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METABOLISM OF PENTACHLORO- AND HEXACHLORO-BIPHENYLS IN THE RAT+

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Many papers are now available on the metabolic conversion of polychlorinated biphenyls in animals[1-6] and microorganisms[7-9]. The dominant metabolites were proved to be hydroxylated compounds and their conjugates.
In the previous papers[10-12], we reported on the metabolism of 2,2'-, 2,4-, 2,3-, 3,4-, 3,3'-, 4,4'-dichlorobiphenyls, 2,4,6-trichlorobiphenyl, 2,3,5,6-tetrachlorobiphenyl and 2,3,4,5,6-pentachlorobiphenyl in the rat. In this paper, we describe the metabolic behavior of higher chlorinated biphenyl compounds in the rat.

EXPERIMENTAL

The following compounds were prepared by the reaction of [U-^{14}C]2,4,6-trichloroiodobenzene and dichloroiodobenzene by Ullmann reaction (see, ref. 13-15) and the desired products were separated by gas chromatography: [$^{14}C_{1,2,3,4,5,6}$] 2,4,6,2',4'-pentachlorobiphenyl (107X10^3 cpm/mg), [$^{14}C_{1,2,3,4,5,6}$]2,4,6,2',6'-pentachlorobiphenyl (103X10^3 cpm/mg), [$^{14}C_{1,2,3,4,5,6}$]2,4,6,3',4'-pentachlorobiphenyl (89.6X10^3 cpm/mg), [$^{14}C_{1,2,3,4,5,6}$]2,4,6,3',5'-pentachlorobiphenyl (120X10^3 cpm/mg) and [U-^{14}C]2,4,6,2',4',6'-hexachlorobiphenyl (160X 10^3 cpm/mg). [U-^{14}C]2,4,6-Trichloroiodobenzene was prepared from [^{14}C]aniline purchased from New England Nuclear, Boston, USA. [$^{14}C_{1,2,3,4,5,6}$]decachlorobiphenyl (99.4X10^3 cpm/mg) was prepared by exhaustive chlorination of [$^{14}C_{1,2,3,4,5,6}$]2,3-dichlorobiphenyl.

2-Hydroxybiphenyl and 4-hydroxybiphenyl were purchased from Wako Pure Chemical Ind., Ltd., Tokyo. 3-Hydroxybiphenyl and 3,4-dihydroxybiphenyl were prepared

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as described in the previous paper[11]. 3-Hydroxy-2,4,6,2',4'-pentachlorobiphenyl, 3-hydroxy-2,4,6,2',6'-pentachlorobiphenyl, 3-hydroxy-2,4,6,3',4'-pentachlorobiphenyl, 3-hydroxy-2,4,6,3',5'-pentachlorobiphenyl and 3-hydroxy-2,4,6,2',4',6'-hexachlorobiphenyl were synthesized starting from 2,4,6-trichlorophenol and chloroanilines according to the procedure described by Colbert et al[16]; the desired compounds were separated by gas chromatography.

Administration of ^{14}C-labeled compounds to the rat, collection of the urine and feces, extraction of polychlorobiphenyls and their conversion products from feces, urine and body were performed as described previously[12]. Three main radioactive fractions were isolated: Fraction I including the unchanged polychlorobiphenyl, Fraction II containing monohydroxylated compounds and Fraction III of conjugated metabolites. Further purifications of the metabolites as well as dehalogenations of the compounds were achieved as described in the former publications[11].

RESULTS AND DISCUSSION

^{14}C-2,4,6,2',4'-Pentachlorobiphenyl, ^{14}C-2,4,6,2',6'-pentachlorobiphenyl, ^{14}C-2,4,6,3',4'-pentachlorobiphenyl, ^{14}C-2,4,6,3',5'-pentachlorobiphenyl and ^{14}C-2,4,6,2',4',6'-hexachlorobiphenyl were administered orally to the rat. The metabolites found in the urine were exclusively those of conjugates (β-D-glucuronides and others). Most of the radioactivity was found in the feces. Main conversion products of the five polychlorobiphenyls were found to be monohydroxylated derivatives as determined by mass spectrometry. On dehalogenation with RDB [11], all the monohydroxylated metabolites gave 3-hydroxybiphenyl (and not 2- nor 4-hydroxybiphenyl); this was identified by mass spectrometry and by comparison with authentic samples. Thus, hydroxylation was occured always on the meta-position of the biphenyls. Moreover, it was proved that 2,4,6,2',4'-pentachlorobiphenyl gave three possible m-hydroxy compounds and 2,4,6,2',6'-pentachlorobiphenyl two m-hydroxy derivatives (one major and one minor); this was identified by gas chromatography, mass spectrometry and by comparison with authentic samples. In the case of 2,4,6,3',4'-pentachlorobiphenyl the formation of 5'-hydroxy compound was not

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proved definitely. An additional metabolite was isolated when 2,4,6, 2',6'-pentachlorobiphenyl was fed to the rat. By comparison of mass spectra before and after dehalogenation and by comparison with authentic material, the compound was shown to be 3',4'-dihydroxy-2,4,6,2',6'-pentachlorobiphenyl. By treatment with sodium acetate and boric acid in ethanol, the compound gave a bathochromic shift typical to catechol. The main conjugate was identified as that of β-glucuronide by incubation with β-glucuronidase. Decachlorobiphenyl remained unchanged after feeding it to the rat. The metabolic behaviors of the polychlorobiphenyls which were discussed here and in the former publications[10-12] are summarized in Fig. 1. Further works on the relation between the structures of PCBs and enzyme inductions are in progress.

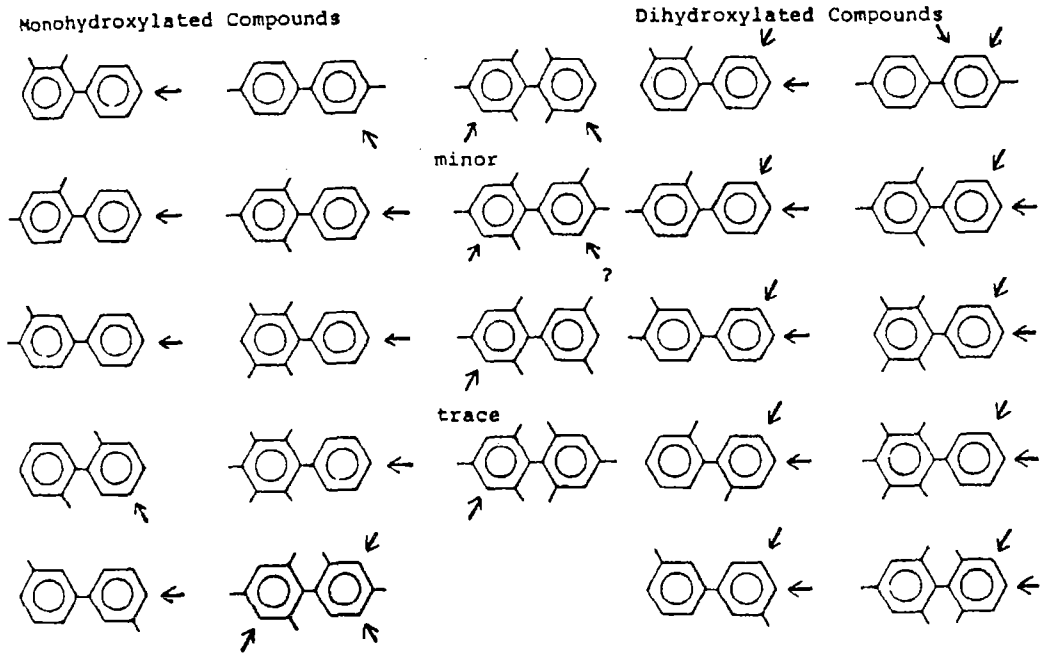


Fig. 1 Hydroxylations of polychlorinated biphenyls in the rat
(Main positions are indicated by arrows)

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