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Synthesis, Characterization, and Binding Property of Isoelectronic Analogues of Nucleobases, B(6)-Substituted 5-Aza-6-borauracils and -thymines

Hiroshi Ito,*,†,§ Kyohei Yumura,† and Kazuhiko Saigo*,†,‡

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan, and School of Environmental Science and Engineering, Kochi University of Technology, Miyanokuch, Tosayamada-cho, Kami-shi, Kochi 782-8502, Japan

h-ito@sci.osaka-cu.ac.jp; saigo.kazuhiko@kochi-tech.ac.jp

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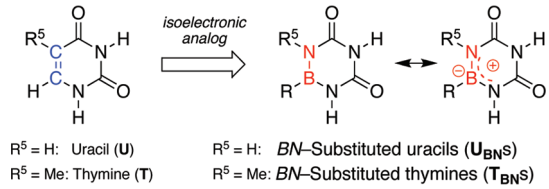
ABSTRACT



As isoelectronic *BN*-containing analogues of 6-substituted uracil and thymine, a series of B(6)-substituted 5-aza-6-borauracils (U_{BN}s) and -thymines (T_{BN}s) were synthesized and fully characterized. The crystallographic and spectroscopic analyses of the analogues revealed that the framework and hydrogen-bonding pattern of T_{BN}s were similar to those of the original nucleobase, thymine.

The substitution of a carbon−carbon double bond with an isoelectronic boron−nitrogen bond (*BN*-substitution) is one of the fascinating strategies for the invention of a new series of heterocycles.[1] Since Dewar and co-workers have reported their pioneering research on *BN*-containing analogues of aromatic and heteroaromatic systems,[2] a numerous number of *BN*-containing compounds have been developed.[3] Recently, the groups of Ashe,[4] Piers,[5] Paetzold,[6] and Liu[7] have reported a new generation of *BN*-substituted heteroaromatics with distinct photophysical and electrochemical properties or biological activity. On the other hand, nucleobases having a recognition site in their molecular frame are typical heterocyclic compounds with carbon−carbon double bond(s) and are extremely important components not only in biochemistry but also in supramolecular chemistry.[8] This

† The University of Tokyo.
‡ Kochi University of Technology.
§ Present Address: Department of Chemistry, Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi-ku, Osaka-shi, Osaka 558-8585, Japan.

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means that *BN*-substituted nucleobases are very attractive as the next generation of *BN*-substituted heterocyclic compounds. Although the synthesis and π electron distribution property of 5-aza-6-borauracil ($\mathbf{U_{BN}}$) and its derivatives, in which the C(6)═C(5) bond of uracil is replaced with a B(6)−N(5) bond, appear in a paper[9] and a patent,[10] these reports are dubious because of irreproducible scant experimental detail and characterization only with an elemental analysis, as Bielawski et al. pointed out.[11] Bielawski et al. have also reported the synthesis of B(6)-phenyl-*BN*-uracil ($\mathbf{PhU_{BN}}$), which was characterized by mass and IR spectra and an elemental analysis; they reported neither NMR data nor X-ray crystallographic data, presumably because of its high moisture sensitivity, insolubility in nonpolar solvents, and/or instability in polar solvents. In this paper, we report the synthesis, full characterization, and binding property of isoelectronic analogues of nucleobases, B(6)-substituted 5-aza-6-borauracils ($\mathbf{U_{BN}}$s) and -thymines ($\mathbf{T_{BN}}$s) (Figure 1).

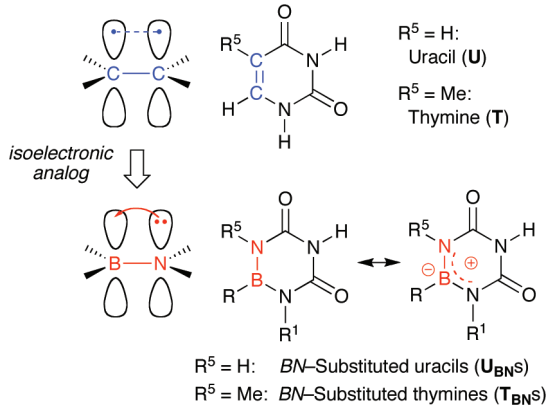
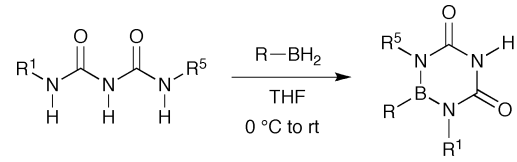


Figure 1. Design of *BN*-substituted uracils and thymines.

To prevent the hydrolysis of $\mathbf{U_{BN}}$s and $\mathbf{T_{BN}}$s and to increase their solubilities in common nonpolar solvents, we considered that a proper substituent should be introduced on the boron atom. Then, we selected thexyl and mesityl groups as typical aliphatic and aromatic substituents, respectively, with the expectation that their obvious bulkiness would obstruct the nucleophilic attack of polar molecules to the boron atom in the $\mathbf{U_{BN}}$s and $\mathbf{T_{BN}}$s and that their hydrophobicity would make the $\mathbf{U_{BN}}$s and $\mathbf{T_{BN}}$s solubile in nonpolar solvents.

The B(6)-substituted $\mathbf{U_{BN}}$s and $\mathbf{T_{BN}}$s (**1a**−**e**) thus designed were synthesized by the one-step cyclization reaction of biurets (**2a**−**c**) with monosubstituted boranes (**3a**,**b**) in THF (Scheme 1). Among the targeted five analogues, $\mathbf{ThxU_{BN}}$ could not be unfortunately isolated, although its formation

Scheme 1. Synthesis of $\mathbf{U_{BN}}$s and $\mathbf{T_{BN}}$s



2a ($R^1 = R^5 = H$)
2b ($R^1 = H$, $R^5 = Me$)
2c ($R^1 = R^5 = Me$)

3a (R = Thx)
3b (R = Mes)

1a–e

1a: $\mathbf{ThxU_{BN}}$	(R = Thx, $R^1 = R^5 = H$);	not isolated
1b: $\mathbf{MesU_{BN}}$	(R = Mes, $R^1 = R^5 = H$);	27%
1c: $\mathbf{ThxT_{BN}}$	(R = Thx, $R^1 = H$, $R^5 = Me$);	53%
1d: $\mathbf{MesT_{BN}}$	(R = Mes, $R^1 = H$, $R^5 = Me$);	26%
1e: $\mathbf{m^1MesT_{BN}}$	(R = Mes, $R^1 = R^5 = Me$);	10%

(Mes = mesityl, Thx = thexyl)

was strongly suggested by a mass spectrum, probably due to its low stability/solubility. In contrast, $\mathbf{MesU_{BN}}$ (**1b**) and $\mathbf{T_{BN}}$s (**1c**−**e**) could be purified by silica-gel chromatography and/or gel permeation chromatography (GPC). $\mathbf{ThxT_{BN}}$ was not so stable as similar *BN*-substituted compounds reported by Dewar et al.[2c] It gradually decomposed under ambient atmosphere to give 1-methylbiuret.[12] On the other hand, *B*-mesitylated $\mathbf{MesU_{BN}}$ (**1b**), $\mathbf{MesT_{BN}}$ (**1d**), and $\mathbf{m^1MesT_{BN}}$ (**1e**) were highly air- and moisture-stable, and no decomposition was observed for up to two months; the high stabilities made the full chracterization of the analogues possible (see Supporting Information). In an aqueous methanol solution under reflux, however, $\mathbf{MesT_{BN}}$ was gradually hydrolyzed to afford mesitylboric acid and 1-methylbiuret.[13]

The replacement of the C(6)═C(5) bond of uracil with a B(6)−N(5) bond results in the same chemical environment for the N(1) and N(5) amide protons in $\mathbf{MesU_{BN}}$; the amide protons were observed to be equivalent in the ^{1}H NMR of $\mathbf{MesU_{BN}}$. Moreover, the chemical shift of the amide protons was dependent on the concentration, implying that the proton at the N(5)-position was also associated in the intermolecular hydrogen-bonding interaction. Thus, $\mathbf{MesU_{BN}}$ was distinctively different from original uracil in molecular symmetry and hydrogen-bonding ability.

The crystalline-state structures of $\mathbf{MesU_{BN}}$ and $\mathbf{MesT_{BN}}$ were determined by X-ray crystallography (Figure 2).[14] In both of the crystals, there are two different molecular forms in each unit cell, depending on the hydrogen-bonding patterns. In the crystal of $\mathbf{MesU_{BN}}$, one of the amide protons interacts with the mesityl group of the neighbored molecule by NH−π interaction,[15] and the other constructs a hydrogen-

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(12) ThxTBN was almost completely decomposed in a few days under ambient atmosphere.

(13) 35% of MesTBN was decomposed, when it was heated in CD_3OD for 20 h at 60 °C (bath temperature). See Figure S5 (Supporting Information) for details.

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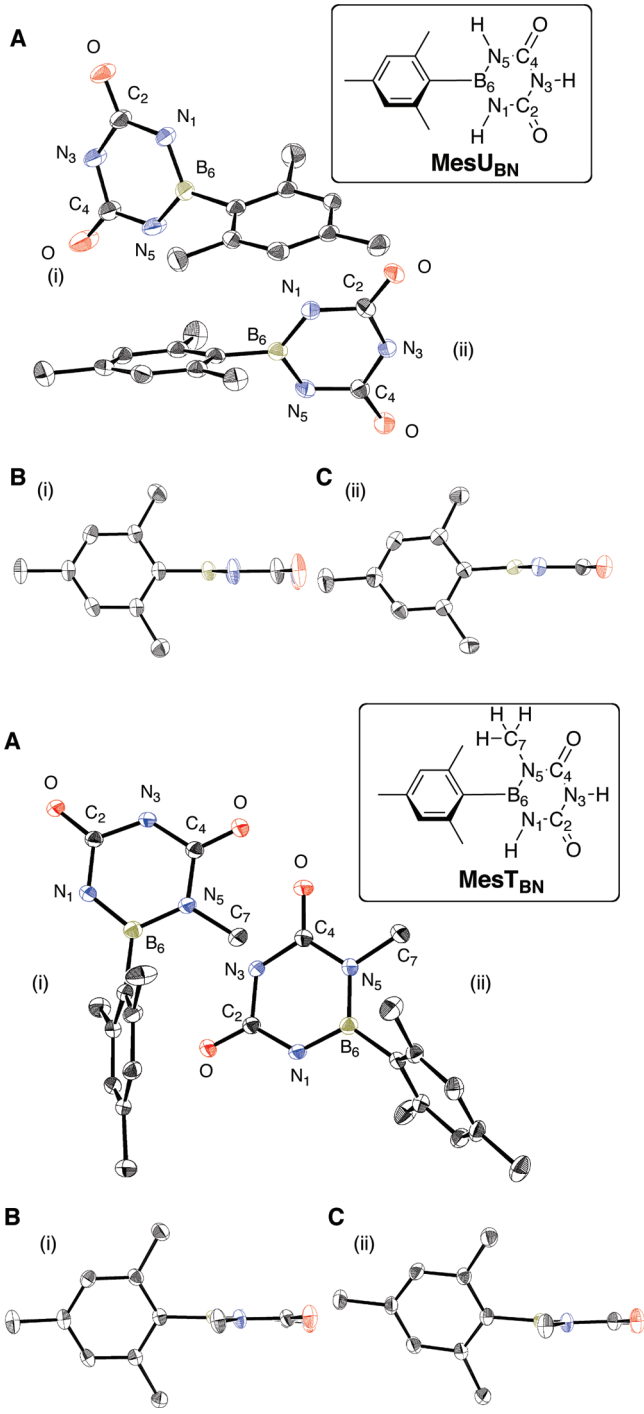

Figure 2. Crystal structure of **MesU$_{BN}$** and **MesT$_{BN}$** (50% thermal ellipsoids; hydrogen atoms are omitted for clarity). A, top view; B, C, side view.

bonding network. On the other hand, a hydrogen-bonding network in the crystal of **MesT$_{BN}$** is similar to that of a thymine derivative crystal.[16] The lengths of the B(6)−N(5) and C(4)═O bonds in **MesU$_{BN}$** and **MesT$_{BN}$** are similar to those of the B(6)−N(1) and C(2)═O bonds, respectively. The lengths of the B(6)−N(5) bonds in **MesU$_{BN}$** (1.418−1.429 Å) and **MesT$_{BN}$** (1.422−1.442 Å) are obviously short, compared to that in the borabenzene/pyridine complex[17] (1.558 Å), and are close to those in *BN*-aromatic hydrocarbons (*BN*-naphthalene,[4c] 1.461 Å; *BN*-phenanthrene,[5b] 1.491 Å; *BN*-pyrene,[5c] 1.456 Å). These lengths suggest a significant double-bond character of the B−N bonds in **MesU$_{BN}$** and **MesT$_{BN}$**. Although the six-membered heterocyclic rings of **MesU$_{BN}$** and **MesT$_{BN}$** are a little deformed by the substitution of the C═C bond with a B−N bond, the almost flat shape of the heterocyclic ring indicates that **MesU$_{BN}$** and **MesT$_{BN}$** can be regarded as nucleobase analogues.

The absorption spectra of **MesU$_{BN}$** and **MesT$_{BN}$** were quite different from those of original nucleobases (Figure 3). The

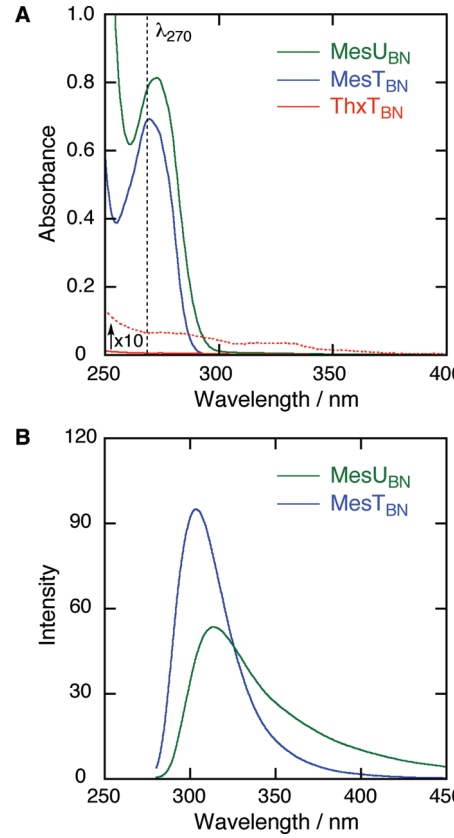

Figure 3. Absorption (A) and fluorescence (B) spectra of **MesU$_{BN}$** and **T$_{BN}$s** (green, **MesU$_{BN}$**; blue, **MesT$_{BN}$**; red, **ThxT$_{BN}$**). 2.0 mM in CH_2Cl_2, λ_{ex} = 270 nm. Dashed red line is the **ThxT$_{BN}$** spectrum multiplied by 10.

absorption of **ThxT$_{BN}$** in CH_2Cl_2 is extremely weak, compared with that of thymine, clearly indicating that the π-electron distribution of **T$_{BN}$s** is not so sufficient; the result is distinctly different from that reported in the previous paper.[9] On the other hand, **MesU$_{BN}$** and **MesT$_{BN}$** in CH_2Cl_2 showed strong absorptions and emissions at 273 and 312 nm and at 270 and 302 nm, respectively, which would be attributable to the interaction between the boron atom and

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the aryl moiety.[18] To the best of our knowledge, this is the first example of a unique emission arising from an atom in the framework of nucleobase analogues. Thus, **MesU$_{BN}$** and **MesT$_{BN}$** would be applied as probes, which would play a role analogously with uracil and thymine, respectively.

The structural characteristics prompted us to examine the molecular-recognition ability of **MesU$_{BN}$**, **MesT$_{BN}$**, and **m^{1}MesT$_{BN}$**. Because 2,6-diaminopyridine (**DAP**) is a typical molecule to form supramolecular complexes with thymine derivatives, in which hydrogen donating (D) and accepting (A) groups complementarily alternate (ADA·DAD),[19] we at first tried the complexation of **MesT$_{BN}$** with **DAP**. Fortunately, the single crystal of a **MesT$_{BN}$/DAP** complex (1:1) was obtained by the slow evaporation of the solvents from an equimolar mixture in chloroform/hexane. The X-ray crystallographic analysis of the complex showed that there exists complementary hydrogen bonds between **MesT$_{BN}$** and **DAP**, which are almost the same as those in the complex of thymine with **DAP** (Figure 4).[20]

In the next stage, we tried to measure the association constant (K_{assoc}) of a **T$_{BN}$** derivative with **DAP**; we used **m^{1}MesT$_{BN}$** in the place of **MesT$_{BN}$** because **MesT$_{BN}$** has possible binding sites not only at the N(3)−H/C(4)═O/N(5)−H but also at the N(1)−H/C(2)═O/N(3)−H in a solution. As a result, the K_{assoc} of **m^{1}MesT$_{BN}$** with **DAP** at 25 °C in $CDCl_3$ was estimated to be 77 M^{-1} by ^{1}H NMR, which is close to that of original thymine.[8c]

In summary, we have successfully synthesized several kinds of novel nucleobase analogues, **U$_{BN}$**s and **T$_{BN}$**s, by the isoelectronic replacement of the C═C bond of uracil and thymine with a B−N bond. Although no distinct ultraviolet absorption was observed arising from the π-electron distribution, B(6)-mesitylated **U$_{BN}$** and **T$_{BN}$**s showed unique absorption and emission, caused by B/aryl interaction. The crystallographic studies on **MesU$_{BN}$**, **MesT$_{BN}$**, and the **MesT$_{BN}$·DAP** complex revealed that the heterocyclic rings of **U$_{BN}$**s and **T$_{BN}$**s were isoelectronic with uracil and thymine, respectively, to show double bond character for the B−N bond to some extent and that **T$_{BN}$**s have a molecular-recognition ability similar to thymine. These results strongly imply that **U$_{BN}$**s and **T$_{BN}$**s are one of the fascinating classes of uracil and thymine analogues. The introduction of these new nucleobase analogues into nucleosides and further applications are now under investigation.

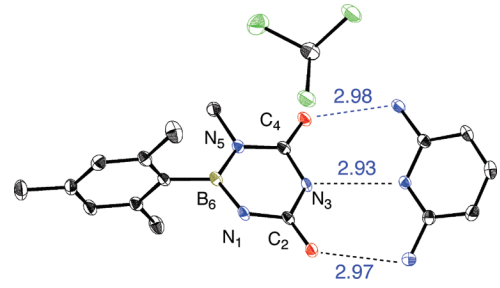

Figure 4. Crystal structure of **MesT$_{BN}$·DAP** (50% thermal ellipsoids; chloroform is included; hydrogen atoms are omitted for clarity) with hydrogen-bonding lengths (angstrom).

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1012058

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