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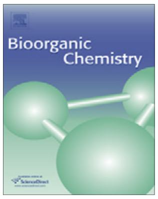

The aromaticity of 5,6-dihydroborauracil, borauracil and benzoborauracil systems

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ABSTRACT

The nucleus-independent chemical shift (NICS) indices of aromaticity, calculated for four boron compounds, 4-hydroxy-5,6-dihydroborauracil, 4-hydroxyborauracil, borazine and 4-hydroxybenzoborauracil, and parent uracil, were analyzed in parallel with the NMR properties, in order to learn more about the aromaticity of those heterocyclic systems. The existence of a unique solvent-dependent aromaticity of 4-hydroxyborauracil is indicated.

1. Introduction

Only a few boron analogues of nucleic acid bases are known, including benzoborauracils and recently presented 5,6-dihydroborauracils, 5,6-dihydrothymines and borauracils [1–4]. Of note is that boron analogues of uracil, thymine or cytosine may be considered unique and important building blocks in search for new inhibitors of enzymes involved in nucleotide metabolism, especially as biologically active boron compounds are capable of enzyme inhibition promoting due to their unique capacity to form, following the nucleophilic attack of an enzyme on the boron atom, highly stable tetrahedral sp^3 hybridized boron “ate” complexes [5–7]. Besides, boron-containing compounds may be considered candidates for application in boron-neutron capture therapy (BNCT), taking advantage of nuclear reaction of ^{10}B isotope [8].

In view of the uracil heterocycle being aromatic, of interest was whether its boron analogues (Fig. 1) would share this property. In order to learn that, we attempted to compare aromatic properties of recently synthesized 4-hydroxy-5,6-dihydroborauracil (**1**) [2,3] and 4-hydroxyborauracil (**2**) [4], as well as borazine(borazol; **3**) and 4-hydroxybenzoborauracil (**4**) [1], with those of uracil (**5**), by following NMR properties and calculating the aromaticity indices (nucleus-independent chemical shift, NICS) [9,10], allowing quantitative estimation of aromaticity.

2. Results and discussion

2.1. Aromaticity of boron compounds

Trigonal boron in the ground state has three electrons available for bonding, with two electrons being formally at 2s, and one at 2p, orbital. Consequently, the trivalent boron compounds are electron-deficient, having only six electrons in the boron nucleus closest electronic surrounding. As a result, trivalent boron compounds are usually very reactive toward nucleophilic reagents (neutral or anionic) that donate an electron pair to each boron atom, thus forming a stable, eight-electron system. The electron pair donation may be a result of coordination of various compounds, e.g. amines, alcohols, water, thiols or carboxylate anions. Boron with eight electrons can also be found in trigonal compounds, with electron octet formed by back-coordination of oxygen, nitrogen or halogen lone pairs. Tetrahedral, compared to trigonal, boron compounds are chemically much more stable. However, although compounds containing eight-electron boron systems are also much less sensitive to autoxidation, due to increased ionic character, they undergo solvolysis reactions easier.

Similar to carbocation, trigonal six-electron boron has a vacant 2p orbital, and therefore should participate in electronic conjugations, processes that may have a significant impact on the stability of boron compounds. Moreover, cyclic boron compounds that meet Hückel’s rule could have aromatic properties. Several seven-membered boron ring compounds are known to have aromatic properties similar to those of tropylium cation – tricyclic dibenzo [b,f]borepins (Fig. 2a) and their derivatives described by Van Tamelen et al. [11].

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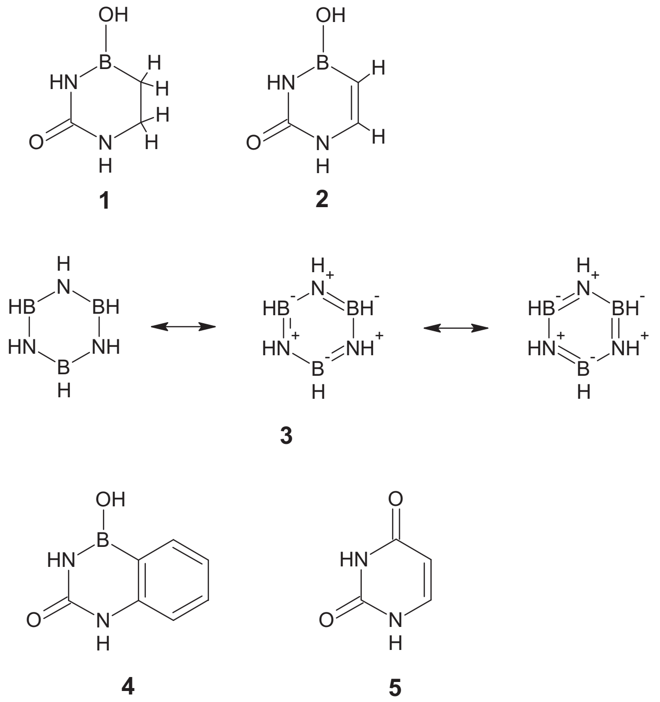

Fig. 1. Analyzed compounds **1**–**5**. For the sake of clarity, the heterocyclic ring of 4 will be referred to as LR (left ring), and the benzene moiety as RR (right ring).

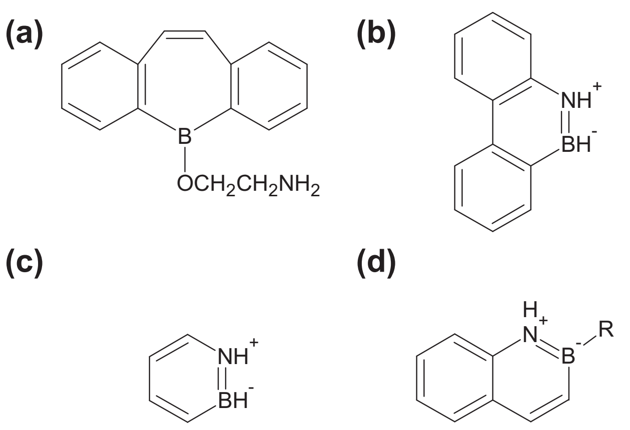

Fig. 2. Molecular structures of 5-hydroxy-5H-dibenzo[b,f]borepin ethanolamine complex (a), 10,9-borazarophenantrene (b), 2,1-borazarene (c) and 2,1-borazaronaphtalene (d).

Considering six-membered ring systems containing boron atom(s), the most commonly known is the borazine **3**, an unstable and highly reactive towards oxygen and protic solvents compound. Another heterocyclic boron compounds – tricyclic derivatives of 10,9-borazarophenantrene (Fig. 2b) [12] that belongs to the 2,1-borazarene group (Fig. 2c) [13] are more stable compounds having aromatic properties. Monocyclic compounds of this type haven't been prepared to date, and various known tricyclic dibenzoboroxins show very weak aromatic properties [12,14–16]. Another group of compounds containing six-membered boron rings that meets Hückel's rule encompasses bicyclic analogues of naphtalene – 2,1-borazaronaphtalenes (Fig. 2d) [15,17,18].

Heterocyclic compounds of another type, containing covalently bound boron atom(s) within the ring structure, are bicyclic benzoborauracils (see Fig. 1) and thiopheneuracil containing hydroxyboron moiety at 4-position of heterocyclic ring [1]. Benzoborauracils were synthesized from *o*-aminobenzeneboronic acids that have a *cis*-orientated 1,2-groups necessary for the ring closing reaction step. Compounds of this type have limited applicability, since a considerable steric hindrance of aromatic ring makes them poor pyrimidine analogues. The closest uracil analogues so far are recently presented monocyclic 5,6-unsaturated boron derivatives of uracil containing boron atom at the 4-position of the heterocyclic ring [4].

2.2. Aromaticity indices

The nucleus-independent chemical shift (NICS) indices of aromaticity [9,10] have been obtained as the negative of absolute NMR shieldings, computed at ring centers (nonweighted mean of the heavy atom coordinates; NICS(0)) and 1 Å above of the ring plane (NICS(1)). In general, highly negative NICS values denote aromaticity whereas positive values of NICS are associated with anti-aromaticity. The indice is one of the most widely used quantitative measures of aromaticity [19,20] that has been demonstrated to be a convenient indicator of aromaticity in several organic and inorganic systems [20–24].

The results of NICS calculations are presented in Table 1. The compound **2** is more aromatic than compound **1**, as clearly indicated by both NICS(0) and NICS(1).

Compounds **1** and **2** have the same ring skeleton but differ by π-bonding between the C5 and C6 atoms, present only in compound **2**. The ability to delocalize the π-electron pair from the double bond C5-C6 toward the boron atom B4, which has an empty p orbital and can accept electrons through resonance, increases π-electron delocalization in the ring and hence the aromatic character of compound **2** relative to **1**.

Aromaticity of compound **3** is similar to that of compound **2**, but higher from that of compound **1**. Thus the alternate arrangement of boron and nitrogen atoms in the ring, producing an electron cloud (unevenly distributed between nitrogen and boron due to their different electronegativities), consisting of 6 p electrons encompassing the nitrogen lone pairs, apparently increases the π-electron delocalization and aromatic character of compound **3**, as compared to compound **1**. The corresponding delocalized electron cloud cannot be formed in compound **1** due to the saturated C5–C6 region.

Although the heterocyclic ring in compound **4** is identical that in compound **2**, the aromaticity of the former is lower than of the latter. This result can be explained by the fact that the π-electron pair from the formally double bond C5–C6 would be delocalized much stronger on the right (Fig. 1) than on the left (heterocyclic) ring of compound **4**, thereby relatively decreasing π-electron delocalization, and hence aromaticity, of the heterocyclic ring. A much stronger delocalization of this π-electron pair on the right ring, where the sextet of π electrons can be engaged in a strong ring current, is reasonable, as that ring is benzene, the prototype of aromatic systems. The strongly negative values

Table 1
NICS(0) and NICS(1) values [ppm] for compounds **1**–**5**.

Compound	NICS (0)	NICS (1)	Literature NICS (0)
1	−1.82	−0.98	–
2	−2.73	−2.40	–
3	−2.47	−2.81	−2.1 [25]
4	−1.59 (LR); −9.11 (RR)[a]	−1.85 (LR); −10.45 (RR)[a]	−9.7 (benzene) [9]
5	−1.68	−2.02	−1.2 [26]

[a] LR – heterocyclic ring of **4** (left ring in Fig. 1); RR – benzene moiety of **4** (right ring in Fig. 1).

of NICS(0) and NICS(1) for the right ring in compound **4** confirm the above reasoning (*cf.* the NICS(0) value for benzene of −9.7 ppm [9]).

Interestingly, the replacement of B4 in compound **2** with C4 in compound **5** results in a decrease of the aromatic character. Apparently the boron atom at the position 4 has a better aromatic complementarity to the electron arrangement in the ring, probably due to the boron atom being less electronegative than the carbon atom and, unlike the latter, having an empty p orbital. For these reasons, the boron atom would be expected to attract, and in consequence delocalize, π-electrons stronger than carbon atom, thereby increasing π-electron delocalization in the ring and aromaticity. Taken together, all the compounds studied have weak aromatic character, except from the right ring (Fig. 1) in compound **4** which is strongly aromatic.

2.3. NMR properties of borauracil systems

Recently synthesized derivatives of 5,6-dihydroborauracil and borauracil, regardless of their low stability, allowed to perform NMR experiments showing coordination equilibria between trivalent, sp^2-hybridized and sp^3-hybridized "ate", complexes with alcohols and amines [2–4]. The latter phenomenon, previously shown with several boronic acid–based inhibitors to take place in active sites of inhibited enzymes, resulting in the formation of sp^3 anionic form covalently bonded to enzyme protein [27,28]. Further analysis of NMR properties of 4-hydroxyborauracil (**2**) and 4-hydroxy-3-methylborauracil revealed the ^{13}C and ^{1}H chemical shifts of borauracil moiety to be relatively close to those of "natural" uracil [4].

The ^{13}C, ^{1}H and ^{11}B chemical shifts of 4-hydroxy-5,6-dihydroborauracil (**1**), 4-hydroxyborauracil (**2**), borazine (**3**), 4-hydroxybenzoborauracil (**4**) and uracil (**5**) are presented in Table 2.

Comparison of 5,6-saturated borauracil **1,** containing boron atom at the position 4, with uracil, containing C4, reveals distinct differences of chemical shifts at most of the analyzed positions (Table 2; Δ column). The ^{13}C chemical shifts, corresponding to carbonyl C2 carbon atom in uracil (**5**) and **1** are relatively close, at 151.0 and 156.2 ppm respectively. The small ^{13}C chemical shift difference isn't surprising, in view of boron atom being relatively far from C2 position. The largest differences can be found in the C5 and C6 regions. The ^{13}C shifts, corresponding to C5 and C6 in **1** and **5** are 17.5 and 35.0 ppm, and 100.0 and 147.2 ppm, respectively (Δ of −82.5 and −112.2 ppm for C5 and C6, respectively). Moreover, the ^{1}H NMR resonances of H5 and H6 hydrogens in **1** are in regions typical for aliphatic systems, in accord with **1** lacking the 5,6-double bond. Additionally, the calculations suggest very low degree of aromaticity in **1**, compared to other analyzed compounds.

The ^{13}C and ^{1}H chemical shifts of unsaturated **2** are very similar to that of uracil (Table 2). In contrast to very similar shifts of H1, H3 and C2 atoms (that in **2** are relatively far from B4) in **2** and **5**, those corresponding to C6 carbon atom show the highest difference (δ of 132.1 with **2**; Δ of −15.1 ppm). The latter 15.1 ppm *upfield shift* in **2** most probably results from the absence of the mesomeric effect of the strongly electron-withdrawing C4 carbonyl group, resulting in a partial positive charge at the C6 position in **5**. The H6 and H5 chemical shifts for **2** are 7.2 and 5.2 ppm, respectively, being very similar to those observed for uracil (Δ_{H6} and Δ_{H5} of −0.2 and −0.3 ppm, respectively).

Of particular interest is observation made by comparing chemical shifts for **2** and 4-hydroxybenzoborauracil **4**. The calculated NICS indices of **4** are suggesting that the π-electrons in the C5–C6 region would be delocalized mainly on the right (Fig. 1) ring, with the heterocyclic ring aromatic character weaker from that of **2** (Table 1). However, the experimental ^{13}C and ^{11}B NMR chemical shift values the two compounds are surprisingly similar, with δ_{C2} of 153.1 and δ_{B4} of 32.1 ppm for **2** and δ_{C2} of 154.6 and δ_{B4} of 31.1 ppm for **4**. The presented NMR data suggest that the electronic delocalization in **2** and heterocyclic moiety of **4** should be very similar, resulting in comparable magnetic deshielding and comparable degree of aromaticity. The analysis of steric effects that affect aromaticity of **2** and **4** suggests that higher steric hindrance from additional benzene ring, especially the repulsion between π-electron clouds of benzene and heterocyclic rings in **4**, may result in destabilization of partially aromatic heterocyclic ring's planar structure.

Table 2
NMR properties of compounds **1**–**5**.

Compound	Nuclei	δ (ppm) in D_2O	δ (ppm)[a]	Δ (ppm)[b]	Ref.
1	H1	–	5.8	−5.1	[2,3]
	C2	–	156.2	5.2	
	H3	–	5.7	−5.2	
	B4	–	24.9	–	
	C5	–	17.5	−82.5	
	H5	1.3	1.31	−4.2	
	C6	–	35.0	−112.2	
	H6	3.5	3.4	−4.0	
2	H1	–	10.4	−0.5	[4]
	C2	–	153.1	2.1	
	H3	–	8.1	−2.8	
	B4	–	32.1	–	
	C5	–	95.0	−5.0	
	H5	–	5.2	−0.3	
	C6	–	132.1	−15.1	
	H6	–	7.2	−0.2	
3	H(N)	–	4.0	–	[29,30]
	H(B)	–	5.0	–	
	B	–	0.3	–	
4[c]	H1	–	10.0	−0.9	[1]
	C2	–	154.6	3.6	
	H3	–	7.9	−3.0	
	B4	–	31.1	–	
5	H1	–	10.9	–	*This work*
	C2	155.9	151.0	–	
	H3	–	10.9	–	
	C4	170.2	164.2	–	
	C5	103.7	100.0	–	
	H5	5.8	5.5	–	
	C6	146.2	147.2	–	
	H6	7.5	7.4	–	

[a] Chemical shifts in aprotic solvents: acetone-*d6* for **1**, DMSO-*d6* for **2**, **4**, **5** and CCl4 for **3**.
[b] Chemical shift differences between analyzed compound (aprotic solvents) and uracil (DMSO-*d6*).
[c] Heterocyclic moiety of **4**.

The aromaticity of borauracil and 5,6-dihydroborauracil systems should not be discussed without boron coordination properties taken into consideration. Almost all of known boron compounds and their derivatives of sp^2 hybridization possess a unique capacity to form stable anionic 'ate'-complexes of sp^3 hybridization upon coordination of an electron pair donor [1–4]. Fig. 3 shows that 4-hydroxyborauracil (**2**, $\delta_{11B} = 32.1$ ppm in DMSO-*d6*, [4]) forms bis-methoxy species containing sp^3-hybridized, negatively charged boron atom in a large excess of methanol. The experiment was controlled by ^{11}B NMR which showed a large *upfield* shift.

(25.6–25.7 ppm) of boron resonance upon sp^3 complex formation. The anionic sp^3 species (**2(CD$_3$OD)$_2$**, $\delta_{11B} = 6.4$ ppm in methanol-*d4*, **2(OR)$_2$** in Fig. 3) has no longer a vacant 2p orbital which is crucial for π-electron delocalization, contributing to the aromatic ring current phenomenon. Consequently, NMR investigation of coordination equilibria of **2**-electron pair donor systems suggests that **2** is aromatic only in non-coordinating aprotic solvents (DMSO-*d6*, acetone-*d6*), whereas in coordinating solvents (methanol-*d4*, D_2O)

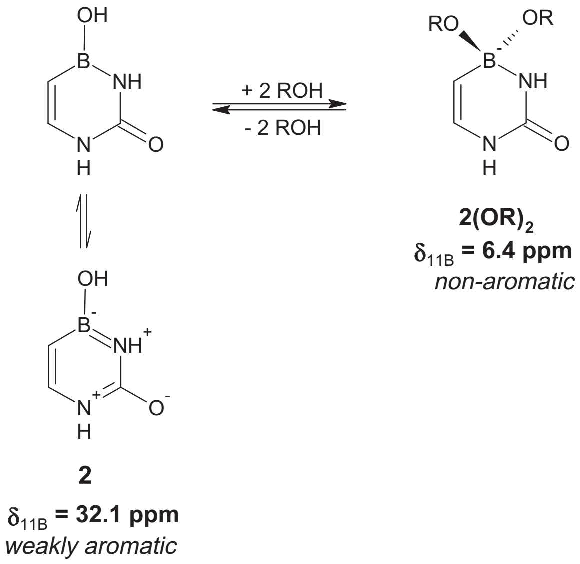

Fig. 3. Coordination equilibrium and ^{11}B NMR data for 2. R=H, alkyl.

form relatively stable sp^3 anionic complexes that are not aromatic. To our knowledge, the described solvent-dependent aromaticity effect should be observable also for benzoborauracils but was never analyzed and described in details. However, coordination equilibrium similar to that described in this work was observed by M.P. Groziak and coworkers for few 2,4,1-oxaza- and diazaborines [29]. Similarly to our results, the reported ^{11}B NMR data showed approx 25–30 ppm *upfield* shift of boron resonances upon formation of tetrahedral, anionic bis-methoxy form [4].

3. Experimental

3.1. Materials and methods

^{1}H and ^{13}C NMR spectra of uracil were obtained with Bruker Avance II spectrometer, operating in the quadrature mode at 500 MHz. The residual peaks of deuterated solvents were used as internal standards. Uracil and deuterated solvents of the highest commercially available grade were purchased from Aldrich and used without further purification (with exception for DMSO-*d6* which was dried with anhydrous sodium sulfate).

The nuclear magnetic resonance data was previously shown [1–4,30,31]. The structures of compounds **1**–**5** have been geometry optimized using the B3LYP hybrid functional [32] with the 6–31G^* basis set and the Gaussian 03 program [33].

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