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Phenyl boronic acid complexes of diols and hydroxyacids

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Cumulative formation constants for the interaction of phenyl boronic acids with 1,2-diols and structurally related α-hydroxy carboxylic acids were determined by potentiometric titration in aqueous solution. Although there is a significant electronic effect on the acidity of phenyl boronic acid ($\rho = 2.1$), there is no marked electronic effect on the stability of the complexes. Rather, the complexes are significantly *destabilised* by adjacent anionic groups, by steric interactions across the face of the cyclic boronate ester and by angle strain within the boronate ester ring. Binding that is nearly independent of pH is observed for some favourably constituted α-hydroxy acid complexes as a result of the relatively high acidity of the acids, which in turn allows tetrahedral boronate complexes to persist in acidic solution (pH < 3).

Keywords: boronic acids; molecular recognition; formation constant; titration

1. Introduction

The recognition of diols by boronic acids is unique in supramolecular chemistry, in that the intermolecular interaction results in the reversible formation of a pair of covalent bonds (*1*). Frequently, a single interaction is sufficiently stabilising that single-point chelate recognition becomes possible. In addition, the complexes form in aqueous or predominantly aqueous solutions permitting recognition of hydrated and polar species such as saccharides. The ability of phenyl boronic acid to discriminate among monosaccharides was reported a half century ago, and that selectivity appears to be retained by all monoboronic acids (*2*, *3*). The core interaction has been very widely exploited with recent emphasis on colorimetric and fluorimetric sensors of saccharides (*3*, *4*), and the discrimination of mono- and oligosaccharides through hosts with multiple boronic acid units (*5*). The related interaction of boronic acids with α-hydroxy acids has also been successfully exploited for sensor applications (*6*–*9*).

Our interest in the interaction is prompted by two potential applications. Both envisaged interactions require 'stable' interactions to occur in an aqueous environment. The first application stems from our recent examination of the energetics of the self-assembly process leading from a mixture of ethylenediamine Pd(II) and 4,4-bipyridine to the square tetramer first reported by Fujita (*10*, *11*). The pairwise interaction at the heart of that system is the Pd—N coordinative bond, which has a 1:1 association constant of approximately $\log K = 5.5$. Our computational investigations showed that values above $\log K = 4.5$ were required in order to drive the overall self-assembly at reasonable reagent concentrations (*10*). This value is about the upper end of known diol–boronic acid formation constants (*12*). We reasoned that if an additional factor of about 10 in stability could be found through judicious choice of diols or hydroxy acids and boronic acids, then an aqueous self-assembly process based on the geometric properties of the complexes could be envisaged, which would be complementary to the geometries accessible via octahedral and/or square planar metal centres.

The second area of potential application is in the development of model ligand-gated ion channel systems in bilayer membranes. In this type of system, the binding of a signal molecule would alter the conductance of an ion channel (*13*). In the ideal case, the signal molecule would switch entirely from an 'off' to an 'on' condition or vice versa. The signal molecule must be hydrophilic since it comes from one of the aqueous compartments of the bilayer system. As in the self-assembly application envisaged above, stable pairwise interactions are required. Strictly speaking, this application requires interactions that persist for periods in excess of tens of microseconds; we assume that thermodynamically stable entities will offer the best possibility to produce the kinetically stable entities required.

Despite the potential for diol–boronic acid complexes to meet the requirements of these applications, they suffer from some potentially limiting characteristics due to the mix of species involved and the pH dependence of the interaction. The key species and equilibria are illustrated in Scheme 1 for the case of phenyl boronic acid and a glycol (or hydroxy acid) (*12*). Phenyl boronic acid is a weak acid with a pK_a of about 9. Both phenyl boronic acid

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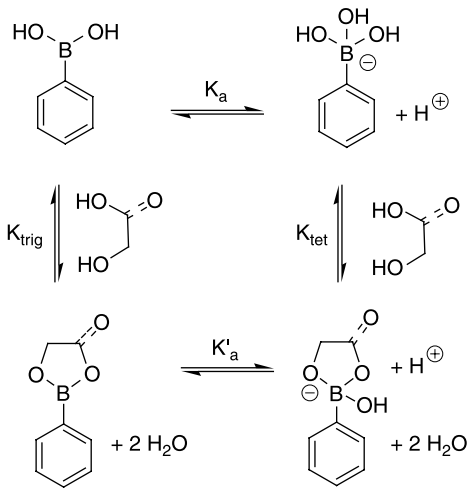


Scheme 1. Equilibria for phenyl boronic acid complexation of diols and hydroxyacids.

itself and its conjugate base, the phenyl boronate anion, can reversibly bind the diol (hydroxy acid) fragment with liberation of two water molecules. The complex from the boronic acid is a trigonal boronic acid ester; the complex from the conjugate base is a tetrahedral boronate ester. In a formal sense, the esters are also related through an acid–base equilibrium, although the system is fully defined without consideration of this additional process. Scheme 1 defines the additional equilibria as K_{tet}, K_{trig}, and K'_a. If the two esters formed from their reactants to the same extent ($\log K_{tet} = \log K_{trig}$), then $pK_a = pK'_a$ and the system would be independent of pH. However, K_{tet} is typically larger than K_{trig} with the result that significant decomposition of the complexes occurs in acidic solution (*12*). For either of the envisaged applications, this pH-dependent binding is tolerable, but there is no doubt that pH independence would greatly simplify the use of this recognition element.

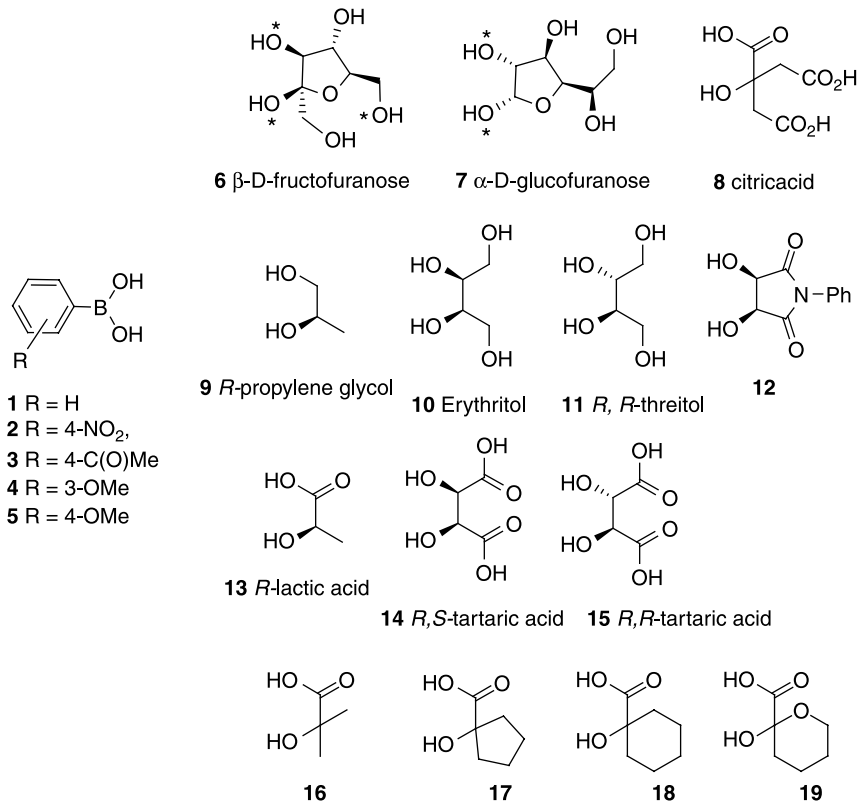
What factors influence the stability of diol–boronic acid complexes? The main factor is geometrical: *cis*-diols bind more strongly than acyclic diols as the diol fragment is preorganised to the conformation required in the ester complex (*12*). Of available rigid *cis*-diols, catechol gives the most stable complex (*2*), but this might also include an electronic component due to the higher acidity of catechol/weaker basicity of the catecholate relative to aliphatic diols. The stable complex of fructose with phenyl boronic acid involves a third coordinative interaction from a co-facial hydroxymethyl group (*14*). Less is known about the factors that influence the stability of α-hydroxy acid complexes, although these are claimed to be significantly more stable than simple diol complexes (*7*). Although certainly correct in this specific case, it is not known whether this is a general result. In short, the dataset is sparse and provides limited guidance in searching for the significantly more stable complexes required in the envisaged applications.

The goal of this paper is to survey the formation constants for complex formation between a number of simple diols and structurally related α-hydroxy acids, together with a number of commercially available phenyl boronic acids bearing electron-donating and electron-withdrawing groups. The key structural variations explored the geometric and electronic influences on the formation of complexes of diols, and the direct comparison between diols and stereochemically related hydroxy acids. These baseline compounds allow an exploration of simple systems prior to investing in a synthesis leading to our envisaged applications.

2. Results

The series of compounds investigated is given in Scheme 2. With the exception of compounds **12** and **19**, all compounds are commercially available. *Cis*-diol **12** was prepared in poor yield by catalytic dihydroxylation of *N*-phenyl maleimide with osmium tetroxide–morpholine *N*-oxide and was most simply isolated by direct crystallisation from the reaction mixture. Other extractive purification methods failed due to the low solubility in organic solvents and a pronounced tendency to isomerise to a mixture of *cis*- and *trans*-isomers. The ^1H and ^{13}C NMR spectra in DMSO-d_6 showed the expected chemical shifts but additional complexity due to intermolecular hydrogen bonding in slow exchange, which lowered the symmetry of the succinimide ring. Compound **19** was previously reported as the major component of a mixture (*15*). We followed the reported method in which a Grignard reagent prepared from TBDMS protected 4-chloro-1-butanol was added to ethyl oxalate. Additional chromatography of the product keto ester gave this key intermediate in high purity and poor yield. Ester hydrolysis and silyl ether cleavage then gave **19** as a pure product. Compound **19** was obtained as a tautomeric mixture of the cyclic and acyclic sodium salts that gave satisfactory $^1H/^{13}C$ NMR and equivalent weight data.

The complex formation constants were determined by potentiometric titration as described previously (*12*). The acidity constants of all ionisable species were determined from the titration of the respective conjugate bases with standard nitric acid in 0.1 M $NaNO_3$ electrolyte solution. For solubility, the substituted boronic acids (**1**–**5**) and diol **12** were measured in a 2:1 (v/v) mixture of water and methanol; the remaining diols and hydroxy acids were measured in water. Following acidity constant determination, a mixture of a boronate (**1**–**5**) and a diol (**9**–**12**) or hydroxy acid (**13**–**19**) was titrated to produce a titration curve that was analysed by HYPERQUAD (*17*) to give the cumulative formation constants of the complex species. Typically, three concentrations of reactants were titrated



Scheme 2. Structures of compounds considered. Hydroxyl groups known to be involved in 1:1 complexes with phenyl boronic acid are indicated with an asterisk (*14*, *16*).

each in duplicate at concentrations that gave 12–20 points per equivalent. The statistical fits in all cases exceeded the expectations at the 95% confidence interval. The precision in acidity constants is $\log\beta \pm 0.05$ and in cumulative formation constants is $\log\beta \pm 0.15$ as assessed by the replicates of separately prepared solutions on different occasions. The precision of the derived stepwise formation constants discussed below is therefore $\log K \pm 0.2$.

The formation constants of protonated species and the derived acidity constants determined are given in Table 1. Table 2 gives the cumulative formation constants of complexes formed between boronic acids and diols

Table 1. Logarithm of cumulative formation constants ($\log\beta_{hx}$) for protonated complexes.

	Methanol–water[a]			Water[b]		
Compound	$\log\beta_{11}$ (= pK_1)	$\log\beta_{21}$	pK_2	$\log\beta_{11}$ (= pK_1)	$\log\beta_{21}$	pK_2
1	9.01			8.78		
2	7.32					
3	7.86					
4	8.76					
5	9.52					
12	11.5	15.8	4.3			
13				3.83		
14				4.57	7.79	3.22
15				4.08	7.11	3.03
16				3.80		
17				3.97		
18				4.05		
19				2.71		

Determined by titration of the conjugate base with HNO_3 at 25°C. Subscripts *h* and *x* define the number of protons bound to the *x* substrate in the complexes considered.
[a] Methanol:water 1:2 (vol%) $I = 0.1$ (NaCl).
[b] $I = 0.1$ ($NaNO_3$).

Table 2. Logarithm of cumulative formation constants ($\log \beta_{hbx}$) for boronic acid complexes of diols and hydroxy acids.

		Methanol–water[a]		Water[b]		Stepwise constants[c]	
Boronic acid	Diol or hydroxy acid	$\log \beta_{211}$	$\log \beta_{311}$	$\log \beta_{011}$	$\log \beta_{111}$	$\log K_{tet}$ or $\log K_1$	$\log K_{trig}$ or $\log K_2$
1	**12**	22.2	27.4			1.7[d]	2.6[d]
2	**12**	22.1	25.8			3.3[d]	2.6[d]
3	**12**	23.2	27.4			3.3[d]	3.7[d]
4	**12**	–[e]	27.2			–[e]	2.8[d]
5	**12**	–[e]	27.2			–[e]	1.8[d]
1	**9**			1.03	–[e]	1.0[d]	–[e]
1	**10**			2.16	–[e]	2.2[d]	–[e]
1	**11**			2.59	–[e]	2.6[d]	–[e]
1	**13**			4.47	13.19	4.5	4.4[f]
1	**14**			2.28	11.16	2.3[f]	2.4[f]
1	**15**			2.21	10.85	2.2[f]	2.1[f]
1	**16**			2.03	10.73	2.0[f]	2.0[f]
1	**17**			–[e]	10.44	–[e]	1.7[f]
1	**18**			2.96	11.66	3.0[f]	2.9[f]
1	**19**			5.01	13.43	5.0[f]	4.6[f]

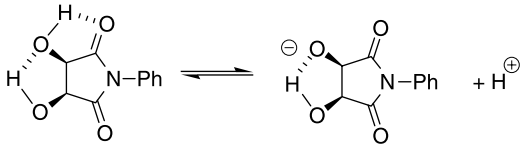
Determined by titration of the conjugate base with HNO_3 at 25°C. Subscripts *h*, *b* and *x* define the number of protons, boronates and diol/hydroxy acids in the complex considered.
[a] Methanol:water 1:2 (vol%) $I = 0.1$ (NaCl).
[b] $I = 0.1$ ($NaNO_3$).
[c] As defined in text.
[d] $\log K_{tet}$ or $\log K_{trig}$.
[e] A complex of this stoichiometry was not required to adequately fit the titration data.
[f] $\log K_1$ or $\log K_2$.

or hydroxy acids, together with derived stepwise constants. Directly comparable data for compounds **6**–**8** and their complexes with **1** in water are given in earlier work (*12*).

3. Discussion

The acidity constants determined (Table 1) are in close agreement with available literature data. The values for **1** in both media are within the experimental errors for values reported previously (*12*). The pK_a values for the substituted boronic acids (**1**–**5**) follow the expected linear free energy relationship with a calculated $\rho = 2.1$ ($r^2 = 0.989$). This is entirely consistent with the expected close electronic coupling of the aromatic system with the empty orbital on the boronic acid.

The pK_a values for **13**–**15** are in good agreement with those in closely related media (*18*). This agreement with reference values is reassuring, given the very anomalous behaviour of **12**; the diprotonated diol as shown in Scheme 2 is a three-fold stronger acid than acetic acid! Even the second deprotonation of **12** occurs several orders of magnitude more readily than simple alcohols and diols. This result goes a long way to explain the difficulties we had in isolating the product from reaction mixtures. We had expected a neutral compound and all purification schemes were planned to isolate this type of compound. Even with relatively poor solubility, **12** is partly ionised near neutral pH, so would be difficult to extract, chromatograph or crystallise. As noted above, the NMR spectrum suggests that the diprotonated compound is involved in significant and kinetically slow intramolecular hydrogen bonding that lowers the overall symmetry of the compound. This is probably a consequence of the enforced *syn* arrangement of the diol groups. A repulsive interaction of this type can be rendered sterically less demanding through ionisation and the resultant conjugate base could well be stabilised by an intramolecular hydrogen bond between the two oxygen centres. This type of effect is the basis for proton sponge, in which a very significant perturbation of the 'normal' pK_a is produced (*19*).



Even though **12** shows anomalous acidity, the complexes it forms with the substituted phenyl boronic acids **1**–**5** are of unremarkable stability. The stepwise constants may be calculated from the determined values of $\log \beta_{hbx}$, where the subscripts *h*, *b* and *x* refer to the stoichiometric ratio of proton:**1**:**12** in the complex. Thus,

$$\log K_{tet} = \log \beta_{211} - \log \beta_{110} - \log \beta_{101} \qquad (1)$$

and

$$\log K_{trig} = \log \beta_{311} - \log \beta_{110} - \log \beta_{201}. \qquad (2)$$

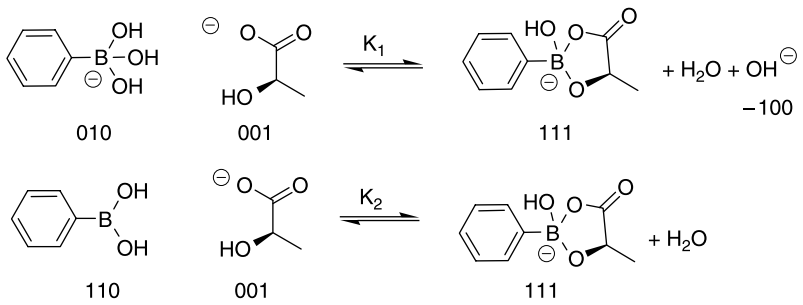
Despite the preorganisation of the *cis*-diols of **12**, neither the trigonal nor the tetrahedral complex with

phenyl boronic acid is remarkably stable. However, $\log K_{tet}$ and $\log K_{trig}$ are within about an order of magnitude of one another for the complexes of **1**–**3**. This is unusual as the trigonal complexes are usually significantly less stable than the tetrahedral complexes (*12*). Indeed, in two cases, the tetrahedral complex stoichiometry was not required to adequately model the titration data. Equally surprising is the lack of a linear free energy relationship for the complexes of **12** with **1**–**5**; the 4-acetyl complexes are relatively stable but the 4-nitro complexes are not proportionately more stable indicating that any electronic effect must be weak. This effectively rules out using electronic effects to enhance the overall formation constants of future more stable complexes.

The other diols (**9**–**11**) also form the expected weak complexes with **1** (in water). Here, the more usual pattern of a stable boronate complex and a weaker boronic complex appears to be respected. There is a small diastereoselection between the stronger threitol and weaker erythritol complexes, which is at the edge of statistical significance. At least in the case of **10**, it is unlikely that the 2,3-diol is the dominant binding pair. If it were, the two hydroxymethyl groups would be eclipsing. This unfavourable situation can be alleviated through binding the 1,2-diol pair. Thus, the difference between **10** and **11** is potentially due to the formation of different esters or different proportions of a mixture of isomeric esters. This issue cannot be resolved through thermodynamic studies of this type; additional structural studies using NMR will be required to explore these questions.

Some of the α-hydroxyacids **13**–**19** do in fact form stable complexes with **1** in water. The comparison between the diol **9** and its oxidised cousin lactic acid (**13**) is particularly striking. However, it is not generally the case that hydroxy acids bind more effectively than structurally related diols: the comparison of $\log \beta_{011}$ of **10** with **14**, or **11** with **15**, indicates only small differences. Where there is a significant difference is in the requirement for two complexes of differing stoichiometries of the hydroxy acids. At first blush, these appear to be related to K_{trig} and K_{tet} of the diol case; they are observed in all systems and in one system (**17**), only the so-called 'trigonal complex' is required to adequately fit the titration data. With the exception of **13** and **19**, none of these are strong complexes of the type sought. Nonetheless, they do point to an underlying difference between diols and hydroxy acids.

Consider the stepwise equilibria for the association to form the lactic acid complexes of overall stoichiometry 011 (*hbx*: no protons; one **1** conjugate base; one **13** conjugate base) and 111:

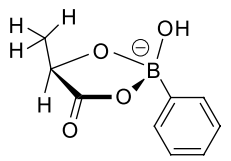


The K_2 equilibrium is unambiguous and the complex of 111 stoichiometry is readily seen to be formed from the boronic acid and the lactate anion. It is not a trigonal complex, but retains the tetrahedral boronate form. A true trigonal complex would have overall 211 stoichiometry since two protons are required to convert both conjugate base forms to the neutrals as envisaged in Scheme 1; a complex of this stoichiometry was not required to model the titration data to pH 2.5 and, if present, would be expected at even lower pH. It follows from this stoichiometry discussion of the partly protonated species that the complex of overall 011 stoichiometry should bear one proton fewer than the 111 complex. Although one could write species in which one of the boronate hydroxy hydrogens was ionised, the more conservative approach is to recognise that the equilibrium of K_1 produces a hydroxide anion. This 'negative proton' has stoichiometry -100, so the sum of the products of the K_1 equilibrium generates the required stoichiometric coefficients ($011 = 111 + - 100$). The stepwise constants calculated for the hydroxy acid complexes are given in Table 2. In all cases, they are numerically equal within experimental error as they should be according to the above discussion.

There appear to be two factors that control the observed complex stabilities. The first is the role that adjacent anionic changes play in destabilising the complexes. Consider the case of citrate binding (compound **8**) in which the previously reported stepwise $\log K_{tet}$ values were 1.5, 1.8 and 1.9 for the binding of citrate^{3-}, Hcitrate^{2-} and H_2citrate^{-}, respectively. Each of these complexes experiences the effect of adjacent carboxylates. In the corresponding tartaric acid complexes (compounds **10** and **11**), the remote carboxylate is protonated, and the corresponding $\log K_{1,2}$ values are

a factor of 3 more stable. Finally, in the lactic acid complex (**13**), there is no possibility of an adjacent carboxylate and a very stable complex is formed. This electrostatic effect has been commonly observed in a range of systems (*12*).

The dominant factor that appears to control complex stability is geometric and steric in origin. The cyclic boronate esters are congested, and the tetrahedral boronate is significantly more congested than the trigonal ester due to the inevitable *pseudo*-axial hydroxyl and phenyl substituents on the boron. Thus, lactic acid **13** forms stable complexes in which the potential diaxial interaction between the methyl group and the phenyl group can be avoided, as in structure **20**. Addition of a second methyl at the α-carbon (**16**) creates an unavoidable diaxial interaction and results in significant complex destabilisation, as in **21**.



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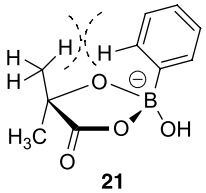

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The difference between the diols and the hydroxy acids might also have a steric origin, as replacing an sp^3 centre (with or without substituents) by an sp^2 centre would be expected to alter angle strain in the cyclic ester and reduce peripheral eclipsing interactions. The angles within the cyclic ester are clearly important as the series of compounds with *spiro*-fused cyclic esters (**17**–**19**) shows very marked differences in the stability and the complexes observed. The *cyclo*-pentyl derivative is expected to impose the most demanding control on the ester ring, and it is this compound that resists ester formation to the greatest extent.

These steric factors can be recognised in the binding of fructose and glucose (**6**,**7**). The structures of fructose complexes reveal a three-point attachment using the *cis*-2,3-diol unit and the 6-hydroxy group, which is arrayed across the face of the furanose ring (*14*). The situation in glucose is more complicated as both pyranose and furanose complexes have been detected, although the complexes of the glucofuranose form appear to dominate (*16*). Recent computational work suggests that the formation of six-membered boronic acid esters is energetically favoured relative to binding *cis*-2,3-dihydroxy fragments on pyranose rings (*20*). The *cis*-2,3 dihydroxy fragments on fructofuranose rings occur in the lowest energy conformation, but the glucofuranose *cis*-diol fragments only occur in higher energy tautomers, so start with an energetic penalty paid by complex formation. Within this context, the strong binding observed for **19** rests on several contributing factors. First, the *spiro*-linkage ties back substituents at the α-carbon. Second, because **19** contains a tetrahydropyran, the resultant 5–6 *spiro*-fusion does not destabilise the boronic acid ester. A possible third factor is the influence of an anomeric effect in lengthening the C—O bond within the cyclic boronic acid ester ring, which would also serve to reduce steric congestion.

Comparisons of stepwise constants reveal pairwise differences and trends such as those discussed above. More important is the overall efficacy of binding which integrates the stabilities of both trigonal and tetrahedral complexes with competing acid–base equilibria. Roelens and co-workers have made this point in their analysis of tripodal receptors for monosaccharides (*21*, *22*). They propose a binding descriptor of the intrinsic median binding concentration (BC_{50}°), which can be derived from a knowledge of the formation constants of multiple complexes between a pair of reactant species. A similar approach has been employed by Reinhoudt and co-workers in the discussion of self-assembled complexes (*23*). Such descriptors are useful for the analysis of binary systems, such as a comparison of different receptors of a common guest or different guests of a common receptor. However, such systems fail in the general case in which there are more than two reactants. These more complex systems deny an analytical solution and must be compared using a numerical method, which is dependent upon a selected set of initial concentration conditions.

Consider the general case of complexes formed from protons, boronic acids (*B*) and a third species (*X*). All species to be considered have the general formula $H_hB_bX_x$, where the stoichiometric coefficients *h*, *b* and *x* indicate the numbers of protons, boronates and third species in a given complex. These coefficients can take positive integral values and zero. We identify 'bound' species of interest as those in which $b \geq 1$ AND $x \geq 1$ (*h* can take any value). For a given set of initial concentrations (pH, $[B]_{tot}$, $[X]_{tot}$) and a knowledge of the cumulative association constants ($\log \beta_{hbx}$) of all $H_hB_bX_x$ species in the system, the equilibrium concentrations ($[H_hB_bX_x]_{eq}$) can be computed, using a program such as HySS (*24*). Usually the comparison under consideration will define one of the reactants of prime importance, such as the boronic acid. In this case, the bound fraction is simply given by $\Sigma[H_hB_bX_x]_{eq}/[B]_{tot}$ ($b \geq 1$; $x \geq 1$). It may be convenient to choose conditions such that $[B]_{tot} = [X]_{tot}$. If this not physically realistic for a particular application or comparison, some other fixed ratio of $[B]_{tot}/[X]_{tot}$ can be chosen to allow comparison between the complexes formed by a range of *X* species. Since the value of *h* can vary, it will usually be interesting to compute the bound fraction as function of pH.

Such a plot is given in Figure 1 for the complexes of **1** with selected diols and hydroxyacids calculated at $[B]_{tot} = [X]_{tot} = 0.01$ M. The factors discussed above

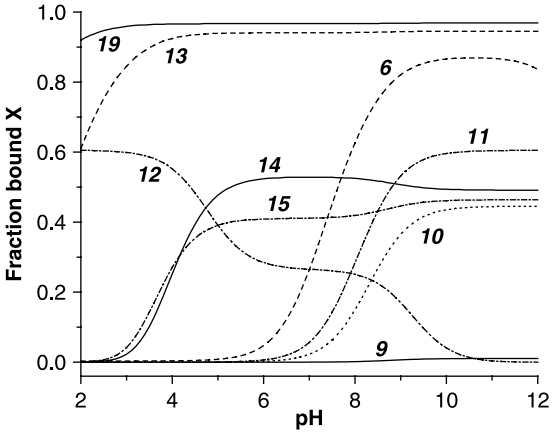

Figure 1. Fraction of the diol or hydroxy acid bound by phenyl boronic acid as a function of pH (calculated for $[B]_{tot} = [X]_{tot} = 0.01$ M).

are evident. Note the substantial difference between diols and structurally related hydroxy acids (compare **9/13**; **10/14**; **11/15**), and the diastereomeric differences (**10/11**; **14/15**). In contrast to the discussion of the tabular data in which only direct comparisons between complexes of like stoichiometry was possible, the overall effect of the competing complexes is directly comparable using Figure 1. Of particular note is the calculated bound fraction of the *cis*-diol **12**, which shows an opposite evolution towards a larger fraction bound at low pH than at high pH. This is an inevitable consequence of the acidity of the diol: at high pH the deprotonated forms effectively compete with boronate complexes, while at pH below that of phenyl boronic acid, the acidic forms can bind to the monoanion and the neutral forms of **12**. As noted above, these complexes are not particularly stable; what is noteworthy is the pH range in which they can be observed.

The goal of a pH-independent binding regime is approximately achieved with hydroxy acids **13** and **19**. The broad range achieved depends on two factors. In basic solution, the complexes of the conjugate bases with the conjugate base of the boronic acid are significantly more stable than any individual component. There are no additional sites to deprotonate (as is the case for the *cis*-diol **12** and to a smaller extent for fructose (**6**)), hence the complex formed resists decomplexation as the pH increases. The second factor is the obverse; in acidic solution, the complexes **13** and **19** resist protonation/decomplexation by being themselves relatively strong acids. As noted above, this would result in the formation of a presumably weak complex of stoichiometry 211 and eventual decomposition as in other cases. The main factor differentiating hydroxyacids relative to diols is that the former give access to boronate complexes up to the pH, where the conjugate base of the hydroxy acid itself begins to undergo protonation. To the extent that the complex is stable, some extension to even more acidic solution is possible, depending upon the specific concentrations of the partners.

4. Conclusions

The data presented in this paper reveal the main structural features that control the stability of complexes of boronic acids with diols and hydroxyacids. The dominant factor is geometric and steric in origin. If more stable complexes are to be created, this factor will require close attention. A second feature is the destabilising role that adjacent anionic charges play in controlling the equilibria. Stabilising electrostatic effects play a major role in carboxylate crown ether recognition of alkali metal cations (*25*), so it is not surprising that the charge reversal condition is also significant. Direct electronic effects are minor, so a remote manipulation of the required interaction appears to be unlikely. Rather, sterically undemanding fluoro substituents might play a significant role on the hydroxy acid partner through a combination of pK_a perturbation and boronate stabilisation. In conjunction with suitably placed neutral donors as found in the fructose complex, it is likely that substantial stabilisation can be developed. Our ongoing investigations in this area will be reported in due course.

5. Experimental

5.1 Cis-*2,3-dihydroxy*-N-*phenylmaleimide (12)*

N-phenylmaleimide (4.33 g, 25 mmol) was added to a solution of citric acid (10.51 g, 50 mmol) in 25 ml v/v 1:1 *t*-butyl alcohol: water. To this mixture was added 4-methylmorpholine *N*-oxide (3.22 g, 27.5 mmol) in 6 ml water followed by potassium osmate (0.020 g, 0.054 mmol). The mixture was stirred at room temperature overnight to give a pale beige solution with white precipitate. The mixture was filtered and the precipitate was washed with 2 × 30 ml 1 M HCl and 2 × 30 ml water to give on drying compound **12** as a white solid (0.211 g, 1.0 mmol, 4%); mp = 132°C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.45–7.56$ (m, 3H), 7.27–7.30 (m, 2H), 6.14–6.19 (m, 2H), 4.54–4.60 (m, 2H); ^{13}C NMR (300 MHz, DMSO-d_6): $\delta = 175.6$, 132.0, 129.0, 128.3, 126.8, 68.2; MS (EI): $m/z = 207$ (M^+); IR (cm^{-1}): 3373 (strong, broad), 1710 (strong, broad). Calculated for $C_{10}H_9NO_4$: C 57.97; H 4.38; N 6.76; O 30.89. Found: C 57.82; H 4.58; N 6.66; O 31.15.

5.2 Potentiometric titrations and simulations

The methodology and procedures previously described in detail were duplicated to the largest extent possible in this work (*12*). Additional details and HYPERQUAD files containing the raw data used for the determination of the cumulative formation constants reported is available as Supporting Information at http://hdl.handle.net/1828/1113.

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