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Study of the Synthesis of Dextran Derivatives

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ABSTRACT

The synthesis of biologically active high-molecular compounds offers an interesting subject for study in polymer chemistry. Dextran, one of the best blood plasma expanders, is a good product for use in synthesizing biologically active water-soluble polymers. This paper discusses the synthesis of water-soluble derivatives of dextran which can be used as drug carriers or as independent physiologically active compounds. The synthesis of these derivatives involved oxidation of dextran, O-alkylation of dextran, subsequent transformation of ethers of dextran containing reactive functional groups, and graft polymerization. Periodate oxidation of dextran resulted in the production of a derivative of dextran containing aldehyde groups: dialdehydedextran. Subsequent oxidation of dialdehydedextran with sodium chlorite permitted the introduction of carboxyl groups into the macromolecule of dextran. In order to introduce sulfonic acid, phosphonic, mercapto, chlorhydrinic, cyano, and aromatic amino groups into the macromolecule of dextran, dextran was alkylated with various alkylating reagents. The synthesized products

were sulfopropyl, phosphonomethyl, mercaptoethyl, 3-chloro-2-hydroxypropyl, cyanoethyl, and 2-(3'-amino-4'-methoxyphenyl)-sulfonylethyl ethers of dextran.
Treatment of the 3-chloro-2-hydroxypropyl ether of dextran with ammonia, amines, and aliphatic and aromatic amino acids produced ethers of dextran containing primary, secondary, and tertiary amino groups and quaternary ammonium groups, as well as residual aliphatic and aromatic amino acids.
Cyanethyl ether of dextran was used to synthesize derivatives of dextran containing thioamide and hydrazidine groups.
Graft copolymers of dextran and polyacrylic acid and of dextran and poly-2-methyl-5-vinylpyridine were synthesized. Redox systems were utilized to initiate graft copolymerization with tetravalent cerium compounds used as oxidants and pentavalent vanadium with dextran or 2-(3'-amino-4'-methoxyphenyl)-sulfonylethyl ether of dextran used as reductant. This method produced graft copolymers with short graft chains.
The availability of the above derivatives of dextran has permitted the linking of drugs to dextran by different types of chemical bonds.

Advances in the chemistry of high-molecular compounds have led to increasing and ever wider applications in solving a variety of problems in biochemistry, biology, and medicine. One aspect of investigations in this field is the synthesis of new polymers and the chemical modification of known natural and synthetic polymers, two processes employed in the production of water-soluble high-molecular compounds that exhibit biological activity [1-7].

Water-soluble polymers are extensively used in the making of blood plasma substitutes. Polymers, specifically polymeric metal complexes, are used as models of enzymes. Another significant field of study concerns production of water-soluble polymers containing residues of chemically combined low-molecular drugs. Compounds of this class are synthesized in order to prolong the period of their efficacy, decrease their toxicity, increase their solubility, and change their distribution in a living organism. Dissolved polymers are used as detoxicators. Some water-soluble polymers containing acidic groups inhibit virus infection.

There is evidence of the possibility of using polymers with electron-exchange properties both in modeling biochemical processes and for medicinal purposes.

Biologically active water-soluble polymers may be based either on synthetic or natural polymers. Most experiments described in the literature have involved the use of synthetic carbon-chain polymers. Evidence of the possibility of the use of carbon-chain polymers in order to modify the properties of medicinal drugs has been provided by studies carried out by Ushakov, Kropachev, et al., who synthesized a large number of polymeric drug compounds based on polyvinyl alcohol, its derivatives, and copolymers of vinyl alcohol and vinylpyrrolidone [2, 4, 8].

In synthesizing polymers intended for introduction into a living organisms, especially by injection, due regard should be given to their ability to be assimilated and then to be rejected by the organism after they have fulfilled their function. Carbon-chain polymers such as polyvinyl alcohol and polyvinylpyrrolidone introduced into a living organism are not susceptible to enzymic decomposition. The high stability of carbon-chain polymers—blood plasma expanders operates both as an advantage (long presence in the organism) and as a significant shortcoming, viz., given too great a molecular weight they tend to accumulate and become deposed in various tissues, thereby disturbing the normal functioning of the organs [9, 10]. For this reason the most promising choices for the production of biologically active water-soluble compounds are offered by natural polymers, specifically polysaccharides. These have a big advantage over carbon-chain polymers in that they are gradually hydrolyzed by the enzymes in the organism. With natural polymers use can probably be made of compounds with high-molecular weights, free of the fear of deposition in organic tissues.

The gradual enzymatic decomposition of polysaccharides that goes on in the organism may not allow medicinal drugs the same prolonged period of efficacy as with synthetic carbon-chain polymers, i.e., 20 to 30 days. Even so, this is not a requirement in many cases, for a few days or hours is often sufficient. The decomposing ability of polysaccharides in the organism is an obvious advantage where the aim in adding a medicinal drug to a polymer is to make the latter soluble and lower its toxicity.

Dextran, one of the best known blood plasma expanders, holds major promise for the synthesis of biologically active water-soluble compounds.

Basically, there are two types of biologically active water-soluble compounds that can be evolved around dextran;

1) Compounds in which dextran and its derivatives are polymeric carriers of low-molecular drugs whose properties they enhance.
2) Dextran derivatives, specifically compounds containing ionogenic, electron-exchanging, and complexing groups used as independent biologically active compounds (detoxication, models of enzymic processes, inhibition of virus reproduction, introduction of micrometric elements into the organism, diagnostics).

Direct interaction between dextran and a drug is not always possible because of the absence of functional groups which could react under mild conditions and maintain the drug's activity. This necessitates a preliminary chemical modification of dextran through the introduction of reactive groups.

The following methods have been employed to synthesize dextran derivatives containing new types of functional groups:

1) Oxidation of dextran and its derivatives.
2) Synthesis of dextran ethers in the O-alkylation reaction and by transformation of dextran ethers containing reactive groups.
3) Synthesis of graft copolymers of dextran.

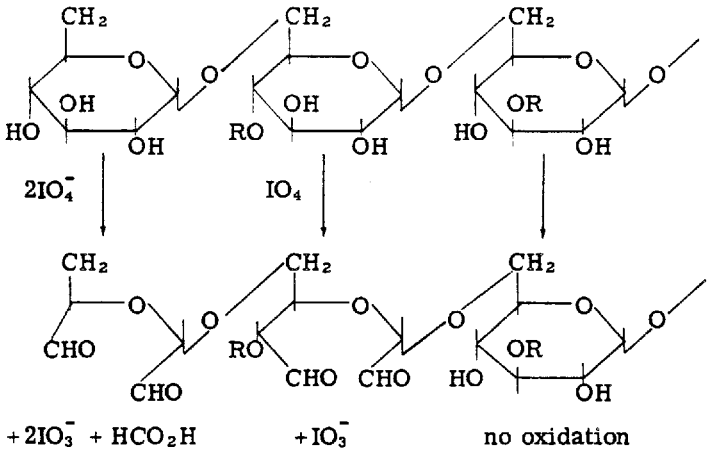
The basic ingredient was dextran with a weight-average molecular weight of 55,000-60,000, synthesized with the strain Leuconostoc mesenteroides SF-4.

SYNTHESIS OF DEXTRAN DERIVATIVES BY OXIDATION

Dextran derivatives containing aldehyde and carboxyl groups [11] were produced by oxidation.

Dialdehydedextran

The simplest way of introducing aldehyde groups into the macromolecule of dextran is provided by oxidation with sodium periodate. In this case the reactions shown possibly depend on the composition of the individual polysaccharide links.



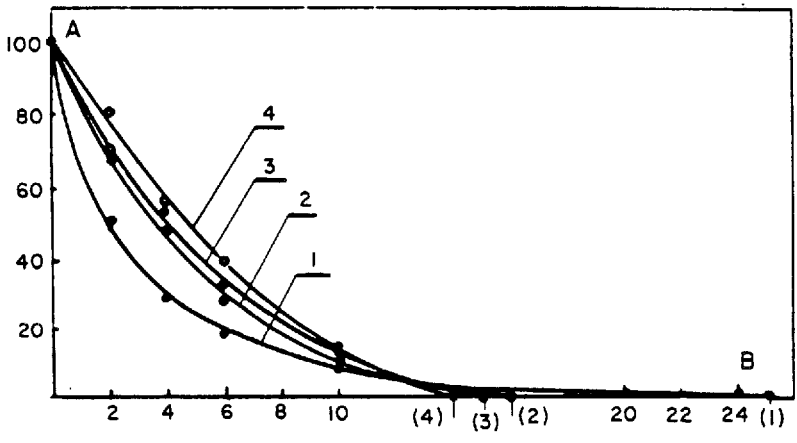


FIG. 1. Concentration of $NaIO_4$ in the oxidation of dextran as a function of the time of reaction. (A) Concentration of $NaIO_4$ (% of initial value). (B) Time of reaction (min). Quantity of molecules of $NaIO_4$ introduced in the reaction per 100 elementary dextran links: (1) 100, (2) 40, (3) 20, and (4) 10.

Dextran was oxidized in a homogeneous medium at a pH of 4.0 and 20°C. The reaction proceeds at a high rate (see Fig. 1).

It will be seen from Table 1 that there are more oxidized

TABLE 1. Degree of Oxidation of Dextran as a Function of the Amount of $NaIO_4$

Amount of $NaIO_4$ (molecules per 100 elementary dextran links)	Iodine value of dialdehyde-dextran	Content of aldehyde groups	
		%	Number of aldehyde groups per 100 elementary dextran links
10	20.8	3.0	16
20	36.7	5.3	28
40	66.8	9.7	52
70	100.3	14.5	78

elementary links in all the products than might be expected if two molecules of $NaIO_4$ were used to oxidize a single link. A possible explanation for this is the presence of side chains in dextran macromolecules. Products of dialdehydedextran are water-soluble, the rate of solution decreasing as the content of aldehyde groups increases.

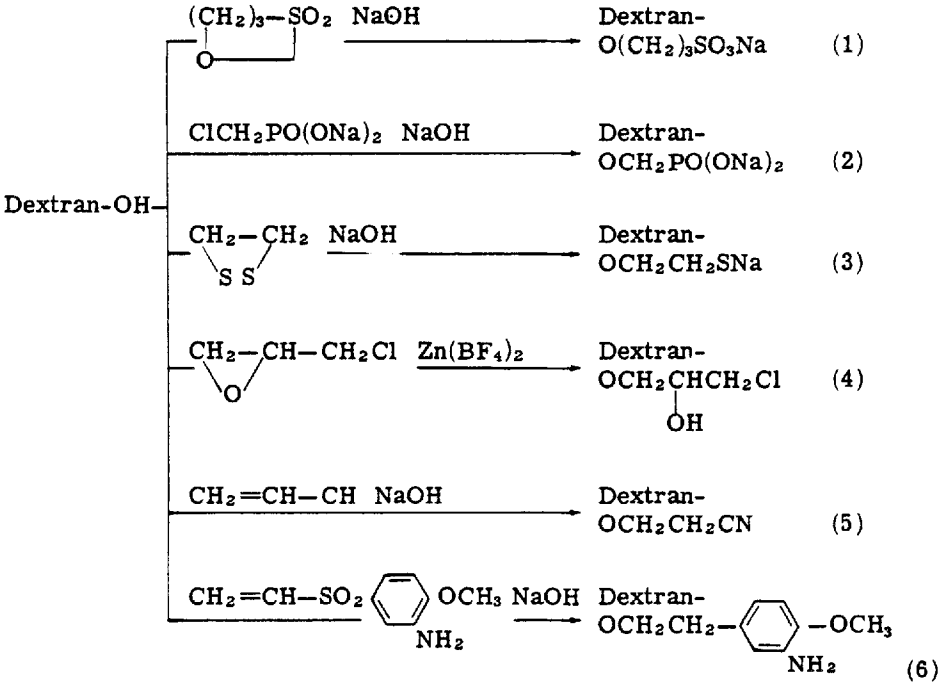
The intensity of the band at 1740 cm^{-1} in the ir spectrum of dialdehydedextran containing 13% aldehyde groups is very small [12]. This shows that aldehyde groups are bonded and are probably part of hemialdal and hemiacetal structures. Such structures have been found in cellulose oxidized with sodium periodate (dialdehydecellulose) [13].

Dicarboxyldextran

When dialdehydedextran is treated with sodium chlorite (10 molecules of $NaClO_2$ per oxidized link of dialdehydedextran, pH 3.0, 20°C), aldehyde groups may be fully oxidized into carboxyl groups. The sodium salt of dicarboxyldextran formed in such a reaction is easily soluble in water. Dicarboxyldextran was obtained in the form of an acid by treating the Na-salt with hydrochloric acid. The dissociation constants of carboxyl groups of dicarboxyldextran, found by potentiometric titration, are $K_1 = 6.03 \times 10^{4}$ and $K_2 = 7.94 \times 10^{-5}$.

SYNTHESIS OF ETHERS OF DEXTRAN

The following ethers of dextran were obtained in the equations listed: sulfopropyl (1), phosphonomethyl (2), mercaptoethyl (3), 3-chloro-2-hydroxypropyl (4), cyanoethyl (5), 2-(3'-amino-4'-methoxyphenyl)-sulfonyl-ethyl (6) [2-(3'-amino-4'-methoxyphenyl)-sulfonylethyl ether was obtained for subsequent use in the synthesis of graft copolymers of dextran (see the section on Synthesis of Graft Copolymers of Dextran)] [14-17].



Sulfopropyl Ether of Dextran [14]

Synthesis of sulfopropyl ether of dextran, which the authors believed to have the properties of a strong polyelectrolyte, has interesting aspects.

Interaction between the alkylating agent sultone of γ-hydroxy-propyl-sulfonic acid and dextran proceeds at a high rate and under relatively mild conditions (35°C, 10-30 min). An important factor affecting the composition of the ether thus formed is provided by the molar ratio of the sultone of γ-hydroxy-propyl-sulfonic acid and sodium hydrate (Table 2). In order to achieve the maximum degree of alkylation, an equimolar quantity of the above compounds should be introduced into the reaction.

The degree of substitution of sulfopropyl ether of dextran may be greatly increased by a second treatment with sultone of γ-hydroxy-propyl-sulfonic acid. Thus by a second reaction with sulfopropyl ether of dextran containing 9.4% sulfur (DS = 0.82) a product was obtained that contained 13.4% sulfur (DS = 1.7). The sulfopropyl ether of dextran is easily soluble in water. The dissociation constant of sulfonic groups is $K = 1.54 \times 10^{-3}$.

Mercaptoethyl Ether of Dextran [15]

By treating dextran with ethylene sulfide in the presence of NaOH, a product is obtained that contains mercapto groups. The product was also found to contain disulfide groups which were reduced to mercapto groups by the action of sodium hydrosulfite. The electron-exchange capacity of synthesized water-soluble mercaptoethyl ether of dextran (DS = 1.65) was 6.2 mg-equiv/g. A by-product of the synthesis of mercaptoethyl ether of dextran is a nonwater-soluble graft copolymer of dextran and polyethylene-sulfide whose quantity was 50% of the weight of mercaptoethyl ether of dextran.

Phosphonmethyl Ether of Dextran [16]

In the synthesis of phosphonmethyl ether of dextran an adequate degree of substitution of hydroxyl groups, one equal to 0.53, was achieved only under fairly rigid conditions (125°C, 1 hr, 25% solution of NaOH), which caused heavy destruction of polymers.

The dissociation constants of the phosphone group are $K_1 = 9.13 \times 10^{-4}$ and $K_2 = 1.45 \times 10^{-7}$.

Cyanoethyl Ether of Dextran [16]

Introduction of cyano groups into the macromolecule of dextran opens up possibilities of the production of dextran derivatives containing electron-exchange and complexing groups.

TABLE 2. Degree of Substitution of Dextran as a Function of the Quantitative Ratio of Reagents

Experiment No.	Quantity of sultone (molecule per elementary dextran links)	Quantity of NaOH		Content of sulfur in sulfopropyl ether of dextran (%)	Degree of substitution of dextran hydroxyl groups (DS)
		Molecule per elementary dextran links	Molecule per molecule of sultone		
1	0.65	0.65	1.00	6.9	0.51
2		0.52	0.40	6.5	0.46
3		0.98	0.75	9.1	0.77
4	1.3	1.30	1.00	9.4	0.82
5		1.63	1.25	8.4	0.68
6		3.25	2.50	6.6	0.46
7	2.6	2.60	1.00	11.2	1.15

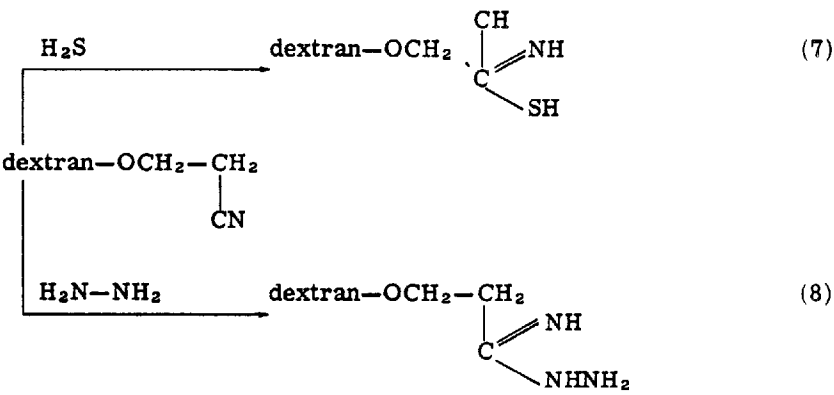
Some of the aspects of the reaction between dextran and acrylonitrite in alkaline medium are shown in Fig. 2.

The reason for the decreasing content of nitrogen in cyanoethyl ether of dextran at temperatures above 60°C is the partial hydrolysis of the C—O bond, which is the result of the I-effect of the cyano group of the alkyl residue as well as the partial saponification of the cyano group into a carboxyl group. A product of cyanoethyl ether of dextran obtained at 78°C contained 1.2% carboxyl groups while products obtained at 60 and 40°C contained no carboxyl groups.

With a degree of substitution equal to 1.0, the cyanoethyl ether of dextran is soluble in water and dimethylformamide. When the degree of substitution is 2.5, it is not soluble in water but is soluble in formamide, dimethylformamide, and dimethylsulfoxide, and exhibits heavy swelling in acrylonitrile. This swelling of the product in acrylonitrile is apparently the reason for the increased rate of reaction during the synthesis of cyanoethyl ether of dextran after the degree of substitution has passed 1.5.

Cyanoethyl ether of dextran with a degree of substitution of 3.0 may also be obtained at 20°C (concentration of dextran in aqueous solution, 33%; NaOH, 3%; quantity of acrylonitrile, 300% of the weight of aqueous solution, period of treatment 48 hr).

Dextran derivatives having electron-exchange and complexing properties [16] were obtained by transforming cyanoethyl ether of dextran as shown in Eqs. (7) and (8).



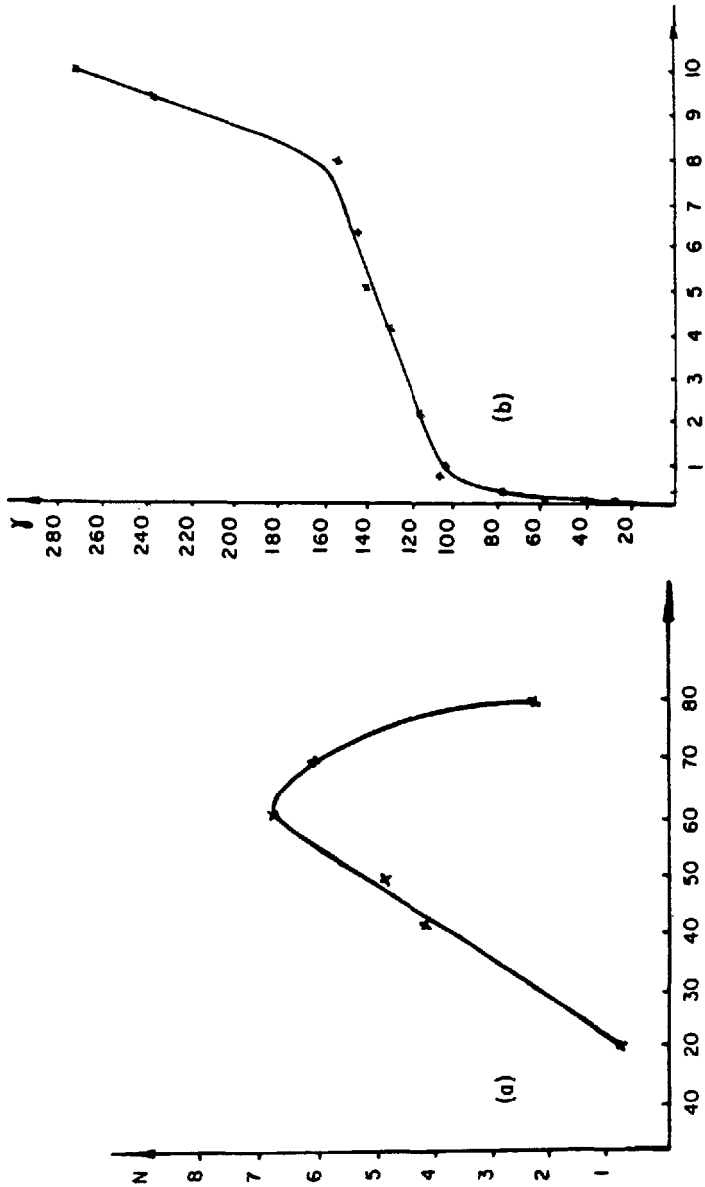


FIG. 2. Effect of temperature (a) and time of reaction (b) on the degree of alkylation of hydroxyl groups of dextran. Content of aqueous solution: dextran, 33%; NaOH, 3%. Quantity of acrylonitrile, 300% of the weight of alkaline solution of dextran. Time of reaction 40 min (a), temperature 60°C (b).

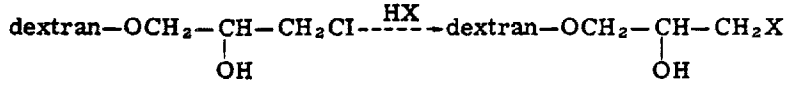
3-Chloro-2-hydroxypropyl Ether of Dextran [14]

Synthesis of the 3-chloro-2-hydroxypropyl ether of dextran is of interest as a method of introducing reactive chlorohydrinic groups into a macromolecule of dextran. The latter may subsequently be used to obtain new derivatives of dextran that contain other functional groups and to join drugs with the dextran macromolecule by means of covalent bonds.

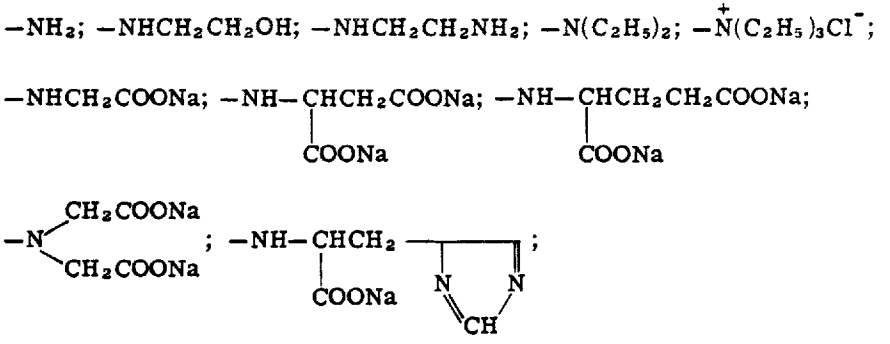
Depending on the concentration of the catalyst $Zn(BF_4)$ in the reaction mixture, the products obtained were varieties of the 3-chloro-2-hydroxypropyl ether which contained from 2.2 to 16.4% Cl (DS from 0.1 to 1.3) and practically no epoxy groups.

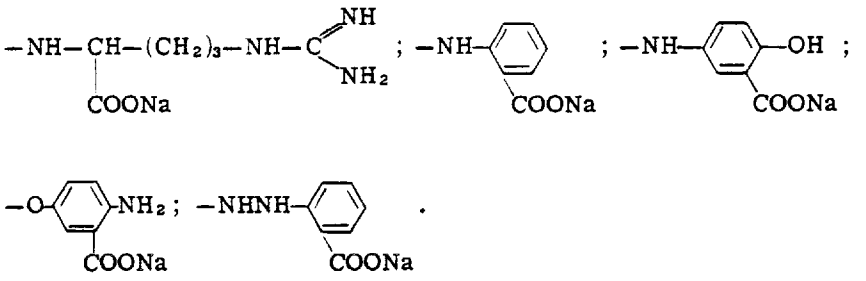
In interacting with the hydroxyl groups of dextran, the epoxy ring of epichlorohydrin is opened as indicated in the above formulas. The reason for this is that, owing to the I-effect of the atom of Cl in the molecule of epichlorohydrin, the polarizability of the adjacent C—O bond is lower and is therefore less susceptible to opening than any other C—O bond of the epoxy group.

The action of nucleophilic reagents (ammonia, aliphatic amines, aliphatic and aromatic amino acids, and hydrazine) was utilized in the general formula



to obtain derivatives of dextran, wherein the X stands for





It should be noted that dextran ethers containing primary and secondary amino groups, hydrazino groups, and residual amino acids cannot be obtained by direct interaction between dextran and an alkylating agent containing the said groups.

Table 3 lists the optimal conditions for the synthesis of various derivatives of dextran obtained by transforming the 3-chloro-2-hydroxypropyl ether of dextran. This ether of dextran reacts with the sodium salts of glycine and other amino acids, but does not react with glycine, glutamic, and aspartic acids. The reason for this is that where the pH value is approximately equal to the isoelectric point of the aqueous solution, α-amino acids are generally found as bipolar ions (e.g., in glycine; $\overset{+}{N}H_3CH_2COO^-$), and protonized amino acids do not react with chlorohydrinic groups of the 3-chloro-2-hydroxypropyl ether of dextran.

The reason for the relatively low rate of interaction of this ether with sodium salts of amino acids compared with amines is the induction effect of the carboxy group. The rate of reaction of the 3-chloro-2-hydroxypropyl ether of dextran with the Na-salt of aminobenzoic acid is much lower than with aliphatic α-amino acids because of the more intensive electrophilic action of the carboxy group in aromatic amino acid. The presence in O-hydrazinobenzoic acid of the hydrazino group, both of whose nitrogen atoms have an undivided electron pair, contributes, owing to the so-called α-effect, to the faster rate of reaction between this compound and the 3-chloro-2-hydroxypropyl ether of dextran.

The structures of synthesized compounds were confirmed by ir spectroscopy [17]. A Van Slyke test to determine the content of amino nitrogen in the product obtained by treating the 3-chloro-2-hydroxypropyl ether of dextran with a large quantity of ammonia showed that all the nitrogen is part of the primary amino groups,

TABLE 3. Conditions of Reaction and Composition of Products Obtained by Transformations of the 3-Chloro-2-hydroxypropyl Ether of Dextran

Expt No.	Reagent	Degree of substitution of original 2-chloro-3-hydroxypropyl ether of dextran	Conditions of reaction: Quantity of reagent (molecule per chlorohydrinic group)	Conditions of reaction: Temperature (°C)	Conditions of reaction: Duration (hr. min)	Content in products of reaction (%): N	Content in products of reaction (%): Cl	Degree of substitution as residual reagent introduced	Degree of useful utilization of chlorohydrinic groups (%)
1	Ammonia	0.32	20	20	6.00	1.8	0.3	0.25	76.5
2	Aminoethyl alcohol	0.32	4	60	4.00	1.8	0.9	0.25	78.0
3	Ethylenediamine	0.25	10	60	6.00	3.7	0.0	0.25	100.0
4	Diethylamine	0.34	4	60	4.00	1.8	0.3	0.26	75.6
5	Triethylamine	0.48	20	20	48.00	1.5	1.3	0.24	50.0
6	Hydrazine	0.25	40	20	2.00	3.8	0.0	0.25	100.0
7	Glycine (Na-salt)	0.19	5	100	7.00	1.3	0.0	0.18	94.0
8	Aspartic acid (disodium salt)	0.19	5	100	9.00	1.3	0.0	0.19	100.0
9	Glutamic acid (disodium salt)	0.19	5	100	9.00	1.2	0.2	0.18	95.0

10	Arginine (Na-salt)	0.32	4	100	0.30	6.1	0.7	0.25	78.1
11	Histidine (Na-salt)	0.32	4	100	1.00	4.3	0.9	0.24	73.4
12	Iminodiacetic acid (disodium salt)	0.25	5	100	15.00	1.6	0.0	0.25	100.0
13	O-Aminobenzoic acid (Na-salt)	0.19	5	100	30.00	1.3	0.0	0.19	100.0
14	5-Aminosalicyclic acid (Na-salt)	0.19	5	100	9.00	1.0	0.3	0.16	83.8
15	O-Hydrazinobenzoic acid (Na-salt)	0.25	5	100	4.00	3.3	0.0	0.25	100.0

hence each molecule of ammonia reacts only with one chlorohydrinic group.

The products of interaction between an ether of dextran with 2-aminoethyl and sodium salts of glycine, aspartic, and glutamic acids did not contain any primary amino groups, which proves that the reaction is based solely on the amino groups of the above nucleophilic reagents.

The association of histidine with a molecule of the 3-chloro-2-hydroxypropyl ether of dextran is based largely (about 90%) on the action of the α-amino groups, as was made obvious by the content of primary α-amino groups in the product of the interaction between the ether of dextran and the Na-salt of histidine. The reason for the ability of the iminazole ring of histidine to react is that one of the two undivided electron pairs of the nitrogen atoms of the iminazole ring does not form part of the π-electronic system.

The pK value of the guanidino group of arginine is 12.5. Where the pH value is 9.0 it has a positive charge and cannot react, so the association of arginine with the polymer is based solely on the α-amino group. About 50% of the nitrogen in the product of interaction between the 3-chloro-2-hydroxypropyl ether of dextran and 5-aminosalicylic acid is found in the primary aromatic amino groups. Consequently, 50% of the molecules of 5-aminosalicylic acid are linked by amino groups, with the remaining 50% linked by phenolic hydroxyls.

The reason for the incomplete substitution of the atoms of chlorine in the 3-chloro-2-hydroxypropyl ether of dextran by nitrogen groups during the synthesis of the above derivatives of dextran is that some of the epoxy groups formed in the first stage are hydrolyzed and that not all chlorine atoms form part of the highly reactive chlorohydrinic groups.

In order to determine the degree of destruction of dextran during chemical transformation, the molecular weight of some of its ethers was found osmometrically. Acetone was used as solvent. In order to make the products acetone-soluble, they were nitrated under conditions that ruled out destruction of polymer. The coefficient of polymerization of the macromolecule of dextran remained practically unchanged in the synthesis of the cyanoethyl ether of dextran (DS = 1.0) and the 2-(3'-amino-4'-methoxyphenyl)-sulfonyl ether of dextran (DS = 0.05). The polymerization coefficient of the 3-chloro-2-hydroxypropyl ether of dextran (DS = 0.32) was 53% less than the polymerization coefficient of the original dextran and failed to change in subsequent treatment of the ether in an alkaline medium (pH = 9.0; t = 100°C; 30 hr).

Synthesized derivatives of dextran containing various complexing groups (compounds Nos. 3 and 12-15 in Table 3) form water-soluble metal-ion complexes with Cu^{2+}, Co^{2+}, and Ni^{2+}. The stability constants of complex polymeric compounds calculated by the Bjerrum formula are close to the stability constants of complex compound formed by appropriate low-molecular complexing compounds.

Experiments have demonstrated that an ether of dextran containing quaternary ammonium groups is in vitro bacteriostatically active, that the sulfopropyl ether of dextran has blood-anticoagulant activity, and that the complexing derivatives of dextran may be used as polymeric catalysts.

It will be seen from Fig. 3 that the initial rate of decomposition of H_2O_2 in the presence of the complex compound 3-(2'-aminoethyl)-amino-2-hydroxypropyl ether of dextran and Cu^{2+} is 20 times higher than that of H_2O_2 in the presence of an equivalent amount of Cu^{2+} ions. Studies conducted jointly with Platte and Davydova have shown that an ether of dextran containing residual l-glutamic acid may be used to modify the catalyst in the hydrogenation of poly-β-ketoethers in order to effect asymmetric induction into a macromolecular substrate.

SYNTHESIS OF GRAFT COPOLYMERS OF DEXTRAN

One of the most effective methods of chemical modification of polymers including saccharides is provided by the synthesis of graft copolymers. This type of synthesis of the dextran derivatives has so far been the subject of only limited study [19-21].

This paper presents a study of the synthesis of graft copolymers of dextran with poly-2-methyl-5-vinylpyridine and polyacrylic acid [16, 22].

Fully aware of the danger inherent in introducing carbon-chain polymers with their high molecular weights into an organism, the authors thought it best to use those methods of synthesis which permit adjustment of the length of grafted chains and obtain graft copolymers with short side-chains.

In order to initiate the reaction of graft copolymerization, the redox system was used in which dextran or 2(3'-amino-4'-methoxyphenyl)-sulfonylethyl dextran ether were reductants and the oxidants were presented as compounds of tetravalent cerium or pentavalent

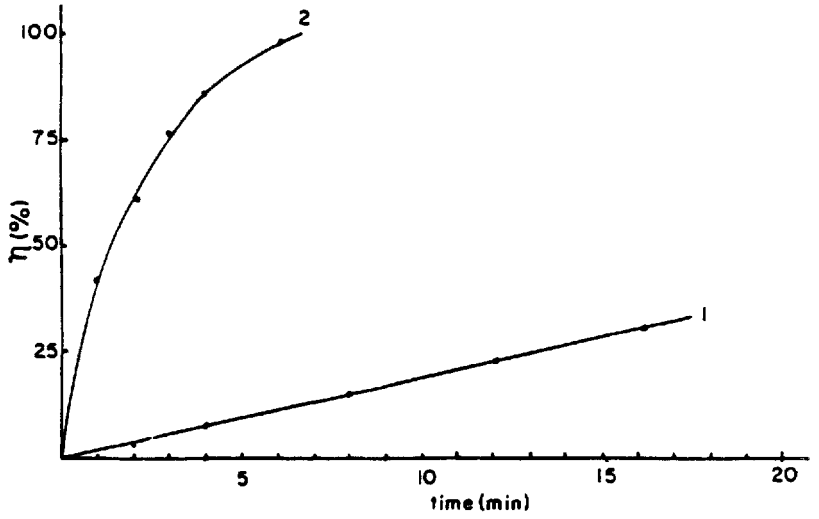
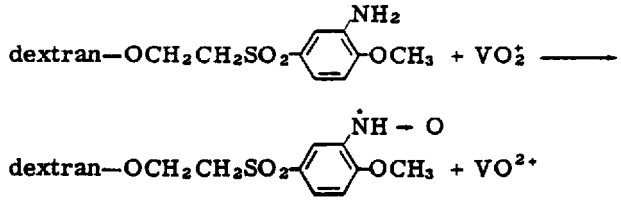


FIG. 3. Quantity of H_2O_2 decomposed in the presence of Cu^{2+}(1) and of the complex compound 3-(N-2'-aminoethyl)-amino-2-hydroxypropyl ether of dextran and Cu^{2+}(2) as a function of reaction time (0.09 N solution of H_2O_2, 30°C, pH = 11, $Cu^{+} = 7.5 \times 10^{-4}$ mole/liter).

vanadium, respectively. In the second case the initiation of graft copolymerization can be represented by Eq. (9) [23].



(9)

These methods of synthesis of graft copolymers permit regulation of the length of the grafted chain and the obtaining of copolymers without the concomitant formation of a carbon-chain homopolymer.

The grafted chains of polyacrylic acid and poly-2-methyl-5-vinylpyridine were separated from the dextran macromolecule by acetolysis and hydrolysis of the latter. The molecular weight

of polyacrylic acid separated by acetolysis of dextran was determined by a viscometric test in a 2-N aqueous solution of NaOH. The molecular weight of poly-2-methyl-5-vinylpyridine separated by hydrolysis of dextran was determined by a viscometric test in absolute dimethylformamide as well as with reference to the content of aldehyde groups bonded with the grafted chains of residual glucose, or with reference to the content of sulfur present in the residual 4-β-hydroxyethylsulfonyl-2-aminoanisole bonded with the separate grafted chains. The readings of molecular weights of the grafted chains of poly-2-methyl-5-vinylpyridine determined as above proved to be close to each other, e.g., M_n = 3200 and M_w = 3700 during initiation with graft copolymerization of Ce^{4+}, or M_n = 1200 and M_w = 1700 during initiation with compounds V^{5+}.

It will be seen from Tables 4 and 5 that the characteristic features of the reaction discussed above are:

1) High rate of reaction. The reaction takes 30 min at 50°C where compounds of pentavalent vanadium are used to initiate graft copolymerization and 5 min where tetravalent cerium is used. It should be noted that the rate of grafting these monomers to cellulose (heterogeneous process) is much slower.

2) Graft copolymers having relatively short chains are formed. A significant effect on the composition of the components of graft copolymers, on the molecular weight of grafted chains, and on the solubility of graft copolymers is exercised by the molar ratio between the HVO_3 and amino groups. When the above molar weight drops to 1.6 (see Table 4, Expt 5) and 2.0 (see Table 5, Expt 14), the molecular weight of grafted chains goes sharply up with the products of the reaction becoming partly or wholly insoluble in water.

In this case the quantity of vanadic acid used in the reaction is probably inadequate to break off the growing chains, and the breaking-off of the chain may partly occur as the result of recombination of the growing macromolecules.

Involved in the reaction of graft polymerization with polyacrylic acid under the conditions of Expts 2 and 8 (see Table 4) are, respectively, 47 and 67% of macromolecules of the 2-(3'-amino-4'-methoxyphenyl)-sulfonylethyl ether of dextran. The polymerization coefficient of the ether of dextran under such conditions is, respectively, 35 and 50% lower. Under the conditions of graft polymerization involving Ce^{4+}, the polymerization coefficient for dextran is 17% lower.

TABLE 4. Effect of Conditions of Reaction on Composition of Graft Copolymer of Dextran and Polyacrylic Acid[a]

Expt No.	Condition of reaction: Molecular ratio of HVO_3/NH_2 groups	Condition of reaction: Reaction time (min)	Condition of reaction: Temperature (°C)	Quantity of grafted polyacrylic acid (% of weight of dextran)	Molecular weight of grafted polyacrylic acid	Water solubility of graft copolymer
1	3.3	15	50	12	-	Yes
2	3.3	30	50	28	12,000	Yes
3	3.3	60	50	26	12,500	Yes
4	9.8	30	50	22	5,400	Yes
5	1.6	30	50	49	63,000	No
6	3.3	30	40	26	14,000	Yes
7	3.3	30	60	37	6,200	Yes
8	3.3	30	70	46	2,700	Yes

[a]Concentrations: ether of dextran, 7.8%; acrylic acid, 1.1 M; H_2SO_4, 0.4 M

TABLE 5. Effect of Conditions of Reaction on Composition of Graft Copolymer of Dextran and Poly-2-methyl-5-vinylpyridine (PMV P)[a]

Expt No.	Oxidant	Conditions of reaction: Temperature (°C)	Reaction time (min)	Concentration of oxidant (10^{-3} M)	Molecular ratio of HVO_3/NH_2 groups	Quantity of grafted PMV P (% of weight of dextran)	Molecular weight of grafted PMV P
1	Ce^{4+}	25	5	3.0	-	11.9	3,700
2		25	10	3.0	-	12.6	3,700
3		25	20	3.0	-	11.4	3,700
4		25	30	3.0	-	11.6	3,700
5		15	10	3.0	-	11.5	6,400
6		10	10	3.0	-	9.9	9,500
7		25	10	1.5	-	12.4	6,100
8		25	10	4.5	-	12.0	2,200
9	V^{5+}	50	15	78	3.3	14.0	-
10		50	30	78	3.3	27.2	2,200
11		50	90	78	3.3	27.2	2,600
12		20	30	78	3.3	24.0	8,000
13		70	30	78	3.3	29.2	1,400
14		70	30		2.0	16.0[b]	14,200

[a]The concentration of 2-methyl-5-vinylpyridine is 0.4 M.

[b]The soluble fraction is about 50%. The water insoluble fraction contains 43% of the grafted PMV P with molecular weight of 48,000.

It will be seen from the available findings that it is feasible to regulate within a wide range the lengths of chains of carbon-chain polymers grafted onto dextran and to obtain copolymers with shorter grafted chains. It can be inferred from this that graft copolymerization is a promising method of modifying dextran and that graft copolymers of dextran can probably be used, in principle, in the synthesis of polymeric compounds containing residual low-molecular drugs.

SYNTHESIS OF DERIVATIVES OF DEXTRAN CONTAINING RESIDUAL DRUGS

The properties of polymeric drug compounds will, to a large extent, depend on the nature of the bond between the polymer and the drug. One interesting study is a comparison of the pharmaceutical properties of polymeric compounds wherein the same drug is linked to the carrier polymer by different types of chemical bonds. The synthesis of such products has been made possible by the existence of the above-described derivatives of dextran containing diverse functional groups.

Typical formulas of reactions whereby drugs are linked with the above dextran derivatives are given below. The basic products used for the synthesis of polymeric drug compounds were dicarboxyldextran (Formula 1), carboxylmethyl (Formulas 2 and 4), sulfopropyl (Formula 3), 3-chloro-2-hydroxypropyl ethers of dextran (Formula 5), and dialdehydedextran (Formulas 6 and 7) [24-27].

1. $\text{dextran—COOH} + \text{H}_2\text{N—drug} \rightarrow \text{dextran—OCH}_2\text{C}\overset{-}{\text{O}}\text{O}\overset{+}{\text{H}}_3\text{N—drug}$
2. $\text{dextran—OCH}_2\text{COONa} + \text{HCl}\cdot\text{H}_2\text{N—drug} \rightarrow$
   $\text{dextran—OCH}_2\text{C}\overset{-}{\text{O}}\text{O}\overset{+}{\text{H}}_3\text{N—drug} + \text{NaCl}$
3. $\text{dextran—OCH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{Na} + \text{HCl}\cdot\text{H}_2\text{N—drug} \rightarrow$
   $\text{dextran—O(CH}_2)_3\overset{-}{\text{S}}\text{O}_3\overset{+}{\text{H}}_3\text{N—drug} + \text{NaCl}$
4. $\text{dextran—OCH}_2\text{COONa} + \text{Cl—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—OC}_2\text{H}_5 \rightarrow$
   $\text{dextran—OCH}_2\text{—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—O—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—OC}_2\text{H}_5 + \text{NaCl}$
   $\text{dextran—OCH}_2\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—O—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—OC}_2\text{H}_5 + \text{H}_2\text{N—drug}$
   $\text{dextran—OCH}_2\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—HN—drug} + \text{HO—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—OC}_2\text{H}_5$

5. $\text{dextran}-OCH_2-\underset{\underset{OH}{|}}{CH}-CH_2Cl + NH_2-\text{drug} \rightarrow$
$\text{dextran}-OCH_2-\underset{\underset{OH}{|}}{CH}-CH_2-HN-\text{drug} + HCl$
6. $\text{dextran}-CHO + H_2N-\text{drug} \rightarrow \text{dextran}-C{=}N-\text{drug} + H_2O$
7. $\text{dextran}-CHO + H_2N-HN-\text{drug} \rightarrow \text{dextran}-C{=}N-NH-\text{drug} + H_2O$

Animal tests have shown that linking with dextran or its derivatives provides one of the ways to improve the properties of low-molecular drugs, i.e., to prolong and improve the efficacy of drug action, lower toxicity, and make the drugs water-soluble [25-28].

Available findings suggest the tentative assumption that curative action is a function of low-molecular drugs whose bond with the polymer is gradually hydrolyzed. In order to modify the properties of low-molecular drugs, they should be linked to a polymer by gradually hydrolyzing covalent bonds. The ionic bond must be such as to assure changes in the properties of low-molecular drugs containing two ionogenic groups. The reason for the latter circumstance is probably the simultaneous linking of a low-molecular drug to two ionogenic polymeric groups.

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