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Preliminary Communications

Synthesis and NMR properties of novel 5,6-dihydroborauracil derivatives

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ABSTRACT

Novel boron compounds – 5,6-saturated borauracil derivatives (4-bromo-5,6-dihydroborauracil, 4-hydroxy-5,6-dihydroborauracil and 4-methoxy-5,6-dihydroborauracil) are presented along with other boron compounds obtained from *N*-vinylurea: *N*-substituted β-boronic amino acid – 2-{[(dihydroxyboranoamino)(dihydroxyboranooxy)methyl]-amino}ethylboronic acid and substituted methoxy-borane O-[(1-amino-1-*N*-vinylamino)methyl]dihydroxyboronate.

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1. Introduction

Hydroboration, an important reaction in synthetic organic chemistry, is accomplished with various hydroborating agents, including borane-tetrahydrofuran, borane-pyridine, borane-dimethyl sulfide, 9-BBN, and thexylborane complexes. Those reagents are commercially available and offer many options for selective hydroboration [1–5].

Little is known about the hydroboration of olefinic ureas compared to other olefinic systems; the published data have been reviewed by Soloway et al. [6,7]. Only a few boronic acids containing urea-derived moieties are known and the intermediates formed during the respective reactions were not described.

In this paper we present novel boron compounds **1**–**6**. Compounds **1** and **2**, i.e. a substituted methoxyborane (*O*-[(1-amino-1-*N*-vinylamino)methyl]dihydroxyboronate), and *N*-substituted β-boronic amino acid, respectively (Fig. 1), could be used as building blocks for pharmaceuticals or as cross-linking agents in polymer chemistry.

The most important aspect of this work are novel boron analogues of 5,6-dihydrouracil (5,6-dihydroborauracils, **4**–**6** see Fig. 2). There are only few boron analogues of nucleic acid bases, with Zhuo group's benzoborauracils as the most important work of the last 20 years [8]. It should be noted that borauracils, borathymines or boracytosines and their derivatives should be key compounds in the search for e.g. new anticancer compounds. Boron analogues of biologically active compounds have very interesting properties. The mechanism of action that is unique for those compounds is believed to be the nucleophilic attack of an enzyme on to the electron deficient sp^2 boron, resulting in the tetrahedral sp^3 hybridized boron "ate" complex. The boron analogue–enzyme "ate" complex is highly stable resulting in effective inhibition of the enzyme [9–11]. Additionally, boron-containing compounds can be considered potentially active in boron–neutron capture therapy (BNCT) [12].

2. Results and discussion

2.1. Hydroboration of N-vinylurea

Of particular interest is the fact that *O*-[(1-amino-1-*N*-vinylamino)methyl]dihydroxyboronate (**1**) was synthesized in the present study by an almost identical method to that used by Soloway's group [12]. Instead of the expected hydroboration product (borane to C=C double bond addition product), compound **1** is the product of addition at the carbonyl group of the vinylurea (Fig. 1). While our synthetic approach allowed the substrates, *N*-vinylurea and borane complex ($BH_3 \cdot THF$), to be used in strictly equimolar quantities, the same reaction would have been difficult to perform using gaseous diborane as reported [6,7,13].

A proposed intermediate compound **1′** resulting from addition of borane to the carbonyl group of *N*-vinylurea undergoes hydrolysis to give **1**. The vinyl moiety of *N*-vinylurea was not affected during the reaction according to NMR spectroscopy. Carbonyl group reduction by diborane gas and borane complexes have been

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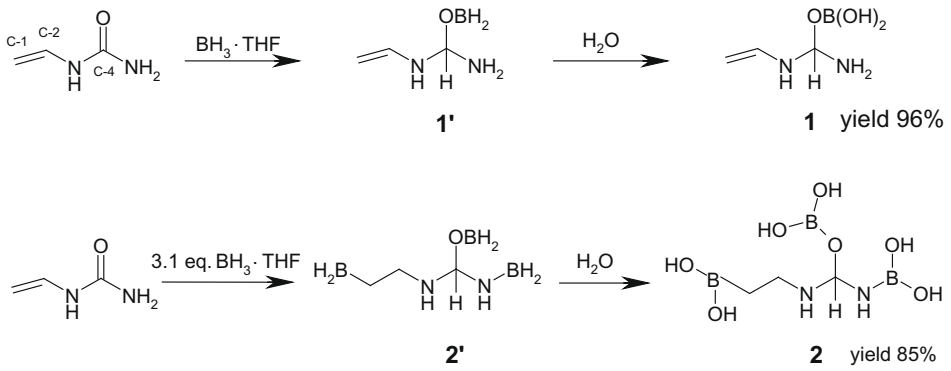

Fig. 1. Synthesis of compounds **1** and **2**.

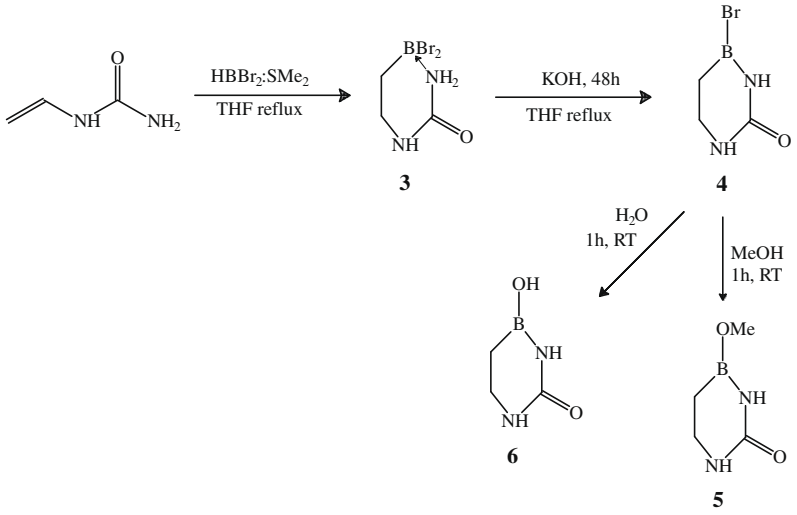

Fig. 2. Synthetic route for preparation of compounds **3**–**6**.

studied widely by both experimental and computational approaches [14–16]. The reduction of urea moiety should not be surprising as boranes also are known to perform reduction of wide range of amides. The typical reduction of amide is performed in mild conditions (66 °C, atmospheric pressure). Reduction with boranes in these conditions can lead even to amines [17]. The proposed reaction mechanism suggests that the methine hydrogen atom originates from the borane complex, with the remaining BH_2 moiety being attached to the oxygen atom. The final dihydroxyboron structural fragment then results from hydrolysis.

The presented experimental data shows that hydroboration of the unsaturated vinyl moiety also resulted in the formation of proposed intermediate **2′**, which could be easily hydrolyzed to dihydroxyboron derivative **2**. When the borane to *N*-vinylurea molar ratio was $\geqslant$1.8, addition of borane to the carbonyl moiety took place, followed by hydroboration of the olefinic fragment and substitution of hydrogen on the peripheral $-NH_2$ group (Fig. 1), giving **2′**, which hydrolyzed to compound **2**. Using borane to vinylurea molar ratios ranging from 1.8 to 2.8 resulted in formation of compounds **1** and **2** in different proportions. Compound **2** was obtained as the major product when the borane to vinylurea molar ratio was $\geqslant$3.1. No products containing two dihydroxyboron moieties were detected. Surprisingly, our synthetic route to **1** is very similar to that previously described, leading to β-ureidoethylboronic acid by direct C=C bond hydroboration, thus having an unreacted carbonyl moiety of boronic acid [6,7]. It should be noted that newly formed *O*-linked boric acid esters (**1** and **2**) could react with water and also with simple alcohols and due to this reactivity the solutions of those compounds for NMR spectra were prepared in aprotic solvents.

2.2. Computational analysis of the regio- and chemoselectivity of N-vinylurea and its derivatives

The alkene and alkyne hydroboration reaction mechanism is well known.[17] Steric effects are responsible for the regioselectivity, especially when using bulky borane reagents, however, for the majority of olefins, the most significant factors are electronic effects. Attack of the electrophilic reagent, e.g. BH_3, causes significant redistribution of the electron density in the target molecule, and as a consequence affects its reactivity. In the present work we considered a simplified mechanism for the hydroboration of *N*-vinylurea by borane-tetrahydrofuran reagent.

The atomic charges calculations show that the sum of the natural charges of the olefinic moiety (C-1, C-2, and adjacent hydrogens) in *N*-vinylurea is more positive (+0.153 a.u.) than in intermediate **1′** (+0.098 a.u.), indicating that *N*-vinylurea should react with the borane complex more slowly than **1′**. This can be rationalized by the lack of a carbonyl-related strong resonance effect in **1** and **1′** which is known for amides and also occurs in urea derivatives. The calculated natural charge on the C-4 carbonyl atom, is +0.771 a.u., and this is the highest positive partial charge found

for *N*-vinylurea. Therefore, it is reasonable to expect that the partially negative hydrogen atom of the borane complex (for comparison, the natural charge of the H atom in BH_3 is −0.107 a.u.) should attack the carbonyl carbon [18–20]. This suggestion agrees with the experimental results. In summary, compounds **2** and **2′** can be obtained from *N*-vinylurea *via* hydroboration of compound **1′** which is a borane-carbonyl addition product (*vide supra*).

2.3. Synthesis of 5,6-dihydroborauracils

The knowledge of small borane (BH_3 and its complexes) reactivity towards carbonyl and amide groups suggested the use of the bulky dibromoborane complex for the reaction with vinylurea. Experimental data proved that dibromoborane–dimethylsulfide complex does not react with carbonyl group as it was observed for BH_3:SMe_2 complex. The possible explanation for this phenomenon is lower reactivity of $BHBr_2$ reagent caused by both much higher steric repulsion and a strong electron withdrawing effect from two bromine atoms. Moreover, tetrahydrofuran could easily form $BHBr_2$:THF complex with even higher steric hindrance. The $BHBr_2$ complex hydroboration step (Fig. 2) was conducted at much higher temperature (66 °C) than in the case of BH_3 complex (0 °C) and unfortunately it resulted in slow loss of dibromoborane. This negative effect was neutralized by multiple additions of dibromoborane complex every hour of reaction time.

The obtained linear product **3** (Fig. 2) is similar to the one obtained by Soloway group having BBr_2 instead of BH_2 group [12]. The work mentioned suggested possibility of formation of six-membered complex where carbonyl oxygen coordinates to boron atom. Such a possibility also exists for compound **3** with coordination of carbonyl oxygen or, more likely, peripheral nitrogen atom (Fig. 2). The same group obtained also a linear boronic acid $(HO)_2BCH_2CH_2NHCONH_2$ but failed to convert it into cyclic product with covalent B–N bond [13].

The reaction of **3** with potassium hydroxide gave cyclic six-membered product 4-bromo-5,6-dihydroborauracil (**4**). To the best of our knowledge, **4** is the first boron-containing 5,6-saturated analogue of uracil. The formation of covalent B–N bond was confirmed by our analytical data, but unfortunately, we were unable to prepare X-ray diffraction quality monocrystal. The ^{11}B NMR chemical shift of compound **4** (54.5 ppm) confirmed that boron atom is covalently connected to carbon, nitrogen and bromine atoms [21–23]. The exceptionally interesting aspect is the possibility of coordination to boron atom of chiral electron pair donors (e.g. lactate, amino acids, etc.) that should result in formation of diastereoisomeric products. Another dihydrouracils – 4-*O*-methoxy-5,6-dihydroborauracil (**5**) and 4-hydroxy-5,6-dihydroborauracil (**6**) were prepared by methanolysis (**5**) or hydrolysis (**6**) of **4**. The ^{11}B chemical shifts of **5** (23.7 ppm) and **6** (24.9 ppm) are in accord with literature data [8,21–23]. There was also observed the formation of tetrahedral bis-methanol adduct of **5** (**5**:CD_3OD) with ^{11}B chemical shift of 1.6 ppm, similar to those described by Zhuo et al. [8]. The problem of determining the atom bound to boron was previously discussed by Zhuo et al. [8]. The authors proved that hydroxyboron compound (B–OH cyclic product) of benzoborauracils contains B–N bond in solid state or in non-coordinating solvent, while the titration with methanol gave bismethanol adduct that may contain B–O (carbonyl oxygen coordinating to boron) form in equilibrium with B–N form in solution. The removal of methanol gave starting B–N form as judged from ^{11}B NMR spectra [8]. Our observations are very similar to that of Zhuo et al. Solution of compound **6** in non-coordinating solvent contains mainly B–N form with ^{11}B chemical shifts value of 24.9 ppm (for **6**), a value that differs significantly from literature data for alkylboronic acids and their esters ((R–$B(OH)_2$ and R–$B(OR)_2$, respectively, R=alkyl) where chemical shifts that are always in 30–34 ppm range [24–28]. It should be noted that methanol (or other alcohol of small steric hindrance) solution could contain some amount of B–O form, the quantitative analysis of B–O/B–N equilibrium is difficult due to process rate that is fast in NMR-scale in analyzed conditions (0–20 °C).

3. Conclusions

The synthesis, reactivity and spectroscopic properties of novel boron compounds are presented. The intermediate compound **1′** is the product of addition of the borane complex at the carbonyl group of *N*-vinylurea giving *O*-[(1-amino-1-*N*-vinylamino)methyl]dihydroxyboronate (**1**) after hydrolysis. No reaction in the vinyl moiety of *N*-vinylurea was apparent under conditions used. Borane to *N*-vinylurea molar ratios higher than 1.8 resulted in addition of borane to the carbonyl moiety, followed by hydroboration of the olefinic fragment and substitution of a hydrogen from the peripheral–NH_2 group. Borane to vinylurea molar ratios ranging from 1.8 to 2.8 resulted in the formation of compounds **1** and **2** in different proportions. The calculated natural charge on the C-4 carbonyl atom of +0.771 a.u. is the highest positive partial charge found for *N*-vinylurea. Therefore, the partially negative hydrogen atom from the borane complex may be expected to attack the carbonyl carbon, in accord with the experimental results.

Reaction of dibromoborane complex with *N*-vinylurea conducted in higher temperature (66 °C) resulted in synthesis of C=C double bond hydroboration product **3**, formally a boronic acid bromide. Its reaction with potassium hydroxide in aprotic solvent resulted in heterocyclic product **4**, a first 5,6-dihydroborauracil derivative. Its hydrolysis gave B–OH moiety at 4-position of saturated ring (**6**), and reaction with methanol resulted in formation of another cyclic compound containing B–OMe structural fragment (**5**).

4. Experimental

4.1. Materials and methods

^1H NMR spectra were obtained with Bruker Avance spectrometer operating in the quadrature mode at 500 MHz. All ^{11}B spectra were performed using 5 mm pure quartz NMR tube. The residual peaks of deuterated solvents were used as internal standards. Elemental analysis was performed using Carlo Erba Elemental Analyser EA 1108. GC–MS analysis was carried out on Agilent Technologies 6890 N apparatus with 5973-Network mass detector. FTIR spectra was recorded on Perkin Elmer Paragon 1000 apparatus. The *N*-vinylurea was prepared using known method [29]. All other reagents and deuterated solvents of the highest commercially available grade were purchased from Aldrich and used without further purification (with exception for acetone-*d*6 which was dried with anhydrous sodium sulfate). Rubber septa joints were purchased from Aldrich. All procedures, including preparation of samples for the NMR measurements, were carried out under nitrogen.

The theoretical calculations have been performed with the density functional theory and the B3LYP functional with the aug-cc-pVTZ basis set implemented in the Gaussian G03 (rev. C.02) suite of programs [30]. The optimal geometries were obtained with default methods achieving the stationary point controlled by four convergence criteria. The electronic density distribution has been analyzed with the use of the NBO 5.G module implemented also in the Gaussian G03.

4.2. Preparation of O-[(1-amino-1-N-vinylamino)methyl]-dihydroxyboronate (1)

1 M Borane–tetrahydrofuran complex in THF (1 g of borane–THF complex, 11.6 mmol) was placed in a dry, 100 ml round-

bottom flask purged with dry nitrogen. The flask was then immersed in an ice bath. *N*-vinylurea [29] (1 g in 5 ml of dry THF, 11.6 mmol) was added dropwise over a period of 30 min and the reaction was allowed to run for another 30 min, with the reaction temperature rising to 5 °C. Distilled and deoxygenated water (630 μL, 35 mmol) was added dropwise. Following completion of hydrogen evolution, all volatile products were removed under reduced pressure. Finally, the resulting solid was dried under high vacuum. Compound **1** was obtained in 96% yield (*ca.* 1.46 g). MS (electrospray ionization, *m*/*z*): 131 + 132 (100%). Elemental Anal. Calcd for $C_3H_9BN_2O_3$: C, 27.31; H, 6.83; N, 21.24. Found: C, 27.21; H, 6.86; N, 21.22. FTIR (KBr, cm^{-1}) 3320 (νN–H, s, br); 3223 (νB–O–H, s, br); 2104 (νC═CH, w); 1663 (νN–H, m); 1617 (νC═C, m); 1560 (νC–O, m); 1345 (νB–O, m); 1026 (νC–N, m); 750–760 (νN–H, w). ^{1}H NMR (acetone-*d*6, ppm): 7.67–7.78 (m, H_{vinyl}, 3H); 5.77 (s, OH, 1H), 3.64 (m, CH, 1H), 1.72 (m, NH, 1H); 1.46 (m, NH_2, 2H). ^{13}C NMR (acetone-*d*6, ppm): 83.2 ($CH_{satur.}$); 115.8, 165.0 (C_{vinyl}). ^{11}B NMR (acetone-*d*6, ppm): 19.21.

4.3. Preparation of 2-{[(dihydroxyboranoamino) (dihydroxyboranooxy)methyl]amino}ethylboronic acid (*2*) (Fig. 1)

1 M Borane–tetrahydrofuran complex in THF (3.1 g of borane-THF complex, 36.1 mmol) was placed in a dry, 100 ml round-bottom flask purged with dry nitrogen. The flask was then immersed in an ice bath. *N*-vinylurea [29] (1 g, 11.6 mmol, in 5 ml of dry THF) was added dropwise over a period of 30 min, and the reaction was run for another 90 min, with the reaction temperature rising to 10 °C. Distilled and deoxygenated water (2 ml, 0.108 mol) was added dropwise. Following completion of hydrogen evolution, all the volatile products were removed under reduced pressure and the resulting solid was dried under high vacuum. Compound **2** was obtained in 85% yield (*ca.* 2.2 g). MS (electrospray ionization, *m*/*z*): 219–222 (100%). Elemental Anal. Calcd for $C_3H_{13}BN_2O_7$: C, 16.26; H, 5.87; N, 12.65. Found: C, 16.22; H, 5.90; N, 12.57. ^{1}H NMR (acetone-*d*6, ppm): 7.0, 7.27, 5.30 (br., OH, 2H + 2H + 2H) 3.30 (m, CH, 1H); 3.13 (m, C*H*$_2$–N, 2H); 2.18 (m, N*H*–CH_2, 1H); 2.14 (d, N*H*–B, 1H) 1.06 (tr., B–C*H*$_2$, 2H). ^{11}B NMR (acetone-*d*6, ppm): 20.24; 19.70, −13.02. Compounds **1** and **2** were also obtained by analogous reactions of *N*-vinylurea with 1 M toluene solution of borane–dimethylsulfide complex, in yields of 92% and 79%, respectively.

4.4. Preparation of *3* and *4*

Dibromoborane–dimethylsulfide complex (1.5 g of dibromoborane–Me_2S complex, 6.4 mmol) was placed in a 100 ml round-bottom flask containing 20 ml of anhydrous THF. The flask was then immersed in a silicon oil bath. *N*-vinylurea [29] (550 mg in 5 ml of dry THF) was added dropwise to the reaction flask at THF reflux conditions over a period of 10 min and the reaction was allowed to run for another 30 min. Other portions of dibromoborane–dimethylsulfide complex (1.5 g) were added every 1 h to the refluxing mixture (total amount of $BHBr_2$:SMe_2 complex used in the reaction was 15 g). All volatile products were removed under reduced pressure. Finally, the resulting solid was dried under high vacuum. Compound **3** was obtained in 85% yield as judged from NMR spectra. Reaction product was dissolved in anhydrous THF (20 ml) containing 3.6 g of dry KOH and refluxed for 48 h. Resulting product was vacuum dried. Compound **4** was washed out with two portions of chloroform (2 × 10 ml). Yield: 880 mg (78% total yield). Analytical data for **4**: MS (electrospray ionization, *m*/*z*): 176–177 (100%). Elemental Anal. Calcd for $C_3H_6BBrN_2O$: C, 20.38; H, 3.42: N, 15.84. Found: C, 20.30; H, 3.46; N, 15.81. ^{1}H NMR (acetone-*d*6, ppm): 5.80–5.56 (br, NH, 2H); 3.35 (m, N–C*H*$_2$, 2H), 1.18 (m, B–C*H*$_2$, 2H). ^{13}C NMR (acetone-*d*6, ppm): 155.2 (C═O); 35.1 (N–C*H*$_2$), 15.6 (B–C*H*$_2$). ^{11}B NMR (acetone-*d*6, ppm): 54.5.

4.5. Preparation of *5*

To the solution of **4** in anhydrous tetrahydrofurane (200 mg in 10 ml of THF) anhydrous methanol was added (50 ml). Reaction mixture was stirred in room temperature for 1 h and vacuum dried (60 °C, 48 h at 0.01 Pa). Compound **5** was obtained in almost quantitative yield (approx. 0.14 g). Analytical data for **5**: MS (electrospray ionization, *m*/*z*): 127–128 (100%). Elemental Anal. Calcd for $C_4H_9BN_2O_2$: C, 37.55; H, 7.09; N, 21.90. Found: C, 37.48; H, 7.11; N, 21.84. ^{1}H NMR (acetone-*d*6, ppm): 5.61–5.72 (br, NH, 2H); 3.61 (s, OMe, 3H), 3.38 (m, N–CH_2, 2H), 1.28 (m, B–CH_2, 2H). ^{13}C NMR (acetone-*d*6, ppm): 157.2 (C═O); 53.1 (OMe); 35.2 (N–CH_2), 17.0 (B–CH_2). ^{11}B NMR (acetone-*d*6, ppm): 23.7. ^{11}B NMR (methanol-d4, ppm): 1.6.

4.6. Preparation of *6*

To the solution of **4** in anhydrous tetrahydrofurane (300 mg in 10 ml of THF) deoxygenated water was added (10 ml). Reaction mixture was stirred in room temperature for 1 h and vacuum dried. Compound **6** was obtained in almost quantitative yield (approx. 0.19 g). Analytical data for **6**: MS (electrospray ionization, *m*/*z*): 113–114 (100%). Elemental Anal. Calcd for $C_3H_7BN_2O_2$: C, 31.6; H, 6.19; N, 24.59. Found C, 31.54; H, 6.23; N, 24.52. ^{1}H NMR (acetone-*d*6, ppm): 8.43 (br, B–OH, 1H); 5.68–5.81 (br, NH, 2H); 3.42 (m, N–CH_2, 2H), 1.31 (m, B–CH_2, 2H). ^{13}C NMR (acetone-*d*6, ppm): 156.2 (C═O); 35.0 (N–C*H*$_2$), 17.5 (B–C*H*$_2$). ^{11}B NMR (acetone-*d*6, ppm): 24.9. ^{1}H NMR (D_2O, ppm): 3.48 (m, N–CH_2, 2H), 1.34 (m, B–CH_2, 2H).

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