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A Re-investigation of the Crystal Structure of Choline Chloride

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The crystal structure of choline chloride, $Cl^-[(CH_3)_3NCH_2CH_2OH]^+$, has been refined with three-dimensional X-ray intensity data from an automatic diffractometer. The positions of all atoms including the hydrogen atoms have been located and refined to a final *R* index of 4·8%; using anisotropic thermal vibration parameters for all atoms except the hydrogen atoms. All bond lengths, interatomic distances and bond angles have normal values, except for the N–C(4) and the C(4)–C(5) bond, which have been determined as 1·559 and 1·461 Å respectively.

Introduction

The crystal and molecular structure of choline chloride, $Cl^-[(CH_3)_3NCH_2CH_2OH]^+$, was first investigated by Senko & Templeton (1960), referred to hereafter as ST. At that time one of us (HS) had collected three-dimensional intensity data for choline chloride in connexion with a research project on choline-like structures. As ST found some anomalous bonds, in particular an exceptionally long bond (1·60 Å) between the tertiary nitrogen atom and the nearest carbon atom in the chain N–C(4), we found it worth while to carry out a refinement based on our intensity data, which comprised more than twice as many reflexions as the data set used by ST.

Experimental

Our first data set, which was obtained from Weissenberg multiple-film photographs, taken with Ni-filtered Cu $K\alpha$ radiation and using visual estimation of the intensities, comprised 565 observed reflexions as compared with 282 reflexions observed by ST. As choline chloride is sensitive to radiation a short exposure to X-rays would be an advantage. Our data set has, therefore, later been remeasured by the aid of an automatic Picker Nuclear FACS-1 diffractometer, using Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å) and the $\theta/2\theta$ scanning mode. Since choline chloride is very hygroscopic the crystal had to be mounted in a glass capillary. The crystal used for the diffractometer measurements was egg-shaped with a length of 0·37 mm (in the direction of the crystallographic *c* axis) and having a diameter of approximately 0·25 mm.

The cell dimensions determined by least-squares refinement of diffractometer data are $a = 11{\cdot}210 \pm 0{\cdot}003$, $b = 11{\cdot}589 \pm 0{\cdot}003$, $c = 5{\cdot}901 \pm 0{\cdot}002$ Å. The space group is $P2_12_12_1$ with $Z = 4$ as determined by ST.

All the 644 reflexions having a 2θ value below 115° were measured, using a 2·5° scan at a scanning speed of $1°.\text{min}^{-1}$ and background measurements of 20 seconds at both sides. The 143 and 610 reflexions were used as standards and were measured after every 20 reflexions. The intensities of the standard reflexions were gradually reduced to 39·1 and 42·2%, respectively, after 35 hours used for the collection of the complete data set. The observed reflexions were brought back on a common scale by using the sum of the intensities of the two standard reflexions as a standard and interpolating linearly between the standard measurements. The axis of the capillary was mounted parallel to the Eulerian φ axis, and the extreme cases of absorption in the capillary wall have been avoided by limiting the measurements to a fairly low 2θ maximum value (115°). The effects of radiation damage could possibly be reduced by using several crystals. The standards did, however, show a very linear and simultaneous decrease on irradiation, with no abrupt changes which would have indicated a sudden breakdown. The use of several crystals would have introduced new problems in scaling the data sets together. The decrease in intensity is too rapid to allow measurements on symmetry related reflexions in order to detect absorption effects. Several crystals were used in recording the photographic intensity data. The agreement between the diffractometer data and the photographic data is in general good, and no systematic deviations between the two series of observed reflexions could be detected.

Refinement of the structure

The refinement described here is based on the diffractometer data. Some results from a refinement based on the photographic intensity data are later given for comparison. The structure was refined by the aid of the full-matrix least-squares program *LSFIV*4 written for the UNIVAC 1107 computer by Borgen & Mestvedt (1966*a*). The function minimized is $\sum w(|F_o| - |F_c|)^2$ where $w = 1$. No weighting was used as we considered a scheme based solely on the counting errors to be of doubtful value since absorption and other systematic errors are likely to be of the same or greater magnitude, though being very difficult to assess. ST's results for the atomic coordinates were used as starting values, and a few cycles of refinement with anisotropic vibration parameters for all atoms, except the hydrogen atoms, brought the *R* index down to a value of 7·9%

($R=\sum||F_o|-|F_c||/\sum|F_o|$). At this stage a difference map was calculated and this map gave the positions of all the hydrogen atoms as maxima of heights 0·26–0·50 e.Å^{-3} except for the hydrogen atom belonging to the hydroxyl group. One of the hydrogen atoms, H(51), bonded to the C(5) carbon atom shifted during the refinement to an evidently false position at a distance of about 1·7 Å from the C(5) carbon atom. The H(51) hydrogen atom was therefore fixed in a stereochemically acceptable position and given a vibration parameter of 8 Å^2. At this point 48 weak reflexions with $\sigma(I)>0{\cdot}33\ I$, $\sigma(I)$ being the statistical counting error, were removed. The continued refinement comprising the remaining 596 reflexions gave a final R index of 4·8%. The final value of the R index in a refinement based on the photographic intensity data was 10·4%.

The refined atomic coordinates are shown in Table 1 and the final atomic vibration parameters are given in Table 2. A final difference map did in fact show a peak of height 0·5 e.Å^{-3} at the position into which H(51) would shift on refinement. The heights of other spurious maxima were below 0·15 e.Å^{-3}, but the hydrogen atom of the hydroxyl group could still not be located. The Fourier program *FOUAL*3 written by Borgen & Mestvedt (1966*b*) was used for the calculation of the difference maps. The scattering factor for Cl$^-$ ion was taken from *International Tables for X-ray Crystallography* (1962). The scattering factors for the C, N and the O atoms are those determined by Hanson, Herman, Lea & Skillman (1964). The scattering factor given by Stewart, Davidson & Simpson (1965) was used for the hydrogen atoms.

Complete lists of observed and calculated structure factors may be obtained from the authors.

Table 1. *Final atomic coordinates of choline chloride*

The least-squares standard deviations of the refined parameters are given in parentheses. The first number in the index of a hydrogen atom refers to the number of the carbon atom to which it is bonded.

	x	*y*	*z*
Cl	−0·2204 (1)	0·2288 (1)	0·1645 (3)
O	0·1222 (5)	0·1085 (4)	0·1167 (8)
N	−0·0045 (4)	−0·0037 (4)	0·5575 (8)
C(1)	−0·0529 (6)	−0·0535 (6)	0·3434 (12)
C(2)	−0·0999 (8)	0·0666 (6)	0·6727 (16)
C(3)	0·0284 (7)	−0·1000 (6)	0·7180 (13)
C(4)	0·1156 (7)	0·0603 (7)	0·5140 (14)
C(5)	0·1092 (8)	0·1518 (6)	0·3442 (13)
H(11)	−0·130 (5)	−0·111 (4)	0·412 (10)
H(12)	0·012 (5)	−0·112 (5)	0·266 (11)
H(13)	−0·084 (5)	0·018 (5)	0·247 (9)
H(21)	−0·182 (6)	0·008 (7)	0·695 (16)
H(22)	−0·064 (6)	0·113 (5)	0·810 (13)
H(23)	−0·132 (6)	0·127 (6)	0·577 (13)
H(31)	0·094 (5)	−0·158 (5)	0·630 (11)
H(32)	−0·049 (5)	−0·154 (5)	0·763 (10)
H(33)	0·075 (5)	−0·062 (5)	0·865 (10)
H(41)	0·147 (6)	0·090 (5)	0·681 (12)
H(42)	0·174 (6)	−0·004 (6)	0·415 (13)
H(52)	0·183 (5)	0·198 (5)	0·375 (11)
H(51)	0·030	0·198	0·330

Discussion

The bond lengths and their standard deviations are given in Table 3, and the structure of the choline group is indicated in Fig. 1. It may be seen that the mean value of the three N–C(Me) bond lengths found in this work is 1·502 ± 0·006 Å. This is significantly longer than the value of 1·479 ± 0·005 Å reported by Sutton (1965) for this type of bond, but our value agrees very well with more recent values for the C–N$^+$ bond reported by Singh & Ahmed (1969): 1·509 ± 0·006 Å, and by Hess (1969): 1·502 ± 0·011 Å. The N–C(Me) bond lengths of choline chloride seem therefore to be quite normal. The important and interesting bond in the structure of choline chloride is the N–C(4) bond, C(4) being the first carbon atom of the chain. ST found a value of 1·60 ± 0·03 Å for this bond, whereas a value of 1·559 ± 0·010 Å was found in this work, both values being significantly longer than the normal value. (The refinement based on the film intensity data gave a bond length N–C(4) of 1·53 ± 0·03 Å.) The next bond of the chain, C(4)–C(5), is 1·461 ± 0·012 Å according to the results obtained in this work. ST reported a value of 1·56 ± 0·03 Å for this bond. Now, a value of 1·461 Å is significantly shorter than a normal C–C single bond. Thus, a somewhat lengthened N–C(4) bond appears to have a shortened C(4)–C(5) bond as its counterpart, implying that the latter bond would have to be ascribed a partial double bond character. In order to verify if these anomalous features of the bonds are real or may come out as the result of some special effects on the refinement, noting that anisotropy is especially prominent in the region of the anomalous bonds, we have constrained the position of the C(4) carbon atom so as to give normal values of 1·494 and 1·534 Å for the N–C(4) and the C(4)–C(5) bond lengths respectively. This led to an increase in the R index from 4·8 to 5·7%, showing a difference which must be considered as significant on the 5% level according to Hamilton (1964). The bond lengths given above are therefore likely to be correct. A weak bond N–C(4) may possibly also be indicated by the observation of Tolbert, Adams, Bennett, Hughes, Kirk, Lemmon, Noller, Ostwald & Calvin (1953) that choline chloride decomposes very rapidly to trimethylamine and acetaldehyde on irradiation. The C(5)–O bond length of

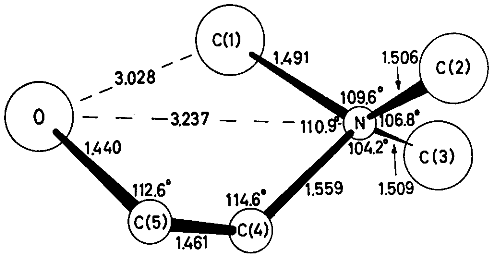

Fig. 1. The structure of the choline molecule in crystals of choline chloride, with interatomic distances and angles.

Table 2. *Final thermal parameters*

(*a*) Final thermal parameters, $\beta_{ij}(\times 10^4)$, for the heavier atoms of choline chloride, where β is defined by $\exp\left[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})\right]$

Standard deviations appear in parentheses.

	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl	87 (1)	68 (1)	317 (5)	9 (1)	−12 (3)	16 (2)
O	128 (5)	98 (4)	269 (15)	−32 (4)	17 (7)	−8 (7)
N	99 (5)	68 (4)	231 (14)	−13 (4)	19 (8)	−16 (7)
C(1)	119 (7)	80 (5)	242 (19)	−25 (6)	−8 (13)	−30 (11)
C(2)	163 (10)	83 (6)	355 (26)	51 (6)	22 (17)	−10 (13)
C(3)	113 (7)	84 (6)	338 (26)	4 (6)	10 (13)	13 (11)
C(4)	127 (8)	114 (8)	392 (28)	−40 (7)	−22 (14)	13 (13)
C(5)	197 (11)	120 (8)	265 (22)	−74 (8)	5 (17)	11 (13)

(*b*) Final thermal parameters of the hydrogen atoms in choline chloride

Standard deviation for the refined parameters are given in parentheses.

	B		*B*
H(11)	5·0 (1·4) Å²	H(31)	5·9 (1·6) Å²
H(12)	5·2 (1·5)	H(32)	5·1 (1·5)
H(13)	4 4 (1 4)	H(33)	4·4 (1·3)
H(21)	10·6 (2·4)	H(41)	6·2 (1·7)
H(22)	6·5 (1·8)	H(42)	9·9 (2·1)
		H(52)	5·2 (1·6)
H(23)	7·9 (2·1)	H(51)	8·0

1·440 ± 0·010 Å is quite normal for a paraffinic C–O bond. The C–H bond distances, which may be found in Table 3, show some fluctuations, but must be considered to lie within reasonable limits. The distances from the oxygen atom to the nearest methyl carbon and to the nitrogen atom come out as 3·028 and 3·237 Å as compared with 3·07 and 3·26 Å found by ST. The bond angles are given in Table 4. It may be seen that all values of the bond angles from the N atom are reasonably close to the tetrahedral angle. The bond angles found in the chain have both normal values. Interatomic distances from the Cl⁻ ion and intermolecular distances found in this work do not differ significantly from the values reported by ST.

Table 3. *Bond lengths of choline chloride*

Standard deviations ($\times 10^3$) of bonds between the heavier atoms appear in parentheses. E.s.d.'s for the bonds with hydrogen atoms are 0·08 Å.

	This work	Senko & Tempelton (1960)
N——C(1)	1·491 (9)	1·53 (3)
N——C(2)	1·506 (10)	1·52 (3)
N——C(3)	1·509 (9)	1·50 (3)
N——C(4)	1·559 (10)	1·60 (3)
C(4)–C(5)	1·461 (12)	1·56 (3)
C(5)–O	1·440 (10)	1·39 (3)
Cl——O	3·070 (6)	3·03 (2)
C(1)–O	3·028 (9)	
N——O	3·237 (10)	
C(1)–H(11)	1·04	
C(1)–H(12)	1·00	
C(1)–H(13)	1·09	
C(2)–H(21)	1·15	
C(2)–H(22)	1·05	
C(2)–H(23)	0·97	
C(3)–H(31)	1·12	
C(3)–H(32)	1·10	
C(3)–H(33)	1·10	
C(4)–H(41)	1·10	
C(4)–H(42)	1·09	
C(5)–H(51)	1·04	
C(5)–H(52)	1·00	
Mean C–H:	1·07	

Table 4. *Bond angles in the structure of choline chloride*

E.s.d.'s are 0·4°.

C(1)–N–C(2)	109·6°	N——C(4)–C(5)	114·6
C(3)–N–C(2)	106·8	C(4)–C(5)–O	112·6
C(4)–N–C(3)	104·2		
C(4)–N–C(2)	115·2		
C(4)–N–C(1)	110·9		

Structure determinations of several choline derivatives have been reported in the literature (see Chothia & Pauling, 1969, and references cited therein). The reported bond lengths vary widely, however, and no clear conlusions can be drawn from a comparison. The other features of the choline-like structures have been extensively discussed by Pauling (1968), who has related the structure of cholinergic molecules to their physiological activity.

The intensity data used in this work was obtained by the aid of the diffractometer at The Crystallography Group, Institute of Medical Biochemistry, University of Göteborg. Our thanks are due to Professor S. Abrahamson for placing this equipment at our disposal and to Dr S. Aleby for giving help and instructions while one of us (JH) was staying at this Institute.

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The Structure of α-Lactose Monohydrate

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α-Lactose monohydrate, $C_{12}H_{22}O_{11}.H_2O$, is monoclinic with $a=7{\cdot}815$, $b=21{\cdot}567$, $c=4{\cdot}844$ Å, $\beta=106{\cdot}2°$. The structure has been found by Patterson methods and refined to an *R* value of 15%. There is one intramolecular O–O distance of 2·82 Å and there are no less than sixteen hydrogen bonds linking one lactose molecule to its neighbours in the crystal.

Introduction

We have now completed work on the crystal structure of α-lactose monohydrate, $C_{12}H_{22}O_{11}.H_2O$. Lactose occurs in the milk of mammals and in the pollen of the Forsythia plant. It is a reducing sugar which hydrolyses into equal quantities of glucose and galactose. In the α form it can be more completely described as α-4-(β-D-galactopyranosido)-D-glucopyranose. The molecule thus contains two six-membered rings with a 1,4 linkage and its conformation and numbering are shown in Fig. 1. X-ray photography was carried out with a Weissenberg camera of 10 cm diameter using normal-beam methods with copper *Kα* radiation from a Raymax continuously evacuated tube. One crystal of dimensions about 0·8 mm was used for all photographs. Layers 0–3 were photographed about the *a* axis, 0–10 about the *b* axis, and 0–2 about the *c* axis.

Crystal data

The 0*k*0 reflexions were absent for *k* odd. Since the molecules are optically active in solution they are likely to be of the one form and thus the space group must be $P2_1$. Crystal system: Monoclinic, $a=7{\cdot}815$ $b=21{\cdot}567$ $c=4{\cdot}844$ Å, $\beta=106{\cdot}2°$. It is thought that these dimensions are correct to ±0·2% and the angle to 0·2°. The values in Groth (1910) are not considered to be very accurate. Our values were obtained by extrapolation of high order spots. $D_x=1{\cdot}52$, $D_m=1{\cdot}53$ g.cm^{-3}, cell contents $2(C_{12}H_{22}O_{11}.H_2O)$.

Determination of the structure

The intensities of the reflexions were estimated visually, corrected for Lorentz and polarization factors, and all brought to a common scale. 1379 intensities were collected in all. Patterson projections were computed using a procedure to sharpen the peaks to 'point atoms at rest' and a three-dimensional sharpened Patterson map was also calculated. A model was made of the value of the function on the surface of a sphere of radius 2·5 Å, this vector distance being of special importance in the sugars (Beevers & Ehrlich, 1959). Having decided on the vectors for each ring it was possible to build up the molecule with the correct orientation. The position of this molecule in the cell was found by consideration of the Harker section at $y=\frac{1}{2}$. Taking chance peaks into account as well as the true Harker peaks a trial structure was found which had one atom

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