Reactions of chlorinated tetrahydrofurans. XIX.*
Polychlorination of chlorotetrahydrofurans

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Polychlorination of tetrahydrofuran has been studied in detail using gas chromatography, high resolution liquid chromatography, and p.m.r. spectrometry for the analysis of products. Pathways of polychlorination, depending upon the reaction temperature and the intensity of u.v. irradiation, have been proposed. Some of the pathways can be utilized in the preparation of desired polychloro derivatives. New chlorinated tetrahydrofuran derivatives have been identified and characterized.

Представления о полихлорировании тетрагидрофуранового цикла были расширены и уточнены при помощи применения комбинации газовой хроматографии, высокоэффективной жидкостной хроматографии и ЯМР спектроскопии. Предлагаются направления реакций полихлорирования зависимые от температуры реакции и интенсивности ультрафиолетового излучения; некоторые из них можно использовать при приготовлении желаемого полихлордеривата. Использованная методика сделала возможными идентификацию и охарактеризование новых хлорпроизводных тетрагидрофурана.

Depending upon the reaction conditions chlorination of tetrahydrofuran proceeds preferentially either as a radical substitution in the α position to the atom of oxygen or as an elimination-substitution in the β position. Sometimes the reaction proceeds almost exclusively in one direction giving the wanted substance. When, however, a complex mixture of isomers is formed, efficient separation into its components, owing to the reactivity and thermal instability of some chlorinated tetrahydrofurans, is almost impossible.

Experimental

Tetrahydrofuran, ethyl ether, and pentane were dried over sodium and distilled. Carbon tetrachloride was dried with anhydrous calcium chloride and distilled. Chlorine and nitrogen were supplied from commercial cylinders and dried by passing through concentrated sulfuric acid. All manipulations with chlorotetrahydrofurans were done under dry nitrogen.

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HMDS — hexamethyldisilazane, TMS — tetramethylsilane.

Gas chromatography was carried out with CHROM II Gas Chromatograph (Laboratorní přístroje, Praha) equipped with a flame ionization detector. A glass column of 150 cm length packed with 10% Apiezon L on Chromaton NAW-DMCS was used. The analyses were run isothermally in the range 100—130°C, using nitrogen as the carrier gas.

Liquid chromatography was done with a self-constructed chromatograph [1, 2] equipped with an LDC (USA) refractometric detector and a TZ-21 recorder (Laboratorní přístroje, Praha). Pentane was used as the mobile phase and this was supplied with an MC-300 micropump (Mikrotechna, Praha). A stainless steel column (500 × 2 mm) was packed with activated silica gel (30—40 μm) coated with 22% (w/w) nitrated polystyrene [1, 2]. For preparative purposes 10—15 μl samples of reaction mixtures were repeatedly injected, the respective fractions were collected and concentrated under diminished pressure. The residue was dissolved in carbon tetrachloride (1 ml), concentrated, and again concentrated after dilution with carbon tetrachloride (1 ml). Carbon tetrachloride (0.5 ml) was added to the residue and the p.m.r. spectrum was taken from the solution formed.

The p.m.r. spectra for solutions in carbon tetrachloride (internal standard HMDS, the found data being recalculated for TMS) were obtained at 25°C and 80 MHz with Tesla BS 474 XA instrument. The spectra of *XIV* were run with a hydrogen standard in the following manner: the spectra of a mixture of the sample (91 mg) and *tert*-butyl methyl ketone (38.6 mg) were taken and the intensity of the signal corresponding to the methyl group was compared with that corresponding to the sample. The found ratio of the signal-height corresponding to the methyl group to that of *XIV* was 171.5 : 63.5. The amounts of the substance (hexa- and heptachlorotetrahydrofuran) corresponding to the found signal ratios were calculated (59.5 and 134 mg for hexa- and heptachlorotetrahydrofuran, respectively). It follows from the results obtained that the substance under investigation was hexachlorotetrahydrofuran *XIV* containing, according to p.m.r. and GC analysis ~ 30% of impurities.

Chlorination

The substance to be chlorinated (neat, or as a solution in carbon tetrachloride) was placed into an insulated chlorinator [3] kept at the given temperature (Table 1) by means of a bath of heated ethylene glycol or ethanol—dry ice mixture. The construction of the chlorinator permitted u.v. irradiation by means of a mercury lamp located in the apparatus. The bottom of the chlorinator was equipped with a sintered-glass inlet through which a mixture of chlorine and nitrogen was supplied. The formed gases were allowed to escape through a reflux condenser (calcium chloride drying tube) into the hood. Samples of the reaction mixtures were periodically withdrawn and analyzed by gas chromatography. Chlorination was terminated by passing a stream of nitrogen through the reaction mixture and the product was distilled at diminished pressure under nitrogen. The p.m.r. spectra were taken after resolution of the mixture by liquid chromatography. Chemical shifts and coupling constants are given in Table 2. In studying the products of thermal elimination of hydrogen chloride (Table 1) the peak-areas corresponding to the substances under investigation eluted during GC analysis were measured and the peak-area ratios (A) and time-dependence of the peak-area ratios were plotted as shown in Fig. 1.

3,3-Dichlorotetrahydrofuran (V)

Compound *VI* (17.5 g; 0.1 mole) was added dropwise into a 50 ml solution of lithium aluminium hydride (1.9 g; 0.05 mole) in ether and the mixture was stirred under reflux for 24 hrs. The excess of the reagent was destroyed by addition of aqueous ammonium chloride, the organic layer was separated and the aqueous phase was extracted with ether (30 ml). The combined ether solutions were dried, distilled and the fraction corresponding to *V* (b.p. 55—58°C/2.4 kPa, n_D^{20} 1.4711) was collected. The same procedure [4] was applied when *XVI* was made by hydrogenolysis of *IV*.

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Table 1
Chlorination of polychlorotetrahydrofurans

| Reaction | Starting material | | Reaction tempera-ture °C | Irradiation | Means of isolation | B.p. °C/kPa | Products of | Calculated found % Cl |
	Compound	Amount in the starting material, %						
1	IV	100	140	—	Distillation	81—83/2.5	VI	60.6 60.77
2	VI	100	170	—	—	—	—	— —
3	VI	100	140	—	Distillation	86—88/1.6	X	67.57 64.12
4	VI	25	−10	+	Distillation	100—101/2.4	XI + (XV)	72.55 65.25
5	IV	25	−10	+	Distillation	95—100/5.3	VII + (VIII)*	
6	IV	25	−10	+	Solvent distillation off	to 40/6.6	IX + (VIII)	
7	VII	100	+150	—	Distillation	85—90/1.7	VIII + (XIII, XIV)	
8	VII	50	+30	+	Solvent distillation off	to 30/4.0	XIV + (XII)	76.3 67.72
9	Product of reaction 5		135, 150	—			HCl elimination	
10	Product of reaction 6		100, 120	—			HCl elimination	
11	XVI	50	−15	+	Distillation	68—72/2.9	IV	
12	XVI	50	+20	—	Distillation	68—72/2.9	IV	—
13	XVI	50	+20	+	Distillation	68—72/2.9	IV	—

* Ref. [6].

Table 2

Chemical shifts and coupling constants calculated from p.m.r. spectra

Compound	Position							
	2		3		4		5	
	δ/p.p.m.	J/Hz	δ/p.p.m.	J/Hz	δ/p.p.m.	J/Hz	δ/p.p.m.	J/Hz
IV	6.14; s	—	4.58; d	5.5	2.78; m		4.28; d	5; 9
					2.19; m			
V	3.88; d	1	—	—	2.50; t	7.5	3.81; t	7.5
VI	6.08; s	—	—	—	2.85; m		4.23; m	
VIIa	6.04; d		4.65; m		3.22; m	15	6.23; d	6
					2.90; m			
VIIb	6.19; d						6.31; d	5.5
VIII	6.16; s	—	4.58; s	—	4.58; s	—	6.16; s	—
IX	6.19; s	—	4.64; m		3.78; m	16	—	—
X	6.30; m		—	—	3.43; m		6.30; m	
XI	6.48; s	—	—	—	3.95; s	—	—	—
XIV	—		4.05; s	—	4.05; s	—	—	—

Peak multiplicities: s — singlet, d — doublet, t — triplet, m — multiplet.

Results and discussion

The analysis of the products formed by chlorination of chlorinated tetrahydrofurans under the above-given conditions widens our knowledge about chlorination of the tetrahydrofuran ring [5—9].

In contrast to earlier reports [7] chlorination of 2,3-dichlorotetrahydrofuran (IV) at 140°C gave [2, 10] 2,3,3-trichlorotetrahydrofuran (VI) as the main product (Scheme 1). Compound VI was isolated from the reaction mixture either by preparative liquid chromatography or, with little decomposition, by repeated distillation. While the two-step procedure developed earlier [8] was found unpractical, high-temperature chlorination of IV described herein gave VI of ~95% purity (GC) in 65—75% yield. The structure of VI follows from the found physical properties (Table 1) and p.m.r. spectral data (Table 2). The direction of the substitution of hydrogen by chlorine in IV can be explained by the reaction conditions applied. Obviously, the elimination of hydrogen chloride proceeds at 140°C faster than does radical substitution at the position 5. The thus formed 2,3-dihydro-4-chlorofuran then takes up a molecule of chlorine to give VI. The solubility of chlorine in the reaction medium at even higher temperature (170°C) is so low that the formation of substitution products is not observed.

The product of further chlorination at 140°C of VI was isolated. It follows from the results of GC analysis (Fig. 2), LC separation as well as from analytical figures
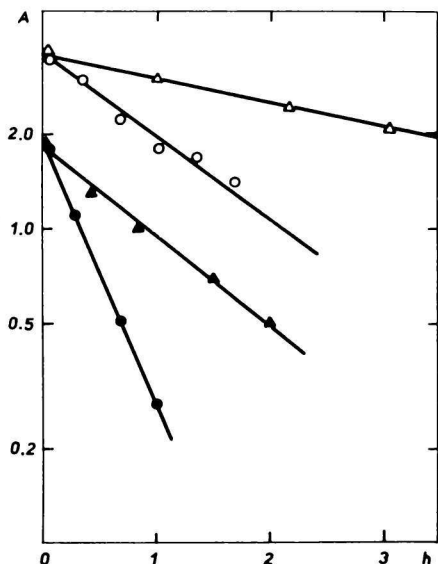
Fig. 1. GC peak-area ratios (A) *vs.* reaction time (t) observed during elimination reaction of polychlorinated tetrahydrofurans.
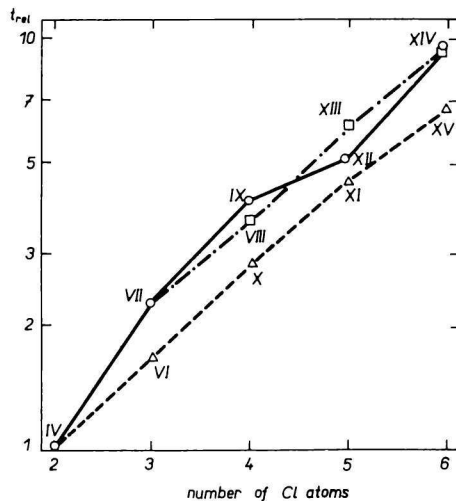△ $IX/VIII$ at 100°C; ○ $IX/VIII$ at 120°C; ▲ $VII/VIII$ at 135°C; ● $VII/VIII$ at 150°C.

Fig. 2. Corrected retention times of polychlorinated tetrahydrofurans relative to IV (t_{rel}) as a function of the number of chlorine atoms (n) in the molecule.
For the operating conditions see the text.
△ Photochlorination of VI at −10°C;
○ photochlorination of VII at 30°C;
□ chlorination of VII at 150°C.

and p.m.r. spectral data (Tables 1 and 2) that the primary reaction product of chlorination of VI carried out at 140°C is 2,3,3,5-tetrachlorotetrahydrofuran (X).

Compound X is primary product also of photochlorination of VI at −10°C. In addition to X and in contrast to the reaction at high temperature 2,3,3,5,5-pentachlorotetrahydrofuran (XI) could also be isolated when the reaction mixture was submitted to separation by liquid chromatography. The structure of XI is proposed on the basis of p.m.r. and GC data. Compounds X and XI are formed by radical substitution at the position 5 and elimination-addition products are not formed.

Another substance found in the reaction mixture of chlorination was 2,2,3,3,5,5-hexachlorotetrahydrofuran (XV). Compound XV, formed by radical substitution of the last available α position in XI, is the final chlorination product of VI at −10°C.

Photochlorination of IV at temperatures up to 60°C gives 2,3,5-trichlorotetrahydrofuran (VII) as the primary product [3, 6, 7]. It follows from p.m.r. data obtained for VII [1] that this material is a mixture of two isomers differing in the orientation of the chlorine atom at the positions 2 and 5 while the chlorine atoms at the positions 2 and 3 always take *trans* configuration (Table 2). The isomer $VIIa$

(2,5-*cis*) predominates in this mixture over its *trans* counterpart *VIIb* by a factor of ~3.

Conformational studies on *IV* using a shift reagent showed [11] that, in carbon tetrachloride solution, the substance exists preferentially in a diaxial half-chair conformation having the carbon atoms C(3) and C(4) twisted. The *cis* configuration of the chlorine atoms at the positions 2 and 5 in *VII* is probably configurationally more advantageous than the *trans* one.

Scheme 1
The proposed reaction pathway of polychlorination of tetrahydrofuran

Further chlorination of *VII* yields a mixture of tetrahydrofuran polychloro derivatives. At the temperature above 40°C the formation of 2,3,4,5-tetrachloro-tetrahydrofuran (*VIII*) is preferred [3, 6, 7] and all four atoms of chlorine take, with respect to each other, a *trans* position, which follows from the p.m.r. spectrum of the substance *VIII* [2, 11], showing only two singlets (Table 2).

The second possible tetrachloro derivative formed by photochlorination of *VII* at temperatures below 40°C is 2,3,5,5-tetrachlorotetrahydrofuran (*IX*) [1, 2]. Under these conditions the concentration of chlorine radicals is high enough for the radical substitution to proceed faster than the elimination-addition reaction at the position 4. The factor determining the introduction of the fourth halogen atom into *VII* during a radical reaction is the stereochemical stability of the just formed radical. Obviously, as a result of above-mentioned conformation of *VII*, the substitution at the position 5 is preferred.

The differences in the composition of the reaction mixtures for reactions run under conditions *5* and *6* (Table 1), as a result of higher reaction temperatures (100—150°C; Fig. 1), are likely to be caused by different rate of elimination of hydrogen chloride from the studied compounds. The fact that hydrogen chloride was evolved from the mixture during the whole reaction period was proved with gaseous ammonia. By monitoring the course of the reaction by gas chromatography neither the formation of a new product nor the increase in the amount of products already formed could be observed. Hence, the compounds under investigation undergo thermal decomposition at the rate *IX* > *VII* > *VIII*. This explains also the fact that in previous preparations of tetrachlorotetrahydrofuran [6], where the isolation was carried out by repeated low-pressure distillation at 100—120°C, only compound *VIII* could be isolated. When, a mixture of *VII*, *VIII*, and *IX*, arising by chlorination from *VII*, was photochlorinated at 30°C and the reaction was monitored by gas chromatography the formation of pentachloro derivatives *XII* and *XIII*, together with their final chlorination product 2,2,3,4,5,5-hexachlorotet-rahydrofuran (*XIV*) could be observed (Table 1).

When *VII* was chlorinated at 150°C (reaction *7;* Table 1) a hexachloro derivative was formed *via* the expected derivative *VIII* and the pentachloro derivative the GC elution time of which was identical with that of the substance formed by photochlorination at 30°C (Fig. 2). As shown in Scheme 1, compound *XIV* can be made from *IX* by reversing the substitution steps at the positions 2 and 4 either through 2,2,3,5,5-pentachlorotetrahydrofuran (*XII*) or through the iso-meric substance *XIII*. Compound *XIV* is, under the given conditions, the sole product of chlorination of *VIII*. The structure of *XIV* is proposed on the basis of GC and p.m.r. spectral data, and the suggested reaction mechanism. The fact that the amount of *XIV* in the product of reaction *8* (Table 1) was ~64% followed from its p.m.r. spectrum run with the addition of a hydrogen standard.

To clarify the course of substitution on the tetrahydrofuran ring chlorination of

3-chlorotetrahydrofuran (*XVI*) was carried out. Under all conditions applied (Table 1) the primary product of the reaction was found to be *IV* and the formation of 2,4-dichlorotetrahydrofuran was not observed.

By analogy with hydrogenolysis of *IV* [4] which gives 3-chlorotetrahydrofuran (*XVI*), hydrogenolysis of *VI* gave 3,3-dichlorotetrahydrofuran (*V*). In both cases the substitution of chlorine atom at the position 2 is more feasible than at the position 3, which is in agreement with the reactivity of haloethers. When excess of lithium aluminium hydride was used the cleavage off of another atom of chlorine from *V* occurred and *XVI* was produced.

The found course of the formation of tetrahydrofuran chloro derivatives agrees with the rules of chlorination of tetrahydrofuran ring [3, 5—9] known so far. Photochlorination gives predominantly α-substituted derivatives which can either be isolated, and this is the case when the reaction is run at low temperature, or further chlorinated at the α position (*e.g.* sequence *I → II → III; VII → IX → XII: VI → X → XI → XV*). When working above certain critical temperature, characteristic of each particular derivative, the primary α-substituted product loses a molecule of hydrogen chloride and a molecule of chlorine is added to the thus formed elimination product. The overall product of these two reactions is a β-substituted derivative. When there is a possibility of a reaction at both positions 3 and 4 the next atom of halogen is linked to the one less occupied (*e.g.* *X ⇌ VII → VIII*), which depends upon the lower temperature necessary for an elimination of hydrogen chloride. The ease with which hydrogen chloride is eliminated governs not only the course of further substitution but also the isolability of the individual products. When distillation is used as a means of isolation, repeated rectification yields normally only the most stable product while the less stable ones decompose (*VII, VIII, IX → VIII; II, IV → IV; IV, VI → VI*). When mono- and disubstituted derivatives are further chlorinated under suitable conditions wanted compounds can be obtained in practical yields (*II, III, IV, VI, VII*). Polychloro derivatives may, however, react in different way and complex mixtures of products are then formed. Hence, only the final products of extensive chlorination can be obtained on a preparative scale (*XIV, XV*).

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