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Transformation Rates of *ortho*-Substituted Thiophene and Benzene Carboxylic Esters: Application to Thifensulfuron-methyl and Metsulfuron-methyl Herbicides

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Abstract: The rate constants for soil degradation and alkaline hydrolysis of two herbicides, metsulfuron-methyl and thifensulfuron-methyl, have been determined. In order to explain the difference in behaviour of the two compounds, the chemical and enzymatic hydrolysis of some *ortho*-substituted methyl benzoates and methyl 3-substituted thiophene-2-carboxylates were studied. The data are consistent with a difference in polar and steric effects of the substituents in benzene and thiophene derivatives.

1 INTRODUCTION

Depending on their structure,[1] degradation rates of sulfonylurea herbicides differ in soils, and can be explained by either microbial degradation or chemical hydrolysis. The introduction of a methyl group on the nitrogen of the urea function of tribenuron-methyl (methyl 2-[4-methoxy-6-methyl-1,3,5-triazin-2-yl (methyl)-carbamoylsulfamoyl]benzoate) makes this compound more susceptible to bridge hydrolysis and explains its fast degradation in soil.[2]

The rapid degradation of thifensulfuron methyl (Fig. 1, **1**, methyl 3-(4-methoxy-6-methyl-1,3,5-triazin-2-ylcarbamoylsulfamoyl)thiophene-2-carboxylate) in soil is mainly related to microbial activity.[2,3] Metsulfuron-methyl (**2**; methyl 2-(4-methoxy-6-methyl-1,3,5-triazin-2-ylcarbamoylsulfamoyl)benzoate) is slowly degraded in soil by both chemical and microbial mechanisms.[4] The two compounds have very similar structures, the only difference being that the benzene ring of **2** is changed to a thiophene ring in **1**. A difference in reactivity has been observed between benzene *ortho*-substituted esters and thiophene *ortho*-like substituted esters by Spinelli *et al.*[5] In order to investigate the reason why the two herbicides **1** and **2** display such differences in reactivity, we report herein the results of chemical hydrolysis and enzymatic and soil degradation rates of these two compounds and some analogues.

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2 EXPERIMENTAL METHODS

2.1 Synthesis of model compounds

2.1.1 Methyl 3-sulfamoylthiophene-2-carboxylate, **5t** *(Fig. 2)*

A solution of sodium nitrite (2·25 g, 0·032 mol) in water (3 ml) was added at 0°C to a solution of methyl 3-aminothiophene-2-carboxylate (4·72 g, 0·03 mol) in glacial acetic acid (10 ml) and 1 M hydrochloric acid (35 ml). The reaction mixture was stirred at 0°C for 1-h added to a mixture of acetic acid (40 ml), sulfur dioxide (12 g) and copper (II) chloride (0·6 g), and stirring continued for 1 h. The mixture was poured into water (50 ml) and extracted with diethyl ether (2 × 50 ml), washed with sodium carbonate solution, dried (sodium sulfate) and evaporated to give crystals (2 g) of methyl 3-chlorosulfonylthiophene-2-carboxylate. This product was dissolved in acetone (20 ml) and ammonium hydroxide (2 ml) was added. The mixture was stirred for 1 h

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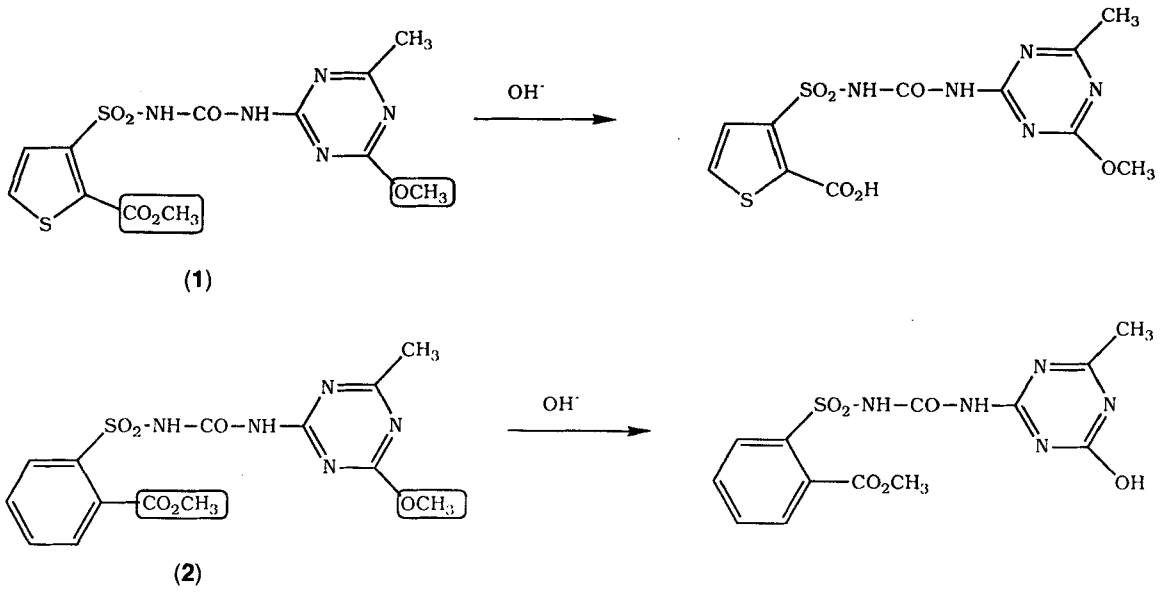
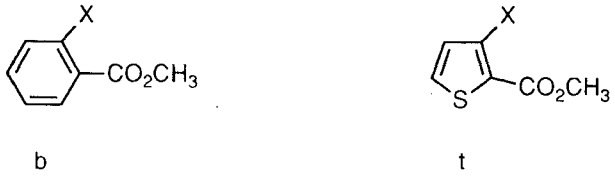


Fig. 1. Structures and alkaline hydrolysis of thifensulfuron-methyl (**1**) and metsulfuron-methyl (**2**).



X	H	NH_2	SO_2NH_2	$SO_2N(C_2H_5)_2$	NO_2	$SO_2NHCOCH_3$
b	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**
t	**3t**	**4t**	**5t**	**6t**	**7t**	**8t**

Fig. 2. Structures of compounds tested.

and evaporated to remove acetone. The precipitated solid **5t** was filtered off and recrystallised from chloroform + hexane (1·8 g, 27 %) m.p. 122–123°C [1H]NMR (400 MHz; deuterochloroform) 3·93 (3H, s, CO_2CH_3), 5·93 (2H, s NH_2), 7·53 (2H, s, CH=CH). *Elemental analysis* (Found: C, 32·82; H, 3·36; N, 6·26. Calc. for $C_6H_7NO_4S_2$: C, 32·57; H, 3·16; N, 6·33)

2.1.2 Methyl 3-(N,N-*diethylsulfamoyl*)*thiophen-2-carboxylate*, **6t**

Methyl 3-sulfamoylthiophene-2-carboxylate (2·4 g, 0·011 mol) was dissolved in benzene (20 ml) and diethylamine (2·6 ml, 0·024 mol) was added dropwise. The mixture was heated at reflux for 2 h. After evaporation of the solvent, the residue was extracted with diethyl ether, washed with water, dried and evaporated to give **6t** (1 g, 46 %) m.p. 72–73°C. [^{1}H] NMR (400 MHz; deuterochloroform) 1·09 (3H, t, J 6·7, CH_2CH_3), 3·36 (2H, q, J 6·7, CH_2CH_3), 3·85 (3H, s, CO_2CH_3), 7·4 (2H, s, CH=CH). *Elemental analysis* (Found: C, 43·32; H, 5·41; N, 5·05. Calc. for $C_{10}H_{15}NO_4S_2$: C, 43·58; H, 5·67; N, 5·05).

2.1.3 Methyl 2-(N,N-*diethylsulfamoyl*)*benzoate*, **6b**

Methyl 2-chlorosulfonylbenzoate (2·34 g, 0·01 mol) was dissolved in benzene (50 ml) and diethylamine (1.5 ml, 0·014 mol) was added slowly. The mixture was heated at reflux for 2 h. After evaporation of the solvent, the residue was extracted twice with diethyl ether, and the extracts were dried and evaporated to give **6b** (1·5 g, 55 %) m.p. 71–72°C. [^{1}H]NMR (400 MHz; deuterochloroform) 1·07 (3H, t, J 6·6, CH_2CH_3), 3·3 (2H, q, J 6·6, CH_2CH_3), 3·9 (3H, s, CO_2CH_3), 7·4–7·9 (4H, m. arom.). *Elemental analysis* (Found: C, 53·03; H, 6·41; N, 5·28. Calc. for $C_{12}H_{17}NO_4S$: C, 53·13; H, 6·27; N, 5·16).

2.1.4 Methyl 3-nitrothiophene-2-carboxylate **7t**

To a solution of methyl 3-sulfamoylthiophene-2-carboxylate (2·36 g) in acetic acid (3 ml) was added concentrated sulfuric acid (1·5 ml) at −5°C. A solution of sodium nitrite (1·1 g) in water (1 ml) was added to the reaction mixture at 5°C. After 10 min, this mixture was added to a solution of sodium nitrite (1·5 g) in water (2 ml)with a catalytic amount of copper (I) chloride and stirred for

10 min at room temperature. The solution was extracted with diethyl ether (2 × 20 ml), dried and evaporated to dryness. Purification on a chromatographic silica gel column with chloroform as the eluent yielded **7t** (0·06 g, 2 %) m.p. 132–133°C. [^{1}H]NMR (400 MHz; deuterochloroform) 3·9 (3H, s, CO_2CH_3), 7·42 (1H, d, J 2·5, CH—), 7·51 (1H, d, J 2·5 CH—). *Elemental analysis* (Found: C, 38·5; H, 2·67; N, 7·48; Calc. for $C_6H_5NO_4S$: C, 39·1; H, 2·83; N, 7·43).

2.1.5 Methyl 2-(N-acetosulfamoyl)benzoate, **8b**
Methyl 2-(sulfamoyl)benzoate (3 g, 0·014 mol) was added to acetyl chloride (15 ml). The mixture was warmed at 50°C for 30 min. The white precipitate of **8b** formed at room temperature was filtered off and recrystallized from benzene (2 g, 63 %) m.p. 156°C. [^{1}H]NMR (400 MHz; deuterochloroform) 2·2 (3H, s, $COCH_3$), 4·07 (3H, s, CO_2CH_3), 7·7–8·4 (4H, m, arom), 8·9 (1H, s, N–H); IR (chloroform) νNH 3364 cm^{-1}; νCO 1727 cm^{-1}. *Elemental analysis* (Found: C, 46·94; H, 4·25; N, 5·52. Calc. for $C_{10}H_{11}NO_5S$: C, 46·69; H, 4·28; N, 5·45).

2.1.6 Methyl 3-(N-acetylsulfamoyl)thiophene-2-carboxylate, **8t**
Methyl 3-sulfamoylthiophene-2-carboxylate (1·1 g, 0·005 mol) was added to acetyl chloride (10 ml) and warmed at 60°C for 12 h. The white precipitate of **8t** formed at room temperature was filtered and recrystallized from benzene. (0·8 g, 61 %) m.p. 186°C. [^{1}H]NMR (400 MHz; deuterochloroform) 2·12 (3H, s, $COCH_3$), 3·95 (3H, s, CO_2CH_3), 7·55 (1H, d, CH), 7·8 (1H, d, CH), 8·95 (1H, s, NH); IR (chloroform) νNH 3365 cm^{-1}; νCO 1720 cm^{-1}. *Elemental analysis* (Found: C, 36·68; H, 3·34; N, 5·36. Calc. for $C_8H_9NO_5S_2$: C, 36·50; H, 3·42; N, 5·32).

2.1.7 Synthesis of acid derivatives
Carboxylic ester (0·005 mol) was dissolved in methanol + 0·1 M potassium hydroxide (20 + 80 by volume). After 24 h at ambient temperature, the mixture was extracted with diethyl ether. The aqueous fraction was acidified and the acid precipitate was filtered off. The [^{1}H]NMR of the compounds was in accordance with their structures.

2.2 Soil degradation

2.2.1 Properties of soils
St Nazaire soil: pH 6·7; organic matter 2 %; clay 22 %; sand 24·3 %. Salanque soil: pH 7·8; organic matter 1·5 %; clay 19·6 %; sand 19 %.

2.2.2 Degradation experiments
An aqueous solution of the product was incorporated into a sample of soil (20 g) to produce an initial concentration of 20 mg kg^{-1} and a soil moisture content of 25 % (w/w). The soil–herbicide mixture was incubated at 29°C. Samples was taken periodically and frozen until analysis. For analysis the sample was extracted with methanol + water + acetic acid (20 + 5 + 0·5 by volume) by shaking for 1 h. After centrifuging, the concentration of parent and degradates of the two herbicides in the clear supernatant was determined using an HPLC method.

2.3 HPLC analysis

Pump: LDC constametric I; detector LDC Spectromonitor I.
Column: Ultrabase C_8; solvent: acetonitrile + water + acetic acid (50 + 50 + 0·5 by volume)
Wavelength detection: 235 nm for benzene derivatives
254 nm for thiophene derivatives.
This method allows simultaneous determination of ester and acid concentration.

2.4 Determination of hydrolysis rate constants

An aliquot (62·5 μl) of a solution of the test compound (40 g litre^{-1} in acetonitrile) was added to carbonate buffer (pH 9·8; 0·2 M; 50 ml) at time $t = 0$. For products having a half-life time >20 h the solution was directly analyzed by HPLC at different times. For products having a half-life time <20 h, a solution of acetic acid in acetonitrile (0·2 M0·5 ml) was added to 0·5 ml of reaction solution at different times to stopping the reaction before analysis. This mixture was analyzed by HPLC.

2.5 Enzymatic hydrolysis

The kinetics were followed by measuring the variation in absorbance at difference wavelengths (**3t**: 270 nm; **3b**: 240 nm; **4t**: 318 nm; **6t**: 236 nm; **6b**: 220 nm; **7t**: 250 nm; **7b**: 220 nm; **8t**: 270 nm; **8b**: 226 nm). Solution of products (10^{-4} M in pH 7 phosphate buffer; 1·5 ml) were treated by pig liver esterase (Sigma Chemical) (1 unit). The results are reported in half-life times to hydrolyse 100 μmoles per liter of solution.

2.6 Determination of pKa

The pKa were measured potentiometrically or by a spectrophotometic method based on the difference of ultraviolet absorption between the neutral and anionic forms of acids.[6]

3 RESULTS AND DISCUSSION

3.1 Degradation of Thifensulfuron-methyl (1) and Metsulfuron-methyl (2) in Soils

In the two soils tested, the degradation rate of **1** was greater than that of **2** (Table 1). Soil sterilization resulted in a decrease of the degradation rate of **1** in accordance

TABLE 1
Degradation Rates of Thifensulfuron-methyl (1) and Metsulfuron-methyl (2) in St Nazaire and Salanque soil

		$t_{\frac{1}{2}}$ (days)	
		St Nazaire	*Salanque*
Thifensulfuron-methyl	Non-sterile	1.6	2
	Sterile	27	25
Metsulfuron-methyl	Non-sterile	27	60
	Sterile	54	108

TABLE 2
Rate of Hydrolysis of Thifensulfuron-methyl (1) and Metsulfuron-methyl (2) at Different pH values

pH	$t_{\frac{1}{2}}$ (days)				
	5	*6*	*8*	*9*	*10*
Thifensulfuron-methyl	346	1950	739	130	12
Metsulfuron-methyl	300[a]	3650[a]	—	—	520

[a] From Ref. 7.

with microbial degradation as the proposed route of degradation. The degradation rates of **2** were also lower in a sterilized soil than in non-sterilized soil, but the half-life in the former was only twice that in the latter.[4]

3.2 Hydrolysis of Thifensulfuron-methyl (1) and Metsulfuron-methyl (2)

The two products have similar rates of acidic hydrolysis, while the rate of alkaline hydrolysis of **1** is greater than that of **2** (Table 2).

The analysis of reaction products revealed that the two compounds follow identical pathways under acidic conditions: cleavage of the sulfonylurea bridge and *O*-demethylation of the triazine ring with **2**[7] and **1** (Cambon, J. P. & Bastide J., unpublished). On the other hand, the alkaline hydrolysis of the two compounds follows different routes (Fig. 1): *O*-demethylation of the triazine ring with **2**[7] and ester hydrolysis with **1**.[8] The hydrolysis of **2** is 43 times slower than the hydrolysis of **1** at pH 10 and the measured reaction for **2** is not ester hydrolysis.

3.3 Hydrolysis of benzene and thiophene derivatives

Some *ortho*-substituted benzene carboxylic esters and 3-substituted thiophen-2-carboxylic esters were studied (Fig. 2).

Kinetics of their hydrolysis are reported in Table 3. Methyl benzoate and methyl thiophene-2-carboxylate have similar hydrolysis rates.[9] An amino substituent decreased the hydrolysis rates equally in the two series of compounds. The sulfamoyl substituent increased the hydrolysis rate of the thiophene derivative **5t**, and the hydrolysis rate of the benzene derivative **5b** was too rapid to be measured. In this latter case the product of reaction was not the corresponding acid, but a cyclized product, a saccharin.[10] Cyclization was not observed with the thiophene analogue. The diethylsulfamoyl-substituted products are not able to cyclize and the hydrolysis rate of the benzene derivative **6b** was slow. Sulfamoyl (**5t**) and diethylsulfamoyl (**6t**) thiophene derivatives were hydrolyzed at the same rate. The difference in hydrolysis rate between the benzene derivative **8b** and the thiophene derivative **8t** was also very large. Another electron-withdrawing group, nitro, gave a similar result; the substitution increased the hydrolysis rate by a factor of 85 in the thiophene derivatives, **7t**, while only by a factor of 3 in the benzene derivative, **7b**. 4- or 5-substituents in the thiophene ring have greater effects on the hydrolysis rate than do the corresponding *meta* or *para* substituents in the benzene ring.[11] The same difference is probably involved in the case of 2-substituents. Moreover, steric factors are more important in the benzene series than in the thiophene series[12] and decrease the hydrolysis rate in *ortho*-substituted benzene esters.

3.4 Acid Dissociation constants

The pKa of *ortho*-substituted benzene acids and thiophene-2-carboxylic acids were measured in aqueous solution by a spectrophotometric method (Table 3). The influence of substituents on pKa values is consistent in both thiophene and benzene series, increasing with electron-withdrawing group and decreasing with electron-donating group. Nevertheless, the ΔpKa values (ΔpKa = pKa(X) − pKa(H)) are different for the two series. For eight different substituents. Spinelli *et al.*[12] obtained a good correlation between ΔpKa and Hammet constants, σ. In *para*-substituted benzene series, the hydrolysis rates of carboxylic esters were related to the pKa of the corresponding acids. In this study, a poor correlation was obtained, possibly due to the small number of substituents. The difference in pKa of compounds **6b–6t** and **8t–8b** is small, whereas the difference in hydrolysis rate is great.

3.5 Enzymatic hydrolysis

To test the biodegradability of these different compounds, the activity of a commercially available esterase was studied. Methyl benzoate and methyl thiophene-2-carboxylate were rapidly hydrolyzed by pig liver esterase. Enzymatic reactions were more sensitive to steric effects than to electronic effects; 3-substituted compounds were less reactive than unsubstituted ones; a larger difference was obtained in benzene derivatives.

TABLE 3
Rate Constants for the Alkaline Hydrolysis, Enzymatic Hydrolysis and Soil Degradation of Methyl Esters and pKa of Corresponding Acids

	3t	3b	4t	4b	5t	5b	6t	6b	7t	7b	8t	8b
$t_{\frac{1}{2}}$(h)[a]	24·3	22	237	200	3·4	[e]	3·4	600	0·28	6·3	14·5	3010
vR enzyme[b]	22	33·6	0·05	—	—	—	1·6	0·12	21	7·8	[f]	[f]
$t_{\frac{1}{2}}$ soil[c] (h)	1	1	—	—	—	—	6·5	408	—		<24	<24
pKa[d]	3·53	4·19	5	4·6	3·3		2·77	2·96	2·68	2·4	3·1	3·1

[a] At pH 9·8 and 29°C.
[b] vR enzyme = Hydrolysis rate by pig liver esterase in μmoles min^{-1} of 10^{-4} M solution.
[c] $t_{\frac{1}{2}}$ soil = half-life time in hours in soil, St Nazaire
[d] In water at 25°C.
[e] Rate too fast to be measured.
[f] Rate too low to be measured.

The enzymatic hydrolysis rates of **6t**, **7t**, **7b** and **8t** are lower than those of **3t** or **3b**, contrary to results under alkaline conditions. In order to determine if the enzymatic reactions occurred in soils, we have investigated the degradation of compounds **3b**, **3t**, **6b**, **6t**, **8t** and **8b** in soil. A rapid degradation of **3b** and **3t** was observed (Table 3). The thiophene derivative **6t** was also hydrolyzed, but more slowly than the unsubstituted compound. The degradation rate of the benzene derivative **6b** was very low, as was observed in soil. The compounds **8b** and **8t** were not transformed by esterase enzyme; in soil a rapid degradation was observed ($t_{\frac{1}{2}} < 24$ h), but hydrolysis of the acetamide bond was responsible for this transformation in these two cases.

4 CONCLUSION

This study confirms that 3-substituents in a thiophene-2-carboxylic acid ester profoundly alter the susceptibility of such compounds to aqueous alkaline hydrolysis compared to *ortho*-substituted benzene carboxylic acid esters, in agreement with the established faster degradation of thifensulfuron-methyl compared to metsulfuron-methyl. These differences can be explained by the effect of *ortho* substitution. The electronic and steric effect of these substituents decreases the reactivity of the carboxylic ester function for electron-donating groups, but has the opposite effect in the case of electron-withdrawing groups. The slow rate of alkaline hydrolysis of compounds **6b** and **8b** can be explained by the greater steric effect in benzene than *ortho*-like substituted thiophenes.

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