Carbohydrate Diacids: Potential as Commercial Chemicals and Hydrophobic Polyamide Precursors

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Carbohydrate diacids (aldaric acids) are derived from oxidation of the terminal carbons of simple aldoses. Several aldaric acids are suggested as being reasonable candidates for commercial development, based on potential applications, and availability and cost of the individual simple sugar precursors. Given that D-glucose, produced on a massive scale worldwide by starch hydrolysis, is by far the most available and inexpensive aldose, the corresponding aldaric acid, D-glucaric acid, would appear to be the most attractive aldaric acid for commercial development. This report will focus on several potentially important aldaric acids, consider some of their applications as standalone chemicals, and describe how they can be used as diacid monomers for the preparation of assorted polyamides, labeled polyhydroxypolyamides (PHPAs) or Hydroxylated Nylons.

The term "carbohydrate diacids" as used in this report represents that class of compounds know as aldaric acids, i.e., simple diacids derived from oxidation of the terminal carbons of aldoses. As a class of compounds aldaric acids have been known for more than a century and some of these diacids played an important role in Emil Fischer's assignment of the relative configurations of naturally occurring D-aldoses *(1)*. Surprisingly, these molecules have seen very little chemical application over the past century but their time may have arrived to be considered as valuable and versatile synthons for preparation of specialty chemicals and polyamides. The material in this report presents an overview of

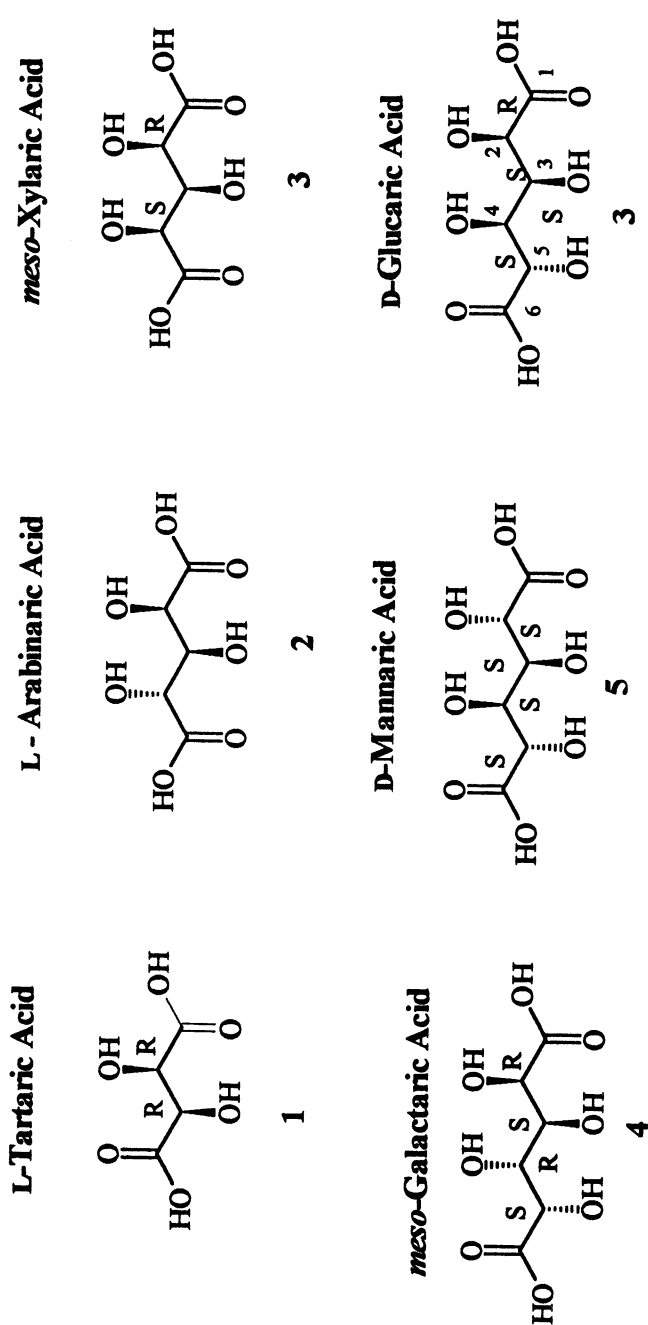© 2001 American Chemical Society

how, in recent years, some of these compounds have been synthetically employed in the author's laboratories, and in those of other investigators. It is hoped that the examples illustrated here will stimulate further development of these small but synthetically versatile molecules.

Aldaric Acid Preparation

Historically, aldaric acids have been prepared principally by nitric acid oxidation of aldoses *(2)*, although catalytic oxidation of aldoses has had some success *(3)*. The nitric acid oxidation method is remarkably selective and in general yields the corresponding aldaric acid (in one form or another) as the major product. Given the long history of this reaction, it is a wonder that aldaric acids haven't been produced in bulk quantities for years and become available and inexpensive compounds. Quite the contrary, only a limited number of aldaric acids can be purchased from chemical suppliers and those are quite expensive. In Figure 1 are structures of aldaric acids that might be considered as potential bulk chemicals, a consideration based primarily on the availability and cost of the starting sugar precursors.

Among the acids shown, only four carbon L-tartaric acid (1), produced as a byproduct of the wine industry, is at present a relatively important commercial aldaric acid. However, five carbon L-arabinaric acid (2) and *meso*-xylaric acid (3), while not available from chemical suppliers as far as this author is aware, could be produced by appropriate oxidation of L-arabinose (from hydrolysis of the plant polysaccharide, arabinogalactan) and D-xylose (wood sugar), a hydrolysis product of woody plant hemicellulosic xylans. In contrast the three six carbon aldaric acids shown, while costly, are available from a number of laboratory chemical suppliers. Crystalline *meso*-galactaric (mucic) acid (4) is synthetically the most well known aldaric acid as its preparation by nitric acid oxidation of lactose represents a classical procedure in synthetic organic chemistry *(4)*. D-Mannaric acid *(5)* is typically prepared by nitric acid oxidation of D-mannose *(5)*, and is sold as its crystalline 1,4:6,3-dilactone. The last and potentially most commercially attractive aldaric acid is D-glucaric acid (6), a direct nitric acid *(2)* or platinum catalyzed *(3)* oxidation product of D-glucose (dextrose). In terms of a large scale bulk chemical, D-glucaric acid is the only acid among this group that offers the opportunity for economy of scale. Precursor D-glucose is inexpensive and available as a major commodity chemical from starch hydrolysis, and in particular corn starch hydrolysis.

D-Glucaric acid, while typically represented in a Fischer projection formula as an acyclic product, is not isolated in this form but is isolated and easy to handle as crystalline 1,4- and 6,3- monolactones, **6a** and **6b**, respectively, or the 1,4:6,3-dilactone (**6c**). Several convenient salt forms of acyclic D-glucaric acid can also be prepared and these include monopotassium (**6d**) - *(6)*, dipotassium (**6e**) - *(7)*, sodium potassium (**6f**) - *(7)*, and calcium D-glucarate (**6g**) - *(6)*. In aqueous solution glucaric acid is present as an equilibrium mixture of principally the acyclic structure, and the 1,4- and 6-3-monolactones *(8,9)*.
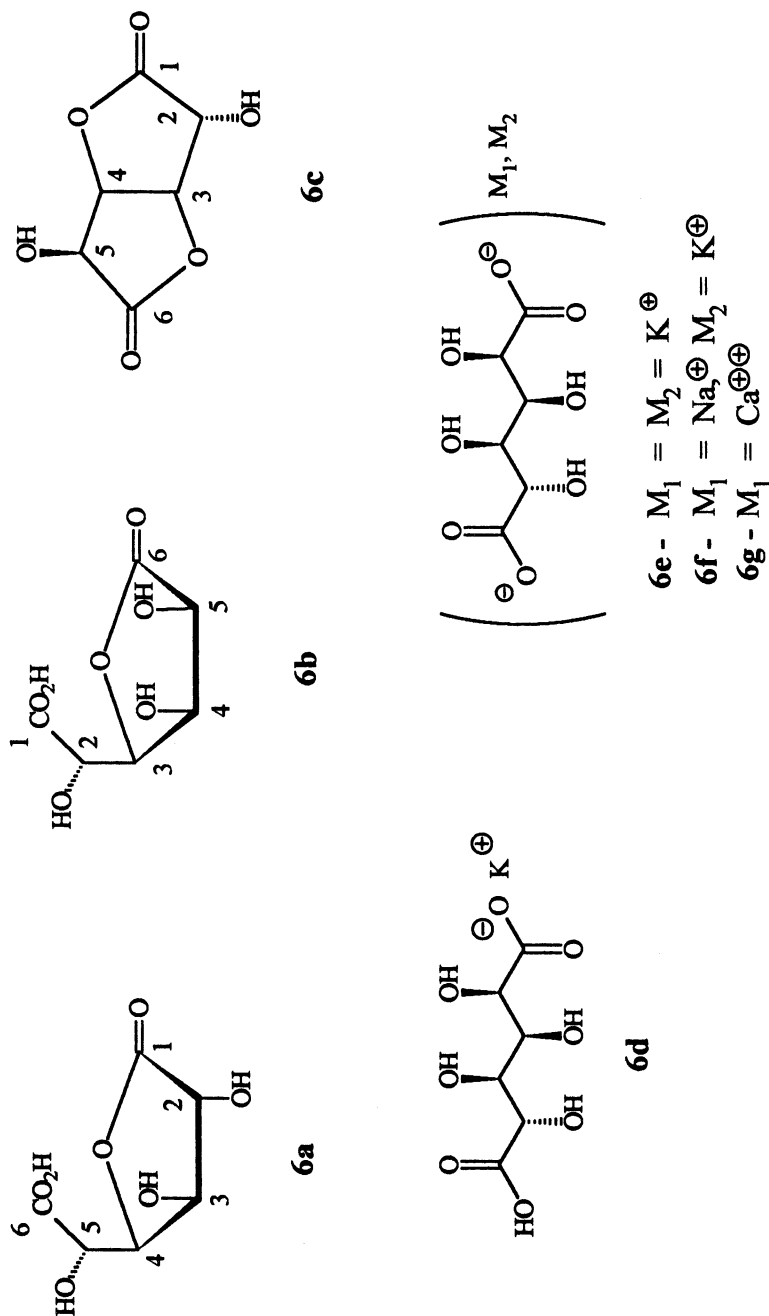
L-Tartaric Acid

1

L - Arabinaric Acid

2

meso-Xylaric Acid

3

meso-Galactaric Acid

4

D-Mannaric Acid

5

D-Glucaric Acid

3

Figure1. Some important aldaric acids and salts

6e - $M_1 = M_2 = K^{\oplus}$
6f - $M_1 = Na_2^{\oplus}$ $M_2 = K^{\oplus}$
6g - $M_1 = Ca^{\oplus\oplus}$

6a

6b

6c

6d

Aldaric Acids as Synthons

Polyhydroxypolyamide Synthesis

Our current major interest in aldaric acids is as monomers for polycondensation reactions with diamines to yield a broad class of polymers called polyhydroxypolyamides (PHPAs) or Hydroxylated Nylons *(10)*. The original reports of examples of this class of polyamides were from the laboratory of N. Ogata and coworkers in Japan, beginning in the 1970s *(11)*. More recent reports on these polymers have come from the laboratories of Hashimoto and coworkers *(12)* and those of author *(13)*. Our general preparation of these polyamides, exemplified with a generic hexaric acid, is outlined in Figure 2.

Typically, condensations to polyamide (**II**), are carried out between an activated, i.e., esterified (diester, ester/lactone, dilactone) form of the aldaric acid (**I**), and a primary diamine in a polar protic solvent such as methanol at room temperature. Under those conditions any starting single "ester" form of a five or six carbon aldaric acid is rapidly converted to an equilibrium mixture of acyclic diester and ester/lactone forms. Dilactone, if formed at all, is present in only small amounts. The starting monomer "esterified" form(s) of the aldaric acid differ from one acid to an other. For example, the monomers of choice for L-tartaric acid (**1**) and *meso*-galactaric acid (**4**) are simple diesters, while for D-glucaric acid suitable monomers are ester/lactones, dilactone, or even the entire alcohol esterified mixture *(10)*. Xylaric acid is also conveniently polymerized as its esterification mixture while the D-mannaric acid monomer is the 1,4:6,3-dilactone *(13a)*.

Given the ease of carrying out these polymerizations, we have prepared a number of polyamides in order to survey how reaction conditions and change in diacid and/or diamine monomers influence the reaction itself and the properties of the polymers obtained. We recently described a number of PHPAs from D-glucaric, *meso*-xylaric, *meso*-galactaric and L-mannaric acid with an assortment of diamines, and our studies indicated several trends *(13a)*. Some typical diamines employed in the polymerizations are shown in Figure 3. Polyamides from conformationally "bent" D-glucaric and *meso*-xylaric acids tend to be more water soluble and have lower melting points then those derived from conformationally "extended" *meso*-galactaric and D-mannaric acids. As the alkylenediamine monomer units become shorter, polyamide water solubility increases. Whereas the poly(alkylene D-glucaramides) from ethylenediamine and tetramethylenediamine are water soluble, those based on hexamethylendiamine to dodecamethylenediamine become increasingly less water soluble. Interestingly, all of these latter polymers have similar melting points (ca. 190 °C) in spite of their range of water solubility. Thus, it is clear that variable degrees of both hydrogen bonding (aldaryl unit) and van der Waals attractive forces (alkylene unit) impact the properties of the polymers. It was further observed that polyamides derived from branched diamines and/or those containing a heteroatom in the backbone had enhanced polymer water solubility,
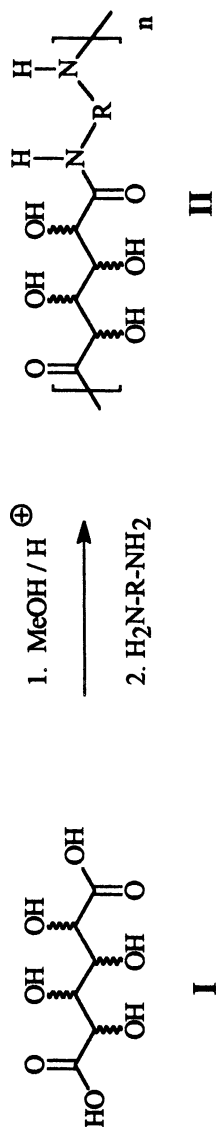
Figure 2. General procedure for converting an aldaric acid, illustrated with a generic hexaric acid **I**, to a polyhydroxypolyamide (PHPA), **II**.
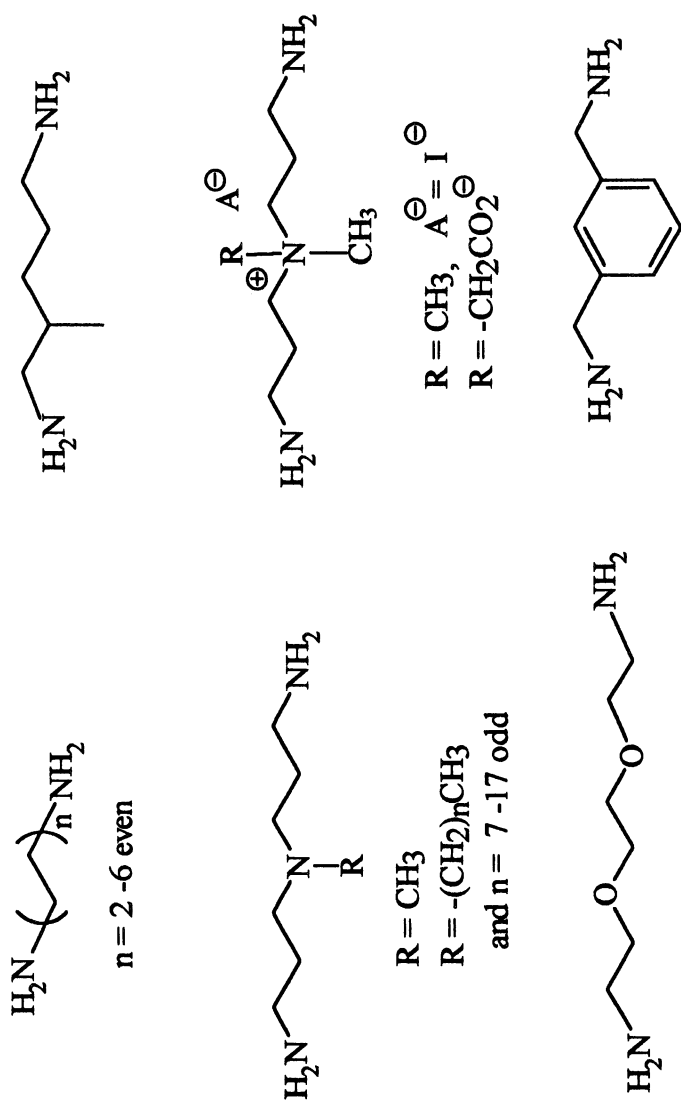
Figure3. Some typical diamine repeating monomer units in the polyhydroxypolyamides

n = 2 -6 even

R = CH₃
R = -(CH₂)ₙCH₃
and n = 7 -17 odd

R = CH₃, A⊖ = I⊖
R = -CH₂CO₂⊖

film forming properties, and adhesive characteristics compared to the poly(alkylene aldaramides) *(13b,13c)*. Three examples of polyamides, with different aldaric acid monomer units, that showed relatively good film forming and adhesive properties are shown in Figure 4. In general, polymers from diamines with heteroatoms in the diamine backbone or branched diamines had superior film forming and adhesive properties than those polyamides with high alkylenediamine monomer content.

Several aspects of this research are particularly exciting. The condensation polymerization method allows for preparation of a broad spectrum of polymers with different primary structures based simply on using different diacid and diamine monomers. As a result, by choice of the acid and diamine monomers, one can alter, in somewhat predictive fashion, such polymer properties as melting point, solvent solubility, crystallinity, film and adhesive characteristics and undoubtedly other polymer properties that remain to be studied. Furthermore, the condensations require no aldaric acid hydroxyl group protection/deprotection, a very important cost consideration in the potential production of any of these materials.

This chemistry also provides the option to prepare stereoisomeric polyamides, again with different properties and potentially different uses. For example, condensing a common diamine monomer with D-mannaric, *meso*-galactaric and D-glucaric acid generates diastereoisomeric polyamides. Whereas the poly(D- mannaramides) are repeating *head-tail* polymers (with C-1 and C-6 of the aldaryl unit representing the head and tail ends, respectively), *(12b,13a)*, the poly(galactaramides) have a random distribution of the head and tail ends of the repeating galactaryl unit, as do the poly(D-glucaramides) prepared as described. However, stereoregular repeating *head, tail*-poly(D-glucaramides) *(14)* and alternating *head, tail - tail, head*-poly(D-glucaramides), *(15)*, can be prepared, using modified procedures, but also without hydroxyl protection/deprotection.

Small molecule synthesis

Figure 5 illustrates the use of *meso*-xylaric acid as a precursor for the preparation of a number of synthetic six-membered carbocylic *(16)* and nitrogen heterocyclic products *(17)*. The routes to the carbocylic products shown were similar and involved first a two carbon extension of tri-*O*-acetylxylaryl dichloride (**7**) with diazomethane to the corresponding bis(diazomethyl)ketone which was readily converted to bis(halo- or azidomethyl)diketones (**8**). The latter undergo efficient and convenient cyclization to branched acetylated cycloses which in turn are easily converted to the branched inositols or six-membered unsaturated carbocycles shown. The diamide **10**, derived from the same xylaryl dichloride, and the diamide **11**, from ribaric acid, both served as direct precursors for the nitrogen heterocycle illustrated.

The six membered carbocyclic compounds shown in Figure 5 were prepared by us in a study designed to prepare new branched cyclitols. Cyclitols, both
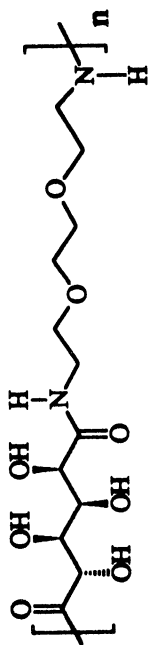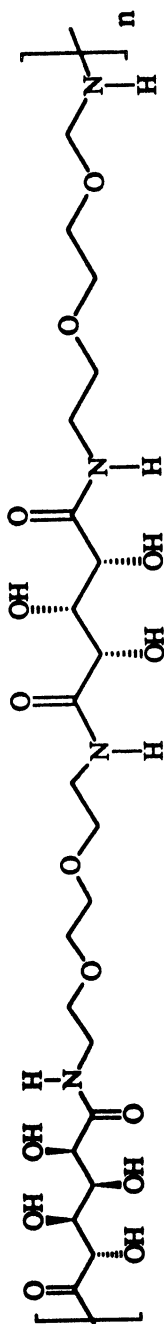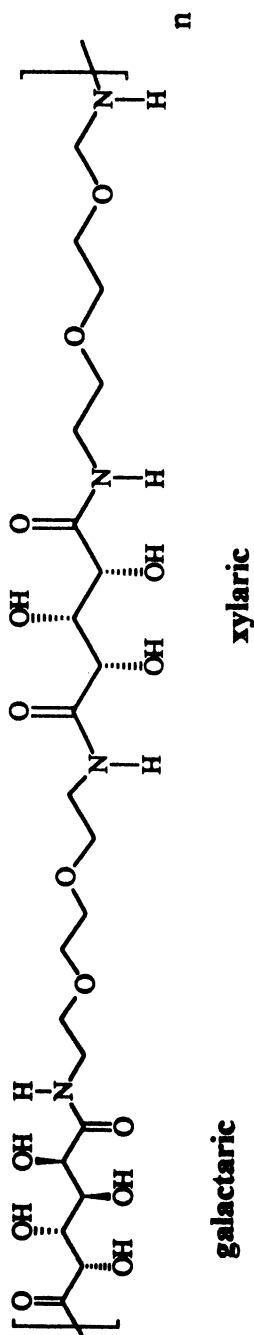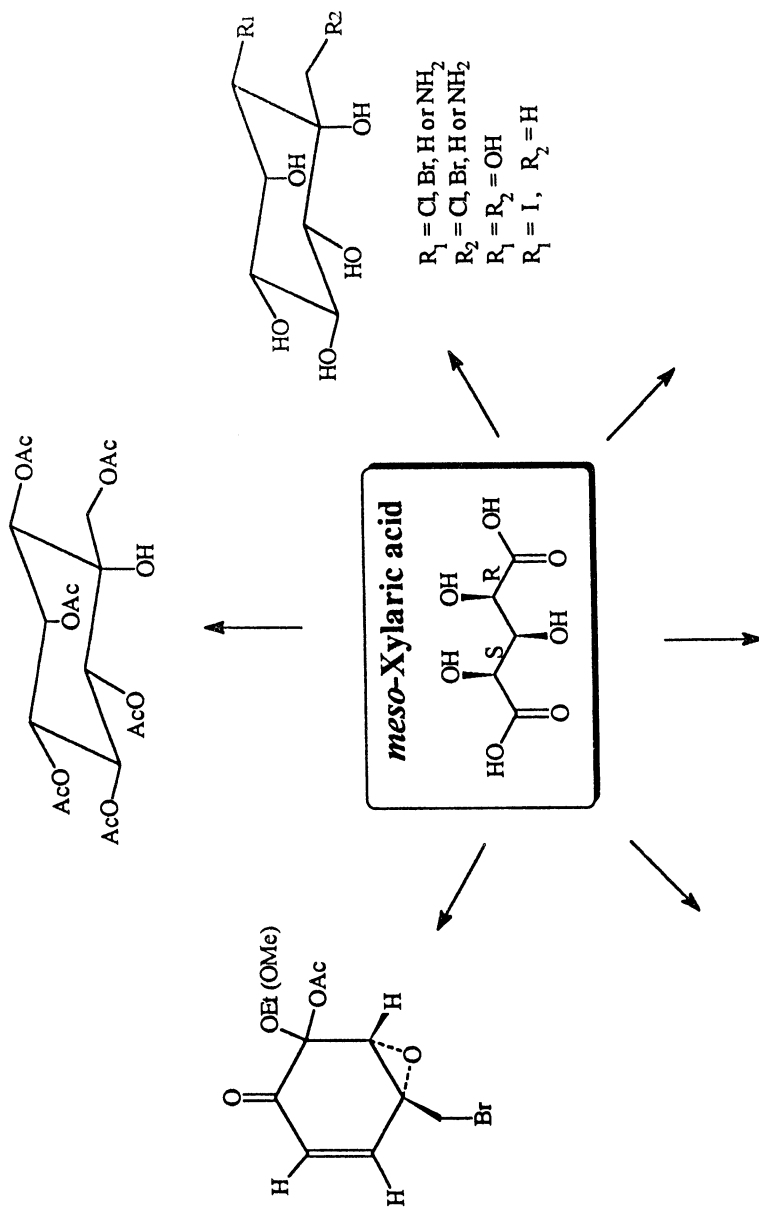
Figure 4. Some polyhydroxypolyamides with adhesive and film forming properties derived from 2,6-dioxaoctane-1,8-diamine and different aldaric acids.

R_1 = Cl, Br, H or NH_2
R_2 = Cl, Br, H or NH_2
R_1 = R_2 = OH
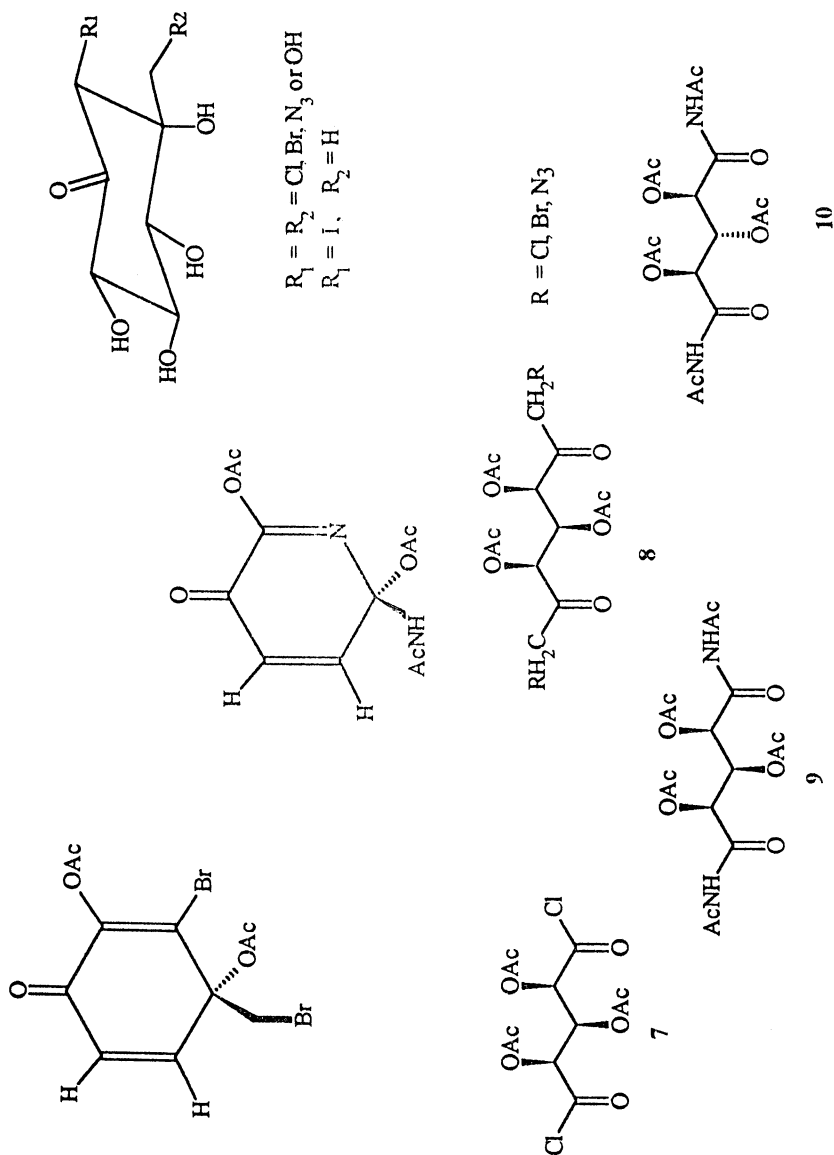R_1 = I, R_2 = H

meso-Xylaric acid

Figure 5. Some branched cycloses, cyclitols and alpha, beta-unsaturated cyclic ketones derived from xylaric acid; some acyclic *xylo* (**8 - 9**) and *ribo* (**10**) ring precurors.

branched and unbranched, were of interest because of their biosynthetic origin from carbohydrates, and as components of aminocylitol antibiotics. The novel cyclitols, unsaturated carbocycles, and unsaturated heterocycle shown were all prepared from xylaric acid, a molecule that has still seen very little use but clearly can be considered as a synthon for preparing small, multi-functional molecules of biological interest. In short, the synthetic value of aldaric acids in organic chemistry and medicinal chemistry is largely unexplored.

Applications of Aldaric Acids and Polyhydroxypolyamides

Glucaric acid applications

Although applications for aldaric acids have not been seriously tapped to date, these molecules clearly offer opportunities as "standalone" chemicals and as chemical precursors for manufacture of other materials, both small molecules and polymers. The applications noted here are those of D-glucaric acid, but in general might also apply to other structurally related aldaric acids. Ultimately, the long range potential economic value of glucaric acid can only be realized when there is at least a moderate supply of less expensive acid available for further applications testing.

Health related applications - D-Glucaric acid is a human metabolite and is generally regarded as a safe compound for human use, making it an attractive compound for health related applications. Currently, the most rapidly growing commercial use of glucaric acid is in the neutraceuticals (diet supplements) area where calcium D-glucarate is being marketed as a nontoxic natural compound for adjuvant cancer prevention, *(18)* and prevention and treatment of hypercholesterolemia *(19)*. Glucaric acid, and other alpha hydroxy acids such as lactic acid, have use in various skin conditioners and skin healing applications *(20)*, skin aging prevention products *(21)*, antibacterial and antiviral compositions *(22)*, and as a hair growth stimulant component *(23)*. It is additionally considered advantageous in the manufacture of a calcium fortified yogurt *(24)*, and calcium fortified powdered milk *(25)*.

Industrial process applications - The following list of applications is taken largely from the patent literature and illustrates the range of applications identified for D-glucaric and/or other aldaric acids: electroplating processes *(26)*, epoxy resin based powder coatings *(27)*, applications in sugar cane *(28)* and sugar beet processing *(29)*, as a cement additive *(30)*, in bleaching textile formulations *(31)*, as a dispersing and milling aid for inorganic fillers and pigments for production of lacquers, dyes, paper, etc. *(32)*, in ceramic materials with dispersed titanium for corrosion resistance *(33)*, and for the manufacture of some antifogging plastics *(34)*.

Other Applications - Other reported applications include glucaric as a component of detergent formulations (assorted patents) *(35-37)*, shampoos *(38)*, calcium and magnesium containing fertilizers *(39)*, fillings (calcium salt) for

ceramics and other porous materials *(40)*, flocculating agents for water clarification *(41)*, as an additive in the manufacture of noodles *(30)*, and as a calcium chelating agent for soil stabilization *(42)*.

A number of the applications also list L-tartaric acid and D-glucaric acid as having comparable properties, both being hydroxy acids and chelators. When inexpensive glucaric acid becomes commercially available on a significant scale, it has applications waiting for a supply and could overtake uses now dominated by tartaric acid. Additional applications unique to glucaric acid will also benefit from a dependable source.

Polyhydroxypolyamides Applications

Opportunities for the polyamides described above, like that of glucaric acid itself, have yet to be realized, and will depend in part on a supply of inexpensive glucaric acid. However, any successful commercial ventures with these polymers are likely to take advantage of one or more factors concerning their preparation and properties. A multitude of these polyamides are possible given their ease of preparation, a method that requires no hydroxyl protection/deprotection. Polymer properties such as hydrophobic/hydrophilic balance, film forming and adhesive properties, water solubility/insolubility, orientation of the chiral D-glucaryl unit in the polymer, charge on the polymer, etc., can be manipulated by the choice of glucaric acid - diamine(s) combination, and whether a procedure to prepare random or stereoregular polyamides is used. Furthermore, given the apparent biodegradability of the polymers *(43)*, applications that take advantage of this property also become important. As biodegradable materials, they have very different properties from the more conventional biodegradable polyester materials, such as poly(lactic acid). The polyamides might not compete with the polyesters in some applications, but the polar properties of the polyhydroxypolyamides might make them better candidates than polyesters for other biodegradable materials applications. Given what we know at present about these polyamides the following potential applications are reasonable: biodegradable adhesives *(44)*, specialty time release fertilizers *(43)*, industrial chemicals for the textile and paper industries, water treatment chemicals, detergent components, hydrogel components, composite material components, and specialty film and fiber materials.

The above are optimistic applications targets for the materials, and while the potential for commercial success has yet to be determined, the challenges associated with commercial development of biodegradable materials are significant and well known. Poly(lactic acid) (PLA) was studied for about forty years before it was announced by Dow - Cargill in January of 2000 that the first large scale production facility for this biodegradable polyester derived from corn starch is now scheduled to be built *(45)*.

Time will tell whether D-glucaric and other aldaric acids will, like L-lactic acid, become important chemical building blocks from renewable agricultural resources.

Potential Commercial Markets - Aldaric acids, and in particular D-glucaric acid, represent a class of molecules whose direct use potential and synthetic potential have yet to be realized. Thus one can only speculate on the market potential they may have. Their monetary value will depend on to what extent they become commercially available and at what cost, and how many applications become economical. However, these acids are derived from renewable agriculture resources (in particular starch), and the growing trend toward adding value to ag materials will sooner or later drive their production and applications development. When that occurs we will know how much they are actually worth.

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