Molecular Crystals and Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl16

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Version of record first published: 17 Oct 2011.

To cite this article: Roger Lamartine , Claude Decoret , Jean Royer & Jacques Vicens (1986): Experimental and Theoretical Study of Organic Solid State : Structure and Reactivity, Molecular Crystals and Liquid Crystals, 134:1, 197-218

To link to this article: http://dx.doi.org/10.1080/00268948608079585

Mol. Cryst. Liq. Cryst., 1986, Vol. 134, pp. 197-218
0026-8941/86/1344-0197$25.00/0

Printed in the United States of America

EXPERIMENTAL AND THEORETICAL STUDY OF ORGANIC SOLID STATE : STRUCTURE AND REACTIVITY.

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Abstract Three of our recent attempts to study the mechanism of organic reactions in the solid phase are presented. The stability of organic crystals of monotropic polymorphic substances is studied. Also described are the rearrangement of orthocyclohexadienone into paracyclohexadienone and the solid state hydrolysis of acetylanthranyl. In all cases it is shown that organic single crystals are useful for the study of reaction mechanisms.

INTRODUCTION

Organic single crystals are useful for the study of reaction mechanisms since molecular conformations, and intermolecular contacts can be precisely defined from x-ray crystal structure analyses. During solid-state or solid-gas reactions the progress of the reaction can be monitored by observing the direction of reaction in relation to the morphology of the crystal and by observing the mode of phase separation of product. The product phase can cause fracturing, powdering, expansion, or sublimation of the crystal, thereby giving additional information about the mechanism of reaction and, in particular, about the cooperative motions of groups of molecules.

Such mechanistic information is unattainable from studies of reactions in mobile phases.

The arrangement of molecules in crystal can be more precisely determined by x-ray or neutron diffraction than in solution. This allows a better knowledge of the environment and localization :

- of reaction processes.
- of reaction pathways.
- of the formation of intermediates and final products.

Such precise details of molecular processes occuring in the solid phase are precious to theoriticians and more efficient for mechanistic studies [1,2,3,4,5].

For example Burgi, Dunitz and Lehn have vizualized the approach of a nucleophile onto a carbonyl function from a series of crystallographic determinations of chosen compounds containing a tertiary amino group and a carbonyl group.

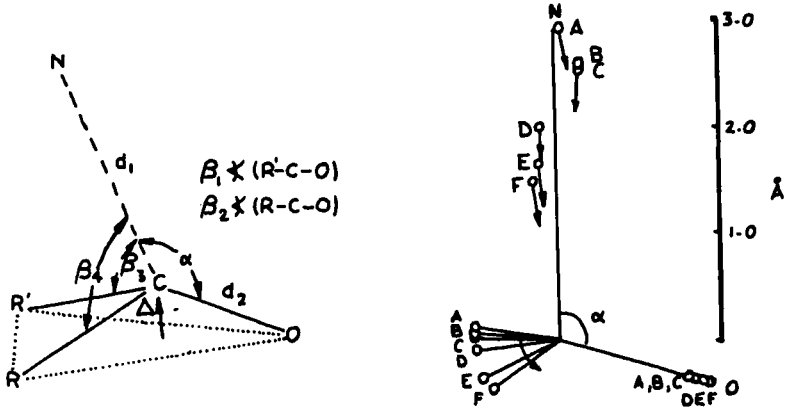


FIGURE 1. Reaction path for addition of amine to carbonyl[6]

As shown on the Figure 1, the approach of the nucleophilic N atom towards the electrophilic C atom is accompanied by a displacement of the C atom out of the plane defined by its three bonded atoms (two substituents R and R', and the carbonyl O atom) towards the nucleophilic center. The out of plane displacement increases as the nucleophile approaches the carbonyl C atom, the two alkyl substituents R and R' bend away and the C-O distance becomes slightly longer [6].

Another way to use the crystalline state to study the mechanism of reactions is to take advantage of its polymorphism and its reactivity.

Three of our recent attempts to study the stability of organic crystals and the mechanisms of organic reactions in the solid state are now presented. In first the stability of organic crystals of monotropic polymorphic substances is studied. In a second section the solid state rearrangement of orthocyclohexadienone into paracyclohexadienone is described and lastly the solid state hydrolysis of acetylanthranyl is discussed.

STABILITY OF ORGANIC CRYSTALS

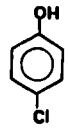
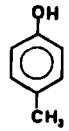
Solid substances are by no means restricted to specific crystalline forms, but on the contrary, they exhibit very often various crystalline forms. Two types of polymorphism are encountered in nature, reversible (enantiomorphism) and irreversible (monotropism). Enantiotropic polymorphs can be interconverted below the melting point of either polymorph, while monotropic polymorphs cannot.

We have studied 4-chlorophenol and 4-methylphenol which are examples of monotropic systems. When 4-chlorophenol is melted, it easily remains in the liquid state for long periods even if the temperature is lower than the melting point. If the liquid is in a sealed glass container, it is possible to induce the crystallization at a low temperature.

Such a crystallization gives transparent needles for the two studied compounds. After a variable time period, the compounds become opaque. A transformation occurs giving more stable form. Each needle becomes a collection of microcrystals. The transformation from metastable form to stable one can be observed at all temperatures below the melting point. The undercooled liquid first crystallizes in a metastable form, then in a stable one except if there is an increase in viscosity of the liquid. In this case the crystallization is immediately followed by the phase transition and the crystal appears opaque. Indeed it is possible to obtain the stable form directly as a transparent crystal. On the other hand it is not possible to transform the stable form into the metastable one.

Molecules of 4-chlorophenol and 4-methylphenol have a similar shape and volume. As indicated on Table I, metastable 4-chlorophenol and stable 4-methylphenol are similar and their space groups are the same $P2_1/c$. These conditions result in an interesting phase diagram, Figure 2. Mixtures of the two products were made and for each mixture we measured the solidus and liquidus values. Three crystal forms, labeled α, β and γ are possible for the two compounds. They correspond to three arrangements of molecules in crystals.

TABLE I. Cell parameters.

	metastable form	stable form
4-chlorophenol 	a = 4.14 (1) Å b = 12.85 (2) Å c = 23.20 (3) Å β = 93°,0 (5) z = 8 $P2_1/c$ F = 34.65°C	a = 8.841 (3) Å b = 15.726 (2) Å c = 8.790 (2) Å β = 92°,81 (2) z = 8 $P2_1/c$ F = 43.45°C
4-methylphenol 	a = 26.412 (5) Å b = 6.001 (2) Å c = 27.842 (5) Å β = 117°,61 (2) z = 24 C2 c F = 31.9°C	a = 5.72 b = 11.74 c = 18,68 β = 98°,0 z = 8 $P2_1/c$ F = 34.7°C

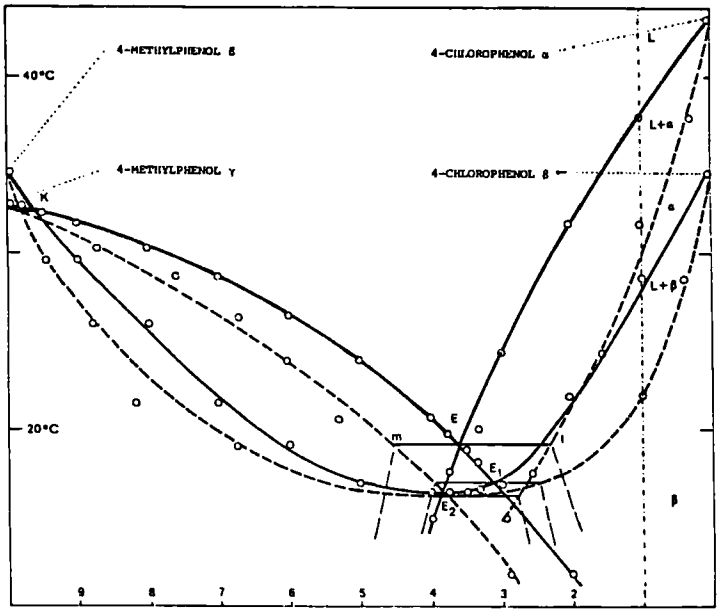


FIGURE 2. Phase diagram of 4-methylphenol and 4-chlorophenol.

It can be noted that the γ form is an intermediate stable form. It is not stable for the two pure compounds but only for the compositions between the peritectic point K and the eutectic point E. This implies that the γ form of 4-chorophenol is not stable[7].

The crystal structure of the three forms were determined by X-ray diffraction.

4 -chlorophenol-α form, stable crystal.

Figure 3 shows that in the structure molecules are hydrogen-bonded to form chains running along the c axis.

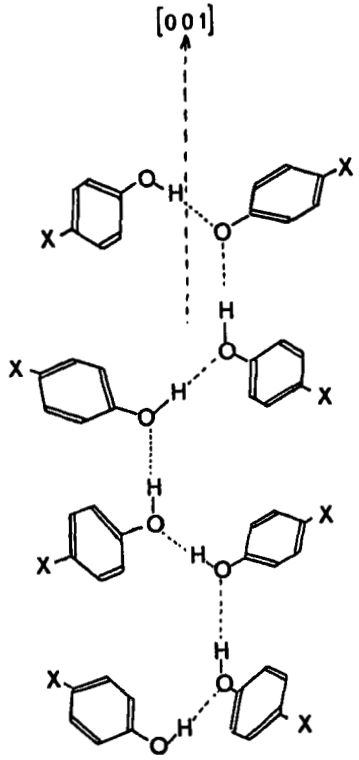


FIGURE 3. Structure of 4-chlorophenol γ form.

4-chlorophenol-βform,metastable crystal.

Figure 4 shows that in this structure molecules are linked by hydrogen bonds to give tetramers.

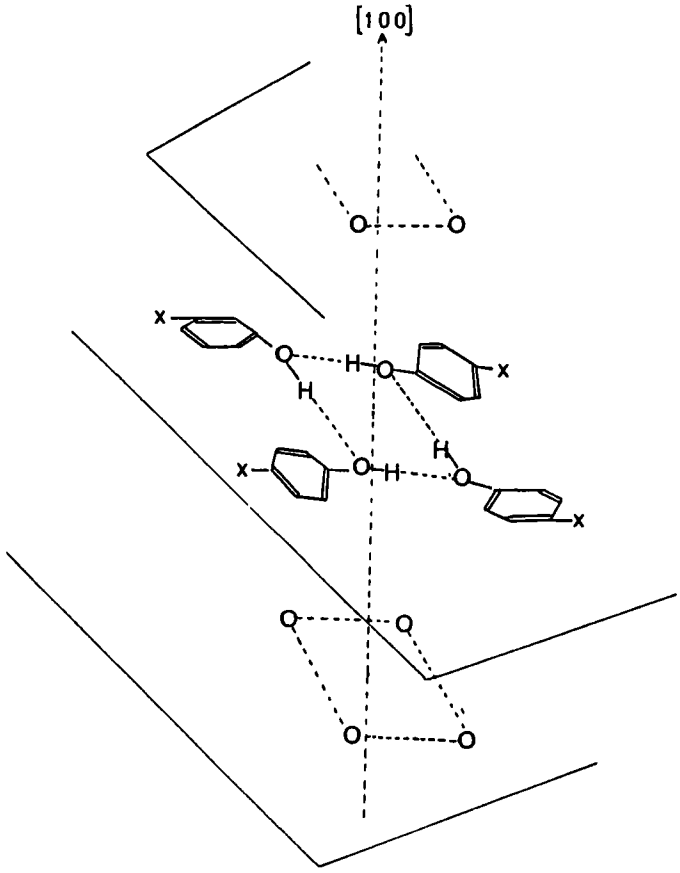


FIGURE 4. Structure of 4-chlorophenol-β form.

4-chlorophenol- γform.

The unit cell is larger and the space group is C 2/c with three independent molecules in the cell, as shown in Figure 5. Chains of hydrogen bonded molecules run along the

[010] direction.

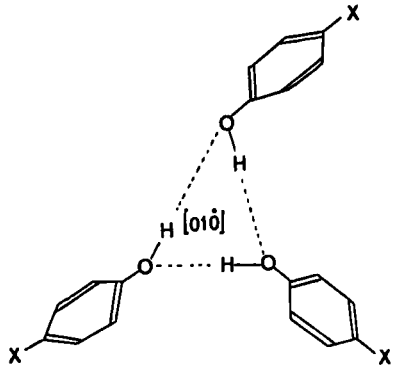


FIGURE 5. Structure of 4-chlorophenol- γ form.

For lattice energy calculations we use Caillet and Claverie's method [8]. The interaction energy, Table II, was evaluated as the sum of four contributions : electrostatic, polarization, dispersion and short-range repulsion. The geometry taken for calculations was that found from X-ray data. The program of calculations minimizes the energy by optimizing the intermolecular geometry.

The results of the lattice energy calculations are summarized in Table III. The calculated order of stability for the different polymorphic varieties of 4-methylphenol and 4-chlorophenol is the same as the experimental one. In particular the β form which is the more stable for 4-methylphenol becomes unstable for 4-chlorophenol.

In the case of a monotropic transformation the upper temperature form is the more stable. On the phase diagram, Figure 2, the α form of 4-chlorophenol is the upper temperature form. This implies that α form is more stable than the β form.

TABLE II. Cohesive forces.

$$F_{cohesive} = F_{elec} + F_{pol} + F_{disp} + F_{rep}$$

ELECTROSTATIC FORCES: Forces between permanent dipole moments.

POLARIZATION FORCES: Forces between induced dipole moment in an electric field. The calculation of polarization forces is specific to the Claverie's method.

DISPERSION FORCES: Forces between instantaneous induced dipole moments for neutral molecules.

REPULSIVE FORCES: between electronic clouds which cannot interpenetrate each other.

TABLE III. Summary of lattice energy calculations.
Crystal energy E tot (kcal/mole). Enthalpies of fusion ΔH.

	4-methylphenol		4-chlorophenol		
	γ	β	β	α	γ
Eelec	- 1.87	- 1.58	- 0.35	- 0.29	- 0.34
E pol	- 0.58	- 0.47	- 0.29	- 0.39	- 0.50
E disp-rep	-11.60	-13.36	-11.36	-12.43	-11.76
E tot	-14.05	-15.41	-12.00	-13.11	-12.60
ΔE	1.36		1.11		
ΔH	3.50 2.70		2.55	3.05	

Concerning the experimental enthalpies of fusion the following remarks can be made. For the two compounds the most stable form has an enthalphy of fusion greater than that of the unstable form. In order to compare calculated energies with crystal stability a more detailed analysis of the total energy was undertaken. A partition of the total energy in two parts was carried out ; a stabilization energy E (intrapile) due to interaction with other molecules in the same pile of tetramers or chains and a stabilization energy E (interpile) due to interaction with molecules from other piles.

TABLE IV. Interpile or interchain contribution energy to the total energy (kcal/mole).

	4-methylphenol		4-chlorophenol		
	β	γ	β	γ	α
E_{inter}	- 8.73	- 8.89	- 5.72	- 9.11	-10.37
E_{intra}	- 6.68	- 5.16	- 6.28	- 3.49	- 2.74
E_T	-15.41	-14.05	-12.00	-12.60	-13.11
% of the interpile contribution energy	57	63	48	72	79
ΔH (kcal/mole)	2.70	3.50	2.55		3.05
Number of chains per 100 $Å^2$	0.95	1.22	0.67	1.39	1.45

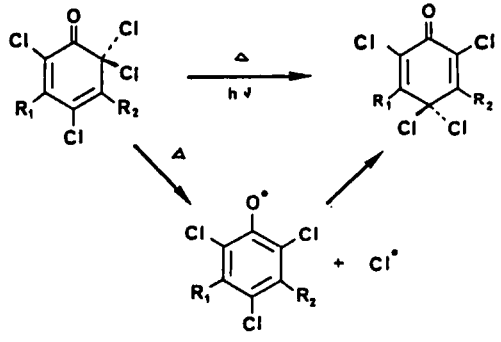
In Table IV are reported the percentage of the interpile contribution to the total energy for each form and it can be seen that for 4-chlorophenol, the more important the interpile contribution to the total energy the greater the stability. It could be thought that the more the piles are linked together the higher the stability is.

It should be noted that chain densities are in good agreement with the interpile contribution order. Such a remark would mean that the main feature in the stability of these crystals is the separation of piles. This remark suggested by our calculations must be made very cautiously, because the phenomenon of stability is very complex. This remark could be confirmed by further application or possible improvement of calculation and could lead to a better understanding of various phenomena in which cohesive energy between chains or piles are involved.

SOLID STATE REARRANGEMENT OF ORTHOCYCLOHEXADIENONE INTO PARACYCLOHEXADIENONE

Halogenocyclohexadienones are known to undergo rearrangements in the solid state.

Orthochlorocyclohexadienones have been observed to rearrange into their parachloro isomer in the solid state at room temperature by warming. We have studied the transformation in the solid state of 2,4,6,6-tetrachloro 3-methyl-5- isopropylcyclohexa-2,4,-dien-1-one, 1, into 2,4,4,6- tetrachloro-3-methyl-5-isopropylcyclohexa-2,5 dien-1- one, 2, under U.V. irradiation or by heating [9,10].



Microscopic observations of single crystals of 1 irradiated under U.V. show the crystals become cloudy in the bulk [11]. Heating solid 1 below the melting point increases the 1 → 2 conversion rate and the reaction is accompanied by a melt. The solid state mechanism is concluded to be homogeneous as defined by Curtin and Paul [12].

Electron spin resonance signals are observed during the thermal transformation of powders and single crystals of 1. A phenoxy radical intermediate is identified. Orthocyclohexadienone 1 is transformed into parachlorocyclohexadienone 2 by a radical mechanism.

The mechanism of the reaction is rationalized on the basis of the crystalline structure of 1. As shown on Figure 6 the distance between one chlorine attached to the C-6 position of a molecules of 1 and C-4 position of neighbouring molecule is 4.6 A, so a chlorine atom can be easily transferred. In agreement with the topological disposition it is assumed that a radical chlorine atom migrates along the C-4... C-6 direction.

The application of the Caillet and Claverie method [8] to a crystal of orthochlorocyclohexadienone provides a model of the crystal.

As shown on Figure 7, by elongation of the C-Cl bond a new position of molecules, allowing the molecular motion pictured at the beginning of the reaction, is obtained (dotted lines). This new position of the atoms shows that the chlorine comes nearer to the C-4 position of the neighbouring molecule [11].

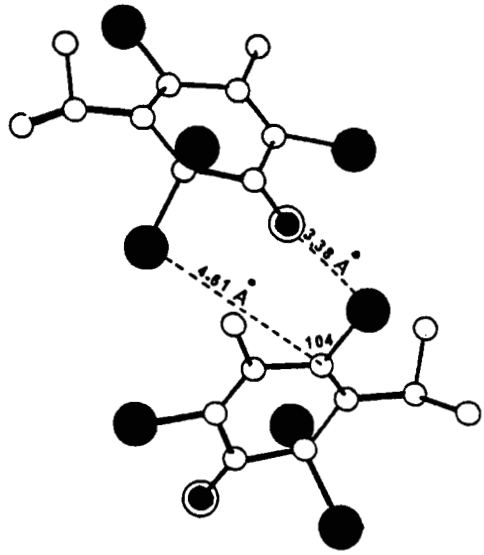


FIGURE 6. Two neighbouring molecules in crystal 1.

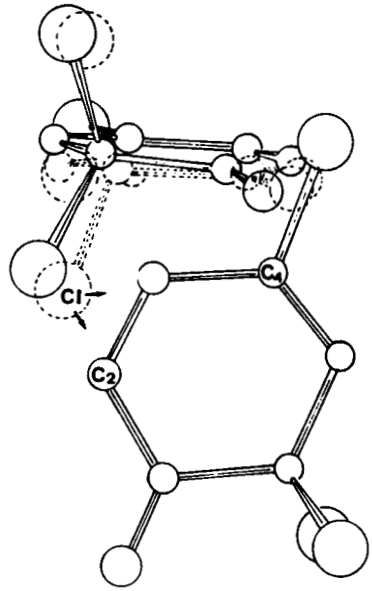


FIGURE 7. Two reacting molecules in crystal 1.

Such a migration is made possible by the presence of free space between the chlorine atom and the position to be reached. This was shown by the use of the Gavezzotti's method evaluating the volumes of cavities within crystals [13]. In this method, molecules are supposed to be made of rigid spheres with Van der Waals radius. Points in the cell are calculated to be either free or occupied. The fraction of occupied space in an elementary volume is given by :

$$D_i = Nocc / (Nocc + Nfree)$$

where Nocc and Nfree are the number of occupied and free points, in the ith elementary volume. A map of D_i at z = 0.32 is drawn as shown on Figure 8.

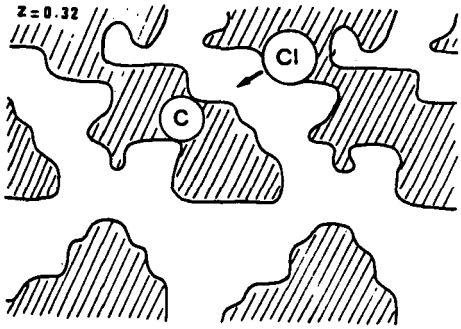


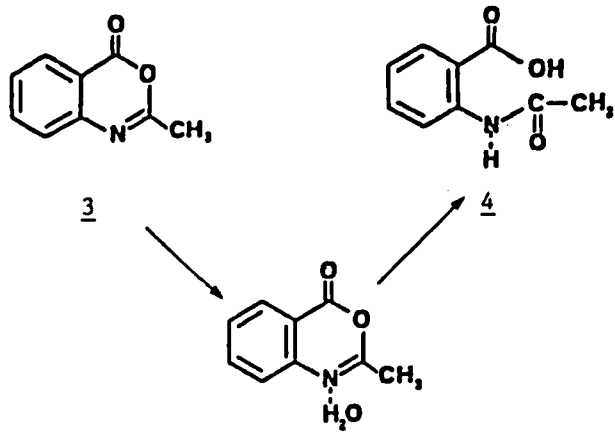
FIGURE 8. D_i map for section perpendicular to z = 0.32.

We note that there is free space between the two reacting atoms which makes possible the chlorine atom transfer [12].

More generally the disposition of atoms and molecules during such reactions can be seen as a model of an sp2 to sp3 carbon transformation during the attack of a chlorine atom on a double bond of a phenyl ring [14].

HYDROLYSIS AND METHANOLYSIS OF ORGANIC SOLID SUBSTANCES.

Solid acetylanthranyl or 2-methyl-3,1 benzoxazin-4-one, 3, reacts with water vapor to give N-acetylanthranylic acid, 4[15].



3 4

a

The reaction is anisotropic and begins at the crystal ends, (100) face, and moves in the a axis direction [16]. This motion is consistent with water molecules diffusing more rapidly along the (001) planes, which were shown to be hydrophylic planes.

Solid state deuteriolysis and acidic hydrolysis show that water molecules attack predominantly the imine function. This is indicative of H-bond participation in the diffusion process [17,18]. Acidic hydrolysis in the solid state is observed to be faster than hydrolysis in neutral water vapor. Kinetic experiments show that the reaction is autocatalytic. This may be due to the formation of the acidic product [19].

A mechanism has been proposed for the solid state hydrolysis which involves hydrogen bonding between water and nitrogen atoms prior to reaction at the C-2 position. Such an interaction assists the water molecules in the reaction at the imino group as proposed for neutral and acidic hydrolysis in solution [19].

Both the reaction mechanism and diffusion process were confirmed by theoretical investigations. On the one hand CNDO/2 calculations on acetylanthranyl and its N-protonated ion were in agreement with a preferential nucleophilic attack on the C-2 position of the protonated intermediate[18]. On the other hand, Gavezotti's theoretical method[13] shows that :

- nitrogen atoms and reaction sites have room to allow the formation of hydrogen-bonds [19].

- the cavities provide channels in the $\underline{a}$ direction in which water molecules have a thermodynamically favorable pathway to approach the reactive centers [19].

A D_i map for section y = 0 is shown on Figure 9.

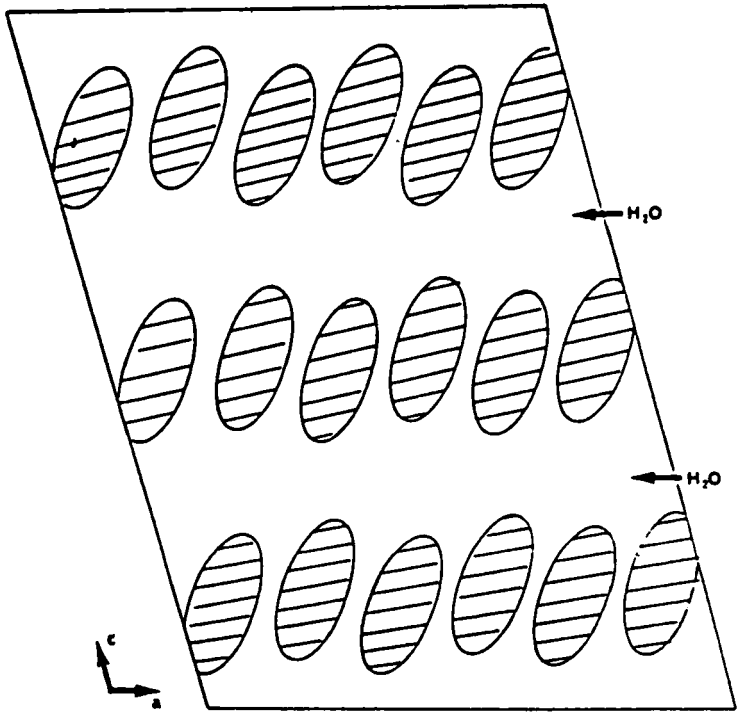
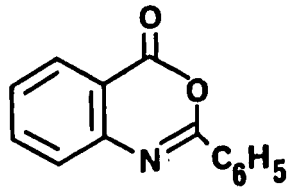


FIGURE 9. D_i map for section y = 0.

Dashed areas give the fraction of occupied space for each molecule. They are indicative of the packing mode of acetylanthranyl which is a parallel arrangement of molecules along the a direction [19].

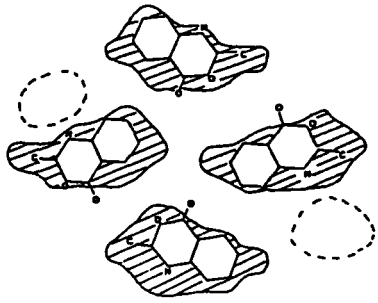
Similar results have been obtained during the solid hydrolysis of phenacetylanthranyl, 5 [20].



5

The reaction is unitropic and proceeds along the b direction. Figure 10 shows the D_i maps for sections perpendicular to z = 0.225, 0.275, 0.725 and 0.775. These values were chosen because they correspond approximatively to the z coordinates of nitrogen atoms in the cell. One observes that nitrogen and imino reactive centers have room to allow the formation of H-bonds and the nucleophile to reach the active sites. All these cavities communicate with each other to form channels in the b direction[20].

Such studies show that an important step in the solid hydrolysis is the penetration of water molecules through channels present in the molecular crystal to form H-bonds with N-atoms borne by the starting material. The cavities provide channels for th penetration of water which can diffuse and interact with the reactive centers.



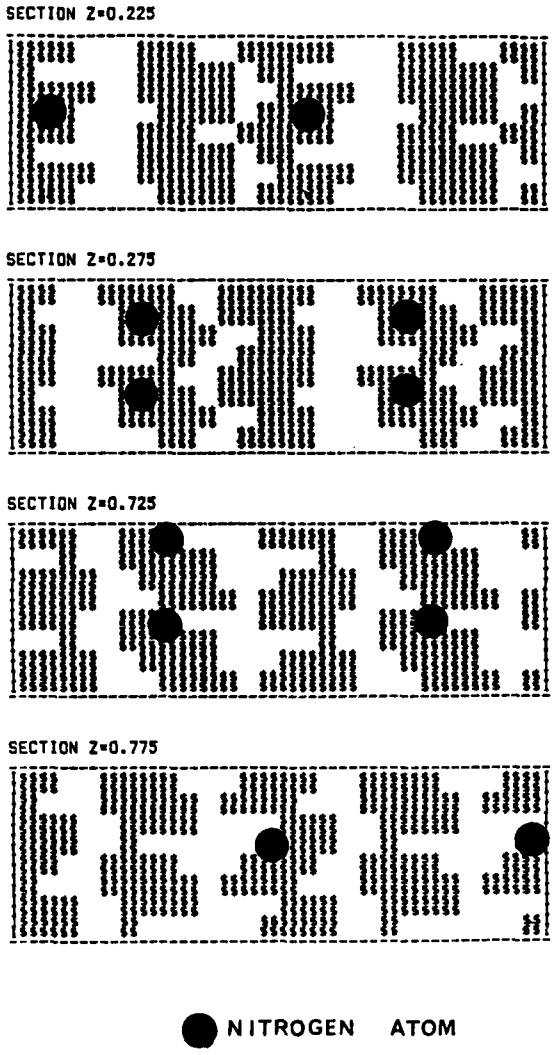
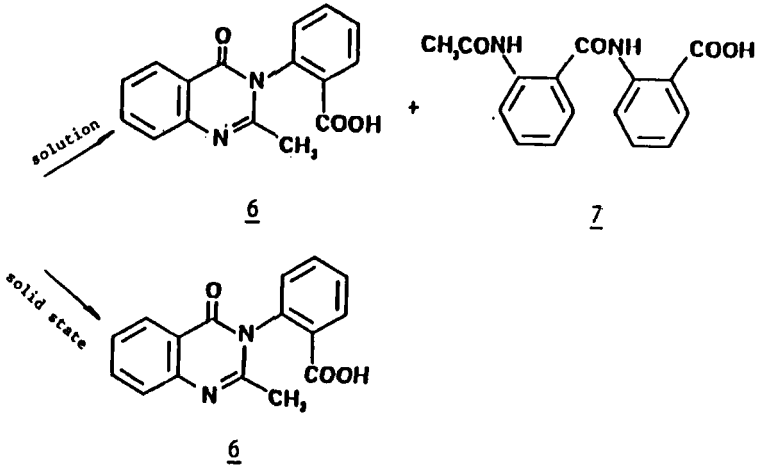


FIGURE 10. D_i maps for sections perpendicular to z = 0.225, 0.275, 0.725 and 0.775 of phenacetylantranyl.

Studies on the penetration of water molecules in organic solids are relevant to the degradation of tablets and powders when exposed to high humidities and consequently are important in the pharmaceutical industry [21].

Lastly we would like to mention that the crystalline arrangement of 2-methyl-3,1-benzoxazin-4-one, 3, is such that gaseous methanolysis of 3 is more specific and more rapid in the solid state than in solution [22,23]. In solution methanolysis of 3 leads to the formation of self condensation products 6 and 7 after fifteen days of reaction. In the solid state only 6 is obtained after twelve hours of reaction [23].



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CONCLUSIONS.

These three studies are relevant to the principal fields of solid state chemsitry. The results are ;

- the packing energies of polymorphs were correlated with the corresponding enthalphies of fusion by taking into account the lability and loosening of intermolecular bonds,

- the dependence of the intramolecular change at the beginning of a reaction path with cooperative effects due to crystal forces has been presented,

- the presence of channels has been proved to be essential for a gas to diffuse in crystals during unitropic reactions.

In conclusion, the results reported here represent an effort to understand the molecular processes involved in solid state and solid-gas reactions. They corroborate the classical four-step process proposed for reaction in organic solid[21]. Moreover the details obtained for each step may lead to a new approach of the dynamic of structures in organized media [24].

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