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DEHYDRATION OF IRRADIATED AND NON-IRRADIATED *L*-α-ASPARAGINE MONOHYDRATE
Part I. Isothermal kinetics

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Dehydration of irradiated and non-irradiated asparagine monohydrate was investigated by means of a computer interfaced PerkinElmer 1B DSC in isothermal conditions and static atmosphere. Isothermal runs were performed at 358, 363, 368 and 373 K. Samples were γ-irradiated at room temperature, using a ^{137}Cs source with an activity of $3\cdot10^{13}$ Bq and a dose rate of $4\cdot10^{2}$ Gy h^{-1}, with irradiation times between 8–116 h. Isothermal kinetics were analyzed via the common factorized rate equation. Šesták–Berggren conversion function was found to best fit the experimental data. Of the three fitting parameters, only the one associated with the activation energy was found to follow a coherent variation with the exposure time. Even within this simple model, that makes the activation energy a useful stability criterion within a set of similar samples.

Keywords: *dehydratin, DSC, irradiation, L-asparagine monohydrate*

Introduction

Thermal dehydration of solids is an important field of solid-state chemistry with wide technical applications. Incorporation of water molecule in crystal structure of organic compounds affects their chemical and physical properties. Therefore the stability study of water incorporated in pharmaceutical compounds and of the dehydration mechanism and kinetics is very important for pharmaceutical industry, food industry and medicine [1–5].

Biological molecules, such as proteins and DNA, are very sensitive to the ionizing radiation and this problem has a fundamental importance in biology and medicine (e.g. mechanism of mutagenesis and radioprotection) [6]. Radiation damage manifests in the disturbance of a long range crystalline or supramolecular order [7–10] and in chemical modification of studied systems through free radical formation [11–13] or mass loss [14–16].

Amino acids, which are the building blocks of proteins, are among the simplest organic molecules of biological relevance and thus serve as convenient model systems in studies of radiation damage.

Asparagine is one of the 20 most common natural amino acids in living organisms. It is stable in both hydrated (with one water molecule) and anhydrous forms, and contains carboxamide as the side chain function group. Asparagine is considered a non-essential amino acid and among other biological substances, it is very important because it plays a role in the metabolic control of some cell functions in nerve and brain tissue and is part of different drugs and foods. In asparagine monohydrate there is a total of seven hydrogen bonds per hydrated molecule, three of which involving the water molecule [17]. Thermal behavior of drugs constituents, especially possible dehydration is extremely important for their preparation, processing and storage.

The aim of this contribution is the study of dehydration of non-irradiated and pre-γ-irradiated *L*-asparagine monohydrate within the temperature range 358–373 K using DSC technique in isothermal conditions.

The dehydration kinetics of powder and single crystals *L*-asparagine monohydrate was previously studied by Dei and Guarini [18] by DSC and FTIR in order to establish the role of ageing upon the thermal behavior of compound and by Kalis *et al.* [19]. Sharma *et al.* have studied the pyrolysis of some amino acids, including asparagine, putting in evidence the products formed by pyrolysis in different conditions [20, 21]

Influence of ionizing radiation (X-rays) upon dehydration kinetics of *L*-asparagine monohydrate was the subject of paper of Tria *et al.* [22] but they have not followed up the variation of kinetic parameters with the radiation dose.

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Experimental

Materials

Commercially available polycrystalline powder of asparagine monohydrate (Merck of purity≥99%) was used.

Methods

Irradiation

A ^{137}Cs source with an activity of $3 \cdot 10^{13}$ Bq and a dose rate of $4 \cdot 10^{2}$ Gy h^{-1} were used for γ-irradiation of asparagine monohydrate at room temperature. The times of exposure were between 8–96 h.

Differential scanning calorimetry

A DSC Perkin-Elmer DSC 1B differential scanning calorimeter (calibrated with indium ($\Delta_{fus}H$= 28.46 J g^{-1}) was used to record thermal curves isothermally. The samples with masses between 2–4 mg were weighted in the standard aluminum sample pans and loosely covered with aluminum lids (not sealed) and were placed in the sample side of the instrument. An identical empty reference pan was placed in the reference side. Scans were performed in static air at four temperatures 358, 363, 368 and 373 K, respectively. After initial rapid heating (64 K min^{-1}) and reaching of the desired temperature the samples were kept at this temperature for 20, 30 and 40 min, respectively. After the runs the weighing of samples was repeated and the mass loss was evaluated to about 11.9%, which corresponds to the stoichiometry of dehydration. The same check was performed on the dehydration startup: during the rapid heating mass losses were below 0.03%.

The acquisition of experimental data was performed by means of a HP 34812A multimeter, serving as an interface with the computer, provided with the Benchlink data acquisition software. The acquired data were transferred to Excel, TableCurve 2D v.5.01 and PeakFit v4.12 (Systat) software, for further processing and fitting.

Results and discussion

A typical curve representing aquired raw dehydration data is presented in Fig. 1.

The first step in data processing was the selection of time range (for which the recorded signal exhibits significant values) which must be extended enough to afford an accurate determination of the baseline. We applied a Savitzky–Golay smoothing, followed by a non parametrical digital filtering and

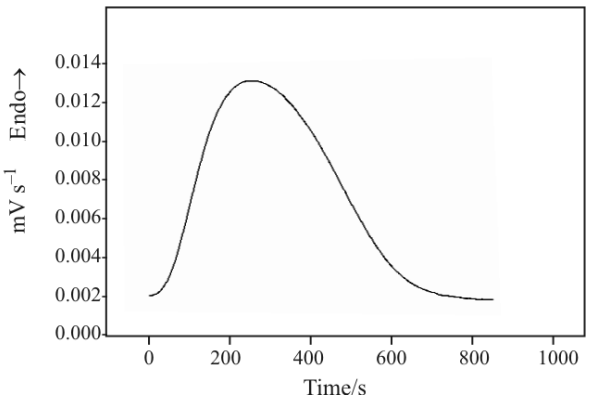

Fig. 1 Dehydration curve of *L*-asparagine at 363 K

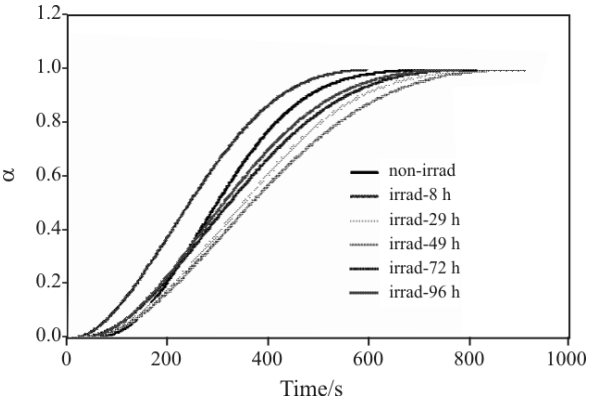

Fig. 2 Conversion–time plots of *L*-asparagine samples with different irradiation dose

getting a sufficient number of equally spaced points to ensure precise numerical integration. Data processing involved the automatically determination and subtraction of the baseline and an extra digital filtering and normalization to peak area leading to the 'normalized heat flow' (NHF) *vs.* time plots [23, 24]. With the usual expression of the adimensional conversion, $\alpha(t)$ as the ratio of partial peak area (corresponding to time t) to the total peak area, the normalized heat flow actually equals the time derivative of conversion, i.e. the reaction rate:

$$\alpha(t)=\int_{t_0}^{t}\mathrm{NHF}(t)\mathrm{d}t;\ 1=\int_{t_0}^{t_f}\mathrm{NHF}(t)\mathrm{d}t;\ \mathrm{NHF}(t)=\frac{\mathrm{d}\alpha}{\mathrm{d}t} \quad (1)$$

The dehydration behavior at 363 K of *L*-asparagine samples with different irradiation degrees is presented in Fig. 2 (conversion–time plots) and Fig. 3 (reaction rate–conversion plots).

The usual factorized form of the reaction rate was applied together with the common simplifying assumption that the conversion function, $f(\alpha)$, is temperature invariant

$$\mathrm{d}\alpha/\mathrm{d}t=k(T)f(\alpha);\ k(T)\propto A_0 \quad (2)$$

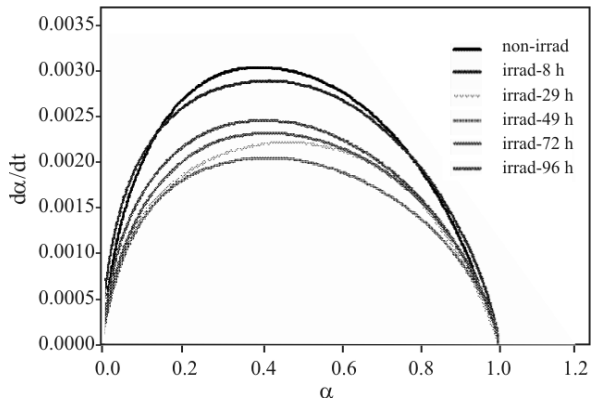

Fig. 3 Reaction rate–conversion plots of *L*-asparagine samples with different irradiation dose

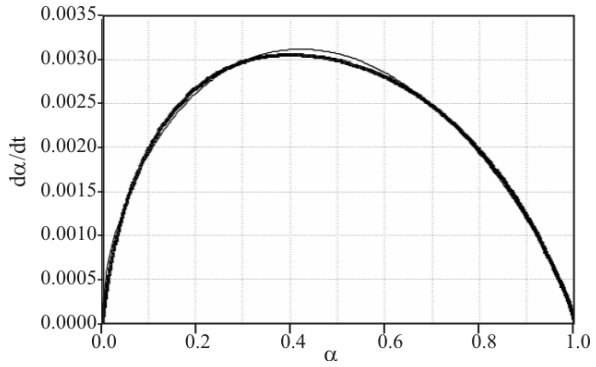

Fig. 4 Curve fit of non-irradiated *L*-asparagine dehydration at 363 K

The best-fit conversion function was given by the Šesták–Berggren expression [25], given in Eq. (3), in contradiction to the results of Guarini and Dei [18] whose experimental data obtained on differently aged *L*-asparagine samples obeyed Avrami–Erofeev (n=3) and first-order kinetics at low to medium and higher temperatures, respectively.

$$f(\alpha)=\alpha^{m}(1-\alpha)^{n} \qquad (3)$$

Fitting in TableCurve the experimental rate–conversion data such as those plotted in Fig. 3 offers a direct estimation of the rate constant, k, that equals the fitting parameter A_0 (or a in TableCurve notations), as expressed in Eq. (2). Arrhenius-type expressing of the later yields the sought for estimates of the activation energy. An example of TableCurve fit is given in Fig. 4: within the software notations, fitting parameters, A_1 (b) and A_2 (c) represent the Šesták–Berggren parameters m and n, respectively. In Fig. 4 'Rank 1' designates the best-fit equation within an entire set (comprising Avrami – 3 and Avrami – n, among others).

As qualitatively evidenced in Figs 2 and 3, the investigated dehydration process is an intricate one, with not so clearly manifested pattern with respect to the irradiation dose. The very fact that an empirical equation, rather than some model-based equation, offered the best fit to experimental data, points towards mechanistic complexity.

All TableCurve fitting parameters are given in Table 1. There is an obvious variation of the Šesták–Berggren exponents (b and c) either for the same sample at different temperatures, for different samples at the same temperature. This may be due to the quest for the fit with best statistical scores, i.e. allowing these parameters to adjust freely. On the other hand, 'mechanistic complexity' is not excluded, as the conversion function may very well change with either temperature or irradiation dose. However, there is no clear trend of variation of these parameters with either temperature or dose, indicating a combined effect of the above hypotheses, as well as a possible contribution of experimental errors.

The only parameter in Table 1 that exhibits a clear trend, i.e. an increase with increasing temperature for all irradiation times, is a (A_0), associated with the rate constant. The Arrhenius plots of these parameters are presented in Fig. 5.

There are two general features of the Arrhenius plots presented in Fig. 5: 1) slopes tend to increase

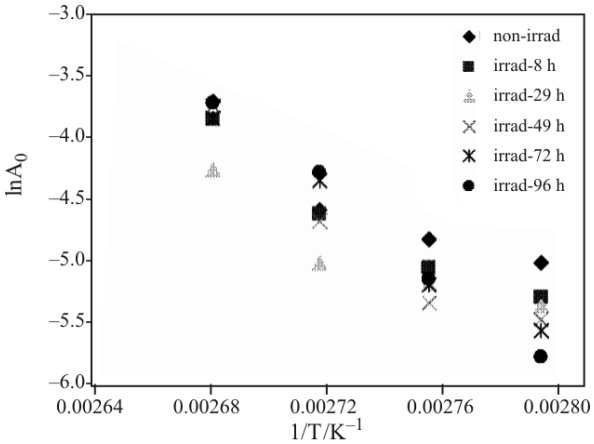

Fig. 5 Arrhenius plots of the fitting parameter A_0 for different doses of irradiation

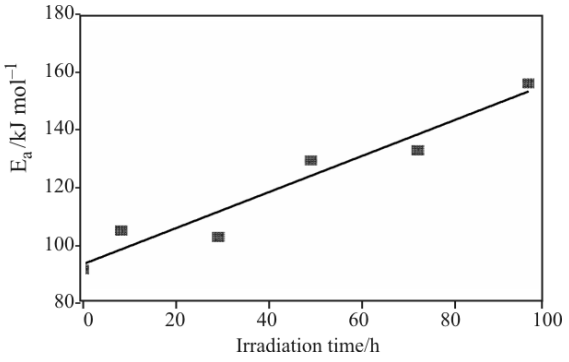

Fig. 6 Activation energies calculated from Arrhenius plots presented in Fig. 5

Table 1 Fit parameters for all experimental runs

	Exposure time/h																	
	0			8			29			49			72			96		
	Fit parameter																	
T/K	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*
358	0.006	0.626	0.812	0.005	0.546	0.734	0.005	0.675	0.833	0.004	0.648	0.666	0.004	0.552	0.685	0.003	0.491	0.665
363	0.007	0.560	0.745	0.006	0.468	0.663	0.006	0.591	0.726	0.005	0.538	0.681	0.006	0.556	0.691	0.006	0.528	0.715
368	0.009	0.565	0.947	0.010	0.463	0.736	0.007	0.459	0.681	0.009	0.553	0.785	0.012	0.586	0.676	0.014	0.543	0.657
373	0.024	0.714	0.971	0.021	0.473	0.671	0.014	0.485	0.625	0.023	0.496	0.622	0.021	0.500	0.688	0.024	0.500	0.658

with increasing the irradiation dose; 2) for all doses, there is an evident 'upwards bending' concerning the 373 K runs, that indicates a change in dehydration mechanism at higher temperatures, as reported previously [18].

The calculated activation energies are plotted in Fig. 6 against the exposure time. There is a manifest increase of the activation energy with the irradiation time (which amounts to more than 50% considering the extremes, non-irradiated and 96 h – irradiated samples). This reccomends the activation energy as the most sensitive kinetic parameter capable to account for the expected alterations of the dehydration process produced by irradiation.

The water of hydration is usually divided into two broad categories: the strongly bound primary hydration, and the more loosely bound secondary hydration [26].

In the case of hydrated asparagine the water of hydration is involved in a complex network of hydrogen bonds which helps to hold the lattice together. Tria *et al.* [22] demonstrated that upon irradiation radicals with considerable stability are formed, as proven by the fact that their decay begins at higher temperatures when dehydration is near completion [22]. Moreover, the increase in decay rate does not seem to be due to an increase in defect – aided diffusion since most of the defects formed by dehydration are present before the rapid process begins [22].

The action of X-rays on non-hydrated amino acids was also investigated by Zubavichus *et al.* [6], by means of XPS, NEXAFS and MS. Aliphatic amino acids undergo chemical changes upon exposure to radiation. In the case of *L*-asparagine the main route involves C–OH breaking with water formation, i.e. a 'chemical' dehydration.

Dei and Guarini [18] modeled the process of dehydration by a three-stage mechanism (TSM), characterized by:

- an initial dehydration of the outer lattice planes to form a dehydrated layer
- diffusion of the volatile reaction product through this layer
- formation of crystalline germs of the product in the dehydrated layer.

According to this model, the dehydration process is determined by the state of crystal surface, initial presence of a dehydrated layer, internal (volume) reactivity.

The results presented in this paper are better supported by profound chemical changes that occur in irradiated samples. Neither Avrami–Erofeev nor first-order kinetic equations are capable to fit experimental data. (The fact is that Dei and Guarini [18] found the Avrami–Erofeev valid only for isothermal runs below 343 K, more than 20 K below our experiments; they investigated well grown/aged crystals, whereas in the present work powder was studied. Discrepancies are thus quite expectable.)

The presence of free radicals within the crystalline structure, as well as its modification by increasing of the irradiation dose, are supposed to alter the dehydration process [6, 22]. This involves an enhancement of the chemical component of dehydration: higher the free radical concentration (produced by higher doses), higher the amount of water formed from amino acid decomposition. As free radicals decay is unimportant as long as hydration water is present, their action could be viewed as stabilizing the hydration structure while labilizing the chemical amino acid structure. This physico-chemical interplay is expected to manifest even more in non-isothermal runs, as will be presented in a subsequent contribution.

Equations (2) and (3) undoubtedly oversimplify the quantitative description of the above process. Nevertheless, there is a significant variation of one of the fitting parameters related to the activation energy. The variation of the latter with the exposure time correctly describes the enhancement of the chemical component of dehydration produced by irradiation. Activation energy calculated via this simplified model and may thus be used as a predictive stability criterion within a series of similar samples.

Conclusions

Isothermal decomposition of *L*-asparagine monohydrate samples exposed to different doses of radiation was investigated by DSC. This complex process was kinetically modeled by means of the usual factorized rate equation. The best fit to the data, in statistical terms, was achieved making use of the empirical Šesták–Berggren expression for the conversion function. Out of the three fitting parameters, only the one associated with the rate constant (and thus to the activation energy) was found to follow a coherent variation with the exposure time.

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