

## THERMOGRAVIMETRIC AND KINETIC STUDY OF A CLODRONIC ACID COMPLEX FORMED WITH SODIUM

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Thermal stability of the clodronic acid complex formed with sodium ( $\text{Na}_2\text{CCl}_2(\text{HPO}_3)_2 \cdot 4\text{H}_2\text{O}$ ) was studied using both dynamic and isothermal thermogravimetric analyses as well as mass spectra. The thermal decomposition has two stages: dehydration and loss of two molecules of hydrogen chloride. Using the isothermal TG data the first step was found to be a phase-boundary reaction while the second step obviously cannot be described with just one reaction mechanism. The final residue of the dynamic TG analyses above 810 K was found to be sodium metaphosphate.

Clodronic acid,  $\text{CH}_4\text{Cl}_2\text{O}_6\text{P}_2$  (dichloromethylenebisphosphonic acid) belongs to a group of diphosphonates of the type P–C–P. These compounds are known to be valuable agents in the regulation of calcium metabolism and also potentially useful therapeutic agents. The sodium complex, for instance, is used in the treatment of bone metastases and hypercalcaemia [1, 2].

In order to characterize the thermal stability and behaviour of the clodronic acid disodium complex we used both dynamic and isothermal thermogravimetric analyses (TG) as well as mass spectroscopy (MS).

### Experimental

The disodium complex of clodronic acid ( $\text{Na}_2\text{L} \cdot 4\text{H}_2\text{O}$ ) was prepared and analyzed by Oy Star Ab (A Finnish pharmaceutical company). The compound was also meant to serve as a standard reference material in clinical experiments and therefore used also here without further purification.

Thermogravimetric analyses were carried out on a Mettler TG50 thermobalance both dynamically and isothermally. The sample size was 8–10 mg. The analyses were performed using standard crucibles in air and/or nitrogen atmospheres (200  $\text{cm}^3/\text{min}$ ). In the dynamic runs the heating rate was 2 deg/min. In order to study the reaction rate the dynamic run was quick and covered a large temperature range whereas isothermal conditions were used to study the reaction mechanism. The kinetic parameters were determined on the basis of the general kinetic relation

$$g(\alpha) = \int_{T_0}^{T_1} k(T) dt \quad (1)$$

where

$$k(T) = k_0 e^{\frac{-E_a}{RT}}$$

(the Arrhenius law),  $k_0$  = the frequency factor,  $E_a$  = the activation energy and  $\alpha$  = the mole fraction. For the isothermal analysis the general equation (1) is simply  $g(\alpha) = kt$ . Values of the correlation coefficient and standard deviation were used as a measure of the linearity for the least-squares fitting in various  $g(\alpha)$  versus  $t$  plots. The principal expressions of  $g(\alpha)$  are given in Table 1.

**Table 1** Kinetic function  $g(\alpha)$  for heterogenous solid-state reactions

$g(\alpha)$	Symbol	Rate-controlling process
$\alpha^2$	$D_1$	One-dimensional diffusion
$\alpha + (1-\alpha)\ln(1-\alpha)$	$D_2$	Two-dimensional diffusion
$(1 - \sqrt[3]{1-\alpha})^2$	$D_3$	Three-dimensional diffusion (Jander)
$1 - \frac{2}{3}\alpha - \sqrt[3]{(1-\alpha)^2}$	$D_4$	Three-dimensional diffusion (Ginstling-Brounshtein)
$\ln \frac{\alpha}{1-\alpha}$	$A_u$	Autocatalytic reaction (Prout-Tompkins)
$1 - \sqrt[n]{1-\alpha}$	$R_n$	Phase-boundary reaction, dimension $n = 1, 2, 3$
$\sqrt[m]{-\ln(1-\alpha)}$	$A_m$	Random nucleation, $m = 1$ Random nucleation and subsequent growth, $m = 2, 3$ and 4 (Avrami-Erofeyev)

The mass spectra was obtained on a Kratos MS 80 RF mass spectrometer using the direct inlet technique with sample heating at a rate of 50 deg/min and using scanning rate of 1 s/decade for recording the spectra.

## Results and discussion

There are two separate reaction stages as seen in the TG curves obtained upon heating the disodium complex of clodronic acid. The first stage being dehydration and the second loss of two molecules of hydrogen chloride.

Finally also carbon burns and the residue was found to be sodium metaphosphate,  $\text{Na}_2\text{PO}_3$ . The TG curves recorded in air and nitrogen atmospheres were rather similar (Fig. 1).

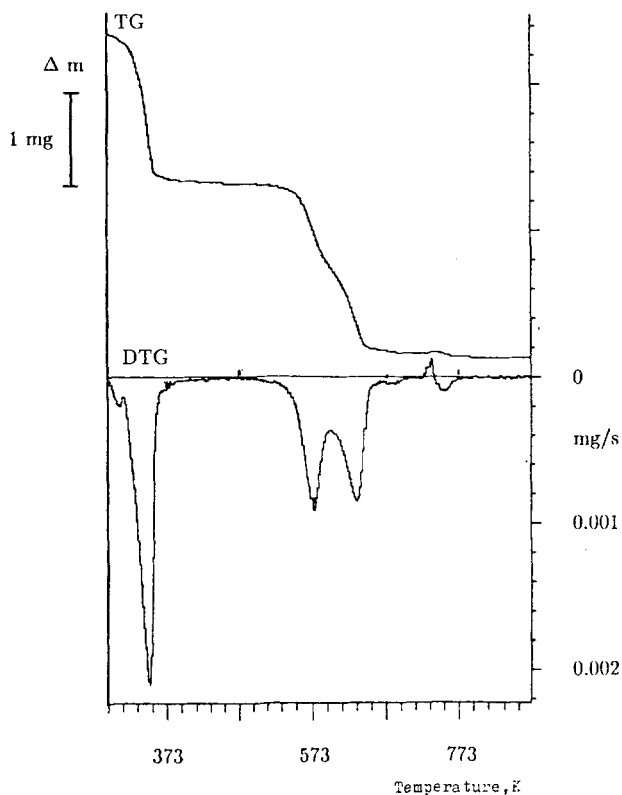


Fig. 1 TG curve for  $\text{Na}_2\text{L}\cdot 4\text{H}_2\text{O}$  heated with a rate of 2 deg/min in air atmosphere.

The dehydration reaction was rather fast and was completed at about 370 K. Figure 2 shows plots of  $\alpha$  (decomposed fraction) vs. time obtained from the isothermal TG data. Using least-squares fitting it can be seen that the dehydration reaction is a phase-boundary reaction (Table 2). The values of the rate constant  $k$  at different temperatures together with the kinetic parameters  $E_a$  (activation energy) and  $\ln k_0$  ( $k_0$  = frequency factor) for the best fitting phase-boundary reaction mechanisms are given in Tables 3 and 4. From the activation energies it can be seen that the compound loses its water molecules with ease.

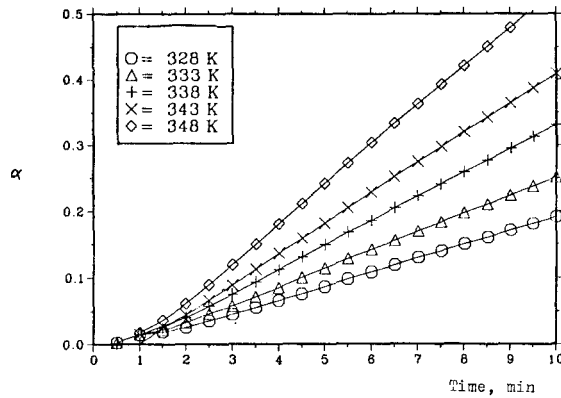


Fig. 2 Plot of degree of dissociation vs. time at different temperatures for the dehydration of  $\text{Na}_2\text{L} \cdot 4\text{H}_2\text{O}$  in isothermal TG runs in air atmospheres.

Table 2 The correlation coefficient  $r$  and standard deviation  $s$  for the least squares fitting of the best fitting  $g(\alpha)$ -functions vs. time  $t$  for the isothermal dehydration of  $\text{Na}_2\text{L} \cdot 4\text{H}_2\text{O}$  in the  $\alpha$  range 0.1–0.8

$T$ , K	$r$ $s \cdot 10^{-2}$	$R_1$	$A_{1,2}$	$g(\alpha)$ $R_{1,2}$	$R_{1,4}$	$R_{1,6}$
328.15	$r$	0.999964	0.999911	0.999966	0.999962	0.999945
	$s$	3.5	8.3	2.9	2.9	2.9
333.15	$r$	0.999976	0.999958	0.999985	0.999975	0.999958
	$s$	4.1	7.3	2.4	2.9	3.5
338.15	$r$	0.999971	0.999978	0.999988	0.999965	0.999927
	$s$	5.5	7.5	3.0	5.0	6.5
343.15	$r$	0.999957	0.999887	0.999990	0.999957	0.999901
	$s$	9.6	21.3	3.1	6.9	9.8

Table 3 The rate constants  $k$  for the isothermal dehydration of  $\text{Na}_2\text{L} \cdot 4\text{H}_2\text{O}$  corresponding the different phase-boundary reaction mechanisms

$T$ , K	$k \times 10^{-4}, \text{s}^{-1}$		
	$R_1$	$R_{1,2}$	$R_{1,4}$
328.15	3.48	2.96	2.58
333.15	4.60	3.95	3.45
338.15	6.09	5.27	4.64
343.15	7.63	6.67	5.93

Table 4 Kinetic parameters derived from the Arrhenius plot by means of isothermal TG

	$E, \text{kJ/mol}$	$\ln k_0, \text{s}^{-1}$	$-r$
$R_1$	$49.3 \pm 1.4$	$10.1 \pm 0.5$	0.999703
$R_{1,2}$	$51.0 \pm 1.3$	$10.6 \pm 0.5$	0.998813
$R_{1,4}$	$52.4 \pm 1.2$	$10.9 \pm 0.4$	1.000266

The second reaction step, loss of two molecules of hydrogen chloride takes place in the region 530–690 K and consists of two rather distinct steps, the first step being from 530 K to about 600 K (Figs. 1 and 3).

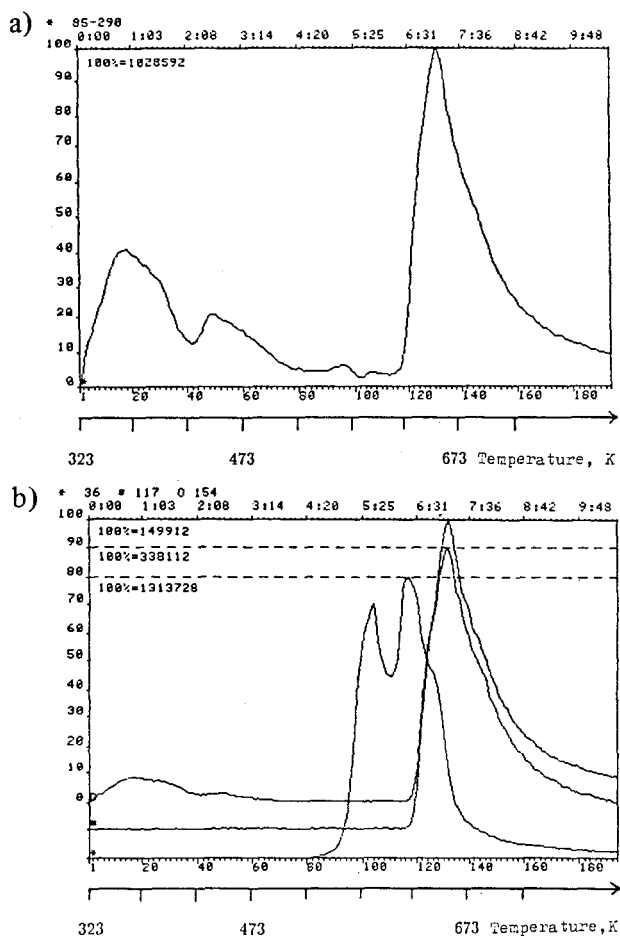


Fig. 3 Total ion chromatograms a) corresponding the masses 85–290 and b) masses 36, 117 and 154 (36 = HCl, 117 =  $\text{POCl}_2^+$  and 154 =  $\text{POCl}_3^+$ ).

Figure 4 shows the plots of  $\alpha$  vs. time obtained from the isothermal TG data for these reactions. However, it was not possible to find the mechanism of the reaction using the method described above. It is obvious that the loss of hydrogen chloride takes place with more than just one single mechanism. This is even probable since according to the X-ray structure data the two chlorine atoms in the compound are not equally coordinated [3].

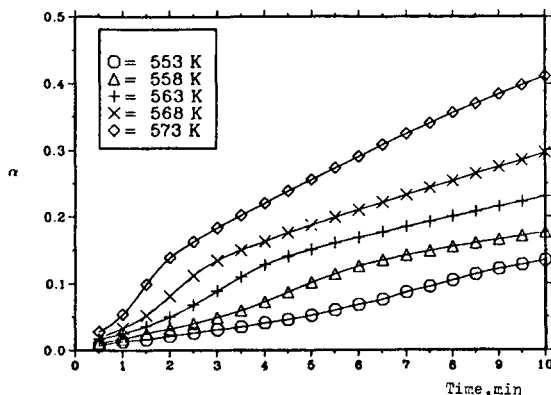


Fig. 4 Plot of degree of dissociation vs. time at different temperatures for the loss of hydrogen chloride from  $\text{Na}_2\text{L}$ .

## References

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**Zusammenfassung** – Sowohl mittels dynamischer und thermogravimetrischer Untersuchungen als auch and Hand von Massenspektren würde die thermische Stabilität des mit Natrium gebildeten Säurekomplexes  $\text{Na}_2\text{CCl}_2(\text{HPO}_3)_2 \cdot 4\text{H}_2\text{O}$  untersucht. Die thermische Zersetzung vollzieht sich in zwei Schritten: Dehydratation und Verlust von zwei Molekülen HCl. Auf Grund der isothermen TG Angaben ist der erste Schritt eine Phasengrenzreaktion, während der zweite Schritt mit einem einzigen Reaktionsmechanismus nicht eindeutig beschrieben werden kann. Das Endprodukt der DTG Analyse oberhalb 810 K erwies sich als Natriummethaphosphat.

Резюме - Термоустойчивость комплекса клодроновой кислоты с натрием -  $\text{Na}_2\text{CCl}_2/\text{HPO}_3/2 \cdot 4\text{H}_2\text{O}$  - была изучена методами динамического и изотермического термогравиметрического анализов, а также масс-спектрологии. Термическое разложение комплекса протекает в две стадии, состоящие, соответственно, из дегидратации и потери двух молекул хлористого водорода. На основе данных изотермического ТГ было найдено, что первая стадия описывается реакцией граничной фазы, тогда как вторая стадия реакции не может быть ясно описана только одним реакционным механизмом. При динамическом ТГ анализе конечным продуктом разложения выше 810 К являлся метафосфат натрия.