

THERMAL PROPERTIES OF TETRAHYDROPERPARINE DERIVATIVES

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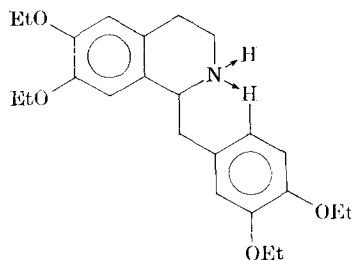
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The thermal behaviour of tetrahydroperparine (THP) and its derivatives with various acids has been investigated. The acid is liberated from the formate derivative basically in two steps, while the other aliphatic acids are released quantitatively before the thermal decomposition of the THP molecule. The thermoanalytical curves, electrical conductivity data measured in the molten phase, and infrared spectra prove that while part of the formic acid is hydrogen-bonded the other part is bound ionically in the molecule. It may be assumed that the marked biological activity of the compound can be explained by this difference in the nature of the bonds.

The knowledge of physico-chemical properties which are dependent on the chemical structure of molecules of therapeutic value can often lead to the recognition and explanation of the mechanism of biological activity.



A series of hydrated compounds with isoquinoline skeleton, described by the formula was prepared by Mészáros and coworkers [1]. Among the dihydroderivatives there was a compound with antispasmodic effect [2]. However, with the preparation of tetrahydrated derivatives the therapeutic utility increased significantly. In the course of systematic research the formic acid derivative (THPF) of tetrahydroperparine (THP) attracted attention [3], since its biological activity differed significantly from the hydrochloric acid (THPHCl), acetic acid (THPA) and propionic acid (TGPP) derivatives. This observation raised the question as to whether the physico-chemical properties of THPF also exhibit some difference from those of the other derivatives. In principle, it can be assumed that there are differences in the strengths of the bonds in the acid derivatives of THP, and that these can be examined by using thermal or spectroscopic methods.

Experimental

The compounds were carefully purified by recrystallization and examined with a Paulik–Paulik–Erdey derivatograph (Hungarian Optical Works). The measurements were performed in an oxygen-free nitrogen atmosphere ensured by a constant gas-flow, with a 4°/min heating rate. The complex thermoanalytical

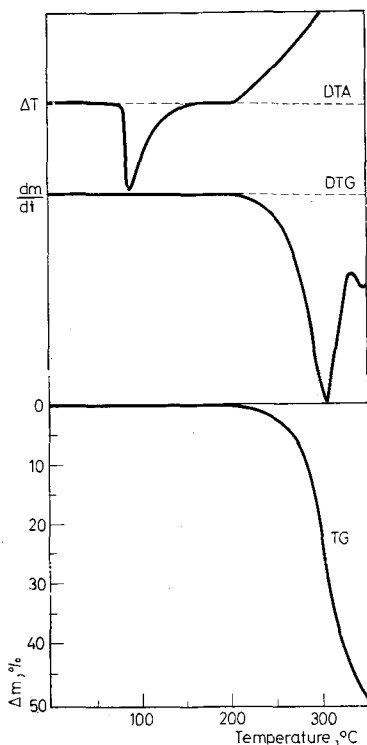


Fig. 1. Simultaneously recorded complex thermoanalytical curves of THP; sample weight: 96.8 mg

curves (TG, DTG, DTA and T) characteristic of the thermal behaviour of the substance are shown in Figures 1–5. The THP melts at 90° and its decomposition in the molten phase begins at 210°. The decomposition has a maximum rate at about 305°, gaseous decomposition products being liberated. The THPHCl decomposes after melting at 170°, with a maximum rate at 285°; the departure of the HCl molecule cannot be identified as a separate process. The TG curves indicate the separate release of one mole acid from both THPA and THPP. It is characteristic of both compounds that the departure of the acid begins in the molten phase immediately after the melting point and the weight change can be

evaluated in spite of the complexity of the DTG curve. Furthermore, for the acetate derivative a slowing down in the departure of the acid can be observed between 150 and 160°. After a relatively long weight constancy, at about 210° the base begins to decompose, attaining the maximum decomposition rate at 290° and 300° for THPA and THPP, respectively.

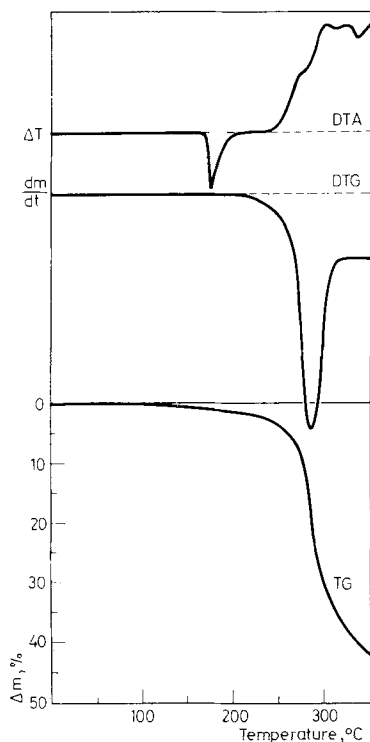


Fig. 2. Simultaneously recorded complex thermoanalytical curves of THPHCl; sample weight: 93.6 mg

The thermal behaviour of THPF differs markedly from that of the other THP derivatives. Even before the melting point is attained at 85°, 2.8% of the weight is lost, with a maximum rate at 75°. Following this an accelerating weight change can be observed, again due to the departure of formic acid. An overall weight loss of 8.9–9.2% results. The two maxima on the DTG curve are due to the departure of formic acid in two steps. The simultaneous formation of a liquid phase causes changes in the evaporation conditions of the volatile component. The assumption was confirmed by the phenomenon that the proportions of the two maxima changed when the heating rate was increased, and also by the observation that in the course of a thermogravimetric investigation on the micro scale,

the formic acid left in a single step. The diffusion does not play a significant role in the departure of volatile products if very small samples (a few mg) are investigated. It was conspicuous that after the departure of formic acid, in the earlier-mentioned amount the temperature interval of weight constancy became significantly broader in comparison with those of the other derivatives. At 160°, due

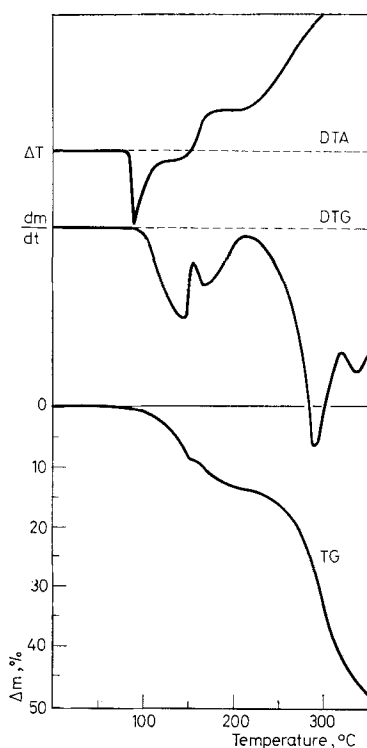


Fig. 3. Simultaneously recorded complex thermoanalytical curves of THPA; sample weight : 87.1 mg

to the lower boiling point of formic acid, the weight became constant. At the same time the further decomposition of the residual base begins at a higher temperature than that of the pure base or even of THPHCl.

The amount of formic acid leaving in the decomposition of THPF up to 160° is much smaller than the 10.4% weight loss calculated for the 1 : 1 molar ratio. When a 10% sulphuric acidic solution of the sample was used to expel the formic acid by steam distillation, then the amount of formic acid was found to be 13.5%. Samples which had already been thermally treated up to 160° were also analysed by the distillation process, and with respect to the original weight a further 4.5% of formic acid could be obtained. Overall, the samples contained 13.7% formic

acid. The great difference in the amounts of formic acid released in the thermal decomposition and by distillation proves that the formic acid is bound in the molecule in two different ways.

Valuable information on the natures of the bonds can be obtained from the specific electric conductivities of the compounds. With an instrument developed

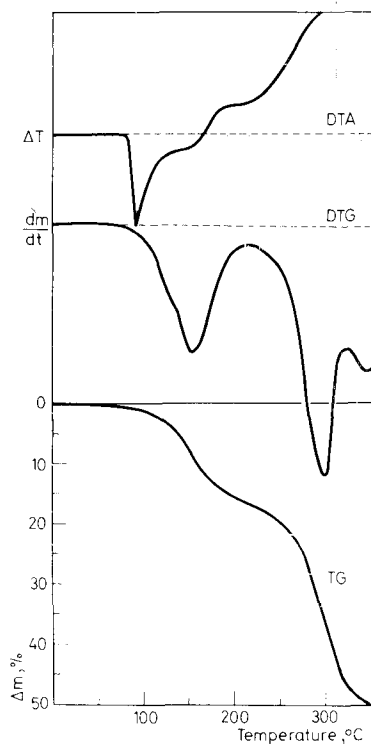


Fig. 4. Simultaneously recorded complex thermoanalytical curves of THPP; sample weight: 96.5 mg

earlier [4], THP and its derivatives were examined at temperatures about 10° higher than their melting points. The data for molten salts are free of solvent effects and reflect with a good approximation the state of the solid salts. In the molten phase, at temperatures near the melting point, the arrangement of the molecules is similar to that in the solid phase, with the restriction that this is valid only for smaller centres.

The results of these measurements are listed in Table 1.

The specific electric conductivity increases in the order: THP < THPP < THPA < THPHCl in good agreement with expectations based upon the dissociation constants of the acids. However, the value obtained for the formic acid

derivative shows a significant deviation, demonstrating that it contains a bond of very polar character. The temperature coefficient of its conductivity is also much larger than those for the other compounds, indicating stronger intermolecular interactions in this case.

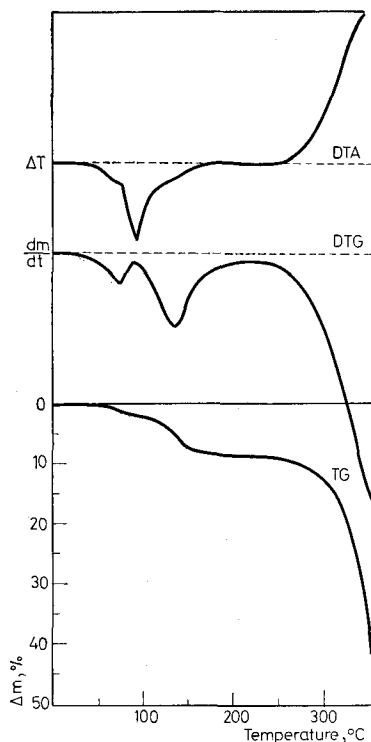


Fig. 5. Simultaneously recorded complex thermoanalytical curves of THPF; sample weight: 92.0 mg

Table 1

Specific conductivity values of THP and its derivatives

Compound	Temperature of measurement °C	$\kappa, \Omega^{-1} \text{ cm}^{-1}$
THP	100	immeasurably small
THPHCl	185	$1.18 \cdot 10^{-4}$
THPF	100	$3.49 \cdot 10^{-4}$
THPA	100	$1.67 \cdot 10^{-5}$
THPP	100	$3.21 \cdot 10^{-6}$

The conductivities of the compounds investigated, however, are smaller by some orders of magnitude than those of the salts of simple aliphatic amines. This difference is due not only to the intermolecular interactions but also to the smaller ionic mobility (this may be assumed because of the largeness of the THP molecule), and even more to the weakly basic nature of the compound. The viscosity of the melts, their glassy stiffening and lengthy crystallization process indicate strong intermolecular interactions.

The conductivity data prove unambiguously that part of the formic acid is bonded in the THPF molecule by a relatively strong ionic bond, while the thermo-analytical results give with a good approximation the ratio of the acid bound by loose hydrogen-bonds and by ionic bonds, respectively.

Our assumptions were also supported by infrared examinations of the compounds. The spectra were obtained with an IR spectrophotometer type Zeiss U. R. 10, using KBr pellets. The diffuse maxima characteristic of protonated nitrogen can be found between $3000-3500\text{ cm}^{-1}$ only in the THPHCl and THPF spectra, for THPA and THPP only a slight elevation of the baseline being observed. The intensity of the $\text{C}=\text{O}$ asymmetric valence vibration of the ionic carboxylate decreases in the order $\text{THPF} > \text{THPA} > \text{THPP}$. Similarly, the intensity of the symmetric $\text{C}=\text{O}$ valence vibration at about 1320 cm^{-1} , characteristic of carboxylates, changes in the same way. The intensity of the peak at $1670-1660\text{ cm}^{-1}$ changes in the order propionate $>$ acetate $>$ formate. This peak is characteristic of the $-\text{COOH}$ group.

Conclusion

The THP derivatives contain acids bound in different ways. In the acetate and propionate derivatives one molecule acid is hydrogen-bonded per molecule. In the case of formic acid a significant part is bound in this way, and can be removed at much lower temperatures. The remainder of the acid is bound in a molar ratio of about 1 : 1/2 by stronger bonds, mainly of an ionic nature. It is characteristic of the strength of these bonds that the acid is released only on the thermal decomposition of the whole molecule, or by steam-distillation from a non-volatile strong acid. The infrared spectra and electrical conductivity of the melt support these assumptions.

The properties established can be of help in the assessment of the pharmacological effect and its mechanism.

References

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RESUMÉ — Les auteurs ont étudié le comportement thermique de la tétrahydroperparine (THP) et de ses dérivés avec divers acides. Il a été établi que le formiate dérivé de l'acide s'échappe en trois étapes dont deux principales, tandis que les autres acides aliphatiques sont libérés quantitativement avant la décomposition thermique de la molécule de THP. A partir des courbes thermoanalytiques ainsi que des données de conductibilité électrique mesurée sur la phase fondue et des spectres d'absorption infrarouge, les auteurs montrent qu'une partie de l'acide formique est liée par pont d'hydrogène et l'autre partie par une liaison ionique dans la molécule. Il est à présumer que l'activité biologique distincte du composé s'explique par cette différence du caractère des liaisons.

ZUSAMMENFASSUNG — Die Autoren prüften das thermische Verhalten von Tetrahydroperparin (THP) und seiner mit verschiedenen Säuren gebildeten Derivate. Es wurde festgestellt, daß aus dem Ameisensäure-Derivat die Säure in drei, grundlegend in zwei Schritten entwich, während die übrigen aliphatischen Säuren vor der thermischen Zersetzung des THP-Moleküls quantitativ freigesetzt wurden. Aufgrund der thermoanalytischen Kurven sowie der in der geschmolzenen Phase gemessenen elektrischen Leitfähigkeit und Infrarotspektren bewiesen die Autoren, daß — während ein Teil der Ameisensäure durch Wasserstoffbrücken gebunden ist — der andere Teil der Säure mittels einer ionischen Bindung im Molekül festgehalten ist. Es kann angenommen werden, daß sich die deutliche biologische Aktivität der Verbindung durch diesen Unterschied der Bindungen erklären läßt.

Резюме — Авторами исследовано термическое поведение тетрагидроперпарина (ТНР) и его производных, образованных с различными кислотами. Установлено, что из формиат-производного кислота выделяется в три, в основном, в две степени, тогда, как алифатические кислоты количественно удаляются до термического распада молекулы ТНР. На основании термоаналитических кривых, инфракрасных спектров и данных электропроводности, измеряемой в расплавленной фазе, авторы считают, что одна часть муравьиной кислоты в молекуле связана водородной связью, а другая — ионной связью. Предполагается, что определенная биологическая активность соединения может быть объяснена этим различием в природе связей.