CHEMICAL REACTIVITY, BIOTRANSFORMATION, AND TOXICITY OF POLYCHLORINATED ALIPHATIC COMPOUNDS

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INTRODUCTION

Chlorinated aliphatic compounds are released, in increasing number and quantity, into the environment. They are used on a large-scale basis as industrial solvents, in textile cleaning shops, and as plastic monomers, pesticides, and drugs. Some of the technically important products have long been known as hepatotoxic agents, and single members of the family (like vinyl chloride and vinylidene chloride) have recently been claimed to be carcinogenic; at present, trichloroethylene is also suspected as a potential carcinogen. In addition, several polychlorinated compounds possess a marked persistence in biological and abiotic systems and may accumulate to health-threatening concentrations.

The means and degree of metabolic transformation of chlorinated compounds, which may vary considerably, are influenced to a great extent by the nature of the chlorine substitution of differently hybridized C-atoms. The tendency of the behavior of the compounds under consideration with respect to metabolic and nonmetabolic activity can be particularly well demonstrated with poly- and perchlorosubstitutions. This report describes some aspects of the interrelationship among polychlorinated aliphatics, chlorine substitution, chemical reactivity, and metabolic fate in biological systems, as well as their toxic properties. The molecular context is emphasized, whereas details of enzyme mechanisms and pathophysiological aspects of toxic reactions are not dealt with.

GENERAL CONSIDERATIONS ON CHLORINE SUBSTITUTION IN ALIPHATIC HYDROCARBONS

In general, chlorine substitution provides a decrease in the electron density of the involved C-atoms by their electron-attracting inductive effect (-I effect) which dominates the mesomeric donator effect. In nuclear magnetic resonance spectroscopy, the frequency of the resonance of an atomic nucleus depends on the electron density of its environment. The diamagnetic protection by the electrons diminishes the effective magnetic field at the nucleus. Thus, the shift of the resonance absorption may serve as a criterion for the electronic influence of substituents.[1] Recent publications[2-5] reveal the possibility of a linear correlation between ^{13}C-NMR shifts and the total electron density of the corresponding C-atoms.

Thus, the position of the ^{13}C-NMR signals is a measure of the electron-attracting effect of chlorine subsututions in organic molecules. The electronic shifts indicated in Table 1 clearly illustrate that an increase in chlorine substitution induces a decrease in electron density at the substituted C-atom; this correlates with a shift of resonance signals to lower fields. Substitution of hydrogen by chlorine in alkenes results in a smaller shift of ^{13}C-signals than it does in alkanes. This is probably due to the interaction of the chlorine with the π-bond. The inductive effect may be dominant in chlorinated alkanes, but in alkenes another effect (magnetic anisotropy, resonance effect) may contribute to the shift.[8]

The mesomeric substitution effect encountered with chlorine substituents may also be demonstrated separately by microwave and radiowave spectroscopy.[9,10] One criterion of the mesomeric effect is the bond extension C–Cl which will be submitted in part to some kind of "double-bond character" and thus to a contraction by the participation of zwitter ionic structures. Thus, for example, the bond extension C–Cl is 1.76 Å with alkanes, 1.69 Å with alkenes (e.g., vinyl chloride), and 1.63 Å with alkynes (e.g., chloroacetylene). The proportion of the double-bond character of the C–Cl bond, according to nuclear quadrupole measurements, amounts to 5 to 6% in the case of vinyl chloride.

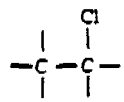
An enforced electron-attracting effect in connection with steric factors resulting from polychloro- or perchlorosubstitution induces decisive changes in reactivity as compared to unsubstituted hydrocarbons. In the series of alkanes, an increasing chlorine substitution with an elongation of the carbon chain results in an enhanced tendency toward destabilization, which leads to C–C fissions or eliminations of HCl or chlorine with consequent formation of alkenes. On the other hand, alkenes are stabilized against electrophilic agents by increasing chlorine substitution; chlorinated olefines are characterized by an elevated thermal stability. Alkynes, unlike alkenes, are considerably destabilized by chlorine substitution.

TABLE 1

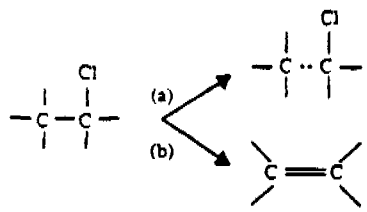
^{13}C-NMR Shifts of Chlorinated Aliphatic Hydrocarbons (ppm Referring to CS_2 = 0 ppm)[4-6]

		C_1	C_2	C_1	C_2
CH_4	194.9	CH_3-CH_3		186.9	186.9
CH_3Cl	167.7	CH_2Cl-CH_3		152.9	174.1
CH_2Cl_2	138.6	$CHCl_2-CH_3$		123.6	160.3
$CHCl_3$	115.6	CCl_3-CH_3		96.9	146.5
CCl_4	96.8	CCl_3-CCl_3		87.3	87.3
		$CH_2=CH_2$		70.0	70.0
		$CHCl=CH_2$		66.7	75.4
		$CCl_2=CH_2$		64.1	77.3
		trans-CHCl=CHCl		71.7	71.7
		cis-CHCl=CHCl		73.5	73.5
		$CCl_2=CHCl$		67.8	75.3
		$CCl_2=CCl_2$		72.1	72.1

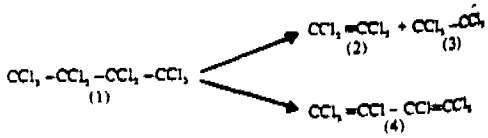
ALKANES



The destabilizing effect in chlorinated alkanes is observed with an increase in the number of chlorine and carbon atoms. The steric hindrance of accumulated chlorine substituents, as well as the electron-attracting effect, favors C–C fissions (a, structure below) and eliminations of Cl_2 or HCl with the formation of more stable olefinic compounds (b, structure below).



For example, thermal decomposition of decachlorobutane (1) renders, by C–C fission, tetrachloroethylene (2) and hexachloroethane (3). Under dechlorinating conditions, hexachlorobutadiene (4) may easily be obtained from decachlorobutane (1).[11]



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sions of chlorinated aliphatic hydrocarbons have focused on C_1 and C_2 compounds; higher homologues of C_3 and C_4 units have occasionally been included. Regarding the C_1 series (the chlorinated methanes), carbon tetrachloride is converted metabolically to chloroform and CO_2,[12] chloroform to CO_2,[13] and dichloromethane to CO.[14]

A deeper insight into the mechanism of the hepatotoxicity of carbon tetrachloride was provided in 1961 by Butler[15] who suggested a homolytic C–Cl fission with the formation of trichloromethyl and chlorine radicals. At present, the most probable subsequent pathochemical reaction mechanism is the interaction of the trichloromethyl radical with unsaturated fatty acid chains, with the formation of chloroform and a fatty acid radical. The latter reacts with oxygen and forms peroxides and hydroperoxides which, in turn, induce the decomposition of the fatty acid chains.[16] At the same time, it was recently demonstrated that the hepatotoxic activity of bromotrichloromethane ($BrCCl_3$) is considerably greater than that of CCl_4 or $CHCl_3$.[17] There is a correlation between the cytotoxic effects produced in vitro and in vivo and the bond-dissociation energies for the fission of the three methane derivatives ($CHCl_3$, CCl_4, and $BrCCl_3$): H–CCl_3, 95.7 kcal/mol; Cl–CCl_3, 73 kcal/mol; Br–CCl_3, 54 kcal/mol.[18,19] A low dissociation energy corresponds to an increased tendency for a homolytic fission to the trichloromethyl radical. Correspondingly, $BrCCl_3$ is considerably more effective than CCl_4 in producing a peroxidative breakdown of the microsomal lipids in rat liver.[17]

In principle, chlorine-substituted alkanes tend to have radical reaction mechanisms because chlorine substituents are capable of delocalizing the unpaired electron via empty d orbitals of low energy. Consequently, the resonance energy of the CCl_3 radical amounts to 8.3 kcal/mol (as compaired to the CH_3 radical = 0). Possible resonance structures of the trichloromethyl radical are shown below.

Carbon tetrachloride forms an enzyme-substrate complex with cytochrome P_{450} of liver microsomes[20] in which the following sequence of reactions takes place.[21]

$$CCl_4 + e^{\theta} \longrightarrow \cdot CCl_3 + |Cl^{\theta}$$
$$\cdot CCl_3 + e^{\theta} \longrightarrow |CCl_3{}^{\theta}$$

The complex cytochrome P_{450}-$|CCl_3{}^{\theta}$ may then decompose in the presence of protons, releasing chloroform as the stable final product.

The work of Heppel and Porterfield[22] has well established that enzymes catalyze the oxidative C–Cl fission of chlorinated organic compounds in the organism. According to Van Dyke[23] and Van Dyke and Chenoweth,[24] the enzyme system involved shares all relevant properties with mixed function oxidases. It is inducible by phenobarbital and benzo-a-pyrene and requires oxygen and NADPH.[25] High rates of dechlorination have been found with this enzyme system in the series of chlorinated ethanes: 1,1-dichloroethanes ($CHCl_2-CH_3$), 1,1,2-trichloroethane ($CHCl_2-CH_2Cl$), and 1,1,2,2-tetrachloroethane ($CHCl_2-CHCl_2$). Ethanes with a trichloromethyl (CCl_3-) group [for example, 1,1,1-trichloroethane (CCl_3-CH_3), 1,1,1,2-tetrachloroethane (CCl_3-CH_2Cl), and 1,1,1,2,2-pentachloroethane (CCl_3-CHCl_2)] are characterized by a low tendency towards oxidative dechlorination; the same is true for tetrachloroethylene ($CCl_2=CCl_2$). Accordingly, acute and chronic hepatotoxicity are high in the former and low in the latter group of chlorinated aliphatics.[26-28]

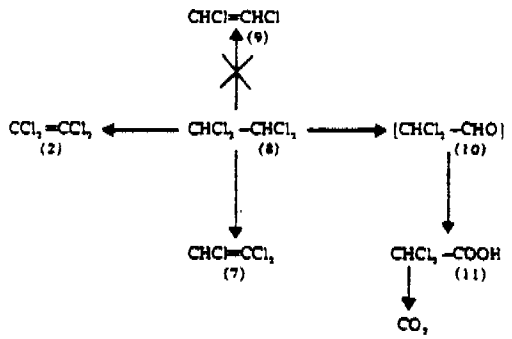
Elimination of Chlorine

The elimination of chlorine with formation of more stable alkenes represents the second type of metabolic conversion of chlorinated alkanes. This is the main pathway and the first step in the metabolic conversion of pentachloroethane (5)[29] and hexachloroethane (6),[30] leading to the formation of trichloroethylene (7) or tetrachloroethylene (2), respectively.

$$\underset{(5)}{CHCl_2-CCl_3} \xrightarrow{-Cl_2} \underset{(7)}{CHCl=CCl_2}$$

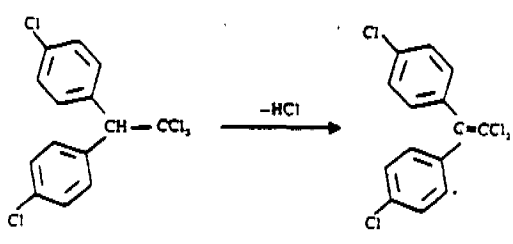
$$\underset{(6)}{CCl_3-CCl_3} \xrightarrow{-Cl_2} \underset{(2)}{CCl_2=CCl_2}$$

However, an analogous mechanism with 1,1,2,2-tetrachloroethane (8) which would yield 1,2-dichloroethylene (9) could not be demonstrated up to now. The predominant pathway in the metabolism of 1,1,2,2-tetrachloroethane (8) goes through the sequence dichloroacetaldehyde-dichloroacetic acid (10-11), while the product of nonenzymatic dehydrocholorination (b) is found only in minor proportion; this reaction is already found in neutral phosphate buffer.[31] In addition, traces of oxidatively formed tetrachloroethylene (2) are found.



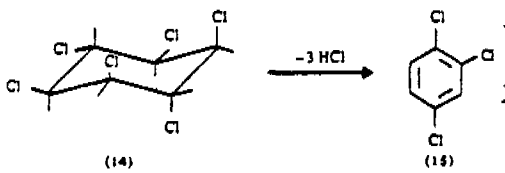
Elimination of HCl

The elimination of hydrogen chloride from polychlorinated alkanes, leading to olefinic structures, also represents a major pathway in the metabolism of *p,p'*-dichlorodiphenyltrichloroethane (DDT) (12), with *p,p'*-dichlorodiphenyldichloroethylene (DDE) (13) as the first metabolite.[32] This conversion is additionally catalyzed by the enzyme "DDT-dehydrochlorinase" (E.C. 4.5.1.1.) in the presence of glutathione.[33]



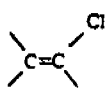
(12) (13)

Dehydrochlorinations are also discussed as primary metabolic pathways of polychlorinated cyclic alkanes, for example as in the case of 1,2,3,4,5,6-hexachlorocyclohexane.[34,35] The γ-isomer of $C_6H_6Cl_6$ (14) is converted, by successive dehydrochlorination, via a γ-pentachlorocyclohexene to 1,2,4-trichlorobenzene (15), which is then conjugated after aromatic hydroxylation.[35]



(14) (15)

ALKENES



Considerations on Stability

Poly- and perchlorosubstitution at sp^2-hybridized C-atoms in unsaturated systems increases the thermal and chemical stability of these molecules. The -I effect dominates the +M effect of the chlorine substituents, thus resulting in a "deprivation" of the electron density of the double-bond system. This provides, in combination with a steric protective effect of the bulky chlorine substituents, an increased stability against electrophilic attack.

A good example of this effect is the reaction of chlorinated ethylenes with ozone. The relative rates of ozonization in the series ethylene:vinylchloride:trichloroethylene:tetrachloroethylene are 2500:1180:3.6:1.[36]

$CH_2=CH-CH=CH_2$ (16) $\qquad$ $CCl_2=CCl-CCl=CCl_2$ (17)

Liquid butadiene (16) (bp_{760} -5.6°C) polymerizes when left open to air for months after some period of induction; light irradiation accelerates the reaction. On the other hand, hexachlorobutadiene (17) (bp_{760} 213°C) is stable up to 500°C and cannot be brought to polymerization by pressure up to 100 atm (17), in addition, is characterized by a remarkable chemical stability, similar to the higher homologous stereoisomeric perchlorohexatrienes.[37] They are fairly stable against strong mineral acids and aqueous alkali even at high temperatures, but are converted to highly chlorinated vinyl ethers by alcoholic alkali at 80°C.[38] At least the action of fuming nitric acid at 130° and additional treatment with concentrated sulfuric acid at 170° are necessary to convert hexachlor
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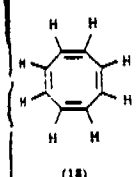
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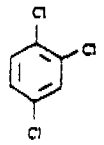

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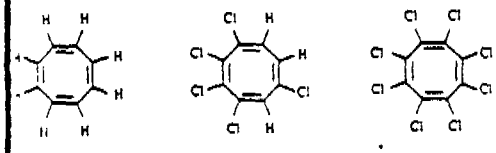
convert hexachlorobutadiene (17) to dichloromaleic acid anhydride.[39]



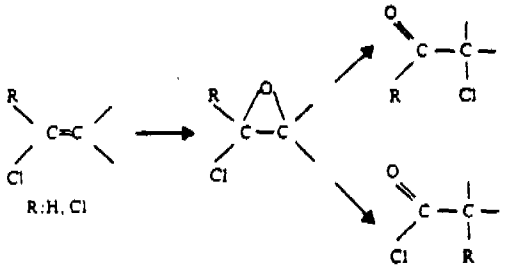
(18) (19) (20)

Cyclooctotetrene (18) (bp_{760} 141°C), a representative of cyclic polyolefines with alternating double bonds, is sensitive against light and oxygen. After an extended stay, or acceleration by heating, it converts to a mixture of dimers and resinous substances. The enormous reactivity of the molecule is again demonstrated by the rapid addition of halogens.[40,41] Attack of oxidants (O_2, $KMnO_4$, and CrO_3) easily results in products with ring contraction. The transition to pentachlorocyclooctatetrene (19) and octachlorocyclooctatetrene (20) coincides with an increase in thermal and chemical stability. After heating in the pressure tube for 6 hr at 250°C, pentachlorocyclooctatetrene (19) can be isolated unchanged. With elemental bromine it reacts to a product of the composition $C_8H_3Cl_5Br_2$.[42] Octachlorocyclooctatetrene (20) does not react with ozone or aqueous $KMnO_4$ and cannot be brominated under varying conditions. It remains thermically stable up to 180°C.[43,44] The reason for this remarkable inertness of the double bonds should be determined in the protection by the accumulated voluminous chlorine atoms which, per se, render an electrophilic attack more difficult due to their -I effect. The validity of the general principle of an extraordinary stabilization of olefinic systems by poly- and perchlorosubstitution may be further demonstrated by some paired examples (Table 2).

Metabolism

Chlorinated ethylenes are metabolically converted to predominantly C_2 alcohols and acids. A significant interrelationship has been demonstrated between the enhanced stability associated with increasing numbers of chlorine substitutions and the metabolic behavior in biologic systems with all chlorinated ethylenes in the isolated perfused rat liver preparation.[51,52] At a given prehepatic concentration of the ethylenes, a significant rise in the proportion metabolized was found in the series tetra-, tri-, and cis-1,2-dichloroethylene vinylidene chloride.

The metabolic changes of chlorinated ethylenes are initiated with the oxidation to corresponding oxiranes[53-56] by monooxygenases. Up to now this class of compounds has only found limited interest. The principal reactions of oxiranes in biological systems are summarized in Figure 1. The main toxic effects, acute as well as chronic, have been associated with electrophilic reactions with essential cellular components (alkylation), whereas the other pathways (reduction, hydrolysis, and conjugation, both enzymatically and nonenzymatically) and rearrangements of carbonylic compounds are considered to be detoxication mechanisms. The type of rearrangement in chlorinated ethylenes depends on the number and position of chlorine substitution(s); it goes to either chlorinated aldehydes or acyl chlorides.



R:H, Cl

Further metabolic steps with the rearrangement products are oxidations or reductions of aldehydes to carboxylic acids of ethanol derivatives or hydrolyses of acyl chlorides to corresponding acids.

With *tetrachloroethylene* (2), the metabolic formation of trichloroacetic acid (23) can plausibly be explained by the primary formation of an oxirane (21) and subsequent rearrangement to trichloroacetyl chloride (22) and its hydrolysis.[52,53] The transition of the oxirane to trichloroacetyl chloride (21 to 22) is, in analogy, found with the tetrachloroethylene oxide (2) which can be synthesized by photooxidation and which rearranges in vitro in different solvents to trichloroacetyl chloride.[57]

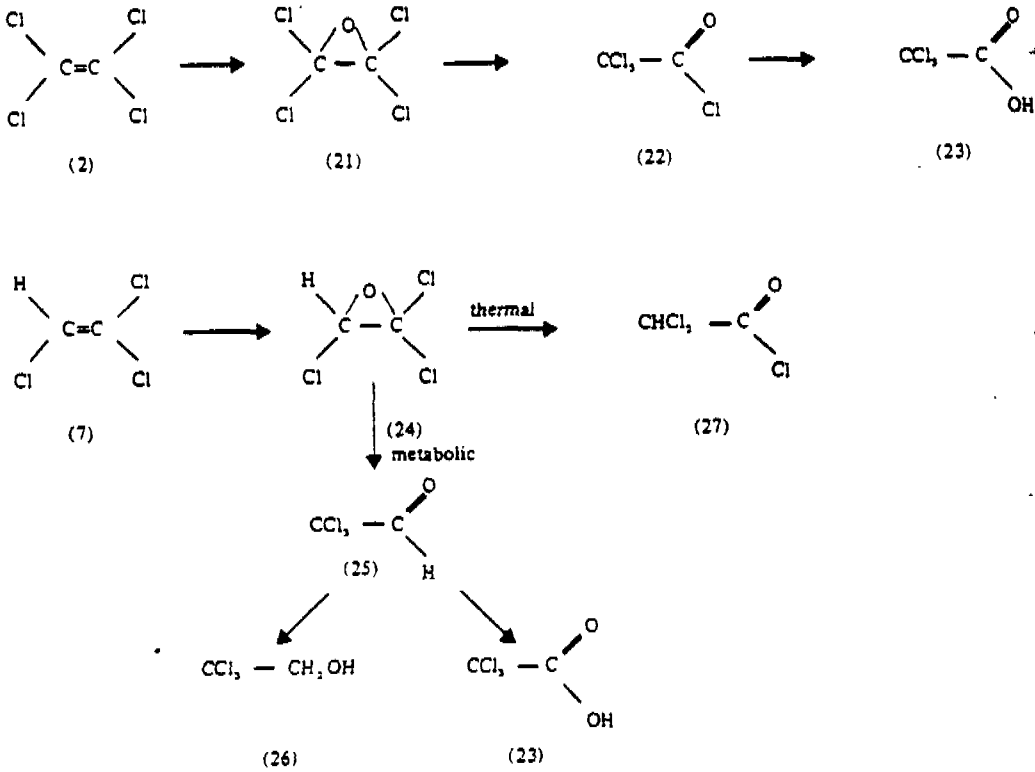
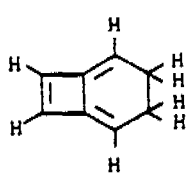


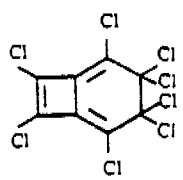
TABLE 2

Comparison of the Stability of Unsubstituted and Perchlorosubstituted Cyclic Polyolefines



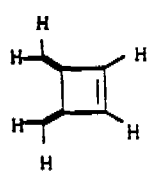
(45)

Bicyclo-(4,2,0) octatrien-(1,5,7); some hours stable at room temperature, rapid polymerization at open air



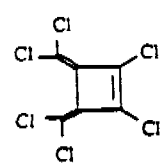
(46)

Stable at room temperature, no tendency to polymerization, rearranges to aromatic compounds at 80°C



(47)

3,4-Dimethylenecyclobutene; rapid polymerization in the presence of light and air



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Stable in air up to 160°C

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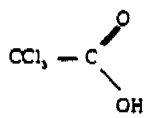

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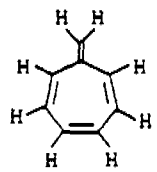
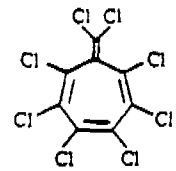
TABLE 2 (continued)

Comparison of the Stability of Unsubstituted and Perchlorosubstituted Cyclic Polyolefines



(49)

Heptafulvene; polymerization in solution already at −80°C



(50)

Stable in air up to 340°C

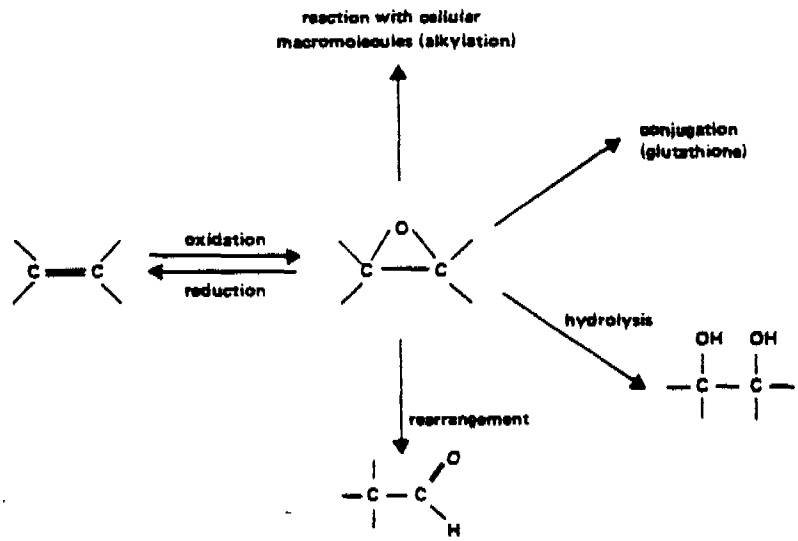
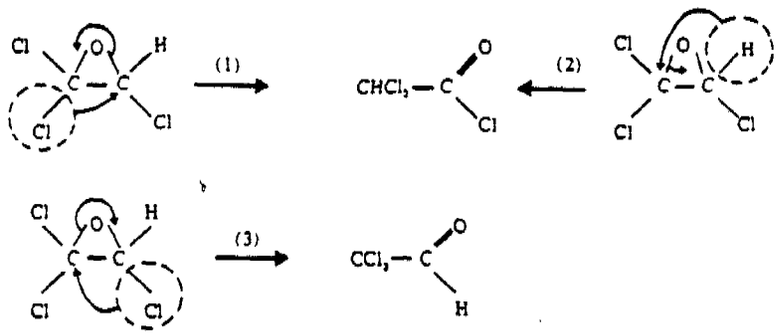


FIGURE 1. Synopsis of metabolic conversions and biological consequences of toxication (alkylation) and detoxication (conjugations, hydrolysis, and rearrangement) of alkenes.

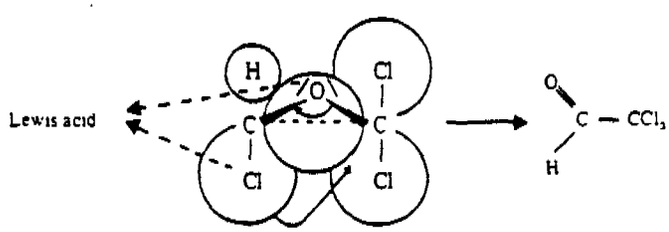
Trichloroethylene (7) is metabolically converted to trichloroethylene oxide (24) and further converted to chloral.[53-55,58,59] In subsequent metabolic reactions, chloral (25) is in part reduced to trichloroethanol (26) or oxidized to trichloroacetic acid (23).[60] The real occurrence of the oxirane (24) as a metabolic intermediate could be substantiated by spectroscopic investigations with the catalytic hemoprotein P_{450} of the converting enzyme monooxygenase.[61]

After administration of ^{36}Cl-labeled trichloroethylene to experimental animals, the specific activity remains unchanged in the recovered metabolites trichloroethanol and trichloroacetic acid; no exchange of ^{36}Cl with the chlorine pool of the organism is observed.[53] Again, this is indicative of an intramolecular chlorine migration in the course of the transition of trichloroethylene oxide to chloral (24 to 25). Surprisingly, at first glance, the trichloroethylene oxide (24) which can be synthesized from trichloroethylene by photochemical oxidation[62] thermally rearranges (in vitro) mainly to dichloroacetyl chloride (27).[63] In vivo, however, no dichloroacetic acid is found as a metabolite.[52,64] This remarkable difference has important practical implications. In principle, there are three possible ways of rearranging the oxirane of trichloroethylene (24).

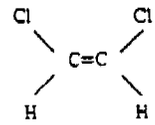


Regarding the two rearrangements leading to dichloroacetylchloride, the hydride shift (2) has low probability, according to investigations by McDonald and Schwab.[65] If one postulates that α-ketocarbonium ions or ion pairs[66-68] are transition forms of the rearrangement (a synchronous process cannot, however, positively be ruled out[69]), the carbonium ion (which after C–O heterolysis is solely destabilized by one direct, liganded Cl atom) should be indicative of a favored rearrangement. Way (3) would involve a carbonium ion with two direct liganded Cl atoms, consequently giving a lower degree of probability. Experiments on the behavior of the oxirane are in accordance with this assumption: rearrangement to dichloroacetyl chloride is accelerated by tertiary amines[70] which, after addition of methanol, render dichloroacetic acid methyl ester.[71] Upon heating to 100 to 140°C for 4 hr in a glass tube, the oxirane is converted in high yields (88%) into dichloroacetylchloride, and only a small proportion of chloral can be detected.[63]

The rearrangement of trichloroethylene oxirane to chloral in vitro can only be elicited by Lewis acids such as $AlCl_3$ or $FeCl_3$.[52] Thus, it has been suggested that in the living organism the "environment" at the site of formation of the oxirane (24) might possess electron acceptor properties and induce the rearrangement in the direction of chloral.[51,52] The most plausible mechanism for the influence of



Lewis acids is an interaction with the oxirane (24) at the site where there is a steric opening of the molecule with the oxirane oxygen, with the nearest chlorine atom, or with both, inducing the final rearrangement according to shift (3) to chloral (25).



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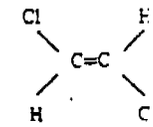

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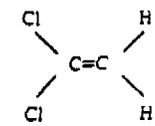

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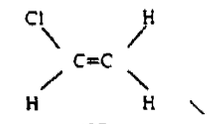

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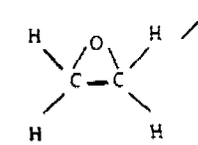

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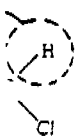

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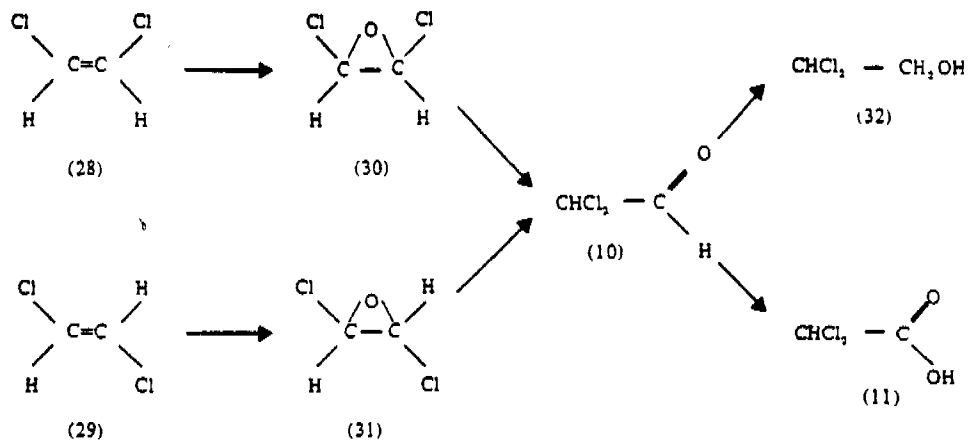
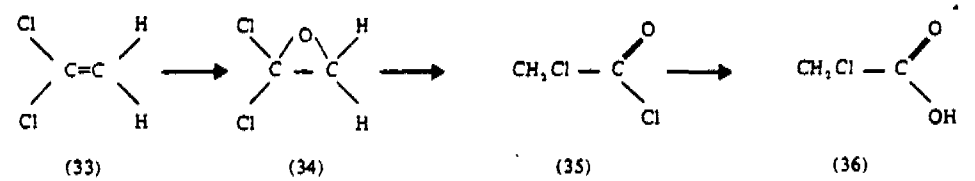
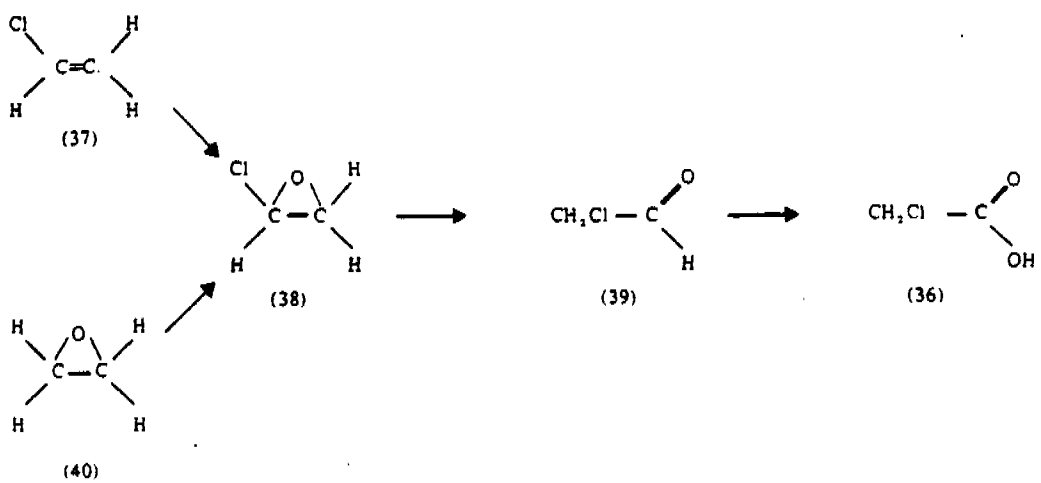


Cis- and trans-1,2-dichloroethylenes (28 and 29) both form the metabolites dichloroethanol (32) and dichloroacetic acid (11) which have been identified in perfusates of the isolated rat liver preparation.[51,52] Their formation can be explained by the primary intermediate oxiranes (30 and 31) and subsequent rearrangement to dichloroacetaldehyde (10), which is then oxidized to dichloroacetic acid (11) or reduced to dichloroethanol (32). The thermal rearrangement of the oxiranes that occurs with chlorine migration to dichloroacetaldehyde (10) has been demonstrated.[66]

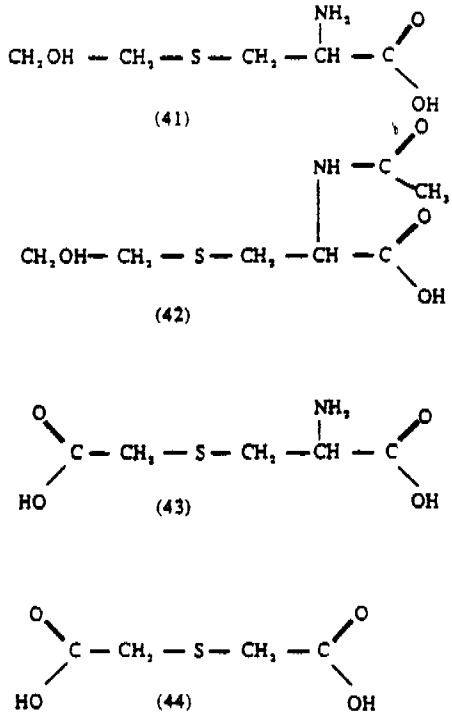


The isomeric *1,1-dichloroethylene* (vinylidene chloride) (33) is metabolized to monochloroacetic acid (36).[64,72] If 1,1-dichloroethylene is oxidized with *m*-chloroperbenzoic acid, only chloroacetyl chloride (35) (the expected rearrangement product of the oxirane) can be isolated. The oxirane itself seems to be extremely unstable and resistive to synthesis under varying conditions.[73] However, from these findings it can be speculated that the oxirane (34) is formed as a metabolic intermediate and rearranges spontaneously to chloroacetyl chloride (35), which is subsequently hydrolyzed to monochloroacetic acid (36).



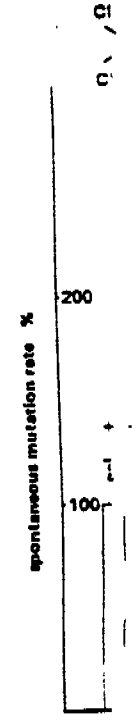
Monochloroacetic acid (36) is likewise formed as a metabolite of *monochloroethylene* (vinyl chloride) (37).[74-76] One possible explanation of the formation of monochloroacetic acid (36) is the primary oxidation of monochloroethylene (37) to vinyl chloride oxirane (38), which rearranges to chloroacetaldehyde[74] (33) followed by further metabolic oxidation to chloroacetic acid (36). In analogy, monochloroacetaldehyde (39) is formed as a rearrangement product of the oxirane of vinyl chloride, which can be synthesized by chlorination of ethylene oxide (40) in the gaseous phase.[77,78]

The further metabolic fate of vinyl chloride oxirane has been elucidated in part. A very small proportion of metabolized vinyl chloride is bound covalently to tissue components, as has been shown in vitro[79] and in vivo.[80] Major metabolites in vivo are 2-hydroxyethylcysteine[81] (41), 2-hydroxyethyl-N-acetylcysteine[81] (42), carboxymethylcysteine[82] (43), and thiodiacetic acid[81,82] (44). The mechanism of the formation of these conjugates can easily be explained by the previous rearrangement of the oxirane to chloroacetaldehyde (39) and oxidation to chloroacetic acid (36) which reacts with glutathione; carboxymethylglutathione is converted to carboxymethylcysteine (43), and the latter, by further oxidations, is converted to thiodiacetic acid (44). Yllner has identified carboxymethylcysteine (43) and thiodiacetic acid (44) as the main metabolites[83] in the urine of mice after dosing with chloroacetic acid. The formation of S-(2-chloroethyl)-cysteine and its N-acetyl conjugate[76] as products of simple addition reactions has been questioned;[81] in fact, this hypothesis is inconsistent with an enzymatic mechanism postulated according to the results of experiments in vivo with enzyme inhibitors.[74,80] The formation of a cyclic vinyl chloride peroxide, in equilibrium with an oxirane-singlet oxygen complex, might account for the observed formation of formaldehyde as a decomposition product and oxidation to carbon dioxide, which has been identified in part, in vivo, after metabolic incorporation into urea or methionine and serine.[76] Another interesting hypothesis is the addition of vinyl chloride to hydrogen sulfide under formation of bis-(2-chloroethyl)-sulfide, which then might account for the formation of thiodiacetic acid[76] (44); the alkylating intermediate could be suspected as one of the carcinogenic metabolites of vinyl chloride. However, further experiments, particularly in isolated biological systems, are necessary to confirm or reject these assumptions.



Mutagenicity and Carcinogenicity

Three chlorinated ethylenes exert mutagenic effects: vinyl chloride,[84-86] vinylidene chloride,[86,87] and trichloroethylene[86] (see Figure 2). The common molecular feature of these compounds is the formation of unsymmetric oxiranes,[86,88] the stability of which (as tested in non polar solvents) is far less[63,73,77] than that of the others which form symmetric oxiranes[57,66] and are not mutagenic. Oxiranes may react in vivo enzymatically or nonenzymatically with SH-compounds to form nonactive conjugates.[89] On the other hand, the highly electrophilic oxiranes may react directly with nucleophilic constituents of the animal cell as a first step in a genetoxic effect. If this mechanism is taken to be essential for the mutagenic effects (as has been elucidated in the case of vinyl chloride),[85] the interrelationship between symmetry/asymmetry and stability/instability of the oxiranes might offer an important rule[88] and possibly a useful criterion which may be used to measure chemical reactivity and predict biologic activity (see Figure 3). Vinyl chloride has been demonstrated to be carcinogenic



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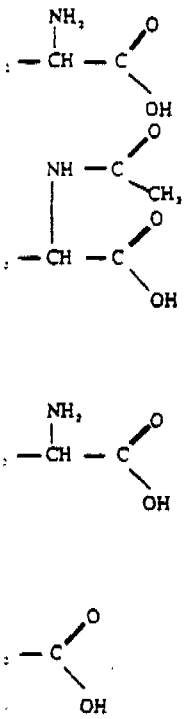

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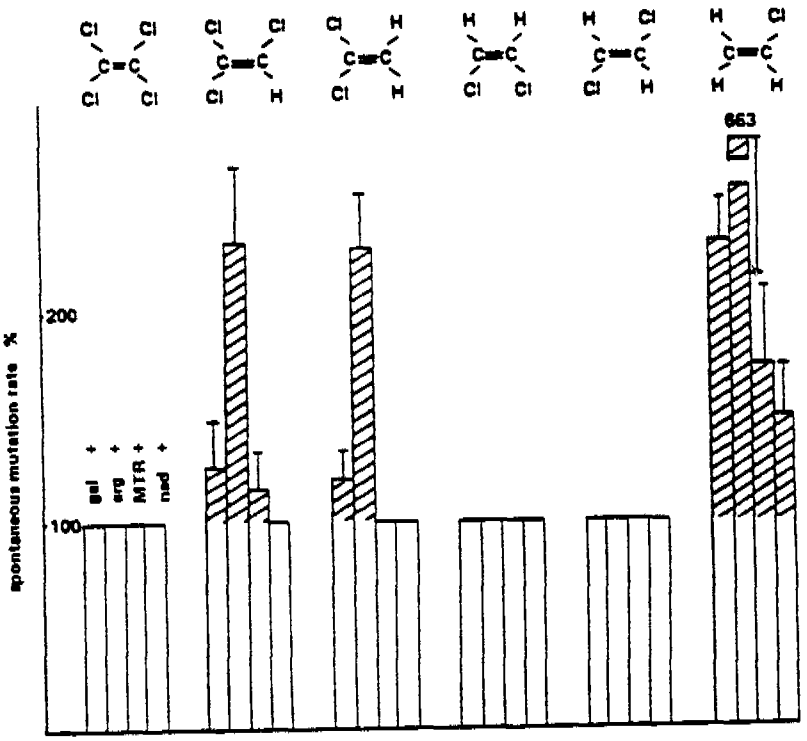


FIGURE 2. Mutagenicity of chlorinated ethylenes in an in vitro test system. Incubation of the compounds in concentrations (aqueous phase) from 0.9 to 10.9 m*M* in a metabolic activating microsomal system. Results as percent of spontaneous (= 100%) mutation rate in different operons of the test germ *E. coli* K_{12}: gal$^+$, galactose; arg$^+$, arginine; MTR$^+$, methyltryptophane; nad$^+$, NAD.[84]

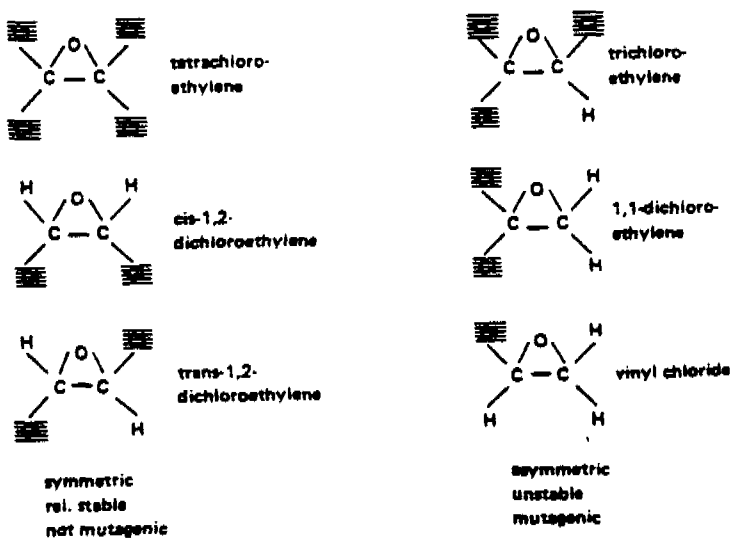


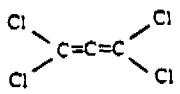
FIGURE 3. Molecular features of oxidative metabolic intermediates (oxiranes) of chlorinated ethylenes in relation to their mutagenic potential in vitro (see Figure 2).

in humans[90] and experimental animals.[91] In high oral doses, trichloroethylene produces malignancies in mice.[92] Vinylidene chloride also has been reported as an animal carcinogen.[93]

ALKYNES

$-C\equiv C-Cl$

In general, chlorine substitution of sp-hybridized C-atoms in allenes and acetylenes results in a destabilization of the molecules. This has been demonstrated with perchloroallene (45), which is stable only below -50°C and starts dimerization from -30°C upward.[94,95] Similar behavior is encountered with tribromoallene, perbromoallene, and trichloroallenes with electronegative substituents.[96-99]



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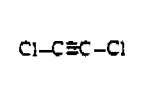

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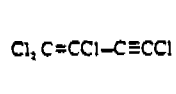

(47)

Dichloroacetylene (46) is also extremely reactive (explosive) and decomposes immediately in the presence of air, to phosgene and carbon monoxide.[100] The destabilizing effect of chlorine substitutions at sp-hybridized bonds has also been demonstrated (though in a less intensity) with perchlorobutenyne[101] (47); this thermally unstable compound forms (slowly above 25°C) a dimer, C_8Cl_8.

The metabolic fate of chlorinated acetylenes and allenes has not yet been investigated. Dichloroacetylene which is formed from trichloroethylene, tetrachloroethane(s), or acetylene in some working environments produces a highly characteristic symptomatology of acute intoxication: irreversible damage to the cranial nerves (predominantly the nervus trigeminus) in humans[102] as well as experimental animals[103-105] and tubular nephrotoxicity in animals.[104,105] Whether these toxic effects are due to the reactive dichloroacetylene or to metabolites is open to further experimentation.

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