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RESEARCH PAPER

Structure-Solubility Relationship and Thermal Decomposition of Furosemide

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ABSTRACT

Furosemide, a high ceiling diuretic, decomposes on heating and is very sparingly soluble in water. The aim of this study was to identify the thermal decomposition product(s) of furosemide and to calculate the activation energy needed for this reaction. This was done to gain a better understanding of the unusually low water solubility of this drug. The main thermal decomposition product was identified by nuclear magnetic resonance (NMR), mass spectrometry (MS), and infrared (IR) analysis as 4-chloro-5-sulfamoylanthranilic acid (saluamine), and the activation energy, calculated from thermogravimetric analysis (TGA) measurements, for this reaction was 47.7 (±1.93) kcal/mol. The experimentally measured activation energy was well below the normal 59 ± 4 kcal/mol needed for the cleavage of the C–N bond to form saluamine. This could possibly be explained by the weakening of the C–N bond through the I–effect of the furane ring and the delocalization of the electrons of the aniline nitrogen in the chlorosulfamoyl benzoic acid entity of furosemide. This decomposition of furosemide indicates the breaking of intramolecular bonds before those of intermolecular bonds (separation of individual furosemide molecules). Strong inter- and intramolecular bonds are a probable cause for the poor water solubility of furosemide because, when some of the inter- and intramolecular bonds that form part of the hydrogen bond network disappeared, as in the structurally related decomposition product saluamine, the aqueous solubility increased.

Key Words: *Furosemide; Molecular bonds; Solubility; Thermal decomposition.*

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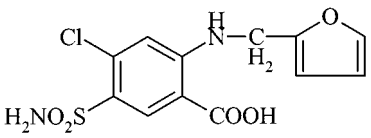
INTRODUCTION

Furosemide (**1**; Scheme 1), a high ceiling diuretic, is weakly water soluble (1,2) and exhibits poor bioavailability with large variations among and within subjects (3,4). In general, a linear relationship between water solubility and dissolution percentage exists, and within boundaries, a linear relationship between the dissolution percentage and bioavailability of furosemide tablets has also been described (5).

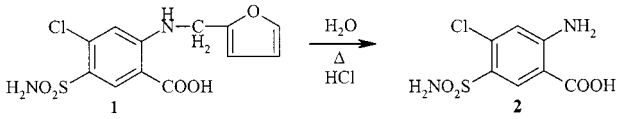
The solubility of a solid depends on the ability of molecules to escape from a crystal to the solvent. The stable form possesses lower free energy at a particular temperature and pressure and therefore has lower solubility or escaping tendency. For the most stable crystal forms within a chemical group, the water solubility increases with a decrease in melting temperatures. This is because a crystal that is bound together by weak forces in general will have a low heat of fusion and a low melting point (6).

It is well known that furosemide undergoes photochemical degradation (7,8) through hydrolysis and a photochemical oxidation process to form *N*-furfuryl-5-sulfamoylanthranilic acid and 4-chloro-5-sulfamoylanthranilic acid (**2**, saluamine). Saluamine (**2**) is also the product of the acid-catalyzed hydrolysis of furosemide in water solution (Scheme 2) and photochemical degradation in the solid state (9–11). According to Doherty and York (12), the melting endotherm for furosemide is accompanied by decomposition of the compound and occurs in the range 217°C–222°C. The degradation products formed during melting have not been described yet.

The decomposition of furosemide before or during melting indicates a ratio between intra- and intermolecular forces in such a way that breaking of intramolecular bonds occurs simultaneous with or before that of intermolecular bonds (6,13). The energy involved in the breaking of inter- and intramolecular bonds during decomposition and melting of furosemide can be obtained from differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Further analysis of the products formed during melting then make it possible to identify the thermal decomposition products.



Scheme 1. Furosemide (**1**).



Scheme 2. Formation of saluamine (**2**) through acid hydrolysis of furosemide (**1**).

The determination of the melting behavior also enables the estimation of the aqueous solubility of the drug and decomposition products; Yalkowsky and coworkers (14–16) have shown in a number of papers that the aqueous solubility of nonelectrolytes can be estimated successfully from its melting point. Data needed to do these calculations include the heat of fusion and melting point, which can also be obtained from a combination of DSC and TGA.

In this study, the thermal decomposition reaction of furosemide was studied as part of an investigation into the unfavorable water solubility of this drug. DSC was used to obtain the melting point and the thermal decomposition product(s) of furosemide. The main decomposition product was identified with nuclear magnetic resonance (NMR), mass spectrometry (MS), and infrared (IR) analysis. The activation energy for this decomposition reaction was determined by TGA (17). Melting point, mass loss on heating, and heat of melting data were also used to calculate the solubility of furosemide and saluamine in water. These values were then compared to experimentally measured values.

EXPERIMENTAL

Materials

Furosemide (**1**) was obtained from Laboratoria Mag (Johannesburg, South Africa; batch 3889). The purity was 99.81%, and it also complied with all other pharmacopoeial specifications. All other solvents and chemicals used were analytical grade.

Differential Scanning Calorimetry

DSC experiments were carried out on a Shimadzu DSC-50 controlled by a Shimadzu TA-501 thermal analyzer (Shimadzu, Kyoto, Japan). Furosemide (5 mg) was loaded into an aluminum sample pan and analyzed under nitrogen (flow rate 35 ml/min). The sample was heated from room temperature to 400°C at a rate of 10°C/min. The decomposition temperature was measured. Furosemide was then heated (10°C/min) to 250°C (a tempera-

ture at which it already decomposed), and the sample was kept at 250°C for 5 min before it was allowed to cool to room temperature. This process was repeated until enough of the decomposition product was obtained for NMR, MS, and IR analysis.

Nuclear Magnetic Resonance

A Varian VXR 300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75.46 MHz in a 1 Tesla magnetic field) with dimethylsulfoxide (DMSO) as the solvent and TMS as the internal standard was used.

Mass Spectrometry

An analytical VG 707OE mass spectrometer with electron ionization at 70 eV was used to obtain mass spectra.

Infrared Spectroscopy

A Shimadzu FTIR-4200 was used for infrared analysis of the product in a solid state as a KBr tablet.

Thermogravimetric Analysis

TGA experiments were carried out with a Shimadzu TGA-50 controlled by the Shimadzu TA-501 thermal analyzer. Furosemide (10 mg) was loaded into a platinum sample pan and analyzed in a nitrogen chamber (flow rate 35 ml/min). The sample was heated from room temperature to 350°C at rates of 10°C, 15°C, 20°C, and 25°C/min.

Activation Energy E_a

The method for determining the activation energy from TGA plots involved the reading of the temperatures at a constant weight loss from several integral thermograms with different heating rates. The negative of the logarithm of the heating rate ($-\log \beta$) was plotted against the inverse of the absolute temperature $1/T$. From the slope of $-\log \beta$ versus $1/T$ (β = °C/sec and T = absolute temperature K), the activation energy could be approximated closely by Eq. 1 below (17).

Solubility Measurements

Experimental solubilities were determined by rotating excess solute with solvent in amber glass bottles maintained at 20°C or 25°C in a constant-temperature water bath. Equilibrium was usually reached within 24 hr. The samples were filtered, diluted with an appropriate solvent, and assayed by high-performance liquid chromatography (HPLC) or spectrophotometry.

Partition Coefficients

A known amount of furosemide or saluamine was dissolved in water-saturated octanol. An equivalent volume of octanol-saturated water was added. The two phases were shaken for 2 hr at 25°C and then allowed to equilibrate. The phases were separated by centrifugation at 1500 rpm for 30 min. The concentration of solute in each phase was determined spectrophotometrically or with HPLC. The logarithm of the ratio between the two phases log $P_{o/w}$ was calculated.

RESULTS AND DISCUSSION

The decomposition of furosemide is clearly visible as a sharp exothermic peak in the DSC thermogram of the compound (Fig. 1). The total heat of this reaction was

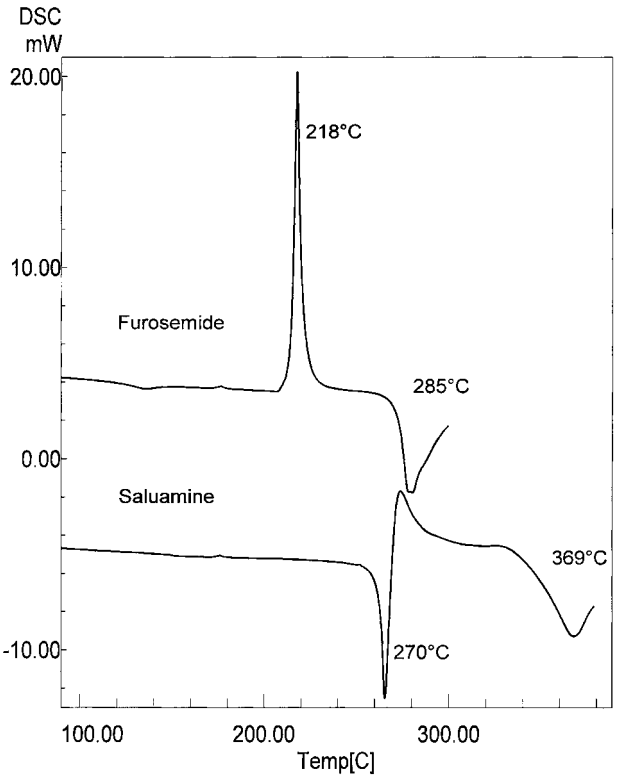


Figure 1. DSC thermograms of furosemide and saluamine.

9.09 (±0.49) kcal/mol, and the temperature at which the decomposition occurred was 218.1°C (±0.83)°C. At the same temperature, a decomposition process was also observed with TGA (Fig. 2). The average weight loss at 218°C was 2.73% (±0.15%).

NMR, MS, and IR analysis confirmed the structure of the recoverable decomposition product as saluamine (**2**; 4-chloro-5-sulfamoylanthranilic acid). Three signals in the aromatic region of the ^{1}H-NMR spectrum (Fig. 3) were identified as the two aromatic protons and the sulfonamide NH_2. The carboxylic acid proton was identified downfield from the aromatic signals. The ^{13}C-NMR spectrum (Fig. 3) indicates the presence of seven carbon atoms, and from the distortionless enhancement of polarization transfer (DEPT) spectrum, two CH– groups and five C– groups (of which four are aromatic and one is from a COOH– group) are visible. With MS, a molecular ion of 251 ($M^+ + 1$) was found, and the isotopic effect of one chlorine atom was also observed in the spectrum. IR spectrometry further confirmed the major functional groups of the thermal decomposition product.

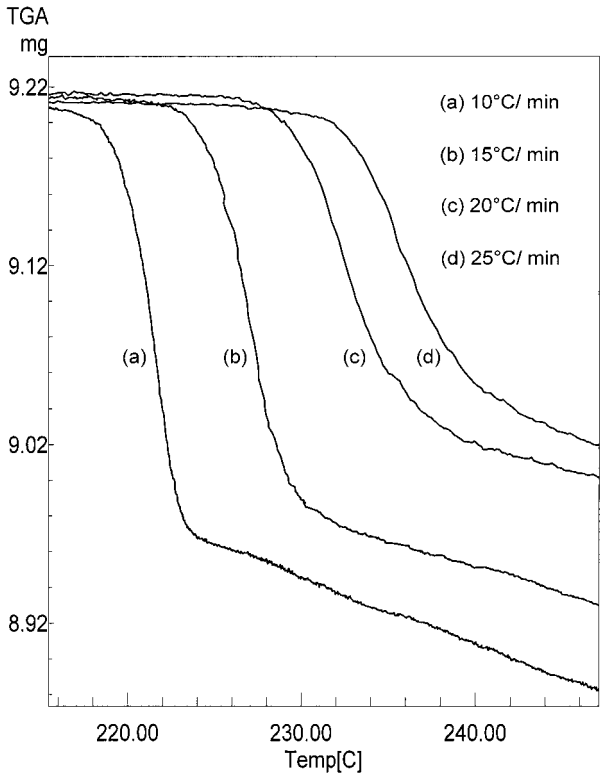


Figure 2. TGA thermograms at different heating rates at the decomposition temperature of furosemide.

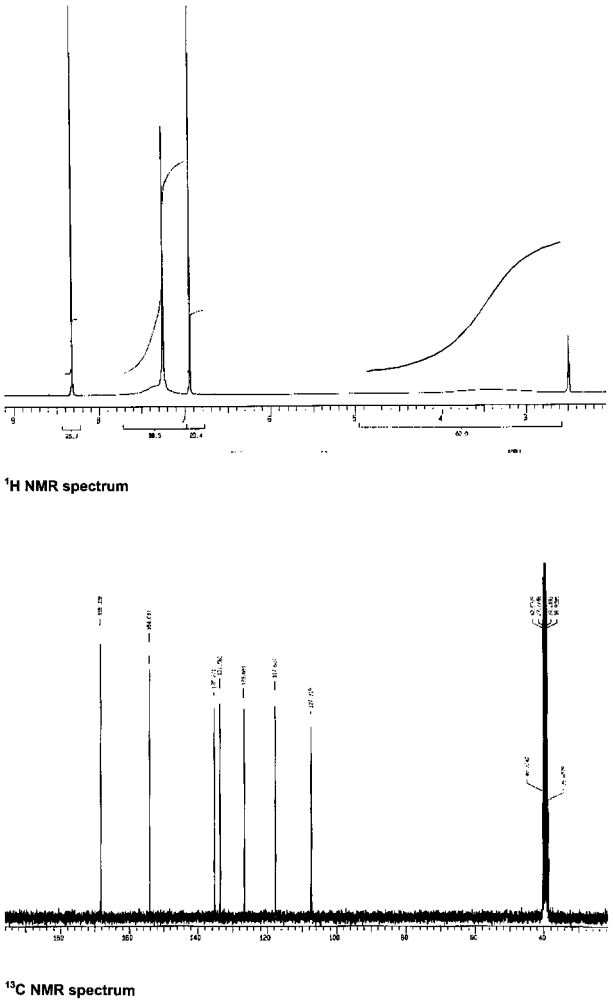


Figure 3. ^{1}H- and ^{13}C-NMR spectra of saluamine (**2**).

The physical data of the decomposition product correlated with that described in the literature (7) for saluamine (**2**) and are as follows: $C_7H_7ClN_2O_4S$; mp 273°C; ν_{max} (KBr) 3500–3100 (NH_2), 3000–2500 (COOH), 1180–1160 (SO_2NH_2); M/Z 251 ($M^+ + 1$), 232, 216, 198, 153, 108, 88, 64, 44; δ_H (300 MHz, DMSO) 6.93 (s, H-3), 7.24 (s, SO_2NH_2), 8.31 (s, H-6), 13.0 (bs, COOH); δ_C (75.16 MHz, DMSO) 107.85 (C), 117.57 (CH), 126.28 (C), 133.93 (CH), 135.86 (C), 154.05 (C), 169.23 (COOH).

The TGAs of furosemide measured at four different heating rates (β_1 = 0.167°C/sec; β_2 = 0.250°C/sec; β_3 = 0.333°C/sec; β_4 = 0.417°C/sec) were used to calculate the activation energy (Fig. 2). At four constant weight losses (C = 0.2, 0.4, 0.6, and 0.8), the logarithm of the

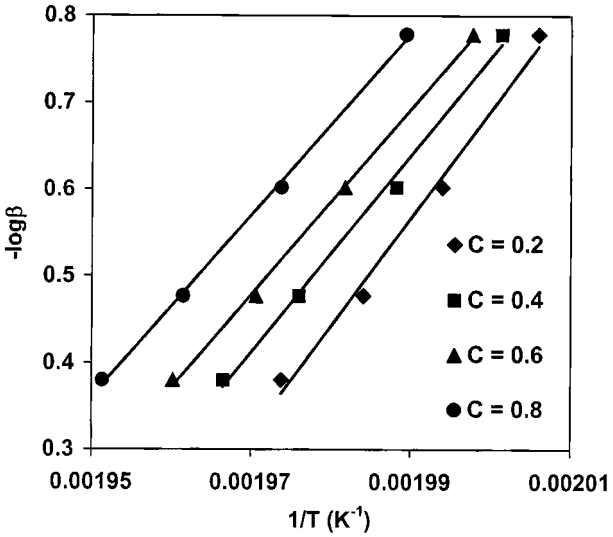


Figure 4. $-\text{Log}\,\beta$ (°C/sec) versus $1/T$ (K^{-1}) for four different weight losses ($R^2 = 0.991$ [$C = 0.2$]; 0.995 [$C = 0.4$]; 0.998 [$C = 0.6$]; 0.998 [$C = 0.8$]).

heating rate β versus the inverse of the absolute temperature T were plotted (Fig. 4). From the slopes of the lines, the activation energy E_a was calculated as 47.7 (±1.93) kcal/mol using Eq. 1.

$$E_a = 4.35 \times \frac{\Delta\ log\ \beta}{\Delta 1/T} \qquad (1)$$

where 4.35 represents a constant approximated from E/RT calculations (17).

From the heat of the reaction (9.09 ± 0.49 kcal/mol), the activation energy (47.7 ± 1.93 kcal/mol), and using the heat evolution method (18) to derive kinetic information from the DSC thermogram, the heat of fusion and an accurate value for the melting point (218.14°C) were obtained. From these values, the aqueous solubility of furosemide at 20°C and 25°C (Table 1) was estimated by the following equation (14):

$$\log S_m \approx -\log P_{o/w} - \frac{\Delta S_f(\text{mp} - 25)}{1364} + 0.80 \qquad (2)$$

where S_m, ΔS_f, $P_{o/w}$, and mp are the aqueous solubility in moles per liter, entropy of fusion, octanol-water partition coefficient of furosemide, and melting point (°C), respectively. The value of 0.8 is a constant that depends on the units chosen for solubility. Equation 2 has been shown to be applicable for a large number of solutes (14–16). The entropy of fusion ΔS_f was calculated from the heat of fusion ΔH_f and the melting point T_m (Kelvin). This is possible since the free energy of fusion ΔG is equal to zero at the melting point and ΔS_f is therefore equal to $\Delta H_f/T_m$. For furosemide, ΔS_f was calculated as 18.52 (±0.01) cal/mol/K when using the DSC results and 34.06 (±0.75) cal/mol/K when using the TGA results. The log $P_{o/w}$ of furosemide was determined to be 0.47.

Solubility values for saluamine were also estimated using Eq. 2. From DSC results, T_m was taken as 273°C and ΔH_f as 7.86 (±0.52) kcal/mol. Using these results, ΔS_f for saluamine was calculated to be 14.2 (±0.52) cal/mol/K. The log $P_{o/w}$ of saluamine was 0.22.

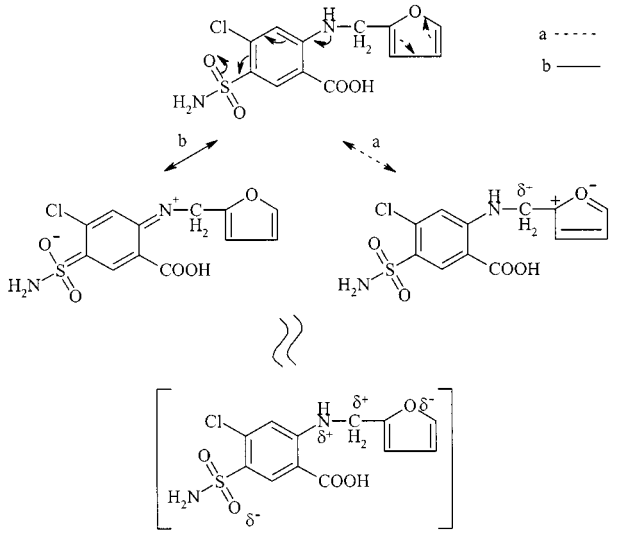
In Table 1, experimentally determined values for the solubility of furosemide and saluamine are also listed. The solubility of furosemide in both water and HCl:KCl buffer at pH 2.0 is very low. Saluamine is significantly more soluble in both. The difference in solubility was more than 0.7 g/L in water at 25°C and 0.5 g/L in buffer at pH 2.0. Calculated solubilities were significantly different from measured solubilities. Since furosemide decomposed on melting, the solubilities were calculated from ΔH_f values obtained from both DSC and TGA results. The solubilities calculated from TGA results were a better approximation of the measured solubilities. Bias

Table 1

Estimated and Measured Solubility of Furosemide and Its Thermal Decomposition Product Saluamine

	Furosemide			Saluamine	
Solvent	Calculated from DSC (g/L)	Calculated from TGA (g/L)	Measured Solubility (g/L)	Calculated from DSC (g/L)	Measured Solubility (g/L)
Water at 20°C	1.52 ± 0.05	0.0086 ± 0.0021	0.0185 ± 0.0007	0.620 ± 0.022	[a]
Water at 25°C	1.77 ± 0.06	0.0115 ± 0.0027	0.0250 ± 0.0006	0.935 ± 0.033	0.754 ± 0.032
Buffer pH 2.0 at 25°C	[a]	[a]	0.0089 ± 0.0001	[a]	0.556 ± 0.006

[a] Values not calculated or determined.



Scheme 3. The weakening of the C–N bond in furosemide through the (a) negative inductive effect of the furane ring and (b) delocalization of the electrons of the aniline nitrogen in the chlorosulfamoyl benzoic acid entity.

was +1.50 g/L at 20°C and +1.75 g/L at 25°C for DSC calculated solubilities and −0.010 g/L at 20°C and −0.014 g/L at 25°C for TGA calculated solubilities. The solubility of saluamine was calculated only from DSC results since no decomposition occurred during melting. For saluamine, calculated and measured solubilities (Table 1) were of the same order of magnitude.

The main thermal decomposition product of furosemide at high temperatures (218°C) was identified as saluamine (4-chloro-5-sulfamoylanthranilic; **2**). For saluamine to form, it is clear that cleavage of a C–N bond must take place within this reaction. The experimentally measured activation energy of 47.7 (±1.93) kcal/mol, however, is well below the normal 59 ± 4 kcal/mol needed for such a cleavage (19). This could possibly be explained by the weakening of the C–N bond through the–I–effect of the furane ring and the delocalization of the electrons of aniline nitrogen in the chlorosulfamoyl benzoic acid entity of furosemide (Scheme 3).

This decomposition of furosemide indicates the breaking of intramolecular bonds before the breaking of intermolecular bonds (separation of individual furosemide molecules). The activation energy for the breaking of intermolecular bonds, therefore, must be higher than the 47.7 (±1.93) kcal/mol needed for decomposition. In the crystal structure of furosemide, there exists one intramolecular hydrogen bond (between the carboxylic and amine entities) and two intermolecular hydrogen bonds between the sulfamoyl groups of adjacent molecules (20). The activation energy needed for cleavage of a hydrogen bond is described as being between 2 and 7 kcal/mol (21). The energy needed to overcome the forces between individual furosemide molecules therefore indicates the presence of more than the two intermolecular hydrogen bonds described.

CONCLUSIONS

Strong inter- and intramolecular bonds are also a possible explanation for the poor water solubility of furosemide (12). When some of the inter- and intramolecular bonds that form part of the hydrogen bond network involving the sulfonamide groups in furosemide disappear, as in the structurally related decomposition product saluamine, the aqueous solubility increases. However, although saluamine is approximately 30 times more soluble in water than furosemide, it can still be classified as a poorly water soluble compound. This poor solubility might thus be attributed to the strong hydrogen bonds between the amine and the carbonyl groups that also exist in furosemide (20).

This study of the melting behavior of furosemide and the decomposition products formed during thermal decomposition gave considerable insight into the reasons for the poor aqueous solubility of this drug.

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