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The Crystal Structures of the Isomeric Squalene Hexahydrochlorides

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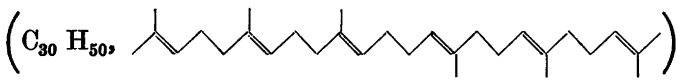
The structures of two isomeric squalene hexahydrochlorides have been investigated by the aid of X-ray methods, supported by the study of the infrared absorption spectra. Detailed molecular structures are proposed for both forms, and their relation to other long carbon chain molecules such as β-guttapercha, rubber hydrochloride and geranylamine hydrochloride is discussed. It is shown that the reason for the isomerism lies in the steric orientation of chlorine atoms and methyl groups at the four asymmetric carbon atoms, and the two crystalline isomers have been identified as the two possible *meso*-forms of the molecule. These structure determinations constitute an independent proof of the accepted structure of the carbon skeleton of the squalene molecule.

Both natural and synthetic squalene



upon saturation with hydrogen chloride yield a mixture of crystalline hexahydrochlorides, which can be separated into two fractions, one of which constitutes about 80 % and melts at 108—110° C, while the other one constitutes about 20 % and melts at 143—145° C (see for instance Karrer and Helfenstein [1]). Sometimes two low melting isomers have been reported in the literature. We have found, by repeated crystallizations, that all crystal crops with deviating melting points are mixtures of the higher melting form and the lower melting form mentioned above (in this paper designated by h.m. form and l.m. form, respectively).

Both isomers have the same composition ($C_{30}H_{56}Cl_6$) and give very similar, though not identical, X-ray diffraction patterns. Nevertheless, they are distinctly different as evidenced by their melting points, solubility properties, specific gravities, X-ray data and infrared absorption spectra. No attempt to clarify the reason for this isomerism has hitherto been made. It could scarcely be connected with isomerism of the parent hydrocarbon for several reasons:

1) Regeneration of the hydrocarbon from both isomers gives indistinguishable products; 2) Both these products, and also synthetic squalene made by different methods, give with hydrogen chloride the same mixture of hexahydrochlorides as obtained from squalene itself, although these hydrocarbons differ from natural squalene with respect to double bond orientation around at least some of the substituted carbon atoms (*cf.* Dauben *et al.*[2]).

It would appear that the only reasonable cause for this isomerism is to be found in the steric orientation of the chlorine atoms and methyl groups at the four asymmetric carbon atoms of the chain, making the fair assumption that chlorine adds to the methylsubstituted carbons according to Markownikoff's rule. The only difficulty is that out of the 6 possible diastereoisomers only two are obtained in crystalline form and in so widely different quantities. Evidently, the addition mechanism must favour the formation of the lower melting isomer. Thus, the structure determination of these crystal modifications is of interest from two points of view, *i. e.*, the stereochemistry of polymeric carbon chains, and the mechanism of the addition of hydrogen chloride to unsaturated hydrocarbons.

The present paper reports the results of X-ray investigations on the structures of the two isomers of squalene hexahydrochloride, supported by chemical and optical observations.

UNIT CELLS AND SPACE GROUPS

Both isomers of squalene hexahydrochloride crystallize in thin transparent plates with perfect cleavage parallel to the plane of the plates. Cleavage in several directions perpendicular to these planes is also observed, giving the small plates a pseudo-hexagonal cross-section. This is most pronounced for the higher melting form, which also looks more homogeneous under the microscope in polarized light than the lower melting one. Both isomers show sharp extinction in polarized light, from which the lack of optical activity may be inferred. No difference can be detected in their X-ray powder photographs. The unit cell dimensions and rules for systematic absences were determined from oscillation and Weissenberg photographs obtained with Cu$K\alpha$-radiation.

For the h.m. form: $a = 56.7_0 \pm 0.1$ Å; $b = 10.23 \pm 0.02$ Å; $c = 5.99_2 \pm 0.01$ Å; $\gamma = 93.2° \pm 0.2°$.

$V = 3\,468$ Å^3, $d_{calc.} = 1.205$ g/cm^3, $Z = 4$ mol./u.c.

For the l.m. form: $a = 56.7_1 \pm 0.1$ Å; $b = 10.40 \pm 0.02$ Å; $c = 5.98_4 \pm 0.01$ Å; $\gamma = 92.0° \pm 0.2°$.

$V = 3\,526$ Å^3, $d_{calc.} = 1.185$ g/cm^3, $Z = 4$ mol./u.c.

Thus, both isomers are monoclinic and pseudo-orthorhombic, but only very small differences are revealed in their cell dimensions. The small but significant difference in specific density has been confirmed by determinations by the floating method, which gave 1.20_8 and 1.18_2 for h.m. and l.m. form, respectively.

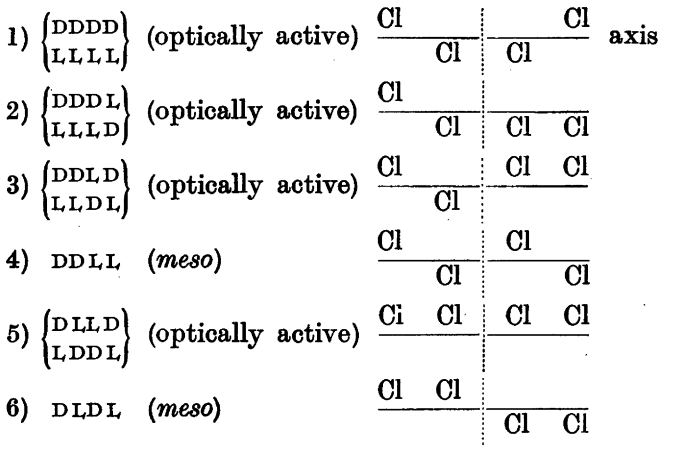
The same systematic absences and pseudo-absences are found for both forms:

$h00$ for h odd; $0k0$ for k odd; $00l$ for l odd; $h0l$ for $h + l$ odd; $hk0$ for k odd.

Since the angle γ deviates from 90° for both forms, only the third and the fifth rule could be strictly valid, the other rules must be due to pseudo-symmetries, but it may be of interest to note that all these rules together would indicate the orthorhombic space group *Pnma* (D_{2h}^{16}) (with the *a*-axis and the *b*-axis interchanged). The systematic absences $00l$ for l odd and $hk0$ for k odd indicate a screw axis parallel to [001] and a glide plane parallel to (001) with translation $b/2$. This corresponds to the space group $P2_1/b(C_{2h}^5)$.

POSSIBLE ISOMERIC STRUCTURES

Six possible diastereo-isomers of squalene hexahydrochloride, four D,L-forms and two *meso*-forms, may be anticipated from the disposition of the chlorine atoms and methyl groups. These six possible isomers may be visualized schematically in the following way:



To the left are given the sequences of the four *asymmetric* orientations, to the right the resulting orientations in the crystal lattice. The horisontal line represents the approximate "plane" of the folded carbon zig-zag chain, which will fit with the length of the unit cell axis (*a*) and which has been shown by Bunn and Garner [3] to exist in the structure of rubber hydrochloride in crystalline form. The chlorine atoms will then have to lie either above or below this "plane".

THE DETERMINATION OF THE STRUCTURES

The Weissenberg photographs of the equatorial layer lines around the principal axes of the crystals show fairly sharp and well-defined reflexions, especially the $h00$-reflexions, for which even orders until the 62nd are observed. Most of the $hk0$-reflexions are very weak, and only very small differences are observed between the intensities for the h.m. form and the l.m.form. The glide plane of symmetry implies that the x-coordinates for corresponding atoms of molecules, lying beside each other in the *b*-axis direction, are the same. This means that a fairly good resolution of the electron density variation might be expected in a Fourier projection on the crystallographic *a*-axis direction. Clear differences in intensities might probably be expected first for the hkl-reflexions. These, however,

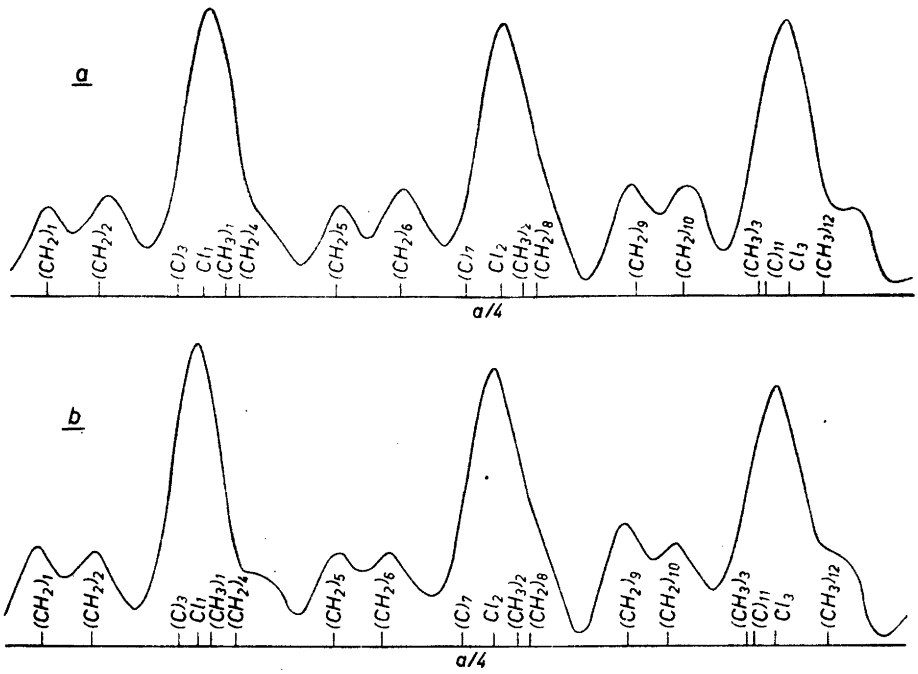


Fig. 1. Projections of electron density on [100] *a) for the higher melting form, b) for the lower melting form of squalene hexahydrochloride. Atomic co-ordinates, as derived by the method of least squares, are indicated.*

would in an ordinary Weissenberg photograph with Cu$K\alpha$ radiation be separated only by about 0.5 mm, and it was in fact found that the reflexions on higher levels are smeared out into lines, making the determinaticn of intensities difficult and uncertain.

In this position it was found that the best way of attacking these structures would be to obtain a maximum of informations from one-dimensional projections of electron densities on [100]. The intensities of the $h00$-reflexions were estimated visually, using a graduated intensity scale of reflexions with approximately the same size and form as those to be determined. The reading of the intensities were repeated five times on different photographs, and corrected in the usual way, the absorption error being neglected since the crystals used were very small (0.1—0.2 mm).

The successive determinations of the signs for the $h00$-reflexions, by means of a direct method to be described elsewhere, led to the projections of electron densities on the long axis for the h.m. form and the l.m. form as shown in Fig. 1. Differences in structure for the two forms could hardly be deduced from these projections, because of the strong overlapping of the densities for the chlorine atoms and the nearest carbon atoms. The carbon skeleton of the chain and the positions of the chlorine atoms and methyl groups were, however, at once evident from these projections. In order to bring out some possible differences between the structures of the two forms, and possibly also a decision for one or the other of the 6 isomeric structures discussed above, both series of x-coordinates were subjected to repeated least squares refinements. This treatment brought out some conspicuous differences in the projected bond lengths, especially for the C—C-bonds on the central sides of the asymmetric carbon atoms. The final x-coordinates and the projections of the bond lengths along the carbon chain are set out in Table 1. The observed and calculated structure factors are listed for both forms in Table 2. The reliability index is 0.126 for the h.m. form and 0.115 for the l.m. form.

THE STRUCTURE OF THE SQUALENE HEXAHYDROCHLORIDES

In order to reconstruct the skeleton of the carbon chain from the knowledge of the projected C—C distances it was necessary to make the assumption of 1.54 Å for the C—C bond length. This value may, however, be considered as very well established and there should be no reason to expect any remarkable deviation from this value in the present case. Secondly, the assumption of 114° for the angle between the bond directions at the chain carbons was preliminarily introduced. In the course of the calculation this value can be corrected, and it was found that the present data would suggest a value of about 115° for the bond angles, with the exception of those at the tetrasubstituted carbons, for which values of 108—109° would fit better with the present observations. The angle ε between a C—C bond and the a-axis direction is calculated for both forms and may be found in Table 1.

There might be some doubt as to the sequence of chain carbons and methyl groups in the projection, for example, whether the fourth or the fifth carbon should be ascribed to the methyl group. If, however, the fifth one were assumed to be the methyl group, the fourth one being a chain carbon, the projection of the C—C bond length of the chain would be 1.73 Å for the h.m. form and 1.93 for the l.m. form, whereas the same projected bond lengths come out to be 1.52 Å and 1.54 Å, respectively, if the fourth carbon belongs to the methyl group and the fifth to the chain. It seems justified to consider these data as a decisive proof of the sequence —C*—Cl—CH_3—CH_2— in the projection, and a similar argument indicates the same sequence at the second

Table 1. Atomic co-ordinates (Θ_1) in degrees, projected bond-lengths on the a*-axis in Å, and angle between bond and* a*-axis for the squalene hexahydrochloride isomers. The middle point of a molecule has been chosen as origin.*

Atom or group	Θ_1 in degrees		Chain carbon distance	Projected bond-length (P_x) in Å		Angle (ε) between bond and a-axis	
	h.m. form	l.m. form		h.m. form	l.m. form	h.m. form	l.m. form
Cl_1	38.7	38.6	$C\bar{l}-C_1$	1.19	1.16	39°	41°
Cl_2	97.7	97.8	C_1-C_2	0.82	0.79	58	59
Cl_3	154.3	154.5	C_2-C_3	1.22	1.38	*37*	*26*
$(CH_2)_1$	7.6	7.4	C_3-C_4	0.97	0.83	51	57
$(CH_2)_2$	18.0	17.5	C_4-C_5	1.53	1.53	·0	0
$(C)_3$	33.5	35.1	C_5-C_6	0.98	0.77	50	60
$(CH_2)_4$	45.8	46.6	C_6-C_7	1.05	1.24	*47*	*36*
$(CH_2)_5$	65.2	66.0	C_7-C_8	1.10	1.05	44	47
$(CH_2)_6$	77.7	75.8	C_8-C_9	1.52	1.54	~0	0
$(C)_7$	91.1	91.6	C_9-C_{10}	0.72	0.65	62	65
$(CH_2)_8$	105.0	105.0	$C_{10}-C_{11}$	1.31	1.34	31	29
$(CH_2)_9$	124.3	124.5	$C_{11}-C_{12}$	0.90	1.12	54	43
$(CH_2)_{10}$	133.4	132.8					
$(C)_{11}$	150.1	149.8					
$(CH_3)_{12}$	161.6	164.3					
$(CH_3)_1$	43.3	41.4					
$(CH_3)_2$	102.2	102.7					
$(CH_3)_3$	148.9	148.1					

tetrasubstituted carbon. Stereochemical considerations will also show that the chlorine atoms and the methyl groups must be connected to the third, eighth and fourteenth carbons of the projection, because the deviations from a planar zig-zag carbon chain are found at these carbon atoms (see below). Furthermore, it is seen that the chlorine atom connected to a tetrasubstituted carbon for both forms, lies closer to the carbon in the projection, than does the methyl group connected to the same carbon.

The structures which emerge from the data given in Table 1 may be described as follows: The four carbons, constituting the central part of the molecule, lie approximately in a plane, which makes an angle of about 40° with the chain direction (*a*-axis), this angle being larger for the l.m. form than for the h.m. form. From the two asymmetric carbons, towards the ends of the molecule, there extend planar groups of four carbons, the planes of these groups being parallel to the *a*-axis. The bonds from the asymmetric carbons, towards the central side, linking the planar groups together, are tilted an angle (ε) of about 30—40° away from the planes of these groups, these angles being appreciably larger for the h.m. form than for the l.m. form. (Strictly ε denotes the angle between a C—C bond and the *a*-axis, but since the planes of the planar groups in question are approximately parallel to the *a*-axis, ε will also approximately indicate the tilting of these bonds with respect to the planar groups). This difference in the tilting of the bonds, linking the planar 4 C-groups together, is the only feature which clearly discriminates between the structures of the two isomeric forms. The result is a more pronounced folding of the carbon chain for the h.m. form than for the l.m. form.

The folding of the chain at each tetrasubstituted carbon atom may be necessary to provide place for the methyl group and chlorine atom, and from molecular models it may also seem likely that the non-planar structure here is mainly due to repulsion between CH_2-groups of the chain.

Only two models can be derived such that they satisfy the requirements of the present observations. First, the bond on the central side of both asymmetric carbons are tilted in the same direction away from the planes of the planar 4 C-groups, the chlorines Cl_1 and Cl_2 must be on the same side of the chain in order to appear on the central side of the methyl group in the projection. Secondly, if these bonds are tilted in opposite direction, the chlorines must, for the same reason, lie on opposite sides of the chain (the argument is, in both cases, based on the assumption of an approximately tetrahedral arrangement of bonds from the asymmetric carbons).

The two structures, which result from these considerations, are indicated in Fig. 2, and may be seen to correspond to models Nos. 4 and 6, *i. e.*, the two *meso*-forms of the six possible diastereoisomers. The other models would correspond to asymmetric molecules, which would give rise to odd orders of the $h00$-reflexions, provided they would be strong enough to be observed. The structure factors F_{h00} are, however, very sensitive to an all over displacement of the atoms. The absence of odd orders of $h00$, therefore, speaks clearly in favour of the two symmetric forms Nos. 4 and 6 above, and consideration of the packing of the molecules points in the same direction. The projection of electron density on [100] can, of course, give no information about the orientation of the molecules around this axis. The packing of the molecules, as well

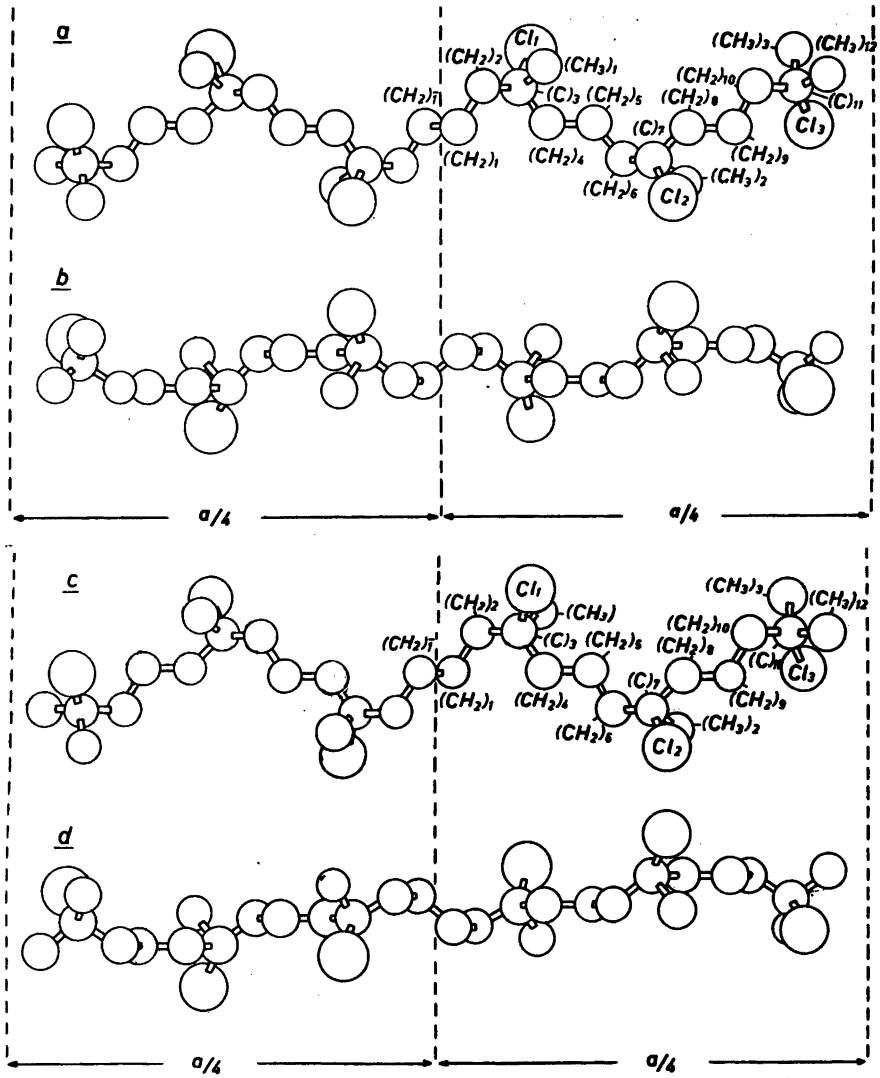


Fig. 2. Molecular structure models for the two crystalline isomers of squalene hexahydrochloride, a) and b) for the higher melting form, c) and d) for the lower melting form. In a) and c) the molecules are viewed along the c*-axis direction, in b) and d) along the* b*-axis direction.*

as comparison with the apparently closely related structure of rubber hydrochloride [3] would suggest that the main plane of the molecule is approximately parallel to the (001)-plane, which implies that the C—Cl-bonds and the C—CH_3-bonds are mainly pointing in the direction of the *c*-axis of the crystal.

As to the orientation of the arrangement around the end tetrasubstituted carbons, this could hardly be deduced with certainty from the obtained pro-

Table 2. Observed and calculated structure factors for the higher melting form and the lower melting form of squalene hexahydrochloride.

*h*00 *	H.m. form		L.m. form	
	$F_{obs.}$	$F_{calc.}$	$F_{obs.}$	$F_{calc.}$
1 0 0	—	−8	—	−9
2 0 0	24	−25	24	−24
3 0 0	—	3	9	4
4 0 0	44	−44	46	−44
5 0 0	45	−53	49	−55
6 0 0	181	−180	163	−166
7 0 0	121	139	125	132
8 0 0	14	13	15	15
9 0 0	54	49	54	47
10 0 0	18	27	25	36
11 0 0	80	71	92	76
12 0 0	32	−14	36	−29
13 0 0	167	−158	168	−164
14 0 0	27	25	16	14
15 0 0	31	−37	33	−32
16 0 0	28	−13	35	−24
17 0 0	22	17	13	13
18 0 0	45	45	44	41
19 0 0	65	56	55	65
20 0 0	40	−46	15	20
21 0 0	14	15	15	17
22 0 0	16	−12	15	−12
23 0 0	12	−12	22	−25
24 0 0	14	−17	28	−30
25 0 0	52	−43	51	−43
26 0 0	15	18	26	23
27 0 0	—	−11	—	−17
28 0 0	—	7	22	29
29 0 0	—	4	—	11
30 0 0	—	9	—	3
31 0 0	35	−42	32	−42

* Strictly, these indices should be doubled.

jections, especially because the arrangement apparently deviates considerably from a regular one. The obtained projections indicate, however, that the end groups could not possibly have a similar orientation as the groups around the other tetrasubstituted carbons, but more likely be turned about 90° away from these orientations; *i. e.*, about 90° around the single C—C bond on the central side of the end tetrasubstituted carbon (see Fig. 2). The direction of the tilting of this bond cannot be derived unequivocally from the one-dimensional projection, but considering the all over directions of these very long chain molecules, the directions indicated in Fig. 2 may reasonably be assumed as the most likely ones.

The question now remains as to which of these structures should be ascribed to the h.m. form and which to the l.m. form. It may then be seen from Fig. 2 that structure model No. 6 has the bonds, connecting the planar 4 C-groups, tilted in the same direction, which implies that the molecule will lie somewhat inclined to the *a*-axis in the crystal. This inclination of the molecules is likely

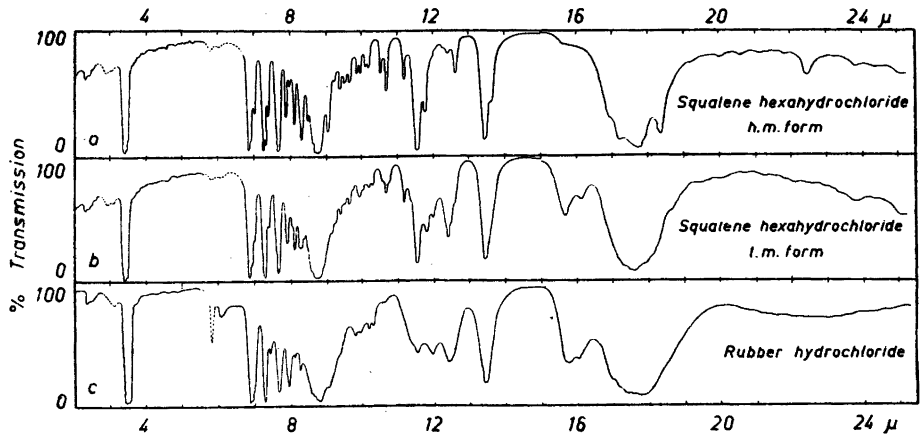


Fig. 3. Infrared absorption spectra from 2—15 μ (NaCl-prism) and from 15—25 μ (KBr-prism) of a) h.m. and b) l.m. squalene hexahydrochloride as pressed KBr-disks and of c) commercial rubber hydrochloride film containing 29 % Cl, or 85 % of the theoretical value.

to reduce the tightness of packing and put a restriction on the deviation from a planar structure. Considering the values of the angle ε in Table 1 for the bonds C_2—C_3 and C_6—C_7, which are 26° and 36° for the l.m. form, against 37° and 47° for the h.m. form, it may be reasonable to suggest that the l.m. form has a structure, corresponding to model No. 6, indicated in Fig. 2 c and d. In structure model No. 4, (Fig. 2) the bonds between planar 4 C-groups are tilted in alternating directions, leaving the main direction of the molecule parallel to the crystallographic *a*-axis. Thus, no strong restriction on the inclination of these bonds is present for this case, and it is likely that the h.m. form has the molecular structure indicated in Fig. 2 a and b. The study of the infrared absorption spectra seems to support this point of view (See next section).

INFRARED ABSORPTION SPECTRA

The infrared absorption spectra of the two squalene hexahydrochlorides are shown in Fig. 3. They were recorded in a Perkin-Elmer double beam instrument, Model 21, as pressed potassium bromide disks. As might be expected the two spectra are rather similar. The most conspicuous differences are the bands at 9.05 μ, 12.6 μ, 18.35 μ and 22.5 μ, present in the h.m. form but absent in the l.m. form, and the bands at 12.4 μ and around 16 μ (15.7 and 16.1 μ) present in the l.m. form but absent in the h.m. form. That these differences are mainly due to differences in crystal structures, is shown by the fact that solutions and undercooled melts give practically identical spectra; thus, the h.m. form most strikingly loses its bands at 18.35 and 22.5 μ and develops a band at around 16 μ. The non-crystallizing mother liquor also gives roughly the same spectrum.

It may be noted that the broad band at 17—18 μ, which is due to the C—Cl stretching vibration and agrees very well with the value 570 cm^{-1} found for *tert*-butylchloride and *tert*-amylchloride [4, 5], and the band (or band group) at 8.5—9 μ, which are the two most prominent bands in both spectra, show more detail in the h.m. form than in the l.m. form. Incidentally, the frequency of the band group at 8.5—9 μ is just twice that of the C—Cl stretching frequency. No overtone is involved, however, since the same strong band is present also in the spectra of the squalene hexahydrobromides.

For comparison the spectrum of a commercial sample of rubber hydrochloride has been recorded (as film) and included in Fig. 3. It is evident that it resembles the l.m. form much more than the h.m. form, although, of course, many details occurring in the squalene hexahydrochloride spectra are lacking in that of rubber hydrochloride. This is taken as a confirmation of the result of the structure determination, indicating that the general shape of the l.m. form, *i. e.* with the chlorines of each half on the same side, is more similar to rubber hydrochloride than is the h.m. form, where the chlorines are alternately on opposite sides and to a greater extent are surrounded by chlorine atoms of neighbouring molecules. The molecules of the h.m. form so to say fit into each other like cog-wheel teeth, and one would expect greater van der Waals forces between molecules, as actually evidenced by tighter packing, higher melting point, lower solubility and thinner plates of the crystals.

DISCUSSION

The present structure determinations of the isomers of squalene hexahydrochloride have been worked out on the basis of a relatively limited amount of experimental data. A two-dimensional projection of electron density on, for example, (001) would possibly give more definite informations, provided that all signs of the numerous weak reflections were obtained with certainty, a task which would involve a vast amount of calculation, and even considerably more if a three-dimensional synthesis were intended. It is reasonable to believe that the intensities of the *h*00 reflexions are fairly accurate, and the method used in deriving the projection of electron density on [100] involved no assumptions as to the structure in beforehand. The present structure determination, therefore, constitutes a direct and completely independent proof of the accepted structure of the carbon skeleton of the squalene molecule. As to the type and location of the double bonds it can only be said from this work that they have to involve the substituted carbon atoms.

The characteristic feature of planar segments of four carbon atoms in the chain connected by C—C bonds at angles of 30—40° is reminiscent of the structures proposed for rubber and β-guttapercha (*cf.* Bunn [6] and Jeffrey [7]) and established in geranylamine hydrochloride by Jeffrey [8]. In these cases the planar isoprene groups are necessitated by the double bond in the middle of each group, whereas the planar groups in the squalene hexahydrochlorides are displaced two carbons along the saturated chain. Molecular models show clearly that the reason for these tilted bonds between planar 4 C-groups is the same in all cases; *viz.* a consequence of steric repulsions between CH_2, CH_3 and CH groups in the former case, and chiefly between CH_2 groups in the latter case. The same structural features are, therefore, to be expected in rubber hydrochloride, in particular since the structure proposed by Bunn and Garner demands unusually large distortions of the tetrahedral arrangement around the substituted carbons (*cf.* the criticism advanced by Jeffrey [7]).

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