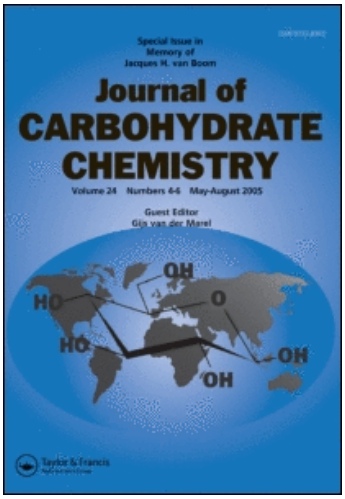

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STUDY ON THE SELECTIVITY OF BENZOYLATION OF METAL CHELATES OF SUCROSE[1]

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ABSTRACT

A study of the selectivity of metal chelate-directed benzoylation of sucrose dianion, relative to unchelated sucrose anion, was conducted as part of a study on new synthetic approaches to the high-potency sweetener sucralose. Ionic complexes of sucrose with various metal ions were prepared in DMF and the resulting complexes reacted at low temperature with benzoic anhydride. Cobalt and manganese salts directed esterification mostly to the 3'-OH on the fructosyl portion. Unchelated sucrose anion and other metals favored esterification at the 2-OH of the glucosyl portion. Migration of the benzoate ester along the glucose portion was observed in the direction *O*-2 to *O*-6 at moderate temperature, but at higher temperature transannular migration was observed from the glucose to the fructose ring. Reaction mixtures were analyzed by HPLC and monobenzoates identified by retention times relative to standards. Six of eight possible monobenzoates of sucrose were isolated from mixtures and identified by their ^{1}H NMR spectra.

INTRODUCTION

Use of carbohydrates as commercial feedstocks for chemical processes is an area of increasing interest because of their ready availability, low cost and high purity.[2] The need to selectively protect sucrose hydroxyl groups for synthetic puposes continues to be an area of

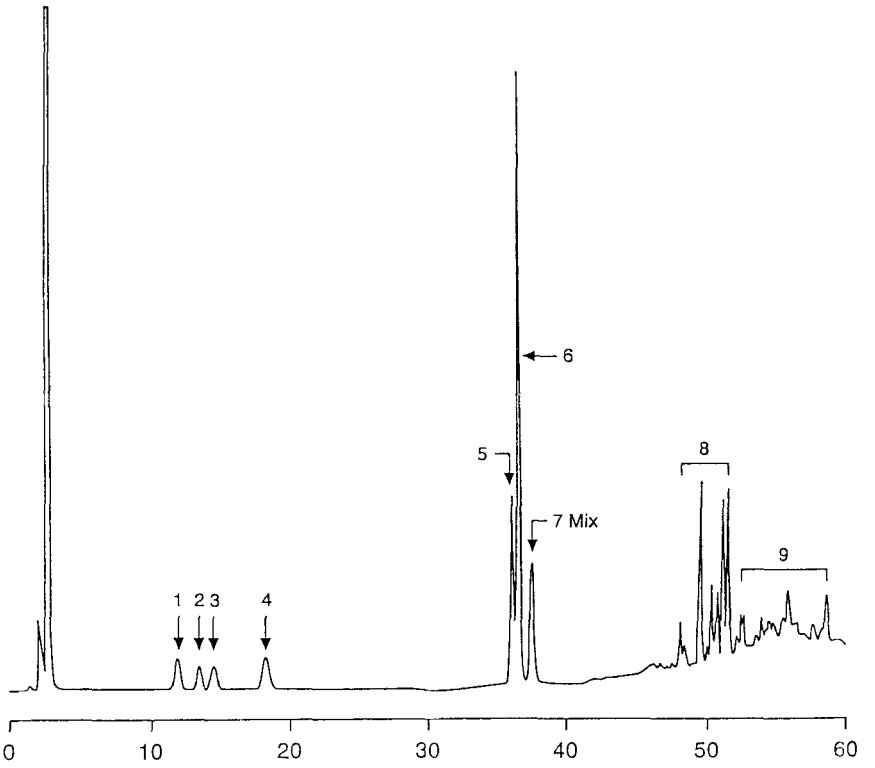

Figure 1. HPLC elution profile of sucrose monobenzoates. Peak assignment: 1 = 2-*O*-benzoate, 2 = 3'-*O*-benzoate, 3 = 4-*O*-benzoate, 4 = 3-*O*-benzoate, 5 = 1'-*O*-benzoate, 6 = 6-*O*-benzoate, 7 = mixture of 4'- and 6'-*O*-benzoate, 8 = dibenzoates, 9 = gradient artifacts. Chromatographic conditions are as described in the General Procedures of the Experimental section.

research interest. Acylation at the primary hydroxyl groups of simple glucosides[3] has been successfully carried out using Mitsunobu chemistry,[4] but similar reactions with sucrose failed to distinguish between the 6 and 6' positions.[5] Another selective method for esterification of the primary hydroxyl of free sugars and simple glycosides with *gluco*, *manno* , and *galacto* configuration has been reported by Baczko and Plusquellec.[6] Chauvin and Plusquellec[7a] have reported the chemoenzymatic synthesis of 6'-*O*-acylsucrose derivatives. Chauvin et al. have reported the highly regioselective acylation of sucrose at O-2 with 3-acylthiazolidine-2-thione.[7b] Dibutyltin oxide has been widely used for selective alkylation and esterification of various carbohydrates.[1,8,9,10] The reaction of sucrose with various organotin derivatives has been reported by Navia,[10a,b] and Vernon and Walkup.[10c]

Studies on the relative reactivity of carbohydrate hydroxyl groups in general have been reviewed by Haines.[11] James, et al.[12] reviewed other studies on the relative reactivity of sucrose hydroxyls. Some of these studies relied on measuring the extent of derivatization at a

Table 1. HPLC Retention Times of Sucrose Monobenzoates

	Glucose			Fructose			
Benzoate Position	2	3	4	6	1'	3'	4'& 6'[b]
Retention time (min.)[a]	9.9	15.8	12.4	35.2	34.7	11.1	36

a. Retention times (R_t) are for HPLC conditions indicated in the general methods; ±0.1 min for R_t<30 min, ±0.3 min for R_t>30 min.
b. Components were partially resolved by analytical HPLC with a Nova-Pak C18 column eluted with 10% acetonitrile in water: R_t (4'-*O*-benzoate) 10.8 min.; R_t (6'-*O*-benzoate) 10.3 min.

position on the molecule in a mixture where a major portion of the molecules were esterified at more than one hydroxyl group. Since the relative reactivity of a given hydroxyl may be different in an unsubstituted molecule than in a substituted derivative, it was of interest to us to investigate the order of reactivity of sucrose hydroxyls in order to produce selected monoesterified derivatives.

In the present study, reaction conditions were chosen so that the extent of derivatization at multiple hydroxyls was minimized and monoesters were the principal components. The non-selective benzoylation of the sucrate anion was used as a point of reference in evaluating the selectivity of the metal chelate directed benzoylations. We chose benzoic anhydride because its low reactivity would enhance the selectivity of the reaction, while the aromatic ring was simple to detect by HPLC using a UV detector. The development of a reliable HPLC method (Figure 1) with which to determine the product distribution in a large number of reactions for the same substrate and products greatly facilitated this study. The retention time for each possible monobenzoate of sucrose is summarized in Table 1.

The chelation of metal ions by carbohydrates is a well studied phenomenon,[13,14,15] however the effect of such chelation on the relative reactivity of carbohydrates, while also extensively investigated, remains a highly empirical area. Avela and coworkers[16] reported on the selectivity of acylation of various sucrose-metal ion complexes but did not identify the structures of the products. Eby and coworkers[15] reported an extensive study on the regioselectivity of alkylation and acylation of the metal chelates of monosaccharide dianions. The locus of anion formation was directed by the positioning of benzyl ethers or acetals on the monosaccharide. The present work builds on the earlier report[16] by identifying the benzoylation products from some of the sucrose-metal ion chelates.

RESULTS AND DISCUSSION

Non-selective esterification of sucrose. The results of non-selective benzoylation of sucrose under various conditions are summarized on Table 2a. When the sucrate anion,

Table 2a. Non-specific Benzoylation of Sucrose.

Solvent	Base	HOAc[a] added	Time (h)	Temp (°C)	Chromatographic Percent of Monobenzoates Esterified at the Specified Position						
					2	3	4	6	1'	3'	4'& 6'
DMF	LiOH	3 eq.	1	0	72.7	1.0	1.0	n.r.[b]	19.6[b]	4.7	1.0
DMF	LiH	3 eq.	3	0	72.1	2.1	4.0	2.5	12.7	6.1	0.6
THF-H_2O[c]	Li_2CO_3	3 eq.	24	0	68.4	4.5	2.9	n.r.[b]	9.3[b]	7.4	7.5
THF-H_2O[c]	Li_2CO_3	0	o.n.	r.t.	8.1	11.4	4.4	63.5	n.r.	5.0	7.7
DMF	Li_2CO_3	0[d]	24	r.t.	14.6	24.9	38.3	5.6	2.5	2.8	11.3
			40	r.t.	14.6	25.4	39.3	5.8	2.6	2.8	9.5

a. Acetic acid was added prior to concentration of the reaction mixture on a rotary evaporator at 50 °C to inhibit benzoate migration.
b. Peaks for the 6- and 1'-*O*-benzoates were not resolved. The latter was the major component.
c. THF-H_2O proportion was 1:1.5.
d. No acetic acid was added because the samples were assayed directly, without work-up.

Table 2b. Benzoate migration in alkaline aqueous DMF[a]

Solvent	Base	HOAc[a] added	Time (h)	Temp (°C)	Chromatographic Percent of Monobenzoates Esterified at the Specified Position						
					2	3	4	6	1'	3'	4'& 6'
DMF/H_2O	Li_2CO_3	0	r.t.	24	14.7	25.9	35.6	9.2	2.6	2.8	9.1
				48	14.7	26.4	30.1	13.9	2.8	2.9	9.3
				72	15.0	26.8	24.2	19.0	2.4	2.8	9.3
			50	24	7.1	11.76	5.7	57.6	4.3	1.8	11.6
				48	6.7	11.1	5.2	56.6	6.4	1.1	12.5
			85	10	6.1	9.2	5.6	48.7	9.6	2.1	18.6
			110	14	3.0	3.7	5.9	18.3	7.7	0	61.4

a. The benzoylation mixture (Table 2: DMF/Li_2CO_3) was quenched with 100 mL water after the aliquot at 40 h was withdrawn. The alkaline aqueous/DMF solution was stirred at ambient temperature and aliquots withdrawn to be assayed at the indicated times. After 72 h at ambient temperature, a further 100 mL portion of water was added to the mixture, the solution was heated to 50 °C and continued to be stirred. Aliquots were withdrawn and assayed at the indicated times. No more water was added prior to raising the temperature of the reaction mixture to 85 or 100 °C. Aliquots were withdrawn and assayed at the indicated times.
abbreviations: n.r.= not resolved; o.n.= overnight; r.t.= room temperature.

generated at low temperature by reaction of sucrose with LiOH or LiH in DMF, or Li_2CO_3 in aqueous THF, was reacted with benzoic anhydride, the major product was the 2-*O*-benzoate. This is consistent with Lichtenthaler's observation[17] that the 2-OH of the glucosyl moiety had the highest electron density based on MNDO calculations. The greater reactivity of the 2-OH position relative to 1'-OH has also been reported by Isaacs et al.,[18] and Lemieux and Barrette[19] for the sulfonylation of sucrose. A likely explanation for this is the existence of the hydrogen bond from O-1' to O-2 which fascilitates the dissociation of H-2.[17]

Non-selective reactions carried out at or above ambient temperature for longer than a few hours are susceptible to acyl migration on the glucose ring (DMF/Li_2CO_3/24-40 h). Water is required to force migration to O-6. Monoesterification at O-2 predominates when the opportunity for acyl migration is minimized by reducing the reaction temperature or by adding acetic acid to the reaction mixture prior to work-up. Reaction of sucrose with benzoic anhydride in the presence of Li_2CO_3 in aqueous THF for 24 hours at 0 °C gave principally benzoylation at O-2 when the mixture was acidified with glacial acetic acid prior to work-up. A similar benzoylation carried out at ambient temperature in which no acetic acid was added resulted in a reduction of the amount of 2-*O*-benzoate and an increase in benzoylation at the other positions in the glucose ring, most notably at O-6.

Benzoate migration on sucrose. The effect of temperature on benzoate migration along the sucrose molecule in aqueous DMF was investigated (Table 2b). A benzoylation

reaction mixture (Table 2a; DMF/Li_2CO_3) was allowed to attain an equilibrium distribution of monobenzoates (40 h at ambient temperature). The solution was diluted with water and again allowed to equilibrate at room temperature over 72 h. During this period, the relative amount of benzoate at O-6 nearly doubled at the expense of 4-*O*-benzoate. The relative amount of other derivatives remained essentially unchanged. When the temperature was raised to 50 °C, the 6-*O*-benzoate became the predominant product. Further increase of the temperature of the solution resulted in a diminution of 6-*O*-benzoylated product and a corresponding increase in the peak containing the mixture of 4'- and 6'-*O*-benzoate. A possible mechanism for the transfer of a benzoyl group across the glycosidic linkage from the glucose to the fructose ring may be by acyl migration from O-2 to O-1'. These two atoms have been shown to be close together in crystalline sucrose[20] as well as in solution,[21] although a number of other conformations are also possible.[22] The further migration of the ester from O-1' to O-4' is readily possible since these two atoms are on the same side of the furanosyl ring plane.

Isolation of sucrose monobenzoates. The non-selective methods proved to be useful methods to prepare and isolate six of the eight monobenzoate derivatives as single compounds. The crude mixture was fractionated on silica to separate the monobenzoates from diesters and unreacted sucrose, then the components of the monobenzoate fraction were separated by preparative HPLC. Ester migration during chromatography on silica could not be avoided completely, but the addition of a small amount of acetic acid in the eluting solvent reduced the extent of isomerization.

It was not possible to effect a preparative separation of the 4'- and 6'-*O*-benzoates, hence this mixture was analyzed by ^1H NMR and structural assignments were made on the basis of homonuclear decoupling experiments and peak areas. The anomeric region of the spectrum showed two anomeric signals of unequal intensity. Decoupling of the larger anomeric doublet (6'-*O*-benzoate) at 5.24 ppm identified H2 at 3.32 ppm. Similar decoupling of H2 identified H3 (3.66 ppm) as a triplet in a crowded region of the spectrum. Irradiation of a triplet at 3.25 ppm (H4) affected the triplet at 3.66 ppm and a complex signal 3.60-3.70 which included H5.

The anomeric doublet (5.34 ppm) of the minor (4'-*O*-benzoate) component overlapped with the H4' triplet at 5.32 ppm. Simultaneous irradiation of these two signals resulted in the collapse of a doublet (H3') at 4.53 ppm to a single peak, of a doublet of doublets (H2) at 3.42 ppm to a doublet and simplification of a complex signal (H5') at 4.05 ppm. Decoupling of a multiplet (H3) at 3.66 ppm caused the collapse of H2 and H4 (triplet, 3.35 ppm) to doublets. Although the complete assignment of the spectrum of both compounds was not possible because of overlapping of signals, confidence in the structural assignments is bolstered by having isolated the other six possible isomers as pure compounds and the interpretation of their ^1H NMR spectra (Table 3).

Metal chelate directed benzoylation of sucrose. The yield of monobenzoate from metal-chelated sucrose was typically 70-85% based on unreacted sucrose versus 30-65% for the non-selective methods on Table 2a. The results are summarized in Table 4. As

Table 3. ^{1}H NMR Assignments for Sucrose Monobenzoates

Benzoate Position	Glucose Ring H1	H2	H3	H4	H5	H6a,b
Glucose						
2-*O*-Bz	5.66 d $J_{1,2}$ 3.7	4.95 dd $J_{2,3}$ 10	4.15 t $J_{3,4}$ 9.2	3.63 t $J_{4,5}$ 9.7	3.97 m	3.80-3.84 m
3-*O*-Bz	5.47 d $J_{1,2}$ 3.9	3.91 dd $J_{2,3}$ 10	5.38 t $J_{3,4}$ 10	3.75-3.82	3.95 m	3.75-3.82
4-*O*-Bz	5.39 d $J_{1,2}$ 3.8	3.63 dd $J_{2,3}$ 9.6	4.06 t $J_{3,4}$ 9.6	5.04 t $J_{4,5}$ 9.6	4.12 m	3.5-3.74 m
6-*O*-Bz	5.40 d $J_{1,2}$ 3.8	3.57 dd $J_{2,3}$ 10	3.76 t $J_{3,4}$ 10	3.43 t $J_{4,5}$ 9.6	4.05 m	4.39 dd $J_{5,6a}$ 2.3; $J_{6a,6b}$ 12.3 4.27 dd $J_{5,6b}$ 5.2
Fructose						
1'-*O*-Bz	5.49 d $J_{1,2}$ 3.8	3.54 dd $J_{2,3}$ 10	3.77 t	3.44 t $J_{3,4}$=$J_{4,5}$ 10	3.83-3.92	3.83-3.92
3'-*O*-Bz	5.43 d $J_{1,2}$ 2.8	3.50 dd	3.78 t	3.70-3.74 m	3.40 m	3.70-3.74 m
4'-*O*-Bz	5.34 d $J_{2,3}$ 3.9	3.42 dd $J_{2,3}$ 10	3.66	3.35 t $J_{3,4}$;$J_{4,5}$ 10	-----	-----
6'-*O*-Bz	5.24 d $J_{1,2}$ 3.9	3.32 dd $J_{2,3}$ 10	3.58 t $J_{3,4}$ 10	3.25 t $J_{4,5}$ 9.4	3.65 m	-----

(continued)

Table 3 (continued). ^{1}H NMR Assignments for Sucrose Monobenzoates

Benzoate Position	Fructose Ring H1'a,b	H3'	H4'	H5'	H6' a,b
Glucose					
2-*O*-Bz	3.47 d 3.35 d $J_{1a',1b'}$ 12	4.15 d $J_{3',4'}$ 8	4.02 t	3.80-3.84 m	3.80-3.84 m
3-*O*-Bz	3.65 s	4.18 d $J_{3',4'}$ 8.5	4.04 t $J_{4',5'}$ 8.5	3.75-3.82	3.75-3.82
4-*O*-Bz	3.61 s	4.14 d $J_{3',4'}$ 8.8	3.98 s $J_{4',5'}$ 8.4	3.81 m	3.4-3.5 m
6-*O*-Bz	3.65 s	4.21 d $J_{3',4'}$ 8.6	4.02 t $J_{4',5'}$ 8.5	3.88 m	3.34 s
Fructose					
1'-*O*-Bz	4.57 d 4.41 d $J_{1a',1'b}$ 12.2	4.28 d $J_{3',4'}$ 8.5	4.07 t $J_{4',5'}$ 8.5	3.83-3.92	3.83-3.92
3'-*O*-Bz	3.52 s	5.62 d $J_{3',4'}$ 7.5	4.52 t $J_{4',5'}$ 7.5	4.11 m	3.88-3.93 m
4'-*O*-Bz	-----	4.53 d $J_{3',4'}$ 8	5.32 t $J_{4',5'}$ 8	4.05 m	-----
6'-*O*-Bz	3.54 s	-----	-----	-----	4.00-4.10 m

preparative methods, the removal of salt during work-up proved to be difficult (data not shown). In the case of the $CoCl_2$, most of the salt could be removed with a chelating resin, but remaining traces lent the product a persistent blue color until it was chromatographed on silica gel.

Table 4. Distribution of Products in Metal Chelate Directed Benzoylation of Sucrose. Molar ratio: sucrose : NaH : M(II)Cl_2 : Bz_2O (2 : 4 : 1 : 2.2)

	Benzoate Position on Sucrose[a]						
	Glucose				Fructose		
Salt	2	3	4	6	1'	3'	4' & 6'
$CaCl_2$	13.3	22.5	4.9	27.1	10.5	2.0	7.1
$MnCl_2$	7.4	---	---	---	2.4	79.8	1.5
$CoCl_2$	8.2	---	---	---	2.6	88.1	---
$NiBr_2$	53.8	1.0	1.0	1.0	7.0	12.2	3.4
$CuCl_2$	68.4	2.7	1.0	5.7	4.7	2.4	2.0
$ZnCl_2$	55.4	4.1	1.0	2.5	12.8	5.7	3.4
$HgCl_2$	39.0	16.3	1.9	3.0	8.0	2.8	5.4

a. Chromatographic percent.

Benzoylation of the calcium chelate resulted in a greater extent of esterification at O-3 and O-6 than at O-2 and O-1'. Each pair was benzoylated to a similar extent which was interpreted to mean that these pairs were involved in the common coordination of the Ca^{+2} ion. It is seductive to suggest that benzoylation at O-6 occurs simply by acyl migration from O-2, but this does not fit with the other data. Benzoylation in DMF/$LiCO_3$ for 24 and 40 h (Table 2a) gives relatively little esterification at O-6 despite a high degree of esterification at O-2, O-3 and O-4. Similarly, reactions in the presence of Ni, Cu and Zn salts (Table 4) show a low degree of benzoylation at O-3, O-4 or O-6 despite a high degree of benzoylation at O-2. Acyl migration simply does not appear to happen under these conditions. Nevertheless, Ca^{2+} may facilitate migration of the benzoate in a way that other metal ions do not. Another possible explanation of the different degree of esterification at each pair may be that the first pair of atoms are close in space and may enter more tightly into the coordination of the calcium ion. A similar observation was made by Eby and coworkers[15] to explain a greater extent of monoacylation at less acidic hydroxyl groups in derivatized monosaccharides. O-3 and O-6 can only be brought in close enough to take part in chelation when the glucose ring is in the higher energy $^1C_4$ conformation, so benzoylation here may be only the result of non-selective benzoylation.

Complexes of cobalt and manganese, which are commonly octahedral when hexacoordinated or tetrahedral when tetracoordinated, gave a high degree of selectivity at O-3' of the fructose ring (79.8% and 88.1% respectively). Benzoylation of sucrose chelates with nickel, copper, zinc or mercury occurred principally at O-2, as in the low-temperature non-selective benzoylation of sucrose in the presence of LiOH, LiH or Li_2CO_3.

The relative reactivity of hydroxyl groups on underivatized sucrose has been extensively studied and reviewed.[11,12,23] It is generally held that the primary hydroxyl groups

at O-6 and O-6' are the most reactive and that O-1' and O-2 may alternate as next most reactive hydroxyls on glucosides depending on the reaction conditions. Under strongly basic conditions the order of reactivity changes such that hydroxyl acidity determines the relative reactivity. Non-selective anionic acylation conditions (LiOH/1 h/ 0 °C) favor the order of reactivity of sucrose hydroxyls O-2>>O-1'>O-3'>O-6,O-6'. Manganese and cobalt change this order to O-3'>>O-2>O-1'> others. Coordination with nickel, copper, zinc or mercury favors acylation at O-2 but vary in the extent of acylation at other positions. Nickel seems to reverse the order of reactivity of O-2 and O-3' (O-2>>O-3'>O-1'> others) from that observed with cobalt and manganese . Zinc also favors benzoylation at O-2, but reverses the order of the next most reactive hydroxyls (O-1'>O-3') relative to that observed for nickel. Coordination with mercury promoted benzoylation primarily on the glucosyl moiety at O-2, and to a lesser extent, on O-3. Benzoylation of the calcium chelate appeared to favor O-6=O-3>O-2=O-1'. The high degree of substitution at different places on the glucose ring is likely an indication of more than one chelation site as discussed above.

In conclusion, non-selective benzoylation of unprotected sucrose was shown to favor O-2. This selectivity was enhanced when the sucrate dianion was complexed with Cu(II), Ni(II), Zn(II), and to a lesser extent, Hg(II) salts. Complexation with Cu(II) or Mn(II) salts changed the selectivity greatly, favoring esterification at O-3'. The position of the hydroxyl group in the ligand field of the metal ion may greatly influence its susceptibility to benzoylation. Depending on the conformation of the sucrose molecule while it is chelated, some of the hydroxyls may be more firmly held than others, and therefore less susceptible towards being esterified, while the nucleophilicity of others is enhanced. The enormous conformational flexibility of sucrose in solution[22] allows for a great diversity in structure and stereochemistry in forming transition metal chelates. While a comprehensive discussion of the stereochemistry of transition metal chelates of the sucrate dianion is beyond the scope of this work, the results presented here offer some insight into the usefulness of metal chelation as a director of esterification and invites further exploration into the structure of sucrate dianion-metal ion chelates.

EXPERIMENTAL

General Procedures. Sucrose and solvents were dried before use. Salts were purchased as anhydrous compounds from Aldrich (Milwaukee, WI). Sucrose benzoate samples were analyzed by high performance liquid chromatography (HPLC) using a Waters 600E system controller, two Waters 510 solvent pumps, a Rheodyne 7125 injector, a Kratos (ABI) Analytical 757 detector and a Waters 746 Data module. Sample components were separated on a Nova-Pak RP C-18 column (8 mm x 100 mm) with gradient elution at 1 mL/min (system A, 10 min; step change to system B, 15 min; linear ramp to system C, 10 min; system C, 25 min; linear ramp to system A, 5 min. System A: 15% methanol/85% 0.01M K_2HPO_4, pH 7.5 buffer; system B: 20% methanol/80% 0.01M K_2HPO_4, pH 7.5 buffer; system C: 50% methanol/50% 0.01M K_2HPO_4, pH 7.5 buffer). Detection was by ultraviolet absorption at 254 nm. Chromatographic purity was calculated from the total area percent.

The sucrose content of sucrose benzoate samples was determined separately by HPLC using a Waters μBondapak-NH_2 column (3.9 mm x 300 mm), an isocratic mobile phase of 85% acetonitrile/15% water, and refractive index detection. The sucrose peak in the sample was compared with that from a sucrose standard solution to allow quantitation.

Preparative HPLC was carried out on a Waters 600E system described above equipped with a UV detector (280 nm) and a Bondapak C18 column (19 mm x 150 mm). Flow rates were 7-10 mL/min. Injection volumes were 0.2-0.4 mL of a solution of 0.1-0.2 g monobenzoate mixture per milliliter of mobile phase (14-25% CH_3OH in H_2O). Fractions were collected manually in flasks containing about 1 mL acetic acid and kept at 5 °C between collection times to avoid acyl group migration. Fractions were concentrated on a rotary evaporator at 0-5 °C to a volume of 1-5 mL then lyophilized.

TLC systems used were 15:10:2 $CHCl_3$-CH_3OH-H_2O (system I) or 15:10:1 $CHCl_3$-CH_3OH-HOAc (system II). Column chromatography was carried out in a 2.5 x 90 cm column of silica gel (Merck) eluted with solvent system A) 6:0.85:0.15 or B) 4:0.85:0.15 $CHCl_3$-CH_3OH-HOAc.

The ^1H NMR data was obtained on a Brücker NMR instrument at 270 or 500 MHz in D_2O at ambient temperature. Chemical shifts are reported relative to tetramethylsilane at 0 ppm (external reference). Samples were freeze-dried from 1% CD_3COD in D_2O to minimize the DOH resonance and to minimize acyl migration during sample preparation. Samples benzoylated on the glucosyl moiety tended to undergo ester migration when stored at ambient temperature overnight. Addition of a drop of acetic acid-d_4 effectively stabilized the samples. Resonance assignments for the eight monobenzoates of sucrose are summarized in Table 3.

Non-Specific Benzoylation of Sucrose (Table 2a)

DMF/LiH. A mixture of sucrose (10.0 g, 29.2 mmol) and LiH (0.23 g, 29.2 mmol) in DMF (250 mL) were stirred at ambient temperature overnight to produce a clear solution. The solution was cooled to 0 °C and benzoic anhydride (6.61 g, 29.2 mmol) was added. Disappearance of anhydride was monitored by TLC ($CHCl_3$). Only a trace of anhydride remained after 1 h. The mixture was stirred for an additional 2 h, then quenched by the addition of glacial acetic acid (5 mL, 86.4 mmol). The quenched reaction mixture was stirred for 30 min at ambient temperature to allow the effervescence to subside, then it was concentrated under diminished pressure to 100 mL. An aliquot was withdrawn for analysis by HPLC.

THF-H_2O/Li_2CO_3 (Acetic acid work-up). A mixture of sucrose (10.0 g, 29.2 mmol), Li_2CO_3 (2.16 g, 29.2 mmol), and water (150 mL) was stirred at ambient temperature to give a thin slurry. THF (100 mL) was added and the slurry cooled to 0 °C. Benzoic anhydride (6.61 g, 29.2 mmol) was added and stirring continued for 24 h at 0-2 °C to afford a homogeneous solution. TLC ($CHCl_3$) showed only a trace of anhydride remained. The solution was allowed to warm to ambient temperature, quenched with acetic acid (5 mL, 86.4 mmol), and the solvent changed to DMF by repeated concentration with two 250 mL portions of DMF. Analysis by HPLC showed that 2-*O*-benzoylsucrose was the major product.

THF-H_2O/Li_2CO_3 (No acetic acid prior to work-up). The same procedure was followed as described above, but the addition of acetic acid was omitted. 6-*O*-Benzoylsucrose was identified as the major monobenzoate product by HPLC analysis.

DMF/Li_2CO_3 (No acetic acid prior to work-up). A mixture of sucrose (10.0 g, 29.2 mmol), Li_2CO_3 (2.16 g, 29.2 mmol), and DMF (250 mL) was stirred at ambient temperature for 6 h under argon. Benzoic anhydride (6.61 g, 29.2 mmol) was added and the mixture continued to be stirred. Aliquot were withdrawn after 24 and 40 h for immediate analysis by HPLC. The remaining solution was used in the benzoate migration study (see Table 2b).

Isolation of Sucrose Monobenzoates.

Isolation of 2-*O*-Benzoyl- and 1'-*O*-Benzoylsucrose. A solution of sucrose (10 g, 29.2 mmol) in DMF (250 mL) was stirred under argon; LiOH (0.7 g, 29.2 mmol) was added all at once and the mixture stirred at ambient temperature overnight. The solution was cooled to 0 °C, benzoic anhydride (6.6 g, 29.2 mmol) was added and the mixture stirred at 0 °C for 1.5 h. The reaction was stopped by addition of 5 mL glacial acetic acid, stirred 15 min then concentrated under reduced pressure to 100 mL. TLC (system I) showed about 40-50% unreacted sucrose, about 40% monobenzoates and a small amount of faster-moving components presumed to be dibenzoates. HPLC analysis of the crude mixture contained the 2-*O*-benzoate, 72.7% (chromatographic peak area of monobenzoates) as the major monobenzoate, the 1'-*O*-benzoate (19.6%) and lesser amounts of all others. Half of this material was fractionated on silica (0.65 L system A followed by 2.5 L system B) to give 5.5 g of colorless syrup containing the monobenzoates.

2-*O*-Benzoyl- and 1'-*O*-benzoylsucrose were isolated by preparative HPLC, and identified by their ^1H NMR spectrum.

Isolation of 3-*O*-Benzoyl- and 4-*O*-Benzoylsucrose. A solution of sucrose (110 g, 321.4 mmol) in DMF (0.55 L) was treated with Li_2CO_3 (23.8 g, 322.1 mmol) and benzoic anhydride (72.8 g, 321.8 mmol) under argon at room temperature overnight. Disappearance of anhydride was monitored by TLC ($CHCl_3$). The mixture was filtered to remove the salt, the filtrate concentrated to about 200 g of syrup which contained about 39 g (35.5%) unreacted sucrose. HPLC analysis showed the principal monobenzoates in the crude mixture were 4-*O*- (36.4%) 3-*O*-benzoylsucrose (20.8%). All other monobenzoates were also present: 2-*O*-benzoate (12.6%), 6-*O*- and 1'-*O*-benzoates (18.7%; partially resolved in the chromatograph), 3'-*O*-benzoate (3.9%), and 4'-*O*- and 6'-*O*-benzoates (7.7%, coeluted). This was diluted with 2-propanol (1 L) and refrigerated to crystallize out most of the sucrose. A portion of the supernatant was chromatographed on silica eluted with system A to give a syrup (1.08 g) containing the monobenzoates. Further fractionation of a portion (297 mg) of the monobenzoate fraction by preparative HPLC gave 70 mg 4-*O*-benzoylsucrose and 32 mg 3-*O*-benzoylsucrose which were identified from their ^1H NMR spectra.

Isolation of 6-*O*-Benzoylsucrose. Sucrose (10 g, 29.2 mmol) in DMF (50 mL) was reacted with trimethyl orthobenzoate (6.6 g, 36.5 mmol) and *p*-toluenesulfonic acid (0.5 mL

from a saturated solution in toluene) under argon at room temperature overnight. Formation of orthoester and concomitant loss of sucrose was followed by TLC (system I). The resultant orthoester was cleaved by addition of 1 mL (55.6 mmol) water and stirring at room temperature for 30 min. *tert*-Butylamine (0.7 g, 9.6 mmol) was added, the mixture was stirred for 30 min at ambient temperature then concentrated under reduced pressure to a syrup, and dried *in vacuo* overnight to a hard syrup (18.8 g). HPLC analysis showed the 4-*O*- and 6-*O*-benzoate to be the major monobenzoates.

This material was combined with two other similar reaction mixtures and 8.8 g chromatographed on silica (3:1 $CHCl_3$-CH_3OH) to obtain the monobenzoates in two fractions. Fraction 1 (1.9 g) contained 61% 3-*O*-benzoate, 35% 4-*O*-benzoate and 4% 6-*O*-benzoate (chromatographic percentage); fraction 2 (2.09 g) contained 82% 6-*O*-benzoate, 13% 2-*O*-benzoate, 2% 4-*O*-benzoate and 1% 3-*O*-benzoate. Further fractionation of fraction 2 by preparative HPLC gave 6-*O*-benzoylsucrose as a chromatographically pure material which was identified by its ^1H NMR spectrum.

Isolation of 6'-*O*-Benzoyl- and 4'-*O*-Benzoylsucrose. A mixture of sucrose (10 g, 29.2 mmol), and benzoic anhydride (6.6 g, 29.2 mmol) in pyridine (250 mL) was stirred under argon for 40 h at ambient temperature, then methanol (50 mL) added to destroy any unreacted anhydride and the mixture concentrated under reduced pressure. Residual pyridine was removed by repeated evaporation with 2 x 200 mL portions of DMF, and the residue diluted with 100 mL DMF. HPLC analysis indicated the presence of unreacted sucrose (5 g, 14.6 mmol), and a mixture of monobenzoates with 6-*O*-benzoylsucrose (34.7%, coeluted with 1'-*O*-benzoate) as the major component. 2-*O*-Benzoylsucrose (19.8%) , and the mixture of 4'- and 6'-*O*-benzoates (23.1%, coeluted) were the next most abundant components. All other monobenzoates were present in lesser amounts.. A portion of the monobenzoates (1.05 g) was isolated by chromatography on silica (1.75 L system A, 0.72 L system B). Further fractionation of the monobenzoates (0.52 g) by preparative HPLC gave about 100 mg each 2-*O*-benzoylsucrose, a mixture of 6-*O*-benzoylsucrose and 1'-*O*-benzoylsucrose, and a mixture two monobenzoates identified as 6'-*O*-benzoylsucrose (major) and 4'-*O*-benzoylsucrose (minor) by ^1H NMR. The latter mixture of two components could be partially resolved by analytical HPLC on a Nova-Pak C18 column (8 mm x 100 mm) eluted with 10% acetonitrile in water and occurred in the proportion 3:2 (6'- to 4'-*O*-benzoate) and retention times 10.27 min. and 10.83 min., respectively.

Transition Metal Salt Mediated Benzoylations (Table 4)

$CoCl_2$. A solution of sucrose (5 g, 14.6 mmol) in 100 mL DMF under argon was cooled to 5 °C and reacted with sodium hydride (0.7 g, 29 mmol) added in portions to control gas and heat evolution. The mixture was allowed to come to room temperature (about 20 min) and stirred for 1 h before adding cobalt chloride (0.95 g, 7.3 mmol) in one portion. The mixture effervesced and warmed slightly. Stirring continued for a further 30 min, then benzoic anhydride (4.3 g, 19 mmol) was added all at once which resulted in further gas evolution and slight warming. This suspension was stirred at ambient temperature overnight,

during which time the mixture formed a purple gel. Addition of 5 mL glacial acetic acid dissolved the gel, and the color changed from purple to dark blue with a small amount of a white precipitate. Stirring was continued for 2 h. TLC (system II) analysis of the supernatant showed monobenzoates to be the major component. Typically, 70-85% yield of monoesters from sucrose was observed for these reactions unless otherwise indicated. Trace amounts of unreacted sucrose, and slower moving components presumed to be dibenzoates, were also evident by HPLC analysis. The main monobenzoate component was 3'-*O*-benzoylsucrose (88.1%).

Isolation of 3'-*O*-Benzoylsucrose. The crude mixture (50 mL) was concentrated under diminished pressure to a syrup which was chromatographed on silica (0.65 L system A, 2.5 L system B). 3'-*O*-Benzoylsucrose was isolated as a pure compound and identified from its ^{1}H NMR spectrum (Table 3).

$MnCl_2$. A reaction mixture was prepared in a similar manner to that described for $CoCl_2$. The manganese(II)-carbohydrate complex formed was colorless. HPLC analysis of the acetic acid quenched mixture showed 3'-*O*-benzoylsucrose to be the major component (79.8%).

$CuCl_2$. A reaction mixture was prepared in a similar manner to that described for $CoCl_2$. On addition of $CuCl_2$ the mixture became a pale green color. The color changed to a brighter, more intense emerald green on addition of benzoic anhydride, and after stirring overnight and adding acetic acid, the solution turned blue. HPLC analysis showed the 2-*O*-benzoate (68.4%) to be the major component with lesser amounts of each of the other possible monobenzoates.

$ZnCl_2$. A reaction mixture was prepared as with $CoCl_2$. No color changes were observed. HPLC analysis after acetic acid quench showed 2-*O*-benzoylsucrose (55.4%) as the major products and 1'-*O*-benzoate (12.8%) as the next most abundant component. All other monobenzoates were also present in amounts less than 6%. Relatively larger levels of sucrose were evident in this reaction mixture than in the $CoCl_2$ reaction.

$NiBr_2$. A solution of sucrose (5 g, 14.6 mmol) in DMF (100 mL) was cooled to 0 - 5 °C and hexane-washed NaH (0.7 g, 29 mmol) was added. After the effervescence and slight exotherm subsided, $NiBr_2$ (1.6 g, 7.3 mmol) was added, and the mixture stirred at ambient temperature overnight to allow the $NiBr_2$ to dissolve. On addition of benzoic anhydride (19 mmol), a slight exotherm was observed to cause a 2 °C rise in temperature. During the subsequent 4 h the mixture became thicker until magnetic stirring was impossible. After two hours additional reaction time acetic acid was added to the mixture, and stirring resumed almost instantly. HPLC analysis of the crude mixture showed 2-*O*-benzoylsucrose (53.8%) as the major product and 3'-*O*-benzoate (12.2%) as the next most abundant. Other monobenzoates were also present as indicated in Table 4.

$HgCl_2$. The reaction was carried out as described previously for $CoCl_2$. No colored complex was observed. HPLC analysis of the acetic acid quenched mixture showed 2-*O*-benzoylsucrose (39%) as the major product, and the 3-*O*-benzoate (16.3%) and 1'-*O*-benzoate

(8%) as the next most abundant isomers. All other benzoates were also present in amounts of about 5% or less.

$CaCl_2$. A reaction mixture was prepared as described previously for $CoCl_2$. After stirring at ambient temperature overnight, the reaction was quenched by the addition of acetic acid (35 mL) in 10-15 mL portions to help dissolve the resulting gelatinous mass. Approximately 15% of the sucrose was recovered unreacted. HPLC analysis of the monobenzoates showed the 3-*O*- (22.5%) and 6-*O*-benzoate (27.1%) derivatives were the major components.

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