

Crystal and Molecular Structure of 1-Azabicyclo[3.2.0]heptane-1-methyl Chloride

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The structure of the compound, 1-azabicyclo[3.2.0]heptane-1-methyl chloride has been determined by a single crystal x-ray diffraction study. The compound crystallizes in space group C_{mcm} with four formula weights in a unit cell of dimensions $a = 8.53$, $b = 10.30$, $c = 9.27 \pm .01$ Å. The molecular cations fit in large holes between the chloride anions and consequently are disordered about the cation positions. The five-membered ring portion is non-planar and bears a strong resemblance to other five-membered rings in bicyclic-fused compounds. The azetidine portion of the molecule is planar. The basic fused ring structure is contrasted to that found in penicillin salts. A final value of $R = 0.10_6$ for the 305 independent reflections was obtained.

INTRODUCTION

Azetidine in the form of various derivatives was first synthesized in the nineteenth century (1) and remained a laboratory curiosity for over fifty years. Interest in bicyclic derivatives of this compound was stimulated by the discovery (2) that penicillin contained azetidine in the form of a β -lactam ring in a bicyclic fusion. Cephalosporin C (3) was later found to also contain a β -lactam ring and then the possibility of azetidine or aziridine compounds acting as alkylating agents in the fight against cancer (4) aroused even greater interest in these compounds.

The molecular parameters obtained in the penicillin and cephalosporin C studies remained the only such measured quantities for an azetidine system for nineteen years. In 1968, molecular parameters for an unfused azetidinium salt (5) were first reported, followed almost immediately by a study of a simple azetidine-2-carboxylic acid derivative (6). The compound to be discussed in this study (I) represents the first fused-ring structure study of

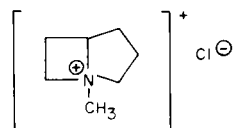
This compound itself is of some pharmacological interest having already been tested as a hypotensive and ganglionic blocking agent (7). Additionally, such a study should be useful in resolving some of the anomalies which exist in the comparison of molecular parameters of unfused azetidine systems (5,6) and those of the more complicated antibiotics (2,3).

EXPERIMENTAL

Crystallographic Data.

Samples of the compound were kindly furnished to us by A. Ebnoether of Sandoz Limited. The crystals of this compound were extremely hygroscopic so all work on them was done in a dry nitrogen atmosphere. Crystals were recovered from acetonitrile and mounted in thin-walled glass capillaries. The best one of these crystals was selected for use in this study.

Intensity data were collected using a Buerger precession camera with filtered $Mo-K_{\alpha}$ radiation. Owing to the difficulties in trying to orient a crystal in a capillary we were able to collect data down only one proper crystallographic axis. This data was taken for the zero and first four levels about the (001) axis. This was supplemented by data from the $(h, 3h - 2n, \ell)$ zones where $n = 0-6$, and finally the $(h, 3h - 4\ell, \ell)$ zero level. Systematic absences for $h + k$ odd for all data and ℓ odd in the $(h0\ell)$ zone indicated that the compound had crystallized in one of



an azetidine ring in which it does not exist as a β -lactam ring and in which the only heteroatom in the fused system is the nitrogen.

three space groups: C_{mcm} , C_{mc2_1} , or C_{2cm} (8).

The orthorhombic cell dimensions were measured as being $a = 8.53$, $b = 10.30$ and $c = 9.27 \pm .01$ Å. The crystal density measured by flotation techniques was 1.17 ± 0.3 g. per c.c. which compared favorably to 1.20 g. per c.c. calculated assuming four molecules per unit cell.

The relative intensities were first determined by visually comparing each reflection to a prepared scale. Reflections which were observed but fell below the lowest reading on the scale (about one-third of the total reflections) were given one of three constant values graduated according to estimates as to whether they were just below the minimum value on the scale, barely visible or at a value intermediate between these two. Each group then used a separate scale factor in the refinement to correctly select the constant value which should be applied to that group. Lorentz and polarization corrections were made and the zones were correlated by use of common spots to give a total of 289 independent reflections.

STRUCTURE DETERMINATION

A. The Refinement.

A three-dimensional Patterson map was calculated using the intensity data which had been evaluated visually. This map showed two possible positions for the chlorine, namely the special position $(0, y, \frac{1}{4})$ and a more general position $(0, y, z)$. Since there were three possible space groups and two non-equivalent alternatives in each space group, it was decided to run all six possibilities concurrently. The approach involved calculating the necessary Fourier maps on the basis of the chlorine positions, using these maps to determine additional atomic peaks, then alternating least squares and difference Fourier maps for all six possibilities.

The results beginning with the more general chlorine position $(0, y, z \neq \frac{1}{4})$ were very poor. The R value refinements for the chlorine only began in the range 0.44-0.50 and even after all "atomic positions" were included refined only as low as $R = 0.25$. The use of anisotropic temperature factors failed to lower these values significantly or to improve the models.

The special position for the chlorine $(0, y, \frac{1}{4})$ led to slightly better results. The more promising space groups (C_{2cm} and C_{mcm}) produced models that refined down to values of $R \approx 0.20$ isotropically and $R \approx 0.19$ anisotropically. The models seemed reasonable chemically except that two of the distances remained longer than 1.70 Å.

At this point it was felt that the quantity of data (less than 300 observed structure factors) and the quality of the data (roughly one-third being assigned a minimum value) would continually hamper our efforts to obtain a really satisfactory solution to the problem.

Shortly after this a Nonius integrating microdensitometer became available in the laboratory and it was used to re-evaluate the film data. This allowed us to obtain an actual numerical value for all of the observed reflections. Again, the new data was correlated, Lorentz and polarization corrections applied and the data combined into one set to give a total of 305 independent reflections.

A three-dimensional Patterson map was recalculated using the new values of the observed structure factors. Not surprisingly, this map also indicated the same two unique possibilities for the chlorine position. Significantly, least squares refinement of the chlorine position led to $R = 0.42$ for the general position and $R = 0.41$ for the special position. Thus we were encouraged to proceed again in testing all possibilities.

In those cases where the chlorine was in the more general position (C_{mcm} and C_{2cm}) and where the z-coordinate was origin determining (in C_{mc2_1} the choice

TABLE I

Coordinates and Temperature Factors

	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Chlorine	0.0000	0.1923	0.2500	0.0204	0.0122	0.0173	0.0000	0.0000	0.0000
C 1	0.5378	0.0857	0.2500	0.0356	0.0094	0.0209	0.0060	0.0000	0.0000
C 2	0.4602	0.1485	0.1225	0.0243	0.0113	0.0215	-0.0001	-0.0002	0.0001
C 3	0.6373	0.3619	0.1640	0.0208	0.0121	0.0191	0.0008	-0.0006	-0.0016
C 4	0.3490	0.3780	0.1010	0.0227	0.0481	0.0098	-0.0013	0.0023	-0.0101
CN	0.4750	0.2942	0.1670	0.0266	0.0102	0.0228	-0.0023	0.0016	0.0010

of the z -coordinate of chlorine is arbitrary) the ultimate refinements led to a poorer final result with $R \geq 0.30$. For the chlorine at the special position $(0, y, \frac{1}{4})$ we arrived finally at a model which refined isotropically to $R = 0.16$ in space groups $C_{1mc}2_1$ and C_{2cm} . However, subsequent refinements in these space groups did not improve our results further and a difference map showed several large positive regions corresponding to mirror images of the model. This same model, refined isotropically in space group C_{1mcm} , led to values of $R, r = 0.14, 0.13$ (9) and to the most reasonable chemical structure. Further refinements using anisotropic temperature factors in C_{1mcm} lowered the values of R, r to 0.12, 0.11.

B. The Models.

A section of the Fourier map generated by chlorine at the special position $(0, y, \frac{1}{4})$ in space group C_{1mcm} (10) is illustrated in Figure I. It should be recalled that if the peaks shown are located at values less than $X = \frac{1}{2}$, then an identical map will be generated at values greater than

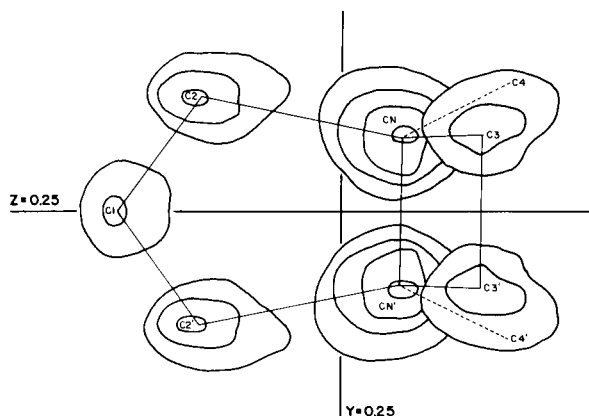


Figure I. Fourier map projected down x -axis based on chlorine phases only. Chlorine omitted for clarity. Each peak shown has a mirror image above (reflected across $X = \frac{1}{2}$). Peaks start at four $e/\text{\AA}^3$. Final structure (with nitrogen-methyl disordered set shown by dotted lines) superimposed for comparative purposes.

$X = \frac{1}{2}$. Thus two peaks corresponding to C_1 are generated at values above and below $X = \frac{1}{2}$. Four peaks are generated equivalent to C_2 (C_2 and its mirror C'_2 across $Z = \frac{1}{2}$; and the mirror images of both peaks across $X = \frac{1}{2}$). Similarly CN, C_3 and C_4 all generate four equivalent positions at the general location of one molecule.

Schematically, all of the peaks in the environment of one molecule are shown in Figure II, Part A, with shaded circles indicating those peaks at values greater than $X = \frac{1}{2}$

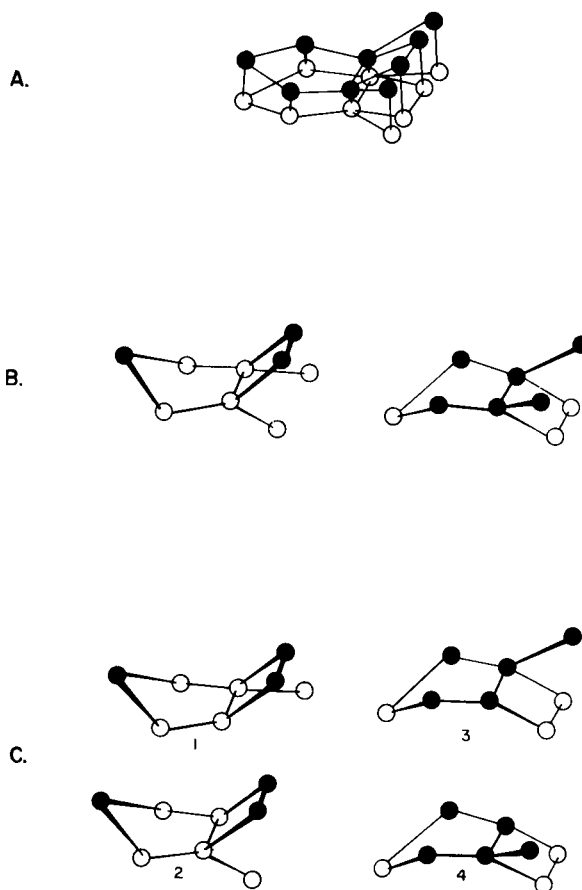


Figure II. A. Schematic drawing of all atomic positions in the vicinity of a molecular cation. Peaks above $X = \frac{1}{2}$ shown by shaded balls, their mirror image counterparts (below $X = \frac{1}{2}$) by unshaded balls. B. Separation of peaks into disordered pair of molecular cations (each containing reasonable bond distances and angles) and related to each other by mirror plane at $X = \frac{1}{2}$. C. Separation of final two isomers in each case, eliminating disordering of CN position (and therefore of methyl group). The superposition of these four models results in peaks observed about each molecular cation position in Fourier map.

and unshaded circles indicating those peaks at values less than $X = \frac{1}{2}$. The problem then arises in connecting the appropriate peaks. For example, starting at C_1 with a value of $X > \frac{1}{2}$, does one proceed to C_2 and C'_2 positions in which both have either $X > \frac{1}{2}$, does one proceed to C_2 and C'_2 positions in which both have either $X > \frac{1}{2}$ or $X < \frac{1}{2}$, or does one of the C_2 atoms have $X < \frac{1}{2}$ and the other $X > \frac{1}{2}$? After this choice, one proceeds to the CN and CN' peaks and must again connect the correct set of peaks.

Section B of Figure II illustrates the only chemically sensible way of interconnecting these peaks. The criteria employed are that C-C bonds will have lengths of 1.5 ± 0.2 Å, angles in the range $100-115^\circ$, etc. It is obvious that even in this case additional disordering exists. Section C of Figure II separates the remaining disordered set.

Since the carbon and nitrogen atoms at the fusion of the two rings occupy equivalent positions, an averaged scattering factor curve ($\frac{f_{C^+} + f_{N^+}}{2}$) was used for the CN peak.

Finally, the multiplicity factor for the methyl carbon must be half as large as that for the other atoms, since it actually appears twice as often in each molecular configuration as its actual multiplicity in the cell would dictate.

The refinement was further complicated because the peaks C_4 and C'_4 on one side of $X = \frac{1}{2}$ very nearly overlapped the mirror images of the C_3 , C'_3 peaks reflected across $X = \frac{1}{2}$. The result of this is that the least squares refinement was incapable by itself of distinguishing between these peaks. To overcome this problem the structure was refined anisotropically by least squares techniques holding the methyl carbon fixed. Then a difference Fourier was calculated omitting the methyl carbon. This map gave a peak which corresponded to an improved methyl position. The new position was held fixed and the process was repeated until no change in the coordinates was observed in the maps. By this time shifts in all other coordinates were less than 0.0001. This model gave R and r values of 0.11 and 0.10. A final difference map was calculated using this model which showed no peaks with height greater than 1.5 electrons per cubic angstroms. This confirmed that the structure was correct and the structure study was considered complete.

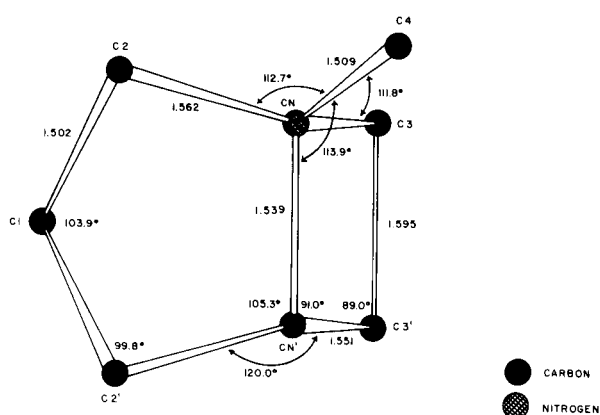


Figure III. Projected view of a single molecular cation with bond distances and bond angles indicated.

RESULTS AND DISCUSSION

Figure III shows a projected view of the molecule with the bond distances and bond angles indicated. Estimated standard deviations for the chlorine are less than 0.004 Å. The estimated standard deviations for the lighter atoms, based on the results of the last cycle of least squares and the gradients observed on difference Fourier maps were less than 0.03 Å for all bond distances and less than 2.5° for all bond angles except those involving the methyl carbon. In the latter case, the E.S.D. were larger, being 0.057 Å for the (CN) - CH_3 distance and 4.7° for the angles involving the methyl carbon. Final coordinates and anisotropic temperature factors in space group C_{2v} are given in Table I.

With the exception of the long $C_3 - C_3$ distance of 1.595 Å, all of the distances are within .035 Å of an averaged bond length of 1.527 Å. Even this longer distance differs by only twice the average deviation from this value. The differences in the various angles are both of geometric and statistical significance and these differences are discussed in detail further on.

Based on geometric considerations ($C-H = 1.10$ Å, $\angle HCH = 109^\circ$, all other angles equally split and near 109°), positions were calculated for all of the hydrogen atoms with the exception of the methyl hydrogens. Figure IV illustrates the molecule with the calculated hydrogen positions and their closest intermolecular contacts. Because of the disordering in the unit cell and the

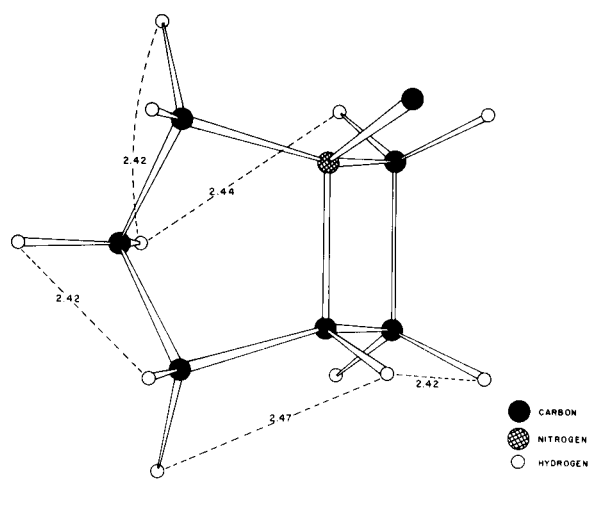


Figure IV. Projected view of a single molecular cation with calculated hydrogen positions shown. Intermolecular hydrogen contact distances less than 2.5 Å indicated.

consequent overlap of peaks and the various mirror images of other peaks, attempts to verify these calculations from a final difference Fourier map were not successful.

Figure V illustrates the contents of the unit cell and shows the closest intra- and inter-molecular contact distances. Only one set of the possible four disordered sets at each molecular position is shown. Reference to Figure II shows the type of disordering which occurs about each molecular position.

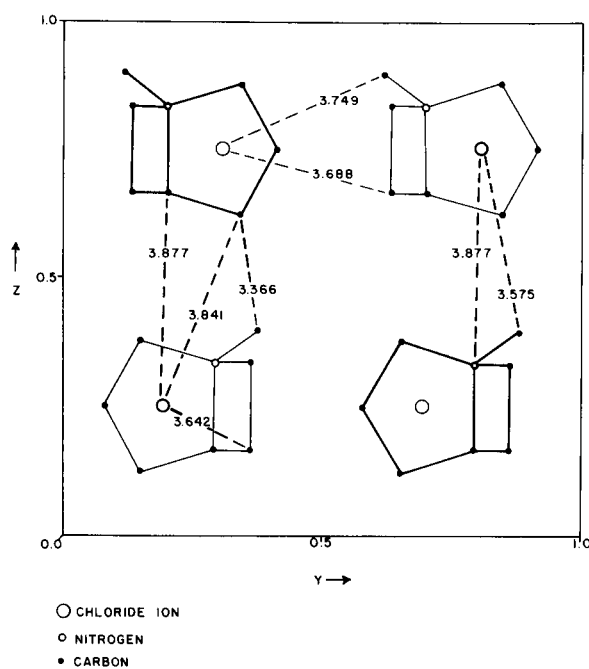


Figure V. Suggested contents of unit cell assuming no disordering. Species chosen so that all C-C distances less than 3.36 Å and all Cl-C distances less than 3.57 Å are omitted. Lack of distortion in molecular cation parameters suggests no close contacts exist.

The five-membered ring part of this molecule is quite distorted from the essentially regular pentagonal, almost planar structure reported for free cyclopentane in an electron diffraction, gas-phase study (11). For example, the non-planarity of the five-membered ring is quite pronounced in this study with the atom C_1 being out of the plane of the remaining four atoms of the ring. The interplanar angle formed by plane C_1, C_2, C'_2 and the plane of the four atoms excluding C_1 is 129.3° . However, if one compares this compound to other bicyclic, fused five-membered rings, a pattern emerges of alternating short and long bond distances and a similar pattern for the bond angles. Figure VI shows the averaged results of two recently completed studies on five-membered rings

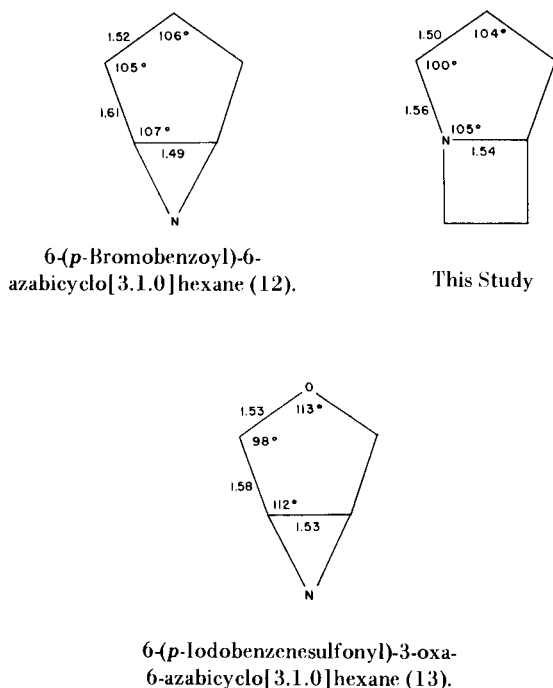


Figure VI. Comparison of this molecule to bicyclic systems in which the smaller ring is an aziridine ring.

fused to an aziridine ring. In one case an aziridine is fused to a cyclopentane ring (12), and in the other case, it is fused to an oxa-cyclopentane ring (13).

One can also compare this compound to the basic ring structure of the penicillin compounds (2) (Figure VII). Because of the great disparity in substituents on the two molecules, the only meaningful comparison would be in the trends observed in the angles. In the azetidine

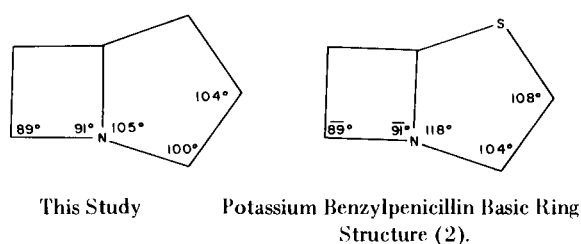


Figure VII. Comparison of this molecule to basic ring structure of penicillin.

portion of the molecule, the averaged value of the angles at the fusion points in penicillin exceed 90° whereas those at the back end of the azetidine ring are less than 90° . The same pattern is obtained in this compound. Similarly,

if one looks at the pattern of angles in the five-membered ring of both compounds, avoiding those angles near the sulfur atom in penicillin, one again perceives this pattern of alternating large and small angles.

In all of these comparisons, the differences are not statistically significant if each angle or distance is compared individually. Yet the same pattern emerges in a comparison of series of such compounds.

Acknowledgments.

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(9) The expressions for the reliability factor (R) and the weighted reliability factor (r) are:

$$R = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|} \quad r = \left[\frac{\sum (wF_o - kF)^2}{\sum wF_o^2} \right]^{1/2}$$

Unit weighting factors were used in refining this structure.

(10) For chlorine only maps, with the chlorine at a special position, the additional symmetry generated made the maps in C_{2cm} identical in all respects to the C_{mcm} maps. Similarly, in C_{mc2_1} the peaks all had the same locations relative to each other but the center of symmetry was not at the origin. Thus the differences in the three space groups did not show up in the maps based on chlorine only. However, when additional atoms were added to the refinement, the maps were no longer identical. For in C_{2cm} the mirror plane at $X = 1/2$ was removed and in C_{mc2_1} the mirror plane at $Z = 1/4$ was removed. If one refers to Figure II, part C, the net effect of this is as follows:

1. C_{mcm} - all four models found at each general molecular position.
 2. C_{2cm} - only models 1 and 2 found at each general molecular position.
 3. C_{mc2_1} - only models 1 and 3 found at each general molecular position.
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