Journal of Thermal Analysis and Calorimetry, Vol. 57 (1999) 157-164

THE MORPHOLOGY OF ETCH PITS DURING THERMAL TREATMENT OF DRUGS AND ITS DEPENDENCE ON THE FEATURES OF THEIR CRYSTALLOCHEMICAL STRUCTURE

M. A. Vasilchenko[1], *T. P. Shakhtshneider*[1], *D. Yu. Naumov*[2] *and V. V. Boldyrev*[1]

[1]Institute of Solid State Chemistry, 630128, Kutateladze, 18, Novosibirsk
[2]Novosibirsk State University, 630090, Pirogova, 2, Novosibirsk, Russia

Abstract

Topochemistry of the initial stages of evaporation and dissolution of monoclinic single crystals of paracetamol and phenacetin was studied. Thermal treatment of these crystals showed that the morphology of etch pits depicts the symmetry of etched planes. The shapes of pits formed during chemical etching of the cleavage plane of a paracetamol crystal by different etchants were not similar to each other. The chemical etching of the cleavage plane of a phenacetin crystal resulted in the formation of pits stretched along the same direction, independently of the chosen solvent. An interpretation of this result is suggested, based on the analysis of the anisotropy of the crystal structure and presence of steric hindrance.

Keywords: chemical etching, morphology of etch pits, paracetamol, phenacetin, thermal etching

Introduction

To improve our knowledge concerning the mechanisms of drug dissolution is important because dissolution of drugs and other organic substances in various liquids is a very common procedure in pharmaceutical research and processing [1]. From this point of view, it is interesting to study the chemical etching of organic compounds, namely, the interconnection between the morphology of etch pits and the structure of molecular crystals. At the same time, it should be kept in mind that the dissolution process depends also on the properties of the solvent used. On the other hand, the method of thermal etching allows us to consider the development of the reaction front when the molecules are removed, independently of the solvent, taking into account the presence of intermolecular interactions in crystals. Paracetamol and phenacetin were chosen as model compounds. These drugs are widely accepted analgesics. They are extensively studied in pharmacy. Good and large crystals of these compounds are readily available. The crystal structure of both these drugs is known [2–5]. Paracetamol [2, 3] and phenacetin [4, 5] are close to each other in chemical structure but differ by packing of the molecules in a crystal and by the presence of

1418–2874/99/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

different intermolecular bonds. The aim of this paper is to study topochemical stages of evaporation and initial stages of dissolution for single crystals of paracetamol and phenacetin.

Experimental

Materials

Paracetamol (J. R. Sharma Overseas Ltd., India), phenacetin (Moscow plant of chemical reagents, Russia), ethyl acetate, acetone, pyridine, dichloroethane, ethanol, and carbon tetrachloride (Angarsk plant of chemical reagents, Russia).

Crystal growth

Paracetamol crystals were grown from ethanol according to the temperature decrease technique from T=35 to T=25°C at a rate of 3°C per 24 h. Phenacetin crystals were grown from ethyl acetate by the method of slow evaporation (T=20°C).

Redetermination of the crystal structure

Within the course of studies, we redeterminated the crystal structure of paracetamol at 150 K [3] and phenacetin at 293 K [5].

Thermal etching

Cleaved planes of paracetamol (010) and phenacetin (100) were heated in vacuum of 10^{-1} Torr (T=96(1)°C) for 7 min and 10^{-1} Torr (T=84(1)°C) for 7 min, respectively. Crystallographic indexes of cleaved planes and habituses of studied crystals were obtained from LAUE and rotation photographs by program LAUE [6].

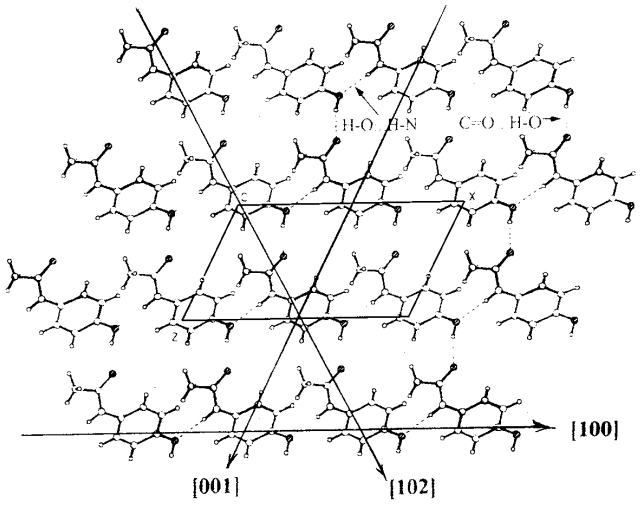

Fig. 1 The projection of the crystal structure of paracetamol along *b*-axis. Broken lines show hydrogen bonds: H–O···H-N, C=O···H–O

Chemical etching

Solutions of the following compositions were used as etching agents (for paracetamol): ethyl acetate/carbon tetrachloride (1.5:1), acetone/carbon tetrachloride (1:1), pyridine/carbon tetrachloride (1:5), acetic anhydride/carbon tetrachloride (1.5:1), dichloroethane. The etching time was 20–25 s for dichloroethane and the solution of ethyl acetate, and 5–10 s for the solution of acetone, acetic anhydride, and pyridine. Solutions used as etching agents (for phenacetin) were: pyridine, ethyl acetate, dichloroethane. The etching time was 20–25 s for dichloroethane and 5–7 s for the solution of ethyl acetate and pyridine.

Results and discussion

Paracetamol crystal structure

The projection of paracetamol structure along the *b*-axis is shown in Fig. 1. It is clearly seen that the molecules are bonded to each other with hydrogen bonds. There are two types of these bonds, N–H···O–H and O–H···O=C. These bonds form parallel layers in the plane (010). Layers of molecules are held together along the [010] direction by van der Waals forces (Fig. 2).

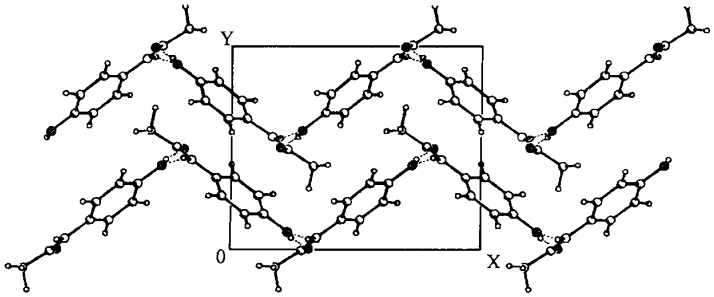

Fig. 2 The projection of the crystal structure of paracetamol along *c*-axis

Phenacetin crystal structure

The projection of phenacetin structure along the *a*-axis is shown in Fig. 3. Phenacetin crystal structure differs from the paracetamol one by the packing of molecules and by the type of intermolecular interactions. The molecules in paracetamol crystals are bound together to form crimped layers with the help of hydrogen bonds of the two types. In the crystal structure of phenacetin, the molecules are held together by the N–H···O=C-type intermolecular hydrogen bonds. They form parallel ribbons in the plane (100). These ribbons are held together along the [001] direction by van der Waals forces.

Thermal treatment of paracetamol and phenacetin single crystals

We began our investigations with thermal treatment of paracetamol and phenacetin single crystals. For paracetamol, thermal etch pits formed during the treat-

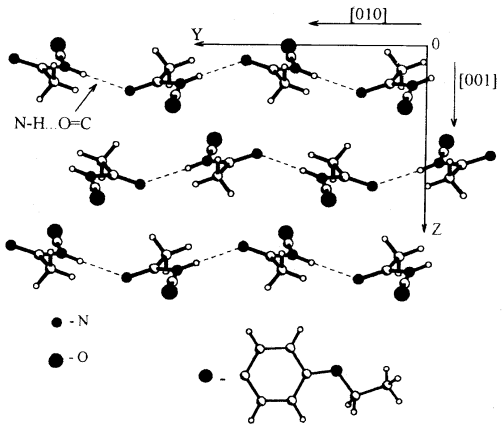

Fig. 3 The projection of the crystal structure of phenacetin on (100)

ment at the (010) plane (which is the cleavage plane) were parallelograms stretched along the *c*-axis (Fig. 4). For phenacetin, the shape of etch pits observed at the (100) plane (cleavage plane) was close to square (Fig. 5). It is known that etch pits inevitably exhibit some symmetry characteristic of the given crystal surface since the shape of etch pits is directly connected with intermolecular forces in the crystal [7]. We can assume that in the case under investigation, the morphology of etch pits during thermal treatment also depicts the symmetry of etched planes (Figs 1 and 3).

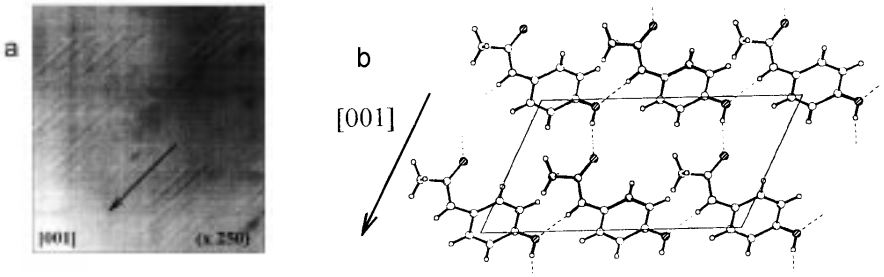

Fig. 4 Thermal treatment of paracetamol single crystals ((010) cleavage plane)

Chemical etching of paracetamol crystals

Two planes of the paracetamol crystals were used in the experiments, namely, the cleavage plane (0l0) and the as-grown (001) face.

The etching of the (001) plane of paracetamol crystal results in the formation of etch pits elongated along the [100] direction, independently of what etching solution is used (Fig. 6). The analysis of crystallochemical features of the structure allowed us to assume that the reaction front anisotropy is connected with the position of hydrogen bonds in crystals. These bonds link molecules in chains along [001] therefore autolocalization during the development of the dissolution front is conditioned by the excitation of molecules linked by hydrogen bonds to the molecule to be removed (Fig. 2).

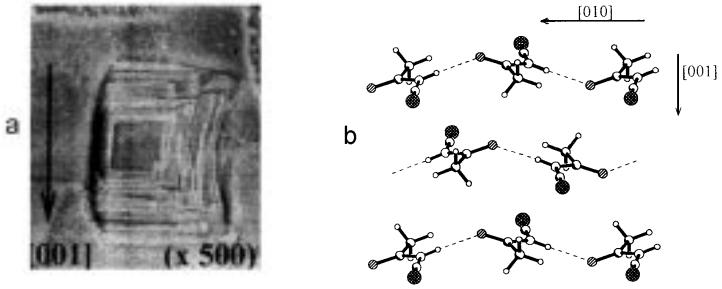

Fig. 5 Thermal treatment of phenacetin single crystals ((100) cleavage plane)

Etching of the crystals of paracetamol at the (010) plane showed that the shapes of pits were not similar to each other (Fig. 7). When we used dichloroethane as an etchant for the (010) plane of paracetamol crystal, we obtained etch pits anisotropic in shape. They were elongated along the [001] direction. When etched with ethyl acetate, the shape of etch pits was close to parallelogram. Treatment with pyridine causes the development of the reaction front in paracetamol crystals in three directions. This leads to the formation of hexagonal etch pits. We suppose that in the case of different etchants the decrease of the reaction front anisotropy results from the increase in the electron donor properties of the solvent molecules. The data on etch pit shapes and the donor numbers of solvents DN^N, according to the Marcus scale, are given in our previous work [8]. The stronger were electron donor properties of an etchant, the less was the extent to which the etchant was sensitive to the choice of crystallochemical directions in paracetamol crystal lattice and the less was the anisotropy of etch pits. In case of an etchant exhibiting weak electron donor properties, the shape of etch pits is sharply anisotropic. The pits are stretched along [001]. On the basis of paracetamol crystallochemical structure analysis, we can assume that dissolution occurs more easily along the [001] direction because this direction is the shortest to pass the 'excitation' from the reacting molecule to neighbouring ones. This assumption (concerning the existence of a direction that is most favourable for the transfer of excitation) is confirmed by the experiments on thermal etching in vacuum. In this case, the molecules are removed preferably along the [001] direction.

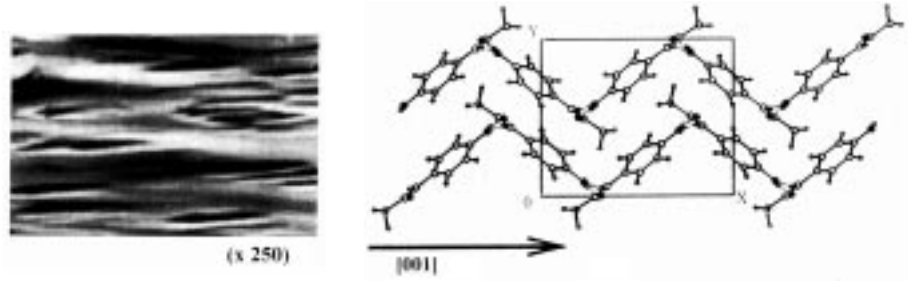

Fig. 6 The chemical etching of the (001) plane of paracetamol crystals in the pyridine solution

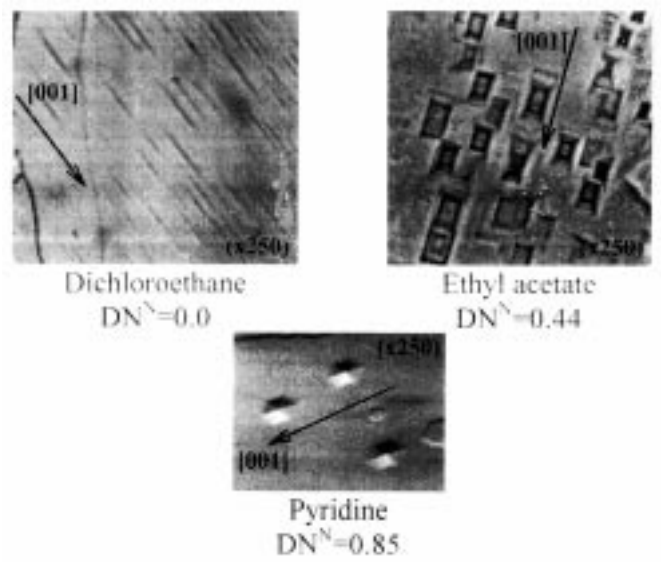

Fig. 7 The chemical etching of the (010) plane of paracetamol crystals in the different solvents

Chemical etching of phenacetin crystals

However, we found that chemical etching of the (100) plane of phenacetin crystal resulted in the formation of pits stretched along [001], independently of the chosen solvent (Fig. 8a). The anisotropy of front development is not connected with the positions of hydrogen bonds in the structure. We believe that different steric features of the interaction between the solvent and molecular crystal can be an explanation for these two cases. As one can see from the projections of the phenacetin crystal structure on *bc* and *ab* planes (Figs 3 and 8b), phenacetin molecules are parallel to [100]; they are packed so that CH_3 groups of the ester and carbonyl ends of the molecules emerge at the (100) plane in an alternating manner. In spite of the carbonyl oxygen being located at a hollow between the neighbouring molecules, it turns out to be more accessible for the solvent molecules than the ester oxygen the access to which is screened by $–CH_2–CH_3$ groups. One can expect from general considerations that the donor properties of carbonyl oxygen are exhibited more vividly than those of the ester oxygen and the C=O group is a reaction centre attacked by the solvent. This attack is accompanied by the solvatation of the substance to be dissolved. So, the first molecules to be removed during the dissolution will be those located in the crystals along [001] because their oxygen atoms are accessible for solvent molecules. This leads to the observed anisotropic movement of the reaction front during the dissolution.

It should be noted that the packing of molecules in paracetamol crystals is not similar to the packing in phenacetin. The former one is characterized by the accessibility of all the reaction centres to the solvent molecules. Because of this, a prevailing factor in this case is the character of intermolecular interactions existing in the crystals.

As regards the absence of a connection between the donor properties of a solvent and the shapes of etch pits formed during phenacetin crystal etching it should be noted that, along with the steric factors mentioned above, another important feature is that in this case only one type of hydrogen bonds (NH···O) is present in the system. Because of this, the possibility of changing the shape of reaction front due to the competition of the reaction development directions along different types of hydrogen bonds is excluded in this case.

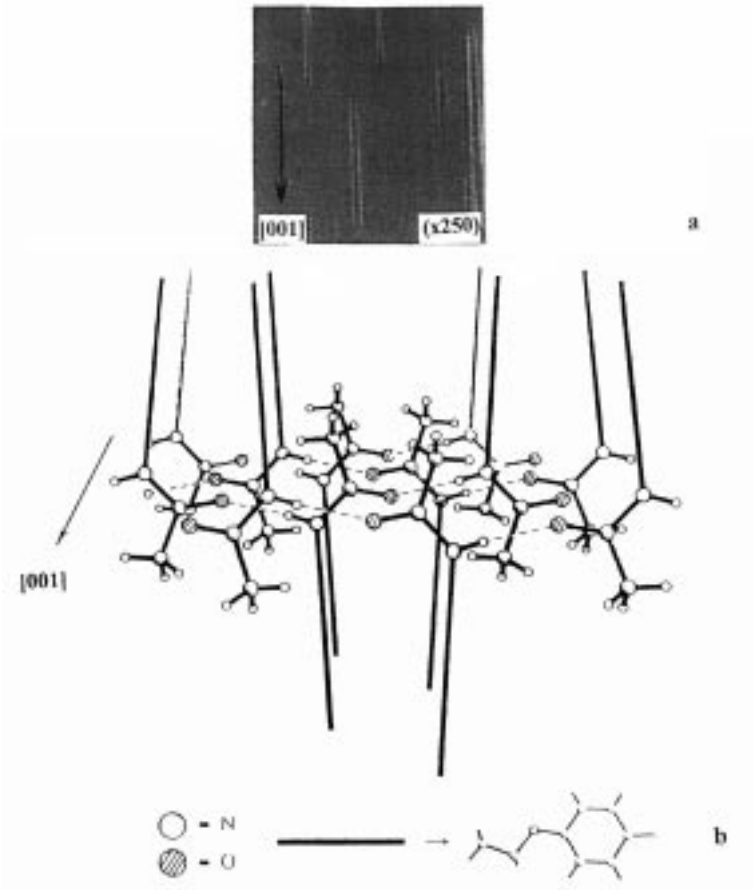

Fig. 8 The chemical etching of the (100) plane of phenacetin crystals in the pyridine solution (a); The projection of the crystal structure of phenacetin along *c*-axis (b)

Thus, the results of our experiments demonstrate an important role which can be played both by steric factors (accessibility of the reaction centre at the molecular crystal to the solvent molecule) and by intermolecular interactions in molecular crystals during the heterogeneous chemical transformations of molecular crystals.

* * *

The study was done under financial support of Russian Foundation of Fundamental Research (N° 96-03-32981) and the Program of supporting of Leading scientific Schools (N° 96-15-97556).

References

1 S. H.Yalkowsky, Techniques of Solubilization of Drugs, Dekker, New York and Basel 1981.
2 M. Haisa, S. Kashino, R. Kawai and H. Maeda, Acta Crystallogr., B32 (1976) 1283.
3 D. Yu. Naumov, M. A. Vasilchenko and J. A. K. Howard, Acta Crystallogr., C54 (1998) 653.
4 U. Patel, T. C. Patel and T. D. Singh, Acta Crystallogr., C39 (1983) 1445.
5 D. Yu. Naumov and M. A. Vasilchenko, Russian Journal of Structural Chemistry, to be published.
6 D. Yu. Naumov, LAUE, Novosibirsk State University, 1995.
7 K. Sangwal, Etching of Crystals (Theory, Experiment and Application), Elsevier, Amsterdam 1987.
8 M. A. Vasilchenko, T. P. Shakhtshneider, D. Yu. Naumov and V. V. Boldyrev, J. Pharm. Sci., 85 (1997) 929.