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Kinetics of interconversion of sulphamethoxydiazine crystal forms

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A quantitative Nujol mull technique is described for the determination of sulphamethoxydiazine crystal forms in mixtures, so that the rates of their interconversion may be determined. The technique is applied to the transformations taking place in the more thermodynamically active as well as biologically available crystal form (Form II). Kinetic parameters indicate a highly temperature dependent transformation ($E_a \simeq 100$ kcal mol^{-1}; 418·6 kJ mol^{-1}) of Form II to the more stable Form I. Suspension in water results in a much faster transformation of Form II ($E_a \simeq 20$ kcal mol^{-1}; 83·7 kJ mol^{-1}, $t_{\frac{1}{2}} \simeq 15$ min) to the water-stable Form III. Water and water vapour are shown to be important factors in the transformation of Form II at room temperature.

The preparation, characterization and interconversion of sulphamethoxydiazine crystal forms has been recently described by Moustafa, Ebian & others (1971). The interconversion of these forms was qualitatively mapped out. Since the bioavailability (Ballard & Nelson, 1962; Higuchi, Lau & others, 1963; Aguiar, Krc Jr & others, 1967; Aguiar & Zelmer, 1969; Haleblian, Koda & Biles, 1971) as well as the physical stability (Frederick, 1961; Moustafa, 1967) of the different forms may be affected by their interconversion, the quantitative study of such transformations seemed important.

Moustafa (1967) studied the rates of interconversion of cortisone acetate crystal forms and derived kinetic parameters for the various transformations. More recently, the kinetics of transformation of sulphathiazole polymorphs using differential scanning calorimetry was reported by Shami, Bernardo & others (1971).

Other investigators developed various techniques for the determination of drug polymorphs in mixtures. However, the use of such techniques in measuring rates of transformation was not fully investigated.

Infrared spectroscopy offers greater opportunities for quantitative studies of polymorphic systems. Although solution and potassium halide methods are not satisfactory for use in such systems because of possible alterations in crystal form (Roberts, 1957; Mesley & Johnson, 1965; Borka & Backe-Hansen, 1968), yet the Nujol mull technique remained as a better alternative. The use of internal standards (Barnes, Gore & others, 1947) or spacers (Garlock Jr & Grove, 1948; Moustafa, 1967) with Nujol mulls have been suggested. However, the use of an absorbance ratio technique (Maruyama, Hayashi & Kishi, 1961) is simpler and perhaps more promising. The latter technique requires the presence of absorption bands having a constant absorbance ratio for a particular crystal form. This ratio should vary quantitatively with the concentration of the crystal form under study.

The present investigation is concerned with the development of an assay technique for the determination of sulphamethoxydiazine crystal forms during their transforma-

tion under standard conditions. Differences in the infrared spectra of Forms I, II & III suggested their use in measuring the rates of interconversion of these forms. The transformations taking place in Form II are the main concern in this work, since the latter was reported (Moustafa & others, 1971; Khalil, Moustafa & others, 1972) to be the more thermodynamically active and biologically available crystal form.

METHODS AND RESULTS

Materials and apparatus

Sulphamethoxydiazine Forms I, II & III (80–90 μm) were prepared as previously described (Moustafa & others, 1971). A Perkin-Elmer double-beam grating infrared spectrophotometer model 237 B was used for the determination of infrared spectra.

Technique of measurement

Approximately 10 mg of sulphamethoxydiazine were mixed lightly with 2 drops of Nujol. The infrared spectrum was recorded for four samples taken from the same mull. Measurement of the absorbance of selected bands (characteristic of each form) was attempted using a variety of methods which fixed different values for the incident light intensity, I_0 (Moustafa, 1967). The method of measurement used by Maruyama & others (1961), shown in Fig. 1 for sulphamethoxydiazine Form II, was found to give

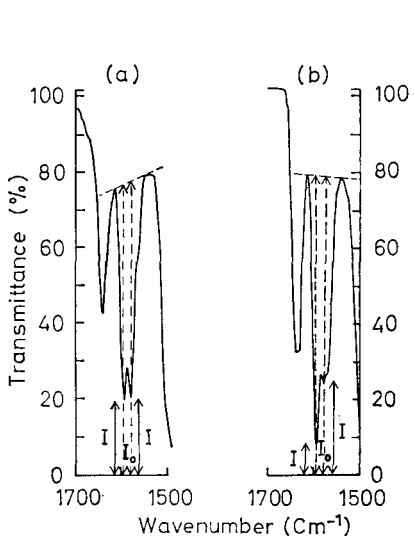

Fig. 1

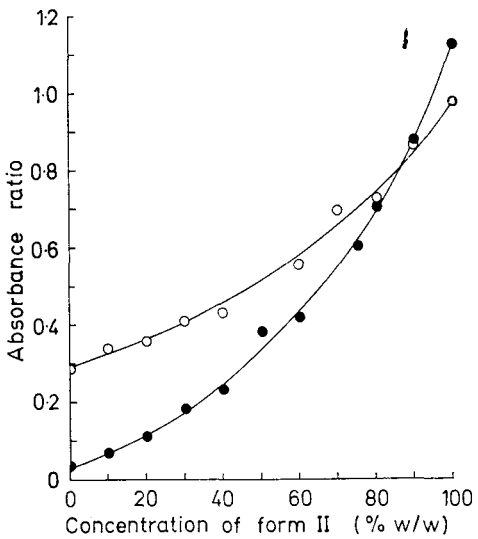

Fig. 2

FIG. 1. Measurement of absorbance ratio of sulphamethoxydiazine Form II (a) alone, (b) in mixture (50% w/w) with Form I.

FIG. 2. Calibration curves of sulphamethoxydiazine Form II. ○——○ Form II in presence of Form I using the ratio A 1580 cm^{-1}/A 1595 cm^{-1}, ●——● Form II in presence of Form III using the ratio A 950 cm^{-1}/A 1595 cm^{-1}.

reproducible results. Constant absorbance ratios (A 950 cm^{-1}/A 1595 cm^{-1}, A 1580 cm^{-1}/A 1595 cm^{-1}) for Form II were observed. The common band at 1595 cm^{-1} was taken as an internal standard. Its absorbance was also found to be constant, as tested in a mull of known concentration in a fixed path-length cell, irrespective of the crystal form. Characteristic bands of Forms I and III did not give sufficiently constant absorbance ratios for quantitative use.

Preparation of calibration curves

Mixtures containing varying quantities of Form II with either Form I, or III were prepared. The infrared spectra of the mixtures were recorded. The absorbance ratio A 950 cm^{-1}/A 1595 cm^{-1} was measured for mixtures of Forms II and III, whereas the ratio A 1580 cm^{-1}/A 1595 cm^{-1} was measured for mixtures of Forms II and I. The calibration curves for Form II in presence of either Form I or III are shown in Fig. 2.

Kinetics of transformation of Form II

A—*Transformation in the solid state.* Form II was shown (Moustafa & others, 1971) to change to Form I by heating. To study the rate of this transformation, about 200 mg samples of Form II were spread on watch glasses and placed in hot air ovens at constant temperatures (100°, 105°, 110° ±0·2°). Samples were taken at various time intervals and assayed for Form II as described above. Results are shown in Fig. 3A.

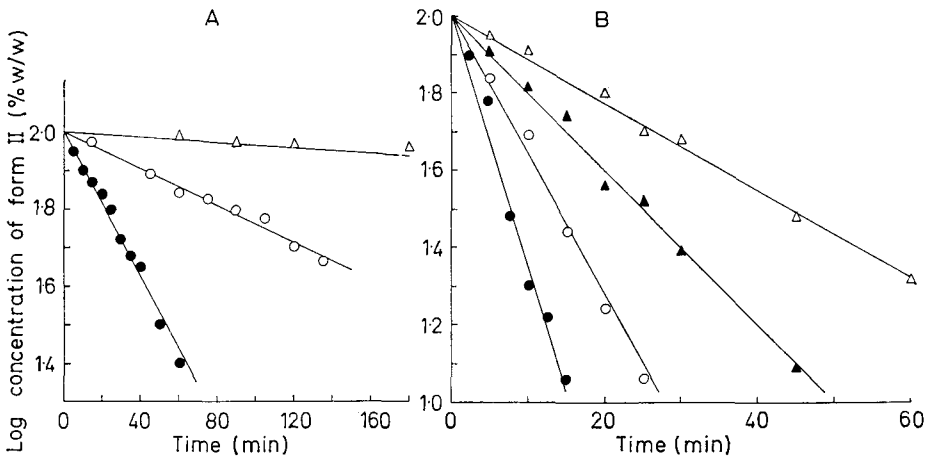

FIG. 3. A. Transformation of sulphamethoxydiazine Form II to Form I in the solid state at various temperatures. △——△ 100°, ○——○ 105°, ●——● 110°.

B. Transformation of sulphamethoxydiazine Form II to Form III in aqueous suspension at various temperatures. △——△ 20°, ▲——▲ 25°, ○——○ 30°, ●——● 37°.

B—*Transformation in suspension.* The transformation of Form II to Form III by suspension in water was previously reported (Moustafa & others, 1971). The rate of such transformation was studied by preparing 1% w/v suspensions of Form II in distilled water and placing them in thermostated water-baths at 20°, 25°, 30°, and 37° ±0·1°. Samples of each suspension were taken at various time intervals, filtered and the residue dried in a current of air at room temperature. The concentration of Form II in the residue (mixture of Forms II & III) was determined as described before. Results are shown in Fig. 3B. The polymorphic transformation was found to be accompanied by a change of habit, from needles of Form II to almost monosized cubic crystals of Form III.

The effect on suspension concentration on the transformation rates was studied by measuring such rates in suspensions containing 1, 3, 5, 7, 10 and 15% w/v of Form II. A linear decrease of the transformation rate constants with increase of suspension concentration was observed when they were plotted on a log-log scale.

C—*Transformation in an atmosphere of 100% relative humidity.* 200 mg of Form II were spread on a watch glass and placed in a humidity cabinet (Gallenkamp & Co. Ltd., London) adjusted to 100% relative humidity and 25° ± 0·1°. Samples were taken at various time intervals and assayed for Form II. Results are shown in Fig. 4.

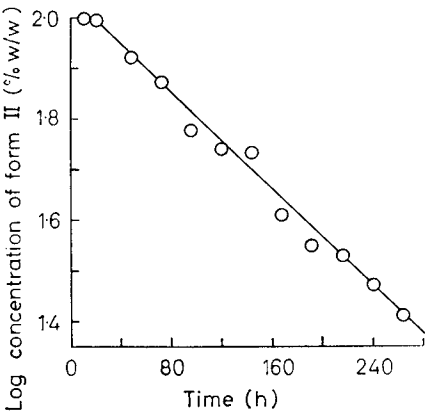

Fig. 4

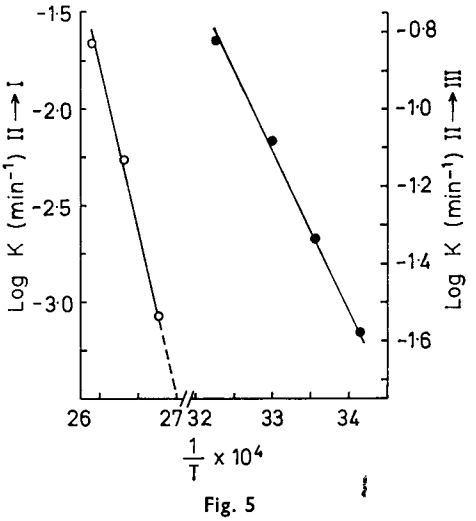

Fig. 5

FIG. 4. Transformation of sulphamethoxydiazine Form II to Form III in an atmosphere of 100% relative humidity at 25°.

FIG. 5. Arrhenius plot of the transformation of sulphamethoxydiazine Form II. ○——○ II → I, ●——● II → III.

DISCUSSION

A quantitative Nujol mull technique has been developed for the determination of sulphamethoxydiazine crystal forms in mixtures, in order to be able to measure the rates of their interconversion. The technique utilizes the constancy of absorbance ratios of characteristic bands in the infrared spectrum of the more energetic crystal form (Form II) for its determination in mixtures with either Form I or III. An absorption band (1595 cm^{-1}) common to all forms had to be used as a reference internal standard since characteristic bands of the various crystal forms were, in most cases, too close to each other to allow their use alone for absorbance ratio measurements. The reproducibility of the technique was better than ±5%. This was found to be acceptable in view of the difficulty encountered by the lack of suitable differences in the infrared spectra of the crystal forms for quantitative use. An example of this difficulty is the limitation of being unable to use the band at 950 cm^{-1} in Form II for its determination in a mixture with Form I due to the presence of a closely interfering band at 943 cm^{-1} in the latter form. Furthermore, absorbance of characteristic bands is sometimes, e.g. 980 cm^{-1} of Form III, not large enough to make their use feasible for quantitative work; greater errors consequently arise. The use of this technique, however, can be recommended for similar polymorphic systems provided that a sufficiently large number of experimental points is adopted.

The transformation of Form II to Form I by heating can be seen from the results (Table 1, Fig. 3A) to be highly temperature dependent. Increase of temperature from 100 to 110° increased the rate of transformation about 25 times. This explains why

Table 1. *Kinetic parameters of the transformation of sulphamethoxydiazine Form II to Form I by heating.*

Rate constant ($K \times 10^3$) min^{-1}				$t_{\frac{1}{2}}$ 25°	E_a
100°	105°	110°	25° (by extrapolation)	min. (calculated)	kcal mol^{-1} (kJ mol^{-1})
0·854	5·520	21·800	infinitely small value	infinitely long time	97·3 (407·5)

the transformation of Form II to Form I is almost instantaneous at 150° (Moustafa & others, 1971) and that the transformation at room temperature is practically negligible. Further evidence is presented by the fact that the activation energy, calculated from an Arrhenius type of plot (Fig. 5) of the results, for the transformation is about 100 kcal mol^{-1} (418·6 kJ mol^{-1}) and that the calculated half-life at 25° is an infinitely long time. A similar highly temperature dependent transformation, in chloramphenicol palmitate, of the α- to the β-form was reported by Borka (1971).

Suspension in water, on the other hand, was found to effect a rather rapid ($t_{\frac{1}{2}}$ = 15 min) transformation of Form II to the water-stable Form III (Table 2, Fig. 3B).

Table 2. *Kinetic parameters of the transformation of sulphamethoxydiazine Form II to Form III by water.*

Rate constant ($K \times 10^2$) min^{-1}					$t_{\frac{1}{2}}$ 25°	E_a
20°	25°	30°	37°	25° (100% rel. humidity)	min	kcal mol^{-1} (kJ mol^{-1})
2·602	4·606	8·280	14·960	0·00912	15·0	19·0 (79·5)

Arrhenius type plot (Fig. 5), shows an activation energy of only about 20 kcal mol^{-1} (83·7 kJ mol^{-1}).

An atmosphere of 100% relative humidity (25°) resulted in a transformation of Form II to Form III. After an initial lag period of about 20 h, the rate of change was found to be about 500 times slower than that of the transformation of Form II to Form III in aqueous suspension at 25° (Table 2, Fig. 4). The initial lag period may be interpreted as the time needed for equilibration of the crystal surfaces with water vapour. These results indicate that water or water vapour is a more important factor in the transformation of Form II at room temperature. A sample of Form II would maintain its identity almost indefinitely in a desiccator, however when placed on the shelf at fairly high relative humidities, transformation to Form III sets in rather slowly. The same phenomenon explains the existence of commercial samples of sulphamethoxydiazine as mixtures of Forms I and III. Form I produced by heating, gradually changes during storage to Form III in an atmosphere of water vapour.

The polymorphic transformation of sulphamethoxydiazine Form II to Form III could be attributed mainly to a water-mediated reversion of the metastable crystal form. According to Carless, Moustafa & Rapson (1968) and Pearson & Varney (1969) this involves dissolution of small particles of Form II, migration of the molecules in aqueous solution and deposition of the nuclei of the water-stable Form III. The changes observed in crystal habit and size distribution provide evidence of this

mechanism (Pearson & Varney, 1969). However, transformation of solid sulphamethoxydiazine in suspension cannot be excluded since, contrary to the findings of Pearson & Varney (1969), seeding with nuclei of the water-stable form was not a prerequisite for the transformation. Nuclei of Form III are produced in suspension by rearrangement of molecules of sulphamethoxydiazine in the solid state. These nuclei continue to grow as described before. Seeding with nuclei of Form III was not found to affect the rate of transformation of Form II in the solid state (Ebian, Moustafa & others, 1973). The polymorphic transformation taking place is perhaps the outcome of an interplay of a number of energy terms which dictate the direction and velocity of the transformation. These include the lattice energies, heats of wetting and solution (Carless & others, 1968). In the present system, the heat of wetting is probably an important term in the energy balance just described, thus wetting with water was found to be the rate controlling factor in the transformation. Changes in the heat of wetting are also probably responsible for the rate retardation observed with suspensions containing higher concentrations of sulphamethoxydiazine Form II, a result which is in disagreement with that of Pearson & Varney (1969).

It was suggested previously (Moustafa & others, 1971) that Form II would be a better choice for use in pharmaceutical preparations. Results of the present study suggest that there is little danger of transformation of Form II in solid dosage forms. Even the compression involved in tablet making was found to affect Form II only slightly. However, the formulation of Form II in aqueous suspensions does not seem appropriate because of the fairly rapid rate of transformation to Form III. The effect of various formulation additives in retarding such transformation has recently been investigated (Ebian, Moustafa & others, 1973).

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