Studies of Tritylated Sucroses. III. NMR Studies of Tritylacetylsucroses

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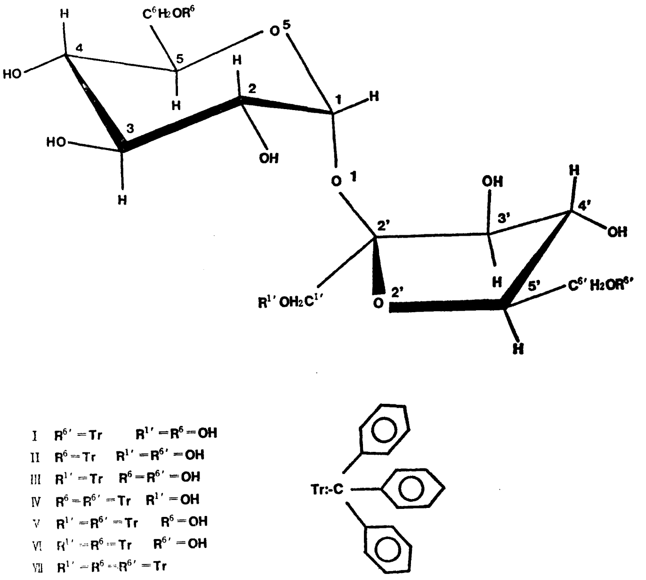
Seven tritylated derivatives have been synthesized by the tritylation of the primary hydroxyl group of sucrose. The ^1H NMR spectra of their peracetyl derivatives have been determined at 100 MHz and 220 MHz in order to assign the sugar-ring-proton signals with the aid of the double-resonance technique and NMR spin simulation. The relationship between the chemical shifts of their methine protons and the substituted position of the bonded trityl groups is discussed. Crystalline 1′-mono-*O*-tritylsucrose derived from 6,6′-di-*O*-palmitolysucrose is also described.

The preparations and the structures of two mono-*O*-tritylsucroses, 6′- (I) and 6-mono-*O*-tritylsucrose (II), and of 1′, 6-di-*O*-tritylsucrose (VI) were reported in previous papers.[1,2] The structures were mainly elucidated by ^1H NMR studies of the corresponding peracetyl derivatives and by gas-chromatographic studies of their partially-methylated derivatives. The structure of the tri-*O*-trityl derivative, 1′,6,6′-tri-*O*-tritylsucrose (VII), was established through complicated reaction routes without refering to the NMR spectra.[3-5]

In the NMR spectra of the tritylacetylsucroses, signals of protons on methylene carbons directly bearing an *O*-trityl group were observed in the region between δ 2 and 3.5. However, the author did not assign the methine proton signals which appear in the region between δ 4.5 and 6.0; these signals show characteristic patterns according to the number and positions of trityl groups on a sucrose molecule. The chemical shifts and coupling constants for the methine and methylene protons of octa-*O*-acetylsucrose (VIII) had already been determined with the aid of the double-resonance technique and the multi solvent method.[6]



I $R^{6'}=Tr$ $R^{1'}=R^6=OH$
II $R^6=Tr$ $R^{1'}=R^{6'}=OH$
III $R^{1'}=Tr$ $R^6=R^{6'}=OH$
IV $R^6=R^{6'}=Tr$ $R^{1'}=OH$
V $R^{1'}=R^{6'}=Tr$ $R^6=OH$
VI $R^{1'}=R^6=Tr$ $R^{6'}=OH$
VII $R^{1'}=R^6=R^{6'}=Tr$

This paper will deal with the assignment of methine-proton signals in the tritylacetylsucroses and with the relationship between the methine chemical shifts and the anisotropic effects exerted by a trityl group. Further, it is suggested that the difference in the chemical shifts of methine or methylene protons between a tritylacetyl and a peracetyl derivative of an oligosaccharide provides valuable information about its stereostructure or conformation in solution.

Results and Discussion

As has been described in previous papers,[1,2] 1′-mono-*O*-tritylsucrose (III) was not found in the reaction product of sucrose with trityl chloride in pyridine, although di- and tri-*O*-tritylsucroses with a trityl group at the 1′-position were found in the product. The reaction of 6,6′-di-*O*-palmitoylsucrose[7] with trityl chloride in a 1 : 2 mole ratio in pyridine gave 1′-mono-*O*-trityl-di-*O*-palmitoylsucrose (IX) as the main product. In the reaction solution, the presence of unreacted trityl chloride and di-*O*-palmitoylsucrose, and a minor amount of poly-*O*-trityldi-*O*-palmitoylsucroses were also observed by thin-layer chromatography. Compound IX which had been isolated by column chromatography, was deacylated to give III. The procedure used to prepare the remaining six tritylacetylsucroses was described in the previous papers.[1,2] Recently, Buchanan[8] and Suami and Ikeda[9] have reported the synthesis of 6′-mono-*O*-tritylhepta-*O*-acetylsucrose (I′) and a peracetyl derivative of 1′,6′-di-*O*-tritylsucrose (V′) from 2,3,6,3′,4′-penta-*O*-acetylsucrose.

Figure 1 shows parts of the 220 MHz NMR spectrum of III′, which gives the expected seven signals of acetyl-methyl-protons at δ 1.85 (3H), 1.97 (3H), 1.99(3H), 2.02(3H), 2.03(3H), 2.08(3H), and 2.10(3H), and also an AB-type quartet at δ 3.17 and 3.24 which arises from the isolated oxymethylene protons at the 1′-position. These signals together with the relative integrated intensity of the trityl group which corresponds to 14.83 protons (theory, 15 protons), and that of the acetyl groups, which corresponds to 20.96 protons (theory, 21 protons), account for the expected structure of III′.

In the NMR spectra of the tritylacetylsucroses with an acetyl group at the 6-position, such as 1′-mono- (III′), 6′-mono- (I′), and 1′,6′-di-*O*-tritylacetylsucrose (V′), all the methine-proton signals except those due to H-5 and H-5′ were readily assigned with the aid of the double-resonance technique, the results are shown in Figs. 1, 2, and 3. The analysis of the complicated signals between δ 5.2 and 5.6 in the spectrum of I′ was made by the spin-simulation method; these results are also shown in Fig. 2.

When a trityl group is situated at the 6-position, as in

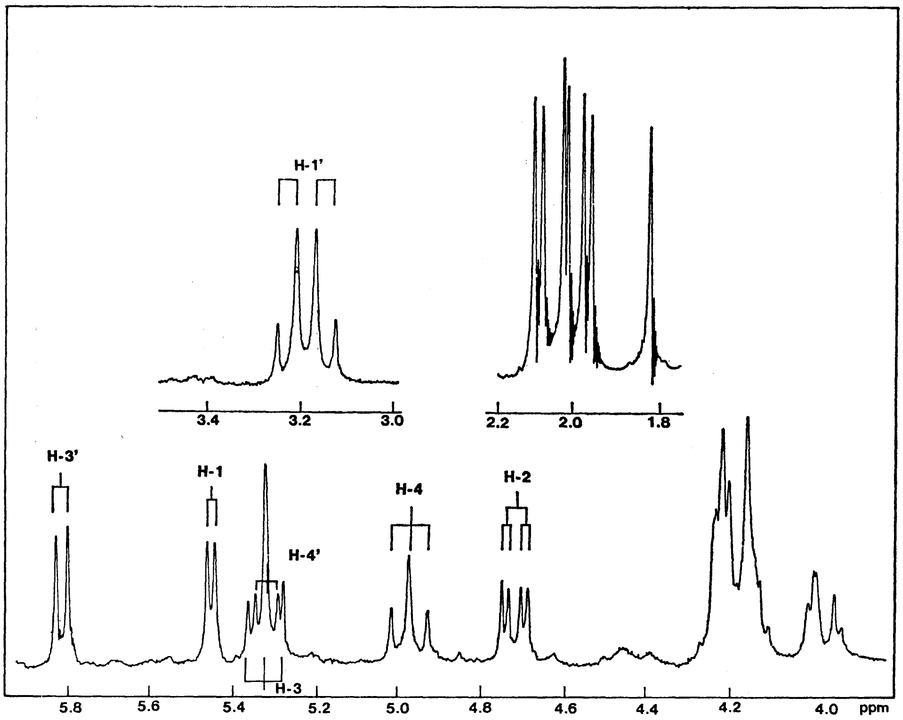


Fig. 1. Parts of the NMR spectrum at 220 MHz of III'.

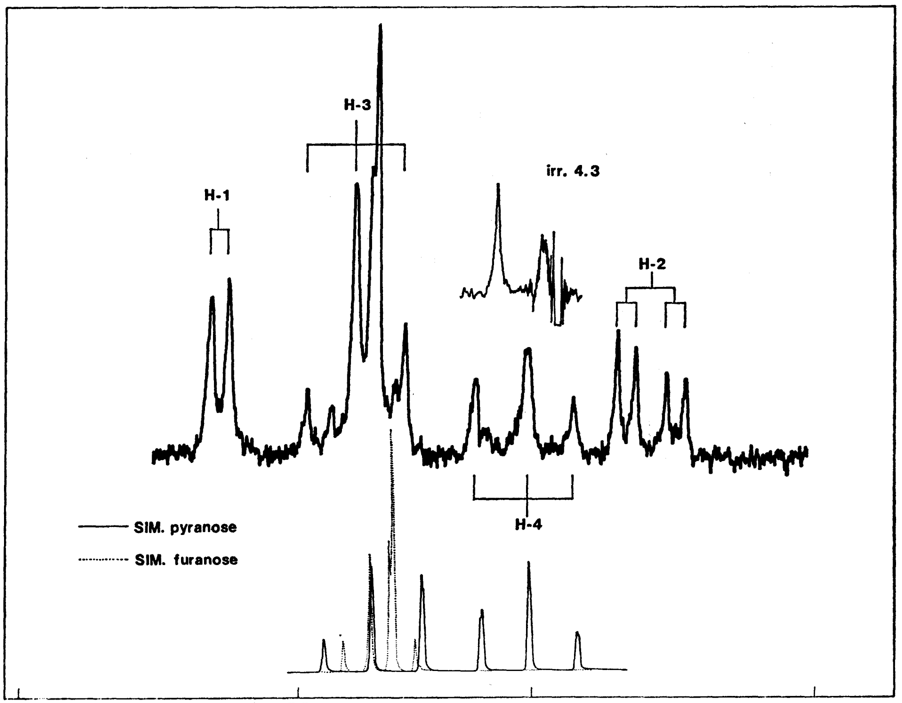


Fig. 2. A part of the NMR spectrum at 100 MHz of I'

the cases of 6-mono- (II'), 6,6'-di- (IV'), 1',6-di- (VI'), and 1',6,6'-tri-*O*-tritylacetylsucrose (VII'), the access of the H-3 and H-4 signals and the overlapping of other signals make their assignments difficult, especially at 100 MHz. An approximate first-order analysis was applied to the methine-proton signals in the 220 MHz spectrum of II', which was confirmed by a spin simulation; the results are shown in Fig. 4. The signals due to H-3 and H-4 in IV' and VII' show symmetrical, but overlapping patterns near δ 5.2 in their 220 MHz spectra and correspond to the AB part of an ABXY system, where J_{AX} equal J_{BY}. They were simulated using appropriate parameters, as is shown in Figs. 5 and 6. In the 220 MHz spectrum of VI', the signals due to H-3 and H-4 lie between δ 5.20 and 5.35 (Fig. 7). By analogy with the cases of IV' and VII', the chemical shifts of H-3 and H-4 may have a value almost equal to that corresponding to

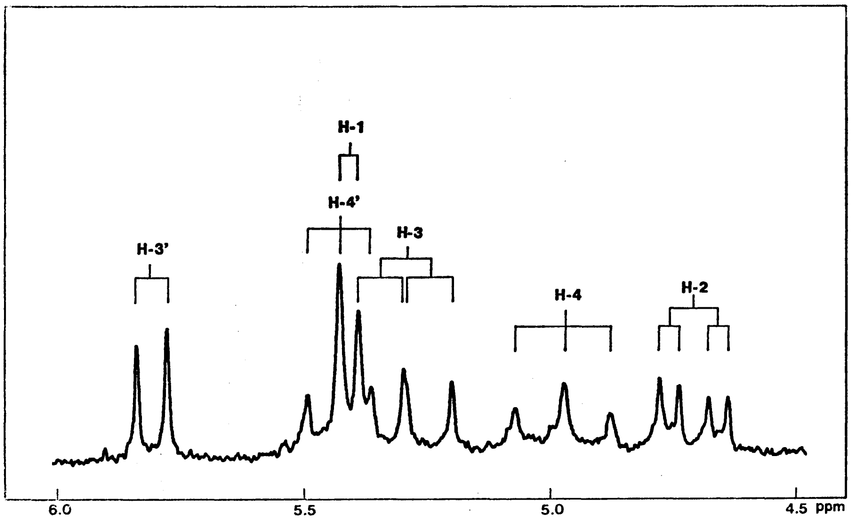


Fig. 3. A part of the NMR spectrum at 100 MHz of V'.

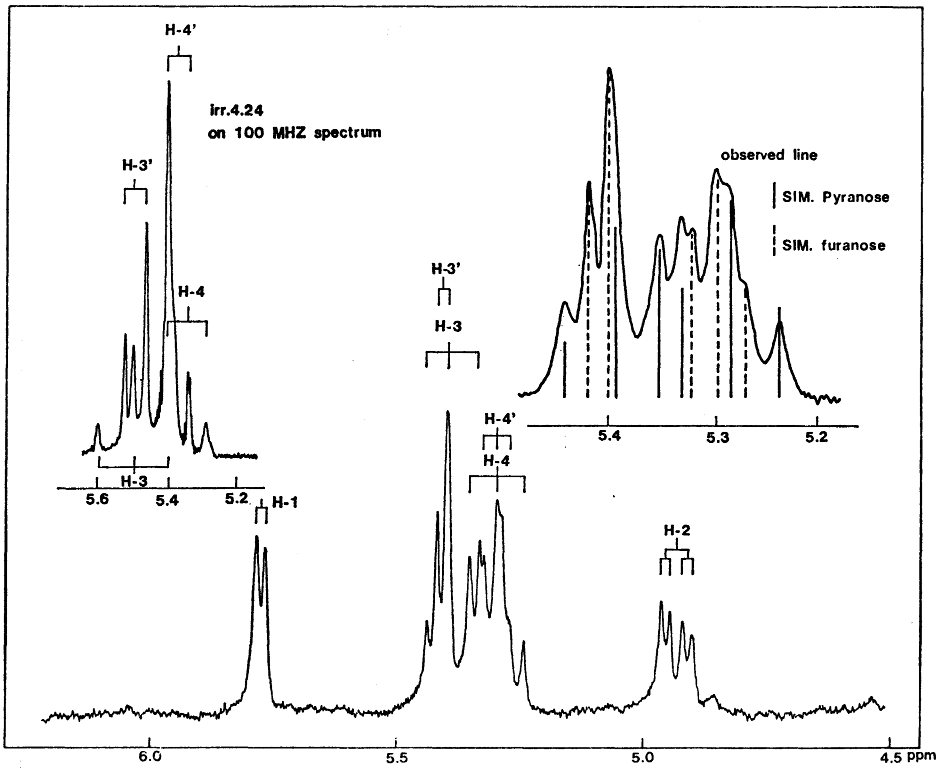


Fig. 4. Parts of the NMR spectrum at 220 MHz of II'.

the frequency of either of the two intense signals appearing in this region, that is, δ 5.31 or 5.27. The remaining methine-proton signals of this group of compounds, II', IV', VII', and VI' are well resolved and were readily assigned at 220 MHz.

The assignment of the signals of H-4 by irradiating H-5 signals was achieved only in the case of II'. For the other compounds of this group, the assignment of the H-4 signals was unsuccessful, because the chemical shifts of H-3 are too close to those of H-4.

Table 1. Coupling constants (Hz) applied to NMR spin simulation for tritylacetylsucroses

Compound	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{3',4'}$	$J_{4'5'}$
I'	9.5	10.0	10.0	5.3	5.5
II'	9.5	10.0	10.0	5.0	5.0
IV'	10.0	10.0	10.0	—	—
VII'	10.0	10.0	10.0	—	—

The coupling constants applied to NMR spin simulation are listed in Table 1. The chemical shifts of all the methine protons except those of H-5 and H-5' in the tritylacetylsucroses examined are listed in Table 2.

The differences in chemical shifts between a methine proton of octa-*O*-acetylsucrose (VIII) and the cor-

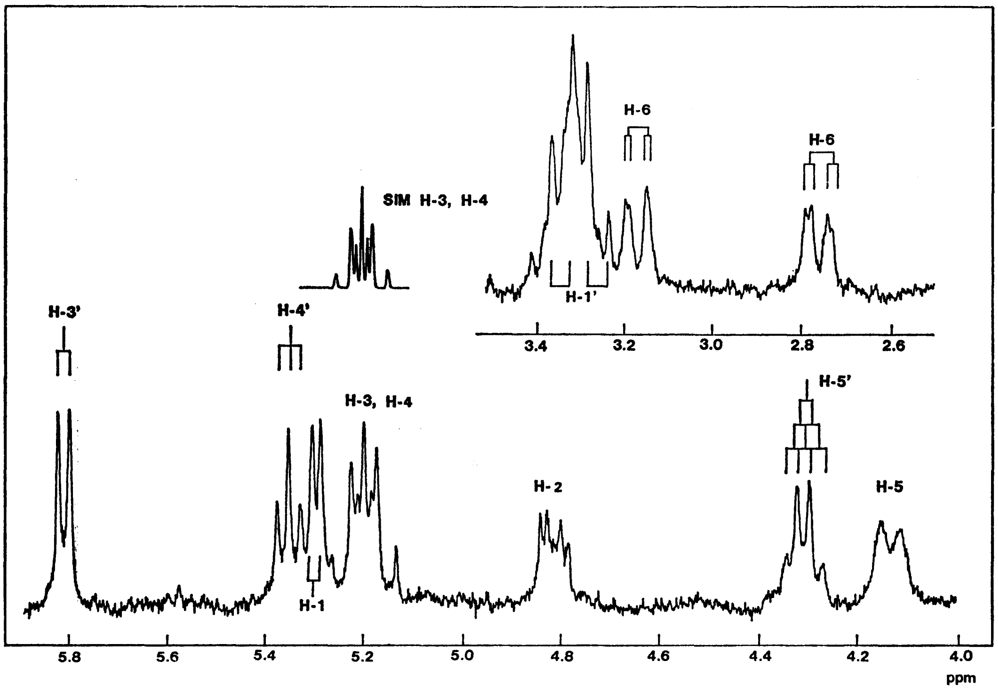


Fig. 5. Parts of the NMR spectrum at 220 MHz of VII′.

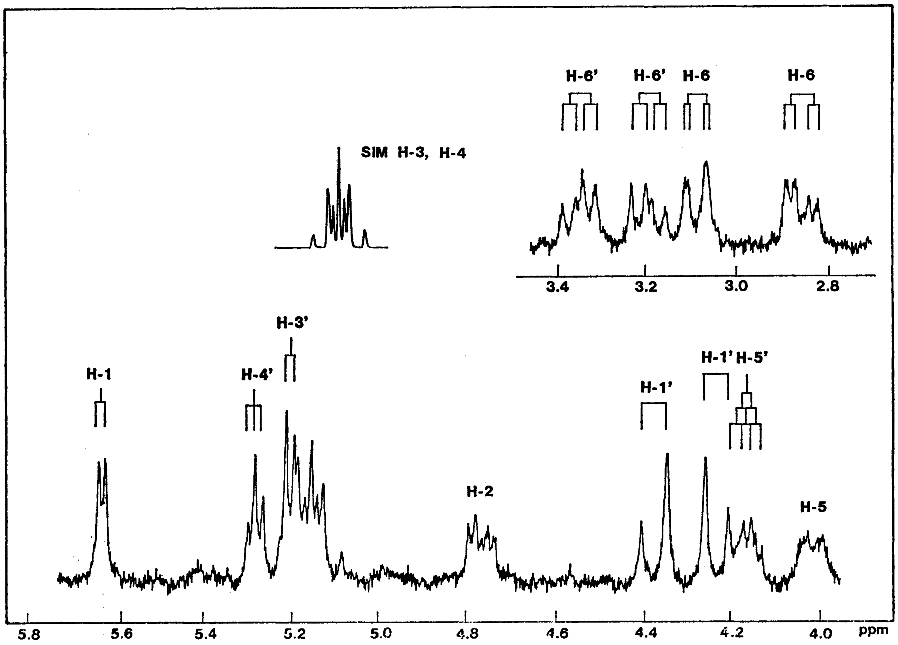


Fig. 6. Parts of the NMR spectrum at 220 MHz of V′.

responding proton of each tritylacetylsucrose (Δ) are listed in Table 3. A positive Δ value represents a downfield shift of a proton signal from VIII to a tritylacetylsucrose.

Each compound has its characteristic set of Δ values. The protons, H-3′ in III′, H-4 in II′, and H-4′ in I′, resonate at lower fields than the corresponding protons in VIII. In spite of the similarity in the positional relationship between each proton and the trityl group, as will be shown below, the difference in the magnitude of the deshielding effects upon these protons should be considerable.

When a methine proton shares a hexose ring with a trityl group, it generally suffers a deshielding effect as in the cases of H-2 and H-3 in II′, and that of H-4′ in III′, but not the case of H-3′ in I′. In all the mono-*O*-tritylacetylsucroses, the methine protons bonded to the hexose ring with no trityl group resonate at a slightly higher field than the corresponding protons in VIII.

The anisotropic shielding effect, σ (expressed in ppm), that is, the ring-current effect of a benzene ring, is well known.[10] The surface where $\sigma=0$ is approximated by a double cone, the axis of which is shared

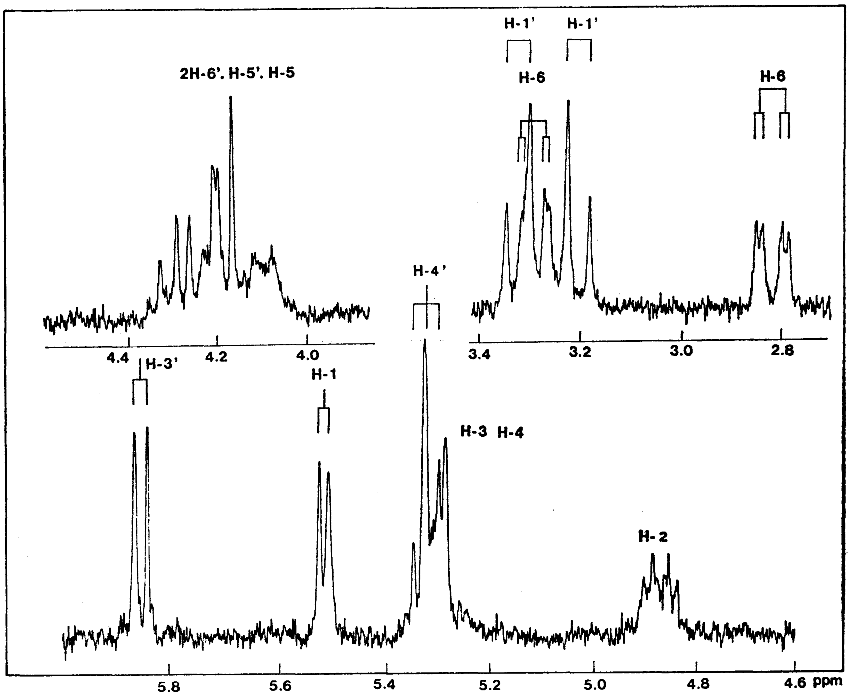


Fig. 7. Parts of the NMR spectrum at 220 MHz of VI'.

with the hexad axis of the ring; the inside of the cone is the shielding region, and the outside, the deshielding region. The rotation of a phenyl of a trityl group about the bond to the methane carbon ♯ (C_{TM}) is sterically hindered, while the trityl group as a whole can rotate around the C–O bond (TOB), thus dividing the space into several regions, as is shown in Fig. 8. A proton in the P region surrounding the TOB bond

Table 2. Chemical shifts (δ) of methine protons in tritylacetylsucroses

Compound	H-1	H-2	H-3	H-4	H-3'	H-4'
I'	5.67	4.79	5.36	5.04	5.34	5.39
II'	5.79	4.96	5.42	5.32	5.43	5.32
III'	5.51	4.77	5.39	5.02	5.87	5.38
IV'	5.73	4.85	5.27 or 5.23	5.23 or 5.27	5.30	5.38
V'	5.52	4.86	5.32 or 5.28	5.28 or 5.32	5.87	5.32
VI'	5.40	4.70	5.29	4.96	5.81	5.42
VII'	5.30	4.79	5.22 or 5.17	5.17 or 5.22	5.82	5.35

Table 3. Chemical-shift differences between a proton of VIII and the corresponding proton of tritylacetylsucroses [$\Delta = \delta$(tritylacetylsucrose) $- \delta$(VIII)]

Compound	H-1	H-2	H-3	H-4	H-3'	H-4'
I'	−0.01	−0.06	−0.06	−0.02	−0.11	+0.03
II'	+0.11	+0.11	−0.03	+0.26	−0.02	−0.04
III'	−0.17	−0.08	−0.06	−0.04	+0.42	+0.02
IV'	+0.05	0.00	−0.18 or −0.22	+0.17 or +0.22	−0.15	+0.02
V'	−0.16	+0.01	−0.13 or −0.17	+0.22 or +0.26	+0.42	−0.04
VI'	−0.23	−0.15	−0.16	−0.10	+0.36	+0.06
VII'	−0.38	−0.06	−0.23 or −0.28	+0.11 or +0.16	+0.37	−0.01

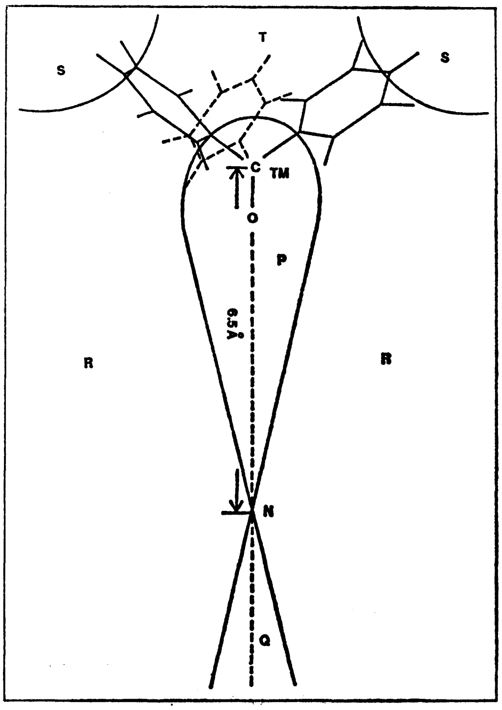
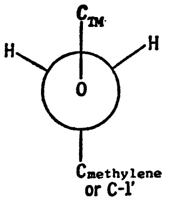


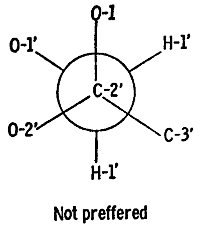
Fig. 8. A schematic representation of the anisotropic shielding effects exerted by a trityl group.

always suffers a deshielding effect, while that in the Q region suffers a shielding effect. The distance between C_{TM} and the node, N, of P and Q is estimated to be about 6.5 Å, with reference to the structure of triphenylmethane in the gas phase, as determined by the electron-diffraction method.[11] In the R region, the outside of the P and Q cores, the sign of the shielding effect, σ, is not clear. However, in view of the cancellation of a positive with a negative effect, the magnitude of σ in this region could not be very large. The methine protons in the tritylacetylsucroses should never be included in the S and T regions.

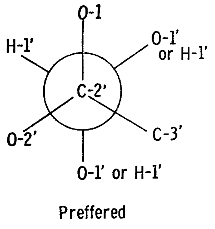
Thus, rotation about the bond which bears a trityl group causes a wide range of shielding or deshielding effects on a proton near this group. In all the tritylacetylsucroses, the rotation about the bond between the methylene carbon and the oxygen atom is appreciably restricted in such a conformation as (A). Any other conformations about the $C_{methylene}$–O bond make the distance between a phenyl group and various parts of the sucrose moiety too short. In III′, such a conformation as (B) is avoided, as by the Δ-2 effect in the case of glycopyranosides,[12] and the conformation illustrated as (C) is perferred. The trityl group is almost fixed; therefore, H-3′ may mostly be included in the P core, the deshielding region.



(A)



(B)



(C)

The C-5′ in I′ and C-5 in II′ are both attached with only one oxygen atom, and so the conformational restriction about C-5′–C-6′ or C-5–C-6 may be less than that about C-2′–C-1′. Then, H-4′ in I′ and H-4 in II′ may experience a shielding-deshielding averaging effect more than does H-3′ in III′. A proton on a ring with no trityl group may be included in the Q core, the shielding region which extends from the node, N.

The applicability of the additive rule for the Δ-value of di-*O*- and tri-*O*-tritylacetylsucroses has been examined. Each Δ value for a certain methine proton in a poly-*O*-tritylacetyl derivative agrees, in general, with the sum of the corresponding Δ values of mono-*O*-trityl derivatives, although there are some exceptions. This fact suggests that the disposition of a trityl group or the conformation of a sucrose moiety remains almost unchanged.

Experimental

General Methods. The NMR spectra were recorded on a Varian HA-100D (100 MHz) and an HR-220 (220 MHz) spectrometer, using chloroform-*d* solutions and with tetramethylsilane as the internal reference. The chemical shifts are expressed in δ. The NMR simulation was accomplished by means of a Varian Spectro System SS-100 equipped with a Varian 620/i computer. Thin-layer chromatography was carried out using Merck silica gel G as an adsorbent in a thickness of 0.25 mm. The developed plate was sprayed with 50% sulfuric acid and heated at 120 °C. Column chromatography was carried out using silica gel, 60—80 mesh (Kanto Chemical Co.).

*1′-Mono-*O*-tritylsucrose* (III). Crystalline 6,6′-di-*O*-palmitoylsucrose (1.278 g, mp 108—109 °C) which had been extracted from commercial sucrose palmitate, followed by crystallization, was reacted with recrystallized trityl chloride (0.834 g) which has twice the molarity of the ester, in dry pyridine (5 ml) at room temperature. Then the solution was allowed to stand for 96 hr. At the end of the reaction period, the solution was concentrated *in vacuo* at 40 °C until it became a hard syrup. Then the syrup was chromatographed on 10 g of silica gel. After the column had been washed with chloroform (200 ml) and 3% methanol-chloroform (70 ml), 6,6′-di-*O*-palmitoyl 1′-mono-*O*-tritylsucrose (IX) was eluted with 5% methanol-chloroform (200 ml). The evaporation of the last solution left 441 mg of IX as an amorphous solid. The thin-layer chromatogram developed by an admixture of methanol-tetrahydrofuran-water-methylene chloride 5 : 7 : 0.2 : 88 (vol/vol/vol/vol) showed the residue to be homogeneous, with an R_f value of 0.59. After the IX (400 mg) had then been dissolved by 5% ammoniac methanol (20 ml), the solution was allowed to stand for 24 hr at room temperature to remove the palmitoyl group. Then the solution was dried *in vacuo*, followed by the addition of methanol and reconcentration. The residue was chromatographed on a silica gel (10 g) column. After washing with 5% methanol-chloroform, III was eluted with 10% methanol-chloroform (200 ml). The residue of evaporation gave 201 mg of III.

Repeated crystallization from a 20% methanol-chloroform solution gave needles which melted at 193—196 °C and which had an $[\alpha]_D^{22}$ of +70.4° (*c* 1, methanol).

Found: C, 63.11; H, 6.40%. Calcd for $C_{31}H_{26}O_{11}$: C, 63.69; H, 6.21%.

*1′-Mono-*O*-tritylhepta-*O*-acetylsucrose(III′).* 1′-Mono-*O*-tritylsucrose, III (100 mg), was dissolved in 2 ml of dry pyridine and then acetylated with acetic anhydride (0.3 ml) for 24 hr. The residue of evaporation *in vacuo* was chromatographed on silica gel (10 g) by washing the gel with 200 ml of toluene and 200 ml of 10% methyl ethyl ketone-toluene. The evaporation of the last washings gave 121 mg of III′, which had an $[\alpha]_D^{20}$ of +76.5° (*c* 1.59, $CHCl_3$).

Found: C, 61.67; H, 5.44%. Calcd for $C_{45}H_{50}O_{18}$: C, 61.50; H, 5.73%.

Other Materials. All the mono- and di-*O*-tritylacetylsucroses except III′ and V′ were prepared by the methods reported previously.[1,2] The tri-O-trityl derivative(VII′) was prepared by the method of Bredereck and his-co-workers. The authentic sample of V′ was synthesized by Suami and Ikeda through 2,3,6,3′,4′-penta-*O*-acetylsucrose; it melted at 100.0—102.0 °C and had an $[\alpha]_D^{20}$ of +58.4° (*c* 2.49, $CHCl_3$).

Found: C, 69.17; H, 5.70%. Calcd for $C_{62}H_{62}O_{17}$: C, 69.01; H, 5.79%.

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