 g) and sodium carbonate (24 g) was then slowly added and the mixture was stirred for 4 h. The yellow precipitate was filtered, thoroughly washed with water and dried for three days in a vacuum oven at 40°C.

The products were not soluble in classical NMR solvents.

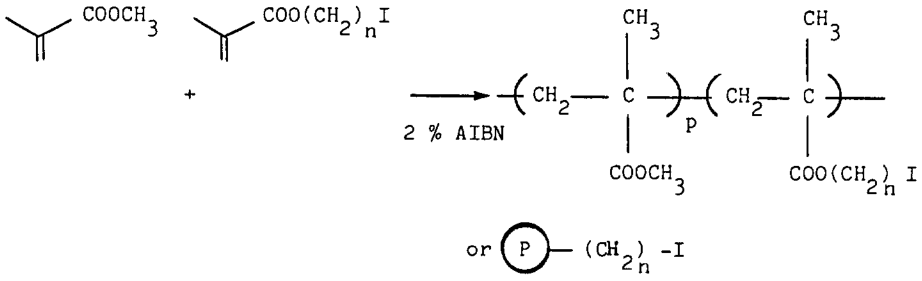
Reduction of p-nitrobenzaldehyde

Reagents: Acetonitrile was distilled over calcium hydride in an athmosphere of argon and was allowed to stand 48 h over molecular sieves (3A) prior to use. p-Nitrobenzaldehyde was purchased from ALDRICH chemical Co. and anhydrous magnesium perchlorate from MERCK Co. A typical run is as follows: 151 mg (1 mmol.) of p-nitrobenzaldehyde, 250 mg (1 mmol.) of magnesium perchlorate and one equivalent of polymer <u>3a</u> or <u>3b</u> were mixed with 10 ml of dry acetonitrile in a sealed tube flushed with argon. The tube was allowed to stand at 60°C during the appropriate time. One ml water was then added and the polymer was filtered and washed with acetonitrile.

The filtrate was evaporated and the residue treated with water and extracted twice with dichloromethane. The organic layer was dried over magnesium sulfate. Removal of solvent gave an oil which was subjected to NMR analysis.

DISCUSSION

Copoliodals are copolymers of methyl methacrylate and n-iodoalkyl methacrylate (with n = 2 or 4). Copolymerisation is achieved with the same weight of the two methacrylates in presence of azoisobutyronitrile (AIBN).



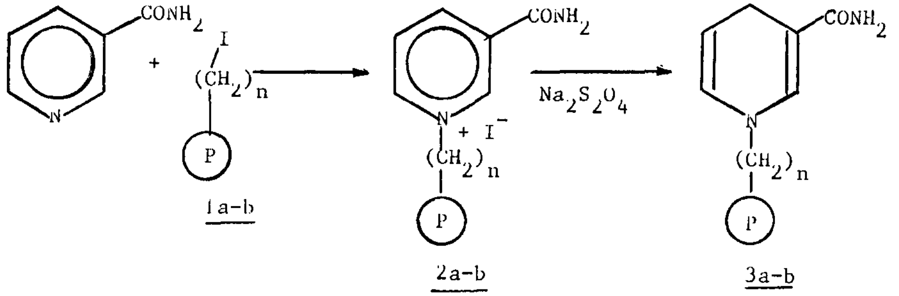
1a-b

<u>1a</u> n = 2 p ∼ 2.4: Copoliodal 2-1-1

<u>1b</u> n = 4 p ∼ 2.7: Copoliodal 4-1-1

<u>Scheme 1: preparation of copoliodals 2-1-1 and 4-1-1</u>

When the copolymers are refluxed with nicotinamide in acetonitrile we obtain the pyridinium derivatives 2a or 2b in very good yields. The structures of compounds 2a and 2b are confirmed ba infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy.



Scheme 2: Synthesis of immobilized NADH models

Polymers 2a and 2b are easily dissolved in water because of the hydrophilic character of the pyridinium moieties. The reduction of 2a and 2b with sodium dithionite proceeds smoothly. During this reduction the dihydronicotinamide compounds 3a or 3b precipitate because of their hydrophobic character. The filtration of the products 3a and 3b is very difficult but after drying the mechanical characteristics of the grafted reagents are good.

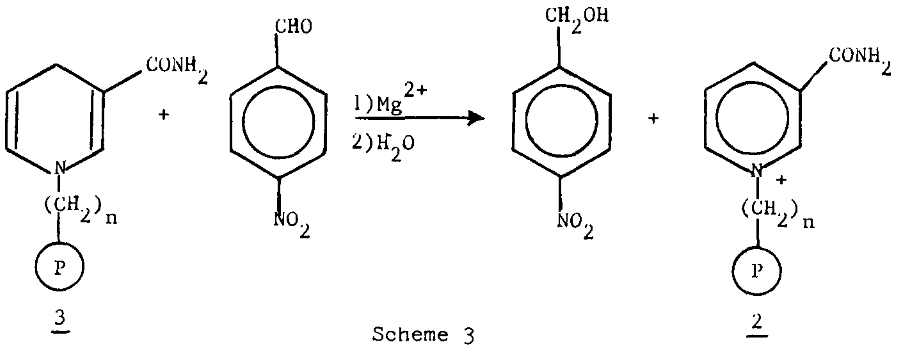
Nicotinamide contents after quaternization and reduction respectively are listed in table I (calculated from the nitrogen content of 2 and 3 determined by elemental analysis).

TABLE I

Compound	2a	2b	3a	3b
Nicotinamide content (mmol./g)	1.9(a)	2.1(a)	1.8	1.7

The efficiency of polymers 3 is improved in the reduction of p-nitrobenzaldehyde (pNBA). This compound has an easily interpretable NMR spectrum which makes the quantitative analysis of reactional mixtures possible.

(a): The elemental analysis shows a slight excess in the nitrogen content due to the trapping of nicotinamide during the precipitation of compounds 2. In the course of reduction nicotinamide remains in water.



Scheme 3

At room temperature, the reduction rate is very slow, so we perform the reactions at 60°C. Reagent 3a is slightly soluble in acetonitrile and a little amount is recovered with alcohol 5. With 3b, the final product 5 is free of polymer and the workup is easier. Figure 1 shows yield variation against reaction time:

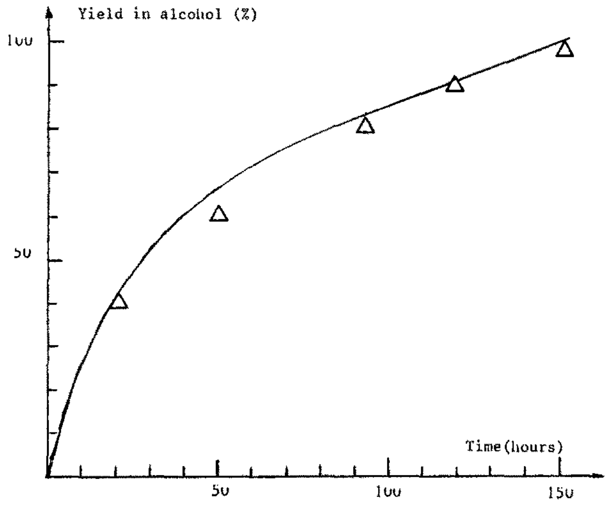


Figure 1: Yield versus reaction time

We obtain the same curves with reagents 3a and 3b: the length of the "spacer" between the dihydronicotinamide moiety and the polymer surface has no significant influence upon the extent of the reduction. The reduction is quantitative in 150 hours at 60°C: The reactivities of these new reagents are comparable with MERRIFIELD based systems (2), but the presence of a swelling agent is not necessary because copoliodals are not cross-linked.

With MERRIFIELD resins we noticed that increasing the amount of magnesium perchlorate (the assistance of divalent ions is generally recognized in reductions with NADH models) lowers the reduction rate. Figure 2 shows yield variation against the amount of magnesium perchlorate (reaction time was 21 hours) with reagent 3b compared to the MERRIFIELD based reducing agent.

The phenomenon observed is quite different in the case of 3b:the higher the amount of catalyst, the higher the yield in alcohol and the variation seems to be linear (in the limits of solubility of magnesium perchlorate in the mixture). With microreticular cross linked systems a great amount of divalent ion hinders access to the reactional sites. Such a drawback disappears with linear polymers like copoliodals.

These new reagents are easier to use in the case of the reactional medium but partially soluble in acetonitrile. So, we have switched to the use of analogous crosslinked systems, and this work is in progress.

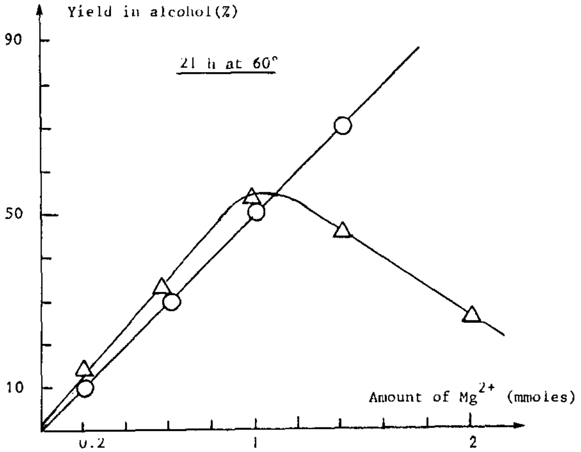


Figure 2: Yield versus magnesium perchlorate
○ reagent 3b
△ dihydro-1,4 nicotinamide on MERRIFIELD resin.

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