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Synthesis of Perfluoro[2.2]paracyclophane

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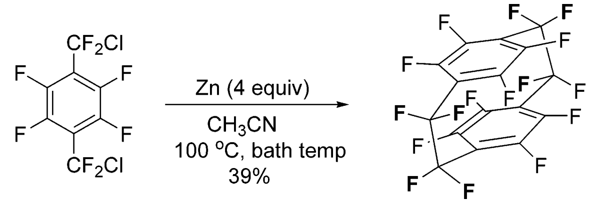
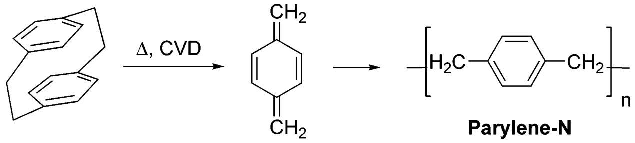


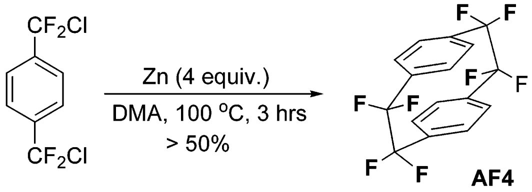
A synthesis of perfluoro[2.2]paracyclophane has been sought ever since the partially fluorinated octafluoro[2.2]-paracyclophane (AF4) was prepared and its chemistry studied. This compound has now been prepared in 39% yield from the precursor, 1,4-bis(chlorodifluoromethyl)-2,3,5,6-tetrafluorobenzene by its reaction with Zn when heated in acetonitrile at 100 °C. Two preparations of the precursor, first from 1,4-dicyano-2,3,5,6-tetrachlorobenzene and an improved method beginning from 1,2,4,5-tetrachlorobenzene, are also described as are key comparisons to our related synthesis of AF4.

[2.2]Paracyclophanes are useful chemical vapor deposition (CVD) precursors of a family of thin film polymers known as Parylenes.[1] Parylene polymers are conformal coatings that are ideally suited for a wide variety of applications within the automotive, medical, electronics and semiconductor industries. Parylene coatings are transparent, chemically inert, and they have excellent barrier properties.

The process of conversion of a [2.2]paracyclophane into a Parylene polymer is exemplified in Scheme 1 for the parent hydrocarbon system. The hydrocarbon version of the polymer, Parylene N, has good thermal stability, remaining useful (for several hours) at temperatures up to 130 °C. However, for those applications that require a coating of greater thermal stability, the bridge-fluorinated Parylene-HT, which exhibits only 0.3% weight loss per hour at 450 °C, is preferred. The precursor for Parylene HT is 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane, commonly known as AF4, and which for the last 15 years has been the subject of considerable synthetic interest. Since our initial published preparation, in 1993,[2] which allowed gram quantities of AF4 to be prepared, four subsequent papers provided procedures that would allow larger, even commercial quantities to be prepared.[3−6] The best of our procedures, that where 1,4-bis(chlorodifluoromethyl)benzene was allowed to react with zinc in dimethylacetamide (DMA) under non-high-dilution conditions, is shown in eq 1.[4] This process is currently used to manufacture AF4 for use in the Parylene industry.

SCHEME 1. [2.2]Paracyclophanes and Their Conversion to Parylene Polymers





(1)

Perfluoro[2.2]paracyclophane, herein referred to as F8, has been the subject of much interest as a potential Parylene precursor ever since the bridge-fluorinated AF4 was found to be so useful. It was predicted that the polymer derived from F8 would retain the high thermal stability of the AF4-derived polymer while having a lower dielectric constant, better dielectric strength, a very low coefficient of friction, plus transparency in regions of spectra (ir spectra, in particular) that involve C−H bonds. Nevertheless, until this report no synthesis of F8 had been reported.[7,8]

The approach to synthesis of F8 that ultimately proved successful emulated the method shown above for AF4. However, significant changes in key steps were required because of the presence of the ring fluorines. For example, a completely different synthesis of the logical [2.2]paracyclophane precursor 1,4-bis(chlorodifluoromethyl)-2,3,5,6-tetrafluorobenzene (**1**) proved necessary because the ring fluorines effectively inhibited both the chlorination and fluorination steps of our published procedure for synthesis of the AF4 precursor.[9]

Instead, we utilized alternative synthetic schemes to prepare precursor **1**. Our initial approach utilized commercially available 2,3,5,6-tetrachloro-1,4-dicyanobenzene as the starting material (Scheme 2). Tetrafluoro compound **2** was prepared in 89% yield by facile Cl−F exchange using KF in DMF along with 2% phase transfer agent tetrabutyl ammonium bromide.[10] The cyano groups were then reduced using DIBAL-H in toluene to form

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[1] Dolbier, W. R., Jr.; Beach, W. F. *J. Fluorine Chem.* **2003**, *122*, 97−104.

[2] Dolbier, W. R., Jr.; Asghar, M. A.; Pan, H. Q.; Celewicz, L. *J. Org. Chem.* **1993**, *58*, 1827−1830.

[3] Amii, H.; Hatamoto, Y.; Seo, M.; Uneyama, K. *J. Org. Chem.* **2001**, *66*, 7216−7218.

[4] Dolbier, W. R., Jr.; Duan, J.-X.; Roche, A. J. *Org. Lett.* **2000**, *2*, 1867−1869.

[5] Dolbier, W. R., Jr.; Rong, X. X.; Xu, Y. L.; Beach, W. F. *J. Org. Chem.* **1997**, *62*, 7500−7502.

[6] Zhu, S.-Z.; Mao, Y.-Y.; Jin, G.-F.; Qin, C.-Y.; Chu, Q.-L.; Hu, C.-M. *Tetrahedron Lett.* **2002**, *43*, 669−671.

[7] F8 has been “mentioned” in a recent patent as a precursor of the respective Parylene polymer.[8] However, no preparation, properties or characterization of F8 is described in this patent.

[8] Kaji, S. JP 2005−183729 (2005).

[9] Dolbier, W. R., Jr.; Duan, J.-X.; Rong, X. X. *J. Fluorine Chem.* **2007**, *128*, 1091−1093.

[10] Zhu, S.; Zhao, J.; Cai, X. *J. Fluorine Chem.* **2004**, *125*, 451−454.

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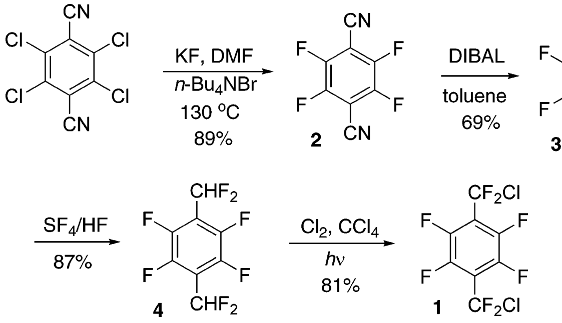
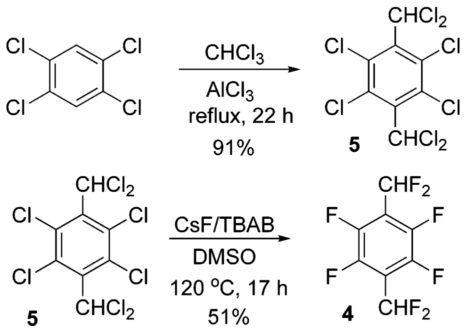
SCHEME 2. First Synthesis of F8 Precursor 1



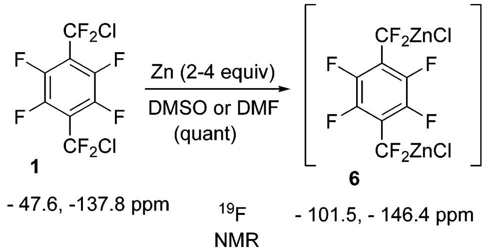
SCHEME 3. Improved Synthesis of F8 Precursor 1



dialdehyde **3** in 69% yield.[10,11] Dialdehyde **3** could be efficiently converted (87%) to the bis(difluoromethyl) compound, **4**, via reaction with SF_4 in the presence of HF, with **4** then being chlorinated to make the desired precursor **1** in 81% yield.

Although this procedure allowed the synthesis of the required dichloride precursor **1**, the required use of DIBAL-H and SF_4 insured that this overall process would be expensive to utilize for making larger quantities of F8. Thus an even more convenient, but potentially much less expensive three-step approach to the synthesis of **1** was developed, based upon the preparation by Castaner and Riera of 1,4-bis(dichloromethyl)-2,3,5,6-tetrachlorobenzene (**5**) by an $AlCl_3$-catalyzed condensation of chloroform with 1,2,4,5-tetrachlorobenzene.[12] Thus, as shown in Scheme 3, 1,4-bis(difluoromethyl)-2,3,5,6-tetrafluorobenzene (**4**) could be prepared with an overall yield of 46% from the inexpensive 1,2,4,5-tetrachlorobenzene. We anticipate being able to further improve this synthesis though the use of KF, instead of the relatively expensive CsF, in the chlorine–fluorine exchange step.

Conversion of dichloride precursor **1** to the paracyclophane F8 provided its own challenges, since the exact procedure used to synthesize AF4 when applied to **1** gave no perfluoro[2.2]-paracyclophane product. Indeed, when precursor **1** was allowed to react with Zn in various polar aprotic solvents, a reaction proceeded very smoothly to consume **1** (eq 2).



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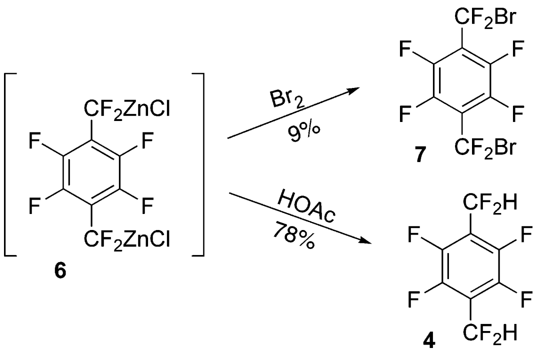
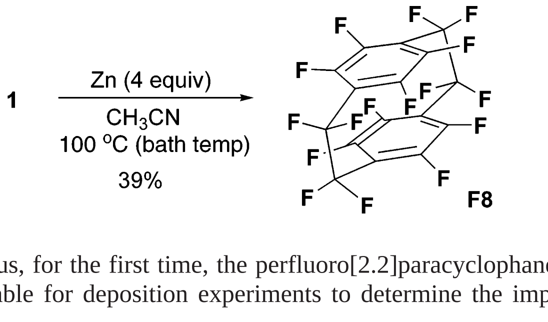
SCHEME 4. Chemical Characterization of Bis-Zn Reagent 6



A fluorine NMR spectrum of the product mixture indicated that **1** had been converted cleanly to a single product that exhibited two singlet signals, at −101.5 and −146.4 ppm, signals that were not inconsistent with the product actually being the desired perfluoro[2.2]paracyclophane. However, any attempt to work the reaction up and isolate a product led to no isolable fluorine-containing product. It finally was concluded that these new signals were due to formation of the over-reduced bis-zinc reagent **6**. This conclusion was based upon two reactions of the intermediate, both of which were consistent with it being bis-zinc intermediate **6** (Scheme 4). Addition of Br_2 to the reaction mixture containing **6** led to formation of *bis*-bromodifluoromethyl product **7**, whereas addition of acetic acid led to formation of the bis-difluoromethyl compound **4**.[13] Also the observed fluorine chemical shift of **6** is consistent with its structure.[14,15]

In view of these results, it was thought that using Zn in a *less polar* solvent might inhibit the over-reduction that led to the bis-Zn reagent **6**. Indeed, when acetonitrile was used as the reaction medium, a new product appeared in relatively low yield (~ 20%) which also had two signals in the fluorine NMR, this time at δ − 102.8 and − 132.4 (eq 3). Upon isolation and characterization, this product proved to be the desired perfluoro-[2.2]paracyclophane, F8, as characterized by ^{13}C, ^{19}F NMR, HRMS and elemental analysis. Upon optimization this yield was able to be increased to an acceptable 39% of high purity product.



(3)

Thus, for the first time, the perfluoro[2.2]paracyclophane is available for deposition experiments to determine the impact

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[11] Yoon, N. M.; Young, S. G. *J. Org. Chem.* **1985**, *50*, 2443–2450.

[12] Castaner, J.; Riera, J. *J. Org. Chem.* **1991**, *56*, 5445–5448.

[13] Bailey, J.; Plevey, R. G.; Tatlow, J. C. *J. Fluorine Chem.* **1987**, *37*, 1–14.

[14] The fluorine chemical shift of HCF_2ZnCl is −126 ppm.[15] Generally, changing a CF_2H group to a CF_2Ph group in various compounds leads to deshielding to the extent of 22–25 ppm, which makes a chemical shift of −101.5 for **6** quite reasonable.

[15] Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2007**, *128*, 1198–1215.

of perfluorination on properties of the respective Parylene polymer. As for the paracyclophane itself, aspects of its unique chemistry and electrochemistry will be reported in due course.

Experimental Section

1,4-Dicyano-2,3,5,6-tetrafluorobenzene (2).[10] 1,4-Dicyano-2,3,5,6-tetrachlorobenzene (purity 95%) (40 g, 0.15 mol), KF (43.7 g, 5 equiv), and tetrabutylamonium bromide (TBAB) 0.99 g (2 mol %) were added to a flask containing 250 mL of dry DMF, and the mixture was stirred overnight at 120 °C under N_2. Then the reaction mixture was poured into a beaker with 2 L of ice−water, and the resulting precipitate was filtered and washed with water. The crude product was recrystallized from acetone to give the yellowish white pure product **2** (25.5 g, 89%): mp 197−199 °C; ^{19}F NMR, δ −128.5 (s).[10]

2,3,5,6-Tetrafluorobenzene-1,4-dicarbaldehyde (3).[10,11,16] To a solution of 1,4-dicyano-2,3,5,6-tetrafluorobenzene (**2**) (20.0 g, 0.1 mol) and toluene (300 mL) at 0 °C was added 250 mL (0.25 mol) of 1 M DIBAL-H (diisopropylaluminum hydride) toluene solution dropwise under N_2. The mixture was stirred at 0 °C for 1 h and then was slowly warmed to room temperature and stirred overnight. The reaction was quenched by addition of 300 mL of 2 N HCl until pH <2, and then the mixture was stirred for 30 min. The resulting precipitate was filtered and washed with CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 6). The organic layer was washed with saturated sodium bicarbonate and brine, dried over $MgSO_4$, and evaporated, and the crude product (16.0 g, yield 78%) was further purified recrystallized from CH_2Cl_2 to give product **3**, 14.2 g (yield 69%): ^{1}H NMR δ 10.33 (s);[10] ^{19}F NMR δ −144.2 (s);[10] MS 207 ($M + H^+$, 100).

1,4-Bis(difluoromethyl)-2,3,5,6-tetrafluorobenzene (4) (Method A).[13] Tetrafluorophthalaldehyde (**3**) (27.3 g, 0.132 mol) and 50 mL of CH_2Cl_2 were added into a 250 mL autoclave, which was then evacuated with a dry ice−acetone bath. HF (8.0 g) and SF_4 (135 g) were filled, and the reaction mixture was stirred at 180 °C for 48 h. The reaction mixture was washed out with 200 mL of CH_2Cl_2 and kept overnight to release HF and other gaseous products. The reaction mixture was filtered, and the filtrate was washed with saturated brine (60 mL × 3), dried ($MgSO_4$), evaporated to dryness, and recrystallized with CH_2Cl_2 to afford product **4** (28.9 g, yield 87%): mp 68−70 °C (lit.[13] mp 45−50 °C); ^{1}H NMR δ 6.97 (t, $^2J_{FH} = 53$ Hz); ^{13}C NMR δ 108.22 (t, $^1J_{FC} = 242$ Hz), 115.97 (br s), 144.79 (d, $^1J_{FC} = 262$ Hz); ^{19}F NMR δ −115.2 (d, $^2J_{HF} = 52$ Hz), −142.2 (s) (equal intensity). Anal. Calcd for $C_8H_2F_8$: C, 38.42; H, 0.81. Found: C, 38.07; H, 0.68.

1,4-Bis(dichloromethyl)-2,3,5,6-tetrachlorobenzene (5).[12] A mixture of 2,3,5,6-tetrachlorobenzene (22.6 g, 0.1 mol) and aluminum chloride (30 g, 0.225 mol) in anhydrous chloroform (300 mL) was refluxed for 22 h. The reaction mixture was cooled to room temperature, diluted with chloroform (200 mL) and poured into a mixture of hydrochloric acid (30 mL) and ice−water (300 mL). The organic layer was separated, dried over magnesium sulfate, and concentrated to give crude product (45 g, wet), which was recrystallized from hexanes (225 mL) to obtain **5** (31.6 g) as a yellow solid. The mother liquor was concentrated to a volume of 45 mL, after which a second crop of product (4.1 g) was obtained. The total yield was 91.1%: mp 134−136 °C (lit.[12] mp 127−129 °C); ^{1}H NMR, δ 7.59 (br s), 7.63 (br s) (equal intensity, due to atropisomers deriving from restricted rotation);[17] ^{13}C NMR δ 66.52, 137.29 (C1/C4 carbons not observed).

1,4-Bis(difluoromethyl)-2,3,5,6-tetrafluorobenzene (4) (Method B). A mixture of **5** (23 g, 60 mmol), cesium fluoride (91.2 g, 600 mmol), and tetrabutylammonium bromide (1.2 g, 3.7 mmol) in anhydrous DMSO (110 mL) was heated to 120 °C for 17 h. The reaction mixture was then cooled to room temperature, poured into ice−water (330 mL), and extracted with diethyl ether (2 × 250 mL). The combined organic layers were washed with water (500 mL), dried with magnesium sulfate, filtered, and concentrated to remove solvent. The residue was distilled to give crude product (8.4 g), which was recrystallized from hexanes (15 mL) to furnish (**4**) (7.6 g, yield 50.6%, mp, 70−72 °C) as white crystals.

1,4-Bis(chlorodifluoromethyl)-2,3,5,6-tetrafluorobenzene (1). Molecular Cl_2 was introduced to a solution of 1,4-bis(difluoromethyl)-2,3,4,5-tetrafluorobenzene (**4**) (18.7 g, 74.8 mmol) in CCl_4 (250 mL) while irradiating with a sunlamp for 20 h. The reaction mixture was slowly evaporated to remove CCl_4 and the residue distilled under reduced pressure (85−87 °C/20 mmHg) to give 1,4-bis(chlorodifluoromethyl)-2,3,4,5-tetrafluorobenzene (**1**) (19.4 g, yield: 81.3%) as a colorless oil: ^{13}C NMR δ 121.10 (t, $^1J_{FC} = 295$ Hz), 143.61 (d, $^1J_{FC} = 268$ Hz)(non-fluorine-substituted C-1/C-4 not observed); ^{19}F NMR δ −47.6 (m, 4F), −137.9 (m, 4F); HRMS calcd for $C_8F_8Cl_2$ 317.9249, found 317.9239; GC−EI-MS ($C_8F_8Cl_2$, 319, C_8F_8Cl, 283, C_8F_8, 248).

1,4-Bis(bromodifluoromethyl)-2,3,5,6-tetrafluorobenzene (7). A mixture of 1,4-bis(chlorodifluoromethyl)-2,3,5,6-tetrafluorobenzene (**1**) (1 g, 3.13 mmol) and zinc (0.82 g, 12.5 mmol) in 5 mL of anhydrous DMSO was heated to 100 °C for 0.5 h. The reaction mixture was then cooled to room temperature, and a ^{19}F NMR spectrum of the mixture revealed two equal intensity singlets at −100.3 and −145.0 ppm. These two peaks were attributed to the presence of bis-zinc intermediate **6**: ^{19}F NMR δ −100.3 and −145.0 ppm (equal intensity).

Bromine (0.65 g, 8 mmol) was then added to the reaction, and this mixture stirred at room temperature for 4 h, quenched with ice−water (30 g), extracted with diethyl ether (2 × 10 mL), dried over magnesium sulfate, and concentrated to give crude product, which was purified by column chromatography (silica gel, hexanes) to provide 1,4-bis(bromodifluoromethyl)-2,3,5,6-tetrafluorobenzene (**7**) (0.11 g, yield: 8.6%) as a sticky colorless oil: ^{13}C NMR δ 110.4 (t, $^2J_{FC} = 308$ Hz), 143.1 (d, $^2J_{FC} = 284$ Hz) (other carbon not seen); ^{19}F NMR −43.8 and −137.9 (both second order mult); HRMS (all three isotopic combinations) calcd for $C_8F_8[79]Br_2$ 405.8239, found 405.8214; calcd for $C_8F_8[79]Br[81]Br$ 407.8219, found 407.8228; calcd for $C_8F_8[81]Br_2$ 409.8198, found 409.8234.

Perfluoro[2.2]paracyclophane (F8). A mixture of 1,4-bis(chlorodifluoromethyl)-2,3,5,6-tetrafluorobenzene **1** (10 g, 31.3 mmol) and zinc (8.2 g, 125.2 mmol) (99.7%, activated by 2% HCl) in anhydrous acetonitrile (100 mL) was heated to 100 °C (oil bath temperature) under N_2 atmosphere. The reaction mixture was refluxed gently for 38 h and then cooled to room temperature, filtered, and washed with acetone (3 × 30 mL). The combined filtrates were concentrated to dryness. The residue was purified by column chromatography (silica gel, hexanes) to give crude product (3.4 g) as a white powder. This crude product was recrystallized from chloroform (40 mL) to furnish 2.7 g of pure product as white needles. The mother liquor was concentrated to dryness and recrystallized from chloroform (10 mL) to obtain a second crop of pure product (0.3 g) as white needles. The yield is 38.6% based on isolated pure F8 and X-ray crystal analysis: mp 195−196 °C; ^{19}F NMR δ −102.8 (s), −132.4 (s) equal intensities; ^{13}C NMR δ 118.0

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(16) Krebs, F. C.; Jensen, T. *J. Fluorine Chem.* **2003**, *120*, 77−84.

(17) When octachloro compound **5** was heated to 70 °C in DMS-d_6, the two broad singlets collapsed to a sharp singlet at 7.90 ppm, this confirming the fact that the pair of peaks at rt was due to the presence of atropisomers. Note that the same phenomenon is not observed for the analogous octafluoro compound **4**.

(tt, $J = 283, 29$ Hz), 147.4 (dd, $J = 267, 22$ Hz), bridgehead carbon not seen; HRMS calcd for $C_{16}F_{16}$ 495.9739, found 495.9719. Anal. Calcd for $C_{16}F_{16}$: C, 38.73; H, 0.00; N, 0.00. Found: C, 39.07; H, 0.00; N, 0.04.

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Supporting Information Available: General experimental information, NMR spectra of compounds **1**−**7** and F8, and crystallographic experimental and data (CIF) for F8. This material is available free of charge via the Internet at http://pubs.acs.org.

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