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Reaction Anisotropy of 2-Amino-5-(4-Fluorophenil)-1,3,4-Oxadiazole Crystals in Acetylation Reactions

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2-amino-5-(4-fluorophenyl)-1,3,4-oxadiazole (1) is a compound of ambident reactivity. Its solid-state acetylation by acetyl bromide vapours results in two monoacetyl derivatives and two diacetyl derivatives. Their structures were confirmed by UV spectra, mass spectra and thin layer chromatography data. The solid-state acetylation of compound (1) is an anisotropic reaction and the different products are formed on different crystal facets: amino-derivatives–on (1 1 0) and ($\bar{1}$ 1 0) crystal facets; imino-derivatives–on (0 0 1) facets. The crystal facets' reactivity is determined by the reactive centres of molecules that break out on the reaction surface. X-ray analysis shows that molecules of the reagent diffuse into channels in aminooxadiazole crystal. There the channels are perpendicular to to the plane of crystal facets; their diameter is about 8 Å.

Keywords: Reaction anisotropy, solid-state acetylation, 2-aminooxadiazoles

1. INTRODUCTION

Organic crystals are anisotropic objects with reactivity depending on the orientation of the crystal facet. Reactions of organic crystals with gases are characterised by the phenomenon of kinetic anisotropy, i.e. intrinsic rates of reaction vary on various crystal facets.

It was G. M. J. Schmidt who began investigations in chemistry of organic crystals in the Weizman Institute of Science (Israel).[1] His work was continued by M. Lahav, L. Leizerowitz *et al.*.[2] Reactions of crystalline carbonic acids and anhydrides with ammonia and amines studied by I. C. Paul and D. J. Curtin provide a classical example of kinetic anisotropy.[3] They have shown that reaction rates along various reaction axes are different and in some cases the reaction rate along one or two axes are equal to 0, i.e. ditropic or unitropic reaction takes place.[4–6] The kinetic anisotropy phenomenon has been described for some other reactions, such as desolvation,[7] oxidation,[8] hydrolysis.[9] Attention is to be called to the fact that in all cases kinetic anisotropy is characterised by crystal structure, i.e. by the different orientation of the molecule reaction centre from different facets.

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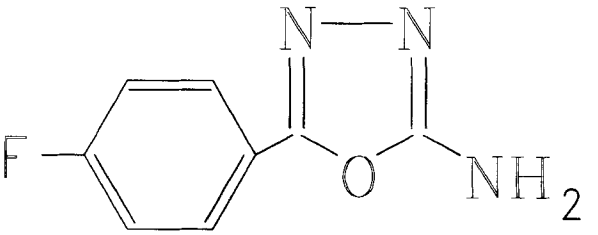
If an organic compound has the property of ambident reactivity in the solid state, this leads to various ratios of reaction products on the different facets of the crystal because the formation of each product is characterised by its own intrinsic rate of reaction on that specific facet. Lamartine and Perrin have demonstrated that chlorination of 2-methylphenol is a gas-molecular solid reaction resulting in a mainly para-substituted product on the perpendicular C-axis facets and in a mainly ortho-substituted product on the parallel C-axis facets,[10-12] i.e. reaction anisotropy takes place.

2-amino-5-aryl-1,3,4-oxadiazoles are ambident nucleophiles.[13] The presence of an ambidental conjugate system N3=C2—NH_2 creates the possibility for an electrophilic agent to combine both with the "cyclic" nitrogen atom N3 or with amino-group. During the alkylation of 2-amino-5-aryl-1,3,4-oxadiazoles four reaction products are formed.[14] The fact that the oxadiazoles dialkyl derivatives are oils with a low melting point,[15,16] makes the corroboration of reaction anisotropy impossible during the investigation of 2-amino-5-aryl-1,3,4-oxadiazole crystals alkylation by the vapours of alkylation agents.



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For the purposes of investigating the anisotropic reaction, the acetylation reaction was chosen because acetyl derivatives are known to have a higher melting point[16] (as the subject for investigations). The 2-amino-5-(4-fluorophenil)-1,3,4-oxadiazole (1) was chosen because it was the only compound that allowed us to obtain crystals large enough with a low concentration of defects.

2. EXPERIMENTAL SECTION

2.1 General Methods

Melting points were determined on a "ПТП" apparatus. Infrared spectra were recorded on a "ИКС-29" spectrophotometer in a KBr pellet. Mass spectra of the crystal substrate and reaction products were recorded on FINNIGAN MAT 90 spectrometer. Molecular ions of the initial compound and mono and diacetyl derivatives were obtained in a chemical ionisation mode (isobutane). Using the electron strike mode with ionisation energy of 70 eV, the following mass spectra were obtained: 221(23), 179(18), 178(27), 136(73), 128(20), 123(91), 121(40), 108(28), 95(82), 81(92), 59(79), 43(100), 28(55). The maximum relative intensities of characterising ions are: $I_1 - 100$, $I_2 - 91$, $I_3 - 73$, $I_4 - 49$, $I_5 - 27$, $I_6 - 20$, $I_7 - 28$, $I_8 - 82$. The solid-state acetylation products were separated through thin-layer chromatography on Silufol UW-254 plates

in a butyl alcohol-chloroform system (1:8) and were analysed using SHIMADZU dual-wavelength thin-layer chromato-scanner model CS-930, P/N 204-03200.

2.2 Materials

2-Amino-5-(4-Fluorophenyl)-1,3,4-Oxadiazole (1)[17]

3.6 g (0.2 moles) of aldehyde semicarbozone were added to a stirred solution of 8.2 g (0.1 mole) anhydrous sodium acetate in 70 ml glacial acetic acid. After that 1.1 ml (0.02 mole) of bromine in 10 ml of glacial acetic acid was added drop by drop to the mixture over 30 min. The solution was stirred for 30 min at 60°C, then poured into 1 l of ice-water. The product was filtered, washed and recrystallised by ethanol to give (1) (2.8 g, 80%) as a white, crystalline solid: m.p. 241–243°C;

Cacl. %: C, 53.63; H, 3.38; N, 23.46.
Found %: C, 53.82; H, 3.45; N, 23.63. $C_8H_6FN_3O$.
IR (in KBr pellet) 3320, 3105, 1640, 1600, 1505 cm^{-1}.

2-Acetylamino-5-(4-Fluorophenil)-1,3,4-Oxadiazole (2)[16]

A mixture of 20.0 g (0.11 mole) of (1) and 100 ml of acetic anhydride was heated under reflux for 1 h and cooled. The precipitate solid was filtered, air dried and recrystallised by butyl alcohol to give (2) (8.3 g, 34%) as white needles. m.p. 210°C dec.

Calc. %: C, 53.3; H, 3.6; N, 19.0.
Found %: 54.21; H, 3.52; N, 19.1. $C_{10}H_8FN_3O_2$.
IR (in KBr pellet) 1740, 1640, 1601, 1500 cm^{-1}.

2.3 Sample Preparation

Small crystals of (1) were recrystallised by butyl alcohol and flowless examples were selected by microscope. Butyl alcohol was saturated with compound (1) being stirred for 24 h and the small crystals were put into the solution. The solvent was allowed to evaporate slowly from a crystallisation dish at room temperature until crystals began to grow. After 2–3 months we obtained single crystals of (1) with edge length about 4–6 mm.

2.4 Acetylation of (1) Crystals in Solid State

A single crystal of (1) was put into a hermetically sealed reactor ($V = 100$ ml) with support for the crystal and a vessel with 10 ml of acetyl bromide, to ensure a constant pressure of its vapours after being treated under a vacuum (10 mm mercury column) for 24 h. The reactor was exposed in thermostat at 40°C for 24 h. After the reaction the crystal was vacuum-treated to remove the acetyl bromide and HBr absorbed on it, then put into gaseous ammonia to prevent a reverse reaction and to resolve the products into corresponding bases. The reaction penetrated the crystal for 30–40% of its thickness. The conversion in the layer of reacted substrate was 80–90%. The products were taken from the centre of the facet, while the adjacent facets and the edges were not affected.

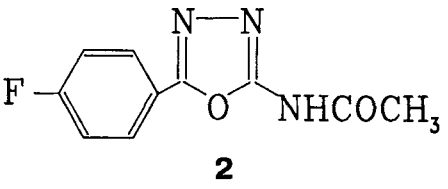
Dimness of the crystal facets and high conversion suggest that products of acetylation of (1) are developed, as is usual, in polycrystalline form. Therefore, the layer of the reaction products does not block diffusion of acetyl bromide vapours to the reaction front.

2.5 Crystal Structure Analysis of Compound (1)

Data was collected on a Syntex R21 diffractometer with graphite monochromated MoKa radiation. Monoclinic unit cell parameters rendered the following: space group $P2_1/n$; $a = 8.204(1)$, $b = 5.9453(8)$, $c = 16.750(2)$ Å; $\beta = 108.51(1)°$; $V = 774.8(4)$ Å^3; $d_{calc} = 1.571(1)$ g/cm^3; unit cell mass was 732.84 a.m.u; number of measured reflections = 630; $R = 0.0383$, $Rw = 0.0390$. The bound dimensions and angles are listed in Table II, the structure of crystal (1) is shown on Figure 2. The crystal of compound (1) belongs to space group $P2_1/n$, which means that it is not polar, i.e., its parallel facets are identical and have the same reaction properties.

3. RESULTS

As the result of solid-state acetylation of compound (1), four reaction products were obtained. The structure of the acetyl products[14] is described as:



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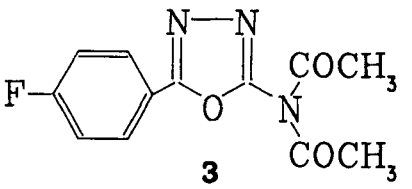

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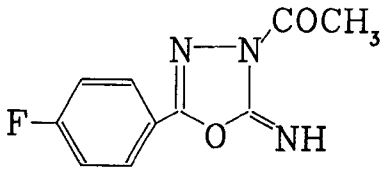

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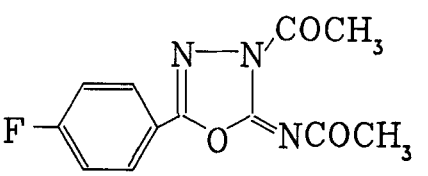

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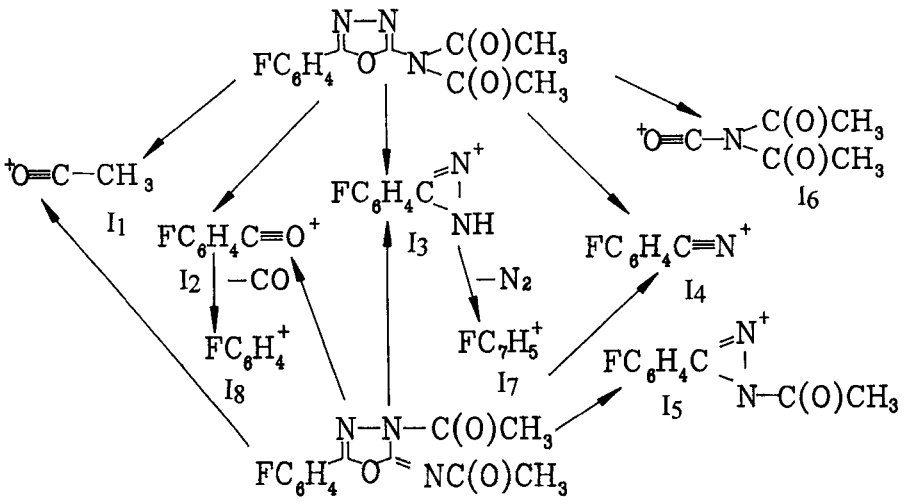
Compound (2) is reported[16] to be the only product of homogeneous acetylation of (1). The acetylation of 2-amino-5-phenyl-1,3,4-oxadiazole, or 2-acetylamino-5-phenyl-1,3,4-oxadiazole in liquid acetyl anhydride renders not more than 3% of 4-acetyl-5-acetylimino-2-phenyl-Δ^2-1,3,4-oxadiazoline.[16] Compounds (3–5) have not been obtained before, nor were unsubstituted analogues of compounds (3) and (4). At the same time the formation of four different products proves conclusively the gas-solid mechanism of acetylation reaction.



Molecular ions of compounds (2–5) were obtained in the mass spectra in chemical ionisation mode. The fragmentation of compound (1) diacetyl products is shown.

The fragmentation paths of monoacetyl products of 2-amino-5-aryl-1,3,4-oxadiazoles were demonstrated.[18] The compound (2) was obtained by acetylation compound (1) with acetyc anhydride and its structure was confirmed by results of elementary analysis and by IR spectra.

The UV spectra and R_f of compound (1) and the products of solid-state acetylation are shown in Table I. The absorbtion line with peak at 288 nm is related to $\pi \rightarrow \pi^*$ transfer in aminophenyloxadiazole chromophore, besides the transmission of influence in oxadiazole cycle is only going in the double bonds system. The similarity of UV spectra of (2) and (3) when R_f differs three times shows that the compound (3) is 2′-N, N′-diacetylamino-5-(4-fluorophenyl)-1,3,4-oxadiazole, the formation of which was demonstrated by mass spectra. The absorbtion lines of compounds (4) and (5) are moved by 30–35 nm relative to absorbtion peak of compound (2) and (3) which proves that the conjugate chain decreases by one double bond. It means that acetylation passed by the ring. Hence, taking into consideration mass spectra, UV spectra and

TABLE I

The UV-spectra and R_f^* of 2-amino-5-(4-fluorophenyl)-1,3,4-oxadiazoles and solid-state acetylation products

Compound	R_f	λ_{max}, nm
1	0.17	288
2	0.29	266
3	0.90	260
4	0.54	230
5	0.79	230

* Butyl alcohol–chloroform system (1:8).

thin-layer chromatography data, it can be postulated that during the solid-state acetylation of compound (1) products (2–5) are actually formed.

4. DISCUSSION

The crystals of compound (1) react anisotropically with acetyl bromide vapours. On (001) facets (see Figure 1) only compound (5) is formed, while on facets (110) and ($\overline{1}10$) only amino-groups react, which leads to the formation of compounds (2) and (3).

Theoretically, compound (3) can be formed only from compound (2). Compound (5) may be a product of substitution of compound (4) or compound (2). However, absence of compound (5) on facets where compounds (2) and (3) are formed certifies that during the actual solid-state acetylation compound (2) converts only to compound (3). This fact can be explained by the influence of the crystal matrix of intermediate product (compound (2)) because the conversion of amino-derivative into imino-derivative is accompanied by greater changes in crystal structure than in the case of conversion to a similar compound (3).

Only a diacetyl derivative (5) was found on facets (001) which means that compound (5) can be formed only from compound (4). There is no compound (4) in the chromatogram because its formation is the limiting stage of reaction. It must be noted that if compound (5) was formed by solid-state acetylation from compound (2), compound (5) on (110) and ($\overline{1}10$) facets would be found apart from compound (2) and (3). Hence during the acetylation of compound (1) in solid-state only the diacetyl derivative (3) is formed from the monoacetyl derivate (2)

It is to be noted that liquid-state acetylation of 2-amino-5-aryl-1,3,4-oxadiazoles leads to 2-acetylamino-5-aryl-1,3,4-oxadiazoles. Syntheses of 4-acetyl-5-(acetylimino)-5-phenyl-Δ^2-1,3,4-oxadiazoline by acetylation of 2-amino-5-phenyl-1,3,4-oxadiazole in acetic anhydride with merely 3% reaction yield are shown in the paper.[16] However

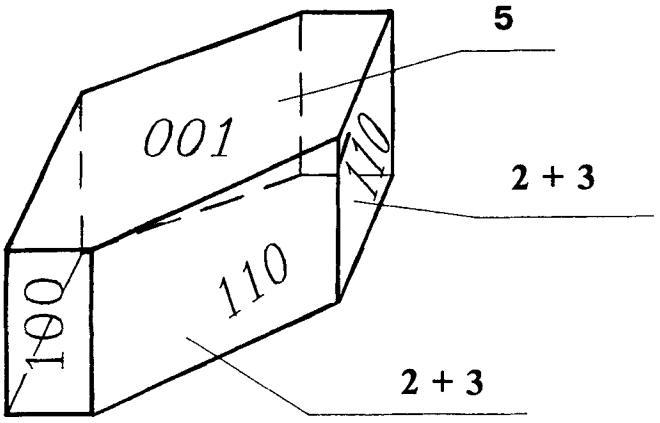


FIGURE 1 A single crystal of 2-amino-5-(4-fluorophenyl)-1,3,4-oxadiazole.

we were not able to obtain compound (5) under the conditions described. At the same time solid-state acetylation of compound (1) results in a whole range of theoretically possible products. This phenomenon is likely to be typical for reactions of organic crystals. For example, the polysubstituted chlorophenole yield in solid-state chlorination is higher than in liquid state.[19] Solid-state alkylation of phenylphenol by isobutene leads to dialkyl derivative, while only monoalkyl derivative is obtained in solution.[20] Consequently one can assume that the formation of four products in solid-state acetylation of compound (1) is the general law-governed phenomenon.

The crystal facets reactivity is determined by the reactive centres of molecules that break out on the reaction surface. The elementary cell structure of compound (1) is shown on Figure 2; the bond dimensions and angles are shown in Table II. Table II shows that both hydrogen atoms of the amino-group in every molecule are linked by hydrogen bonds with cyclic nitrogen atoms of two neighbouring molecules, and the hydrogen bond with atom N3 is shorter than in the case of nitrogen atom N4.

The projection of crystal structure on the facet (110) is shown in Figure 3, while the projection of the same structure on the facet (001) is shown in Figure 4. Figure 3 and Figure 4 lead us to expect that reagent molecules can diffuse into the channels dividing molecule (1). These channels are perpendicular to the plane of facets, and their diameter is 8 Å. The only accessible reaction centres on the facets (110) are amino-groups because

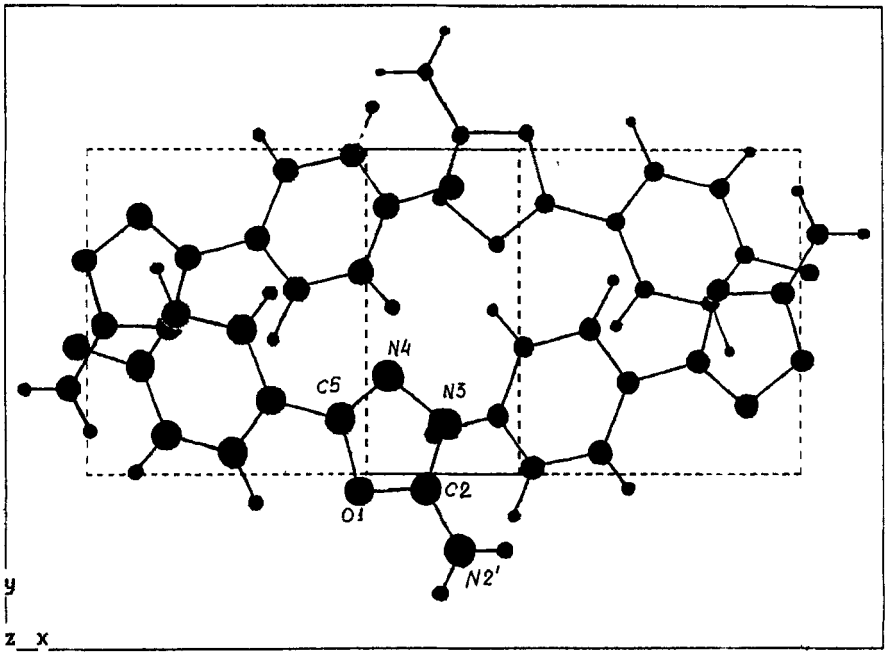


FIGURE 2 Structure of 2-amino-5-(4-fluorophenyl)-1,3,4-oxadiazole crystal.

TABLE II

Bond distances (Å) and angles (deg) in 2-amino-5-(4-fluorophenyl)-1,3,4-oxadiazole crystal

	Bond Distances		
N4–N3	1.416(5)	C5–N4	1.279(5)
N4–C5	1.279(5)	C5–O1	1.371(5)
N3–N4	1.416(5)	C2–N3	1.298(6)
N3–C2	1.298(6)	C2–N2′	1.336(6)
N2′–C2	1.336(6)	C2–O1	1.360(4)
N2′–H2	0.980(4)		
N2′–H1	0.920(6)		
O1–C5	1.371(5)		
O1–C2	1.360(4)		
	Bong Angles		
	N3–N4–C5	106.8(3)	
	N4–N3–C2	105.2(3)	
	C2–N2′–H2	118.6(27)	
	C2–N2′–H1	118.7(31)	
	C5–O1–C2	102.3(3)	
	H2–N2′–H1	122.6(41)	
	N4–C5–O1	112.6(3)	
	N3–C2–N2′	129.1(4)	
	N3–C2–O1	113.1(3)	
	N2′–C2–O1	117.9(3)	
	Hydrogen Bond Distances and Angles		
	H2–N3*	2.01(4)	
	H2–N2′	0.98(4)	
	H1–N4*	2.21(6)	
	H1–N2′	0.92(6)	
	N3*–H2–N2′	166.2(40)	
	N4*–H1–N2′	159.1(3)	

* Atom belongs to the neighbouring molecule.

they are perpendicular to the reaction front and parallel to crystallographic axis. The reaction of solid-state acetylation is topochemical, i.e. the reaction front in the crystal remains parallel to its facets, and the reaction properties of crystal reacting surfaces do not change. Simultaneously, the amino-group shields another potential reaction centre N3. Following the reaction of the amino-group with the acetylation agent the shielding of "cyclic" nitrogen increases, and secondary acetylation also goes with the amino-group, and as a result only amino-group reactions are possible on the facet (110). Figure 4 shows that both reactive nitrogen atoms of the molecule are open to the acetylation agent on the facet (001). The reaction, though, begins from atom N3, because this type of substitution causes rupture of one hydrogen bond while the amino-group reaction causes a rupture of two hydrogen bonds. The secondary substitution happend with the nitrogen atom of the amino-group.

Thus, the reactive anisotropy takes place in the solid-state acetylation of 2-amino-5-(4-fluorophenyl)-1,3,4-oxadiazole, this phenomenon being caused by the orientation of molecules in crystal and the hydrogen bonds between them.

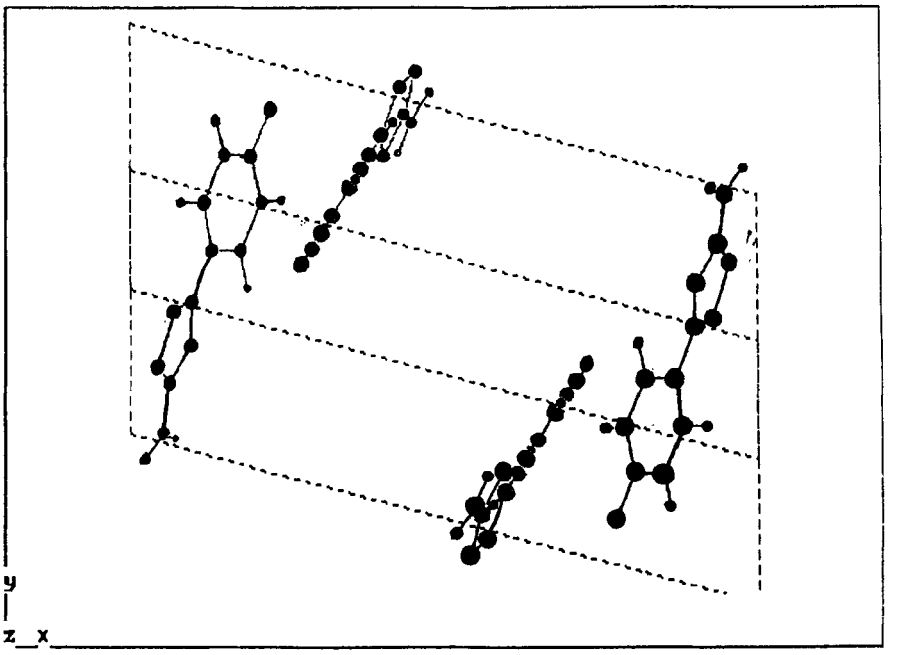


FIGURE 3 Projection of crystal structure on facet (110).

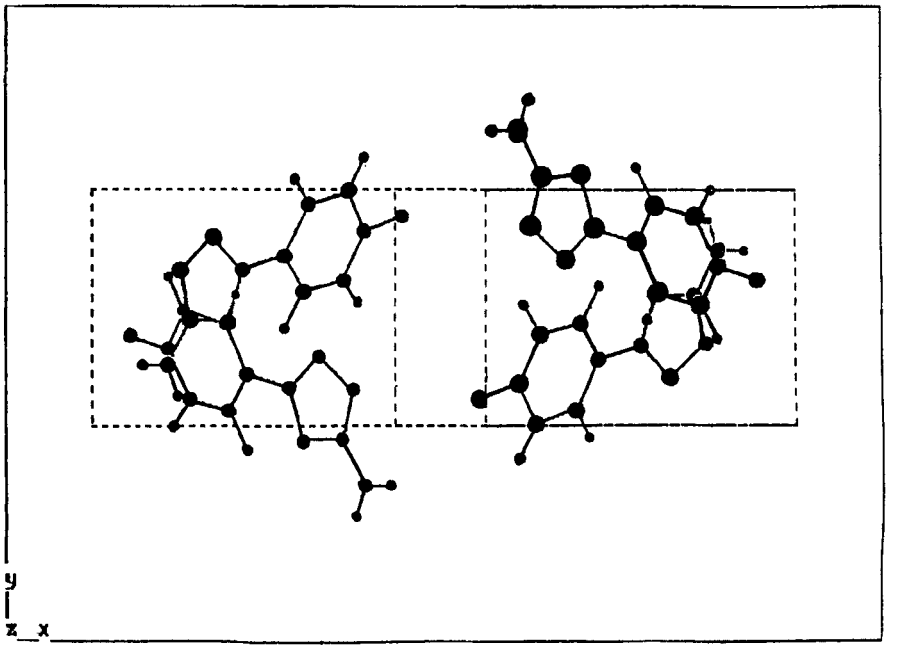


FIGURE 4 Projection of crystal structure on facet (001).

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