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SOLID STATE DECOMPOSITION STUDIES ON SOME ISOPROPYL CLODRONATE SODIUM SALTS

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SUMMARY

Thermal decomposition of four isopropyl clodronate sodium salts were interpreted from the TG and DTG curves with help of mass spectrometry. The compounds studied were {[hydroxy(1-methylethoxy)phosphino] dichloromethyl}phosphonic acid trisodium salt or monoisopropyl clodronate trisodium salt (compound 1), {[bis(1-methylethoxy)phosphino]dichloromethyl}phosphonic acid disodium salt or P,P-diisopropyl clodronate disodium salt (compound 2), (dichloromethylene)bisphosphonic acid P,P'-bis(1-methylethyl) ester disodium salt or P,P'-diisopropyl clodronate disodium salt (compound 3), {[bis(1-methylethoxy)phosphino]dichloromethyl}phosphonic acid mono(1-methylethyl) ester monosodium salt or triisopropyl clodronate monosodium salt (compound 4)

INTRODUCTION

Isopropyl esters of clodronic acid [(dichloromethylene)bisphosponic acid] belong to a group of diphosphonates of the type P-C-P. There has been an increasing biological and clinical interest in these compounds since they are known to be valuable agents in the regulation of calcium metabolism and also potentially useful therapeutic agents.

In order to characterize the thermal stability and behaviour of the sodium salts of these compounds dynamic thermogravimetric analysis (TG and DTG) and mass spectrometry (MS) were used.

EXPERIMENTAL

Preparation of the compounds

Compounds 1, 2, 3 and 4 were prepared according to the procedures described in the literature (ref. 1).

Thermogravimetric analyses

TG runs were carried out on a Mettler TG50 thermobalance in a temperature range 25-900 deg. The sample quantity varied between 8 and 10 mg. The dynamic runs were made in air or nitrogen at a flow rate of 200 ml min^{-1} and a heating rate of 2 deg min^{-1} was used.

Mass spectrometry

The mass spectra of the decomposition products were recorded at a scanning rate of 1 s/decade on a Kratos MS 80 RF mass spectrometer, using the direct inlet technique and heating the sample at a rate of 50 deg min^{-1}.

RESULTS AND DISCUSSION

The TG and DTG curves given in Fig. 1 show that none of the compounds contain crystal water. The thermal decomposition of compounds 1, 2 and 4 takes place in three steps, but the compound 3 decomposes directly in one step. TG data on the decomposition of the compounds studied are given in Table 1. Thermal decomposition in air and nitrogen was practically the same for each compound with minor exceptions. In each case an amorphous residue was obtained. Phosphates are known to form with sodium rigid homogeneous single phase glasses with varying stoichiometry (ref. 2). To detect the reactions, volatile decomposition products were identified by mass spectrometry.

HCl, propene, propyne, methane, acetylene, acetone or 2-propanol are possible volatile decomposition products of the esters studied (ref. 3). The break of oxygen-carbon bond gives propene or propyne, whereas the reaction with oxygen will give acetone or 2-propanol. Also the break of the phosphorus-oxygen bond gives acetone or 2-propanol. The release of methane from the isopropyl group will affect the formation of acetone. Carbon from phosphorus-carbon-phosphorus group can be released as carbon monoxide or dioxide by reacting with oxygen.

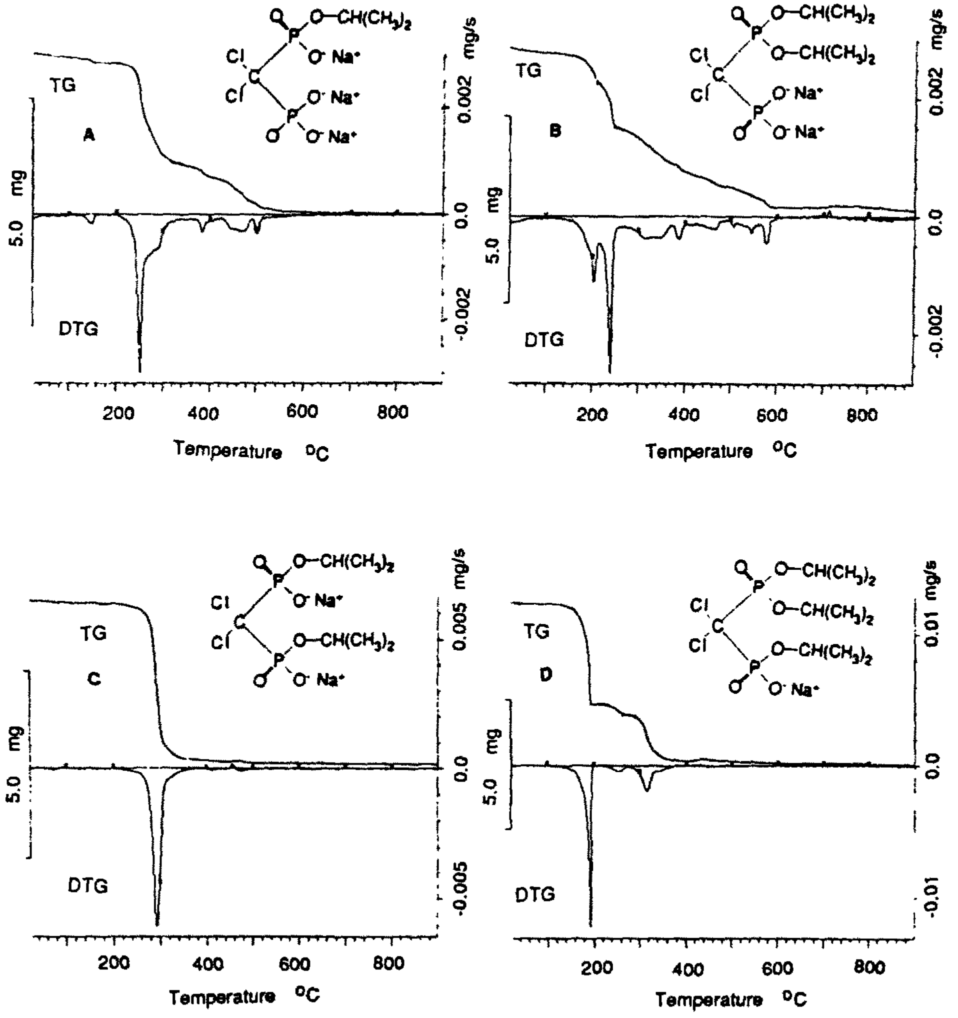


Fig. 1. TG and DTG curves of the compound 1 (A), 2 (B), 3 (C) and 4 (D) in air.

TABLE 1

TG data on the decomposition of isopropyl clodronate sodium salts.

T range (°C)	weight loss (%)	Calculated weight loss (%)	Leaving group
Compound 1			
In air flow:			
25-200	2.28		
200-340	22.64	24.54	$2 \cdot HCl + 1/3 \cdot C_3H_5 \cdot$
340-700	10.54	11.16	$2/3 \cdot C_3H_5 \cdot + C$
Residue (%)	64.54	64.30	$P_2O_6Na_3$
In nitrogen flow:			
25-190	3.03		
190-360	23.04	24.54	$2 \cdot HCl + 1/3 \cdot C_3H_5 \cdot$
360-720	9.72	11.16	$2/3 \cdot C_3H_5 \cdot + C$
Residue (%)	64.21	64.30	$P_2O_6Na_3$
Compound 2			
In air flow:			
25-140	1.84		
140-216.1	8.46	9.77	HCl
216.1-263	12.13	11.28	C_3H_6
263-660	21.65	24.27	$HCl + C_3H_6 + C$
Residue (%)	55.92	54.68	$P_2O_6Na_2$
In nitrogen flow:			
25-140	1.55		
140-209.1	8.28	9.77	HCl
209.1-250	11.93	11.28	C_3H_6
250-690	20.21	21.05	$HCl + C_3H_6$
690-900	7.85	7.51	CO
Residue (%)	50.18	50.39	$P_2O_5Na_2$
Compound 3			
In air flow:			
25-220	0.00	0.00	
220-400	45.37	45.32	$2 \cdot HCl + 2 \cdot C_3H_6 + C$
Residue (%)	54.63	54.68	$P_2O_6Na_2$
In nitrogen flow:			
25-240	0.00	0.00	
240-470	42.88	42.10	$2 \cdot HCl + 2 \cdot C_3H_6$
470-600	2.66	3.21	C
Residue (%)	54.45	54.68	$P_2O_6Na_2$
Compound 4			
In air flow:			
25-120	0.00	0.00	
120-210	39.04	39.08	$HCl + C_3H_6O + C_3H_7O \cdot$
210-280	4.11	4.08	CH_4
280-700	19.10	18.95	$HCl + C_2H_2 + C$
Residue (%)	37.75	37.89	P_2O_4Na
In nitrogen flow:.			
25-120	0.00	0.00	
120-210	40.16	39.08	$HCl + C_3H_6O + C_3H_7O \cdot$
210-270	3.87	4.08	CH_4
270-700	18.30	18.95	$HCl + C_2H_2 + C$
Residue (%)	37.67	37.89	P_2O_4Na

The smooth weight loss at 25-200 ^{o}C in the TG curves of the compound 1 is due to the volatilation of adsorbed water. In the first decomposition step the weight loss and mass spectra reveal to a simultaneous release of HCl and $C_3H_5\cdot$. Then the rest of $C_3H_5\cdot$ is released in second step together with carbon (in the form of CO or CO_2).

The smooth weight loss at 25-200 ^{o}C in the TG curves of the compound 2 is due to the volatilation of adsorbed water. The first and second reaction steps reveal to a release of HCl and propene, respectively. In the third stage HCl, propene and carbon monoxide or dioxide are formed. In nitrogen flow, carbon is released in a separate step at 690-900 ^{o}C by burning to CO.

The compound 3 decomposes in air at one very sharp reaction step, which corresponds to the volatilation of two molecules of HCl and propene, and one molecule of CO or CO_2. In nitrogen flow two reaction steps can be observed. The first step is due to the simultaneous release of HCl and propene. The second step correspond to the burning of the carbon left in the crucible.

In the first decomposition step of the compound 4, the weight loss and mass spectra suggest to a simultaneous release of one molecule of HCl, acetone and $C_3H_7O\cdot$. The weight loss of second step corresponds to a release of methane, and that of third step to a simultaneous release of HCl, acetylene and carbon (CO or CO_2).

The most stable of the present compounds is P,P'-diisopropyl clodronate disodium salt (compound 3). This can be explained by the symmetric structure of the compound.

The procedure of the mass spectrometric studies is visualized in Fig. 2-4 for compound 2. The total ion chromatogram obtained by heating the compound 2 in the direct inlet probe using a constant heating rate is shown in Fig. 2, and corresponding mass spectra of the peaks at 215, 254, 299 and 392 ^{o}C are presented in Fig. 3. Total ion chromatogram shows that the decomposition takes place mainly in two steps. The main fragments found were $C_2H_3^+$ (m/z = 27), $C_2H_4^{+\cdot}$ (28), $HCl^{+\cdot}$ (36), $C_3H_5^+$ (41), $C_3H_7^+$ or $C_2H_3O^+$ (43) and $C_2H_5O^{+\cdot}$ (43). Mass chromatograms of these ions are shown in Fig. 4.

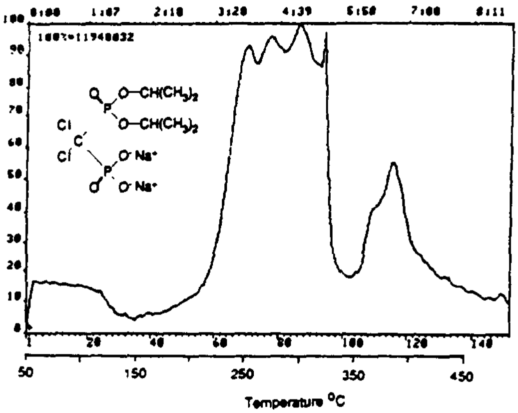


Fig. 2. The total ion chromatogram of the compound 2 as a function of scan numbers and temperature taken with the straight inlet system of the sample.

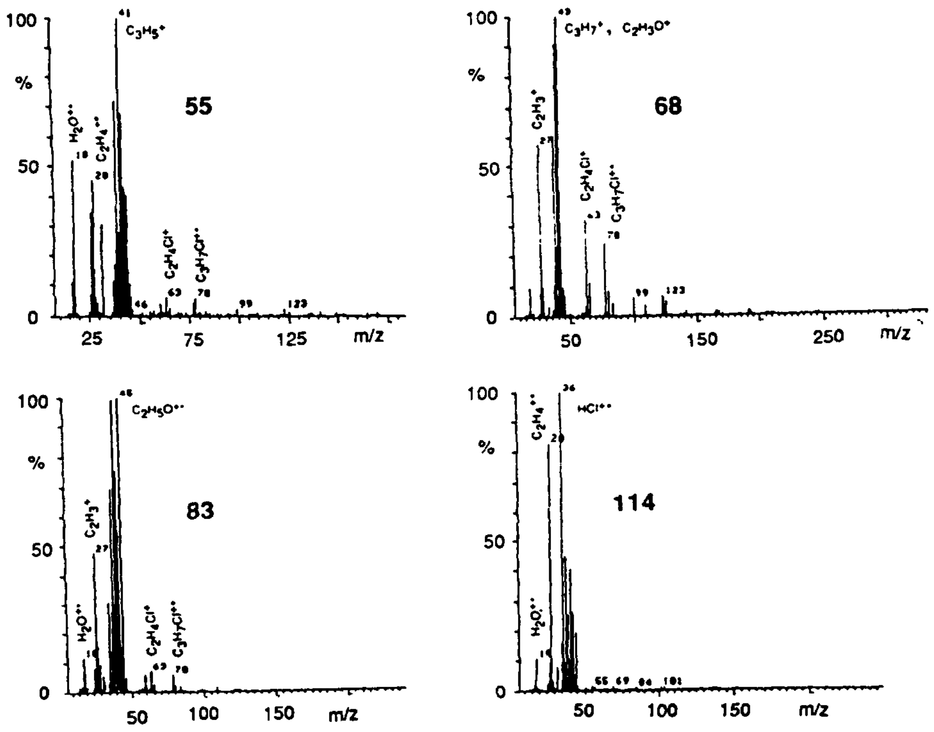


Fig. 3. Mass spectra of the compound 2 taken from the points of scan numbers 55, 68, 83, 114 of the total ion chromatogram presented in Fig. 2.

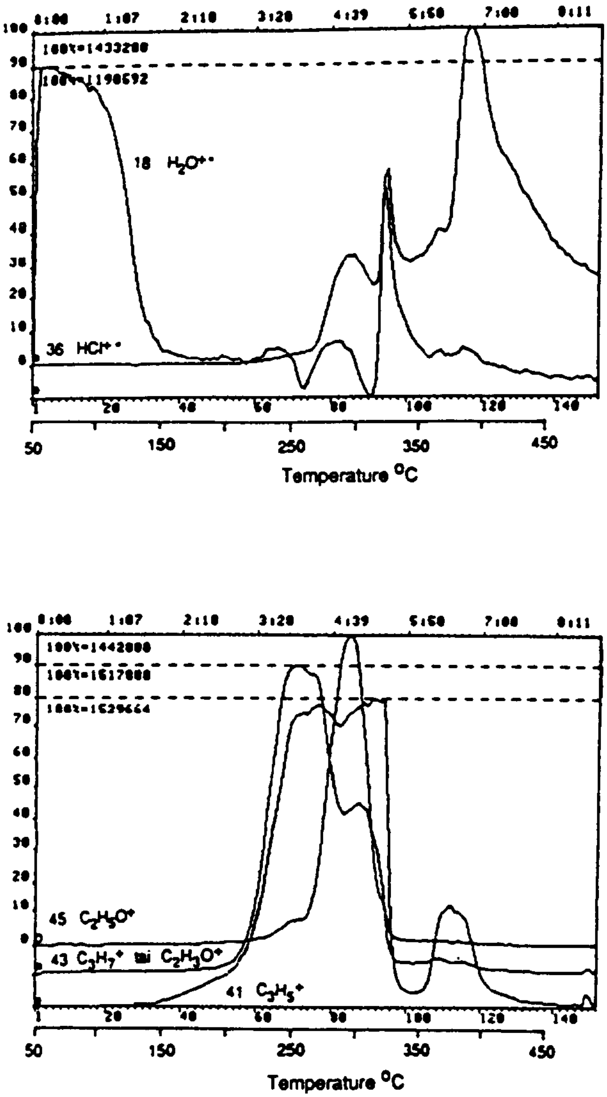


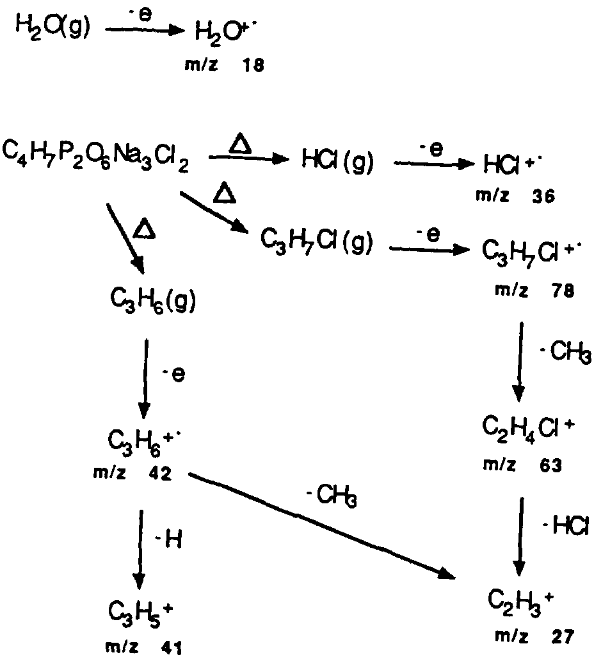
Fig. 4. Mass chromatograms of ions 18, 36, 41, 43 and 45 (m/z).

The release of adsorbed water is seen at 50-150 °C. Similar observation was also made for the other esters studied indicating these compounds to be little hygroscopic. $HCl^{+\cdot}$ ions are formed at three temperatures (about 290, 320 and 400 °C), $C_3H_7^+$ or $C_2H_3O^+$ ion at two temperatures (between 200 and 320 °C and 370 °C).

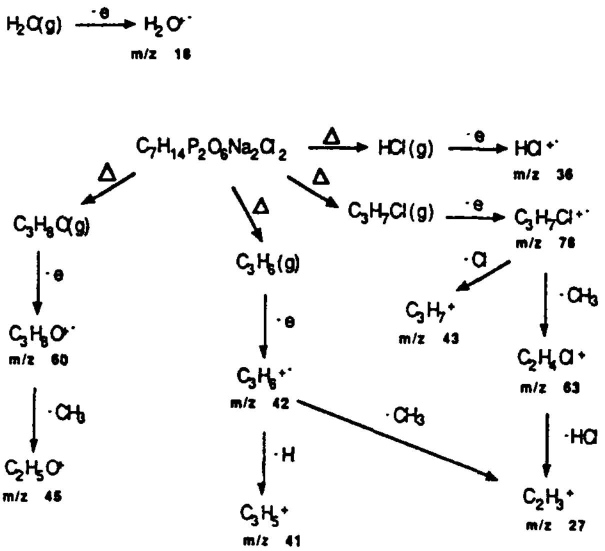
The fragmentation of each compound studied is presented in Scheme 1-4. The fragments with m/z = 55 or 69 are probably formed by the reaction of two ions in the gas phase:

$$C_2H_5^+ + C_2H_4^{+\cdot} \Rightarrow C_4H_7^+ \text{ (m/z = 55)}$$

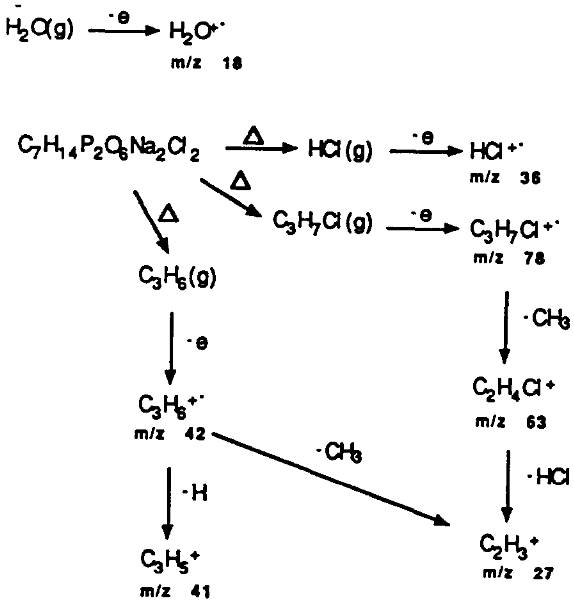
$$C_2H_4^{+\cdot} + C_3H_5^+ \Rightarrow C_5H_9^+ \text{ (m/z = 69)}$$



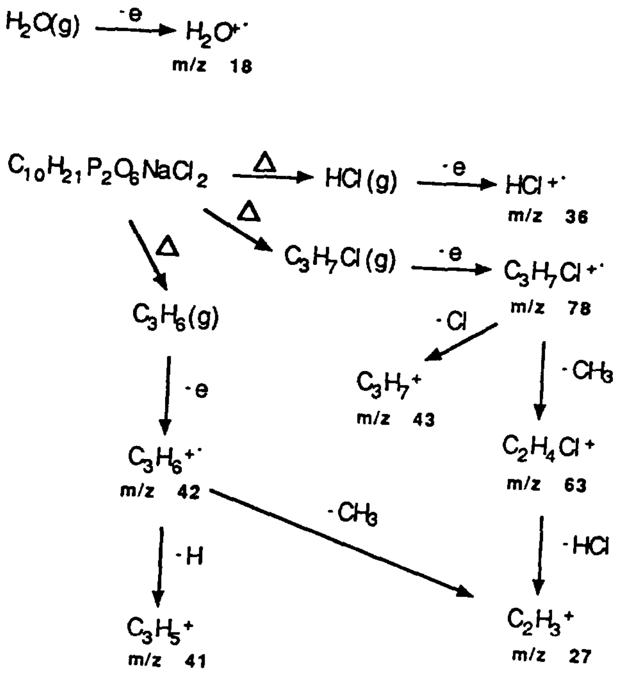
Scheme 1. The fragmentations of the compound 1.



Scheme 2. The fragmentations of the compound 2.



Scheme 3. The fragmentations of the compound 3.



Scheme 4. The fragmentations of the compound 4.

The interpretations for the main decomposition reactions given in Table 1 are based on the mass spectrometric analyses and amounts of the weight losses.

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