Molecular Packing of the Crystal, N-methyl acetamide *

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Dedicated to Prof. Dr. G. Borrmann on the occasion of his 65th birthday

The molecular packing of the crystal N-methyl acetamide has been studied, taking into account van der Waals and electrostatic interactions, together with the hydrogen bonds between the molecules. Contact criteria were used to obtain the molecular position in the unit cell approximately, which was then refined using the potential energy functions. This involved three position parameters, consisting of two translations and one rotation of the molecule in the $a-c$ plane. The calculated values of these parameters are in reasonable agreement with the observed values in the crystal structure, particularly if hydrogen atoms are included in making the energy calculations.

Introduction

It is well known that the calculation of the potential energy serves as a good means of predicting the probable conformational states of biological molecules. However, there is a wide choice of different potential functions for calculating the potential energy. Recently Ramachandran has pointed out the differences in the shapes of the potential energy curves adopted by workers in this field [1]. Even though none of their predictions differs significantly from the observed conformations of the biological molecules, many attempts are being made to refine the potential parameters based on crystal structure data [2–5]. But how far these refined functions are capable of being applied to different problems is yet to be seen. In fact Scheraga has even pointed out that it may be necessary to use different functions for intra- and inter-molecular interactions [6]. On the other hand, in our first paper on the molecular packing [7] we have concluded that the potential functions used in our laboratory [8] for the conformational analysis could also explain the observed crystal structure of benzene and sulfur dioxide without any modification. In continuation of this study we have chosen another crystal, N-methyl acetamide, whose crystal structure is known [9]. This structure contains hydrogen bonds, and therefore the accuracy and utility of the potential functions for hydrogen bonds proposed by us [10] could be tested in this case.

The crystal and the molecular structure of N-methyl acetamide is of particular importance since it forms a model compound for the studies on polypeptide conformation. The crystal structure of this compound at −35 °C has been reported [9]. The unit cell is orthorhombic with the space group Pnma. The cell edges are $a=9.61$ Å, $b=6.52$ Å and $c=7.24$ Å. The heavy atoms of the molecule occupy special positions and they are arranged in layers at $\frac{1}{4}b$ and $\frac{3}{4}b$. During the X-ray analysis the interesting observation was made that the molecules in a layer were connected to one another by NH ... O hydrogen bonds nearly parallel to the a direction in a zig-zag manner. This is probably responsible for the growth of the crystal along the a axis. Hence the formation of such a hydrogen bond was taken for granted in the present investigation.

Method of Study

The Pauling-Corey dimensions commonly used for the peptide geometry were assumed for the N-methyl acetamide molecule. The methyl groups were assumed to form CH_3 groups and suitable potential functions were used for their interactions with other atoms, as has been done for the calculation of the potential energy for an alanyl dipeptide [11, 8]. Since the molecule is in the mirror plane it has only two translational freedoms, namely the shifts along the a and c axis with respect to a chosen origin. In addition, it has a rotational freedom about an axis parallel to b. There are four ways of orienting the molecule in the $a-c$ plane which are mirror reflections of one another. Since the space group has these mirror (glide) symmetries, it is sufficient to

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consider only one orientation and this arrangement is shown in Figure 1. For convenience the initial position of the molecule is defined such that the molecule is in the $a-c$ plane at $\frac{1}{4}\,b$ with the N(2) – C(4) bond coinciding with the a axis and the origin at the mid-point of the N(2) – C(4) bond. In general, the position of the molecule in the unit cell is defined by three parameters x and z defining the fractional coordinates of the mid-point of the N(2) – C(4) bond with respect to the chosen origin and Θ which defines the clockwise rotation of the molecule about the b axis from the initial orientation. The molecule can be oriented in between the two glide planes at $\frac{1}{4}$ and $\frac{3}{4}$ along a and c directions. Hence x and z can take up values from 0 to 0.5. In general, Θ can vary from 0° to 360°. But because of the space-group symmetry it is sufficient to vary Θ from 0° to 180°. The parameters x and z were varied at intervals of 0.02 and Θ at intervals of 20°.

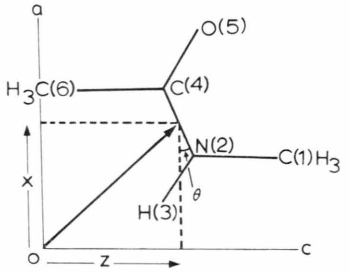

Fig. 1. Definition of the variable parameters (x, z, Θ) representing the location and orientation of the molecule in the unit cell.

Only those molecules whose centres are within a distance of 10 Å from the centre of the molecule at (x, 0.25, z) were considered for calculating interatomic interactions. Accordingly, 37 molecules had to be considered in all. These molecules are arranged in layers at $y = 0.25\,b$, $0.75\,b$ and $1.25\,b$ above and below the $a-c$ plane at $y = 0$. It was found that, because of the symmetry, the interaction between some of these molecules were the same and hence only the interactions of the first molecule listed in Tab. 1 with the others listed in it had to be calculated. The multiplicity factor of each contribution required for calculating the total energy of intermolecular interaction is also given in Table 1.

For each combination of x, z and Θ, the formation of the hydrogen bond (NH ... O) between the first molecule and the others was checked under the condition that the hydrogen-bond length should be within 2.6 – 3.4 Å, the hydrogen-bond angle being less than 35°. If a satisfactory hydrogen bond was formed according to the above criteria, then the nonbonded contact distances were checked whether they were allowed according to the contact criteria of Ramachandran, Ramakrishnan and Sasisekharan[12].

Table 1. The positions of the centres of the molecules considered for the study.

Molecule number	Equivalent positions			Multiplicity factor
1	x	$^1/_4$	z	—
2	$^1/_2+x$	$^1/_4$	$^1/_2-z$	2
3	$1-x$	$^3/_4$	$1-z$	2
4	$^1/_2+x$	$^1/_4$	$^3/_2-z$	2
5	x	$^1/_4$	$1+z$	2
6	$^1/_2-x$	$^3/_4$	$^1/_2+z$	2
7	x	$^5/_4$	z	2
8	$^1/_2-x$	$^3/_4$	$-^1/_2+z$	2
9	$-x$	$^3/_4$	$1-z$	2
10	$-x$	$^3/_4$	$-z$	2
11	$-^1/_2+x$	$^1/_4$	$-^1/_2-z$	2
12	$1-x$	$^3/_4$	$-z$	2
13	$-^1/_2-x$	$^3/_4$	$^1/_2+z$	2
14	$-^1/_2-x$	$^3/_4$	$-^1/_2+z$	2
15	$-^1/_2+x$	$^5/_4$	$^1/_2-z$	4
16	$1+x$	$^5/_4$	$1+z$	2
17	x	$^5/_4$	$1+z$	4

Potential energy calculations were also made using the **6-exp** form of the nonbonded interaction energy and a value of 4 for the effective dielectric constant in the electrostatic energy term[8, 12]. The values of the partial charges were assumed to be the same as given for peptides by Ramachandran and Sasisekharan[8]. Recently Giacommello and Giglio have used the Stockmayer's relation[14] to calculate the hydrogen-bond energy in their packing study of a diketopiperazine[15]. Sikka and Chidambaram have studied the hydrogen-bonded crystal of tetrachlorohydroquinone in which they have used a modified form of the Lippincott-Schroeder function[16]. However, our group has suggested an empirical function for the calculation of the hydrogen-bond energy, which is very easy to calculate, based on a large number of observed data on crystal structures[10]. Their function has the form

$$V_{\mathrm{hb}} = V_{\min} + p_1\,\Delta^2 + p_2\,\Delta^3 + \exp\{p_3\,\Delta\}\ \ (q_1\,\Theta^2 + q_2\,\Theta^3)$$

where $\Delta = R - R_{\min}$ and R and Θ are the hydrogen-bond length and angle respectively. This function was used with the constants $p_1 = 75$, $p_2 = -230$, $p_3 = -5.1$, $q_1 = 0.008$, $q_2 = 0.000165$, $R_{\min} = 2.8$ Å and $V_{\min} = -5$ kcal/mole as given in Reference[10].

Results and Discussion

It was found that only two types of hydrogen bonds were possible, stabilizing the molecules in the crystal. In the first type the oxygen atom of molecule 1 (see Tab. 1) accepts a proton from a molecule whose position relative to the first molecule is obtained by an *a*-glide with translation along the positive *a* direction; in the second type the nitrogen atom of molecule 1 is a donor to the oxygen atom of a molecule which is obtained again by an *a*-glide, but with translation along the negative *a* direction. Only the former type of hydrogen bond is crystallographically independent, since the latter type is obtained from it by simple translation along the *a* axis. It is to be noted that no other type of hydrogen bond was found to be possible, since the other molecules were in different layers, or they are too distant to form the hydrogen bond. Also, since the hydrogen-bonded molecules are related by the *a*-glide, the hydrogen-bond parameters are dependent only on the values of the parameters z and Θ. It was found that this type of hydrogen bond was formed within a wide range of values of Θ, namely, from 0° to 60°, in a large range of z (approximately from 0.14 to 0.36) and in the whole range of x. It was also seen that a large volume was allowed according to the contact criteria in (x, z, Θ)-space for the hydrogen-bonded structures. Hence it was impossible to pick out the stablest structure from these data.

Then the calculation of the total potential energy was performed including the nonbonded, electrostatic and hydrogen-bond energies. The minimum of the energy was found for a value less than 40° and for values of $x \approx 0.16$ and $z \approx 0.3$. The calculations were therefore repeated for a smaller interval of Θ (2°). A section of the energy profile in the $x-z$ plane corresponding to the value of Θ for which the energy has a minimum ($\Theta = 32°$) is shown in Figure 2. The values of the parameters corresponding to the minimum energy position are $\Theta = 32°$, $x = 0.16$ and $z = 0.30$. The corresponding observed values are $\Theta = 39.5°$, $x = 0.12$ and $z = 0.29$. The hydrogen-bond lengths and angle corresponding to the theoretical minimum energy structure of the molecule are 2.82 Å and 0.4° respectively. The hydrogen-bond length observed is 2.82 Å in the crystal structure determination[9]. Since the hydrogen positions have not been located, the hydrogen-bond angle is not given for this structure. The molecules corresponding to the theoretical and observed orientations are shown in Figure 3. The deviation of the calculated position from the observed position of each of the heavy atoms is listed in Table 2. As can be seen the deviation is large for the atom C(6). It is to be noted that in the crystal structure analysis[9] a short methyl-methyl separation of the order of 3.5 Å between the atoms C(1) and C(6), translated along the c axis, has been reported. Looking at Fig. 3 it can be seen that this distance is considerably shorter in the theoretically predicted structure. This might be the reason for the large deviation in the position of the C(6) atom.

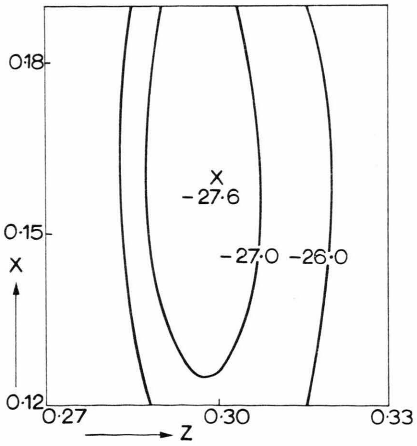

Fig. 2. A section of the energy surface for a value of Θ (= 32°) which corresponds to the minimum energy orientation. The energy values marked are in kcal/mole.

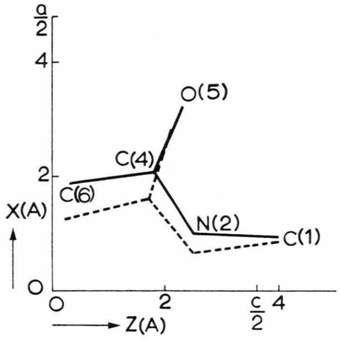

Fig. 3. Arrangement of the atoms in the $a-c$ plane. (———) corresponds to the theoretical calculations and (— — —) to the x-ray structure determination.

An attempt was also made to include the methyl hydrogens in order to see whether it improves the results. At each end of the molecule one hydrogen must be placed in the plane of the molecule; the

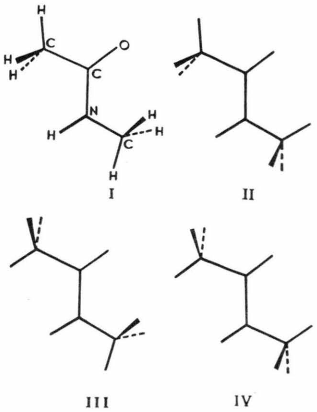

Fig. 4. The four possible ways of orienting the methyl hydrogens. The symbols I, II, III, IV correspond to those used in the text and in Table 3.

Table 2. Distance between the observed and calculated positions of the heavy atoms of the molecule.

Atom	C(1)	N(2)	C(4)	O(5)	C(6)
diviation (Å)	0.09	0.35	0.48	0.48	0.63

Table 3. Minimum energy orientations corresponding to the four models shown in Figure 4.

Model	Minimum energy orientation			
	Θ	x	z	Energy (kcal/mole)
I	35°	0.14	0.29	−40.4
II	30	0.20	0.29	−42.0
III	30	0.12	0.29	−41.1
IV	30	0.18	0.29	−41.3
Observed	39.5	0.12	0.29	—

other two are arranged in such a way that one is the mirror of the other and that they are rotated by +120° and −120° to the one which is in the plane about N(2)−C(1) or C(4)−C(6). There are two possible ways of arranging hydrogens of each methyl group and hence there are four possibilities defining the orientation of the hydrogen atoms which are shown in Figure 4. It is to be noted that only the models I and IV would correspond to an arrangement where the hydrogens C(1) would be interleaved with the hydrogens of C(6) translated along the c axis. For each of the four models, the total potential energy due to inter-molecular interactions, including the hydrogen-bond energy, was computed for the molecular orientations near the minimum energy position obtained from calculations without considering the methyl hydrogens. The parameters corresponding to the minimum energy conformations of the four models are listed in Table 3. As can be seen the agreement between the theory and the observation is good only for the two models I and III. Even though they are energetically favourable the other two models show large deviations in the positional parameters from the observed values. The question of locating the hydrogens by a refinement of the structure from X-ray data is under study.

Acknowledgement

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