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Effect of type and extent of crystalline order on chemical and physical stability of carbamazepine

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Summary

Three crystalline phases of carbamazepine (C), namely (i) the needle-shaped form **I** (tempered) with high crystalline order, (ii) beam-shaped form **I** (anhydrate) with lower crystalline order, which was prepared by dehydration of the dihydrate, and (iii) the prismatic form **III**, which is stable at room temperature, were prepared and their physical properties were determined Then they were separately mixed with 40% (w/w) colloidal silica and stored open under climatic stress at 4 temperatures (56–72 °C) and 3 relative humidities (41–71%) The physial and chemical stability of C was followed for 200 days Form **I** (anhydrate) transformed under all conditions to form **III**, with the highest rate at 51 °C, while the other phases were physically stable C degraded chemically by hydrolysis to iminostilbene (IS), about 10 mol% were formed at the highest stress after 200 days Small amounts of secondary products were detected An initial constant degradation rate up to 1 mol% IS was followed by a slower, again linear degradation The initial rates of formation of IS per unit surface area of the crystals (°k, mol%/day) were highest for form **I** (anhydrate) and lowest for form **I** (tempered) The calculated Arrhenius activation energies up to 67 °C were of the order form **III** > form **I** (anhydrate) > form **I** (tempered) with 135, 125 and 104 kJ/mol, respectively The energies of activation for chemical degradation correlate well with the content in free enthalpy of the respective crystalline phases and their correspondent physical stability

Introduction

Drug compounds with low solubility and/or dissolution rate may cause stability problems in addition to the extent of chemical degradation, namely alterations in rate and extent of dissolution by physical transformations. Besides the surface area of the drug particles accessible for solvent, both the type of crystalline order, i.e. polymorphic modification, and its extent, i.e. degree of crystallinity, are to be considered (York, 1983). These properties of solid phases in turn may modify the rates of chemical reactions, as was reviewed by Byrn (1976) for polymorphic modifications, and was introduced as part of the general concept of "molecular pharmaceutics" by Hüttenrauch (1978). The interdependence of physical state and chemical reactivity has been tested in this work using carbamazepine as a model drug.

The antiepileptic drug carbamazepine has been investigated by several authors with respect to polymorphism and the physical stability of various solid phases (for review, see Krahn and Mielck,

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1987). Consistent data have been obtained for a form with normally prismatic habit, which is termed modification **III** in this work and is the form usually obtained from the market, and for a usually needle-shaped form, which forms at higher temperatures. The latter form is termed modification **I** according to the rules for ordering polymorphs as recommended by Burger (1982). Several findings point to the existence of at least two more modifications. In addition, a dihydrate (Kaneniwa et al., 1984; Krahn and Mielck, 1987; Laine et al., 1984) and an acetonate (Kala et al., 1986) have been described.

From a semischematic energy–temperature diagram we deduced that form **III** is thermodynamically stable at room temperature (Krahn and Mielck, 1987), while form **I** is less stable due to a higher free-energy content. Apparently the degree of crystallinity then determines the rate of physical transformation: needles of form **I** obtained by tempering were stable for at least 3 years, while crystals of the same modification, but obtained by dehydration of carbamazepine dihydrate and thus less ordered, formed increasing amounts of modification **III** with time.

The chemical stability of carbamazepine has only been investigated quantitatively so far in aqueous solution (Beyer et al., 1971; Brazier et al., 1973; Robson and Sharples, 1984) and in suspension (Burckart et al., 1981).

Since differences in energy content exist between the forms **I** and **III** at an equally high degree of order and also between phases with different degrees of order within the same polymorphic modification, differences in the solid-state chemical stability of these materials should also occur (Byrn, 1976). Since chemical reactions which involve other components as reactants can only start at the surface of the particles, rates of reaction have to be normalized with respect to surface area for comparison of different materials. Differences in surface concentration of defects, however, may not yet be accounted for by this normalization.

As judged from the standpoint of a pharmaceutical manufacturer, carbamazepine is considered to be chemically stable.

In order to relate the chemical and physical stability of several crystalline phases, in this model study the chemical stability is reduced by combination with an excipient.

Since the degradation of carbamazepine involves hydrolysis in an early step, a hydrophilic excipient is chosen which reversibly adsorbs considerable amounts of water from the atmosphere and which has been shown to accelerate hydrolytic reactions of rather lipophilic compounds, i.e. colloidal silica (Czaja and Mielck, 1982; Daniels et al., 1986). Therefore, the chemical stability of carbamazepine has been investigated in mixtures with colloidal silica and under climatic stress, i.e. elevated temperatures and relative humidities.

Materials and Methods

*Carbamazepine, modification **III***

Carbamazepine (C) USPXX was obtained from Pfannenschmidt, Hamburg, F.R.G. (lot 001819) and consisted of agglomerates of prismatic crystals. From this material, all other crystalline phases were prepared.

A size fraction of 40–80 μm was obtained by air-jet sieving (Model 200, Alpine).

*Carbamazepine, modification **I** (tempered)*

Six g C were dissolved in 20 ml methanol (analytical grade) at 80 °C. The solution was cooled for 30 s under running tap water. The solvent was evaporated at room temperature (r.t.) by an air stream; the resulting crystals were dried for 3 h at 65 °C in an oven and subsequently carefully dispersed by mortar and pestle. The powder was tempered for 2 h at 175 °C in an oven. Particles below 40 μm and above 224 μm were separated by air-jet sieving and hand sieving, respectively. The resulting product consisted of fine needles partly agglomerated in bundles.

*Carbamazepine, modification **I** (anhydrate)*

Thirty g C were dissolved on a water bath at 80 °C in 220 ml ethanol of analytical grade under stirring and refluxing. 84 ml of distilled water were added dropwise. The mixture was slowly cooled to r.t. during 5 h. The crystals were filtered off, washed with a cold mixture of ethanol and

water, dried for 3 h at r.t. and carefully dispersed as above. The product was dehydrated by heating it in a thin layer in an oven at 65 °C.

A size fraction 40–224 μm was obtained as described above. The resulting particles were beam-shaped.

Powder-technological characteristics

Samples were analyzed by microscopy (Orthoplan, Leitz), and by scanning electron microscopy (SEM) (Stereoscan S4 with Ortec 6230 micro analysis system, Cambridge Scientific Instr.); particle size distributions were obtained by measuring diameters of equivalent circles (Videoplan image analysis system, Kontron); true densities were determined by gas pycnometry, using helium and measuring each of the 4 samples 4 times (Stereopycnometer, Quantachrome); specific surface areas were determined by air permeametry at porosities of 0.38–0.42 (Luftdurchsatzprüfer, Toni-Technik, methanol as measuring fluid).

Physical stability

To obtain X-ray diffractograms, the powders were strewn into the specimen holder and lightly compacted with a glass slide in a diffractometer (Iso-Debyeflex 1001, Seifert, Cu-/K_α anode and goniometer, Philips, and counting electronics, Berthold); quantitative I.R. spectrophotometry was carried out with a Microlab 600 (Beckman) by suspending the powders in Nujol (Uvasol, E. Merck) and reading against Nujol. The analytical method has been described (Krahn and Mielck, 1987). The error in the determination of the ratio of form **I** to form **III** in the sample was 5%. The presence of 40% colloidal silica had no effect on the determination. All samples were heated for 2 h at 65 °C in an oven prior to analysis in order to dehydrate any dihydrate formed during storage. The latter is transformed to form **I** by this treatment (Krahn and Mielck, 1987).

Preparation of mixtures

The respective crystalline materials were mixed with colloidal silica (Aerosil 200, Degussa, Frankfurt, F.R.G., lot 0049). The materials were stored for 1 day at 75% r.h. and r.t. To destroy agglomerates, the silica was hand-sieved through a 180 μm sieve. 24 g of a crystalline phase were mixed with 16 g colloidal silica with the aid of 70 g glass beads of 3 mm diameter in a 1 liter glass bottle by a shaking mixer (Turbula 2 C, Bachofen) for 30 min.

TABLE 1

Apparent zero-order rate constants for the initial formation of iminostilbene (< 1 mol%) in powder mixtures of carbamazepine and colloidal silica (60 + 40, w + w) under climatic stress

Crystalline phase	T (°C)	°k (10^3 mol%/day)		
		41% r.h	60% r.h	71% r h
Form I (tempered)	56 2	8 3± 3.8	11 4± 3 8	11 7± 3.5
	61.8	17 7± 4.4	19 2± 5 0	22 2± 5 1
	67 1	31 4±10 6	33 6± 9 5	40.6±12 9
	72 3	47 6±16 4	43.9±12 8	48 9±18 0
Form I (anhydrate)	56.2	7 9± 1 8	8.5± 2.4	7.4± 2.8
	61 8	17.0± 3 2	14 1± 2 4	19.2± 4 4
	67 1	32.4± 8.4	32.4± 7 9	35.9±10.4
	72 3	47 4±12.9	37 0±16.4	48 3±14 2
Form III	56.2	5.1± 2.0	7 1± 2.8	7 0± 2.8
	61 8	14 8± 3 7	15.5± 3 8	17 1± 4.7
	67 1	32 0± 7 1	39.3± 9.7	35 2± 8 8
	72.3	55 8±12 8	56 8±14 8	58.6±11.1

T, average kinetic temperature
° k, values are mean ± 95% confidence intervals

Preparation of samples and storage

Aliquots of 125 mg mixture were weighed into 5 ml vials. These were stored open in 5-liter glass jars at 41, 60 and 71% r.h. These humidities were produced by saturated solutions of potassium nitrate, sodium nitrate and sodium chloride, respectively, with excess salt. The containers were stored in precision ovens (B 5050 E, Heraeus) at each of the temperatures 55, 62, 67 and 72 °C. The actual temperatures were read by precision thermometers every day for 14 days and subsequently twice a week. The relative humidities within the containers were controlled several times (Humidat IC II, Nova Sina).

The average kinetic temperatures were calculated for the first 20 days of storage (Table 1). During the longer storage times of up to 200 days, the maximum deviation was 0.1 °C.

The average content of C in the mixtures was determined using all samples with contents of less

than 0.25 mol% iminostilbene as main degradation product since the precision in determination of C by HPLC was ±0.3%. The sampling plan warranted an unbiased distribution of the data for the degree of mixing.

Chemical stability

The following materials were used in the analysis by TLC and by HPLC:

Carbamazepine (C): Pfannenschmidt, Hamburg, F.R.G., lot 18009; iminostilbene (IS): Fluka, Buchs, Switzerland, lot 259672; acridine (AI): Sigma, Deisenhofen, F.R.G., lot 103F-3427; acridone (AO): Riedel-de Haen, Hannover, F.R.G., lot 4082; acridone-9-carboxylic acid: Aldrich, Steinheim, F.R.G., lot 00520 KM; 9-methyl acridine: synthetized according to Jensen and Rethwish, 1928: melting temperature, I.R. spectrum and ^{1}H-NMR spectrum were identical with those in the literature.

Thin-layer chromatography

From a solution of 10 mg C in 1 ml methanol, 2–4 µl were placed in bands onto TLC plates (Kieselgel 60 F 254 10 × 10 cm, E. Merck). They were developed horizontally for 70 mm with a mixture of methanol, ethylacetate and toluene (1 + 5 + 4 volume parts). After drying in an air stream, the compounds were detected by inspection in the UV at 254 and 366 nm.

High-pressure liquid chromatography

A column of 250 mm length filled with Nucleosil 5 C8 (Macherey and Nagel, Düren, F.R.G.) was used, and in addition a similar precolumn of 40 mm length and 4 mm inner diameter. A mixture of acetonitrile (Lichrosolv, E. Merck, Darmstadt, F.R.G.) and freshly distilled water (55 + 45 volume parts) was pumped (twin piston pump, Knauer) at 19 to 24 MPa with 1.2 ml/min through a valve (20 µl injection volume, Rheodyne), the columns, and a flow-through cell (8 µl, 10 mm light path) in a photometer (UV photometer at 254 nm, Knauer). The absorbance readings were fed into an integrator (SP 4100, Spectra-Physics).

The sample was transferred to a 25 ml volumetric flask and made up to volume with acetonitrile, analytical grade. After treating for 15 s in an ultrasonic bath, the silica was separated 15 min later by centrifugation. Exactly 1 ml of the supernatant was diluted with 9.00 ml of a mixture of equal volumes of acetonitrile and water and degassed for 15 s. The solution then contained 300 µg/ml C.

External standard solutions were used, where C was combined with IS, and AI with AO. Calibration was performed every day of analysis.

For C, AI and AO the ratios of amount injected and peak area detected were constant during analysis within a known concentration range. Therefore, a single linear calibration curve was used for calculation of concentrations of the respective compound in samples during one day.

The concentration ranges of standard solutions and their number within this range (n), precision of determination (c.v.), and limits of detection were:

C: 260 to 325 µg/ml, $n = 4$, c.v. ± 0.31% at $n = 9$;

IS: 0.1 to 15 µg/ml, $n = 7$, c.v. ± 0.19% at $n = 6$ at 0.26 µg/ml, lower limit for determination

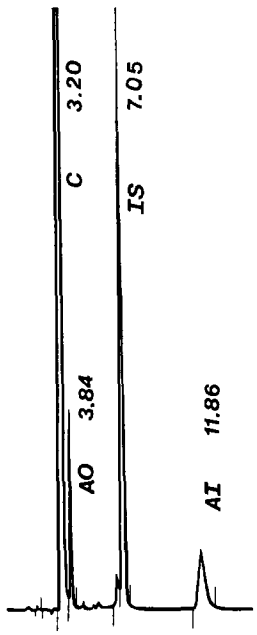


Fig 1 HPLC chromatogram after injection of 20 µl of standard solution with 300 µg/ml carbamazepine (C), 4 µg/ml iminostilbene (IS), 0 7 µg/ml acridine (AI) and 0 5 µg/ml acridone (AO), eluent acetonitrile + water 55 + 45 (v + v) at 1 2 ml/min, retention times in s.

0.1 μg/ml, lower limit for detection 0.05 μg/ml;
AI: 0.2, 0.5 and 0.9 μg/ml, c.v. ± 2.5% at $n = 9$ at 0.2 μg/ml;
AO: 0.2, 0.5 and 0.9 μg/ml, c.v. ± 3.3% at $n = 8$ at 0.2 μg/ml.

The iminostilbene standard contained less than 5% (w/w) impurities, made up by ≤ 1% 9-methyl acridine, ≤ 3% acridine, ≤ 0.1% acridone, and one other compound, which has not been identified.

It was impossible to purify IS further permanently by recrystallization. In solid state after 12 h an equilibrium between IS and its degradation products was re-established.

Within the first hours of analysis, the column demonstrated saturation effects for IS. Therefore, sample preparations and calibrating standards of similar concentrations were injected alternatively for the first hours.

A typical chromatogram resulting from injection of 20 μl of a solution containing the 4 standards is given in Fig. 1.

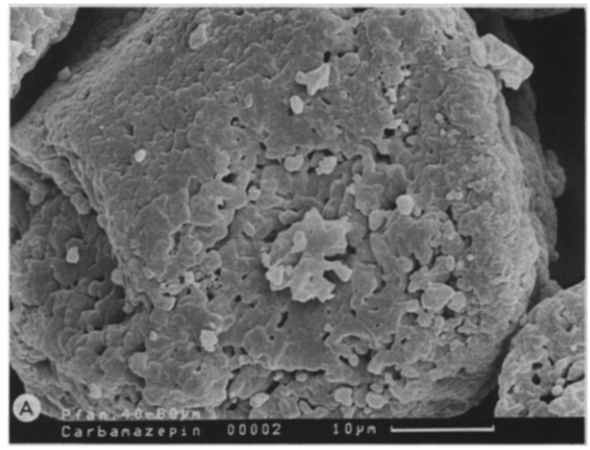
Results and Discussion

Powder – technological characteristics

Particles of the original material (form **III**) are illustrated by S.E.M. in Fig. 2A. The depicted particles of about 80 μm diameter have a porous surface to which very small particles adhere.

Form **I** obtained by tempering is shown in Fig. 2B. Primary particles of needle shape have lengths to about 40 μm, while secondary particles in the form of bundles have edge lengths of up to 120 μm. The surfaces apparently are free of pores. Form **I** obtained by dehydration (Fig. 2C) consists of beam-like fragments with edge lengths of about 100 μm. The surfaces are porous and are covered with numerous small thin particles.

The particle size distributions are skewed; a narrow distribution with d_{max} at 10 μm and another d_{max} at 60 μm was found for form **III**, a wider distribution with one d_{max} at 10 μm for form **I** (tempered) and the broadest distribution with a d_{max} of 10 and another d_{max} at 70 μm for form **I** (anhydrate).



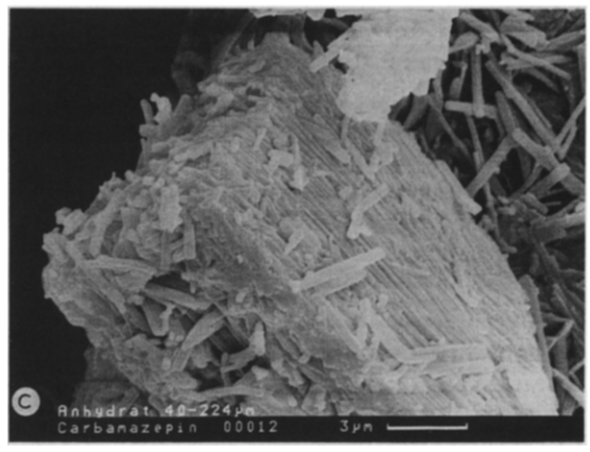


Fig. 2. SEM of 3 crystalline phases of C under study. A form **III** B: form **I** (tempered) C form **I** (anhydrate).

TABLE 2

The physical properties of the 3 crystalline phases of C under study

Polymorphic modification	True density ± S.D. (kg/m^3)	Sieve fraction (μm)	Specific surface area ± S D (m^2/g)	Physical purity; content of I (% (w/w) ± S.D. rel.)
I (tempered	1.301 ± 0.008	40–224	0.50 ± 0 01	97.0 ± 1 1
I (anhydrate)	1 328 ± 0 008	40–224	0 19 ± 0 01	96.2 ± 5 6
III	1.345 ± 0.008	40–80	0.29 ± 0.03	0 0 ± 2.0

The specific surface areas have been obtained by air permeametry and are included in Table 2. Since the chemical degradation was expected to be accelerated by surface contact with the colloidal silica, it seemed more reasonable to determine the 'outer' surface instead of a surface (e.g. by gas adsorption) including pores and crevices, which are not likely to be entered by the silica particles during mixing.

Degree of mixing

The mixtures of the respective crystalline phases of C with colloidal silica had the following mean contents and coefficients of variations, derived from n determinations: form **I** (tempered) 60.21 ± 0.84% ($n = 62$); form **I** (anhydrate) 60.21 ± 1.69% ($n = 88$); form **III** 60.24 ± 1.37% ($n = 80$).

Structural characteristics

The X-ray diffractograms did not point to any alteration in the modification due to the mechanical treatment. Instead, the patterns were identical to those already described (Krahn and Mielck, 1987).

The respective initial contents of form **I** within all 3 products as quantitatively determined by IR spectrophotometry are given in Table 2.

Physical stability

During storage under climatic stress the powder mixtures were analyzed at various times by microscopy, SEM, I.R. spectrophotometry, and X-ray diffractometry.

I.R. spectrophotometry

As described earlier (Krahn and Mielck, 1987), the samples were dried by short heating prior to analysis. Samples containing modifications **I** (tempered) or **III** exhibited negligible changes. However, the anhydrate demonstrated a marked reduction in the content resembling the structure of form **I**, depending on climatic stress, (Fig. 3). Samples of mixtures were also stored at −20 °C and samples of the crystalline phases at r.t. for reference. Even at r.t. the content in form **I** linearly decreased during 200 days to 50%. At higher temperatures, 10% of form **III** have been formed after only 10–15 days.

The rate of transformation of form **I** to form **III** is higher at 56 °C than at 72 °C; since the transition temperature between forms **III** and **I** lies slightly above 100 °C, the rate of transition of form **I** and **III** should be slowed at temperatures closer to this point.

The relative humidity exposes an accelerating effect on the rate of formation of form **III** only at 56 °C, but none at 72 °C. Since the anhydrate

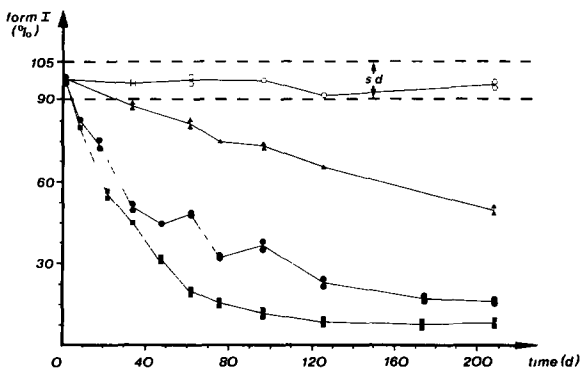


Fig. 3. Residual contents (% w/w) of modification **I** in form **I** (anhydrate) mixed with colloidal silica, transforming to form **III** under different storage conditions. (○), −20 °C; (▲), +20 °C, (●) 72 °C and 71% r h., (■) 56 °C and 71% r.h

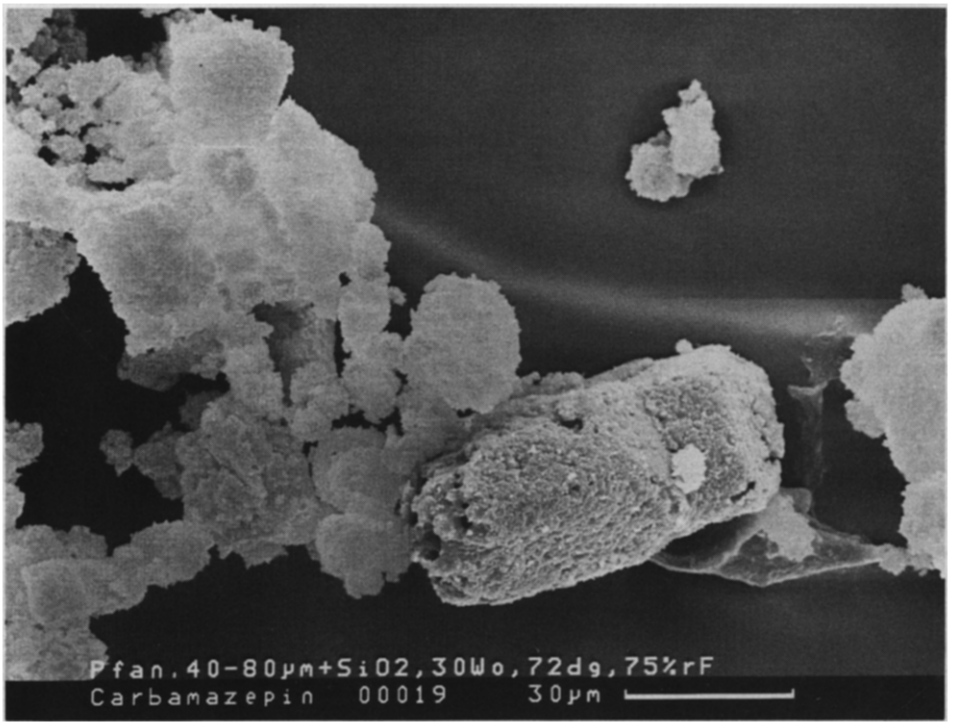


Fig 4 SEM of a sample of form **III**, mixed with colloidal silica, stored for 200 days at 72° C and 71% r.h

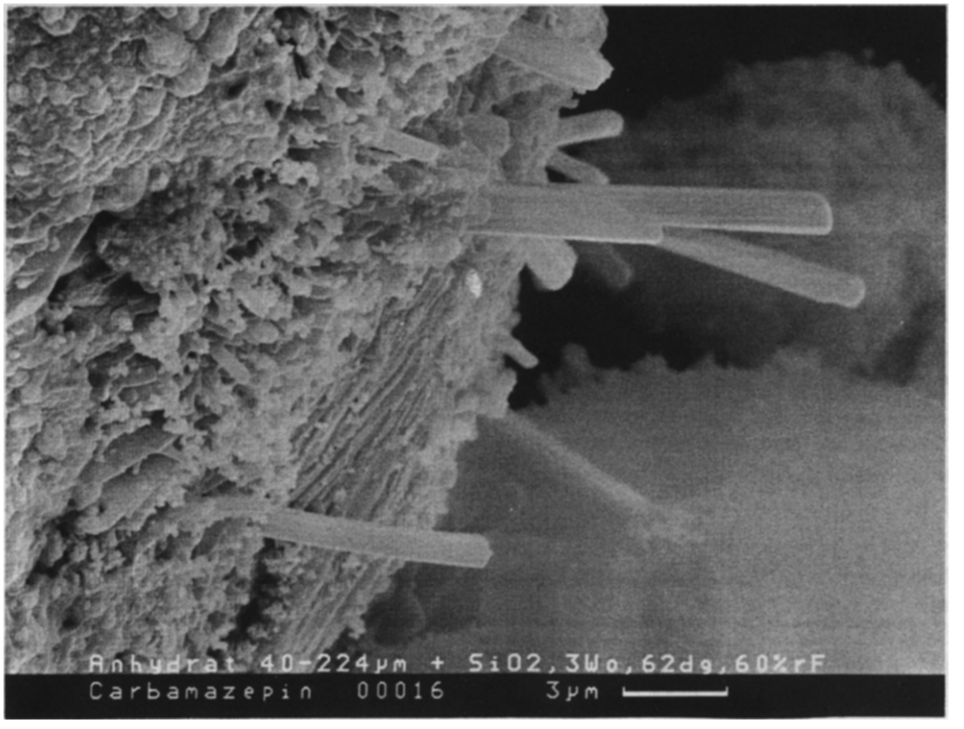


Fig. 5. SEM of a sample of form **I** (anhydrate), mixed with colloidal silica, stored for 21 days at 62° C and 60% r h.

adsorbs more water than the needles or prisms, the rate of transition via molecular dissolution of carbamazepine adsorbed at the surface of the highly disordered anhydrate may favor the formation of form **III**, the stable one under these conditions.

X-ray diffraction

Although the presence of colloidal silica in the powder mixture caused considerable noise in the diffractograms, no changes were detected for the powders containing either needles or prisms. However, the anhydrate exhibited reflexions typical for modification **III**, especially at 15 and 25° (2θ), which increased with time.

Light microscopy

Samples stored for more then 100 days at 72° C macroscopically exhibited dark yellow particles. Under the microscope these were composed of primary particles unchanged in form which apparently were completely chemically degraded. Interactions between the carbamazepine and colloidal silica are supposed since the surface of the agglomerates was transparent and like a gel at various locations.

Scanning electron microscopy

The complete coverage of the surface of the particles of C by colloidal silica was evident from this method. In addition, an excess of silica was present in form of agglomerates. A sample of form **III** with silica stored for 200 days at 72° C (Fig. 4) clearly exposed in the foreground a long crystal already chemically degraded and with an altered surface structure. The other crystals captured by this photograph exhibit the original appearance. This resembles the observation of Okamura et al. (1980), that within a population of particles structural changes occur at points on some of the crystals, where these particles subsequently degrade completely, while others remain unchanged for extended times. At the surface of crystals of anhydrate, stored for 21 days at 62° C (Fig. 5) small needles have grown perpendicular to the original surface.

Earlier investigations of aged anhydrate by thermal microscopy (Krahn and Mielck, 1987) suggested that needles grown from this structure

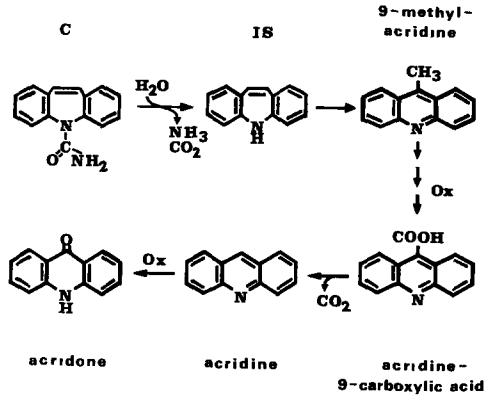


Fig. 6 Reaction scheme for the solid-state degradation of C in mixture with colloidal silica under climatic stress

at about 125° C consisted of pure form **I**. Therefore it may be assumed that depending on temperature not only form **III** may grow (forward reaction) but that at points energetically and structurally favored needles of pure form **I** may grow already at temperatures below the transition temperature (reverse reaction). Since such needles may grow undisturbed during long times they will be of high order and therefore rather stable. In addition, as can be seen from the figure, they pierce the coat of colloidal silica and thus will chemically degrade only to a very small extent.

Chemical stability

Qualitative results

By TLC and by HPLC, 5 degradation products were identified: the main product IS, 9-methylacridine, acridine-9-carboxylic acid, acridine and acridone. Three additional peaks were detected by HPLC after extended storage, which have not been identified. The main reaction path derived from the data is depicted in Fig. 6. Initially, hydrolysis of the carboxamide function leads to IS. Rearrangements of C_{10} and C_{11} lead to 9-methyl acridine, an aromatic, planar three-ring system which subsequently is oxidized. This reaction path is identical with part of the known metabolism of C in vivo (Faigle et al., 1976).

Via an epoxide at the carbon atoms 10 and 11 further products may be formed (Robson and Sharples, 1984); however, they were not detected

in this study. With respect to the rearrangement as well as to the subsequent oxidation a proof for the existence of 9-methyl acridine was important. By comparison with a synthetized standard, traces of this intermediate were detected by TLC and by HPLC (less than 0.001 mol%) in samples stored for extended times. These very small amounts support the lability of this compound for oxidative degradation.

Quantitative results

Since only small amounts of C were degraded, the interpretation of the rates of degradation of the various crystalline phases cannot be based on the losses of C. Only at 72°C the amount of C decreased to 90% within 200 days, with an apparent zero order rate constant of 0.037 mol%/day. Influences of r.h. were not detected.

More informative is the rate of appearance of IS in accordance with the concept of stability-indicating assay methods, as already discussed by Chafetz (1971). The formation curves were non-linear for all crystalline forms. Especially at 72°C, the initially faster formation of IS was seen clearly. When about 1 mol% IS had been formed, the rate decreased and a slower, again apparently linear degradation followed. It is not likely that the secondary degradation products inhibit the formation of IS since even after 200 days at 72°C and 71% r.h. only 0.36 mol% acridine and 0.09 mol% acridone are formed.

From the initial degradation phase (Fig. 7) apparent zero-order rate constants were calculated by weighted linear regression (Carstensen, 1972). In a stepwise procedure, progressively more data (mol% IS) were included until the slope changed significantly by inclusion of the next value, as indicated by exceeding the 90% confidence limits for the regression line obtained so far. The resulting rate constants are listed in Table 1. The influence of temperature is evident. An influence of relative humidity is not detectable since the confidence limits for the rates at constant temperature, but varying r.h., overlap. During the later phase of degradation, an increase in r.h. slightly accelerates the degradation rate.

Comparative stability

For evaluation of reactivities, the rates have to be normalized with respect to surface areas of the crystalline phases (Table 2). The resulting rates are highest for form **I** (anhydrate) and lowest for form **I** (tempered) under all conditions. This is consistent with the concept that a higher crystalline order is obtained by tempering as compared to dehydrating the dihydrate.

The normalization of rates by surface area tacitly assumes comparable concentrations of surface defects per unit area for all crystal phases. No method was available to determine the individual surface concentrations of disorder, as was proposed for total defect concentration per unit mass by Suryanarayanan and Mitchell (1985).

Apparent activation energies were calculated according to the Arrhenius relationship. Statistical evaluation (Stricker, 1977; Zierenberg, 1977) justified a linear relationship and thus a constant energy of activation only for 3 temperatures up to 67°C. Weighted linear regression led to the values listed in Table 3.

The higher energy of activation for the chemical degradation of form **III** correlates with the highest physical stability of this form at temperatures below 100°C. Form **I** (tempered), although physically unchanged during 200 days, is the form physically less stable below 100°C with a lower energy of activation. Yet, it is degraded most slowly under all conditions (Fig. 7). This may be due to the higher degree of crystalline order of the tempered product in comparison to that of form **III**. Then the effect of the higher energy content of the former due to the type of crystalline order is over-compensated.

TABLE 3

Apparent activation energies for the formation of iminostilbene from mixtures of carbamazepine and colloidal silica (60 + 40, w + w) at 56–67°C and 41–71% r.h.

Crystalline phase	E_A (kJ/mol) ± 95% confidence interval
Form **I** (tempered)	104.3 ± 13.2
Form **I** (anhydrate)	125.1 ± 3.5
Form **III**	135.2 ± 8.9

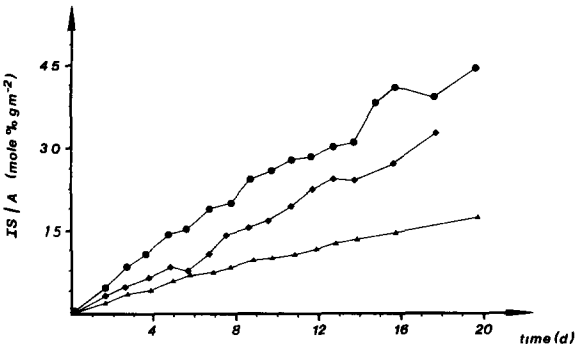


Fig. 7. Amounts of iminostilbene (IS) formed per unit surface area (A), in 3 crystalline phases of carbamazepine in mixtures with colloidal silica and stored at 72° C and 41% r h.: (●), form I (anhydrate); (◆), form III; (▲), form I (tempered).

Form I (anhydrate) has an intermediate activation energy, while its rate of degradation was the highest. This phenomenon may be the result of (i) continuing loss of disordered and thus less stable form I by physical transformation to form III, and (ii) increase in order by recrystallization of highly disordered regions into form I. The activation energy then mainly correlates with the type of order, and the rate of reaction with the degree of order.

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