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PREFACE

This work was carried out at the Department of Chemistry, University of Jyväskylä, during the years 1986-1989.

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Jyväskylä, December 1989

Kari Rissanen

ABSTRACT

The structures of nine organic compounds containing bromine or chlorine were studied by single crystal X-ray diffraction. The compounds belong to two different classes of halogenated organics. Three of the compounds were polybrominated polycyclic ethers formed through transannular reactions during the treatment of two isomers of cyclododeca-1,5,9-triene with *N*-bromosuccinimide in methanol. These compounds were *endo,endo*-5,9-dibromo-*cis-transoid-cis*-13-oxa-tricyclo[8.2.1.$0^{2,6}$]tridecane (**I**), *endo,endo,exo*-2,6,10-tribromo-*exo*-5-methoxy-13-oxa-*trans*-bicyclo[7.3.1]tridecane (**II**) and *(E)-exo,endo*-2,5,10-tribromo-*exo*-6-methoxy-13-oxa-*cis*-bicyclo[7.3.1]tridec-4-ene (**III**). The remaining six compounds were polychlorinated aromatics used as model compounds in environmental analyses: 1,2,3,4-tetrachlorodibenzo-*p*-dioxin (**IV**), pentachloromethoxybenzene (**V**), 2,2',3,4',5'-pentachloro-4-methoxybiphenyl (**VI**), 2,2',4,4',5',6-hexachloro-3-methoxybiphenyl (**VII**), bis(2,4-dichlorophenyl) ether (**VIII**) and 2,2',3,4,4',5'-hexachlorodiphenyl ether (**IX**).

All structures were solved by Direct Methods, but the procedure used for the three brominated polycyclic ethers differed from the normal one. These compounds were taken for structure analysis directly from the synthesis, with no other information available about their chemical composition except that provided by the synthesis. A qualitative procedure for estimating the chemical composition from experimental crystallographic data and information about the synthesis is described and is applied as an expedient to structure solution for the three compositionally indeterminate polycyclic bromo compounds.

CONTENTS

ABBREVIATIONS

CSD	= **C**ambridge **S**tructural **D**atabase
PBDDs	= **P**oly**b**rominated **d**ibenzo-*p*-**d**ioxins
PBDFs	= **P**oly**b**rominated**d**ibenzo**f**urans
PBNs	= **P**oly**b**rominated **n**aphthalenes
OCs	= **O**rgano**c**hlorine compounds
TCDD	= 2,3,7,8-**T**etra**c**hloro**d**ibenzo-*p*-**d**ioxin
LD_{50}	= **L**ethal **d**ose for **50%** of the population
PCAs	= **P**oly**c**hlorinated **a**romatic compounds
PCBzs	= **P**oly**c**hlorinated **b**en**z**enes
PCPs	= **P**oly**c**hlorinated **p**henols
PCBs	= **P**oly**c**hlorinated **b**iphenyls
PCDDs	= **P**oly**c**hlorinated **d**ibenzo-*p*-**d**ioxins
PCDFs	= **P**oly**c**hlorinated **d**ibenzo**f**urans
PCPPs	= **P**oly**c**hlorinated **p**henoxy**p**henols
PCGs	= **P**oly**c**hlorinated **g**uaiacols
PCCs	= **P**oly**c**hlorinated **c**atechols
PCAs	= **P**oly**c**hlorinated **a**nisols
PVCs	= **P**oly**c**hlorinated **v**eratroles
PCBAs	= **P**oly**c**hlorinated **b**iphenyl **a**nisoles
PCAns	= **P**oly**c**hlorinated **an**thracenes
PCFls	= **P**oly**c**hlorinated **fl**uorenes
PCPys	= **P**oly**c**hlorinated **py**renes
PCFns	= **P**oly**c**hlorinated **fl**uora**n**thenes
AHH	= **A**ryl **h**ydrocarbon **h**ydroxylase
Ah receptor	= dioxin receptor
PBBs	= **P**oly**b**rominated **b**iphenyls
PAHs	= **P**oly**a**romatic **h**ydrocarbons
PCB-OHs	= **P**oly**c**hlorinated **b**iphenylols
PCDEs	= **P**oly**c**hlorinated **d**iphenyl **e**thers
ACEs	= **P**oly**c**hlorinated **e**thers

1. INTRODUCTION

Rapid evelopments in the computer field during the 1970's have provided crystallographers with new and powerful tools for crystal structure analysis.[1] The computers and programs available for solving crystal structures in the 1960's were difficult to use and generated results slowly, unlike the computers and sophisticated Direct Methods programs made available during the 1970's and 1980's. The dramatic increase in the number of crystal structure studies encouraged by the new technology can be seen by investigating entries in the Cambridge Structural Database[2] (CSD) (Figure 1.1).

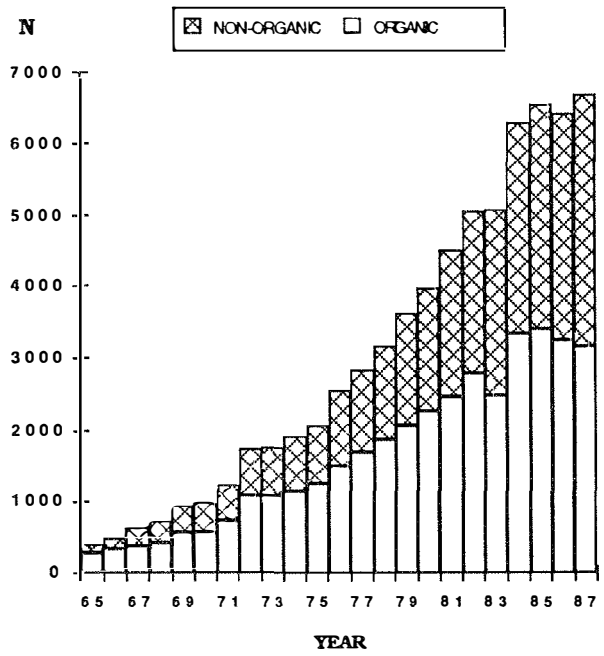


Figure 1.1. Growth of the CSD, expressed as number of entries (N) per publication year, for the period 1965-1987. The shaded area represents organometallics and metal complexes, the unshaded area organics.

The present version of the CSD (4.1, JUL89) contains information on 73893 structural studies, of which 40531 are classified[3] as organic. Of the 40531 organic entries 2544 (6.3%) contain at least one carbon-bromine bond and 5141 (12.7 %) at least one carbon-chlorine bond. Relative to all entries those containing bromine or chlorine as substituents make up 3.4 % and 7.0 %, respectively. The number of entries in the CSD has been increasing steadily at a rate of approximately 10% a year. The more rapid increase during the 1970's was associated with the publication of the first good Direct Methods programs: the first versions of the two principal Direct Methods programs, MULTAN[4] and SHELX[5] were published in 1970 and 1975, respectively. The steady increase in entries continued up until 1984 (the year 1983 was an exception) when more than 6000 were made. The growth of the CSD now appears to have levelled off at this figure. The percentage of organic entries in the CSD has dropped from 70% during the 1960's to approximately 50% during the 1980's, at the same time as the number of organometallic entries has increased.

The present work comprises nine single-crystal X-ray structural studies on organic compounds, of which three contain two or three bromine atoms as substituents in a polycyclic ether skeleton (**I**-**III**) and six contain four to six chlorine atoms attached to an aromatic ring (**IV**-**IX**). The compounds were synthesized and provided by the chemists presented in Table 1.1.

The work on the organobromine compounds is a continuation of the crystallographic studies on methoxybromination products of 12- and 13-membered trienes done at Karl-Marx-University,[6,7] while the work on the organochlorine compounds is a sequel to a series of synthetic and analytic studies on environmentally hazardous compounds done at the Department of Chemistry, University of Jyväskylä during the 1980's.[8–14]

Table 1.1. Origin of the compounds studied.

Compound	Synthesized by	Place
I	Doc. Günter Haufe	Jyväskylä*
II	Doc. Günter Haufe	Jyväskylä*
III	Doc. Günter Haufe	Jyväskylä*
IV	Analabs Company	USA
V	Doc. Juha Knuutinen	Jyväskylä#
VI	Birgitta Mannila, M.Sc.	Jyväskylä#
VII	Birgitta Mannila, M.Sc.	Jyväskylä#
VIII	Dr. Tarmo Humppi	Lakiala&
IX	Dr. Tarmo Humppi	Lakiala&

* On leave from Karl-Marx-University, GDR (December 1986)

\# Organic Chemistry Section, Department of Chemistry,
University of Jyväskylä, Finland

& Research Centre of the Finnish Defence Forces, Lakiala, Finland

The three organobromine compounds were new compounds whose chemical composition was not precisely known. Although knowledge of the chemical composition is a general presequisite for structure analysis of a compound, it is well-known to empirical crystallographers, and also has been noted in a recent crystallography text,[15] that the Direct Methods programs[16–18] can be applied to compounds of uncertain composition, provided that the estimated composition does not deviate too much from the correct composition. In this work, a systematic procedure was developed and applied, for estimating the chemical composition of the organobromine compounds from experimental data, *viz.* from particulars of the synthesis, unit cell volume and measured density; the estimate obtained for the composition was then used as input to a Direct Methods program. This procedure was used in place of the more time-consuming trial-and-error method of finding a composition, and is superior to it being less time-consuming.

2. POLYBROMINATED POLYCYCLIC ETHERS

2.1. General

Organobromine compounds are widely used in various forms and areas of industry and everyday life. They find use as antiseptics, germicides and fungicides, catalysts, dense liquids for solid separations, ingredients of fire-extinguishing fluids and fire retardants, fumigants and contact poisons, herbicides, lacrimators and warning fluids, reagents in microscopy and refractometry, ingredients in pharmaceutical and medicinal products, solvents, intermediates in synthesis and ingredients in heat-transfer media and transformer oils.[19] Some of the organobromine compounds, especially polybrominated dibenzo-*p*-dioxins (PBDDs), dibenzofurans (PBDFs) and naphthalenes (PBNs), are toxic and pose an environmental risk but in general organobromine compounds are less harmful to the environment than their polychlorinated analogues.[20]

After proper syntheses were developed for the cyclic hydrocarbons it became evident that the physical and chemical properties were quite different for compounds with common (five- to seven-membered), medium (eight- to eleven-membered) and large (twelve-membered and larger) rings. The special properties of these ring compounds are mainly attributable to steric effects within the molecule.[21] Transannular interactions, *viz.* steric interferences between non-adjacent atoms, govern the conformations and reactivities of the cyclic hydrocarbons, especially unsaturated ones.

The reactions taking place within the cyclic molecule are called transannular reactions.[21–23] Transannular reactions proceed mainly through carbonium ions, but also through carbanions, carbenes, free radicals and as yet unknown intermediates. The major route is through carbonium ions.[21,22,24–26,28–31,34] Brominated reaction products can be obtained by treatment of medium and large rings

containing double bonds with *N*-bromosuccinimide (NBS) in methanol[24,26–33] (methoxybromination), in water[29–32,34] (hydroxybromination), in acetic acid[32] (acetoxybromination) or in trimethylamine-HF[25] (bromofluorination). Under similar methoxybromination conditions, transannular π-cyclizations are the main processes for nine- to eleven-membered 1,5-dienes,[35] whereas transannular *O*-heterocyclization occurs in twelve- and thirteen-membered 1,5-dienes and 1,5,9-trienes.[24,27] Transannular π-cyclization leads to the formation of a new ring inside the molecule (bicyclo compounds) and transannular *O*-heterocyclization to transannular *O*-bridging (oxabicyclo or oxatricyclo compounds). Transannular *N*-heterocyclization is observed when cycloocta-1,5-diene is treated with NBS in the presence of cyanamide in diethylether, yielding dibromo-9-azabicyclo[4.2.1]nonanes.[36]

Applying a methoxybromination procedure to 12- or 13-membered trienes always yields a mixture of normal *anti*-1,2-addition products and their products together with transannular *O*-heterocyclization products (oxabicyclic) or transannular π-cyclization and *O*-heterocyclization products (oxatricyclic).[6,7,24,27] The reaction solution always contains a mixture of compounds, which have to be separated by column chromatography. The structures of these transannular reaction products can normally be verified by chemical reactions and spectroscopic techniques, but sometimes they remain uncertain even after such studies.

Single crystal X-ray diffraction study is the best way unambiguously to resolve the structure of a crystalline compound. Two crystal structure studies have earlier been published on the methoxybromination products of 12- and 13-membered trienes: *viz.* on (*E*)-2,6,11-tribromo-14-oxabicyclo[8.3.1]tetradec-6-ene (**1**)[6] and *anti*,*exo*,*exo*-5,10,12-tribromo-13-oxa-*exo*-tricyclo[7.3.1.$0^{2,6}$]tridecane (**2**).[7] The first was obtained by methoxybromination of (*Z,E,Z*)-cyclotrideca-1,5,9-triene *via* transannular *O*-heterocyclization and the second together with compound **II**, by methoxybromination of (*E,E,E*)-cyclododeca-1,5,9-triene *via* transannular π-cyclization and subsequent transannular *O*-heterocyclization. The detailed comparision of compounds **1** and **2** with

those studied in **I**, **II** and **III** is presented in Section 2.3.

The interesting structural features of these methoxybromination compounds are the conformations of the rings and the effect of the conformation on the carbon-bromine bond distances and angles and intramolecular non-bonded distances. A search of the Cambridge Structural Database[2] for carbon-bromine bond distances in this type of compound (the fragment searched was $C_{sp^3}(1)$–$C_{sp^3}(2)$–$C_{sp^3}(3)$, where one hydrogen and one bromine are bonded to carbon (2) with single bonds) yielded 149 non-disordered C–Br bonds. The mean of the bond distances was 1.957 Å with S.D.mean = 0.003 and S.D.sample = 0.038. The maximum bond distance was 2.108 and minimum 1.818 Å. The distribution of the distances is presented in Figure 2.1.1.

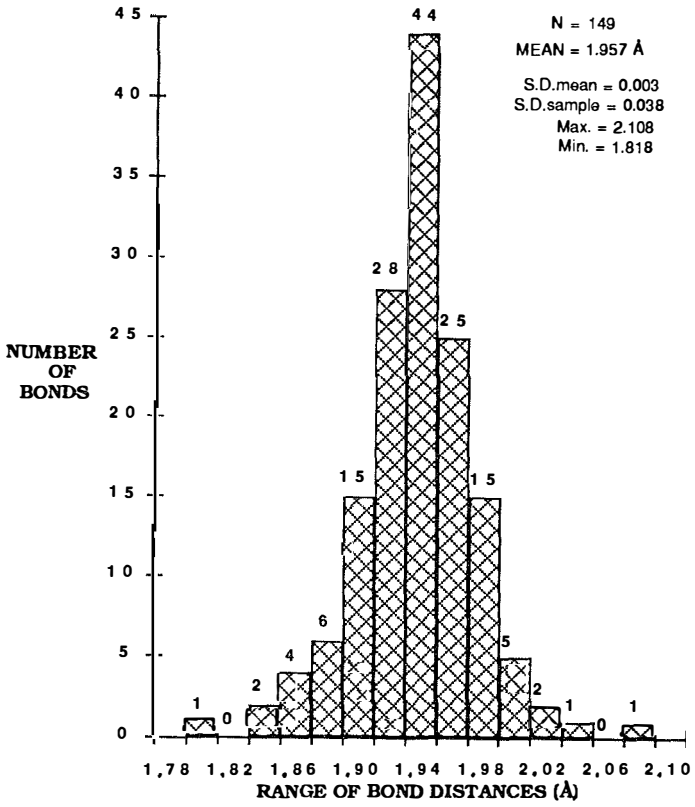


Figure 2.1.1. The distribution of C-Br bond distances

The difficulties expected in determining the chemical composition after synthesis and separation of compounds **I**, **II** and **III** led to the development of a systematic procedure for estimating the chemical composition from experimental data: from particulars of the synthesis, unit cell volume and measured density. The obtained estimate was used directly as input to the Direct Methods structure solution program MULTAN11/82[16]. The procedure and its application in the structure solution of compounds **I**, **II** and **III** are described below.

2.2. Direct Methods structure solution of compounds of uncertain chemical composition

Crystallographers are frequently asked to perform a crystal structure study on a compound of uncertain chemical composition. This kind of situation may arise when there is such a small amount of the compound to be studied that normal analytical methods cannot be applied, or the results of analyses are not available and the structure has to be determined without the analytical data. This section presents a concise qualitative answer to the question: When and how and when is it possible to solve the crystal structure of a compound of uncertain chemical composition?.

A 'normal' structure solution using Direct Methods starts from knowledge of the chemical composition of the compound. The basic principles of the structure solution by Direct Methods, as discussed in various excellent crystallographic texts,[15,37–40] are all valid in this presentation and therefore not discussed in any detail. When the chemical composition of a compound is not exactly known, some extra procedures needs to be carried out before the Direct Methods programs can be applied. Cases like these can be described as 'analytical' because the successful structure solution reveals the chemical composition of the compound as well as the structure, or else corrects a previously wrong structure.

The general formula for a compound can be presented as follows:

$$X_a Y_b Z_c Q_d \ldots, \tag{2.1}$$

where $X, Y, Z, Q \ldots$ are the types of atoms and $a, b, c, d \ldots$ are the number of atoms of each type. In the case of the structure solution of a compositionally uncertain compound, four categories of different complexity, depending on the number of unknowns in the formula, can be represented as follows:

A X,Y,Z,Q... are partly known and a,b,c,d... are unknown
eg. $C_a Y_b Br_c Q_d$, where Y,Q,a,b,c,d = ?

B X,Y,Z,Q... and a,b,c,d... are partly known
eg. $C_a H_b Br_c Q_d$, where Q=N,O,S,P, a=10-15, b=10-25, c=0-5, d=0-5

C Chemical composition is considered as known but during structure solution (*ss*) it turns out to be incorrect
eg. $C_{10}H_{15}Br_3O_4 \xrightarrow{ss} C_{13}H_{18}Br_4O$

D Chemical composition and the overall structure (eg. carbon skeleton) are known, but the exact structure can only be solved by X-ray diffraction; for instance *endo* or *exo* isomerism in a complex systems
eg. *endo,exo,endo*-$C_{13}H_{15}Br_3O_2 \xrightarrow{ss}$ *exo,endo,endo*-$C_{13}H_{15}Br_3O_2$

Structure determinations of types **A** and **B** are classified as 'analytical', while those of types **C** and **D** are merely special cases of 'normal' structure analysis and are not discussed here.

The difficulty in the structure solution of a compound of uncertain composition arises from the inability to present the structure factor,[15] *F(hkl)*, unambiguously.

$$F(hkl) = \sum_{j=1}^{N} f_j e^{-T_j} e^{2\pi i(hx_j + ky_j + lz_j)}, \tag{2.2}$$

where hkl are the Miller indices, N is the number of atoms, f_j is the scattering factor of a particular atom (j) type, T_j is the temperature factor expression and x, y and z are the fractional coordinates of the atom (j). In the case of an imprecisely known composition at least N and f_j's are unknown. The scaled structure factor,[15] $F_{rel}(hkl)$, is related to the measured intensity, $I(hkl)$, by the equation.

$$F_{rel}(hkl) = +k \cdot \sqrt{\frac{I(hkl)}{LpA}}, \tag{2.3}$$

where Lp is the Lorentz and polarization correction term, k is the statistically obtained scale factor and A is the effect of absorption. Direct Methods programs do not use $F_{rel}(hkl)$'s directly but instead they use so-called 'normalized structure factors' or E-values, $E(hkl)$.[15]

$$E(hkl)^2 = \frac{\mid F_{rel}(hkl) \mid^2}{(\sum_{j=1}^{N} f_j^2) \cdot \varepsilon}, \tag{2.4}$$

where N is the number of atoms, f_j's are the scattering factors of atoms and ε is a small integer related to some symmetry properties of the space group. *Fortunately, the calculation of E values during the normalization process in Direct Methods programs is not very sensitive to even quite large deviations in atom types and numbers.*[15]

To be able to apply Direct Methods to the structure solution of a compound of uncertain composition, some estimate must be made of the chemical composition. A systematic procedure for doing this is presented in the following section.

2.2.1. A procedure for estimating chemical composition from experimental crystallographic data

A considerable amount of information about the chemical composition of a compound can be obtained from crystallographic experiments and from details of the synthesis. From good quality crystals the crystal symmetry and unit cell are easily obtained by photographic or diffractometric techniques. Data collection is done by automated diffractometers and the space group(s) is determined from the systematic absences in the reflection data file. The density can be measured by standard flotation techniques. From the measured density value, d [Mg m^{-3}], some general conclusions about the types of the atoms in the compound can be made in the following way:

$d < 1.30$, only light atoms present; organic compound

$d = 1.30$ - 2.00, one or more heavier atom present;
organic compound with halogen, sulfur, phosphorous... etc. or
metal complex with organic ligand

$d > 2.00$, many heavy atoms present;
inorganic or organometallic compound

Nothing certain can be deduced from the density value alone and the above is merely a guideline as to what kinds of atoms are likely.

The formula weight of the compound, $F.W.$, and the number of formula units within the unit cell, Z, depend upon each other as shown[40] in equation (2.5) and are not known in the case of compositionally indeterminate compound.

$$F.W. = \frac{N_A \cdot d \cdot V}{Z}, \tag{2.5}$$

where $F.W.$ is the formula weight [kg mol^{-1}], N_A Avogadro's number [mol^{-1}], d the density [kg m^{-3}] and V the unit cell volume [m^3]. Only the product of Z and $F.W.$, which can be defined as the unit cell weight, $U.W.$, can be calculated directly from experimental data.

$$U.W. = Z \cdot F.W. = N \cdot d \cdot V, \tag{2.6}$$

where d is the measured density and V the measured unit cell volume. A procedure for estimating the value of Z in the case of partially known composition is presented later in this text.

The $F(000)$ is defined[15] as follows:

$$F(000) = \sum_{j=1}^{N} z_j \tag{2.7}$$

where z is the atomic number of the j atom. Thus $F(000)$ is the sum of all electrons in the unit cell and contains information about the number of formula units in the unit cell, Z:

$$F(000) = Z \cdot F_m, \tag{2.8}$$

where F_m is the number of electrons in one formula unit. Dividing $F(000)$ by unit cell volume (V) and plotting this quotient versus calculated density (d_x) yields a positive linear correlation ($y = a + bx$, where $y = \frac{F(000)}{V}$ and $x =$ density, d_x) (Figure 2.1).

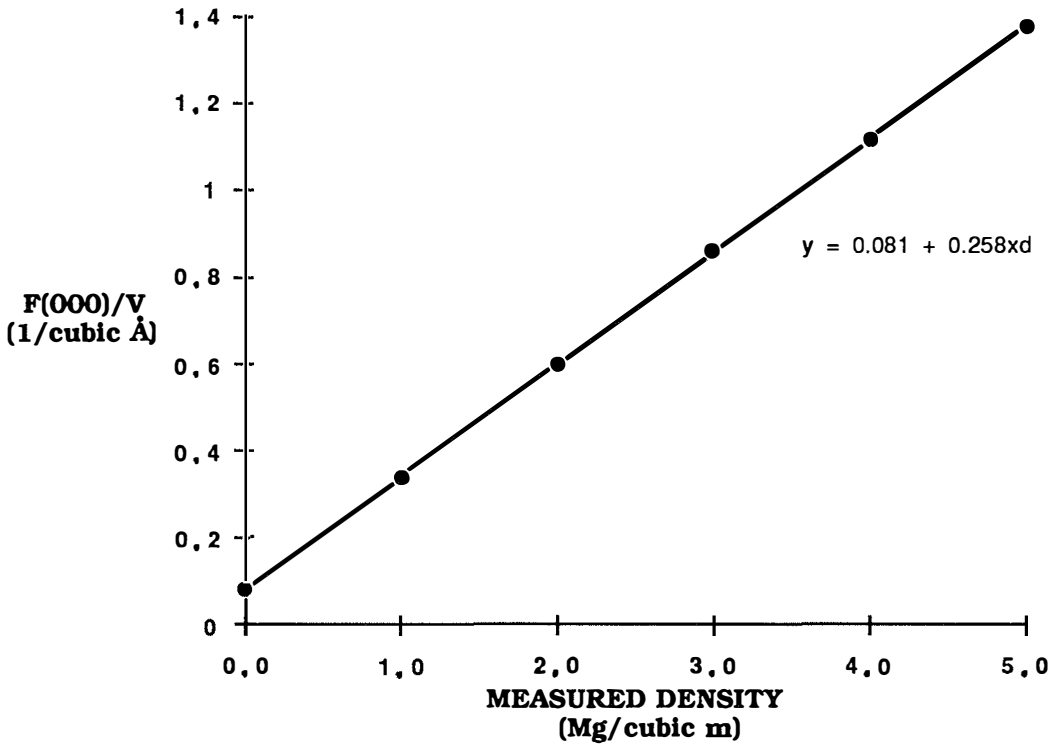


Figure 2.1. $\frac{F(000)}{V}$ versus d_x.

In this work the estimating parameters, a and b, were calculated by least-squares procedure using empirical values of $F(000)$, V and d_x from 77 crystal structure determinations found in *Acta Crystallographica* **C44** (1988), Part 11, pp. 1867-2037. The density variation was 0.819 - 5.128 Mg m^{-3}. The following least-squares line with correlation r = 0.997 was obtained:

$$\frac{F(000)}{V} = 0.081 + 0.258 \cdot d \tag{2.9}$$

From this equation a value for $F(000)$ can be estimated, without knowledge about the chemical composition, as follows:

$$F(000) = 0.081 \cdot V + 0.258 \cdot d \cdot V, \tag{2.10}$$

where $F(000)$ is the estimate of the total number of electrons within the unit cell, V is the measured unit cell volume [Å^3] and d is the measured density [Mg m^{-3}]. Because of the high correlation between y and x the errors in a and b are negligible compared with the errors in V and d and can be ignored. The errors in V and d are obtained experimentally and normally are between 0.1 and 0.2 and 1.0 and 1.5%, respectively. The error in estimated $F(000)$ can be obtained simply by adding the experimentally obtained errors in V and d.

$$\sigma F(000) = 2 \cdot \sigma V + \sigma \boldsymbol{d}, \tag{2.11}$$

By calculating $F(000)$ from equation (2.10), the overall scattering power of the compound of uncertain composition can be fairly reliably estimated. From equations (2.6) and (2.10) a value can be found for the ratio of the unit cell weight, $U.W.$, and the number of electrons in the unit cell, $F(000)$:

$$\frac{U.W.}{F(000)} = \frac{0.6022 \cdot \boldsymbol{d}}{0.081 + 0.258 \cdot \boldsymbol{d}} \tag{2.12}$$

Equation (2.12) shows the ratio $\frac{U.W.}{F(000)}$ to depend only on the density, not on Z, and to have nearly the same value as obtained by dividing the atomic weight, A, by the number of electrons in that atom (≈ 2). If the exact chemical composition is known, the ratio $\frac{U.W.}{F(000)}$ for a compound can be calculated directly, without using equation (2.12).

$$\frac{U.W.}{F(000)} = \frac{\sum_{j=1}^{M} A_j}{\sum_{j=1}^{M} Z_j} = \frac{F.W.}{F_m}, \tag{2.13}$$

where A_j is the atomic weight of atom (j), Z_j is the atomic number of atom (j) and M is the number of atoms in the formula unit.

When there is sufficient information available about the atom types and number of each composing the compound, *viz.* from synthesis and recrystallization

conditions, the possible values for Z can be calculated using the equations (2.10) and (2.14) together with the F_m's calculated for a large group of possible theoretical compositions.

$$Z = \frac{F(000)}{F_m}, \tag{2.14}$$

where F_m is the number of electrons in the theoretical composition. Calculations are done with a small computer program, which uses the estimate of $F(000)$, the possible atom types and number of each, and the space group information to sort out possible values of Z. The program permutes all possible combinations of compositions using the inputted atom types and minimum and maximum number of atoms, and calculates F_m for each composition. After this it computes values for Z (which must be integer numbers) from known $F(000)$, using equation (2.14), and selects the possible values on the basis of the space group information. If the information about the possible atom types and number is precise enough, only one or two possible Z values are obtained. After Z has been fixed to one or two values, the estimate for the $F.W.$ can be calculated using equation (2.5).

The values obtained for $F(000)$, $\frac{U.W.}{F(000)}$ and $F.W.$ can now effectively be used to sort out the most probable compositions from among the large number permuted from a certain group of atom types. The calculated values for the permuted composition are compared with the observed values (derived from density, unit cell volume and space group information), and those whose values of $F(000)$, $\frac{U.W.}{F(000)}$ and $F.W.$ are all within the specified error range (based on experimental errors) are accepted as 'trial' compositions to be used in Direct Methods programs. The narrower the error range within which compositions are accepted, the smaller will be the number of trial compositions accepted. Sorting is done using the same small computer program that permutes the compositions and calculates the possible Z values.

Even with moderate experimental errors the compositions accepted will be close enough to the actual compositions that every one can be accepted and used as 'trial' composition for the compound in Direct Methods programs and is likely

to produce the true solution. It needs to be emphasized, however, that without the availability of information from the synthesis and recrystallization to restrict the number of possible atom types, a solution for the structure would be almost impossible to find.

In some cases the values of density, $F(000)$, $\frac{U.W.}{F(000)}$ and $F.W.$ may be uninformative about the presence of a heavy atom(s) in the compound. The presence of heavy atom(s) can be investigated by calculating a Patterson synthesis for the data set, since this can be done without any knowledge of the composition. If the Patterson map is relatively flat, there are no heavy atoms present, or most of the atoms are of equal weight. This knowledge is relevant, together with the $F(000)$, $\frac{U.W.}{F(000)}$ and $F.W.$ values, when constructing a reasonable 'trial' composition to be used in structure solution by Direct Methods. The 'trial' composition constructed according to the procedure outlined above will normally be so close to the real composition that the subsequent E-value calculation will produce reasonably good phasing, allowing an electron density map of recognizable structure to be calculated and the structure to be solved.

2.2.2. Advantages and limitations of the procedure

+ Excellent quality crystals straight from synthesis can be used for structure analysis without the chemical composition first being determined by conventional analytical methods (eg. elemental analysis, IR, NMR, MS,... etc.). In normal cases the time required for the structure analysis will be reduced at least by a factor of three, in some difficult cases even more.

+ Medium-sized structures can be solved within a few days and small compounds in approximately 24 hours (including data collection).

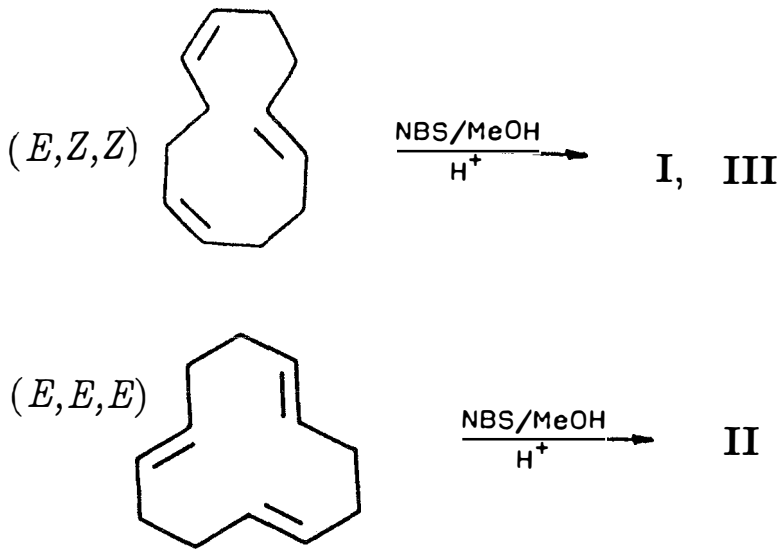
+ The whole analysis is made by one trained crystallographer, not by three or four persons from different fields as is the normal procedure.

- To be able to arrive at a reasonable 'trial' composition for the Direct Meth-

ods programs, two things need to be known about the compound: (1) how it was synthesized (*viz.* the atom types) and (2) the recrystallization conditions (additional atom types, solvent molecules). If this information is not available, it will be practically impossible to solve the structure by the proposed method, except in rare cases where the compound can be presumed to be merely organic (containing C, H, perhaps O).

2.2.3. Application of the procedure

The (*E,Z,Z*) and (*E,E,E*) isomers of cyclododeca-1,5,9-triene were treated with *N*-bromosuccinimide in methanol using the methoxybromination procedure according to Haufe.[24,27]



Colourless crystals of unknown chemical composition were isolated from the reaction mixtures. No attempt was made to analyze the chemical composition of these products, but instead crystals suitable for X-ray analysis were immediately chosen. The crystals turned out to be of excellent quality and good unit cells were obtained (Table 2.2.3.1).

Table 2.2.3.1. Unit cells for **I**, **II** and **III**

Compound	**I**	**II**	**III**
a [Å]	6.352(1)	6.739(1)	10.442(1)
b [Å]	12.002(1)	12.270(3)	9.681(2)
c [Å]	16.378(3)	19.231(2)	19.558(3)
α [^{o}]	90	90	90
β [^{o}]	97.17(1)	90	129.42(1)
γ [^{o}]	90	90	90
V [Å^3]	1238.8(3)	1590.3(8)	1527.3(9)
σV [%]	0.02	0.05	0.06

After data collections the systematic absences indicated the space groups to be

$P2_1/c$ with Z = 2,4,8... for **I**
$P2_12_12_1$ with Z = 4,8,12... for **II**
$P2_1/c$ with Z = 2,4,8...for **III**

From earlier studies[10,11,24,27] is was known that this type of methoxybromination product is likely to have a formula $C_aH_bBr_cO_d$, where a = 12 - 15, b = 15 - 25, c = 0 - 4 and d = 0 - 4. To allow for more combinations, the ranges were expanded to a = 12 - 17, b = 15 - 30, c = 0 - 5 and d = 0 - 7 in the computer run (see Section above). These products belong to category **B**, where atom types and numbers of atoms are only partly known. The densities were known to be approximately 1.7 – 1.9 Mg/m^3, varying with the number of bromine atoms in the product.

Except for the density values, all the data needed to construct a 'trial' composition by the procedure described above are now available. The densities of the products were measured by normal flotation technique, and the values obtained are presented in Table 2.2.3.2.

The estimates of $U.W.$ and $F(000)$ for the products could now be calculated, using equations (2.6) and (2.10), respectively (Table 2.2.3.2). The ratios $\frac{U.W.}{F(000)}$ were calculated using equation (2.11) and the measured density values. The Z value was obtained from a computer run and, with the given atom types and amounts, was found to be 4 for all three products. The estimate for $F.W.$ was calculated using equation (2.5) and the accepted Z value. The error in $F(000)$ was calculated with equation (2.11) from the errors shown in Table 2.2.3.2; the same error was also used for $\frac{U.W.}{F(000)}$ and $F.W.$ The error in the density value arrived at by flotation density measurements is normally $\pm$ 0.02 Mg m^{-3}.

Table 2.2.3.2. Estimates for $U.W.$, $F(000)$ and $\frac{U.W.}{F(000)}$.

Parameter\Compound	**I**	**II**	**III**
d [Mg/m^3]	1.79(2)	1.89(2)	1.93(2)
σd [%]	1.12	1.06	1.04
$U.W.$ [g/mol]	1335.35	1810.01	1775.10
$F(000)$	672	904	884
$\sigma F(000)$ [%]	1.16	1.16	1.14
$\frac{U.W.}{F(000)}$	1.986	2.002	2.008

Supplied with the above estimates and errors for $F(000)$ and $\frac{U.W.}{F(000)}$ and the data available from synthesis, the computer program produced the following compositions for compounds **I**, **II** and **III** (Table 2.2.3.3).

Table 2.2.3.3. Computer generated compositions for **I**, **II** and **III**

Variable\Compound	**I**	**II**	**III**
Number of comp.	1326	1032	989
Accepted*	10	34	39
min.# $F(000)$	668	896	876
max. $F(000)$	680	912	892
min. *F.W.*	329.13	447.13	438.09
max. *F.W.*	336.10	456.11	447.13
min. $\frac{U.W.}{F(000)}$	1.965	1.983	1.983
max. $\frac{U.W.}{F(000)}$	2.007	2.023	2.023
min. C	12	13	12
max. C	17	17	17
min. H	15	15	15
max. H	26	30	30
min. Br	1	2	2
max. Br	2	3	3
min. O	0	0	0
max. O	6	7	7

* based on selected atom range and the errors shown in Tables 2.2.3.1 and 2.2.3.2

\# calculated only for the accepted compositions

The 'trial' compositions (Table 2.2.3.4) to be used as input to the Direct Methods program MULTAN11/82[16] were chosen using the estimated values of $F(000)$ (equation 2.10) as criterion (the first composition, which had the same $F(000)$ value, was taken).

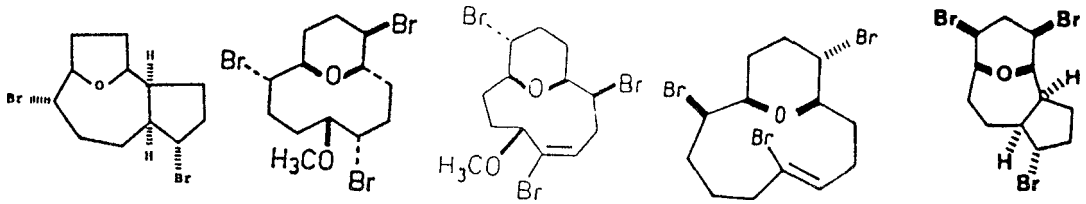
Only a few phase sets all had a very high combinated figure of merit (CFOM) and low residual (RESID) values in the MULTAN runs, the others having low CFOM and high RESID values. This indicates with high propability that one of the high CFOM value phase sets produces the true solution. In the case of product **I** with 'trial' composition $C_{13}H_{20}Br_2$, the best solution has CFOM = 2.564 and the electron density map shows one huge peak, one intermediate peak and a slowly fading background. The high maximum was assigned to bromine, but since the intermediate may or may not be bromine, at this stage only the highest peak was accepted as bromine. Product **II** with 'trial' composition $C_{14}H_{16}Br_2O_7$ had CFOM = 2.936 and gave an electron density map with two high, almost equal peaks, one intermediate peak and a slowly fading backround. The two high peaks were assigned to bromine atoms, but, as in the case of **I**, no assigments was made of the intermediate peak. Product **III** with 'trial' composition $C_{16}H_{15}Br_2O_5$ had CFOM = 2.805 and the electron density map again showed two equally high peaks, one intermediate peak and a slowly fading backround. The two high peaks were assigned to bromine atoms. After least-squares refinement with one, two and two bromine atoms for **I**, **II** and **III**, respectively, the subsequent difference Fourier calculations revealed one high maximum for all three compounds. These were the same intermediate peaks as in the peak list produced by MULTAN, which were now assigned to bromine atoms. Least-squares refinements with two, three and three bromine atoms for **I**, **II** and **III**, respectively, gave R-factors around 30%. All missing C and O atoms (and in the case of **I** the H atoms) were located from subsequent difference Fourier calculations. The 'trial' compositions deviated considerable from the actual compositions (Table 2.2.3.4), but MULTAN runs with the same parameter set gave the same true solutions with the 'trial' and the actual compositions. The crystallographic details and descriptions of structures are presented in the following section and in papers **I**, **II** and **III**.

Table 2.2.3.4. Differences between the 'trial' and actual compositions.

	'Trial"	Actual	Difference
I			
Composition	$C_{13}H_{20}Br_2$	$C_{12}H_{18}Br_2O$	+C,+2H,-O
Density	1.79	1.81	-0.02
F.W.	336.10	338.09	-1.99
$F(000)$	672	672	0
$\frac{U.W.}{F(000)}$	2.001	1.988	0.013
II			
Composition	$C_{14}H_{16}Br_2O_7$	$C_{13}H_{21}Br_3O_2$	+C,-5H,-Br,+6O
Density	1.89	1.88	0.01
F.W.	456.07	449.04	7.03
$F(000)$	904	880	24
$\frac{U.W.}{F(000)}$	2.018	2.041	-0.023
III			
Composition	$C_{16}H_{15}Br_2O_5$	$C_{13}H_{19}Br_3O_2$	+3C,+H,-Br
Density	1.93	1.94	-0.01
F.W.	447.08	447.02	0.06
$F(000)$	884	872	12
$\frac{U.W.}{F(000)}$	2.023	2.051	-0.028

2.3. Structures of the compounds

Data collection and experimental parameters together with crystallographic details are presented in papers **I-III**. The formation of *endo,endo*-5,9-dibromo-*cis-transoid-cis*-13-oxabicyclo[8.2.1.$0^{2,6}$]tridecane (**I**), *endo,endo,exo*-2,6,10-tribromo-*exo*-5-methoxy-13-oxa-*trans*-bicyclo[7.3.1]tridecane (**II**), (*E*)-*exo,endo*-2,5,10-tribromo-*exo*-6-methoxy-13-oxa-*cis*-bicyclo[7.3.1]tridec-4-ene (**III**), (*E*)-2,6,11-tribromo-14-oxabicyclo[8.3.1]tetradec-6-ene[6] (**1**) and *anti,exo,exo*-5,10,12-tribromo-13-oxa-*exo*-tricyclo[7.3.1.$0^{2,6}$]tridecane[7] (**2**) involves transannular *O*-heterocyclization, leading to oxabicyclo structure for **II**, **III** and **1** and, with transannular π-cyclization as well to oxatricyclo structures for **I** and **2** (Figure 2.3.1). In place of the long and complex IUPAC names, abbreviations **I-III**, **1** and **2** are used.



I **II** **III** **1** **2**

Figure 2.3.1. Structures of the compounds.

Two completely different compounds are obtained from the same reaction mixture: the tricyclic **I** and bicyclic **III** from (*E.E.E*)-cyclododeca-1,5,9-triene and the bicyclic **II** and tricyclic **2** from (*E.Z.Z*)-cyclododeca-1,5,9-triene. The formation of these compounds can be explained by the different reaction mechanisms. The oxatricyclic compounds are formed through a carbonium ion leading to transannular π-cyclization, whereas the oxabicyclic compounds are formed through a more-or-less bridged bromonium ion leading to *O*-heterocyclization. *O*-heterocyclization leads to formation of a six-membered tetrahydropyran ring

in case of **II**, **III**, **1** and **2**, but a five-membered tetrahydrofuran ring is formed in case of **I**. The tricyclic **I** and **2** have *cis-transoid-cis* configuration on the polycyclic skeleton, whereas the bicyclic **II**, **III** and **1** have *trans-*, *cis-* and *cis-*configurations, respectively. It is interesting to find that, from the same reaction mixture, different oxa-rings are formed with the same configuration (**I** and **III**) or the same oxa-ring with different configurations (**II** and **2**). The formation of the oxa-ring and the positions of the bromine atoms are dependent on the structure and conformation of the unisolable, mechanism-dependent, transition-state complex.

Carbon-bromine bond distances and conformations of the rings within the molecule are presented in Table 2.3.1. The carbon-carbon and carbon-oxygen bond distances and angles in **I** - **III** are normal and comparable to the values observed in **1** and **2**, the minimum C-C distance being 1.483(11) Å for **II** and maximum 1.561(13) Å for **II**. The mean of all C-C distances for **I** - **III** is 1.528 Å (n = 36) and is comparable to the mean for **1** and **2**, 1.521 Å (n = 25). The C-C double bond in **III** and **1** has the same value of 1.31 Å in each.

Table 2.3.1. Carbon-bromine bond distances and ring conformations for **I**-**III**, **1** and **2**.

Compound	I	II	III	1	2
Reaction type	$\pi + O$	O	O	O	$\pi + O$
C_{sp^3}-Br [Å]	1.969(5) 1.984(4) -	1.950(8) 1.984(9) 1.981(8)	1.965(7) 1.946(6) -	1.962(8) 1.991(8) -	2.01(1) 1.96(1) 1.98(1)
C_{sp^2}-Br [Å]	-	-	1.909(7)	1.954(9)	-
Conformation					
5-ring	envelope	-	-	-	envelope
6-ring	-	chair	chair	chair	twist-boat
7-11-ring	Dist. crown	dist. B-C-B	very dist. B-C-B	undefined	very twisted chair
Reference	I	II	III	10	11

The mean of the C_{sp^3}-Br bond distances for **I**-**III**, 1.968 Å (n = 7), is relatively close to the mean of 1.957 Å (n=149) calculated for non-disordered C_{sp^3}-Br distances in similar structural fragments present in the CSD[2] (see above p. 11).

The mean value calculated for **1** and **2** is 1.981 Å (n = 5) and is somewhat larger but still quite acceptable for such a small set of distances. Earlier,[41] based on a smaller amount of data, a mean value of 1.94 Å was suggested for C_{sp^3}-Br bond distances. The length of the C_{sp^3}-Br bond can vary within a wide range of values, the acceptable variation range being (3σ = 3 x S.D.sample = 0.114 Å) 1.843 – 2.071 Å. The carbon-bromine distance is affected at least by the electronegativities of the adjacent carbon atoms, steric effects within the molecule, large thermal motion of the Br atom and, to a minor extent, by intermolecular contacts and packing forces. An exact explanation of the variation of the C-Br distance cannot be given.[41]

The ring conformations for the five- and six-membered rings within the molecules are normal envelope (5-ring) for **I** and **2** and chair (6-ring) for **II**, **III** and **1**; the rarely encountered twist-boat (6-ring) is present in **2**. The seven- to eleven-membered rings all have more or less distorted crown or boat-chair-boat (B-C-B) conformations.

The strained conformations of large rings usually occasion some short intramolecular non-bonded contacts, most importantly the hydrogen-hydrogen, -H....H-, contacts. The van der Waals radius of the hydrogen atom is 1.20 Å, so the unstrained non-bonded contact should be larger than the sum of the van der Waals radii, 2.40 Å. The intramolecular non-bonded -H....H- contacts shorter than 2.40 Å for compounds **I**-**III** are presented in Table 2.3.2.

Table 2.3.2. Non-bonded contact -H....H- distances for **I**-**III**.

I	**II**	**III**
H11-H18, 2.27(8)	H1-H7, 1.98(4)	H4-H6, 2.02(5)
H6-H10, 2.31(8)	H1-H11, 2.15(4)	
H7-H9, 2.32(8)	H7-H11, 2.00(5)	
	H12-H14, 2.28(5)	

Some tentative conclusions can be drawn about the degree of strain within the molecules from the -H....H- contacts. Molecule **II**, which has many extremely short (about 0.4 Å shorter than the sum of the van der Walls radii) non-bonded contacts is the most strained of the compounds. Compound **III** has one very short contact, indicating moderate strain, and compound **I** has only marginally short contacts, indicating an almost strainless conformation.

3. POLYCHLORINATED AROMATICS

3.1. General

The majority of the organochlorine compounds (OCs) are considered as environmentally hazardous due to their toxicity, resistence to biodegraration and bioaccumulation into adopose tissues of animals. This is especially true of the planar and coplanar polychlorinated aromatic compounds. Coplanar compounds have an essentially non-planar conformation but are able to adopt planarity. Recent pollution by OCs has been found to cause ecological damage, initially by causing declining populations.[42] Organochlorine compounds are extensively used, in the same ways as their organobromine analogues, and additionally as insecticides, starting materials for plastics, intermediates in the manufacture of fluorohydrocarbons, adhesives, aerosol products, extraction solvents, paint and coating solvents, dry cleaning agents, metal cleaning agents, textile processing agents and starting materials for the synthesis of freons (chlorofluorocarbons).[43]

The extreme toxicity of certain chloroaromatics was discovered in the aftermath of industrial accidents during the production of 2,4,5-trichlorophenol from 1,2,4,5-tetrachlorobenzene by alkali treatment. The first accident, in the Monsanto Nitro plant in Virginia, USA, in 1949, caused chloroacne disease in 228 workers. After several such accidents and occupational chloroacne poisonings in the USA, France and the Federal Republic of Germany, the toxic substance

was identified as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or TCDD (Figure 3.1.1). TCDD was found to be acutely toxic to man and animals, the LD_{50} value for guinea pig being only 0.6 μg/kg.[42]

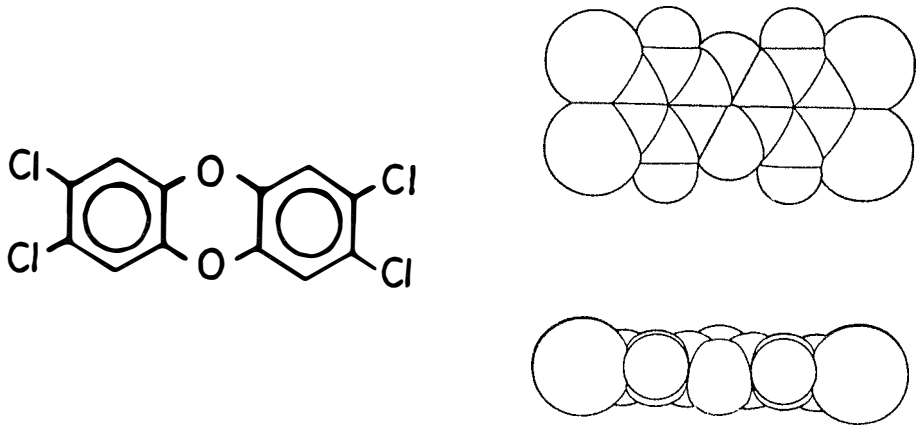
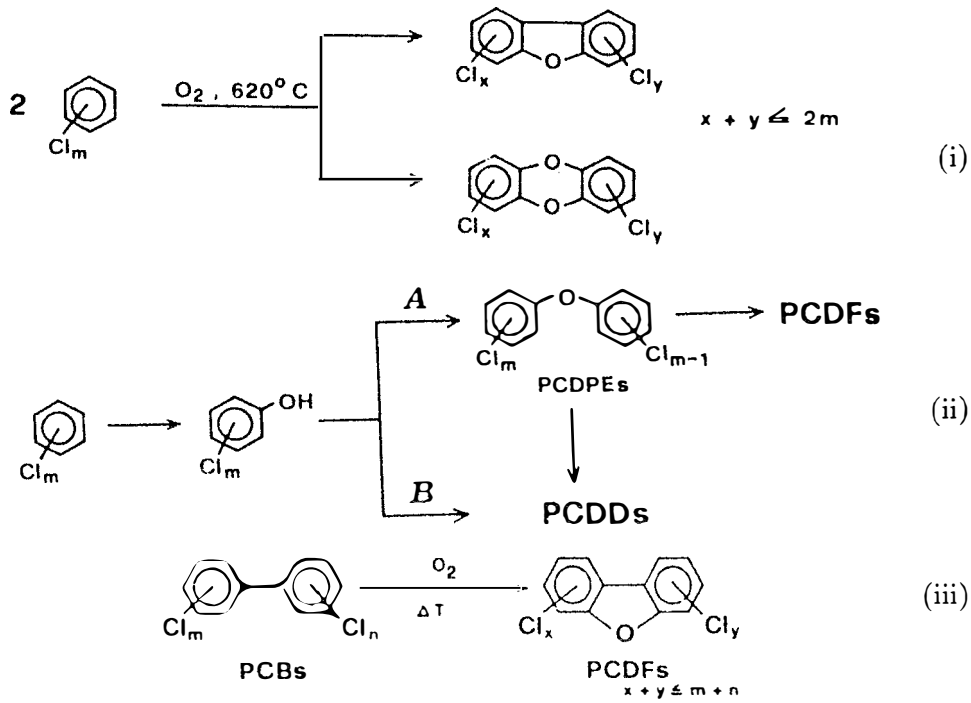


Figure 3.1.1. The structure of 2,3,7,8-tetrachloro-*p*-dioxin, TCDD.[44]

On the basis of the molecular dimensions of TCDD,[44] a model was proposed for a receptor into which the TCDD molecule exactly fits, disturbing its normal functioning and causing toxic effects.[45,46] The size of the receptor, now called the dioxin receptor, was later increased to take into account the van der Waals radii of the atoms, so explaining the similar toxic effects observed for other TCDD-type planar and coplanar compounds.[47]

Owing to the high dissociation energy of the C_{arom}–Cl bond, the polychlorinated aromatic compounds (PCAs) are resistant to degration under normal conditions, so that incineration or combustion[48,49] at low temperatures (< 700 ^{o}C) produces PCA compounds that are even more toxic and persistent. This is particularly true of the polychlorinated benzenes (PCBzs), phenols (PCPs) and biphenyls (PCBs) which generally are only moderaterly toxic, but upon incomplete combustion transform to supertoxic polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) (Scheme 3.1.1).



Scheme 3.1.1. The formation of PCDDs and PCDFs from PCBzs (i), PCPs (ii) and PCBs (iii).[48]

The industrial processes used to produce PCBzs, PCPs and PCBs involve elevated temperatures, at which the commercial PCBz, PCP and PCB products become contaminated with the supertoxic PCDDs and PCDFs.[49] The nonpolar and moderately polar PCAs are fat-soluble and bioaccumulate into food chains, representing a serious environmental hazard for higher animals such as fish, birds and mammals including humans.[42,49]

The supertoxic PCAs are planar or coplanar compounds with specific molecular geometry and electronic properties. The molecular geometry is mainly governed by the hydrocarbon skeleton and the electronic properties by the aromatic nature of the carbon backbone and the polarizable chlorine substituents. A condition for supertoxicity is that the chlorine substituents be located at specific positions in the molecule. The polarizability of the chlorine atoms and the carbon-chlorine bond distances are important factors in determining the electronic properties and molecular geometry, which afford an affinity towards

the dioxin binding receptor and inducing toxic or supertoxic effects.[45–47,53–55]

The C_{arom}–Cl bond distance like the C_{sp^3}–Br bond distance, varies within a wide range of values, but the distribution is much narrower around the mean value. A search of the CSD[2] for C_{arom}–Cl bond distances produced 1117 non-disordered bonds, with a mean value of 1.725 Å, S.D.mean = 0.001 and S.D.sample = 0.022. The maximum bond distance was 1.824 and minimum 1.629 Å. The distribution of the C_{arom}–Cl bond distances is presented in Figure 3.1.2.

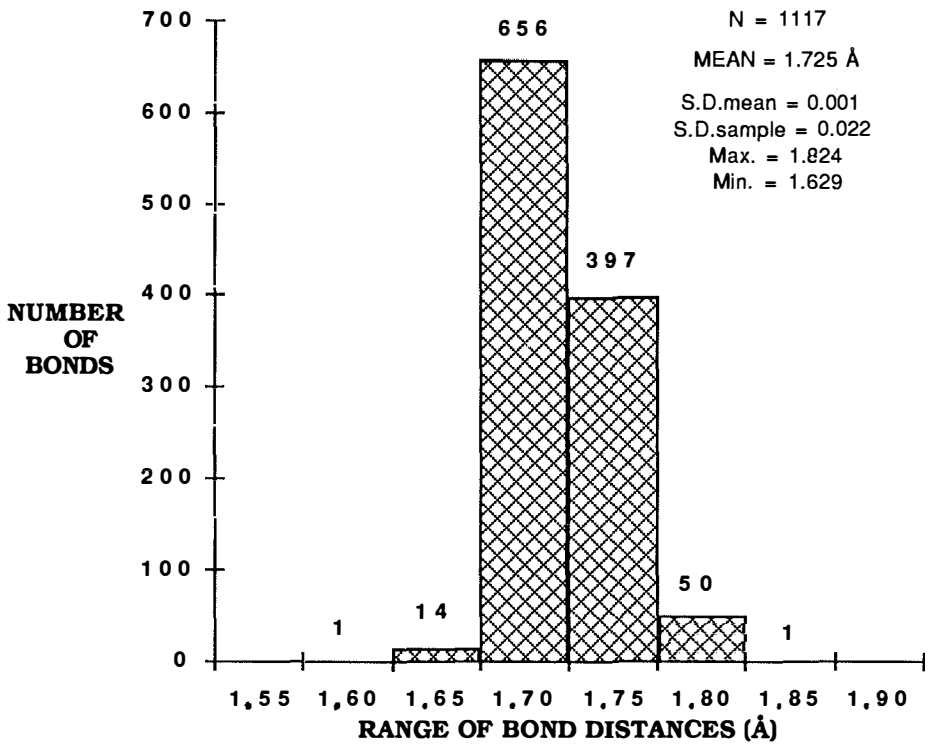


Figure 3.1.2. The distribution of C_{arom}–Cl bond distances.

3.2. Polychlorinated aromatics in the environment

Polychlorinated aromatic compounds are released into the environment from various sources, including industrial accidents, pesticide uses, dumping of chlorophenol wastes, chlorobleaching of pulp, chlorodisinfection of water and combustion of organochlorine compounds or chlorine-containing materials (Figure 3.2.1).[42] The harmful ecological effects of organochlorine compounds first came to light in the early 1960's in connection with the pesticide DDT. The compound responsible for the toxic effects was DDE, the major persistent metabolite. After a number of TCDD poisonings caused by industrial accidents, the importance of the organochlorine compounds and their metabolites as an environmental hazard was gradually recognized.[42,48,49] Hundreds of organochlorine compounds, including the supertoxic PCDD, PCDF and PCB congeners, are now being analyzed from environmental samples in every step of the food chain.[42,50,52]

The concept of TCDD-equivalent has just recently been introduced into the environmental analysis of PCA compounds.[50,51] Developed on the basis of the dioxin receptor theory (Section 3.3) and the toxicity studies, the TCDD-equivalent is a measure of the total dioxin-type toxicity load to the environment caused by TCDD and its related compounds. Recent studies have indicated that the major TCDD toxicity load comes from the coplanar PCB congeners.[50–52]

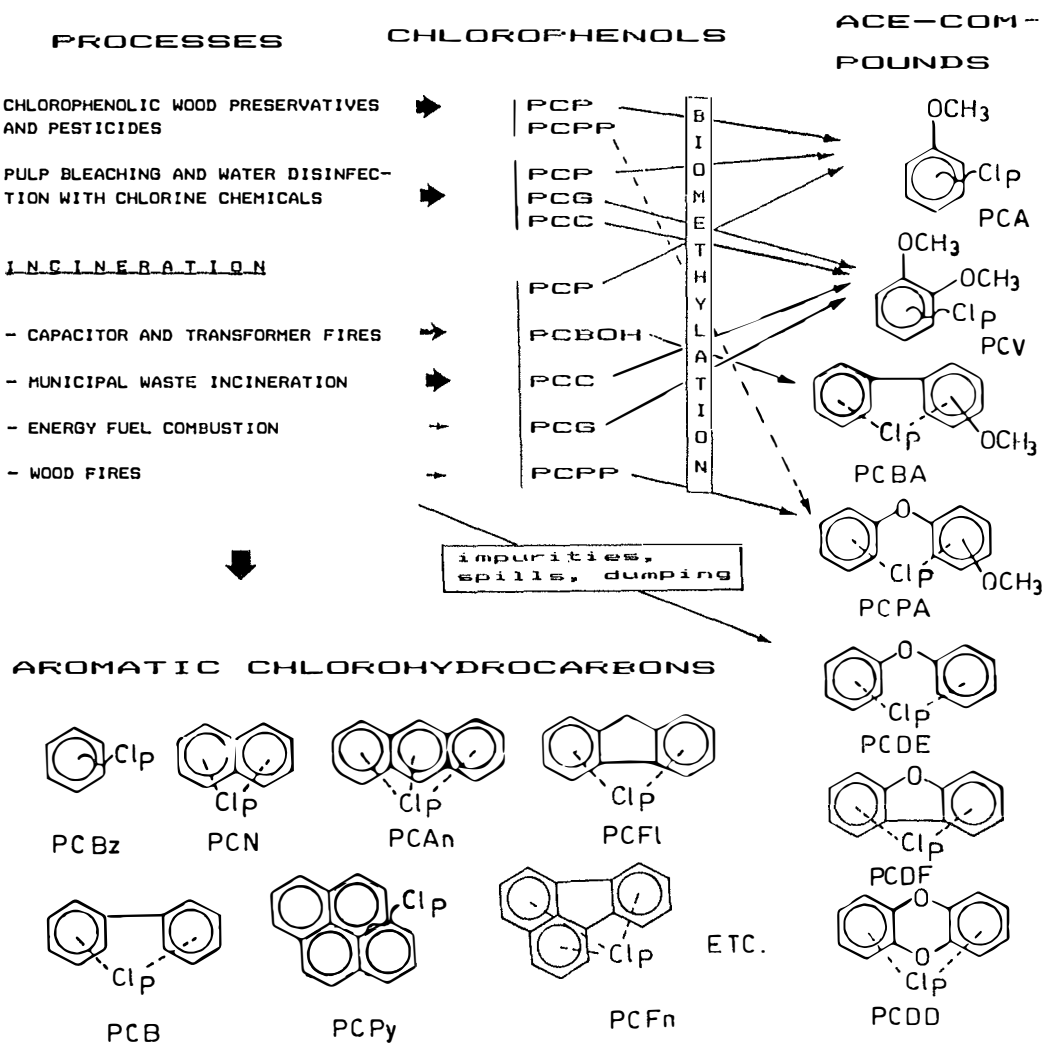


Figure 3.2.1. Sources of environmentally important PCAs.[42]

3.3. Structure vs. toxicity; the dioxin receptor theory

The crystal structure study[44] of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD, confirmed the planarity of the dibenzo-*p*-dioxin skeleton. TCDD is a completely planar molecule with four lateral chlorine substituents (see Figure 3.1.1) with approximate dimensions of 3 x 10 Å (height x width). Based on the molecular dimensions of TCDD, Poland[45,46] proposed a model for a particular high-affinity TCDD-binding cytosolic receptor protein, now called the dioxin or *Ah* receptor. TCDD binds into the hydrophobic 3 x 10 Å rectangular receptor site and causes hepatic aryl hydrocarbon hydroxylase (AHH) induction. The abnormal funtioning of this important drug-metabolism enzyme is manifested in humans with symptoms of chloracne, porphyria, liver damage, raised serum hepatic enzyme levels, disorders of fat and carbohydrate metabolism, cardiovascular, urinary and respiratory track disorders, pancreatic disorders, peripheral polyneuropathies, sensorial impairments, central lassitude, weakness, impotence and loss of libido.[53]

Although Polands dioxin receptor theory was feasible for TCDD, it was unable to explain the similar toxic effects observed for coplanar PCB and polybrominated biphenyl (PBB) congeners, polybrominated and non-halogenated TCDD analogues and polyaromatic hydrocarbons (PAHs).[20,47,49,54–58] To rectify this deficiency Gillner *et al.*[47] expanded the size of the receptor to 6.8 x 13.7 Å (Figure 3.3.1) making it big enough to receive the TCDD molecule, expanded to van der Waals size.

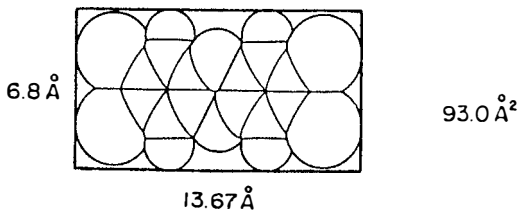


Figure 3.3.1. Model of the *Ah* receptor expanded to its van der Waals dimensions, with 'height' 6.8 Å, 'width' 13.67 Å and incumberance area 93.0 Å^2.[20,47]

Table 3.3.1. LD_{50} values for guinea pig for TCDD and related compounds.[20,54]

Name of Compound	No. in Fig. 3.3.2.	LD_{50} [μg/kg]
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	1	2
2,3,7,8-Tetrachlorodibenzofuran	2	7
3,3',4,4',5,5'-Hexachlorobiphenyl	3	223
2,3,7-Trichlorodibenzo-*p*-dioxin	4	29444
2,3,3',4,4',5,5'-Heptachlorobiphenyl	5	>3000
3,3',5,5'-Tetrafluoro-4,4'-dichlorobiphenyl	6	>3000
3,3',4,4'-Tetrachlorobiphenyl	7	<552
3,3',4,4'-Tetrachlorobiphenyl ether	8	inactive
2,3,6,7-Tetrachloronaphthalene	9	>3000
1,2,4,7,8-Pentachlorodibenzo-*p*-dioxin	10	1125
1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin	11	3
2,3,4,7,8-Tetrachlorodibenzofuran	12	<10
3,3',4,4',5-Pentachlorobiphenyl	13	active
2,3,7,8-Tetrabromodibenzo-*p*-dioxin	14	active
2,3,7,8-Tetrabromodibenzofuran	15	<15
2,3,7-Tribromodibenzo-*p*-dioxin	16	active
2,3,6,7-Tetrabromonaphthalene	17	242
1,2,4,6,7-Pentabromonaphthalene	18	200
1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin	19	73
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	20	70-100
1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin	21	60-100
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	22	>600
1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin	23	inactive
2,3,4,6,7,8-Hexachlorodibenzofuran	24	120
1,2,3,4,6,7-Hexabromonaphthalene	25	361
1,2,3,5,6,7-Hexabromonaphthalene	26	>3610
2,3,6,7-Tetrachlorobiphenylene	27	active
2,3,7,8-Tetrachloroanthracene	28	active
2,3,7,8-Tetrachlorofluorenone	29	>100
3-Methylcholanthrene	30	>10000
2,3,6,7-Tetrabromobiphenylene	31	<10

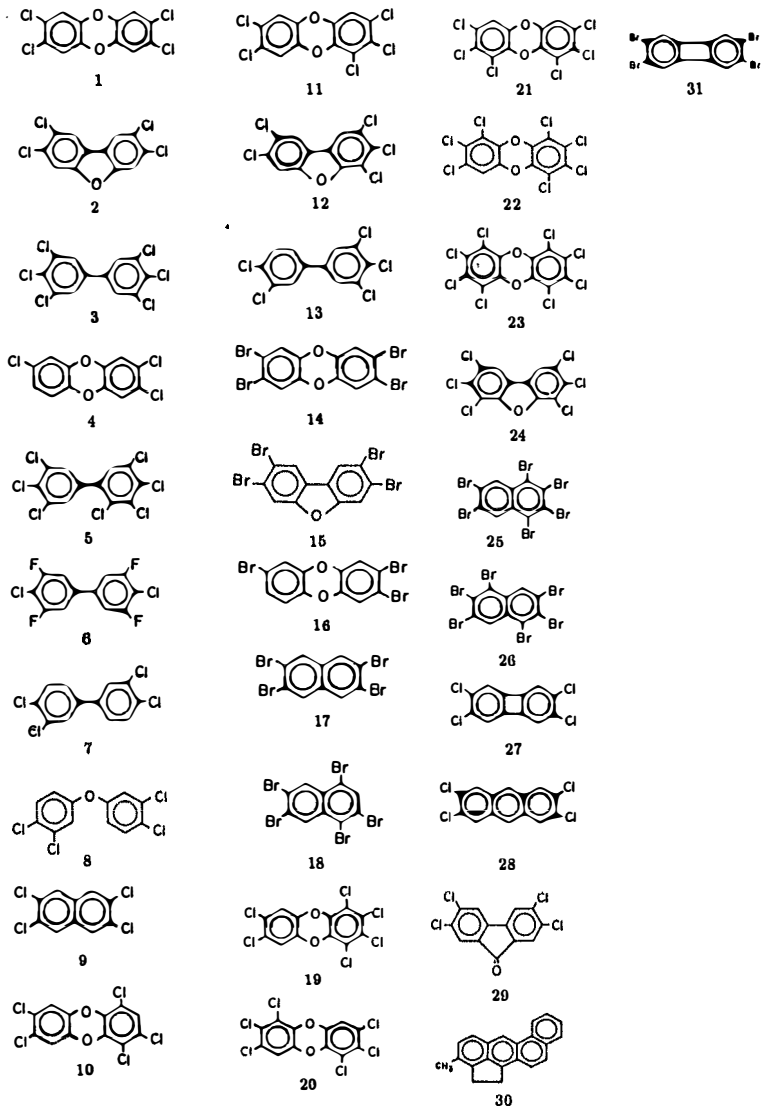


Figure 3.3.2. Structures of the compounds presented in Table 3.3.1.

The expanded receptor is capable of binding other TCDD-type compounds, thereby explaining the toxicity observed for some of these compounds. TCDD and those of its related compounds with extremely low LD_{50} values are associated with high *Ah*-receptor affinity and AHH-type enzyme induction (Table 3.3.1).[20,54] All compounds possessing high toxicity have planar or coplanar molecular geometry with easily polarized substituents in lateral positions (Figure 3.3.1).

The marked difference in the toxicity between the supertoxic TCDD and essentially non-toxic 3-methylcholanthrene (3-MC) and 2,4,6-triiodophenol, which all bind into the *Ah*-receptor with equal affinity, are informative of the electronic requirements for supertoxicity.[20]

The diversity of structural types (Table 3.3.1 and Figure 3.3.2) bound at the *Ah*-receptor suggests a stacking *viz.* charge-transfer type of complexation. Some proof of this kind of complexation has been obtained by NMR spectroscopy.[54] The rectangular 6.8 x 13.7 Å size with halogens in the four corners serves as a rough approximation for the generalized structure-activity relationship involving the *Ah* receptor.[47,54] However, MaKinney *et al.*[54] argue that molecular size and shape are not the controlling factors in binding the *Ah* receptor, and have developed a better model based on molecular polarizability and equilibrium separation between receptor and effector. This model assumes π-complexation between the receptor site and the inducer molecule and is more broadly applicable in being able to handle the expections not explained by the rectangular box model. Figure 3.3.3 provides a descriptive illustration of polarization through π-complexation.

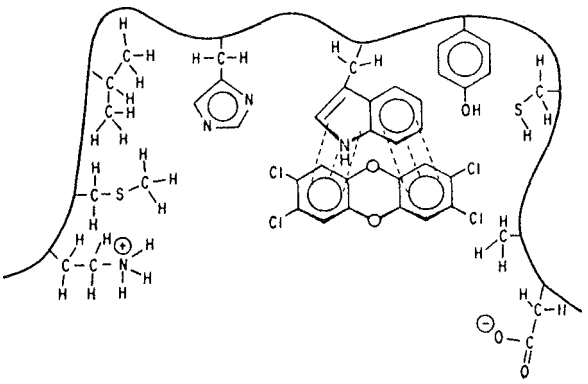


Figure 3.3.3. *Ah* receptor stacking π-interaction model.[54]

In the structure-toxicity relationship, planarity or coplanarity of structure and

lateral halogenation are apparently more important than the specific placement of halogens in effecting a sufficient condition for polarization and its right location. This would be more consistent with a non-stacking "pocket" type receptor model[54] as descriptively illustrated in Figure 3.3.4.

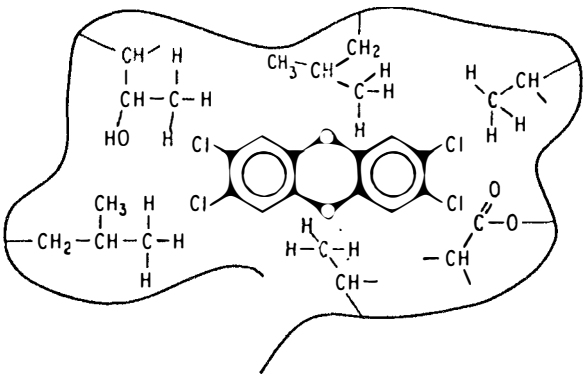


Figure 3.3.4. A non-stacking lateral halogen polarization interaction model for putative toxic "pocket"-type dioxin receptor.[54]

The model for the mechanism of action of toxic halogenated aromatics (Figure 3.3.5) is based on the mechanism of action of steroid hormones in which the process is initiated by the non-covalent interaction between a ligand (i.e., a coplanar toxic haloaromatic) and a receptor protein. The ligand-receptor complex is then translocated into the nucleus, and presumably interacts with a specific region of the nucleus DNA. These events trigger synthesis of m-RNA and protein, which ultimately leads to the pleiotypic responses observed in the host animals. Although considerable evidence for a receptor-mediated mechnism of action is found, the mechanistic details for the individual steps involved in the process are not well defined.[59–61]

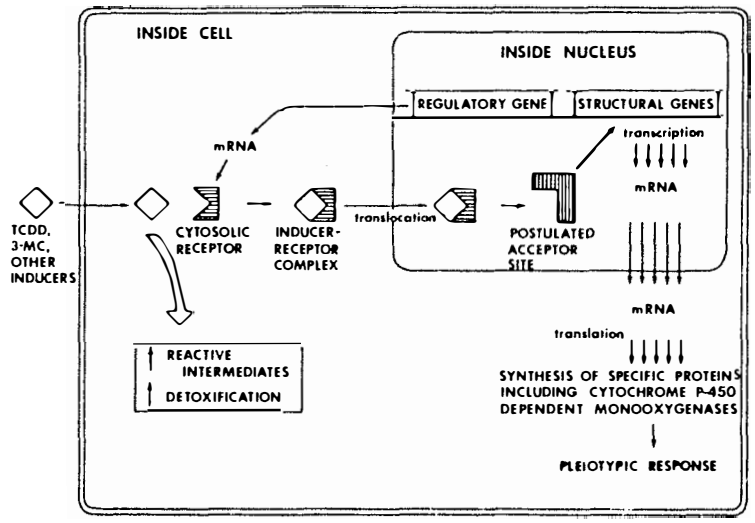


Figure 3.3.5. Proposed mechanism of action for TCDD and related toxic halogenated aromatics.[59]

A detailed description of the structure of the *Ah* receptor and the mechanism of action becomes even more difficult because the receptor has been identified and characterized in cytosol from a diversity of animals. Although the molecular properties of the *Ah* receptor were found to be similar in all species in which it was detected, subtle differences in receptor properties were found among animal species, indicating that the *Ah* receptor protein is not identical in all species.[62]

Toxicity studies done on various species of animals have also shown differences in the susceptibility to intoxication. The LD_{50} values for guinea pig and hamster, for example, are 0.6 and 5051 μg/kg, respectively.[63] Also the clinicopathological syndrome is different in each species of animals and intoxication more readily occurs in young animals than in adults. At lethal doses the time between exposure and death was about two weeks longer in adult than in young animals.[63]

In spite of the difficulties in explaining the exact structure of the *Ah* receptor

and the mechanism of action, some general requirements for the supertoxic compounds can be given (Table 3.3.1 and Figure 3.3.1).[20,58]

PCDDs and related planar compounds

1) Approximately 6.8 x 13.7 Å rectangular size with aromatic nature and about 93-96 $Å^3$ incumberance area

2) Molecular thickness about 3.6-3.9 Å (van der Waals radii of chlorine or bromine atoms)

3) From three to six polarizable (chlorine 4-6, bromine 3-6) substituents in lateral (corner) positions.

PCBs and related non-planar compounds

4) Ability to adopt planar or near planar conformation

5) Molecular geometry and polarizability as defined in 1)–3)

Any major deviations from the above requirements will result in lower affinity towards the *Ah* receptor and/or lower toxicity.[20,54–58]

3.4. Structures of the compounds

The compounds studied in papers **IV** - **IX** represent four different types of PCA compounds. 1,2,3,4-Tetrachlorodibenzo-*p*-dioxin (**IV**) is an isomeric form of the supertoxic TCDD thus representing the planar polychlorodioxins (PCDDs). Pentachloromethoxybenzene (**V**) is an example of the biomethylation products of polychlorophenols (PCPs). 2,2',3,4',5'-Pentachloro-4-methoxybiphenyl

(**VI**) and 2,2',4,4',5',6-hexachloro-3-methoxybiphenyl (**VII**) are biomethylation products of polychlorobiphenylols (PCB-OHs), closely resembling polychlorobiphenyls (PCBs). Bis(2,4-dichlorophenyl) ether (**VIII**) and 2,2',3,4,4',5'-hexachlorodiphenyl ether (**IX**) are representatives of the polychlorodiphenyl ethers (PCDEs) (Figure 3.4.1). All six compounds are members of a larger group of aromatic chloroethers (ACEs) and were synthesized for use as model compounds in environmental analyses.[42]

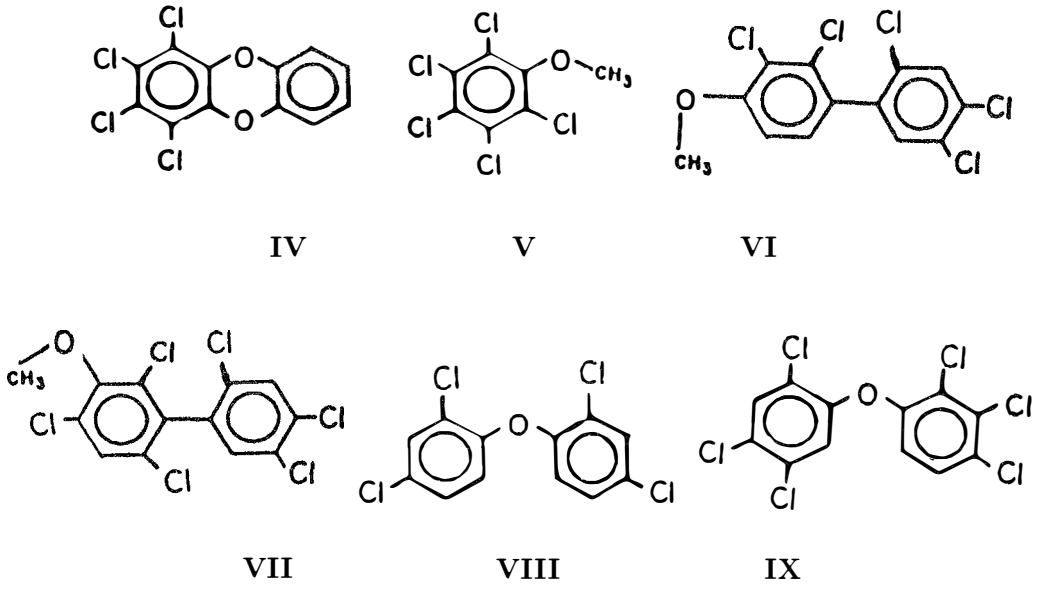


Figure 3.4.1. Structures of compounds **IV-IX**.

Data collection and experimental parameters together with the crystallographic details are presented in papers **IV** - **IX**. The focal point of the studies **IV** - **IX** was to determine the molecular geometry, *viz.* the planarity and shape of the molecules and study the relationships between structure and toxicity as suggested by the dioxin receptor theory. A summary of the carbon-chlorine bond distances, the parameters defining planarity, the twist and the C–O–C bond angles for compounds **IV** - **IX** is presented in Table 3.4.1.

Table 3.4.1. C_{arom}-Cl bond distances, planarity, twist and C–O–C angles for **IV** - **IX**.

Compound	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
C_{arom}-Cl [Å]	1.710(11)	1.698(10)	1.729(3)	1.728(4)	1.738(7)	1.720(4)
	1.736(11)	1.714(9)	1.721(3)	1.723(4)	1.749(8)	1.713(4)
	1.701(12)	1.727(13)	1.734(3)	1.734(5)	-	1.717(4)
	1.697(11)	1.704(11)	1.721(3)	1.729(5)	-	1.725(3)
	-	1.711(9)	1.712(2)	1.727(4)	-	1.723(4)
	-	-	-	1.730(4)	-	1.727(4)
Planarity* [Å]						
above the ls-plane	0.081(4) [Cl(2)]	1.182(13) [C(7)]	0.050(1) [Cl(2)]	1.253(5) [C(7)]	0.092(2) [Cl(4)]	0.090(1) [Cl(4')]
below the ls-plane	-	0.135(9) [O(1)]	0.208(4) [C(7)]	0.072(1) [Cl(2)]	-	0.089(1) [Cl(4)]
Twist angle [°]	-	-	73.35(9)	82.72(11)	68.4(8)	85.46(8)
C–O–C angle [°]	115.2(8)	112.2(9)	117.6(2)	114.7(3)	120.0(6)	117.2(3)
	114.5(8)	-	-	-	-	-

* Maximum deviation from the calculated least-squares plane

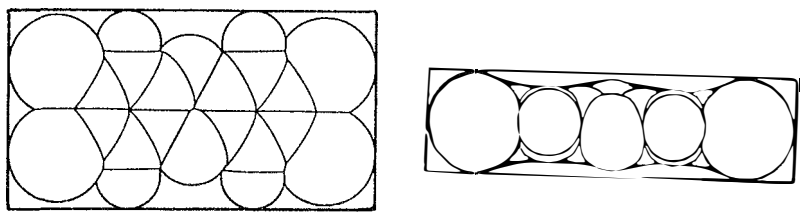
The carbon-chlorine bond distances are very similar in all compounds studied, the mean value being 1.721 Å (n = 28) with maximum = 1.749 and minimum = 1.697 Å. The mean calculated for these compounds is almost the same as that calculated from CSD (1.725 Å, n = 1117, p. 33) for a very large set of C_{arom}–Cl bonds. Similar although slightly larger values [1.736 (n = 83)[64] and 1.74[41] Å] were calculated earlier from a smaller set of bonds. The acceptable range for the C_{arom}–Cl bond distance based on CSD calculations (3σ = 3 x 0.022 = 0.066 Å) is from 1.659 to 1.791 Å. Although the range is quite wide, there seem to be certain small systematic alterations in the bond distances due to the positions and number of other chlorine substituents within the same benzene ring.[41,64] In compounds with two chlorine substituents in *ortho* position to each other, or three in non-*ortho* positions, the bond distance is about 1.725 - 1.735 Å. With a single chlorine substituent the bond distance is a little longer (≈ 1.74-1.75 Å). Three chlorine substituents in *ortho* position to each other and four or more chlorine substituents in the same benzene ring will result in a bond distance of about 1.705 - 1.715 Å.[64] This tendency is also seen in compounds **IV**-**IX** (Table 3.4.1 and Figure 3.4.1). The C-C, C-O and C-H bond distances and angles in compounds **IV**-**IX** are normal, the ether angle C–O–C being the only one that is markedly affected by the steric effects.

The only compound of those studied which can be regarded as planar is compound **IV**, which has a rigid planar dibenzo-*p*-dioxin skeleton. In pentachloromethoxybenzene (**V**), the methoxy group carbon is sterically fixed perpendicular to the benzene ring resulting in a rigid non-planar structure. Compounds **VI** and **VII** have a definite twist angle around the single bond between the phenyl rings in the biphenyl moiety. The twist angle is caused by the chlorine substituents occupying the *ortho* positions, two (2,2') in **VI** and three (2,2',6) in **VII**. Because of the large *ortho* substituents these molecules can not adopt coplanar structure, at least not in the crystalline state, unlike some of the non-*ortho* substituted biphenyls.[65–69] The PDCE compounds **VIII** and **IX** also have a large twist angle, even though the structural moiety is different from that in **VI** and **VII**. The phenyl rings are bonded to an etheric oxygen

which, through the C–O–C angle ($\approx 120^o$), induces steric repulsion between the phenyl rings. Four different conformational forms have been proposed[70] for the diphenyl ether moiety: planar, 'butterfly', skew and twist. Studies **VIII**, **IX** and that on bis(3,4-dichlorophenyl) ether[71] (see no. 8 in Figure 3.3.2, p. 38) have shown that only the twist conformation is encountered.

The orientation of the methoxy group towards the benzene ring and the size of the ether angle C–O–C are affected by the adjacent substituents. Theoretical studies[72] have shown that the methoxy group tends to prefer coplanar orientation toward the benzene ring when there is no or only one large substituent adjacent to it. After *ortho* disubstitution (towards the methoxy group) a perpendicular orientation as in **V** and **VII** is found. The C–O–C angle is affected sterically by the large substituents adjacent to it and a closing of 3-5^o is observed for the perpendicular orientation (Table 3.4.1).

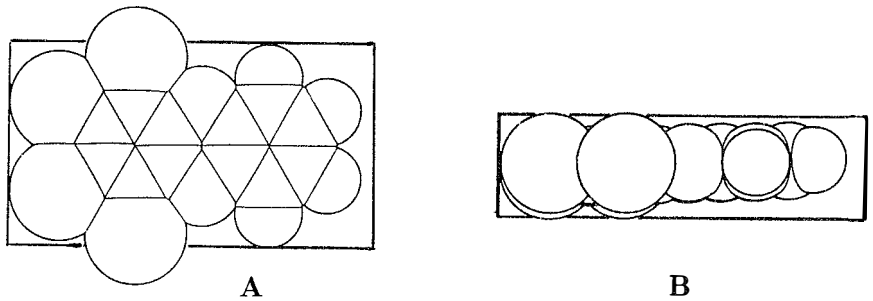
The molecular size and the polarizable chlorine substituents in compounds **IV**-**IX** (Figure 3.4.1.) suggests that if these molecules were planar or could adopt planarity, the major requirements for supertoxicity as presented in Section 3.3 (p. 36) would be fulfilled. The molecular fit of these compounds into the dioxin receptor can be tested qualitatively by examining the size and the planarity of the molecules against the rectangular dioxin receptor model. Figure 3.4.2 shows the rectangular receptor model from top and side view with the TCDD molecule inside.



A **B**

Figure 3.4.2. Rectangular dioxin receptor model
from top (**A**) and side (**B**) view.

Comparing now the molecular fit of compound **IV** into the rectangular receptor model (compound **IV** is an isomeric form of TCDD), we see that although the planarity is about the same, the 'height' of the compound is too great for an exact molecular fit (Figure 3.4.3).

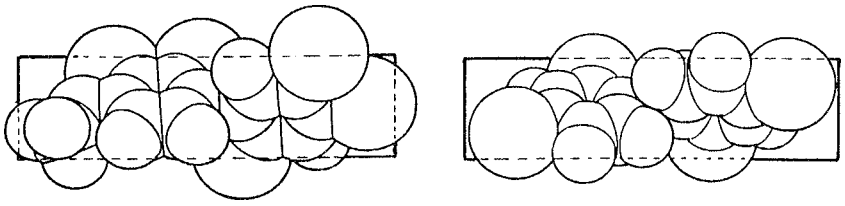


A **B**

Figure 3.4.3. The molecular fit of **IV** into the dioxin receptor model; top (**A**) and side (**B**) view.

The less than exact molecular fit does not alone explain the absence of supertoxicity since even larger chlorinated dibenzo-*p*-dioxins, like 1,2,3,7,8-penta-, 1,2,3,4,7,8-hexa-, 1,2,3,6,7,8-hexa- and 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin, are supertoxic (nos. 11, 19-21 in Table 3.3.1 and Figure 3.3.2, pp. 37-38). Rather, the different polarizability of the molecule in the same way as in 2,3,7-trichlorodibenzo-*p*-dioxin (no. 4 in Table 3.3.1 and Figure 3.3.2, pp. 37-38), is the main determinant for the absence of supertoxicity for compound **IV**.

Compounds **V**-**IX** are all non-planar and the compound **V**, in addition, is too small to fit into the receptor. The marked non-planarity of compounds **VI**-**IX** makes them sterically unfavourable for supertoxicity. The molecular fit of compounds **VI**-**IX** is exemplified with the two most planar of these compounds, **VI** and **VIII**, in Figure 3.4.4.



A **B**

Figure 3.4.4. Molecular fit of compounds **VI** (**A**) and **VIII** (**B**) into the dioxin receptor.

The non-toxicity of bis(3,4-dichlorophenyl) ether[71] (Table 3.3.1, p.37), which is structurally very similar to compounds **VI-IX**, is supportive of the sterical requirements proposed for supertoxicity.

4. CONCLUSIONS

Single crystal X-ray diffraction study on a crystalline compound is the best way unambiquosly to determine the crystal and molecular structure of that compound. The easy use and effectiveness of the modern Direct Methods computer programs, together with the development of faster computers, has led to a dramatic reduction in the time required for complete crystal structure study. The flexibility of the Direct Methods programs allows their successful use also for compounds of uncertain composition providing that a reasonable estimate of the chemical composition can be given. A systematic procedure for this purpose, *viz.* to provide a reasonable estimate of the composition needed as starting data for the Direct Methods programs, has been presented in this work. The proce-

dure, which substitutes for the more time-consuming 'trial-and-error' method, makes use of experimental crystallographic and synthetic data and thus has limitations in general use. However, it be applied as an expedient when a crystal structure is to be done on a compound of uncertain composition.

The exact and unambiguously determined molecular structure can be used, together with accurate synthetic details, to explain the formation of that compound. The reaction mechanism, or at least the possible reaction route leading to the compound, can normally be given after complete crystal structure study. This is especially true when very different compounds are formed within the same reaction mixture. A typical example of this is provided by the treatment of various isomers of 1,5,9-cyclodocecatrienes (12-membered hydrocarbons with three double bonds) with *N*-bromosuccinimide (NBS) in methanol. In this work, transannular *O*-heterocyclization of (*E.Z.Z*)-1,5,9-cyclodocecatriene led to the formation of (*E*)-*exo,endo*-2,5,10-tribromo-*exo*-6-methoxy-13-oxa-*cis*-bicyclo[7.3.1]tridec-4-ene (**III**), an oxabicyclo compound, while at the same time transannular π-cyclization followed by transannular *O*-heterocyclization lead to *endo,endo*-5,9-dibromo-*cis-transoid-cis*-13-oxatricyclo[8.2.1.$0^{2,6}$]tridecane (**I**), an oxatricyclo compound. Following a similar reaction pattern, the oxabicyclic *endo,endo,exo*-2,6,10-tribromo-*exo*-5-methoxy-13-oxa-*trans*-bicyclo[7.3.1]tridecane (**II**), was obtained from (*E.E.E*)-1,5,9-cyclododecatriene. Compound **I** is the first example of a tricyclic tetrahydrofuran derivative obtained from methoxybromination applied to 12- or 13-membered trienes. The bond distances and angles in compounds **I-III** are normal, ranging from 1.946 to 2.01 Å for C_{sp^3}–Br, from 1.909 to 1.954 Å for C_{sp^2}–Br and from 1.483 to 1.561 Å for C_{sp^3}–C_{sp^3}. The conformations of the oxacyclo and 6-membered rings are normal envelope, chair and chair for compounds **I-III**, respectively. The distorted boat-chair-boat conformations of the larger rings occasion some short non-bonding intermolecular contact distances, especially between the hydrogen atoms. As a result compound **II** is strongly strained, compound **III** is moderately strained and **I** is virtually strainless.

The exa

dependent properties if the proper structure-activity reference data is available. The polychlorinated aromatic compounds **IV**-**IX** were studied from their structure-toxicity relationships, using as reference the most toxic man-made chemical compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Structure-toxicity relationships are quite well defined for TCDD although not quantitatively explained, and can be used to decide whether a particular compound might be toxic or supertoxic. Supertoxicity is observed when the compound fulfills specific requirements of molecular geometry and substituent polarizability. Compounds **IV**-**IX** (except **V**) fulfill many of these requirements, especially compound **IV** which is an isomeric form of TCDD. Careful inspection of the molecular dimensions and planarity and comparison with the proposed model for the dioxin binding receptor site shows, however, that only 1,2,3,4-tetrachlorodibenzo-*p*-dioxin, **IV**, has a suitable molecular geometry for supertoxicity. Unsuitable molecular geometry rules out the possibility of a TCDD-type supertoxicity for compounds **V**-**IX**. Moreover, although compound **IV** has the required molecular geometry, the absence of polarizable chlorine substituents in one of the benzene rings in the dibenzo-*p*-dioxin moiety changes the polarizability so much that supertoxic effects are ruled out. The above observations are all consistent with the sterical and polarization requirements specified earlier in the literature[20,45–63] for TCDD-induced supertoxicity. The bond distances and angles are normal in compounds **IV**-**IX**. The aromatic carbon–chlorine, C_{arom}–Cl, bond distances range between 1.697 and 1.749 Å. The compounds that have a twist angle within the molecule (**VI**-**IX**) have definite non-planar conformation, the values for the twist angle being 73.35, 82.72, 68.4 and 85.46^o for **VI**-**IX**, respectively. The orientation of the methoxy group, present in compounds **V**-**VII**, was found to be governed by the substitution at adjacent carbon atoms. When both these carbon atoms have chlorine substituents (*ortho* disubstitution), the methoxy group is forced into a perpendicular orientation with respect to the benzene ring (compounds **V** and **VII**) and the C–O–C angle closes by 3-5^o. Correspondingly, a coplanar orientation of the methoxy group towards the benzene ring is observed (**VI**) in the absence of *ortho* disubstitution.

REFERENCES

I. Kari Rissanen, Jussi Valkonen and Günter Haufe, *endo,endo*-5,9-Dibromo-*cis-transoid-cis*-13-oxa-tricyclo[8.2.1.$0^{2,6}$]tridecane, *Acta Crystallogr., Sect. C43* (1987), 1961.

II. Kari Rissanen and Günter Haufe, *endo,endo,exo*-2,6,10-Tribromo-*exo*-5-methoxy-13-oxa-*trans*-bicyclo[7.3.1]tridecane, *Acta Crystallogr., Sect. C44* (1988), 1803.

III. Kari Rissanen and Günter Haufe, *(E)-exo,endo*-2,5,10-Tribromo-*exo*-6-methoxy-13-oxa-*cis*-bicyclo[7.3.1]tridec-4-ene, *Acta Crystallogr., Sect. C45* (1989), 1617.

IV. Kari Rissanen, Jussi Valkonen and Juhani Tarhanen, 1,2,3,4-Tetrachlorodibenzo-*p*-dioxin, *Acta Crystallogr., Sect. C43* (1987), 488.

V. Kari Rissanen, Jussi Valkonen and Juha Knuutinen, Conformational Effects in Methoxybenzenes Caused by *Ortho* Disubstitution. I. Pentachloromethoxybenzene, *Acta Crystallogr. Sect. C43* (1987), 1966.

VI. Kari Rissanen, Jussi Valkonen and Birgitta Mannila, Structures of Chlorinated Methoxybiphenyls. I. 2,2',3,4',5'-Pentachloro-4-methoxybiphenyl, *Acta Crystallogr., Sect. C44* (1988), 682.

VII. Kari Rissanen, Jussi Valkonen and Birgitta Mannila, Structures of Chlorinated Methoxybiphenyls. II. 2,2',4,4',5',6-Hexachloro-3-methoxybiphenyl, *Acta Crystallogr., Sect. C44* (1988), 684.

VIII. Kari Rissanen, Jussi Valkonen and Liisa Virkki, Bis(2,4-dichlorophenyl) Ether, *Acta Crystallogr., Sect. C44* (1988), 1644.

IX. Kari Rissanen and Liisa Virkki, 2,2',3,4,4',5'-Hexachlorodiphenyl Ether, *Acta Crystallogr., Sect. C45* (1989), 1408.

1. Woolfson, M.M., *Acta Crystallogr., Sect A43* (1987), 593.

2. Allen, F.H., Bellard, S., Brice, M.D., Cartwright, B.A., Doubleday, A., Higgs, H., Hummelink, T., Hummelink-Peters, B.G., Kennard, O., Motherwell, W.D.S, Rodgers, J.R. and Watson, D.G., *Acta Crystallogr., Sect. B35* (1979), 2331.

3. *Cambridge Crystallographic Data Centre User Manual* (1988), 4^{th} edition, p. 34.

4. Germain, G., Main, P. and Woolfson, M.M., *Acta Crystallogr., Sect. A26* (1970), 274.

5. Sheldrick, G.M., SHELX. Program for crystal structure determination. University of Cambridge, England 1975.

6. Sieler, J., Richter, R., Haufe, G. and Faure, R., Cryst. Res. Techn. 22 (1987), 371.

7. Haufe, G., Faure, R. and Loiseleur, L., J. Cryst. Spect. Res. 17 (1987), 653.

8. Sattar, M.A., *Research Report No. 10* (Dissertation) (1980), Department of Chemistry, University of Jyvskyl, Finland.

9. Knuutinen, J., *Research Report No. 18* (Dissertation) (1984), Department of Chemistry, University of Jyvskyl, Finland.

10. Humppi, T., *Research Report No. 23* (Dissertation) (1985), Department of Chemistry, University of Jyvskyl, Finland.

11. Paasivirta, J., (Ed.), *Research Report No. 28* (1988), Department of Chemistry, University of Jyvskyl, Finland.

12. Paasivirta, J., (Ed.), *Research Report No. 29* (1989), Department of Chemistry, University of Jyvskyl, Finland.

13. Sinkkonen, S., *Research Report No. 30* (Dissertation) (1989), Department of Chemistry, University of Jyvskyl, Finland.

14. Kuokkanen, T., *Research Report No. 32* (Dissertation) (1989), Department of Chemistry, University of Jyvskyl, Finland.

15. Luger, P., *Modern X-ray Analysis on Single Crystals*, de Gruyter, New York 1980, pp. 209–266.

16. Main, P., Fiske, S.J., Hull, S.E., Lessinger, L., Germain, G., Declercq, J.-P. and Woolfson, M.M., MULTAN11/82 *A System of Computer Programs for the Automated Solution of Crystal Structures from X-ray Diffraction Data*, Universities of York, England and Louvain, Belgium 1982.

17. Dabaerdemaeker, T., Germain, G., Main, P., Tate, C. and Woolfson, M.M., MULTAN87 *Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*, Universities of York, England and Louvain, Belgium 1987.

18. Sheldrick, G.M., SHELXS-86, in *Crystallographic Computing 3*, Sheldrick, G.M., Krüger, C. and Goddard, R. (Eds.), Oxford University Press, Oxford 1985, pp. 175–189.

19. Kirk-Othmer, *Encyclopedia of Chemical Technology*, 3^{rd} edition, John Wiley & Sons, New York 1978, Vol. 4., pp. 249-263.

20. McKinney, J. and McConnell, E. in *Chlorinated Dioxins and Related Compounds, Impact on the Environment*, Hutzinger, O., Frei, R.W., Merian, E. and Pocchairi, F. (Eds.), Pregamon Press, Oxford 1982, p. 367.

21. Cope, A.C., Martin, M.M. and McKervey, M.A., *Q. Rev., Chem. Soc. 20* (1966), 119.

22. Haufe, G., Wolf, A. and Schultze, K., Tetrahedron 42 (1986), 4719.

23. Sutherland, J.K., *Tetrahedron 30* (1974), 1651.

24. Haufe, G., *J. Chem. Res.* (1987), 100.

25. Haufe, G., Alvernhe, G. and Laurent, A., *Tetrahedron Letters 27* (1986), 4449.

26. Fresnet, P. and Dubois, J.-E., *Tetrahedron Letters 23* (1979), 2137.

27. Haufe, G. and Mühlstadt, M., *Tetrahedron Letters 25* (1984), 1777.

28. Haufe, G., *Tetrahedron Letters 25* (1984), 4365.

29. Haufe, G., Kleinpeter, E., Mühlstädt, M. and Graefe, J., *Monats. Chem. 109* (1978), 575.

30. Haufe, G., Mühlstädt, M. and Graefe, J., *Monats. Chem. 108* (1977), 803.

31. Haufe, G., Mühlstädt, M. and Graefe, J., *Monats. Chem. 108* (1977), 1431.

32. Haufe, G., Mühlstädt, M. and Graefe, J., *Monats. Chem. 107* (1976), 653.

33. Graefe, J., Haufe, G. and Mühlstädt, M., *Z. Chem. 16* (1976), 180.

34. Haufe, G., Mühlstädt, M. and Graefe, J., *Z. Chem. 16* (1976), 100.

35. Haufe, G. and Mühstädt, M., *Z. Chem. 19* (1979), 170.

36. Haufe, G. and Kleinpeter, E., *Tetrahedron Letters 23* (1982), 3555.

37. Ladd, M.F.C. and Palmer, R.A., *Structure Determination by X-ray Crystallography*, 2^{nd} edition, Plenum Press, New York 1985, pp. 295–334.

38. Allegra, G. in *Theory and Practice of Direct Methods in Crystallography*, Ladd, M.F.C. and Palmer, R.A. (Eds.), Plenum Press, New York 1980, pp. 1-22.

39. Woolfson, M.M., *An Introduction to X-ray Crystallography*, Cambridge University Press, Cambridge 1970, pp. 252–322.

40. Stout, G.H. and Jensen, L.H., *X-ray Structure Determination, A Practical Guide*, The Macmillan Company, New York 1968, pp. 315–338.

41. Trotter. J., in *The Chemistry of the Carbon-Halogen Bond, Part 1*, Patai, S. (Ed.), John Wiley & Sons, London 1973, pp. 49-62.

42. Paasivirta, J., *Wat. Sci. Tech. 20* (1988), 119.

43. Kirk-Othmer, *Encyclopedia of Chemical Technology*, 3^{rd} edition , John Wiley & Sons, New York 1978, Vol 5., pp. 668-872.

44. Boer, F.P., van Remoortere, F.P., North, P.P. and Neuman, M.A., *Acta Crystallogr., Sect. B28* (1972), 1023.

45. Poland, A., Glover, E. and Kende, A.S., *J. Biol. Chem 251* (1976), 4936.

46. Poland, A. and Knutson, J.C., *Ann. Rev. Pharmacol. Toxicol. 22* (1982), 517.

47. Gillner, M., Fernström, B., Gustafsson, J.-Å., Bergman, J. and Cambillau, C., *Chemosphere 15* (1986), 1673.

48. Hutzinger, O., Choudhry, G.G., Chittim, B.G. and Johnston, L.E., *Environ. Health Persp. 60* (1985), 3.

49. Paasivirta, J., *Kemia-Kemi 11* (1984), 452.

50. Tarhanen, J., Koistinen, J., Paasivirta, J., Vuorinen, P.J., Koivusaari, J., Nuuja, I., Kannan, N. and Tatsukawa, R., *Chcmosphcrc 18* (1989), 1067.

51. Kannan, N., Tanabe, S. and Tatsukawa, R., *Bull. Environ. Contam. Toxicol. 41* (1988), 267.

52. Paasivirta, J., Koistinen, J., Mannila, E. and Tarhanen, J., (*SETAC 10th Annual Meeting, 28.10.–2.11.1989*), Canada. Abstracts.

53. *Chlorinated Dioxins and Related Compounds, Impact on the Environment*, Hutzinger, O., Frei, R.W., Merian, E. and Pocchairi, F. (Eds.), Pregamon Press, Oxford 1982, p. 639.

54. McKinney, J.D., Chae, K., McConnell, E.E. and Birnbaum, L.S., *Environ. Health Persp. 60* (1985), 57.

55. Sweatlock, J.A. and Gasiewicz, T.A., *Chemosphere 15* (1986), 1687.

56. Vecchi, A., Sironi, M., Sfreddo-Galotta, E., Graziani, A. and Cantoni, L., *Chemosphere 15* (1986), 1707.

57. Hahn, M.E., Gasiewicz, T.A., Goldstein, J.A. and Linko, P., *Chemosphere 15* (1986), 1691.

58. Safe, S., Parkinson, A., Robertson, L., Cockerline, R., Safe, L., Bandiera, S. and Okey, A. in *Chlorinated Dioxins and Related Compounds, Impact on the Environment*, Hutzinger, O., Frei, R.W., Merian, E. and Pocchairi, F. (Eds.), Pregamon Press, Oxford 1982, p. 383.

59. Safe, S., Bandiera, S., Sawyer, T., Robertson, L., Safe, L., Parkinson, A., Thomas, P.E., Ryan, D.E., Reik, L.M., Levin, W., Denomme, M.A. and Fujita, T., *Environ. Health Persp. 60* (1985), 47.

60. Poellinger, L., Wilhemsson, A., Lund, J. and Gustafsson, J.-Å., *Chemosphere 15* (1986), 1681.

61. Bunce, N.J., Landers, J.P. and Safe, S.H., *Chemosphere 18* (1989), 731.

62. McConnell, E.E., *Environ. Health Persp. 60* (1985), 29.

63. Denison, M.S., Wilkinson, C.F. and Okey, A.B., *Chemosphere 15* (1986), 1665.

64. Rissanen, K., *Licenciate Thesis* (1987), Department of Chemistry, University of Jyväskylä, Finland.

65. Trotter, J., *Acta Crystallogr. 14* (1961), 1135.

66. Hargreaves, A. and Rivzi, S.H., *Acta Crystallogr. 15* (1962), 365.

67. Charbonneau, G.P. and Delugeard, Y., *Acta Crystallogr., Sect. B32* (1976), 1420.

68. Charbonneau, G.P. and Delugeard, Y., *Acta Crystallogr., Sect B33* (1977), 1586.

69. Brock, C.P. and Morelan, G.L., *J. Phys. Chem. 90* (1986), 5631.

70. Edlund, U. and Norström, Å., *Org. Magn. Reson. 9* (1977), 196.

71. Singh, P. and McKinney, J.D., *Acta Crystallogr., Sect. B36* (1980), 210.

72. Anderson, G.M., Kollman, P.A., Domelsmith, L.N. and Houk, K.N., *J. Am. Chem. Soc. 101* (1979), 2344.

To my wife and children

ORIGINAL PAPERS

Acta Cryst. (1987). C**43**, 1961–1964

endo,endo-5,9-Dibromo-*cis-transoid-cis*-13,oxatricyclo[8.2.1.$0^{2,6}$]tridecane

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UHLENBROEK, J. H. & BIJLOO, J. D. (1960). *Recl Trav. Chim. Pays. Bas*, **79**, 1181–1196.

VERACINI, C. A., MACCIANTELLI, D. & LUNAZZI, L. (1973). *J. Chem. Soc. Perkins Trans.* 2, pp. 751–754.

Acta Cryst. (1988). C**44**, 1803–1805

***endo,endo,exo*-2,6,10-Tribromo-*exo*-5-methoxy-13-oxa-*trans*-bicyclo[7.3.1]tridecane**

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