Mixed *Intra*molecular Hydrogen Bonding in Dihydroxythiophene-based Units and Boron and Technetium Chelation

Sangwon Ko,[a] Sang Hyun Park,[†,b] Hui Jeong Gwon,[†] Junseong Lee, Min Jeong Kim, Yeonju Kwak, Youngkyu Do, and David G. Churchill[*]

Department of Chemistry and Molecular Science (BK 21), Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Korea. [*]E-mail: dchurchill@kaist.ac.kr

[†]Center for HANARO Application Research, Korea Atomic Energy Research Institute, Daejeon 305-353, Korea

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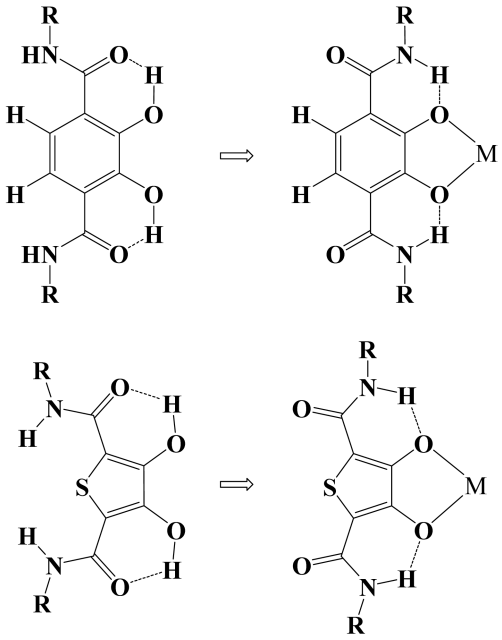
Three novel potential metal ion chelating units have been synthesized and characterized: 5-hexylcarbamoyl-3,4-dihydroxythiophene-2-carboxylic acid methyl ester (**5**), 3-benzyloxy-4-hydroxythiophene-2,5-dicarboxylic acid bis-hexylamide (**6**), and 3,4-dihydroxythiophene-2,5-dicarboxylic acid bis-hexylamide (**7**). The crystal structure of **6** was obtained and suggests the presence of three distinct intramolecular hydrogen bonds, namely [N_{amide}-H···O] [O-H···O_{amide}] and [N_{amide}-H···S]. Boron chelation with **5**, **6** and **7** through the use of BF_3, $B(OH)_3$ or $B(OMe)_3$ was probed by ^1H, ^{11}B, and ^{13}C NMR spectroscopy. Technetium (I) chelation with **5**, **6** and **7** was also studied via HPLC elutions using $[^{99m}Tc(CO)_3(OH_2)_3]^+$.

Key Words : Dihydroxythiophene, Hydrogen bonding, Boron chelation, Technetium-99m chelation, ^{99m}Tc tricarbonyl

Introduction

Ligand design that promotes selective metal ion binding continues to be a crucial aspect of developing new chelating agents.[1,2] The 2,3-dihydroxyterephthalamides (Scheme 1) that have been thoroughly investigated by the research group of K. N. Raymond have lead us to synthesize analogous systems in which the [*HCCH*] unit across from the hydroxyl groups is formally replaced by a sulfur atom. This substitution creates ring constriction and a wider [O_{phen}···O_{phen}] bite distance over that of the catecholate-type binding unit which may induce different metal ion binding selectivity. Stabilizing internal hydrogen bonding in multidentate ligand design has been an element of rational ligand design and has been observed structurally in 2,3-dihydroxyterephthalamide units.[3-5] Complexation has involved a variety of metals that include aluminum,[3] titanium,[3] vanadium,[3] gallium,[3,6,7] iron[3,6-9] and molybdenum.[5] The wide variety of metals that undergo binding make it interesting to study whether related units that differ by slight geometric differences can exhibit the same or different patterns.

When the [*HCCH*] unit is formally replaced by a sulfur atom, the pentacyclic thiophene core is produced and the [O_{phen}···O_{phen}] bite distance is widened from 2.6 to 2.7 Å. It is this change and the resulting bite angle that is at the core of our interest since this subtle change may give rise to differences in binding selectivity. So far we have focused our attention here away from main-stream metal ions, and more on the chelation of boron and technetium. The interest in boron chelation involves sensing technologies as well as the process of boron recovery and reuse. In aqueous media boron is commonly present as boric acid and extraction by resins that possess vicinal diol groups have been the focus of much research effort. In this article we explore potential boron binding with ligands based on amides of the 2,5-dicarboxy-3,4-dihydroxythiophene framework, and using NMR spectroscopy. These uncomplexed units appear to display varied stabilizing internal hydrogen bonding interactions. This hydrogen bonding involving the amide and



Scheme 1. Hydrogen bonding – and metal ion chelation schemes for the 2,3-dihydroxyterephthalamides (top pair) and 2,5-dicarboxy-3,4-dihydroxythiophene (bottom pair)

[a]Present affiliation: Chemistry Department, Texas A&M University
[b]Present address: Advanced Radiation Technology Institute, Korea Atomic Energy Research Institute, Jeongeup, Jeollabuk-do 580-185, Korea

hydroxyl groups may reveal new possible sites for boron binding. The thiophene group contains the 3,2-dihyroxy groups that can form a stable 5-membered catecholate-type chelate ring with [B-X] fragments. The extension of this chelation ability to transition metals known widely for the 2,3-dihydroxyterephthalamide units has been approached through the use of $[^{99m}Tc(CO)_3(OH_2)_3]^+$ labeling studies. Technetium ion chelation is interesting in terms of investigating new potential ligands for use in nuclear medicine. The ^{99m}Tc species is one of the most commonly used radioisotopes in diagnostic pharmaceuticals. The amides at the 2- and 5-positions in units **6** and **7** signify connection points for macromolecular assembly. These groups also supply the amide hydrogen which can direct ligand and chelation conformations. This has been true for multipodal designs in which multiple 2,3-dihydroxyterephthalamide units are present; these interactions are especially important in allowing the ligand and complex to adopt preferred ligand based conformations.

Results and Discussion

The 3,4-dihydroxy-thiophene-2,5-dicarboxylic acid systems have been prepared and new diamides of this class are accessed from the previously reported disodium salt **1**[10,11] which underwent benzylation to give compound **2** (Scheme 2, R = *n*-hexyl).[12] Importantly, products of symmetric amide formation (**3**) with primary amine (*n*-hexylamine or propylamine) or asymmetric mono-amide formation (**4**) can both be isolated (Scheme 2). To the best of our knowledge there are no reports of such asymmetric amide derivatives that bear 2,5-carboxy substitution *and* contain unprotected OH groups.[13,14]

Standard reduction with H_2 and Pd/C of derivative **3** under reflux conditions afforded the monobenzylated product (**6**) and the fully deprotected bishydroxyl derivative (**7**), controlled by reaction time.[15] No monobenzylated derivative was isolated from compound **5** in our hands.

Description of the molecular structure of 6. Single-crystal X-ray characterization of 3-benzyloxy-4-hydroxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (**6**) reveals diverse internal hydrogen bonding based on substituent directionality and heteroatomic internuclear distances. Thus, three distinct hydrogen bonding interactions exist: the

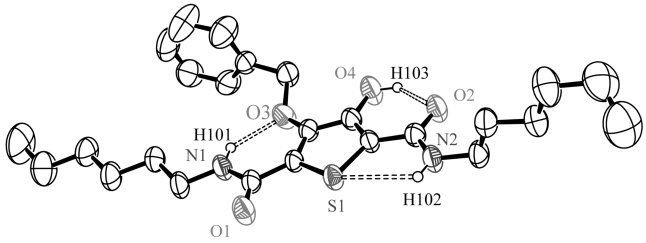


Figure 1. Molecular structure of **6**. Cell dimensions a = 10.111(3) Å, b = 11.761(3) Å, c = 12.014(3) Å, α = 72.987(5)°, β = 88.576(5)°, γ = 71.441(5)°, V = 1291.3(6) Å^3, Z = 2.[20] C-H hydrogens are omitted for clarity. Select hydrogen bonding parameters: [N1-H101···O3]: N-H = 0.88(2) Å, H···O = 2.06(2) Å, ∠ N-H···O = 138.8(19)°; [O4-H103···O2]: O-H = 0.91(3) Å, H···O = 1.80(3) Å, ∠ O-H···O = 147(3)°; [N2-H102···S1]: N-H = 0.81(2) Å; H102···S1 = 2.76(2) Å, ∠ N-H···S = 110.0(17)°.

hydroxyl oxygen and amide oxygen are at an [O···O] distance of 2.60 Å, above the range observed for terephthalamide units (2.49-2.54 Å).[3-5] The amide N-H benzyloxy [N···O] interaction stands at 2.78 Å (Figure 1). Bonds in the range of 2.5-3.2 Å may possess a stabilization energy of 16-60 kJ mol^{-1}. As expected this amide interaction is wider than those observed in terephthalamide metal complexes in which [N···O] distances range from 2.54-2.73 Å.[3,5-9] Lastly the positioning of the benzyloxo group allows for an [N···S] internuclear distance of 3.14 Å which supports the presence of a third and probably weakest hydrogen bond. While there are terephthalamide (**1**) type groups with symmetrical dihydroxy alkylation,[4,16,17] the absence of structural examples of related monoalkylated units underscores the

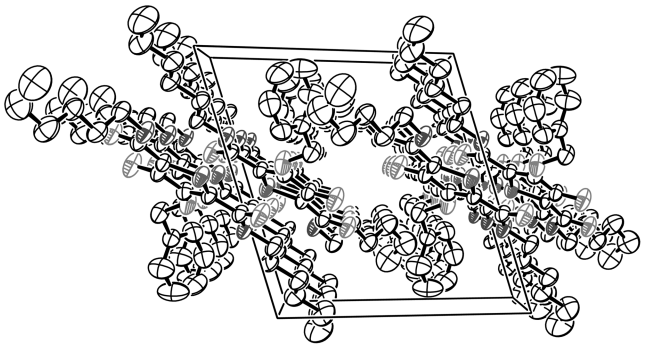
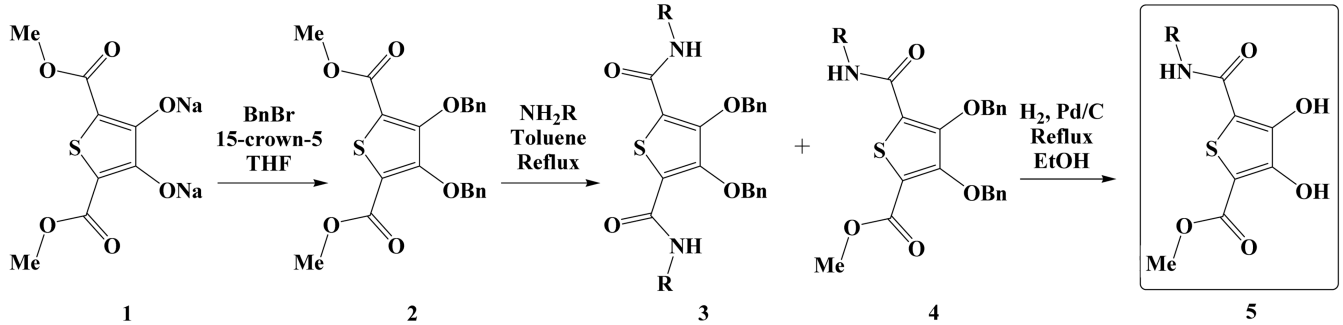


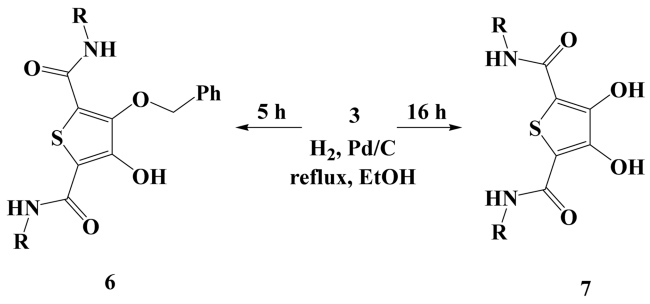
Figure 2. Packing diagram for compound **6** as viewed along the b-axis. Hydrogens are omitted for clarity.



Scheme 2. Benzyl protection/deprotection to give the amide ester derivative **2**.

Table 1. Crystal data and structure refinement for **6** (CCDC # 268969)

Empirical formula	$C_{25}H_{36}N_2O_4S$
Formula weight (g/mol)	460.62
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	Triclinic, P $\bar{1}$
a (Å)	10.111(3)
b (Å)	11.761(3)
c (Å)	12.014(3)
α (°)	72.987(5)
β (°)	88.576(5)
γ (°)	71.441(5)
Z, Calculated density (Mg / m^3)	2, 1.185
Volume (Å^3)	1291.3(6)
θ range for data collection (°)	1.78 to 27.93
Reflections collected / unique	14426 / 5685 [R(int) = 0.0531]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5685 / 0 / 433
Goodness of fit	1.007
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0533, wR2 = 0.0932
R indices (all data)	R1 = 0.1244, wR2 = 0.1065



Scheme 3. Benzyl deprotection of **3** to give singly (**6**) and doubly (**7**) deprotected species.

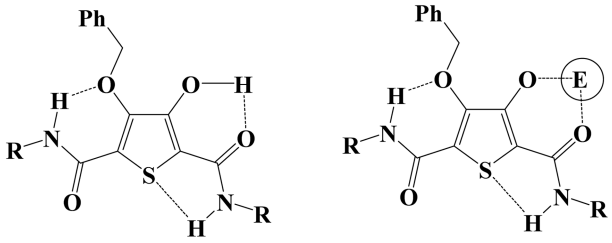
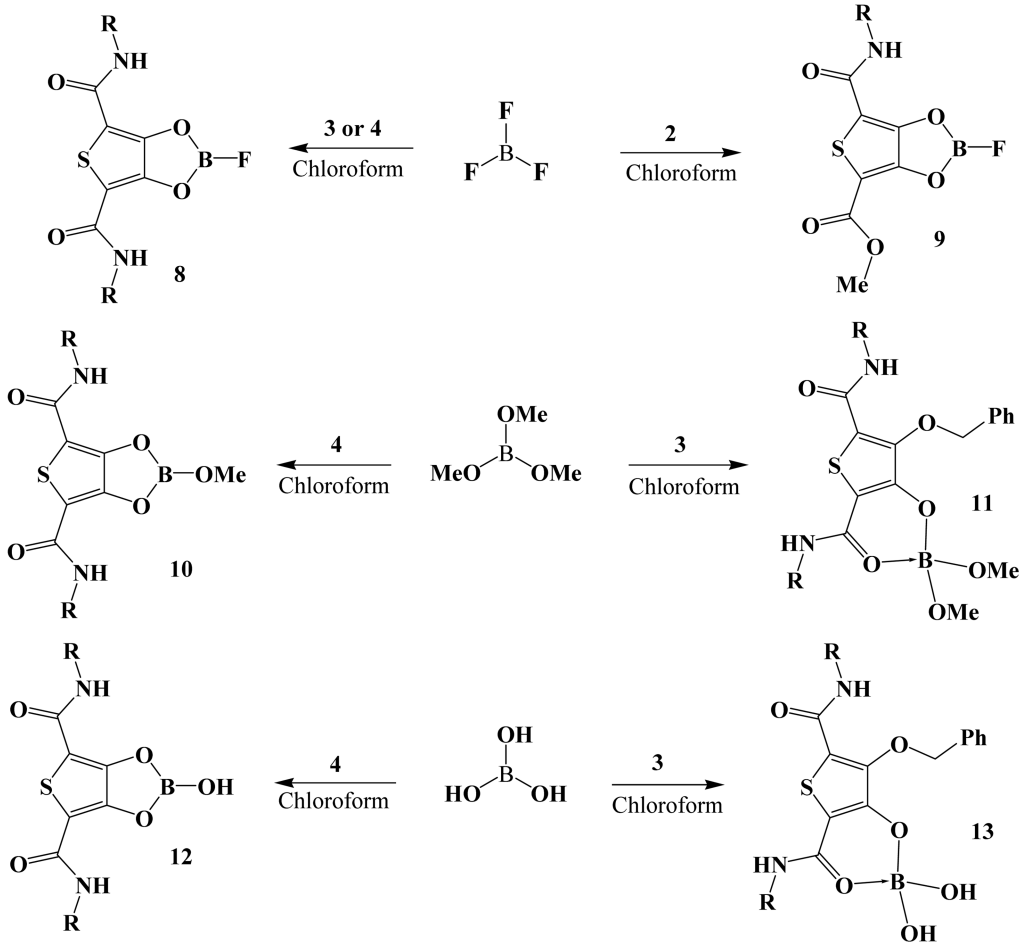
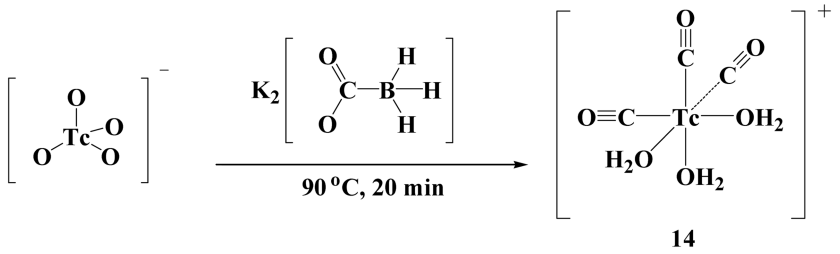


Figure 3. *Intra*molecular hydrogen bonding scheme for **6** and its proposed complexation. R = *n*-hexyl. E = metal, boron.



Scheme 4. Proposed chelation of boron that may switch modality with the benzyl group present.



Scheme 5. Preparation of **14**. Tc = ^{99m}Tc

enhancement here in asymmetric deprotection.

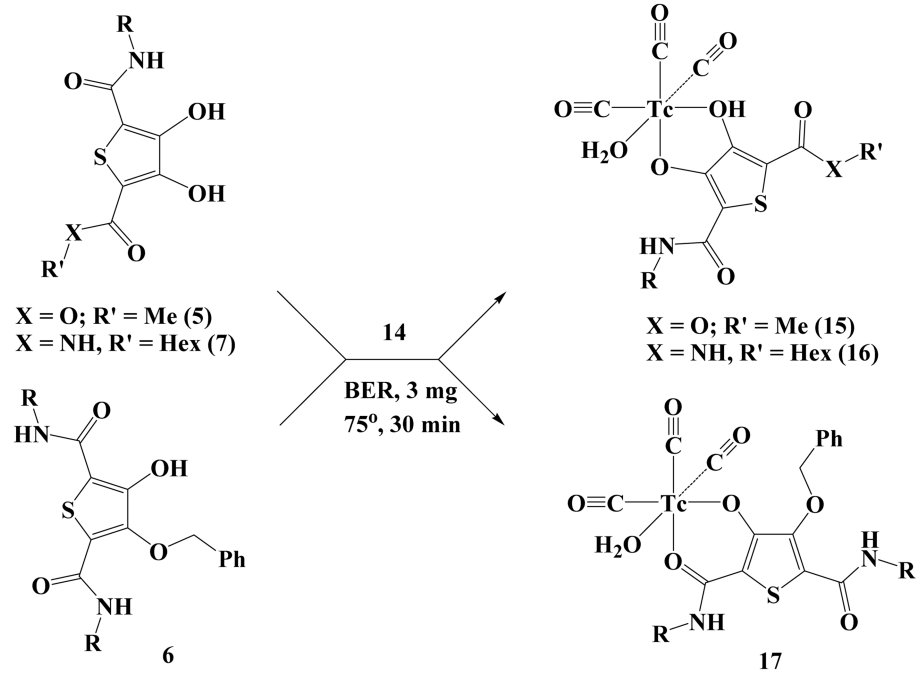
The packing diagram provided by Figure 2 shows how compound **6** is arranged in 3 dimensions. This view indicates that the the benzyl group and both hexyl groups exhibit stacking.

The structure of a single thiophene diester analogous to **1** characterized by X-ray diffraction in the form of the chelate [Rh{$(OC)_2C_2(CO_2Et)_2S$}(η^5-C_5Me_5)(PPh_3)] has been reported previously in the literature.[18] This thiophene 3,4-dihydroxylate moiety does not have the capacity for internal hydrogen bonding, but could in theory give rise to intermolecular hydrogen bonding through its carbonyl groups in the presence of protic solvents as has been observed recently for a different system recently reported in this Journal.[19] Importantly, the internal hydrogen bonding scheme for **6** is expected to remain extensive upon metal complexation, *i.e.*, the metal is expected to take the place of the chelated proton in **6** (Figure 3).

We first attempted chelation in a simplified way using three different boron compounds BF_3, $B(OMe)_3$, and $B(OH)_3$. Such reactivity is important as model compounds in applications that include recovery of boron from radiation waste streams.

We wanted to study these potential chelating agents in the context of metal ions that have medicinal and diagnostic significance. Such relevance for these types of derivatives comes from related thiophene carboxamides reported in the context of pharmacy,[14,21] and pendant benzyloxy groups as in **6** known in blood protein binding.[22] Thus, the ligands were assayed *via* [^{99m}Tc$(CO)_3(OH_2)_3$]$^+$ labeling studies, since ^{99m}Tc is a widely used radionuclide in nuclear medicine. The ^{99m}Tc(I) tricarbonyl precursor **14**, was successfully prepared with 100% radiolabelling using a modification of a literature procedure (Scheme 5).[23,24]

^{99m}Tc complexation occured after treating **14** separately with **5**, **6** and **7** through the use of a tetrahydroborate exchange resin (BER) as a reducing agent (Scheme 6). HPLC chromatograms of $^{99m}TcO_4^-$ (**14**), **15**, **16**, and **17** showed retention times of 4.6, 10.4 10.6, and 10.3 minutes, respectively (see Table 2 and Supporting Information). It is thought that complexation results in the formation of metal : ligand species in a 1 : 1 ratio due to the displacement of the technetium-bound waters with the chelating oxygen atoms of the incoming ligand unit, by inspection of available



Scheme 6. Proposed binding in complexes with a 1 : 1 metal : ligand ratio. R = *n*-hex; Tc = ^{99m}Tc. BER = tetrahydroborate exchange resin.

Table 2. Labeling yield and retention time in ^{99m}Tc compounds **14-17**

Compound (Ligand)	Labeling yield[a]	Retention time (min)
14 (–)	100%	4.6
15 (5)	100%	10.4
16 (7)	100%	10.6
17 (6)	90.3%	10.3

[a]Determined by HPLC

related crystallographic structures in which molecular structure is unequivocal. There is one such example in which a $Tc(CO)_3$ fragment accommodates three oxygen donor atoms.[25] Additionally, for rhenium, there are several mono- and multimeric complexes $Re(CO)_3$[O,O]X in which related [O,O] donors form a pentacyclic coordination ring.[26-29]

The labeling extent was less extensive with regard to the proposed structure of **17**. This is thought to be due to the flexible chelate interaction that ensues from the swiveling amide group.

Conclusions

In summary, the preparation and characterization of the asymmetric and symmetric 3,4-dihydroxythiophene-based chelators **5-7** include the molecular structure of the mono-benzylated species **6** that reveals internal hydrogen bonding which suggests the possibility for rich metal ion coordination isomerization. Compound **6** is the first such structurally characterized example of the 3,4-hydroxy-2,5-dicarboxylic type complex, not only for the thiophenes but also for the analogous furans and pyrroles currently being investigated in this laboratory, and for the heavier selenophenes and phospholes.[30] For the three chelation units 5-7, complexation was evident by way of NMR spectroscopy with boron. The technetium labeling allowed for the isolation of species with proposed complexation in a 1 : 1, ligand: ^{99m}Tc ratio.

Experimental Section

General considerations. All solvents and chemicals used herein were of analytical grade. All solvents used for spectral analysis were of spectroscopic grade. The synthesis of dimethyl thiodiglycolate and disodium 2,5-dicarboxy-3,4-dioxythiophene were prepared by the literature procedure.[11] Infrared spectra were recorded with a Bruker Equinox 55 spectrophotometer. A Vario EL III CHNS elemental analyzer was used for microanalysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with Bruker Avance 300 and Bruker Avance 400 spectrometers, and $SiMe_4$ was used as internal standard. Crystallizations were performed inside a glove box under nitrogen atmosphere.

Synthesis of 3,4-bis-benzyloxy-thiophene-2,5-dicarboxylic acid dimethyl ester (2). 15-crown-5 (11.7 g, 53.2 mmol) and benzyl bromide (11.4 g, 66.5 mmol) was added into a heterogeneous solution of disodium 2,5-dicarboxy-3,4-dioxythiophene (7.34 g, 26.6 mmol) in THF (200 mL). After refluxing for 12 h, the reaction mixture was cooled and quenched with brine. The product was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel (4 : 1 hexane/ethyl acetate) to give 8.99 g (82%) of 4-bis-benzyloxy-thiophene-2,5-dicarboxylic acid dimethyl ester as a yellowish solid. HRMS (EI) calcd 412.0981, found 412.0976; IR (KBr disk, cm^{-1}) 750, 971, 1056, 1156, 1276, 1434, 1489, 1720, 2954; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 6H, methyl protons), 5.17 (s, 4H, aliphatic protons), 7.33 (m, 6H, aromatic protons), 7.41 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 52.3, 76.5, 120.2, 128.4, 128.6, 136.2, 153.0, 161.0.

Synthesis of 3, 4-benzyloxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (3). *N*-hexyl amine (8.80 g, 87.0 mmol) was added to a 4-bis-benzyloxy-thiophene-2,5-dicarboxylic acid dimethyl ester (5.99 g, 14.5 mmol) in toluene (50 mL). After refluxing for 6 hours, the reaction mixture was cooled to room temperature, quenched with brine solution, and extracted with ethyl acetate. The organic phase was dried and concentrated. The residue was purified by chromatography on silica gel (3 : 1 hexane/ethyl acetate) to give 3,4-benzyloxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (6.30 g, 79%) as a yellowish solid. HRMS (EI) calcd 550.2865, found 550.2861; IR (KBr disk, cm^{-1}) 699, 750, 903, 1028, 1300, 1366, 1468, 1523, 1661, 2858, 2930, 3032, 3395; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 6H, J = 6.4 Hz, methyl protons), 1.22 (m, 12H, aliphatic protons), 1.35 (m, 4H, aliphatic protons), 3.23 (q, 4H, J = 6.9, aliphatic protons), 5.21 (s, 4H, aliphatic protons), 7.00 (m, 2H, amide protons), 7.38 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 26.5, 29.2, 31.3, 39.3, 76.3, 126.0, 128.5, 128.9, 129.2, 135.0, 146.0, 160.2.

Synthesis of 3,4-bis-benzyloxy-5-hexylcarbamoyl-thiophene-2-carboxylic acid methyl ester (4). *N*-hexyl amine (4.42 g, 43.7 mmol) was added to 4-bis-benzyloxy-thiophene-2,5-dicarboxylic acid dimethyl ester (3.00 g, 7.28 mmol) in toluene (30 mL). After refluxing for 3 hours, the reaction mixture was cooled to room temperature, quenched with brine solution, and extracted with ethyl acetate. The organic phase was dried and concentrated. The residue was purified by chromatography on silica gel (4 : 1 hexane/ethyl acetate) to give 3,4-bis-benzyloxy-5-hexylcarbamoyl-thiophene-2-carboxylic acid methyl ester (2.70 g, 77%) as a yellowish solid. HRMS (EI) calcd 481.1923, found 481.1924; IR (KBr disk, cm^{-1}) 737, 1050, 1167, 1291, 1363, 1476, 1532, 1656, 1719, 2858, 2930, 3391; ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 3H, methyl protons), 1.22 (m, 6H, aliphatic protons), 1.33 (m, 2H, aliphatic protons), 3.24 (q, 2H, J = 6.7, aliphatic protons), 3.88 (s, 3H, methyl protons), 5.19 (s, 2H, aliphatic protons), 5.26 (s, 2H, aliphatic protons), 7.26-7.51 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 26.4, 29.1, 31.3, 39.3, 52.1, 76.0, 77.2, 118.7, 126.4, 128.3, 128.5, 128.6, 128.8, 129.0, 135.4, 136.1, 147.2, 152.1, 160.1, 160.9, 161.1.

Synthesis of 5-hexylcarbamoyl-3,4-dihydroxy-thiophene-2-carboxylic acid methyl ester (5). Pd/C (298 mg, 0.28 mmol) was added to 3,4-bis-benzyloxy-5-hexylcarbamoyl-thiophene-2-carboxylic acid methyl ester (2.70 g, 5.61 mmol) in ethanol (50 mL). After removing air under vacuum, the round bottom flask was filled with H_2. The reaction mixture was refluxed for 16 hours and was cooled to room tempurature. Pd/C was filtered and the residue solution was concentrated. The residue was purified by chromatography on silica gel (methanol) to give 5-hexylcarbamoyl-3,4-dihydroxy-thiophene-2-carboxylic acid methyl ester (1.59 g, 94%) as a white solid. HRMS (EI) calcd 301.0984, found 301.0980; IR (KBr disk, cm^{-1}) 749, 1030, 1327, 1441, 1557, 1633, 2860, 2934, 3298; ^{1}H NMR ($CDCl_3$) δ 0.77 (m, 3H, methyl protons), 1.15-1.26 (m, 6H, aliphatic protons), 1.47-1.54 (m, 2H, aliphatic protons), 3.34 (q, 2H, J = 6.4, aliphatic protons), 3.80 (s, 3H, methyl protons), 7.13 (m, H, amide protons), 9.9 (br, 2H, hydroxyl protons); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.5, 26.5, 29.4, 31.4, 39.8, 52.3, 104.1, 112.9, 147.8, 152.3, 164.0, 166.0.

Synthesis of 3-benzyloxy-4-hydroxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (6). Pd/C (287 mg, 0.27 mmol) was added to 3,4-benzyloxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (3.00 g. 5.45 mmol) in ethanol. After removing air under vacuum, the round bottom flask was filled with H_2 using a balloon. The reaction mixture was refluxed for 5 hours and was then cooled to room temperature. Pd/C was filtered, and the solution was concentrated. The residue was purified by chromatography on silica gel (3 : 1 hexane/ethyl acetate) to give 3-benzyloxy-4-hydroxy-thiophene-2,5-dicarboxylic acid bis-propylamide (2.23 g, 89%) as a white solid. HRMS (EI) calcd 460.2865, found 460.2389; IR (KBr disk, cm^{-1}) 745, 1030, 1265, 1324, 1478, 1538, 1619, 2931, 3308; ^{1}H NMR ($CDCl_3$) δ 0.83-0.90 (m, 6H, methyl protons), 1.17-1.24 (m, 6H, aliphatic protons), 1.30-1.36 (m, 8H, aliphatic protons), 1.57 (m, 2H, aliphatic protons), 3.24 (q, 2H, J = 6.1 Hz, aliphatic protons), 3.39 (q, 2H, J = 6.6 Hz, aliphatic protons), 5.41 (s, 2H, aliphatic protons), 5.94 (br, 2H, amide protons), 7.34-7.40 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 22.5, 26.5, 26.6, 29.1, 29.6, 31.3, 31.4, 39.4, 39.6, 74.8, 107.2, 121.9, 128.6, 128.7, 128.8, 135.9, 143.7, 154.3, 160.8, 165.9.

Synthesis of 3,4-dihydroxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (7). Pd/C (319 mg, 0.30 mmol) was added to 3,4-benzyloxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (3.30 g. 6.00 mmol) in ethanol. After removing air under vacuum, the round bottom flask was filled with H_2 with the aid of a gas filled balloon. The reaction mixture was refluxed for 16 hours and then cooled to room temperature. Pd/C was filtered, and the residue solution was concentrated. The residue was purified by chromatography on silica gel (methanol) to give 3,4-dihydroxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (2.09 g, 96%) as a white solid. HRMS (EI) calcd 370.1926, found 370.1923; IR (KBr disk, cm^{-1}) 750, 1276, 1333, 1458, 1542, 1603, 2361, 2928, 3007; ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 6H, methyl protons), 1.31 (m, 12H, aliphatic protons), 1.56 (m, 4H, aliphatic protons), 3.39 (q, 4H, J = 6.9, aliphatic protons), 5.79 (br, 2H, amide protons), 10.2 (br, 2H, hydroxyl protons). ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 26.6, 29.5, 31.4, 39.7, 114.1, 149.4, 164.3.

General procedure for the preparation of boron containing compounds. Thiophene-based units (0.06 mmol) were dissolved in $CDCl_3$ (0.50 mL); a sample of boron reagent (0.10 mmol) was then added to the reaction mixture. After stirring, the reaction mixture was characterized by NMR spectroscopy. Products are characterized by ^{1}H NMR and in some cases ^{11}B and ^{13}C NMR spectroscopy.

The reaction of 3,4-dihydroxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (4) with BF_3·OEt_2. ^{1}H NMR ($CDCl_3$) 0.86 (m, 6H, methyl protons), 1.30 (m, 12H, aliphatic protons), 1.68 (m, 4H, aliphatic protons), 3.57 (m, 4H, aliphatic protons), 8.10 (s, 2H, amide protons); ^{13}C NMR ($CDCl_3$) 13.8, 22.3, 26.2, 28.2, 31.1, 42.3, 105.7, 154.8, 163.1; ^{11}B NMR ($CDCl_3$) 1.00.

The reaction of 5-hexylcarbamoyl-3,4-dihydroxy-thiophene-2-carboxylic acid methyl ester (2) with BF_3·OEt_2. ^{1}H NMR ($CDCl_3$) δ 0.86 (m, 3H, methyl protons), 1.36 (m, 6H, aliphatic protons), 1.68 (m, 2H, aliphatic protons), 3.56 (q, 2H, aliphatic protons), 3.91 (s, 3H, aliphatic protons), 7.89 (m, 1H, amide proton), 8.54 (br, 1H, hydroxyl proton); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.4, 26.2, 28.4, 31.1, 42.1, 53.0, 102.6, 110.0, 151.7, 155.3, 163.7, 165.1; ^{11}B NMR($CDCl_3$) δ 0.90.

The reaction of 5-hexylcarbamoyl-3,4-dihydroxy-thiophene-2-carboxylic acid methyl ester (2) with $B(OMe)_3$. ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 3H, methyl protons), 1.31-1.40 (m, 6H, aliphatic protons), 1.54-1.61 (m, 2H, aliphatic protons), 3.37-3.44 (m, 2H, aliphatic protons), 3.91 (s, 3H, aliphatic protons), 6.02 (br, 1H, amide proton), 10.45 (br, 1H, hydroxyl proton).

The reaction of 5-hexylcarbamoyl-3,4-dihydroxy-thiophene-2-carboxylic acid methyl ester (2) with $B(OH)_3$. ^{1}H NMR ($CDCl_3$) δ 0.88-1.91 (m, 3H, methyl protons), 1.32 (m, 6H, aliphatic protons), 1.59-1.61 (m, 2H, aliphatic protons), 3.39-3.44 (m, 2H, aliphatic protons), 3.89 (s, 3H, methyl protons), 5.82 (s, 1H, amide proton), 9.30 (s, 1H, hydroxyl proton), 10.51 (s, 1H, hydroxyl proton).

The reaction of 3-benzyloxy-4-hydroxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (3) with BF_3·OEt_2. ^{1}H NMR ($CDCl_3$) δ 0.84-0.87 (m, 6H, methyl protons), 1.28-1.34 (m, 12H, aliphatic protons), 1.65-1.67 (m, 4H, aliphatic protons), 3.58 (br, 4H, aliphatic protons), 7.99 (s, 2H, amide protons); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 26.2, 28.2, 31.1, 42.4, 105.8, 154.9, 163.2; ^{11}B NMR ($CDCl_3$) δ 0.98.

The reaction of 3-benzyloxy-4-hydroxy-thiophene-2,5-dicarboxylic acid bis-hexylamide (3) with $B(OMe)_3$. ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6H, methyl protons), 1.22 (m, 6H, aliphatic protons), 1.31 (m, 8H, aliphatic protons), 1.63 (m, 2H, aliphatic protons), 3.24 (m, 2H, aliphatic protons), 3.48 (m, 2H, aliphatic protons), 3.64 (s, 3H, methyl protons), 5.54 (s, 1H, amide proton), 7.38-7.40 (m, 5H, aromatic protons), 7.52 (br, 1H, amide proton), 8.32 (br, 1H, hydroxyl proton).

Preparation of ^{99m}Tc tricarbonyl precursors. $Na^{99m}TcO_4$

was obtained by solvent extraction from a commercial ^{99}Mo/^{99m}Tc generator (Unitech 500, Samyoung Inc., Seoul). Labeling yield was characterized by high performance liquid chromatography (HPLC) equipped with a radiometric detector using a reversed phase μ-Bondapak C-18 column (3.9 × 300 mm, Waters, USA) applying a gradient system with 0.05 M tetraethylammoniumphosphate (TEAP) buffer and 100% methanol. HPLC gradient: 0-30 min: a linear gradient to 0% TEAP/100% methanol from 100% TEAP/0% methanol. The flow rate was 1 mL per min.

Preparation of $[^{99m}Tc(CO)_3(OH_2)_3]^+$ (14). The ^{99m}Tc tricarbonyl precursor **14** $[^{99m}Tc(CO)_3(OH_2)_3]^+$ was prepared using a modification of the procedure described by Alberto *et al.*[23,24] A 10 mL-vial containing potassium boranocarbonate (5.9 mg, 0.043 mmol), sodium tetraborate (2.85 mg, 0.007 mmol), potassium sodium tartrate (10.4 mg, 0.037 mmol) and sodium carbonate (7.15 mg, 0.067 mmol) was capped with a rubber stopper and lyophilized. One mL of sodium pertechnetate ($Na^{99m}TcO_4$) with up to 3.7 GBq was added into the vial via syringe and then heated to 90 °C in a boiling water bath for 20 min. After rapid cooling to room temperature, 0.15 mL of 0.1 N HCl and 1.0 mL of buffer solution (0.05 M phosphate buffer, pH 7.4) were added to neutralize **14**.

Preparation of compound 15. One mL (370 MBq) of ^{99m}Tc(I) tricarbonyl precursor **14** and a solution 0.1 mL (1 mg) of **5** were added into a 10 mL vial containing 3 mg of BER and the reaction mixture was heated at 75 °C for 30 min. After cooling it to room temperature, ^{99m}Tc tricarbonyl complex **5** was characterized by HPLC.

Preparation of compound 16. One mL (370 MBq) of ^{99m}Tc(I) tricarbonyl precursor **14** and a 0.1 mL (1 mg) solution of **7** were added into a 10 mL vial containing 3 mg of tetrahydroborate exchange resin (BER) and the reaction mixture was heated 75 °C for 30 min. After cooling it to room temperature, ^{99m}Tc tricarbonyl compound **16** was characterized by HPLC.

Preparation of compound 17. ^{99m}Tc(I) tricarbonyl precursor **1** (1 mL, 370 MBq) and a solution of **6** (0.1 mL, 1 mg) were added into a 10 mL vial containing 3 mg of BER. This reaction mixture was heated at 75 °C for 30 min. After cooling it to room temperature, ^{99m}Tc tricarbonyl **6** was characterized by HPLC.

Crystallographic Structural Analysis. Compound **6** was dissolved in $CHCl_3$, and allowed to evaporate slowly. A crystal of the size $0.4 \times 0.2 \times 0.1$ mm^3 was selected. Reflection data for **3** were collected on a Bruker 1K SMART CCD-based diffractometer with graphite-monochromated MoKα radiation (λ = 0.7107 Å). The hemisphere of reflection data were collected as ω scan frames with 0.3°/frame and an exposure time of 5 s/frame. Cell parameters were determined and refined by the SMART program (SMART, version 5.0, Data collection software, Bruker AXS, Inc., Madison, WI, 1998). Data reduction was performed using SAINT software.[31] The data were corrected for Lorentz and polarization effects. An empirical absorption correction was applied using the SADABS program.[32] The structures of the compounds were solved by direct methods and refined by full matrix least-squares methods using the SHELXTL program package with anisotropic thermal parameters for all non-hydrogen atoms.

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Supporting Information. Cif file of **6**, ^{1}H, ^{11}B, ^{13}C NMR spectra, HPLC Data.

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