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Characterization of two terfenadine polymorphs and a methanol solvate: kinetic study of the thermal rearrangement of terfenadine from the methanol solvate to the lower melting polymorph

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Abstract

Terfenadine was crystallized from solutions of the drug in ethanol, acetone, and methanol. Two polymorphic forms and a methanol solvate were obtained and characterized using X-ray diffraction (XRD), differential scanning calorimetry (DSC), and thermogravimetry (TG). Kinetic parameters were determined for a structural change that the methanol solvate went through during the desolvation reaction which was found to be completed by heating. On the basis of the X-ray diffractogram and the DSC scan the desolvated product was identified as the lower melting polymorph.

Keywords: DSC; Kinetics; Polymorphism; Terfenadine; TG; XRD

1. Introduction

Terfenadine, α-[4-(1,1-dimethyl ethyl)phenyl]-4-(hydroxy diphenyl methyl)-1-piperidine butanol, is a histamine H_1 receptor antagonist devoid of the usual sedation side effect of antihistamines [1]. Solid terfenadine is known to exist in two polymorphic forms. Characterization of terfenadine polymorphs has been carried out, for example by Badwan et al. [2], who also made the assertion that a third

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polymorph may be recrystallized from popylene glycol and had the lowest melting point.

Terfenadine forms can be obtained by crystallization from solutions of different organic solvents. In certain cases, solvent molecules appear in the crystal lattice of the crystallized product and they may be removed by heating. In this work the thermal rearrangement of terfenadine from the methanol solvate to the lower melting polymorph (i.e. the structural change through which the methanol solvate of terfenadine goes during its desolvation reaction which can be completely done by heating) is of particular interest.

Santos-Buelga et al. [3] have studied the thermal decomposition kinetics (i.e. the reaction rate of the thermal decomposition and its temperature dependence) of terfenadine by two thermodynamic methods, DSC and TG. In this work, the kinetics of the thermal rearrangement of terfenadine have been studied by X-ray diffraction together with DSC.

2. Materials and methods

The crystalline forms of terfenadine were prepared by crystallization from solutions of ethanol, acetone, or methanol. The purity of the raw materials was 99.9%. The assay confirmed the chromatographic purity tests of USP XXII [4]. Terfenadine was supplied by Orion Corporation Farmos, Finland. The quality of used solvents was pro analysi (p.a). The minimum volumes were ethanol 99.7%, acetone 99.8%, and methanol 99.5%.

Terfenadine was dissolved by adding an excess of solvent and heating the solution; complete dissolution was assessed by visual observation. Thus the initial polymorphic state of the material was eliminated. Crystallization was accomplished by slow evaporation of the solvent at room temperature.

X-ray diffraction measurements were carried out using a Philips PW 1820, APD 1700 automated diffractometer system with a hot stage assembly. Nickel-filtered copper radiation was used in the measurements.

A Perkin-Elmer DSC 7 and a Perkin-Elmer TGA 7 were used for the themodynamic investigations. The temperature ranges were 25–170°C (DSC) and 20–200°C (TG). The scanning rate was 10°C min^{-1} for both devices. The devices were calibrated at this scanning rate. The calibration materials were indium and gallium (DSC two-point temperature calibration), indium (DSC enthalpy calibration), alumel and nickel (TG two-point temperature calibration). Atmospheres of nitrogen were created by passing the gas at 30 ml min^{-1} through the sample cell (DSC) or at 60 ml min^{-1} through the oven (TG).

3. General principles for studying the reaction kinetics using empirical rate equations

The rate of any reaction may be studied using empirical rate equations. Phase transformations have been classified by Ehrenfest [5]. The order of the phase

transformation is defined by the lowest order pressure or temperature derivate of the thermodynamic potential function of the transforming phase which goes through a discontinuity during the phase transformation. A real reaction usually involves intermediate phases and so the order of the reaction rarely approximates to an integer. For example a polymorphic phase transition has intermediate phases such as nucleation and interfacial growth and a chemical reaction usually has more than one initial reactant and may, for example, have an ion as an intermediate. The order of the reaction can be defined in an empirical manner. According to common chemical kinetics a differential form of an empirical rate equation of order n can be written as

$$\frac{da}{dt} = k_T(1-a)^n \tag{1}$$

where a is the degree of the reaction, da/dt is the rate of the reaction, k_T is the reaction rate constant at the absolute temperature T, and n is the empirical order of the reaction.

Use of the concentration of the initial phase V/V_0 (which is the decreasing concentration) instead of $1-a$ in Eq. (1) gives

$$\frac{-d(V/V_0)}{dt} = k_T(V/V_0)^n \tag{2}$$

Separation of variables in Eq. (2) leads to integration

$$-\int (V/V_0)^{-n}\, d(V/V_0) = k_T \int dt \Rightarrow V/V_0 = [(n-1)k_T t]^{1/(1-n)} \tag{3}$$

The singularity in $n = 1$ in Eq. (3) can be eliminated by writing

$$V/V_0 = e^{-(k'_T t)^{n'}} \tag{4}$$

In $n = n' = 1$ the integration of Eq. (2) gives Eq. (4). Eq. (4) as well as Eq. (3) is an empirical rate equation and has the ability to describe the S-shaped curve of the concentration of the final phase $V'/V_{\text{final}} = 1 - V/V_0$ (which is the increasing concentration) versus time (Fig. 1). The rate constant k'_T in Eq. (4) and also k_T in Eq. (3) can be used for determining the temperature dependence of the reaction rate by using the well-known Arrhenius equation

$$k_T = k_0 e^{-Q/RT} \tag{5}$$

where k_T is the reaction rate constant at the absolute temperature T, k_0 is an empirical constant having the same unit as k_T, Q is the activation energy in J mol^{-1}, R is the molar gas constant ($=8.3145$ J mol^{-1} K^{-1}) and T is the absolute temperature in kelvin.

The reaction rate is proportional to the number of the activated complexes which naturally follow the Maxwell–Boltzmann distribution. The activation energy Q can be thought of as the energy required for excitation of one mole of molecules or ions to the transition state (according to the transition state theory). It describes the peak height in the energy–reaction progress diagram (Fig. 2).

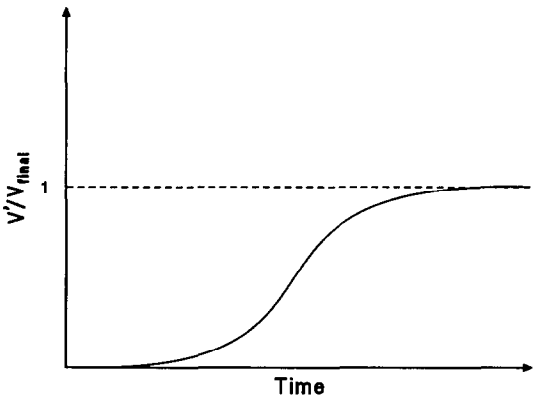

Fig. 1. S-shaped curve of the increasing concentration V'/V_{final} versus time.

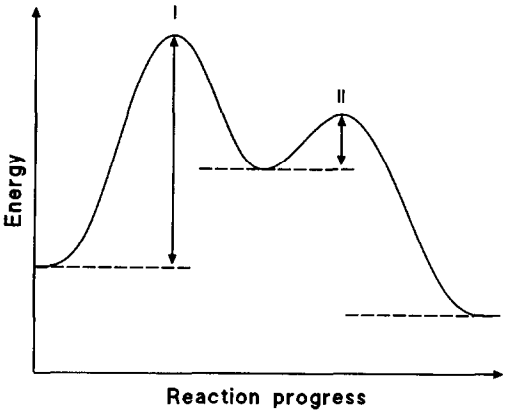

Fig. 2. Energy reaction progress profile of the desolvation reaction. Peak I is the bond breaking between the mother molecules and the solvated molecules, an endothermic phase with a large activation energy. Peak II is the rearrangement of the crystal structure, an exothermic phase with a small activation energy.

The kinetic parameters, such as the empirical order of the reaction or the activation energy, are dependent on the mechanisms of the reaction. They are usually constant in a certain termperature range but can often be altered by changing the temperature range. The reaction rate is determined by the slow phase of the reaction. A change in the reaction mechanism means that the slow phase is not the same.

4. Results and discussion

The higher melting polymorph of terfenadine was crystallized from a solution of ethanol and was characterized by its X-ray diffractogram (diffracted intensity versus

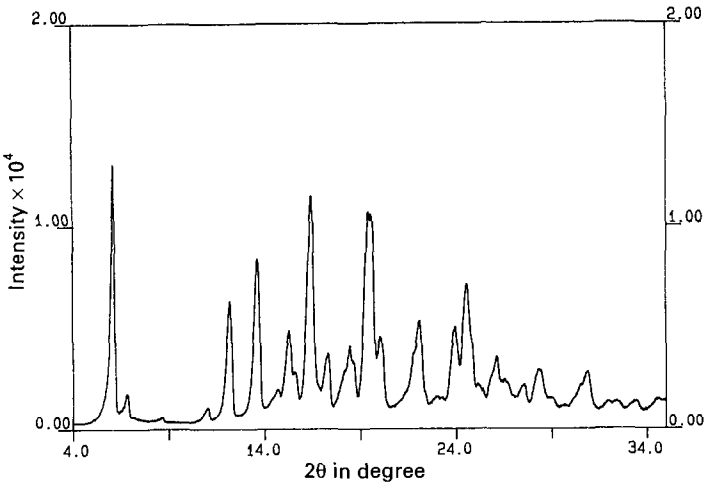

Fig. 3. X-ray diffraction pattern of the higher melting polymorph of terfenadine.

2θ angle or scattering angle, Fig. 3), DI file (relative diffracted intensity versus interplanar distance, see Table 1), and DSC scans (differential change of enthalpy versus temperature, see Fig. 4). The melting point of this form was determined by the onset temperature in the DSC scan as about 150°C.

The lower melting polymorph of terfenadine was crystallized from a solution of acetone and was characterized by the diffractogram (Fig. 5), DI file (see Table 1), and DSC scan (Fig. 6). The melting point of the form was determined by the onset in the DSC scan and was about 146°C.

The methanol solvate of terfenadine was crystallized from a solution of methanol. It was characterized by the diffractogram (Fig. 7), DI file (see Table 1),

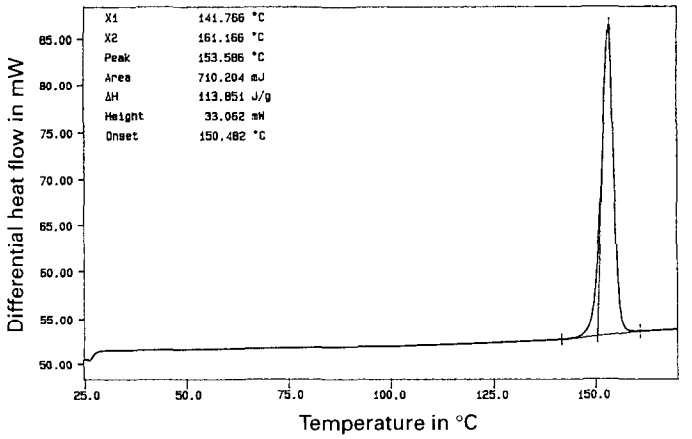

Fig. 4. DSC curve of the higher melting polymorph of terfenadine.

Table 1
The most significant X-ray diffraction reflections of the higher melting polymorph, the lower melting polymorph, and the methanol solvate of terfenadine listed as a DI file

Higher melting polymorph		Lower melting polymorph		Methanol solvate	
d/Å [a]	I/I_{max} in % [b]	d/Å	I/I_{max} in %	d/Å	I/I_{max} in %
14.5	85	14.4	73	15.1	7
12.9	14	7.21	30	13.2	9
8.01	8	6.45	5	10.8	6
7.23	57	6.03	100	8.73	100
6.46	77	5.62	14	7.99	16
5.79	39	5.53	12	7.59	26
5.37	100	5.19	9	6.40	22
5.12	23	5.12	9	5.43	33
4.79	24	4.68	71	5.09	34
4.58	87	4.37	20	4.55	49
4.41	29	3.75	43	4.29	16
4.01	41	3.69	54	4.02	4
3.87	4	3.62	18	3.79	23
3.72	37	3.39	4	3.70	13
3.62	57	3.28	2	3.59	4
3.41	20	3.13	7	3.49	7
3.34	7	3.02	13	3.42	2
3.23	6	2.70	5	3.23	5
3.16	10			3.12	5
3.07	2			3.03	5
2.89	17			2.91	4
2.68	4			2.84	7
2.60	6			2.71	3
				2.62	2

[a] Interplanar spacings; 1 Å = 10^{-10} m. [b] Percentage relative intensity.

DSC scan (Fig. 8), and TG curve (Fig. 9). On the basis of the DSC scan and TG curve the desolvation reaction of the methanol solvate was completed by heating. The desolvated product was identified to be the lower melting point polymorph on the basis of the diffractogram and the DSC scan. The melting point of the form determined by the onset in the DSC scan was about 146°C.

The desolvation of the methanol solvate of terfenadine can be thought of as a combination of two different phases which overlap. These are firstly, an endothermic phase involving the breaking of the hydrogen bonds between the terfenadine and the methanol molecules, and secondly, an exothermic phase caused by the structural change of the crystal lattice (see Fig. 2). The endothermic phase is the slow phase of the reaction characterized by a large activation energy and the exothermic phase is the fast phase of the reaction characterized by a small activation energy.

In this case there is an exothermic peak in the DSC scan of the methanol solvate (see Fig. 8) after all the solvent has evaporated (confirmed on the basis of the TG

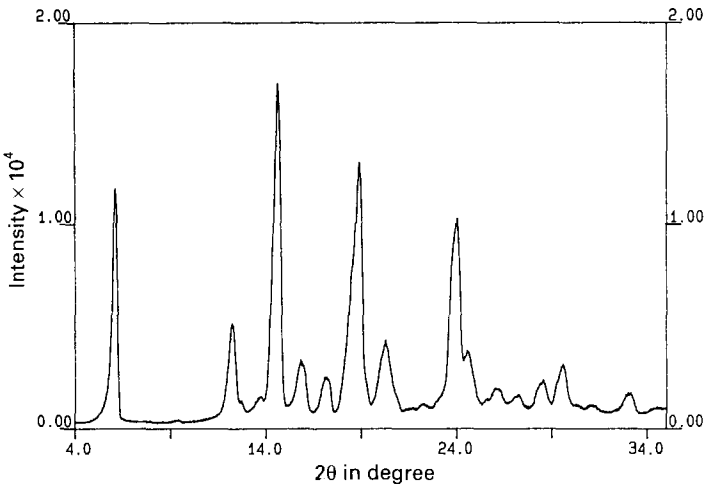

Fig. 5. X-ray diffraction pattern of the lower melting polymorph of terfenadine.

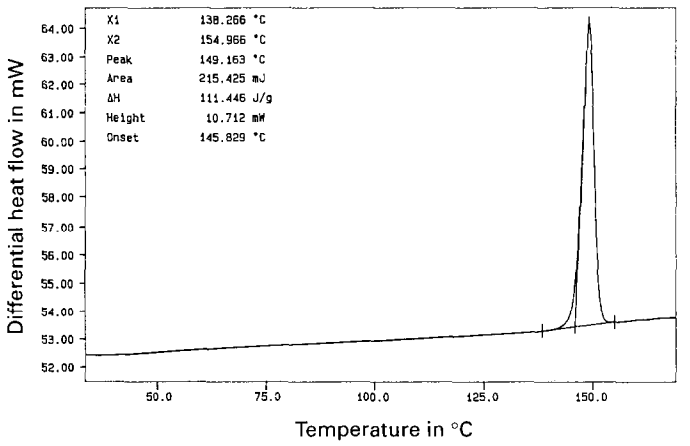

Fig. 6. DSC curve of the lower melting polymorph of terfenadine.

curve, Fig. 9), and its shape is characteristic of the structural change of the form. By taking the natural logarithms of both sides in Eq. (1) and by using linear regression analysis by the least squares (LS) method the rate constant k_T was determined at several temperatures (see Fig. 10). The rate of the reaction (da/dt) in Eq. (1) was replaced by the relative differential change of enthalpy $(dH/dt)\Delta H^{-1}$, where ΔH is the total area of the exothermic peak. Then by taking the natural logarithms of both sides in Eq. (5) and by using linear regression analysis by the LS methods, the activation energy for the structural change was found to be 380 ± 20 kJ mol^{-1} (see Fig. 11). The error limits are $\pm\sigma_m$, where σ_m is the standard

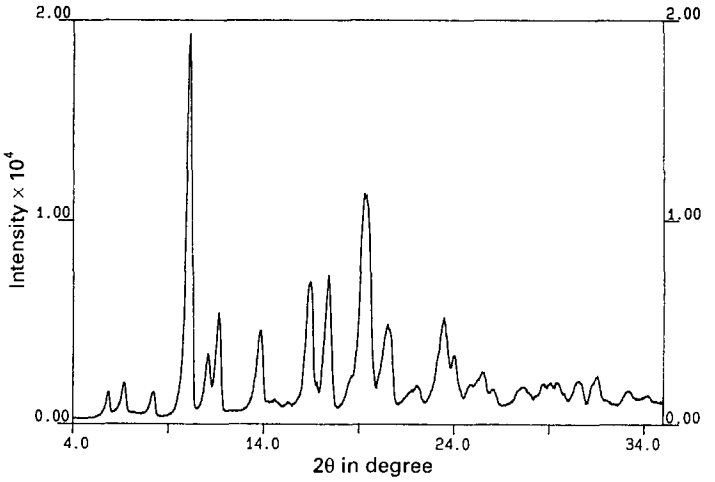

Fig. 7. X-ray diffraction pattern of the methanol solvate of terfenadine.

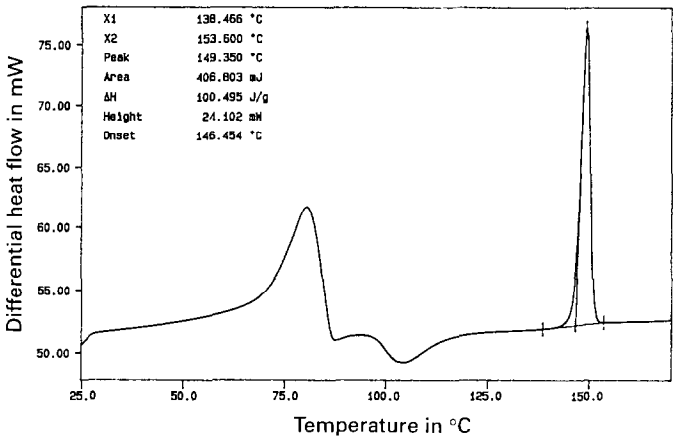

Fig. 8. DSC curve of the methanol solvate of terfenadine.

error of the mean. If the results follow a normal distribution the probability that the correct value appears between the error limits is 68.3%.

The kinetics of the structural change could also be studied by X-ray diffraction with a hot stage assembly and the fact that the strongest reflection in the diffractogram of the methanol solvate decreased as a function of time with a rate which depended on temperature. By taking the natural logarithms twice of both sides in Eq. (4) and by using linear regression analysis by the LS method, the rate constant k'_T was determined at five temperatures (see Fig. 12). If the temperature

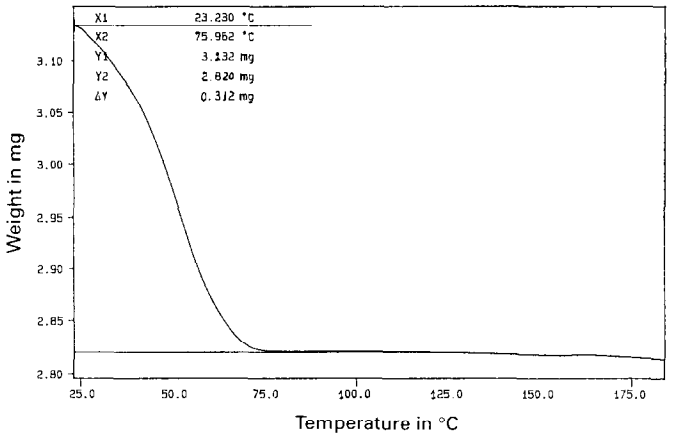

Fig. 9. TG curve of the methanol solvate of terfenadine.

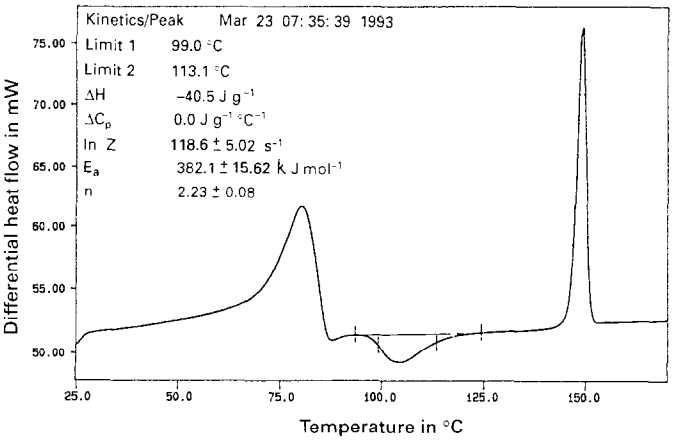

Fig. 10. DSC kinetics of the methanol solvate of terfenadin.

had been elevated above 50°C when an angle-resolved diffraction system was used the number of the observation points would have become too small for statistical analysis. The decreasing concentration V/V_0 in Eq. (4) was replaced by the relation of the integrated diffracted intensities, I/I_0. Then by taking the natural logarithms of both sides in Eq. (5) and by using linear regression analysis by the LS method the activation energy for the structural change was determined to be 380 ± 60 kJ mol^{-1}. The error limits are $\pm\sigma_m$, where σ_m is the standard error of the mean. The quite large deviation of the ln k'_I values (see Fig. 13) can be explained by the macroscopic inhomogenity of the samples. The manual loading of the sample holders had an effect on the density of the samples and thus on the heat conduction from the heating plate to the sample.

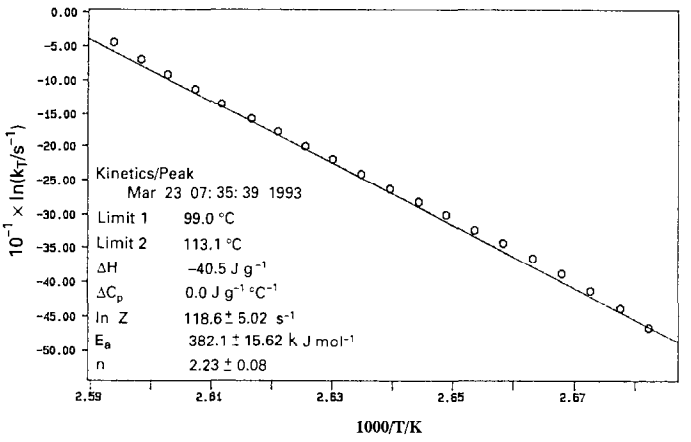

Fig. 11. DSC Arrhenius plot of the methanol solvate of terfenadine.

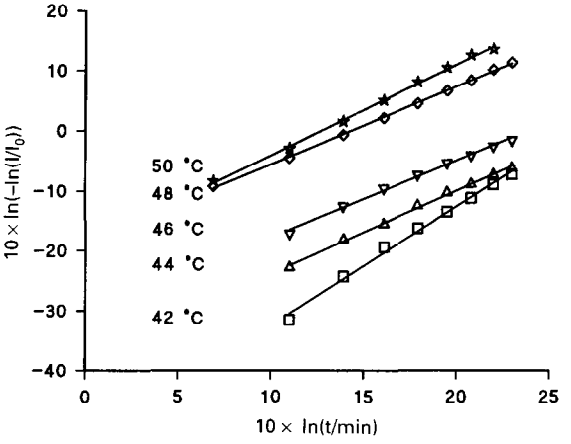

Fig. 12. XRD kinetics of the methanol solvate of terfenadine.

The activation energies for the structural change measured by using two different techniques over different temperature ranges (DSC 99–113°C and XRD 42–50°C, see Figs. 10–13) were approximately equal indicating a constant reaction mechanism over a wide temperature range. Our assertion is that this kinetic parameter is characteristic of the methanol solvate of terfenadine.

The kinetic analysis of the endothermic phase is much more difficult. The crystal structure of the methanol solvate causes steric hindrance which has an effect on evaporation of the freed methanol molecules. There is an intermediate phase which may be compared with a diffusion process.

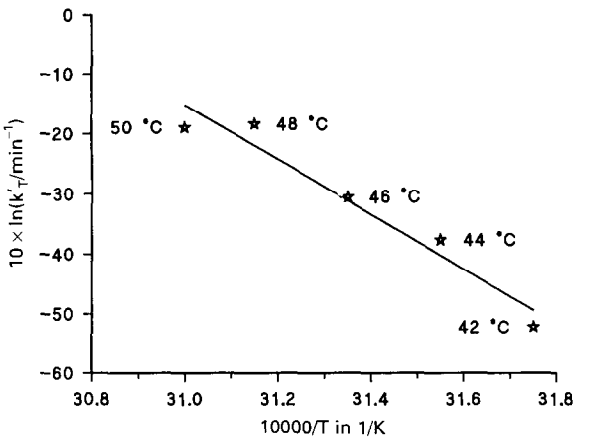

Fig. 13. XRD Arrhenius plot of the methanol solvate of terfenadine.

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