ORGANIC LETTERS

2003
Vol. 5, No. 8
1241−1244

Easy Preparation of Cobalt Corrole and Hexaphyrin and Isolation of New Oligopyrroles in the Solvent-Free Condensation of Pyrrole with Pentafluorobenzaldehyde

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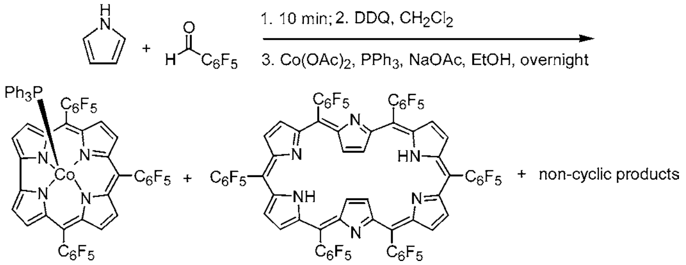
Received January 22, 2003

ABSTRACT



Following the discovery that meso-substituted corroles are formed in solvent-free condensation of pyrrole with aldehydes, we demonstrate that a small variation in the methodology is suitable for facile synthesis of cobalt(III) corrole and hexaphyrin. These compounds, as well as three noncyclic products, were fully characterized by spectroscopy and X-ray crystallography.

The year 1999 signaled a real renaissance of corrole chemistry, induced by the first facile syntheses of the hitherto almost unknown triarylcorroles.[1] Most significant, and in sharp contrast to the preceding three and a half decades, corrole-based applications began to be reported.[2] In this aspect, the most important corrole is **1** (Scheme 1), for which two efficient syntheses were reported: condensation of pyrrole with pentafluorobenzaldehyde,[3a] either neat or on alumina support, followed by DDQ oxidation.[1a,b] The two additional products shown in Scheme 1 were also fully characterized, and **3** was shown to be an excellent precursor to sapphyrin.[3b]

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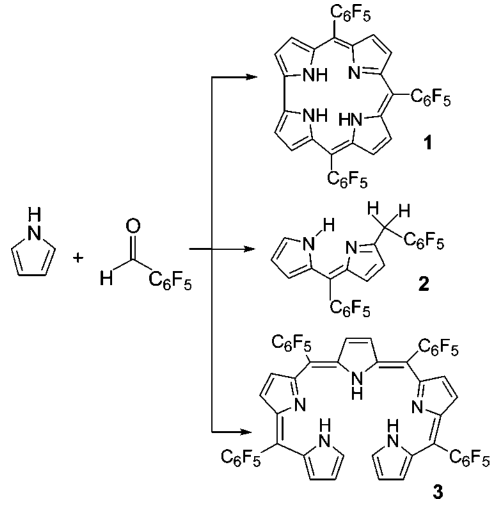
(1) (a) Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem., Int. Ed.* **1999**, *38*, 1427. (b) Gross, Z.; Galili, N.; Simkhovich, L.; Saltsman, I.; Botoshansky, M.; Bläser, D.; Boese, R.; Goldberg, I. *Org. Lett.* **1999**, *1*, 599. (c) Paolesse, R.; Jaquinod, L.; Nurco, D. J.; Mini, S.; Sagone, F.; Boschi, T.; Smith, K. M. *Chem. Commun.* **1999**, 1307. (d) For a review of the recent methodologies for synthesis of corroles, see: Gryko, D. T. *Eur. J. Org. Chem.* **2002**, 1735−1743.

(2) (a) Gross, Z.; Simkhovich, L.; Galili, N. *J. Chem. Soc., Chem. Commun.* **1999**, 599. (b) Simkhovich, L.; Mahammed, A.; Goldberg, I.; Gross, Z. *Chem. Eur. J.* **2001**, *7*, 1041. (c) Simkhovich, L.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 8089. (d) Grodkowski, J.; Neta, P.; Fujita, E.; Mahammed, A.; Simkhovich, L.; Gross, Z. *J. Phys. Chem. A* **2002**, *106*, 4772. (e) Gross, Z.; Golubkov, G.; Simkhovich, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 4045−4047. (f) Aviezer, D.; Cotton, S.; David, M.; Segev, A.; Khaselev, N.; Galili, N.; Gross, Z.; Yayon, A. *Cancer Res.* **2000**, *60*, 2973−2980. (g) Golubkov, G.; Bendix, J.; Gray, H. B.; Mahammed, A.; Goldberg, I.; DiBilio, A. J.; Gross, Z. *Angew. Chem., Int. Ed.* **2001**, *40*, 2132−2134. (h) Segev, A.; Aviezer, D.; Safran, M.; Gross, Z.; Yayon, A. *Cardiovasc. Res.* **2002**, *53*, 232−241. (i) Simkhovich, L.; Goldberg, I.; Gross, Z. *J. Porphyrins Phthalocyanines* **2002**, *6*, 439−444. (j) Eikey, R. A.; Khan, S. I.; Abu-Omar, M. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3592−3595.

10.1021/ol0341142 CCC: $25.00

Scheme 1. Formulas of Previously Fully Characterized Compounds from the Solvent-Free Condensation of Pyrrole and Pentafluorobenzaldehyde[1b]



The objectives of this work were the isolation of additional interesting compounds that might be present in the reaction mixture and to check if reaction with cobalt(II) acetate prior to purification of **1** is an efficient way for easy preparation of the corresponding metal complex. To accomplish these tasks, we choose the solvent- and support-free method for the synthesis of **1**.[1b] Particular attention was paid to the two compounds whose polarity is similar to **1** (**4** and **5**, Scheme 2) and to compound **6** because of its formation in a reasonable yield (4−6%).[4] For the orange **4** we obtained X-ray quality crystals, and the MS and ^{19}F and ^{1}H NMR data were all consistent with the molecular structure shown in Figure 1.[5] This includes the intramolecular NH- - -N hydrogen bond, evident both in the crystal structure and from the ^{1}H NMR chemical shift of 12.0 ppm. The spectroscopic data of the green compound **5** is indicative of an open-chain oligopyrrole. Its ^{1}H NMR displays four types of β-pyrrole hydrogen atoms at relatively high field (6.0−6.7 ppm), five aryl rings are detected by ^{19}F NMR, and its MS (m/z 1171.7 ($[M]^-$, 10), 1155.8 ($[M - OH]^-$, 100)) is also consistent with the formula shown in Scheme 2.

Scheme 2. Proposed Mechanism for the Formation of Compounds **2**, **4**, and **5**

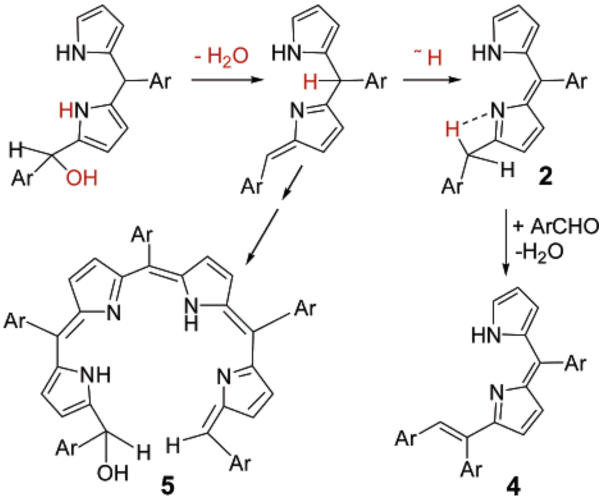
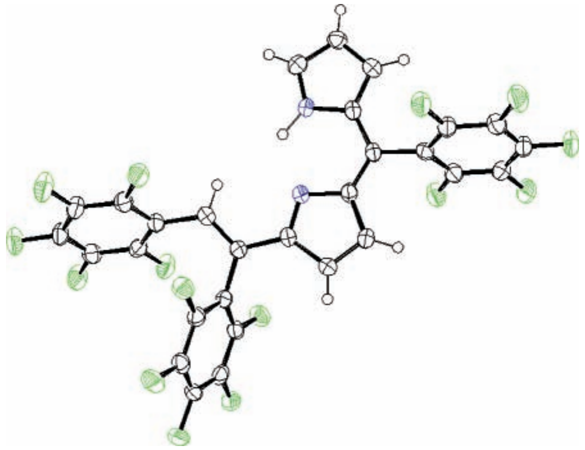


Figure 1. Molecular structure of compound **4**. The atomic thermal displacement parameters are represented by 50% probability ellipsoids in all figures.



Apparently, **2**, **4**, and **5**, are all dead-end byproducts that are responsible for decreasing the yield of the desired macrocyclic compounds. A mechanism that may account for the formation of these three products is proposed in Scheme 2, which starts with elimination of water from the growing chain. Compound **2** is obtained via a 1,5-H-shift, and the formation of **4** seems to indicate that the presence of a basic nitrogen atom in the vicinity of the benzylic proton induces a Knoevenagel condensation with the electron-poor aldehyde. Compound **5** appears to be an analogue of the green compounds that accompany the desired corroles in other synthetic strategies, which have been proposed to be one-electron oxidized corroles (π-cation radicals).[6] Our results clearly show that **5** is an open-chain tetrapyrrole, presumably

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(3) (a) For expanded porphyrins from this very reactive aldehyde, see: Shimizu, S.; Shin, J.-Y.; Furuta, H.; Ismael, R.; Osuka, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 78−82, and references therein. (b) Simkhovich, L.; Rosenberg, S.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 4929−4931.

(4) Injection of pyrrole (0.55 mL, 8 mmol) into a 100 mL flask loaded with pentafluorobenzaldehyde (1 mL, 8 mmol) initiates a strongly exothermic reaction. After 10−15 min, the resulting black-brown resin-like material is dissolved in dichloromethane (100−120 mL), DDQ (0.75 g, 3.3 mmol) is added, and the compounds are separated by chromatography (silica gel, n-hexane/EtOAc = 200/1). The R_f values (silica gel, n-hexane/CH_2Cl_2 = 2/1) of compounds **4**−**6** are 0.57, 0.40, and 0.31, respectively.

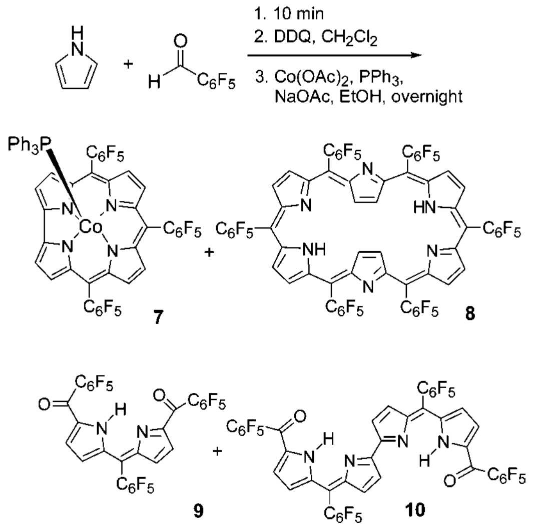
(5) Crystal data of **4** (crystallized from a mixture of dichloromethane and n-hexane): $C_{29}H_7F_{15}N_2$, formula weight 668.37, monoclinic, space group $P2_1$, $a = 11.8050(7)$ Å, $b = 7.0160(5)$ Å, $c = 15.3170(7)$ Å, $\beta = 102.900(2)°$, $V = 1236.59(14)$ Å^3, $Z = 2$, $T = 110$ K, $D_{calc} = 1.795$ g·cm^{-3}, 5199 unique reflections ($2\theta_{max} = 55.7°$). The final $R_1 = 0.054$ for 3630 observations with $F_o > 4\sigma(F_o)$, $R_1 = 0.091$ ($wR_2 = 0.143$) for all unique data, $|\Delta\rho| \leq 0.31$ e/Å^3.

(6) Gryko, D. T.; Jadach, K. *J. Org. Chem.* **2001**, *66*, 4267−4275.

resulting from further reaction of the α-free pyrrole position in **2** or its precursor. In fact, the only macrocycle that was obtained in the synthesis except of **1** is the very polar blue compound **6** that is discussed in a later section.

The main traditional methodologies for preparation of corroles rely on addition of $Co(OAc)_2$ and PPh_3 to reaction mixtures of corrole precursors, from which the corresponding (triphenylphosphine)cobalt(III) corroles are obtained.[7] Although this is not necessary in the modern syntheses, we decided to try to prepare $Co(tpfc)(PPh_3)$ (**7**) directly from the reaction mixture without prior chromatographic separation of the corrole.[8] The number and kind of easily isolated compounds from the reaction mixture is quite surprising (Scheme 3). In addition to the expected product (5−7% yield), it was possible to adjust the reaction conditions as to isolate the purple-violet hexaphyrin **8** in 2.5−3% yield and compounds **9** and **10** in yields of 0.5−1.5%. All four compounds are very stable and were fully characterized by X-ray crystallography (Figures 2−4).

Scheme 3. One-Pot Procedure for Preparation of Compounds **7**−**10**



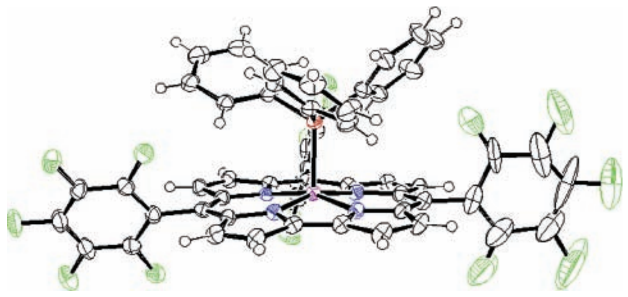


Figure 2. The molecular structure of $Co(tpfc)(PPh_3)$, **7**. The large ellipsoids of one of the aryl rings represent its partial (unresolved) disorder, which however has little effect on the precision of the core corrole structure.

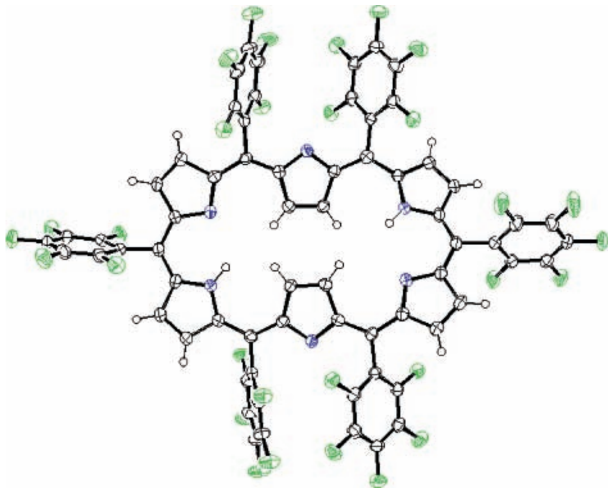


Figure 3. Molecular structure of hexaphyrin **8**.

Since cobalt is the most common metal in all corrole complexes and **1** is the most extensively studied triarylcor-

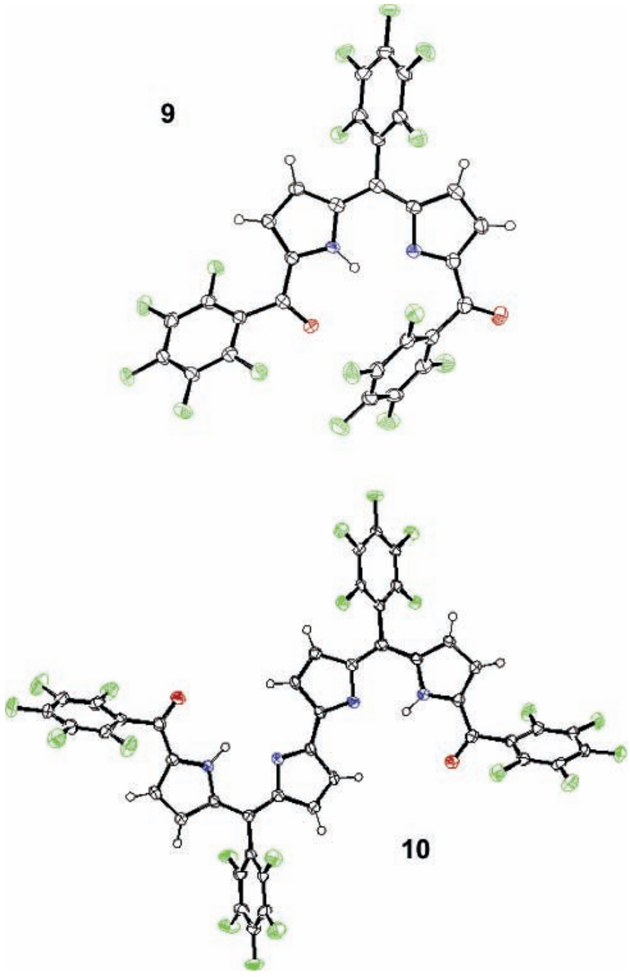


Figure 4. Molecular structures of **9** and **10**.

role, there is a significant interest in the crystal structure of the previously reported complex **7**.[9] This task was only achieved after many attempts (via recrystallization from acetonitrile).[10] The observed structure of **7** (obtained as an acetonitrile solvate) is significantly different from that of the isoelectronic and isostructural rhodium(III) complex Rh(tpfc)(PPh_3), mainly due to the smaller size of the cobalt ion. The former complex is much less domed than the latter [the metal out-of-corrole-plane displacements are 0.324(7) and 0.469(5) Å, respectively], has much shorter metal−nitrogen bonds [1.871(3)−1.886(3) vs 1.957(5)−1.973(5), respectively], and also has a shorter metal−phosphorus bond [2.2052(10) and 2.2217(16) Å, respectively]. On the other hand, the structure of **7** is very similar to that of Co(tpc)(PPh_3), for which the following structural parameters were reported: metal ion displacement from the corrole plane = 0.389 Å, Co−N (corrole) bond lengths = 1.863(2)−1.891(2) Å, and Co−P bond length = 2.201(1) Å.[1c]

The violet compound **8**, of which 70−87 mg (3.5−4.5% yield) can be obtained from a single synthesis,[11] was identified via a combination of spectroscopic methods (UV−vis, MS, and ^1H and ^{19}F NMR) and X-ray crystallography (Figure 3).[12] By all these aspects, **8** is identical to the hexaphyrin that was previously obtained by Neves et al. together with the earlier mentioned blue compound **6** in a combined yield of 1%.[13] Interestingly, **6** but not **8**, was obtained when $Co(OAc)_2$ was omitted. Moreover, isolated **6** was fully converted into **8** within 10−15 min in the presence of $Co(OAc)_2 \cdot 4H_2O$ in ethanol. The much larger polarity of **8** relative to **6** is also very useful for synthetic purposes; these two compounds can be separated by repeated washing with *n*-hexane in which only **6** is soluble. The opposite transformation was performed by adding a few drops of hydrazine hydrate to a solution of **8** in ethanol/dichloromethane. All attempts to obtain X-ray quality crystals of **6** failed, but we agree with the conclusion of Neves et al. that **6** is a partially reduced hexaphyrin.[13a]

Compound **9** is another proof that despite the unusual reaction conditions, the earlier steps that eventually lead to the corrole are identical to those leading to porphyrins and other polypyrrolic macrocycles. Its structure (Figure 4) presents the oxidized form of an immature chain-growing intermediate, with either DDQ or cobalt(II)/O_2 as the oxidants of the hydroxyl groups in the process.[14] The structure of **10** (Figure 4) is more unique[15] because it demonstrates for the first time that the coupling between two pyrrole units does not necessarily occur only in the final cyclization to corrole.

We demonstrated the easy preparation of cobalt corrole and hexaphyrin in methodologies that involve less synthetic steps and minimal workup procedures. In addition, we isolated several noncyclic products in the solvent-free condensation of pyrrole with pentafluorobenzaldehyde. We hope that such obtained mechanistic information will assist in the design of optimal reaction conditions for increasing the yield of corroles and other desired polypyrrolic macrocycles.

Acknowledgment. This research was supported by the Israel Science Foundation, under Grants 368/00 (Z.G.) and 68/01 (I.G.), and the Petroleum Research Fund (ACS, Z.G.).

Supporting Information Available: Detailed spectroscopic data forcompounds **4−6** and **8−10**, and crystallographic data for compounds **4** and **7−10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Paolesse, R. In *Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 2, Chapter 11, pp 201−232. (b) Erben, C.; Will, S.; Kadish, K. M. In *Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 2, Chapter 12, pp 265−273.

(8) After the oxidation step with DDQ, the solvent was evaporated and the product mixture was dissolved in ethanol. $Co(OAc)_2 \cdot 4H_2O$ (0.25 g, 1 mmol), PPh_3 (0.25 g, 0.95 mmol), and NaOAc (0.8 g, 10 mmol) were added, and the reaction was stirred overnight at room temperature. Column chromatography (silica, *n*-hexane/EtOAc = 170:1) afforded **7−10**, which were eluted in the listed order.

(9) Simkhovich, L.; Galili, N.; Saltsman, I.; Goldberg, I.; Gross, Z. *Inorg. Chem.* **2000**, *39*, 2704−2705.

(10) Crystal Data of **7**: $C_{55}H_{23}CoF_{15}N_4P \cdot CH_3CN$, formula weight 1155.73, orthorhombic, space group *Pbca*, $a = 25.4510(1)$ Å, $b = 13.4560(2)$ Å, $c = 28.1280(4)$ Å, $V = 9633.0(2)$ Å^3, $Z = 8$, $T = 110$ K, $D_{calc} = 1.594$ g·cm^{-3}, 11596 unique reflections ($2\theta_{max} = 56.5°$). The final $R_1 = 0.066$ for 7495 observations with $F_o > 4\sigma(F_o)$, $R_1 = 0.114$ ($wR_2 = 0.185$) for all unique data, $|\Delta\rho| \leq 1.01$ e/Å^3. One of the pentafluorophenyl rings is severely disordered, but its disorder could not be resolved. Hence, the relatively high residual peaks in the final electron-density map.

(11) The best yields of **8** were obtained by adding only 0.1 g (0.4 mmol) of $Co(OAc)_2 \cdot 4H_2O$ and 0.1 g (0.38 mmol) of PPh_3 in the last step.

(12) X-ray quality crystals of **8** were obtained via recrystallization from mixtures of dichloromethane/*n*-hexane or benzene/*n*-heptane. Crystal data of **8**: $C_{66}H_{14}F_{30}N_6$, formula weight 1460.83, monoclinic, space group $P2_1/c$, $a = 10.6687(2)$ Å, $b = 26.9481(7)$ Å, $c = 19.4308(4)$ Å, $\beta = 90.065(2)°$, $V = 5586.4(2)$ Å^3, $Z = 4$, $T = 110$K, $D_{calc} = 1.737$ g·cm^{-3}, 11837 unique reflections ($2\theta_{max} = 55.8°$). The final $R_1 = 0.051$ for 6425 observations with $F_o > 4\sigma(F_o)$, $R_1 = 0.123$ ($wR_2 = 0.124$) for all unique data, $|\Delta\rho| \leq 0.29$ e/Å^3. The molecular structure of **8** determined in this study at 110 K is considerably more precise than that reported in ref 13a.

(13) (a) Neves, M. G. P. M. S.; Martins, R. M.; Tomé, A. C.; Silvestre, A. J. D.; Silva, A. M. S.; Félix, V.; Drew, M. G. B.; Cavaleiro, J. A. S. *Chem. Commun.* **1999**, 385−386. (b) For a 16−20% yield of **8**, see: Shin, J.-Y.; Furuta, H.; Yoza, K.; Igarashi, S.; Osuka, A. *J. Am. Chem. Soc.* **2001**, *123*, 7190−7191.

(14) Crystal data of **9**: $C_{29}H_5F_{15}N_2O_2$, formula weight 698.35, monoclinic, space group $P2_1/c$, $a = 15.4480(3)$ Å, $b = 10.9440(2)$ Å, $c = 15.1680(3)$ Å, $\beta = 97.462(1)°$, $V = 2542.63(8)$ Å^3, $Z = 4$, $T = 110$K, $D_{calc} = 1.824$ g·cm^{-3}, 5959 unique reflections ($2\theta_{max} = 55.8°$). The final $R_1 = 0.052$ for 3577 observations with $F_o > 4\sigma(F_o)$, $R_1 = 0.109$ ($wR_2 = 0.143$) for all unique data, $|\Delta\rho| \leq 0.38$ e/Å^3.

(15) Crystal data of **10**: $C_{44}H_{10}F_{20}N_4O_2$, formula weight 1006.56, triclinic, space group *P*-1, $a = 10.3440(3)$ Å, $b = 13.6840(4)$ Å, $c = 15.2040(5)$ Å, $\alpha = 101.462(2)°$, $\beta = 98.328(2)°$, $\gamma = 105.560(2)°$, $V = 1986.6(1)$ Å^3, $Z = 2$, $T = 110$ K, $D_{calc} = 1.683$ g·cm^{-3}, 7299 unique reflections ($2\theta_{max} = 51.4°$). The final $R_1 = 0.075$ for 4751 observations with $F_o > 4\sigma(F_o)$, $R_1 = 0.130$ ($wR_2 = 0.171$) for all unique data, $|\Delta\rho| \leq 0.35$ e/Å^3.