New Non-ionic Polyol Derivatives with Sucrose Mimetic Properties

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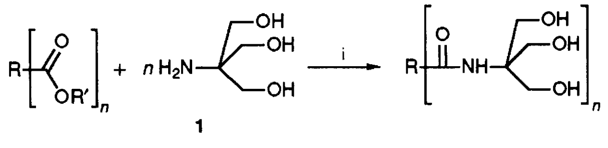
New tris(hydroxymethyl)amidomethane and other non-ionic polyols derived from Cannizzaro condensations are reported, which feature molecular masses and carbon atom to hydroxy group ratios similar to those of sucrose; these materials are (*in vitro*) non-fermentable and accurately reproduce the non-gustatory properties of sucrose, which renders them useful as sugar macronutrient substitutes in low-calorie formulated foods.

Significant efforts have been aimed in recent years at the development of reduced-calorie foods and beverages. Although the use of small amounts of high potency sweeteners such as aspartame is successful in reproducing the sensory profile of sucrose, sweeteners of this type fail to adequately mimic other sucrose characteristics that are important to its function in foods. Included among these properties are freezing point depression, retardation of starch gelatinization, viscosity and mouthcoating, glass formation, and space-filling or 'bulking'. Since high-potency sweeteners deliver none of these properties, a second non-caloric adjuvant, a sugar 'macronutrient substitute' (MNS),† is required for the formulation of low-calorie food products.

A substantial number of materials have been reported to offer utility as sugar MNSs, including various di- and oligo-saccharide alditols[1,2] as well as products with higher[3] or lower molecular weights.[4–6] Problematical with the use of many available sugar MNSs is that they are all either substantially caloric, since at best they permit calorie reductions of only 40–50%,[7,8] or they display undesirable physiological effects, such as flatulence and laxation.[9,10] Our approach to sugar MNSs with optimum properties was directed at the design of non-ionic polyhydroxylic compounds that resemble sucrose in molecular mass (M_w = 342) and their ratio of carbon atoms to hydroxy moieties (C/OH = 1.5). We report here some of these sugar MNS materials based on amides of tris(hydroxymethyl)aminomethane (tris, **1**), as well as formaldehyde condensation products.

The syntheses of tris(hydroxymethyl)amidomethane derivatives could be accomplished readily by condensing tris and appropriate mono-, di-, or tri-carboxylic acid esters in alcohol at reflux temperatures (see Scheme 1). Thus, heating a mixture of **1** and diethyl oxalate (2:1 equivalent ratio) at 140 °C for 1 h afforded a solid, which was dissolved in hot aqueous ethanol (80%), and upon cooling and subsequent recrystallization from water, yielded quantitatively the tris amide **2** (M_w 296, C/OH 1.7, m.p. 224 °C).‡ Similarly, condensation of **1** and diethyl L-tartrate (1:2) in boiling methanol (4 days) afforded the tris amide **3** (89% yield, M_w 356, C/OH, 1.5, m.p. 144 °C) after recrystallization from ethanol (95%).§

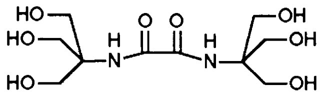


Scheme 1 *Reagents and conditions*: i, heat, MeOH, −*n*R′OH.

A second class of sugar MNSs was obtained *via* Cannizzaro condensation reactions. Thus, cyclohexanone and cyclopentanone were treated with formaldehyde to give the tetramethylol derivatives **4** (71% yield, M_w 220, C/OH 2.0, m.p. 129–130 °C)[11] and **5** (93% yield, M_w 206, C/OH 1.8, m.p. 99 °C), respectively.¶

The sugar MNSs reported here are highly water soluble materials (up to 80%), which feature sucrose-like solution properties over a range of concentrations relevant to typical food applications. Aqueous solutions of the MNSs displayed, for instance, Newtonian viscosities at concentrations of up to 80 w/v% over a shear rate regime of 1–500 s^{-1} (20 °C). A solution of amide **3** (44 w/v%, 50 s^{-1}) had a viscosity of 9.8 mPa s, compared with viscosities of 8.1, 11.29 and 18.8 mPa s for equivalent solutions of sucrose, and the MNS materials Palatinit (a 1:1 mixture of 6-*O*-α-D-glucopyranosyl-D-sorbitol and 6-*O*-α-D-glucopyranosyl-D-mannitol),[12] and Polydextrose (a glucose polycondensation product, M_w ~5000),[3] respectively. Other MNS characteristics bore similar resemblance to sucrose. Thus, the MNS **3** (at 30 w/v%) exhibited osmolality and freeze point depression values of 990 mOsm kg^{-1} and 1.8 °C, compared with corresponding sucrose values of 1013 mOsm kg^{-1} and 1.9 °C, respectively. Compound **3** was also non-hygroscopic, displaying a weight gain of 0.286% at a relative humidity of 83% at 25 °C, as compared with values of 0.292 and 2.893% for sucrose and Palatinit, respectively.

The sugar MNSs produced clear, colourless films upon melting, and were distinguished by good thermal and hydrolytic stabilities. A 20 w/w% aqueous glycerol (70%) solution of polyol **4**, in particular, was found to be undegraded at 110 °C and either pH 3 or pH 7 after periods exceeding 103 days.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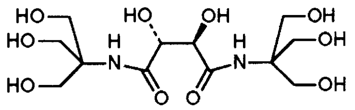
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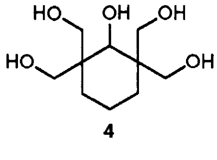
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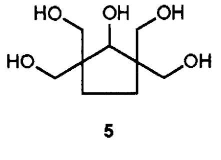
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† The term reflects the high consumption levels of these materials as distinct from the relatively low use levels of high-potency sweeteners. MNSs are also sometimes referred to as 'bulking agents.'

‡ *Spectroscopic data* for **2**: ^1H NMR [$(CD_3)_2SO$]: δ 7.70 (s, 1H), 4.71 (t, *J* 5.3 Hz, 3H), 3.53 (d, *J* 5.3 Hz, 6H); ^{13}C NMR [$(CD_3)_2SO$]: δ 149.7, 61.9, 59.6.

§ *Spectroscopic data* for **3**: ^1H NMR [$(CD_3)_2SO$]: δ 7.43 (s, 2H), 6.01 (d, *J* 6.3 Hz, 2H), 4.90 (t, *J* 5.8 Hz, 6H), 4.19 (d, *J* 6.3 Hz), 3.52 (d, *J* 5.8 Hz, 12H); ^{13}C NMR (D_2O): δ 176.5, 75.4, 64.6, 63.4.

¶ *Spectroscopic data* for **4**: ^1H NMR [$(CD_3)_2SO$]: δ 4.71 (d, *J* 5 Hz, 1H), 4.45–4.55 (m, 4H), 3.30–3.75 (m, 9H), 0.90–1.55 (m, 6H); ^{13}C NMR [$(CD_3)_2SO$]: δ 75.0, 66.3, 60.9, 43.1, 27.5, 16.6. *Spectroscopic data* for **5**: ^1H NMR (CD_3OD): δ 3.84 (s, 1H), 3.68 and 3.76 (ABq, *J* 11 Hz, 4H), 3.49 and 3.58 (ABq, *J* 11 Hz, 4H), 1.40–1.65 (m, 4H). ^{13}C NMR (CD_3OD): δ 81.6, 66.9, 64.8, 52.6, 28.7.

Aqueous solutions of the sugar MNSs (at 20 w/v%) exhibited moderate sweetness corresponding to a sweetness equivalence of about 10–50% with respect to sucrose.

The MNSs were also found to be non-fermentable upon *in vitro* exposure to human fecal microflora,[13,14] which strongly suggests that they are non-caloric. These results indicate, therefore, that the above types of MNS structures do not sufficiently resemble natural polyols or conventional MNSs to be recognized as substrates by the human colonic microflora.

The above findings for the sugar MNSs demonstrate our C/OH ratio model to be effective for the rational design of novel, cleanly sweet and fully functional polyols. Noteworthy is the observation that application of our design criteria seems to permit a degree of flexibility, since deviations of about 30% from the sucrose M_w and C/OH values did not noticably interfere with the desired functionality of the present MNSs. The functionality of sugar in foods appears to be largely colligative in nature as evidenced by the excellent performance of the above sugar MNSs when they were used to fully substitute for sucrose in different food products. We have extended our investigations of non-caloric sugar MNSs to other polyol classes with similar success.[15,16]

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