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Synthesis of amidoxime-containing modified dextran

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Dextrans partially modified with cyanoethyl groups were obtained by reaction of dextran with acrylonitrile in alkaline medium. The structure of the resulting polymers was determined by means of infra-red spectroscopy and ^{1}H and ^{13}C nuclear magnetic resonance (n.m.r.) spectroscopy. The influence of solvent composition, temperature and acrylonitrile concentration as well as the type and concentration of catalyst was evaluated. ^{13}C n.m.r. spectra at 75.4 MHz of partially modified dextran with cyanoethyl groups were studied in order to evaluate the selectivity of the reaction of dextran with acrylonitrile in the homogeneous phase. Analysis of the spectra of ring carbons in the anhydroglucose units shows that the reactivity of the individual hydroxyl groups decreases in the order C2 > C4 > C3. Nitrile groups in cyanoethylated dextran were converted to amidoxime groups by reaction with hydroxylamine. The activation energy was found to be 42.7 kJ mol^{-1}. Preliminary experiments showed the Cu^{2+} complex formation ability of amidoximated dextran. Copyright © 1996 Elsevier Science Ltd.

(Keywords: cyanoethylated dextran; characterization; amidoxime groups)

INTRODUCTION

Polymers carrying amidoxime groups are a class of materials with very interesting properties. On the one hand, polymeric amidoximes would be expected to have a polyampholytic character and, on the other, amidoxime groups, known as being very reactive, offer the possibility of preparing new polymeric derivatives as well as of binding metal ions. The last application has prompted a number of papers dedicated mainly to the synthesis of chelating resins containing amidoxime groups prepared by reaction of the homopolymer or copolymers of acrylonitrile with hydroxylamine[1,2]. However, syntheses of modified polymers with amidoxime groups from other polymeric structures have been little reported.

The present work is concerned with the incorporation of amidoxime groups into dextran through the cyanoethylation of the polysaccharide with acrylonitrile, followed by the reaction with hydroxylamine. Preliminary experiments on the chelating ability of amidoximated dextran were also carried out.

EXPERIMENTAL

Materials

The dextran was a commercial product (T-70 from Pharmacia Fine Chemicals) with a linear structure (as revealed by ^{13}C n.m.r.) and a weight-average molecular weight (from light scattering) of $M_w = 70\,000$. The polymer was dried *in vacuo* for a few days at 80°C in the presence of phosphorus pentoxide to constant weight. Acrylonitrile (from Merck) was purified prior to use by distillation under normal pressure. Hydroxylamine hydrochloride (from Panreac) was used as received. Dimethylsulfoxide (DMSO) (from Ferosa) was distilled *in vacuo* and then dried for a few days with a Merck 4 Å molecular sieve. *N*,*N*-Dimethylformamide (DMF) (from Ferosa) was purified following a conventional method[3]. Other reagents were of analytical grade and were used without further purification.

Cyanoethylation of dextran

The dextran was dissolved in DMSO/water mixtures at 30°C using a double-walled reactor equipped with a magnetic stirrer. The solution obtained was thermostatted at the reaction temperature and the calculated amounts of catalyst (tetramethylammonium hydroxide or sodium hydroxide) and acrylonitrile were added with stirring. The reaction was allowed to proceed for 2 h. Different precipitants were used to isolate the polymer, depending on the degree of substitution (*DS*). All samples were purified by reprecipitation, using distilled water or acetone as solvent and ethanol or ethanol/diethyl ether mixtures as precipitants, and then dried *in vacuo* in the presence of phosphorus pentoxide.

Characterization of cyanoethylated dextran

The i.r. spectra were obtained on a Perkin-Elmer 457 spectrometer on KBr discs. The ^{1}H n.m.r. spectra were registered in DMSO-d_6 or deuterated water at 50°C using a 200 MHz Bruker AM-200 spectrometer. ^{13}C n.m.r. spectra were obtained in DMSO-d_6 at 70°C using a 75.4 MHz Varian XL-300 in the proton noise-decoupled

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mode. Chemical shifts were measured with respect to that of the central peak of the methyl carbon of DMSO, which was taken to be at 39.7 ppm downfield from tetramethylsilane. The spectral measurement conditions were similar to those of the structural analysis of cellulose derivatives[4]. The spectra were accumulated for about 16 000 scans with a repetition time of 3 s. The resonance areas were measured by electronic integration as well as by planimetry and the weight cut out from Xerox copies. The degree of substitution (*DS*) was determined by means of Kjeldahl determination of nitrogen.

Amidoximation of cyanoethylated dextran

Free hydroxylamine was prepared by neutralization of a hydroxylamine hydrochloride solution in DMF with sodium carbonate, following a known method[5]. The hydroxylamine concentration of the solution obtained was determined by titration with 0.1 M hydrochloric acid in the presence of methyl red[6]. For the amidoximation of cyanoethylated dextran, the polymer was dissolved in DMF, using a double-walled reactor. The calculated amounts of hydroxylamine were added with stirring. In the kinetic study, the extent of modification was followed by sampling the reactant solution, taking aliquots at definite periods of time. Different precipitants were used to isolate the modified polymer, depending on the extent of modification. All samples were purified by reprecipitation, using distilled water or distilled water/acetone mixtures as solvent and ethanol or ethanol/diethyl ether mixtures as precipitants, depending on the extent of modification, and then dried *in vacuo* in the presence of phosphorus pentoxide.

Characterization of the amidoximated dextran

The i.r. spectra were obtained on a Perkin-Elmer 457 spectrometer on KBr discs. The ^1H n.m.r. spectra were registered in DMSO-d_6 at 50°C using a 200 MHz Bruker AM-200 spectrometer. The extent of modification of the amidoximated dextran was determined from the ^1H n.m.r. spectra by comparing the peak at 2.2 ppm (ascribed to $-\underline{CH_2}-C(NH_2)=NOH$ protons) with the signal centred at 2.8 ppm (corresponding to $-\underline{CH_2}-CN$ protons).

Complexes of amidoximated dextran with Cu^{2+} ions

The copper chelates of amidoximated dextran were prepared by mixing a 1 wt% solution of the polymer in tetrahydrofuran/water mixtures with an excess of 0.1 M copper acetate aqueous solution. The stirring is continued for 60 min. The chelates were isolated by precipitation using methanol/diethyl ether 1 : 1 (v/v) as precipitant. The resulting green precipitates were filtered off and washed thoroughly with methanol/diethyl ether mixtures. The chelates obtained were dried *in vacuo* in the presence of phosphorus pentoxide. The copper content of the chelate complex was determined iodometrically after decomposition of the product in 3 M hydrochloric acid[7].

RESULTS AND DISCUSSION

Dextrans modified with cyanoethyl groups with different degrees of substitution were synthesized in a homogeneous medium by using DMSO/water mixtures as solvent, according to the following:

$$D-OH + CH_2=CH-CN \xrightarrow{OH} D-O-CH_2-CH_2-CN$$

where D–OH is dextran. The structure of the resulting polymers was confirmed by i.r., ^1H and ^{13}C n.m.r. spectroscopies. The i.r. spectra of partially cyanoethylated dextran show the bands of the pendent groups at 2240 cm^{-1} (nitrile groups) and a decrease of the alcoholic vibration at 3415 cm^{-1}. The ^1H n.m.r. spectra of the same polymers show the characteristic chemical shifts of cyanoethyl groups at 2.8 and 3.9 ppm[8,9]. The ^{13}C n.m.r. spectra exhibit characteristic chemical shifts at 18.2, 64.4 and 118.6 ppm, which correspond to cyanoethyl groups. The bands between 64.4 and 98.3 ppm can be assigned to the sugar carbon atoms.

Table 1 shows the effect of the solvent, temperature, type of catalyst and acrylonitrile concentration on the reaction of dextran with acrylonitrile. The results obtained show that an increase in the concentration of DMSO in the DMSO/water mixture has a negative influence on the extent of modification. This experimental behaviour might be explained by considering that the cyanoethylation reaction of alcohols is essentially an equilibrium reaction, which may be reversed by the presence of high concentrations of alkaline catalyst[10,11]. It is also known that the basicity of the catalyst increases as the DMSO concentration increases in the DMSO/water mixture[12,13]. Thus, it seems reasonable to accept that the reversible reaction with the regeneration of the original alcohol might be favoured by an increasing of the DMSO concentration in the DMSO/water mixture.

On the other hand, nitrile groups are susceptible of hydrolysis under alkaline conditions to give carboxylate groups, but it is well known that decyanoethylation due

Table 1 Reaction of dextran with acrylonitrile in the presence of a basic catalyst[a]

Experiment No.	Catalyst	[Acrylonitrile] (mol l^{-1})	Temperature (°C)	Solvent DMSO/water (v/v)	Extent of modification (mol %)
1	$N(CH_3)_4OH$	1.23	25	2:1	20.3
2	$N(CH_3)_4OH$	1.23	25	1:2	57.3
3	$N(CH_3)_4OH$	1.23	40	1:2	24.3
4	$N(CH_3)_4OH$	1.72	25	1:2	62.3
5	NaOH	1.23	25	1:2	56.7

[a] Conditions: [hydroxyl groups] = 0.37 mol l^{-1}; [catalyst] = 0.25 mol l^{-1}; time, 2 h

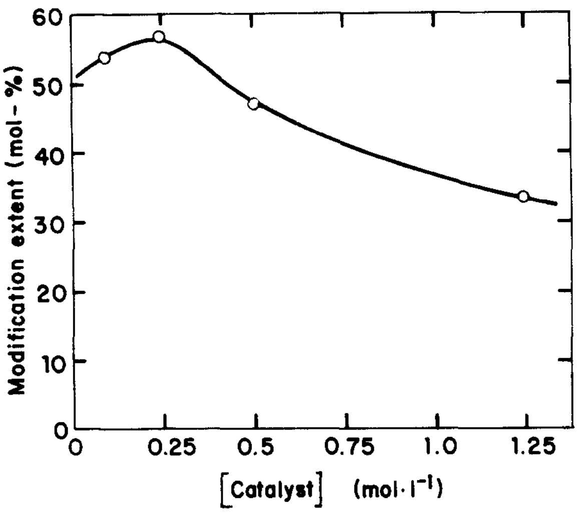


Figure 1 Plot of the extent of modification vs. catalyst (tetramethylammonium hydroxide) concentration in the reaction of dextran ([OH] = 0.37 mol l^{-1}) with acrylonitrile (1.23 mol l^{-1}) in DMSO/water 1 : 2 (v/v) at 25°C

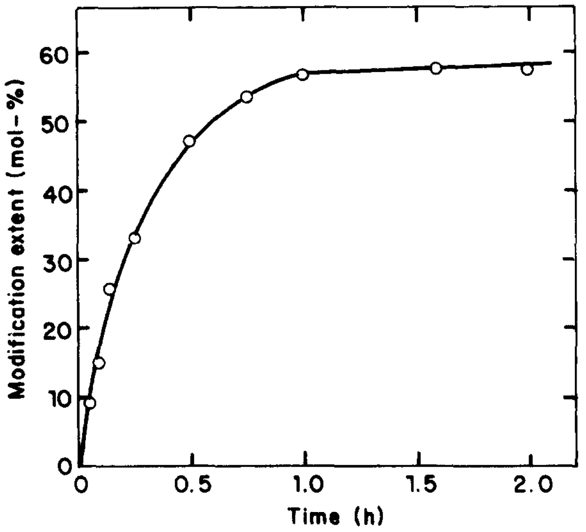


Figure 2 Plot of the extent of modification vs. time in the reaction between dextran ([OH] = 0.37 mol l^{-1}) and acrylonitrile (1.23 mol l^{-1}) using tetramethylammonium hydroxide (0.25 mol l^{-1}) as catalyst and DMSO/water 1 : 2 (v/v) as solvent at 25°C

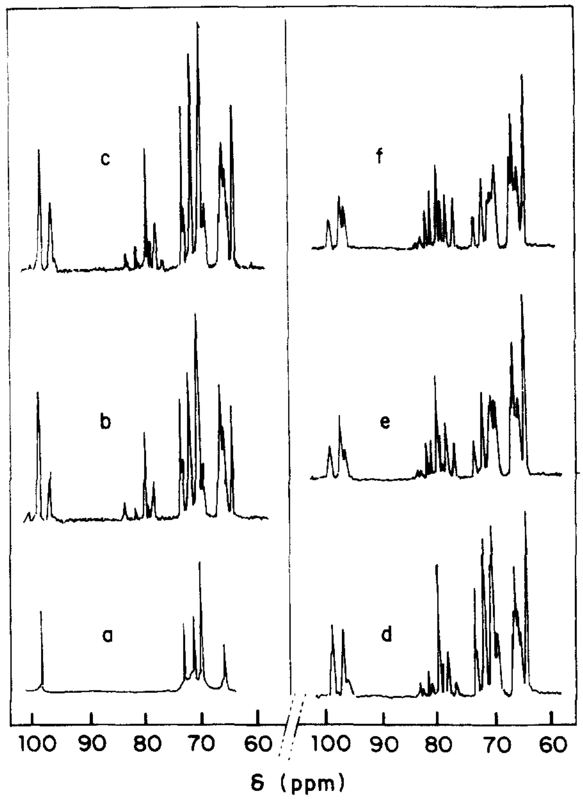


Figure 3 ^{13}C n.m.r. spectra of the ring carbon region of some partially modified dextrans with cyanoethyl groups measured in DMSO-d$_6$: (a) *DS* = 0.00, (b) *DS* = 0.52, (c) *DS* = 0.79, (d) *DS* = 1.07, (e) *DS* = 1.58, (f) *DS* = 1.81

to the reversibility of the cyanoethylation reaction results rather than the hydrolysis of the nitrile groups[11]. Under the experimental conditions used in this work, the content of carboxylate groups in partially cyanoethylated dextrans was negligible as checked experimentally.

It is seen from *Table 1* that the extent of modification decreases as the temperature increases. In agreement with the literature[10], raising the temperature tends to reverse the cyanoethylation process and lower yields will therefore be obtained. The type of catalyst seems not to influence the extent of modification. According to Kamel *et al.*[14], the extent of modification increases with increasing acrylonitrile concentration.

Figure 1 shows the dependence of the extent of modification with the catalyst (tetramethylammonium hydroxide) concentration. As is evident, increasing the catalyst concentration from 0.25 to 1.25 mol l^{-1} causes an outstanding decrease in the extent of modification. This result could be associated with the fact that high concentrations of alkaline catalyst usually tend to reverse the cyanoethylation process[12].

Figure 2 shows the kinetic results for the reaction between dextran and acrylonitrile in the presence of tetramethylammonium hydroxide as catalyst at 25°C. An increase in the reaction time to 1 h has a positive influence on the degree of cyanoethylation. A further increase in the reaction time leads to a practically constant degree of cyanoethylation.

On the other hand, a special feature of polysaccharide derivatization is that, in many cases, only the partial substitution of its three alcoholic groups is desired or achieved. The *DS* and also the partial *DS* in the different positions of the anhydroglucose (AHG) units are of great importance for determining physical, chemical and biochemical properties[15,16]. The relative reactivity of the hydroxyl groups in the AHG units of dextran in the reaction with acrylonitrile was evaluated by ^{13}C n.m.r., which has been suggested as an adequate method to determine the substitution pattern of polysaccharide derivatives[17,18].

The ^{13}C n.m.r. spectra of the ring carbon region of the original dextran and several samples of partially modified dextrans prepared by reaction with acrylonitrile (*DS* ranging from 0.52 to 1.81) are shown in *Figure 3*. The ^{13}C n.m.r. spectra of modified polymers show a decrease in the intensity of the signals assigned to C1 (98.4 ppm), C2 (71.8 ppm), C3 (73.3 ppm), C4 (70.4 ppm) and C5 (70.4 ppm) carbon atoms in the original dextran, together with the appearance of several new peaks at

96.2, 83.1, 82.4, 81.5, 80.7, 79.7, 78.9, 78.0 and 76.7 ppm. The presence of these new peaks is consistent with the fact that the etherification of a hydroxyl group of glucopyranosic compounds not only causes a low-field shift (8.8 to 9.7 ppm) of the resonance of the carbon directly linked to a modified hydroxyl group, but also the resonance of the adjacent carbons is shifted (0.5 to 2.6 ppm) up-field with respect to the chemical shift of the carbon bearing an unsubstituted hydroxyl group[19].

In the present study, the assignments of these signals were made on the basis of a comparison with the substituent-induced shifts observed for 2-, 3- and 4-monomethyl-α-glucose[20], 2-hydroxyethyl-α-glucose[21], ethyl-α-glucose[22] and partially methylated dextran[23] as well as for 2,3,4-trimethyldextran[24]. These assignments were also correlated with the systematic variation of the relative intensity of each individual peak with the total *DS*.

The peak at 96.2 ppm may be ascribed to C1 carbons adjacent to C2 carbons bearing a substituted hydroxyl group. The peak at 83.1 ppm may be attributed to C3 carbons bearing a substituted hydroxyl group in monosubstituted AHG units. The peak at 82.4 ppm can be assigned to C3 carbons bearing a substituted hydroxyl group in 3,4-disubstituted AHG units. The signal at 81.5 ppm was attributed to C3 carbons bearing a substituted hydroxyl group in 2,3-disubstituted AHG units. The peak at 80.7 ppm is assumed to result from the C3 carbons in trisubstituted AHG units. The band at 79.7 ppm is considered to belong to C2 carbons in monosubstituted, 2,4-disubstituted and trisubstituted AHG units. The peak at 78.9 ppm may be assigned to C2 carbons bearing a substituted hydroxyl group in 2,3-disubstituted AHG units. The peak at 78.0 ppm was ascribed to C4 carbons in monosubstituted AHG units as well as to C4 carbons bearing a substituted hydroxyl group in 2,4-disubstituted AHG units. The peak at 76.7 ppm is considered to belong to C4 carbons bearing a substituted hydroxyl group in 3,4-disubstituted and trisubstituted AHG units.

These assignments permit us to estimate the relative reactivities of the three hydroxyl groups. In this sense, according to several authors[4,25,26] it may be considered that, under the experimental conditions used in the present work, the spin–lattice relaxation times and the nuclear Overhauser effect factors of all six carbons of the AHG units must be very similar. Therefore, the peak area measurements can be used for evaluation of the relative *DS* values for individual hydroxyl groups attached to C2, C3 and C4 carbons. The mole fractions (A) of monosubstituted AHG units at C2 (A_2), C3 (A_3) and C4 (A_4), of disubstituted AHG units at C2, C3 ($A_{2,3}$), C2, C4 ($A_{2,4}$) and C3, C4 ($A_{3,4}$), and of trisubstituted AHG units ($A_{2,3,4}$) were calculated from the expanded forms of the spectral ranges at 67–100 ppm, using in each case an adequate combination of the relative intensities of the signals at 96.2, 83.1, 82.4, 81.5, 80.7, 79.7, 78.9, 78.0 and 76.7 ppm.

The relative *DS* values (DS_i) of individual hydroxyl groups attached to the C2, C3 and C4 carbons have been estimated from the following equations:

$$DS_2 = A_2 + A_{2,3} + A_{2,4} + A_{2,3,4}$$

$$DS_3 = A_3 + A_{2,3} + A_{3,4} + A_{2,3,4}$$

$$DS_4 = A_4 + A_{2,4} + A_{3,4} + A_{2,3,4}$$

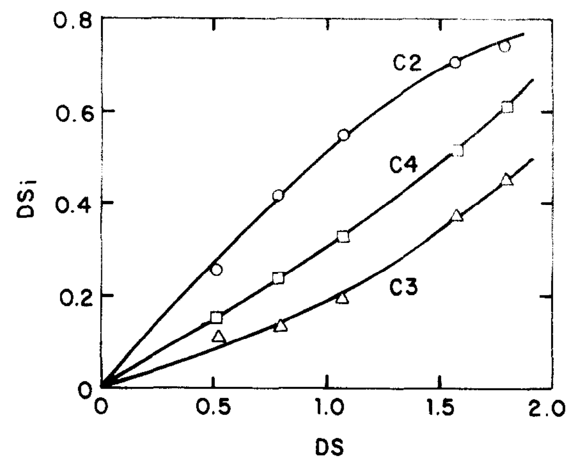


Figure 4 Variation of the degree of substitution at individual hydroxyl groups (DS_i) with the total degree of substitution in modified dextrans prepared by reaction with acrylonitrile

The average degree of substitution of each polymer sample was calculated from:

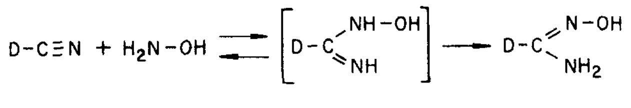
$$DS = DS_2 + DS_3 + DS_4$$

It may be noted that in all cases the magnitude of the total *DS* determined by means of Kjeldahl determination of nitrogen and those obtained from the sum of the partial *DS* values of individual hydroxyl groups attached to C2, C3 and C4 carbons are in good agreement.

Figure 4 shows the variation of the relative DS_i of individual hydroxyl groups in the reaction of dextran with acrylonitrile, as a function of the total *DS* value. The analysis of data shown in *Figure 4* clearly indicates that the relative reactivities of the three hydroxyl groups of AHG units decreased in the order C2 < C4 < C3.

As mentioned above, the functionalization of dextran with acrylonitrile is a reversible reaction, and thus subject to thermodynamic control. Thus, the distribution of substituents in cyanoethylated dextran may be affected by the reversible character of the reaction. However, it may be noteworthy that the relative reactivities of hydroxyl groups at C2, C3 and C4 positions that we have obtained in the reaction of dextran with acrylonitrile follow the same order reported for partially methylated dextrans obtained by rate-controlled reaction of dextran with dimethyl sulfate[27].

Nitrile groups in cyanoethylated dextran are converted into amidoxime groups by reaction with hydroxylamine. The reaction can be represented as follows:



$$\text{D-C}\equiv\text{N} + \text{H}_2\text{N-OH} \rightleftharpoons \left[\text{D-C}\begin{matrix}\nearrow \text{NH-OH}\\ \searrow \text{NH}\end{matrix}\right] \longrightarrow \text{D-C}\begin{matrix}\nearrow \text{N-OH}\\ \searrow \text{NH}_2\end{matrix}$$

where D–C≡N is cyanoethylated dextran. The structure of amidoximated dextrans was determined by means of i.r. and ^{1}H n.m.r. spectroscopy. The i.r. spectra of modified polymers with amidoxime groups show that conversion of cyanoethyl groups to amidoxime ones is accompanied by a decrease of absorption at 2240 cm^{-1}. The most characteristic bands of the amidoxime polymers are those from C=N stretching and from =N–O stretching. The former are located at 1655 cm^{-1}

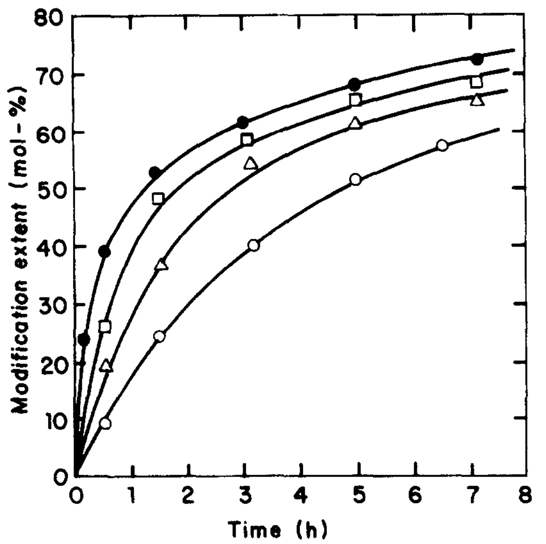


Figure 5 Kinetics of the reaction between a partially modified dextran with cyanoethyl groups ($DS = 1.60$, [cyanoethyl groups] = $0.43\,\mathrm{mol\,l^{-1}}$) and hydroxylamine ($0.86\,\mathrm{mol\,l^{-1}}$) in DMF at various temperatures: (○) 50°C, (△) 60°C, (□) 70°C, (●) 80°C

and the latter at $920\,\mathrm{cm^{-1}}$ (ref. 28). The ^{1}H n.m.r. spectra of the same polymers show peaks at 2.2, 3.7 and 5.4 ppm, which are due to hydrogen atoms of amidoxime groups[29]. The presence of some residual cyanoethyl groups was confirmed by the band at 2.8 ppm, which corresponds to the $-CH_2-CN$ methylene protons.

Figure 5 shows the kinetic results for the reaction between cyanoethylated dextran and hydroxylamine at various temperatures. It may be noted that a high yield was obtained in all cases. However, total completion was not attained for each of the four reactions that we carried out. It is quite probable that this effect may be explained to some extent by the steric effects of amidoxime groups previously incorporated into the polymeric chain. These groups may be considered to complicate the reaction of residual cyanoethyl groups in the last stages of the reaction.

The analysis of the kinetic results in the initial stages of the reaction of cyanoethylated dextran with hydroxylamine enables us to conclude that the reaction shows second-order kinetics. This behaviour was also observed in the reaction of polyacrylonitrile with hydroxylamine[5]. The activation energy for the amidoximation reaction was estimated as $42.7\,\mathrm{kJ\,mol^{-1}}$ from the Arrhenius plot, which is in good agreement with the values found for other amidoximation reactions[30].

Amidoxime groups can coordinate some metal ions selectively[31]. Preliminary experiments have shown that partially modified dextrans with amidoxime groups form chelates with Cu^{2+}, as evidenced by i.r. spectroscopy. A strong band appears at $1560\,\mathrm{cm^{-1}}$, which is due to binding of free NH_2 of the amidoxime groups with copper ions[2]. The fact that the peak at $1655\,\mathrm{cm^{-1}}$ (C=N) becomes weaker also indicates the coordination of Cu^{2+} with amidoxime groups. A ratio of [amidoxime groups]/[Cu^{2+}] = 1.3 was obtained. Further investigations on the chelating mechanism are now in progress.

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