^{11}B NMR Together with IR Spectroscopy Provides Insight into Structural Elucidation of Quadrivalent Diazaborines & Cyclic Boronate Esters: The Chemist's Perspective

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Abstract

Imidazo-fused diazaborines which serve as intermediary structures somewhat along benzene and borazine had been of particular interest to Dewar and Snyder more than 60 years ago. To this end, Dewar utilised his '*π-complex theory*' so as to represent '*borazaros*' as '*quadrivalent*' species; however, sadly modern representations have deviated and leapt into '*trivalent*' counterparts. Inasmuch as bonding in boron species has never been straightforward to such an extent that the orthodox '*ethane*' like diborane *i.e.* $H_3B–BH_3$ which conferred to the paradigmatic rules of molecular structure, in particular, hybridisation and electronegativity was later evolved to a more realistic '*3-centre 2-electron*' bonding, so as to give the lie to the purported diborane structures of X-ray diffractors, herein ^{11}B NMR together with IR spectroscopy sheds light on the nature of bonding in borazaros and '*caged*' cyclic oxazaborons so as to reenforce and reinvigorate the old literature which could be of interests to the synthetic and medicinal chemist alike.

Keywords

^{11}B NMR, IR spectroscopy, borazaros, oxazaboron derivatives, *in crystallo*, caged cyclic boronate esters, 2-formylphenylboronic acid (2-FPBA), heterocycles, synthetic and medicinal chemistry.

Introduction

Unlike ^{1}H and ^{13}C with a '*nuclear spin*' $I = ½$, both naturally occurring isotopes of boron *i.e.* ^{10}B ($I = 3$) and ^{11}B ($I = 5/2$) are NMR active; however, the latter is more versatile than the erstwhile for NMR investigations by virtue of the fact that ^{10}B has a natural abundance of only 19.6%, whereas ^{11}B exhibits a natural abundance of 80.4%,[1] as such ^{10}B comes with a much lower receptivity *i.e.* receiver gain, and quadrupole moment almost thrice as much as that for ^{11}B, which broadens ^{10}B NMR signals. Moreover, the Larmor frequency of ^{10}B is almost three times lower than that for ^{11}B, resulting in a much lower signal resolution and coupling constants *i.e.* J (in Hz) in ^{10}B NMR spectra.[2] Despite these drawbacks ^{10}B NMR can be particularly useful in niche mechanistic studies such as rearrangements.[3]

NMR spectroscopy much to contemporary efforts has proved exceptionally advantageous in elucidating structures of boron compounds, and their behaviour in solutions.[4,5] The extrapolation of NMR activities of other common NMR active nuclei such as ^{1}H, ^{13}C, ^{15}N, ^{31}P *etc.*, to ^{11}B NMR suggests that the following factors should determine chemical shifts (δ) in ^{11}B NMR spectra:

- Electron density
- Coordination number
- Hybridisation
- Ring current

However, the above is found not to be true for many ^{11}B NMR spectra. For example, the signals from B^1 and B^2 in the ^{11}B NMR spectrum of *n*-B_9H_{15} are ~ 64.7 ppm apart, such that B^2 resonates at the highest field and B^1 at the lowest field in the aforementioned ^{11}B NMR spectrum,[6] in spite of both B^1 and B^2 in *n*-B_9H_{15} exhibiting identical connectivity, hybridisation and even immediate bonding environment (Fig. 1).

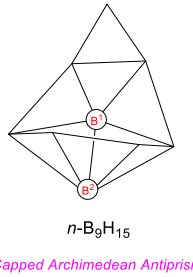


Figure 1. Despite having identical coordination and chemical environment the signals from B^1 & B^2 are the furthest apart from each other in B^{11} NMR spectrum of n-B_9H_{15}. Both B^1 & B^2 are connected to five other boron atoms and one proton in the capped Archimedean antiprism n-B_9H_{15}; *nota bene*: for simplicity protons are omitted from the borane cluster.

On the other hand, in stark contrast to other NMR active nuclei, electron density does not appear to preponderate over other factors in determining the position of chemical shifts in ^{11}B NMR spectra, as the boron atoms of higher electron density in $B_7H_7^{2-}$ are less shielded than their counterparts of lower electron density in the same cluster.[7] To this end, there are no hard and fast rules as yet to fully predict or explain some of the anomalies that have been observed for ^{11}B NMR spectra, and each and every single boron compound can give rise to distinctive and unexpected ^{11}B NMR spectra, which have been observed for the novel boronate esters herein, and forms the basis of the discussions below.

Results and Discussion

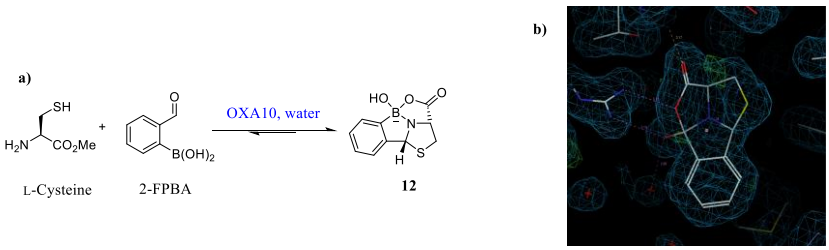
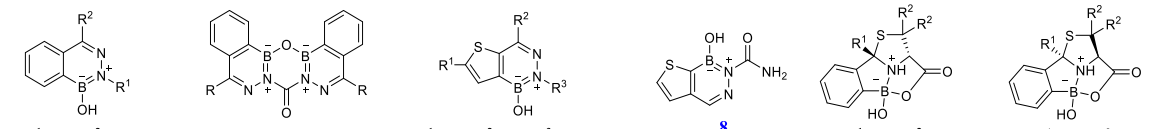


Figure 2. a) *in crystallo* Dynamic combinatorial chemistry of L-cysteine methyl ester with 2-FPBA on the surface of OXA-10; b) X-ray crystal structure of the boronate ester 12 on OXA-10 (courtesy of Dr Jürgen Brem).

Recent protein-directed dynamic combinatorial chemistry studies of L-cysteine derivatives with 2-formylphenylboronic acid (2-FPBA) on the surface *i.e. in crystallo* of oxacillinases *e.g.* OXA-10 brought home to us an intriguing quadrivalent cyclic boronate ester *i.e.* **12** (unpublished) (Fig. 2), given that the same observed '*tetracyclic caged*' structure for **12** has been reported in solution elsewhere,[8] it is conceivable that based on the observed spectroscopic and X-ray crystallographic data, boronate esters **11** & **13**–**18** (Fig. 3) should also follow suit.



3: R^1 = H, R^2 = H
1: R^1 = $CONH_2$, R^2 = H
2: R^1 = $CONH_2$, R^2 = Me
9: R^1 = $CSNH_2$, R^2 = H
10: R^1 = $CSNH_2$, R^2 = Me

4: R = H
5: R = Me

6: R^1 = H, R^2 = H, R^3 = $CONH_2$
7: R^1 = H, R^2 = Me, R^3 = $CONH_2$
21: R^1 = Me, R^2 = H, R^3 = H
23: R^1 = Me, R^2 = H, R^3 = $SO_2(CH_2)_2CH_3$

8

11: R^1 = H, R^2 = H
14: R^1 = H, R^2 = Me
15: R^1 = Me, R^2 = H
17: R^1 = Me, R^2 = Me

12: R^1 = H, R^2 = H
13: R^1 = H, R^2 = Me
16: R^1 = Me, R^2 = H
18: R^1 = Me, R^2 = Me

Figure 3. Benzodiazaborines, diazaborines & boronate esters.

Inasmuch as, both the diazaborines and boronate esters herein presumably, almost certainly feature '*quadrivalent*' boron species, a comparison of chemical shifts (*vide infra)* in ^{11}B NMR spectra of the thus obtained diazaborines and boronate esters (Fig. 3) not only provides structural insight into these intriguing scaffolds, but also paves the way for a better understanding of bonding in such boron species, and salient factors in their ^{11}B NMR resonance frequencies.

Reference has already been made to the unpredictability and irregularity of trends in ^{11}B NMR resonance frequencies (*vide supra*); however, typically, though it need not of necessity, the vacant $2p_z$ orbital of boron plays a crucial role in the position of chemical shifts in ^{11}B NMR spectra. Strictly speaking, trivalent boron species resonate at much lower fields than their quadrivalent counterparts. For instance, trimethyl borane as a true trivalent boron species resonates at the lowest field, whereas trimethyl borate as a somewhat quadrivalent boron species with considerable π-bonding character resonates at much higher fields in ^{11}B NMR. The belief that the determinant factor in the position of chemical shifts in ^{11}B NMR spectra is the π-donating ability of substituents on boron, implies that diethylamino substituents on boron should bring about upfield shifts for the ^{11}B signals in their NMR spectra, relative to that from –OMe by virtue of the fact that –NEt_2 is mesmerically more π-donating than –OMe. However, this effect appears to be reversed in aliphatic boron species, as such $B(NEt_2)_3$ resonates at a much lower field in ^{11}B NMR than that observed for $B(OMe)_3$.[9]

The chemical shift $\delta_R{}^C$ (in ppm) between a compound C and reference R is given by the following equation:

$$\text{Eq. I} \qquad \delta_R{}^C = 10^6\,(H_C - H_R)\,/\,H_R \approx 10^6(\sigma_C - \sigma_R)$$

Where H_C and H_R are the resonance frequencies of the applied magnetic field for compounds C and R, respectively, and σ_C and σ_R are the resulting shielding tensors. Ramsey[10,11] devised an expression for calculating the NMR shielding tensor σ, as such for most solution NMR applications the shielding tensor σ can be replaced by a scalar quantity σ to give the following equation:

$$\text{Eq. II} \qquad \sigma = \frac{e^2}{2mc^2}\langle 0|\sum_j (x_j^2 + y_j^2)/r_j^3|0)\rangle$$

Neglecting the deferential overlaps of the above expression can lead to the following simplified expression for the chemical shift δ_i of the nucleus of atom *i*:[12]

$$\text{Eq. III} \qquad \delta_i = Aq_i + \sum_{j\neq i} Bq_j/r_{ij}^3$$

Where q_i is the π-electron density of atom *i*, r_{ij} is the internuclear distance between atom *i* and *j*, and *A* and *B* are constants. To this end, another salient factor other than the π-donating capabilities of the substituents attached to boron in ^{11}B NMR, would be the '*electronic cloud*' of the substituents attached to boron *i.e.* the availability of lone pairs above and below of the plane of the π-bond.[12] As exemplified by the last equation above (Eq. III), atoms *j* with lone pairs orthogonal to the plane of the covalent bond would have a significant impact on the chemical shift by virtue of a large q_j and small r_{ij} (Table 1).

Table 1. ^{1}H, ^{13}C, ^{11}B and IR Data for 2-FPBA, Diazaborines & Boronate Esters

Entry	^{11}B[§]	C*HO*/*γ*-C*H*/*δ*-C*H*[¥]	*C*HO/*γ*-C/*δ*-C[¶]	IR: C=O[†]
2-FPBA	29.9	10.05	197.0	
1	29.8	8.08	142.7	1673s
2	29.8		146.9	1687s
3	27.7	7.96	140.4	
4	16.2[‡]	8.35[‡]	175.5[‡]	1682s
5	28.3			1683s
6	28.6	8.20	140.0	1698s
7	28.4		142.4	1699s
8	28.8	8.15	145.0	1700s
9	29.9	8.13	144.0	
10	30.0		147.6	
11[*]	11.4	6.16	65.6	1730s
13[*]	11.3	6.25	71.2	1713s
15[*]	11.1		66.8	1715s
17[*]	11.5		76.2	1723s

[*]; Boronate esters **11**, **13**, **15** and **17** are enantiomers of **12**, **14**, **16** and **18**, respectively, with identical spectroscopic data. [§]; 193 MHz, acetonitrile-d_3. [¥]; 600 MHz, acetonitrile-d_3. [¶]; 151 MHz, acetonitrile-d_3. [‡]; benzodiazaborine **4** is much less soluble in acetonitrile-d_3, its NMR spectra were recorded in methanol-d_4 instead. [†]; ν_{max}/cm^{-1} (ATR), s stands for sharp.

Analysis of the ^{1}H, ^{13}C and ^{11}B NMR data above (Table 1), on looking more closely, reveals that whilst the boron in 2-FPBA has a much greater trivalent character, less shielded and non-aromatic relative to that of quadrivalent diazaborines which should be more shielded, they all absorb at about the same field in their ^{11}B NMR; on the other hand, the proton of the formyl group in 2-FPBA, resonates at a much lower field than that from *γ*-C*H* of the benzofused-imadazo ring in their ^{1}H NMR by virtue of greater shielding that the *γ*-C*H* moieties of benzofused-imadazo rings experience, which is in marked contrast to that observed for ^{11}B NMR. The same is also true for ^{13}C NMR data, the *γ*-*C*H and *γ*-*C*Me of the imidazo rings are significantly upshifted compared to the non-ring carbon of the formyl group in 2-FPBA (Table 1). Intriguingly, the solvation effects of methanol-d_4 on benzodiazaborine **4** (*vide infra*) relative to that of acetonitrile-d_3 for its closely related benzodiazaborine **5** has clearly been echoed by both the upshifted and downshifted signals from boron and *γ*-*C*H of benzodiazaborine **4** in its ^{11}B and ^{13}C NMR spectra, respectively. The ^{11}B chemical shifts from the boronate esters, in comparison with those from the diazaborines, exhibit a whopping three-fold upfield shift in their spectra, in spite of the fact that both species are quadrivalent, and potentially negatively charged.

Whilst the aromaticity of diazaborines can play a crucial role in the observed data, as illustrated above (Eq. III) the electronic cloud of heteroatoms with available lone pairs adjacent to the boron centre in question can account for the aforementioned large upfield shift of almost 20 ppm in their ^{11}B NMR spectra (Fig. 4).

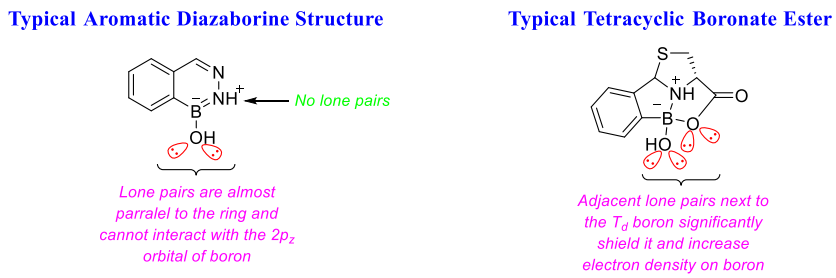


Figure 4. The accessible electronic cloud of the oxygens on boron can account for the upfield shift in ^{11}B NMR of the '*tetracyclic caged*' boronate esters.

In view of the above, it is conceivable that the boronate esters are tetracyclic and '*ring-closed*', as if they were '*ring-open*' and tricyclic, the thus C_{3h} boron species, would be less shielded, and would absorb at about the expected field in ^{11}B NMR, just like that of 2-FPBA with similar chemical environment and shielding effects (Fig. 5).

Figure 5. Both ^{11}B centres *i.e.* D_{3h} in 2-FPBA, and that *i.e.* C_{3h} in the '*ring-open*' boronate esters should resonate with similar frequencies in ^{11}B NMR by virtue of similar bonding and shielding effects; however, the boron signal is upshifted in ^{11}B NMR spectra of '*ring-closed*' boronate esters (Table 1).

The effects of electronic cloud of adjacent substituents on boron (Fig. 4) is further evident from the upshifted signal of the boron in benzodiazaborine **4** in its ^{11}B NMR spectrum in methanol-d_4 *i.e.* δ_B 16.2 (Fig. 6), relative to that obtained in acetonitrile-d_3 for benzodiazaborine **5** *i.e.* δ_B 28.3 (Table 1).

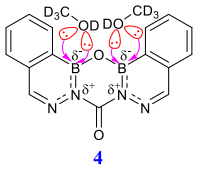


Figure 6. No matter what the hybridisation of boron, the solvation effect of methanol-d_4 is sufficient to significantly shield the boron centres in benzodiazaborine 4.

Further support for the assertion that the aforementioned boronate esters (Fig. 3) are '*ring-closed*' and tetracyclic is provided by the upfield shift of their *δ-C*H and *δ-C*Me signals in ^{13}C NMR, relative to that observed for the *C*=O of their precursors *i.e.* 2-FPBA and 2-acetylphenylboronic acid (2-APBA), which suggests that the D_{3h} carbon of the formyl or acyl moieties, is now a T_d centre, bonded to four substituents, and fully saturated. This arrangement brings the carboxyl moiety in the '*ring-open*' structure in close proximity to the boronic acid so as to further cyclise, close the ring and form a '*tetracyclic caged*' structure. This is in agreement with the observed IR frequencies *i.e.* ~ 1730–1710 cm^{-1} expected for esters (Table 1), as the parent carboxyl moieties should resonate at lower frequencies *i.e.* ~ 1600–1550 cm^{-1}.

Conclusion

Gao and coworkers[8] have reported that on reacting 2-FPBA and 2-APBA with L-cysteine in 0.10 M phosphate-buffered saline (PBS) buffer at physiological pH, bicyclic or tricyclic heterocycles form, which led to the survey of an array of borazaros and oxazaborons described herein (Fig. 3); however, in this work such reactions exclusively furnished tetracyclic and heteroaromatic structures. Whilst almost all the diazaborines as well as boronate ester **12** described in this work have, one way or another, been reported in the literature, by all means, this work is a first-of-its-kind to delineate a '*tetracyclic caged*' structure for novel boronate esters **11** & **13**–**18**, and report full chemical characterisation *i.e.* mp, optical rotation, IR, NMR (^{1}H, ^{13}C & ^{11}B), LC-MS and HRMS of the aforementioned benzodiazaborines, diazaborines and novel boronate esters *cf.* ESI S4–S21 & S24–S26† for which so far as this work is concerned there are no known precedents, and the specific applications, and of the broad implications of these intriguing heterocycles may, hopefully, be of interests to the synthetic and medicinal chemist alike.

Conflicts of Interest

The author declares no conflicts of any kind.

Acknowledgements

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