diffusion coefficients for I and II increased as the calcium concentration increased and then decreased at the 50 m*M* level. The corresponding permeability coefficients agreed fairly well with the sequence of the results. At 0 m*M* calcium, the estimated permeability coefficient of I is almost double that of II, which is also in the order of magnitude of the ratios of their partition coefficients. The permeability coefficients increased with an increase in the calcium-ion concentration, followed by a decrease at the 50 m*M* calcium level.

It is, therefore, proposed that both the prostaglandin molecules and the calcium ions constituting the aggregates crossed intact the diffusion barrier into the mucosal surface. Both species were self-carried in a fashion similar to a carrier-mediated process through the intestinal membrane.

These results may be important in understanding prostaglandin movement through biological fluids and membranes.

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Thermal Decomposition of Amorphous β-Lactam Antibacterials

M. J. PIKAL [x], A. L. LUKES, and J. E. LANG

Abstract □ Thermal decomposition rates for amorphous samples of penicillin G potassium, cephalothin sodium, cefamandole sodium, and cefamandole nafate were determined as a function of water content and temperature. Even when rigorously dry, amorphous cephalosporins were at least one order of magnitude less stable than the corresponding unsolvated crystalline form. Absorbed water generally increased both the number of decomposition products and the net decomposition rate. Reaction kinetics were usually apparent first order, but an anomalously high effective reaction order was observed in several systems. Nonlinear Arrhenius plots were observed, and a qualitative model based on molecular relaxation in glasses is proposed. Although decomposition rates at 25° were small for dry samples, even slight decomposition produced visually detectable changes. Thus, the unsolvated crystalline form was noticeably more stable, even at 25°.

Keyphrases □ Decomposition, thermal—amorphous samples of various antibacterials, effect of water content and temperature □ Cephalosporins, various—thermal decomposition of amorphous samples, effect of water content and temperature □ Penicillin G potassium—thermal decomposition of amorphous samples, effect of water content and temperature □ Antibacterials, various—thermal decomposition of amorphous samples, effect of water content and temperature

Cephalosporins are often difficult to obtain in crystalline form and, even when crystallized, the products may be partially amorphous (1). Thus, information on the stability of amorphous forms is necessary. Several organic reactions were studied in crystalline solids (2–4), but amorphous solids have received little attention. The intuitive notion that an amorphous solid is more reactive than the corresponding crystalline form has some experimental support (5–11) and is probably a useful generalization. However, crystalline reactions are often only slightly slower than the corresponding reactions in the liquid state (2) and some crystalline reactions are considerably faster (12, 13). While the decomposition of cephalosporins and penicillins in aqueous solution has been studied (14–22), data regarding thermal decomposition in the amorphous solid state are limited to several brief reports where the water content of the sample was either high or unspecified (8–11).

This study investigated the thermal decomposition rates of several β-lactam antibacterials in their amorphous and unsolvated crystalline forms as a function of temperature and water content. The amorphous samples studied were amorphous to X-rays and were nonbirefringent when examined microscopically under polarized light. The compounds chosen were penicillin G potassium and three cephalosporins: cephalothin sodium, cefamandole sodium, and cefamandole nafate.

EXPERIMENTAL

Materials—Crystalline cephalothin sodium and crystalline penicillin G potassium were commercial samples[1]. The corresponding amorphous samples were prepared by freeze drying from a 20% aqueous solution. To avoid partial crystallization, the solutions were frozen and partially dried at low temperature (−20°) before allowing the temperature to increase

[1] Eli Lilly and Co., Indianapolis, Ind.

gradually to 25°. The resulting amorphous plugs were then lightly mortar ground and vacuum dried[2]. Water contents were then determined by Karl Fischer assay.

Cefamandole nafate was recrystallized from methanol by addition of 2-propanol, yielding nonsolvated crystalline material. The "wet" crystals were first air dried and then vacuum dried (1). The amorphous sample was prepared as described for cephalothin sodium.

Since no unsolvated crystalline forms of cefamandole sodium have been prepared, only amorphous forms were studied. To optimize purity, crystalline solids (solvates) were used. The dioxane solvate of cefamandole sodium was obtained by adding dioxane to a concentrated aqueous solution. The resulting crystals were repeatedly dissolved in water, freeze dried to remove dioxane, and finally spray dried (1) from an aqueous solution to yield amorphous cefamandole sodium. The sample was dried at reduced pressure[2]. Residual dioxane was less than 0.1% (w/w) (NMR). The freeze-dried cefamandole sodium sample used in the decomposition studies was prepared from the methanol solvate of cefamandole sodium using the procedure described for cephalothin sodium. Crystalline methanol solvate was obtained by adding sodium acetate to a methanol solution of purified cefamandole acid.

Samples containing water were prepared by allowing the dried samples to absorb water from saturated aqueous salt solutions of fixed water vapor pressure. The amount of water absorbed was determined gravimetrically.

Procedures—All samples were protected from light during storage. Cephalothin sodium, cefamandole nafate, and penicillin G potassium were stored in glass sealed ampuls; ~300 mg of sample was sealed with about 10 ml of dry air. Cefamandole sodium was stored in 15-ml ampuls sealed with butyl rubber closures. To ensure that the dry sample did not absorb water during ampul filling, filling was carried out at near zero relative humidity[3]. Karl Fischer assay indicated that no measurable water (<0.1%) was absorbed during the filling and sealing operations. In general, each sample for a given time–temperature aging condition was prepared in duplicate.

Some amorphous cephalothin sodium samples were subjected to high vacuum drying conditions. The sample, dried as previously discussed, was pumped on at 10^{-6} Torr and 25° for 24 hr and was then sealed in vacuum.

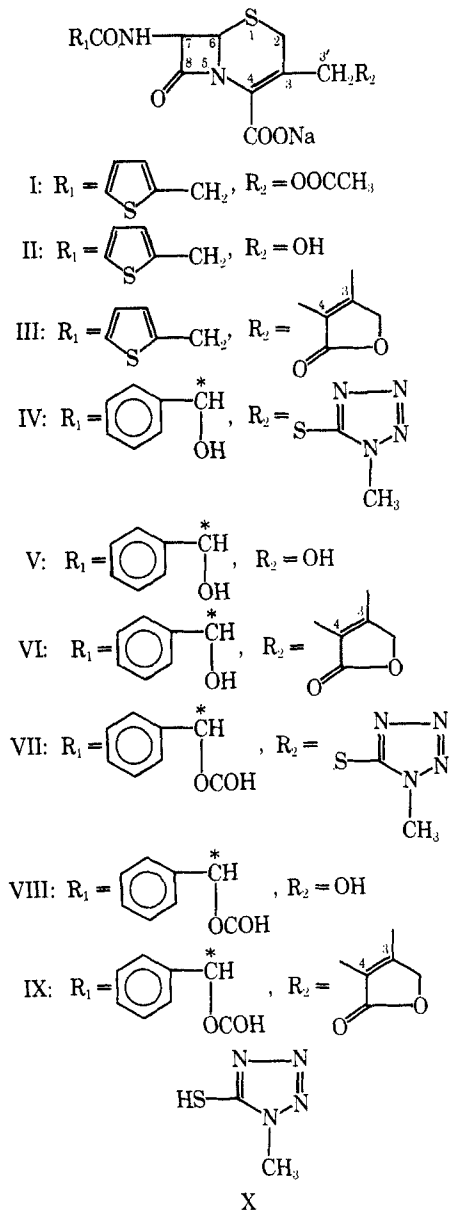
Assay Methods—Cephalothin sodium and penicillin G potassium were assayed by an automated iodometric titration procedure (23). This assay measures intact β-lactam[4]. The mean difference between assays on the duplicate samples was 1.8%. To check accuracy, a number of decomposed cephalothin sodium samples were assayed both by the iodometric procedure and by a microbiological automated assay[5] using *Staphylococcus aureus* (ATCC 9144) (23). The extents of decomposition measured by the two techniques differed by less than 2%.

Cefamandole nafate and cefamandole sodium were assayed by a polarographic technique (24) that determines intact cefamandole and cefamandole nafate. The method does not distinguish between cefamandole nafate and cefamandole sodium. The difference between assays on duplicate samples averaged 1.4%. All cefamandole nafate and cefamandole sodium samples were assayed for the decomposition product, 1-methyl-5-mercapto-1,2,3,4-tetrazole (X), by polarography (25, 26).

Thin-layer chromatograms were obtained by loading a 250-μg sample on a precoated 0.25-mm silica gel 60 F-254 TLC plate[6]. The developing solvent was ethyl acetate–acetone–acetic acid–water (5:2:1:1). Chromatographic zones were examined by shortwave UV light (254 nm).

RESULTS

Decomposition Products—Decomposition products of aqueous and amorphous cephalosporins, as revealed by TLC, are compared in Fig. 1. The extent of decomposition was in the 10–50% range for all samples. The degree of shading used to indicate a zone is a rough indication of the intensity of that zone as observed on the TLC plate. A broken line indicates streaking. The R_f values for the cephalosporins and their hydroxymethyl



X

and lactone derivatives were: cephalothin sodium (I), 0.65; deacetylcephalothin (II), 0.46; deacetylcephalothin lactone (III), 0.88; cefamandole sodium (IV), 0.50; V, 0.34 (25); cefamandole lactone (VI), 0.82 (25); cefamandole nafate (VII), 0.59; cefamandole nafate lactone (IX), 0.92; and X, 0.92.

The decomposition products present (Fig. 1) depended strongly on the water content of the decomposition medium. For cephalothin sodium, the leading component had the same R_f value as the lactone analog (III). Although little lactone was found in decomposed, dry (≤0.1% H_2O) cephalothin sodium, lactone was a major decomposition product for the wet solid (4.4% H_2O)[7]. The 3-hydroxymethyl analog (II) of cephalothin, R_f 0.46, was not present in either solid sample but appeared to be a major product for the aged aqueous sample (Fig. 1). Similarly, the 3-hydroxymethyl analogs of cefamandole and cefamandole nafate[8] were present *only* in the aged aqueous solutions.

Decomposition to form the 3-hydroxymethyl or lactone analogs is accompanied by formation of an equal molar quantity of the free 3′-side chain (X, R_f 0.92). Rupture of the β-lactam bond should be accompanied by release of the 3′-side chain, provided the 3′-group is a good leaving group (17, 22). Thus, the usual decomposition reactions would be expected to yield 1 mole of X for each mole decomposed. However, for decomposed amorphous cefamandole nafate and cefamandole sodium, the

[2] Dried at reduced pressure (≃ 15 Torr) with a dry air bleed (100 ml/min) for ~16 hr at 25° and ~20 hr at 40°.

[3] The glove bag (Instruments for Research and Industry, Cheltenham, Pa.) was continuously purged with air at equilibrium with anhydrous calcium sulfate.

[4] The cephalothin decomposition product, deacetylcephalothin lactone, contains an intact β-lactam and, therefore, should not be distinguished from cephalothin by the iodometric assay. However, samples of pure lactone gave essentially zero β-lactam content by the iodometric method, presumably due to the insolubility of the lactone in the aqueous systems used in the assay.

[5] Autoturb.

[6] Merck.

[7] The wet solid (4.4% H_2O) contained ~10% (w/w) crystalline III (identified by X-ray diffraction).

[8] Presumably, the components at R_f 0.36 and 0.43 were the 3-hydroxymethyl analogs of cefamandole and cefamandole nafate, respectively.

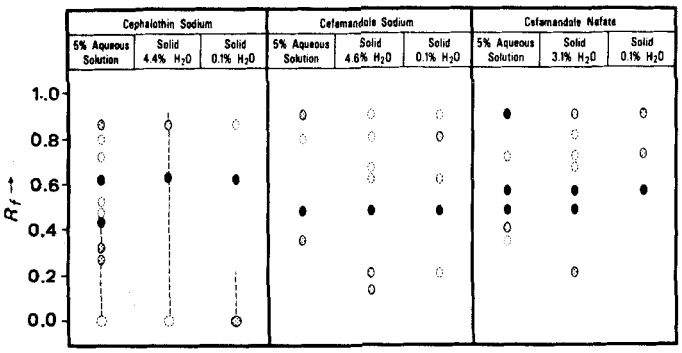


Figure 1—*TLC of decomposed cephalosporins; a comparison between aqueous solution and amorphous solids. Cephalothin sodium 5% aqueous solution was aged 1 hr at 75° and solids were aged 1 week at 75°; cefamandole sodium 5% aqueous solution was aged 2 hr at 50° and solids were aged 1 month at 50°; and cefamandole nafate 5% aqueous solution was aged 2 hr at 50° and solids were aged 2 months at 50° (0.1% H_2O) and 3 weeks at 50° (3.1% H_2O).*

mole percent of X (by assay) was less than the mole percent decomposition. Either one of the decomposition products contains an intact 3′-side chain or X is unstable.

Amorphous cephalothin sodium rapidly developed an amber color upon aging. Even samples that showed no evidence of decomposition by iodometric assay or TLC were highly colored both in the solid form and when dissolved in water. Although column chromatography[9] suggested that the colored products were polymeric, details of the structures are unknown. For amorphous cefamandole and cefamandole nafate, the extent of color formation was *much* less than that noted for cephalothin sodium aged under similar conditions[10].

Decomposition Rates—*Amorphous Cephalothin Sodium*—In general, samples were assayed over a period corresponding to at least 10% decomposition. Periodic microscopic examination verified that the samples remained amorphous during the stability study. Typical data are shown in Fig. 2. Assay data are expressed relative to the initial assays as percent of initial, *P*. Thus, the percentage decomposition is $100 - P$. Although in most cases insufficient decomposition had occurred to establish the reaction order unambiguously, all data were consistent with first-order kinetics.

First-order rate constants were evaluated by least-squares analysis. *No differences* in decomposition or extent of color formation between dry samples (≤0.1% H_2O) stored in air and those stored in vacuum were observed. Thus, these data were combined for the rate constant calculations (Table I). For the dry samples stored at 25°, no decomposition could be demonstrated over 600 days. However, the powder did develop an amber color, indicating that some decomposition occurred.

Amorphous Penicillin G Potassium—Microscopic examination of aged

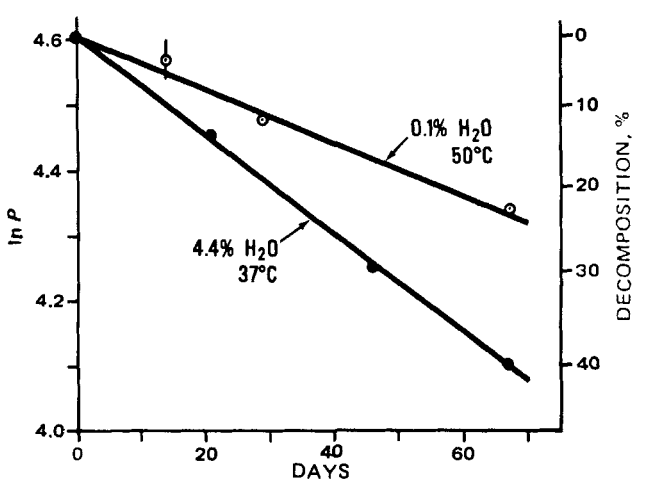


Figure 2—*Kinetics of thermal decomposition of amorphous cephalothin sodium. P is the iodometric assay in percent of initial.*

[9] Sephadex.

[10] Exposure of cefamandole nafate to laboratory light significantly increased the color formation rate.

Table I—First-Order Rate Constants for the Thermal Decomposition of Amorphous Freeze-Dried Cephalothin Sodium

	100 × First-Order Rate Constant, $10^2 k_1$, day^{-1}			
Water, %	25°	37°	50°	75°
0.1	0.000 ± 0.002[a]	0.022 ± 0.005	0.40 ± 0.1	4.9 ± 0.4
0.9	—	0.051 ± 0.016	0.55 ± 0.04	—
1.8	—	0.18 ± 0.02	0.70 ± 0.07	—
4.4	0.084 ± 0.008	0.76 ± 0.02	0.9 ± 0.1	4.2 ± 0.9

[a] The uncertainties given are the standard deviations of the parameters.

samples indicate that, while the dry sample (0.5% H_2O) at 50° remained essentially amorphous[11], the wet samples (5.7% H_2O) partially crystallized early during the stability study (Fig. 3). The dry samples showed no decomposition either by iodometric assay or by visual examination. By contrast, the wet samples decomposed rapidly at both 25 and 50°, with the decomposition rate decreasing much faster with time than would be consistent with first-order kinetics.

Amorphous Cefamandole Nafate and Cefamandole Sodium (Figs. 4 and 5)—Microscopic examination of aged samples showed no evidence of crystallization. Dry (0.1% H_2O) cefamandole nafate at 25° decomposed slightly (3.6%) within 3 months, but the assays remained essentially constant between 3 and 12 months. The line drawn in Fig. 4 reflects the apparent invariance of the assay with respect to time after 3 months. If this plateau effect is rejected as an artifact and all data are fitted to a first-order decay model, $10^2 k_1 = 0.005$ day^{-1}.

Since the stability study for cefamandole sodium was terminated after 3 months, no information regarding a plateau effect for this compound was obtained. The solid line and the value of $10^2 k_1$ in Fig. 4 for dry cefamandole sodium at 25° assume first-order decomposition. Clear deviations from first-order decomposition were observed for wet (3.1% H_2O) cefamandole nafate at 50° and for wet (4.6% H_2O) cefamandole sodium at 40 and 50°. For these samples, therefore, the solid lines and values of $10^2 k_1$ shown in Figs. 4 and 5 are intended only as crude approximations for the initial decomposition rates.

Spray-dried and freeze-dried cefamandole sodium, although both amorphous, are not identical forms. Spray-dried material appears to be an annealed form of the freeze-dried material (1), having an energy about 2 kcal/mole less than the freeze-dried form. Thus, in principle, the reactivity of spray-dried cefamandole sodium may be different from the reactivity of freeze-dried material (1). Decomposition data for freeze-dried and spray-dried cefamandole sodium are compared in Fig. 5. Although the data are insufficient to reveal small differences in reactivity, reactivities of freeze-dried and spray-dried samples are clearly of the same order of magnitude.

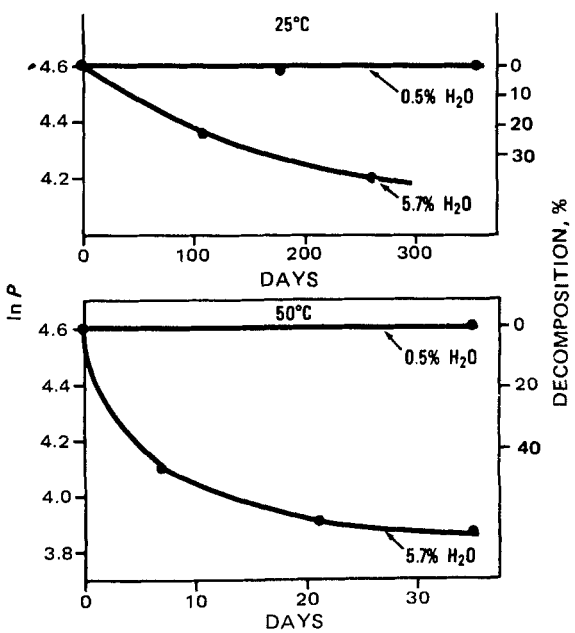


Figure 3—*Kinetics of thermal decomposition of penicillin G potassium. P is the iodometric assay in percent of initial.*

[11] After 12 months at 25°, the dry sample had crystallized.

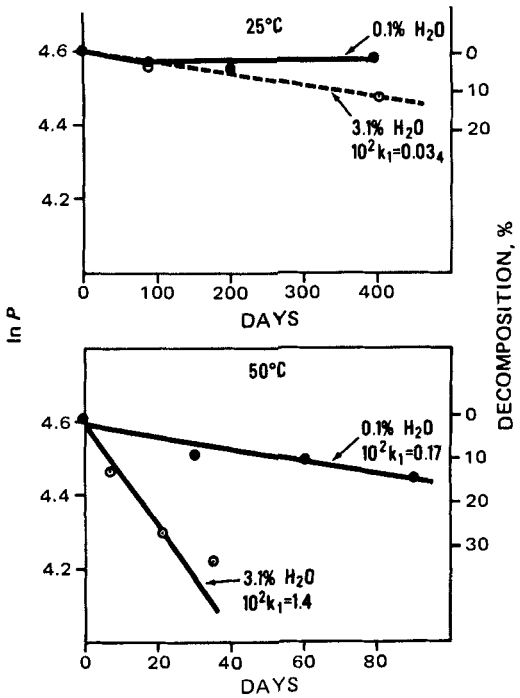


Figure 4—*Kinetics of thermal decomposition of cefamandole nafate. P is the polarographic assay in percent of initial.*

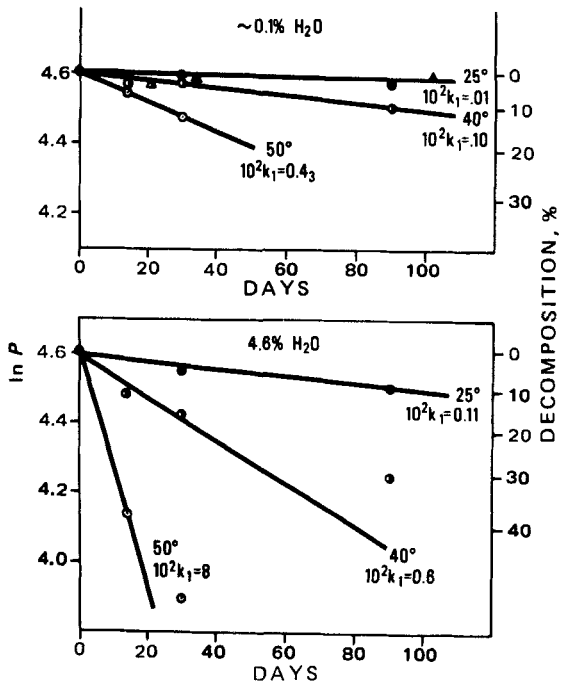


Figure 5—*Kinetics of thermal decomposition of cefamandole sodium. P is the polarographic assay in percent of initial. The circles are spray-dried samples; the triangles are freeze-dried samples.*

Crystalline Forms—The unsolvated crystalline forms of cephalothin sodium, penicillin G potassium, and cefamandole nafate were subjected to aging conditions at least as severe as those used for the corresponding amorphous samples. Assay data did not reveal decomposition under any test condition. From the precision of the assay data and the duration of the stability studies, the decomposition rates, k_1 (day^{-1}), for the crystalline materials studied are estimated to be less than 10^{-4} day^{-1} at 50°. Thus, at least for the cephalosporins studied, the effect of crystallinity is to increase the thermal stability by *at least* one order of magnitude.

DISCUSSION

Kinetics—The amorphous materials studied did not exhibit the sigmoid or "S"-shaped decomposition curves frequently observed with crystalline solids (3). In general, the data are consistent with first-order kinetics, although clear deviations from first-order behavior occurred in several cases. With wet (5.7% H_2O) penicillin G potassium, the sharp decrease in decomposition rate with increasing time was probably due to sample crystallization. The interpretation of the high temperature kinetic data for wet cefamandole sodium and wet cefamandole nafate is less obvious. Here, no crystallization was observed. Similar kinetics for amorphous ampicillin led to the speculation (8) that, upon aging, the amorphous form initially present underwent a transition to a less reactive amorphous form.

While amorphous freeze-dried cefamandole nafate and cefamandole sodium apparently undergo a structural change (annealing) upon aging, amorphous spray-dried cefamandole sodium *is* an annealed form (1). Since similar kinetics are observed for both freeze-dried and spray-dried (*i.e.*, annealed) samples, the deviations from first-order decomposition apparently are not the result of an annealing phenomenon.

If a major decomposition pathway involves attack on the β-lactam by water, the reaction rate would depend on the concentration of water in the system. If a solution model were used for the amorphous solids studied, second-order kinetics are predicted[12]. However, the effective reaction order for the data under discussion is ~5. Therefore, the observed deviations from first-order behavior constitute an anomaly for which no convincing explanation can be offered.

Effect of Water—In general, the decomposition rate was increased significantly by the presence of water. This effect was particularly striking for penicillin G potassium (Fig. 3). At low water content (0.5%), decomposition was not measurable; but at high water content (5.7%), decomposition was faster than for any other solid studied. Although the effect of moisture on the decomposition of amorphous cephalothin sodium was quite significant at low temperatures, the decomposition rate at 75° was essentially independent of water content (Table I).

Effect of Temperature/Mechanisms—Arrhenius plots for the cephalothin sodium data (Table I) are given in Fig. 6. The measured rate constant for dry cephalothin sodium at 25° was zero. Although this point could not be included in Fig. 6, the smooth curve was drawn to reflect a very low decomposition rate at 25°. Significant curvature exists in the Arrhenius plots, particularly for dry material where the effective activation energy decreased from ~40 kcal/mole at low temperature to ~20 kcal/mole at high temperature. At least at low temperature, the effective activation energy for the wet (4.4% H_2O) solid was significantly less than the corresponding activation energy for the dry solid.

If amorphous cephalothin sodium decomposed *via* two degradation pathways with significantly different activation energies, nonlinear Ar-

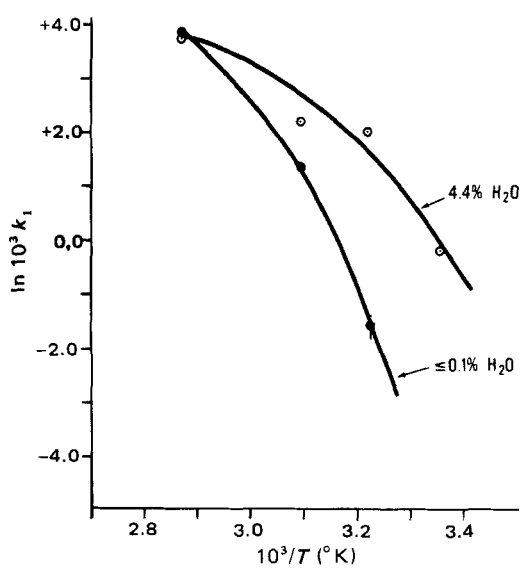


Figure 6—*Arrhenius plots of first-order rate constants for the thermal decomposition of amorphous cephalothin sodium.*

[12] For a solution model, the rate is proportional to the product of the cephalosporin concentration and the water concentration. In the moisture-containing amorphous systems studied, the initial mole ratio of cephalosporin to water was about unity. Thus, for a 1:1 reaction stoichiometry, the cephalosporin and water concentrations would be roughly equal at all times, leading to second-order kinetics.

rhenius plots would result. However, in such a case the effective activation energy, defined by the slope of the Arrhenius plot, would *increase* with increasing temperature. This intuitive conclusion is supported by the following mathematical argument. The observed rate constant, k, is:

$$k = \sum_{i=1}^{n} k_i = \sum_{i=1}^{n} A_i \exp(-E_i/RT) \qquad \text{(Eq. 1)}$$

where A_i, E_i, and k_i represent the preexponential factor, activation energy, and rate constant, respectively, for the ith decomposition pathway. The effective activation energy, E^*, is defined by:

$$E^* = -R \frac{d \ln k}{d(1/T)} \qquad \text{(Eq. 2)}$$

Performing the indicated differentiation yields:

$$E^* = \sum_{i=1}^{n} \frac{k_i}{k} E_i \qquad \text{(Eq. 3)}$$

Differentiation of Eq. 3 and algebraic manipulation then yield:

$$RT^2 \frac{dE^*}{dT} = \sum_{i=1}^{n} \frac{k_i}{k} [E_i - E^*]^2 \geq 0 \qquad \text{(Eq. 4)}$$

Thus, provided two or more degradation pathways exist ($E_i \neq E^*$), dE^*/dT is always positive; *e.g.*, an increase in temperature increases E^*. Experimentally, however, the effective activation energy *decreases* as the temperature increases.

The observed temperature dependence (Fig. 6) is consistent with the following qualitative model. For decomposition to occur, the reacting molecule and its immediate neighbors must undergo considerable reorientation. For example, if attack on the β-lactam by a nucleophilic group from a neighboring molecule is involved, reorientation must occur to provide the geometry needed for the reaction to proceed. This model assumes that molecular reorientation is the rate-determining step for thermal decomposition. Thus, the reaction rate is proportional to a molecular relaxation rate.

For liquids at low temperature (24) and glassy polymers (27), molecular relaxation rates may show pronounced non-Arrhenius behavior near the glass transition temperature; the activation energy for molecular relaxation decreases as the temperature increases. Similar behavior might be expected for amorphous cephalosporins near 25°, provided the glass transition temperature is near 25°. The glass transition temperature, T_g, for dry cephalothin sodium may be estimated[13] as $T_g \approx 300$ °K. Thus, according to the described model, the non-Arrhenius behavior demonstrated in Fig. 6 is a consequence of the decreasing activation energy for molecular relaxation as the temperature increases from T_g.

CONCLUSIONS

Even when rigorously dry, the amorphous cephalosporins studied are much less stable than their crystalline forms. In general, absorbed water increases the number of decomposition products and greatly increases the net decomposition rate. The activation energy is high and, at least for cephalothin sodium, the effective activation energy increases with decreasing temperature.

Provided the solid is dry, decomposition rates at 25° are small[14]. If potency were the only consideration, the amorphous compounds studied would be viable product forms in the dry state. Loss of product elegance is the more serious problem. Amorphous cephalothin sodium develops excessive amber color well before a potency loss is measurable. With amorphous cefamandole sodium and cefamandole nafate, even slight decomposition lowers the pH of a reconstituted solution to the point where the cephalosporin acid precipitates.

[13] As a rough rule, $T_g/T_m \approx 0.6$ (28, 29), where T_m is the melting point (°K) of the crystalline solid. Crystalline cephalothin sodium melts (with decomposition) at ~470 °K.

[14] Amorphous dry cephalothin sodium stored at 25° maintains initial potency for 2 years. However, upon equilibration of the solid with 30% relative humidity (4.4% H_2O), the projected shelflife (less than 10% potency loss) at 25° is only 4 months.

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