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Nitrite Esters of Polyhydroxy Polymers[1]

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Nitrite esters of polysaccharides and synthetic polyhydroxy polymers are obtained by reaction of polyhydroxy polymer with dinitrogen tetroxide or nitrosyl chloride in a medium containing a suitable proton acceptor. The polymeric nitrite esters are relatively unstable compounds and can be isolated only at low temperatures as wet, fibrous materials from a neutral or alkaline medium. In the presence of a protic solvent, such as water or alcohol, and catalytic amounts of mineral acid, they decompose immediately with formation of nitrous acid or alkyl nitrite and regeneration of the corresponding polyhydroxy polymer. Results suggest that nitrosation of alcoholic hydroxyl groups, irrespective of their origin, follows the same mechanism and is subject to an equilibrium $ROH + N_2O_4 \rightleftharpoons RONO + HNO_3$, whose equilibrium constant depends greatly on the stability of the nitrite ester.

It has been found previously that cellulose can be solubilized with nitrogen dioxide or nitrosyl chloride in *N,N*-dialkylacylamide, with formation of clear and viscous solutions.[2] More recent results indicate that the reason for this solvation lies in the formation of cellulose trinitrite ester, a compound that decomposes immediately in the presence of a protic solvent and mineral acid as a catalyst with regeneration of the cellulose.[3] A reaction mechanism has been proposed[3] in which the nitrosyl nitrate form,[4] not the symmetric nitrogen dioxide dimer, is the reactive agent that quantitatively esterifies the cellulose molecule. Nitrosyl chloride reacts in a similar fashion producing nitrite ester and, instead of nitrate ion, chloride ion. However, a 2.5- to 3-fold excess of nitrosyl chloride is required for completion of the reaction probably as a result of a higher stability, i.e., lower reactivity, of nitrosyl chloride.

It is postulated that the *N,N*-dialkylacylamide functions as a proton acceptor, so the equilibrium as shown in Scheme I would shift to the right to provide for an essentially quantitative nitrite ester formation. Consistent with this mechanism, the rate of esterification increases and the conversion with nitrosyl chloride can be completed with

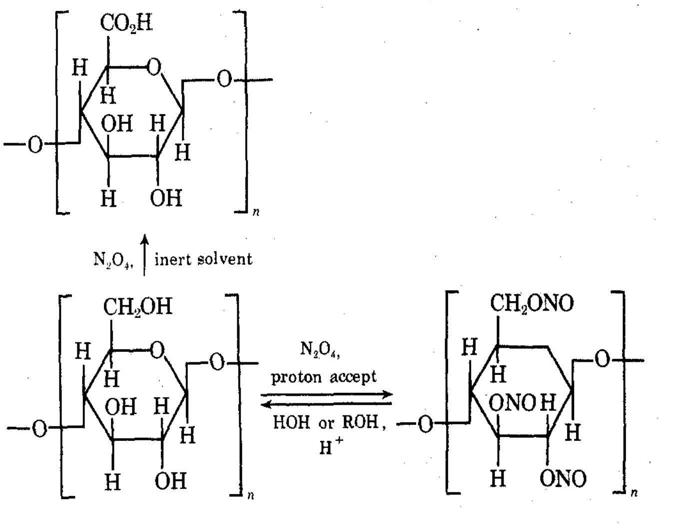
Scheme I

$$ROH + ONONO_2 \rightleftharpoons RONO + HNO_3$$
$$ROH + ONCl \rightleftharpoons RONO + HCl$$

stoichiometric amounts of reagent if the more strongly basic tertiary amines, such as pyridine or quinoline, are used as solvent. The reaction proceeds also in inert solvents, such as benzene, chloroform, acetone, or ethyl acetate, provided that at least 1 mol of amine per mole of nitrosating agent is present. However, if a strongly basic tertiary amine, such as trialkylamine, is used, no nitrite ester formation occurs but, instead, a highly exothermic reaction of the nitrosating reagent with the amine is observed making nitrosyl nitrate or chloride unavailable for nitrosation of the cellulose.

Previously it was believed that the only principal reaction of cellulose (and other hexosans) with nitrogen dioxide was oxidation of *primary* hydroxyl groups at C-6 to form carboxyl groups with minor side reactions being oxidation of *secondary* hydroxyl groups and nitration.[5] The present results establish that, in a medium containing cellulose and nitrogen dioxide, an equilibrium as shown in Scheme I exists and, depending on the medium, the reaction may proceed either toward oxidation or nitrite ester formation as shown in Scheme II. In relatively inert solvents, the equilibrium is very much in favor of the left side, i.e., cellulose and free dinitrogen tetroxide, and practically no nitrite ester is detectable. Then, oxidation of *primary* hydroxyl groups, a relatively slow reaction, will take place. No such oxidation, however, is possible in the presence of a suitable proton acceptor even with an excess of nitrogen dioxide since the rate of nitrite ester formation is much higher than that of oxidation and, once the nitrite ester is formed, the hydroxyl groups are protected from oxidative attack.

Scheme II



Nitrite ester formation as shown above is not limited to cellulose but is a reaction common to all polysaccharides and synthetic polyhydroxy polymers. Thus, other polysaccharides, such as starch, guar gum, locust bean gum, alginic acid, and hemicellulose, and polyvinyl alcohol form clear and viscous solutions in *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), pyridine, or quinoline when a sufficient amount of nitrogen dioxide or nitrosyl chloride is introduced. The amounts of dinitrogen tetroxide necessary to solubilize the various polyhydroxy polymers are shown in Table I. During introduction of the nitrogen dioxide, the mixtures remain colorless to very lightly colored until the ratios in Table I are closely approached. Then, an intensive color change toward bluish green occurs indicative of free nitrogen dioxide. The molar ratio, polyhydroxy polymer:nitrosyl chloride, is essentially the same if pyridine or quinoline is used as the proton acceptor. With DMF or DMA, a 2.5- to 3-fold excess of nitrosyl chloride is required for completion of the reaction. In all cases, the ratio coincides remarkably well with the number of free hydroxyl groups per polymer unit, i.e., three for hexosans, two for polyuronic acid and pentosans, and one for polyvinyl alcohol. Slight deviations from the theory toward higher values may be due to the presence of impurities, such as protein, and, in the case of hemicellulose, to a small percentage of anhydrohexose as a molecular building unit. The yellow color of regenerated guar and locust bean gums may be an indication of protein impurities that have reacted with nitrogen dioxide.

Table I
Reactions of Dinitrogen Tetroxide with Polyhydroxy Polymers in DMF

Polyhydroxy polymer	Molar equiv of N_2O_4 reacted	Number of free OH groups in polymer units
Cellulose	2.7–2.8	3
Starch	2.7–2.8	3
Guar gum	3.0–3.2	3
Locust bean gum	3.0–3.2	3
Alginic acid	1.8–1.9	2
Hemicellulose	2.0–2.1	2
Polyvinyl alcohol	0.9–0.95	1

The nitrite esters of polyhydroxy polymers can be isolated by addition of their solution, neutralized with a tertiary amine, to water. All nitrite esters prepared exhibit similar solution properties and an instability similar to that of the cellulose nitrite ester described previously.[3] Thus, they can be isolated only at a low temperature, they cannot be dried without decomposition unless the temperature is extremely low, and they decompose immediately in the presence of a protic solvent and mineral acid as a catalyst. The consumptions given in Table I indicate that all polymers form fully substituted nitrite esters. This has been established by direct analysis of the nitrite ester through decomposition with acid, determination of the regenerated polymer by weight, and titration of the nitrous acid with permanganate followed by isolation of the nitric acid formed as nitron nitrate. Degrees of substitution calculated from the weight of the polymer and the amount of nitrous acid titrated were found to be 2.8–3.0 for the hexosans (including cellulose), 1.9–2.0 for polyuronic acid and pentosans, and 0.9–1.0 for polyvinyl alcohol.

Regeneration of the polyhydroxy polymer is accomplished by addition of a protic solvent, such as water or alcohol, to the nitrite ester solution containing mineral acid. With water, this is a simple hydrolysis while, with alcohol, it is a transesterification producing alkyl nitrite as the most stable nitrite ester in this system. Stoichiometric amounts of protic solvent are sufficient to remove the nitrite groups quantitatively from the polymer molecule as this has been demonstrated previously for cellulose.[3] Nitrogen determinations of the regenerated materials are negative or do not show an increase of the nitrogen content originally present, and ir spectra are identical with those of the corresponding starting materials indicating that the regenerated polyhydroxy polymers are chemically unmodified.

Comparison of the viscosities of the regenerated polysaccharides with those of the corresponding starting materials is made in Table II. It indicates that degradation is negligible with the exception of galactomannans, which appear to

Table II
Viscosity of Original and Regenerated Polysaccharide

Material	Concn, %	pH	Viscosity	
			Original	Regenerated
Cellulose[a]	0.5		28.8	28.8
Starch	1.0	6.0	30.4	29.3
Guar gum	0.25	6.3	287	70.7
Locust bean gum	0.25	6.6	255	117.2
Alginic acid[b]	0.25	6.5	114	104.6
Hemicellulose	2.0	6.7	146.2	138.5
Water			12	

[a] The viscosity of cellulose was determined in cuprammonium hydroxide solution as described previously.[3]
[b] EDTA (0.1%) was added to exclude any influence on viscosity by traces of calcium ions.

depolymerize to a significant extent as shown by the reduction of their solution viscosity.

Apparently, all polyhydroxy polymers irrespective of their structure or composition are subject to the equilibrium in Scheme I, producing polymeric nitrite ester if a suitable proton acceptor is present. Aliphatic alcohols undergo the same reaction with dinitrogen tetroxide,[3] but the presence of a proton acceptor is not necessary for alkyl nitrite formation, and the reaction proceeds with or without the addition of an inert solvent.[4,6] Assuming that the formations of alkyl nitrite and polymeric nitrite proceed along the same reaction path so both are subject to the equilibrium in Scheme I and ignoring the fact that there are one- and two-phase reactions, the principal remaining difference is in the stability of the nitrite esters. Such difference is expressed in the value of the equilibrium constant, $C = [ROH][N_2O_4]/[RONO][HNO_3]$, which is reversely proportional to nitrite ester stability. Relatively large constants favoring unsubstituted hydroxyl groups and free dinitrogen tetroxide would thus be expected for the relatively unstable polymeric nitrite esters while relatively small constants would be typical of the more stable alkyl nitrites.

Experimental Section

Cellulose Trinitrite Ester. Cellulose trinitrite ester was prepared by treating cellulose (10 g) with N_2O_4 or NOCl as described previously,[3] but instead of DMF, 100 ml of (a) pyridine, (b) quinoline, (c) benzene–pyridine, 1:1 and 4:1, (d) acetone–pyridine, 4:1, and (e) ethyl acetate–pyridine, 4:1, was used. All mixtures formed viscous solutions with about 1 mol of N_2O_4 or NOCl per mole of hydroxyl radical. Experiments c–e formed some white precipitate consisting probably of pyridinium nitrate.

Similar results were obtained when a benzene–pyridine mixture was used in which the amount of pyridine was about 1 mol per mole of N_2O_4 or NOCl.

If triethyl- or tripropylamine was substituted for the pyridine, a strongly exothermic reaction occured on addition of N_2O_4 or NOCl without esterification of the cellulose. The same exothermic reaction was observed when N_2O_4 or NOCl was added to trialkylamine without cellulose being present.

Nitrite Esters of Polymers Other Than Cellulose. Pregelatinized corn starch (4 g) was dried at 60° in vacuo for 3 hr and suspended in 100 ml of DMF or DMA, and N_2O_4 was introduced at room temperature with mechanical stirring and under exclusion of moisture. After introduction of 5 g of N_2O_4, the mixture had thickened but still contained a considerable amount of suspended particles. The color of the mixture was slightly bluish green. Complete solubilization and deepening of the color occurred with about 6.1 g, and further addition of N_2O_4 did not increase the viscosity but only intensified the deep green color of the solution. Without pregelatinization of the starch, no solubilization was achieved under these reaction conditions.

Four-gram portions of guar gum, locust bean gum, alginic acid, hemicellulose, and polyvinyl alcohol were treated under identical conditions in 400, 400, 150, 150, and 40 ml of DMF or DMA, respectively. Prior to the reaction with N_2O_4, guar and locust bean gums were dissolved in water, precipitated and dehydrated with methanol, and dried in vacuo at 60° for 2 hr. Alginic acid was obtained from Kelco Gel HV[7] by dissolution in water, precipitation with $CaCl_2$, washing of the precipitate with 0.1 *N* HCl followed by water, dehydration with alcohol, and drying in vacuo at 50° for 2 hr. Hemicellulose was prepared by alkaline extraction of corn hulls[8] and purified by redissolving in water, precipitation with methanol, and drying at 110° for 2 hr. Polyvinyl alcohol (fully hydrolyzed) was used as supplied without further treatment.

Table III

Polyhydroxy polymer	Amount of N_2O_4 introduced, g	Observation
Guar	4.3	Thickening, light color
	6.2	Gelatinous, clear, deeper color
	7.2	Gelatinous, clear, deep green
Locust bean	5.6	Thickening, light color
	6.4	Gelatinous, clear, deeper color
	7.4	Gelatinous, clear, deep green
Alginic acid	3.5	Thick solution, light color
	3.8	Clear viscous solution, bluish green
Hemicellulose	5.5	Thick solution, undissolved particles
	5.8	Clear solution, bluish green
Polyvinyl alcohol	4.0	Thickening, colorless
	8.0	Clear solution after prolonged stirring, bluish green

The observations in Table III were made after introduction of various amounts of N_2O_4. With NOCl and DMF or DMA, the molar amount of reagent had to be increased substantially to obtain similar results. In the presence of pyridine, however, stoichiometric quantities of NOCl were sufficient. Similar results were also obtained when solvent mixtures as described above for cellulose were used.

Regeneration of Polyhydroxy Polymer. The nitrite ester solution in DMF was poured in a thin stream and with vigorous agitation into about 3 volumes of methanol, and the precipitate was filtered off and pressed out on a Büchner funnel, resuspended in fresh methanol, filtered off again, and dried in vacuo at 60°. All regenerated polymers were practically colorless, with the exception of guar and locust bean gums being light yellow. Films were obtained by spreading the solution on a glass plate and contacting it with aqueous methanol. The film was removed, washed with methanol, and dried in vacuo at 60°.

Analytical Procedures. Ir spectra were obtained with a Perkin-Elmer spectrophotometer, Model 257. All samples were used in the form of films prepared as described above.

Nitrogen was determined by the Kjeldahl method, and each polymer was analyzed before solvation and after regeneration.

For viscosity measurements, the polysaccharides were kept in DMF–N_2O_4 for 24 hr at 5°, regenerated, and the viscosities of their aqueous solutions determined at a pH of 6–7 with a Cannon Fenske Viscometer at 25°. pH values, if too low, were adjusted by the addition of dilute sodium hydroxide. Alginic acid prepared as described above was transformed into the ammonium salt before the viscosity measurement. Viscosities of aqueous solutions of the corresponding starting materials were measured under the same conditions, and results are given in Table II. Evidence of alkyl nitrite formation during regeneration of polysaccharide or polyvinyl alcohol by the addition of stoichiometric amounts of alcohol was obtained by isolation of the alkyl nitrite formed as described previously for cellulose.[3]

Isolation and Analysis of Polymeric Nitrite Ester. The nitrite ester solution in pyridine (or in DMF to which an excess of trialkylamine had been added) was poured slowly and with stirring into ice-cold water. The fibrous precipitate was removed, washed with ice-cold water, and pressed out on a Büchner funnel. Care had to be taken to maintain the temperature at below about 5° to avoid decomposition of the nitrite ester.

The moist nitrite esters thus obtained decomposed on drying.

They were soluble in DMF, pyridine, ethyl acetate, benzene, toluene, chloroform, acetone, and other common solvents for polymeric esters even in the presence of a protic solvent, such as alcohol. Solutions gelled on standing over an extended period of time finally resulting in separation of the corresponding polysaccharides or polyvinyl alcohol. On addition of mineral acid, the regenerated polymer separated immediately. The nitrite esters were analyzed by suspending the moist fibrous material in water, acidifying with sulfuric acid, and keeping the mixture in a closed Erlenmeyer flask with occasional shaking. After about 1 hr, a portion of the sample was neutralized with sodium hydroxide and the nitrite titrated with permanganate solution. The nitrate formed during titration was precipitated and identified as nitron nitrate.[9] The other portion was poured slowly and with agitation into 3–4 volumes of isopropyl alcohol to precipitate the polysaccharide and the precipitate was removed, dried in vacuo over P_2O_5 at 60°, and weighed.

Registry No.—Cellulose nitrite, 57255-90-0; starch nitrite, 57255-91-1; quar gum nitrite, 57108-91-5; locust bean gum nitrite, 57108-95-9; alginic acid nitrite, 57108-92-6; hemicellulose nitrite, 57108-93-7; polyvinyl alcohol nitrite, 57108-94-8; dinitrogen tetroxide, 10544-72-6; nitrosyl chloride, 2696-92-6.

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Selective Chlorinations in Sulfuric Acid. Synthesis of Some 2-Amino-5-chloro-, 2-Amino-3-chloro-, and 2-Amino-3,5-dichloropyridines

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A convenient and general process is described for the selective monochlorination of 2-aminopyridine and a number of methyl-substituted 2-aminopyridines. The chlorination of 2-aminopyridine at various sulfuric acid concentrations and the distribution of chlorinated products has been studied in detail. The results show that with increasing acidity dichlorination decreases, and in 72% sulfuric acid only traces of dichlorination occur. The selectivity of the chlorination reaction is ascribed to differences in the rate of chlorination of protonated vs. nonprotonated substrates.

We wish to report a convenient and general process for the selective monochlorination of 2-aminopyridine and a number of methyl-substituted 2-aminopyridines.

Several procedures for the chlorination of 2-aminopyridine have appeared in the literature. Chichibabin[1] reported the chlorination of 2-aminopyridine in ethanol. Later workers,[2,3] unable to duplicate the literature results, utilized 20% aqueous sulfuric acid at 25° as the solvent. However, in each of these procedures the desired monochlorinated product was found to be contaminated with significant amounts of 2-amino-3,5-dichloropyridine. A 70% yield of 2-amino-5-chloropyridine, with only slight formation of dichlorinated product, was obtained by treating 2-aminopyridine in concentrated hydrochloric acid with hydrogen peroxide.[4] These results on the chlorination of 2-aminopyridine in highly acidic media, and the varied selectivity reported in the halogenation of other aminopyridines,[5,6] led us to undertake a systematic investigation of this reaction.

Results

Chlorination of 2-Aminopyridine. Reaction of 2-aminopyridine (**1**) with a 2 molar excess of chlorine gas at various sulfuric acid concentrations gave the products listed in Table I. The distribution clearly shows that with increasing acidity dichlorination decreases, and in 72% sulfuric acid only traces of 2-amino-3,5-dichloropyridine (**1c**) are formed. Under optimum conditions (see Table II) the crude product 2-amino-5-chloropyridine (**1b**) had 99% purity and was obtained in 82–85% yield (98% based on recovered **1**).

Table I
Chlorination of 2-Aminopyridine in Sulfuric Acid

Sulfuric acid concn		% product distribution	
Wt %	H_0	5-Chloro-	3,5-Dichloro-
17	−0.8	50	50
30	−1.5	52	48
45	−2.7	77	23
55	−3.7	92	8
72	−5.8	98	2

Chlorination of Substituted 2-Aminopyridines. The generality of the chlorination process and the specificity toward monochlorination were demonstrated by chlorination of the compounds listed in Table II. As one might anticipate, the methyl groups facilitate 3 substitution. The combined effect of the methyl group on product distribution in the case of the 2-amino-4-methyl- and 2-amino-6-methylpyridines (**3** and **5**) when compared with 2-amino-4,6-dimethylpyridine (**6**) was very close to an average. The structure of each chlorinated product was easily determined by ^1H NMR spectroscopy except in the case of 2-amino-6-methylpyridine (**5**). Each monochloro derivative of **5** displayed an AB system for the aromatic protons, and the spectra were almost identical. A literature search revealed that Parker and Shive had prepared the nitro derivative (**9**) of 2-amino-3-chloro-6-methylpyridine by an alternate route.[7] Using their procedure we nitrated **5** and separated the mononitro products (**7** and **8**), and subsequent