Structure and Stability, as a Function of pH, of Borate Esters of Carbohydrate Oximes and Related Compounds in Aqueous Media Studied by ¹¹B and ¹³C NMR Spectroscopy

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Borate ester formation of carbohydrate oximes and related compounds, including acetohydroxamic acid, has been studied using ¹¹B and ¹³C NMR spectroscopy. It is shown that the oxime hydroxyl is involved in the borate ester formation. The resulting six-membered ring borate monoesters are more stable than the five-membered ring *erythro*- or *threo*-borate monoesters involving a vicinal diol function.

Complexation of transition metal ions by oximes has been studied for many years [1] and hydroxyoximes have found some important industrial applications, *e.g.* in solvent extraction processes.[2,3] The cation sequestering abilities of polyhydroxycarboxylic acids are known to increase upon addition of borate.[4,5,6] The synergic cation sequestration of these systems finds its origin in the good cation coordinating sites that are formed upon linking two sugar acid molecules by borate.

In polyhydroxycarboxylic acid–borate systems,[7] at pH > 9, borate mono- (B^-L) and borate diesters (B^-L_2) involving adjacent (1,2-diol type) or alternate hydroxyl functions (1,3-diol type) are formed (Fig. 1), leaving the carboxylate functions free for coordination with metal ions. Mixtures of polyhydroxy oximes (carbohydrate derived oximes) and borate may, likewise, possess good cation sequestering abilities. Here we report on a study of the borate ester formation of polyhydroxy oximes and related compounds, which has been undertaken in order to understand the cation sequestering abilities of such mixtures. The structures and the stabilities of the borate esters were determined using ¹¹B and ¹³C NMR spectroscopy. The cation sequestration by these systems will be the subject of a future report.

Although borate is known to interact with benzohydroxamic acids and with oxime hydroxy groups in the solid state,[9,10] studies by ¹¹B NMR spectroscopy on the interaction between borate and polyhydroxy oximes or hydroxamic acids in aqueous solution have not been published hitherto.

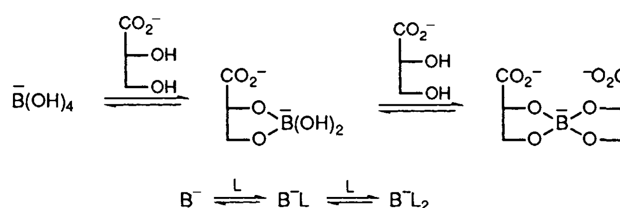

Fig. 1 Equilibria between borate (B^-) and a diol function of a polyhydroxycarboxylate (L) at pH > 9

Table 1 *E*/*Z* Ratio of the oxime compounds as determined from the ¹³C NMR peak intensities at 25 °C in D_2O

Oxime	*E*/*Z*
Acetaldehyde oxime (**2**)	1.3
Acetole oxime (**4**)	1.0
DL-Glyceraldehyde oxime (**5**)	3.0
D-Arabinose oxime (**6**)	4.0
D-Mannose oxime (**7**)	10.0
D-Glucose oxime (**8**)	4.2
D-Galactose oxime (**9**)	2.9
D-Glucosamine oxime (**10**)	4.0
Potassium-D-*xylo*-5-hexulosonate-5-oxime (**11**)	1.5

Results and Discussion

Oxime Compounds.—The borate ester formation of a series of carbohydrate oximes and related compounds (Fig. 2), including acetohydroxamic acid, has been studied as a function of pH. Oximes usually occur as two geometric *E*- and *Z*-isomers; in the case of aldoximes the *E*-isomer with the oxime OH *syn* to the imine C–H is predominant.[11] Hydroxamic acids exist in two tautomeric forms of which the enol form dominates in alkaline medium.[12] Oxime derivatives of carbohydrates may also adopt cyclic structures: in aqueous solution, at equilibrium, D-glucose oxime (**8**) exists as a mixture of the cyclic α-pyranose (23%) and β-pyranose (7%) forms, and the acyclic *E* (56.5%) and *Z* (13.5%) forms.[13] From ¹³C NMR spectroscopic data it can be concluded that all other compounds studied occur almost exclusively in the acyclic forms. The ratios of the *E*- and *Z*-isomers as determined from ¹³C NMR peak intensities are given in Table 1. The *E*/*Z* ratios of compounds **6**–**9** show a good agreement with literature values.[13,14]

In aqueous solution, at equilibrium, the composition of isomers of oximes can differ from that in the solid state.[13] Thus upon dissolution in aqueous medium, these oximes will isomerise at a certain rate, leading to an equilibrium mixture as described by eqn. (1).

$$E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Z \qquad (1)$$

For D-arabinose oxime (**6**) the isomerisation [eqn. (1)] behaves kinetically as a two component, first-order, reversible reaction with an observable rate constant $k_e = k_1 + k_{-1}$, which has been shown to be pH dependent.[15] The isomerisation probably proceeds by a pathway involving cyclic *N*-arabinosylhydroxylamine intermediates and is catalysed by both acid and base leading to rate constants of 4.1 and $0.6 \times 10^{-3}\ s^{-1}$ at pH 4.4 and 9.0, respectively.[15] This means that upon dissolving D-arabinose oxime (and most probably also the other carbohydrate oximes **6**–**11**) in aqueous medium, an equilibrium mixture will be reached, at room temperature, within a few minutes to a few hours, depending on the pH. By contrast,

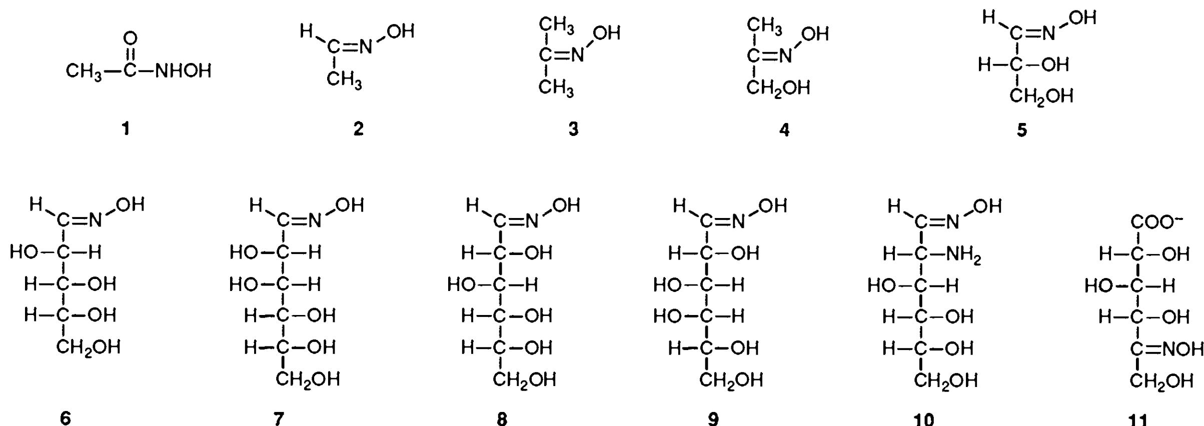

Fig. 2 Structures of the major isomers of the polyhydroxy (amino) oximes (D_2O, 25 °C). For **5** the D-enantiomer is depicted; the major isomer of **11** has not been determined.

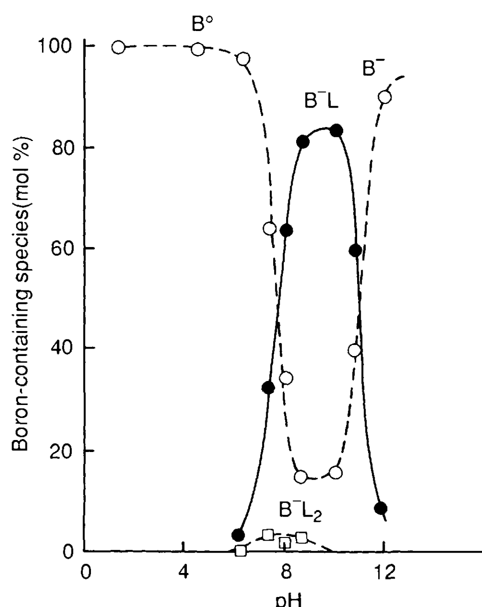

Fig. 3 Borate ester formation of acetohydroxamic acid (**1**) as a function of pH; 0.10 mol dm^{-3} borate and 0.23 mol dm^{-3} acetohydroxamic acid; molar percentage boron-containing species

isomerisation for acetole oxime (**4**) and DL-glyceraldehyde oxime (**5**) appeared to be much slower, which is probably caused by the fact that these oximes cannot form cyclic carbinolamine intermediates as carbohydrate oximes [15] do.

Borate Ester Formation Studied by ^{11}B and ^{13}C NMR Spectroscopy.—^{11}B and ^{13}C NMR [7,16,17] spectroscopy have proved to be useful techniques for both the identification of borate esters and the estimation of their relative stabilities. Borate ester formation has been shown to occur usually across adjacent (1,2-diol-type) or alternate (1,3-diol-type) hydroxy functions, resulting in bidentate mono- or di-esters. Recently we have shown that on borate ester formation with amino acids and amino diols, in aqueous solution, no borate esters having boron–nitrogen bonds are formed.[18]

The exchange rate between borate, borate monoesters and diesters is slow on the ^{11}B NMR time-scale,[19,20] hence enabling the determination of the chemical shifts, linewidths and association constants of the various boron-containing species. The exchange rate between the various boron-containing species and the free ligand is also often slow on the ^{13}C NMR time-scale.[4,7,16,17] When the exchange is slow, addition of borate to aqueous solutions of ligands such as polyols, or in our case carbohydrate oximes, results in ^{13}C NMR spectra which contain a large number of new resonances. A new set of resonances for each different borate ester appears, and both small up- and down-field shifts with respect to the free ligands are observed. This may be explained by conformational changes upon borate ester formation and by the inductive effect of the borate group. Moreover, due to the presence of a chiral boron centre in most of the spiro borate diesters, two diastereoisomeric borate diesters are formed, each of which give rise to separate sets of signals.

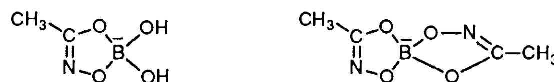

Fig. 4 Structures of borate esters of acetohydroxamic acid

Acetohydroxamic Acid (**1**).—For acetohydroxamic acid **1** the ^{11}B NMR spectrum showed not only the signal for the equilibrium between boric acid and borate, but also signals from two other boron containing species (Fig. 3), with chemical shifts of −11.7 and −11.0 ppm, respectively. Although the *exact* values of the chemical shifts are unique, they are within the chemical shift range of borate mono- and di-esters of '1,2-diol-type' borate esters (*i.e.* −9 to −14 ppm).[19,20] The greatest amount of borate esters of acetohydroxamic acid is at pH 9–10. Borate ester formation is most favoured at that pH where the sum of the charges of the free esterifying species is equal to the charge of the ester ('pH rule of thumb'),[19] and as a consequence the optimum pH for borate monoester formation is attained at pK(boric acid) < pH < pK(acetohydroxamic acid). Thus, upon increasing the pH above 10 (pK_a of acetohydroxamic acid is 9.36; H_2O, 25 °C [21]) the borate esters will dissociate because of the ionisation of the acetohydroxamic acid. As monodentate borate esters are only very weak,[22] it can be concluded that the acetohydroxamic acid is bound in a bidentate fashion *via* the two hydroxy groups (Fig. 4).

The linewidths of ^{11}B NMR signals are dominated by quadrupolar relaxation.[23] In '1,2-diol-type' borate diesters the boron atom can be more distorted from tetrahedral symmetry than in borate monoesters or in free borate,[20,22] which would result in an increase of the quadrupolar relaxation and thus a broadening of the signals. In addition, the larger size of the borate diester will give rise to a relatively long correlation time which also leads to greater linewidths. Therefore, as of the two borate ester signals that at −11.0 ppm has the biggest linewidth (see Table 2), it is assigned to the B^-L_2 ester. Analogously, the signal at −11.7 ppm is assigned to the B^-L ester.

^{13}C NMR spectroscopy of a solution of acetohydroxamic acid, at pH 9.2, showed signals at 171.0 and 20.1 ppm, which

Table 2 Chemical shifts/ppm and linewidths/Hz of the various borate esters (D_2O, 25 °C)

Polyhydroxy oxime	Ester type	Chemical shift		Linewidth	
		B^-L	B^-L_2	B^-L	B^-L_2
1; Acetohydroxamic acid	1,1	−11.7	−11.0	22	49
2; Acetaldehyde oxime	1,1	−6.3	—	222	—
3; Acetone oxime	2,2	−6.3	—	272	—
4; Acetole oxime	1,2-oxime	−18.7	−19.1	8	21
	1,2-diol	−14.3		44	
5; DL-Glyceraldehyde oxime	1,2-oxime	−18.4	−19.0	14	—
	2,3-diol	−13.6	−9.5	19	44
	1,2 + 1,3	—	−14.0	—	40
6; D-Arabinose oxime	1,2-oxime	−18.2	−18.8	34	—
	threo-2,3	−13.6	−9.7	35	94
	erythro-3,4	−14.4	—	42	—
7; D-Mannose oxime	1,2-oxime	−18.0	−18.3	26	52
	threo-3,4	−13.3	−8.9	36	95
	erythro-4,5	−14.5	—	37	—
8; D-Glucose oxime	1,2-oxime	−18.2	−18.7	22	28
	threo-2,3/3,4	−13.3	−8.9	41	97
	erythro-4,5	−14.4	—	38	—
9; D-Galactose oxime	1,2-oxime	−18.2	−18.6	32	50
	threo-2,3/4,5	−13.5	−9.4	47	124
	erythro-3,4	−14.5	—	37	—
10; Glucosamine oxime	*threo*-3,4	−13.4	−9.3	—	100
	erythro-4,5	−14.5	—	—	—
11; Potassium-D-*xylo*-5-hexulosonate-oxime	1,2-oxime	−18.3	−18.6	35	45
	threo-2,3/3,4	−13.0	−8.9	34	—
	?	−14.0	—	—	—
	?	−14.2	—	—	—

were assigned to the imine carbon and the methyl group, respectively. Upon ionisation of acetohydroxamic acid the imine ^{13}C signal shifted from 172.2 (pH 2.4) to 166.7 ppm (pH 12.2). Upon addition of borate, at pH 9.2, three new signals appeared at 164.7, 13.7 and 13.2 ppm. The signal at 164.7 ppm is due to the imine carbon of the borate mono- and di-esters, the signal at 13.7 ppm is assigned, on the basis of its intensity, to the methyl group of the borate monoester, leaving that at 13.2 ppm as the methyl group of the borate diester. Both the signal of the imine carbon and of the methyl carbon exhibit an upfield shift upon borate ester formation, which probably reflects the increase of negative charge on the C=N–O moiety upon borate ester formation.

Acetaldehyde Oxime (**2**), *Acetone Oxime* (**3**) *and Acetole Oxime* (**4**).—Immediately after dissolving acetole oxime the *E*-isomer (*i.e.* the isomer with the oxime OH *syn* to the methyl group) alone is present in solution. Prior to borate ester formation an isomerisation from *E* to *Z* is required. This isomerisation process has a low rate constant, k_e, since the relatively fast pathway *via* cyclic carbinolamine intermediates is impossible here. For acetole oxime (**4**), at pH 10.4, the low rate of the isomerisation of the oxime resulted in an exceptionally slow formation of the borate esters. Normally, in the case of polyols or polyhydroxycarboxylic acids, borate ester formation is fast and equilibrium mixtures between borate and borate esters are obtained almost immediately after preparation of the samples. However, for acetole oxime, the spectra appeared to be time-dependent up to three weeks after preparation of the sample. Spectra recorded after three weeks and seven months did not differ significantly, indicating that after about three weeks an equilibrium mixture has been reached.

Apart from the signal for boric acid/borate, three new signals appeared in the ^{11}B NMR spectra, having chemical shifts of −18.7, −19.1 and −14.3 ppm (Table 2). The signals at −18.7 and −19.1 ppm, are in the chemical shift range of '1,3-diol-type' borate esters[19,20] and were assigned to the B^-L and B^-L_2 borate esters of (*Z*)-acetole oxime. The signal at −14.3 ppm

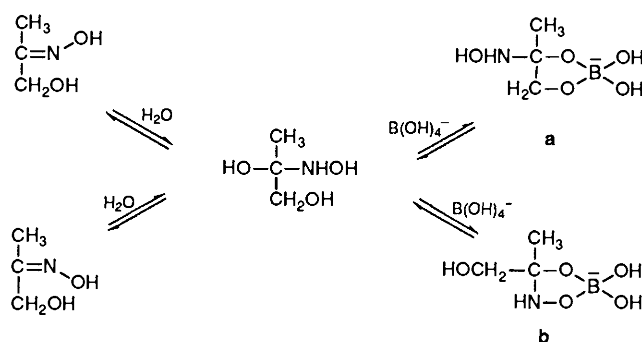

Fig. 5 Borate esters derived from hydrated forms of acetole oxime (**4**)

could not be assigned unambiguously, but its chemical shift points to a borate ester of the '1,2-diol-type', probably derived from a hydrated form of acetole oxime (see Fig. 5).

The amount of B^-L and B^-L_2 esters gradually increased until the equilibrium was reached, whereas the amounts of B^0/B^- and of the borate ester corresponding to the peak at −14.3 ppm decreased. At equilibrium, the latter could no longer be detected. Similarly with acetohydroxamic acid, the amount of borate esters reached its maximum at pH 10–11 and decreased at higher pH due to the ionisation of the oxime hydroxy group.

Assigning the signal at −14.3 ppm to a borate ester derived from a hydrated form of acetole oxime leaves two possibilities for its structure (see Fig. 5, structure **a** or **b**). In order to discriminate between structures **a** and **b** some ^{11}B NMR measurements were performed on mixtures of borate and acetaldehyde oxime (**2**) or acetone oxime (**3**); these ligands are only able to form monodentate borate esters or borate esters of a structure similar to that denoted as **b** in Fig. 5. For both oximes the ^{11}B spectra showed no signals at about −14.3 ppm but, between pH 8 and 10, other than the signal for the equilibrium between B^0 and B^- only a small signal (5–8% of total boron) having a chemical shift of −6.3 ppm was observed.

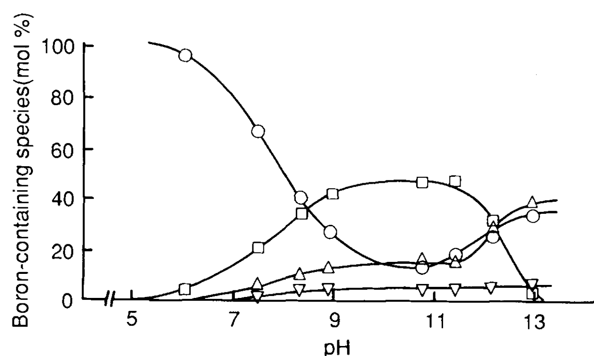

Fig. 6 Borate ester formation of DL-glyceraldehyde oxime (**5**) as a function of pH, 0.10 mol dm^{-3} borate and 0.25 mol dm^{-3} DL-glyceraldehyde oxime; molar percentage boron-containing species (B^-, ○; B^-L, △; B^-L(oxime), □; B^-L_2, ▽)

Therefore it may be concluded that the ^{11}B NMR signal at −14.3 ppm for compound **4** most likely originates from a borate ester species with structure **a** (see Fig. 5). No hydrated forms of the oximes **2**–**4** were detected in the ^{13}C NMR spectra. In mixtures of acetole oxime (**4**) and borate no separate signals for the borate esters were detected in the ^{13}C NMR spectra. This probably results from fast exchange on the ^{13}C NMR time-scale between the borate esters and the free ligand.

DL-*Glyceraldehyde Oxime* (**5**).—^{11}B NMR spectroscopy on mixtures of boric acid and DL-glyceraldehyde oxime (**5**), showed the borate ester formation also to be time-dependent. The equilibrium was reached in about two weeks. The pH dependence of the borate ester formation, at equilibrium, is shown in Fig. 6.

In the ^{11}B NMR spectra the signals at about −13.5 and −9.5 ppm (Table 2) were assigned to the '1,2-diol-type' borate mono- and di-esters, respectively. From their chemical shifts and disappearance at pH values above 11, it was concluded that the signals at −18.4 and −19.0 ppm are from '1,3-diol-type' borate mono- and di-esters, respectively, which include the oxime hydroxy group. These '1,3-diol-type' borate esters with participation of the oxime hydroxy group will, hereafter, be denoted as B^-L_n(oxime) borate esters (n = 1 or 2). At −13.9 ppm a signal was present, which on the basis of its chemical shift may be assigned to a mixed B^-L_2(oxime + 2,3-diol) ester, or a borate ester derived from a hydrated form of the oxime as in the case of acetole oxime (**4**). The signals of the '1,2-diol-type' borate mono- and di-esters showed an upfield shift (0.1–0.2 ppm), upon raising the pH from 10 to 12, while the chemical shifts of the B^-L_n(oxime) esters remained constant at −18.4 and −19.0 ppm, respectively. This reflects the deprotonation of the unbound oxime hydroxy group in the borate esters (pK_a values of oximes are usually 10–11 [21]); a similar, small upfield shift was observed upon the deprotonation of amino groups in the borate esters of amino diols.[18] Though the '1,2-diol-type' borate mono- and di-esters can have the oxime hydroxyl *E* or *Z*, no distinct signals for these forms were observed.

^{13}C NMR spectroscopic studies on mixtures of DL-glyceraldehyde oxime and borate (Table 3), showed a single signal for the imine carbon atoms of the B^-L_n(oxime) esters and the *Z* form of the free ligand. A broad signal at 155.2 ppm was assigned to the imine carbons of the B^-L and B^-L_2 esters, since it did not disappear at pH values above 11. Signals for borate esters at 66.4 ppm showed the involvement of the CH_2OH carbon in the borate ester formation, while a signal at 71.9 ppm could be assigned to the CHOH carbon of the borate esters. The downfield shifts upon borate ester formation of the CHOH (1.1 ppm) and CH_2OH (1.8 ppm) carbon atoms, are of the same magnitude as observed for borate esters of glycerate and for borate esters with the borate moiety at a terminal vicinal diol group.[7]

The borate ester formation of DL-glyceraldehyde oxime (**5**) can be summarised as depicted in Fig. 7. Borate esters which might be derived from hydrated forms of the oxime are not included in Fig. 7 as they are weak compared to the other borate esters.

^{11}B *NMR Spectroscopy of the Carbohydrate Oxime–Borate Systems*.—^{11}B NMR spectroscopy of mixtures of the carbohydrate oximes and boric acid, as a function of pH, essentially shows the same features as the spectra of DL-glyceraldehyde oxime, although the number of different borate ester species is larger as the compounds contain more hydroxy groups. With the aid of the results obtained for acetole oxime (**4**), DL-glyceraldehyde oxime (**5**) and previous work on polyols and polyhydroxycarboxylic acids,[22,24] almost all ^{11}B NMR resonances for the borate esters of the carbohydrate oximes could be assigned (see Table 2).

As a consequence of the large number of hydroxy groups, diborate (B_2L^{2-}) or triborate (B_3L^{3-}) esters may also be formed. These esters, however, will only be formed at high boron to ligand ratios,[24] which is not the case in our study. Therefore the amounts of di- and tri-borate esters are supposed to be negligible. Borate esters involving *threo*-diol functions usually give resonances at −13.0 to −13.8 ppm,[22] whereas borate esters involving *erythro*-diol functions resonate at −14.0 to −14.6 ppm.[22]

In the case of potassium D-*xylo*-5-hexulosonate-5-oxime (**11**), minor components with peaks at −14.0 and −14.2 ppm were observed. As this ligand contains no *erythro* position the borate esters are most probably derived from hydrated forms of the oxime, which is consistent with the observations for acetole oxime (**4**). '1,3-Diol-type' borate monoesters, involving alternate diol functions, are known to be formed in mixtures of borate and polyhydroxy acids or polyols[22] and have chemical shifts of −17.9 to −18.5 ppm. In our case such esters would overlap with the signals of the B^-L_n (oxime) borate esters. '1,3-Diol-type' borate mono- and di-esters of polyols and polyhydroxy-carboxylic acids are, however, usually unstable and consequently only formed above pH 10 in (under our conditions) at most a few percent compared to the other borate esters. In the case of D-glucosamine oxime (**10**) no borate esters with involvement of the oxime group could be detected. This confirms that no seven-membered ring borate esters are formed (the amino group does not participate in borate ester formation in aqueous solution[18]). '1,3-Diol-type' borate esters could also not be detected, which again demonstrates that such borate esters, certainly at pH values below 10, do not have to be taken into account for carbohydrate oximes. For all carbohydrate oximes, at high magnetic field (9.4 T), shoulders could be detected on the signals of the B^-L (oxime) esters. Since these signals also disappeared at high pH (pH > 11), they have been assigned to B^-L_2(oxime) esters.

^{13}C *NMR Spectroscopy on Mixtures of the Carbohydrate Oximes and Borate*.—The measurements were performed at pH 9.5–12. Chemical shifts, for a single pH value, are compiled in Table 3. Since ^{11}B NMR spectroscopy indicates that, above pH 12, almost no borate esters involving the imine carbon are present, comparing the ^{13}C NMR spectra at pH 12 with those at pH 10 is useful in discriminating between borate esters in which the oxime hydroxy is involved and other borate esters. Addition of borate to solutions of D-glucose oxime (**8**), D-galactose oxime (**9**) and potassium-D-*xylo*-5-hexulosonate-5-oxime (**11**), gave, apart from the (at least) twelve resonances of the free ligands, such a large number of resonances that an unambiguous

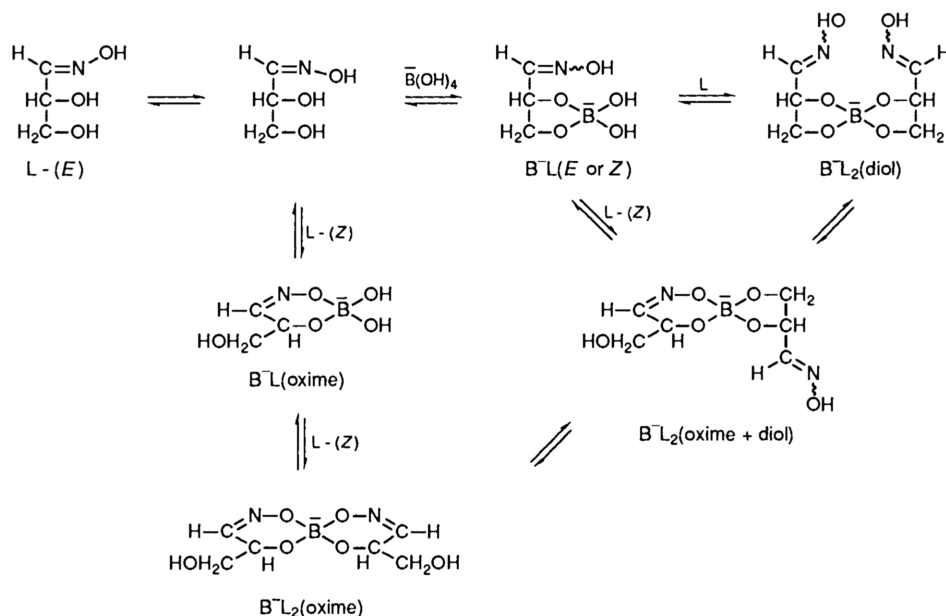

Fig. 7 Borate ester formation of DL-glyceraldehyde oxime

Table 3 ^{13}C NMR chemical shifts of the free ligands and their borate esters at various pH values[a] (D_2O, 25 °C)

		C=NOH		CHOH		CH_2OH		CH_3	
Polyhydroxy oxime	Species	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
1; Acetohydroxamic acid	L	171.0							20.1
	B^-L	164.7							13.6
	B^-L_2	164.7							13.2
4; Acetole oxime	L		161.0			64.5	64.1	12.5	17.8
	B^-L		161.0				64.1		17.8
	B^-L_2	161.0					64.1		17.8
5; DL-Glyceraldehyde oxime	L	153.2	154.0	70.8	67.4	64.6	64.0		
	B^-L	155.2		71.9		66.4			
	B^-L_2	155.2		71.9		66.4			
	B^-L(oxime)		154.0		71.9				
6; D-Arabinose oxime	L	151.8	153.8			64.1	64.4		
	B^-L	154.4	156.8			64.5	64.8		
	B^-L_2	153.7	156.1			64.3	64.8		
		153.6	155.9			64.2	64.8		
	B^-L(oxime)		151.6			64.2	64.8		
7; D-Mannose oxime	L	154.0	153.9			64.6			
	B^-L	154.0	151.4			64.8			
	B^-L_2	154.0	151.3			64.6			
		154.0	151.3			64.6			
	B^-L(oxime)		153.8			64.8			
10; D-Glucosamine oxime	L	151.7	153.4			64.6	64.9		
	B^-L	152.4	151.7			64.9			
	B^-L_2	152.5	151.7			64.8			
		152.4	151.7			64.7			

[a] pH: **1**, 9.2; **4**, 10.5; **5**, 8.9; **6**, 11.2; **7**, 10.1; **10**, 11.5.

assignment was impossible. For this reason, these oximes have not been included in Table 3. The borate esters of D-glucose oxime (**8**), nonetheless, appeared to possess acyclic structures, as the intensity of signals with chemical shifts characteristic of cyclic compounds (free ligand + borate bound ligand) decreased upon addition of borate. The ^{13}C NMR spectra of D-arabinose oxime (**6**) and D-mannose oxime (**7**), upon addition of borate, gave fewer new resonances, by virtue of the fact that these ligands possess only one *threo*-diol position. As the individual CHOH carbons of the carbohydrate oximes have not been assigned so far, no attempt was made to assign the CHOH resonances of the corresponding borate (di)esters. Assignment of ^{13}C resonances was restricted to the imine carbons and the CH_2OH carbons. Both the chemical shifts for the free ligands and those for the borate esters were shown to be pH dependent: upon deprotonation of the oxime OH the imine carbons of the free ligands showed an upfield shift of 2.5–3.4 ppm for the *E*-isomers and 0.2–2.4 ppm for the *Z*-isomers. The CHOH carbons at the C(2) position showed a downfield shift of *ca.* 1 ppm for the *E* forms and of about 3 ppm for the *Z* form.

For D-arabinose oxime (**6**) at pH 12.5, ^{11}B NMR spectroscopy showed the occurrence of mainly *threo*-borate mono- and di-esters. The ^{13}C NMR spectra showed, apart from the signal of the carbonyl oxime carbon of the free ligand, two sets of three new signals in the carbonyl signal region. These signals are assumed to belong to the *threo*-borate mono- and di-esters, of which the latter exists as a pair of diastereoisomers, resulting in peak doubling. Thus ^{13}C NMR spectroscopy

Table 4 Association constants of the borate esters (0.1 mol dm^{-3} borate, 0.1–0.4 mol dm^{-3} ligand in D_2O at 25 °C, pH 8–10)

Polyhydroxy oxime	Ester type	Association constant (log K)	
		log K_1	log K_2
1; Acetohydroxamic acid	1,1	1.8	−0.6
2; Acetaldehyde oxime	1,1	0.2	—
3; Acetone oxime	2,2	0.2	—
4; Acetole oxime	1,2-oxime	1.6 (±0.2)	—
5; DL-Glyceraldehyde oxime	1,2-oxime	2.1 (±0.2)	−0.5 (±0.1)
	2,3-diol	1.1 (±0.2)	0.08
6; D-Arabinose oxime	1,2-oxime	3.6 (±0.2)	—
	threo-2,3	2.8 (±0.2)	1.3
	erythro-3,4	1.7 (±0.1)	—
7; D-Mannose oxime	1,2-oxime	4.0 (±0.3)	—
	threo-3,4	3.1 (±0.3)	2.3 (±0.2)
	erythro-4,5	2.0 (±0.3)	—
8; D-Glucose oxime	1,2-oxime	3.0	—
	threo-2,3/3,4	2.2 (±0.2)	1.4 (±0.1)
	erythro-4,5	1.9	—
9; D-Galactose oxime	1,2-oxime	4.1 (±0.4)	—
	threo-2,3/4,5	3.6 (±0.3)	2.4
	erythro-3,4	2.6	—
10; D-Glucosamine oxime	*threo*-3,4	2.6 (±0.2)	2.1 (±0.2)
	erythro-4,5	1.5 (±0.1)	—

indicates the existence of borate esters having the oxime hydroxy group E and Z. At pH 11.2 apart from the signals of the *threo*-borate esters and of the free ligand, a signal was observed, which on the basis of its intensity and practical disappearance at pH 12.5, is assigned to the B^-L (oxime) ester. This imine carbon signal showed an upfield shift of 2.3 ppm with respect to the signal for the Z form of the free ligand. Addition of borate to solutions of D-mannose oxime (**7**) at pH 10.1 and 12.3 again showed two sets of three new resonances for the imine carbon of the *threo*-borate mono- or di-esters having the oxime hydroxy group E and Z (Table 3). For D-glucosamine oxime (**10**), at pH 8–12 no separate signals for borate esters having the oxime hydroxy E or Z could be detected. It could not be established whether this indicates that, at the measured pH values, only borate esters having the oxime hydroxy E or Z are formed, or that the signals merely coincide. Upon forming borate esters the signals of the CH_2OH carbons for all ligands measured showed downfield shifts of only 0.1–0.3 ppm, which confirms that no borate esters involving the terminal diol functions are formed.[7]

Association Constants.—Having identified the various borate esters formed in solution, by means of ^{11}B and ^{13}C NMR spectroscopy, association constants for the borate mono- and di-esters can be determined from the relative amounts of the borate esters by peak integration of the various ^{11}B NMR signals. The association constants, compiled in Table 4, are defined as in eqns. (2) and (3), and are the mean values obtained

$$K_1 = [B^-L]/[B^-][L] \quad (2)$$

$$K_2 = [B^-L_2]/[B^-L][L] \quad (3)$$

from measurements at various borate/ligand ratios and at various pH values between 8 and 10. In this pH region the oxime groups of the free ligands and *threo*- or *erythro*-borate esters are not ionised. As the association constants have been calculated from ^{11}B NMR spectroscopy, no distinction was made between (*threo*- or *erythro*-) borate esters having the oxime hydroxy group E or Z. In the calculation of the association constants of the B^-L (oxime) esters, only the amount of free ligand in the Z form ($[L]_Z$) has been taken into account, as this is the only isomer capable of giving B^-L (oxime) esters. This way all association constants of Table 4 refer to one-step processes, making comparison of the association constants for B^-L (oxime) esters with those for *threo*- and *erythro*-borate esters reasonable from a thermodynamic point of view: taking the total amount of free ligand into account would lead to association constants for B^-L (oxime) esters which would refer to constants for two consecutive steps, *i.e.* the constant for the equilibrium between the E and Z form of the free ligand and the association constant for the borate ester formation between borate and the Z form of the free ligand. Association constants for the borate esters of acetaldehyde oxime and acetone oxime were calculated with the assumption that they are borate monoesters. For acetohydroxamic acid association constants have been calculated using data measured between pH 7 and 12, with the assumption that the pK_a of acetohydroxamic acid is 9.9 ± 0.1 in D_2O.

The relative stabilities of the borate monoesters of acetohydroxamic acid (**1**) and acetole oxime (**4**) show that the 1,2-bidentate ester and the 1,3-bidentate ester are of about equal stability. The association constants for **4** and **5** are higher than those of small diols such as ethane-1,2-diol or propane-1,3-diol.[20] This can be explained by the relatively high acidity of **4** and **5** (pK_a =NOH, 10–12[21,25]), compared to diols: from a study covering borate ester formation between various boron acids and ligands, Babcock and Pizer[26] concluded that the stability constants of borate esters increase as the boron acids and ligands become more acidic. The rate-limiting step in borate ester formation appeared to be the proton transfer involved in the ring closure step. The forward rate constant (k_f) was found to be higher when the OH of the ligand is more acidic, while the reverse rate constant (k_r) increases with higher pK_a values of the ligands, leading to higher k_f/k_r ratios and larger association constants for more acidic ligands. The stabilities of borate esters involving the oxime hydroxyl [B^-L(oxime)], for ligands **5**–**9**, demonstrate that these '1,3-diol-type' esters are more stable than the borate esters involving *threo*- or *erythro*-diol functions. This is in contrast to borate esters of alditols, where 1,3-bidentate borate esters or esters involving terminal diol functions are found to be much less stable. The lower stability of the 1,3-bidentate borate esters of polyols with respect to the 1,2-bidentate borate esters is ascribed to the larger decrease of rotational freedom of the ligands upon borate ester formation.[27] However, as oximes and their borate esters contain a C=N double bond, the loss of rotational freedom and decrease in

entropy upon borate ester formation will be about the same as for 1,2-bidentate borate esters. Here again the relatively higher acidity of the oxime hydroxy groups compared to the alcoholic hydroxy groups seems a major factor determining the association constants of the borate esters. For the B^-L_2(oxime) esters of the carbohydrate oximes, association constants have not been calculated as the intensities of these signals were always quite low compared to the B^-L(oxime) esters and the signals were never well resolved.

Association constants for the '1,2-diol-type' *threo*- and *erythro*-borate mono- and di-esters of the carbohydrate oximes confirmed that *threo*-borate esters are more stable than *erythro*-borate esters, which is already well known from previous studies.[22,24] These differences in stability are mainly caused by differences in steric interactions between the substituents on the borate moiety, which are less in case of a *threo*-configuration. The larger number of hydroxy groups for D-galactose oxime (**9**) and D-mannose oxime (**7**), compared to D-arabinose oxime (**6**) and D-glucosamine oxime (**10**), increase the possibilities for the borate anion to bind the ligand, while total hydrolysis (*i.e.* the stepwise hydrolysis of two B–O ester bonds, where hydrolysis of one B–O bond competes with the formation of another B–O bond) becomes more difficult when increasing the number of hydroxy groups.[23] These two features can be translated into stabilising factors, which explain the relatively high association constants for compounds **7** and **9** compared to **6** and **10**.

Conclusions

In summary, it may be concluded that addition of borate to (poly)hydroxy(amino) oximes, leads to a new class of borate [B^-L(oxime)] esters, for which factors determining characteristics such as optimum pH of formation ('pH rule of thumb'), chemical shifts and association constants (loss of rotational freedom, acidity, number of hydroxy groups) are consistent with those derived in previous studies dealing with polyols and polyhydroxy acids. Furthermore, due to the presence of an oxime, or an oxime and an amino group in the ligands, the polyhydroxy(amino) oximes have interesting cation sequestering abilities, which may be enhanced upon addition of borate.

Experimental

Acetohydroxamic acid (**1**), acetaldehyde oxime (**2**) and acetone oxime (**3**) were purchased from Janssen Chimica and used without further purification. DL-Glyceraldehyde oxime (**5**), D-arabinose oxime (**6**), D-mannose oxime (**7**), D-glucose oxime (**8**), D-galactose oxime (**9**) and D-glucosamine oxime (**10**) were synthesised according to the method of Finch and Merchant[13] and purified by recrystallisation from methanol. Acetole oxime (**4**) was synthesised following the same procedure but the purification was achieved by distillation. Potassium D-*xylo*-5-hexulosonate-5-oxime (**11**) was synthesised according to the method of Inoye *et al.*[28] The amount of absorbed water for the oxime compounds was determined by Karl Fischer titration.

^{11}B NMR spectra were recorded at 25 °C on a Varian VXR-400 S spectrometer at 128.3 MHz or on a Nicolet NT-200 WB spectrometer at 64.2 MHz with 0.1 mol dm^{-3} boric acid in D_2O as external reference (δ 0.0). Baseline correction was applied to remove the broad signal of the boron incorporated in the glass sample tube and in the insert. Usually a deconvolution program was used to obtain all the signal characteristics. ^{13}C NMR spectra were recorded at 25 °C using the same spectrometers at 100.6 and 50.3 MHz respectively, with *tert*-butanol as internal standard. The total boron concentration was always 0.10 mol dm^{-3}, whereas the concentration of the polyhydroxy compounds varied between 0.1 and 0.4 mol dm^{-3}. Samples were prepared by dissolution of the appropriate amounts of boric acid and organic compound in D_2O. The pD was adjusted with NaOH or DCl and measured with a calibrated MI 412 Micro-combination probe from Microelectrodes, Inc.

^{11}B NMR spectra for samples of carbohydrate oximes **6–11** were recorded immediately after preparing the samples. After 24 h no significant differences in the ^{11}B NMR spectra were observed. Samples of acetole oxime (**4**) or DL-glyceraldehyde oxime (**5**) showed a remarkable time dependence of the borate ester formation. For determination of the association constants of acetole oxime (**4**) and DL-glyceraldehyde oxime (**5**), spectra recorded three and two weeks, respectively, after preparation of the solutions were used.

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