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Dextran and Its Derivatives

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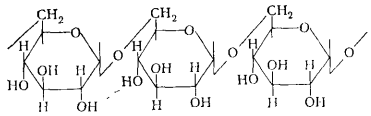
The Review covers the physicochemical properties of dextran, the preparation of various types of derivatives, and the study of their properties and possible fields of application. Consideration is given also to the preparation of dextranates of alkali and alkaline-earth metals, complexes of dextran with multivalent metals, oxidation products of dextran and their derivatives, deoxy-derivatives, esters and ethers, dextran derivatives having a three-dimensional cross-linked structure, graft copolymers, and derivatives containing chemically attached medicinals. The production of many of the above derivatives is shown to extend considerably the possible applications of dextran. A list of 335 references is included.

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I. INTRODUCTION

"Dextran" is the group name for polysaccharides, obtainable by microbiological synthesis, whose main molecular chain consists of anhydro-D-glucopyranose units linked predominantly by α-1,6-glycosidic bonds



The macromolecules of various dextran preparations may contain also various quantities of α-1,2-, α-1,3-, and α-1,4-glycosidic bonds, by means of which side-chains are usually attached to the main chain. Dextrans have been obtained whose molecules are almost entirely unbranched, while the monomer units are 95% linked by α-1,6-glycosidic bonds.

Dextran is obtained from cultures of the micro-organisms—*Leuconostoc mesenteroides*, *Leuconostoc dextranicum*, *Streptobacterium dextranicum*, etc.—in a medium containing sucrose or other carbohydrates in which anhydro-D-glucopyranose units are present, including a dextran of low molecular weight. The product of microbiological synthesis is termed "native dextran".

Many strains of the above micro-organisms exist, and produce dextrans differing in structure and properties, i.e. in molecular weight, degree of branching of the macromolecules, relative contents of particular types of glycosidic links, solubility, optical activity, and physiological action. The molecular weight of native dextran is usually lowered by acid hydrolysis, generally with simultaneous decrease in the degree of branching of the macromolecules.

The polysaccharide dextran has become widely known because aqueous solutions of certain preparations of molecular weight $(35-70) \times 10^3$ and low degree of branching are effective substitutes for blood plasma. The advantage of dextran over carbon-chain polymers also employed for this purpose (polyvinylpyrrolidone, polyvinyl alcohol) consists in its gradual hydrolysis by enzymes in the organism. This eliminates the danger that the polymer will accumulate in organs of the macro-organism. A very important use of dextran is as starting material for the production of Sephadexes, which are widely employed in gel chromatography. Dextran and its derivatives are finding increasing applications for other purposes.

The microbiological synthesis, structure, biological properties, and application of the polysaccharide in medicine have been described in detail in reviews and monographs[1-13]. However, no systematic surveys have been made of the physicochemical properties of dextran and the preparation and properties of its derivatives. The present Review covers work published mainly during the past decade.

II. PHYSICOCHEMICAL PROPERTIES OF DEXTRAN AND ITS APPLICATION

Native dextran is a polymer of high molecular weight (reaching 10^7-10^8) and high polydispersity ($M_w/M_n = 10^2-10^3$).[14] Information on the determination of the molecular weight of native dextran will be found in Refs. 15 and 16.

The molecular weight of native dextran can be reduced by acid hydrolysis[17,18], enzymic depolymerisation[19], alcoholysis[20], thermal degradation[21], treatment with hydrogen peroxide[22], γ-irradiation[23-26], ultraviolet and X-ray irradiation[27,28], and the action of ultrasonic vibrations[29]. Under industrial conditions acid hydrolysis is used for this purpose. The nature of the acid—hydrochloric, perchloric, nitric, sulphuric, or orthophosphoric—has little effect on the quantitative proportions of the hydrolysis products[17]. Hydrolysis followed by fractionation enables the ratio M_w/M_n to be reduced to 1.2-1.5. Acid hydrolysis results also in a diminished degree of branching of the

dextran macromolecules, owing to the relatively high stability of the α-1,6-glycosidic bond to acid hydrolysis. A systematic investigation has been made by electron spin resonance of the nature of the radicals formed when dextran is exposed to ultraviolet radiation, X-rays, and γ-rays, and of the kinetics of their accumulation and destruction[24,25,27].

Partly hydrolysed dextran can be fractionated and its polydispersity determined by fractional precipitation from solution on addition of an oxidising agent[30,31], gel permeation using Sephadexes[32-35] and other gels[36-39], filtration through microporous membranes[40], and turbidimetric titration[41]. It dissolves in water, formamide, and dimethyl sulphoxide; various alcohols and acetone do not dissolve dextran, but precipitate it from solution.

Many physicochemical researches have been aimed at establishing a relation between the properties and the structure of dextran preparations. The infrared absorption band at 794 cm^{-1}, due to the presence of α-1,3-glycosidic links in the macromolecules, varies in intensity in the spectra of dextrans formed by different micro-organisms[42]. Measurement of the intensity has been used to determine the content of this type of glycosidic link in various dextran preparations[43]. The conformation of the monomer unit of carbohydrates has a significant influence on the infrared spectrum in the range 700–1000 cm^{-1}. Investigation of this region in the spectrum of dextran and its derivatives[44] led to the suggestion that the most probable conformation of the anhydro-D-glucopyranose units in dextran macromolecules is $C1$. Nuclear magnetic resonance and Raman spectra have been determined for dextran[45-47].

Thermogravimetric investigation of the structure of dextran[48,49] reveals endothermic peaks in the range 130–310°C on the thermograms of all the dextran preparations investigated. The peak in the region of 200°C is typical of dextrans containing mainly α-1,6-glycosidic links; the thermograms of dextrans containing a considerable quantity of α-1,3-glycosidic links included a peak near 245°C.

The structure of dextran macromolecules also influences the sorption of water vapour by the polymer[50,51]. The quantity of water sorbed by specimens in which the α-1,6-glycosidic links were accompanied by a considerable number of α-1,3- and α-1,4-bonds increased monotonically with increase in the relative water vapour pressure. With preparations having a high content of α-1,6-glycosidic links the quantity of sorbed water increased with the vapour pressure to 75–85%, after which it decreased. This phenomenon was attributed to crystallisation of the dextran. Preparations whose macromolecules are only slightly branched, with the branches consisting mainly of one or two anhydro-D-glucopyranose units, are evidently able to crystallise. Study of such a preparation[52] by means of an original method for determining the lengths of side-chains established that approximately 40% of the branches contained one glucose residue, 45% contained two residues, and only 15% had a longer chain. Examination of eight different preparations by X-ray diffraction established[53] that all the dextran polymers were amorphous.

During recent years investigations have been made[54,55] on several physicochemical properties of dextran produced in the USSR, obtained by the partial acid hydrolysis of native dextran formed by the strain *Leuconostoc mesenteroides* SF-4 (molecular weight 55 000). X-Ray diffraction and thermomechanical examination have shown that spray-dried dextran is amorphous (glass point 140°C, flow point 180°C), but is able to crystallise when certain temperature–time heat-treatment schedules are used (with relatively slow cooling from 190 to 20°C or with slow heating), and also on treatment with liquids in which it swells (water, formamide)[55]. The possibility of converting dextran into states of rubberlike elasticity and viscous flow is the first observation of these phenomena in polysaccharides. The crystallisation of dextran on heat-treatment and when treated with water or formamide results in the appearance of new absorption bands in the infrared spectrum and in selective increase in the relative intensity of individual bands, which can be explained by the predominance of certain types of rotational isomers that favour crystallisation. The heat of interaction of amorphous dextran with water is 29.5 cal g^{-1}, and the "water surface" calculated from the water-vapour sorption isotherm is 228 m^2 g^{-1}.[54]

Many studies have been made of dextran solutions, an important physical characteristic of which is their optical activity, which depends on the structure of the macromolecules—the content of α-1,3-glycosidic bonds—and on the nature of the solvent[58]. The value of $[\alpha]_D$ for aqueous solutions of various dextran preparations varies from +199° to +235°. Extrapolation to zero content of such bonds gives 194.6°.[56,57] The optical activity of dextran solutions is unaffected by the presence of α-1,4-glycosidic bonds[56,57]. The influence of the solvent on $[\alpha]_D$ has been investigated[58]. Study of the optical rotation of dextran in cuprammonium solution indicates that the monomer units in the dextran macromolecules have the $C1$ conformation[59]. Similar conclusions were reached[60] from an n.m.r. study of a solution of dextran in dimethyl sulphoxide.

Several investigations have been made recently of the interaction of dextran macromolecules with the solvent. The macromolecules of several preparations of native dextrans form structural association complexes with the solvent[61]. The possibility of such association was examined in terms of the helical structure of native dextran stabilised by intramolecular hydrogen bonds and of the character of the hydrogen bonds formed in solution. The form of the macromolecules and the viscosity of aqueous solutions are affected by the presence of other substances: the asymmetry of the macromolecules of native dextran is greater in aqueous solutions of urea and glucose and in concentrated salt solutions than in water, but is less in aqueous methanol[15].

Study of the rheological properties of aqueous solutions of dextran (M_W = 120 000) over a wide concentration range revealed a sharp change at concentrations of 40–43%.[62] This was attributed to the structure of the hydration sheath of the macromolecules: an abrupt change in viscosity occurs when the composition corresponds to the formation of $1\frac{1}{2}$ layers of water molecules around each dextran macromolecule. Nuclear magnetic resonance has been used to study the interaction of water with dissolved dextran macromolecules[63], and electron microscopy to determine the size and configuration of the macromolecular aggregates in solution[64].

Viscosimetry has certain limitations as a method for determining the molecular weight of dextran. The constants K and α in the formula $[\eta] = KM^{\alpha}$ are different for dextran preparations differing in degree of branching or in the proportions of the various types of glycosidic bonds in the macromolecules. Examination of various dextran preparations by light scattering established[65] that, when 15–20 α-1,6-glycosidic bonds are present per glycosidic bond of a different type, the molecular weight of the dextran can be calculated by means of the formula $[\eta] = 0.00218M^{0.43}$; with greater branching of the macromolecules, when the ratio becomes 2–3, the coefficients K and

α are respectively 0.0044 and 0.34. Soviet dextran (polyglucin) preparations conform to the expression $[\eta] = 0.000966M^{0.5}$ over the range of molecular weights 40 000–100 000.[66]

The intrinsic viscosity of aqueous solutions of hydrolysed dextran is increased by the addition of potassium thiocyanate and calcium chloride, but diminished by lithium and potassium chlorides[67]. It depends also on the solution pH.[68] The variation in viscosity is attributed to variation in the character and number of intramolecular hydrogen bonds. The relation between the degree of branching of the macromolecules of dextrans and other natural polymers and the viscosity of their solutions has been studied[69,70]. The effects of the nature of the solvent (water, formamide, aqueous methanol, and aqueous dimethylformamide), the molecular weight of the dextran (M_n = 4100–32 000), and the temperature on the intrinsic viscosity of the solutions have been investigated[71]. Various aspects of the use of viscosimetry to determine the molecular weight of dextran have also been discussed[72–76].

Several papers have also appeared during recent years on the conformational transitions of dextran macromolecules in solution[77], the determination of virial coefficients[72,78], increments of the refractive indices of aqueous solutions of dextran[79], the heat and entropy of mixing of dextran with water over a wide concentration range[78], and the study of osmotic pressure and the scattering of light in aqueous solutions[72,78,80–82].

Applications of Dextran

As mentioned above, dextran is widely used to prepare most effective plasma substitutes for application in shock and the loss of blood; these are manufactured in various countries under the names polyglucin, dextran, Macrodex, Expandex, Intradex, and Dextraven[7]. The use of dextran for the production of Sephadexes is discussed in Section VIII. Other uses of dextran have also been reported—for preparing various forms of medicines (tablets, capsules for pharmaceutical preparations, eye-drops)[83–85], in the foodstuffs industry[86], in drilling, and in the production of cosmetic agents[87]—and the production of fibres from dextran has been patented. As mentioned above, dextran is hydrolysed by enzymes in the organism[88–92], so that considerable interest attaches to obtaining from dextran fibres or other articles (e.g. pins for joining bones in fractures) for use in surgery, when they would be gradually absorbed in the organism.

III. DEXTRANATES OF ALKALI AND ALKALINE-EARTH METALS AND COMPLEXES OF DEXTRAN WITH MULTIVALENT METALS

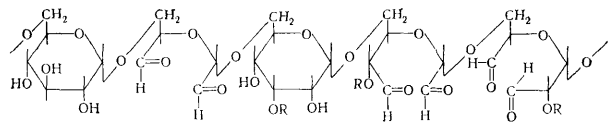
With alkali and alkaline-earth metals dextran forms alkoxides termed "dextranates". Sodium dextranate is produced when dextran is treated with a solution of sodium in liquid ammonia[93,94]; calcium dextranate, containing up to 20% of calcium, can be obtained according to a patent[95] from dextran and a calcium alkoxide of a lower alcohol. Dextranates are used as intermediates in the preparation of other dextran derivatives, e.g. its graft copolymers[94] and ethers[93].

Complex compounds of dextran have been described with Cuoxene $[Cu(NH_2CH_2CH_2NH_2)_2](OH)_2$ and Cadoxene $[Cd(NH_2CH_2CH_2NH_2)_3](OH)_2$.[96] The scientific and patent literature contains reports of the formation of compounds of dextran (probably complex) with hydroxides of several multivalent metals—calcium(II), bismuth(III), lead(II), cerium(III), lanthanum(III), chromium(III), aluminium(III), copper(II), cobalt(II)[97–99], and also iron(III)[100–108]—the exact structure of most of which has not been established. They are generally obtained by reaction between dextran and salts of the metals in an alkaline medium (sometimes in the presence of other compounds of low molecular weight, in particular those possessing complexing properties). In some cases dextran is pretreated with a reductant (e.g. sodium tetrahydroborate) or an oxidant (hydrogen peroxide). The largest number of patents and scientific papers deal with the preparation and study of the compound of dextran with iron(III) hydroxide, which is used for the treatment of anaemia in veterinary practice and is produced in several countries. Information is available also on the biological properties of compounds of dextran with hydroxides of other multivalent metals[97,99].

IV. PREPARATION OF OXIDATION PRODUCTS AND THEIR DERIVATIVES

The main lines of development of this branch of the chemistry of dextran during the past decade have been the use of additional oxidants to obtain carbonyl-containing derivatives and the preparation of several new derivatives from oxidation products of dextran.

Complete oxidation with periodic acid has long been used, together with other methods, to study the structure of dextran macromolecules. Investigation of the influence of the conditions of oxidation on the content of formyl groups in the water-soluble reaction product (which can provisionally be named "dialdehydodextran" by analogy with "dialdehydocellulose") showed[109] a high rate of reaction in a homogeneous medium (oxidation was complete in 25 min in the presence of 1 mole of periodic acid per monomer unit). The structure of the product of the partial oxidation of dextran by periodic acid can be represented by



Since the 1740-cm^{-1} band in the infrared spectrum of this polymer is very weak[110], however, it may be concluded that most of the aldehyde groups are not in the free state but probably involved in the formation of acetal, hemiacetal, and hemialdol[110] bonds or are present in the hydrated form. Study of the stability in an alkaline medium (pH $\geq$ 10) of dextran oxidised with periodic acid shows that hydrolysis of the glycosidic links is then accompanied by the Cannizzaro reaction with the formation from two formyl groups of one carboxy- and one hydroxy-group[111,112].

The oxidation of dextran by lead tetra-acetate in dimethyl sulphoxide, which also yields dialdehydodextran, is more rapid than oxidation by sodium periodate in aqueous solution[113]. Oxidation with a mixture of dimethyl sulphoxide and acetic anhydride gives a polymer containing keto-groups[114,115]. Under these conditions oxidation involves mainly hydroxy-groups at position 3 in the monomer unit of dextran[114]. A side-product of oxidation with dimethyl sulphoxide and acetic anhydride is the methylthiomethyl ether of dextran. The aqueous solubility of preparations from this dextran derivative depends both on the degree of

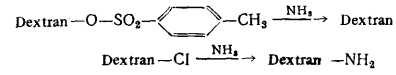
oxidation and on their sulphur content[115]. Water-soluble keto-derivatives can be obtained by oxidising dextran with chlorobenzotriazole[115]. In contrast to dialdehydodextran, the above keto-derivatives are quite resistant to alkaline hydrolysis (pH 9.5 at 20°C).[115]

Dialdehydodextran has been used to prepare derivatives containing carboxy- and amino-groups, the former by oxidation with sodium chlorite[109] and the latter by treatment with liquid ammonia in the presence of Raney nickel under pressure[116]. Degradation accompanying the action of aqueous ammonia on dialdehydodextran at high temperatures leads to the formation of imidazole and 4-methylimidazole[117].

The above dextran derivatives containing formyl, carboxyl, and keto-groups have been used to prepare derivatives containing chemically attached medicinal compounds (isonicotinohydrazide, novocaine, sulphanilamide, serotonin, morphine, Promedol, and various antibiotics)[118-124]. The infrared spectra of several of these compounds have been published[110,115,121]. Intraperitoneal injection of dialdehydodextran enhances the resistance of mice to infection with pathogenic strains of *Escherichia coli* [125, 126].

V. DEOXY-DERIVATIVES OF DEXTRAN

Study of the preparation of deoxy-derivatives of dextran containing halogen, thiol, and amino-groups has begun during recent years. Deoxyiodo-derivatives have been obtained[115] by nucleophilic substitution when dextran is treated with methyltriphenoxyphosphonium iodide and when sodium iodide acts on dextran toluene-*p*-sulphonate or nitrate. The fact that deoxyiododextran having a degree of substitution of 0.71 can be obtained from dextran toluene-*p*-sulphonate shows the possibility of replacing by halogen toluene-*p*-sulphonyloxy-groups attached to secondary carbon atoms in the anhydro-D-glucopyranose monomer unit. A water-soluble chlorodeoxydextran has been prepared by treating dextran with thionyl chloride in dimethylformamide[115,127]. Aminodeoxy-derivatives have been obtained[115,127] by nucleophilic substitution:



A deoxymercapto-derivative of dextran has been obtained by pyrolysis of the product of the oxidation of dextran xanthate with sodium nitrite followed by treatment of the resulting polymer with alkali[128].

VI. DEXTRAN ESTERS

Development of this branch of the chemistry of dextran in recent years has been characterised by the study of new methods for preparing already known esters, the elaboration of methods for obtaining new types of esters (including those containing residues of natural compounds—α-amino-acids and heterocyclic bases present in ribonucleic and deoxyribonucleic acids), and investigation of the properties and possible fields of application of dextran esters.

Esters with Inorganic Acids

The most fully studied ester is dextran sulphate, usually obtained by treating dextran with chlorosulphuric acid in absolute pyridine. Sulphur trioxide, sulphuryl chloride, oleum, concentrated sulphuric acid, and piperidine-*N*-sulphonic acid can also be used[129-134]. The reaction can be conducted in dimethylformamide, formamide, methylpyridine, dioxan, or dimethyl sulphoxide. Treatment of dextran with piperidine-*N*-sulphonic acid dissolved in dimethyl sulphoxide enables a uniformly substituted dextran sulphate to be obtained without significant fall in the degree of polymerisation[133]. The distribution of sulphate groups in the dextran sulphate macromolecule obtained in a heterogeneous system is non-uniform[135].

Alkaline saponification of dextran sulphate followed by complete acid hydrolysis of the product yields not only glucose but also altrose, mannose, and gulose[135,136]. Formation of such monomer units in the polysaccharide macromolecules is due to change in the configuration of the hydroxy-groups accompanying cleavage in an acid medium of the α-oxide rings formed by saponification of the sulphate groups.

Measurement of the viscosity of dextran sulphate solutions of different ionic strengths indicates that the macromolecules are highly flexible[137]. The interaction of dextran sulphate with various inorganic cations and organic cations of low molecular weight has been studied[138-142].

The ability of dextran sulphate to form compounds with various biopolymers enables it to be used to separate, isolate, and purify proteins, nucleic acids, lipoproteins, and viruses[143], and is also the reason for various aspects of its biological activity. Much work has been done on the possibility of using dextran sulphate as a blood anticoagulant. Despite the pronounced effect obtained with a dextran sulphate of high molecular weight, however, the strong toxic action on the organism has prevented its practical application.

During recent years, however, interest has been renewed in the preparation of less toxic forms of dextran sulphate, and in the study of its possible application as a blood anticoagulant[133, 144,145] and for other purposes in biology, biochemistry, and medicine. The results obtained from investigation of the medicobiological properties of dextran sulphate are summarised below. Dextran sulphate intensifies the antiviral activity of interferon in experiments *in vitro*[146,147], and itself possesses antiviral activity *in vitro*[148-150], but was inactive in experimental influenzal infections of white mice[148,151]. Dextran sulphate inhibits the activity of proteinases[152,153] and lipoprotein lipase[154], when its molecular weight has a significant influence on the degree of inhibition. It is therefore suggested[152] that dextran sulphate can be used to treat gastric ulcers. Products of its reaction with aluminium salts have been patented for this purpose[155,156]. Dextran sulphate possesses antilipaemic activity[130,133], and inhibits the template activity of deoxyribonucleic acids[157] and the respiratory activity of the mitochondria of rat liver cells in a medium of low ionic strength[158]. In the latter case it was assumed that the sulphate prevents the entry of nucleotides into the mitochondria. In experiments on mice spleen cells dextran sulphate inhibited the formation of antibodies on the injection of sheep erythrocytes[159]. It has been proposed also for the preparation of polymeric medicinals[160] and of photographic films[161].

According to the patent literature dextran phosphates can be prepared by the action of phosphoryl chloride in pyridine followed by treatment of the product with caustic soda or directly in the presence of the alkali. They have recently been obtained by treating dextran with a mixture of polyphosphoric acid and a trialkylamine[162]. Dextran phosphates form complexes with lipoproteins[163], and can

be used to obtain polymeric medicinals and photographic materials[164].

Studies have been made on the effect of the reaction conditions on the composition of nitric esters formed by the nitration of dextran with concentrated nitric acid and various nitrating mixtures[55,165-167]. Nitration with a mixture of 64% of nitric acid, 26% of orthophosphoric acid, and 10% of phosphorus pentoxide produces no decreases in the degree of polymerisation of dextran[168]. Highly substituted dextran nitrates are soluble in acetone, dimethylformamide, cyclohexanone, and oxolan. The infrared spectra over the range 700–1000 cm^{-1} indicate that the monomer units of dextran nitrate macromolecules have the same conformation ($C1$) as those of dextran itself[55,167]. Dextran trinitrate is an amorphous polymer[55], which absorbs water vapour[54]. Dextran xanthates have been obtained[169] and proposed for use in fibre production and the finishing of paper and textiles. Dextran methyl xanthate has been prepared and subjected to pyrolysis at 160°C.[170]

Esters with Organic Acids

Detailed investigations on the acetylation of dextran with various acetylating mixtures have yielded dextran acetates having degrees of substitution up to 3.0[55,167,171-173]. The rate of acetylation depends significantly on the conditions of preliminary activation of the dextran: a sharp increase in rate was observed after preliminary activation by reprecipitation from water into glacial acetic acid[55,167]. The infrared spectrum over the range 1270–1420 cm^{-1} of dextran activated in this way differs markedly from those of non-activated dextran and of dextran activated by treatment with glacial acetic acid[55,167].

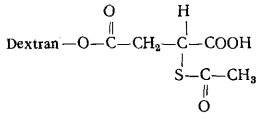
Investigation of the distribution of substituents in partly substituted dextran acetates has shown that acetylation of dextran with acetic anhydride in the presence of sodium acetate gives a product in which the 2-, 3-, and 4-hydroxyls are approximately equally reactive, whereas the 2-hydroxy-groups are most reactive in the product obtained with acetic anhydride in an equimolecular mixture of formamide and pyridine[172]. Since the infrared spectrum of dextran triacetate at 700–1000 cm^{-1} is identical with that of dextran, the monomer units in the corresponding macromolecules can be assumed to have the same conformation ($C1$). Only one solvent—symmetrical tetrachloroethane—is at present known for the triacetates of various dextran preparations[167,171,173,174]. The formula $[\eta] = 10^{-3}M^{0.5}$ has been proposed[171] for the viscosimetric determination of the molecular weight of dextran triacetate in this solvent.

Thermomechanical examination and X-ray diffraction indicate that dextran triacetate is a crystalline polymer (melting point 210°C).[55] The crystalline structure was improved by heating in tetrachloroethane and evaporating off the solvent. The heats of interaction of dextran triacetate with water and with dimethylformamide are respectively 3.0 and −9.4 cal g^{-1}, while the "water surface" calculated from the water-vapour sorption isotherm is 45 m^2 g^{-1}.[54]

Esters of dextran with aromatic carboxylic acids (benzoic, acetylsalicylic, cinnamic, nitrobenzoic) have been prepared by treating the polysaccharide with the acid chlorides in absolute pyridine[175] and by nucleophilic substitution of dextran nitrate by the action of the sodium salts in aqueous dimethylformamide[176]. The latter reaction has an S_N2 mechanism. Dextran phenyl diphenylcarbamate is obtained by the action of phenyl isocyanate on dextran[177]. The succinate, maleate, and phthalate, which are able to form complexes, have been obtained by the action of the acid anhydrides in formamide and pyridine[178,179]. Treatment of dextran maleate with sodium hydrogen sulphite yields an ester containing both carboxylate and sulphonate groups:

$$\text{Dextran}\!-\!OCOCH\!=\!CH\!-\!COOH + NaHSO_3 \rightarrow \text{Dextran}\!-\!OCOCH_2\!-\!\underset{\displaystyle SO_3Na}{\underset{|}{CH}}\!-\!COOH .$$

Dextran reacts with S-acetylthiosuccinic anhydride to give the corresponding ester[180]:

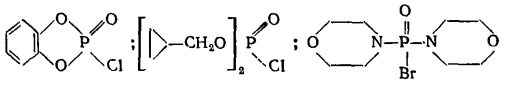


A systematic investigation has been made of the preparation of dextran esters of N-substituted α-amino-acids and the possibility of obtaining from them derivatives of dextran containing a free amino-group[181-188]. The esters were obtained by the action of the acids in the presence of NN'-dicyclohexylcarbodi-imide[181,182] by a method providing for the formation of mixed anhydrides[183-185] (these are formed when the amino-acids are treated with ethyl chloroformate, phosphoryl chloride, toluene-p-sulphonyl chloride, or benzenesulphonyl chloride in the presence of an organic base), by treating dextran with imidazolides of N-protonated α-amino-acids (obtained by the reaction of trifluoroacetates or hydrochlorides of the α-amino-acids with thionyl- or carbonyl-bi-imidazolyl)[186,187], and also by transesterification of p-nitrophenyl esters of the N-substituted α-amino-acids with dextran in dimethyl sulphoxide in the presence of excess of imidazole[188].

Of the various groups used to protect the amino-group in the acids nitrophenylsulphonyl is the most easily removed, by treatment with thiophenol in a mixture of dimethyl sulphoxide and pyridine or in the sodium thiosulphate–potassium iodide system in aqueous solution[183]. When dextran is treated with N-protonated imidazolides of α-amino-acids, poly(amino-acid) residues are added to the macromolecule[186]. Adenine, thymine, and uracil residues are introduced into the macromolecule by treating dextran with the carboxymethylated bases in the presence of dicyclohexylcarbodi-imide[189]; the resulting dextran esters form compounds with polynucleotides.

Toluene-p-sulphonic and methanesulphonic esters of various polysaccharides are widely used as intermediates for preparing derivatives of the polysaccharides by nucleophilic substitution. Considerable interest therefore attaches to the recent preparation of the dextran esters from the acid chlorides[115,190]. A similar scheme has been used to prepare the 5-dimethylaminonaphthalene-1-sulphonic ester (which is fluorescent)[191] and the p-iodobenzenesulphonic ester[192]. The latter has been proposed for preparing tissues of various animal organs for electron microscopy.

Phosphorus-containing esters can be obtained[193] by treating dextran with compounds of the type



A compound which may be used to detect specific immunoglobulin receptors on the surface of tumour cells is obtained by the action of fluorescein isothiocyanate on dextran[194]. A water-soluble ester is obtained from dextran and a chlorotriazine reactive blue dye (Dextran Blue

2000), which can be used to determine the dead space in column gel permeation, to check that the column is correctly packed, and as substrate in estimating the activity of enzymes that hydrolyse dextran[195-202]. Dextran coloured with a reactive orange dye has been suggested for use in thin-layer gel permeation[203,204].

VII. DEXTRAN ETHERS

The main lines of development at present are the preparation of ethers containing various reactive functional groups, elaboration of new methods for preparing already known ethers, determination of the distribution of alkyl groups at carbon atoms in the anhydro-D-glucopyranose unit, and study of the properties and possible fields of application of dextran ethers.

The completely substituted methyl ether of dextran had been obtained earlier by repeatedly treating sodium dextranate with methyl iodide or dextran with dimethyl sulphate or methyl iodide in the presence of alkali. This ether has now been obtained[205] by treating dextran acetate, which is soluble in acetone, first with dimethyl sulphate and then with methyl iodide in the presence of silver oxide. A single-stage preparation of the completely substituted methyl ether involves treating dextran in dimethyl sulphoxide with methyl iodide in the presence of the methylsulphonylmethyl carbanion in an atmosphere of nitrogen[206].

In the methylation of dextran with dimethyl sulphate in a homogeneous medium the relative rate constants for the hydroxyls at positions 2–4 are 8 : 1 : 3.5.[207] The probable reason is that the 2-hydroxyl, in the α-position to the glycosidic link and arranged equatorially in the monomer unit of dextran, is more acidic than the hydroxyls at positions 3 and 4. The 3-hydroxyl shows the lowest reactivity also in the methylation of dextran with methyl iodide[55]. Infrared spectra have been published for methyl ethers of dextran of different degrees of substitution[167]. An ethyl ether has been obtained by treating dextran dissolved in 10% caustic soda with ethyl bromide[55,167].

Dextran ethers containing hydroxyalkyl groups—2-hydroxyethyl, 2-hydroxypropyl, 2-hydroxybutyl—can be obtained, according to the patent literature, by the action of compounds containing α-oxide rings or 1,2-halogenohydrin groups on dextran in alkaline medium. Reaction between dextran and epoxides may yield not only the ether but also graft copolymers by interaction of the epoxides with the hydroxy-groups in the alkyls:

$$\text{Dextran}-\text{O}-\text{CH}_2-\text{CH}_2\text{OH} + n\,\text{CH}_2-\text{CH}_2 \rightarrow \text{Dextran}-\text{O}(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2\text{OH}\,.$$

The distribution of alkyl groups in a 2-hydroxyethyl ether obtained by the action of oxiran on dextran dissolved in 0.25% caustic soda has recently been examined[208]. Analysis by gas–liquid chromatography with reference samples of the products of the acid hydrolysis of the ether shows that the alkyls are distributed among positions 2–4 in the proportions 5.8 : 1 : 3.

Preparation of the water-soluble 3-chloro-2-hydroxypropyl ether by treating dextran with epichlorohydrin in the presence of zinc tetrafluoroborate[209]

$$\text{Dextran}-\text{OH} + \text{CH}_2-\text{CH}-\text{CH}_2\text{Cl} \xrightarrow{\text{Zn}(\text{BF}_4)_2} \text{Dextran}-\text{O}-\text{CH}_2-\underset{\text{OH}}{\text{CH}}-\underset{\text{Cl}}{\text{CH}_2}$$

is of considerable interest as a method of introducing reactive chlorohydrin groups into the macromolecule. This ether is the starting material for the preparation of other dextran ethers[210-212] and polymeric medicinals[115,119,121,123,124]. A dextran derivative labelled with radioactive iodine can be obtained by first treating dextran with allyl bromide and then iodinating the resulting allyl ether with radioactive iodine[213,214].

Cyanoethyl and carbamoylethyl ethers of various degrees of substitution have been prepared by nucleophilic addition to dextran of acrylonitrile and acrylamide in the presence of caustic soda[167,168,210,211,215]:

$$\text{Dextran}-\text{OH} + \text{CH}_2=\underset{\text{CN}}{\text{CH}} \rightarrow \text{Dextran}-\text{O}-\text{CH}_2-\underset{\text{CN}}{\text{CH}_2}$$

$$\text{Dextran}-\text{OH} + \text{CH}_2=\underset{\text{O=C-NH}_2}{\text{CH}} \rightarrow \text{Dextran}-\text{O}-\text{CH}_2-\underset{\text{O=C-NH}_2}{\text{CH}_2}\,.$$

Investigation of cyanoethyl ethers of low degrees of substitution has established that cyanoethylation of one of the secondary hydroxyls in a monomer unit of dextran diminishes the rate of cyanoethylation of the other secondary hydroxyls in that unit[55,167]. In the initial stage acrylonitrile reacts mainly with the 2- and 4-hydroxyls[55]. A cyanoethyl ether of degree of substitution 3.0 is crystalline (melting point 80°C)[55], and its crystal structure is improved by heating it in dimethylformamide and then evaporating off the solvent. Data have been published on the sorption of water vapour and the heats of interaction with water and with dimethylformamide for this ether[54], and infrared spectra for cyanoethyl ethers of dextran having various degrees of substitution[167,216].

A trityl ether can be prepared[168,217] by treating dextran with chlorotriphenylmethane in the presence of pyridine:

$$\text{Dextran}-\text{OH} + \text{ClC}(\text{C}_6\text{H}_5)_3 \rightarrow \text{Dextran}-\text{O}-\text{C}(\text{C}_6\text{H}_5)_3\,.$$

An ether has been prepared also with oxan-2-ol[218]. The addition of D-mannose and D-xylose to dextran has been reported[219].

Dextran Ethers containing Ionogenic, Complexing, or Electron-exchange Groups

Increasing interest has been taken during recent years in the preparation, properties, and fields of application of dextran ethers containing ionogenic, complexing, or electron-exchange groups. A considerable number of scientific papers and patents have been published on the preparation and application of the carboxymethyl ether[220-222], obtained by treating dextran with sodium chloroacetate in the presence of caustic soda:

$$\text{Dextran}-\text{OH} + \text{ClCH}_2\text{COONa} \xrightarrow{\text{NaOH}} \text{Dextran}-\text{OCH}_2\text{COONa}\,.$$

The patent literature describes the application in veterinary practice of compounds (probably complex) formed in an alkaline medium between dextran carboxymethyl ether and iron hydroxide (for the treatment of anaemia), as well as cobalt and copper hydroxides. The product obtained from the ether with a basic aluminium salt has been proposed for the treatment of ulcers. The ether can be used also for the preparation of polymeric medicinals[115,119,120,123,124], the production of long acting forms of medicines (tablets), X-ray contrast media, cosmetic preparations, paints and varnishes, and in the foodstuffs industry[9,223,224]. Various methods for preparing derivatives of dextran carboxymethyl ether containing α-amino-acid residues have been studied in detail[225-228].

In the presence of caustic soda dextran reacts with the sultone of 3-hydroxypropanesulphonic acid, chloromethylphosphonic acid, and thi-iran to give the water-soluble

sulphopropyl, dihydroxyphosphinylmethyl, and mercaptoethyl ethers[209,210,229]:

$$\text{Dextran}-OCH_2CH_2CH_2SO_3Na, \quad \text{Dextran}-OCH_2PO(ONa)_2, \quad \text{Dextran}-OCH_2CH_2-SNa$$

The first of these ethers is a strong polyelectrolyte; the second and third ethers possess respectively complexing and electron-exchange properties. The infrared spectra have been published[230]. The sulphopropyl ether exhibits anticoagulant activity, and has been used to obtain polymeric medicinals[115,119-124,231].

Several new water-soluble dextran derivatives containing various ionogenic, complexing, and electron-exchange groups have been prepared[115,121,168,210-212,232] by the action on the 3-chloro-2-hydroxypropyl ether of ammonia, aliphatic amines, aliphatic and aromatic amino-carboxylic acids, hydrazine, sodium sulphide, and other compounds according to the general scheme

$$\text{Dextran}-OCH_2-\underset{OH}{CH}-CH_2Cl \xrightarrow{HX} \text{Dextran}-OCH_2-\underset{OH}{CH}-CH_2X + HCl$$

where X is a molecular residue of one of the above monomeric agents. Water-soluble dextran ethers containing thiocarbamoyl and amidrazone groups, which possess complexing properties, have been prepared[168,213] from the cyanoethyl ether:

$$\text{Dextran}-OCH_2-CH_2CN \xrightarrow{H_2S} \text{Dextran}-OCH_2-CH_2C(=NH)SH$$

$$\text{Dextran}-OCH_2-CH_2CN \xrightarrow{H_2NNH_2} \text{Dextran}-OCH_2-CH_2C(=NH)NH-NH_2 .$$

The infrared spectra of these ethers have been published[219]. The above dextran derivatives, containing various complexing groups and prepared from the 3-chloro-2-hydroxypropyl and cyanoethyl ethers, form water-soluble complexes with several bivalent metals—copper, cobalt, nickel, and mercury—whose stability constants have been given in Ref. 168.

Treatment of dextran in alkaline medium with 1-diethylamino-2,3-epoxypropane and 1-chloro-2-diethylaminoethane yields[233,234] the 3-diethylamino-2-hydroxypropyl and diethylaminoethyl ethers

$$\text{Dextran}-O-CH_2-\underset{OH}{CH}-CH_2-N(C_2H_5)_2, \quad \text{Dextran}-O-CH_2CH_2-N(C_2H_5)_2 .$$

The diethylaminoethyl ether has been quaternised with benzyl chloride[235]. Dextran ethers containing primary and tertiary aliphatic amino-groups have been investigated by potentiometric titration[121,236-238]. Viscosity measurements on solutions of carboxymethyl, diethylaminoethyl, and quaternised diethylaminoethyl ethers of dextran at various ionic strengths[137] suggest that the ether macromolecules are very flexible. A water-soluble ether containing aromatic amino-groups has been prepared[210] by treating dextran in alkaline medium with the sulphuric ester of 2-(3-amino-4-methoxyphenylsulphonyl)ethanol:

$$\text{Dextran}-OH + NaO_3SOCH_2-CH_2-O_2S-C_6H_3(NH_2)(OCH_3) \xrightarrow{Na_2CO_3}$$

$$\rightarrow \text{Dextran}-OH + CH_2=CH-SO_2-C_6H_3(NH_2)(OCH_3) \xrightarrow{NaOH}$$

$$\rightarrow \text{Dextran}-OCH_2CH_2SO_2-C_6H_3(NH_2)(OCH_3) .$$

The resulting 2-(3-amino-4-methoxyphenylsulphonyl)ethyl ether was used for the preparation of graft copolymers of dextran[214,239,240]. Dextran reacts also with chlorotrialkyl(aryl)silanes and hexa-alkyldisilazanes[241].

Several workers have shown that the diethylaminoethyl ether of dextran enhances interferon formation and antiviral activity caused by the introduction of polynucleotides into animals or into a cellular culture[242-244]. Pretreatment of the cells (before introduction of polynucleotides) with the diethylaminoethyl ether also increases viral resistance. The 3-diethylamino-2-hydroxypropyl ether of dextran possesses similar properties[245]. Nevertheless, the diethylaminoethyl ether increases the infective activity of viruses[246-249]. The reasons for these phenomena are firstly that this dextran ether protects nucleic acids and polynucleotides (by forming compounds with them) from the degrading action of nucleases and secondly that it promotes penetration of polynucleotides and nucleic acids into the cells by reacting with the cell membrane[242,246,248-250]. However, it has been stated[251,252] that dextran diethylaminoethyl ether is also able to suppress the growth of viruses.

VIII. DERIVATIVES WITH A THREE-DIMENSIONAL CROSS-LINKED STRUCTURE

Derivatives of dextran having a three-dimensional cross-linked structure, known under the general name Sephadexes, are obtained by treatment with epichlorohydrin in an alkaline medium[253-256]. Intermolecular bonds are formed by the reactions

$$\text{Dextran}-OH + CH_2-\underset{O}{CH}-CH_2-Cl \xrightarrow{NaOH}$$

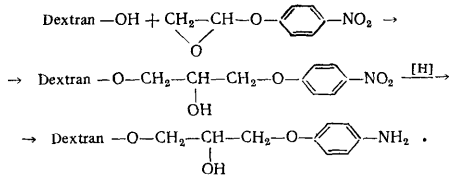
$$\rightarrow \text{Dextran}-O-CH_2-\underset{OH}{CH}-CH_2-O-\text{Dextran} .$$

Sephadexes of different degrees of cross-linking, differing in gel pore size and in ability to swell in water, are obtained by varying the reactant concentrations and also the molecular weight of the dextran. Several brands of Sephadex G are marketed at the present time, and are widely used in gel permeation in aqueous media for preparative and analytical purposes[257-260]. Other cross-linking agents suitable for application to dextran are glycidyl tetramethylene ether[261] and 1,2 : 3,4-diepoxybutane[256]. Cross-linked dextran derivatives can be used in perfumery and cosmetics[262].

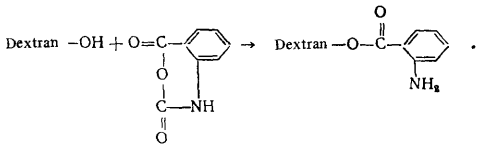
Alkylation or acylation of the hydroxy-groups of the dextran macromolecules in Sephadexes yields derivatives which swell well in organic solvents while retaining the ability to fractionate substances according to molecular dimensions. The hydroxyls of the dextran can be blocked by subjecting Sephadexes to acetylation[263,264], benzoylation[265], methylation[266], or treatment with aliphatic isocyanates[267] or aliphatic α-oxides[268]. Thus Sephadex LH-20 is Sephadex G-25 treated with an aliphatic epoxide.

Cross-linked dextran derivatives have been obtained containing aminoethyl[269], sulphoethyl[270] and sulphopropyl, carboxymethyl[270,271], diethylaminoethyl[270,272], and quaternary ammonium groups[273]; the last four are marketed under the respective names SP, CM, DEAE, and QAE Sephadexes[274]. These Sephadexes possess ion-exchange properties and are widely used for the separation of biologically active substances such as proteins, hormones, nucleic acids, etc.

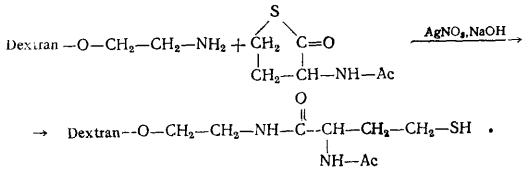
Cross-linked dextran ethers containing aromatic amino-groups have been prepared in three ways. Firstly, treatment of a cross-linked dextran derivative with 1,2-epoxy-1-*p*-nitrophenoxypropane is followed by reduction of the nitro-groups to amino[275,276]:



The second method consists in reaction between a cross-linked dextran derivative and the sulphuric ester of 2-(3-amino-4-methoxyphenylsulphonyl)ethanol[277]. Thirdly, carbon dioxide is evolved when dextran is treated with *N*-carboxyanthranilic anhydride[278]:



A derivative containing isothiocyanato-groups was obtained by treating a cross-linked 3-*p*-aminophenoxy-2-hydroxypropyl ether of dextran with thiocarbonyl chloride[275]. These polymers, containing isothiocyanato- or aromatic amino-groups, are used to prepare insoluble derivatives of enzymes and antibodies. A cross-linked dextran derivative containing mercapto-groups was prepared[269] by the reactions



This polymer can be used to prevent the oxidation of compounds containing thiol groups[279,280].

A cross-linked dextran derivative containing an organomercury residue (which can be used to isolate proteins containing thiol groups) has been obtained[281] by alkylating dextran with 1-allyloxy-2,3-epoxypropane and then treating with mercury acetate. Patents and scientific papers[282-284] have reported the preparation of cross-linked dextran derivatives possessing complexing properties. An insoluble cross-linked dextran derivative coloured with a reactive dye can be used as substrate in studying the activity of enzymes that hydrolyse dextran[261]. The rate of oxidation of Sephadexes by periodic acid is not much lower than the rate of oxidation of dextran in solution[285].

IX. PREPARATION OF GRAFT COPOLYMERS OF DEXTRAN

Graft copolymers of dextran have been obtained with carbon-chain polymers, starch, polypeptides, and biologically active proteins (enzymes, antigens, and hormones). Detailed investigations of the preparation of graft copolymers with polyacrylic acid and with poly-2-methyl-5-vinylpyridine used as initiators redox systems in which the oxidants were cerium(IV) or vanadium(V) compounds and the reductants respectively dextran or its 2-(3-amino-4-methoxyphenylsulphonyl)ethyl ether[214,239,240]. These methods of preparation enabled the length of the grafted chain to be controlled, and water-soluble graft copolymers of dextran with polyacrylic acid or with poly-2-methyl-5-vinylpyridine containing up to 30–40% of the grafted polymer to be obtained without accompanying formation of a carbon-chain homopolymer.

These methods are characterised by high reaction velocities, the formation of comparatively short grafted chains, and a high degree of involvement of macromolecules of the 2-(3-amino-4-methoxyphenylsulphonyl)ethyl ether of dextran (up to 70% in the grafting of polyacrylic acid), which are explained by the occurrence of copolymerisation in a homogeneous medium. Cerium(IV) compounds have been used to initiate the graft copolymerisation of comparatively short polyacrylamide chains with dextran[286]. A graft copolymer of dextran and poly(methyl methacrylate) has recently been synthesised by anionic polymerisation involving treatment of a dextranate with methyl methacrylate in the presence of dimethyl sulphoxide[287]. A graft copolymer of dextran and polytyrosine is obtained by treating the aminoethyl ether of dextran with the anhydride of *N*-carboxy-L-tyrosine[288]. Graft copolymers of dextran and polypeptides have been obtained also by treating sodium dextranate with anhydrides of other *N*-carboxy-*α*-amino-acids[184], by reaction between the carboxymethyl ether of dextran and a peptide in the presence of dicyclohexylcarbodi-imide, and by acylating dextran with a succinyloligopeptide in the presence of dicyclohexylcarbodi-imide[289].

The starting material in the preparation of a graft copolymer with starch is a cyclic carbonate obtained by treating dextran with chloroform, whose ester groups react with starch[290]. The addition of insulin to dextran pretreated with cyanogen bromide is of great interest[291,292]. The activity of the relatively non-toxic water-soluble product is closely similar to that of the original insulin both *in vitro* and *in vivo*; its immunochemical activity is less than that of free insulin, but the lipoglycaemic action is stronger and more prolonged. A graft copolymer of dextran and insulin (when injected in smaller doses than the original insulin) induced the formation of several enzymes in the liver of animals suffering from diabetes. Yet other workers state[293] that the biological activity of the insulin derivative obtained in this way is considerably below that of the initial insulin.

During recent years increasing interest has been aroused by the preparation of insoluble derivatives of biologically active proteins (enzymes, antigens, antibodies), which can be used as specific catalysts, immunosorbents, or sorbents for affinity chromatography[294-298]. Starting materials used for the addition of enzymes have been cross-linked dextran derivatives containing carboxyl[299], diethylaminoethyl[300,301], or isothiocyanate[275,276] groups or aromatic amino-groups[302,303], as well as Sephadexes treated with phenyl isocyanate[304] or cyanogen bromide[305-310]. In these insoluble derivatives the enzyme macromolecules are attached to the dextran macromolecules by ionic[300,301] or covalent[275,276,302-310] bonds.

Interesting results have been obtained[309] showing that the activity of trypsin added to Sephadex pretreated with cyanogen bromide is 15–35% of that of the original enzyme; but if the dextran in this compound is subjected to enzymic hydrolysis with dextran glucosidase, the activity of the resulting water-soluble trypsin derivative is 60–100% of the original. This technique can probably be widely used

in the future to analyse the reasons for the decrease in activity of enzymes attached to insoluble dextran derivatives. A graft copolymer of cross-linked dextran and trypsin can be used[310] to isolate the ovomucoid glycoprotein by affinity chromatography. The properties of nucleases can be improved by addition to soluble dextran derivatives[311].

Table 1. Reactions used to obtain medicinal polymers based on dextran and its derivatives. (D = dextran macromolecule; M = residue of medicinal molecule; DCCD = dicyclohexyldi-imide).

1. $D{-}OH + C(=O)(OH){-}M \rightarrow D{-}O{-}C(=O){-}M$[121,322];

2. $D{-}OH + Cl{-}C(=O){-}M \rightarrow D{-}O{-}C(=O){-}M$[9,175,323,324];

3. $D{-}OH + HOOC{-}M \xrightarrow{DCCD} D{-}O{-}C(=O){-}M$[289];

4. $D{-}COOH + H_2N{-}M \rightarrow D{-}COO^-(H_3\overset{+}{N}{-}M)$[116,121];

5. $D{-}OSO_3Na + HCl \cdot H_2N{-}M \rightarrow D{-}OSO_3^-(H_3\overset{+}{N}{-}M)$[160,325–328];

6. $D{-}OCH_2CH_2CH_2SO_3H + H_2N{-}M \rightarrow D{-}OCH_2CH_2CH_2SO_3^-(H_3\overset{+}{N}{-}M)$[115,119–121,123,124,231];

7.* $D{-}O{-}CH_2CH_2SO_3H + H_2N{-}M \rightarrow D{-}O{-}CH_2CH_2SO_3^-(H_3\overset{+}{N}{-}M)$[329];

8. $D{-}OCH_2COOH + H_2N{-}M \rightarrow D{-}O{-}CH_2COO^-(H_3\overset{+}{N}{-}M)$[115,119–121,123,124];

9. $D{-}O{-}CH_2{-}CH(OH){-}CH_2{-}\overset{+}{N}(C_2H_5)_3\,\overline{O}H + HOOC{-}M \rightarrow$

$\rightarrow D{-}O{-}CH_2{-}CH(OH){-}CH_2{-}\overset{+}{N}(C_2H_5)_2(\overline{O}OC{-}M)$[115,123,124];

10*. $D{-}O{-}CH_2CH_2{-}N(C_2H_5)_2 + HO_3S{-}M \rightarrow$

$\rightarrow D{-}O{-}CH_2{-}CH_2{-}\overset{+}{N}(C_2H_5)_2(O_3\bar{S}{-}M)$[330];

11. $D{-}O{-}CH_2{-}C(=O){-}O{-}C(=O){-}O{-}C_2H_5 + H_2N{-}M \rightarrow D{-}O{-}CH_2{-}C(=O){-}NH{-}M$[120,121]

12. $D{-}O{-}CH_2{-}COOH + H_2N{-}M \xrightarrow{DCCD} D{-}O{-}CH_2{-}C(=O){-}NH{-}M$[288];

13. $D{-}O{-}CH_2{-}CH(OH){-}CH_2Cl + H_2N{-}M \rightarrow D{-}OCH_2{-}CH(OH){-}CH_2{-}NH{-}M$[116,119,121,123,124]

14. $D{-}O{-}CH_2{-}CH(OH){-}CH_2{-}NH{-}C_2H_4{-}OH + H_2CO + H_2N{-}C(=O){-}M \rightarrow$

$\rightarrow D{-}O{-}CH_2{-}CH(OH){-}CH_2{-}N(CH_2{-}NH{-}C(=O){-}M){-}C_2H_4OH$[115,123,124];

15. $D{-}Cl + H_2N{-}M \rightarrow D{-}NH{-}M$[116];

16. $D{-}NH_2 + H_2CO + H_2N{-}C(=O){-}M \rightarrow D{-}NH{-}CH_2{-}NH{-}C(=O){-}M$[218];

17. $D{-}C(H)=O + H_2N{-}M \rightarrow D{-}C(H)=N{-}M$[115,118–124,231,232];

18. $D{>}C=O + H_2N{-}M \rightarrow D{>}C=N{-}M$[115];

19. $D{-}OR{-}C_6H_4{-}CH(=O) + H_2N{-}M \rightarrow D{-}O{-}R{-}C_6H_4{-}CH=N{-}M$[116].

* Dextran derivatives having a three-dimensional cross-linked structure are used in reactions 7 and 10.

When an animal is immunised by the hypodermic, intramuscular, or intraperitoneal injection of an insoluble graft copolymer of cross-linked dextran and an antigen, the synthesis of antibodies in the organism lasts longer than on immunisation with a soluble antigen[312,313]. A repeat immunisation with a soluble antigen of an animal previously injected with the above graft copolymer caused extraordinarily intense production of antibodies, in numbers exceeding by factors of 10–20 those formed if the first immunisation had been made with a soluble antigen. This work established that the injected insoluble graft copolymer of dextran and antigen is gradually absorbed, probably by the action of dextran glucosidase present in the animal organism.

X. DERIVATIVES CONTAINING ATTACHED MEDICINALS

During the past decade the achievements of the chemistry of macromolecular compounds have been used ever more frequently and widely in the solution of medical problems[314–321]. An urgent line of research is the synthesis of polymeric medicinals by attaching drugs of low molecular weight to water-soluble or -insoluble polymers.

Table 2. Brief summary of effects achieved by the attachment of medicinals of low molecular weight to dextran.

Reaction	Dextran derivative	Medicinal	Effect	Ref.
1	Dextran	pelentan	water solubility	121, 322
2	Dextran	aspirin	less toxic	175
2	Dextran	nicotinic acid	prolongation	9
3	Dextran	oligopeptide analogue of eledoisin	prolongation	289
5	Sulphate	streptomycin, neomycin	prolongation, increased concn. in lymphatic system	160, 325
5	Sulphate	mitomycin	increased antitumour activity	326
6	Sulphopropyl ether	cystamine	prolongation, more effective	121, 231
7	Cross-linked sulphoethyl ether	papaverine, codeine	better taste, less toxic	329
8	Carboxymethyl ether	Tubazid	prolongation	119, 121
8	Carboxymethyl ether	kanamycin	prolongation	115
11	Carboxymethyl ether	serotonin	less toxic	120, 121
12	Carboxymethyl ether	peptide analogue of eledoisin	prolongation	289
17	Dialdehydo	kanamycin	prolongation	115
17	Dialdehydo	Tubazid	prolongation, less toxic	119, 121, 122
17	Dialdehydo	serotonin	prolongation, less toxic	120, 121
17	Dialdehydo	4-methylthiosemi-carbazide	antitumour activity	331
17*	Dextran	tetracycline	prolongation	333, 334
17*	Dextran	thyrocalcitoin hormone	prolongation	335

* Probably complex compounds.

The purpose is to improve the properties of the drugs—to prolong their action and enhance their activity, lower the toxicity, change the distribution in the organism, improve solubility, and increase stability to the action of enzyme systems in the organism that tend to destroy them.

In the preparation of polymeric medicinals for introduction into the organism, especially by injection, it is necessary to take into account the ability of the polymer to be assimilated in the organism and to be isolated from

the latter after fulfilling its functions. From this point of view the use of dextran for the production of physiologically active polymers is of considerable interest, as it is gradually hydrolysed by enzymes in the organism, which eliminates the danger of accumulation of the polymer in the tissues of various organs. The gradual enzymic cleavage of dextran in the organism may not permit the action of drugs to be prolonged to the extent achieved by the use of synthetic carbon-chain polymers, which are not broken down in the organism, but in many cases this is not required: it is sufficient to increase the period of action of the medicinals to a few hours or days. Table 1 lists the reactions used to obtain medicinal polymers based on dextran. Table 2 summarises the information in the scientific literature on the effects achieved by the chemical attachment of drugs of low molecular weight to derivatives of dextran.

Several workers have shown that the nature of the chemical bond between the dextran derivative and the attached medicinal has a significant influence on the biological properties of the resulting medicinal polymer, e.g. on the antibacterial activity of polymeric derivatives of isonicotinohydrazide[119,121] and antibiotics (kanamycin, ampicillin, tetracyclines)[115,123,124], and on the toxicity of polymeric derivatives of serotonin[120,121]. Available experimental results show that attachment to dextran and its derivatives can be regarded as a method for improving the properties of medicinal drugs.

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