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The thermal stability of some thiadiazole derivatives in relation to antimicrobial activity

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Abstract

Fourteen thiadiazole derivatives have been prepared and their thermal behaviours determined using DSC technique. The results suggested that an alkyl substituent at the 2- and 5-positions increases the thermal stability and antimicrobial activity, whereas a benzyl or allyl substituent at both positions exerts the opposite effect.

INTRODUCTION

In recent years, thiadiazoles and, in particular, 1,3,4-thiadiazole derivatives have been among the various heterocyclic compounds that have received special attention as antimicrobial agents [1–3]. Most derivatives involve substitution on the 2- and 5-positions of the thiadiazole ring, and include amino [4, 5], alkylthio [6] and carbamate [7] groups, and unsaturated groups [8, 9]. Thermal stability and thermogravimetric techniques are important in the pharmaceutical industry [10]. Previously we have investigated the possible relationships between thermal stability and antimicrobial activity of certain heterocyclic compounds, namely mercaptothiazole and triazoles [11–14].

In this communication, the thermal stabilities of certain thiadiazole derivatives, designated 1–14, have been measured and correlated to their antimicrobial activities. The structure of the investigated compounds is shown in Structure 1 (the R′ and R groups are listed in Table 1).

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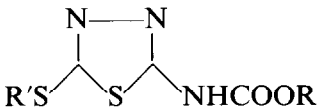

Structure 1. Thiazole derivatives 1–14. See Table 1 for the R and R′ groups.

EXPERIMENTAL

Compounds 1–14 were prepared according to procedures described by Muhi-Eldeen and coworkers [15, 16]. Melting points were determined in an open glass capillary using an electrothermal apparatus and are uncorrected. Differential scanning calorimetry (DSC) measurements were carried out on a Heraeus TA-500 thermal analyser under static air. Aluminium oxide was used as a stable inert reference. The heating rate was $10°C\,min^{-1}$. The thermodynamic properties were calculated according to ref. 17.

RESULTS AND DISCUSSION

Table 1 lists the melting points, thermal melting temperature T_M, decomposition temperatures T_{dec}, and decomposition enthalpies ΔH_{dec}, of compounds 1–14. Table 2 shows the antimicrobial activity of the reported compounds against *Pseudomonas aeruginosa* and *Candida albicans*. Representative DSC curves are shown in Figs. 1 and 2. Using T_{dec} as a measure of thermal stability, the following trends could be observed. In compounds 1, 4, 6 and 9, where R

TABLE 1

Thermal data for compounds 1–14

No.	R′	R	M.P./ °C	T_M/ °C	T_{dec}/ °C	ΔH_{dec}/ J mol^{-1}
1	CH_3	CH_2–CH_3	163	164	313	191.96
2	CH_3	CH_2–CH=CH_2	136	119	230	93.15
3	CH_3	CH_2–Ph	144	166	220	152.76
4	C_2H_5	CH_2–CH_3	130	143	250	190.00
5	C_2H_5	CH_2–CH=CH_2	128	108	245	79.87
6	CH_2=CH–CH_2	CH_2–CH_3	120	95	205	237.2
7	CH_2=CH–CH_2	CH_2–CH=CH_2	94	121	252	245.01
8	CH_2=CH–CH_2	CH_2–Ph	110	113	200	427.05
9	Ph–CH_2	CH_2–CH_3	129	123	287	199.73
10	Ph–CH_2	CH_2–CH=CH_2	125	117	250	245.93
11	Ph–CH_2	CH_2–Ph	140	118	178	315.33
12	CH_3–$(CH_2)_3$	CH_2–CH_3	119	112	210	189.20
13	CH_2–$(CH_2)_3$	CH_2–CH=CH_2	90	78	240	26.40
14	CH_3–$(CH_2)_3$	CH_2–Ph	122	93	195	61.35

TABLE 2

Antimicrobial activity of compounds 1–14

Compound No.	Diameter of inhibition [a]		Compound No.	Diameter of inhibition [a]	
	Pseudomonas aeruginosa	*Candida albicans*		*Pseudomonas aeruginosa*	*Candida albicans*
1	+	+	8	–	+
2	–	+	9	+	+
3	+	–	10	–	–
4	++	++	11	–	–
5	+	–	12	++	++
6	–	+	13	+	–
7	–	+	14	+	–

[a] The diameters of the inhibition zone are an average of three measurements: –, no inhibition; +, 7–10 mm diameter of growth inhibition; ++, 11–15 mm diameter of growth inhibition.

is an ethyl group, the thermal stabilities decrease in the order methyl > benzyl > alkyl > allyl. However, if R is an allyl group, as in compounds 2, 5 and 7, the thermal stability decreases in the order allyl > benzyl > alkyl.

When R is a benzyl group, as in compounds 3, 8, 11 and 14, the thermal stabilities decrease in the order methyl > allyl > *t*-butyl > benzyl.

In other words, if R is kept constant, as either methyl, ethyl or benzyl, and R′ is changed to various moieties as outlined in Table 1, the trend in thermal stability is ethyl > allyl > benzyl. However, if R′ is allyl or *t*-butyl the observed thermal stability decreases in the order ethyl > benzyl > allyl.

It is interesting to note from Figs. 1 and 2 that when R′ or R or both are alkyl substituents, the endothermic process of melting is followed by an exothermic or an endothermic process, and then an endothermic process, whereas compounds with an aryl group substituted at R′ or R or both, show two endothermic peaks, representing the decomposition and evaporation of the compound.

The antimicrobial screening results summarized in Table 2 indicate that the presence of alkyl substitutents at the 2- and 5-positions increases the antimicrobial activity, i.e. compounds 1, 4 and 12. However, when substituents at both positions are allyl or benzyl, the antimicrobial activity decreases. These observations suggest that if the substituents at the 2- and 5-positions are benzyl or allyl, i.e. compounds 4, 8, 10, 11, which cause a charge delocalization throughout the whole molecule, the antimicrobial activity and the thermal stability decrease, whereas if the substituents at both positions are an alkyl group, i.e. compounds 1, 4, 12, which result in a charge localization, the antimicrobial activity and the thermal stability increase.

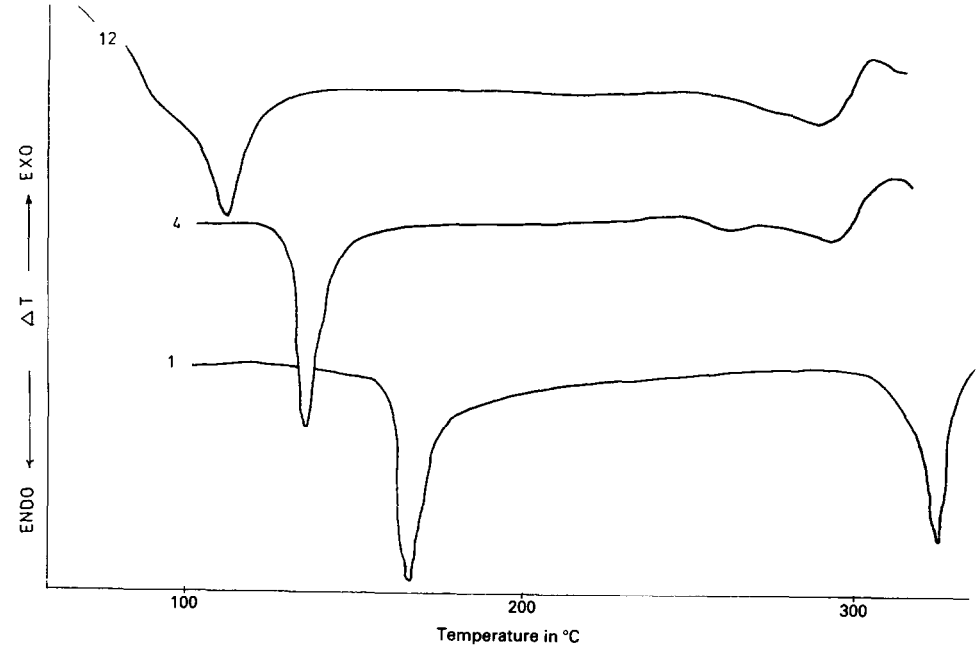

Fig. 1. DSC for compounds 1, 4 and 12.

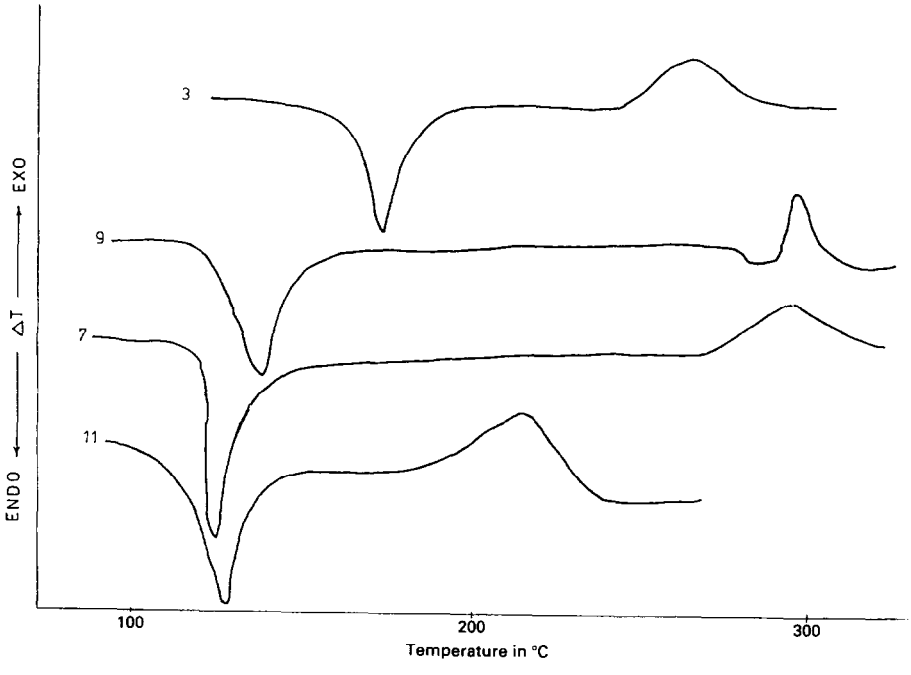

Fig. 2. DSC for compounds 3, 9, 7 and 11.

It may be concluded that the increases in the thermal stability and charge localization enhance the ability of the thiadiazole ring to interact with the cell membrane of the microoganisim to exert its antimicrobial activity. In other words, charge delocalization weakens the electronic interaction between these compounds and the microorganism, which might favour charge localization.

Of course, other factors, such as differences in absorption distribution and metabolism, may contribute to the activity differences observed.

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