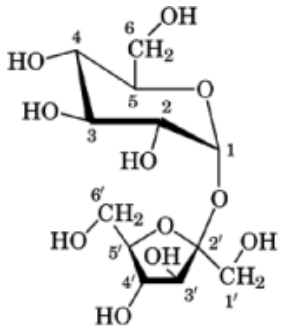
Kirk-Othmer Encyclopedia of Chemical Technology.

SUGAR, SUGAR DERIVATIVES

Sucrose, commonly known as sugar, has been used as a natural sweetening agent for almost 4000 years. It is isolated from sugarbeet (*Beta vulgaris*) in Europe and from sugarcane (*Saccharum officinarum*) in the tropics. Its total world production in 1994–1995 was 116 million metric tons.

Sucrochemistry has seen rapid advances since the 1960s. Whereas well-characterized sucrose derivatives numbered only about 15 in 1965, over 300 well-identified sucrose compounds have been described more recently in the literature (1).

1. Structure of Sucrose



(1)

Sucrose is systematically named as α-D-glucopyranosyl β-D-fructofuranoside **1** [57-50-1]. It exists in two crystalline forms: a stable A-form crystallized from water, mp 184–185°C, and a metastable B-form recrystallized from methanol, mp 169–170°C (1). It is a nonreducing disaccharide with eight hydroxyl groups, of which three are primary (6, 1′, and 6′) and the remaining five are secondary (2, 3, 4, 3′, 4′). The carbon atoms in sucrose are numbered as primed and unprimed in **1**. The correct ring structure of sucrose was first deduced by methylation studies (2, 3). The configurations at the glycosidic centers were determined as a result of specific enzymic hydrolysis studies (4) and x-ray (5, 6) and neutron diffraction data (7, 8) (see Carbohydrates).

1.1. Conformation

Neutron diffraction studies of sucrose revealed the presence of two strong intramolecular hydrogen bonds: O-2–HO-1′ and O-5–HO-6′ in the crystal form (7, 8). These interactions hold the molecule in a well-ordered and rigid conformation. The two rings are disposed at an angle close to 90°, with the glucopyranosyl and fructofuranosyl residues adapting $^4C_1$ chair and $_3T^4$ twist conformations, respectively.

The conformation of sucrose in solution has been extensively investigated. Hard-sphere exoanomeric (HSEA) methods, supported by ^{1}H- and ^{13}C-nmr data, revealed that sucrose in dilute solution had a similar conformation to the crystal state but with only one intramolecular H bond between O-2 and HO-1′ (9). Further support of this conformation was provided by ^{13}C-nmr spin relaxation studies (10, 11). An additional conformation containing a hydrogen bond between HO-3′ and O-2 was shown to be important (12). Using x-ray and Raman techniques, no evidence for intramolecular hydrogen bonds in dilute solution ($<0.7\ M$) was found, but at saturated solution the conformation resembled that of the crystal structure (13). Further nmr studies on sucrose in water have indicated that the O-2–HO-1′ hydrogen bonding was not permanently maintained (14). The solid state ^{13}C-nmr spectra of partially deuterated crystalline sucrose has been reported (15). The spectrum showed some marked differences over the solution spectrum, not the least that C-1′ was observed at lower field with C-6 and C-6′ resonances at higher field. However, these differences are not unexpected considering the differences in electronic environments on going from solid to solution states.

2. Ethers

2.1. Trityl Ethers

Treatment of sucrose with four molar equivalents of chlorotriphenylmethyl chloride (trityl chloride) in pyridine gives, after acetylation and chromatography, 6,1′,6′-tri-*O*-tritylsucrose [35674-14-7] and 6,6′-di-*O*-tritylsucrose [35674-15-8] in 50 and 30% yield, respectively (16). Conventional acetylation of 6,1′,6′-tri-*O*-tritylsucrose, followed by detritylation and concomitant C-4 to C-6 acetyl migration using aqueous acetic acid, yields a pentaacetate, which on chlorination using thionyl chloride in pyridine and deacetylation produces 4,1′,6′-trichloro-4,1′,6′-trideoxygalactosucrose [56038-13-2] (sucralose), a low calorie sweetener (17).

2.2. Methyl Ethers

Methylation of sucrose is generally conducted under basic conditions. Etherification occurs initially at the most acidic hydroxyl groups, HO-2, HO-1′, and HO-3′, followed by the least hindered groups, HO-6 and HO-6′. Several reagents have found use in the methylation of sucrose, including dimethyl sulfate–sodium hydroxide (18, 19), methyl iodide–silver oxide–acetone, methyl iodide–sodium hydride in *N, N*-dimethylformamide (DMF), and diazomethane–boron trifluoride etherate (20). The last reagent is particularly useful for compounds where mild conditions are necessary to prevent acyl migration (20).

2.3. Other Alkyl Ethers

Sucrose has been selectively etherified by electrochemical means to generate a sucrose anion followed by reaction with an alkyl halide (21, 22). The benzylation of sucrose using this technique gives 2-*O*-benzyl- (49%), 1′-*O*-benzyl- (41%), and 3′-*O*-benzyl- (10%) sucrose (22). The benzylation of sucrose with benzyl bromide and silver oxide in DMF also produces the 2-*O*-benzyl ether as the principal product, but smaller proportions of 1′- and 3′-ethers (23). Octadienyl ether derivatives of sucrose, intermediates for polymers, have been prepared by a palladium-catalyzed telomerization reaction with butadiene in 2-propanol–water (24).

2.4. Silyl Ethers

The preparation of per-*O*-trimethylsilyl ethers of sucrose is generally achieved by reaction with chlorotrimethylsilane and/or hexamethyldisilazane in pyridine (25, 26). However, this reaction is not selective and in general per-trimethylsilyl ethers are only used as derivatives for gas chromatographic studies.

Sterically hindered silyl ethers such as *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, and tricyclohexylsilyl have been proposed as alternatives to trityl ethers. Reaction of sucrose with 3.5 molar equivalents of *tert*-butyldimethylsilyl chloride produces the 6,1′,6′-tri-*O*-silyl derivative in good yield (27). Silylation of sucrose with 0.65 equivalents of *tert*-butyldimethylsilyl chloride in pyridine gives the corresponding 6′-, 6,6′-di-, and 6,1′,6′-tri-*O*-*tert*-butyldimethylsilyl ethers in yields of 10.5, 36.4, and 33.5%, respectively. Monosubstitution at C-6 and C-1′ under the conditions employed was not observed. When sucrose was treated with one molar equivalent of the more sterically hindered *tert*-butyldiphenylsilyl chloride in pyridine, 6′-*O*-*tert*-butyldiphenylsilylsucrose was isolated in 49% yield (28). 6,6′-Di-*O*-*tert*-butyldiphenylsilylsucrose (78%) is obtained as the principal product when three molar equivalents of the silylating reagent are used. The 6,1′,6′-tri-*O*-*tert*-butyldiphenylsilylsucrose is the principal product on treatment of sucrose with 4.6 molar equivalents of the silylating reagent. These results clearly show that HO-6′ is the most reactive site toward silylation.

These hindered silyl ethers are generally more stable to acid hydrolysis than their trityl ether equivalents and can be removed using tetrabutylammonium fluoride. However, deprotection can be difficult and if there are ester groups they can hydrolyze and/or migrate. These difficulties and the relative expense of the reagents mean that trityl ethers have seen more use as selective protecting groups in industrial sucrochemistry.

2.5. Cyclic Acetals

One of the most significant developments in the chemistry of sucrose was the synthesis of cyclic acetals which, despite many attempts, were not synthesized until 1974. The first synthesis of 4,6-*O*-benzylidenesucrose was achieved from the reaction of sucrose with α, α-dibromotoluene in pyridine (29). Since then, many new acetalating reagents have been used to give a variety of sucrose acetals, generally by transacetalation reactions.

Treatment of sucrose with 2,2-dimethoxypropane, DMF, and toluene-*p*-sulfonic acid gives 4,6-*O*-isopropylidenesucrose and 4,6:2,1′-di-*O*-isopropylidenesucrose (30, 31). The 4,6-mono- and 4,6:1′2-diacetals are obtained in 60 and 70% yields, respectively, using the kinetic acetalating reagent, 2-methoxypropene (32). The unique eight-membered 2,1′-cyclic acetal bridges the two rings in sucrose, is more stable to acid than the 4,6-acetal linkage, and has been effective in providing access to selective reactions at C-2 and 1′ positions in sucrose. Interesting 8- and 12-membered ring cyclic acetals of sucrose have been synthesized by using 2,2-dimethoxydiphenylsilane, DMF, and toluene-*p*-sulfonic acid to give the 2,1′- and 2,1′:6,6′-diphenylsilylene derivatives in 45 and 10% yields, respectively (33).

3. Esters

3.1. Acetates

Because of the significant interest in selective acetylation reactions of sucrose, the need for a convenient and unambiguous method of identification has been recognized (34, 35). The position of an acetyl group in a partially acetylated sucrose derivative can be ascertained by comparison of its ^{1}H-nmr acetyl methyl proton resonances after per-deuterioacetylation with those of the assigned octaacetate spectrum. The synthesis of partially acetylated sucroses has generally been achieved either by way of selectively protected derivatives such as trityl ethers and cyclic acetals or by direct selective acetylation and deacetylation reactions.

6-*O*-Acetylsucrose [63648-81-7] has been prepared in 40% yield by direct acetylation of sucrose using acetic anhydride in pyridine at 40°C (36). The 6-ester has subsequently been obtained in greater than 90% yield, by way of 4,6-cyclic orthoacetate. Other selective methods for the 6-acylated derivatives include the use of alkyl tin reagents such as dibutyl tin oxide (37) and of dibutyl stannolane derivatives (38). Selective acetylation of sucrose by an enzymic process has also been described. Treatment of sucrose with isopropenyl acetate in pyridine in the presence of Lipase P Amano gave, after chromatography, 6-*O*-acetylsucrose (33%) and

4′,6-di-*O*-acetylsucrose (8%). The latter compound has been obtained in 47% yield by the prolonged treatment (39).

The selective deacetylation of sucrose octaacetate [126-14-7] provides another route to partially acetylated sucrose derivatives. The selective chemical deacetylation of sucrose octaacetate has been the subject of much investigation (40–44). Reaction of the octaacetate absorbed on aluminium oxide produces heptaacetates that have the 6′-OH, 4-OH and 4′-OH groups free, but in low yield (40). This method has been modified (41–43); methanolic solutions of sucrose octaacetate and heptaacetates are adsorbed onto alumina impregnated with potassium carbonate. The various reactions produce heptacetates that have free hydroxyl groups at C-1′,3′,4′,6′ positions (41); hexaacetates with free hydroxyl groups at C-3′,4′ and C-1′,3′ (42); and pentaacetates with free hydroxyl groups at C-3′,4′,6′, C-1′,3′,4′, and C-2,3′,4′ positions (43), in low to moderate yields. More recently, sucrose octaacetate has been deacetylated using primary amines in the absence of solvents, to produce 2,3,4,6,1′,6′-hexa-*O*-acetylsucrose in 22% yield (44).

Sucrose octaacetate has been selectively deacetylated with a number of lipases and proteases in buffer solutions or biphasic media to produce 2,3,4,6,1′,3′,6′-hepta-*O*-acetylsucrose (45), 2,3,4,3′,4′-penta-*O*-acetylsucrose [34382-02-2], and 2,3,6,1′,6′-penta-*O*-acetylsucrose [35867-25-5] (46–51). Wheat germ lipase exclusively deacetylates in the fructose ring to produce 2,3,4,6,1′,3′-hexa-*O*-acetylsucrose and 2,3,4,6,1′-penta-*O*-acetylsucrose (52). Enzymic deacetylation of sucrose octaacetate with various lipases and proteases in organic solvents containing minimal amounts of water has been investigated (53). Prior to use, commercial enzymes are precipitated from a pH-adjusted buffer, dried, and then rehydrated. Identified were a 3:1 mixture of 3′- and 1′-hydroxy-heptaacetates using lipase AY 30 (*Candida cylindracea*), the 3′-hydroxy-heptaacetate from porcine pancreatic lipase, the 6′-hydroxyheptaacetate using lipase SP-435 (*Candida antartica*), and a 1:1 mixture of 4- and 6-hydroxy-heptaacetates with lipase AP 12 (*Asperilligus niger*). Of the protease enzymes, protease N (*Bacillus subtilis*) produces a 1:1:1 mixture of 3′-, 1′-, and 6′-hydroxy-heptaacetates. The 6′-hydroxy-heptaacetate was the predominant product with the serine protease proleather (*Bacillus subtilis*) and alcanase (*Bacillus licheniformis*). On prolonged treatment with the latter enzymes, a mixture containing unreacted starting material, 1′- and 6′-hydroxy-heptaacetates, 1′,6′-dihydroxy-hexaacetate, and the 6,1′,6′- and 4,1′,6′-trihydroxy-pentacetates were identified. The 4,1′,6′-trihydroxy-pentaacetate was reportedly isolated as a single compound but no yield was given (53).

3.2. Benzoates

The selective debenzoylation of sucrose octabenzoate [2425-84-5] using isopropylamine in the absence of solvents caused deacylation in the furanose ring to give 2,3,4,6,1′,3′,6′-hepta- and 2,3,4,6,1′,6′-hexa-*O*-benzoylsucroses in 24.1 and 25.4% after 21 and 80 hours, respectively (54). The unambiguous assignment of partially benzoylated sucrose derivatives was accomplished by specific isotopic labeling techniques (54). Identification of any benzoylated sucrose derivative can thus be achieved by comparison of its ^{13}C-nmr carbonyl carbon resonances with those of the assigned octabenzoate derivative after benzoylation with 10 atom % benzoyl–carbonyl ^{13}C chloride in pyridine.

Reaction of 4,6:1′,2-di-*O*-isopropylidenesucrose in pyridine–chloroform with 3.3 molar equivalents of benzoyl chloride at 0°C eventually produced 3′,6′-di-*O*-benzoylsucrose (36%) as the major and 3′,4′,6′- and 3,3′,6′-tribenzoates as the minor products. The relative reactivities of the hydroxyl groups toward benzoylation was HO-3′ $\approx$ HO-6′ $>$ HO-4′ $>$ HO-3 (55).

3.3. Pivalates

The selective pivaloylation of sucrose with pivaloyl (2,2-dimethylpropionyl) chloride has been thoroughly investigated (56). The reactivity of sucrose toward pivaloylation was shown to be significantly different from other sulfonic or carboxylic acid chlorides. For example, reaction of sucrose with four molar equivalent of

toluene-*p*-sulfonyl chloride in pyridine revealed, based on product isolation, the reactivity order of O-6 $\approx$ O-6′ $>$ O-1′ $>$ O-2 (57). In contrast, a reactivity order for the pivaloylation reaction, under similar reaction conditions, was observed to be O-6 $\approx$ O-6′ $>$ O-1′ $>$ O-4. Two divergent routes to sucrose octapivalate by way of this reaction have been suggested, each the result of different reactivities of the partially pivalated derivatives toward further acylation: (*1*) 6,6′-OH $>$ 1′-OH $>$ 4′-OH $>$ 2-OH $>$ 4-OH $>$ 3′-OH $>$ 3-OH, and (*2*) 6,6′-OH $>$ 1′-OH $>$ 3′-OH $>$ 3-OH $>$ 4′-OH $>$ 2-OH and 4-OH.

3.4. Fatty Acid Esters

There has been much interest in the selective esterification of sucrose with fatty acids, primarily to produce surfactants, emulsifiers, detergents, and fat replacers (58–66), which comprise an ever-increasing market. These derivatives can be produced on an industrial scale by solventless or melt reactions. The transesterification reaction of sucrose with fatty acid methyl esters or triglycerides in the presence of a base, such as potassium carbonate, at 130–150°C, has been reported to give the corresponding fatty acid esters (58). Reactions using methyl esters are conducted under reduced pressure, thus removing methanol and driving the equilibrium to favor the formation of the sucrose fatty acid derivative.

The monofatty acid esters are surfactants and emulsifiers and have the advantage that they are biodegradable, nontoxic, edible, and can inhibit the growth of microorganisms in some cases (67). Produced by Dai-Ichi Kogyo Seiyaku Company, Ltd. in Kyoto and Mitsubishi Corporation in Tokyo, Japan, they are approved by the U.S. FDA as food additives. Sucrose monofatty acid esters are used in food formulations and, because of their excellent skin compatibility, find application in shampoos and cosmetics (qv). They are also used on fruits and vegetables as edible semipermeable coatings to retard ripening and reduce wastage resulting from rotting.

A commercially interesting low calorie fat has been produced from sucrose. Proctor & Gamble has patented a mixture of penta- to octafatty acid ester derivatives of sucrose under the brand name Olestra. It was approved by the FDA in January 1996 for use as up to 100% replacement for the oil used in preparing savory snacks and biscuits. Olestra, a viscous, bland-tasting liquid insoluble in water, has an appearance and color similar to refined edible vegetable oils. It is basically inert from a toxicity point of view as it is not metabolized or absorbed. It absorbs cholesterol (low density lipoprotein) and removes certain fat-soluble vitamins (A, D, E, and K). Hence, Olestra has to be supplemented with these vitamins. No standard LD_{50} tests have been performed on Olestra; however, several chronic and subchronic studies were performed at levels of 15% in the diet, and no evidence of toxicity was found. No threshold limit value (TLV), expressed as a maximum exposure per m^3 of air, has been established, but it is estimated to be similar to that of an inert lipid material at 5 mg/m^3.

Olestra is prepared by a solventless transesterification process in which sucrose is treated with methyl ester of fatty acids in the presence of sodium methoxide between 100–180°C for 14 hours (68). The manufacturing process involves removal of the unreacted fatty acid esters by enzymic hydrolysis with lipases, refining, bleaching, and deodorizing to produce sucrose polyesters containing five or more fatty acid ester groups.

3.5. Other Carboxylic Esters

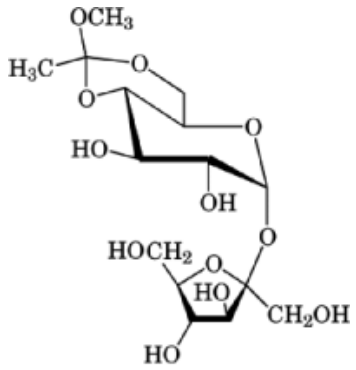
Selective 2-*O*-acylation of sucrose has been achieved by way of the 2-oxyanion compound. Treatment of sucrose in DMF with 3-lauryl-, 3-stearyl-, 3-hydrocinnamoyl-, and 3-(4-phenylbutyryl)-thiazolidine-2-thione derivatives and sodium hydride produced the corresponding 2-*O*-acyl derivatives in good yield (69). Syntheses of 6-*O*-acylsucroses were also achieved by acylation with 3-acylthiazolidine-2-thione and 3-acyl-5-methyl-1,3,4-thiadiazole-2(3*H*)-thione derivatives in the presence of sodium hydride in DMF, followed by acyl migration using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or aqueous triethylamine. 6-*O*-Acylsucroses were obtained directly when only DBU was used (70).

Enzymatic acylation reactions offer considerable promise in the synthesis of specific ester derivatives of sucrose. For example, reaction of sucrose with an activated alkyl ester in *N*,*N*-dimethylformamide in the

presence of subtilisin gave 1′-*O*-butyrylsucrose, which on further treatment with an activated fatty acid ester in acetone in the presence of lipase *C. viscosum* produced the 1′,6-diester derivative (71, 72).

3.6. Orthoesters

The value of cyclic orthoesters as intermediates for selective acylation of carbohydrates has been demonstrated (73). Treatment of sucrose with trimethylorthoacetate and DMF in the presence of toluene-*p*-sulfonic acid followed by acid hydrolysis gave the 6-*O*-acetylsucrose as the major and the 4-*O*-acetylsucrose [63648-80-6] as the minor component. The latter compound underwent acetyl migration from C-4 to C-6 when treated with an organic base, such as *tert*-butylamine, in DMF to give sucrose 6-acetate in >90% yield (74). When the kinetic reagent 2,2-dimethoxyethene was used, 4,6-*O*-(1-methoxyethylidene) sucrose [116015-72-6] **2**, the intermediate for 6-*O*-acetylsucrose was obtained in near quantitative yield (75). The synthesis of 4,6-*O*-(1-ethoxy-2-propenylidene)sucrose has also been reported (76). Mild hydrolysis of this unsaturated cyclic orthoester derivative produced 4-*O*- and 6-*O*-acrolylsucrose for polymerization studies. The use of orthoester derivatives in the synthesis of 6-*O*-acetyl-2,3,4-tri-*O*-(3*S*-methylpentanoyl)sucrose, a precursor of tobacco flavor, has been described (77).



(2)

3.7. Phosphate Esters

The phosphorylation of sucrose using sodium metaphosphate has been reported (78). Lyophilization of a sodium metaphosphate solution of sucrose at pH 5 for 20 hours followed by storage at 80°C for five days produced a mixture of sucrose monophosphates. These products were isolated by preparative hplc, with a calculated yield of 27% based on all organic phosphate as sucrose monoesters. Small proportions of glucose and fructose were also formed.

3.8. Sulfonate Esters

Sucrose sulfonates are valuable intermediates for the synthesis of epoxides and derivatives containing halogens, nitrogen, and sulfur. In addition, the sulfonation reaction has been used to determine the relative reactivity of the hydroxyl groups in sucrose. The general order of reactivity in sucrose toward the esterification reaction is OH-6 $\approx$ OH-6′ $>$ OH-1′ $>$ HO-2.

The selective tosylation of sucrose using limited amounts of tosyl chloride has been studied. Treatment of sucrose with three molar equivalents of toluene-*p*-sulfonyl chloride (tosyl chloride) in pyridine at 0°C for six days produced crystalline 6,6′-di-*O*-tosylsucrose (18%) (57, 79), a mixed syrupy tritosylate fraction (57, 80), and

a small amount of 2,6,1′,6′-tetra-*O*-tosylsucrose (80). The tritosylate fraction gave, after high pressure liquid chromatography, 6,1′,6′-tri-*O*-tosylate (26%) and 2,6,6′-tri-*O*-tosylate (7%). Tetramolar tosylation of sucrose in pyridine at 0°C gave 6,1′,6′-tri-*O*-tosylate (40%) and 2,6,1′,6′-tetra-*O*-tosylsucrose (32%) (81). The use of sterically hindered sulfonates such as 2,4,6-trimethyl- (82, 83) or 2,4,6-triisopropyl- (84) benzenesulphonyl chloride (trimsyl and tripsyl chloride, respectively) offered greater selectivity, resulting into crystalline 6,1′,6′-tri-*O*-trimsylsucrose (50%) and 6,1′,6′-tri-*O*-tripsylsucrose (54%) (82–84).

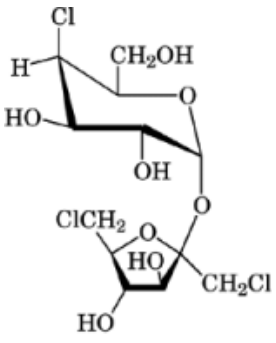
4. Deoxyhalogeno Derivatives

The application of bimolecular, nucleophilic substitution (S_N2) reactions to sucrose sulfonates has led to a number of deoxhalogeno derivatives. Selective displacement reactions of tosyl (79, 85), mesyl (86), and tripsyl (84, 87) derivatives of sucrose with different nucleophiles have been reported. The order of reactivity of the sulfonate groups in sucrose toward S_N2 reaction has been found to be $6 > 6' > 4 > 1'$.

Direct halogenation of sucrose has also been achieved using a combination of DMF–methanesulfonyl chloride (88), sulfuryl chloride–pyridine (89), carbon tetrachloride–triphenylphosphine–pyridine (90), and thionyl chloride–pyridine–1,1,2-trichloroethane (91). Treatment of sucrose with carbon tetrachloride–triphenylphosphine–pyridine at 70°C for 2 h gave 6,6′-dichloro-6,6′-dideoxysucrose in 92% yield. The greater reactivity of the 6 and 6′ primary hydroxyl groups has been associated with a bulky halogenating complex formed from triphenylphosphine dihalide ($(C_6H_5)_3P{=}CX_2$) and pyridine (90).

The first S_N2 displacement reaction at C-2 position in carbohydrates was achieved during the study of sulfuryl chloride reaction with sucrose (92). Treatment of 3,4,6,3′,4′,6′-hexa-*O*-acetylsucrose 2,1′-bis(chlorosulfate) with lithium chloride in hexamethylphosphoric triamide at 80°C for 20 h led to the corresponding 2,1′-manno derivative in 73% yield.

4,1′,6′-Trichloro-4,1′,6′-trideoxygalactosucrose (sucralose) **3** has 650 times the sweetness of sucrose. It was discovered by the carbohydrate chemistry research groups of Philip Lyle Memorial Research Laboratory in Reading and Queen Elizabeth College in London, England (17). It is poorly absorbed by the intestines and passes unchanged through the body. An average daily intake (ADI) of 3.5 mg per kg body weight has initially been recommended for sucralose. It is being developed and marketed by Tate & Lyle in England in collaboration with Johnson & Johnson in the United States. Sucralose has been approved for use in food in Canada, Australia, and the CIS, and is awaiting approval as a food and drink additive by the FDA in the United States and by European and other health authorities.

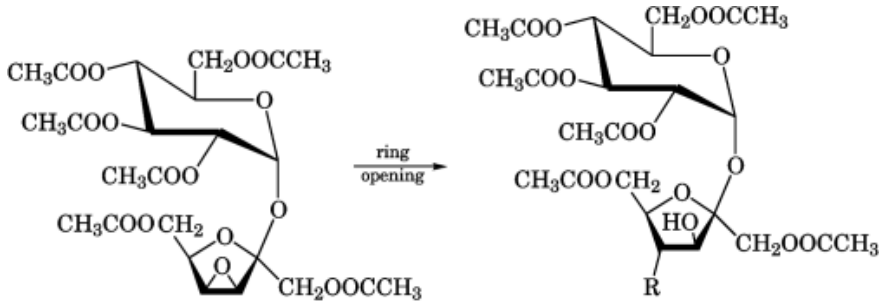


(3)

An economic synthesis of **3** has been patented (74, 91). The process involves (*1*) synthesis of sucrose 6-acetate by way of sucrose 4,6-cyclic orthoacetate **2**, and (*2*) selective chlorination using thionyl chloride–pyridine–1,1,2-trichloroethane, followed by removal of the acetate group.

5. Anhydrides and Epoxides

Anhydride derivatives of sucrose are generally synthesized by intramolecular nucleophilic displacement reactions of the respective sulfonate or deoxyhalogeno derivatives. Synthesis of 3,6- (88), 2,1′- (93), 2,3- (94), and 3′,4′- (95, 96) anhydrides have been described. The base-catalyzed reaction of 2-*O*-tosyl-6,1′,6′-tri-*O*-tritylsucrose produced the expected 2,3-mannoepoxide as the principal product. A small proportion of the 3,4-altroepoxide was also isolated and occurred as a result of migration of the epoxide ring (94). A facile synthesis of sucrose 3′,4′-epoxide, α-D-glucopyranosyl-3,4-epoxy- β-D-lyxohexulofuranoside **4** in 42% yield has been achieved, using triphenylphosphine and diethyl azodicarboxylate in DMF and incorporating acetic acid to prevent the formation of 3,6- and 1′,4′-anhydro rings (96). The sugar epoxides are important intermediates for a variety of derivatives. For example, ring-opening reactions of sucrose hexaacetate 3′,4′-epoxide **4** have led to a number of C-4′-substituted sucrose compounds, eg **5**, where R = N_3 or Cl (97).



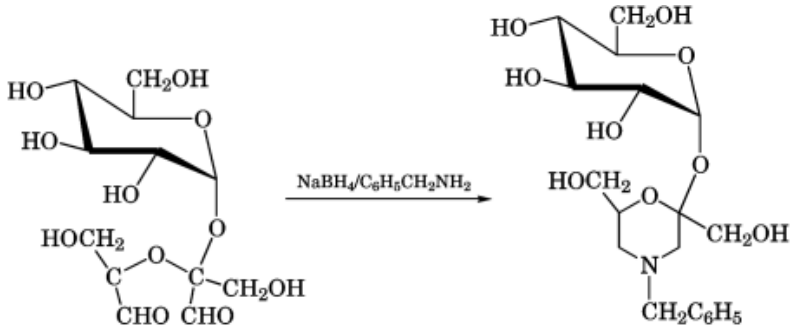
(4) **(5)**

6. Nitrogen-Containing Compounds

The aminodeoxy derivatives of carbohydrates are of interest because they are components of such biologically active materials as antibiotics, glycoproteins, and bacterial polysaccharides. They are usually synthesized by catalytic reduction of the corresponding azido derivatives. Treatment of peracetylated sucrose-3′,4′-lyxo- **4** and sucrose-3′,4′-sorboepoxides with lithium azide in aqueous ethanol in the presence of ammonium chloride, at 80°C for 72 h, gives stereoselectively 4′-azido-4′-deoxysucrose (**5**, R = N_3, 63%) and 2,3,4,6-tetra-*O*-acetyl- α-D-glucopyranosyl-4′-azido-4′-deoxy- β-D-sorbofuranoside (82%), respectively (97). The 4′-azido derivatives have then been converted to the corresponding 4′-amines by catalytic hydrogenation. The ring-opening reaction of sucrose 2,3-manno-epoxide with azide as the nucleophile resulted in axial attack to produce 3-azido-3-deoxy-α-D-altropyranosyl β-D-fructofuranoside (94). 6,6′-Diazido-6,6′-dideoxysucrose has been used as an intermediate for the synthesis of 1-deoxymannonojirimycin (98). The 6,6′-diazido compound was hydrolyzed using ion-exchange resin (Amberlite IR 120 H^+ in water to produce a mixture of 6-azido-6-deoxy-D-glucose and 6-azido-6-deoxy-D-fructose. The latter compound was separated by chromatographic method in 62% yield. The corresponding crystalline glucose derivative was isolated in 64%. The 6-azido-6-deoxy-D-fructose was converted to 1,5-dideoxy-1,5-imino-D-mannitol (78%) by reductive cyclization in methanol–water in the presence

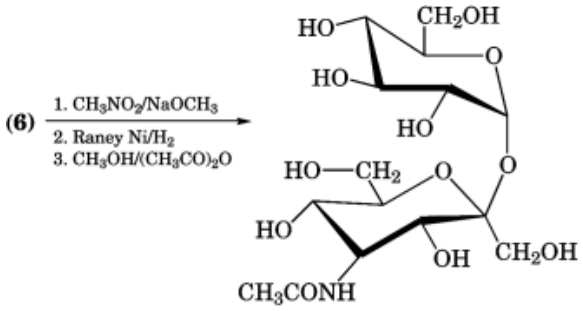
of palladium-on-carbon. The 6-azido-6-deoxy-D-glucose was partially transformed to 6-azido-6-deoxy-D-fructose using glucose isomerase.

Morpholinoglucopyranosides have been synthesized from sucrose by selective lead tetraacetate oxidation of the fructofuranosyl ring to a dialdehyde **6**. This product was subjected to reductive amination with sodium borohydride and a primary amine such as benzylamine to produce the *N*-benzylmorpholino derivative **7** (99).



(6) **(7)**

The dialdehyde also underwent a Fischer cyclization with nitromethane and base to produce a mixture of four diasteriomeric nitropyranosides. The principal product was isolated by chromatography, hydrogenated using Raney nickel and then *N*-acetylated to give α-D-glucopyranosyl-4-acetamido-4-deoxy- β-D-glucoheptulopyranoside **8** (100). The oxidation of sucrose with sodium periodate cleaved both the rings to give the corresponding tetraaldehyde, which on treatment with nitromethane and sodium methoxide produced 3-nitro-3-deoxy- α-D-glucopyranosyl-4-nitro-4-deoxy- β-D-glucoheptulopyranoside as the principal product (100).



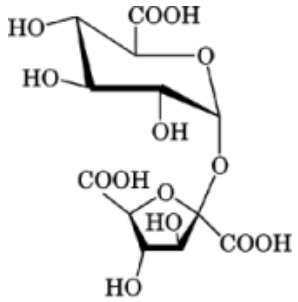
(8)

7. Sulfur-Containing Compounds

The reaction of sucrose 2,3-manno-epoxide with potassium thioacetate and ammonium chloride in aqueous ethanol gave the expected 3-*S*-acetyl-3-thio-altropyranoside (101). Treatment of 6,6′-dibromo-6,6′-dideoxysucrose hexaacetate with potassium thioacetate and *N,N*-dimethylthiocarbamate gave the corresponding derivatives of 6,6′-dithiosucrose. The air oxidation of 6,6′-dithiolsucrose gave the bridged 6,6′-episulfide. A detailed conformational study of sucrose 6,6′-dithiol and sucrose 6,6′-episulfide revealed that they are similar but distinguishable (102).

8. Oxidation Products

Sucrose can undergo two distinct types of oxidation reaction: (*1*) conventional oxidation of primary hydroxyl groups to aldehydes or carboxylic acid residues and a secondary hydroxyl to a ketone, and (*2*) oxidative cleavage of vicinal diols to produce dialdehyde species. The catalytic oxidation of carbohydrates with oxygen and noble-metal catalysts such as platinum and palladium is a well-known and selective reaction (103). The catalytic oxidation of sucrose with platinum and oxygen at pH 7 and at 100°C gave selectively the 6- and 6′-mono- and 6,6′-dicarboxylic acid derivatives. The 1′-OH group under these conditions was not oxidized (104). When the reaction was performed at pH 9 and 100°C, some oxidation occurred at the C-1′ position to produce sucrose 6,6′-dicarboxylate as the major and sucrose 6,1′,6′-tricarboxylate as the minor product. The reaction rate was dependent on temperature; oxidation was slow below 80°C (105). An industrial synthesis of sucrose 6,1′,6′-tricarboxylate **9** (35%), using platinum on carbon in alkaline solution, has been claimed (106). The carboxylate derivatives of sucrose are of interest as chelators, detergent builders, and for application in food and drink formulations.



(9)

Sucrose on treatment with lead tetraacetate undergoes oxidative cleavage of the C-3′ and C-4′ bond to produce the corresponding 2′,5′-dialdehydo derivative. Oxidation with sodium periodate cleaved both rings of the sucrose molecule to give the tetraaldehydo derivative and one molar equivalent of formic acid. The periodate oxidation of sucrose in water and aqueous DMF has been studied (107–109). Oxidation at 25°C and pH 7 in aqueous solution produces the dialdehyde derivatives; no initial selectivity in favor of either of the ring is observed (107). The initial oxidation at C-2 and C-3 is rapidly followed by oxidation at C-4 with the formation of formic acid. The temperature and pH have a strong influence on the selectivity. Increasing the temperature to 75°C and decreasing the pH to 5 favor the formation of the dialdehyde resulting from oxidation in the glucose ring (108). The oxidation of the glucosyl moiety is also favored in 50% aqueous DMF, but the rate of reaction is much slower than in water alone (109).

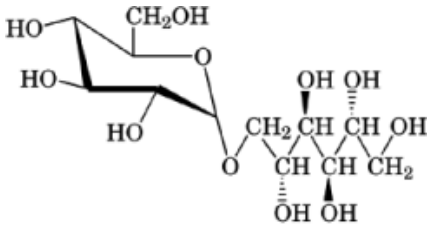
9. Compounds from Enzymic Isomerization

The synthesis of some commercially important bulk sweeteners such as isomaltulose (Palatinose), isomaltitol (Palatinit), and Actilight (formerly Neosugar) has been achieved by enzymatic transformations of sucrose.

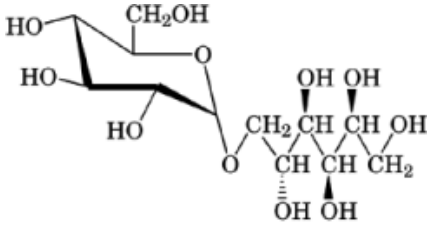
Palatinose, 6-*O*-(α-D-glucopyranosyl)-D-fructose, is produced from sucrose using an immobilized α-glucosyl transferase enzyme from *Protanimobacter rubrum* (110). It is produced by Mitsui Sugar Company in Tokyo, Japan. The annual production is roughly 10,000 metric tons per year. The main market for Palatinose is in Japan, where it is used as a noncariogenic sweetener promoting bifidogenus flora. Palatinose is a

free-flowing, nonhygroscopic, crystalline material (mp 123–124°C). Its sweetness intensity is 42% of that of sucrose. It is not utilized by the microbial flora of the mouth and consequently no organic acid or polysaccharides are formed. It is hydrolyzed in the small intestine and has an energetic value of 16.7 kJ/g (4 kcal/g).

Palatinit is produced by catalytic hydrogenation of Palatinose, which is a mixture of 6-*O*-(α-D-glucopyranosyl)-D-mannitol **10** and 6-*O*-(α-D-glucopyranosyl)-D-sorbitol **11** (111). The process steps involve catalytic hydrogenation (Raney nickel catalyst), filtration and ion-exchange treatment to remove the catalyst, evaporation, and crystallization from hot water. The sweetness of Palatinit is neutral, whereas that of sucrose is round and balanced. Palatinit, which has a caloric value of 8.36 kJ/g (2 kcal/g), is claimed to be a noncariogenic and a suitable sweetener for diabetics. It is produced by the Sudzucker company of Germany. The annual production is 20,000 metric tons.



(10)



(11)

Actilight, a mixture of D-glucose, sucrose, and fructooligosaccharides with one to three fructofuranosyl residues linked by way of β-(1 ⟶ 2) bonds to the fructosyl moiety of sucrose, is commercially produced by microbial fermentation of sucrose using fructosyl transferase enzyme from *Aspergillus niger* (112). These products are claimed to be noncariogenic, reduced caloric sweeteners and promote bifidogenus flora. In Japan, Actilight is produced by Meiji Seika Company, in France by Beghin Meiji Industries, and in the United States by Meiji Seika and Golden Technologies Company. However, it has not yet been approved as a food additive in the United States.

Leucrose, 6-*O*-(α-D-glucopyranosyl)-β-D-fructopyranose [7158-70-5], is synthesized from sucrose using a dextranase enzyme from *Leuconostoc mesenteriodes* and a small proportion of fructose (2%). Pfeifer & Langen of Germany have developed a production process for leucrose that involves extraction of the enzyme, treatment with 65% aqueous solution of sucrose and fructose (1:2 wt/wt) at 25°C, separation of the product from fructose by ion-exchange column chromatography, and crystallization. The product has not yet been launched on the market as of this writing (1996).

Table 1. World Production of White Sucrose for 1994–1995[a]

Area	Sucrose production, 10^6 t
North America	7.498
Central America	11.491
South America	18.542
Europe	27.502
Africa	7.508
Asia	37.782
Oceania	5.798
Total	*116.121*

[a]Sugar Economy (Berlin, Germany).

Table 2. Price of Sucrose, Alditols, and Synthetic Sweeteners

	$/kg			
Product	Europe	United States	World	Sweetness
sucrose	1	0.69	0.27	1
HFCS-55[a]	0.83	0.43		0.95
sorbitol			3	0.6
xylitol			6	0.1
isomalt			5	0.5
aspartame			65	200
acesulfame-K			80	200
saccharin			4.5	300
cyclamate			4.5	25

[a]HFCS = high fructose corn syrup.

10. Polymeric Intermediates

A series of reactive sucrose derivatives as intermediates to a variety of different polymers has been reported. They are still a chemical curiosity and their commercial potential has yet to be established as of this writing. Interesting polymers or polymer intermediates such as sucrose methylacrylate gels, chelating resins, sucrose derivatives with carbonic acid amide groups or *N*-methylated groups as condensation components for formaldehyde, sucrose with photoactive groups, and sucrose derivatives with primary amino groups and their fatty acid amides have all been reported (113).

Monomethylacryloyl and vinylbenzyl derivatives of sucrose have been prepared as intermediates for polymers, and preparation of a range of copolymers of styrene and *O*-methylacryloylsucrose has been described (114). Synthesis of 4- and 6-*O*-acryloylsucrose has been achieved by acid-catalyzed hydrolysis of 4,6-*O*-(1-ethoxy-2-propenylidene)sucrose (76). These acryloyl derivatives have been polymerized and copolymerized with styrene (qv).

11. Sucrose Economics

The total world production of centrifugal sucrose in 1994–1995 exceeded 116 million metric tons; total production in each region is shown in Table 1.

Table 3. World Consumption of Sweeteners, 10^9 kg

Product	1975	1995
sucrose	76.4	116
high fructose corn syrup	0.7	10.1
synthetics	<4	10

The three single biggest producers were India, Brazil, and the United States, with 15.85, 12.6, and 7.24×10^9 kg, respectively. The average world market price for raw sucrose in 1994–1995 was $0.27/kg. A comparison of the price of sucrose and other sweeteners (qv) is given in Table 2.

Sucrose occupies a unique position in the sweetener market (Table 3). The total market share of sucrose as a sweetener is 85%, compared to other sweeteners such as high fructose corn syrup (HFCS) at 7%, alditols at 4%, and synthetic sweeteners (aspartame, acesulfame-K, saccharin, and cyclamate) at 4%. The world consumption of sugar has kept pace with the production. The rapid rise in the synthetic sweetener market during 1975–1995 appears to have reached a maximum.

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