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Paper Electrophoretic and NMR Studies of Complexes Between Polyols and Diphenylborinic Acid

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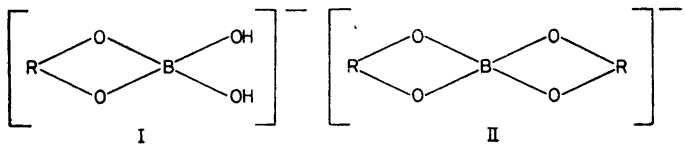
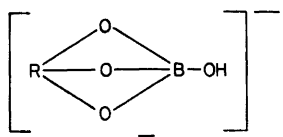
The electrophoretic mobilities of various aldoses, ketoses, xylose and glucose monomethyl ethers, glycosides, glycitols, and inositols in diphenylborinate at pH 10 have been examined and compared with those in borate. Whereas borate can form different types of cyclic complexes with polyols, only one such complex is possible with diphenylborinate. Nevertheless, the mobilities for the various polyols in this buffer closely parallel those obtained in borate. The NMR spectrum of *epi*-inositol in borate at pH 10 shows inversion of the cyclohexane ring into the conformationally less stable chair form, presumably in order to form the favoured tridentate complex involving three *cis*-axial oxygens and boron. By contrast, no such inversion occurs in the presence of diphenylborinate, although strong complexing (non-tridentate) is observed. The results lend support to the view that in aqueous solutions and under favourable steric conditions, strong tridentate complexes are formed between borate and polyols.

Polyhydroxy compounds form charged complexes with the borate anion according to I-III of which III (tridentate complex) is only formed under favourable steric conditions. The relative mobilities of various polyhydroxy



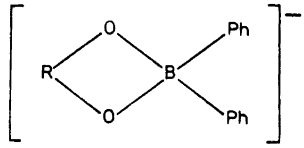
I

II



III

compounds on paper electrophoresis in borate reflect the equilibrium constants for the formation of the various complexes.[1-4] In the case of diphenylborinate, only one type of charged species resulting from the interaction with polyhydroxy compounds is possible, IV, analogous to I above. Since complexes



IV

analogous to II and III are precluded, it seemed possible that significant differences in the relative mobilities of polyols in borate on the one hand, and diphenylborinate on the other might be observed.

Table 1. Aldoses and ketoses.

$$M_G = \frac{\text{true distance of migration of substance}}{\text{true distance of migration of glucose}}$$

Substance	$10^2 M_G$ in diphenylborinate	$10^2 M_G$ in borate
L-Arabinose	80	96
D-Lyxose	75	71
D-Ribose	75	77
D-Xylose	95	100
L-Rhamnose	40	52
D-Altrose	90	97
D-Galactose	80	93
D-Glucose	100	100
D-Mannose	65	72
D-Fructose	80	90
L-Sorbose	100	95
D-Tagatose	90	95

Table 2. Xylose and glucose methyl ethers.

Substance	$10^2 M_G$ in diphenylborinate	$10^2 M_G$ in borate
D-Xylose	95	100
2-*O*-Methyl-D-xylose	30	39
3-*O*-Methyl-D-xylose	75	66
4-*O*-Methyl-D-xylose	10	21
3,5-Di-*O*-methyl-D-xylose	70	73
D-Glucose	100	100
2-*O*-Methyl-D-glucose	30	23
3-*O*-Methyl-D-glucose	75	80
6-*O*-Methyl-D-glucose	65	80

The paper electrophoretic mobilities, in borate and in diphenylborinate at pH 10 of some aldoses, ketoses, xylose and glucose monomethyl ethers, glycosides and glycitols, are shown in Tables 1 – 4. For these substances,

Table 3. Glycosides.

Substance	10^2 M_G in diphenylborinate	10^2 M_G in borate
Methyl β-D-xylopyranoside	0	0
Methyl α-D-rhamnopyranoside	30	34
Methyl α-D-galactofuranoside	30	41
Methyl β-D-galactofuranoside	30	31
Methyl β-D-glucofuranoside	65	62
Methyl α-D-glucopyranoside	20	11
Methyl β-D-glucopyranoside	30	19
Methyl α-D-mannofuranoside	100	80
Methyl α-D-mannopyranoside	40	42
Methyl β-D-mannopyranoside	25	31

Table 4. Glycitols.

Substance	10^2 M_G in diphenylborinate	10^2 M_G in borate
Glycol	5	11
Glyceritol	45	49
Erythritol	75	75
D-Threitol	80	75
L-Arabinitol	95	87
Ribitol	100	85
Xylitol	90	79
Galactitol	105	97
D-Glucitol	100	83
L-Iditol	95	81
D-Mannitol	100	91
2-*O*-Methyl-D-xylitol	85	74
3-*O*-Methylxylitol	50	67
5-*O*-Methyl-D-xylitol	90	76
2-*O*-Methyl-D-galactitol	85	82
3-*O*-Methyl-D-galactitol	85	72
6-*O*-Methyl-D-galactitol	95	91
2-*O*-Methyl-D-glucitol	85	72
3-*O*-Methyl-D-glucitol	70	73
6-*O*-Methyl-D-glucitol	65	79

complexes of types I and II are feasible with borate. In some instances, complexes of type III are possible. This latter type of interaction is, however, only of importance if the polyol can adopt a conformation similar to that of a six-membered carbocylic ring with three axial *cis*-1,3,5-hydroxyls. Since this leads to conformationally untenable structures, tridentate complexes

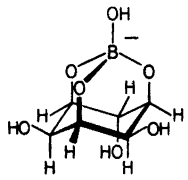
in the above compounds are probably precluded. Although only one type of complex (IV) is possible with diphenylborinic acid as compared with two for borate, the relative mobilities in the two buffers closely parallel one another.

The paper electrophoretic mobilities of some cyclitols in the two buffers are shown in Table 5. A difference between the patterns of relative mobilities

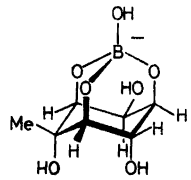
Table 5. Cyclitols.

Substance	10^2 M_G in diphenylborinate	10^2 M_G in borate
myo-Inositol	30	42
D-Inositol	55	70
epi-Inositol	95	76
Laminitol	100	76
cis-Inositol	114	76

may, however, be observed. In borate, "tridentate", *i.e.* *cis*-1,3,5-complexes, in addition to types I and II complexes are formally possible in one of the two chair conformations of each of *myo*-, *epi*-, and *cis*-inositol as well as with laminitol.[4] In the conformation required for tridentate complex formation (*c.f.* *epi*-inositol, V, and laminitol, VI) the number of axial hydroxyls not participating in tridentate complex formation for the three former is two,



V



VI

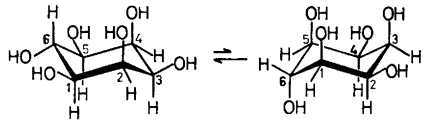
one, and none, respectively, and for laminitol two. Laminitol forms a much stronger tridentate complex than *myo*-inositol, which is ascribed to the presence of an axial *C*-methyl group in laminitol in the most stable chair conformation. This becomes equatorial in the tridentate complex.

The changes in pH, caused by successive additions of cyclitols to sodium tetraborate, have been examined. The results have revealed a clear correlation between the number of non-participating axial hydroxyl groups in the conformation of the cyclitol required for tridentate complex formation on the one hand, and the equilibrium constant for complex formation on the other.[4,5] For *cis*-inositol, where the non-participating hydroxyls occupy equatorial positions, a strong complex is formed. These findings have been adduced as evidence for the existence of tridentate complexes between borate and cyclitols with the appropriate steric arrangement of the hydroxyl groups.[4,5] In the

instances where tridentate complexes have been postulated, clear evidence for a 1:1 ratio of borate:inositol has been obtained.[4,5]

The differences in the patterns of relative paper electrophoretic mobility in borate and in diphenylborinate, depicted in Table 5, could be due to the formation of tridentate complexes with the three faster-moving cyclitols in borate, whereas in diphenylborinate this possibility is precluded.

The most stable chair conformation of *epi*-inositol is depicted in VIIa. In this conformation, several possibilities for the formation of *cis*-1,2-complexes with borate and with diphenylborinate exist. However, for the cyclitol to form a tridentate complex with borate, an inversion of the cyclohexane ring must take place (VIIb).



VII a VII b

The NMR spectra of *epi*-inositol in (a) deuterium oxide, (b) deuterium oxide containing borate, and (c) deuterium oxide containing diphenylborinate are depicted in Fig. 1. In the former spectrum, the triplet at 0.64 ppm (upfield from DOH), 2H, $J = 3$ Hz, is probably due to H-2 and to H-4 (equivalent) in the conformer VIIa. These protons being equatorial are expected to give signals at lower field than the other protons, which are axially orientated.[6] In this spectrum, the magnitude of the expected coupling constants for the other signals relative to the differences in chemical shifts should give rise to second-order effects. These are clearly seen in the spectrum, which is consistent with conformation VIIa.

By contrast, the spectrum of *epi*-inositol in the presence of two moles sodium borate per mole cyclitol, shown in Fig. 1b, is consistent with inversion of the chair conformation, leading to VIIb. The triplet at 0.45 ppm, 1H, $J = 4$ Hz, is due to the equatorial hydrogen H-6, which, being coupled to a position not involved in complex formation, is not shifted upfield. The high-field triplet, 2H, $J = 2$ Hz, is assigned to H-2 and H-4 (equivalent) both of which are axial, and are adjacent to equatorial hydrogens. Of the remaining protons, H-1 and H-5 are identically situated. H-1, H-3, and H-5 are all equatorial and are shielded by the oxygens at these positions, which are linked to negatively charged boron. The chemical shifts of H-1 and H-5 on the one hand, and H-3 on the other, may therefore be expected to be similar. The broad signal at 0.6 – 0.9 ppm, 3H, is in agreement with these expectations.

The spectrum of *epi*-inositol in the presence of two moles sodium diphenylborinate is shown in spectrum 1c. A complex second order spectrum is observed. In contrast to the first two spectra, where the inherent symmetry of either conformations VIIa or VIIb gives rise to relatively simple spectra, it is clear that in the present instance, complex formation has resulted in non-equivalence

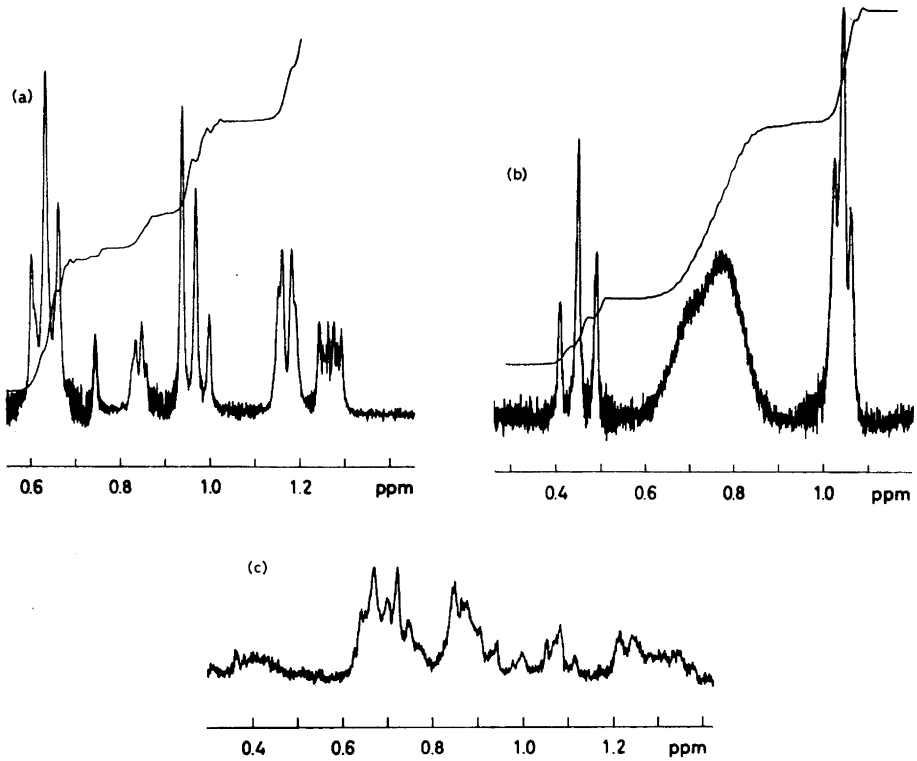


Fig. 1. Partial 100 MHz spectra of *epi*-inositol in (a) deuterium oxide, (b) deuterium oxide containing 2 mol sodium borate/mol cyclitol, and (c) deuterium oxide containing 2 mol sodium diphenylborinate/mol cyclitol.

of all the protons. As tridentate complexing is precluded, it would seem most likely that conformations approaching that of VIIa are involved in complex formation. In this conformation, four *cis*-1,2-complexes and one *cis*-1,3-complex (between positions 2 and 4) with boron are feasible. *cis*-1,2-Complexes are only possible if the oxygens involved are nearly eclipsed.[7] This implies that complexing between O-1 and O-2, together with O-3 and O-4, is sterically permissible, while that between O-1 and O-2 with O-4 and O-5 is not. Complexing across O-2 and O-4 would prevent further complexing in the molecule. The high mobility of *epi*-inositol on paper electrophoresis in diphenylborinate suggests that more than one boron is complexed with the cyclitol. Complex formation between O-1 and O-2, and O-3 and O-4 would explain the high electrophoretic mobility, and is consistent with the NMR spectrum insofar as the resulting flattening of the cyclitol ring would lessen the difference between axial and equatorial hydrogens as described above. Furthermore, the complexing leads to an asymmetrical molecule with a complex NMR spectrum.

The distinct differences in the NMR spectra 1b and 1c indicate a considerable difference in the conformations of *epi*-inositol in the two buffers. Since tridentate complexing is precluded in diphenylborinate, no free energy can be gained by the cyclitol assuming the conformation VIIb in that buffer. Spectrum 1c therefore corresponds to the boron complex with a "flattened" conformation of VIIa. It follows that in the presence of borate, *epi*-inositol assumes conformation VIIa, as a result of the tridentate complex across O-1, O-3, and O-5. The results therefore lend support to the view [4,5,8] that in aqueous solution and under favourable steric circumstances, strong tridentate complexes are formed between borate and polyols.

EXPERIMENTAL

Melting points are corrected. Evaporations were carried out under diminished pressure at temperatures below 40°.

Diphenylborinic acid. Tributyl borate [9] (230 g, 1 mol) was dropped into a solution of phenylmagnesium bromide (358 g, 2 mol) in dry diethyl ether (1200 ml) at −70° with vigorous stirring. The time of addition was about 90 min. After a further 20 min at the same temperature, the product was hydrolyzed with water (70 ml) for 5 min, and then treated with sulphuric acid (28 ml) in water (566 ml) for 15 min. The neutral mixture was extracted three times with light petroleum (60 – 80°). The combined extracts were dried over magnesium sulphate, filtered, and concentrated to yield 132 g (73 %) crude diphenylborinic acid. The crude product was purified by conversion into the ethanolamine ester, as described by Coates and Livingstone.[10] The crystalline ester had m.p. 193 – 195°. Coates and Livingstone report m.p. 188 – 189°. The yield of diphenylborinic acid in the form of crystalline ethanolamine ester was 65 %. The diphenylborinic acid was obtained, as required, by hydrolysis of the ester.[10]

Substances. The various aldoses, ketoses, aldose methyl ethers, glycosides, and some cyclitols were available at this Laboratory. The various monomethyl alditols were obtained by Raney nickel reduction of the corresponding monomethyl aldoses.[11] *cis*- and *epi*-Inositol were prepared as previously described.[12,13]

Buffers: A. Borate buffer 0.1 M at pH 10.[2,14] B. Phenylborinic acid (0.1 M) in water, to which sodium hydroxide was added with vigorous stirring to pH 10. Diphenylborinate is slowly oxidized when exposed to air at this pH to yield phenol. The buffer was therefore periodically examined by removing an aliquot, acidifying and extracting the aqueous solution with chloroform. The chloroform phase was examined by thin layer chromatography (silica gel GF_{254} nach Stahl, hexane/diethyl ether 2:1) which gave clear separations of diphenylborinic acid, phenol, and phenylboronic acid. Only buffer containing undegraded diphenylborinic acid was used in the experiments.

Electrophoresis. The apparatus was similar to that described by Kunkel and Tiselius,[15] and the procedure to that described by Foster.[2,14] Whatman 3 MM filter paper was used. Hydroxymethylfurfural was used as starting line marker, and glucose as the standard reference for the relative rate of migration. The starting line was placed 20 cm from the cathode end of the cooling plate; the latter was cooled with tap water. Each electrophoresis was performed at 1000 V (20 V/cm) for 2½ h. After each run, the electrolyte in the two electrode vessels was mixed to avoid build-up of a difference in pH between the two vessels. Reducing sugars were located by spraying the papers with anisidine hydrochloride, the other substances by spraying with periodate followed by benzidine.[16] Distances of migration were measured from the centre of the spots.

NMR spectra were obtained on a Varian A-60 and on an HA-100 spectrometer. Chemical shifts were measured from that of DOH in each spectrum.

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