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Synthesis and Characterization of Twenty-two Purified Polychlorinated Dibenzofuran Congeners

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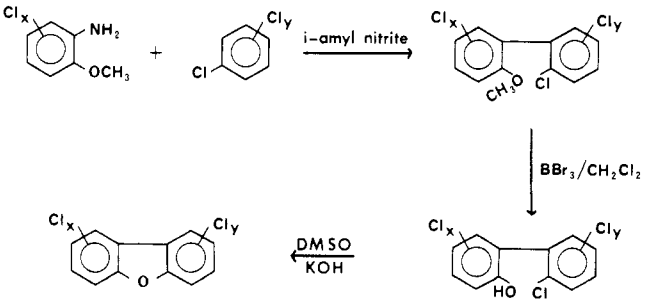
The identification of toxic polychlorinated dibenzofurans (PCDFs) in diverse environmental matrices requires the availability of purified standards for analytical, toxic, and biologic studies. This study reports the synthesis and characterization of 22 purified PCDF congeners by the base-catalyzed cyclization of their corresponding hydroxypolychlorinated biphenyl (PCB) precursors containing *o*-chloro and -hydroxy substituents on the two phenyl rings. The synthesis of the hydroxy PCBs (from their methoxy analogues) was accomplished by using two main routes, namely, (1) the diazo coupling of chlorinated anisidines and symmetrical chlorinated benzenes and (2) the diazo coupling of chlorinated anilines and chlorinated anisoles. By the judicious selection of the synthetic precursors it is conceivable that these schemes could be used to prepare most of the PCDF congeners.

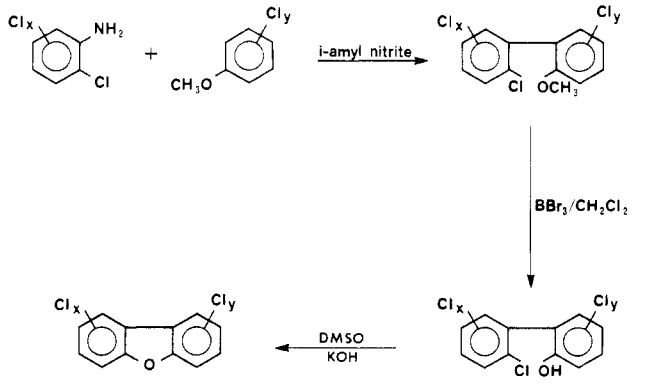
Halogenated aromatic hydrocarbons are among the most widespread and persistent environmental contaminants (Landrigan, 1980; Safe, 1982). Included in this group of structurally related compounds are the polychlorinated biphenyls (PCBs), naphthalenes (PCNs), polybrominated biphenyls (PBBs), polychlorinated dibenzofurans (PCDFs), and dibenzo-*p*-dioxins (PCDDs). The PCDDs and PCDFs are not primary industrial products but are formed as impurities in chlorinated phenol, PCB, and PCN formulations (Buser and Bosshardt, 1976; Blaser et al., 1976; Buser, 1975; Levin and Nilsson, 1977; Nilsson and Renberg, 1974; Firestone, 1977; Rappe et al., 1978a; Norstrom et al., 1979; Vos et al., 1970; Buser et al., 1978c; Bowes et al., 1975) or are formed as byproducts in diverse combustion processes (Olie et al., 1977; Lustenhouwer et al., 1980; Ahling et al., 1977; Buser et al., 1978b,c; Buser, 1979; Lindahl et al., 1980; Kooke et al., 1981; Hutzinger et al., 1980; Eiceman et al., 1979; Nestrick et al., 1982; Gizzi et al., 1982; Choudhry and Hutzinger, 1982; Buser and Rappe, 1978, 1979). PCDDs and PCDFs are the most toxic halogenated aromatic pollutants, and it has been shown that although there are 75 and 135 possible PCDD and PCDF isomer congeners, only a limited number of these compounds are toxic (Poland and Knutson, 1982). The most active individual compounds within each class are approximate isostereomers of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and 2,3,7,8-tetrachlorodibenzofuran (TCDF); however, the precise number of toxic congeners and their relative activities has not been fully delineated.

Analysis and quantitation of PCDFs in the environment are complicated by the lack of analytical standards available. There are several synthetic routes that have been utilized for the synthesis of specific PCDF congeners (Gara et al., 1981) and these include the following: (1) chlorination of dibenzofuran and its chlorinated homologues; (2) the reduction of chlorinated *o*-nitrodiphenyl ethers followed by internal diazo coupling (Gray et al., 1976); (3) internal cyclization of *o*-chloro-substituted diphenyl ethers by chemical or photolytic techniques (Choudhry et al., 1977; Norstrom et al., 1976, 1977; Gara et al., 1979); (4) pyrolysis of PCBs, chlorinated phenols and derived products, and chlorinated diphenyl ethers (Ahling

Scheme I. Synthesis of Purified Polychlorinated Dibenzofurans



Scheme II. Synthesis of Purified Polychlorinated Dibenzofurans



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et al., 1977; Buser et al., 1978a; Buser, 1979; Lindahl et al., 1980; Rappe et al., 1978b; Mazer et al., 1983). A major drawback with some of these synthetic schemes is the formation of product mixtures that require extensive purification or difficulties in the preparation of precursors.

This paper reports the development of synthetic routes for the synthesis of hydroxylated PCBs that possess ortho-substituted chloro and hydroxyl groups on different phenyl rings. This substituent orientation is required for the base-catalyzed formation of an ether linkage between the two phenyl rings to give a PCDF. Scheme I illustrates a synthetic route that involves the Cadogan coupling condensation (Cadogan, 1962) of a chlorinated anisidine and specific symmetrical chlorinated benzenes such as pentachlorobenzene, 1,2,4,5-tetrachlorobenzene, 1,2,3,4-tetrachlorobenzene, 1,3,5-trichlorobenzene, and 1,4-dichlorobenzene. The resulting chlorinated methoxybiphenyls can be readily demethylated to give the hydroxylated PCBs (Hutzinger et al., 1974), which in turn are cyclized to yield a single PCDF product. Scheme II illustrates a modification of Scheme I in which the hydroxylated PCB is synthesized from a chlorinated aniline precursor (containing a 2-chloro substituent), which is coupled to a chlorinated anisole. This reaction scheme may yield two or more coupling products as shown in the scheme. however, only one of the hydroxy-PCBs (pre-PCDFs) contains the structural features (i.e., *o*-hydroxy and -chloro substituents on different phenyl rings) that are required for the ultimate base-catalyzed condensation reaction and, therefore, a single PCDF product is formed. Chlorinated anisoles that can be used in this reaction to give a single PCDF coupling product include 3,4,5-trichloroanisole, *p*-chloranisole, and all the *o*-chloro-substituted anisoles (i.e., *o*-chloroanisole, 2,3-dichloro-, 2,4-dichloro-, and 2,5-dichloroanisole, 2,3,4-, 2,3,5-, 2,4,5-trichloroanisole, and 2,3,4,5-tetrachloroanisole). Scheme II can also be extended to include chlorinated *o*-nitroanilines, which give the appropriate nitrohydroxy-PCBs, which also cyclize to yield PCDFs. By the judicious selection of precursors both reaction pathways can be used to synthesize hydroxy-PCB mixtures in which only one specific isomer will undergo intramolecular base-catalyzed cyclization. *This synthetic strategy greatly facilitates the separation and purification procedures, which in turn reduce the risk of exposure to potentially toxic PCDFs.* This paper reports the synthesis and characterization of 22 congeneric PCDFs by using the reaction sequences summarized in Schemes I and II.

EXPERIMENTAL SECTION

Chemicals. All the chemical precursors required for this study are commercially available. The 2,3-, 2,4-, 2,5-, and 2,6-dichloroanilines, 2,3,4- and 2,4,5-trichloroanilines, 2,3,4,5- and 2,3,5,6-tetrachloroanilines, pentachloroaniline, pentachlorobenzene, 1,2,4,5- and 1,2,3,4-tetrachlorobenzene, 1,3,5-trichlorobenzene, 1,4-dichlorobenzene, anisole, 2,3,4-trichloroanisole, 3,4,5-trichlorophenol, boron tribromide, and 3-chloro-*o*-anisidine were purchased from the Aldrich Chemical Co., Milwaukee, Wi. Isoamyl nitrite was purchased from Pfaltz and Bauer, Inc., Stamford, Ct. *o*-Anisidine and 5-chloro-*o*-anisidine were purchased from Eastman Organics, Rochester, N.Y. The 3,4,5-trichlorophenol was converted into the corresponding anisole by using dimethyl sulfate and potassium carbonate in acetone (Bickoff et al., 1958).

Synthesis. The substituted aniline or anisidine (3.0 g) and an excess of the substituted benzene or anisole (8–12 g) were placed in a 50-mL round-bottomed flask with a magnetic stirrer and heated at 120 °C. To the stirring mixture an excess of isoamyl nitrite (2.0 mL) was added over a period of 30 min and the reaction mixture maintained, with stirring, at 120 °C for 18 h. The excess of the substituted benzene was removed by distillation in vacuo and the residue adsorbed on to silica gel. The adsorbed material was layered on top of a 10-cm column of silica gel and the crude chlorinated methoxybiphenyl eluted with 500 mL of petroleum spirit, which was concentrated and the residue further purified by thin-layer chromatography (TLC) on silica gel HF_{254} using petroleum spirit as the elution solvent. The crude bands representing the methoxy product(s) (R_f 0.3–0.6) were scraped from the plate, eluted with diethyl ether, concentrated, and redissolved in methylene chloride; excess boron tribromide (5-8 mL, 1 M) in methylene chloride was added to the solution, with was allowed to stand for 24 h at 20 °C. The demethylation reaction was quenched by the dropwise addition of water (5 mL) and the reaction mixture was partitioned between methylene chloride–water (100 mL:100 mL). The methylene chloride was removed, the aqueous phase was extracted with methylene chloride, the extracts were combined, dried, and concentrated, and the residue was purified by TLC using petroleum spirit–ether (9:1) as the eluting solvent. The iodine-sensitive phenolic products were removed from the plate and the product was eluted from the silica gel with ether. The hydroxy-PCBs were concentrated, transferred to a 25-mL two-necked flask, and 0.7 mL of a 1 N potassium methoxide solution (potassium hydroxide in methanol) was added under a stream of dry nitrogen. After the solvent was removed 3 mL of dimethyl sulfoxide (Me_2SO) was added and the mixture refluxed with stirring at 180–200 °C for 18 h. The crude reaction mixture was diluted with water (100 mL) and extracted with 2 × 100 mL of methylene chloride, the combined extracts were dried and concentrated, and the residue was adsorbed onto silica gel. An alternative and more convenient procedure can be used to circumvent the extraction procedures since the crude reaction mixture can be adsorbed on to silica gel and the Me_2SO allowed to evaporate in a well-ventilated fume hood. The adsorbed material is layered on top of a 10-cm silica gel column and the PCDF eluted with 500 mL of petroleum spirit; the eluate is concentrated and the residue crystallized from methanol, filtered, and dried.

Characterization. The 220-MHz proton magnetic resonance (^1H NMR) spectra were recorded on a Varian XL-200 spectrometer; molecular weights were confirmed by mass spectral analysis and a detailed study of structure-dependent fragmentation pathways is in progress. The electron capture (EC) and flame ionization (FI) gas chromatographic analysis of the purified PCDFs was carried out by using a Tracor 360 chromatograph equipped with a glass column (6 ft × $^3/_{16}$ in.) packed with 1% OV-17/2% OV-210 on Gas-Chrom Q (Chromatographic Specialties, Brockville, Ontario, Canada); the oven temperature was 250 °C.

RESULTS AND DISCUSSION

Table I summarizes the reactants used for the preparation of the PCDF congeners, their relative GC retention times, and their response factors relative to that of lindane. Table II summarizes the ^1H NMR spectral data obtained for these compounds. The relative retention times of the PCDF congeners paralleled results that have previously been reported for related halogenated aromatics such as the PCBs (Ballschmiter and Zell, 1980; Mullin et al., 1981). There was in increase in both relative retention times and response factors with increasing chlorine content. Other effects of structure on the EC-GC retention times were not

Table I. Summary of PCDF Synthesis

chlorinated aniline or anisidine	chlorinated anisole or benzene	PCDF product	overall yield,[a] mg
2,6-dichloroaniline	anisole	1-chlorodibenzofuran	28
2,5-dichloroaniline	anisole	2-chlorodibenzofuran	97
2,4-dichloroaniline	anisole	3-chlorodibenzofuran	170
2,3-dichloroaniline	anisole	4-chlorodibenzofuran	102
2,4,5-trichloroaniline	anisole	2,3-dichlorodibenzofuran	240
5-chloro-*o*-anisidine	1,4-dichlorobenzene	2,8-dichlorodibenzofuran	170
2,4-dichloroaniline	4-chloroanisole	2,7-dichlorodibenzofuran	35
3-chloro-*o*-anisidine	1,4-dichlorobenzene	2,6-dichlorodibenzofuran	106
2,3,4-trichloroaniline	4-chloroanisole	2,6,7-trichlorodibenzofuran	320
5-chloro-*o*-anisidine	1,3,5-trichlorobenzene	1,3,8-trichlorodibenzofuran	170
2,4-dichloro-6-nitroaniline	4-chloroanisole	1,3,8-trichlorodibenzofuran	75
2,3,4,5-tetrachloroaniline	anisole	2,3,4-trichlorodibenzofuran	38
3-chloro-*o*-anisidine	1,3,5-trichlorobenzene	1,3,6-trichlorodibenzofuran	148
2,4,5-trichloroaniline	4-chloroanisole	2,3,8-trichlorodibenzofuran	199
3-chloro-*o*-anisidine	1,2,3,4-tetrachlorobenzene	2,3,4,6-tetrachlorodibenzofuran	30
5-chloro-*o*-anisidine	1,2,3,4-tetrachlorobenzene	2,3,4,8-tetrachlorodibenzofuran	170
5-chloro-*o*-anisidine	1,2,4,5-tetrachlorobenzene	1,2,4,8-tetrachlorodibenzofuran	10
2,3,5,6-tetrachloroaniline	4-chloroanisole	1,2,4,8-tetrachlorodibenzofuran	184
2,4,5-trichloroaniline	3,4,5-trichloroanisole	1,2,3,7,8-pentachlorodibenzofuran	94
5-chloro-*o*-anisidine	pentachlorobenzene	1,2,3,4,8-pentachlorodibenzofuran	83
2,4,5-trichloroaniline	2,3,4-trichloroanisole	2,3,4,7,8-pentachlorodibenzofuran	145
2,3,4,5-tetrachloroaniline	2,3,4-trichloroanisole	2,3,4,6,7,8-hexachlorodibenzofuran	117
2,3,4,5-tetrachloroaniline	3,4,5-trichloroanisole	1,2,3,6,7,8-hexachlorodibenzofuran	142
2,3,5,6-tetrachloroaniline	2,3,4-trichloroanisole	1,2,4,6,7,8-hexachlorodibenzofuran	56

[a] The overall yield of product represents the amount of material obtained after the three reaction steps; the yield of the Cadogan coupling reaction is low (5–15%), whereas the demethylation and base-catalyzed ring closure reactions are high (70–95%).

Table II. GC and Spectral Properties of Synthetic PCDFs

PCDF congener	retention[a] time	response[a] factor	^{1}H NMR chemical shifts, ppm[b]
1-MCDF	0.86	0.008[c]	m, 7.20–8.10
2-MCDF	0.86	0.044	m, 7.20–8.10
3-MCDF	0.85	0.02[c]	m, 7.20–8.10
4-MCDF	0.87	0.01[c]	m, 7.20–8.10
2,3-DCDF	1.35	0.05[c]	m, 7.20–8.20
2,8-DCDF	1.34	0.10	m, 7.20–8.20
2,6-DCDF	1.38	0.07	m, 7.20–8.20
2,7-DCDF	1.36	0.07	m, 7.20–8.20
2,6,7-TrCDF	2.22	0.28	7.46 (H3, dd, J = 8.2, 2.4 Hz), 7.48 (H8, d, J = 8.4 Hz), 7.63 (H4, dd, J = 8.2, 0.6 Hz), 7.99 (H9, d, J = 8.4 Hz), 8.08 (H1, dd, J = 2.4, 0.6 Hz)
1,3,8-TrCDF	1.72	0.27	7.55 (H2, d, J = 1.6 Hz), 7.64 (H7, dd, J = 8.4, 2.2 Hz), 7.76 (H6, dd, J = 8.4, 0.6 Hz), 7.79 (H4, d, J = 1.6 Hz), 8.27 (H9, dd, J = 2.2, 0.6 Hz)
2,3,4-TrCDF	2.20	0.52	m, 7.25–8.25 (H6, H7, H8, H9), 8.39 (H1, s)
1,3,6-TrCDF	1.74	0.23	7.50 (H8, t, J = 8.1 Hz), 7.55 (H2, d, J = 1.6 Hz), 7.68 (H7, dd, J = 8.1, 1.2 Hz), 7.85 (H4, d, J = 1.6 Hz), 8.27 (H9, dd, J = 8.1, 1.2 Hz)
2,3,8-TrCDF	2.08	0.19	7.45 (H7, dd, H = 8.6, 2.2 Hz), 7.56 (H6, d, J = 8.6 Hz), 7.82 (H4, s), 8.09 (H9, d, J = 2.2 Hz), 8.27 (H1, s)
2,3,4,6-TCDF	3.54	0.66	7.51 (H8, t, J = 7.8 Hz), 7.69 (H7, dd, J = 7.8, 1.2 Hz), 8.18 (H9, dd, J = 7.8, 1.2 Hz), 8.39 (H1, s)
2,3,4,8-TCDF	3.56	0.96	7.64 (H7, dd, J = 8.8, 2.2 Hz), 7.78 (H6, d, J = 8.8 Hz), 8.25 (H9, d, J = 2.2 Hz), 8.39 (H1, s)
1,2,4,8-TCDF	2.84	1.00	7.58 (H7, dd, J = 9.0, 2.3 Hz), 7.71 (H6, d, J = 9.0 Hz), 7.76 (H3, s), 8.25 (H9, d, J = 2.3 Hz)
1,2,3,7,8-PCDF	5.49	1.15	8.06 (H4, s), 8.08 (H6, br s), 8.52 (H9, br s)
1,2,3,4,8-PCDF	5.23	1.50	7.74 (H7, dd, J = 8.6, 2.2 Hz), 7.89 (H6, dd, J = 8.6, 0.08 Hz), 8.37 (H9, dd, J = 2.2, 0.8 Hz)
2,3,4,7,8-PCDF	5.90	1.81	8.09 (H6, s), 8.43 (H1, s), 8.46 (H9, s)
2,3,4,6,7,8-HCDF	9.57	1.82	8.32 (H1, H9, s)
1,2,3,6,7,8-HCDF	8.80	1.43	8.16 (H4, s), 8.51 (H9, s)
1,2,4,6,7,8-HCDF	7.55	1.47	7.99 (H3, s), 8.54 (H9, s)

[a] Relative to lindane where R_t = 1.0 and the molar response factor = 1.0. [b] In acetone-d_6. [c] Estimated due to impurities.

apparent when the 1% OV-17/2% OV-210 packed column was used.

The results illustrate the feasibility of this approach for the unambiguous synthesis of >95% pure PCDF congeners. The only compounds that were not obtained with this degree of purity were the 4-, 3- and 1-chlorodibenzofurans and 2,3-dichlorodibenzofuran, which were only 90, 90, 30, and 88% pure as determined by FI detector-GC analysis. These products were contaminated with a single major impurity containing an additional chlorine atom; however, the identities of these byproducts were not determined. *Since the PCDF congeners are potentially toxic, all the*

experimental procedures for the conversion of the hydroxy-PCBs into PCDFs were carried out in a well-ventilated fume hood.

Further research is continuing on the synthesis of additional congeners that are being used to identify specific PCDFs in environmental matrices and to study their biologic and toxic effects.

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Registry No. 2,6-Dichloroaniline, 608-31-1; 2,5-dichloroaniline, 95-82-9; 2,4-dichloroaniline, 554-00-7; 2,3-dichloroaniline, 608-27-5; 2,4,5-trichloroaniline, 636-30-6; 5-chloro-*o*-anisidine, 95-03-4; 3-chloro-*o*-anisidine, 51114-68-2; 2,3,4-trichloroaniline, 634-67-3; 2,4-dichloro-6-nitroaniline, 2683-43-4; 2,3,4,5-tetrachloroaniline, 634-83-3; 2,3,5,6-tetrachloroaniline, 3481-20-7; anisole, 100-66-3; 1,4-dichlorobenzene, 106-46-7; 4-chloroanisole, 623-12-1; 1,3,5-trichlorobenzene, 108-70-3; 1,2,3,4-tetrachlorobenzene, 634-66-2; 1,2,4,5-tetrachlorobenzene, 95-94-3; 3,4,5-trichloroanisole, 54135-82-9; pentachlorobenzene, 608-93-5; 2,3,4-trichloroanisole, 54135-80-7; 1-chlorodibenzofuran, 84761-86-4; 2-chlorodibenzofuran, 51230-49-0; 3-chlorodibenzofuran, 25074-67-3; 4-chlorodibenzofuran, 74992-96-4; 2,3-dichlorodibenzofuran, 64126-86-9; 2,8-dichlorodibenzofuran, 5409-83-6; 2,7-dichlorodibenzofuran, 74992-98-6; 2,6-dichlorodibenzofuran, 60390-27-4; 2,6,7-trichlorodibenzofuran, 83704-45-4; 1,3,8-trichlorodibenzofuran, 76621-12-0; 2,3,4-trichlorodibenzofuran, 57117-34-7; 1,3,6-trichlorodibenzofuran, 83704-39-6; 2,3,8-trichlorodibenzofuran, 57117-32-5; 2,3,46-tetrachlorodibenzofuran, 83704-30-7; 2,3,4,8-tetrachlorodibenzofuran, 83704-32-9; 1,2,4,8-tetrachlorodibenzofuran, 64126-87-0; 1,2,3,7,8-pentachlorodibenzofuran, 57117-41-6; 1,2,3,4,8-pentachlorodibenzofuran, 67517-48-0; 2,3,4,7,8-pentachlorodibenzofuran, 57117-31-4; 2,3,4,6,7,8-hexachlorodibenzofuran, 60851-34-5; 1,2,3,6,7,8-hexachlorodibenzofuran, 57117-44-9; 1,2,4,6,7,8-hexachlorobenzofuran, 67562-40-7; 1,1'-biphenyl, 92-52-4.

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