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Thermal decomposition of new ruthenium(II) complexes containing *N*-alkylphenothiazines

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Niinistö"s Special Chapter

Abstract Thermal decomposition of chlorpromazine hydrochloride (CP·HCl), trifluoperazine dihydrochloride (TF·2HCl) and thioridazine hydrochloride (TR·HCl), and the ruthenium complexes with dimethyl sulfoxide (dmso) of composition $[RuCl_2(dmso)_4]$ and $L[RuCl_3(dmso)_3]\cdot x$EtOH, L = CP·HCl, TF·2HCl or TR·HCl is described. The phenothiazines are stable to temperature range of 200–280 °C with an increasing stability order of TF·2HCl < CP·HCl < TR·HCl. The decomposition of all the compounds takes place in superposing steps. For detection of chlorides and sulfides, EGD analysis was performed. The decomposition pattern of the complexes, due to their similar structure, is similar. The thermal data unambiguously resolve the contradiction between the elemental analysis and X-ray structural data for $(TF\cdot 2HCl)[RuCl_3(dmso)_3]Cl\cdot$EtOH. The compound crystallizes with one EtOH, evaporating in part at room temperature.

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Introduction

The search for effective anticancer compounds based on metal centers has been developed in the last few decades of the twentieth century. Ruthenium complexes are potential alternative drugs to cisplatin, some of them exhibit even a better cytotoxic effect [1]. Ruthenium complexes with dimethyl sulfoxide (dmso) showed selective antitumor properties in preclinical testing [2]. Biological studies in *cis*- and *trans*-$RuX_2(dmso)_4$ complexes (X = Cl and Br) refer to different tumor toxicity and anti-metastasis properties of the isomers [3]. Dmso can be coordinated to ruthenium as a metal center either through the sulfur (dmso-S) or through the oxygen atom (dmso-O). Dimethyl sulfoxide (dmso) provides a moderate acceptor site for π-electron donors and bound through sulfur stabilizes ruthenium in lower Ru(II) oxidation state, more reactive toward tumor cells [4].

The biological activity of complexes can be modified by addition or change of the ligands. Phenothiazines and their *N*-alkyl derivatives are themselves biological active compounds, suitable to take part in complex formation. In medicine, they are used as antipsychotic and antihistaminic drugs [5], show antimicrobial and antifungal properties [6], and exhibit a strong in vitro antitumor activity in numerous and various tumor cell lines [7, 8]. Only a few mononuclear metal complexes of *N*-alkylphenothiazines are described with coordination through their heterocyclic atoms, sulfur [9, 10], or nitrogen [11].

In our previous article, we described the synthesis, structure, in vivo activity on superoxide dismutase (SOD),

and catalase (CAT), and in vitro cytotoxicity of new Ru(II) complexes with *N*-alkylphenothiazines [12]. The selective cytotoxicity of these complexes against some human carcinoma cell lines is promising for development of new anticancer drugs. In this article, we report the thermal behaviors of the new compounds and their precursors, which are of general interest in the case of potential bioactive compounds [13–15]. Besides, the thermal decomposition pattern may help us to estimate the bond strength, redox properties, and exchangeability of the central atoms in the molecule [16], thus offering a basis for a better understanding of the mechanisms regulating their activity.

Experimental

Materials

Chlorpromazine hydrochloride (CP·HCl), trifluoperazine dihydrochloride (TF·2HCl), and thioridazine hydrochloride (TR·HCl) were used as supplied (Aldrich). The preparation of the starting $[RuCl_2(dmso)_4]$ complex [17] and the corresponding $L[RuCl_3(dmso)_3]$ complexes with *N*-alkylpheno-thiazine derivatives with L = CP·HCl, TF·2HCl or TR·HCl, [12] is described elsewhere.

Methods

Thermal data were measured using TA Instruments SDT Q600 TG/DSC thermal analyzer. Simultaneous TG/DSC measurements were carried out up to 700 °C at a heating rate of 20 °C min^{-1} in nitrogen gas carrier (100 cm^3 min^{-1}) and a sample mass of ~3 mg. The runs were taken in an open alumina pan and a corresponding empty referent pan. The thermal decomposition of selected samples was followed in flowing synthetic air atmosphere, also. For EGD, an acidic (HNO_3) solution of $AgNO_3$ was applied.

Results and discussion

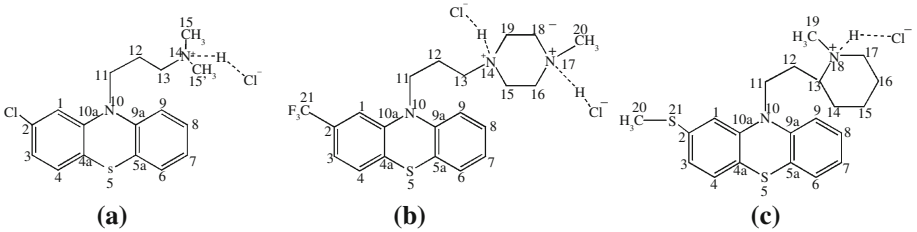
The structure of the phenothiazines is presented in Scheme 1. As can be seen, the phenothiazine skeleton in all the three compounds is substituted at positions 2 and 10 with different substituents, forming thus a series.

The $L[RuCl_3(dmso)_3]$ complexes **1**, **2**, and **3** were synthesized by the reaction of $[RuCl_2(dmso)_4]$ and CP·HCl, TF·2HCl or TR·HCl, respectively. The molecular structure of the complex with TF·2HCl (**2**) was determined by single crystal X-ray analysis [12] and is presented in Fig. 1. The complex consists of $[RuCl_3(dmso)_3]^-$ anionic unit and the protonated trifluoperazine, being in the outer coordination sphere. The molecule crystallizes with one ethanol molecule. The spectral data (absorption, IR and NMR spectra) of all three compounds are very similar referring to their similar structure. Comparison between the proton spectrum of the phenothiazines and the corresponding complexes suggests that the alkylphenotiazines are in outer sphere in all the three complexes. The ^{13}C NMR spectra of the complexes show a high-field shift of the N10 substituent carbon atoms [12].

As both the phenothiazines and the corresponding complexes belong to series, the thermal analysis could give valuable data on the relationship between the structure and thermal data.

Thermal decomposition

The DTG curves of the phenothiazines are presented in Fig. 2. The decomposition of the phenothiazines takes place in the range of about 200 to 280 °C with an increasing stability order of TF·2HCl < CP·HCl < TR·HCl. The decomposition is a complex process with hardly distinguishable steps in TF·2HCl, and almost completely overlapped peaks in CP·HCl and TR·HCl. EGD analysis refers to the evaporation of HCl around 300 °C. In TR·HCl, it is almost immediately followed by the splitting of the methylthio group detected by the precipitation of black Ag_2S in an acidic $AgNO_3$ solution. The decomposition of



Scheme 1 The structure of the phenothiazines: **a** Chlorpromazine hydrochloride (CP·HCl), 10-[3-(dimethyl amino)propyl]-2-chloro phenothiazine hydrochloride. **b** Trifluoperazine dihydrochloride (TF·2HCl), 10-[3-(4-methyl-1-piperazinyl)propyl]-2-trifluoromethyl phenothiazine dihydrochloride. **c** Thioridazine hydrochloride (TR·HCl), 10-[2-(1-methyl-2-piperidinyl)ethyl]-2-(methylthio)-phenothiazine hydrochloride

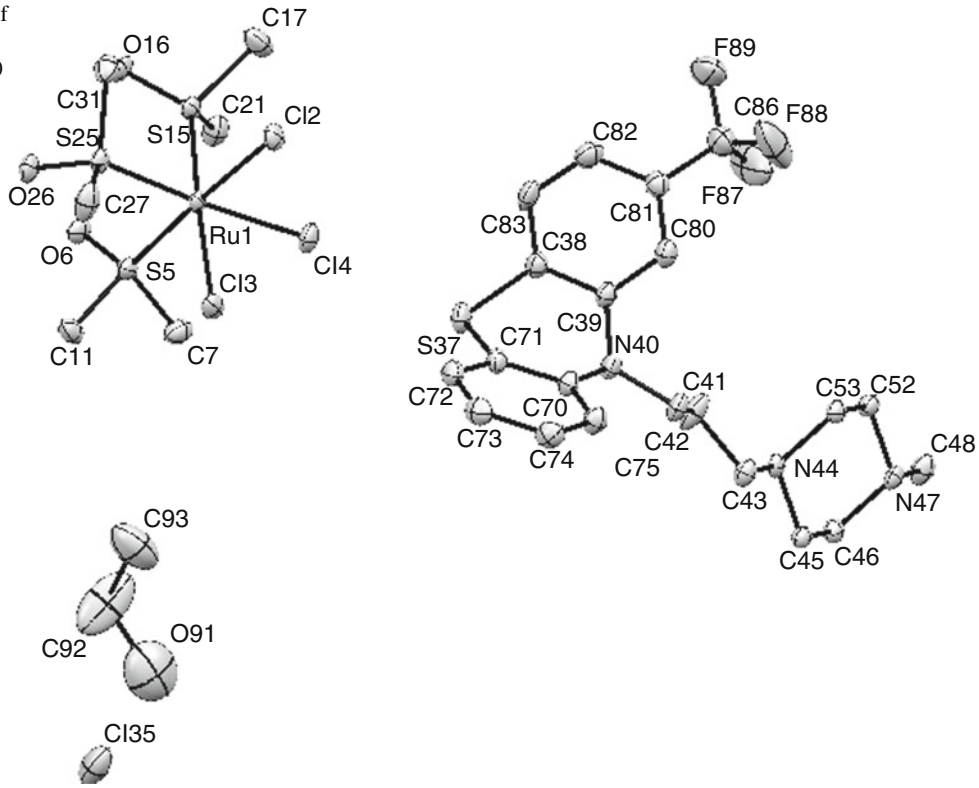


Fig. 1 ORTEP representation [18] of the asymmetric unit of $TF{\cdot}H_2[Ru(dmso)_3Cl_3]Cl{\cdot}C_2H_5OH$ (**2**) with the crystallographic numbering scheme

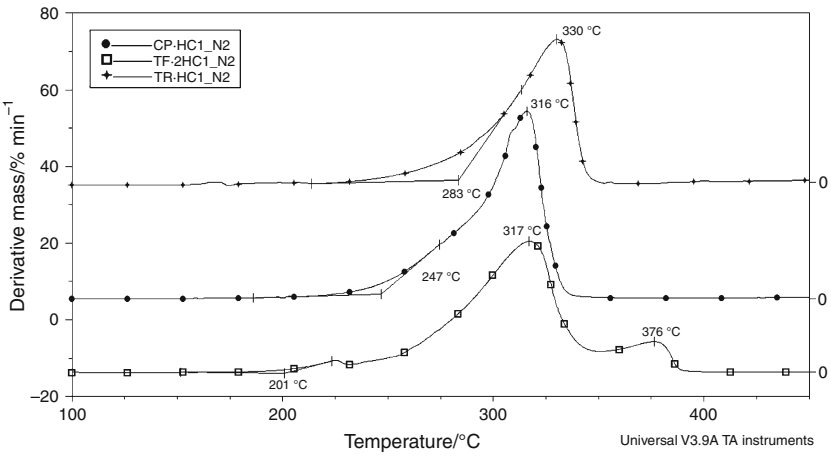


Fig. 2 DTG curves of TF·2HCl, CP·HCl and TR·HCl

TF·2HCl in nitrogen is completed at around 400 °C without residue, while the decomposition of the other two phenothiazine molecules proceeds with a steady, very slow rate from around 350 °C and is not finished up to 500 °C.

All the three compounds melt (onsets: 160 °C, TR·HCl; 197 °C, CP·HCl; 211 °C, TF·2HCl, see DSC curves in Fig. 3; visible to the naked eye, too). The melting of TF·2HCl is accompanied by its decomposition. The most significant difference in DSC curves of the phenothiazines is the intensive exothermic peak with a maximum at 334 °C in TR·HCl, while the decomposition of the other two compounds to about 350 °C is endothermic. Whether this difference could be related to the considerably higher cytotoxicity of this compound against MDA-MB-432 (breast cancer), SW-480 (colon adenocarcinoma), and IM9 (myeloma multiple) cell lines [12] requires further research.

The thermal curves of the starting $[RuCl_2(dmso)_4]$ complex are presented in Fig. 4. The complex is stable to 200 °C (onset: 204 °C). Instead of the stepwise release of dmso ligands, the decomposition takes place by complex exothermic processes. The endothermic peak with a minimum at 212 °C refers to the melting. The decomposition proceeds most probably through oxidation of Ru(II) to Ru(III) and coordination change between O and S ligating atoms of dmso which are originally bonded through both the S and O atoms in the *cis* isomer, while in the

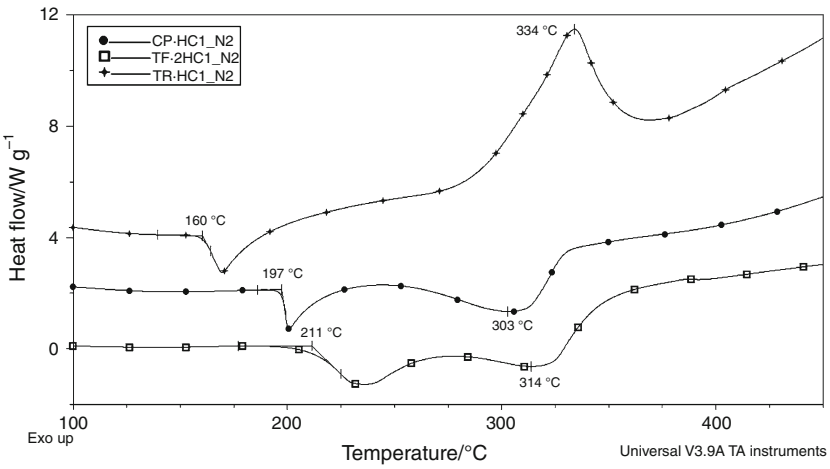


Fig. 3 DSC curves of TF·2HCl, CP·HCl and TR·HCl

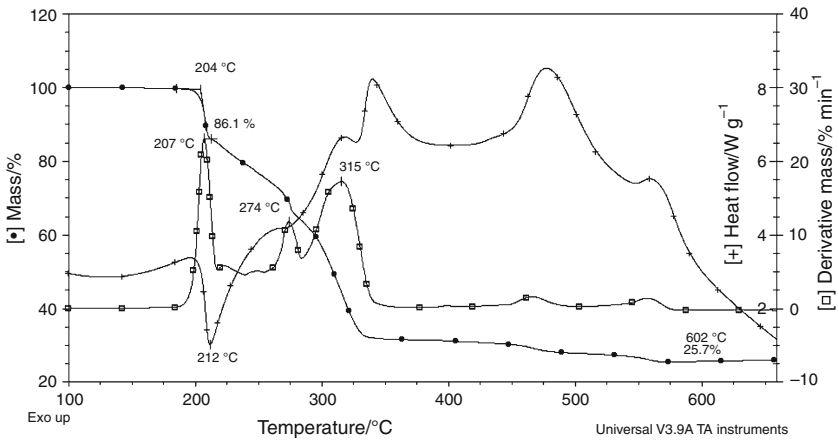


Fig. 4 TA curves of the starting $[RuCl_2(dmso)_4]$ complex

corresponding *trans* configuration only through S atoms [3]. The residue at about 360 °C may belong mostly to RuS_2 (exp. 31.5%, teor. 34.09%). At about 500 °C, most of the residue consists of RuO (exp. 27.8%, teor. 27.48%) while above 600 °C a partial reduction to elemental Ru is observed (exp. 25.7%, teor. 24.17%) in both flowing nitrogen and air atmosphere. This is in accordance with decomposition of some palladium complexes [19]. On the contrary, the residue at the decomposition of some ruthenium complexes in air [14, 15] is Ru(IV) oxide.

The decomposition pattern of the $L[RuCl_3(dmso)_3]$ complexes **1**–**3** are similar (see Figs. 5 and 6; the curves are shifted compared to each other) and can be divided in three separate parts. The first part from room temperature to about 200 °C belongs to the desolvation and most probably to demethylation. Twin peaks at around 180 °C in **1**, with aliphatic dimethylamino group (chlorpromazine hydrochloride, CP·HCl) might support this proposition in spite of the fact that the corresponding peak is not detected in the thermal curves of the phenothiazines. In other words, by the complex formation, the properties of the constituents are usually changed.

In the next part, up to ~320 °C the phenothiazines fragmentation and the evaporation of the dmso take place. The decomposition rate of **1** is higher compared to that of the complexes with piperazine (**2**) and piperidine (**3**) derivative. Around 250 °C, the evaporation of HCl is detected by EGD in all the three compounds (AgCl formation with an acidic $AgNO_3$ solution). In TR·HCl, it is followed by splitting of the methylthio group. The processes are accompanied by small endothermic effect. Above 320 °C, the course of the decomposition changes to highly exothermic. This is most probably related to the departure of the rest of dmso with structural rearrangements through sulfide and oxide formation, alike to $[RuCl_2(dmso)_4]$ decomposition. The decomposition is not accomplished up to 700 °C and proceeds with a very slow rate, into elemental ruthenium. Around 1000 °C in air, the only residue of the decomposition is elemental ruthenium in all the three complexes.

The thermal data unambiguously resolve the contradiction between the elemental analysis and X-ray structural data [12]. By single crystal X-ray analysis, one ethanol molecule per formula unit was found in **2**, while elemental

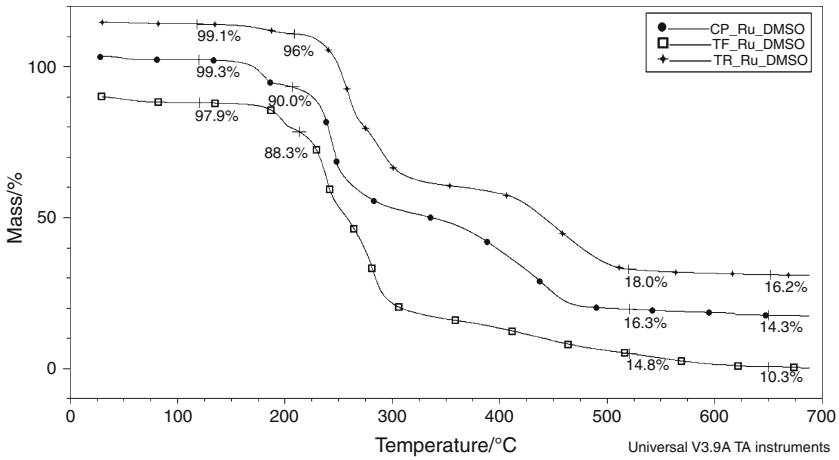


Fig. 5 TG curves of $L[RuCl_3(dmso)_3]$ complexes

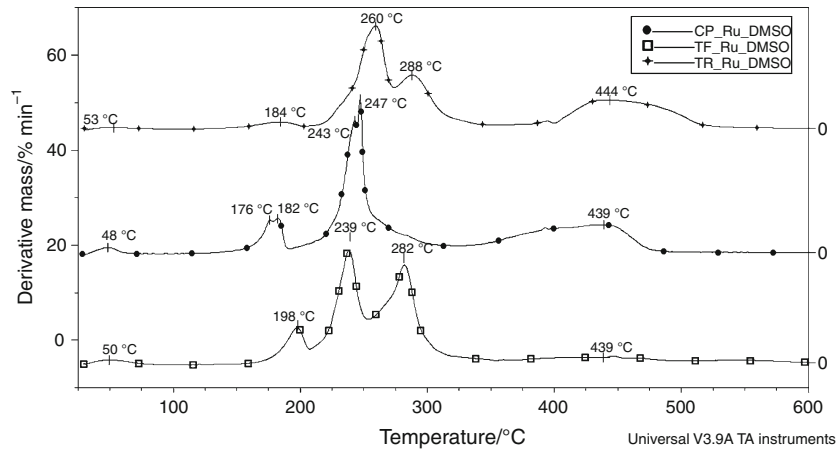


Fig. 6 DTG curves of $L[RuCl_3(dmso)_3]$ complexes

analysis data match with only a half of EtOH. As the ethanol evaporation starts at room temperature with a DTG maximum at 50 ± 3 °C in all the three complexes, the elemental analysis data agree with a less ethanol content, depending on the time period between the preparation of the complexes and their analyses and the storage temperature. Therefore, **2**, and probably the other two complexes, too, crystallize with one EtOH which in part evaporates between the measurements. In **1**, **2**, and **3,** by thermal analysis 0.4, 0.2, and 0.1 mol (2.1, 1.0, and 0.8%) ethanol per formula unit was found, respectively. The desolvated complexes are not stable either. Most probably, the low evaporation temperature of the crystal solvent and the low stability of the desolvated compounds prevented the preparation of the other complexes in the form suitable for X-ray structure determination.

The decomposition of **1**–**3** is accompanied by melting of the complexes that was observed visually. The thermal decomposition pattern of the complexes does not depend on the atmosphere. This observation might have an impact on their specific reaction mechanism in biological systems.

Conclusions

The thermal stability of the phenothiazines increases in the order of TF·2HCl < CP·HCl < TR·HCl from 200 to 280 °C. The decomposition of TF·2HCl and CP·HCl is endothermic to 350 °C while the decomposition of TR·HCl around this temperature is accompanied by a highly exothermic peak.

The decomposition of $[RuCl_2(dmso)_4]$ starts at 204 °C onset involving several overlapping exothermic processes. The decomposition proceeds most probably through oxidation of Ru(II) to Ru(III) and coordination change between O- and S-ligating atoms of dmso with residua containing mostly RuS_2, RuO, and Ru at around 400, 500, and 600 °C, respectively.

The evaporation of EtOH in complexes of $L[RuCl_3(dmso)_3]\cdot x$EtOH starts at room temperature with 50 ± 3 °C DTG peak maximum. As a consequence, the compounds lose a part of crystal solvent during storage. The next fragment most probably belongs to methyl group departure. Around 250 °C, the loss of HCl occurs in all the

three complexes, while in **3**, it is followed by splitting of the methylsulfonyl group. Above 320 °C, the decomposition becomes highly exothermic. The reaction is probably related to the departure of the rest of dmso with structural rearrangements through ruthenium sulfide and oxide formation. The decomposition is not completed to 700 °C. Near 1000 °C, the residue is elemental ruthenium.

The decomposition pattern of the complexes is not affected by the atmosphere: the thermal curves are almost identical in nitrogen and air atmospheres. This property of the complexes might be of importance regarding the mechanism of their biological activity.

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