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THE THERMOGRAVIMETRY OF SULFANILAMIDE AND RELATED SULFA DRUGS

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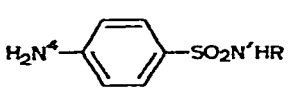
ABSTRACT

TG curves are shown for 12 sulfa drugs up to a temperature of 800 °C. With some minor refinements, the curves can be used for a qualitative identification of the drugs. Currently, there is not a good method for rapidly identifying this type of drug qualitatively. Sample sizes were about 2 mg, and a 2.2-mg sample gave a full scale deflection with the instrument used. Some of the evolved gases were also analyzed with SO_2 found to be the major component of pyrolysis.

INTRODUCTION

Sulfa drugs are used for the treatment of bacterial infections, such as eye infections, influenza, meningitis, and other meningides, actinomices infections, and urinary tract infections. They can also be used as model compounds for investigations of mechanisms of the action of drugs[1,2]. Sulfa drugs are generally N′-substituted derivatives of the parent compound, sulfanilamide:



They may also be N^4 substituted.

Presently, there is only one rapid method for determining qualitatively the presence of the most common sulfa drugs. To determine the components of a simple mixture of drugs such as sulfadiazine, sulfamerazine and sulfamethazine is a difficult task. It was felt that a qualitative analysis could be made from the TG curves of unknown sulfa drug samples by comparing their curves with the curves of known sulfa drugs obtained under identical conditions.

Because of the difference of the R groups attached to the N′ nitrogen on sulfanilamide, it was anticipated that each individual sulfa drug would give a unique TG curve. This research was conducted to see if the curves could be obtained and if

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they were unique, so that analysis of sulfa drugs may become a more practical analysis. Further development of the technique could lead to the determination of components of a mixture and eventually to a quantitative analysis of the drugs.

INSTRUMENTATION

The thermobalance used was constructed similarly to one built by Jensen and Swensen[3]. The balance itself is a double pan chainomatic from Christian Becker, Inc., with the pans removed. The right balance pan was replaced by a 25 × 1/8 in. copper tube. 6 in. down from the balance beam are mounted two bar magnets. The bar magnets are glued together at one end at a 15° angle and mounted open end down. A Model BH 700 transverse Hall element[4,5] from F. W. Bell, Inc., is mounted inside the angle of these magnets. The Hall element is sensitive to changes in the magnetic field caused by the movement of the balance beam from which the magnets are suspended. The left pan is also replaced by a 25 × 1/8 in. copper tube that is suspended down to about 6 in. above the oven. A 100-mg platinum boat is suspended from the end of a piece of platinum wire that extends into the oven 5 in. The Hall element is powered by two Lambda Model LME 3 power supplies connected in series to give 6-V DC. The power supplies are controlled by a variable resistor to 50 mA. A 2.3-mg sample gives full scale deflection on a 10 in., 1 mV Beckman Model 100500 recorder; most of the sample sizes were about 2 mg. A 1.35 V mercury battery is used as a bucking potential on the Hall crystal to zero the instrument. The oven is a Lindberg Heviduty Model 56201 which is capable of 1200°C at 460 W. The oven is controlled by a Powerstat Variable Transformer Model 21 series turned by a 1/5 rph timing motor. By starting the transformer at 30%, a temperature calibration was obtained with the Platinel II thermocouple in the oven and a potentiometer. For the first 12 min of operation, the temperature rise was non-linear. For the remainder of the run, the temperature rise followed a linear plot of 5°C/min. The temperatures of each plot are within ±5°C. The balance is vibration isolated from the rest of the instrument and the instrument is vibration isolated from the floor to reduce the noise to a minimum.

EXPERIMENTAL AND RESULTS

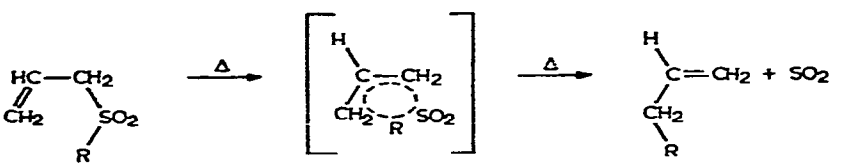
Calibration of the instrument was completed by repeating some of Duval's[4] work on inorganic compounds. A number of calibration runs were made to determine the relationship between temperature and the number of units on the chart paper by using the Platinel II thermocouple in the oven and a potentiometer. The temperature was allowed to rise to 1200°C. After completing the calibration, the collection of thermograms of the twelve drugs was started. It was found that the thermograms of any one drug were reproduceable for both the percent weight loss at a specific temperature and the temperature at which the weight loss occurred. The uncertainty of the temperature is ±5°C, and the uncertainty of the weight loss is a maximum at ±.05 mg

or 2.5 vertical units on the chart paper. At the end of each curve (750–800 °C), there was no residue of any kind left in the sample boat which indicated that all of the final products of the reactions that take place at various points on the curve were gases or solids volatilized at these temperatures. TG curves were obtained for sulfanilamide, sulfacetamide, sulfadiazine, sulfaquanidine, sulfamerizine, sulfamethizine, sulfamethizole, sulfapyrazine, sulfapyridine, sulfathiazole, phthalsulfacetamide, and phthalylsulfathiazole; and they are shown in Fig. 1. The buoyancy of the platinum sample boat from 25 to 750 °C was negligible because of the low coefficient of thermal expansion of platinum. The general shape of each curve can be used as a qualitative tool in identifying an unknown sulfa drug by comparing its shape to the shapes of the curves obtained from a set of standard drugs that have been obtained previously.

An attempt was made to identify the products of the reactions at each plateau of the thermograms. Several articles concerning the thermal decomposition of sulfones[5,6] according to reaction (1) have appeared in the literature. It has been stated that available evidence points to a radical intermediate and that rate is independent of the

$$R\text{–}SO_2\text{–}R' \xrightarrow{\Delta} R\text{–}SO_2^{\cdot} + R^{\cdot} \xrightarrow{\Delta} R^{\cdot} + SO_2 \qquad (1)$$

leaving group R. In work reported by Kloosterziel and Backer[7] and Paquette[8,9], a cyclic three-membered ring intermediate has been isolated and it has been shown that the reaction goes by an ionic rather than a radical mechanism. Another article by La Combe and Stewart[10] proposed a four-centered intermediate at lower temperatures:



Alkylsulfonyl chlorides also split out SO_2 as a product and evidence for these reactions seems to support both the ionic and the radical intermediate mechanism[11–15]. A hydrazine-like compound, ϕ–CH_2–SO_2–N=N–ϕ, also splits out SO_2 as a product[16]. From the literature, it might be expected that the sulfa drugs decompose by a similar mechanism and lose SO_2 as one of their pyrolysis products. This was shown for sulfapyridine by heating a 20-mg sample of the drug to 310 °C for ½ h in a sealed tube. The temperature of 310 °C is at the top of the first plateau of the thermogram for sulfapyridine which indicates a stable intermediate in the heating process. The sealed tube was oxygen purged before the sample was heated. After heating the sample, the evolved gases were analyzed by mass spectroscopy (DuPont 21-421) and the main component was found to be SO_2. This has been shown conclusively only for sulfapyridine; other gases present could not be positively identified. Work is progressing on other drugs in the series.

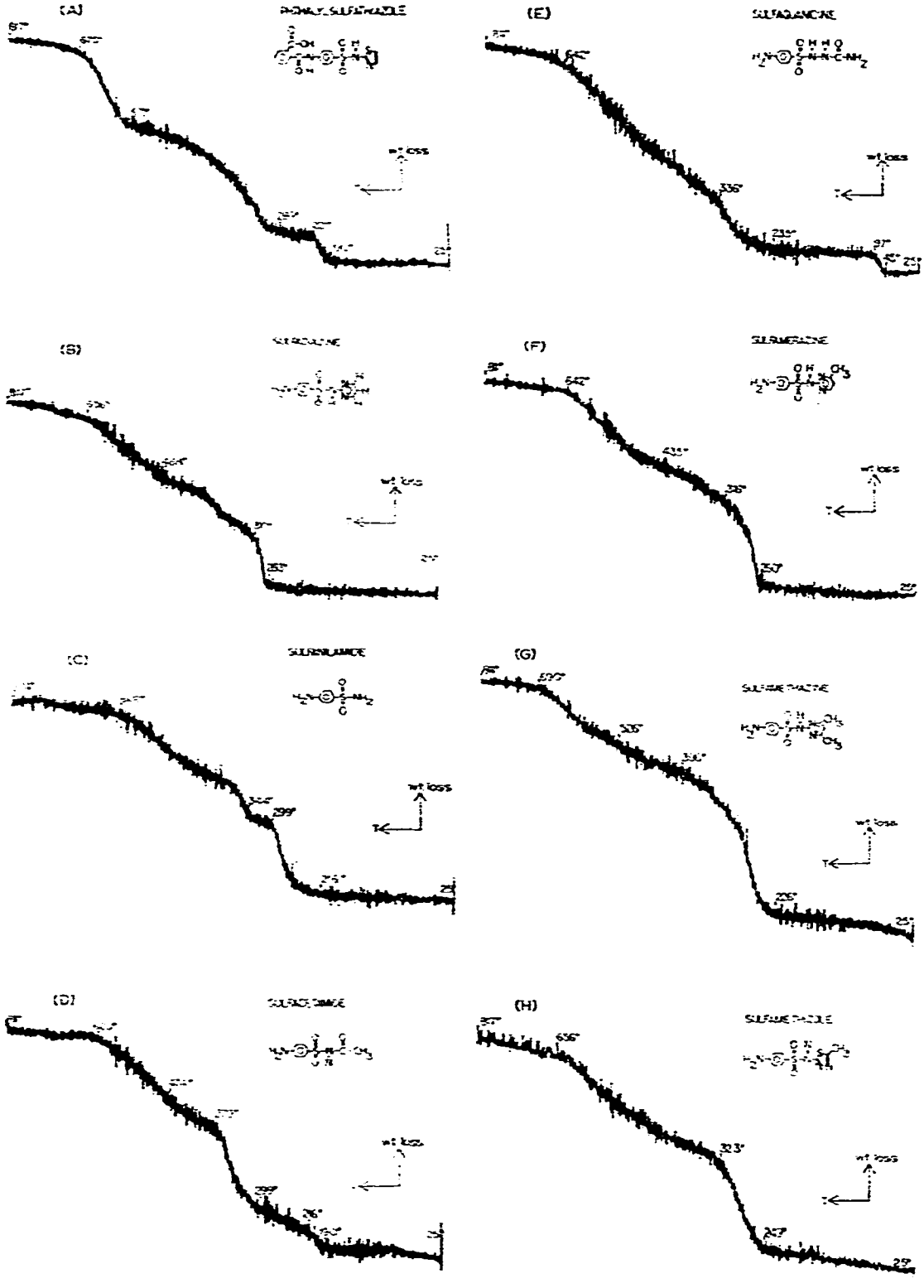


Fig. 1. TG curves of sulfa drugs.

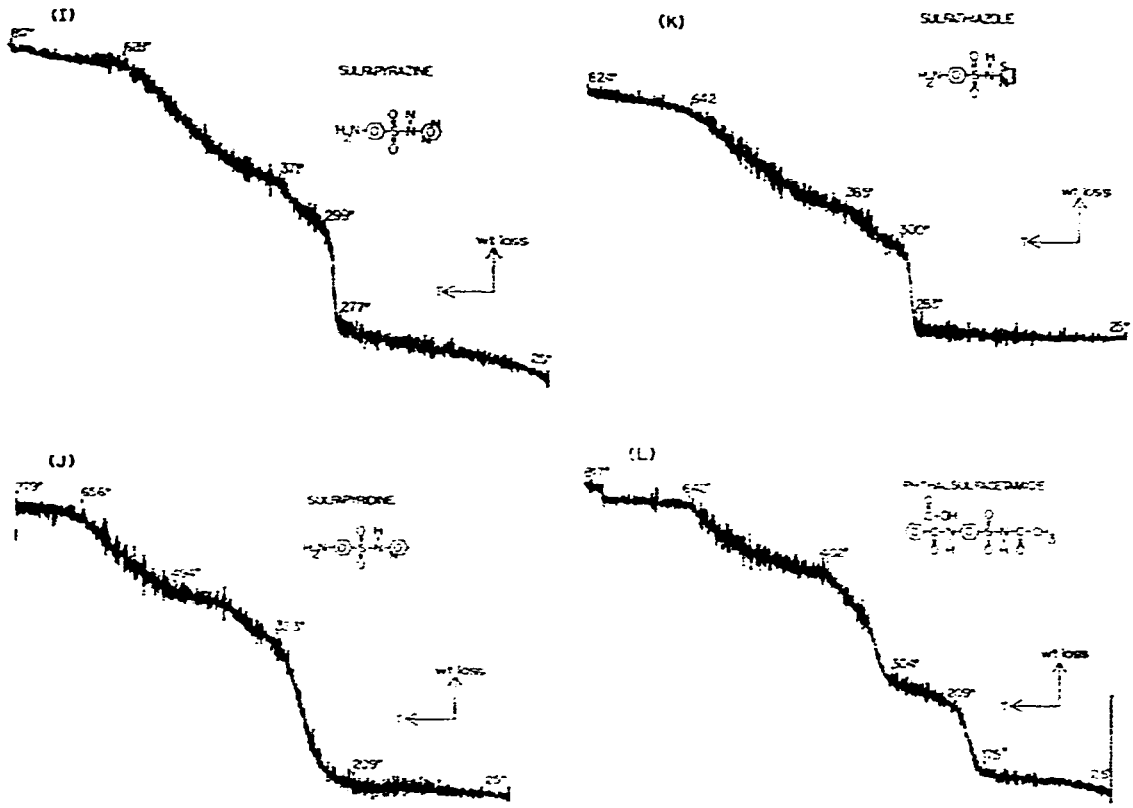


Fig. 1.

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