PSEUDOPOLYMORPHISM AND PHASE STABILITY OF 7-PIPERIDINO-1,2,3,5-TETRAHYDROIMIDAZO-[2,1-b]QUINAZOLIN-2-ONE (DN-9693)

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Abstract

The phase stabilities of three pseudopolymorphs of DN-9693 were studied by using thermogravimetry and differential thermal analysis. The thermal dehydration of DN-9693·2HCl·H$_2$O proceeds by the mechanism of two-dimensional growth of nuclei. The thermal dehydration of 0.5 mol of H$_2$O per mol of DN-9693·2HCl·2H$_2$O, and that of 2 mol of H$_2$O per mol of DN-9693·2HCl·3H$_2$O, proceed by the mechanisms of three-dimensional diffusion and three-dimensional phase boundary reaction, respectively, but the dehydration followed overlaps with the thermal elimination of HCl. The half-lives for the dehydration at 25°C show that DN-9693·2HCl·H$_2$O is the most stable form.

Keywords: DTA, phase stability, pseudopolymorphism, TG

Introduction

7-Piperidino-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-2-one (DN-9693) is a new phosphodiesterase inhibitor (Chart 1). In the solid state, DN-9693 has been found to exist in at least three different physical forms: form I (dihydrochloride monohydrate), form II (dihydrochloride dihydrate) and form III (dihydrochloride trihydrate).
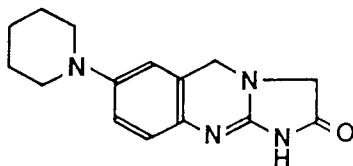

Chart 1 The structural formula of DN-9693

It is well known that physical forms such as pseudopolymorphs affect physical and chemical stabilities, solubilities and bioavailabilities. As the solubilities

of these pseudopolymorphs are sufficiently high, the phase stability is the most important factor in selection of the physical form for the bulk substance.

The present study was conducted to clarify the processes of elimination of crystal water and hydrogen chloride from these pseudopolymorphs, the thermogravimetric technique being used to select the most stable physical form.

Experimental

Materials

Form I (DN-9693·2HCl·H₂O) was of pharmaceutical grade; it was synthesized in our laboratory [1], and was used without further purification.

Preparation of form II (DN-9693·2HCl·2H₂O)

Form I (1.0 g) was dissolved in water (2 ml) and the solution was filtered. The filtrate was allowed to cool at 5°C for 1 day, and crystallization was then induced by scratching the wall of the flask. The resulting crystals were collected by filtration and were air-dried at room temperature for 24 h.

Preparation of form III (DN-9693·2HCl·3H₂O)

Form I (0.5 g) was dissolved in water (1 ml) and the solution was filtered. The filtrate was concentrated to one-third of its original volume. The solution was allowed to cool at 5°C for 24 h. The resulting crystals were collected by filtration and were air-dried at room temperature for 24 h.

Powder X-ray diffraction

The measurement was made with a powder X-ray diffractometer (Rigaku Denki model GEIGER FLEX 2012) under the following conditions: target, nickel-filtered CuK_α radiation, $\lambda = 1.5418$ Å; voltage, 35 kV; current, 20 mA; receiving slit, 0.15 mm; scanning speed, 2° 2θ/min.

Measurement of water content

The water contents of the samples were determined by the Karl Fischer method (type MK-II, Kyoto Denshi Kogyo).

Thermal analysis

The thermal curves of the samples were recorded by thermogravimetry (TG) and differential thermal analysis (DTA) (model SSC/580 TG/DTA20, Seiko Denshi Kogyo). The conditions for TG-DTA were as follows: sample mass,

ca. 10 mg; sample holder, an open aluminum pan; atmosphere, N_2 gas flow (100 ml/min); heating rate, 1, 2, 4, 5, 10 or 15 deg·min^{-1}.

The data obtained from the TG curves were processed on a Burroughs 6800 computer and/or a FACOM M760 computer in the same manner as described previously [2].

Elucidation of the eliminated molecule

In order to elucidate the eliminated molecule, elemental analysis and thin-layer chromatography (TLC) were performed. The sample was prepared by use of TG at a heating rate of 5 deg·min^{-1}. TLC was carried out under the following conditions.

Plate: Silica gel 60 F_{254} (E. Merck, Darmstadt, Germany)

Developing solvents: a) $CHCl_3$/MeOH (6:1 v/v); b) n-BuOH/AcOH/H_2O (1:1:2 v/v)

Detection: 254 nm

Results and discussion

Elemental analysis

The results of elemental analysis and water contents for the pseudopoly-morphs are shown in Table 1. These data prove that forms I, II and III are DN-9693·2HCl·H_2O, DN-9693·2HCl·$2H_2O$ and DN-9693·2HCl·$3H_2O$, respectively.

X-ray powder diffraction

The powder X-ray diffraction patterns of forms I, II and III are shown in Fig. 1, which reveals that the diffraction patterns differ distinctly from each other. Form I exhibits characteristic peaks at 12.3, 17.5, 25.9 and 29.0 degrees, form II at 8.8, 21.6, 26.2 and 27.7 degrees, and form III at 8.4, 22.2, 24.4 and 26.2 degrees. These substantial differences in both the intensities and the positions of the diffraction peaks permit their discrimination from one another.

Thermal analysis

Figures 2–4 depict the TG and DTA curves of forms I, II and III.

For form I, the loss in mass takes place in three steps. Elemental analyses and TLC demonstrate that the first loss in mass (5.4%), which occurs at about 106–152°C, is due to the release of 1 mol of H_2O (calcd. 4.99%). The second loss in mass (19.8%), which occurs in the interval 152–280°C, is due to the elimination of 2 mol of hydrogen chloride (calcd. 20.18%). The last loss in

Table 1 Elemental analyses and water contents of DN-9693 pseudopolymorphs

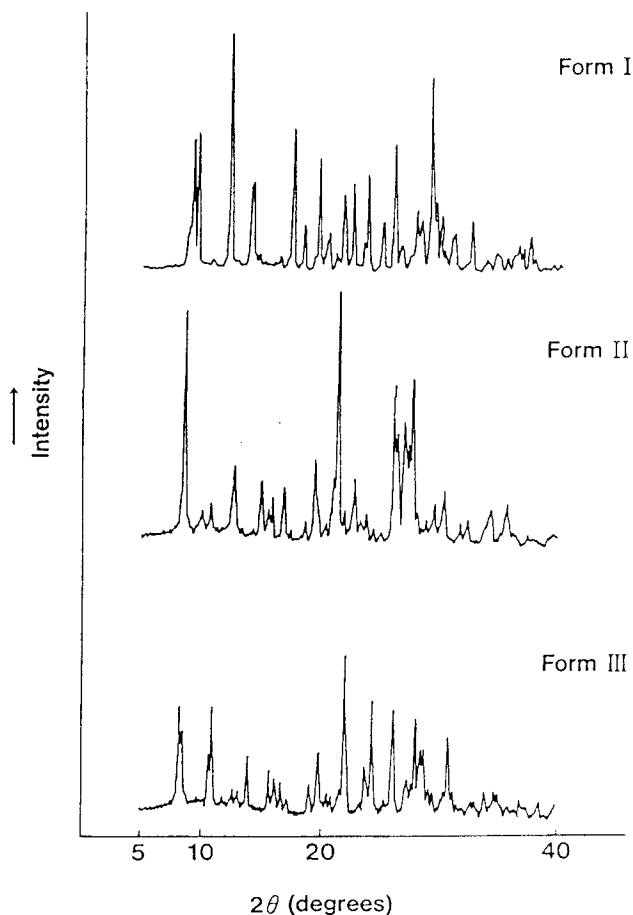| Pseudo-polymorph	Formula		Elemental analysis /%					H$_2$O /%
			C	H	N	Cl		
Form I	C$_{15}$H$_{18}$N$_4$O·2HCl·H$_2$O	Calcd.	49.87	6.14	19.63	15.51	Calcd.	5.0
		Found	49.70	6.17	19.44	15.40	Found	5.4
Form II	C$_{15}$H$_{18}$N$_4$O·2HCl·2H$_2$O	Calcd.	47.50	6.38	14.77	18.69	Calcd.	9.50
		Found	47.59	6.23	14.83	18.49	Found	9.58
Form III	C$_{15}$H$_{18}$N$_4$O·2HCl·3H$_2$O	Calcd.	45.37	6.60	14.10	17.85	Calcd.	13.60
		Found	45.33	6.41	14.12	17.72	Found	14.07

Fig. 1 Powder X-ray diffraction patterns of form I, form II and form III

mass, which begins at about 280°C, is due to the decomposition of DN-9693. The DTA curve shows an endotherm at 138°C, corresponding to the dehydration, with others at 221 and 270°C, corresponding to the elimination of hydrogen chloride, and at 323 °C, corresponding to the decomposition of DN-9693. The TG-DTA observations may be summarized as follows:

1st step: DN-9693·2HCl·H$_2$O → DN-9693·2HCl·+H$_2$O
2nd step: DN-9693·2HCl → DN-9693+2HCl
3rd step: DN-9693 → decomposition

For form II, the loss in mass takes place in four steps. Elemental analyses and TLC show that first loss in mass (3.1%), which occurs at about, 35–96°C, is due to the release of 0.5 mol of H$_2$O (calcd. 2.37%). The second loss in mass (16.1%),which occurs in the interval 96–233°C, is due to the elimination
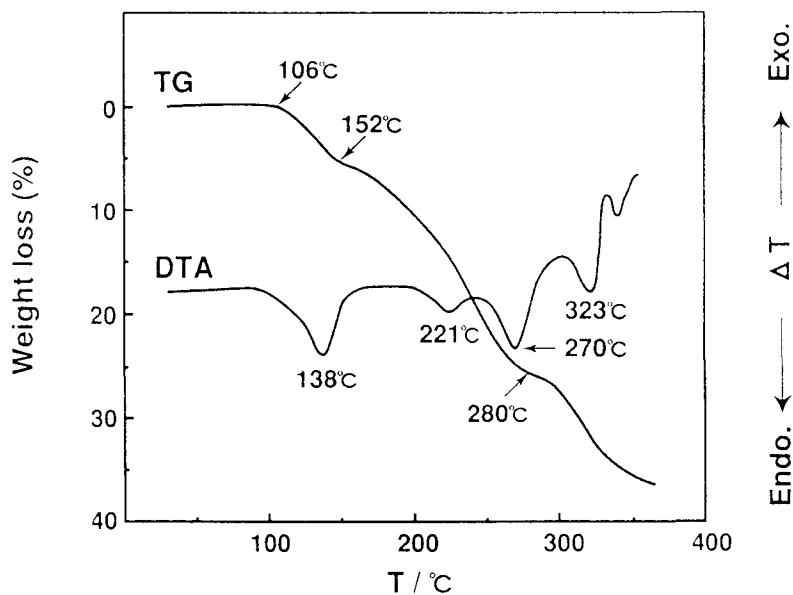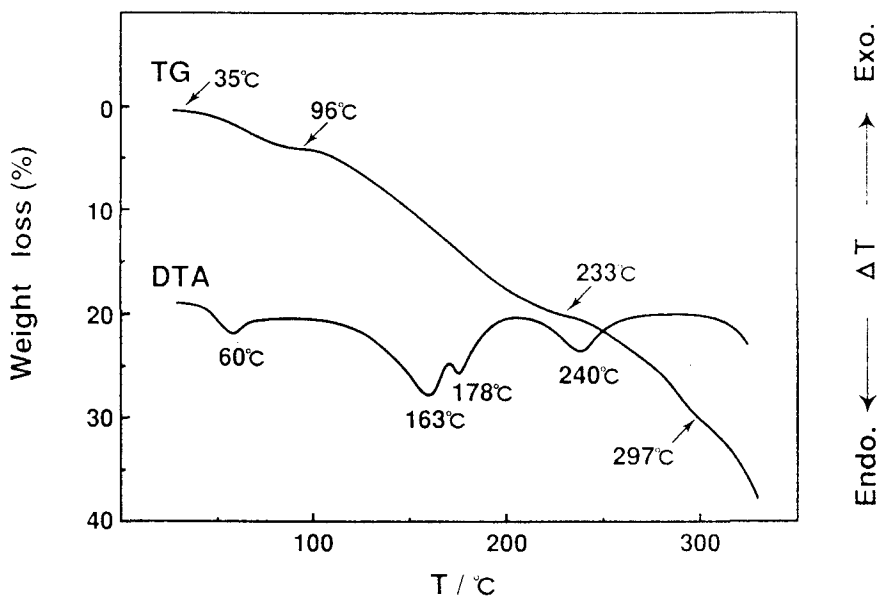
Fig. 2 TG and DTA curves of form I

Fig. 3 TG and DTA curves of form II

of both 1.5 mol of H_2O and 1 mol of hydrogen chloride (calcd. 16.74%). The third loss in mass (9.6%), which occurs in the range 233–297°C, is due to the
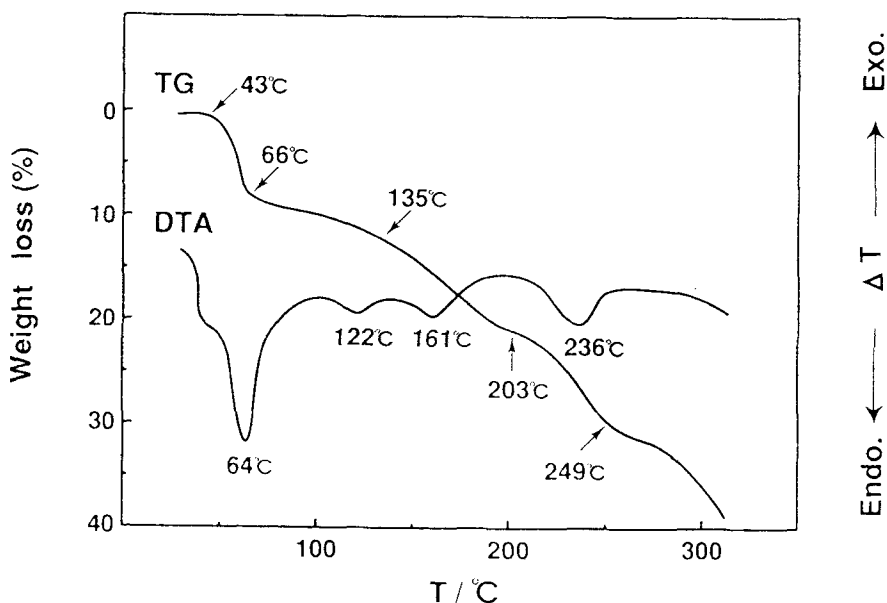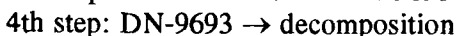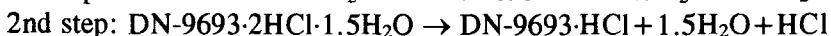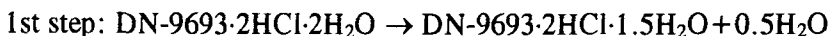
Fig. 4 TG and DTA curves of form III

elimination of 1 mol of hydrogen chloride (calcd. 9.61%). The last loss in mass, which begins at about 297°C, is due to the decomposition of DN-9693. The DTA curve shows endothermic peaks at 60°C, corresponding to the dehydration, at 163 and 178°C, corresponding to the simultaneous elimination of crystal water and hydrogen chloride, and at 240°C, corresponding to the elimination of hydrogen chloride. The TG-DTA observations may be summarized as follows:

1st step: $DN\text{-}9693 \cdot 2HCl \cdot 2H_2O \rightarrow DN\text{-}9693 \cdot 2HCl \cdot 1.5H_2O + 0.5H_2O$
2nd step: $DN\text{-}9693 \cdot 2HCl \cdot 1.5H_2O \rightarrow DN\text{-}9693 \cdot HCl + 1.5H_2O + HCl$
3rd step: $DN\text{-}9693 \cdot HCl \rightarrow DN\text{-}9693 + HCl$
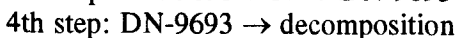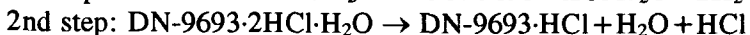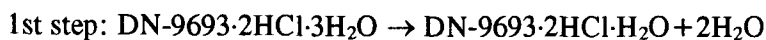4th step: $DN\text{-}9693 \rightarrow$ decomposition

For form III, the loss in mass takes place in four steps. Elemental analyses and TLC demonstrate that the first loss in mass (9.7%) which occurs at about 43–66°C, is due to the dehydration of 2 mol of H_2O (calcd. 9.07%). The second loss in mass (12.7%), which occurs in the interval 66–203°C, is due to the simultaneous elimination of both 1 mol of H_2O and 1 mol of hydrogen chloride (calcd., as $HCl + H_2O$, 13.71%). The TG curve indicates a bending point at 135°C. It seems that the mechanism of the reaction changes at about 135°C and the loss in mass occurs in two steps in the intervals 66–135°C and 135–203°C. Several detailed examinations of the loss in mass clarified that the loss (3.3%) in the interval 66–135°C was mainly due to the release of 1 mol of H_2O, while

Table 2 Kinetic parameters of the pseudopolymorphs of DN-9693

Pseudopolymorph	Reaction	Mechanism	E /kJ·mol^{-1}	A /h^{-1}
Form I (DN-9693·2HCl·H$_2$O)	DN-9693·2HCl·H$_2$O→DN-9693·2HCl+H$_2$O↑	Two-dimensional growth of nuclei. Avrami-Erofe'ev equation.	93.3	2.8×10^{11}
	DN-9693·2HCl→DN-9693·HCl+HCl↑	First-order mechanism. Random nucleation.	90.0	1.5×10^{9}
	DN-9693·HCl→DN-9693+HCl↑	Two-dimensional growth of nuclei. Avrami-Erofe'ev equation.	106.7	5.0×10^{9}
Form II (DN-9693·2HCl·2H$_2$O)	DN-9693·2HCl·2H$_2$O→DN-9693·2HCl·1.5H$_2$O+0.5H$_2$O↑	Three-dimensional diffusion. Jander equation.	88.7	6.9×10^{13}
	DN-9693·2HCl·1.5H$_2$O→DN-9693·HCl+1.5H$_2$O+HCl↑	–	–	–
	DN-9693·HCl→DN-9693+HCl↑	Two-dimensional growth of nuclei. Avrami-Erofe'ev equation.	59.4	3.9×10^{6}
Form III (DN-9693·2HCl·3H$_2$O)	DN-9693·2HCl·3H$_2$O→DN-9693·2HCl·H$_2$O+2H$_2$O↑	Contracting sphere equation. Phase boundary reaction.	182.4	3.9×10^{29}
	DN-9693·2HCl·H$_2$O→DN-9693·HCl+H$_2$O↑+HCl↑	–	–	–
	DN-9693·HCl→DN-9693·HCl+HCl↑	Two-dimensional growth of nuclei. Avrami-Erofe'ev equation.	120.1	3.4×10^{13}

The symbol – represents not to be able to analyse

that (9.4%) at 135–203°C was mainly due to the elimination of 1 mol of hydrogen chloride. The third loss in mass (9.2%), in the range 203–249°C, is due to the elimination of 1 mol of hydrogen chloride (calcd. 9.18%). The last loss in mass, which begins at about 250°C, is due to the decomposition of DN-9693. The DTA curve shows endothermic peaks at 64°C, corresponding to the dehydration, at 122 and 161°C, corresponding to the simultaneous elimination of crystal water and hydrogen chloride, and at 236°C, corresponding to the elimination of hydrogen chloride. The TG-DTA observations may be summarized as follows:

1st step: DN-9693·2HCl·3H$_2$O → DN-9693·2HCl·H$_2$O + 2H$_2$O
2nd step: DN-9693·2HCl·H$_2$O → DN-9693·HCl + H$_2$O + HCl
3rd step: DN-9693·HCl → DN-9693 + HCl
4th step: DN-9693 → decomposition

Kinetics and mechanisms of the thermal reaction

Kinetic analysis with respect to the dehydration and the elimination of hydrogen chloride from the pseudopolymorphs was carried out according to the Ozawa method [3]. The activation energies (E) obtained by the Ozawa method are given in Table 2.

In the case of form I, the activation energies of the 2nd step, the elimination of 2 mol of hydrogen chloride, differ between the first half (90.0 kJ/mol) and the second half (106.7 kJ/mol). These observations suggest that the elimination of 2 mol of hydrogen chloride involves two unit processes. On the other hand, the activation energies of the 2nd step for form II and form III, which consist in the simultaneous elimination of crystal water and hydrogen chloride, gradually decrease with the progress of the reactions. Therefore, the activation energies of these reactions could not be determined.

These activation energies were extended to determine the reaction mechanisms through the use of Eq. (1):

$$g(\alpha) = A\theta \qquad (1)$$

where α is the fraction of reaction, A is the preexponential factor in the Arrhenius equation, and θ is the reduced time [4]. In this study, 10 mechanistic models ($g(\alpha)$) were used for curve-fitting of the TG data [5] to determine the reaction mechanism and A, respectively.

Table 2 presents data on the reaction mechanism, E and A for the dehydration and the elimination of hydrogen chloride from DN-9693 pseudopolymorphs.

The stability of the crystal water for forms I, II and III was predicted by kinetic calculations with the kinetic parameters show in Table 2. The half-lives ($t_{1/2}$) of dehydration at 25°C were calculated to be 8.7 years for form I, 2.2 years for form II, and 51.1 h for form III. On the basis of these $t_{1/2}$ values, it is concluded that form I is the most stable of the three pseudopolymorphs.

References

1 F. Ishikawa, J. Saegusa, K. Inamura, K. Sakuma and S. Ashida, J. Med. Chem., 28 (1984) 1387.
2 H. Kitaoka, K. Ohya and M. Sano, Yakugaku Zasshi, 102 (1982) 428.
3 T. Ozawa, Bull. Chem. Soc. Jpn., 38 (1965) 1881.
4 T. Ozawa, Bull. Chem. Soc. Jpn., 57 (1984) 639.
5 J. H. Sharp, G. W. Brindley and B. N. N. Achar, J. Am. Ceram. Soc., 49 (1966) 379.

Zusammenfassung — Mittels TG und DTA wurde die Phasenstabilität von drei Pseudopolymorphen von DN-9693 untersucht. Die thermische Dehydratation von DN-9693·2HCl·H$_2$O erfolgt über einen zweidimensionalen Kernwachstumsmechanismus. Die thermische Dehydratation von 0.5 mol Wasser pro Mol DN-9693·2HCl·2H$_2$O bzw. die von 2 mol Wasser pro Mol DN-9693·2HCl·3H$_2$O erfolgt über den Mechanismus der dreidimensionalen Diffusion beziehungsweise einer dreidimensionalen Phasengrenzschichtreaktion, jedoch ist die Dehydratation durch die thermische Eliminierung von HCl überlagert. Die Halbwertszeit für die Dehydratation bei 25°C zeigt, daß DN-9693·2HCl·H$_2$O die stabilste Form ist.