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THE INTERACTION OF SOME CARBOHYDRATE DERIVATIVES WITH SODIUM IONS IN ACETONE SOLUTION

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ABSTRACT

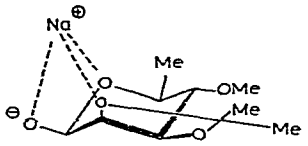
The changes induced in the chemical shifts of certain protons in some carbohydrate derivatives and some other poly-oxygenated compounds, on addition of sodium iodide to their solutions in acetone-d_6, are reported The H-1 resonances of β-glycosides of 2,3-*O*-isopropylidene-4-*O*-methyl-L-rhamnopyranoside were significantly affected by the addition of sodium ions, whereas with the α-L-glycosides, these resonances were virtually unaltered Methoxyacetaldehyde diethyl acetal, triethyl orthoformate, and tris(2-methoxyethyl) orthoformate all showed significant induced-shifts in their acetal-proton resonances on the addition of sodium ions, and all the proton resonances of 1,4-anhydroerythritol were affected, but to differing degrees With the *cis*- and *trans*-5-methoxy-2-phenyl-1,3-dioxanes, it is the former isomer, which can in principle simultaneously use all three oxygen atoms in the molecule to complex a sodium ion, which shows the greatest induced-shift in the acetal-proton resonance

INTRODUCTION

There has been considerable recent interest in the complexing of metal ions with oxygen-containing organic molecules[1–3]. In particular, the co-ordination chemistry of the alkali and alkaline-earth metal ions has been considerably expanded by the discovery that they can form stable complexes with macrocyclic[4] and macrobicyclic[5] polyethers It has also been demonstrated that polyols having a suitable arrangement of three oxygen atoms form complexes with these cations in aqueous solution[6]

Our interest in this subject was initiated during studies on the methylation of reducing-sugar derivatives using sodium hydride–methyl iodide[7]. The ratio of α- to β-glycosides obtained under various conditions could be rationalized if the relative stabilities of the two possible alkoxides were influenced by preferential complexing of sodium ions in an ion pair of one of the alkoxides Thus, methylation of 2,3-*O*-isopropylidene-4-*O*-methyl-L-rhamnopyranose (**2**) in tetrahydrofuran gave, unexpectedly, 91% of the β-glycoside **3**, suggesting that the presence of sodium ion might stabilise the β-alkoxide **1** as a result of simultaneous interaction with the negatively

charged O-1 and lone-pair orbitals on O-ring and O-2 In agreement with this idea, similar alkylation in the presence of dicyclohexyl-18-crown-6[4], which effectively prevents interaction of sodium ions with the alkoxide through preferential complexing, yielded the α-glycoside **4** in 86% yield



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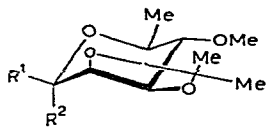


2 $R^1 = R^2 = H$ OH
3 R^1 = OMe $R^2 = H$
4 R^1 = H, R^2 = OMe
5 $R^1 = OCH_2CH_2OH$ $R^2 = H$
6 $R^1 = H$ $R^2 = OCH_2CH_2OH$

Angyal and Davies have noted that a particularly favourable arrangement for complexing cations is an *ax,eq,ax* sequence of oxygen atoms on consecutive carbon atoms in a six-membered ring[8] The β-alkoxide **1** partly satisfies these requirements, and it appeared useful, therefore, to investigate the interaction of the β- and α-glycosides, **3** and **4**, with sodium ions to gain evidence in support of, or against, the above hypothesis concerning the role played by the metal ion in glycosidation reactions We now report a study of shifts induced in the n m r spectra of **3** and **4** by sodium iodide in acetone-d_6, and also similar studies on some related compounds, with a view to ascertaining stereochemical features which favour complex formation

RESULTS AND DISCUSSION

The chemical shift of H-1 in methyl 2,3-*O*-isopropylidene-4-*O*-methyl-α-L-rhamnopyranoside (**4**) is virtually unaffected on the addition of sodium iodide, in contrast, for the β anomer **3**, a move to lower field occurs for the H-1 signal (see Fig 1a), since only one signal for H-1 is observed, the equilibrium between complexed and uncomplexed species is fast on the n m r time-scale, and the chemical shift represents an average value Although the induced chemical shift ($\Delta\delta$) is only moderate (~0 37 p p m for a salt/glycoside ratio of 10), shifts of a similar magnitude have been reported for H-3 in *epi*-inositol in the presence of calcium[8] and lanthanum[6] ions, and it has been suggested that the metal ion in these complexes is located approximately in the direction of the H–C bond on the opposite side of C-3 to H-3 The observed chemical-shift behaviour of the H-1 signal in **3** therefore appears consistent with a complex related to that depicted by **1**, and lends credence to the concept of the sodium ion affecting the α,β-alkoxide equilibrium in favour of the β derivative. Coupling constants observed in **3** and **4** were fully consistent with these compounds existing in approximate-chair conformations, distorted from the idealised geometry as a result of a decrease in the dihedral angle O(2)–C(2)–C(3)–O(3), through fusion of the dioxolane ring

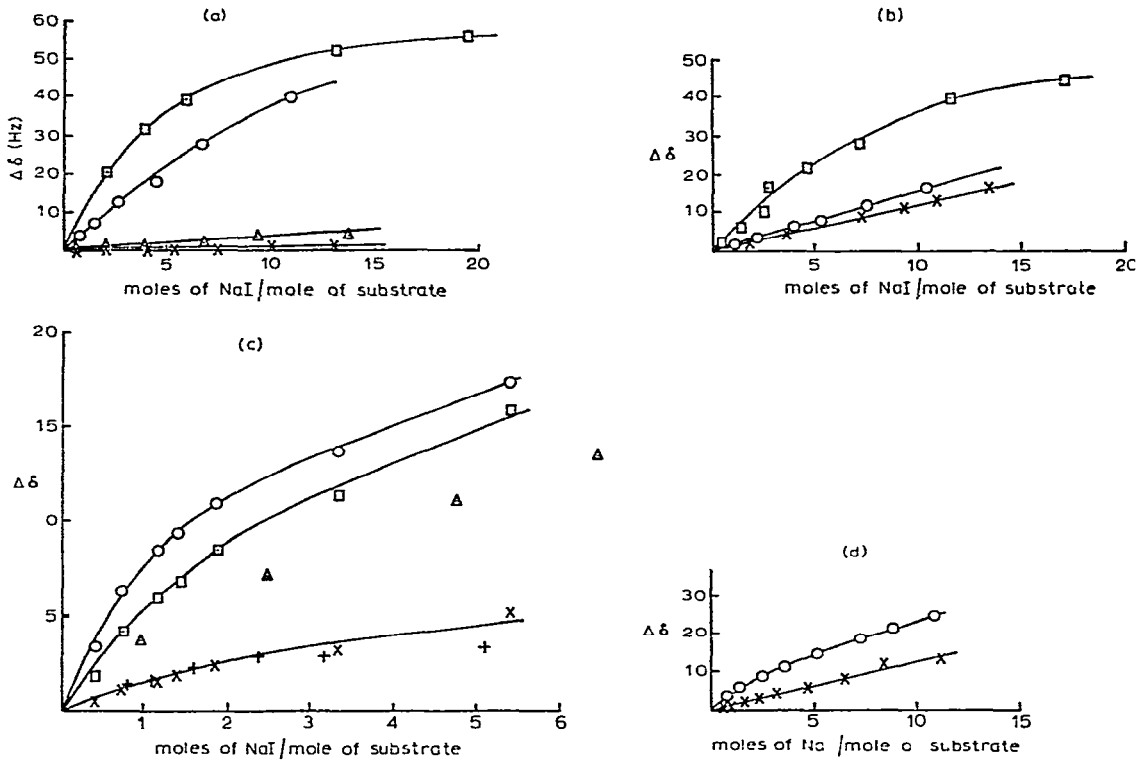
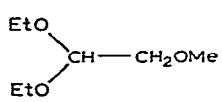


Fig 1 Induced chemical shifts ($\Delta\delta$) in certain proton resonances of some carbohydrate derivatives in acetone-d_6 solution on addition of sodium iodide (a) Anomeric proton in **3** (—○—), **4** (—×—), **5** (—□—), and **6** (—△—) (b), Acetal proton in **7** (—○—), **8** (—×—), and **9** (—□—) (c) H-1 (—○—), H-2 (—×—), and H-3 (—□—) in **10** (numbering as in formula), methine protons (△) in cyclopentane-*cis*-1,2-diol, and H-1 (+) in **10** with NBu_4I replacing NaI (d) Acetal proton in **11** (—○—) and **12** (—×—)

Since the structural unit O–C–C–O is found in many ligands effective for complexing sodium ions[9], we prepared and similarly investigated the (2-hydroxyethyl) β- and α-glycosides **5** and **6** It is apparent (Fig 1a) that, for the α-glycoside **6**, there is little increase in the interaction with sodium ions on replacing MeO-1 by a 2-hydroxyethyl function In the β-series, however, assuming a similar geometry of the complex in both cases, the replacement causes a marked increase in the interaction, at a salt/glycoside ratio of 10, the induced shift is approximately 0 48 p p m

Entropy considerations suggest that cyclic compounds containing a favourable arrangement of oxygen atoms will be more effective ligands than acyclic compounds containing a similar structural sequence of atoms, since in the latter case the favoured geometry for complexing may only be obtained in a few of the many possible conformations of these molecules Methoxyacetaldehyde diethyl acetal (**7**) possesses the structural features of the proposed site of complexation in **3**, but it is apparent (Fig 1b) that although the resonance of the acetal proton is affected by the addition



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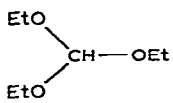

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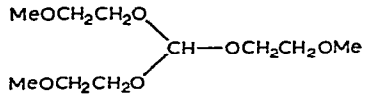

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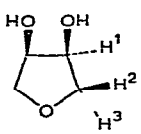
of sodium ions, the effect is smaller than in **3** Interestingly, in triethyl orthoformate (**8**), the chemical shift of the orthoformyl proton shows a similar dependence on the salt concentration, but in tris(2-methoxyethyl) orthoformate (**9**), which incorporates threefold the favourable O–C–C–O spacing, an induced-shift curve similar to that of **3** is found The ranking of complexing ability by comparison of such induced-shift behaviour must assume similar geometries of the complex in all cases This assumption may be reasonable in compounds having similar structure[10] around the complexing site

Further consideration of carbohydrate-derived molecules containing the O–C–C–O unit led us to examine 1,4-anhydroerythritol (**10**) as a possible ligand for sodium ions We recently reported[11] the preparation of crystalline complexes from



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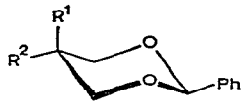

11 R^1 = OMe, R^2 = H
12 R^1 = H, R^2 = OMe

10 and sodium thiocyanate, sodium iodide, and sodium perchlorate, and also the structure of the perchlorate complex[12] The complex nature of the spin system in **10** necessitated the use of spectral simulation to obtain accurate data for chemical shifts and coupling constants The induced chemical shifts of H-1, H-2, and H-3 in **10** with increasing concentration of sodium iodide are shown in Fig 1c, the proton (H-1) geminal to the hydroxyl group is most affected The importance of the *cis*-vicinal diol function in **10** in aiding complexing is suggested by the sensitivity of the chemical shifts of the methine protons in cyclopentane-*cis*-1,2-diol under similar conditions (see Fig 1c) However, the ratio of the induced chemical shift of the methine proton in **10** (*i e*, H-1) to that in cyclopentane-*cis*-1,2-diol, for any given salt/substrate ratio, was always greater than unity, suggesting that the ring oxygen does play some part in the interaction of **10** with sodium ions The allocation of the least and most affected of the methylene protons in **10** as H-2 and H-3 (see formula), respectively, is based on the calculated induced-shifts* in their resonances, using the

*For this calculation, the co-ordination of sodium by the *cis*-diol function was assumed, with a geometry similar to that found in the crystal of the perchlorate complex[12]

formula[13]

$$\Delta\sigma = -2\times10^{-12}\,E_z - 10^{-18}E^2,$$

where $\Delta\sigma$ is the change in the proton-screening constant of an X–H bond when it is subject to an electric field E, E_z being the component of E in the bond direction The induced chemical shifts calculated thereby were found to be in the ratios for H-1 H-3 H-2 of 5 2 3 2 1 Observed values in **10** at salt/substrate ratios of 1 85, 3 32, and 5 4 to 1 were 4 7 3 7 1, 4 4 3 7 1, and 3 32 3 1·1, respectively Although this allocation is contrary to that which might be made on the basis of the general observation for five-membered rings that $J_{cis} > J_{trans}$, (*c f* in **10**, $J_{1,2}$ 5 45, $J_{1,3}$ 4 61 Hz), it is noteworthy that calculation of coupling constants in **10**, using a recently described, modified Karplus equation[14], gives $J_{1,2} > J_{1,3}$ by ~0 5 Hz

Analysis of the chemical-shift data for H-1, H-2, and H-3 by the method of Martin and co-workers[15] yielded equilibrium constants for complex formation of approximately 6, 1, and 2 5M^{-1}, respectively The variation in these values may be a result of the non-validity of an inherent assumption in this treatment, *i e*, that only 1 1 complex-formation occurs The crystal structure of the (**10**)–$NaClO_4$ complex and 2(**10**)–NaI complex[16] suggests that interaction of **10** with two sodium ions may not be ruled out As expected, addition of tetrabutylammonium iodide to **10** in solution induced much smaller shifts than sodium iodide.

Addition of sodium iodide to the isomeric *cis*- and *trans*-5-methoxy-2-phenyl-1,3-dioxanes, **11** and **12**, produced the greatest effect on the benzylic hydrogen atom of the *cis* isomer (Fig 1d) Dreiding models show that a sodium ion placed 2 4Å* from all three oxygen atoms of the *cis* isomer, on the side of the acetal carbon opposite to the benzylic hydrogen, lies close to the axis of the C–H bond at the acetal centre, a particularly favourable orientation for producing a shielding change at that hydrogen nucleus In contrast, the *trans* isomer in its preferred conformation is not able to achieve a similar, simultaneous complexing to all three oxygen atoms

EXPERIMENTAL

Compounds **2**[17], **3**[7], **4**[18], **10**[19], **11**[20], and **12**[21] were prepared by literature methods N m r spectra were measured on a Varian HA-100 instrument, using Me_4Si as an internal standard, unless stated otherwise, chemical shifts were measured at 250-Hz sweep-widths with chart calibration by a pen-coupled frequency counter Spectral simulation was performed using a LACX programme[22], and computation of the equilibrium constants from chemical-shift data of **10** was performed using Scott's modification[23] of the Benesi–Hildebrand equation[24] with the aid of the programme SHEBA[25] Sodium hydride was prepared oil-free immediately before use by washing the commercially available 60% dispersion in oil with light petroleum; it was then maintained briefly under reduced pressure prior to weighing Optical

*This figure lies in the range of many Na–O distances determined by X-ray crystallography

rotations were measured at ambient temperature on a Perkin–Elmer 141 polarimeter

2-Hydroxyethyl 2,3-O-isopropylidene-4-O-methyl-β- and α-L-rhamnopyranoside (**5** and **6**) — To a stirred solution of 2,3-*O*-isopropylidene-4-*O*-methyl-α-L-rhamnopyranose[17] (**2**) (0 65 g) in 1,2-dimethoxyethane (10 ml) was added, with stirring, a suspension of sodium hydride (0 2 g) in 1,2-dimethoxyethane (5 ml), the reaction being maintained under dried nitrogen After 2 h, methyl bromoacetate (1 6 g) was added and the mixture was stirred for a further 2 h T l c (benzene–ethyl acetate, 4 1 v/v) indicated the disappearance of starting material Methanol (5 ml) was added and the mixture was then concentrated to a thick slurry which was partitioned between chloroform (50 ml) and water (20 ml) The aqueous layer was extracted with chloroform (2 × 10 ml), and the combined extracts were washed with water (10 ml), dried, and concentrated The syrupy residue was dissolved in dried ether (10 ml), and a suspension of lithium aluminium hydride (0 6 g) in dried ether (10 ml) was added dropwise with stirring After 3 h at room temperature, water (0 6 ml) was added, and then aqueous sodium hydroxide (0 6 ml of a 15% solution) and water (1 8 ml) After filtration, the ether solution was dried and concentrated to give a syrup which contained (t l c in ethyl acetate) two components, the slower-running component (β-glycoside **5**) preponderated, the ratio of **5** **6** was visually estimated from t l c to be ~7 3 A portion of this syrup was subjected to p l c , and the lower band (R_F 0 25), after extraction and distillation, gave 2-hydroxyethyl 2,3-*O*-isopropylidene-4-*O*-methyl-β-L-rhamnopyranoside (**5**), b p 100°(bath)/0 04 mmHg, $[\alpha]_D$ +43 4° (*c* 0 9, chloroform) N m r. (acetone-d_6) data δ 1 23 (d, $J_{5,6}$ 6 Hz, H-6), 1 30, 1 46 (2s, CMe_2), 3 46 (s, OMe), 4 13 (t, $J_{2,3}$ 6, $J_{3,4}$ 6 Hz, H-3), 4 26 (dd, $J_{1,2}$ 2 Hz, H-2), 4 81 (d, H-1)

Anal Calc for $C_{21}H_{22}O_6$. C, 54 95, H, 8 45 Found C, 55 0, H, 8 3

The faster-running band (R_F 0 4), after extraction, yielded 2-hydroxyethyl 2,3-*O*-isopropylidene-4-*O*-methyl-α-L-rhamnopyranoside (**6**), b p 86°(bath)/0 03 mmHg, $[\alpha]_D$ −38 6° (*c* 0 8, chloroform) N m r (acetone-d_6) data δ 1 18 (d, $J_{5,6}$ Hz, H-6), 1 30, 1 47 (2s, CMe_2), 3 47 (s, OMe), 3 9–4 3 (complex, H-2,3), and 4 95 (s, H-1)

Anal Calc for $C_{21}H_{22}O_6$ C, 54 95, H, 8 45 Found C, 54 4; H, 8 4.

N m r data on **3**, **4**, *and* **10** — **3** ($CDCl_3$) δ 1 34 (d, $J_{5,6}$ 6 3 Hz, H-6), 1 39, 1 58 (2s, CMe_2), 3 09 (dd, $J_{3,4}$ 6 5, $J_{4,5}$ 9 5 Hz, H-4), 3 30 (m, H-5), 3 52 (s, OMe), 3 59 (s, OMe), 4 11 (t, $J_{2,3}$ 6 3 Hz, H-3), 4 25 (dd, $J_{1,2}$ 2 3 Hz, H-2), 4 6 (d, H-1)

4 ($CDCl_3$) δ 1 28 (d, $J_{5,6}$ 6 Hz, H-6), 1 35, 1 54 (2s, CMe_2), 2 96 (m, H-4), 3 36 (s, OMe), 3 50 (s, OMe), 3 50–3 62 (m, H-5), 4 08–4 13 (complex, H-2,3), and 4 84 (s, H-1)

4 (C_6D_6) δ 1 23, 1 47 (2s, CMe_2), 1 36 (d, $J_{5,6}$ 6 3 Hz, H-6), 3 05 (s, OMe), 3 05–3 2 (m, H-4), 3 45 (s, OMe), 3 63–3 79 (m, $J_{4,5}$ 10 Hz, H-5), 4 16 (t, $J_{3,4}$ 6 Hz, H-3), 4 25 (d, $J_{2,3}$ 6 5 Hz, H-2), 4.91 (s, H-1)

10 (acetone-d_6) δ 3 55 (m, $J_{1,3}$ 4 61 Hz, H-3), 3 81 (m, $J_{2,3}$ −9 06 Hz, H-2), 4 15 (m, $J_{1,1'}$ 5 74, $J_{1,2}$ 5 45 Hz, H-1)

Tris(2-methoxyethyl) orthoformate (**9**) — Triethyl orthoformate (16 4 ml) and 2-methoxyethanol (16 2 ml) were heated at 80° in the presence of *p*-toluenesulphonic

acid (0 1 g) for 24 h Ethanol (~11 ml, theory, 17 4 ml) formed in this reaction was then distilled from the mixture The residue was distilled at 12 mmHg, and after a fore-run of ~8 ml, material of b p 131–140° was collected The n m r spectrum (60 MHz, neat liquid) showed two singlets at δ 5 2 and 5 15, indicating incomplete reaction To this material was added 2-methoxyethanol (16 ml), and the reaction and isolation procedure were repeated The product had b p 145–148°/12 mmHg, n m r (neat) δ 3 3 (s, 3MeO), 3 4–3 8 (complex, $-CH_2$ CH_2-), 5 2 (s, H–C–)

Anal Calc for $C_{10}H_{22}O_6$ C, 50 4; H, 9 3 Found C, 50 3, H, 9 1

Measurement of induced chemical shifts — The following procedure was generally used To the substrate (~50 μmoles) in an n m r tube was added acetone-d_6 (0 5 ml) The capped tube and contents were weighed, and the n m r spectrum was recorded A small portion (~0 5 molar equivalent) of previously dried sodium iodide was then added and the tube reweighed to yield the accurate weight of iodide added The n m r spectrum of the solution was measured Further additions of known weights of sodium iodide were made, and a spectrum was run after each addition In the case of **10** the following procedure was used. Aliquots (0 1 ml) of a solution of **10** (99 mg) in acetone-d_6 (1 ml) were added to calibrated (volume) n m r tubes containing weighed portions of sodium iodide so as to achieve a range of molar ratios of salt/substrate between 0 4 and 6 Further acetone-d_6 was added to make up the final volume to 0 7 ml The n m r spectrum of each solution was then determined

For **10** and cyclopentane-*cis*-1,2-diol, simplification of spectral analysis was achieved by exchange of the hydroxyl protons by treatment with deuterium oxide For example, **10** (~0 1 g) was dissolved in D_2O (1 ml), and the solution was then concentrated to dryness using an oil pump This process was repeated four times, after which the residue was stored over phosphorus pentaoxide in a vacuum desiccator I r spectroscopy confirmed the conversion of –OH to –OD groups

Equilibrium constants for complex formation by **10** — In the Scott modification of the Benesi–Hildebrand analysis for calculation of the equilibrium constant for complex formation by **10**, using the programme SHEBA, the values obtained from the chemical-shift data for H-1, H-2, and H-3 were $6 \pm 0\,6$, $1 \pm 0\,2$, $2\,5 \pm 0\,3$ M^{-1} The error ranges are based on standard deviations in computed line-positions for H-1, H-2, and H-3 of approximately 0 13, 0 05, and 0 05 Hz, respectively

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