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### Poly-Sugar: Modification of Poly(vinyl Alcohol)

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## Poly-Sugar: Modification of Poly(vinyl Alcohol)

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### ABSTRACT

This paper describes the attachment of sugar (sucrose) onto low molecular weight poly(vinyl alcohols) (etherification) to produce a new class of synthetic sweetener. Because of its regulated molecular weight, the new sweetener would pass through the digestive tract and be excreted in its original molecular form. We have termed the new class of sweeteners poly-sugar. The etherification of sucrose with poly(vinyl alcohol) can be carried out either in dimethyl sulfoxide or water. We have prepared poly-sugars with varying degrees of etherification (3.4-5.4). Highly etherified products were bitter, but a poly-sugar with a 4.23 degree of etherification was sweet without any bitter aftertaste.

### INTRODUCTION

The artificial sweetener cyclamate has been banned, and the fate of saccharin is uncertain. Sugar (sucrose) has some adverse effects even on healthy people because of its high food value, and it cannot be tolerated by many diabetics at all.

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Thus, there continues to be a pressing need for a safe artificial sweetener. What is needed is a commercially utilizable sweetener that will make foods and beverages more palatable and yet pass through the digestive tract without being metabolized, to be excreted in the same molecular form it had when consumed.

The concept of "anatomical compartmentalization" of chemical substances by regulating their molecular size and/or solubility has been applied to pharmacological agents. More recently, this concept has been extended by Weinshenker and co-workers [ 1 ] of Alza Corporation to produce several nonconventional food colors.

Alza researchers have successfully attached color-producing groups to suitable polymer molecules. The increased molecular size of the new colors prevents their absorption through the intestinal lining. Thus, they are excreted without change. The Alza group has determined that their new food colors are stable to the conditions occurring in the gastrointestinal (GI) tract. Had the new molecular entity degraded or depolymerized in the GI tract, the entire idea of adding color-producing functional groups to the polymeric chain would have been defeated. Alza chemists considered the condition of microflora, enzyme, and pH in the GI tract.

Montemarano et al. [ 2 ] (Naval Ship Research and Development Center) have copolymerized organometallic monomers (e. g., tributyltin methacrylate and triphenyllead methacrylate) with methyl methacrylate and fluoro monomers in an attempt to couple the anti-sliming and nonwetting characteristics of each into an optical material for underwater use. Similarly, the naval ship researchers attached organometallic monomers to polymer backbones such as polystyrene and polyester for use as coatings and structural plastics where antifouling protection was needed.

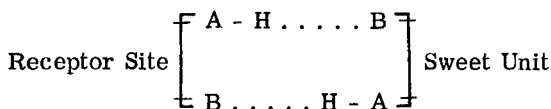
This paper describes a project undertaken to adapt Weinshenker's work by attaching sugar (sucrose) onto a suitable biologically acceptable polymer to produce a new class of synthetic sweetener.

## THEORETICAL BACKGROUND ON TASTE

There are four basic taste sensations: sweet, sour, salty, and bitter. The sour taste stems from protons. The salty taste is caused by ions. Both of these tastes lack molecular specificity. Sugars are noted for their sweet taste and have distinct molecular characteristics; e. g., a polyhydroxy feature, a carbonyl character, and four or five different asymmetric centers of optical activity.

In the last ten years, taste has been placed on molecular basis. Configurational changes in a sugar molecule affect sweetness dramatically. This led Shallenberger [ 3 ] to hypothesize that the degree of sweetness must be a function of the way in which the

hydroxyl groups that participate in hydrogen bond formation are arranged. Thus, Shallenberger suggested that a molecule can be modified to taste sweet. Shallenberger's AH, B system is depicted below.



A molecule containing an AH, B system is sweet due to hydrogen bonding of the taste receptor with another similar AH, B system. Development of two hydrogen bonds stabilizes the entire complex. The degree of sweetness depends on strength of the hydrogen bonded complex.

Taste depends on the number, character, and position of the substituents in substituted sugars. In general, a high degree of substitution renders the molecule tasteless. A bitter taste begins to emerge when substituents are placed on the molecule in specific positions.

#### Sweetness and Bitterness in Substituted Sugars: Structural Considerations

The  $\beta$  configuration at the hemiacetal carbon atom of sugars, imparts bitterness to the molecule, whereas the  $\alpha$  configuration does not produce bitterness. For example,  $\beta$ -D-mannose is bitter, while the  $\alpha$ -anomer is not. Addition of quinine sulfate to sucrose solutions results in a logarithmic decrease in the sweetness of the latter with increasing concentrations of the former. It is also well known that the subjective intensity of sweetness increases logarithmically with the concentration of a sweet-stimulating compound. The same relationship holds for a bitter stimulus. The effect of either sweetness or bitterness on the other is to lower the taste response by the following relationship:

$$\Delta T = K \log (C/C_m)$$

where  $\Delta T$  = lowering in taste (sweetness or bitterness),  $C$  = concentration of taste stimulus (e. g., quinine sulfate or sucrose solution) producing the taste reduction,  $C_m$  = maximum concentration having no effect on taste, and  $K$  = constant. If  $K$  remains constant for methyl glycosides, it should be possible, by using the above equation, to estimate the effect of bitterness or sweetness of a compound containing

both bitter and sweet stimuli. Sweetness and bitterness are usually present in a molecule and may interfere with one another in a predictable way. In extremes, the bitterness of an aglycone may completely overwhelm and totally eliminate the sweetness of the sugar residue.

### General Taste Panel Considerations

There are two primary methods for quantitatively testing the taste of sugars and artificial sweeteners: the threshold method and the method of successive approximation. Also, an effect of "impact time" is noticed when different sugars are tasted which, if combined with a low solubility problem, may cause considerable differences in sweetness to be recorded. This is one reason why tasting of solid sugars can give only qualitative, or at least, semiquantitative results.

The gustatory (taste) properties of methyl ethers of sucrose has been studied by Khan and co-workers [4] in England. Their results are shown in Table 1.

## RESULTS AND DISCUSSION

### Requirements of Polymer-Modified Sugar

The general requirements for a sweetener of commercial utility are: sweetness intensity; sweetness quality (no long sweet taste impact); low cost; safety; stability, both thermal and hydrolytic; non-cariogenic. Different sweetening agents possess the above properties in varying degrees. The modified entity we propose to make in this project by attaching sucrose onto a polymer chain should meet the following chemical and biological requirements.

It must maintain the taste of the parent sweetener. Some reduction in sweetness would be acceptable, but much deviation in taste properties would be unacceptable. Water solubility is desirable.

The molecular weight of the material should be high so that it is not absorbed through the intestinal lining.

It should be stable to conditions prevalent in the GI tract. The polymer-to-sugar bonds, as well as the glycoside bond of the sugar molecule, should be hydrolytically stable.

It should meet biological requirements.

It should be stable during actual use (e. g., boiling, baking, and frying). Prolonged shelf stability is also required.

TABLE 1. Gustatory Properties of Methyl Ethers of Sucrose

Compound	Gustatory properties <sup>a</sup>	
	Sweetness	Bitterness
Sucrose	vs	0
6'-O-Methyl sucrose	vs	0
4-O-Methyl sucrose	s	0
6,6'-Di-O-methyl sucrose	vs	tr
4,6'-Di-O-methyl sucrose	s	tr
4,6-Di-O-methyl sucrose	s	tr
1',6'-Di-O-methyl sucrose	s	tr

<sup>a</sup>Properties: s = sweet; vs = very sweet; tr = trace; 0 = zero response.

### Synthesis Strategies

The four possibilities listed below were considered for synthesis of a poly-sugar: (1) polymerize or copolymerize sucrose with other step-growth type monomers; (2) polymerize a vinyl which has had sucrose molecules attached to it; (3) attach a sugar molecule to a preformed polymer to produce linear and branched structures; (4) attach the sugar molecule to more than one preformed polymer. The third approach was selected.

### Requirements of the Attachable Polymer

Characteristics required for the polymer to which the sugar was to be attached were (1) nonbiodegradable backbone; (2) high molecular weight; (3) permanent sugar-polymer attachment.

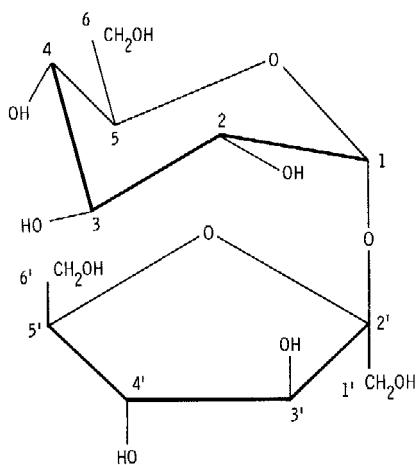
The C-C and C-O-C bonds are nonbiodegradable and preferred over ester bonds, which are slightly biodegradable.

The molecular weight was required to be large enough to make the size of poly-sugar sufficiently high to prevent any absorption through the intestinal lining. A polymer molecular weight in the 3000-10,000 range was desired. A molecular weight above 20,000 would produce a sweetener of high molecular weight and low water solubility.

A permanent attachment of sugar to the polymer, i. e., a nonbiodegradable link such as an ether linkage between the sugar and the polymer, is highly desirable.

### Etherification of Sucrose

Sucrose is a nonreducing disaccharide. The numbering of the carbon positions in the molecule is shown in the structure I.



I

Sucrose contains eight hydroxyl groups; three are primary (C-1', 6 and 6') and the remaining are secondary. In transesterification reactions, C-6 and 6' react preferentially, as demonstrated by Reinfield [5]. The reactions of sulfuryl chloride with sugars (including sucrose) have been shown to give products where the primary hydroxyls were replaced by chlorine. It has been reported [6] that the substitution of four sucrose hydroxyls by four chlorine atoms produced a sweetener that was sweeter than sucrose itself.

The selected substitution of hydroxyl groups in sucrose is difficult to achieve. This is shown in Table 2, which lists the number of isomers produced on derivatization.

In our work, sugar (sucrose) bought from a supermarket was used as obtained. Three different grades of poly(vinyl alcohol) were utilized in the etherification reactions. Their characteristics are shown in Table 3.

TABLE 2. Number of Possible Isomers Obtained by Substitution of Hydroxyl Groups in Sucrose

No. OH	No. isomers
Mono	8
Di	28
Tri	56
Tetra	70
Penta	56
Hexa	28
Hepta	8
Octa	1

The sugar hydroxyls are less reactive than water; therefore, it is difficult to make derivatives of sugar in an aqueous medium. Pyridine has been used as a solvent by carbohydrate chemists, but it is noxious and not a good solvent for polyvinyl alcohol. Pyridine was therefore not used. *N,N*-Dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) dissolve significant quantities of sugar, contain unreactive hydrogen, and seem useful nonaqueous media for conversion of sugar to poly-sugar. DMSO was found to be a better solvent for polyvinyl alcohol than DMF; therefore, the former was selected as the nonaqueous medium.

In initial etherification reactions, 0.05% *p*-toluenesulfonic acid (PTSA) was tried as a catalyst. Use of PTSA slightly yellowed the etherified product in solution, and the products charred during flash evaporation of the poly-sugar solutions to the solid state. This being the case, use of catalyst (e. g., PTSA, phosphoric acid, and potassium acid sulfate) in the etherification reaction was abandoned. Instead, a 3 Å Molecular Sieve was used in reactions conducted in nonaqueous media to pick up the water of reaction. In aqueous runs, obviously, no Molecular Sieve was used.

### Preparation of Poly-Sugar

A 20% solution of sucrose was prepared in DMSO. Complete solubility was achieved by stirring. A 7.7% solution of PVOH (Elvanol 90-50) was also prepared in DMSO. Complete solubility was obtained by prolonged heating (50°C) and stirring. Solutions



TABLE 3. Characteristics of Poly(vinyl Alcohol)

Resin grade	Supplier	Viscosity (Cps) <sup>a</sup>	Residual poly(vinyl acetate) (%) <sup>b</sup>	Hydrolyzed (%)	Approx. $\frac{M_w}{M_n}$	Ash (%) (maximum)
Gelvatol I-30	Monsanto	4-6	0-3	100-98.5	14,000	1
Gelvatol 40-20	Monsanto	2-3	37-42	77-72.9	3,000	1
Elvanol 90-50	Du Pont	-	-	99.0-99.8	43,000	1

<sup>a</sup>Viscosity of a 4% aqueous solution at 20° C.<sup>b</sup>Determined on a weight basis.

of 20% of other PVOH, e. g., Gelvatol I-30 and 40-20, were prepared in DMSO by moderate heating (40°C) and stirring. No problem was encountered in dissolving poly(vinyl alcohol) in water. Poly(vinyl alcohol) and sugar solutions were weighed into a 250-ml standard taper rimmed Erlenmeyer flask (Table 4). If solid sugar and PVOH were used in the reaction, complete solubility in the processing solvent was achieved by stirring at room temperature. Molecular Sieves, 3 Å (Grace), were now added. The condenser was then attached and the flask was placed in a 100°C water bath (1000-ml beaker). A magnetic stirrer was used to keep the reactants well mixed. After completion of the reaction the product was cooled. It was filtered if Molecular Sieves were used in the reaction, then the solution was flash evaporated to dryness. For complete solvent removal, drying was done in a vacuum oven for 16 hr at 80°C.

Because of the solubility of sugar, poly(vinyl alcohol), and poly-sugar in DMSO and water, the poly-sugar product could not be readily purified by crystallization. Poly-sugar processed in DMSO could retain residual amounts of DMSO. This is objectionable. Therefore, these poly-sugars were dissolved in water at 70°C, and the water and trace DMSO were removed by flash evaporation to dryness. Complete removal of the solvent was achieved by subsequent drying in a vacuum oven at 80°C for 24 hr.

The physical forms and colors of the poly-sugars are described in Table 5.

#### Determination of the Extent of Etherification

Infrared spectra of poly(vinyl alcohol), sugar, and poly-sugars were recorded on a Perkin-Elmer Model 137 spectrophotometer. Because of the presence of C-O in both the starting material and in the poly-sugar, it was difficult to establish by infrared spectroscopy that etherification had taken place. The 100 MHz proton NMR spectra of poly-sugars and the starting materials were run in DMSO and D<sub>2</sub>O. Because of insufficient resolution, the extent of etherification was not conclusively established. To follow the extent of etherification, we had to resort to the determination of OH content by a wet method. The method of Fritz-Schenk [7] was used, following the procedure given below.

A sample of poly-sugar containing about 2 μmole of hydroxyl was accurately weighed into a 125-ml glass stoppered flask. A 5 ml portion of pyridine and 5 ml DMSO were added and the mixture heated to 70°C with stirring for 2-4 hr or until solution was achieved. Then, exactly 5 ml of 2 M freshly prepared acetic anhydride in pyridine containing 3% p-toluenesulfonic acid was pipetted into the flask. The acetylation was allowed to proceed for 2 hr at room temperature.

TABLE 4. Poly-Sugars: Composition and Reaction Conditions

Sample	Composition (reactants)			Reaction time at 100°C (hr)	Mole reactants		Mole OH		Mole ratio		
	20% Sucrose in DMSO (g)	PVOH (g)	3 Å Mol. Sieve (g)		Sucrose	PVOH unit	From sucrose	From PVOH (normalized) <sup>a</sup>	OH	sucrose	PVOH
204247	50	130 (7.7% 90-50 PVOH in DMSO)	-	7	0.0292	0.2275	0.2339	0.2264	1.0334	1.0334	
204248	50	100 (7.7% 90-50 in DMSO)	-	7	0.0292	0.1750	0.2339	0.1741	1.3434	1.3434	
204249	50	50 (20% 40-20 in DMSO)	20	7	0.0292	0.2273	0.2339	0.1705	1.3723	1.3723	
204250	50	130 (7.7% 90-50 in DMSO)	20 <sup>b</sup>	7	0.0292	0.2275	0.2339	0.2264	1.0334	1.0334	
204251	50 (in water)	50 (20% I-30 in water)	-	24	0.0292	0.2273	0.2339	0.2261	1.0344	1.0344	

## POLY-SUGAR

204252	50 (in water)	50 (20% 40-20 in water)	-	24	0.0292	0.2273	0.2339	0.1705	1.3723
204256	15 (solid)	15 (I-30)	20 + 1120 g DMSO	7	0.0439	0.3409	0.3509	0.3392	1.0344
204257	50	50 (20% 40-20 in DMSO)	20 <sup>b</sup>	24	0.0292	0.2273	0.2339	0.1705	1.3717
204259	30 (solid)	30 (I-30)	60 + 240 g DMSO	24	0.0877	0.6818	0.7018	0.6982	1.0050

<sup>a</sup> Percent of hydrolysis of PVOH (used for normalization): I-30, 99.5%; 40-20, 75.0%; 90-50, 99.5%.  
<sup>b</sup> Molecular Sieves disintegrated into fine particles at the end of reaction.

TABLE 5. Form and Color of Poly-Sugar

Material	Form and color
Sugar	Water white crystals
PVOH 90-50	Water white, free flowing powder
PVOH I-30	Very slightly yellow, free flowing powder
PVOH 40-20	Slightly yellow granules
204247	Water white, spongy film former; gummy
204248	Water white, spongy film former; gummy
204249	Very slight straw color; granular
204250	Straw color, spongy film former; gummy
204251	Very, very slightly brown; granular
204252	Very, very slightly brown; granular
204256	Very slightly brown; gummy
204257	Slightly yellow; slightly sticky; gummy
204259	Slightly brown; gummy

Then 5 ml of water and 10 ml of pyridine/water (3/1) solution were added, and the solution was titrated with standardized 0.5 N methanolic NaOH solution to an apparent pH of 9.8 by using a pH meter with glass-calomel electrodes. A reagent blank was also run. The OH content was calculated as

$$\% \text{ OH} = \frac{\text{ml (sample - blank)} \times \text{N NaOH} \times 100}{\text{g Sample} \times 1000}$$

The results of the wet analysis are shown in Table 6.

### Taste Results

Several researchers served as panelists on the gustatory properties of poly-sugars. Both solid poly-sugar and a 5% solution in water that had been cooled to about 4°C were tasted. The results are presented in Table 7. It was found that the poly-sugars stimulated the back of the tongue.

TABLE 6. Extent of Etherification in Poly-Sugars

Poly-sugar sample	OH (%)	Extent of etherification (%)	Degree of substitution (etherification)
204247	20.80	46.94	3.76
204248	16.30	58.42	4.67
204249	18.48	52.86	4.23
204250	16.70	57.40	4.59
204251	22.47	42.68	3.41
204252	21.63	44.82	3.59
204256	17.00	56.63	4.53
204257	12.78	67.40	5.39
204259	21.41	45.38	3.63

### Hydrolysis Studies

The stability profile data are quite favorable for poly-sugar. All poly-sugars were resistant to prolonged heat treatment with boiling water. Poly-sugars should tolerate the pH conditions in the stomach; i. e., they should have good stability against acidic conditions. The method of testing is described below.

The pH of 1.5-2.5 (average 2.0) is prevalent in the human stomach. Therefore, it seemed appropriate to check the hydrolytic resistance of poly-sugar in an aqueous solution of pH 2.0, at body temperature (98.6° F). The pH of a master batch of deionized water was adjusted to 2.0 by addition of hydrochloric acid. Then 50 ml of this solution was pipetted into a 4-oz. glass jar. To this, 2.5 g of poly-sugar was added, and the jar was placed in a 38° C oven for 4 hr. The solution was cooled to room temperature and allowed to stand overnight. The samples were then flash-evaporated, and solids were recovered. Differences between starting and hydrolyzed materials were observed. The recovered solids were then further allowed to remain at 70° C for 24 hr. Observations regarding discoloration were noted. Results of hydrolysis are shown in Table 8.

The base hydrolysis has not been studied. Resistance to basic conditions may be important to survival of the material in the intestine.

TABLE 7. Gustatory Properties of Poly-Sugars<sup>a</sup>

Compound	Solid material			5% Aqueous solution		
	Sweetness	Bitterness	Remarks	Sweetness	Bitterness	Remarks
204247	SS	0	Crunch tasting	SS	0	Slightly syrupy
204248	0-SS	0	Hard to chew	SS	0	-
204249	S	0	-	S	0	-
204250	SS	B	-	0	B	-
204251	S	tr	-	SS	B	-
204252	S	-	Buttery taste and smell	S	tr	-
204256	S	B	-	0	B	-
204257	0	BB	-	-	-	-
204259	S	tr	Crunchy	S	tr	-

<sup>a</sup> Properties: SS = slightly sweet; S = sweet; 0 = zero response; tr = trace; B = bitter; BB = extremely bitter.

TABLE 8. Poly-Sugars: Hydrolysis Results and Stability Profile

Poly-sugar sample	Initial color	4-Hr hydrolysis <sup>a</sup>		24-Hr/70°C heat treatment <sup>b</sup>	
		Observation	Stability rating <sup>c</sup>	Observation	Stability rating <sup>c</sup>
204247	Water white	Very slight off white	2	Considerably dark and charry smell	8
204248	Water white	Very slight off white	2	Darkened and charry smell	8
204249	Very slightly straw color	Slightly straw color	2	Slightly brown	3
204250	Straw color	Maintains color	1	Maintains initial color	1
204251	Very, very slight brown	Maintains color	1	Brownish grey; slightly charry smell	4
205252	Very very slight brown	Slightly darkened	2	Considerably dark and charry smell	8
Sugar	Water white	Black, foamed and bad charry smell	10	Black; foamed and bad charry smell	10

<sup>a</sup>Hydrolysis: 2.5 g compound + 50 ml water of 2 pH; stirred at 98.6° F/4 hr, then recovered by flash evaporation.

<sup>b</sup>Recovered hydrolysis product compound heat treated at 70° C/24 hr.

<sup>c</sup>Stability rating (1-10): 1 = no change, extremely stable to hydrolysis; 10 = extremely sensitive to hydrolysis.



## CONCLUSIONS

The poly-sugar with the highest degree of etherification, 5.39 (sample 204257), was extremely bitter. Sample 204249 with a 4.23 degree of substitution was sweet without any bitter aftertaste. Based on our work and that of Khan [4] (methyl ethers of sugar), it would seem logical to prepare 6'-O-polyvinylated and 6,6'-di-O-polyvinylated sucrose (using PVOH) type poly-sugars. They might be quite sweet.

Poly-sugars showed good stability towards acid hydrolysis. No toxicological testing was done on poly-sugars.

We believe that the poly-sugar concept wherein a suitable polymer, e. g., poly(vinyl alcohol), is attached to sucrose can lead to a viable product of importance. The limited work we did indicates that the concept of anatomical compartmentalization might be used to produce a commercially viable sweetener.

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