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Determination of the Molecular Packing in Diketopiperazine Crystal by means of van der Waals and Hydrogen Bonding Energy Calculations

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The crystal packing of diketopiperazine may be predicted from the approximate molecular geometry and space group symmetry. The van der Waals and hydrogen bonding energies were computed as a function of three rotational degrees of freedom (space group $P2_1/a$ and $Z=2$). The Eulerian angles, relative to the deepest minimum, correspond to a good approximation to the real structure. The calculations were carried out using potential functions tested in some crystals and in the conformational analysis of synthetic and biological macromolecules. A potential function proposed by Stockmayer was chosen to describe the hydrogen bond formation. The rigid-body translations of the molecules in the crystal, known from an analysis of the anisotropic atomic thermal parameters, were qualitatively checked. For this purpose the van der Waals potential energy was computed by moving one chain of molecules and leaving the surrounding chains fixed. The good results obtained again confirm the validity of this method for the solution of the phase problem. It is hoped that this approach may be useful in crystal structure determinations of organic molecules of biological interest.

Introduction

Semi-empirical potential functions have been used in the study of the conformational stability of synthetic polymers and biopolymers (Liquori, 1959; De Santis, Giglio, Liquori & Ripamonti, 1962, 1963, 1965; Liquori, 1966*a*,*b*, 1969). This method was later extended to the solution of the phase problem in molecular crystals (Giglio & Liquori, 1967; Damiani, Giglio, Liquori & Mazzarella, 1967; Giglio, 1969) where the molecular geometry is approximately known and the unit-cell parameters together with the space group have been determined. Similar analyses have been reported by other researchers, *e.g.* Kitaigorodskii, Mirskaya & Tovbis (1968), Williams (1969), Craig, Mason, Pauling & Santry (1965), Rabinovich & Schmidt (1966) and Mason & Rae (1968).

Moreover, the validity of some potential functions available in the literature was investigated in crystals when the unit-cell dimensions and some rotational degrees of freedom, allowed by symmetry conditions, were permitted to vary (Liquori, Giglio & Mazzarella, 1968; Giglio, Liquori & Mazzarella, 1968, 1969; Di Nola & Giglio, 1970). Potential functions describing pairwise interactions between the more common atoms in organic compounds such as hydrogen, carbon, nitrogen, oxygen, sulphur and chlorine, have been chosen for this analysis.

In addition we have undertaken a research programme to study forces other than van der Waals in crystals. To begin with the hydrogen bond, which is one of the most important forces in biological systems, was considered. For this purpose the crystal structure of dimethylglyoxime was successfully calculated by locating the deepest minimum of the van der Waals and hydrogen bonding energies (Giglio, 1969). This paper concerns a similar analysis of the molecular packing in the crystal structure of diketopiperazine, which belongs to a class of biologically interesting model compounds.

Table 1. *Bond lengths* (Å) *and bond angles* (°) *of the diketopiperazine molecule used in the analysis* (GG) *compared with those found by Degeilh & Marsh* (DM)

	GG	DM		GG	DM
C(1)C(2)	1·53	1·499	C(2)C(1)O(1)	120	118·5
C(4)N(1)	1·47	1·449	N(1)C(1)O(1)	120	122·6
N(1)C(1)	1·32	1·325	C(2)C(1)N(1)	120	118·9
C(1)O(1)	1·24	1·239	C(1)C(2)N(2)	113	115·1
N(1)H(1)	1·00	0·86	C(1)N(1)C(4)	127	126·0
C(2)H(2)	1·08	0·93	C(1)N(1)H(1)	116·5	123
C(2)H(3)	1·08	0·95	C(4)N(1)H(1)	116·5	111
			H(2)C(2)H(3)	110	109
			C(1)C(2)H(2)	108·5	104
			C(1)C(2)H(3)	108·5	107
			N(2)C(2)H(2)	108·5	113
			N(2)C(2)H(3)	108·5	108

Energy calculations

Diketopiperazine crystallizes in space group $P2_1/a$, $Z=2$, with unit-cell dimensions (Degeilh & Marsh, 1959): $a=5{\cdot}228$ Å, $b=11{\cdot}554$ Å, $c=3{\cdot}980$ Å; $\beta=97°\,59'$.

The crystal structure was determined by X-ray (Degeilh & Marsh, 1959; Corey, 1938) and electron diffraction methods (Vainshtein, 1955). The molecule, lying on a crystallographic centre of symmetry, has been considered planar in our calculations with the exception of the methylene hydrogen atoms, and the bond lengths and angles correspond to normal values (see Table 1 for a comparison with those found by Degeilh & Marsh).

Fig. 1 shows the atomic numbering and the starting position of the molecule which has three rotational degrees of freedom ψ_1, ψ_2 and ψ_3. These are Eulerian angles of rotation defined according to Goldstein (1951). The rotations occur in a rigid orthogonal framework $OXYZ$, where OY and OZ coincide respectively with the Ob and Oc axes of the monoclinic crystallographic system. The $OXYZ$ and $Oabc$ reference systems are both right-handed.

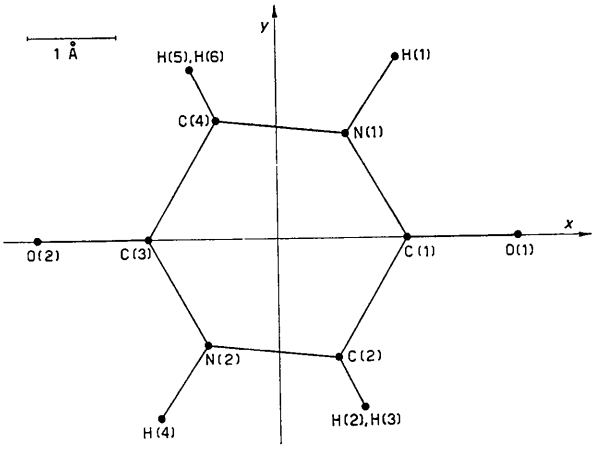

Fig. 1. Atomic numbering and position of the molecule corresponding to $\psi_1=\psi_2=\psi_3=0°$. The plane of the heavy atoms coincides with the XY plane.

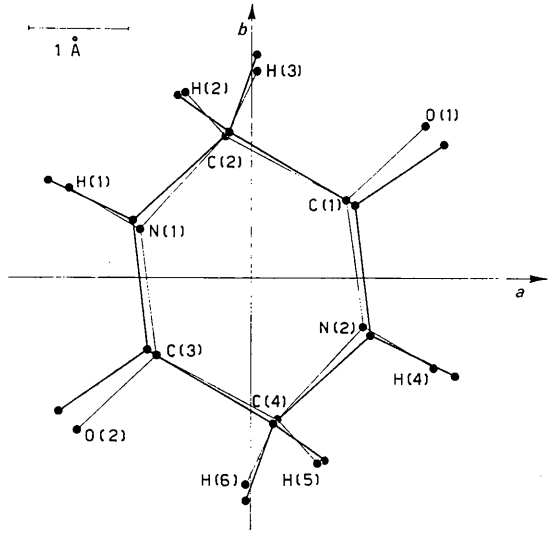

Fig. 2. Projections on the *ab* plane of the GG molecular model at $\psi_1=96°$, $\psi_2=150°$ and $\psi_3=62°$ (thick line) and of the experimental molecule as found by the X-ray diffraction method (thin line).

All the interactions between one molecule and the fourteen nearest molecules were computed. Ten potential functions, chosen among those tested in the analysis of crystals, were used in the calculations and are reported in a previous paper (Giglio, 1969). A potential function, proposed by Stockmayer (1941) for interactions between two polar gas molecules, was considered in order to describe intermolecular hydrogen bonds between C=O and N–H groups. This function has given good results in dimethylglyoxime and in the conformational analysis of helical polypeptides. Its parameters have been calculated as in the dimethylglyoxime case (Giglio, 1969). The function was minimized at a distance O...H of 1·85 Å, while the Lennard-Jones part yielded a minimum at 3·18 Å, which is the sum of the hydrogen and oxygen van der Waals radii in the best potential functions found. The lowest value of the potential, −5 kcal, is obtained when the C=O and N–H bonds are collinear.

The calculations were performed on a UNIVAC 1108 computer with angular increments of 10° for the first run, and showed the existence of a large minimum which was much deeper than the others. This region was explored using angular increments of 2° in a second run. The position of the minimum was located at $\psi_1=96°$, $\psi_2=150°$ and $\psi_3=62°$.

The atomic coordinates corresponding to the deepest minimum are compared with those found by Degeilh & Marsh in Table 2. The projections on the *ab* plane of these two molecules are shown in Fig. 2.

Rigid body translations of diketopiperazine

Lonsdale (1961) analysed the anisotropic thermal parameters of diketopiperazine and calculated that the principal rigid body translations of the molecule occur along the average directions [101], [010] and along the normal to (10$\bar{1}$). Hereafter these three directions will be called **A**, **B** and **C**. The amplitudes of the translational movements appeared to be of the order of 0·11, 0·14 and 0·13 Å along **A**, **B** and **C** respectively.

Since the shape of the potential energy minimum, computed as a function of the molecular translations in the crystal unit cell, may supply information about the thermal movement of the molecule, it was decided to undertake this type of calculation using the GG model of Table 1 at $\psi_1=96°$, $\psi_2=150°$ and $\psi_3=62°$.

The potential energy was thus calculated translating only one chain of hydrogen-bonded molecules with respect to the nearest chains. The sixteen closest molecules were taken into account.

Fig. 3 shows that the potential energy minimum has an ellipsoidal shape and its principal axes lie to a good approximation, along **A**, **B** and **C**. There appears to be satisfactory qualitative agreement between predicted and experimental rigid body translations.

Discussion

Diketopiperazine is the second molecule investigated in our laboratory having non-collinear hydrogen bonding. Once again the potential functions involving hydrogen, carbon, nitrogen and oxygen have been successfully used.

Departures from linear hydrogen bonding are fairly common and it is important to point out that much experimental evidence on this subject (Hamilton & Ibers, 1968; Donohue, 1968) is available. For this reason we have chosen the Stockmayer potential function, which is less sensitive to non-linearity than, for example, the semi-empirical functions closely related to the Lippincott–Schroeder potential (Lippincott & Schroeder, 1955; Lippincott, 1957). The results obtained to date are good enough to justify this choice.

Both hydrogen bonding and van der Waals energies are very close to the lowest value found in the analysis. As with dimethylglyoxime, no competitive effect is present.

The agreement between the atomic coordinates corresponding to the deepest minimum and those derived from X-ray diffraction is satisfactory, although it is worse than in the case of dimethylglyoxime.

This situation arises, in our opinion, because of the great difference in the molecular geometry of the heavy atoms in our model as compared with that of the experimental model. The limit of error in the hydrogen positional parameters of the X-ray crystal structure is very high (see the hydrogen-bond distances of Table 1) and a comparison for these atom positions is impossible.

The outcome of this investigation, regarding a model compound, is also useful in the conformational analysis of polypeptides as far as the choice of van der Waals and hydrogen bonding potential functions is concerned. Hopefully, this method could be applied to the solving of crystal structures of model compounds and of large biological molecules.

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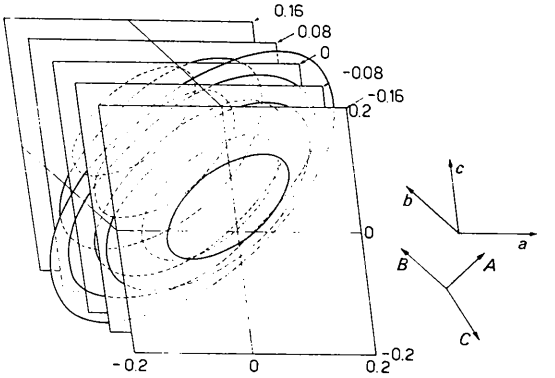

Fig. 3. Sections of the potential energy map along the *b* axis of the crystal. Contour lines are drawn starting from −23·60 kcal with increments of 0·2 kcal. The values of the coordinates are in Å.

Table 2. *Atomic fractional coordinates of the asymmetric unit diketopiperazine which refer to the lowest minimum found in the analysis* (GG) *compared with those of Degeilh & Marsh* (DM)

The distances between corresponding atoms are given in the last column.

	GG			DM			
	X/a	*Y/b*	*Z/c*	*X/a*	*Y/b*	*Z/c*	*d*
C(1)	0·1981	0·0620	0·2163	0·1820	0·0697	0·2170	0·12 Å
C(2)	−0·0469	0·1249	0·0586	−0·0515	0·1233	0·0150	0·17
N(1)	−0·2282	0·0491	−0·1543	−0·2198	0·0432	−0·1902	0·17
O(1)	0·3685	0·1153	0·4023	0·3311	0·1328	0·4044	0·28
H(1)	−0·3921	0·0857	−0·2642	−0·3510	0·0780	−0·2970	0·28
H(2)	−0·1429	0·1589	0·2609	−0·1320	0·1610	0·1780	0·34
H(3)	0·0079	0·1949	−0·0966	0·0090	0·1790	−0·1310	0·23

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Une Formule Optimale pour la Correction par Compteur Moniteur

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The counter method with a time basis has the disadvantage that it includes the systematic error resulting from the variation of the source. The counter method with a monitor counter gets rid of this systematic error but introduces a statistical error originating in the uncertainty of the flux received by the monitor counter. The author proposes a formula which is a compromise between the two methods and which partially retains the advantages of the two methods.

1. Avantages et inconvénients de l'emploi d'un compteur moniteur

Les compteurs détecteurs de quanta possèdent certains avantages et désavantages sur les films photographiques. Leur sensibilité est en général plus grande que celle des films. Cependant, pour certaines applications cet avantage est contrebalancé par la possibilité qu'offre le film d'enregistrer simultanément tout le diagramme à étudier. Il faut avoir à l'esprit, en particulier que toutes les portions d'un cliché photographique sont obtenues dans des conditions instrumentales identiques, ce qui permet automatiquement de rapporter les intensités à une base strictement équivalente. Au contraire le compteur est un détecteur local et il doit parcourir successivement tous les points décrivant le domaine du diagramme. Aussi les intensités recueillies de cette manière sont-elles sujettes à des erreurs (résultant de la variation de la source) qui se produisent pendant la course du compteur.

Si la précision recherchée pour les intensités est supérieure à celle du flux probable de la source, on peut corriger les intensités observées d'un facteur déduit de la mesure du flux incident venant de la source. Cette mesure doit évidemment être faite simultanément et pendant la même durée que celle d'un point du diagramme. Le détecteur servant à cette mesure est appelé compteur moniteur.

Il est des cas où indubitablement l'usage d'un compteur moniteur est indispensable: lorsque la source n'est pas stabilisable et fluctue grandement.

Par contre, lorsque la source est très stable et que les taux de comptage du compteur récepteur sont élevés (voisins de la limite acceptable pour avoir une bonne durée de vie, ou pour rester dans le domaine des approximations valables concernant le temps de résolution), alors l'emploi d'un compteur moniteur ne ferait qu'augmenter la fluctuation des résultats. L'incertitude sur le flux déduit du nombre de quanta reçus par le compteur moniteur serait alors plus grande que les fluctuations possibles de la source pendant le même temps.

Si on se trouve dans des cas intermédiaires, il est alors tentant d'utiliser à la fois l'information sur le temps et l'information du compteur moniteur.

2. Choix d'un mode opératoire

Certains modes d'emploi du compteur moniteur peuvent conduire à des formules de calcul du flux probable n'ayant pas les propriétés statistiques courantes.

Nous allons examiner ces cas pour des chaînes de comptage ayant un temps de résolution négligeable. Nous aurons ainsi des expressions plus simples sans restreindre les propriétés statistiques.

Premier mode d'emploi

On déclenche et on arrête le comptage à des instants