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THE INFLUENCE OF CHEMICAL STRUCTURE OF SULFONAMIDES ON THE COURSE OF THEIR THERMAL DECOMPOSITION

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Abstract

The thermal decomposition of several sulfonamides and potassium salts of sulfonamides was investigated. The analyses were performed using a derivatograph in an air atmosphere, sample sizes were from 50 to 200 mg and heating rate from 2.5 to 20 K min^{-1}. It has been established, that the thermal destruction of studied compounds occurs via three stages with formation of potassium carbonate as a final product of the complete combustion of potassium salts of sulfonamides. The temperature ranges, in which the analyzed compounds undergo thermal transformations were established. For evaluation of the results the principal component analysis (PCA) was applied. By this method the influence of the specific functional groups on the thermal decomposition of sulfonamides and potassium salts of sulfonamides was determined. It has also been recognized, that better discrimination among the analyzed compounds is obtained for the data set of the DTA.

Keywords: differential thermal analysis, principal component analysis, sulfonamides, thermal decomposition, thermogravimetry

Introduction

In recent years, thermoanalytical methods, i.e. DSC, DTA and TG, have played an important role in the solution of a variety of scientific and industrial problems in pharmacy [1–5]. They are finding increasing applications for the determination of the temperatures of phase transitions of drugs and the values of their thermodynamic constants, the determination of phase diagrams and purity, the evaluation of compatibility among the components of dosage forms, the qualitative and quantitative analysis of drug formulations, stability tests and the determination of kinetic parameters.

Tests on the stability and the thermal decomposition of therapeutic organic substances have revealed, that in many cases the differences in chemical structure of substances covered by analysis find a reflection in the shape of DTA, TG and DTG curves of their thermal decomposition [6–11]. Taking above into consideration, the purpose of these studies is testing of chemical structure influence of the selected groups of therapeutic substances for characteristics of their thermal decomposition.

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Purpose of this work was effected by the determination of the decomposition course of sulfonamides and potassium salts of sulfonamides having a general formula p-$R_1C_6H_4SO_2NHR_2$ and by use of the advanced statistic analysis method, principal component analysis (PCA) as identification tool of influence of compound's chemical structure on the thermal decomposition character.

Experimental

Materials

The following compounds prepared at the Department of Inorganic Chemistry of the Medical University of Gdańsk were used:

a) monopotassium salts of sulfonamides: (**1**) 4-amino-N-(aminocarbonyl)benzenesulfonamide (sulfacarbamide); (**2**) 4-amino-N-(4-isopropoxybenzoyl)benzenesulfonamide (sulfaproxyline); (**3**) 4-amino-N-(4-methyl-2-pyrimidinyl)benzenesulfonamide (sulfamerazine); (**4**) 4-amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide (sulfamethazine); (**5**) 4-amino-N-(2,6-dimethoxy-2-pyrimidinyl)benzenesulfonamide (sulfamethoxine); (**6**) 4-amino-N-2-thiazolyl-benzenesulfonamide (sulfathiazole); (**7**) 4-amino--N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide (sulfafurazole); and (**8**) 4-amino-N-(5-methyl-3-isoxazolyl)benzenesulfonamide (sulfamethoxazole);

b) sulfonamides: (**9**) 2-pyridinebenzenesulfonamide; (**10**) 4-methyl-N-2-pyridinebenzenesulfonamide; (**11**) 4-chloro-N-2-pyridinebenzenesulfonamide; (**12**) 4-bromo-N-2-pyridinebenzenesulfonamide; (**13**) 4-phthalyloamino-N-(4,6-dimethyl-2-pyrimidinyl)-benzenesulfonamide (phthalylsulfamethazine); and (**14**) 4-phthalyloamino-N-(5-methyl--3-isoxazolyl)-benzenesulfonamide (phthalylsulfamethoxazole).

Thermal decomposition

The DTA, TG and DTG curves of the thermal decomposition were carried out using an OD-103 derivatograph (MOM, Hungary). 100 mg samples were heated in a platinum crucible at a heating rate of 2.5, 5, 10 and 20 K min^{-1}. Additionally, 50 and 200 mg samples were heated at a heating rate of 5 K min^{-1}. The analyses were performed in air up to the final temperature of 1073 K. As the reference material α-Al_2O_3 was employed. Each DSC curve was recorded at least three times.

The interpretation of the DTA curve consists of designating the temperatures of the onset (T_i), end (T_f) and peak (T_p), and the temperature ranges of endo- and exothermic peaks (ΔT) in three consecutive stages of the thermal decomposition of the analyzed compounds. In the case of the TG and DTG curves, the temperatures of beginning (T_i) and end (T_f) of the mass losses, the temperature ranges of reaction intervals (ΔT) and losses of mass (Δm) for the second and third stage of decomposition were determined. Moreover, the temperatures of the DTG peaks (T_p) were also determined.

Calculations

PCA was applied for interpretation of the results [11–15]. Starting point for calculations was matrix of the data X with dimensions np, where n – is a number of objects

(rows) and p – is a number of variables (columns). In each matrix sulfonamides and potassium salts of sulfonamides were used as the rows. Columns were the thermal parameters read from the DTA (T_i, T_f, T_p and ΔT), and the TG and DTG (T_i, T_f, ΔT, Δm and T_p) curves of thermal decomposition of the analyzed compounds.

Matrix X is at first standardized, then matrix R is calculated according to it. After further calculations, columns in matrices P and W were obtained, which were called principal components (PC). New matrix P reflects main relations among objects and makes possible classification of the tested compounds according to their chemical structure, whereas matrix W illustrates main relations among variables and enables selection of key thermal parameters, which make the best classification of the analyzed compounds.

Results and discussion

Structural formulas of the sulfonamides and potassium salts of sulfonamides are given in Fig. 1, whereas the most important data about these compounds are compiled in Table 1. From the chemical point of view, sulfonamides are classified as the organic compounds

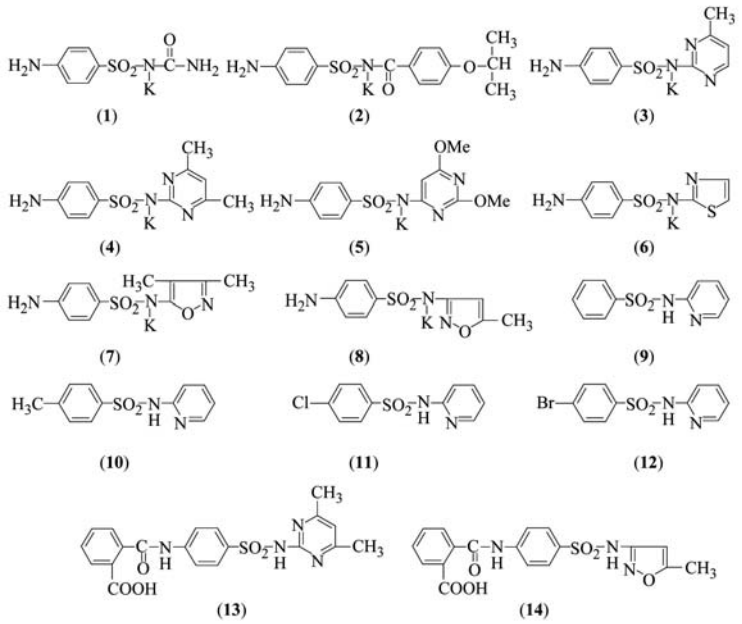

Fig. 1 The chemical structure of:
– monopotassium salts of sulfonamides: (**1**) sulfacarbamide; (**2**) sulfaproxyline; (**3**) sulfamerazine; (**4**) sulfamethazine; (**5**) sulfadimethoxine; (**6**) sulfathiazole; (**7**) sulfafurazole; and (**8**) sulfamethoxazole;
– sulfonamides: (**9**) 2-pyridinebenzenesulfonamide; (**10**) 4-methyl-N-2-pyridinebenzene sulfonamide; (**11**) 4-chloro-N-2-pyridinebenzenesulfonamide; (**12**) 4-bromo-N-2-pyridinebenzenesulfonamide; (**13**) phthalylsulfamethazine and (**14**) phthalylsulfamethoxazole

Table 1 Chemical formulas, molecular masses and melting points of sulfonamides as well as theoretical contents of potassium carbonate in potassium salts of sulfonamides

Sample	Compound	Formula	Molar mass	Melting point/K
1	Potassium salt of sulfacarbamide	$C_7H_8N_3O_3SK$	253.32	27.28[a]
2	Potassium salt of sulfaproxyline	$C_{16}H_{17}N_2O_4SK$	372.48	18.55[a]
3	Potassium salt of sulfamerazine	$C_{11}H_{11}N_4O_2SK$	302.39	22.85[a]
4	Potassium salt of sulfamethazine	$C_{12}H_{13}N_4O_2SK$	316.42	21.84[a]
5	Potassium salt of sulfadimethoxine	$C_{12}H_{13}N_4O_4SK$	348.42	19.83[a]
6	Potassium salt of sulfathiazole	$C_9H_8N_3O_2S_2K$	293.40	23.55[a]
7	Potassium salt of sulfafurazole	$C_{11}H_{12}N_3O_3SK$	305.39	22.63[a]
8	Potassium salt of sulfamethoxazole	$C_{10}H_{10}N_3O_3SK$	291.37	23.72[a]
9	2-pyridinebenzenesulfonamide	$C_{11}H_{10}N_2O_2S$	234.27	462–464[b]
10	4-methyl-N-2-pyridinebenzenesulfonamide	$C_{12}H_{12}N_2O_2S$	248.30	481–486[b]
11	4-chloro-N-2-pyridinebenzenesulfonamide	$C_{11}H_9N_2O_2SCl$	268.72	398–341[b]
12	4-bromo-N-2-pyridinebenzenesulfonamide	$C_{11}H_9N_2O_2SBr$	313.17	477–481[b]
13	Phthalylsulfamethazine	$C_{20}H_{18}N_4O_5S$	426.45	489–492[b]
14	Phthalylsulfamethoxazole	$C_{18}H_{15}N_3O_6S$	401.40	467–473[b]

[a]Percentage content of K_2CO_3 in potassium salts of sulfonamides
[b]Physicochemical guide-book, 2nd Ed., WNT, Warsaw 1974

of sulfur, which are derivatives of amide of *p*-aminobenzenesulfonic acid, which differ from each other by the kind of substituents in the $–SO_2NH_2$ group [16]. Sulfonamides are solids, crystalline, with high melting points, slightly soluble in water but well soluble in acid and alkaline solvents. The antibacterial activity of sulfonamides depends mainly on the free $–NH_2$ group in the *para* position of the benzene ring.

The analysis of the results compiled in Table 2 and illustrated in Fig. 2 allowed to find out, that the thermal decomposition of sulfonamides and potassium salts sulfonamides courses in three stages. The first stage comprises the range of temperatures, in which loss of mass on the TG and DTG curves was not registered. The first stage is present only in case of six compounds, potassium salts of sulfamerazine (**3**), sulfathiazole (**6**) and sulfafurazole (**7**) and also 2-pyridinebenzenesulfonamide (**9**), 4-chloro-N-2-pyridinebenzenesulfonamide (**11**) and 4-bromo-N-2-pyridinebenzenesulfonamide (**12**). Narrow and sharp ended endothermic peaks connected probably with phase transition of the first degree were observed on the DTA curves of these compounds.

In the second stage of decomposition several dozen percent mass loss was observed. In this stage intermediate products of decomposition are formed. The chemical constitution and structure of these products could not be determined due to multi-

Table 2 Results of the thermal decomposition of sulfonamides and potassium salts of sulfonamides. 100 mg samples were heated at 5 K min^{-1} heating rate

Sample	Decomposition stages			
	Temperature range of DTA peak, ΔT/K, temperature of DTA peak, T_p/K, temperature range of decomposition stage, ΔT/K, temperature of DTG peak, T_p/K, mass loss in TG, Δm/%			
	Stage II			Stage III
1		428–513; 498 448–526; 523 (18.0)	513–693; 543 526–708; 673 (25.0)	693–868; 788 708–918; 803 (30.0)
2	338–518; 358 313–518; 353 (10.5)	518–683; 628 518–628; 588 (33.0)	683–833; 823 628–733; 683 (16.5)	833–938; 898 733–933; 893 (21.5)
3		503–538; 528 513–563; 553 (11.0)	538–793; 613 563–703; 583 (19.0)	793–968; 853 703–963; 913 (47.0)
4	348–518; 378 313–503; 378 (6.0)	518–603; 533 503–523; 513 (29.0)	603–758; 628 523–713; 603 (6.0)	758–893; 858 713–908; 858 (37.0)
5	303–508; 343 308–498; 343 (8.0)	508–573; 568 498–553; 538 (20.5)	573–773; 668 553–726; 563 (29.0)	773–948; 913 723–933; 903 (22.5)
6		463–698; 558 453–658; 473 (20.0)		698–923; 858 658–918; 863 (56.5)
7		423–478; 453 433–483; 463 (17.5)	478–653; 633 483–533; 503 (11.5) 653–713; 708 533–653; 640 (7.5)	713–928; 898 653–928; 868 (40.5)

Table 2 Continued

Sample	Decomposition stages			
	Temperature range of DTA peak, ΔT/K, temperature of DTA peak, T_p/K, temperature range of decomposition stage, ΔT/K, temperature of DTG peak, T_p/K, mass loss in TG, Δm/%			
	Stage II			Stage III
8	398–448; 418 303–443; 343 (6.0)	448–513; 483 443–513; 488 (26.5)	513–768; 513 513–658; 648 (10.0)	768–983; 878 658–983; 923 (34.0)
9		453–653; 603 408–540; 530 (28.5)	653–698; 673 540–648; 568 (33.5)	698–788; 738 648–828; 733 (38.0)
10		433–503; 443 433–568; 558 (40.0)	503–703; 603 558–643; 620 (36.5)	703–883; 793 643–868; 808 (23.5)
11		468–583; 573 433–580; 578 (72.0)	583–728; 715 578–673; 670 (8.0)	728–843; 783 673–833; 788 (13.0)
12		488–613; 583 443–593; 588 (61.0)	613–693; 633 593–683; 643 (23.0)	693–883; 798 683–848; 803 (16.0)
13	303–478; 348 303–498; 343 (8.5)	478–673; 583 498–643; 548 (39.0)		673–933; 793 643–903; 793 (52.5)
14	408–478; 428 358–463; 433 (7.0)	478–553; 498 463–533; 493 (12.0)	553–718; 673 533–623; 605 (17.0)	718–978; 808 623–993; 818 (64.0)

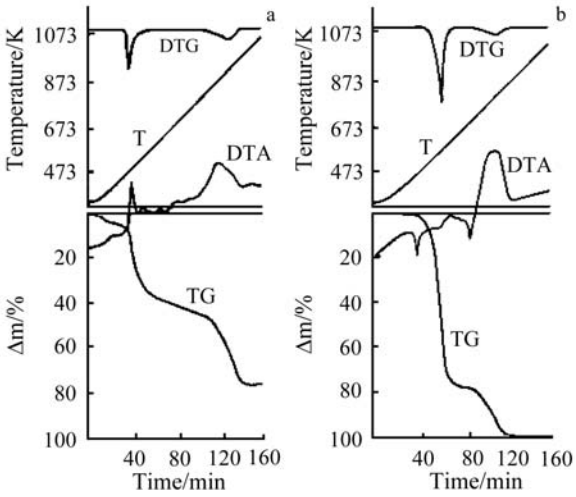

Fig. 2 DTA, TG and DTG curves of the thermal decomposition of: a – potassium salt of sulfamethoxazole (**8**) and b – 4-methyl-N-2-pyridinebenzene-sulfonamide (**10**). 100 mg samples were heated at 5 K min^{-1} heating rate

directional course of thermal destruction of organic matter. As shown in Table 2, the second stage has been divided into several substages. This is caused by the parallel and consecutive reactions of the formation of intermediate products and by overlapping their thermal effects.

The third stage includes the final compound decomposition which is based on combustion of high temperature carbonization residues. In this stage for each compound a strong exothermic effect on the DTA curve and a small peak on the DTG curve reflecting the mass loss on the TG curve can be observed. Qualitatively detected final product of the decomposition of potassium salts of sulfonamides is potassium carbonate.

The thermal parameters determined on the basis of DTA, TG and DTG curves of decomposition for tested compounds were used for the calculations of PCA. On their base seven matrices were constructed (X) – three for the DTA curves, two for the TG and DTG curves, and two for the connected results from the DTA, TG and DTG curves. The matrix for the first stage of decomposition consists of 6 rows, because this stage was found during thermal analysis of only six compounds. For the remaining stages (II and III), matrices consisted of 14 rows (all compounds under analysis). In contrary to the results received from the TG and DTG curves, matrices of which included 30 columns (6 weighed samples at four heating rates and for each weighed sample 5 parameters determined from the TG and DTG curves – T_i, T_f, ΔT, Δm and T_p), the matrices elaborated basing on data received from the DTA curves consisted of 24 columns (6 weighed samples at four heating speeds and for each weighed sample 4 parameters from the DTA curves – T_i, T_f, T_p and ΔT). The matrices for the connected data sets received from the DTA, TG and DTG curves consisted of 14 rows and 54 columns.

The results of PCA calculations are compiled in Table 3. An analysis of these data, separately for the DTA curves as well as for the TG and DTG curves have revealed, that the first two main components PC1 and PC2 explain totally more than

Table 3 Results of PCA calculations for the DTA and for the TG and DTG data sets of the studied compounds

Decomposition stage / Thermoanalytical databases	PC1		PC2		PC3	
	Eigen-values	Variances/ %	Eigen-values	Variances (cumulative variances)/ %	Eigen-values	Variances (cumulative variances)/ %
I (DTA)	16.9	70.6	3.8	15.7 (86.3)	1.7	7.3 (93.6)
II (DTA)	12.4	51.7	6.0	25.2 (76.9)	3.2	13.2 (90.2)
II (TG, DTG)	12.3	41.0	8.2	27.4 (68.5)	4.5	15.0 (83.5)
II (DTA, TG, DTG)	21.2	50.6	9.8	23.4 (74.0)	4.9	11.7 (85.7)
III (DTA)	10.6	44.0	7.2	29.9 (73.9)	2.2	9.1 (83.0)
III (TG, DTG)	13.0	43.4	8.3	27.8 (71.2)	2.7	9.0 (80.2)
III (DTA, TG, DTG)	15.3	36.5	13.0	31.3 (67.8)	3.9	9.3 (77.1)

70% variances, and eigenvalues of PC1 and PC2 are greater than unity. This creates sufficient condition for investigation on the relation between tested compounds in two-dimensional space, PC1 against PC2.

The interpretation of PCA results for the DTA curves has revealed, that for the arrangement of potassium salts of sufamerazine (**3**), sulfathiazole (**6**) and sulfafurazole (**7**) as well as 4-bromo-N-2-pyridinebenzenesulfonamide (**12**) on the PCA diagram for the first stage of decomposition did not have influence of similarity of chemical structure of tested compounds. This results from the fact, that this stage is connected explicitly with phase transitions. The exception is 2-pyridinebenzenesulfonamide (**9**) and its chloroderivative (**11**), which is in the narrow range of PC2 values.

As shown in Fig. 3, in the case of the second stage of decomposition, sulfonamides and potassium salts are localized on the PCA diagrams in this way, that they create groups of compounds of similar chemical constitution. Substances having in their structure the pyrimidine arrangement, i.e. potassium salt sufamethazine (**4**) and sulfadimethoxine (**5**), as well as phthalylsulfamethazine (**13**) and also compounds with five members heterocyclic substituent of numbers **6** (potassium salt of sulfathiazole), **7** (potassium salt of sulfafurazole), **8** (potassium salt of sulfamethoxazole) and **14** (phthalylsulfamethoxazole) are localized in the separate clusters, in relatively narrow range of PC1 values for the DTA results (Fig. 3a) and PC2 for the TG and DTG results (Fig. 3b).

In the case when the data were received from the DTA curves, compounds of numbers **1** (potassium salt of sulfacarbamide) and **3** (potassium salt of sulfamerazine) are

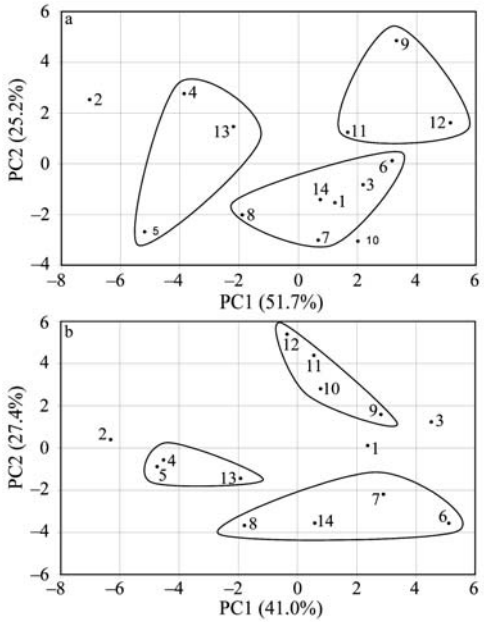

Fig. 3 Two-dimensional plot PC1 *vs*. PC2 for the second stage of the thermal decomposition of analyzed compounds based on the: a – DTA and b – TG and DTG data sets

placed in two-dimensional space with sulfonamides of numbers **6** (potassium salt of sulfathiazole), **7** (potassium salt of sulfafurazole), **8** (potassium salt of sulfamethoxazole) and **14** (phthalylsulfamethoxazole) but it has no connection with their chemical constitution and localization in this group is accidental. In the range of similar values of PC1 and PC2 the derivatives of 2-pyridinebenzenesulfonamide (**9**, **10**, **11** and **12**) also were localized. However in the case of the DTA results, 4-methyl-N-2-pyridinebenzenesulfonamide (**10**) is outside from this group of compounds.

The results of PCA calculations for the third stage of decomposition are illustrated in Fig. 4. In this case, for the data taken also from the DTA as well as from the TG and DTG curves, tested compounds were placed similarly as in the previously described cases, depending on the substituent, which they comprised in their structure. An exception is potassium salt of sulfacarbamide (**1**), which is located on the PCA diagram for data assigned basing on the DTA curves together with compounds of numbers **9**, **10**, **11** and **12**. This arrangement is however accidental and there is no connection between chemical constitution of this sulfonamide and derivates of 2-pyridinebenzenesulfonamide. The influence of phthalyl group for thermal decomposition of compounds of numbers **13** (phthalylsulfamethazine) and **14** (phthalylsulfamethoxazole) which were localized in similar ranges of PC1 and PC2 values, is evident.

In order to make full evaluation of the thermal analysis results of sulfonamides and potassium salts of sulfonamides, the two new matrices for stages II and III pro-

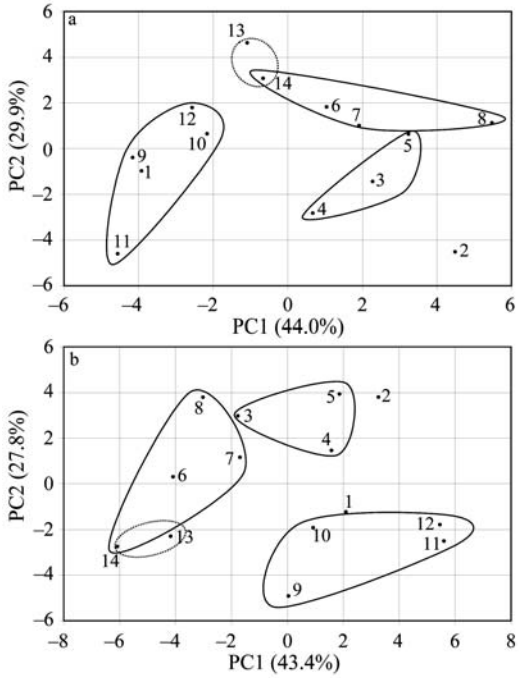

Fig. 4 Two-dimensional plot PC1 *vs*. PC2 for the third stage of the thermal decomposition of analyzed compounds based on the: a – DTA and b – TG and DTG data sets

duced as a result of connection of the DTA matrix with the TG and DTG matrix, were subjected to PCA calculations. The results of PCA calculations listed in the Table 3 have revealed, that PC1 and PC2 describe relations between compounds basing on smaller variance, than in the case of matrices tested separately.

On the diagram of PC1 against PC2 for the second stage of decomposition, the tested compounds are localized according to their chemical constitution. Sulfonamides and potassium salts are grouped in similar way as in the previously described matrices. In narrow scope of PC1 the potassium salts of sulfamethazine (**4**) and sulfadimethoxine (**5**) as well as phthalylsulfamethazine (**13**) and methyl- (**10**), chloro- (**11**) and bromo- (**12**) derivatives of 2-pyridine-benzenesulfonamide were found. Potassium salts of sulfathiazole (**6**), sulfafurazole (**7**) and sulfamethoxazole (**8**) as well as phthalylsulfamethoxazole (**14**) were found in the narrow scope of PC2 values.

Then for the third stage of decomposition, the sulfonamides and potassium salts of sulfonamides were located on two-dimensional diagram as it was in the cases described previously. So in the separate clusters, the compounds having five-members and six-members heterocyclic substituents, the derivatives of 2-pyridinebenzenesulfonamide as well as sulfonamides with phthalyl arrangement are found.

Conclusions

The graphical interpretation of PCA results has revealed that points on PC1 *vs*. PC2 diagrams corresponding to the compounds of similar chemical constitution are localized in the similar ranges of the first two PC's values. This proves that thermal decomposition reflects similarity in the structure of sulfonamides groups and potassium salts of sulfonamides. The compounds which include the same basic chemical structure comprising specified aromatic or heterocyclic arrangements are characterized first of all by similar course of their thermal decomposition. The presence of functional groups and other substituents, both in basic arrangement and in R_2 substituent in sulfonamides group is an important factor which decides on the direction of thermal decomposition.

In this way it has also been recognized, that better discrimination among tested compounds is obtained for the data sets received from the DTA curves, both for the second and the third stage of decomposition. The distribution of sulfonamides and potassium salts in two-dimensional space is determined by higher percentage of total variability, than at the same time for the data sets received from the TG and DTG curves.

Generally, all determined thermal parameters may be useful for the assessment of influence of substituents on the thermal decomposition of basic structure of sulfonamides.

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