the ^{35}Cl resonance frequency by less than 0.8 MHz and hence confirms that the large difference between axial and equatorial chlorine atoms in α chloroethers reported in [1] arises from a specific interaction with the oxygen atom.

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172. Nuclear Quadrupole Resonance and Stereochemistry III. Trichloromethyl Derivatives

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(11. IV. 73)

Summary. ^{35}Cl nuclear quadrupole resonance frequencies are reported of the chlorine atoms in the trichloromethyl group of benzotrichlorides and trichloromethyl derivatives of heterocyclic molecules. They are compared with previously reported results for the same group attached to other planar conjugated radicals. In such compounds the three chlorine atoms cannot be equivalent and all the results are discussed from the point of view of possible orientation-dependant hyperconjugation between the C-Cl bonds and the conjugated moiety, particularly with reference to the marked effects observed in trichloromethyl ethers reported in part I of this series. In the benzotrichloride and indeed most of the compounds discussed such effects are small.

In part I of this series [1] it was shown that the ^{35}Cl resonance frequency of a cyclic α-chloro ether had a marked dependence on the axial or equatorial nature of the carbon-chlorine bond. In part II [2] it was shown that there was no such marked orientation-dependence in saturated carbocyclic systems and it may thus be concluded that the effect in the ethers is due to a specific interaction between the C–Cl bond and the oxygen atom. A model (no doubt much oversimplified), of such an interaction which predicts a frequency variation in accord with experiment [3] [4] is afforded by the resonance structure I which would have its least importance when the four atoms C, O, C, Cl are coplanar.

$$CH_3{-}O{-}CH_2Cl \longleftrightarrow \underset{\text{I}}{CH_3{-}O^{\oplus}=CH_2Cl^{\ominus}}$$

It is of interest to see whether potentially conjugating groups other than oxygen have such a marked effect on the ^{35}Cl resonance frequency, and in particular whether an unsaturated carbon atom would do so. Such an effect is already well-known in the field of ultra-violet spectroscopy where the spectra of α-haloketones can be used as a reliable diagnosis of the axial or equatorial configuration of the carbon-halogen bond. The two ^{35}Cl resonance frequencies of 2,2-dichlorocyclohexanone – where almost certainly one chlorine atom is axial and the other equatorial – differ however by only 0.2 MHz [5]. On the other hand in [2] the only example of a marked configurational effect in carbocyclic systems was found in *cis*- and *trans*-dichloroacenaphthylene where a frequency-difference of 2.4 MHz was observed between the two isomers and where a crystal structure of the trans isomer – having the lower frequency – showed that the C_8-C_1-Cl fragment lies in a plane almost perpendicular to the aromatic plane. Furthermore, in an analysis of the resonance frequencies of various substituted benzyl chlorides *Dewar* & *Herr* [6] suggested that the normal configuration of the chloromethyl group is one in which the C_1-C_7-Cl fragment lies in a plane perpendicular to that of the benzene ring – where an interaction similar to that in I would be a maximum – while the presence of an ortho substituent forces the C-Cl bond to lie in the plane of the benzene ring where the hyperconjugative interaction of I is non-existent. In this way they give an explanation for the fact that in *o*-substituted benzyl chlorides the ^{35}Cl resonance frequencies are about 0.5 MHz higher than those expected from the known effects of the various substituents. In support of this a recent detailed single crystal study of *p*-chlorobenzotrichloride showed [7] that in the crystalline state one of the three C–Cl bonds lies in a plane perpendicular to the benzene ring and has a ^{35}Cl resonance frequency 0.84 MHz lower than that of the other two chlorine atoms. Finally, the frequencies of two trichloromethyl ethers of unknown conformation showed the same frequency spread as had been observed in a variety of cyclic α-chloro ethers of known crystal structure [1].

These observations suggest that an extended study of benzotrichlorides and of trichloromethyl groups attached to potentially conjugable groups might well be profitable and reveal consistent differences between the resonance frequencies of the three atoms of the CCl_3 group which could be ascribed to specific orientation-dependent hyperconjugation.

Experimental. *Instrumentation*, see [1].

Preparation: Benzotrichloride, *o*- and *m*-chlorobenzo-trichloride, *o*-, *m*- and *p*-fluorobenzotrichloride were redistilled commercially-available compounds. $\omega,\omega,\omega,\omega',\omega',\omega'$-hexachloro-*p*- and *m-xylene* were recrystallised commercial samples whereas 2-(trichloro methyl)-4(3*H*)-quinazoline and 2-(trichloromethyl)-benzimidazole were used without previous recrystallisation.

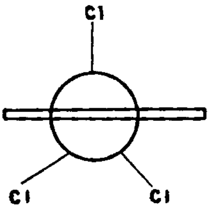
Results and Discussion. – Table 1 shows the resonance frequencies of substituted benzotrichlorides and of two heterocyclic compounds carrying the trichloromethyl substituent. Hexachloro-*p*-xylene was previously studied by *Hooper* & *Bray* [8] who only reported six resonances at 38,302; 38,722; 38,901; 39,200; 39,406 and 39,627. These essentially coincide with six of the resonances reported here whereas the three additional resonances at 39,275; 39,344 and 39,369 are sandwiched between two resonances separated by only 0.2 MHz. All these resonances had essentially the same intensity and the pattern was the same in both the unpurified commercial sample and that recrystallised from ethanol. It seems likely therefore that the nine resonances correspond to just one crystalline phase and we attribute the failure of *Hooper* & *Bray* to observe these resonances to the overlapping of side bands of their superregenerative oscillator. This drawback was overcome in the present case by the 'side-band suppression' facility of the *Decca* spectrometer. The spectrum of hexachloro-*m*-xylene is even more complex and it is noteworthy that all three benzotrichlorides containing only trichloromethyl substituents evidently crystallise with more than one molecule per unit cell. Two sets of frequencies are given for *o*-fluorobenzotrichloride corresponding to two different crystalline phases. This compound is liquid at room temperature and on cooling either yields pure I or a mixture of I and II. Pure II was never obtained but pure I was obtained if the sample was rapidly cooled.

Table 1. *^{35}Cl resonance frequencies (MHz at 77K) of substituted benzotrichlorides and trichloromethyl derivatives of heterocyclic compounds*

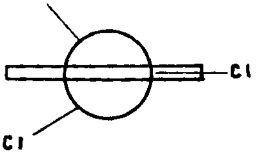
Compound	^{35}Cl resonance frequency at 77 K (MHz)	Ref.
Benzotrichloride	38,288; 38,702; 38,713 38,786; 38,824; 38,898	[9]
o-chlorobenzotrichloride	35,794; 39,158; 39,602 [a]	
m-chlorobenzotrichloride	35,013; 39,044; 39,064; 39,509	
p-chlorobenzotrichloride	34,829; 38,441; 39,280 [a]	[7]
p-fluorobenzotrichloride	38,785; 39,105; 39,454	
m-fluorobenzotrichloride	38,996; 39,029; 39,512	
o-fluorobenzotrichloride I	39,335 [a]; 39,365	
II	39,084; 39,506; 39,802	
ω,ω,ω,ω′,ω′,ω′, hexachloro-*m*-xylene	38,440; 38,462; 38,570; 38,640; 38,692; 38,761; 38,913; 38,987; 39,084; 39,307; 39,461; 39,481	
ω,ω,ω,ω′,ω′,ω′ hexachloro-*p*-xylene	38,300; 38,717; 38,906; 39,195; 39,275; 39,344; 39,369; 39,404; 39,625	[8]
2-(trichloromethyl)-benzimidazole	39,146; 39,526; 39,644; 39,730; 40,107; 40,179	
2-(trichloromethyl)-4(3*H*)-quinazolinone	39,073; 39,451; 39,789; 40,298; 40,730; 40,735.	

[a] This resonance was twice as intense as the neighbouring one and presumably arises from two equivalent chlorine atoms.

The two most symmetric arrangements of the trichloromethyl group in benzotrichlorides are II and III where one C–Cl bond is in a plane which is respectively perpendicular to or coplanar with the benzene ring.



II



III

On the other hand, particularly in the crystalline state other intermediate orientation may occur. The simplest monotonic orientation dependance which can be imagined for the ^{35}Cl resonance frequency is

$$\nu = \nu_0 - \nu_1 \sin^2\theta \tag{1}$$

where θ is the angle between the plane containing the C–Cl bond and the plane of the benzene ring. Implicit in this equation is the assumption that hyperconjugation, by increasing the ionicity of C–Cl bond, decreases the ^{35}Cl resonance frequency. Also implicit in this equation is the assumption that the benzene ring retains its two-fold symmetry axis between atoms 1 and 4: thus it strictly could only be used for *para*-substituted benzotrichlorides although *meta* derivatives may probably also be reasonably well described; however *ortho* substituted derivatives are unlikely to be compatible with equation (1), since direct interactions with the *o*-substituent will almost certainly be significant.

The configuration of the trichloromethyl group in *p*-chlorobenzotrichloride is known to be II from the single crystal study, the data for *m*-chlorobenzotrichloride and *m*- and *p*-fluorobenzotrichloride (Phase II) where only three resonances occur, can be analysed to yield values of ν_0, ν_1, and θ. These results are summarised in Table 2. Not too much importance should be attached to the values of θ since the intermolecular field gradients will not necessarily affect the three frequencies to the same extent; furthermore there is nothing in the analysis of the data which indicates where the reference point for θ should be taken. More important is the value of ν_1 which indicates the magnitude of the conformational effect. Its average value is 0.65 MHz, very much less than that observed in the case of the ethers. Such an effect, although by no means negligeable in terms of electronic structure (it represents a transfer of about 0.01 units of electron population) is too small to provide a reliable indication of conformation since it is of the same order as the coupling resulting from intermolecular field-gradients.

Table 2. *Analysis of ^{35}Cl NQR. frequencies in terms of Equation (1)*

Substituent	ν_0	ν_1	θ
p-Cl	39.56	1.18	30°
m-Cl	39.51	0.61	0°
p-F	39.50	0.77	14°
m-F	39.51	0.67	0°

The situation in *o*-substituted derivatives is even worse. The two resonances in 2:1 intensity ratio for *o*-chlorobenzotrichloride shows that, as indeed consideration of steric effects would indicate, the molecule has the conformation III. Equation (1) and the implied hyperconjugation mechanism, together with the experimental results for the *p*-chloro derivative indicates that for conformation III the line of relative intensity 2 has the lowest frequency but experimentally the opposite is found. Either therefore it is the result for *p*-chlorobenzotrichloride which is 'anomalous' or a direct interaction between the chlorine atom in the *o*-position and the two equivalent chlorine atoms of the benzotrichloride group with which it is in contact, opposes and overwhelms the conformational effect.

A large number of trichloromethyl derivatives in which the trichloromethyl group is attached to planar conjugating groups other than benzene have also been studied but in almost every case the conjugable group lacks a two fold-axis so that the resonance frequency would have to be expressed by a four-parameter equation. Without additional information, therefore, is is impossible to analyse the resonance frequencies in any meaningful way except insofar as the total spread in frequencies gives an indication of the conformational effect. Fig. 1 is a stick diagram of the resonance frequencies of a variety of such trichloromethyl derivatives, mostly taken from the literature. The spread in frequency is in almost all cases comparable with that observed in the benzotrichlorides. It is perhaps significant that in the three molecules containing the fragment IV

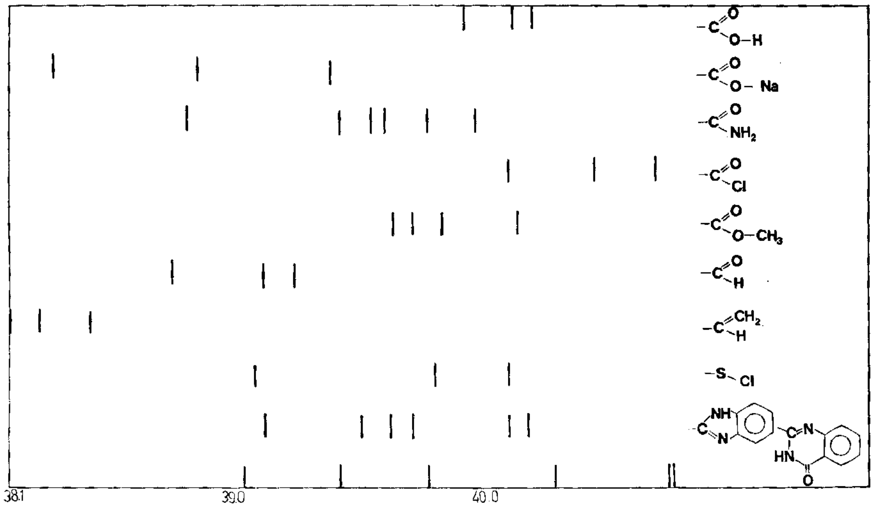
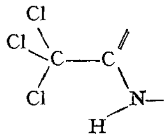


Fig. 1. *^{35}Cl NQR resonances (MHz at 77) of the CCl_3 group in trichloromethyl derivatives*



IV

the total spread is greater than 1.0 MHz, pointing perhaps to the existence of an internal hydrogen bond.

It is clear from the above that there is no general pronounced effect of hyperconjugation on the resonance frequencies of the trichloromethyl group and in this respect the trichloromethyl ethers appear to be unique. More precisely whatever effect there may be is usually smaller than or at most comparable in magnitude with the effects of intermolecular field-gradients and of other intramolecular interactions. This perhaps casts doubt on the mechanism which has been proposed in [1] to explain the marked frequency variation of the α-chloroethers and [2] the difference between *cis*- and *trans*-1,2-dichloroacenaphthylene. In this respect the frequencies of the trichloromethyl group in compounds of the type $Cl_3C\ (CH_2)_n\ CH_2Cl$ are of interest [10] for sufficiently long chain-lengths ($n = 8, 10, 12$) the resonances fall into two groups: one resonance at 38.6 MHz and two others very close together at 37.3 MHz. This is in contrast to the situation with short chain lengths where, despite the proximity of the CH_2Cl group, the resonances of the CCl_3 group spread over only 0.6–0.7 MHz. This observation is likewise in agreement with the results presented [2] for the variously oriented 1,2-dichloro compounds. The frequency variations which have been observed may thus well be due to stronger sigma-sigma interactions between vicinal C–Cl and C–C bonds than between two vicinal C–Cl bonds.

In conclusion this survey of ^{35}Cl resonances of the trichloromethyl group shows that with most planar conjugating groups the change in frequency with orientation is less than of 1.0 MHz, far less than has been clearly demonstrated for the α-chloro ethers. When the trichloromethyl group is attached to a tetracoordinated carbon atom, shifts of at least the same order of magnitude can occur.

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173. Repetitive Excess Mixed Anhydride (REMA) Synthesis of Peptides. The Protected C-terminal Hexadecapeptide of Secretin

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(30. IV. 73)

Summary. The usefulness of the repetitive excess mixed anhydride (REMA) method of peptide synthesis was demonstrated by the prompt synthesis of the protected C-terminal hexadecapeptide of the gastrointestinal hormone secretin, Boc-Arg(NO_2)-Leu-Arg(NO_2)-Asp(Bzl)-

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[1] Taken in part from the Doctoral Dissertation to be submitted by *A. van Zon*.