ALTERNATIVE SWEETENERS
SECOND EDITION, REVISED AND EXPANDED

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L-Sugars: Lev-O-Cal™

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INTRODUCTION

The L-sugars comprising Lev-O-Cal™ are simple 6-carbon sugars (hexose monosaccharides). They are L-sugars by virtue of having left-handed molecular configurations at the fifth carbon atom. They offer the prospect of providing a low-calorie, true sugar flavor sweetener and bulking agent.

On April 14, 1981, U.S. Patent No. 4,262,032 (1) for use of the L-sugars L-allose, L-altrose, L-fructose, L-galactose, L-glucose, L-gulose, L-idose, L-psicose, L-tagatose, and L-talose as low-calorie sweeteners in foods, beverages, and drugs was awarded and assigned to Biospherics Inc. Corresponding patents in a number of foreign countries where obesity or sugar-implicated diseases are significant problems have also been filed.

BACKGROUND

The natural occurrence of L-sugars is rare, although they have been variously reported as minor unquantitated constituents in natural products. Until recently, L-sugars used in research were chemically synthesized using processes that result in equal amounts of L- and D-forms (2–13). When the L/D mixtures were fed to bacteria, the D- form was consumed, but the L-form was left intact. Despite this easily demonstrated biochemical difference, with its indication that L-sugars might be noncaloric, apparently no one thought to use them as sweeteners. This was probably because of their scarcity and, also, the possibility that they would not taste sweet. However, L-sugars have long been used as chemical markers and for other research purposes.

The structural aspect of importance in L-sugars can best be described by beginning with the carbon atom, generally represented as the center of a tetrahedron with four bonding arms, each extending outward from the center to the four points (Fig. 1). Numerous other atoms or groups of atoms can bond with the carbon atom (Fig. 2). Considering two carbon atoms side by side, each bonding with an atom A at all four of its bonding sites, it can be seen that the resulting structures are identical (Fig. 3). If each carbon atom bonds with three As and a B in the manner shown in Figure 4, they may, at first glance, appear to differ. However, by rotating one of the carbon atoms, the molecules can be superimposed and become identical (Fig. 5). The same identity prevails if the carbon atoms form four bonds with four groups of three different types (e.g., ABCA, ABCB, or ABCC) regardless of which bonds are made with which types. However, if all four bonded groups are different (ABCD), then the configuration cannot be rotated into superposition (Fig. 6). If

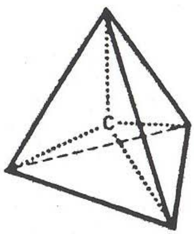

Figure 1 Carbon atom.

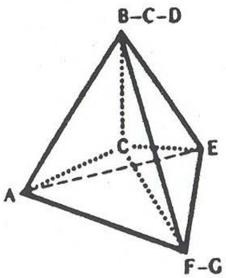

Figure 2 Carbon molecule.

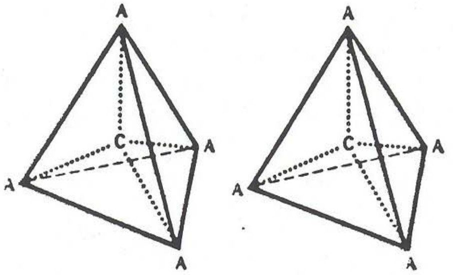

Figure 3 Identical carbon molecules.

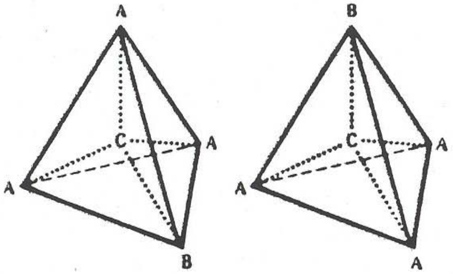

Figure 4 Two apparently different carbon molecules.

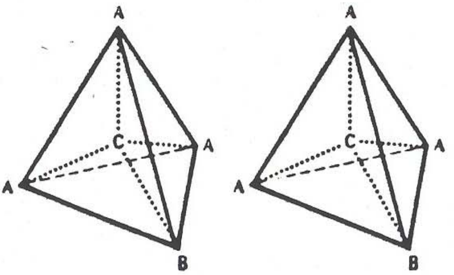

Figure 5 Superimposable mirror images.

these groups are rotated to place any two of the bonds in identical positions, the remaining two will be reversed. These configurations are thus nonsuperimposable mirror images of each other, as are our two hands, and so these compounds have come to be called "left-handed" and "right-handed" sugars. According to the universally accepted system of nomenclature, the configurations are termed "levo" and "dextro" and abbreviated L- and D- (the letters are distinct from the lowercase prefixes l- and d-, or the symbols + and −, used to indicate the direction of rotation of polarized light passing through a sugar solution).

The asymmetric carbon structures of glucose, i.e., dextro-glucose (or D-glucose) and levo-glucose (or L-glucose), are shown in Figure 7. Having the same constituents, mirror-image molecules behave almost identically in chemical reactions. However, in the realm of biochemistry, this similarity may not hold true. In biochemistry, enzymes play an essential role by promoting reactions that would otherwise not occur. This role

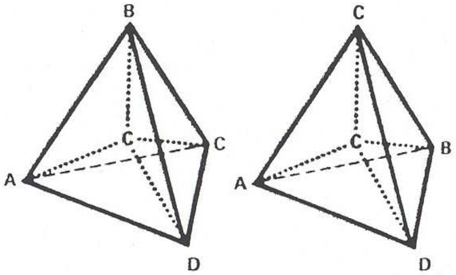

Figure 6 Nonsuperimposable mirror images

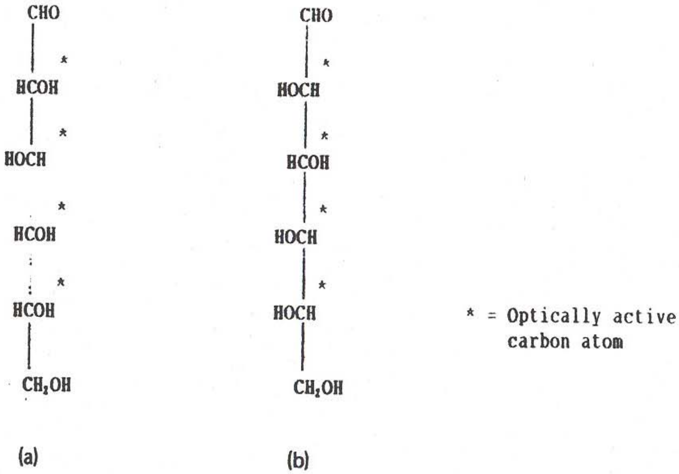

Figure 7 Asymmetric carbon structures of glucose: (a) dextro-glucose (b) levo-glucose.

requires that the enzymes physically fit the shapes of the reacting chemicals in order to bring them together for the reaction to take place. Hence, left-handed (L) sugars cannot fit the enzymes required for sugar metabolism (14) and, extrapolated to humans, should not give us their calories. This difference in caloric availability has been recognized since the time of Pasteur, and more recent findings (15) have supported the nonmetabolizable character of L-sugars.

PHYSICAL AND CHEMICAL PROPERTIES

Differing only because of their mirror image relationship, the L- and D-forms of a particular sugar have identical physical characteristics, such as melting point, solubility, viscosity, texture, hygroscopicity, density, color, and appearance.

Chemical properties of the L- and D-forms in symmetrical (nonbiological) environments are likewise identical. For example, thermal and pH stabilities in various aqueous solutions were identical for the glucose and fructose enantiomers. Unlike all currently available low-calorie sweeteners, the L-sugars brown upon baking. Therefore, L-sugars are expected to yield food products similar to those using D-sugars, but without the calories.

TASTE

Taste testing and sensory profiles of three L-sugars were performed by both trained and expert human panels in accordance with recognized techniques. The taste profiles were similar to those of D-hexoses. Neither cooling effect on the tongue nor any aftertaste was detected. Levels of sweetness were somewhat less than sucrose, but acceptable for product use either directly or enhanced with a small quantity of high-intensity sweetener.

SAFETY AND EFFICACY

An essential step in bringing L-sugars to market is the approval of the U.S. Food and Drug Administration (FDA). To satisfy FDA requirements, three of the 10 L-sugars (under the Biospherics patent) were selected for extensive toxicological testing at a high percentage of diet. So far, two of the sugars have been tested in the three animal species requested by the FDA and the third in rats alone; studies ranged from single-dose acute oral administration up to 6 months feeding at high level in the diet. Organs and tissues were examined for indications of toxicity. No toxic effects were found.

The three selected L-sugars were examined for possible mutagenic activity by in vitro testing recognized and recommended by the FDA. They were all negative.

Sophisticated metabolism testing using radiolabeled L-sugar studies and retained energy balance techniques have been performed on rats fed the three L-sugars in order to gain a detailed picture of how they are dealt with by the host animal. The retained energy balance study on one of the L-sugars showed it to be completely noncaloric to the host animals.

Carefully controlled and monitored single-dose human testing has been performed on two of the three selected L-sugars in a European clinical testing facility. The findings of these studies continue to support the expected nontoxic and low-caloric nature of these L-sugars. However, human acceptability of the two L-sugars tested to date indicates that at least these two may be subject to acceptable daily intake limitations, as are currently available sugar alcohols and nonsweet bulking agents.

Two of the selected L-sugars have been tested for transplacental transfer to rat fetuses and one of these L-sugars tested for potential effect on the normal delivery of baby rats. The findings were negative.

Preliminary in vitro studies on the three selected L-sugars show them to be noncariogenic. Tests for anticariogenicity will be performed.

PRODUCTION PROCESSES

Proprietary process technologies and engineering projections of full-scale production plants have been developed for each of the three selected L-sugars. Technoeconomic evaluations, based on these designs, have yielded detailed manufacturing cost estimates. A variety of process patents has been applied for and should add considerably to the patent protection already afforded by Biospherics' basic L-sugar "use" patent and existing process protection. Current efforts should make possible L-sugar products at reduced manufacturing costs in order to address broader markets. Starting materials are common, low-cost, agricultural materials.

Sample production runs for the three selected L-sugars have yielded quantities of up to 500 pounds used in animal testing and a variety of other research activities. Highly pure crystalline products have been obtained in all cases.

Analytical methods have been developed for a variety of L-sugars and derivatives. The samples produced have been carefully scrutinized for purity and consistency.

MARKET PROSPECTS

Currently, there are three "intense sweeteners" that have been approved by the FDA for use in certain food products: saccharin, acesulfame-K, and aspartame. Of these, aspartame has had the greatest market success—registering close to a billion dollars in worldwide sales this year—principally in the beverage sector where product "bulk" is provided by water.

Applications for high-intensity sweeteners outside of the beverage market sector have been limited primarily because of their lack of bulk. Taste, shelf-life, and heat stability limitations also exist for many of these same uses. The all-important structural functions that natural sugars provide to products like cakes, cookies, ice creams, and candy bars cannot be provided by high-intensity sweeteners alone. While other bulking agents exist or are being developed, none is known to address fully all these needs.

In a talk given at the May 1988 meeting of the International Sweeteners Association, Landell Mills Commodities Studies, authors of *Alternative Sweeteners: Where Will Starch Sweeteners and High Intensity Sweeteners Go from Here?*, described current limitations of low-calorie sweeteners in a market place where the further development of diet sectors is "dependent upon the availability of a good tasting, heat resistant, intense sweetener and an adequate bulking agent." In looking to the future, they concluded that in nonbeverage applications "where there is a sizeable potential, the technical shortcomings of the intense sweeteners frequently restrict their use. The greatest technical difficulty is the absence of an ideal bulking agent, and if such an agent were to be developed then the market for intense sweeteners could be transformed."

L-Sugars offer the prospect of being a combined sweetening and bulking agent—thus providing a possible solution to the issues raised by Landell Mills.

L-Sugars as low-calorie "bulk sweeteners" combine several elements that may be the key to open up these currently inaccessible diet sectors in the food product market. L-Sugars provide a clean, sweet taste and lowered calories while also furnishing the bulk, texture, crystallinity, browning, and other properties so necessary for effective formulation of food products. Testing by our food science staff has produced a number of product prototypes with both low-calorie sweetness and good structural qualities.

Initial target markets include gum, confectionery, baked goods, heat-processed foods, frozen desserts, and ice cream. Considerable interest from manufacturers has been shown. Early discussions with these companies indicate a willingness to pay a premium for the very significant advantages of Lev-O-Cal.

The advantages offered to the consumer by Lev-O-Cal may be unique. Whether used alone or in combination with current or the anticipated heat-stable intense sweeteners, the L-sugars should significantly extend the range and quality of low-calorie foods. They will appeal to those constantly looking for better ways to enjoy great-tasting foods while keeping their waistlines under control and to the significant portion of the population, such as diabetics, who must deny themselves sugar for health reasons.

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