Thermochimica Acta, 159 (1990) 85–91
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CONFORMATIONAL POLYMORPHISM OF A BIOLOGICALLY ACTIVE SCHIFF'S BASE DERIVED FROM SULPHONAMIDE

AHMED M. DONIA and HANAN SALOUM

Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Kom (Egypt)

MOHAMED A. EL-RIES

National Organization for Drug Control and Research, Cairo (Egypt)

(Received 10 May 1989)

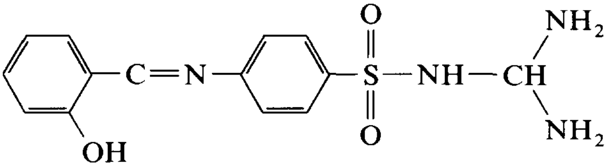
ABSTRACT

The biologically active Schiff's base derived from sulphonamide displays conformational polymorphism and thermochromic behaviour upon heating. The solid state reaction of the polymorphic transformation has been studied using differential thermal analysis, thermogravimetric analysis, electrical conductivity, X-ray powder diffraction and IR spectral techniques.

INTRODUCTION

Polymorphic transformations convert one crystal form of a chemical compound to another. The product of these transformations is the most stable crystal form. On the other hand, polymorphs are interconvertible via dissolution and recrystallization processes as well as solid state reactions. Crystal polymorphs are common in the field of drug manufacture. The presence of a polymorph can alter both the chemical reactivity and the pharmaceutical properties, including the bioavailability, of a compound [1]. The polymorphism of sulphonamides has been studied extensively [1–5]. Results indicate that the widespread polymorphism of these drugs is probably due to (a) the availability of a variety of sites for hydrogen-bonding, and (b) the occurrence of a number of ring–ring stacking modes [1]. Studies have also been made of the conformational polymorphism (i.e. polymorphism in which the conformation of the molecule is strikingly different in the two polymorphs) of various Schiff's bases [6]. The present work investigates the conformational polymorphism of a biologically active [7] Schiff's base (**I**) derived from sulphonamide.

0040-6031/90/$03.50



(I)

EXPERIMENTAL

The Schiff's base I was prepared according to a method reported in previous works [7,8]. Crystallization and recrystallization of the compound were performed in ethanol. Differential thermal analysis (DTA) was performed using a Shimadzu XD-30 thermal analyser with a heating rate of 10 °C min^{-1}. Thermogravimetric (TG) analysis was carried out by recording the weight of the sample before and after a DTA run up to 180 °C. The conductivity measurements were taken using a Keithley 175 autoranging multimeter with applied voltage of 250 V. X-ray diffraction analysis was performed using a Shimadzu XD-3 diffractometer with Cu $K\alpha$. IR spectra were measured quantitatively on KBr discs using a Perkin–Elmer 598 (4000–200 cm^{-1}) spectrophotometer.

RESULTS AND DISCUSSION

Thermal studies

The compound under investigation **I** shows a polymorphic transformation upon heating up to 170 °C, giving another polymorph **Ia**. This solid state transformation reaction and the polymorphs obtained were studied using DTA, TG and electrical conductivity techniques. The DTA curve for **I** (Fig. 1) shows an endothermic peak in the temperature range 100–165 °C. This peak can be assigned to phase transition; on the basis of TG measurements which show no weight loss within that temperature range. The phase transition reaction is irreversible, as can be seen from the absence of its peak in the DTA curve for **Ia** (Fig. 1). The polymorph **Ia** does not revert to **I** either on standing in air or on crystallization from ethanol (Fig. 1). The phase transition peak is followed by two endothermic peaks at 246 and 280 °C (Fig. 1), which can be assigned to melting and material decomposition, respectively. The energy of activation E_a and the order of this phase transition reaction were evaluated from the DTA peak. The value of E_a, as obtained by the method of Piloyan et al. [9] (Fig. 2), is 3.16 kJ mol^{-1}. The order value, as obtained by Kissinger's peak asymmetry method [10], is 0.8.

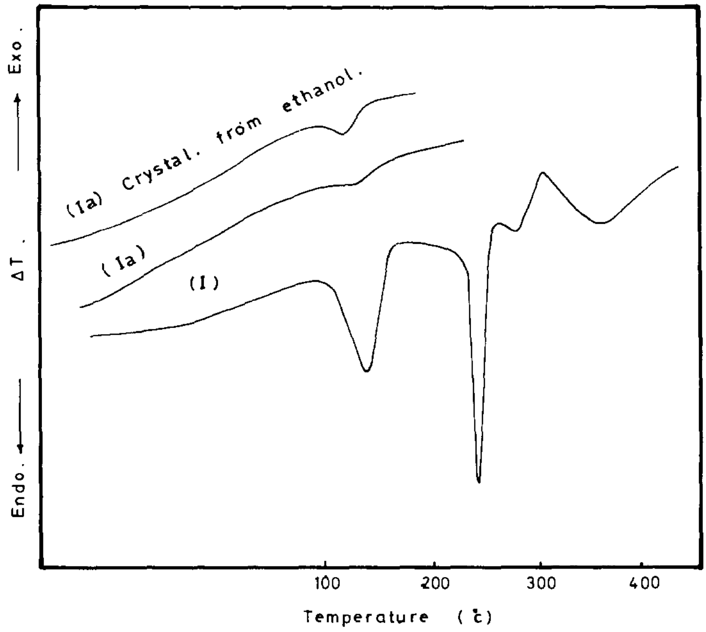
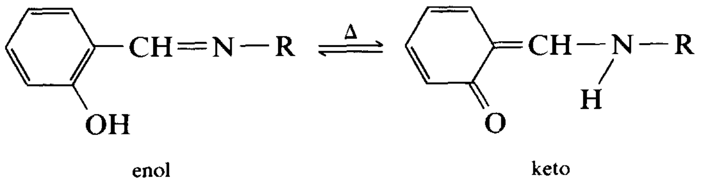


Fig. 1. DTA curves for **I** and **Ia**.

It is interesting that both **I** and **Ia** display thermochromic behaviour (a reversible colour change from yellow to orange) upon heating up to 110 °C. The same phenomenon has been observed for many Schiff's bases, especially salicyl derivatives, and has been attributed to keto–enol tautomerism [11].



This may explain the very weak reversible endothermic peak observed at 110 °C in the DTA curve for **Ia**.

Further evidence for the present phase transition and its irreversibility is furnished by the electrical conductivity behaviour of **I** with changing temperature. The conductivity was recorded through ascending and descending temperature within the range 30–206 °C. The ascending run (Fig. 3) indicates semi-conducting behaviour with activation energy ΔE of 0.50 eV above the knee temperature of 181 °C. Within the range 30–115 °C the conductivity values are nearly constant. The temperature range within which decreasing conductivity is observed (115–166 °C) coincides exactly with that of the endothermic DTA peak. This suggests that the energy of the system is involved in the phase transition rather than in the thermal agitation of

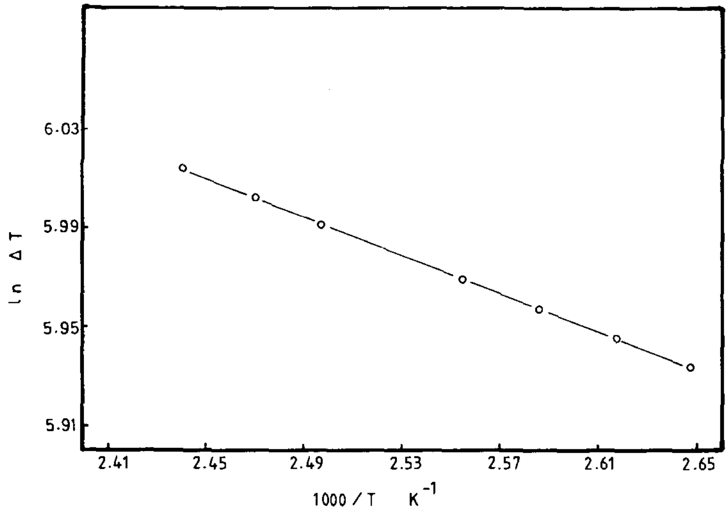


Fig. 2. A plot constructed from the DTA curve for **I**.

electrons, resulting in lower conductivity values. The descending run also shows semi-conducting behaviour with the same activation energy ΔE of 0.50 eV above the knee temperature of 167 °C. The constant conductivity values within the temperature range 30–167 °C, and especially 115–166 °C, suggest that the process under investigation is irreversible.

Spectroscopic studies

The phase transition was also studied using X-ray diffraction. Figure 4 shows the different X-ray diffraction patterns of **I** and **Ia**, indicating the

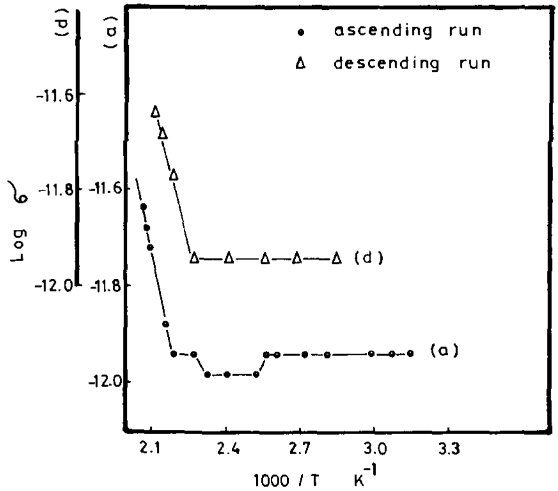


Fig. 3. Temperature dependence of electrical conductivity of **I**.

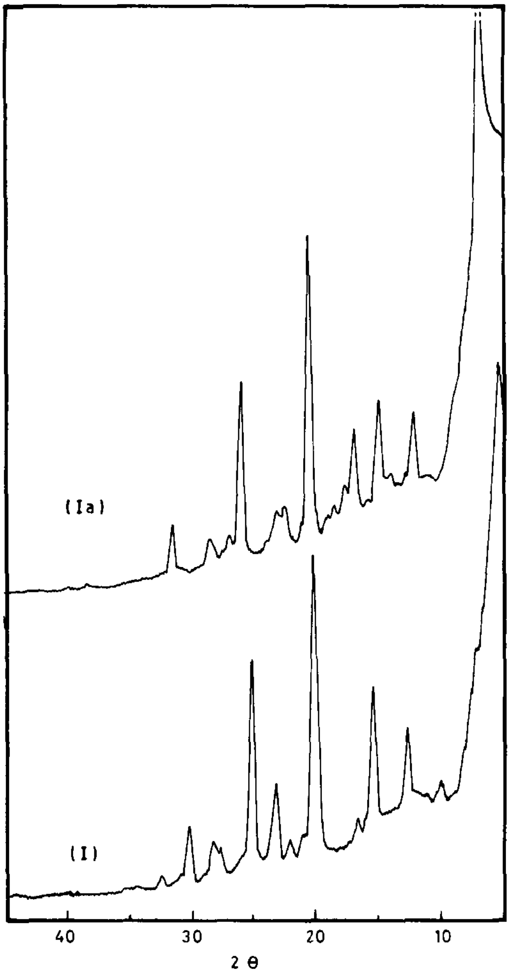


Fig. 4. X-ray powder diffraction patterns of **I** and **Ia**.

presence of two phases (two polymorphs). IR spectroscopy can also be a useful tool in the investigation of conformational polymorphism [1]. The IR spectra of polymorphs **I** and **Ia** are significantly different (Fig. 5). Conformational polymorphism is indicated by differences in the intensity, shape and in some instances position of some peaks, especially those for νNH_2, phenyl ring overtones and combinations, νC–N, ring vibration and CH out-of-plane deformation [12], in the regions 3500–3200, 2100–1800, 1350–1100, 1000–900 and 850–700 cm^{-1}, respectively [1,13,14]. In other words, the conformation of the molecule is strikingly different in the two polymorphs **I** and **Ia**.

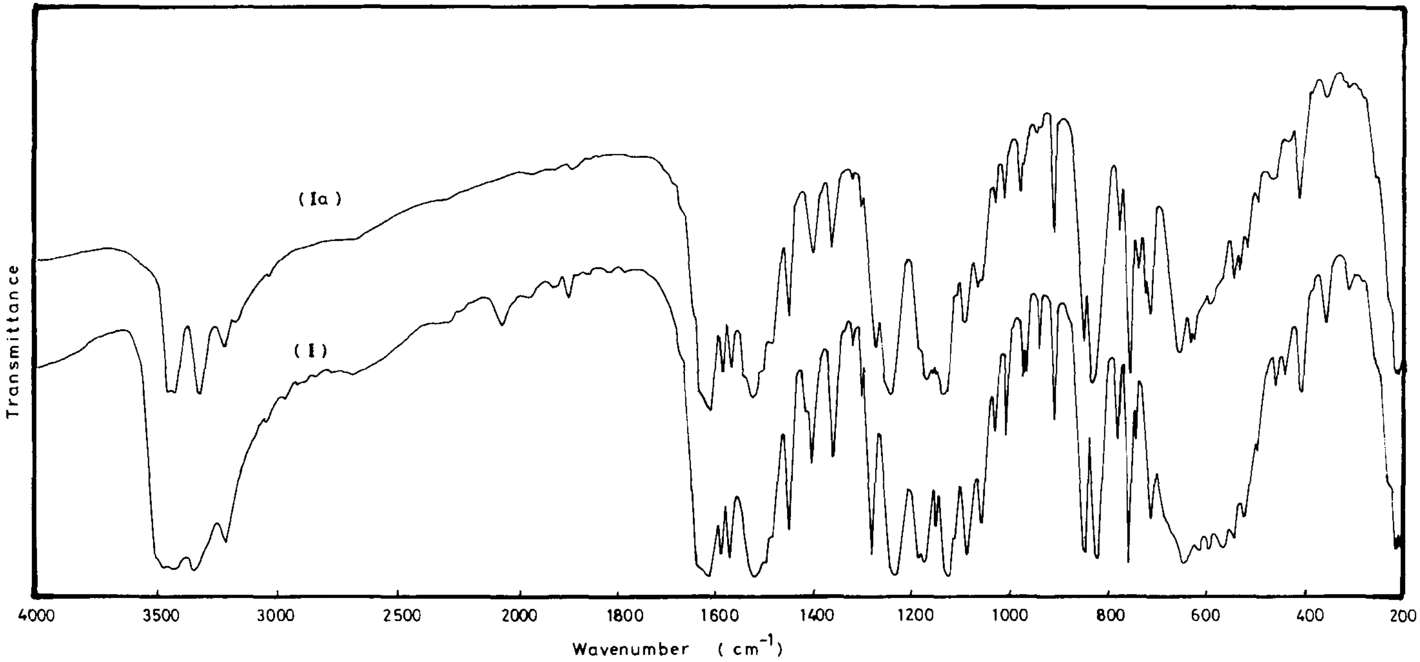


Fig. 5. IR spectra of **I** and **Ia**.

REFERENCES

1 S.R. Byrn, Solid-State Chemistry of Drugs, Academic Press, New York, 1982.
2 B.H. O'Connor and E.N. Masken, Acta Crystallogr., 18 (1965) 363.
3 P.M. Alleaume and J. Decap, Acta Crystallogr., 18 (1965) 731.
4 P.M. Alleaume and J. Decap, Acta Crystallogr., 19 (1966) 934.
5 M.A. Moustafa, A.R. Ebian, S.A. Khalil and M.M. Motawi, J. Pharm. Pharmacol., 23 (1971) 868.
6 J. Bernstein and A.T. Hagler, J. Am. Chem. Soc., 100 (1978) 673.
7 M.A. El-Ries, S.M. Abu El-Wafa and S.M. El-Kousy, J. Pharm. Belg., 43(2) (1988) 93.
8 H. Diehl and C.C. Hach, Synthesis, 3 (1950) 196.
9 G.O. Piloyan, I.D. Ryabchikov and O.S. Novikova, Nature, (1966) 1299.
10 H.E. Kissinger, Anal. Chem., 29 (1957) 1702.
11 E. Hadjoudis, M. Vittorakis and I. Moustakali Mavridis, Tetrahedron, 43 (1987) 1345.
12 J.B. Lambert, H.F. Shurvell, L. Verbit, R.G. Cooks and G.H. Stout, Organic Structural Analysis, Macmillan, New York, 1976.
13 G. De, P.K. Biswas and N. Ray Chaudhuri, J. Chem. Soc., Dalton Trans., (1984) 2591.
14 A.M. Donia, Thermochim. Acta, 152 (1989) 335.