polymer communications

Synthesis of polymer supports based on dimethylacrylamide and 3-formamidopropyl acrylate

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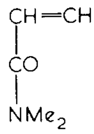
Suspension copolymerization of dimethylacrylamide, 3-formamidopropyl acrylate, and bis-acrylamide crosslinkers provides beaded resins with high or low degrees of functionality. Conversion of the resulting formamido polymers to the corresponding isocyano or amino resins, and the preparation of carbodiamide and nitrophenol derivatives of the latter, are described.

Keywords 3-Formamidopropyl acrylate; dimethylacrylamide resins; amino functionality; isocyano functionality

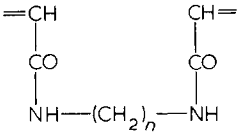
Since the introduction of the so-called solid-phase technique in peptide synthesis[1] a large number of styrene-based polymer supports and polymeric reagents have been developed to affect an increasingly wide range of chemical transformations[2]. These polymers, although satisfactory for many applications involving aprotic organic solvents, are not compatible with the use of highly polar media. More recently, however, a new type of polymer support has been developed[3] which is derived from dimethylacrylamide (1) and bisacrylamide crosslinkers (2). These resins, as well as similar resins derived from acryloylmorpholine[4], are equally well permeated by most common solvents including aqueous, protic, and aprotic organic media. A major difficulty in the synthesis of these resins has been the design, and incorporation into the polymer, of suitable functional monomers. Among the functional monomers thus far reported[3-4] acryloyl sarcosine methyl ester (3a) is the most readily available and is structurally more suitable for copolymerization with (1). However, post-polymerization conversion of the methoxy-carbonyl groups is not completely satisfactory for the preparation of highly functionalized resins. This communication reports a new functional monomer, 3-formamidopropyl acrylate (3b), which is readily accessible and which can be employed to prepare formamido polymers having low or high degrees of functionality. An additionally interesting feature of the new functional monomer is that the formamido groups on the polymer can be converted to either free amino or the highly versatile isocyano[5] functionality.

(1)



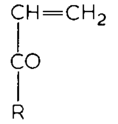
$CH{=}CH_2-CO-NMe_2$

(2)



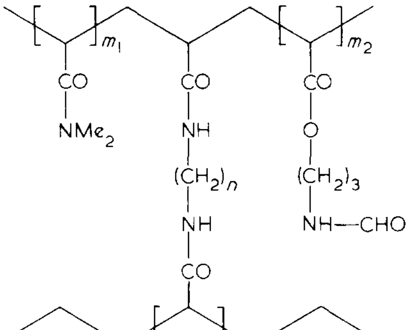
$CH_2{=}CH-CO-NH-(CH_2)_n-NH-CO-CH{=}CH_2$

(3)



$CH{=}CH_2-CO-R$

a: $R{=}N(Me)CH_2CO-OMe$
b: $R{=}O(CH_2)_3-NH-CHO$



(4)

4a: $n{=}2$; $m_2{=}6{\cdot}5$
4b: $n{=}6$; $m_2{=}3{\cdot}9$
4c: $n{=}6$; $m_2{=}1{\cdot}0$
4d: $n{=}6$; $m_2{=}33$
$m_1 + 8 + m_2 {=} 100$

The new monomer (3b, b.p. 141/2 mm Hg) was prepared by selective formylation of 3-aminopropanol by methyl (or ethyl) formate in methanol, followed by reaction with acryloyl chloride in dichloromethane and in the presence of triethylamine (1.1 eq.) and a catalytic amount of 4-dimethylaminopyridine. The resins were prepared by suspension copolymerization as will be described below. All of the resins were obtained in high yields (85–95%) and in the form of relatively homogenous beads which are, as a rule, adequate for chemical transformations without any sieving.

The suspension polymerization procedure used to

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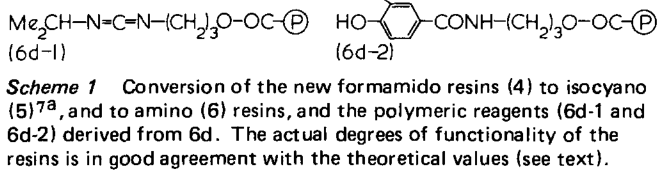
prepare the resins is illustrated by the preparation of resin 4d. The polymerization apparatus[6] was secured in a water bath at 50°C, and was charged with 2.1 g cellulose acetate butyrate (CAB) and 1,2-dichloroethane (DCE) (70 ml). A small scale stirrer was fitted and set at 500 rpm until the CAB was completely dissolved. The stirrer was then stopped, the solution was flushed with nitrogen for about 5 minutes, and a very slow stream of nitrogen was allowed to pass over the solution. The well-mixed monomer solution, comprising dimethylacrylamide (1, 5.9 g, 59 mmol), 3-formamidopropyl acrylate (3b, 5.2 g, 33 mmol), and hexamethylene-bis-acrylamide (2b, 1.8 g, 8 mmol), dimethylformamide (13 ml), water (26 ml), and ammonium persulphate (1 g), were then carefully added and the polymerization was allowed to continue for 5 h. Fresh DCE was added during polymerization to compensate for evaporation losses and so maintain the approximate total volume. The beaded polymer product was added to acetone and freed from the solvents and non-beaded polymeric materials by stirring with acetone (4 × 250 ml) followed by decantation. For some applications the polymer was taken through further washing and decantation cycles with water and acetone.

Considerable quantitative differences exist between the different resins, but their general behaviour is remarkably similar. For example, all of the polymers have an expanded volume of about 10 ml/g in a wide range of solvents including water, methanol, dimethylformamide, and dichloromethane.

The conversion of the new formamido polymers (4) to isocyano (5), and amino (6) resins, and the polymeric reagents (6d-1 and 6d-2) derived from (6d), are shown in *Scheme 1*. The degree of functionality of the resins has been determined by estimation[7b] of the isocyano derivatives (5), and/or glycine incorporation, followed by amino acid analysis, of the amino derivatives (6). The former is simpler and has generally produced results which are in good agreement with the theoretical values indicated in *Scheme 1*. Selective removal of the formyl protecting group has been achieved by treatment of the resins with 1M hydrochloric acid for 5 days at room temperature. This is a convenient procedure, but the use of alternative reagents may be desirable in shortening the reaction time. Conversion of the formamido resins (4) to the corresponding isocyano derivatives (5) is accomplished by the use of *p*-toluenesulphonyl chloride in pyridine. Thus, addition of tosyl chloride (0.5 g/ml pyridine) to the pyridine-swelled polymer leads, usually within 5 minutes, to complete generation of the isocyano groups as indicated by i.r. (2150 cm^{-1}) and titration[7b] of the isocyano resin product. Although ester linkages are basically labile towards both acids and bases, in practice the present resins are stable in the presence of amines and a pH range of about 1–9, and can therefore be employed for most routine applications.



Scheme 1 Conversion of the new formamido resins (4) to isocyano (5)[7a], and to amino (6) resins, and the polymeric reagents (6d-1 and 6d-2) derived from 6d. The actual degrees of functionality of the resins is in good agreement with the theoretical values (see text). The brackets do not indicate a block copolymer structure

A particularly important feature of the new functional monomer is that it is highly compatible (miscible) with the monomer solution employed for suspension polymerization. It is (within experimental error) quantitatively incorporated into the polymer and thus low or highly functionalized resins are obtained equally easily (see *Scheme 1*). Polymer samples 4a–c have loading capacity similar to polar supports currently employed in peptide and oligonucleotide synthesis[3-4], whereas sample 4d carries functionality of about 2.6 mmol/g and is suitable for the preparation of polymeric reagents[2]. For example, reaction of the amino resin 6d with excess isopropyl isocyanate in dimethylformamide (room temperature, 15 h), followed by that of *p*-toluenesulphonyl chloride and triethylamine in dichloromethane (reflux, 4 h) produced the corresponding polymeric carbodiamide 6d-1 (i.r., 2125 cm^{-1}). The polymeric 2-nitrophenol derivative 6d-2 was also prepared by treatment of the amino resin with excess 4-hydroxy-3-nitrobenzoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiamide in dimethylformamide solvent. The highly versatile chemical reactivity of the isocyano functionality combined with the more or less general solvent compatibility of the polymer backbone means that the presently described isocyano resins (5) are potentially suitable for use in several major areas of polymer mediated processes. The isocyano resins are being presently employed for peptide synthesis by four component condensation[8]. Various transition metal derivatives of resin 5d, including those of rhodium(I) and palladium(II), have been prepared and characterized[9]. The isocyano resins should also be suitable for enzyme immobilization as well as general organic synthesis (c.f., ref. 5a).

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