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BIGUANIDES
PART 1. THE THERMAL DECOMPOSITION AND MASS SPECTRAL BEHAVIOUR OF BIGUANIDE AND SOME OF ITS SALTS

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ABSTRACT

The thermal decomposition of biguanide, the biguanidinium chlorides, sulphates and carbonate have been studied. Biguanide decomposes in definite steps, producing an almost quantitative yield of ammonia leaving initially a solid residue, melamine, which then sublimes unchanged at higher temperatures. The biguanidinium chlorides and sulphates are thermally more stable than the parent base and do not decompose in well-defined steps, whereas the carbonate is thermally less stable than the parent base but does decompose in definite steps. In addition, the fragmentation of biguanide and biguanidinium carbonate in a mass spectrometer is reported.

INTRODUCTION

Biguanides have considerable industrial importance as intermediates in the production of dyestuffs, pesticides and photographic chemicals. In the pharmacological field, substituted biguanides undergo regular testing as potential antimalarials, oral hypoglycaemic and anorexia inducing agents.

The chemistry of biguanides, admirably reviewed by Kurzer and Pitchfork[1] has provided a fertile field of work since the first preparation of the parent base by Rathke[2] in 1879, but little work has been done to investigate their thermal behaviour. Phenylbiguanide (I, R = Ph) decomposes on heating to yield a mixture which contains phenylguanidine (II), cyanamide (III), guanidine (IV) and phenylcyanamide (V), (R = Ph). When phenylbiguanide is heated in the

$$\underset{\text{(I)}}{2\text{RNH-C(=NH)NHC(=NH)NH}_2} \rightarrow \underset{\text{(II)}}{\text{RNHC(=NH)NH}_2} + \underset{\text{(III)}}{\text{H}_2\text{NCN}} + \underset{\text{(IV)}}{\text{H}_2\text{NC(=NH)NH}_2} + \underset{\text{(V)}}{\text{RNHCN}}$$

presence of aniline hydrochloride, 1,3-diphenylguanidine hydrochloride (VI) is an additional product formed by reaction of the amine hydrochloride with phenylcyanamide (V, R = Ph)[3]. The decomposition of methylbiguanide

$PhNH_2HCl + PhNHCN \rightarrow PhNH\,C(=NH)\,NHPh\,HCl$
(VI)

(I, R = Me) proceeds similarly[4] while acylbiguanides produce guanamines[5, 6]. According to the patent literature, pyrolysis of biguanide in closed vessels provides melamine in almost quantitative yield[7] while under the thermal conditions of gas chromatography or mass spectrometry, the formation of substituted s-triazines from substituted biguanides has been demonstrated[8].

As part of a programme of work on biguanides, we have studied the thermal behaviour of biguanide and some of its salts.

EXPERIMENTAL

Thermal measurements were made using a DuPont Model 900 thermal analyser in conjunction with their thermogravimetric attachments. Thermogravimetric analyses were conducted in a dynamic atmosphere (250 $cm^3\ min^{-1}$) of oxygen-free nitrogen at atmospheric pressure or under a similar flow of air. Samples of 5–10 mg contained in platinum boats were heated at a rate of 5 or 15°C min^{-1}. Aluminium sample holders, loosely sealed with aluminium caps were used for the differential scanning calorimetry. The heating rate in a dynamic flow of nitrogen was 5°C min^{-1}. The instrument was calibrated using the latent heats of fusion of gallium, indium and tin.

Mass spectra were recorded using an AEI MS 12 mass spectrometer operating at 70 eV and a source temperature of 260°C unless otherwise stated. High resolution data were obtained with an AEI MS 9 mass spectrometer. The solid samples were introduced via a direct insertion probe.

Biguanide

Using a modification of a previously described method[12, 13], biguanide was prepared by reaction of the sulphate ($C_2H_9N_5SO_4$) with sodium methoxide in stoichiometric quantities in methanol. The solution was stirred overnight, precipitated sodium sulphate filtered off and then the filtrate evaporated to dryness. The white solid residue was recrystallised from absolute ethanol as white silky *needles* which were dried in vacuo; m.p. 132°C; lit.[14] 133–134°. The base was stored in a desiccator in the absence of carbon dioxide.

Biguanidinium sulphates

The salts were commercially available and were purified by recrystallisation from water and dried in vacuo ($C_2N_5H_9$)SO_4, m.p. 240°C; $(C_2N_5H_8)_2SO_4$, m.p. 250°C dec.

Biguanidinium chlorides

The 1:1 and 1:2 salts were obtained by mixing biguanide and hydrogen chloride in 1:1 and 1:2 mole ratio in ethanol. The products were filtered off and recrystallised from ethanol/water as white *needles* and white *plates*, respectively. $C_2N_5H_8Cl$, m.p. 235°C; lit.[15] 235°C; $C_2N_5H_9Cl_2$, m.p. 248°C, lit.[15] 248°C.

Biguanidinium carbonate

Carbon dioxide was bubbled through an ethanolic solution of biguanide. The white salt was filtered off, washed with ethanol and dried in vacuo.

(Found: C, 22.28; H, 6.15; N, 51.69%. $C_5H_{16}N_{10}O_3$ *requires:* C, 22.72; H, 6.06; N, 53.03%.)

RESULTS AND DISCUSSION

The thermograms for biguanide, biguanidinium chloride ($C_2H_8N_5Cl$), sulphate ($C_2H_9N_5SO_4$) and carbonate ($(C_2H_8N_5)_2CO_3$) in either a dynamic atmosphere of nitrogen or air, are shown in Fig. 1. The decomposition of biguanide which starts at 130°C at a heating rate of 15°C min^{-1}, produces an intermediate which is thermally stable from 180 to 210°C. At a slower heating rate, the temperature, at which onset of decomposition occurs, is slightly lowered. The mass loss between 130 and 180°C (18.9%) corresponds closely to the required loss (16.8%) of one mole of ammonia per mole of biguanide. The residue was identified as melamine by comparison of its i.r. and n.m.r. spectra with those of an authentic sample. The weight loss is slightly greater than the required value since even at temperatures as low as 180°C, there is slow evaporation of melamine but this does not become appreciable until temperatures of 210–220°C are reached. Above 225°C, a white sublimate collects rapidly on the cooler parts of the apparatus. This sublimate was also identified as melamine by its i.r. and n.m.r. spectra. The weight loss observed between 200 and 350°C varied from 77.3 to 79.3%, slightly less than that required (83.2%) for quantitative decomposition according to eqn (1). The residue left at 350°C (always less than 4%) may well be a polymeric material since it is involatile at temperatures up to 500°C, has

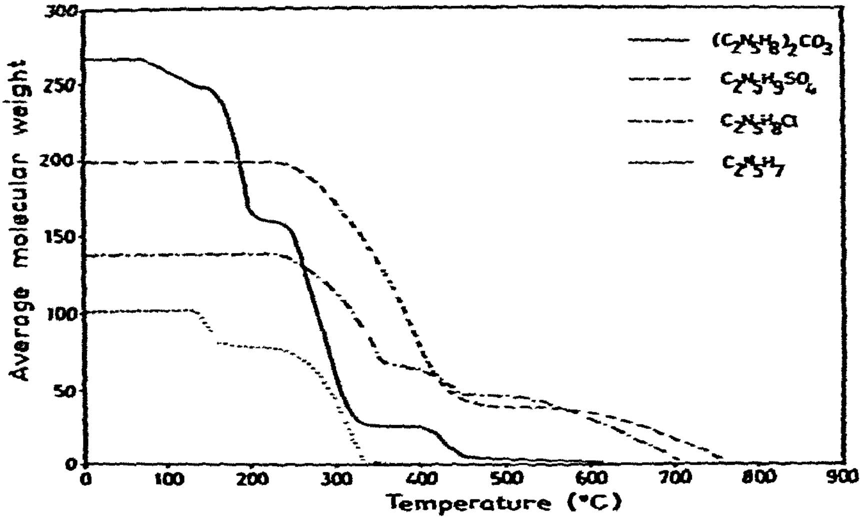


Fig. 1. Thermogravimetric traces for $(C_2N_5H_8)_2$ CO_3, $C_2N_5H_9SO_4$, $C_2N_5H_8Cl$ and $C_2N_5H_7$ in air or nitrogen at a heating rate of 15°C min^{-1}.

a glassy appearance and gives broad infrared absorptions. Accordingly, we suggest that biguanide decomposes thermally in the following manner:

$$3H_2N\text{-}C(=NH)\text{-}NH\text{-}C(=NH)NH_2 \rightarrow 3NH_3 + 2(H_2NC=N\text{-})_3 \qquad (1)$$

Melamine has been produced industrially by the pyrolysis of biguanide in the presence of ammonia[7] and by heating dicyandiamide. As we had expected that dicyandiamide ($H_2NC(=NH)NHCN$) rather than melamine would be formed in the thermal decomposition of biguanide, we recorded the thermogram of dicyandiamide under conditions identical to those used for biguanide. The thermogram from the onset of decomposition at 220 up to 380°C was complex and we found that the sublimate which collected was melamine.

From the area of differential scanning calorimetry (DSC) traces, the enthalpies of physical or chemical changes have been calculated. These data for the thermal decomposition of biguanide are shown in Table 1.

TABLE 1

DSC DATA FOR THE THERMAL BEHAVIOUR OF BIGUANIDE[a]

T_i[b]	T_m[c]	T_f[d]	ΔH (kJ mol^{-1})
120	132	134	5.3
134	139	170	−25.4

[a] Heating rate 5°C min^{-1}. [b] T_i, temperature (°C) at which trace first deviates from baseline. [c] T_m, temperature at which the enthalpy change is at a maximum. [d] T_f, temperature at which trace returns to baseline.

At 132°C, the endothermic maximum corresponds to the fusion of biguanide (visual m.p. 132°C). This is followed almost immediately by an exothermic reaction which occurs over the range 134–170°C resulting in the breakdown to ammonia and melamine (eqn (1)).

The pyrolysis patterns of the sulphates and chlorides (both 1:1 and 2:1 salts) was not as clear-cut as for the parent base. These salts were thermally more stable than biguanide but the products of decomposition could not be clearly established. The sulphates lost mass continuously from 230 to 730°C though most of the mass had been lost by 400 to 450°C where there was some flattening of the thermogram. In the case of the chlorides, although there was stronger evidence for the formation of an intermediate, it was not possible to establish the identity of the decomposition products. These were probably ammonium chloride and dicyandiamide (or melamine) but both were found to vaporize rapidly at just above 200°C under the conditions used in the thermogravimetric experiment. As dicyandiamide starts to vaporize at 230°C and ammonium chloride at 150–160°C, it was hoped that isothermal decomposition of biguanidinium chloride ($C_2H_8N_5Cl$) might provide some indication as to the nature of the decomposition products. However, at the lowest temperature at which decomposition could be detected (220°C), isothermal mass loss showed no evidence for the formation of an intermediate and decomposition continued for over 8 h.

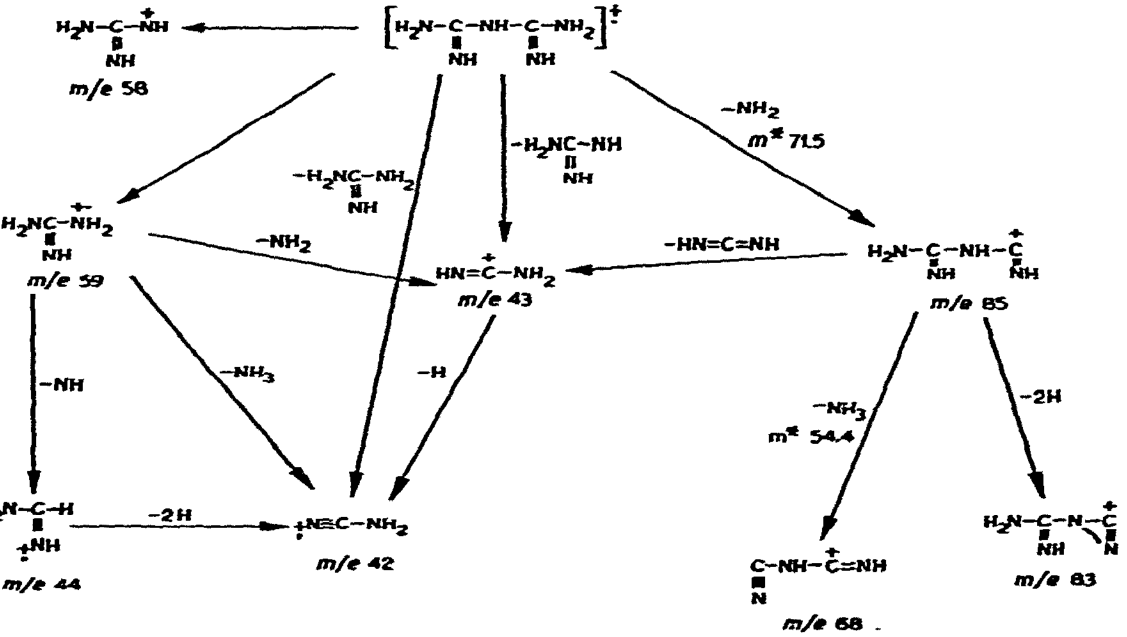
Biguanidinium carbonate decomposes by loss of water over the range 80–135°C at a heating rate of 15°C min^{-1} (mass loss required, 6.8%; found, 7.1%). Almost immediately, further decomposition occurs liberating carbon dioxide and ammonia over the range 140–210° (mass loss required 29.5%; found 33.0%). The residue which was shown to be melamine by its i.r. and n.m.r. spectra, sublimes between 220 and 320°C, leaving a solid (10%) which is insoluble in the common solvents and may therefore be polymeric. This solid vaporizes slowly from 370–450°C leaving a final white residue (ca. 2.5%). Thus the mode of decomposition of biguanidinium carbonate is primarily:

$$2(C_2H_8N_5)_2\,CO_3 \rightarrow 2H_2O + 2(C_2H_8N_5)^+\,(C_3H_6N_5O_2)^-$$

$$\searrow 4NH_3 + 2CO_2 + 3\,C_3N_6H_6$$

Using the minimum thermogravimetric decomposition temperature as the criterion of thermal stability, the order of stability is $(C_2H_8N_5)_2\,CO_3 < C_2H_7N_5 < C_2H_9N_5Cl_2 < C_2H_8N_5Cl < C_2H_9N_5SO_4 \approx (C_2H_8N_5)_2SO_4$.

Reports[9, 10] have appeared indicating that the behaviour of compounds in a mass spectrometer can resemble that induced by thermal action. In view of these findings, the behaviour of biguanide, biguanidinium carbonate, chloride ($C_2H_8N_5Cl$) and sulphate ($C_2H_9N_5SO_4$) have been examined in a mass spectrometer operating under a range of bombarding voltages and probe temperatures. Unsatisfactory spectra were obtained with both the chlorides and sulphates in that there was an absence of



Scheme 1.

peaks which could be assigned to the molecular ion of either the species introduced into the mass spectrometer or the free base (biguanide, $M^{+\cdot} = m/e$ 101). The results of the thermal examination also suggested that these salts were thermally fairly stable. However, the mass spectra of various samples of the carbonate gave prominent peaks at *m/e* 101 (and *m/e* 44), and this behaviour of the carbonate is consistent with Beynon's findings[11] that salts of guanidines dissociate on the direct insertion probe to produce the free base. A typical spectrum obtained with biguanidinium carbonate is given in Table 2 and a suggested fragmentation pathway in Scheme 1. Peaks of less than 10% abundance have not been quoted unless they are structurally significant. Several of the transitions are similar to those reported by Beynon for guanidines[11].

TABLE 2

MASS SPECTRAL DATA FOR BIGUANIDINIUM CARBONATE

m/e	189	188	187	186	101	85	83	68
% relative abundance	0.308	0.382	26.4	10.9	96.3	82	27.3	20
m/e	59	58	46	45	44	43	42	
% relative abundance	52.7	12.7	10.0	10.9	100	98.2	23.6	

Metastable peaks at 185.0, 71.5 and 54.4.

The accuracy with which the metastable peak at *m/e* 185 could be measured did not allow distinction between the transitions 264 → 221, 189 → 187 and 187 → 186. However, loss of 43 amu from biguanidinium carbonate, *m/e* 264, does not seem likely, as 44 amu (CO_2) are lost so readily. Considerations of relative abundance suggest that 189 → 187 is more likely than 187 → 186. Clarification of this point was complicated by the very variable (and lower) relative abundance of *m/e* 264, 221, 189, 187 and 186 in the mass spectra of the various samples of biguanidinium carbonate.

The mass spectral data that were obtained when biguanide was introduced into the mass spectrometer are given in Table 3. High resolution data were obtained for some of these ions (Table 4). Several of these species could have arisen from the thermal reactions, shown in Scheme 2, which are reminiscent of the thermogravimetric behaviour of biguanide.

TABLE 3

MASS SPECTRAL DATA FOR BIGUANIDE

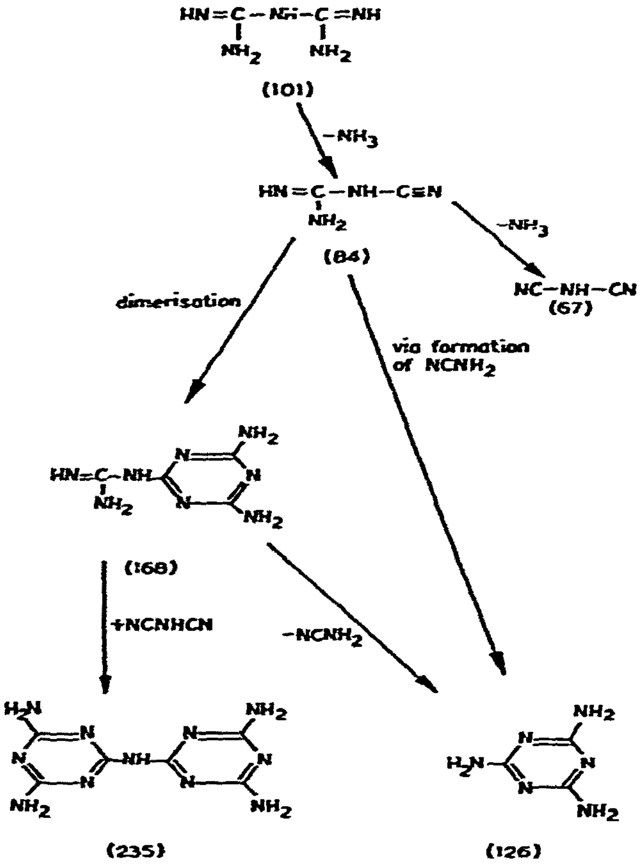
m/e	236	235	194	193	192	169	168	152	151
% relative abundance	0.16	0.80	0.16	0.30	0.09	0.88	3.60	1.84	2.24
m/e	128	127	126	125	110	101	99	86	85
% relative abundance	1.12	17.6	100	0.88	2.88	0.62	1.44	2.08	40
m/e	84	83	69	68	67	59	58	56	53
% relative abundance	4.8	12.0	1.36	20	1.92	2.96	1.84	1.92	2.32
m/e	44	43	42	41	40				
% relative abundance	2.56	9.76	2.72	4.8	0.48				

Metastable peaks at 94.5, 57.3.

TABLE 4

HIGH RESOLUTION MASS SPECTRAL DATA FOR BIGUANIDE

m/e	*Observed relative molecular mass*	*Possible constitutional formula*
235	235.1036	$C_6H_9N_{11}$
168	168.0872	$C_4H_8N_8$
127	127.0497	$C_3H_5N_5O$
126	126.0655	$C_3H_6N_6$



Scheme 2.

However, the metastable peaks at 94.5 and 57.3 correspond to the transitions 168 → 126 and 126 → 85, respectively, showing that the formation of species with *m/e* 126 and 85 arises, at least in part, by electron impact processes. The high resolution data for *m/e* 127 suggested a constitutional formula of $C_3H_5N_5O$ and this could correspond to the formation of 2,3-diamino-6-hydroxy-1,3,5-triazine, although the source of the oxygen is not clear.

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