Synthesis of Cyclic Tetrabenzimidazole Ligands Elaborated with Hydrogen Bonds in the Secondary Coordination Sphere

Minkyu Kim
Department of Chemistry, Seoul National University

Abstract

New ligands based on a cyclic tetrabenzimidazole structure have been designed to install hydrogen bonds in the secondary coordination sphere of the metal–ligand complex. Two synthetic pathways have been pursued, each having penta- and tetrasubstituted benzene as a target monomer. The latter requires a pyridyl halide derivative with an alkyl chain to enhance the solubility. Two different derivatives have thus been designed and synthesized. If the synthesis is completed, the resulting products are anticipated to have unusual structural and electronic properties as ligands. Specifically, a cyclic array of hydrogen bonds from the pyridine nitrogen atoms should be able to "remotely" control the electronic environment immediate to the metal.

Keywords: macrocycle, tetrabenzimidazole, secondary coordination sphere, hydrogen bond

1 Introduction

The importance of secondary coordination sphere has been investigated in a few metal-ligand complex, mostly in biological systems. According to the Poulos—Kraut mechanism, which is a hypothesis to explain the formation of Compound I from the $[\mathbf{L}Fe(H_2O_2)]^+$ (**L** = porphyrinate) species in horseradish peroxidase (HRP), the proton associated with the proximal oxygen atom does not migrated directly to the distal oxygen due to a high energy barrier. Instead, the ferric hydrogen peroxide complex is first deprotonated by a distal histidine, and the distal OH group is subsequently pulled by an arginine and re-protonated by the protonated histidine to produce Compound I and a water molecule (Figure 1).

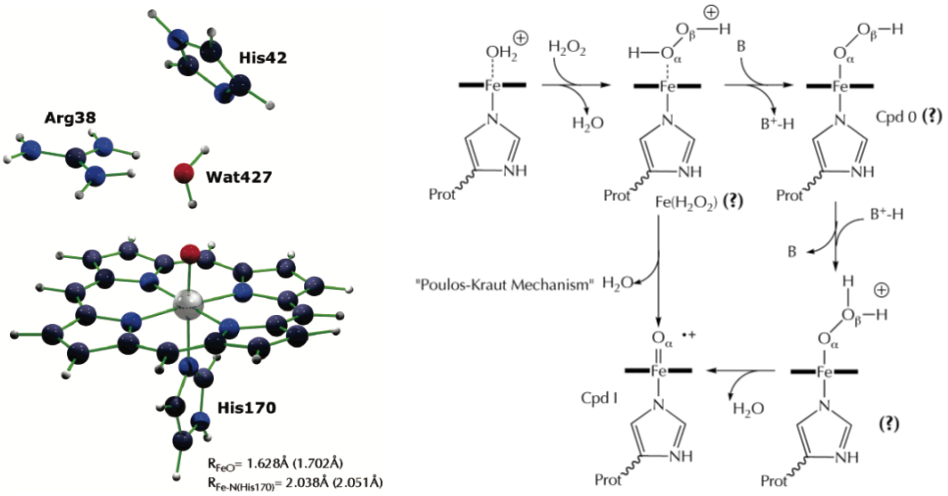


Figure 1. Schematic description of the mechanism for the formation of Compound I in presence of H_2O_2

In this report is described the design of new ligands to mimic such process: protonation and deprotonation of the atoms that are distal from the central metal center result in the change of the electronic environment of the metal. In this study, cyclic tetrabenzimidazole structure is targeted. As shown in Figure 1, this molecule has a "porphyrin-like" macrocyclic N4 skeleton. The C–H bonds at the 2- and 4-positions of benzimidazole are essentially perpendicular to each other, allowing the molecule to form a rigid tetramer via direct C–C linkage (Figure 2).

Around the cyclic tetrabenzimidazole core are introduced heterocyclic motifs to function as hydrogen bond acceptor (HBA) groups. Introduced at the 7-position of the benzimidazole "repeat", such HBA units form tight hydrogen bonds with exocyclic N–H groups. In addition, alkyl chains need to be installed as solubility-enhancing groups for the otherwise intractable tetrabenzimidazole. Based on our design, these alkyl chains can be attached either to the 5- or 6-position, or to the heterocycle on the 7-

position of the tetrabenzimidazole core.

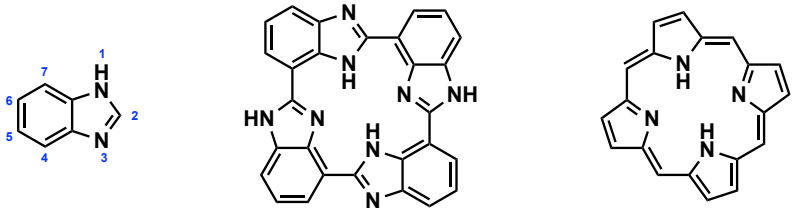
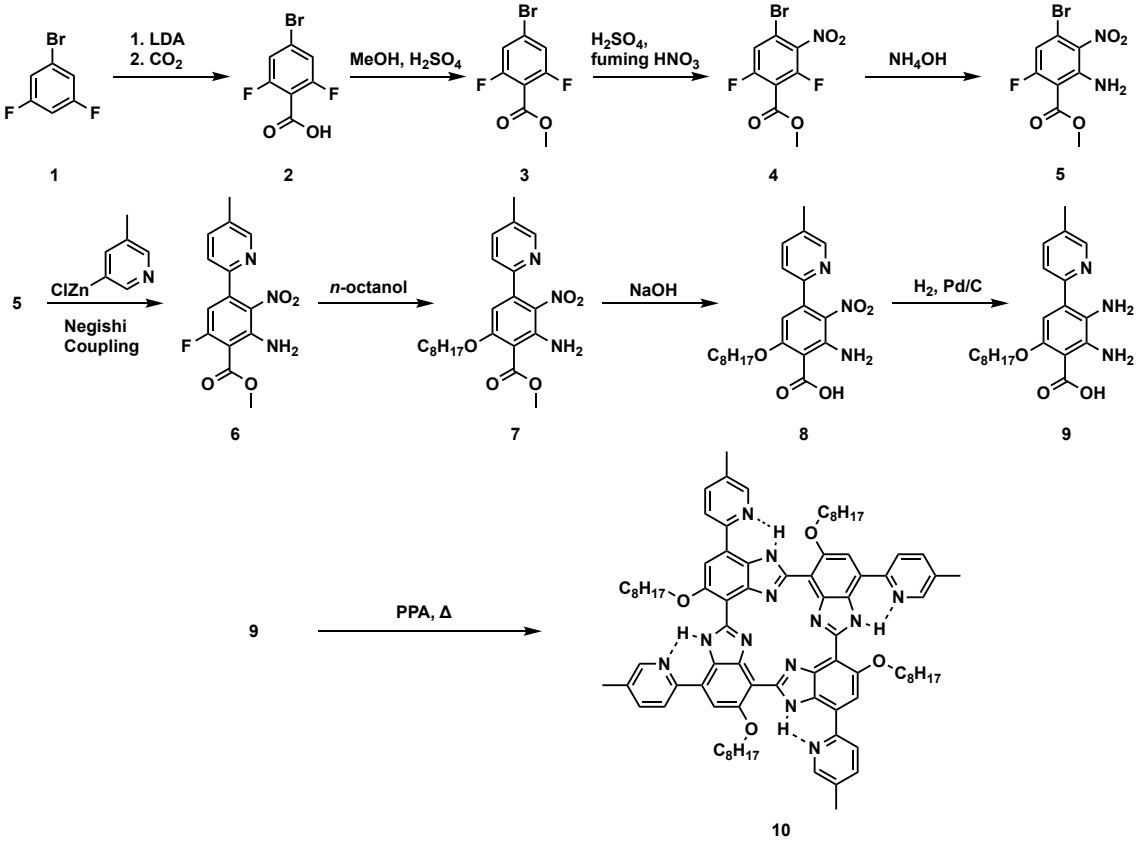


Figure 1. Chemical structure of the benzimidazole, cyclic tetrabenzimidazole, and porphyrin (left to right).

2 Results and Discussion

Two synthetic routes have been explored to prepare cyclic tetrabenzimidazole derivatives. As outlined in Scheme 1, synthetic route **A** commences with 1-bromo-3,5-difluorobenzene (**1**) to acquire a penta-substituted benzene (**9**) as the key building block. Five functional groups attached to the benzene are 2-pyridyl, alkyl ether, diamino, and carboxylic acid group. Among them, the pyridyl group, which can be introduced through a variety of (hetero)biaryl coupling reactions such as Negishi coupling, serves as HBA in the secondary coordination sphere of the target compound. The alkyl ether group is installed to increase the overall solubility of the material. A condensation reaction of the two amino groups and the carboxylic acid group forms a benzimidazole structure, connecting four monomers into a cyclic tetramer. Consequently, eight water molecules are released per one product molecule in the last step of the synthesis.

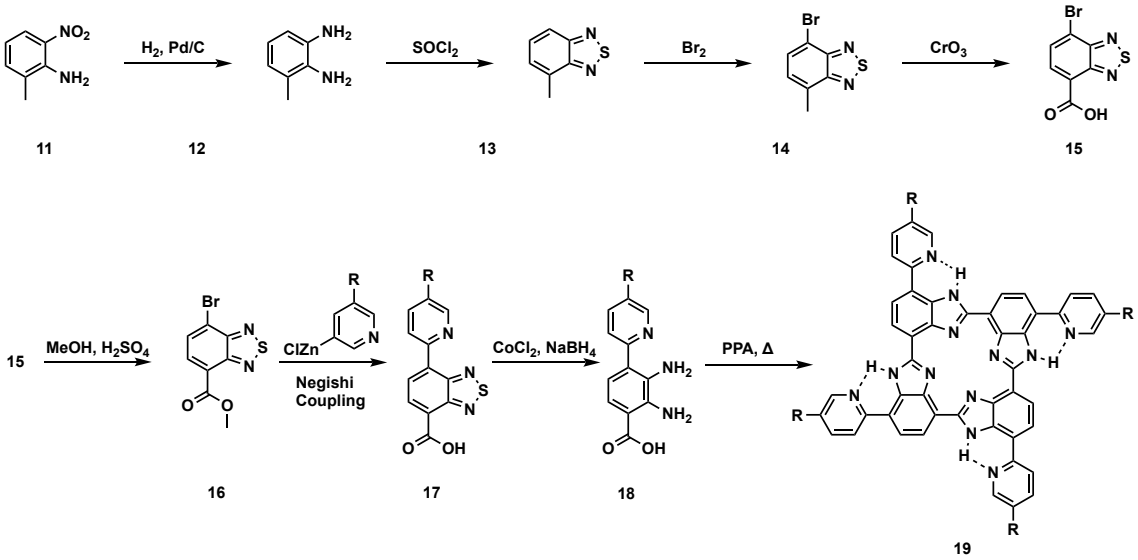


Scheme 1. Synthetic route **A** toward a cyclic tetrabenzimidazole **10**.

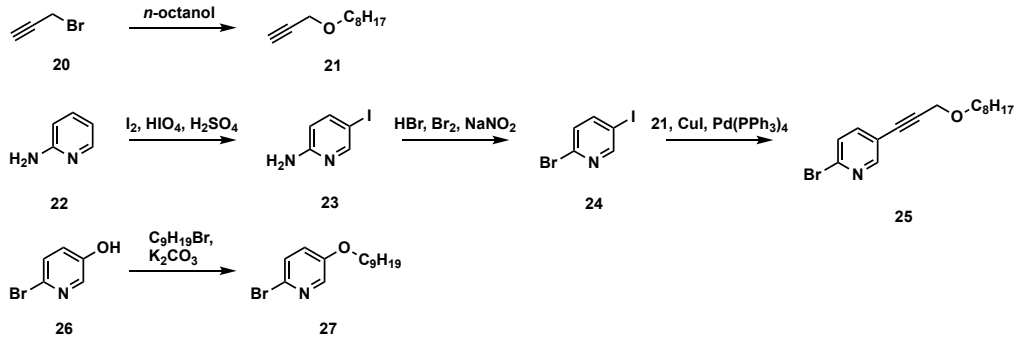
On the other hand, synthetic route **B** commences with 2-methyl-6-nitroaniline (**11**) to arrive at a tetrasubstituted benzene (**18**) as the key intermediate (Scheme 2). In this case, the solubilizing alkyl chain

is attached to the pyridyl group, instead of the benzene ring. This strategy requires preparation of pyridyl halide derivatives having an alkyl chain. For this, two different methods have been devised. As shown in Scheme 3, one route involves a Sonogashira cross-coupling reaction to install a terminal alkyne group to furnish **25**. The other route installs an alkyl ether group on hydroxypyridine via simple S_N2 reaction to afford **27**. Both **25** and **27** could be used as a pyridyl moiety to be attached to the benzene ring in the synthetic route **B** shown in Scheme 2.

Over a period of the 9 weeks for the Undergraduate Winter Internship Program, the first four steps of the synthetic route **A** were carried out to obtain **5**. In addition, two pyridine derivatives **25** and **27** were designed and pepared. Detailed experimental procedures are provided in the following Section. In each synthetic step, flash column chromatography and ^{1}H-NMR spectroscopy were mainly used to purify and characterize the product. Among the products obtained, **25** needed further purification to eliminate byproducts.



Scheme 2. Synthetic route **B** toward a cyclic tetrabenzimidazole **19**.



Scheme 3. Synthetic routes to pyridine derivatives having alkyl chain.

3 Summary and Outlook

Two different synthetic pathways were designed and executed toward the synthesis of cyclic tetrabenzimidazole derivatives. Three compounds **5**, **25**, and **27** were obtained. In the future, these aryl halides would be subjected to coupling reactions to afford penta- or tetrasubstituted benzenes by straightforward functional group transformations.

4 Experimental Section

4.1 4-Bromo-2,6-difluorobenzoic acid[1] (**2**)

To a degassed solution of 1-bromo-3,5-difluorobenzene **1** (1.60 mL, 13.9 mmol) in dry THF (30 mL) at –78 ºC was added lithium diisopropylamide (2.0 M in THF/heptane/ethyl benzene, 7.0 mL) under nitrogen.

The resulting dark brown mixture was allowed to react at –78 ˚C for 2 h. Excess amount of dry ice was then added and the mixture was allowed to warm to room temperature and left to react for an additional 41 h. Volatile fractions were removed under reduced pressure, and the residual material was dissolved in water (150 mL), filtered, and washed with ether (100 mL × 2). Aqueous layers were combined, and acidified by adding conc HCl. The resulting white solidified material was isolated by filtration, washed with water, and dried at r.t. for 5 h to furnish **2** as a white solid (1.74 g, 7.36 mmol, 53%). The product was used in the following step without further purification. R_f = 0.18 (EA). ^{1}H NMR (300 MHz, acetone-d_6): δ ppm 7.35 – 7.56 (m, 2H).

4.2 Methyl 4-bromo-2,6-difluorobenzoate[1] (**3**)

To a solution of **2** (1.74 g, 7.36 mmol) in methanol (45 mL) was slowly added conc H_2SO_4 (1.18 mL). The mixture was refluxed at 75ºC for 44 h. Volatile fractions were removed under reduced pressure and the residual material was dissolved in EA (20 mL), washed with sodium hydrogen carbonate solution (30 mL × 3) and brine (20 mL). Volatile fractions were removed under reduced pressure to furnish **3** as a pale pink solid (1.32 g, 5.26 mmol, 72%). The product was used in the following step without further purification. R_f = 0.68 (EA/hex, 1:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ ppm 3.96 (s, 3H) 7.13 – 7.23 (m, 2H).

4.3 Methyl 4-bromo-2,6-difluoro-3-nitrobenzoate[2] (**4**)

To concentrated sulfuric acid (2.00 mL, 37.5 mmol), cooled to 0ºC, was added fuming nitric acid (1.00 mL, 23.8 mmol) dropwise and the resulting mixture was stirred at 0ºC for additional 5 min. To the mixture was slowly added **3** (1.24 g, 4.94 mmol) with a spatula and was stirred at 0ºC for 1 h. The mixture was poured into ice-cold water (50 mL), stirred for 30 min, and filtered. The residual material was washed with water until the pH becomes ~7 and then dried at r.t. for 1 d to furnish **4** as a yellow solid (1.28 g, 4.31 mmol, 82%). The product was used in the following step without any further purification. R_f = 0.50 (EA/hex, 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ ppm 3.94 (s, 3H) 6.74 (d, 1H, J = 10.27 Hz).

4.4 Methyl 2-amino-4-bromo-6-fluoro-3-nitrobenzoate (**5**)

To a solution of **4** (0.50 g, 1.7 mmol) in ethanol (20 mL) was slowly added ammonium hydroxide (29% v/v in water, 0.34 mL, 2.5 mmol). The resulting brown mixture was stirred at room temperature for 22 h. Volatile fractions were removed under reduced pressure and the residual material was poured into $NaHCO_3$ solution (50 mL) and extracted with dichloromethane (30 mL × 3). Organic layers were combined, dried over Na_2SO_4, and filtered. Volatile fractions were removed under reduced pressure and the residual material was purified by flash column chromatography on SiO_2 (EA : hexane = 1:9, v/v) to furnish **5** as a yellow solid (0.378 g, 1.29 mmol, 76%) and methyl 2,6-diamino-4-bromo-3-nitrobenzoate (0.144 g, 0.496 mmol, 29%) as a minor product. R_f = 0.53 (EA/hex, 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): δ ppm 3.94 (s, 3H) 6.74 (d, 1H, J = 10.27 Hz) 7.09 (br s, 2H).

4.5 1-(Prop-2-yn-1-yloxy)octane[3] (**21**)

To a solution of propargyl bromide **20** (1.20 mL, 10.8 mmol) in THF (7 mL) was added *n*-octanol (1.0 mL, 6.4 mmol) and sodium hydroxide (1.07 g, 26.7 mmol). The resulting light brown mixture was allowed to warm to room temperature and stirred for 60 h. The mixture was poured into ether (20 mL) and water (50 mL). Aqueous fraction was extracted by ether (30 mL × 2) and the combined organic extracts were washed with HCl (10% v/v, 50 mL), $NaHCO_3$ solution (30 mL × 3), and brine (20 mL), dried over Na_2SO_4, and filtered. Volatile fractions were removed under reduced pressure. The residual material was purified by flash column chromatography on SiO_2 (EA : hexane = 1:5, v/v) to furnish **21** as a yellow oil (0.545 g, 3.24 mmol, 30%). R_f = 0.63 (EA/hex, 1:5). ^{1}H-NMR (300 MHz, $CDCl_3$): δ ppm 0.83 – 0.95 (m, 3H) 1.27 (br s, 10H) 1.59 (m, 2H) 2.41 (t, 1H, J = 2.35 Hz) 3.51 (t, 2H, J = 6.69 Hz) 4.13 (d, 2H, J = 2.26 Hz).

4.6 2-Amino-5-iodopyridine[4] (**23**)

To a solution of 2-aminopyridine **22** (0.941 g, 10.0 mmol), periodic acid (0.456 g, 0.2 equiv.), and iodine (1.015 g, 0.4 equiv.) in acetic acid (6 mL) and water (1.2 mL) was slowly added concentrated sulfuric acid (0.18 mL, 3.4 mmol). The resulting dark purple mixture was refluxed at 80ºC for 4 h to give light brown mixture. The mixture was quenched with diluted sodium hydroxide solution and the unreacted iodine was removed by adding excess amount of aqueous $Na_2S_2O_3$ solution. The mixture was extracted by ether (30 mL × 3) and the combined organic extracts were washed with $NaHCO_3$ solution (30 mL × 3) and brine (20 mL), dried over Na_2SO_4, and filtered. Volatile fractions were removed under reduced pressure . The residual material was purified by flash column chromatography on SiO_2 (EA : hexane = 1:1, v/v) to furnish **23** as a

white pellet-like solid (0.726 g, 3.30 mmol, 33%) and 2-amino-3,5-diiodopyridine (0.380 g, 1.10 mmol, 11%) as a minor product. R_f = 0.13 (EA/hex, 1:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ ppm 4.45 (br s, 2H) 6.36 (d, 1H, *J* = 8.67 Hz) 7.63 (dd, 1H, *J* = 8.67, 2.26 Hz) 8.23 (d, 1H, *J* = 2.07 Hz).

4.7 2-Bromo-5-iodopyridine[4] (**24**)

To a solution of **23** (0.142 g, 0.646 mmol) in hydrobromic acid (1.00 mL), cooled below 0ºC in an ice salt bath, was added aqueous sodium nitrite solution (3.36 M, 0.50 mL) dropwise to give a dark brown solution. Bromine (0.10 mL, 3.0 equiv.) was then added and the mixture was allowed to warm to room temperature and left to react for 23 h. The mixture was quenched with diluted NaOH solution (10 mL) and the unreacted bromine was removed by adding excess amount of aqueous $Na_2S_2O_3$ solution (50 mL). The mixture was extracted by ether (50 mL × 3) and the combined organic extracts were washed with Na_2HCO_3 solution (50 mL × 2) and brine (50 mL), dried over Na_2SO_4, and filtered. Volatile fractions were removed under reduced pressure. The residual material was purified by flash column chromatography on SiO_2 (EA : hexane = 1:1, v/v) to furnish **24** as a white solid (0.098 g, 0.34 mmol, 53%). R_f = 0.80 (EA/hex, 1:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ ppm 7.29 (d, 1H, *J* = 8.29 Hz) 7.82 (dd, 1H, *J* = 8.29, 2.45 Hz) 8.59 (d, 1H, *J* = 2.45 Hz).

4.8 2-Bromo-5-(3-(octyloxy)prop-1-yn-1-yl)pyridine[5] (**25**)

A degassed solution of **24** (0.098 g, 0.34 mmol), **19** (0.061 g, 0.37 mmol), copper iodide (1.96 mg, 3 mol%), and palladium tetrakis(triphenylphosphine) (11.9 mg, 3 mol%) in 3 mL of dry triethylamine (3.0 mL) and toluene (1.5 mL) was stirred for 42 h at 60ºC in a sealed flask under nitrogen. Volatile fractions were removed under reduced pressure and diluted in ether (30 mL). It was then washed with $NaHCO_3$ solution (30 mL × 2) and brine (30 mL), dried over Na_2SO_4, and filtered. The residual material was filtered through through a silica gel column (EA/hexane, 1:1) to furnish *crude product* containing **25** as a yellow oil (yield not measured). R_f = unknown. ^{1}H-NMR: messy. (Further purification is needed.).

4.9 2-Bromo-5-(nonyloxy)pyridine[6] (**27**)

To a solution of 2-bromo-5-hydroxypyridine (0.348 g, 2.00 mmol) in 20 mL of DMF was added nonyl bromide (0.573 mL, 1.5 equiv.) and potassium carbonate (0.553 g, 2.0 equiv.) and the mixture was stirred for 19 h at 75ºC in a sealed flask. Volatile fractions were removed under reduced pressure and diluted in ether (50 mL). It was then washed with $NaHCO_3$ solution (30 mL × 3) and brine (50 mL), dried over Na_2SO_4, and filtered. The residual material was purified by flash column chromatography on SiO_2 (dichloromethane only) to furnish **27** as a white solid (0.308 g, 1.22 mmol, 61%). R_f = 0.76 (dichloromethane). ^{1}H-NMR: (300 MHz, $CDCl_3$): δ ppm 0.79 – 1.00 (m, 3H) 1.18 – 1.51 (m, 14H) 1.71 – 1.90 (m, 2H) 3.97 (t, 2H, *J* = 6.50 Hz) 7.08 (dd, 1H, *J* = 3.20 Hz) 7.35 (dd, 1H, *J* = 8.67, 0.57 Hz) 8.05 (d, 1H)

Acknowledgements

This work was done as a part of the Undergraduate Winter Internship Program in the Department of Chemistry, Seoul National University. I would like to thank Professor Dongwhan Lee and Seyong Kim for all the help and advice.

References

1. Chen, Z. *et al*. Chen, Z.; Ginn, J. D.; Hickey, E. R.; Liu, W.; Mao, C.; Morwick, T. M.; Nemoto, P. A.; Spero, D.; Sun, S. Substituted benzothiophene compounds and uses thereof WO 2005012283 A1, Feb 10, 2005.
2. Colón, M.; Fitch, D. M. Prolyl Hydroxylase Inhibitors US 20100305133 A1, Dec 2, 2010.
3. Francis, D. V.; Miles, D. H.; Mohammed, A. I.; Read, R. W.; Wang, X. Towards functional fluorous surfactants. Synthesis of hydrophilic fluorous 1,2,3-triazolylmethyl ethers and di(1,2,3-triazolylmethyl) ethers. *J. Fluor. Chem.*, **2011**, *132*, 898–906.
4. Hama, Y.; Nobuhara, Y.; Aso, Y.; Otsubo, T.; Ogura, F. "Preparation and properties of pyridine-analogue of TCNQ dianion salt." *Bull. Chem. Soc. Jap.*, **1988**, *61*, 1683–1686.
5. Grave, C.; Lentz, D.; Schäfer, A.; Samori, P.; Rabe, J. P.; Franke, P.; Schlüter, A. D. Shape-persistant macrocycles with terpyridine units: Synthesis, characterization, and structure in the crystal. *J. Am. Chem. Soc.*, **2003**, *125*, 6907–6918.
6. Preston, D.; Tucker, R. A.; Garden, A. L.; Crowley, J. D. Heterometallic $[M_nPt_n(L)_{2n}]^{x+}$ Macrocycles from Dichloromethane-Derived Bis-2-pyridyl-1, 2, 3-triazole Ligands. *Inorg. Chem.*, **2016**, 55, 8928–8934.