Highly Effective PQQ Inhibition by Alkynyl and Aryl Mono- and Diiodonium Salts†

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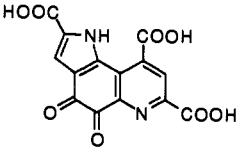
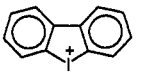
Abstract: PQQ (methoxatin), a bis(quinone) tricarboxylic acid, is an organic cofactor in a variety of biological redox processes. It is effectively inhibited on a micromolar scale by alkynyl and aryl monoiodonium salts, whereas bis(iodonium)triflates **5** and **8** are PQQ inhibitors at nanomolar levels.

PQQ (methoxatin, **1**), a bis(quinone) tricarboxylic acid, is an organic cofactor in an increasing number of biological redox processes. As a consequence, there is considerable current interest and enhanced research activity in the biochemical roles of PQQ-mediated redox cycling in biological processes.[1] Recent evidence suggests that PQQ is an essential nutrient for mouse pups.[2] Furthermore, PQQ, given to animals in pharmacological amounts, affords protection against (1) hepatotoxicity caused by liver poisons in rats,[3a] (2) acetaldehyde accumulation following ethanol loading in rats,[3b] (3) oxidative-stress-induced cataract formation in hydrocortisone-treated chick embryos,[3c] (4) inflammation induced by carrageenin in rat paws,[3d] and (5) neuroexcitatory agents like *N*-methyl-D-aspartic acid tha t target the glutamate receptor redox site in neurons.[3e] Recent evidence indicates that PQQ, first found as a bacterial cofactor for alcohol dehydrogenases,[3f] is widely distributed in animal cells, tissues, and fluids and also functions as a redox cofactor in mitochondrial complex I.[3g,h] PQQ also diminishes brain necrosis in a rat model of a stroke.[3i]

A common way of investigating the role of PQQ in biological processes is to inhibit these processes with agents that effectively sequester PQQ. PQQ is a trianionic quinoid compound with three carboxyl groups that are ionized at physiological pH. PQQ chelates metal ions and forms charge-transfer complexes with aromatic amino acids.[3j] We have found that organic cations like *N*-methylphenazonium (phenazine methosulfate), berberine, and MPP^+ (*N*-methylphenylpyridinium) sequester PQQ and inhibit its ability to catalyze glycinate-fueled redox cycling.[4] PQQ is also sensitive to metal ions, especially indium, manganese, lead, vanadyl and trialkyltin. An especially useful organic cation with profound physiological actions is the diphenyleneiodonium cation,[5] DPI, **2**, a member of the family of polycoordinated iodine species.[6] We found that DPI sequesters PQQ and expect that this accounts for the physiological actions of DPI that include (1) its induction of hypoglycemia and lactic acidosis caused by blockage of gluconeogenesis following mitochondrial toxicity,[5b] (2) the inhibition of respiratory burst in stimulated neutrophils,[5c] (3) the inhibition of nitric oxide synthase in endothelial cells,[5d] and (4) the induction of myopathy in rats, chronically treated with sublethal amounts of DPI.[5e,f]



1 PQQ



2 DPI

Likewise, there is a renaissance in polycoordinated iodine chemistry[6] and, in particular, in new iodonium species.[7,8] With the known[6] wide-ranging biological activity of iodonium

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(1) (a) Paz, M. A.; Flückiger, R.; Gallop, P. M. In *Principles and Applications of Quinoproteins*; Davidson, V. L., Ed.; Marcel Dekker, Inc.: New York, 1992; pp 381-393. (b) Xu, F.; Mack, C. P.; Quondt, K. S.; Shlafer, M.; Massey, V.; Hultquist, D. E.; *Biochem. Biophys. Res. Commun.* **1993**, *193*, 434.

(2) (a) Steinberg, F. M.; Smidt, C.; Kilgore, J.; Romero-Chapman, N.; Tran, D.; Bui, D.; Rucker, R. B. In *Principles and Applications of Quinoproteins*; Davidson, V. L., Ed.; Marcel Dekker, Inc.: New York, 1992; pp 367-379. (b) Kilgore, J.; Smidt, C.; Duich, L.; Romero-Chapman, N.; Tinker, D.; Reiser, K.; Melko, M.; Hyde, D.; Rucker, R. B. *Science* **1989**, *245*, 850. (c) Smidt, C. R.; Steinberg, F. M.; Rucker, R. B. *Proc. Soc. Exp. Biol. Med.* **1991**, *197*, 19.

(3) (a) Watanabe, A.; Hobara, N.; Tsuji, T. *Curr. Ther. Res.* **1988**, *44*, 896. (b) Hobara, N.; Watanabe, A.; Kobayashi, M.; Tsuji, T.; Gomita, Y.; Araki, Y. *Pharmacology* **1988**, *37*, 264. (c) Nishigori, H.; Yasunaga, M.; Mizumara, M.; Lee, J. M.; Iwatsuru, M. *Life Sci.* **1989**, *45*, 593. (d) Hamagishi, Y.; Murata, S.; Kamei, H.; Oki, T.; Adachi, O.; Ameyama, M. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 980. (e) Aizenman, E.; Hartnett, K. A.; Zhong, C.; Gallop, P. M.; Rosenberg, P. A. *J. Neurosci.* **1992**, *12*, 2362. (f) Salisbury, S. A.; Forrest, H. S.; Cruse, W. B. T.; Kennard, O. *Nature* **1979**, *280*, 843. (g) Mah, J.; Paz, M. A.; Flückiger, R.; Gallop, P. M. *FASEB J.* **1993**, *7*, A53. (h) Paz, M. A.; Mah, J.; Flückiger, R.; Stang, P. J.; Gallop, P. M. *Addendum LB80*, ASBMB/DBC-ACS Joint Meeting, San Diego, CA, 1993. (i) Gardner, G.; Gallop, P. M.; Aizenman, E.; Rosenberg, P. A.; Jensen, F. E. *Soc. Neurosc.* **1992**, *18*, A321.6. (j) Ishida, T.; Doi, M.; Tomita, K.; Hayashi, H.; Inoue, M.; Urakami, T. *J. Am. Chem. Soc.* **1989**, *111*, 6822.

(4) (a) Flückiger, R.; Paz, M. A.; Bergethon, P. R.; Henson, E.; Gallop, P. M. In *Principles and Applications of Quinoproteins*; Davidson, V. L., Ed.; Marcell Dekker, Inc.: New York, 1992; pp 331-341. (b) Paz, M. A.; Flückiger, R.; Boak, A.; Kagan, H. A.; Gallop, P. M. *J. Biol. Chem.* **1991**, *266*, 689. (c) Flückiger, R.; Paz, M. A.; Mah, J.; Bishop, M.; Gallop, P. M. *Biochem. Biophys. Res. Commun.* **1993**, *196*, 61-68.

(5) (a) Steward, G. A.; Hanley, T. In *Oral Hypoglycemic Agents: Pharmacology and Theurapeutics*; Campbell, G. D., Ed.; Academic Press: London, New York, 1969; pp 348-407. (b) Holland, P. C.; Clark, M. G.; Bloxham, D. P.; Lardy, H. A. *J. Biol. Chem.* **1973**, *248*, 6050. (c) Cross, A. R.; Jones, O. T. G. *Biochem. J.* **1986**, *237*, 111. (d) Stuehr, D. J.; Fasehun, O. A.; Kwon, N. S.; Gross, S. S.; Gonzales, J. A.; Levi, R.; Nathan, C. F. *FASEB J.* **1991**, *5*, 98. (e) Cooper, J. M.; Petty, R. K. H.; Hayes, D. J.; Challiss, R. A. J.; Brosnan, M. J.; Soubridge, E. A.; Radda, G. K.; Morgan-Hughes, J. A.; Clark, J. B. *J. Neurol. Sci.* **1988**, *83*, 335. (f) Cooper, J. M.; Petty, R. K. H.; Hayes, D. J.; Morgan-Hughes, J. A.; Clark, J. B. *Biochem. Pharmacol.* **1988**, *37*, 687.

(6) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers, Inc.: New York, 1992.

(7) For a review see: Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274.

(8) For reviews see: Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365. Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431. Merkushev, E. B. *Russ. Chem. Rev. (Engl. Transl.)* **1987**, *56*, 826. Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244. Ochiai, M.; Nagao, Y. *Kyokai Yuki Gosie Kagaku Kyeokaishi* **1986**, *44*, 660. Varvoglis, A. *Synthesis* **1984**, 7099. Koser, G. F. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds; Wiley-Interscience, Chichester, U.K., 1983; Chapters 18, 25, pp 721-811, 1265-1351.

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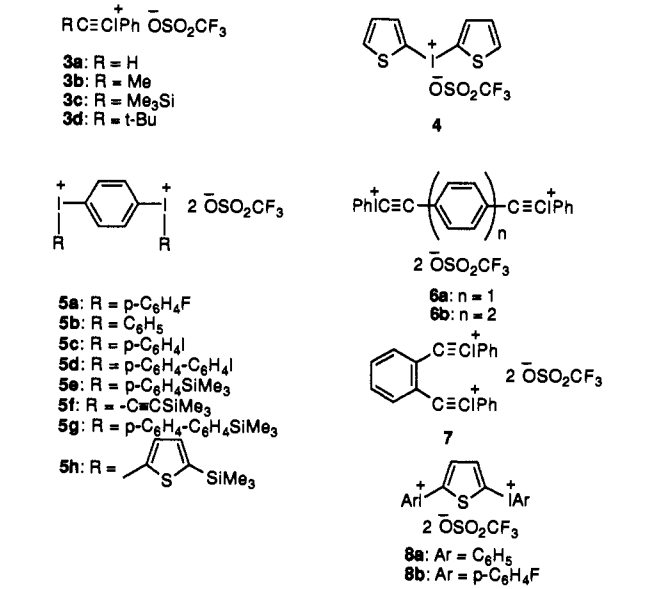
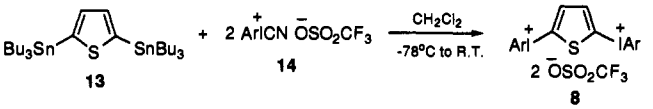
Scheme I



Scheme II



salts and the specific inhibition of PQQ by DPI in mind, we decided to examine the inhibition of PQQ by new types of iodonium salts. Two major classes of new iodonium salts were investigated monoiodonium salts, as exemplified by **3** and **4**, and bis(iodonium) species **5–8**. The preparation of **3**,[9c] **4**,[10] **6**,[11a] and **7**[11b] has been previously described. Bis(iodonium) salts **5** were prepared[12] as described in Scheme I.

Commercial diiodobenzene **9** was oxidized to **10** by CF_3CO_3H in 85% yield. Reaction of **10** with 2 equiv of the appropriate $RSiMe_3$ **11** and $Me_3SiOSO_2CF_3$ (**12**), respectively, in CH_2Cl_2 gave **5a–d** in 66–97% isolated yields.[13] Likewise, **5h** was prepared as outlined in Scheme I using 2,5-bis(trimethylsilyl)thiophene instead of **11**. Compounds **8** were prepared by the iodonium-transfer reaction[9] of 2,5-bis(tributyltin)thiophene (**13**) with arylcyanoiodonium triflates **14**.[9b]

All new compounds had both HRMS and spectral properties in accord with the proposed structures and expectations[6,7] for iodonium salts as detailed in the experimental procedure.

(9) (a) Stang, P. J.; Zhdankin, V. V. *J. Am. Chem. Soc.* **1991**, *113*, 4571. (b) Zhdankin, V. V.; Scheuller, M. C.; Stang, P. J. *Tetrahedron Lett.* **1993**, submitted for publication. (c) Bar-Ner, N.; Crittell, C. M.; Stang, P. J.; Williamson, B. L. *J. Org. Chem.* **1991**, *56*, 3912.

(10) Stang, P. J.; Tykwinski, R.; Zhdankin, V. V. *J. Heterocycl. Chem.* **1992**, *29*, 815.

(11) (a) Stang, P. J.; Tykwinski, R.; Zhdankin, V. V. *J. Org. Chem.* **1992**, *57*, 1861. (b) Stang, P. J.; Tykwinski, R. *J. Am. Chem. Soc.* **1992**, *114*, 4411.

(12) Select members of **5** as a tosylate, p-$CH_3C_6H_4SO_3^-$, have previously been prepared by a different procedure in generally low yields; see: Koser, G. F.; Carman, C. S. U. S. Patent 4,513,137, 1985. Likewise, for **8a** as a tosylate see: Jezic, Z. U.S. Patent 3,712,920, 1973.

(13) See the Experimental Section for individual compounds and yields. The isolated yield of the deactivated p-FC_6H_4 **5a** was only 6%.

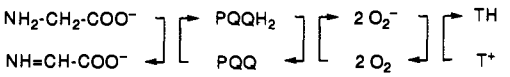
Table I. Inhibition of PQQ-Catalyzed Redox Cycling by Iodonium Compounds

entry	compound	IC_{50}[a]
1	BPI, Ph_2I^+	10.0 μM
2	DPI, **2**	1.5 μM
3	**3a**	6.0 μM
4	**3b**	3.0 μM
5	**3c**	19 μM
6	**3d**	437 nM
7	**4**	667 nM
8	**5a**	7 nM
9	**5b**	13 nM
10	**5c**	33 nM
11	**5d**	77 nM
12	**5e**	333 nM
13	**5f**	667 nM
14	**5g**	63 nM
15	**5h**	36 nM
16	**6a**	1.3 μM
17	**6b**	667 μM
18	**7**	2.0 μM
19	**8a**	29 nM
20	**8b**	13 nM

[a] Using 13.3 nM PQQ.

PQQ inhibition studies were carried out via the PQQ-catalyzed redox-cycling assay[4a,b] using 13.3 nM PQQ and adding various concentrations of the inhibitor to determine the IC_{50}. A stock solution of the inhibitor was prepared in DMSO and then further diluted in water to the desired concentration. PQQ without inhibitor and the various concentrations of the inhibitors were run in parallel, the latter to control for any direct reduction of NBT.

In this assay, glycine present in large excess is oxidized at pH 10 in air in a reaction catalyzed by small amounts of PQQ. As reduced PQQ is generated, it is oxidized by dioxygen back to PQQ and superoxide is generated. Superoxide then reduces nitroblue tetrazolium (T^+) to formazan (TH). In 20 min at 37 °C, about 2000 redox cycles occur such that nanomolar concentrations of PQQ generate micromolar amounts of formazan dye. Agents that sequester PQQ like the iodonium compounds inhibit this redox-cycling assay.



The results are summarized in Table I. Perusal of the data in Table I reveals that as a group the bis(iodonium) compounds are clearly better inhibitors of PQQ than the monoiodonium compounds, in the redox-cycling assay for PQQ. Two of the bis(iodonium) compounds (**5a** and **5b**) have been tested in mitochondria, and both compounds strongly inhibit NADH-fueled mitochondrial electron transport.[3h] The inhibition is reversed by the addition of PQQ. Physiologically, the new iodonium compounds may also show selective permeability for certain cells. For instance, while DPI is especially useful for preparing animal models of myopathies,[5e] bis(iodonium) compounds may show a selective toxicity for other cells and tissues. Inhibition by the new type of alkynyl monocations **3a–c** (entries 3–5) is comparable to inhibition of PQQ by diphenyliodonium (entry 1) and DPI (entry 2), whereas inhibition of PQQ by the most active bis(iodonium) salts **5a–c** (entries 8–10) is 10^2–10^3 better than that of BPI and DPI. Likewise, bis(iodonium) salts **8** are nearly 1000 times better inhibitors of PQQ than DPI. Hence, we expect widespread use of these bis(iodonium) species as highly effective inhibitors of biological processes involving PQQ.

Experimental Section

General Methods. Melting points (uncorrected) were obtained with a Mel-Temp capillary melting-point apparatus. Infrared spectra were recorded on a Mattson FT-IR spectrophotometer. NMR spectra were

recorded on a Varian XL 300 spectrometer at 300 MHz (^{1}H NMR), 75 MHz (^{13}C NMR), and 282 MHz (^{19}F NMR). Chemical shifts for ^{1}H and ^{13}C NMR are reported in parts per million (ppm) relative to internal tetramethylsilane or the proton resonance due to the residual protons in the deuterated NMR solvent; the chemical shifts for ^{19}F NMR are relative to external $CFCl_3$. Mass spectra were obtained with a VG Micromass 7050E double-focusing high-resolution mass spectrometer with the VG data system 2000 under positive ion fast atom bombardment (FAB) conditions at 8 keV. 3-Nitrobenzyl alcohol was used as a matrix in CH_2Cl_2 or $CHCl_3$ as the solvent, and polypropyleneglycol was used as a reference for peak matching. Microanalyses were performed by Atlantic Microlab Inc., Norcross, GA.

Materials. All commercial reagents were ACS reagent grade and used without further purification. Arylcyanoiodonium triflates **14a,b** were prepared from (bis(trifluoroacetoxy)iodo)arenes, trimethylsilyl triflate, and cyanotrimethylsilane.[9b] Iodonium salts **3**,[9c] **4**,[10] **6**,[11a] and **7**[11b] were prepared by known methods. All solvents used were dried by distillation over CaH_2. The reaction flasks were flame-dried and flushed with nitrogen.

***p*-Bis[bis(trifluoroacetoxy)iodo]benzene (10).** *p*-Diiodobenzene (**9**) (3.3 g, 10 mmol) was added by small portions during 30 min to a stirred mixture of CF_3CO_3H (prepared from trifluoroacetic anhydride (10 mL, 71 mmol) and 80% hydrogen peroxide (2 mL, 47 mmol) by a known procedure[14]). The reaction mixture was stirred for 0.5 h at −78 °C and then for 2 h at −20 °C and left overnight at room temperature. Concentration of the resulting clear solution and crystallization of the product by addition of ether afforded analytically pure **10** as a white microcrystalline solid, yield 6.64 g (85%); mp 195–197 °C dec. IR (CCl_4, cm^{-1}): 3084, 3061 (C_6H_4), 1664, 1146, 982 (all CF_3CO_2). ^{1}H NMR ($CF_3CO_2H/CDCl_3$ 1/10): δ 8.43 (s, C_6H_4). ^{19}F NMR ($CF_3CO_2H/CDCl_3$ 1/10): δ −78.9 (s, CF_3CO_2). ^{13}C [^{1}H] NMR ($CF_3CO_2H/CDCl_3$ 1/10): δ 118.7 (q, CF_3), 126.0 (s, C_{ipsoAr}), 137.9 (s, CH_{Ar}), 162.4 (q, C=O). Anal. Calcd for $C_{14}H_4I_2O_8F_{12}$: C, 21.50; H, 0.52. Found: C, 21.16; H, 0.78.

General Procedure for the Preparation of (*p*-Phenylene)bis(iodonium) Salts 5. To a stirred solution of **10** (0.78 g, 1 mmol) in CH_2Cl_2 (20 mL) were added the corresponding silylated arene **11** (2.5–3 mmol) and Me_3SiOTf (**12**) (0.5 mL, 2.5 mmol) at −78 °C under N_2. The reaction mixture was allowed to warm to room temperature and additionally stirred for 3–5 h. Colorless microcrystalline products **5a–f** precipitated in analytically pure form.

5a: yield 0.05 g (6%); mp 252–260 °C dec. IR (CCl_4, cm^{-1}): 3086 (Ar), 1245, 1167, 1028 (all CF_3SO_3). ^{1}H NMR (DMSO-d_6): δ 7.25 (dd, 4H, J = 7.0 Hz), 8.12 (m, 8H). ^{19}F NMR (DMSO-d_6): δ −78.5 (s, CF_3SO_3), −106.1 (s, ArF). ^{13}C [^{1}H] NMR (DMSO-d_6): δ 121.3 (q, J = 318 Hz, $CF_3SO_3^-$), 120.1, 120.4, 137.3, 138.4, 138.7, 139.2 (all Ar).

5b: yield 0.7 g (90%); mp 280–290 °C dec.[15]

5c: yield 0.95 g (92%); mp 270–275 °C dec. IR (CCl_4, cm^{-1}): 3082 (Ar), 1265, 1170, 1024 (all CF_3SO_3). ^{1}H NMR (DMSO-d_6): δ 7.82 (d, 4H, J = 7.3 Hz), 7.87 (d, 4H, J = 7.4 Hz), 8.12 (s, 4H). ^{19}F NMR (DMSO-d_6): δ −77.8 (s, CF_3SO_3). ^{13}C [^{1}H] NMR (DMSO-d_6): δ 121.3 (q, J = 318 Hz, $CF_3SO_3^-$), 96.5, 120.1, 120.5, 138.4, 138.9, 141.2 (all s, Ar). HRMS (FAB) for $C_{19}H_{12}SI_4O_3F_3$ (M − TfO$^-$)$^+$ calcd 884.663334, found 884.661143. Anal. Calcd for $C_{20}H_{12}I_4O_6F_6S_2$: C, 23.23; H, 1.17; I, 49.09. Found: C, 23.40; H, 1.20; I, 49.22.

5d: yield 0.79 g (66%); mp 275–278 °C dec. IR (CCl_4, cm^{-1}): 3082 (Ar), 1247, 1168, 1026 (all CF_3SO_3). ^{1}H NMR (DMSO-d_6): δ 7.36 (d, 4H, J = 7.5 Hz), 7.70 (d, 4H, J = 7.6 Hz), 7.80 (d, 4H, J = 7.5 Hz), 8.12 (s, 4H), 8.14 (d, 4H, J = 7.5 Hz). ^{19}F NMR (DMSO-d_6): δ −78.4 (s, CF_3SO_3). ^{13}C [^{1}H] NMR (DMSO-d_6): δ 121.0 (q, J = 318 Hz, $CF_3SO_3^-$), 95.2, 120.3, 120.6, 131.4, 136.5, 136.8, 136.9, 137.5, 138.4, 138.6 (all Ar). HRMS (FAB) for $C_{31}H_{20}SI_4O_3F_3$ (M − TfO$^-$)$^+$ calcd 1036.725934, found 1036.723128. Anal. Calcd for $C_{32}H_{20}I_4O_6F_6S_2$: C, 32.40; H, 1.70; I, 42.79. Found: C, 32.24; H, 1.69; I, 42.61.

5e: yield 0.9 g (97%); mp 255–257 °C dec.[15]

5f: yield 0.7 g (85%); mp 183–185 °C dec.[16]

5g: yield 0.93 g (86%); mp 256–258 °C dec. IR (CCl_4, cm^{-1}): 3082 (Ar), 2957 (Me_3Si), 1245, 1167, 1027 (all CF_3SO_3). ^{1}H NMR (DMSO-d_6): δ 0.21 (s, 18H), 7.62 (m, 8H), 7.74 (d, 4H, J = 7.6 Hz), 8.12 (s, 4H), 8.15 (d, 4H, J = 7.5 Hz). ^{19}F NMR (DMSO-d_6): δ −78.2 (s, CF_3SO_3). ^{13}C [^{1}H] NMR (DMSO-d_6): δ −1.5 (s), 121.0 (q, J = 318 Hz, $CF_3SO_3^-$), 120.1, 120.7, 131.4, 136.5, 136.8, 136.9, 137.5, 138.4, 138.6, 141.5 (all Ar). HRMS (FAB) for $C_{37}H_{38}SSi_2I_2O_3F_3$ (M − TfO$^-$)$^+$ calcd 929.011939, found 929.012254.

5h: yield 0.8 g (85%); mp 225–230 °C dec. IR (CCl_4, cm^{-1}): 3075, 2965, 1474, 1384, 1282, 1235, 1165, 1026, 977. ^{1}H MMR (CD_3CN): δ 8.03 (s, 4H), 7.90 (d, 2H, J = 8.0 Hz), 7.24 (d, 4H, J = 8.0 Hz), 0.21 (s, 18H, 2Me_3Si). ^{19}F NMR (CD_3CN): δ −78.3 (s, CF_3SO_3). HRMS (FAB) for $C_{21}H_{26}S_3Si_2I_2O_3F_3$ (M − TfO$^-$)$^+$ calcd 788.862184, found 788.861207.

General Procedure for the Reaction of 2,5-Bis(tributyltin)thiophene (13) with Arylcyanoiodonium Triflates 14. To a stirred solution of reagent **14** (1 mmol) was added a solution of the appropriate tributyltin derivative **13** (1–1.5 equiv) in CH_2Cl_2 (15 mL) at −40 °C. The mixture was warmed to room temperature and stirred until the formation of a clear solution. The product was precipitated from the reaction mixture by the addition of dry hexane (20–30 mL). The microcrystalline iodonium triflate salt was filtered under nitrogen, washed with dry hexane (30 mL) and dried in vacuo. Analytically pure materials were obtained by recrystallization from a concentrated solution of the iodonium salt in CH_2Cl_2 by the addition of hexane and ether.

8a: yield 0.39 g (49%); mp 193–194 °C dec. IR (CCl_4, cm^{-1}): 3097, 3066, 1241, 1159, 1023. ^{1}H NMR (DMSO-d_6/CD_3CN): δ 7.55 (t, 4H, J = 8.0 Hz), 7.71 (t, 2H, J = 8.0 Hz), 7.83 (s, 2H), 8.19 (d, 4H, J = 8.0 Hz). ^{19}F NMR (DMSO-d_6/CD_3CN): δ −78.74 (s, $CF_3SO_3^-$). ^{13}C [^{1}H] NMR (DMSO-d_6/CD_3CN): δ 111.0, 119.4, 121.2 (q, J = 320.7 Hz, $CF_3SO_3^-$), 132.3, 132.9, 135.1, 140.9. Anal. Calcd for $C_{18}H_{12}I_2O_6F_6S_3$: C, 27.43; H, 1.53; S, 12.20. Found: C, 27.35; H, 1.56; S, 12.12.

8b: yield 0.21 g (25%); mp 170 °C dec. IR (CCl_4, cm^{-1}): 3098, 1575, 1246, 1170, 1027. ^{1}H NMR (CD_3CN): δ 8.15 (dd, 4H), 7.85 (s, 2H), 7.3 (dd, 4H). ^{19}F NMR (CD_3CN): δ −78.1 ($CF_3SO_3^-$), −105.0 (FC_6H_4). ^{13}C MMR (CD_3CN): δ 162.5 (d), 138.7, 136.3, 136.2, 121.0 (q, CF_3SO_3), 117.7, 110.5. HRMS (FAB) m/z 674.804664 (M − $CF_3SO_3^-$)$^+$, calcd for $C_{17}H_{10}I_2S_2F_5O_3$ 675.807858.

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(14) Yagupolskii, L. M.; Maletina, I. I.; Kondratenko, N. V.; Orda, V. V. *Synthesis* **1978**, 835.

(15) Stang, P J.; Zhdankin, V. V.; Zefirov, N. S. *Mendeleev Commun.* **1992**, 159.

(16) Stang, P. J.; Zhdankin, V. V.; Arif, A. M. *Mendeleev Commun.* **1992**, 158.