Thermochimica Acta, 56 (1982) 125–133
Elsevier Scientific Publishing Company, Amsterdam—Printed in The Netherlands

APPLICATION OF THERMAL ANALYTICAL METHODS TO PHARMACEUTICAL PRODUCTS. CEPHALOSPORINS *

U. BIADER CEIPIDOR, M. TOMASSETTI
Istituto di Chimica Analitica, Università degli Studi di Roma, Rome (Italy)

R. CURINI
Istituto Chimico, Università di Camerino, Camerino (Italy)

(Received 5 January 1982)

ABSTRACT

A series of sodium salts of antibiotics belonging to the cephalosporin group has been analyzed by such thermoanalytical techniques as TG, DTG and DSC. No melting processes have been identified. The heating process, mainly carried out in a stream of oxygen, shows thermal reactions starting at about 150°C. Sodium sulphate was found as residue at temperatures around 600–650°C. From the residue, which has a well-defined composition, it is possible to dose the sodium to a higher degree of accuracy than that obtained by flame photometry. In addition, the analytical time required for pretreatment of the sample is shorter.

INTRODUCTION

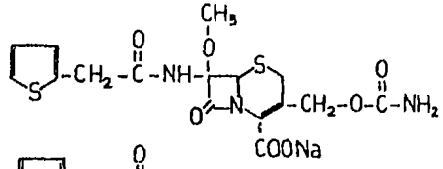
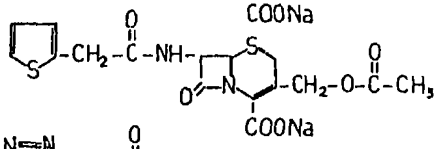
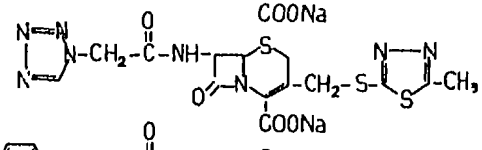
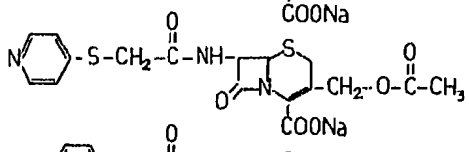
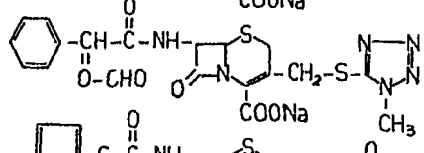
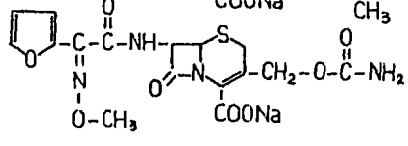
Analysis of antibiotics is of interest at both the industrial level (production control) and at forensic level (frauds control). Commonly, this class of antibiotic is analyzed by biological methods (agar diffusion) [1], ion exchange and gel filtration [2] or by HPLC [3]. Reliable analytical techniques requiring minimal sample treatments are therefore of great interest. Thermoanalytical techniques are recognized as useful and flexible tools in the analysis of drugs [4,5] and clinical analysis [6,7]. The present work examines the determination of the sodium salts of the cephalosporins by thermoanalytical techniques. Analysis of the same salts was also carried out by flame photometry, for which quite a long time is required for pretreatment of samples. The analytical method was realized via sodium determination either by thermal analysis or by flame photometry. The investigation was carried out on compounds present in the most common commercial drugs, and

* This work was supported by the National Research Council (CNR) of Italy.

0040-6031/82/0000–000C/$02.75

TABLE I

Compounds examined

Antibiotic (sodium salt)	Structural formula	Empirical formula	Molecular weight
Cefoxitin		$C_{16}H_{16}N_3NaO_7S_2$	449.44
Cephalothin		$C_{16}H_{15}N_2NaO_6S_2$	418.43
Cefazolin		$C_{14}H_{13}N_8NaO_4S_3$	476.50
Cephapirin		$C_{17}H_{16}N_3NaO_6S_2$	445.45
Cefamandole nafate		$C_{19}H_{17}N_6NaO_6S_2$	512.50
Cefuroxime		$C_{16}H_{15}N_4NaO_8S$	446.37

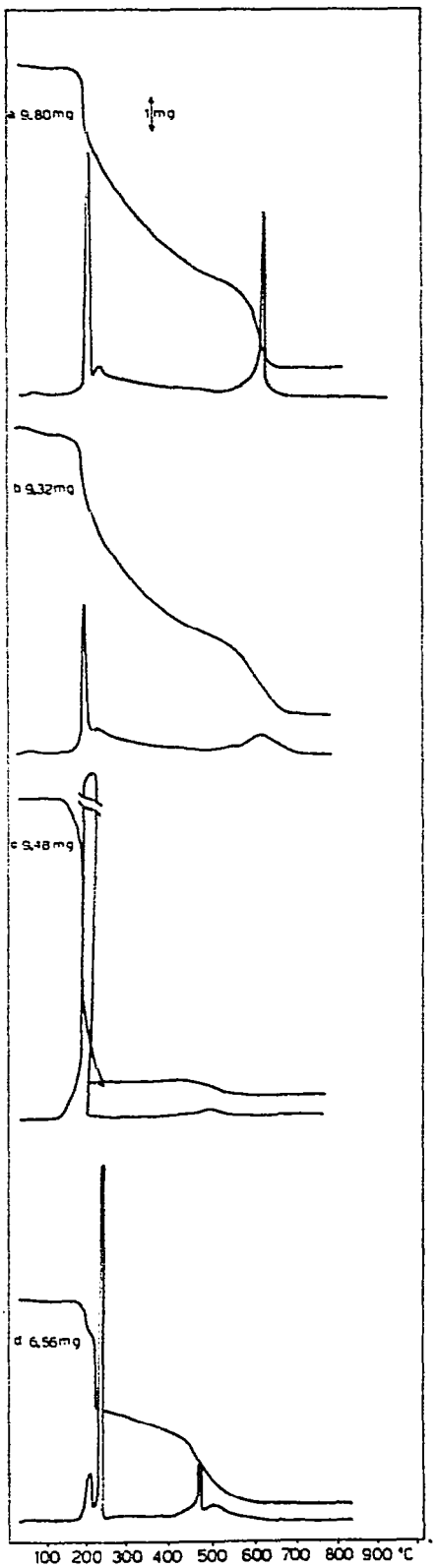
listed in Table 1. Quantitative analysis was carried out by TG, while the characteristics of the thermal decompositions were determined by DSC.

MATERIALS AND METHODS

Sodium salts were supplied by Merck (cefoxitin), Istituto Biochimico Italiano (cephalothin), Carlo Erba (cefazolin), Berlifarm (cephapirin), Lilly (cefamandole nafate), and Glaxo (cefuroxime). The TG and DTG curves of the compounds examined were obtained using a DuPont model 951 thermobalance. The heating rate used was 10°C min^{-1}; the furnace atmosphere was oxygen at a flow rate of 100 ml min^{-1} or static air. The DSC curves were obtained using a Perkin-Elmer DSC-2 instrument at a heating rate of 10°C min^{-1} in an atmosphere of oxygen at a flow rate of 100 ml min^{-1} or in static air. The flame photometric measurements were carried out using an Instrumentation Laboratory Flame Photometer 243; the IR spectra were obtained using a Perkin-Elmer 177 IR spectrophotometer.

RESULTS

The TG curves were obtained in static air or in a stream of oxygen. The TG curves for sodium cefoxitin were clean and reproducible in a stream of oxygen, as shown in Fig. 1. The behaviour of the other compounds agrees well with this. Only in the case of sodium cefuroxime did heating in a stream of oxygen give rise to violent reactions and sputtering. Defective values were obtained for the residual weight (14–15%) found as compared with the theoretical value of 15.9% as sodium sulphate. For this compound better data were obtained working in static air where a residue of 15.6% was found, in good agreement with the theoretical value. Figure 2 shows the TG curves obtained in a stream of oxygen for all the other compounds examined. Table 2 summarizes the results in a stream of oxygen for all the compounds except sodium cefuroxime for which results were obtained in static air. The thermal decomposition, after the loss of water, has been described as a two-step process. The first step gives a mixed residue of sodium sulphate and carbon through a number of overlapping decomposition reactions. The IR spectrum of this residue is shown in Fig. 3 together with the IR spectra of the initial compound and the pure sodium sulphate heated at 500°C. The spectra confirm the hypothesis concerning the nature of the residue: the bands corresponding to the original compounds disappear and the spectrum shows a trend similar to that of the sodium sulphate, while the dark background and the higher weight account for excess carbon. The second TG step corresponds to the oxidation of the carbon to give a pure white sodium sulphate residue as shown by the IR spectrum and by chemical assay



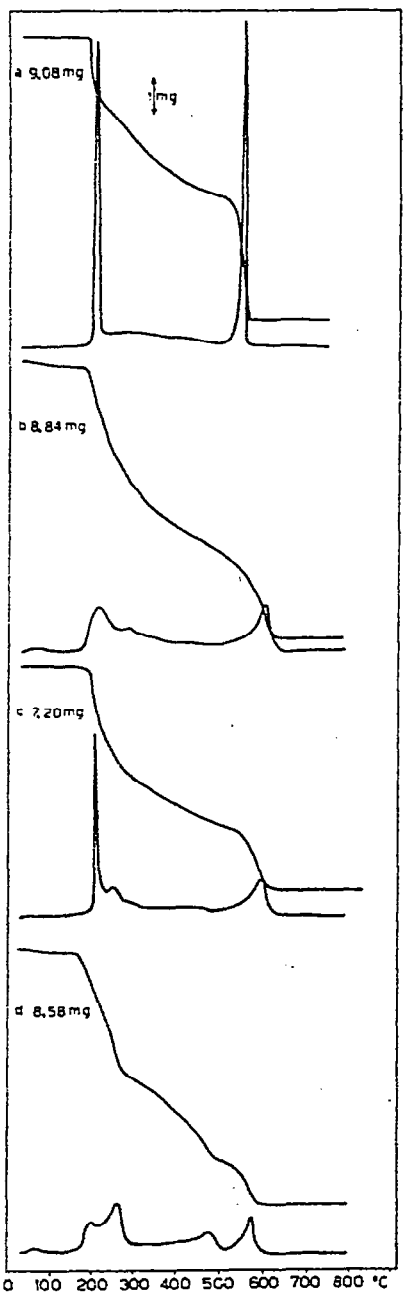


Fig. 1. TG and DTG of some sodium cephalosporins. Heating rate 10°C min^{-1}; static air or oxygen with 100 ml min^{-1} flow rate. (a) Cefoxitin in oxygen; (b) cefoxitin in air; (c) cefuroxime in oxygen; (d) cefuroxime in air.

Fig. 2. TG and DTG of some sodium cephalosporins. Heating rate 10°C min^{-1}; atmosphere of oxygen with 100 ml min^{-1} flow rate. (a) Cephalothin; (b) cefazolin; (c) cephapirin; (d) cefamandole nafate containing 5.93% (w/w) sodium carbonate.

TABLE 2

Thermal analysis of compounds in oxygen

The wt.% residue at the end of each step is referred to the anhydrous compound. Evaporated water is expressed as a fraction of the anhydrous compound.

Sodium salt	Humidity %	pdt	Step 1			Step 2		
			Calcd. %	Found %	pdt	Calcd. %	Found %	pdt
Cefoxitin	1.2	35		41.1	135	15.8	15.9	500
		60			195			600
		95			500			630
Cephalothin				52.6	175	17.0	16.7	500
					215			570
					500			600
Cefazolin	2.1	30		43.1	170	14.9	15.8	500
		65			220			610
		95			500			650
Cephapirin				40.6	165	15.9	15.8	500
					215			600
					500			650
Cefamandole	1.4	30		34.1	155	20.8 [a]	20.8	510
nafate (with		60			200			575
5.93% Na_2CO_3)		90			510			630
Cefuroxime [b]				29.8	160	15.9	15.6	480
					210			510
					480			650

[a] The wt.% of sodium sulphate was calculated considering also the excess sodium present in the drug as carbonate at 5.93% weight.

[b] Values obtained by TG in static air.

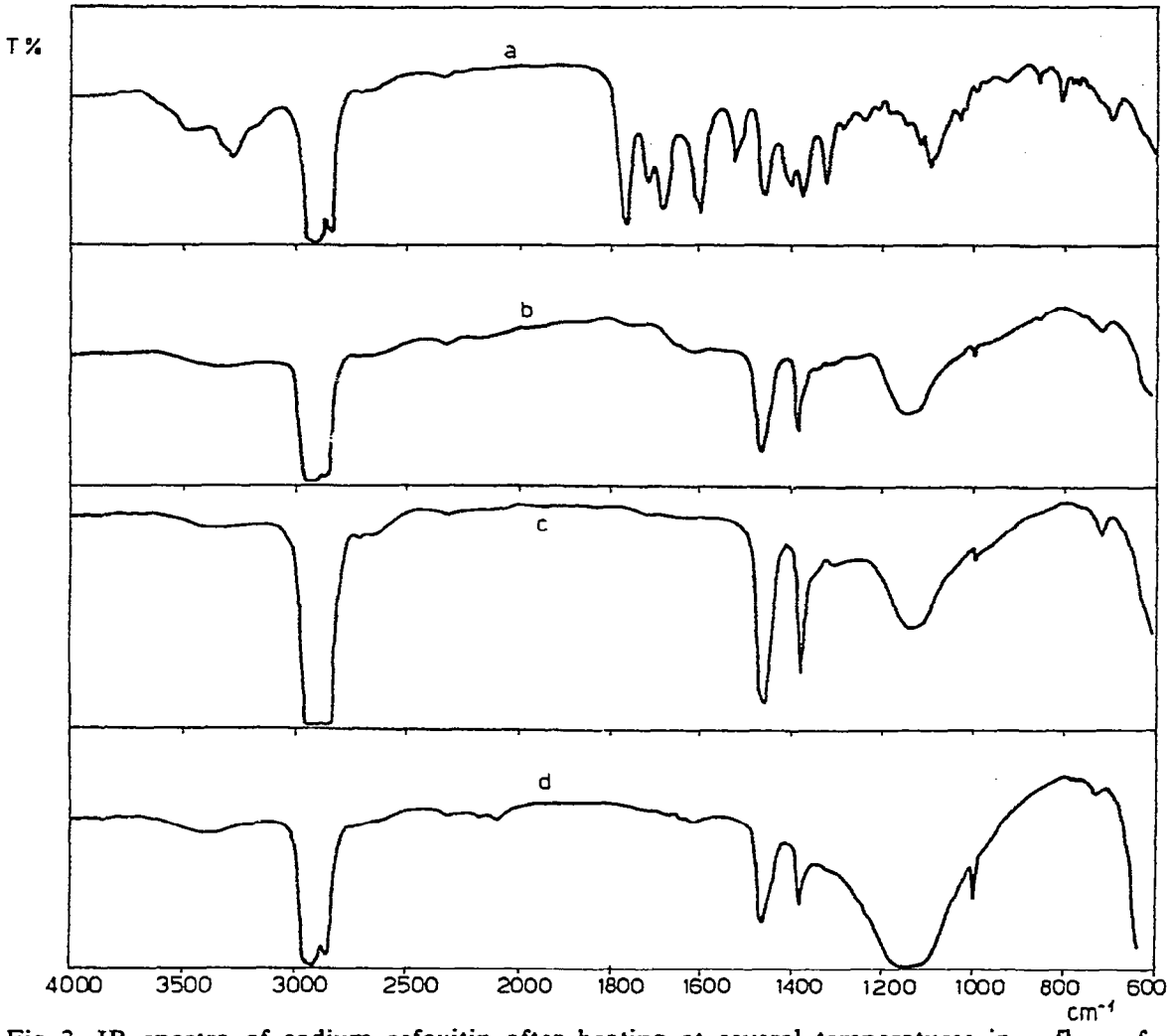


Fig. 3. IR spectra of sodium cefoxitin after heating at several temperatures in a flow of oxygen; nujol used as solvent. (a) Before heating; (b) end of step 1 (~500°C); (c) end of step 2 (~630°C); (d) pure sodium sulphate after heating at 500°C.

(dissolution and precipitation by barium chloride in an acidic medium). During this step, carbon dioxide evolution was verified by bubbling the gas flowing from the furnace over barium hydroxide solution. The DSC curves of the compounds examined are shown in Fig. 4. Calorimetric data show a sequence of very close exothermic reactions occurring in the temperature range corresponding to the first TG decomposition step. The endothermic process due to water loss of the wet compounds (sodium cefoxitin, sodium cefazolin, and sodium cefamandole nafate) appears very weak; in addition, it is impossible to identify any appreciable melting process before thermal decomposition. The quantitative determinations of the sodium content obtained by TG and flame photometry are summarized in Tables 3 and 4. It is thus possible to compare the accuracy of the two methods.

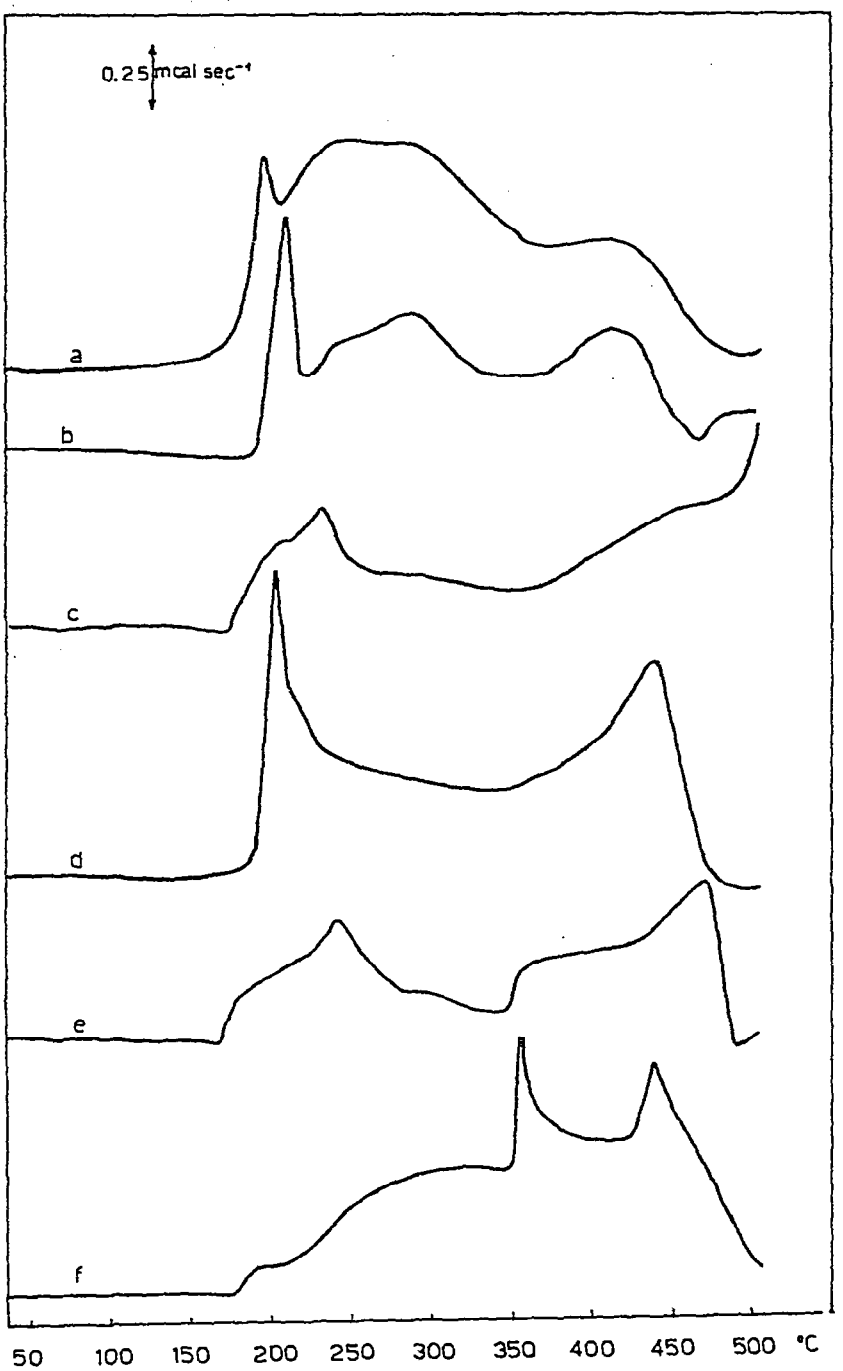


Fig. 4. DSC of sodium cephalosporins at a heating rate of 10°C min^{-1}. Flow of oxygen with 100 ml min^{-1} flow rate: (a) cefoxitin, (b) cephalothin, (c) cefazolin, (d) cephapirin, (e) cefamandole nafate containing 5.93% (w/w) sodium carbonate; air atmosphere: (f) cefuroxime.

TABLE 3

Precision of the analysis of sodium in sodium cefoxitin. Sodium contents (% w/w) obtained by TG and flame photometry
The values obtained by flame photometry are the mean of three readings.

Thermogravimetric method				Flame photometric method			
Calcd.	Found	Mean	S.D.	Calcd.	Found	Mean	S.D.
5.12	5.12 5.24 5.02 5.24 5.34 4.82	5.13	0.19	5.12	4.93 5.03 5.10 4.68 4.82 5.52	5.01	0.29
% Difference between calcd. and mean values: +0.2				% Difference between calcd. and mean values: −2.1			

TABLE 4

Sodium contents (% w/w) of the compounds examined. Comparison of the results obtained by TG and flame photometry
Values are the mean of three determinations.

Sodium salt	% Sodium			% Difference between calcd. and mean values	
	Calcd.	Found by TG	Found by flame photometry	TG	Flame photometry
Cefoxitin	5.12	5.13	5.02	0.2	−2.0
Cephalotin	5.49	5.40	5.47	−1.6	−0.4
Cefazolin	4.83	4.88	4.93	1.0	2.1
Cephapirin	5.15	5.12	5.48	−0.6	6.4
Cefamandole nafate (with 5.93% Na_2CO_3)	6.80	6.77	6.78	−0.4	−0.3
Cefuroxime	5.16	5.06	5.37	−1.9	4.1

DISCUSSION

Thermal analysis of the compounds examined shows that it is impossible to identify and characterize melting reactions. The decomposition induced by heating always starts before the appearance of evaluable endothermic phenomena. In static air, the thermal decomposition in general, starts at a temperature 10°C higher than in a stream of oxygen (for sodium cefuroxime the difference is about 25°C). The better reproducibility of the results

suggests working in a stream of oxygen (with the exception of compounds such as sodium cefuroxime which explode or sputter) where the processes are more determinate. Because of the absence of melting processes, it is impossible to evaluate calorimetrically the purity of the compounds examined. Nevertheless, DSC analysis may be useful in identifying and characterizing the compounds in quality control (calorimetric "finger print"). By TG, it is possible to obtain an accurate analysis of the sodium present in the drugs. The procedure is simple and whether the accuracy is better than that obtained by flame photometry is shown by the data collected in Tables 3 and 4. In the examined cephalosporins, sulphur is generally in excess, when compared with sodium, to form the residual sulphate. In this way, a small, known quantity of sodium carbonate mixed with the compound (as in the case of the sodium cefamandole nafate), increases the final quantity of the residual sodium sulphate, with a consequent correct determination of the total sodium. The sodium determination by this technique, if the final residue is well defined, can be applied to similar drugs giving a good alternative to the traditional quality control methods, especially when it is considered that pretreatment of samples is not required. Since the method is indirect, however, it is not selective.

REFERENCES

1 L.D. Sabath, J.J. Casey, P.A. Ruch, L.L. Stumpf and M. Finland, Antimicrob. Agents Chemother., (1970) 83.
2 T.W. Miller, R.T. Geogelman, R.G. Weston, I. Putter and F.J. Wolf, Antimicrob. Agents Chemother. (1961–1970), 2 (1972) 132.
3 A.L. Wheeler, M. De Meo, B.D. Kirby, R.S. Jerauld and M. Fine, J. Chromatogr., 183 (1980) 357.
4 U. Biader Ceipidor, R. Curini, G. D'Ascenzo and M. Tomassetti, Thermochim. Acta, 46 (1981) 279.
5 U. Biader Ceipidor, R. Curini, G. D'Ascenzo and M. Tomassetti, Thermochim. Acta, 46 (1981) 269.
6 A. Marino, M. Bicchieri, R. Curini, G. D'Ascenzo, V. Carunchio and A. Pierucci, Thermochim. Acta, 46 (1981) 289.
7 G. D'Ascenzo, R. Curini, V. Carunchio, R. Amato and A. Sambenedetto, Thermochim. Acta, 37 (1980) 333.