Fluoride Ion Complexation and Sensing Using Organoboron Compounds

Casey R. Wade,[†] Alexander E. J. Broomsgrove,[‡] Simon Aldridge,*,[‡] and François P. Gabbaï*,[†]

Chemistry Department, Texas A&M University, 3255 TAMU, College Station, Texas 77843-3255, and Inorganic Chemistry, University of Oxford, South Parks Road, Oxford OX1 3QR, United Kingdom

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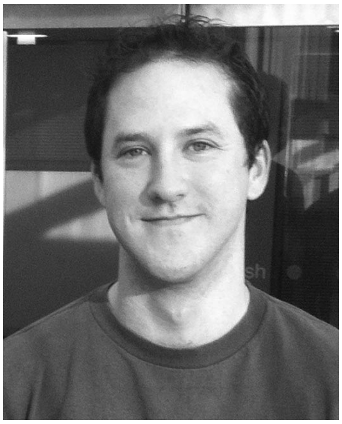
Contents

1. Introduction

Fluoride is often added to drinking water and toothpaste because of its beneficial effects in dental health. It is also administered in the treatment of osteoporosis.[1] While the beneficial effects of fluoride are well documented, chronic exposure to high levels of this anion can lead to dental or even skeletal fluorosis.[2−4] Taking into account these adverse effects, a great deal of attention has been devoted to the discovery of improved analytical methods for the detection of fluoride, especially in water. This field of research has also been stimulated by the potential use of such methods for the detection of phosphorofluoridate nerve agents such as Sarin or uranium hexafluoride, which release fluoride upon hydrolysis. In addition to these applications, the capture of fluoride, especially in water, is a stimulating academic challenge because of the high hydration enthalpy of this anion ($\Delta H° = -504$ kJ mol^{-1}).

Casey Wade was born in 1983 in Lynch, Nebraska. He earned a B.S. degree from the University of Nebraska—Lincoln in 2006. During his time there, he worked as an undergraduate researcher under the supervision of J. A. Belot and participated in a joint research internship at the American Air Liquide Chicago Research Center. In 2007, he joined the group of F. P. Gabbaï at Texas A&M University, where he currently studies anion recognition using main group Lewis acids.



Alexander Broomsgrove received his M.Chem. degree from Cardiff University in 2005 and, following a year in which he spent some time traveling, started his D.Phil. in January 2007, joining the group of Simon Aldridge at Oxford University. He is currently working on the development of ferrocene-based sensors for the recognition of cyanide and fluoride.

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* To whom correspondence should be addressed. E-mail: simon.aldridge@chem.ox.ac.uk (S.A.) and francois@tamu.edu (F.P.G.).

[†] Texas A&M University.

[‡] University of Oxford.

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Simon Aldridge was born in Shrewsbury, England, in 1970 and received his B.A. and D.Phil. degrees from the University of Oxford—the latter in 1996 with Tony Downs. After undertaking postdoctoral stints with Tom Fehlner at Notre Dame (as a Fulbright Scholar) and Mike Mingos FRS at Imperial College, he took up his first academic post in Cardiff in 1998. After 8 years sampling the delights of south Wales, he returned to Oxford in 2007, where he is currently University lecturer and Fellow of The Queen's College. His interests (http://users.ox.ac.uk/~quee1989) are broadly in unsaturated and strongly Lewis acidic main group and transition metal systems and encompass fundamental studies of new types of chemical bonds and reactivity, together with applications, for example, in sensor technologies. To date, efforts in these areas have given rise to 100 papers, articles, and patents.

François Gabbaï was born in 1968 in Montpellier, France. Before joining the research group of A. H. Cowley at the University of Texas at Austin, he studied chemistry at the Université de Bordeaux, France. In 1992 and 1993, he fulfilled his French National Duties by taking part in a Franco-American cooperation under the supervision of G. Bertrand and A. H. Cowley. After he completed his Ph.D. degree in 1994, he was awarded an Alexander von Humboldt Fellowship as well as a Marie Curie Fellowship from the European Commission, which allowed him to work with H. Schmidbaur at the Technische Universität München, Germany, as a postdoctoral fellow and later as an "Habilitand". Upon completion of his habilitation work in 1998, he joined Texas A&M University, where he now holds a Davidson Professorship in Science. His research interests revolve around the chemistry of p-block and late transition metal elements with applications in the domain of materials chemistry and molecular recognition.

Efficient analytical methods have been developed and are currently employed for measuring fluoride concentrations in water. These methods rely on ion-selective electrodes or on colorimetric assays based on the fluoride-induced displacement of a dye from a fluorophilic metal ion.[3,4] These molecular-based colorimetric methods, which are appealing from a practical and economical point of view, suffer from a number of drawbacks, including interferences from other anions.[3−5] In turn, a great deal of current research has been devoted to the discovery of alternative molecular-based strategies.

Organic receptors that interact with the fluoride anion via the formation of hydrogen bonds have been at the forefront of this effort.[6] In most cases, the binding sites of the sensors consist of amide, urea, thiourea, guanidinium, or pyrrole functionalities that are capable of hydrogen bonding with the anionic guest.[7−26] Implementation of this strategy has led to the design of very selective fluoride receptors and sensors, which sometimes tolerate aqueous environments.[27−29] However, as recently noted, fluoride recognition by these derivatives mostly takes place in organic solvents, which greatly limits the scope of their use.[30] Faced with these limitations, alternative strategies based on the use of Lewis acidic compounds have attracted increasing attention.[31−44] Out of these broad efforts geared toward the development of superior fluoride ion receptors has emerged an impressive body of work dealing with boron-based Lewis acids as fluoride sensors, a topic that now warrants a comprehensive and topical review.[6,45−57]

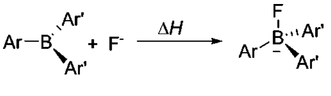
2. The Basic Chemical Reactions

2.1. Reaction of Triarylboranes with Fluoride—Formation of $[Ar_3BF]^-$ Species

Because of their intrinsic Lewis acidity, triarylboranes react with small nucleophilic anions including fluoride to afford fluoroborate anions. This reaction is traditionally described as an addition reaction, which occurs via donation of an electron pair of the fluoride anion into the p_z-orbital of the boron center. While this reaction relieves the inherent unsaturation of the boron center, it occurs at the expense of any stabilizing π-interactions between the boron center and the aryl ligand. It is also important to point out that coordination of fluoride induces a notable pyramidalization of the boron center accompanied by an increase in repulsive steric interaction between the aryl substituents. On the basis of these simple considerations, it can easily be understood that the fate of this reaction will depend on the electronic properties of the aryl substituents as well as their steric bulk. The latter consideration plays a role in governing the selectivity of triarylborane receptors for fluoride. In the absence of steric protection of the boron center, larger and less basic anions may interact, causing interference in fluoride detection.

The complexation of fluoride by the simplest triarylborane, namely, Ph_3B, has been observed but not experimentally explored from a thermodynamic viewpoint.[60] Theoretical calculations show that the gas-phase reaction is exothermic by $\Delta H = -342$ or -344.7 kJ mol^{-1}, depending on the level of theory used (Scheme 1 and Table 1).[58,61] These calculations also indicate that the C−B−C angles decrease from 120° in Ph_3B to 111° in $[Ph_3BF]^-$.[58] While these thermodynamic and geometric parameters are indicative of the formation of a strong bond in the gas phase, it should be kept in mind that solvation effects may significantly reduce

Scheme 1



Ar = Aryl group

Table 1. Computed Thermodynamic and Metrical Parameters for the Reaction Shown in Scheme 1[58,59]

Ar	Ar′	ΔH (kJ mol^{-1})	d(B−F) (Å)	Σ(C−B−C) (°)
Ph	Ph	−344.7	1.465	333
Ph	Mes	−268.7	1.491	340.5

the exothermicity of this reaction in solution. Comparable calculations have been carried out on Mes_2PhB (**1**), affording $\Delta H = -268.7$ kJ mol^{-1}.[59] These results indicate that the fluoride ion affinity (FIA = $-\Delta H$) of **1** is significantly lower than that obtained for Ph_3B, thus demonstrating that an increase in the bulk of the substituents is detrimental to fluoride binding. Presumably, steric repulsions impede tetrahedralization at boron, thereby weakening the boron−fluoride interaction.[59] This view is further supported by the length of the B−F bond, which increases from 1.465 Å in $[Ph_3BF]^-$ to 1.491 Å in [**1**-F]$^-$. A notable effect is also detected in the extent of pyramidalization at the boron atom, as indicated by the sum of the C−B−C angles [Σ(C−B−C)] of 340.5° in [**1**-F]$^-$ vs 333° in $[Ph_3BF]^-$. These metrical data for [**1**-F]$^-$ are given added weight by their closeness to recently determined structural data for the $[{}^nBu_4N]^+$ salt [d(B−F) = 1.481(2) Å, Σ(C−B−C) = 339.8°] (Figure 1).[62] Interestingly, the pyramidalization of the boron center in [**1**-F]$^-$ is essentially identical to that found in the related cyanide-containing species [K(18-crown-6)]$^+$[**1**-CN]$^-$ (340.9°) (Figure 1).[62] The crystal structure of the K^+/[2.2.2]crypt salt of $[Ant_3BF]^-$ has also been determined (Figure 1). The boron atom is distinctly pyramidalized, as indicated by the Σ(C−B−C) = 345.2°. This sum of angles is larger than that determined for [**1**-F]$^-$ (exp., 339.8°; calcd, 340.5°), in agreement with the sterically more hindered boron center of the Ant_3B. The observed B−F bond of 1.466(5) Å in $[Ant_3BF]^-$ is close to that computationally determined for $[Ph_3BF]^-$ and measured crystallographically for [**1**-F]$^-$ [1.481(2) Å].[58,59,62]

From a spectroscopic and structural point of view, fluoride binding to the boron center has been studied by a number of methods. For example, the ^{11}B NMR resonance of the triarylboranes, which is typically detected in the 60 to 75 ppm range, is shifted to the −10 to +10 ppm range in the fluoroborate species. These upfield shifts reflect the change in coordination number and geometry of the boron atom. The ^{19}F NMR resonance of the boron-bound fluorine nucleus typically appears as a broad signal in the −150 to −180 ppm range, shifted significantly upfield from free fluoride anions, which usually appear in the −120 to −130 ppm range.

The low-energy edge of the UV−vis absorption spectrum of triarylboranes is typically dominated by electronic transitions from filled molecular orbitals into the lowest unoccupied molecular orbital (LUMO), an orbital often dominated by the boron p_π-orbital (Figure 2).[63] Fluoride binding, which leads to population of the boron p_π-orbital, induces a quenching of all transitions involving the LUMO. Titration experiments, carried out by monitoring this quenching as a function of fluoride ion concentration, have been used to determine the fluoride ion binding constant of triarylboranes such as Mes_2PhB (**1**),[64] Mes_3B (**2**),[65] or Ant_3B(**3**)[63] (Ant = 9-anthryl). These boranes complex fluoride ions in tetrahydrofuran (THF) with binding constants $K = [Ar_3BF^-]/([Ar_3B][F^-])$ of 5×10^6, $3.3\ (\pm 0.3) \times 10^5$, and $2.8\ (\pm 0.3) \times 10^5$ M^{-1}, respectively, at room temperature.[63,65] The lower binding constants of **2** and **3** can be assigned to the steric protection provided by the three mesityl and Ant substituents to the boron center of these derivatives. Boranes such as **1**−**3** show a high selectivity for fluoride anions. This selectivity has been assigned to the steric protection of the boron atom, which prevents coordination of larger anions for triarylboranes featuring at least two mesityl or anthryl groups. Some interference can, however, be observed in the case of small anions, including cyanide, hydroxide, and sometimes acetate.

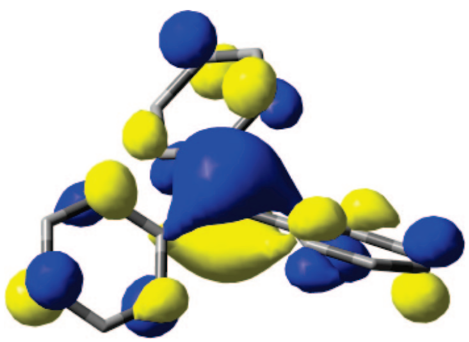
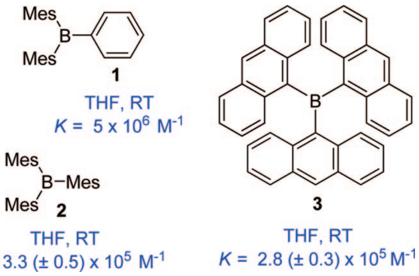


Figure 2. DFT LUMO of Ph_3B [b3lyp/6-31 g(d)].



While it can be assumed that the formation of the fluoroborate species is enthalpically favored, the entropy change involved in such reactions has not been determined. As illustrated in the remainder of this review, the fluoride binding constants of **1**−**3** are quite typical of triarylboranes that feature a moderately encumbered boron center. Although

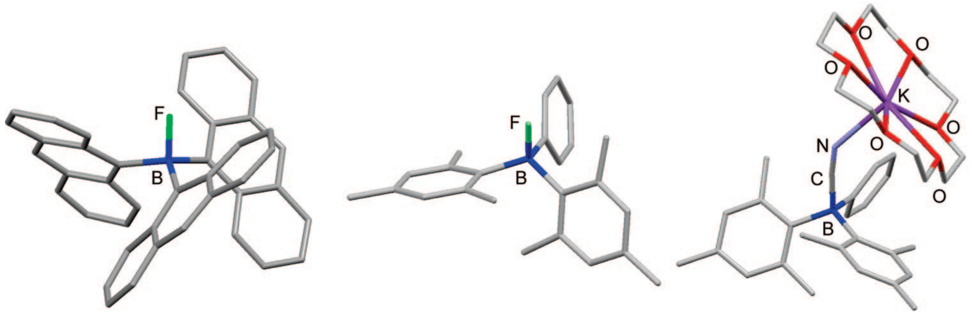


Figure 1. Crystal structure of [**3**-F]$^-$ in the K^+/[2.2.2]crypt salt (left), [**1**-F]$^-$ in the $[{}^nBu_4N]^+$ salt (middle), and [K(18-crown-6)]$^+$[**1**-CN]$^-$ (right).

these binding constants are elevated, available studies indicate that the fluoroborates dissociate in the presence of water. This process has been confirmed in the case of $[\mathrm{Ant_3BF}]^-$ ($[\mathbf{3}\text{-F}]^-$), which reverts to $\mathrm{Ant_3B}$ by the addition of water to a THF solution of the fluoroborate. Analogously, the fluoride binding constant of **2** in THF is reduced from 3.3 ($\pm$0.3) $\times$ 10^5 to about 1 ($\pm$0.3) $\mathrm{M^{-1}}$ when 10% of water is added to the THF solution.[65] This drastic reduction of the binding constant in the presence of water can be attributed to the high hydration enthalpy of the fluoride anion ($\Delta H_{\mathrm{hyd}} = -504$ kJ $\mathrm{mol^{-1}}$).

2.2. Reaction of Boronic Acids and Esters with Fluoride

The lability of the B−O bond under protic conditions means that in contrast to triarylboranes, a series of equilibria are typically established on exposure of an arylboronic acid to fluoride, involving not only complexation of the fluoride ion at boron but also $\mathrm{OH^-/F^-}$ exchange facilitated by protonation of the hydroxide group (Scheme 2).[66,67] In the case of the $\mathrm{PhB(OH)_2/F^-}$ system, stepwise equilibrium constants $\beta_x = [\mathrm{ArB(OH)}_{3-x}\mathrm{F}_x]/[\mathrm{ArB(OH)}_{4-x}\mathrm{F}_{x-1}][\mathrm{F^-}][\mathrm{H^+}]$, corresponding to the sequential formation of $[\mathrm{PhB(OH)}_{3-x}\mathrm{F}_x]^-$ by hydroxide protonation/substitution of $10^{9.4}$, $10^{6.2}$, and $10^{6.5}$, have been determined in water for x = 1, 2, and 3, respectively.

Even in this superficially simple case, the reaction with fluoride in water can also generate the three-coordinate fluoroboranes PhB(OH)F and $\mathrm{PhBF_2}$; the corresponding equilibria in 60% aqueous methanol are displaced significantly in favor of these charge neutral species, in keeping with the less polar nature of the solvent. Thus, the anionic borates $[\mathrm{PhB(OH)_2F}]^-$ and $[\mathrm{PhB(OH)F_2}]^-$ are not observed under such conditions. PhB(OH)F and $\mathrm{PhBF_2}$ are generated from $\mathrm{PhB(OH)_2}$ by hydroxide protonation/substitution with stepwise formation constants of $10^{4.7}$ and $10^{6.7}$, respectively, values that exceed those measured in water ($10^{4.5}$ and $10^{4.4}$, respectively) due to the less heavily solvated nature of the fluoride ion in the mixed solvent medium. Stronger Lewis acids such as 3-nitrophenylboronic acid show higher affinity for $\mathrm{OH^-/F^-}$, and as such, the concentrations of neutral three-coordinate species [i.e., $3\text{-}\mathrm{O_2N\text{-}C_6H_4B(OH)F}$ and $3\text{-}\mathrm{O_2N\text{-}C_6H_4BF_2}$] in water do not reach detectable levels. Similar enhancement in Lewis acidity can be brought about by the incorporation of a pendant (cationic) ammonium function (see sections 3.1 and 3.4). ^{19}F NMR spectroscopy represents a convenient approach for monitoring these systems, with signals of δ_{F} −127, −137, and −148, for example, having been measured for $[\mathrm{PhB(OH)}_{3-x}\mathrm{F}_x]^-$ (x = 1, 2, and 3, respectively).[68] The magnitude of the overall formation constant corresponding to the conversion of an arylboronic acid into the corresponding aryltrifluoroborate K_3 {defined as $[\mathrm{ArBF_3}^-]/[\mathrm{ArB(OH)_2}][\mathrm{F^-}]^3$} is known to be dependent on the electronic properties of the aryl substituent, with values of 1.04 $\times$ 10^4 and 1.08 $\times$ 10^4 $\mathrm{M^{-1}}$ having been determined for phenylboronic acid and 2-naphthylboronic acid in a 1/1 $\mathrm{H_2O}$/MeOH solution by fluorescence-monitored titration experiments.[68]

The influence of pH on the equilibria outlined above is such that acidic conditions (pH 3−4) are typically employed to drive the formation of aryltrifluoroborates, with the protonation of RO groups in $\mathrm{ArB(OR)_2}$ (R = H, alkyl) facilitating displacement by $\mathrm{F^-}$. Consequently, at pH > 7 and concentrations in water on the order of 5 $\times$ 10^{-3} M, solutions of $[\mathrm{ArBF_3}]^-$ are found by ^{19}F NMR to revert to free fluoride and $\mathrm{ArB(OH)_2}$ to such an extent that the aryltrifluoroborate is effectively undetectable.[69] While the *extent* of reversion to the boronic acid is therefore appreciable, the *rate* at which individual aryltrifluoroborates undergo hydrolysis varies markedly, with rate constants varying by some 3 orders of magnitude ($10^{-1} > k_{\mathrm{obs}} > 10^{-4}$ $\mathrm{min^{-1}}$), depending on the substitution pattern of the aryl substituent.[69−73] Thus, the rate of hydrolysis is enhanced by electron-donating substituents and retarded by electron-withdrawing groups; a linear free energy plot reveals that $\log_{10}(k_{\mathrm{obs}})$ correlates well with the substituent Hammett σ parameter with a ρ value of ca. −1. Thus, the use of relatively long-lived $[\mathrm{ArBF_3}]^-$ systems in vivo (for pharmaceutical or radiopharmaceutical applications) necessitates the use of substitution patterns similar to those found in **4** (for which $k_{\mathrm{obs}} \approx 1.2 \times 10^{-4}$ $\mathrm{min^{-1}}$ at pH 7.5 and $[\mathrm{F^-}] = 10^{-1}$ M).

Scheme 2

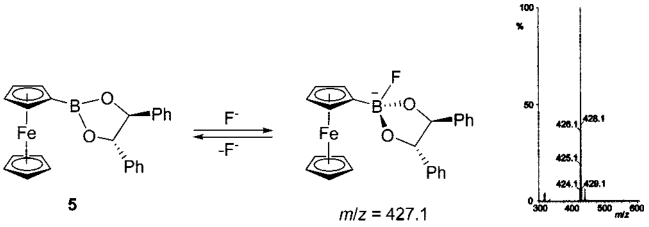
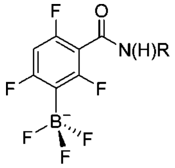


Figure 3. Simple fluoride binding to chelating dialkylboronic ester **5** in chloroform.



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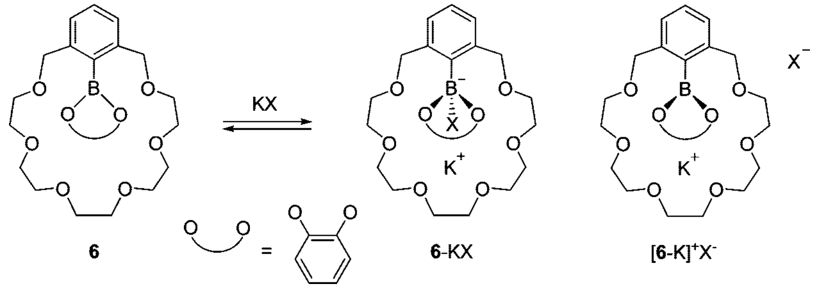
Under nonaqueous solvent conditions, boronic ester systems show disparate stability to fluoride exposure. Thus, for example, compound **5** can be shown in chloroform solution by in situ electrospray mass spectrometry (Figure 3) and by the appearance of a doublet in its ^{11}B NMR spectrum (δ_{B} 7.8, $^1J_{\mathrm{BF}} = 47.1$ Hz) simply to bind a single fluoride ion on exposure to $[^n\mathrm{Bu_4N}]\mathrm{F}\cdot x\mathrm{H_2O}$, with little evidence for further exchange.[74] By contrast, related arylboronic esters featuring aryloxo based on calixarene frameworks are more prone to B−O bond cleavage, presumably reflecting the weaker B−O bonds typically associated with B−O(aryl) vs B−OH or B−O(alkyl) linkages. Thus, under similar conditions, $\mathrm{(FcB)_2}$calix-4 is cleaved to give $[\mathrm{FcB(OH)F_2}]^-$ as the predominant borate product.[74−76]

The high selectivity of fluoride binding in the presence of potentially competitive anions, such as chloride, bromide, and iodide, has been reported for a number of arylboronic esters.[74,77−82] This selectivity has been ascribed to thermodynamic factors, most notably the strong B−F bond that is formed (cf. B−Cl, B−Br, or B−I) and that compensates for the attendant loss of B−O π-bonding (and increased steric crowding) brought about on anion coordination. Some measure of the relative strengths of the bonds formed—distinct from any π-bonding effects—can be obtained by comparing

Scheme 3



the corresponding (calculated) binding energies of F^- and Cl^- to BH_3 (265.7 and 141.8 kJ mol^{-1}, respectively).[83] Thus, Reetz and co-workers have shown that the reaction of the catecholboryl-functionalized crown ether **6** with KF results in the formation of the corresponding heterotopic adduct (i.e., **6**-KX), while KCl and KBr do not appear to react with **6** at all; reaction *is* observed with KI and KSCN, but in this case, ^{11}B NMR spectra are consistent with the formation of products of the type $[\mathbf{6}\text{-K}]^+X^-$ in which the potassium cation is encapsulated, but the counteranion does not interact significantly with the boron center (Scheme 3). Competition experiments also reveal that the binding of F^- by **6** is stronger than that of CN^-.[82]

The structure of **6**-KF determined by X-ray diffraction reveals a B−F bond length of 1.407(7) Å, which is somewhat shorter than those typically found in association with fluoride bound to triarylboranes (as outlined above) but similar to those found for aryltrifluoroborates {e.g., 1.409(3), 1.418(3) and 1.426(3) Å for $[PhBF_3]^-$};[84] the sum of the O−B−O and O−B−C angles is 330.5°. Spectroscopically, the binding of fluoride in this archetypal system is signaled by an upfield shift of 20 ppm in the ^{11}B NMR spectrum from δ_B +30 to δ_B +10.

Finally, with a view to understanding the change in electronic properties at the boron center on fluoride coordination, which underpin many applications of this binding event, it is noteworthy that the Hammett parameters for the $-B(OH)_2$ and $-B(OH)_3^-$ groups [the latter being assumed to be similar to that for $-B(OH)_2F^-$] are σ_p 0.12 and σ_m −0.01 and σ_p −0.44 and σ_m −0.48, respectively.[85] As such, the trihydroxyborate (and, by implication, fluorodihydroxyborate) substituents are among the strongest inductively donating systems known.

3. Strategies To Enhance the Fluoride Affinity of Triarylboranes and Arylboronic Acids/Esters

3.1. Use of Electron-Withdrawing Substituents

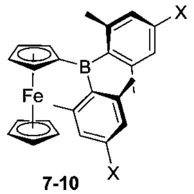
Because of the electron-withdrawing properties of fluorine, tris(pentafluorophenyl)borane $(C_6F_5)_3B$ is one of the most Lewis acidic organoboranes. This derivative, which has found numerous applications in organometallic and organic catalysis, is readily converted into the corresponding fluoroborate[86−91] by reaction with fluoride ion sources such as LiF[86] or Ph_3CF.[87] The structure of the $[(C_6F_5)_3BF]^-$ anion has been determined. It shows a very short B−F bond of 1.43 Å, in agreement with the increased acidity of the boron center.[90] The boron-bound fluorine atom can be detected as a broad signal at −187 ppm in d_8-toluene with $[Ph_3C]^+$ as a counterion.[88] Although the water stability of this anion does not appear to have been investigated, its use as a counterion for cationic metallocene-based olefin polymerization catalysts attests to its chemical robustness. This conclusion is supported by computational results, which show that the FIA of $(C_6F_5)_3B$ (FIA = 454 kJ mol^{-1}) exceeds that of Ph_3B by 110 kJ mol^{-1}.[58] A high FIA is also exhibited by the more complex fluorinated boranes including tris(2,2′,2″-nonafluorobiphenyl)borane, which forms a robust fluoroborate anion when mixed with Ph_3CF.[88] These properties augur well for the use of fluorinated triarylboranes as receptors for fluoride ions. Unfortunately, however, such boranes form highly acidic water adducts such as $[(C_6F_5)_3B(OH_2)]$, thus complicating the development of applications involving aqueous fluoride ions. A lack of steric protection and the exceptional Lewis acidity of $(C_6F_5)_3B$ preclude selectivity for fluoride and result in a tendency for it to bind various larger and less basic anions. This behavior stresses the importance of "tuning" the steric and electronic properties of triarylborane-based receptors to balance anion selectivity and Lewis acidity.

Table 2. Fluoride Binding Constants (*K*) and Electrochemical Data for Ferrocenyldiarylboranes

compound	X	σ	$E_{1/2}$ (mV)[a]	K (M^{-1})[b]
7	OMe	−0.27	+95	6.6 (±0.4) × 10^4
8	Me	−0.17	+131	7.8 (±1.2) × 10^4
9	H	0	+153	4.4 (±0.5) × 10^5
10	F	0.06	+184	4.3 (±0.7) × 10^5

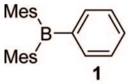
[a] In dichloromethane; referenced with respect to ferrocene/ferrocenium. [b] Dichloromethane solvent.

While its reactivity toward water tends to restrict the anion binding applications of $(C_6F_5)_3B$, triarylboranes in which two of the aryl groups feature a pair of *ortho*-methyl substituents [i.e., systems of the type ArB(*o*-Xyl)$_2$] tend to be moisture stable. Systematic variation, for example, in the xylyl *para*-substituent, then allows for an assessment of the fluoride binding affinity as a function of electron-withdrawing/-donating capabilities, free from steric complications. A recent study centered around compounds **7**−**10** has coupled such an approach to an assessment of the redox properties of a pendant ferrocenyl unit, showing that the Fe(II/III) redox potential follows the trend expected based on the Hammett σ parameter for the *para*-substituent (Table 2); the fluoride binding affinities follow a similar trend, although the magnitude of the changes in the fluoride binding constant K is relatively small.[85,92]



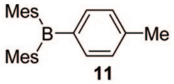
7-10

Another illustration of the inductive effect imparted by peripheral groups can be derived from a comparison of the fluoride binding constants of **1**, **11**, **12**, and **13**, which steadily increase with the electron-withdrawing properties of the substituent at the 4-position of the phenylene group.[64] In fact, **13** is sufficiently fluorophilic to bind fluoride with an association constant of 5.0 (±0.3) × 10^3 M^{-1} in THF in the presence of 10% water (volume).



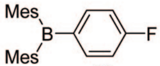
1

THF, RT
$K = 5 \times 10^{6}\ M^{-1}$



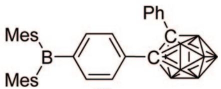
11

THF, RT
$K = 2.5 \times 10^{6}\ M^{-1}$



12

THF, RT
$K = 5 \times 10^{7}\ M^{-1}$



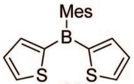
13

THF, RT
$K > 10^{7}\ M^{-1}$

The electronic properties of peripheral substituents have also been shown to influence the Lewis acidity of arylboronic acids. Thus, the values of *K* {defined as $[ArB(OH)_2F^-]/[ArB(OH)_2][F^-]$}, which have been determined in water for phenylboronic and 3-nitrophenylboronic acids ($10^{0.6}$ and $10^{0.9}$, respectively) reflect the electron-withdrawing capabilities of the nitro group.[66,67] The influence of more remote functional groups has also been shown to influence binding capabilities, at least in systems where appreciable conjugation between the various component is conceivable. Thus, *trans*-stilbene receptors featuring a boronic acid in the 4-position and either a cyano or *N*,*N*-dimethylamino group in the 4′-position have been shown to give rise to overall binding constants {$K_3 = [ArBF_3^-]/[ArB(OH)_2][F^-]^3$ in H_2O/MeOH, 2/1}, which differ by ca. 1 order of magnitude (section 5.2).[93] The high FIA of phenylboronic acids bearing between one and five fluorine substituents at the aryl ring has also been exploited in the synthesis of the corresponding $[ArBF_3]^-$ species.[94] An added complication of such systems, however, is their propensity to undergo hydrodeboronation reactions (i.e., formal replacement of the boronic acid moiety by H) under basic conditions.[95]

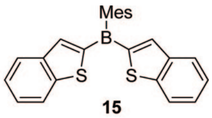
3.2. Extending π-Conjugation

Another efficient method for increasing the Lewis acidity of conjugated organoboranes consists of extending the π-conjugated system containing the boron atom. This strategy has been demonstrated in the case of bis(thienyl) derivatives **14** and **15** whose fluoride binding constants increase by 1 order of magnitude upon substitution of the thienyl substituents in **14** by benzothienyl substituents in **15**.[96] This increase is substantial and can be assigned to a lowering of the LUMO energy upon extension of the π-conjugated systems. This proposal is supported by a red shift of absorbance of the boron center chromophore from 328 nm in **14** to 362 nm in **15** when measured in CH_2Cl_2.



14

CH_2Cl_2, RT
$K = 2.3 \times 10^{6}\ M^{-1}$

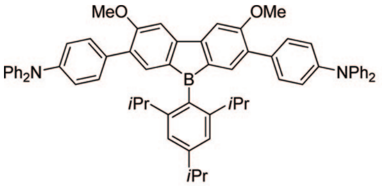


15

CH_2Cl_2, RT
$K = 6.2 \times 10^{7}\ M^{-1}$

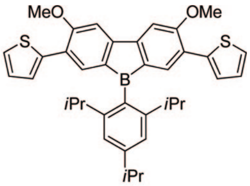
3.3. Incorporation of the Boron Atom in an Anti-Aromatic π-System

The Lewis acidity of boron compounds can be increased by incorporation of the boron atom into an antiaromatic π-system. Examples of such compounds include fluorinated 9,10-dihydro-9,10-diboraanthracene[97,98] and borafluorenes derivatives.[99,100] In the latter case, the Lewis acidity is also enhanced by relief of strain energy in the five-membered ring upon pyramidalization of the boron center. Although this strategy has not been explicitly applied to the design of fluoride receptors, such effects may be invoked in the fluoride binding properties of a series of extended borafluorenes (**16**−**18**).[101] Despite the presence of electron-donating methoxy groups para from the boron atom, these derivatives feature fluoride binding constants as high as 1.4 (±0.3) × 10^6 M^{-1} for **18** in THF at 20 °C. Such binding constants exceed those of simple monofunctional boranes, which could potentially be attributed to the antiaromatic character of the five-membered borole ring. It is, however, important to point out that the steric bulk around the boron atom significantly differs from that of Ant_3B or Mes_3B. Hence, caution should be exercised in assigning the origin of this increased fluoride affinity.



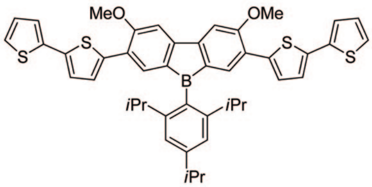
16

THF, 20°C
$K = 3.5\ (\pm 0.4) \times 10^{5}\ M^{-1}$



17

THF, 20°C
$K = 1.1\ (\pm 0.5) \times 10^{6}\ M^{-1}$



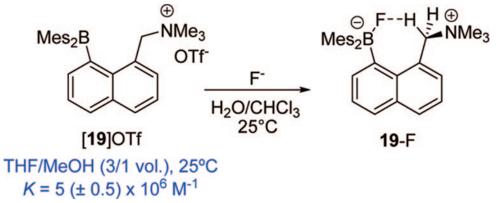
18

THF, 20°C
$K = 1.4\ (\pm 0.3) \times 10^{6}\ M^{-1}$

3.4. Decoration of the Boranes by Peripheral Cationic Substituents

As illustrated by the preceding sections, several strategies have been identified to increase the Lewis acidity of the boron center in triarylboranes. Despite these advances, none of the neutral boranes investigated thus far as fluoride receptors have proven capable to bind fluoride in aqueous environments. Because of these limitations, recent efforts have been devoted to the discovery of an alternative strategy that relies on the decoration of triarylboranes with pendant cationic functionalities. One of the first examples of such a compound is the cationic borane [**19**]$^+$, which was isolated as a triflate salt (Scheme 4). This cationic borane is compatible with protic environments and binds fluoride in THF/MeOH (3/1 volume) with a binding constant of 5.0 (±0.5) × 10^6 M^{-1}. In comparison, Mes_3B does not form a fluoride adduct under these conditions, thus pointing to the favorable influence of the ammonium group on the anion affinity of [**19**]$^+$. Unlike Mes_3B, [**19**]$^+$ also reacts with aqueous fluoride ions under biphasic conditions ($H_2O/CHCl_3$) to form the corresponding zwitterion **19**-F.[102] Structural and computational studies indicate that **19**-F is stabilized by an

Scheme 4



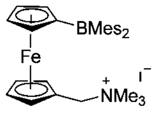
[**19**]OTf

19-F

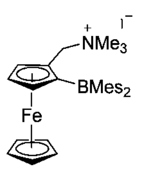
THF/MeOH (3/1 vol.), 25°C
$K = 5\ (\pm 0.5) \times 10^6\ M^{-1}$

intramolecular CH•••FB hydrogen bond (Scheme 4). Despite the presence of a cationic functionality, this borane retains a high selectivity for the fluoride anion. It does, however, react with cyanide to form the corresponding cyanoborate adduct. Titration experiments carried out in THF show that the cyanide binding constant [$K = 8.0\ (\pm 0.5) \times 10^5\ M^{-1}$] is significantly lower than the fluoride binding constant ($K > 10^8\ M^{-1}$ in THF). Presumably, steric crowding around the boron center hampers coordination of the larger cyanide anion.

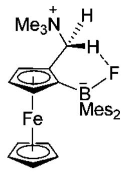
Similar effects are also thought to be responsible for the widely differing fluoride affinities of the isomeric ammonium-functionalized ferrocenyldimesitylboranes [1,1′-**20**]$^+$ and [1,2-**20**]$^+$, each of which has been synthesized as the iodide salt.[92] Thus, the 1,1′-isomer has a fluoride binding constant of $9.4\ (3.6) \times 10^5\ M^{-1}$ in dichloromethane, which is only marginally greater than that of charge neutral FcBMes$_2$. The corresponding 1,2-isomer, despite having a very similar Fe(II/III) redox couple (+367 mV with respect to ferrocene/ferrocenium, cf. +314 mV for [1,1′-**20**]$^+$) binds fluoride nearly 4 orders of magnitude more strongly [$5.6\ (2.3) \times 10^9\ M^{-1}$ in dichloromethane], and indeed is capable of sequestering fluoride from water in a biphasic chloroform/water system. ^{1}H and ^{1}H{^{19}F} NMR data are consistent with the presence of a supplementary CH•••FB hydrogen bond for 1,2-**20**-F in solution, analogous to that found in **19**-F.



[1,1′-**20**]I



[1,2-**20**]I



1,2-**20**-F

The cationic boranes [*o*-**21**]$^+$ and [*p*-**21**]$^+$ have also been synthesized and investigated.[103] Both of these cations, which have been isolated as their triflate salts, react quantitatively with fluoride in CHCl$_3$ to afford the corresponding fluoroborate/ammonium zwitterions *o*-**21**-F and *p*-**21**-F. Interestingly, the behavior of these two isomers becomes drastically different in aqueous solution, with only [*o*-**21**]$^+$ forming the fluoride adduct in H$_2$O/DMSO 60:40 volume (HEPES 6 mM, pH 7) with an association constant of 910 (±50) M^{-1}. The contrasting behavior of [*o*-**21**]$^+$ and [*p*-**21**]$^+$ can be most easily explained by invoking a greater inductive effect of the ammonium group on the boron center in the case of [*o*-**21**]$^+$. This proposal is supported by theoretical calculations that indicate that the LUMO of [*o*-**21**]$^+$ has a lower energy than that of [*p*-**21**]$^+$. Although not explicitly stated in the original report, the zwitterion *o*-**21**-F may also be stabilized by a CH•••FB hydrogen bond involving the nitrogen-bound methyl groups (Figure 4). The cationic borane [*o*-**21**]$^+$ is selective for fluoride in aqueous solution where it does not interact with the more basic cyanide anion. Presumably, the steric protection of the boron center is responsible for this selectivity since [*p*-**21**]$^+$, bearing a more accessible boron center, displays a high cyanide binding constant of $K = 3.9\ (\pm 0.1) \times 10^8\ M^{-1}$ (H$_2$O/DMSO 60:40 volume, pH 7).

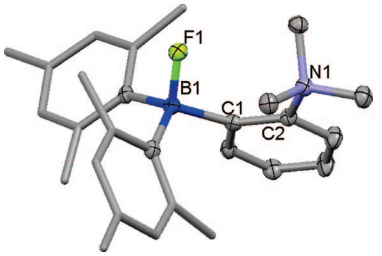
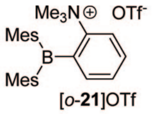
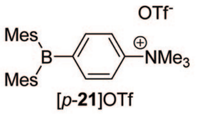


Figure 4. Crystal structure of *o*-**21**-F.



[*o*-**21**]OTf

H$_2$O/DMSO (6/4 vol.), pH 7, 25°C
$K = 910\ (\pm 50)\ M^{-1}$



[*p*-**21**]OTf

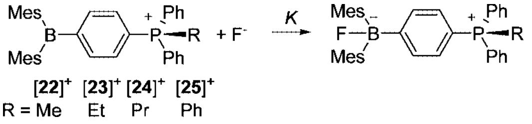
H$_2$O/DMSO (6/4 vol.), pH 7, 25°C
does not bind F$^-$

Table 3. p$K_R$$^+$ Values and Fluoride Binding Constants for Phosphonium Boranes

R	compound	p$K_R$$^+$	K (M^{-1})[a]
Me	[**22**]$^+$	7.3	840
Et	[**23**]$^+$	6.9	2500
Pr	[**24**]$^+$	6.6	4000
Ph	[**25**]$^+$	6.1	10500

[a] H$_2$O/MeOH, 9/1 volume; 9 mM pyridine buffer, pH 4.6−4.9.

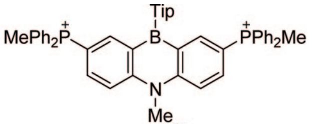
Scheme 5



In parallel to the study of ammonium boranes as fluoride receptors, a series of related phosphonium boranes of general formula [*p*-Mes$_2$B-C$_6$H$_4$-PPh$_2$R]$^+$ with R = Me ([**22**]$^+$), Et ([**23**]$^+$), Pr ([**24**]$^+$), and Ph ([**25**]$^+$) were also investigated.[104,105] These boranes are water stable but undergo conversion to the corresponding zwitterionic hydroxide species (**22**-OH to **25**-OH) upon elevation of the pH. This process can be easily followed by monitoring the absorbance of the boron-centered chromophore as a function of pH. The resulting data can be modeled on the basis of eq 1 to afford the p$K_R$$^+$ values shown in Table 3. These p$K_R$$^+$ values indicate that the Lewis acidity of the boranes increases with their hydrophobicity. A similar trend is observed in the fluoride affinity of these compounds as shown by the fluoride binding constant of [**25**]$^+$, which exceeds that of [**22**]$^+$ by more than 1 order of magnitude (Scheme 5 and Table 3).[105] Presumably, the increased hydrophobicity and decreased solvation of [**25**]$^+$ facilitate the covalent ion pairing process that occurs upon reaction with fluoride (or hydroxide). Like [*o*-**21**]$^+$, none of these phosphonium boranes interact with other commonly encountered anions, such as Cl$^-$, Br$^-$, I$^-$, OAc$^-$, NO$_3$$^-$, H$_2PO_4$$^-$, and HSO$_4$$^-$. From an applied perspective, these hydrophobic effects are significant as [**25**]$^+$ is capable of detecting fluoride ions in water below the maximum contaminant level of 4 ppm set by the U.S. Environmental Protection Agency.

$$[R_3B]^+ + 2H_2O \overset{K_{R^+}}{\rightleftharpoons} R_3B{-}OH + H_3O^+ \qquad (1)$$

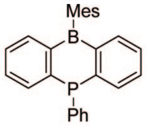
The diphosphonium azaborine $[\mathbf{26}]^{2+}$ has also been investigated.[106] Despite its dicationic character, which should lead to a notable enhancement of the fluoride binding constant, this derivative displays only a moderate affinity for fluoride anions in H_2O/DMSO 1/3 volume. Formation of the fluoride complex can no longer be observed when the volumetric fraction of water is greater than 1/3. A possible cause for this low affinity may be the large bulk of the Tip ligand, which sterically passivates the boron center. It is also probable that the aromaticity of the azaborine ring reduces the electron deficiency of the boron atom. The aromatic stabilization affecting the Lewis acidity of such compounds could, in principle, be reduced if not eliminated upon substitution of the nitrogen atom by a heavier group 15 congener. Such congeners include the phosphaborine **27**, which was alkylated to afford the phosphonium derivatives $[\mathbf{28}]^+$ and $[\mathbf{29}]^+$.[107] Titrations carried out in CH_2Cl_2 indicate a drastic increase in the fluoride binding constant on going from **27** to $[\mathbf{28}]^+$ caused by the inductive and Coulombic influence of the phosphonium center. Analogous results have been obtained with P-methylated phosphonioborins $[\mathbf{29}]^+$ and $[\mathbf{30}]^+$.[104,108] The high fluorophilicity of these derivatives is reflected by their ability to transport fluoride from water into organic phases. Interestingly, cation $[\mathbf{30}]^+$ is also able to scavenge fluoride ions as a solid in water.



$[\mathbf{26}]^{2+}$

H_2O/DMSO (1/3 vol.), 25°C

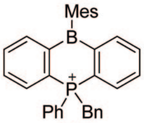
K = 190 (± 30) M^{-1}



27

CH_2Cl_2

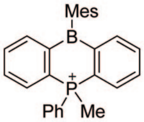
$K = 2.1(3) \times 10^4\ M^{-1}$



$[\mathbf{28}]^+$

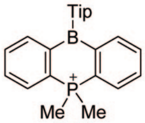
CH_2Cl_2

K = too high to measure



$[\mathbf{29}]^+$

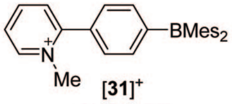
transfers F^- from water into $CHCl_3$



$[\mathbf{30}]^+$

acts as a F^- scavenger in water

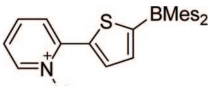
Cationic boranes such as $[\mathbf{31}]^+$ and $[\mathbf{32}]^+$ have also been obtained by alkylation of pyridyl boranes.[109] Both $[\mathbf{31}]^+$ and $[\mathbf{32}]^+$ extract fluoride ions biphasically ($H_2O/CHCl_3$) to form the zwitterionic fluoroborates **31**-F and **32**-F, which have been structurally characterized. In $CHCl_3$, the fluoride binding constants of these cationic boranes are above the 10^7-10^8 M^{-1} range. Moreover, the addition of chloride, bromide, or iodide anions does not affect the UV−vis spectra of the cationic boranes, indicating that these anions do not bind to the borane. A related series of cationic compounds, such as the Ir(III) derivative $[\mathbf{33}]^+$, in which a transition metal center bears the formal cationic charge, have been obtained by metalation of pyridyl boranes. This derivative binds 2 equiv of fluoride ions in MeCN.[110] Comparison of the $K_{1,1}$ (Scheme 9) measured for $[\mathbf{33}]^+$ with the fluoride binding constant of the free ligand **34** indicates a substantial increase in the fluoride affinity in $[\mathbf{33}]^+$. Related results have been obtained with the Ru(II) complex $[\mathbf{35}]^+$ whose fluoride binding constant exceeds that of the free 2-(4′-dimesitylborylphenyl)pyridine ligand (**36**) in chloroform/DMF, 9/1 volume.[111] These results point to the beneficial influence of the cationic transition metal moiety, which increases the anion affinity of the boron center through both inductive and Coulombic effects.



$[\mathbf{31}]^+$

$CHCl_3$, RT

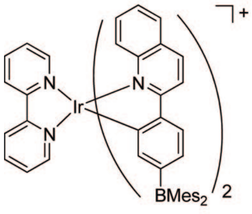
$K > 10^8\ M^{-1}$



$[\mathbf{32}]^+$

$CHCl_3$, RT

$K > 10^8\ M^{-1}$

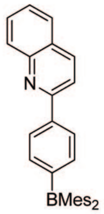


$[\mathbf{33}]^+$

MeCN, RT

$K_{1,1} = 1.29 \times 10^6\ M^{-1}$

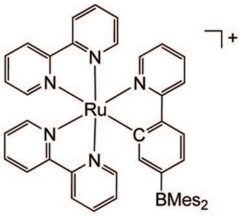
$K_{1,2} = 4.27 \times 10^5\ M^{-1}$



34

MeCN, RT

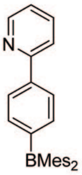
$K = 4.7 \times 10^4\ M^{-1}$



$[\mathbf{35}]^+$

$CHCl_3$/DMF 9/1 vol., RT

$K = 1.1\ (\pm 0.1) \times 10^4\ M^{-1}$



36

$CHCl_3$/DMF 9/1 vol., RT

$K = 7.5\ (\pm 0.5) \times 10^2\ M^{-1}$

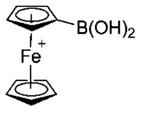
Table 4. Binding Constants of Ferroceniumboronic Acid $[\mathbf{37}]^+$ with Various Anions

X^-	$K\ (M^{-1})$[a]
F^-	700 (±50)[b]
Cl^-	<2
Br^-	<2
SCN^-	2 (±1)
SO_4^{2-}	20 (±10)
$H_2PO_4^-$	10 (±10)

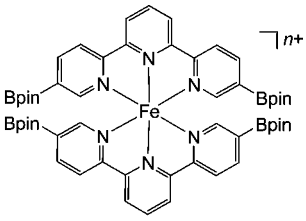
[a] For the formation of $FcB(OH)_2X$ in aqueous solution. [b] A value of 1000 (±50) M^{-1} has been determined in H_2O/MeOH, 9/1 volume.

The introduction of positively charged peripheral substituents has also been employed to enhance the Lewis acidity of arylboronic acids and esters, with the cationic component typically being incorporated by protonation or alkylation protocols or by the oxidation of a pendant ferrocenyl substituent. In an early example of such an approach, Shinkai and co-workers demonstrated electrochemically that the fluoride binding affinity of ferroceniumboronic acid, $[\mathbf{37}]^+$ in aqueous solution, far exceeds that of other halides, thiocyanates, or oxyanions such as sulfate or dihydrogenphosphate, thus demonstrating its usefulness in fluoride recognition (Table 4).[77] Moreover, analysis of the electrochemical data led to the conclusion that the introduction of a cationic substituent by oxidation of the iron center leads to an increase in the fluoride binding constant (over the corresponding neutral ferroceneboronic acid) by 3.5 orders of magnitude.[77] A more modest increase (by a factor of ca.

500) has been reported for the fluoride binding affinity of the pinacolboronate-functionalized terpyridine complexes [**38**]$^{n+}$ on oxidation of the iron center (from n = 2−3).[112]

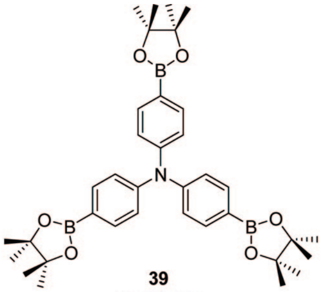


[**37**]$^+$

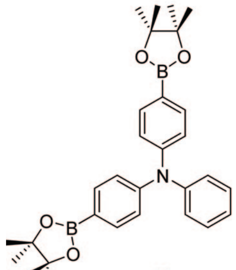


[**38**]$^{n+}$

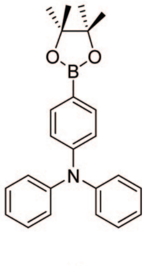
Redox enhancement of fluoride binding has also been reported for aniline-derivatized pinacolboronate esters. Thus, the binding constants K (for 1 equiv of fluoride) determined for the neutral mono-, bis-, and tris-pinacolate esters **39**, **40**, and **41** in acetonitrile solution vary between 2.1 × 10^2 and 2.8 × 10^2 M^{-1}; the corresponding values for the radical cations generated on electrochemical oxidation fall in the range 0.9 × 10^7 to 1.6 × 10^7 M^{-1}.[113,114]



39
MeCN, RT
$K = 2.4 \times 10^2\ M^{-1}$
[**39**]$^{\bullet+}$
MeCN, RT
$K = 1.6 \times 10^7\ M^{-1}$



40
MeCN, RT
$K = 2.8 \times 10^2\ M^{-1}$
[**40**]$^{\bullet+}$
MeCN, RT
$K = 1.2 \times 10^7\ M^{-1}$

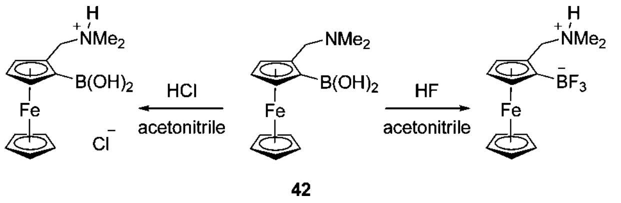


41
MeCN, RT
$K = 2.1 \times 10^2\ M^{-1}$
[**41**]$^{\bullet+}$
MeCN, RT
$K = 9.0 \times 10^6\ M^{-1}$

Alkylation or protonation of pendant amine functions has also been employed to enhance the Lewis acidity of ferrocenylboranes. Thus, in addition to the −BMes$_2$ systems [**20**]$^+$ outlined above, protonation of the pendant tertiary amine function of (dimethylamino)methyl ferroceneboronic acid, **42**, facilitates fluoride binding at the boron center and formation of the corresponding zwitterionic ferrocenyltrifluoroborate CpFe{η^5-$C_5H_3(BF_3)(CH_2NMe_2H)$} (Scheme 6). Under analogous conditions, chloride does not interact significantly with the boron center, thereby providing a mechanism for electrochemical discrimination between HCl and HF (section 5.4).[79]

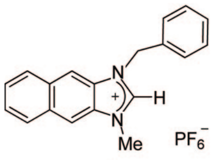
A consequence of protonation (rather than alkylation) at proximal tertiary amine functions appears to be the increased lability of the boron-bound substituents, even those linked via B−C bonds. Thus, while CpFe{η^5-$C_5H_3(BMes_2)(CH_2NMe_2)$} can be methylated to give the air- and moisture-stable [CpFe{η^5-$C_5H_3(BMes_2)(CH_2NMe_3)$}]$^+$, [CpFe{$\eta^5$-$C_5H_3(BMes_2)(CH_2NMe_2H)$}]$^+$ hydrolyzes readily to give the corresponding borinic acid [CpFe{η^5-$C_5H_3(BMesOH)(CH_2NMe_2H)$}]$^+$, with the loss of mesitylene presumably being facilitated by the proximity of B-Mes and N−H$^+$ functions.[92]

Scheme 6

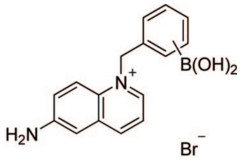


The use of cationic side chains, or related systems that can be converted as such by in situ protonation, has also been investigated in the binding of fluoride by arylboronic acids. Thus, a binding constant K of 360 (±72) M^{-1} has been determined for the interaction of a single equivalent of fluoride with *ortho*-[(methyl)benzylamino]methylphenylboronic acid (**43**) at pH 5.5, under which conditions the tertiary amine group is believed to be protonated. A cooperative NH•••FB mode of binding of the fluoride ion has been proposed (Scheme 7).[115]

The influence of pendant imidazolium functions in fluoride binding has also drawn attention, in particular due to the fact that this particular hydrogen bond donor has previously been shown to be competent for anion recognition in aqueous solution.[116−119] Thus, the isomeric imidazolium-functionalized phenylboronic acids *o*-, *m*-, and *p*-[**44**]$^+$ have been synthesized as the PF_6^- salts, and their relative binding capabilities for fluoride in acetonitrile solution have been examined by ^{19}F NMR and fluorescence titration methods. In each case, sequential binding of three fluoride anions was demonstrated by NMR methods, with the *ortho*-functionalized derivative displaying enhanced affinity (Scheme 8) due to the possibility for cooperative CH•••FB binding. The *m*- and *p*-isomers, on the other hand, show fluoride affinities that are not enhanced as compared to the parent imidazolium salt [**45**]$^+$. The greater binding affinity of *o*-[**44**]$^+$ allows it to function as a fluorescence-based sensor for fluoride in the presence of a range of other anions (Cl^-, Br^-, AcO^-, HSO_4^-, and $H_2PO_4^-$) and in a 20/1 MeCN/HEPES mixture.[116]



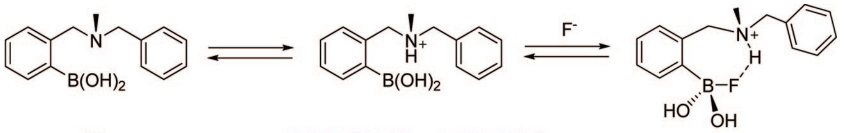
[**45**]$^+$
MeCN, RT
$K = 1.1(\pm0.2) \times 10^4\ M^{-1}$



o-, *m*- and *p*-[**46**]$^+$
H_2O, RT
o-[**46**]$^+$: $K_D = 40.0\ mM^3$
m-[**46**]$^+$: $K_D = 10.8\ mM^3$
p-[**46**]$^+$: $K_D = 55.6\ mM^3$

A related study has been carried out on a series of quinolinium-derived systems [**46**]$^+$, which, although cationic, do not offer the possibility for cooperative binding via intramolecular hydrogen bonding. The binding constants for the *o*-, *m*-, and *p*-isomers are, not unexpectedly, more similar, with values in the order of 40 mM^3 having been determined for K_D (= $1/K_3$) in water.[120,121]

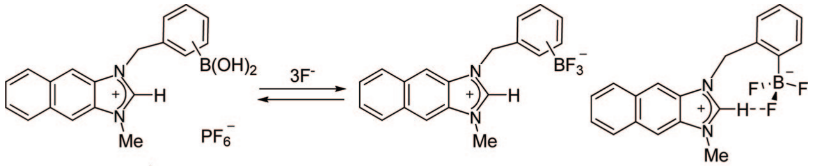
Scheme 7



43
$pK_a = 5.63$

H_2O/MeOH, 1/4 vol., RT, pH 5.5
$K = 360(\pm72)$ M^{-1}

Scheme 8



o-, *m*- and *p*-**[44]**$^+$

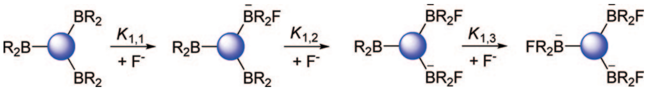
MeCN, RT
o-**[44]**$^+$: $K_3 = 5.1(\pm0.2) \times 10^5$ M^{-3}
m-**[44]**$^+$: $K_3 = 6.7(\pm0.2) \times 10^3$ M^{-3}
p-**[44]**$^+$: $K_3 = 5.7(\pm0.2) \times 10^3$ M^{-3}

4. Fluoride Binding by Polyfunctional Organoboron Compounds

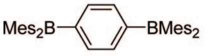
4.1. π-Conjugated Polyfunctional Boranes

Early investigations by Kaim have shown that conjugated diboryl species such as 1,4-bis(dimesitylboryl)benzene **47** have a significantly more anodic reduction potential than mononuclear triarylboranes.[122] This effect, which has been observed in a number of other conjugated diboranes, arises from a lowering of the LUMO caused by participation of a second boron atom to the π-system. This effect, which has been confirmed for a number of other diboranes,[123,124] should also lead to an increase in the Lewis acidity of the derivatives. On the basis of this assumption, the fluoride binding properties of diboranes **47** and **48** have been investigated.[125] Although the 1:1 fluoride binding constant ($K_{1,1}$) of these derivatives has not been determined, titration studies suggest that binding of the first fluoride anion by these receptors is elevated versus mononuclear triarylboranes. In both cases, fluoride binding occurs sequentially, indicating that the binding constant for the formation of the 2:1 adduct should be much lower than that for the formation of the 1:1 complex. This can be realized, as depicted in Scheme 9, by considering the proximity of two or more boron centers and the resulting negative cooperativity caused by the build-up of electrostatic repulsion upon formation of the anionic fluoroborate moieties.

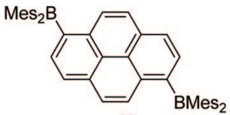
Scheme 9. General Scheme Showing the Multistage Complexation of Fluoride Ions by a Polyfunctional Borane[a]



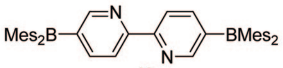
[a] $K_{1,n}$ is equivalent to K ([Ar_3BF]/[Ar_3B][F^-]), where *n* denotes the stage in successive fluoride binding to polyfunctional receptors.



47

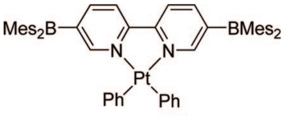


48

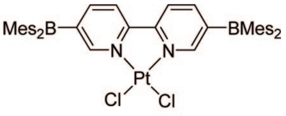


49
CH_2Cl_2, RT
$K_{1,1} > 10^8$ M^{-1}
$K_{1,2} \approx 10^6$ M^{-1}

More quantitative results have been obtained with 5,5′-bis($BMes_2$)-2,2′-bipy (**49**).[126] As shown by electrochemical measurements, this compound ($E_{1/2}^{red} = -1.69$ V vs Fc/Fc$^+$) is more easily reduced than its biphenyl analogue (Mes_2B)-(C_6H_4)$_2$-($BMes_2$) ($E_{1/2}^{red} = -1.96$ V vs Fc/Fc$^+$). Presumably, the increased electron affinity of this compound results not only from the π-conjugation of the two boron centers but also from the presence of electronegative nitrogen atoms in the pyridine rings. In agreement with this conclusion, **49** displays a very high FIA. Indeed, the first fluoride binding constant $K_{1,1}$ in CH_2Cl_2 has been estimated to be equal or greater than 10^8 M^{-1}. This binding constant is much larger than that measured for simple triarylboranes such as Mes_3B in THF (AN = 8 with AN = acceptor number as defined by Gutmann[127]), a solvent less electrophilic and thus a less competing solvent than CH_2Cl_2 (AN = 20.4). The second binding constant $K_{1,2}$ is also very high and comparable to that measured for simple triarylboranes. Presumably, the relatively large spacing between the two boron centers lessens the negative cooperativity occurring between these two centers. The high Lewis acidity of this compound makes it a viable receptor in more competing protic environments. For example, **49** captures fluoride in THF/ethanol (7/3) with a binding constant in the 10^4-10^5 range.



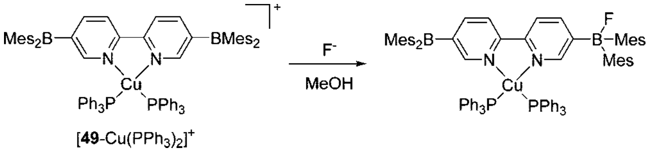
49-$PtPh_2$

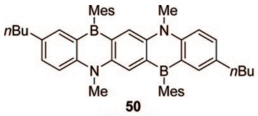


49-$PtCl_2$
CH_2Cl_2, RT
$K_{1,1} > 10^9$ M^{-1}
$K_{1,2} \sim 10^6$ M^{-1}

Further tuning of the fluoride binding properties of **49** has been achieved by its coordination to transition metals as in **49**-$PtPh_2$, **49**-$PtCl_2$, and [**49**-Cu(PPh_3)$_2$]$^+$.[126,128] Cyclic voltammetry measurements suggest that metal coordination leads to a significant increase in the electron-accepting abilities of the boron centers when compared to the free ligand **49**. Although exact fluoride binding constants for these metal complexes have not been determined, they display a high affinity for fluoride anions. For example, [**49**-Cu(PPh_3)$_2$]$^+$ precipitates as a monofluoride adduct when mixed

Scheme 10

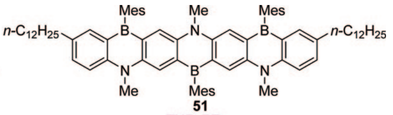




50

THF, RT

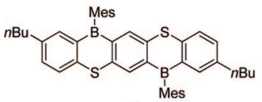
$K_{1,1} = 7(1) \times 10^4\ M^{-1}$



51

THF, RT

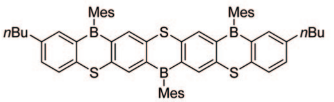
$K_{1,1} = 2.8(8) \times 10^5\ M^{-1}$



52

THF, RT

$K_{1,1} = 3.2(7) \times 10^5\ M^{-1}$

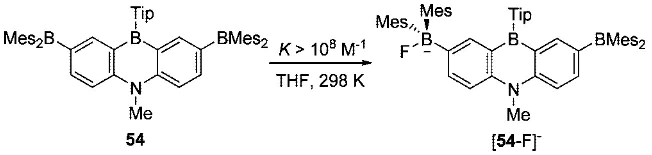


53

THF, RT

$K_{1,1} = 8(4) \times 10^6\ M^{-1}$

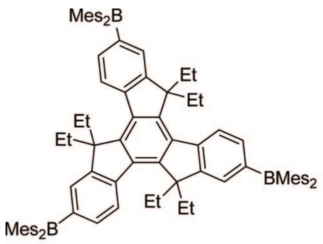
Scheme 11. Structures of the Diborylated Azaborin 54 and Its Reaction with Fluoride Ions



with fluoride ions in methanol (Scheme 10).[126] Complex **49**-PtPh$_2$ binds 2 equiv of fluoride in CH$_2$Cl$_2$ with $K_{1,1} \geq 10^9$ M^{-1} and $K_{1,2} \sim 10^6$ M^{-1}.

Another elegant illustration of the effects caused by extension of the π-system in polyfunctional boranes has been obtained in a study of the ladder type azaborins **50** and **51** and thiaborins **52** and **53**.[129] This study reveals that the heptacene type heteraborins **51** and **53** display a significantly higher fluoride affinity than their pentacene type congeners **50** and **52**. Comparison of these fluoride binding constants also indicates that the azaborins are less Lewis acidic than the thiaborins, which can be rationalized by the greater π-donating ability of nitrogen when compared to sulfur. A further enhancement in the fluoride affinity of this class of compounds can be obtained by simple diborylation of a simple azaborin as in the case of **54**.[130] Theoretical studies show that the LUMO of this compound, which bears strong contribution from the three boron atoms, is significantly lower than that of an unsubstituted azaborin. This lowering of the LUMO reflected a drastic increase in the fluoride binding constant $K_{1,1}$, which exceeds 10^8 M^{-1}. While the site of coordination for the first fluoride anion has not been discussed in the cases of **51** and **53**, ^{11}B NMR studies in the case of **54** indicate that the first fluoride coordination occurs at one of the peripheral dimesitylboryl units rather than at the boron atom of the azaborin system (Scheme 11). While the exact origin of this regioselectivity has not yet been unraveled, one factor that may contribute is the possible alleviation of the electron deficiency of the central boron atom by the aromaticity of the azaborin ring. It is also important to point out that the steric protection of the central boron atom, which bears a single Tip ligand, is significantly different from that of the peripheral dimesitylboryl moieties. In general, coordination of additional fluoride ions to **50**−**54** to form the 2:1 or 3:1 fluoride adducts is affected by a significant negative cooperativity.

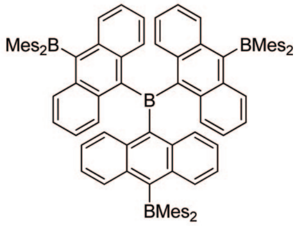
Multistage fluoride ion binding has been observed in **55** and **56**, which contain three and four individual boron centers, respectively.[63,131] For both derivatives, the binding constant $K_{1,1}$ is significantly higher than $K_{1,2}$ and $K_{1,3}$, once again illustrating the negative cooperativity occurring between the boron centers. The UV−vis spectrum of **56** in the presence of an excess of fluoride anion is similar to that of Ant$_3$B (**3**), thus suggesting that the central boron atom remains uncoordinated. While it could have been expected that the extended conjugation present in this compound would lead to an increase of the fluoride affinity, its fluoride binding constant $K_{1,1}$ is actually smaller than those measured for both **2** and **3**. This unexpected observation may reflect the increased steric constraints present in **56**.



55

THF, RT

$K_{1,1} = 3.9 \times 10^5\ M^{-1}$
$K_{1,2} = 2.5 \times 10^4\ M^{-1}$
$K_{1,3} = 1.6 \times 10^4\ M^{-1}$



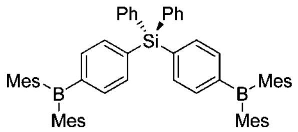
56

THF, 25°C

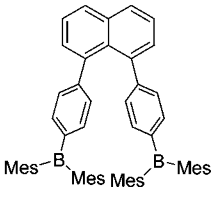
$K_{1,1} = 6.9\ (\pm 0.2) \times 10^4\ M^{-1}$
$K_{1,2} = 9.0\ (\pm 0.6) \times 10^2\ M^{-1}$
$K_{1,3} = 2.1\ (\pm 0.4) \times 10^2\ M^{-1}$

4.2. Bifurcated and Polymeric Polyfunctional Boranes

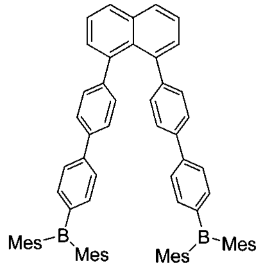
The effects of spacial separation of triarylborane groups on fluoride affinity have been observed in the series of receptors **57**−**59**.[125,132] Although distinct fluoride binding constants for **57** and **58** have not been determined, comparative studies carried out in CH$_2$Cl$_2$ indicate that **57** has a higher fluoride affinity than **58**. This observation is rationalized on the basis of the proximity of the two dimesitylboryl moieties in **58** and the ensuing steric interactions that hamper the anion-induced tetrahedralization of the boron center. These unfavorable steric interactions are somewhat relaxed in **59** because of a larger spacing between boryl moieties.[132] Its fluoride binding isotherm has been obtained in chloroform but not fitted to a model accounting for the sequential binding of fluoride to both boron centers. Hence, its affinity cannot be compared to simple triarylboranes.



57

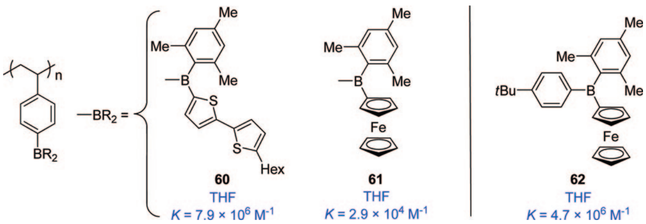


58



59

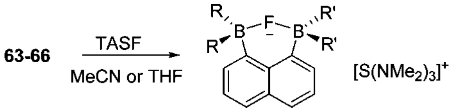
Triarylboryl moieties have also been incorporated into polymers and used for the sensing of anions including fluoride. Borylated polystyrenes **60** and **61** are unique examples of such polymers.[133,134] Although such compounds readily interact with fluoride anions, the fluoride affinity of the polymeric system tends to be lower than that of the monomeric model compounds. For example, the fluoride binding constant of **61** is 2 orders of magnitude lower than that of the model monomeric compound **62**. This net decrease in anion affinity may originate from steric interactions between the neighboring boryl functionalities of the polymer.

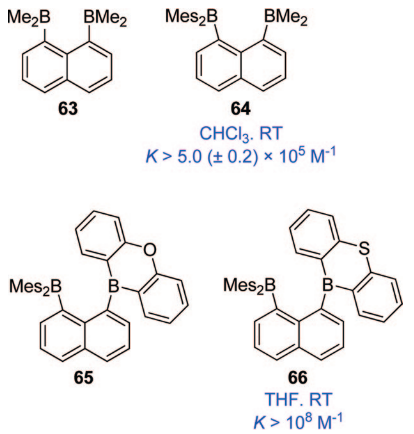


4.3. Bidentate Diboranes

Early studies in the chemistry of polydentate Lewis acids have shown that anion complexation can be efficiently enhanced via chelation. In application of this strategy to increasing the fluoride affinity of boron-based Lewis acids,[135] a great deal of attention has been devoted to 1,8-diborylnaphthalenes such as **63**,[136−138] **64**, **65**, and **66**. Structural analysis of **64**, **65**, and **66** indicates that the boron centers are separated by only 3.2−3.4 Å and thus predisposed to cooperatively interact with incoming anions.[59,65,139−141] Accordingly, reaction of these compounds with $[S(NMe_2)_3][Me_3SiF_2]$ (TASF) affords the anionic chelate complexes [**63**-μ_2-F]$^-$, [**64**-μ_2-F]$^-$, [**65**-μ_2-F]$^-$, and [**66**-μ_2-F]$^-$ (Scheme 12).[59,65,141] Complexation of larger halides or polyatomic anions such as NO_3^- and $H_2PO_4^-$ is not observed with this type of derivative, thus indicating that fluoride anion complexation is selective. The size of the binding pocket provided by these bidentate boranes may be responsible for this selectivity. Structural analysis of [**64**-μ_2-F]$^-$, [**65**-μ_2-F]$^-$, and [**66**-μ_2-F]$^-$ shows that the fluorine atom is located between the two boron atoms with B−F bond lengths in the 1.58−1.64 Å range (Figure 5). The formation of the B−F−B bridge results in B−F bond lengths that are distinctly longer than the distance of 1.48 Å observed in typical triaryfluoroborate moieties.

Scheme 12





To assess the impact of the chelate structure on the fluoride binding properties of these diboranes, the fluoride binding constant of **66** has been measured. This fluoride binding constant is greater than 10^8 M^{-1} in THF, thus exceeding that of neutral monofunctional boranes by at least 3 orders of magnitude.[65] Analogous results have been obtained with **64**, whose fluoride binding constant in $CHCl_3$ exceeds that of simple boranes such as **36** [7.5 (±0.5) × 10^2 M^{-1} in $CHCl_3$/DMF, 9/1 volume]. The net enhancement observed in the fluoride affinity of the diboranes can be assigned to the stability imparted by chelation of the anion. In agreement with this observation, the addition of water to [**66**-μ_2-F]$^-$ does not lead to decomplexation of the fluoride anion as typically observed for fluoride adducts of monofunctional boranes.[63] Theoretical calculations corroborate these experimental findings. Indeed, the computed gas-phase FIAs of **64** (314.2 kJ mol^{-1}) and **65** (306.6 kJ mol^{-1}) substantially exceed those of monofunctional model compounds such as $PhBMes_2$ (**1**) (FIA = 254.1 kJ mol^{-1}).[59,141] However, these naphthalene-based diboranes decompose in the presence of water and thus cannot be used for fluoride detection in aqueous solution.

Fluoride ion chelation has also been demonstrated with 1,2-bis[bis(pentafluorophenyl)boryl]tetrafluorobenzene (**67**), which readily forms the anionic complex ([**67**-μ_2-F]$^-$) upon reaction with KF/18-crown-6[142] or $[Ph_3C]^+[BF_4]^-$ (Scheme 13).[143] The ability of **67** to abstract a fluoride from $[BF_4]^-$ is a testament to its powerful Lewis acidity. Although the crystal structures of these salts have not been determined, NMR data unambiguously support the existence of symmetrical bridged structures. In particular, the bridging fluoride

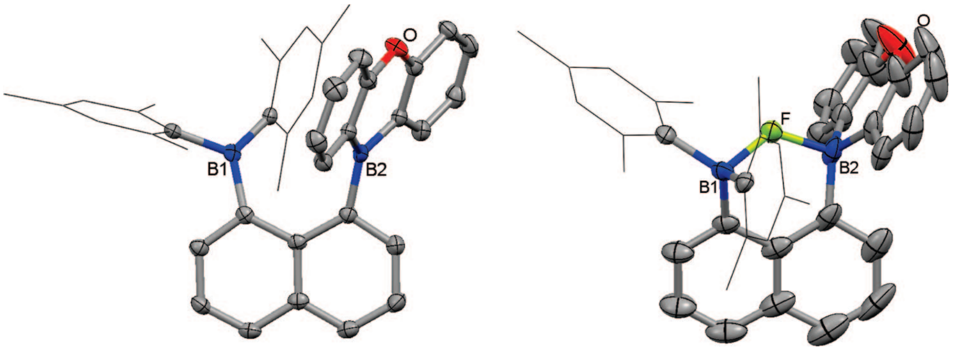
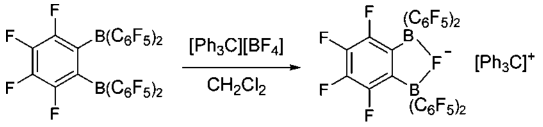


Figure 5. View of the crystal structure of **65** (left) and [**65**-μ_2-F]$^-$ (right) outlining the structural changes induced by fluoride complexation. The mesityl groups are represented by thin lines for clarity.

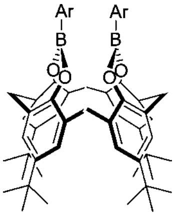
Scheme 13



67 **[67-μ_2-F]$^-$**

atom in [**67**-μ_2-F]$^-$ gives rise to a ^{19}F NMR resonance at −167.2 ppm (in CH_2Cl_2 at 213 K). This chemical shift is similar to that observed for the bridging fluoride in [**66**-μ_2-F]$^-$ (−188 ppm in d_6-acetone at 298 K). Although the fluoride binding constant of **67** has not been determined, theoretical calculations indicate that its FIA (510 kJ mol^{-1}) is significantly larger than that of $(C_6F_5)_3B$ (444 kJ mol^{-1}).[61] This large FIA difference illustrates the impact of chelation on the stability of the anionic complex.

Chelation of fluoride by a bidentate boronic acid or ester based receptor has yet to be demonstrated by crystallographic methods, although systems have been reported—for example, based on a calyx[4]arene backbone—in which the B···B separation (ca. 3.42 Å) would appear to be appropriate for such a mode of binding (e.g., **68** and **69**).[74−76] In reality, it seems likely that relatively labile B−O bonds in such systems render them labile in the presence of hydrated sources of fluoride.



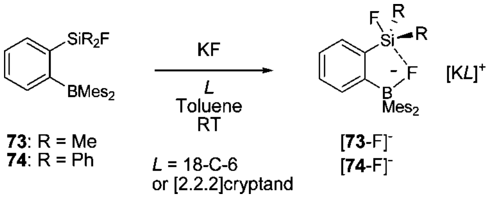
68 (Ar = Ph)
69 (Ar = Fc)

The only structurally authenticated example of chelated fluoride derived from the reaction of a bis(boronic) acid with a fluoride source is that outlined in Scheme 14. The reaction of **70** with potassium hydrogen bifluoride results in the formation of an equilibrium mixture of the dianionic bis(trifluoroborate) [**71**]$^{2-}$ and the corresponding monoanionic B−F−B chelate [**72**]$^-$; the position of equilibrium is reported to be dependent on the amount of water present in the system. From a spectroscopic perspective, the boron-bound fluorines in [**72**]$^-$ are characterized by signals at −143.4 and −139.7 ppm (in a ratio of 4:1), and the B−F distances relating to the bridging fluoride [1.487(4) Å] are lengthened by ca. 5% with respect to the terminal B−F linkages [1.405(4) Å]. Interestingly, fluoride can readily be abstracted from either [**71**]$^{2-}$ or [**72**]$^-$ to give the corresponding neutral 1,2-bis(difluorboryl)benzene system by the addition of BF_3.[100]

4.4. Heteronuclear Bidentate Boranes

Fluoride ion chelation has also been observed in heteronuclear bidentate systems combining a boryl group with another Lewis acidic moiety. Examples of such systems include the *ortho*-phenylene derivatives **73** and **74**, which react with KF in toluene to afford the corresponding fluoride complexes (Scheme 15).[144] Evidence for the chelate structure of these complexes has been derived from ^{19}F NMR spectroscopy, which shows coupling of the two fluorine nuclei coordinated to the silicon atom. Moreover, the resonance of the bridging fluorine {δ = −152 ([**73**-F]$^-$); −148 ([**74**-F]$^-$) in d_8-THF} appears slightly upfield from that of the terminal fluorine {δ = −147 ([**73**-F]$^-$); −145 ([**74**-F]$^-$)}. Interaction of the bridging fluoride with the silicon atom also results in an upfield shift of the ^{29}Si NMR resonance. Structural analysis of [**73**-F]$^-$ and [**74**-F]$^-$ shows linear F−Si−F angles as expected for a difluorosilicate (Figure 6). The lengths of the Si−F bonds in the Si−F−B bridge of these complexes lie in the 2.25−2.53 Å range. These short distances, which are well within the sum of the van der Waals radii of the two elements, confirm the presence of an interaction. Competition experiments carried out by reaction of $[PhMes_2BF]^-$ with **73** and **74** indicate that the presence of the silyl substituents increases the fluoride affinity of the derivatives by 14.6 kJ mol^{-1} in **73** and 6.3 kJ mol^{-1} in **74**.

Scheme 15



Related results have been obtained with boron/tin derivatives such as **75**.[145] This compound forms a fluoride chelate complex when mixed with 1 equiv of KF in THF in the presence of 18-crown-6 (Scheme 16). The crystal structure of the complex shows that the fluorine atom is engaged in a B−F−Sn bridge with a B−F bond length of 1.53 Å and a Sn−F bond length of 2.43 Å. The B−F bond is distinctly longer than that observed in simple fluoroborate compounds (1.48 Å), suggesting a relatively strong interaction with the tin center. Accordingly, the Sn−F bond length is well within the sum of the van der Waals radii of the two elements. In

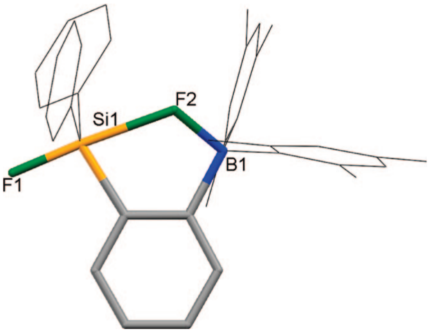
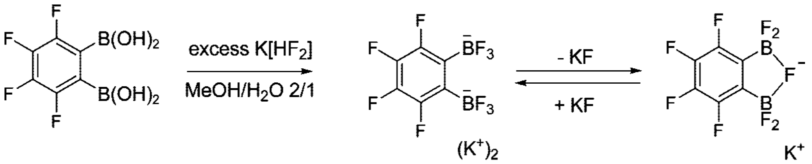


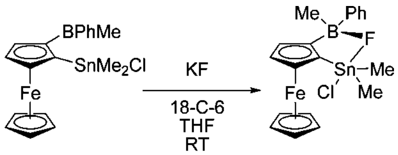
Figure 6. Structure of the [**74**-F]$^-$ in the [K(18-crown-6)THF$_2$]$^+$ salt.

Scheme 14



70 K$_2$[**71**] K[**72**]

Scheme 16



75 **[75-μ_2-F]$^-$**

solution, this complex exists as two diastereomers, both of which display coupling between the ^{119}Sn and the ^{19}F nuclei ($^1J_{Sn-F}$ = 344 or 365 Hz), indicating that the chelate structure subsists in solution. Fluoride ion chelation has also been observed with several other ferrocene-based boron/tin derivatives closely related to **75**.[145]

Another important class of heteronuclear bidentate boranes that have been recently investigated contain mercury as a secondary Lewis acidic element. Examples of such compounds include **76**, **77**, and **78**, which have been characterized by conventional means including ^{199}Hg NMR spectroscopy.[141,146,147] Structural analyses of these compounds indicate that the boron and mercury atoms are separated by approximately 3.3−3.5 Å. This short separation, which is close to that observed between the boron atoms of 1,8-diborylnaphthalenes, shows that the boron and mercury atoms are ideally positioned to cooperatively bind anions. In line with this expectation, compounds **76** and **77** selectively complex fluoride to form the corresponding anionic chelate complexes [**76**-μ_2-F]$^-$ and [**77**-μ_2-F]$^-$.[146,147] Unlike diboranes such as **65** and **66**, compounds **76** and **77** are stable in aqueous media and are sufficiently fluorophilic to bind fluoride in THF/water 9/1 volume. The higher fluoride binding constant of **76** can be assigned to the electron-withdrawing properties of the C_6F_5 group, which increases the Lewis acidity of the mercury center. Because simple boranes such as Mes_3B only display a low fluoride binding constant [1.0 (±0.3) × M^{-1}] in the same THF/water mixture, the ability of these boron/mercury derivatives to bind fluoride under these condition is assigned to a chelate effect, which stabilizes the resulting complexes. The existence of a B−F−Hg chelate motif in [**76**-μ_2-F]$^-$ and [**77**-μ_2-F]$^-$ has been confirmed using NMR spectroscopy.[146,147] The ^{199}Hg nucleus is coupled to the bridging fluoride ($^1J_{Hg-F}$ = 135.2 Hz for [**76**-μ_2-F]$^-$, $^1J_{Hg-F}$ = 109.8 Hz for [**77**-μ_2-F]$^-$), indicating the presence of a direct Hg−F interaction. The crystal structure of [S(NMe$_2$)$_3$][**76**-μ_2-F]$^-$ (Figure 7) shows that the bridging fluorine atom forms a short bond of 1.483(4) Å with a boron atom and a longer one of 2.589(2) Å with the mercury atom. The latter is well within the sum of the van der Waals radii of the two elements and is, in fact, comparable to the distances observed in a fluoride adduct of a tetranuclear mercuracarborand (2.56 and 2.65 Å).[40]

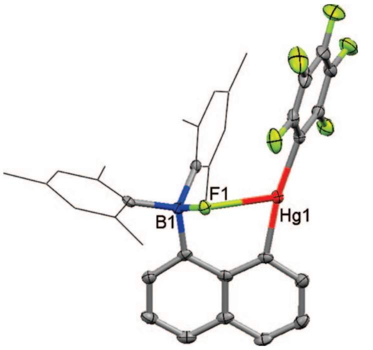
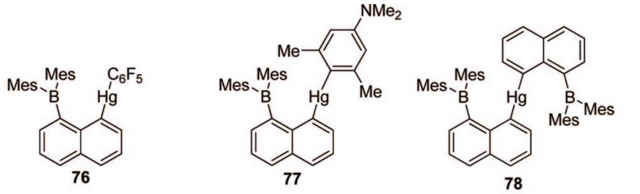


Figure 7. Crystal structure of [**76**-μ_2-F]$^-$. The mesityl groups are represented by thin lines for clarity.



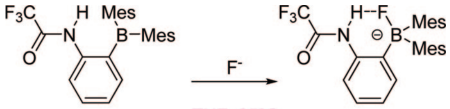
76 **77** **78**

THF/H$_2$O 9/1 vol., RT
K = 2.3 (± 0.2) × 10^4 M^{-1}

THF/H$_2$O 9/1 vol., RT
K = 1.3 (± 0.1) × 10^2 M^{-1}

THF, RT
$K_{1,1}$ > 10^8 M^{-1}
$K_{1,2}$ = 5.2 (± 0.4) × 10^3 M^{-1}

Scheme 17



79 THF, 25°C K > 10^7 M^{-1} **[79-F]$^-$**

Two-stage anion binding is observed for **78** in THF.[141] As expected, the first fluoride binding constant ($K_{1,1}$ > 10^8 M^{-1}) is much larger than the second one [$K_{1,2}$ = 5.2 (±0.4) × 10^3 M^{-1}]. Again, this trend is likely due to electrostatic repulsion associated with the formation of a dianionic species and possibly steric factors. The crystal structure of [**78**-μ_2-F]$^-$ shows a B−F−Hg bridge similar to that observed for [**76**-μ_2-F]$^-$.

4.5. Hybrid Borane/Hydrogen Bond Donor Derivatives

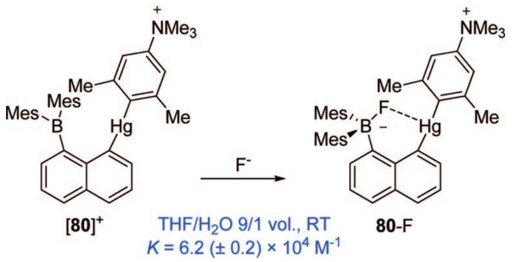
Fluoride ion chelation has also been observed in hybrid borane/hydrogen bond donor derivatives such as *o*-(dimesitylboryl)trifluoroacetanilide (**79**).[148] Reaction of this borane with TBAF in THF affords the corresponding fluoroborate complex, [**79**-F]$^-$ (Scheme 17), which has been characterized by NMR spectroscopy only. The most notable spectroscopic feature of [**79**-F]$^-$ concerns the amide proton resonance at 11.43 ppm, which is split into a doublet through coupling with the bridging fluoride ($^1J_{H-F}$ = 36 Hz). The presence of this intramolecular hydrogen bond may be responsible for the elevated fluoride binding constant measured for **79** in THF. This conclusion is supported by computational results, which show that the FIA of **79** (314.4 kJ mol^{-1}) is substantially larger than that of Mes$_2$BPh (257.4 kJ mol^{-1}).

4.6. Cationic Bidentate Boranes

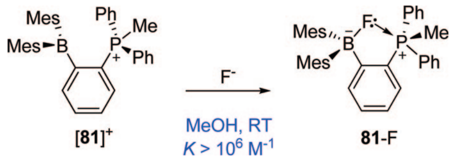
On the basis of the premise that chelate effects could be combined with Coulombic effects to further enhance the FIA of boron-based receptors, recent efforts have been devoted to the synthesis of bidentate cationic boranes such as the heteronuclear B/Hg compound [**80**]$^+$, which was obtained by methylation of **77** (Scheme 18).[147] As shown by fluoride titration experiments carried out in THF/water (9:1 volume) mixtures, the fluoride binding constant of [**80**]$^+$ [6.2 (±0.2) × 10^4 M^{-1}] is substantially higher than that of its neutral precursor **77** [1.3 (±0.1) × 10^2 M^{-1}].

Phosphonium borane [**81**]$^+$, the ortho isomer of [**22**]$^+$ (Scheme 19), exemplifies the advantage of combining cationic and chelate effects.[149,150] Unlike [**22**]$^+$ (p$K_R$$^+$ = 7.3), [**81**]$^+$ is not stable in water around neutral pH. It can, however, be observed by UV−vis spectroscopy at pH 2.3 in water, but the absorption band associated with the cationic borane quickly disappears above pH 3.5. These experiments indicate that the p$K_R$$^+$ of [**81**]$^+$ is in

Scheme 18



Scheme 19



the 3−4 range. Because of its elevated acidity, the fluoride binding constant of this compound has been evaluated in methanol rather than water. Under these conditions, its fluoride binding constant exceeds the measurable range and is at least 4 orders of magnitude higher than that measured for the para isomer [**22**]$^+$ [$K = 400\ (\pm 50)\ \text{M}^{-1}$]. While an increase in inductive effects can be invoked in [**81**]$^+$ when compared to the para isomer [**22**]$^+$, a structural analysis of **81**-F shows that the phosphonium center acts as a Lewis acid and engages the fluoride anion in a B−F → P donor−acceptor interaction with a P−F distance of 2.66 Å (Figure 8). A natural bond orbital (NBO) analysis indicates that this interaction, which involves donaton of a fluorine lone pair into a P−C σ^*-orbital, contributes 5.0 kcal/mol to the stability of the complex.

4.7. Multifunctional Metallocene-Based Lewis Acids

Strong fluoride anion chelation has been observed upon reaction of 1,1′-bis(dialkylboryl)cobaltocenium cations such as [**82**]$^+$ with 1 equiv of fluoride (Scheme 20).[151] The structure of the resulting complex **82**-μ_2-F, which has been determined crystallographically, shows that the fluorine atom is positioned at 1.64 Å from each boron center. While it could be argued that this fluoride complex is stabilized by both chelate and Coulombic effects, solution studies monitored by NMR studies point to the existence of a dynamic process involving the reversible opening and closing of the B−F−B bridge. In agreement with the observed lability of this bridge, addition of an excess of fluoride leads to the formation of the anionic difluoride complex [**82**-F$_2$]$^-$.

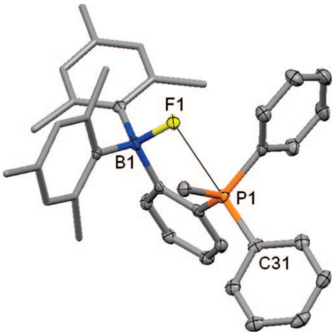
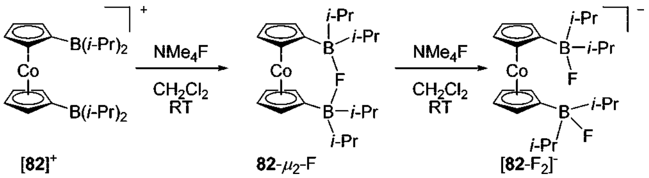
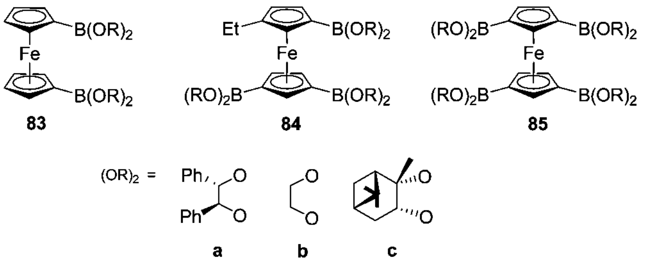


Figure 8. Crystal structure of **81**-F. The mesityl groups are represented by thin lines for clarity.

Scheme 20



Weaker metallocene-based multifunctional Lewis acids show significantly reduced propensities to chelate fluoride. Thus 1,1′-bis(diarylboryl)ferrocenes have been shown from NMR and structural studies to bind either a single equivalent of anion (to a single boron center) or 2 equiv (one at each boron center), with no evidence for cooperativity in binding.[152] Ferrocenyl alkoxyboranes—which feature even weaker binding domains—also provide no evidence for the formation of B−F−B bridges. A range of bis-, tris-, and tetrakis-ferrocene compounds (**83**−**85**) have been reported, and their fluoride binding capabilities have been investigated.[81]

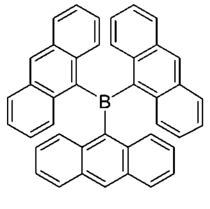


In common with other arylboronic esters,[81,82] these systems act as selective fluoride receptors in chloroform solution; no reaction is observed on addition of Cl$^-$, Br$^-$, I$^-$, BF$_4^-$, PF$_6^-$, H$_2$PO$_4^-$, HSO$_4^-$, or NO$_3^-$. Large electrochemical shifts in the Fe(II/III) redox couple are observed upon fluoride binding due to the conversion of a π-electron-withdrawing boronic ester to a σ-electron-donating anionic borate. In the case of **83a**, cyclic voltammetry shows iron-centered oxidation at +206 mV; on addition of excess fluoride, two waves are seen at −384 and −746 mV, due to the formation of the mono- and bis-fluoride adducts. The latter potential is consistent with aerobic oxidation of the bis-fluoride adduct by atmospheric O$_2$, and **83a** consequently acts as an orange to green (ferrocene to ferrocenium) fluoride sensor.[81] The related tris- and tetrakis-boronic esters **84a** and **85a** also sense fluoride colorimetrically. Moreover, kinetic studies have shown that (i) the rates of oxidation of the ferrocene centers in **84a** and **85a** are an order of magnitude faster than those measured for **83a** [$k = 5.4 \times 10^{-2}$ and $6.0 \times 10^{-2}\ \text{s}^{-1}$, respectively, vs $2 \times 10^{-3}\ \text{s}^{-1}$ for **83a**] and (ii) both **84a** and **85a** are oxidized as the bis-fluoride adducts (i.e., only two fluoride ions are bound prior to oxidation). The latter observation is thought to relate to the relative rates of electron transfer vs fluoride coordination for the dianionic bis-fluoride adducts. The enhanced rates of oxidation for **84a** and **85a** have been postulated to be due to the remaining three-coordinate boron sites, offering a facile pathway for electron transfer.[81]

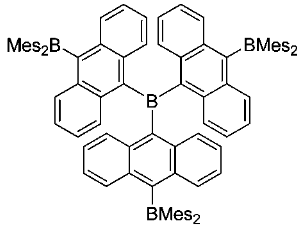
5. Photophysical and Electrochemical Response Induced by Fluoride Binding

5.1. Colorimetric Response

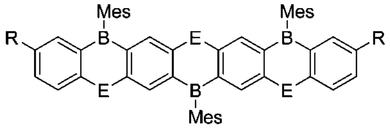
As explained in the first part of this review, the low-energy edge of the UV−vis absorption spectrum of triarylboranes is typically dominated by electronic transitions from filled molecular orbitals into the LUMO. Because the boron p_π-orbital contributes largely to the LUMO of most boranes, these transitions are quenched upon coordination of fluoride to the boron center. For many boranes containing simple aryl substituents, these transitions remain in the UV region such that no visible color change can be detected with the naked eye upon fluoride coordination. By contrast, the use of highly delocalized aryl substituents may push the low-energy edge of the borane absorption into the visible range such that fluoride binding results in a drastic visible color change. Such a colorimetric response has been observed in the case of derivatives such as **3**[63] whose λ_{max} shifts from 470 to 410 nm upon fluoride binding. These spectral changes produce a loss of the orange color of the solution, which can be easily detected with the naked eye. A similar behavior has been observed upon fluoride binding by **56** and **66**, which triggers a progressive change of the color of the solution from red to orange for **56**[63] and yellow to colorless for **66**.[65]



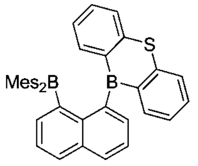
3



56



51: R=*n*-$C_{12}H_{25}$; E = NMe
53: R=*n*-Bu; E = S

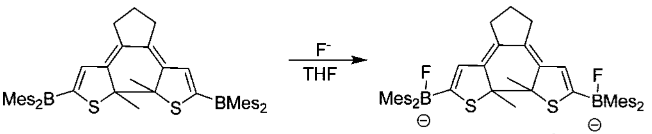


66

By virtue of their extended structures, the heteraborins **51** and **53** display a low-energy absorption peak near 610 and 560 nm, respectively, in THF.[129] Binding of the first equivalent of fluoride by **51** leads to a quenching of the band observed at 610 nm accompanied by the appearance of a new band at around 460 nm. Accordingly, fluoride binding to **51** induces a red to orange colorimetric response. In the case of **53**, binding of the first fluoride anion results in a quenching of a band at 560 nm and is accompanied by the appearance of a new band at 440 nm. Binding of additional fluoride anions quenches the 440 nm absorption band. This multistep process produces a pink to yellow to colorless colorimetric response, which can be easily observed with the naked eye.

A colorimetric response to fluoride is also observed for the closed form of photochromic, borylated dithienylcyclopentene derivatives[153] such as **86**.[154] The main absorption peak of **86** appears at 655 nm in THF, giving the compound a characteristic green color in solution. The addition of fluoride and the formation of the 2:1 adduct [**86**-F_2]$^{2-}$ results in quenching of this band and the appearance of a higher energy absorption band at 490 nm, producing a colorimetric change from green to orange (Scheme 21). The presence of such a low-energy transition indicates that, in the closed form, this diborane is highly π-conjugated, a conclusion supported by density functional theory (DFT) studies. The extent of this π-conjugation can be easily modulated by the light-induced opening of the central ring, which shifts the main absorbance band of the diborane below 400 nm.

Scheme 21



86
λ_{max} = 655 nm (green)

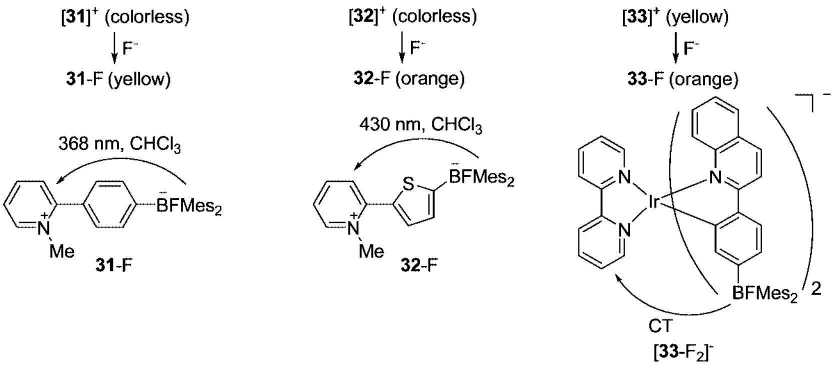
[**86**-F_2]$^{2-}$
λ_{max} = 490 nm (orange)

Although chromophore quenching and a turn-off colorimetric response are commonly observed for fluoride binding to triarylboranes with extended π-conjugation, charge transfer (CT) mechanisms have been shown to provide positive responses in some receptors. For example, fluoride binding to pyridinium boranes [**31**]$^+$ and [**32**]$^+$[109] induces a red shift of the low-energy absorption band of these boranes (from 319 to 368 nm for **31**/**31**-F and from 355 to 430 nm for **32**/**32**-F), leading to the appearance of a yellow color (Scheme 22). The origin of this turn-on colorimetric response is attributed to an intramolecular charge transfer (ICT) process involving the dimesitylfluoroborate moiety as the donor and the pyridinium moiety as the acceptor. A similar phenomenon has been invoked to explain the color change from yellow to orange induced by fluoride binding to the iridium complex [**33**]$^+$.[110] Rather than resulting in the appearance of a new band, fluoride binding induces a red shift of the broad band that appears in the 420−600 nm range. On the basis of theoretical studies, this red shift is proposed to originate from a CT transition involving the dimesitylfluoroborate moiety as the donor and the bipyridyl ligand as the acceptor.

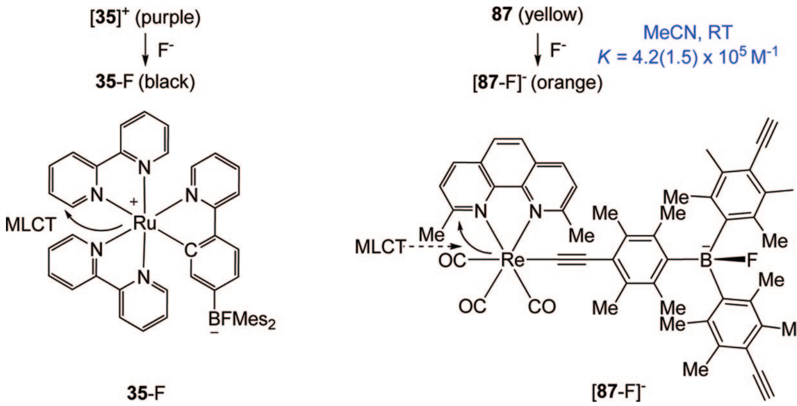
Colorimetric responses have also been obtained when fluoride binding to the boron center of borylated ligands in transition metal complexes influences metal-to-ligand charge transfer (MLCT) absorption bands. In complexes [**35**]$^+$ and **87**,[111,155] fluoride binding to the boron center effectively increases the electron-releasing properties of the borylated ligands, leading to a more electron-rich metal center. The increased energy of the filled metal orbitals results in a red shift of the MLCT band where the accepting orbital in both cases is located on the diimine chelate ligand. This phenomenon has been clearly observed in the ruthenium and rhenium derivatives [**35**]$^+$ and **87**, which go from purple to black in the case of [**35**]$^+$ and from yellow to red in the case of **87** (Scheme 23).

In the reverse scenario, when a CT acceptor ligand is decorated with dimesityl boryl groups, the MLCT energy gap should increase upon fluoride binding as the ligand π-based LUMO goes up in energy. Indeed, this is the case in complexes containing the diborylated bipyridyl ligand **49**.[126] The red color of **49**-$PtPh_2$, which results from a MLCT band at 542 nm in CH_2Cl_2, is blue-shifted to about 435 nm upon binding of the first fluoride anion to afford an orange monofluoride complex (Scheme 24). Binding of a second fluoride anion induces a further shift of the band to

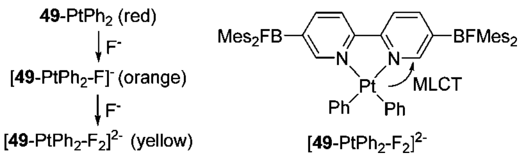
Scheme 22



Scheme 23



Scheme 24

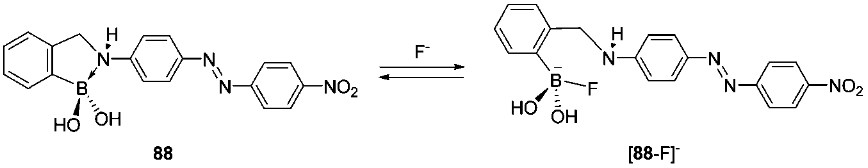


below 380 nm. These results have been rationalized by invoking the stepwise increase in energy of the bipyridyl-based unoccupied orbital triggered by binding one and then two fluoride anions. Similar results have been obtained with **49**-PtCl$_2$. In this case, however, the electronegative character of the chlorine results in a set of transitions that are more blue-shifted when compared to those observed for **49**-PtPh$_2$.

A number of fluoride ion sensors have been developed based around boronic acid/ester binding sites, which give rise to an intrinsic colorimetric response (see section 5.4 for two-component systems, which give rise to an electrochemical response, which can then be coupled with a redox-active dye to give a color change). In 2001, James and co-workers reported an orange-to-claret colorimetric sensor for fluoride in methanol solution, utilizing the fluoride binding equilibrium shown in Scheme 25.[156] Titration of azo dye **88** with chloride, bromide, or iodide leads to an *increase* in the intensity of the band at 450 nm responsible for the orange color, presumably due to a change in the dielectric constant of the medium. The addition of fluoride, on the other hand, leads to a *decrease* in intensity of the 450 nm band and the growth of a second feature at 563 nm, with attendant color change from orange to claret. At a molecular level, this change is thought to reflect the cleavage of the N → B coordinate bond in **88** on the formation of the monofluoride adduct. A similar response is observed in pH titration experiments, implying that a similar binding event also occurs with hydroxide. For fluoride, a value for K of between 130 (±10) and 190 (±20) M^{-1} has been determined by fitting the UV absorption data at 450 and 563 nm, respectively, values that are in broad agreement with those determined for the closely related *ortho*-[(methyl)benzylamino]methylphenylboronic (**43**).[68]

Push−pull systems **89**−**92**, based on the coordination of fluoride at a boronic ester binding site linked to variously nitrated stilbene units, have also been reported to act as colorimetric sensors, resulting from a red shift in λ_{max} (of up to 61 nm) on anion binding (Table 5).[157] The greatest shifts were observed for the trinitro derivative **92**, which acts as a yellow-to-red colorimetric indicator of the presence of fluoride.

Scheme 25



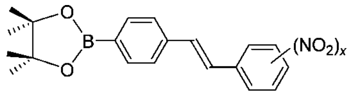
88
λ_{max} = 450 nm
(orange)

[88-F]-
λ_{max} = 563 nm
(claret)

Table 5. Shifts in λ_{max} on Fluoride Binding for Nitrated Stilbene Derivatives 89−92

compound	nitration pattern	$\Delta\lambda_{max}$ (nm)[a]
89	none	0
90	4-NO_2	30
91	2,4-$(NO_2)_2$	50
92	2,4,6-$(NO_2)_3$	61

[a] UV−vis spectra for the free receptor measured in cyclohexane solution; those for the fluoride adducts in dichloromethane.

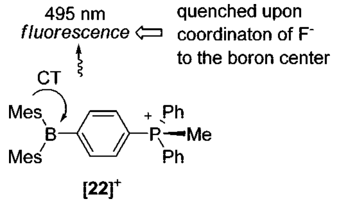


89-**92**

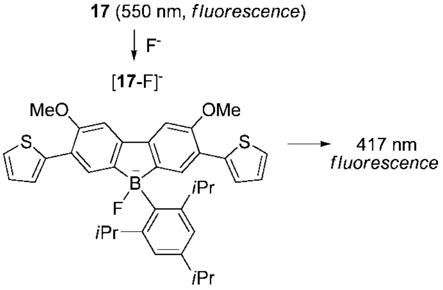
5.2. Fluorescence Response

Triarylboranes such as [*p*-**21**]$^+$ and [**22**]$^+$ are brightly fluorescent.[103,104] Theoretical calculations carried out on [*p*-**21**]$^+$ suggest that the fluorescence of these cationic boranes originates from a "ligand-to-element" CT exited state involving a mesityl-based orbital as the donor and the boron vacant p-orbital as the acceptor (Scheme 26).[103] Because fluoride coordination blocks the boron vacant p-orbital, this fluorescence is readily quenched leading to a turn-off response, which can be easily detected with the naked eye as confirmed in the case of [**22**]$^+$.[104] This type of fluorescence quenching response is quite common and has also been observed for polymer **60**.[133]

Scheme 26



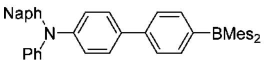
Scheme 27



While fluoride coordination to triarylboranes effectively blocks emission resulting from CT to the boron center, other emission bands, often at higher energy, may arise from the isolated chromophores. Such effects can be illustrated by the behavior of the borafluorene **17** whose emission band at 550 nm is quenched upon coordination of fluoride to the boron center, while a new intense band appears at 417 nm (Scheme 27).[101] A related effect is observed in the case of **93**.[158] As depicted in Scheme 28, an efficient energy transfer occurs between the triarylborane, which acts as an energy donor, and the porphyrin, which acts as the acceptor. As a result of this energy transfer, the derivative emits a porphyrin-based fluorescence at 692 nm. Coordination of fluoride to the boron center interrupts the energy transfer, decreasing the efficiency of this emission, while a new emission band appears at 356 nm, originating from the electronically isolated terminal diarylalkyne ligands.

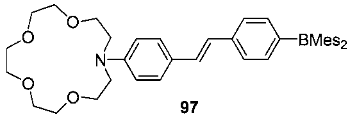
An unusual fluorescence turn-on response has been observed in the ladder type diborane **94**.[159] In the absence of fluoride, this compound fluoresces at 450 nm. Coordination of fluoride to one extremity of this molecule induces the appearance of a broad feature at 520 nm, which originates from a CT excited state involving the negatively charged triarylfluoroborate as the donor and the three-coordinate triarylborane as the acceptor (Scheme 29). A related phenomenon has been observed in polymeric fluorenylboranes such as **95**,[160] which also develop a CT excited state fluorescence at about 460 nm upon coordination of fluoride anions to half of the boron atoms.

Triarylboranes decorated by peripheral electron donor groups also often feature CT transitions in which the CT excited-state is sometimes emissive. This behavior is observed in **96**[47,132] and **97**,[161] whose CT fluorescence at 475 and 550 nm, respectively, is quenched upon coordination of fluoride to the boron center.



96

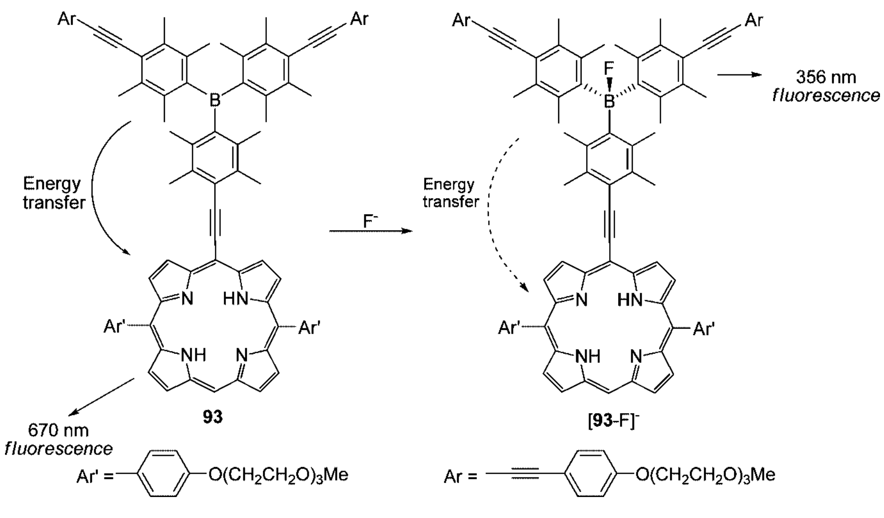
475 nm
fluorescence



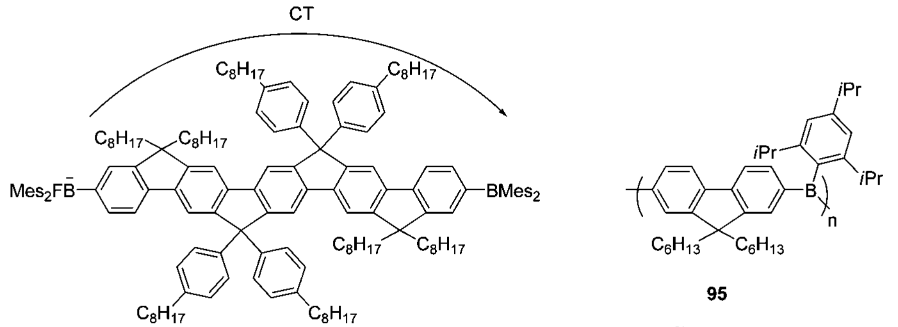
97

540 nm
fluorescence

Scheme 28



Scheme 29



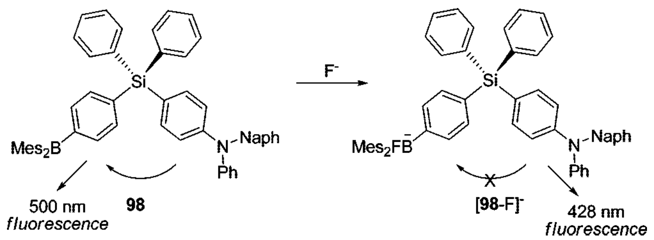
[**94**-F]$^-$

fluorescence
450 nm for **94**
520 nm for [**94**-F]$^-$

95

fluorescence
403 nm for **95**
460 nm for [**95**-0.5F]$^{-0.5}$

Scheme 30



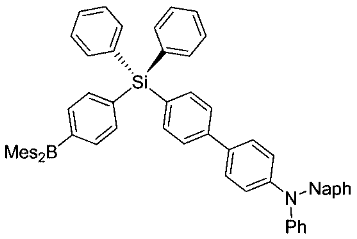
98

[**98**-F]$^-$

In some instances, this process is accompanied by a revival of the $\pi-\pi^*$ fluorescence of the isolated donor-containing chromophore, thus producing a very useful turn-on response. This is the case for **98**, in which fluoride induces a quenching of the weak emission of the CT excited state as well as the appearance of an intense $\pi-\pi^*$ fluorescence arising from the excited triarylamine chromophore (Scheme 30).[162] The simultaneous fluorescence turn-off/turn-on observed in these systems provides a ratiometric response, which can be harnessed to more accurately monitor fluoride concentrations.

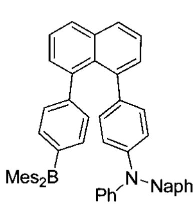
The photophysical properties of triarylboranes exhibiting CT emission appear to depend on the spatial separation between the donor and the acceptor functionalities. The emission spectrum of **98** is dominated by the CT fluorescence (λ_{em} = 500 nm) with a shoulder at λ_{em} = 428 nm, corresponding to $\pi-\pi^*$ fluorescence. However, the main emission band in **99** originates from $\pi-\pi^*$ fluorescence (λ_{em} = 432 nm) with the CT emission band (λ_{em} = 510 nm) appearing as a shoulder of lower intensity.[162] These spectral differences can be assigned to the increased separation between the amine donor and the borane acceptor groups on going from **98** to (B−N ≈ 10 Å) to **99** (B−N ≈ 14 Å). While in both cases, the addition of F$^-$ results in quenching of the CT emission band and an increase in intensity of the $\pi-\pi^*$ fluorescence band, **98** provides a more pronounced turn-on response due to the lower intensity of the $\pi-\pi^*$ emission prior to fluoride binding. Evidence for this effect is also observed in **100** and **101**.[132,162] The B−N separation in **100** and **101** was calculated to be 6.7 and 9.7 Å, respectively. In agreement with the short B−N separation, the emission spectrum of **100** shows a single band at λ_{em} = 504 nm, corresponding to CT emission, and **101** displays a similar band with a weak shoulder at λ_{em} = 450 due to $\pi-\pi^*$ fluorescence. Related properties have been displayed by several other triarylamine/triarylborane conjugates, including **102**−**105**.[128,131,159,162]

In addition to dual emission fluorescence, the amine/borane conjugates **106** and **107** have been shown to exhibit two-



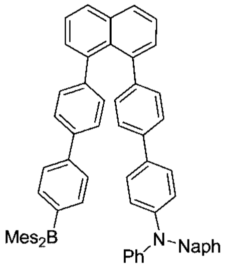
99

fluorescence
510 nm for **99**
432 nm for [**99**-F]$^-$



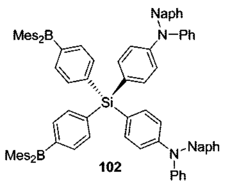
100

fluorescence
504 nm for **100**
450 nm for [**100**-F]$^-$



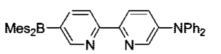
101

fluorescence
504 nm for **101**
450 nm for [**101**-F]$^-$



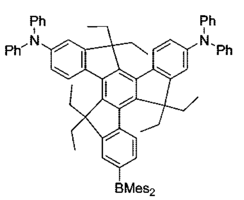
102

fluorescence
500 nm for **102**
428 nm for [**102**-F]$^-$



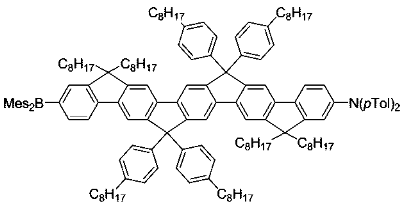
103

fluorescence
501 nm for **103**
400 nm for [**103**-F]$^-$



104

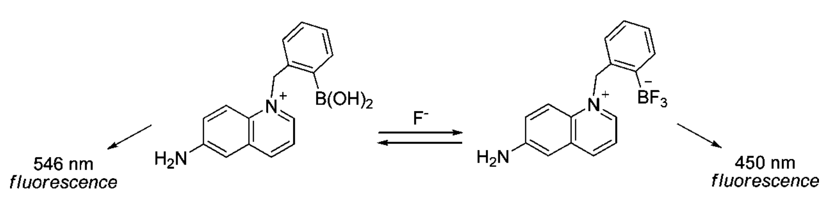
fluorescence
496 nm for **104**
380 nm for [**104**-F]$^-$



105

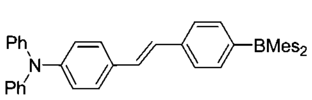
fluorescence
532 nm for **105**
450 nm for [**105**-F]$^-$

Scheme 31



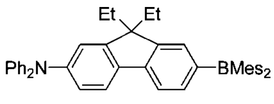
o-[**46**]$^+$

photon excited fluorescence (TPEF).[163,164] While the single-photon excited fluorescence (SPEF) spectra of these molecules all display quenching of a CT emission band and appearance of a $\pi-\pi^*$ fluorescence band upon fluoride binding, the TPEF spectra display only a single emission band, which is quenched upon addition of the anion. Improvement in the TPEF properties can also be achieved by enhancing the two-photon absorption cross-section of the chromophore. The latter tends to be elevated in symmetrical quadrupolar CT systems such as **108** and **109**, which have also been investigated.[163,165,166] Such properties may be of interest for imaging fluoride anions in biological tissues.



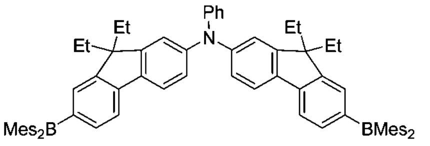
106

fluorescence
λ_{max} = 520 nm for **106**
λ_{max} = 411 nm for [**106**-F]$^-$

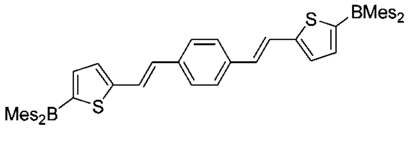


107

fluorescence
λ_{max} = 482 nm for **107**
λ_{max} = 380 nm for [**107**-F]$^-$



108



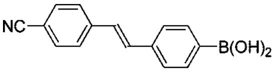
109

Lakowicz and Geddes have developed a series of water-soluble fluoride sensors based on the fluorescence response triggered on conversion of an electron-withdrawing boronic acid moiety to the corresponding electron-donating aryltrifluoroborate.[52,120,121] These systems are typically centered around a quinolinium core, a motif known previously to be effective in sensing the heavier halide ions (Cl^-, Br^-, and I^-) based on collisional quenching of fluorescence. Collisional quenching by the lighter fluoride ion, however, is typically not significant.[167-169] In the case of fluoride, the boronic acid to trifluoroborate conversion brings with it the growth in intensity of a CT emission band at 450 nm (λ_{ex} = 358 nm), with simultaneous loss of intensity of the band at 546 nm (Scheme 31). Interestingly, *o*-[**46**]$^+$ does not display the binding affinity for monosaccharides (such as glucose and fructose) typically found for boronic acids, and as such, this system is able to act as a sensor for the fluoride ion in water in the 1−300 mM concentration range *in the presence of such sugars*. Synthetic studies have indicated that the quinolinium $-NH_2$ function is key to this selectivity, with related systems featuring less strongly electron-donating substituents (e.g., H, Me, and OMe) showing enhanced affinity for sugars. The *m*- and *p*-isomers of [**46**]$^+$ have been reported to show similar behavior, with the *m*-substituted boronic ester reported to display the highest fluoride binding affinity (see section 3.4).[120] Similar ratiometric fluorescence responses to fluoride have also been reported for related imidazolium/boronic acid receptors.[116]

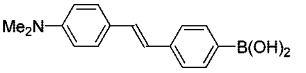
Table 6. Fluorescence Responses and Binding Constants for the Interaction of 110−115 with Fluoride

compound	λ_{ex}	λ_{em}	λ_{em} (F^-)	K_3 (M^{-3})[a]
110	326	389	420	2.9×10^3
111	347	497	455	3.0×10^2
112	373	531	488	6.6×10^3
113	438	585	570	1.2×10^4
114	449	668	654	1.5×10^4
115	347	554	490	6.6×10^3

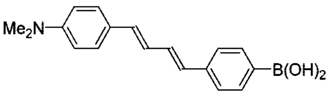
[a] In H_2O/MeOH, 2/1 volume.



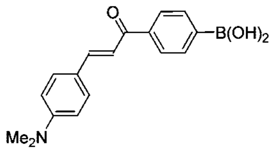
110



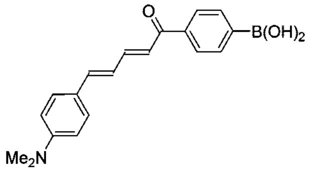
111



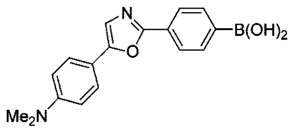
112



113



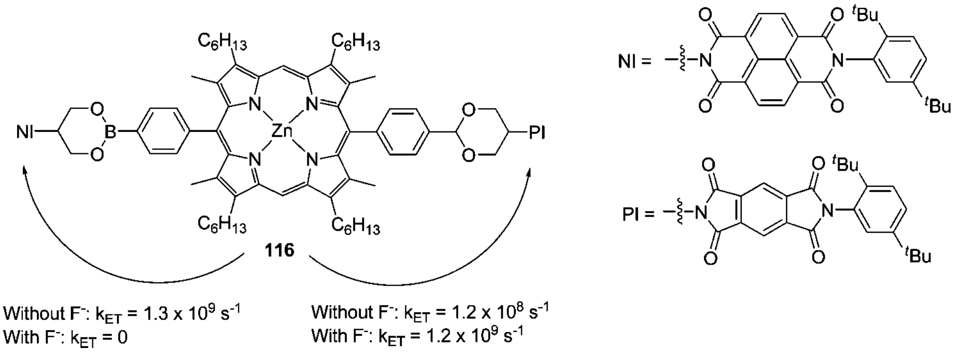
114



115

Similar principles underpin the use of the fluorophores **110**−**115** in fluoride sensing; each features an arylboronic acid receptor component linked via an unsaturated spacer to a second arene unit featuring either an electron-donating dimethylamino or an electron-withdrawing cyano group. The excited state ICT, which is responsible for the fluorescence response, is highly sensitive to the electronic properties of the system—particularly at the receptor site—being derived as it is from the presence of electron-donating and -withdrawing components at either end of the molecule.[93] Thus, if an electron-withdrawing function, such as cyanide, is present (as in **110**), a photoinduced CT state can be formed only when the boronic acid has assimilated fluoride to give an electron-donating fluoroborate function. Conversely, for systems such as **111**, bearing a pendant electron-donating

Scheme 32



amino group, the CT effect is lost on conversion of the electron-withdrawing boronic acid to the fluoroborate.

Compound **110** undergoes a red shift (by 30 nm) in the emission band on addition of fluoride (Table 6), which is interpreted as being indicative of the *switching-on* of an intramolecular CT process; the corresponding spectroscopic response of amino-substituted **111** to fluoride exposure involves a 40 nm blue shift, interpreted as being due to the removal of ICT.[170] In the case of **110**, the spectral changes are identical to those observed at high pH in the absence of fluoride, suggesting a competing binding response for hydroxide; competing responses in the presence of other halide ions are uniformly absent. Fluorescence sensing of fluoride based on ICT has also been reported recently for boronic acid/ester derivatives of 4-(*N*,*N*-dimethylamino)benzonitrile[171] and for pinacolboryl derivatives of dithienophospholes.[172]

An elegant example of the influence of fluoride binding at a boronate ester binding site on *selectivity* in electron transfer has been reported by Osuka and co-workers (Scheme 32).[173] In the system reported (**116**), a zinc porphyrin donor function is linked via a boronic ester linkage to a naphthalene-1,8:4,5-tetracarboxylic diimide (NI) acceptor and via an acetal bridge of similar length to a pyromellitic diimide (PI) acceptor. In the absence of fluoride, electron transfer to the NI function occurs more rapidly, reflecting the fact that it is the stronger of the two acceptor functions (by ca. 0.3 V). In the presence of fluoride, binding at the boronate ester to give a four-coordinate fluoroboronate not only blocks electron transfer to the NI function but also accelerates that to the alternative PI acceptor, presumably on electrostatic grounds.[173]

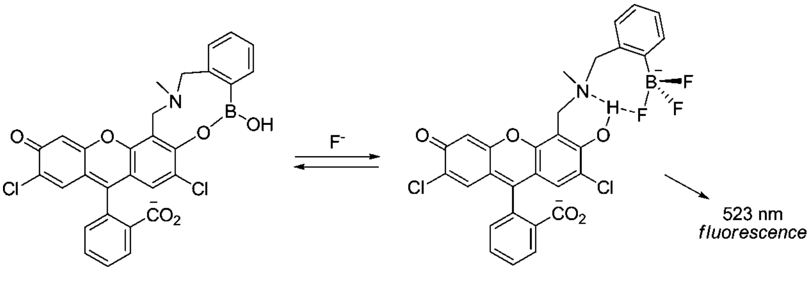
An alternative mechanism by which fluoride ion binding at a boronic acid receptor can be used to switch-on a fluorescence response has been described by Yoon and co-workers.[174] The system in question (**117**, Scheme 33) features a boronic acid binding domain linked to a fluorescein reporter. In the "free" state, fluorescence is largely quenched as a result of a photoinduced electron transfer process involving the effectively three-coordinate nitrogen atom of the benzylamine moiety.[175] On conversion of the boronic acid to a trifluoroborate, the resulting phenolic proton can hydrogen bond strongly not only to the $-BF_3^-$ unit but also to the benzylamine nitrogen, thereby blocking the PET quenching pathway and switching on fluorescence emission.

5.3. Phosphorescence Response

Because of spin−orbit coupling imparted by the presence of a heavy atom, many complexes containing elements such as iridium, platinum, and mercury are phosphorescent. Because the phosphorescence of such complexes usually arises from ligand-centered excited states, borylated examples of such complexes have emissive properties that can be modulated by the addition of fluoride. One of the earliest examples of such a complex includes **76**, in which the spin−orbit perturbation provided by the mercury atom induces a red phosphorescence of the dimesitylborylnaphthalene chromophore with $\lambda_{max} = 531$ nm.[146] Upon fluoride binding to the boron center, conjugation of the naphthalenediyl and mesityl substituents is interrupted. As a result, the naphthalene moiety of [**76**-μ_2-F]$^-$ behaves as an isolated chromophore, which emits its characteristic green phosphorescence ($\lambda_{max} = 480$ nm) (Scheme 34). A similar effect has been observed in several platinum complexes[176,177] such as **118** in which fluoride binding to the boron atom switches the dimesitylboryl-phenylpyridyl-based phosphorescence at $\lambda_{max} = 532$ nm to a phenylpyridyl-based phosphorescence at $\lambda_{max} = 489$ nm in CH_2Cl_2 under an atmosphere of nitrogen (Scheme 34).

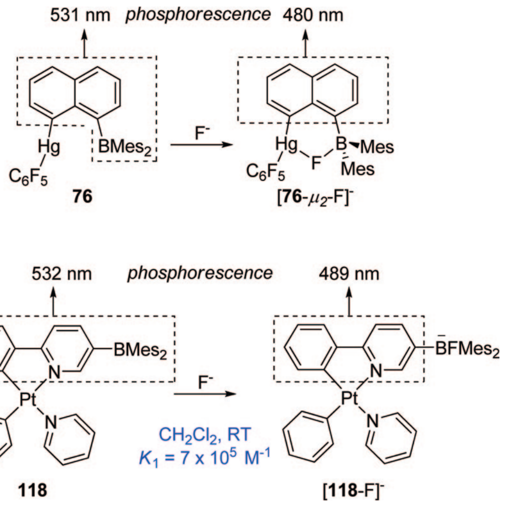
A slightly different behavior is observed for [**33**]$^+$.[110] In this case, red phosphorescence observed at $\lambda_{max} = 592$ nm and assigned to a mixed ^{3}MLCT/^{3}LLCT excited state is quenched upon titration with fluoride anions (Scheme 35). Unlike **76**,

Scheme 33

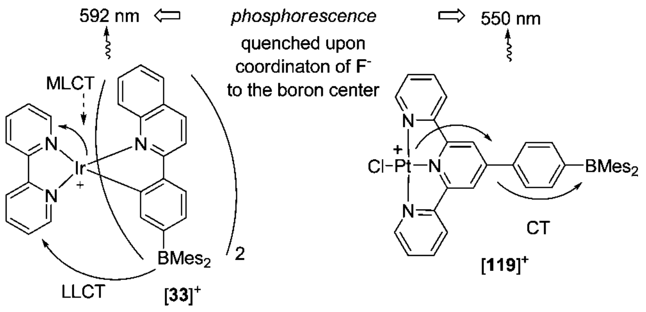


117

Scheme 34



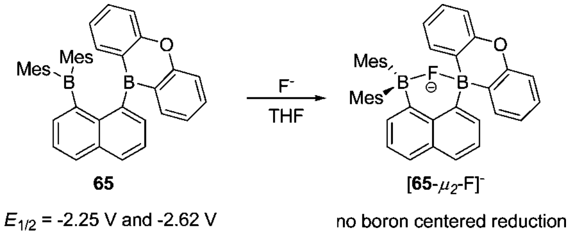
Scheme 35



there is no appearance of emission associated with the isolated chromophores. The exact origin of the response has not been firmly delineated and is assigned to "changes of the excited-state property of the complex" upon fluoride binding. A similar behavior is displayed by [**119**]$^+$ (Scheme 35).[178] In this case, the emitting triplet excited state is thought to arise from a MLCT transition that is relayed by a ligand-to-boron CT transition. The addition of fluoride to this compound leads to a complete quenching of the phosphorescence because of the population of the boron empty p-orbital.

In some instances, fluoride binding can also result in a drastic increase of the phosphorescence of platinum complexes. This is, for example, the case of **120**, whose emission spectrum displays a fluorescence emission at 399 nm originating from the triarylborane chromophore as well as a heavy atom-induced phosphorescence from the *N*-(2′-pyridyl)-7-azaindolyl (NPA) ligand at 494 nm (Scheme 36).[177] Remarkably, coordination of the fluoride to the boron atom annuls the extended triarylborane chromophore, which no longer competes for photoexcitation with the NPA chromophore. In turn, the exited-state population of the NPA chromophore is increased, leading to an increase of its triplet emission at 494 nm.

Scheme 37

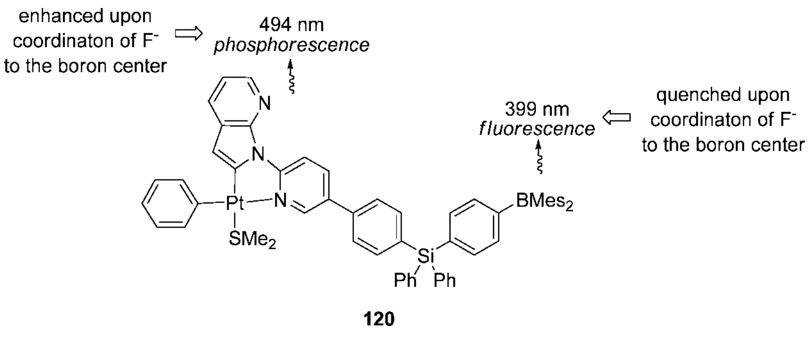


5.4. Electrochemical Response

Triarylboranes typically undergo a reversible one-electron reduction, which can be easily observed by cyclic voltammetry.[179−188] This process produces a radical anion in which the unpaired electron occupies a molecular orbital bearing a large contribution from the boron p-orbital. Because anion binding to triarylboranes induces saturation of the boron atom, this reversible reduction becomes compromised by anion coordination. This simple effect has been used to monitor anion binding to a number of triarylboron derivatives such as the diborane **65**.[59] For this diborane, incremental addition of fluoride to the electrochemical cell results in the synchronous disappearance of the two reduction waves at $E_{1/2} = -2.25$ and -2.62 V, in line with the simultaneous coordination of the fluoride ion to both boron centers (Scheme 37). A different behavior has been observed in the case of **78**, which displays two reduction waves at $E_{1/2} = -2.31$ and -2.61 V.[141] The addition of 1 equiv of fluoride results in the disappearance of the first reduction wave, indicating formation of the 1:1 complex [**78**-μ_2-F]$^-$ with fluoride bound to only one boron center (Scheme 38). Further addition of fluoride leads to a more progressive decrease of the remaining reduction wave in accordance with the negative cooperativity, affecting the two-stage anion binding of this derivative.

An alternative approach for signaling the binding of fluoride at a boron-centered Lewis acid is via the electrochemical response of a peripheral reporter group. In this regard, a number of studies have employed ferrocenyl substituents, given the widely precedented and well-understood response of the Fe(II/III) redox couple in such systems to changes in the electronic properties of pendant substituents and the ease of synthesis of borylated ferrocenes in which the Lewis acid binding site is directly linked to the ferrocenyl reporter.[189]

Scheme 36



Scheme 38

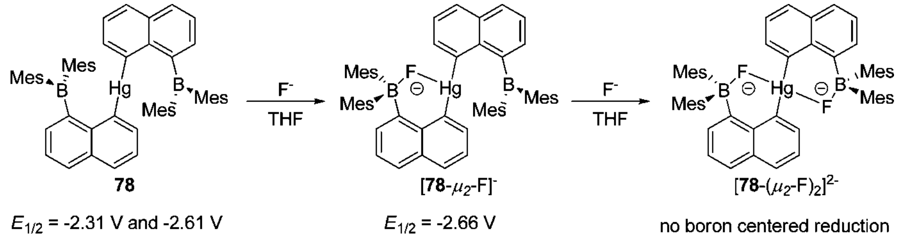
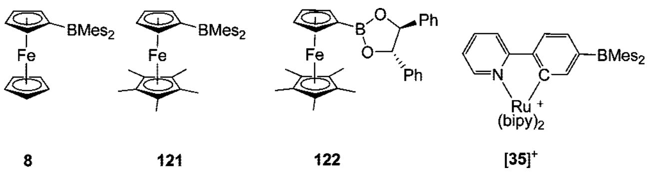


Table 7. Changes Observed in the Potential of the $Fe^{II/III}$ (8, 121, and 122) or $Ru^{II/III}$ ($[35]^+$) Couples upon Fluoride and Cyanide Binding

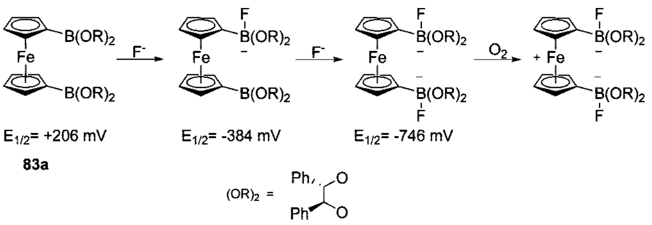


	mV			
	$E_{1/2}(Ar_3B)$	$\Delta E_{1/2}(Ar_3BF)$	$\Delta E_{1/2}(Ar_3BCN)$	solvent
8	+181	−550	−564	MeCN
121	−176	−550	−550	MeCN
122	+181	−580		CH_2Cl_2
$[\mathbf{35}]^+$	+51	−242	−198	DMF

A pioneering example of this approach was reported by Shinkai and co-workers in 1995;[77] ferroceneboronic acid was shown to bind fluoride selectively in aqueous environments (both in pure water and in H_2O/MeOH, 9:1 volume) and an electrochemical shift of −100 mV found to accompany the binding event. Conversion of the electron-withdrawing boronic acid binding site in the free receptor to the strongly electron-donating anionic fluorodihydroxyborate moiety in the adduct is responsible for the observed cathodic shift. In subsequent work, Shinkai showed that by coupling this electrochemical response with an appropriate redox active dye (in this case methylene blue), the complexation event could be detected visually.[190] Such an assay relies on redox matching between the ferrocene and the dye components, such that $[FcB(OH)_2F]^-$ is capable of reducing the dye molecule, while $FcB(OH)_2$ is not.

More recent investigations in this area utilizing ferrocenyldimesitylborane (**8**) reveal substantially larger binding-induced electrochemical shifts in nonaqueous media.[80] Compound **8** is competent for the binding of both fluoride and cyanide, with association constants K of 7.8 (1.2) × 10^4 and 8.3(2.0) × 10^4 M^{-1}, respectively, having been determined by UV−vis titration in dichloromethane solution. With regard to its electrochemistry, **8** is oxidized at a potential of +181 (80) mV with respect to ferrocene/ferrocenium; upon fluoride binding, a shift of approximately −550 mV occurs, consistent with conversion of the pendant three-coordinate Lewis acid to an anionic four-coordinate borate (Table 7). A similar shift of −564 mV from +181 (80) to −383 (100) mV is seen in the presence of cyanide. Such shifts are not without precedent in the Lewis acid/base chemistry of ferrocenylboranes, with a similar shift being reported by Piers for the coordination of trimethylphosphine to $FcB(C_6F_5)_2$.[191] A related behavior has been observed for the $Ru^{II/III}$ redox couple of $[\mathbf{35}]^+$ ($E_{1/2}$ = +0.051 V vs Fc/Fc^+), which undergoes a cathodic shift upon F^- ($\Delta E_{1/2}$ = −0.242 V vs Fc/Fc^+) or CN^- ($\Delta E_{1/2}$ = −0.198 V vs Fc/Fc^+) binding (Table 7).[111]

Scheme 39

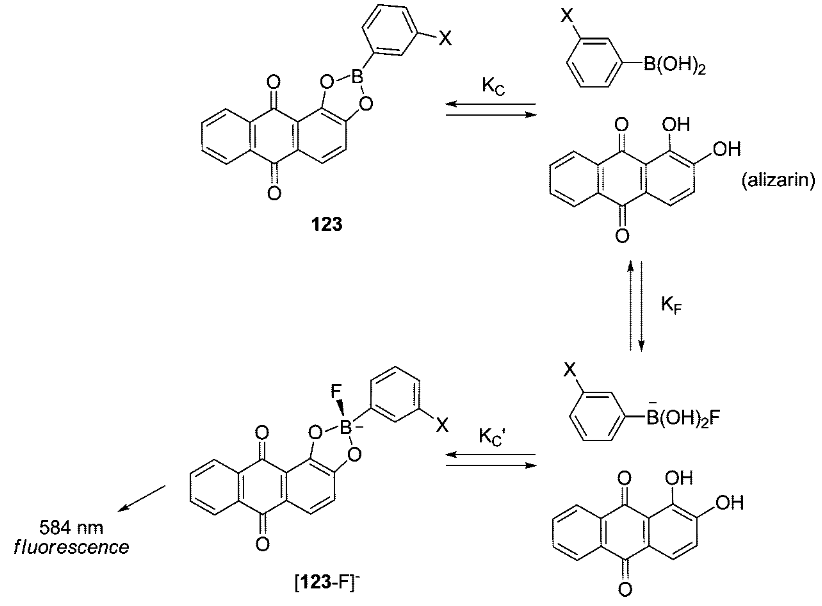


In theory, **8** might be partnered with a suitable redox-active dye to produce a colorimetric system, indicating the presence of fluoride or cyanide. In practice, the related pentamethylcyclopentadienyl derivative **121** undergoes oxidation at potentials more convenient for partnering with dyes such as terazolium violet. Electrochemical studies of **121** reveal an $E_{1/2}$ value of −176 (75) mV for the free receptor and anion-induced shifts of ca. −550 mV on binding of either fluoride or cyanide (Table 7).[80] The difference in the absolute values of these potentials with respect to **8** ($\Delta E_{1/2} \approx -350$ mV) reflects the electron-donating nature of the five methyl groups of the Cp* ring.

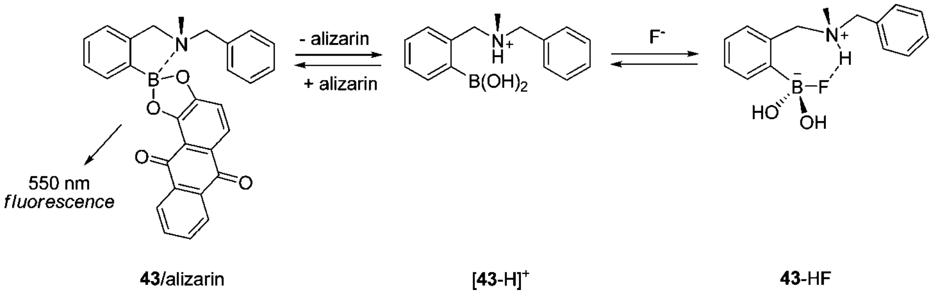
The electrochemical shifts revealed for **121** on anion binding occur in a convenient window for partnering with the redox-active dye, tetrazolium violet, and hence, in conjunction with the reporter response of this system, the presence of fluoride or cyanide can be signaled colorimetrically in acetonitrile/methanol solution (>100/1 vol).[191] Moreover, the tetrazolium dye undergoes an irreversible color change under such conditions, and this together with the large extinction coefficient of the chromophore means that dosimetry can be envisaged on 25−40 nmol of analyte. Although receptor **121** binds both fluoride *and* cyanide, the weaker Lewis acidic receptor **122** binds only fluoride under analogous conditions and hence allows for the construction of a two-component system, which will discriminate between fluoride and cyanide. Thus, in combination with the same tetrazolium dye, dimesitylboryl system **121** gives positive colorimetric responses for both fluoride and cyanide, while boronic ester **122** senses fluoride but not cyanide; discrimination between the two anions is thus achieved by Boolean AND/NOT logic.

Given the magnitudes of the electrochemical shifts brought about at ferrocene reporter units on fluoride binding in non-aqueous media, in favorable cases, the simple oxidation of the Fe(II) center by atmospheric dioxygen can be envisaged.[192] While the magnitude of the fluoride-induced redox shift for monofunctional boronic ester derivatives such as **122** (ca. −580 mV in dichloromethane, Table 7) is not sufficient to render the corresponding monofluoride adduct capable of reducing O_2, the incorporation of further binding sites offers the possibility for greater binding-induced redox shifts.[74,78,81] Investigation of the redox properties of the bis-, tris-, and tetrakis-boronic esters **83a**, **84a**, and **85a** reveals an anodic shift of ca. 100 mV per boronic ester function for the free receptors, consistent with the π-electron-withdrawing nature of the boronic ester groups (Scheme 39). Upon addition of fluoride to **83a**, **84a**, and **85a**, however, all three systems undergo irreversible orange to green color changes, consistent

Scheme 40



Scheme 41



with aerobic oxidation of the ferrocene moiety. In the case of **83a**, the addition of excess fluoride reveals two oxidation events at -384 and -746 mV by cyclic voltammetry (cf. $+206$ mV for the free receptor), the second of which is assigned to the oxidation of the bis(fluoride) adduct (Scheme 39). In fact, in the cases of each of **83a**, **84a**, and **85a**, the binding of 2 equiv of fluoride in dichloromethane solution can be shown to induce sufficiently large redox shifts so as to render the bis(fluoride) adduct amenable to oxidation by O_2.

The use of metal complexes of terpyridine ligands bearing peripheral boronic ester substituents in the sensing of fluoride has been outlined above (e.g., [**38**]$^{n+}$, section 3.4). Cyclic voltammetry experiments carried out on this system in H_2O/MeOH (1/1 volume) reveal a cathodic shift of ca. 160 mV in the Fe(II/III) redox couple in the presence of fluoride, as compared to 20 mV in the presence of chloride and essentially zero for Br^-, NO_3^-, and SO_4^{2-}.[112] UV−vis studies are consistent with the formation of both 1:1 and 2:1 fluoride adducts. The immobilization of such complexes by electropolymerization has also been investigated with the aim of developing ion-selective electrodes.[193]

5.5. Displacement Assays and Sensing Ensembles

A number of multicomponent sensing systems have been developed for fluoride in protic media that make use of a switching-on or switching-off of an alizarin-derived fluorescence response.[115,194,195] A "turn-on" fluorescence-based sensor system has been reported, which makes use of the fact that the equilibrium constant (K_C) for the boronic ester condensation reaction between alizarin and an arylboronic acid (in this case either phenyl or 3-nitrophenylboronic acid) in methanol is minimal. However, in the presence of fluoride (Scheme 40), the resulting tetrahedral fluoroboronate, $[ArB(OH)_2F]^-$, is formed, which binds the alizarin-based diol unit with an equilibrium constant (K_C') of 4.8 ($\pm$0.15) $\times$ 10^3 M^{-1}. Thus, in the presence of fluoride, anion-induced association is brought about between the arylboronic acid and the alizarin components to give [**123**-F]$^-$. This condensation reaction results in a switching-on of a fluorescence response ($\lambda_{em} = 586$ nm) due to the alizarin component, which is otherwise efficiently quenched.[194,195] Interestingly, a competing fluorescence response is found with acetate, for which the corresponding equilibrium constant for anion-induced boronic ester condensation is found to be 17 ($\pm$0.7) $\times$ 10^3 M^{-1}.

Displacement assays, typically relying on the release into solution of a reporter "tag" on anion binding, have also been employed in the sensing of fluoride. A highly fluoride-specific example of such a system has also been reported by Kubo and James, involving a complementary approach to that outlined above, that is, release of the alizarin unit into solution and consequent fluorescence quenching. The system in question makes use of the fact that the equilibrium between the [**43**-H]$^+$ and the **43**/alizarin complex at pH 5.5 is displaced on addition of fluoride due to preferential binding of fluoride to [**43**-H]$^{+}$ (Scheme 41 and section 3.4). “Free” alizarin in solution has no fluorescence over the pH range of the experiment and, so, because of the **43**/alizarin complex (λ_{em} = 550 nm), is quenched on fluoride-driven alizarin displacement.[115]

6. Summary/Outlook

The strength of the B−F bond formed between a three-coordinate borane and the fluoride anion makes the use of such systems in sensing a potentially attractive alternative to more widely used hydrogen bond-based receptors, especially in highly competitive protic media. Thus, potential applications of borane-derived sensors, for example, for monitoring fluoride in drinking water or in the detection of fluorinated chemical warfare agents (such as Sarin), can be envisaged. In addition, such strength of binding also flags up the use of aryltrifluoroborates for in vivo PET imaging as a significant potential application.[69,196] Recent work has indeed established that borane systems are capable of sequestering fluoride from water and, in optimal cases, of actually binding fluoride in aqueous media.

With sensor applications in mind, issues of recognition and reporting have been addressed in recent research efforts. *Selectivity* of anion recognition by boranes typically relies on the steric bulk of pendant substituents to subvert binding of larger anions at triarylboranes or on simple thermodynamics (i.e., the strength of the B−F bond formed) for more weakly Lewis acidic boronic acid/ester-based systems. That said, save for a number of exceptional cases that have recently been reported, competitive binding is often found for hydroxide and/or cyanide ions—the former dictating the pH range in which sensing for fluoride can effectively be carried out. In terms of sensor response, the conversion of an electron-deficient three-coordinate boron center to a highly electron-rich fluoroborate provides the fundamental change in electronic structure upon which most reporter responses are based—be they CT fluorescence, electrochemical, or colorimetric.

The competing responses often observed for cyanide and the similar basicities of F^{-} and CN^{-} in nonaqueous media[197] mean that many of the recognition/reporter principles developed for fluoride may well be amenable to the design of workable systems for cyanide detection. That said, it is conceivable that such receptors will require further developments in synthetic methodology to allow for the placement of Lewis acid functions around a preorganized cavity and hence the sort of size/shape-based anion selectivity that is currently the preserve of hydrogen bond-based systems.

7. Acknowledgments

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8. Note Added in Proof

After submission of this review, the group of Bourissou has reported that the low temperature reaction (−60 °C) of collidine-(HF)$_{1.7}$ with [*o*-*i*Pr$_2$P(C$_6$H$_4$)BMes$_2$] affords the corresponding zwitterionic adduct [*o*-*i*Pr$_2$HP(C$_6$H$_4$)BFMes$_2$] which has been characterized spectroscopically (Moebs-Sanchez, S.; Saffon, N.; Bouhadir, G.; Maron, L.; Bourissou, D. *Dalton Trans.* **2010**, *39*, 4417−4420). This adduct is not stable and produces, upon warming, the starting phosphinoborane and [*o*-*i*Pr$_2$HP(C$_6$H$_4$)BF$_3$].

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