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THERMAL BEHAVIOUR OF PHARMACOLOGICALLY ACTIVE LITHIUM COMPOUNDS

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Abstract

The thermal decompositions of a series of simple lithium compounds (carbonate, sulfate, acetate, citrates, aspartates and glutamates) currently used in the treatment of manic-depressive psychosis and related disorders were investigated by means of TG and DTA measurements in oxygen atmosphere. Pyrolysis residues were characterized by infrared spectroscopy. The stabilities of the hydrates and intermediate phases generated during the degradation processes are discussed.

Keywords: lithium drugs, thermal decomposition, thermal stability

Introduction

The effectivity of lithium compounds in the treatment of affective disorders and manic-depressive psychosis has been well established [1–4], whereas recent investigations also point to the possible essentiality of this element [3, 5].

Although lithium carbonate is the most frequently used lithium drug, other compounds have also been used or tested, and some of them are commercially distributed by the pharmaceutical industry [2, 6].

As part of our studies on the physicochemical properties of this type of drugs [7, 8], we have now investigated the thermal behaviour of all of the compounds so far suggested as being useful in medicine.

Although a certain amount of general information is available on the thermal behaviour of the sulfate and the carbonate [9], we have also re-measured these salts for the sake of completeness in order to make comparisons with the other investigated substances measured under the same experimental conditions.

Experimental

High-purity samples of lithium carbonate (Sigma) and lithium sulfate (Merck) were used as provided. Lithium acetate was obtained by reaction between stoichiometric

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amounts of Li_2CO_3 and 50% acetic acid solutions, followed by slow evaporation of the resulting solution at room temperature. Trilithium citrate was obtained in the following way: 0.95 g (4.5 mmol) of citric acid was slowly added to 0.50 g (6.77 mmol) of Li_2CO_3 suspended in 10 ml of distilled water. The final pH ranged between 6.0 and 7.0. The solution was heated at 60°C during 30–45 min and then cooled. Well-formed crystals were obtained after some weeks. The monolithium salt was obtained in a similar way [8].

Lithium *L*- and *DL*-aspartates and the two investigated lithium *L*-glutamates (the mono- and dilithium salts) were obtained by direct interaction of stoichiometric amounts of Li_2CO_3 with aqueous solutions of the respective acids (ca 50 ml) [10]. After the cessation of CO_2 evolution, the solutions were heated during 3 h at 60°C and then concentrated to 1/3 of the original volume in a rotary evaporator. After some weeks, well-formed crystals were collected in all cases, which were dried between filter-paper sheets.

The compositions of the different salts obtained were confirmed by elemental analysis.

The thermal behaviour was investigated with a Shimadzu thermoanalytical system (TG-50 and DTA-50 models), with compounds in platinum crucibles under a constant oxygen flow of 50 ml min^{-1}. The heating rate was 10°C min^{-1}, with Al_2O_3 as a DTA standard.

Infrared spectra were recorded on a Perkin Elmer 580 B spectrophotometer, the KBr pellet technique being used.

Results and discussion

Li_2CO_3

The DTA curve obtained is shown in Fig. 1a. A very weak endothermic DTA peak at ca 430°C is probably related to the known phase change (from the monoclinic C2/C to an as yet unknown structure) [11]. This solid melts at around 730°C [11, 12] and, as seen from the TG trace, CO_2 loss begins at ca 800°C. The main DTA signal, centred at 755°C, may be related to both processes.

$Li_2SO_4 \cdot H_2O$

As shown in Fig. 1b, the thermolysis of this compound is rather simple. Water is given off in the temperature range between 105 and 195°C (experimental mass loss, 14.10%; loss calculated for 1 mol of water, 14.07%). This dehydration is related to the well-defined endothermic DTA signal centred at 148°C. The other two observed DTA signals (594 and 865°C) correspond, respectively, to a phase change of the anhydrous sulfate and to its fusion. In the older literature, the polymorphic transition is reported to lie in the interval 575–585°C and the fusion temperature at 859°C [13].

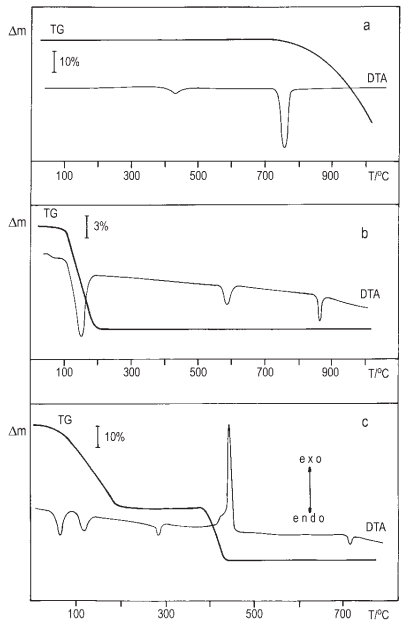

Fig. 1 TG and DTA curves of a – Li_2CO_3; b – $Li_2SO_4 \cdot H_2O$ and c – $Li(CH_3COO) \cdot 2H_2O$

$Li(CH_3COO) \cdot 2H_2O$

The thermal curves of this compound (Fig. 1c) shows that the 2 water molecules are released in a single step in the temperature range between 50 and 195°C, accompanied by two weak endothermic DTA signals, at 63 and 133°C (observed mass loss, 35.55%; loss expected for $2H_2O$ molecules, 35.35%). The anhydrous acetate is stable up to ca 380°C; at this temperature, decomposition with the generation of Li_2CO_3 takes place. A mass loss of 28.46% is expected for this process, in excellent agreement with the experimentally found value of 28.50%. This main degradation is accompanied by a strong exothermic DTA signal at 438°C. The other weak DTA signal found, at 730°C, is related to the fusion of the carbonate, the presence of which in the final residue was confirmed by IR spectroscopy. In the range of stability of the anhydrous phase, a weak DTA signal, observed at 287°C, may be related to a phase transition.

$Li_3(Cit) \cdot 5H_2O$

The thermal curves of this citrate is shown in Fig. 2. In this case, the water is released in two steps. The first 2 molecules are given off between 97 and 130°C (mass loss, 11.90%; calculated loss, 12.00%). The other 3 molecules are given off up to 150°C (mass loss found, 18.75%; calculated loss, 18.02%). These processes are related to the endothermic DTA doublet at 95 and 124°C. Moreover, in this case the decompo-

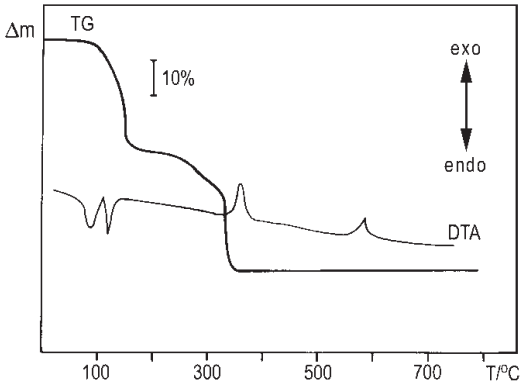

Fig. 2 TG and DTA curves of $Li_3(Cit)\cdot 5H_2O$

sition of the anhydrous compound begins immediately after the dehydration and two well-defined TG steps can be observed. Mass constancy begins at ca 330°C, and IR spectroscopic analysis of the residues collected after heating up to 700°C clearly demonstrates the generation of Li_2CO_3. Therefore, the full process can be represented by the following equations:

$$Li_3(C_6H_5O_7)\cdot 5H_2O \rightarrow Li_3(C_6H_5O_7)\cdot 3H_2O + 2H_2O \quad (1)$$

$$Li_3(C_6H_5O_7)\cdot 3H_2O \rightarrow Li_3(C_6H_5O_7) + 3H_2O \quad (2)$$

$$2Li_3(C_6H_5O_7) \rightarrow 3Li_2CO_3 + 9CO_2 + 5H_2O \quad (3)$$

The total mass loss represented by the full degradation of the citrate to carbonate implies a theoretical mass loss of 63.04%, which is in excellent agreement with the experimentally found value of 63.4%. In the final degradation step, two weak exothermic DTA signals can be observed, at 365 and 585°C.

As mentioned in the Experimental part, another salt of this type has been characterized: lithium citrate monohydrate, $Li(C_6H_7O_7\cdot H_2O$ [8]; this is rather unstable and highly hygroscopic, a situation which hampers its manipulation. Its thermal curves, although scarcely reproducible, show that dehydration occurs in the temperature range between 70 and 95°C, to the accompaniment of a weak endothermic DTA signal at 93°C. Degradation of the anhydrous compound starts immediately after dehydration.

Li(DL-Asp)·H_2O

As can be seen from Fig. 3a, this hydrate is rather stable, as the water molecule is retained up to 178°C. Dehydration is completed at 195°C and the process is accompanied by the endothermic DTA peak at 190°C. The experimentally found mass loss of 11.50% is in good agreement with the calculated value of 11.46%. After the water release, a rapid degradation of the sample takes place, generating a somewhat irregular

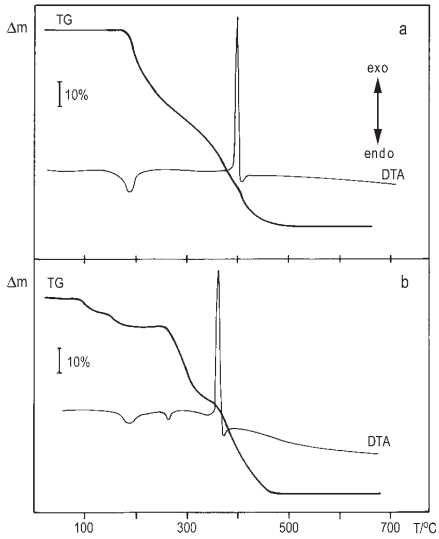

Fig. 3 TG and DTA curves of a – Li(*DL*-Asp)·H_2O and b – Li(*L*-Asp)·H_2O

and complex TG trace, but related to the appearance of a unique and very strong exothermic DTA peak at 401°C. Constant mass is attained at around 470°C; no further changes are observed up to 700°C. The IR spectra of the residues collected after treatment at this temperature again show the presence of Li_2CO_3. The total decomposition, schematized as follows:

$$2Li(C_4H_6O_4N)\cdot 2H_2O \rightarrow Li_2CO_3+7CO_2+8H_2O+2NO \quad (4)$$

implies a total mass loss of 76.41%, in agreement with the experimentally observed value of 77.20%.

Li(L-Asp)·H_2O

In this case, the dehydration begins earlier and covers a wider temperature range, between 95 and 210°C (cf. Fig. 3b), with an observed mass loss of 11.70%. This process is accompanied by a weak endothermic DTA signal at 185°C. The anhydrous species generated has a short stability range (of ca 50°C, between 210 and 260°C). The degradation of the anhydrous species occurs more quickly than for the *DL*-aspartato complex, and constant mass is attained at around 450°C. The total observed mass loss is 77.63%, in agreement with expectations (76.41%), and in this case too the IR spectra reveal formation of the carbonate. During this degradation, a weak endothermic DTA signal (273°C) and a strong and sharp exothermic DTA peak (355°C) are observed.

$Li(Glu)\cdot 2H_2O$

The TG curves of this compound is shown in Fig. 4a; it may be seen that the 2 water molecules are released in a single step between 260 and 275°C (observed mass loss, 22.20%; loss calculated for $2H_2O$, 19.05%; the difference probably indicates that decomposition of the anhydrous compound begins together with the release of water), a process which is related to the weak endothermic DTA signal at 264°C.

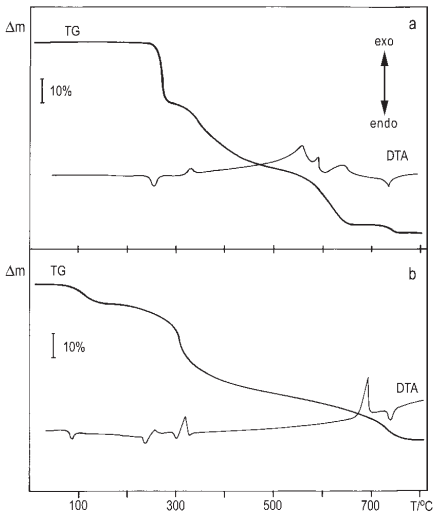

Fig. 4 TG and DTA curves of a – $Li(Glu)\cdot H_2O$ and b – $Li_2(Glu)\cdot 2H_2O$

The subsequent degradation takes place in three well-defined steps, accompanied by DTA signals at 327°C (weak, exo), 562/584°C (weak, exo) and 636°C (broad, exo), and showing again the peak relating to the fusion of Li_2CO_3, the presence of which was confirmed in this case too by IR spectroscopy. The total mass loss for

$$2Li(C_5H_8O_4N)\cdot 2H_2O \rightarrow Li_2CO_3+9CO_2+10H_2O+2NO \quad (5)$$

is 80.45%, in excellent agreement with the experimentally observed loss of 79.50%.

$Li_2(Glu)\cdot 2H_2O$

For this compound, the water release occurs in two consecutive steps (Fig. 4b) between 50 and 300°C, with endothermic DTA signals at 82, 242 and 265°C. The observed mass loss is 18.00% (calculated for $2H_2O$, 18.47%). Three consecutive steps, extending up to 750°C, follow the dehydration process, involving a total mass loss of 63.50%, in agreement with the calculated one (62.10%). The final product is again Li_2CO_3, as confirmed in this case too by IR spectroscopy and by the appearance of the

DTA signal related to its melting point. The last-mentioned three steps are accompanied by the following DTA signals: 304 (weak endo), 321 (weak exo) and 688°C (sharp exo).

Conclusions

Investigation of the thermal behaviour of a series of lithium-containing drugs by means of TG and DTA measurements allows establishment of the stabilities of the hydrates and the anhydrous compounds. In an oxygen atmosphere, all the lithium salts of these organic acids were transformed to Li_2CO_3. However, the temperature at which the carbonate is generated is highly variable: it occurs at relatively low temperatures in the cases of trilithium citrate (330°C) and acetate (380°C), and at very high ones for the two glutamates investigated (ca 750°C). The carbonate produced remains stable up to ca 800°C. In the case of $Li_2SO_4 \cdot H_2O$, dehydration occurs up to 195°C and the anhydrous compound remains stable up to at least 1050°C.

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