Interaction between Dimethyl Sulfoxide and the Anomeric Proton in Anomeric Glycopyranosides

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Chromatography on dimethyl sulfoxide impregnated papers was devised in the late 1950's. It provided a means for separating lipophilic compounds not amenable to the usual paper chromatographic technique using water-saturated cellulose as the stationary phase. Preparative separations using dimethyl sulfoxide as the stationary phase on impregnated silica gel were also described.[1,2] These preparative separations were often better than the corresponding ones on paper. Similar separations can also, most conveniently, be carried out on impregnated silica gel thin-layer plates. Separations of moderately polar compounds such as aromatic amines, phenols, aldose and alditol acetates, aldose methyl ethers and acetylated methyl glycosides were readily accomplished. With the advent of thin-layer chromatography and of gas-liquid chromatography, the technique of chromatographic separation on dimethyl sulfoxide as stationary phase fell into disuse. It does, however, remain as an excellent method for the separation of anomeric glycoside derivatives. Anomers are frequently separated much better than are positional and other stereoisomers, those with axial aglycons in the more stable conformation, generally the α-forms, having the higher mobility. These observations have interested us for some time and is the subject matter of this communication.

A current rationale of the anomeric effect is represented in Fig. 1.[3,4] In glycosides with axial aglycones *1*, the antibonding orbital of bond *a* is stabilized by the *trans*-periplanar free electron pair *a'* at O-5. In the same manner, the antibonding orbital of the C-1 – O-5 bond *b* is stabilized by the *trans*-periplanar free electron pair *b'* at O-1. By contrast in

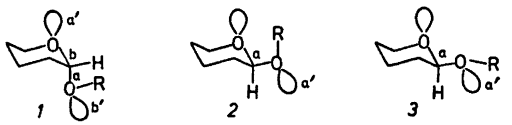

Fig. 1. Orbital representations of the anomeric and *exo*-anomeric effects. For the sake of clarity, only the participating electron pair on each oxygen atom is represented. The argument is independent of the state of hybridization at the oxygen atoms (sp^2 or sp^3).

glycosides with equatorial aglycons *2* and *3* only one such orbital interaction is possible, that of the C-1 – O-5 bond *a* with the free electron pair *a'*. In the absence of other effects the β-D-anomer (*2*, *3*) should be the less stable of the two anomers, with a lower electron density at C-1 and, hence at H-1 than that for the α-D-anomer *1*.

Cations are solvated by dimethyl sulfoxide. Since H-1 of β-D-anomers has a lower electron density than H-1 of α-D-anomers the former should interact more strongly with dimethyl sulfoxide when this is employed for example as the stationary phase in chromatography.

This possibility has now been examined by NMR, for the fully acetylated anomeric methyl hexopyranosides with the D-*galacto*-, D-*gluco*- and D-*manno*-configurations. Spectra were recorded for each glycoside in deuteriochloroform containing increasing concentrations of hexadeuteriodimethyl sulfoxide (from 0 to 100 %). In the spectra obtained for the α-D-glycosides, upfield shifts in δ values for all individual protons except one, including acetoxyl and methoxyl protons, were recorded. The magnitude of this shift for individual protons varied from 0.40 to 0.21 on changing the solvent from chloroform to dimethyl sulfoxide. The exception was the δ value for H-1 of the α-mannoside for which maximum down-field shift of 0.04 ppm was observed. By contrast, the δ values recorded for H-1, H-3 and H-5 in the β-D-glycosides were shifted down-field; upfield shifts were recorded for other protons. The maximum down-field shift for H-3 was only 0.05 ppm, but those for H-1 and H-5 for the three β-D-glycosides ranged from 0.18 to 0.28 ppm on changing the solvent from chloroform to dimethyl sulfoxide (Table 1). We interpret this as being due to interaction of H-1 of the β-D-glycosides with the partially negative oxygen atom in dimethyl sulfoxide and the down-field shifts of H-1, H-5 and, to a much lesser degree H-3, as being due to the anisotropy of the S=O bond.[5] The stronger interaction between the β-D-glycosides and dimethyl sulfoxide correlates well with the differences in chromatographic mobility between α-D- and β-D-glycosides using dimethyl sulfoxide as the stationary phase.

Experimental. The spectra of the six methyl hexopyranosides (~25 mg in 0.50 ml $CDCl_3$ containing ~0.1 % tetramethylsilane as internal standard) were recorded using a Varian XL 100 spectrometer. $(CD_3)_2SO$ was added incrementally between recording the spectra. Values of shift gradients thus determined are recorded in Table 1.

NMR assignments. Since significant down-field shifts were obtained for the β-D-anomers and not for the corresponding α-D-anomers, assignments for the former only will be described here.

Methyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside. Solvent, $CDCl_3$. Decoupling irradiation

Table 1. Variations with solvent composition of δ for H-1, H-3 and H-5 of three methyl 2,3,4,6-tetra-*O*-acetyl-β-D-hexopyranosides.

	$CDCl_3$	$CDCl_3/(CD_3)_2SO$ 5:2	$CDCl_3/(CD_3)_2SO$ 1:1	$(CD_3)_2SO$
galacto configuration				
H-1	4.39	4.48	4.54	4.59
H-3	4.99	—	—	5.04
H-5	3.91	—	—	4.09
gluco configuration				
H-1	4.43	4.52	4.59	4.68
H-3	5.21	5.23	5.24	5.26
H-5	3.70	3.82	(3.89)[a]	(3.98)
manno configuration				
H-1	4.56	4.72	4.78	4.84
H-3	5.04	—	—	(5.09)
H-5	3.66	—	—	3.86

[a] Values in parentheses are less accurate due to overlapping signals or second-order effects and those not given could not be determined, for the same reasons.

at the centre of frequency of the presumed H-5 signal (identified from its chemical shift and spin coupling pattern) caused a simplification of the H-6 and H-6′ signals and a sharpening of the H-4 broad doublet. Irradiation at δ 5.18 (H-2) caused the presumed H-1 signal to collapse into a singlet. The converse collapse of the presumed H-2 triplet into a doublet when irradiating at the presumed H-1 frequency was also observed. Irradiation at the H-4 frequency caused collapse of the H-3 signal (dd) into the expected doublet. The following assignments were therefore made: δ values: H-1 4.39, H-2 5.18, H-3 4.99, H-4 5.39, H-5 3.91, H-6 and H-6′ 4.10-4.22. First-order coupling constants: $J_{1,2}$ 8 Hz, $J_{2,3}$ 10 Hz, $J_{3,4}$ 4 Hz, $J_{4,5} < 1$ Hz.

*Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside.* Solvent $CDCl_3/(CD_3)_2SO$ 5:1. Using decoupling techniques similar to those described above, the following assignments were made: δ values: H-1 4.51, H-2 4.89, H-3 5.23, H-4 5.00, H-5 3.80, H-6 4.08, H-6′ 4.28. First-order coupling constants: $J_{1,2}$ 8 Hz, $J_{2,3}$ 8 Hz, $J_{3,4}$ 8 Hz, $J_{4,5}$ 8 Hz, $J_{5,6}$ 3 Hz, $J_{5,6'}$ 5 Hz, $J_{6,6'}$ 12 Hz.

*Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside:* Solvent $CDCl_3$. Using decoupling techniques similar to those described above, the following assignments were made: δ values: H-1 4.56, H-2 5.48, H-3 5.04, H-4 5.26, H-5 3.66, H-6 4.13, H-6′ 4.33. First-order coupling constants: $J_{1,2} < 1$ Hz, $J_{2,3}$ 4 Hz, $J_{3,4}$ 10 Hz, $J_{4,5}$ 10 Hz, $J_{5,6}$ 4 Hz, $J_{5,6'}$ 6 Hz, $J_{6,6'}$ 12 Hz. The various integrals and shift gradients were in accordance with the above assignments.

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Studies on the Kolbe Electrolysis. XI.* Racemization of Optically Active *sec*-Butyl Radicals in a Mixed Coupling Reaction

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In the preceding article of this series,[1] the mixed Kolbe coupling between radicals from ethyl hydrogen (+)-ethylmethylmalonate and isovaleric acid was found to give ethyl ethylisobutylmethylacetate which was racemic to an extent of at least 99.98%. From the theoretical point of view, one possible objection against this system is that the radical center of the optically active radical is strongly conjugated with an ethoxycarbonyl group, thus (1) providing a strong driving force for the radical to attain a planar structure and (2) causing a weakening of any chemisorption bond between the radical and the electrode surface (platinum). Both factors would de-

* Part X. See Ref. 1.

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