its three hydroxyl groups can possibly chelate with a metal ion. The *cis*-axial orientation of these two hydroxyls, located at C-2 and C-4, and the inflexibility of the carbohydrate ring appear to favor high complex stability and, consequently, a high M_R value. *cis*-Inositol (II), which has hydroxyl groups similarly positioned and oriented, is known to have exceptional mobility in *aqueous* solutions of alkali metal salts.[11]

Mills[11] has shown that carbohydrates such as aldoses and alditols have low migration rates in aqueous solutions of alkali metal salts. The order of decreasing effectiveness in promoting carbohydrate movement was $Na^+ > K^+ > Li^+ > NH_4^+$. Present studies in *alcoholic* media show an almost identical order, $Na^+ > K^+ > NH_4^+ > Li^+$, but the migration rates are greater in alcoholic than in aqueous media.

The ease with which carbohydrates complex with alkali metal cations in alcohol, relative to their ease of complexing in water, may be biologically significant. The environment in cell walls undoubtedly is largely nonaqueous, which condition favors the formation of complexes between polyhydroxy compounds and alkali metal cations.

Polarimetric Studies.—The effect of dissolved alkali metal salts upon the optical rotation of carbohydrates is greater in alcohol than in water, the influence increasing in the order water < methanol < ethanol. Wiklund[12] and Ramaiah and Vishnu[13] made use of Job's principle[14] and the property of optical rotation to show that the predominant combining ratio for adducts formed in homogeneous *aqueous* solution from the reaction of various alkali metal halides with either sucrose or D-fructose is 1:1. Wiklund also observed the formation of a 1:1 adduct from sodium acetate and sucrose. In the present study, methyl β-D-glucopyranoside and potassium acetate were chosen as reactants because of their relatively high solubilities in ethanol.

According to Job's principle, at a fixed combined molar concentration of salt and carbohydrate, the change in optical rotation effected by a salt is maximal when the ratio of total carbohydrate (free and complexed) to total salt in the solution equals the ratio of carbohydrate to salt in the adduct. Ethanolic solutions were thus prepared in which the mole fraction of salt varied from zero to one. The combined concentration of carbohydrate and salt was 0.3 *M* in each solution. The optical rotation was measured rapidly because the majority of the solutions were metastable. After the measurements, the solutions were shaken to induce precipitation. Precipitates from those solutions with carbohydrate-to-salt ratios of 1:1 and 4:1 were isolated and found to be 1:1 adducts. The polarimetric analyses, given in Table III, indicate that predominantly a 1:1 adduct is formed in homogeneous ethanolic solution, in complete harmony with the fact that only a 1:1 adduct was isolated under two widely differing sets of concentration conditions.

Unfortunately low carbohydrate solubility precludes a similar study of α-D-glucose and sucrose. Each of these compounds is capable of forming adducts of 1:1 and 2:1 carbohydrate-to-salt ratio.

Acknowledgment.—The author is indebted to Mr. J. E. Hodge for general supervision and to Mrs. Clara E. McGrew and Mrs. Bonita Heaton for the microanalyses.

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[14] P. Job, *Ann. Chim.*, **9**, 113 (1928).

Alkali Metal Complexes of Carbohydrates. II. Interaction of Bases with Carbohydrates in Alcoholic Media[1]

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Received September 20, 1965

Reaction between alkali metal hydroxides and carbohydrates in anhydrous alcoholic media at 25° produces isolable carbohydrate alcoholates, probably chelates. A minor fraction of the product appears to be a carbohydrate–alkali metal hydroxide adduct. Adducts are produced exclusively if the reaction medium contains 10% or more water. Some adducts can be thermally converted to alcoholates, provided the carbohydrate moiety does not simultaneously decompose. Under the proper conditions, most alcoholates combine with one or, in rare instances, two additional molecules of carbohydrate. Reactions that produce carbohydrate–metal hydroxide adducts show a stoichiometry of even greater variability. Combining ratio is a function of cation radius, hydroxide concentration, and carbohydrate geometry. Alkali metal cyanides react with carbohydrates in ethanolic media to give a mixture of carbohydrate alcoholate and carbohydrate–metal cyanide adduct. The alcoholate predominates. Sodium 1-butoxide, prepared from sodium hydroxide and 1-butanol by removing water of formation by azeotropic distillation, reacts with methyl α-D-glucopyranoside in refluxing 1-butanol to give the monosodium alcoholate.

The reaction of simple carbohydrates with alkali metal hydroxides and alkoxides in alcoholic and aqueous alcoholic media has been described often in the literature. In only a few instances has there been any degree of certainty regarding the composition of the isolated reaction product. Various investigators have described the products from reactions with hydroxides as either alcoholates (carbohydrate salts formed by the loss of one or more hydroxylic protons)[3] or carbohydrate–metal hydroxide adducts. With one possible exception, no one has ever offered sufficient evidence to permit the two types of product to be differentiated.

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[1] Part I: J. A. Rendleman, Jr., *J. Org. Chem.*, **31**, 1839 (1966).

[2] This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

[3] The term "alcoholate" is used rather than "alkoxide" to differentiate between the oxyanion of a carbohydrate and that of a monohydric alcohol. In no instance does "carbohydrate alcoholate" signify a carbohydrate solvated with alcohol.

The exception is Wolfrom and El-Taraboulsi,[4] who formed the monosodium alcoholate of methyl α-D-glucopyranoside by refluxing the glucoside with sodium hydroxide in 1-butanol while removing the water of formation by azeotropic distillation. The hydroxide ion was assumed to have reacted directly with the carbohydrate and not with the 1-butanol.

This work was designed to define the extent of each of several possible reactions between carbohydrates and alkali metal bases in anhydrous alcoholic and aqueous alcoholic media. A method of analysis was devised to determine the alcoholate content of products isolated from various alkali metal hydroxide reactions.

Experimental Section

Solvents.—For electrophoretic studies and for general preparative work, commercial absolute ethanol (0.04% water) and reagent grade methanol (0.05% water) were used without further purification. For near-infrared studies, more anhydrous ethanol (0.003% water) was employed. 2-Pyrrolidinone, *N*-methyl-2-pyrrolidinone, and 1-butanol were anhydrous and distilled before use; ether and ethyl acetate were anhydrous and reagent grade.

Inorganic reactants were sodium hydroxide (97.4%, Baker[5] reagent grade), potassium hydroxide (86.1%, Baker reagent grade), lithium hydroxide (prepared by dehydrating $LiOH \cdot H_2O$ at 150° under vacuum), cesium hydroxide (an ethanolic solution prepared by dissolving cesium metal in absolute ethanol and then adding the calculated amount of water necessary to convert the ethoxide to hydroxide), sodium cyanide (97.9%, Baker reagent grade), potassium cyanide (95%, Baker reagent grade), and permanganate–periodate spray reagent.[6]

Organic Reactants.—α-D-Glucose and sucrose were National Bureau of Standards' samples of the highest purity. All other compounds were the purest available. Carbohydrates possessing water of hydration were dehydrated under vacuum at a temperature at or below the melting point. Anhydrous tartaric acid was Mallinckrodt reagent grade.

Analyses.—Standard microanalytical methods were employed for metal, nitrogen, and alkoxyl. Metal contents of alcoholates and of carbohydrate–metal hydroxide adducts were often determined by titration with standard hydrochloric acid and methyl red indicator. Cyanide ion was determined by silver nitrate titration. Butoxide ion (butoxyl) was determined by first dissolving a sample of complex in water and removing the resulting butanol by azeotropic distillation and then analyzing the distillate for alkoxyl by the method of McGrew and VanEtten.[7]

The difference between total alkali metal and unreacted hydroxide ion was assumed to represent alcoholate content. Hydroxide ion was found by a modified Karl Fischer analysis in which the complex was treated with anhydrous tartaric acid (reaction 6, Results and Discussion) and the water of formation was titrated with Karl Fischer reagent. For example, a weighed sample of complex (0.5–1.0 g) was dissolved in 50 ml of absolute methanol in a nitrogen-flushed 50-ml volumetric flask, and an excess of tartaric acid (usually about 1 g) was added to convert hydroxide ion to water. The entire mixture was then titrated with standard Karl Fischer reagent. The volume of reagent consumed by this mixture, less the volume consumed by a blank (tartaric acid in methanol), was assumed to be proportional to the hydroxide ion content of the unknown sample.

Near-infrared spectra of alcoholic solutions containing hydroxide or water, or both, were obtained in quartz cells 1 cm long in a Cary recording spectrophotometer, Model 14, containing a lead sulfide detector and a tungsten lamp source. The region between 1.8 and 2.0 μ was scanned.

Preparation of Alcoholate Complexes. A. Reaction of Carbohydrates with Hydroxides in Ethanolic Media. General Procedure.—A weighed sample of carbohydrate was first dissolved in a small volume of 2-pyrrolidinone or *N*-methyl-2-pyrrolidinone. Often a little ethanol was added to make the mixture less viscous. An ethanolic solution of alkali metal hydroxide was then added dropwise with stirring (see Results and Discusson for effects of hydroxide concentration on stoichiometry). When the complex was completely soluble under these conditions, precipitation was effected by adding ether or ethyl acetate to the reaction medium either before or after addition of hydroxide. Care was taken not to create a condition in which carbohydrate or metal hydroxide would coprecipitate with the complex. Precipitates were separated by filtration or centrifugation, washed with ethanol or with an ethanol–ether or ethanol–ethyl acetate mixture (depending upon complex solubility), and finally dried at 25° under 1-mm pressure for 16 hr. No special precautions were necessary to protect the complex during its preparation when the atmosphere was relatively dry and the operations could be performed rapidly. Otherwise, an inert atmosphere of dry nitrogen was used.

Yields varied according to the carbohydrate employed. Most aldohexoses and oligosaccharides were precipitated 95% or better by reaction with a stoichiometric amount of alkali metal hydroxide in ethanolic solution. Yields with aldopentoses were lower, but could be improved by the addition of ether or ethyl acetate to the reaction medium. In general, precipitation of a complex diminished with decreasing number of hydroxyl groups.

An isolated complex usually retained a small amount of alcohol of solvation, even after being vacuum dried for 16 hr at 25° (see Table I). Nitrogen analysis showed that 2-pyrrolidinone and *N*-methyl-2-pyrrolidinone were not retained.

B. Reaction of Methyl α-D-Glucopyranoside with Sodium Hydroxide in 1-Butanol.—A hot solution of methyl α-D-glucopyranoside (30 mmoles) in 1-butanol (160 ml) was added to a solution of sodium hydroxide (38 mmoles) in 1-butanol (40 ml). The resulting mixture was refluxed under a dry nitrogen atmosphere until all water of formation had been removed by azeotropic distillation (volume of distillate, 90 ml). After the reaction mixture had cooled, a portion of the solid was removed, washed with 1-butanol, and dried under vacuum at 25° for 16 hr.

Anal. Found: total alkoxyl (as methoxyl, Zeisel), 16.84; butoxyl, 6.7; Na (by acidimetry), 8.16; equiv wt (based on Na), 282.

This analysis indicates 1.24 moles of glucoside (ROH) and 0.26 mole of butoxyl/g-atom of sodium, and suggests the composition $0.74(NaOR \cdot 0.24ROH) \cdot 0.26(NaOBu \cdot 1.24ROH)$.

Reaction of hydroxide and glucoside in exactly equimolar amounts (30 mmoles), and under the same conditions used above, gave a product that, after being dried under vacuum at 70° for 3 hr, contained 1.31 moles of glucoside and 0.21 mole of butoxyl/g-atom of sodium. Further heating at 70° under vacuum reduced the butoxyl content to 0.12 mole/g-atom of sodium.

C. Reaction of Methyl α-D-Glucopyranoside with Sodium 1-Butoxide in 1-Butanol.—A hot solution of methyl α-D-glucopyranoside (30 mmoles) in 1-butanol (65 ml) was added to a warm butanolic solution of sodium 1-butoxide prepared by refluxing a solution of sodium hydroxide (37 mmoles) in 1-butanol (150 ml) and removing all water of formation by azeotropic distillation (volume of distillate, 100 ml). The glucoside–butoxide mixture was refluxed gently for 45 min and then allowed to cool and solidify. All operations were carried out under a protective atmosphere of dry nitrogen. A portion of the reaction product was subsequently washed with 1-butanol and dried at 25° under vacuum for 16 hr.

Anal. Found: total alkoxyl (as methoxyl, Zeisel), 15.88; butoxyl, 7.5; Na (by acidimetry), 8.18; equiv wt (based on Na), 281.

This analysis indicates 1.23 moles of glucoside (ROH) and 0.28 mole of butoxyl/g-atom of sodium, and suggests the composition $0.72(NaOR \cdot 0.23ROH) \cdot 0.28(NaOBu \cdot 1.23ROH)$.

D. Reaction of Carbohydrates with Sodium Cyanide in Ethanol. α-D-Glucose.—To a solution of α-D-glucose (0.20 g, 1.1 mmoles) in 3 ml of *N*-methyl-2-pyrrolidinone was added, dropwise, 11 ml (0.55 mmole) of 0.05 *M* sodium cyanide in ethanol. Ether (5 ml) was then added to increase the yield of precipitated product. The colorless, powdery precipitate was separated, washed with a 2:1 ether–ethanol mixture, and dried for 2 hr under vacuum at 25°: yield 0.13 g.

Anal. Calcd for $0.88(NaOR \cdot 1.2ROH) \cdot 0.12(NaCN \cdot 2.2ROH) \cdot 0.24EtOH$, where ROH = D-glucose: cyanide, 0.72; Na, 5.31; ethoxyl, 2.50. Found: cyanide, 0.76; Na, 5.41; ethoxyl, 2.51.

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[4] M. L. Wolfrom and M. A. El-Taraboulsi, *J. Am. Chem. Soc.*, **75**, 5350 (1953).

[5] The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

[6] R. U. Lemieux and H. F. Brown, *Anal. Chem.*, **26**, 920 (1954).

[7] Clara McGrew and C. H. VanEtten, *J. Assoc. Offic. Agr. Chemists*, **43**, 772 (1960).

D-Glucitol.—Reaction of sodium cyanide with D-glucitol according to the procedure used for α-D-glucose gave a colorless, powdery solid: yield 0.08 g.

Anal. Calcd for $0.63(NaOR \cdot 0.9ROH) \cdot 0.37(NaCN \cdot 1.9ROH) \cdot 1.6EtOH$, where ROH = D-glucitol: cyanide, 2.13; Na, 5.09. Found: cyanide, 2.10; Na, 5.10.

It was assumed that there are 1.6 molecules of solvation per atom of Na.

Preparation of Alkali Metal Hydroxide–Carbohydrate Adducts.—The method of preparing hydroxide adducts is similar to that of preparing alcoholates, except that water is used in place of 2-pyrrolidinone or *N*-methyl-2-pyrrolidinone to dissolve the carbohydrate. Sufficient water is employed to make the final reaction mixture, after addition of hydroxide, at least 10% water by volume. A description of the preparation of the following sucrose–sodium hydroxide adducts should serve to illustrate the general preparative techniques and the effect of hydroxide concentration on combining ratio.

$NaOH \cdot 2$Sucrose.—To a rapidly stirred solution of sucrose (3.4 g, 10 mmoles) in 4 ml of water was added, dropwise, 120 ml (4.8 mmoles) of 0.04 *M* NaOH in 95% ethanol. The precipitate, an amorphous solid, was separated by decantation of the supernatant mother liquior, washed twice with 3-ml portions of absolute ethanol and once with 20 ml of ether, and then dried at 25° under 1-mm pressure for 20 hr.

Anal. Calcd for $NaOH \cdot 1.7$sucrose$\cdot 0.3H_2O$: Na, 3.67. Found: Na, 3.70; equiv wt (based on Na), 622; combined NaOH and H_2O of hydration (by modified Karl Fischer analysis), 1.3 moles/g-atom of Na.

Sucrose$\cdot$5NaOH.—To a solution of sucrose (1.03 g, 3.0 mmoles) in 0.5 ml of water was added a solution of sodium hydroxide (1.6 g, 40 mmoles) in 2.5 ml of water. The resulting mixture, a homogeneous solution, was treated with ethanol (15 ml) to effect precipitation of adduct. The precipitate, a heavy viscous liquid, was washed several times with 10-ml portions of ethanol and then once with 5 ml of ether. The adduct became an amorphous white solid upon being dried at 25° under 1-mm pressure for 20 hr.

Anal. Calcd for sucrose$\cdot 5NaOH \cdot H_2O$, assuming ethanol of solvation is negligible: Na, 20.5; $NaOH + H_2O$, 1.20 moles/g-atom of Na. Found: Na, 20.3; equiv wt (based on Na), 113; combined NaOH and H_2O (by modified Karl Fischer analysis), 1.15 moles/g-atom of Na; ethanol of solvation, 1.74.

Electrophoresis.—The procedure was identical in nearly all respects with the one used previously for carbohydrate–salt interactions.[1] The electrophoretic behavior of various carbohydrates was studied on glass fiber paper in 0.3 *M* solutions of sodium hydroxide and lithium hydroxide in absolute alcohol. Electroosmotic movement in these solutions is toward the anode and was assumed to occur at a rate equal to the rate of movement of the nonmigrating marker, chrysene. A potential of 15 v/in. was employed. Salicylaldehyde was at all times visible during electrophoresis, because of its yellow color; carbohydrate spots were disclosed by spraying the dried paper with permanganate–periodate reagent.

Results and Discussion

Alkali Metal Hydroxides in Anhydrous Alcoholic Media.—In anhydrous alcoholic media, the hydroxides (MOH) of lithium, sodium, potassium, and cesium react rapidly with simple "nonacidic" carbohydrates (ROH) at room temperature to give colorless, amorphous, hygroscopic precipitates that are preponderantly mono(alkali metal) carbohydrate alcoholates (reaction 1). Under the proper concentration conditions, most

$$MOH + ROH \rightleftharpoons H_2O + MOR \qquad (1)$$

$$MOR + nROH \rightleftharpoons MOR \cdot nROH \; (n = 1, 2) \qquad (2)$$

$$MOH + nROH \rightleftharpoons MOH \cdot nROH \; (n = 1, 2, \text{ and possibly } 3) \qquad (3)$$

$$MOR \cdot nROH + H_2O \rightleftharpoons MOH \cdot (n + 1)ROH \; (n = 0\text{–}2) \qquad (4)$$

$$MOR \cdot nROH + H_2O \rightleftharpoons MOR \cdot nROH \cdot H_2O \; (n = 0\text{–}2) \qquad (5)$$

metal alcoholates combine with an additional molecule of carbohydrate to give products whose molar ratios of carbohydrate:alkali metal are 2:1 (reaction 2). Ratios of 3:1 or approximately 3:1 have been obtained in a few instances. In this report, all carbohydrate alcoholates, regardless of molar ratio, are considered to be chelates, because of the great probability that a metal ion associated with an anionic oxygen atom is chelated to neighboring donor groups (hydroxyl or carbonyl) within the same carbohydrate moiety. Chelation should increase the stability of an alcoholate anion and thereby act as a driving force to enhance the formation of alcoholate.

A small percentage (generally about 15%) of each isolated complex is either a carbohydrate–alkali metal hydroxide adduct (reactions 3 and 4) or a monohydrated alcoholate (reaction 5). Unfortunately, there is no known method for distinguishing between the two. At present, the hydrate seems to be the less likely because of the improbability of a water molecule remaining attached to a metal alcoholate in an almost anhydrous alcoholic medium. Even lithium hydroxide and sodium hydroxide, both of which have strong affinities for water, can be isolated in an anhydrous state by evaporation of their 10% aqueous ethanolic solutions at 25° under vacuum. The existence of an alcoholate hydrate seems especially unlikely in those reactions where the combining ratio of carbohydrate to metal is 2:1 or greater. In a 2:1 complex, the bulkiness of two carbohydrate moieties would act as a great hindrance to the attachment of a water molecule to either the metal ion or the anionic oxygen atom.

The method of analysis devised for determining hydroxide ion in an adduct involves treating the adduct with anhydrous tartaric acid to liberate water (reaction 6). This water, which is equivalent to the hydroxide

$$MOH \cdot nROH + H^+ \longrightarrow M^+ + H_2O + nROH \qquad (6)$$

originally present in the adduct, is then determined by Karl Fischer titration. Obviously a hydrated alcoholate would give the same result.

Carbohydrate acidity (ease of proton release) in alcoholic media appears to have little or no effect upon the ratio of alcoholate to adduct in an *isolated* complex. This apparent lack of effect was shown by the similarity in alcoholate content between alkali metal complexes of D-glucitol, D-glucose, D-mannose, and methyl α-D-glucopyranoside (Table I). This similarity could be caused possibly by greater insolubility or greater chelate stability of the alcoholate form. Reliable information on relative carbohydrate acidities in alcoholic solution is needed for clarification.

Abstraction of hydroxylic protons by hydroxide ions occurs before or during precipitation of complex. That little or no abstraction occurs when the precipitate is dried under vacuum at 25° was shown by examination of both mother liquor and precipitate from a reaction between stoichiometric amounts of D-glucose and sodium hydroxide in an ethanolic medium. Precipitation was almost quantitative; acid titration of a portion of the liquor showed that 99% of the sodium hydroxide had been lost. Quantitative near-infrared analysis of the mother liquor at 1.94 μ showed that 92% of the theoretical yield of water had been formed and released into solution and that only a trace of hydroxide remained. The isolated complex was analyzed by the modified Karl Fischer method (see Experimental Section) and found to consist of 88% al-

TABLE I

COMPOSITION OF VARIOUS ALCOHOLATE COMPLEXES PRECIPITATED FROM ANHYDROUS ETHANOLIC MEDIA

Ligand	Metal cation	Molar ratio, ligand:cation	Compn of complex[a] % alcoholate	% hydroxide adduct	Ethanol of solvation,[b] molecules/cation
D-Arabinose	Na	1.18	87	13	0.2
D-Glucose	Na	2.0	90	10	0.3
D-Glucose	K	1.9	85	15	0.3
D-Mannose	Na	1.16	88	12	0.05
Maltol	K	2.0	97	3	0.07
Methyl α-D-glucopyranoside	Na	1.8	88	12	0.4
Methyl β-D-glucopyranoside	Na	2.3	70	30	Undet
D-Glucitol	Na	1.5	82	18	1.6
D-Glucitol	Li	1.0	88	12	1.4
Sucrose[c]	Na	2.1	80	20	0.2
Sucrose	Na	1.4	77	23	0.2

[a] The assumption is made that the combining ratio for alcoholate is identical with that for hydroxide adduct. [b] Solvent remaining after vacuum treatment at 25° for 16 hr. [c] Use of methanol instead of ethanol gave a 1.8:1 complex that consisted of 70% alcoholate and 30% adduct.

coholate and 12% adduct. The results of analysis of the precipitated complex are in excellent agreement with the results of the liquor analysis.

When an alkali metal hydroxide is dissolved in alcohol, an equilibrium between alkoxide and hydroxide ions is established: $\text{AlkOH} + \text{OH}^- \rightleftharpoons \text{AlkO}^- + H_2O$. No definite conclusions can yet be made with regard to the position of this equilibrium. Some investigators have contended (on the basis of kinetic data) that conversion of hydroxide to alkoxide is nearly complete in ethanol, even in a solution that contains a few percent water.[8] Gas chromatographic analyses now in progress at this laboratory indicate that in a 1 *M* solution of sodium hydroxide in ethanol hydroxide predominates over ethoxide; if the solvent contains 2% water, virtually no ethoxide is formed. Removal of protons from carbohydrates in anhydrous alcoholic media at 25° probably involves attack primarily by hydroxide ions rather than by alkoxide ions, in view of a report by Percival[9] that D-glucose reacts with alkali metal alkoxides under these conditions to form exclusively D-glucose–alkoxide adducts.

Certain noncarbohydrates, such as pentaerythritol and the phenollike kojic acid [5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one], maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one), and salicylaldehyde, react with alkali metal hydroxides in ethanolic media to give salts (alcoholates) of variable combining ratio. Unlike the carbohydrate alcoholates, these salts are crystalline and nonhygroscopic. The salicylaldehyde salts were previously studied by other investigators.[10,11]

A. Combining Ratio.—Maximum carbohydrate: metal ratios for a large number of isolated complexes are given in Table II. Almost all were calculated solely on the basis of acidimetric titration data, with the assumption that "adduct" content and ethanol of solvation are negligibly small. Such an assumption would rarely introduce more than a 10% error in the calculation of a ratio. Retention of a large amount of solvent by the complex is rarely encountered and is governed largely by the nature of the polyhydroxy compound (compare complexes of D-glucitol with those of other compounds in Tables I and II).

The ratio of carbohydrate:metal in an alcoholate complex is a function of several factors: cation radius, concentration of metal hydroxide in the preparative medium, and carbohydrate configuration. At hydroxide concentrations of about 0.05 *M* or less, and where the carbohydrate is present in either stoichiometric or excess amount, ratios approximate maximum values (Table II). These are usually 2:1 for alkali metals other than lithium, although there are exceptions where maximum ratios are 1:1 and 3:1. Lithium alcoholate complexes do not show ratios greater than 1.5:1; many are 1:1.

High hydroxide concentrations lead to smaller ratios. At about 2 *M* concentration, ratios generally approach a minimum of 1:1 for monosacharides and their derivatives. For oligosaccharides, smaller ratios are possible. However, a large fraction of the metal in these low-ratio complexes probably is present as alkali metal hydroxide. Studies of sucrose in the presence of a high concentration of potassium hydroxide indicate that, although the resulting complex contains more than 1 atom of potassium/carbohydrate moiety, no more than 1 hydroxylic proton is removed from the sugar molecule. Ethanolic potassium hydroxide (20%) reacted with sucrose to give a complex of 1:2 carbohydrate:metal ratio. Modified Karl Fischer analysis indicated that less than 1 proton had been given up by each carbohydrate moiety and that the complex had the approximate composition $C_{12}H_{20}O_9\text{–}(OH\cdot KOH)_{1.3}\text{–}(OK)_{0.7}$. Conceivably large molecules with reaction sites (hydroxyl groups) separated by relatively great distances will function as polybasic acids that release 2 or more protons. Gaver[12] claims to have prepared sodium "starchate" by treating starch with alcoholic sodium hydroxide solution. A polysodium alcoholate was presumed to have formed by the release of a proton from each D-glucose residue. No conclusive proof that each sodium was associated with a carbohydrate oxyanion was given.

The ability of a metal alcoholate to accommodate an additional molecule of carbohydrate generally increases with increasing ionic radius, Li < Na < K < Cs. The difference in stoichiometry between lithium and sodium is much greater than that between either sodium and potassium or potassium and cesium.

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(8) R. G. Burns and B. D. England, *Tetrahedron Letters*, **No. 24**, 1 (1960).

(9) E. G. V. Percival, *J. Chem. Soc.*, 1160 (1934).

(10) N. V. Sidgwick and F. M. Brewer, *ibid.*, 2379 (1925).

(11) F. M. Brewer, *ibid.*, 361 (1931).

(12) K. M. Gaver, U. S. Patent 2,397,732 (1946).

TABLE II

MAXIMUM COMBINING RATIOS OF ALCOHOLATE COMPLEXES ISOLATED FROM ANHYDROUS ETHANOLIC MEDIA[a]

	Maximum combining ratio of ligand:cation			
Alcoholate (Ligand)	Li^+	Na^+	K^+	Cs^+
Oligosaccharides				
Melezitose			1.5	
Raffinose	1.4	2.2	2.0	2.0
Cellobiose		1.6		
Maltose			2.0	
Sucrose	1.4	2.1 (0.2 EtOH)	2.1	
α,α-Trehalose			2.3	
Aldoses and ketoses				
Erythrose			2.3[b]	
DL-Glyceraldehyde			2.3[b]	
D-Arabinose		1.2 (0.2 EtOH)	1.9 (0.5 EtOH)	2.3
D-Lyxose		1.8	1.9 (0.3 EtOH)	
D-Ribose		1.7	1.9 (0.3 EtOH)	
D-Xylose		1.9	1.9 (0.3 EtOH)	2.1
D-Galactose			2.3	
D-Glucose	1.5 (no EtOH)	2.0 (0.3 EtOH)	2.0 (0.3 EtOH)	2.0 (0.1 EtOH)
D-Mannose		1.2 (0.1 EtOH)	2.1 (0.4 EtOH)	
L-Rhamnose		1.6		
2-*O*-Methyl-D-glucose		1.9	2.0	
3-*O*-Methyl-D-glucose		2.0	2.3	
D-Fructose		1.5	1.9	2.2
L-Sorbose		2.1	2.2	2.3
Glycosides				
Methyl β-D-xyloside		2.3	2.0	
Methyl α-D-glucopyranoside	1.1	1.9 (0.4 EtOH)	2.2	
Methyl β-D-glucopyranoside	1.3	2.3	2.1	
Polyhydric alcohols				
Erythritol		2.0	2.3	2.4
Arabitol		1.8		
Ribitol	1.4		2.0	1.9
D-Glucitol	1.0 (1.4 EtOH)	1.5 (1.6 EtOH)	1.9[c]	
meso-Inositol			2.0	
Pentaerythritol	1.5 (0.5 EtOH)	2.6 (1.0 EtOH)		
Miscellaneous				
1,6-Anhydro-β-D-glucopyranose	1.5	2.2	3.0 (0.3 EtOH)	2.6
1,4-Anhydro-D-glucitol			2.4	
Kojic acid			2.0	
Maltol			2.0 (0.1 EtOH)	
Salicylaldehyde			2.0	

[a] A minor, but significant, fraction of each isolated complex is an alkali metal hydroxide adduct, except those of kojic acid, maltol, and salicylaldehyde, which are all alcoholate. All complexes were treated as pure alcoholate in the calculations for combining ratio. Except where indicated by superscript *c*, ratios are corrected for ethanol content only in those cases where solvent content is known (ethanol of solvation, if known, is reported as molecules per cation in parentheses next to combining ratio). [b] Based on dimeric form of the aldose. Each complex is actually composed of approximately four aldose residues. [c] Estimated on basis of a possible molecule of solvation (ethanol) per cation.

The relation between ionic radius and combining ratio is probably due largely to the ability of a cation of greater surface area to accommodate a larger number of donor groups or carbohydrate ligands. The exceptionally small ability of the lithium ion may be attributed not only to its small surface area, but also to the fact that solvent molecules are more strongly attached to cations of smaller radius, and these solvent molecules may not be easily displaced by carbohydrate molecules.

The importance of carbohydrate configuration in complex formation is exemplified by the behavior of certain isomeric sugars. For example, each of the four aldopentoses (D-arabinose, D-xylose, D-lyxose, and D-ribose) reacts with potassium hydroxide or cesium hydroxide to form a complex of 2:1 carbohydrate: metal ratio. However, with sodium hydroxide, only D-xylose, D-lyxose, and D-ribose form 2:1 complexes; D-arabinose gives a 1:1 complex. Similarly, D-mannose reacts with sodium hydroxide to form a complex of 1:1 maximum ratio, whereas both D-glucose and D-galactose form 2:1 complexes. With potassium hydroxide all three hexoses react to give 2:1 complexes. A 3:1 complex is formed by the reaction of levoglucosan (1,6-anhydro-β-D-glucopyranose) and potassium hydroxide.

B. Electrophoresis.—Many factors other than alcoholate formation might influence the rate and direction of electrophoretic migration: (1) degree of dissociation of metal alcoholate into free ions, (2) size of carbohydrate anion, (3) degree to which metal cations combine with carbohydrate to give free positively charged carbohydrate species, and (4) carbohydrate:metal combining ratio.

The competition between hydroxide ion and metal ion for carbohydrate was demonstrated in a combination of electrophoretic experiments, the results of which are graphically presented in Figure 1. In methanolic lithium hydroxide solution, all movements are toward the anode. In methanolic sodium hydroxide solution,

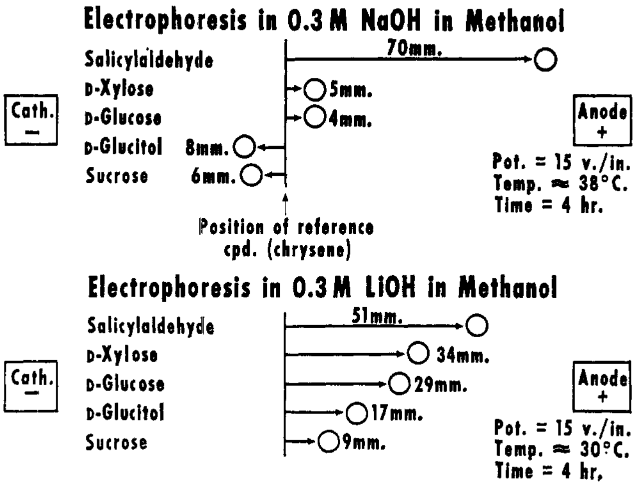

Figure 1.—Migration of salicylaldehyde and carbohydrates in alcoholic hydroxide solutions.

movement of salicyaldehyde, D-xylose, and D-glucose is toward the anode, whereas movement of sucrose and D-glucitol is in the opposite direction. A reasonable interpretation of these phenomena rests solely on the assumption that a competition exists between metal cation and hydroxide ion for carbohydrates (or multidonor compounds). Free alcoholate anions, as well as any free carbohydrate–hydroxide ion species, would migrate toward the anode. Cationic species, produced by the chelation of a free metal cation with one or more multidonor molecules, would migrate toward the cathode. Both negative and positive species should exist; however, the mobility of each species and the extent to which each is formed determine the actual observed rate and direction of carbohydrate migration. In alcoholic sodium hydroxide solution, the two opposing movements almost cancel each other, and migration is slow. The high mobility of salicylaldehyde toward the anode is attributed to ease of release of the phenolic proton to form the anion. The somewhat acidic sugars, D-xylose and D-glucose, migrate slowly as an anion, but the much less acidic carbohydrates, sucrose and D-glucitol, which do not have an acidic hemiacetal hydroxyl group, maintain a net positive charge and migrate toward the cathode. In methanolic lithium hydroxide solution, all carbohydrates migrate toward the anode because of the extremely weak ability of lithium cations to form positively charged carbohydrate species.

Electrophoresis does not show the presence of uncharged species such as undissociated metal alcoholate or carbohydrate–metal hydroxide adducts. These species probably are present in alcoholic solution, but their concentration has not been ascertained. The possible existence of free carbohydrate–hydroxide ion species cannot be disregarded because of the hydrogen-bonding properties of hydroxide ion.[13] Agarwal and Diamond[14] have published evidence for the formation of 3:1 complexes between certain monohydric alcohols and hydroxide ion. Nevertheless, the existence of carbohydrate–hydroxide ion species has not been proved.

Alkali Metal Hydroxides in Aqueous Alcoholic Media.—The presence of water in an alcoholic medium containing carbohydrate and alkali metal hydroxide leads to the formation of an isolable complex that is either a carbohydrate–metal hydroxide adduct or a metal alcoholate hydrate. For the reasons stated earlier, the former is the more probable. Percival and coworkers[9,15–17] reported the preparation of a number of such adducts but offered no proof that they were not hydrated alcoholates. Insufficient water in the reaction medium may result in the production of some alcoholate in addition to adduct. In this work it was found that reaction of methyl α-D-glucopyranoside with potassium hydroxide in an ether–ethanol medium containing about 2% water does not give exclusively adduct as reported by Heddle and Percival.[17] Instead, the isolated product has been shown by modified Karl Fischer analysis to be a mixture of alcoholate (71%) and adduct (29%). If water is excluded from the reaction medium, a complex is obtained that is 88% alcoholate.

In Table III are listed various adducts isolated from aqueous ethanolic media. All are amorphous (nonbirefringent), colorless, hygroscopic solids. Maximum carbohydrate:metal ratios for adducts are generally the same as those for corresponding alcoholate complexes and are usually attained with low hydroxide concentration. With increasing alkali concentration, ratios may vary widely, especially with oligosaccharides. Ratios ranging from 2:1 to 1:5 were obtained for sucrose–sodium hydroxide adducts by varying the hydroxide concentration from 0.2 to 40% (by weight).

TABLE III

ALKALI METAL HYDROXIDE ADDUCTS OF SUGARS

Adduct	Molar ratio, ligand:metal	Water of solvation,[a] molecule/cation	Ethanol of solvation,[b] molecule/cation
D-Arabinose–NaOH	1.1:1	c	c
D-Glucose–LiOH	1.5:1	0	c
D-Glucose–NaOH	2.0:1	0.1	0.08
D-Glucose–KOH	1:1.2	0.2	c
D-Mannose–NaOH	1.2:1	c	c
Sucrose–NaOH	1.7:1	0.3	c
Sucrose–NaOH	1:1.8	c	c
Sucrose–NaOH	1:2.5	0	c
Sucrose–NaOH	1:5.1	0.22	0.04
Sucrose–CsOH	2:1	0.5	c

[a] Solvent remaining after vacuum treatment at 25° for 20 hr equals difference between total gram-atoms of metal and moles of combined OH^- and water as determined by modified Karl Fischer analysis. [b] Solvent remaining after vacuum treatment at 25° for 20 hr. [c] Undetermined.

Conversion of NaOH·2sucrose into the corresponding alcoholate was accomplished by heating the former at 110° under vacuum (Scheme I). Reaction was 94% complete in 4 hr, as shown by modified Karl Fischer analysis. Similar treatment of sucrose·5NaOH resulted in only partial conversion. Approximately 2.4 molecules of sodium hydroxide remained with each sucrose moiety. Higher reaction temperatures were not investigated.

Alkali Metal Alkoxides in Anhydrous Alcoholic Media.—Percival[9] established that alkali metal alkoxides combine with sugars at room temperature to

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[13] A. F. Wells, "Structural Inorganic Chemistry," Clarendon Press, Oxford, England, 1947, Chapters 10 and 11.

[14] B. R. Agarwal and R. M. Diamond, *J. Phys. Chem.*, **67**, 2785 (1963).

[15] E. G. V. Percival, *J. Chem. Soc.*, 648 (1935).

[16] E. G. V. Percival and G. G. Richie, *ibid.*, 1765 (1936).

[17] W. J. Heddle and E. G. V. Percival, *ibid.*, 1690 (1938).

SCHEME I

$$\mathrm{NaOH \cdot 2sucrose} \xrightarrow[\text{4 hr}]{110^\circ,\ 1\ \text{mm}} \mathrm{NaC_{12}H_{21}O_{11} \cdot sucrose} + \mathrm{H_2O}$$

(94% conversion)

$$\Big\downarrow \text{glacial HOAc, } 25^\circ$$

sucrose (90% yield),
mp 167–170°,
$[\alpha]^{20}\mathrm{D}$ +65.2 (c 1, H_2O)

form adducts. He treated D-glucose with sodium methoxide in anhydrous methanol and with sodium ethoxide in anhydrous ethanol; alkoxyl analysis and acid titration of both isolated products (vacuum dried at 60°) indicated a 1:1 alkoxide adduct. Traces of moisture in the preparative medium precluded the formation of alkoxide adduct. Early reports that D-glucose[18] and D-fructose[19] react with sodium ethoxide in anhydrous ethanol at room temperature to give alcoholates are questionable, because the investigators did not analyze the products for ethoxyl content.

Butoxide ion in boiling 1-butanol is capable of abstracting a proton from methyl α-D-glucopyranoside to give the corresponding alcoholate. The product obtained with sodium 1-butoxide is identical with the one obtained by refluxing a mixture of the glucoside and sodium hydroxide in 1-butanol and removing water of formation by azeotropic distillation. If sodium hydroxide is employed, possibly *both* hydroxide ion and butoxide ion react directly with the glucoside to produce alcoholate. Sodium 1-butoxide was formed easily and in quantitative yield by refluxing a solution of sodium hydroxide in excess 1-butanol under dry nitrogen while water of formation was removed by azeotropic distillation. Completion of reaction was determined by Karl Fischer (water) analysis of distillate fractions.

Reactions 7–10 summarize the major reactions that occur when equimolar amounts of sodium hydroxide and methyl α-D-glucopyranoside (ROH) are refluxed together in 1-butanol (BuOH). After the reaction was forced to completion by removal of the water azeotrope, the ratio of glucoside moiety:sodium in the isolated product was slightly greater than 1:1. Furthermore, the product contained a small, but significant, amount of butoxyl even after being dried at 70° under vacuum. Reaction 8 evidently occurs to a significant extent to give sodium 1-butoxide, which combines with glucoside to form an alkoxide–carbohydrate adduct (reaction 10). An alternative explanation for the presence of butoxyl is that the isolated reaction product is an alcoholate complex containing 1-butanol of solvation. The severe drying conditions and the probable presence of sodium 1-butoxide in the total reaction product mixture lead to the conclusion that the butoxyl is in the form of butoxide ion. The ease with which butoxide ions remove hydroxylic protons from carbohydrates in refluxing butanolic solution suggests that alcoholates of alkali-stable carbohydrates can be prepared from other alkali metal alkoxides in other alcoholic media at elevated temperatures.

$$\mathrm{NaOH + ROH \rightleftharpoons NaOR + H_2O} \quad (7)$$

$$\mathrm{NaOH + BuOH \rightleftharpoons NaOBu + H_2O} \quad (8)$$

$$\mathrm{NaOBu + ROH \rightleftharpoons NaOR + BuOH} \quad (9)$$

$$\mathrm{NaOBu + ROH \rightleftharpoons NaOBu \cdot ROH} \quad (10)$$

Alkali Metal Cyanides in Anhydrous Media.—Sodium and potassium cyanide in ethanolic solution react with polyhydroxy compounds at room temperature to form alcoholates that precipitate from solution. The isolated complex is not entirely alcoholate, however. A certain percentage is carbohydrate–alkali metal cyanide adduct. Proton abstraction, presumably by cyanide ion, occurs predominantly before or during precipitation, or both; little occurs during drying. This order was shown by analyzing a complex, prepared from sodium cyanide and α-D-glucose, both before and after it was dried for 2 hr at 25° under vacuum. Before the complex was dried, 21% of its total sodium was present as NaCN; after it was dried, 12%. A longer drying period (45 hr) had little effect upon the cyanide content. Ethanol of solvation was only 0.2 molecule/atom of sodium after a drying period of 16 hr. D-Glucitol is less acidic than α-D-glucose toward sodium cyanide in ethanol. Thirty-seven percent of the sodium in the D-glucitol complex remained as NaCN after a 2-hr drying period. A longer period had little effect on cyanide content. Maximum carbohydrate:metal ratios are attained when low concentrations of cyanides are used in the preparative process. Both α-D-glucose and D-glucitol react with dilute sodium cyanide to form complexes of 2:1 maximum ratio.

Acknowledgment.—The author is indebted to Mr. J. E. Hodge for general supervision, to Mrs. Clara E. McGrew and Mrs. Bonita Heaton for the microanalyses, and to Mrs. Helen M. Peters for the absorption spectra.

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[18] M. Hönig and M. Rosenfeld, *Chem. Ber.*, **10**, 871 (1877).

[19] M. Hönig and M. Rosenfeld, *ibid.*, **12**, 45 (1879).