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Kinetics and Hydrolysis Mechanism of Chlorsulfuron and Metsulfuron-Methyl*

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Abstract: In acidic media, hydrolysis of chlorsulfuron and metsulfuron-methyl occurs via two consecutive reactions which were followed by ultraviolet spectrophotometry. For these two reactions, the pseudo-first-order rate constants increase proportionally to the concentration of hydronium ion in the more acidic media and to the square of this concentration at higher pH values.

A kinetic study by HPLC shows that the first reaction leads to the formation of 4-methoxy-6-methyl-1,3,5-triazin-2-amine and (*o*-chlorophenylsulfonyl) carbamic acid for chlorsulfuron or (*o*-methoxycarbonylphenylsulfonyl) carbamic acid for metsulfuron-methyl. The second reaction is the conversion of these sulfonylcarbamic acids to sulfonamides and carbon dioxide. The complete lack of saccharin and of *o*-sulfamoyl benzoic acid proves that the ester function of the methoxycarbonyl group is stable.

The lack of general acid-base catalysis and a solvent deuterium isotope effect less than unity are consistent with a rate-determining cleavage of the protonated substrate.

In the basic pH range (10–14) a single reaction occurs, the nucleophilic substitution of the methoxy group on the triazine by a hydroxide group.

1 INTRODUCTION

Sulfonylureas are herbicides which inhibit acetolactate synthase (ALS), which is the first common enzyme in the biosynthesis of branched amino acids (valine, leucine and isoleucine) specific to plants and microorganisms.[1–3] The inhibition of this enzyme stops the development of the roots and of the aerial parts of the plant.

The most important pathways of sulfonylureas' degradation in soil are chemical hydrolysis and microbial degradation. Photolysis and volatilization are relatively minor processes.[4] Chemical hydrolysis produces breakdown of the sulfonylurea bridge, yielding sulfonamide and s-triazine derivatives. This cleavage, which is pH-sensitive, is observed during hydrolysis in aqueous solution.[5] Several authors have shown that the degradation rate of sulfonylureas decreases with the increase of soil pH. This has been observed for both sterile and non-sterile soil.[6–9]

Since these herbicides are weak acids with pK_a values ranging from 3·3 to 5·2, the neutral form of the sulfonylurea bridge is especially sensitive to hydrolysis, yielding the herbicidally inactive sulfonamide and s-triazine fractions of the parent molecule.[10]

Although chemical hydrolysis of these herbicides is considered to result from breakdown of the sulfonylurea bridge,[3,5,11] Sabadie[12] has noticed, while studying acidic hydrolysis of metsulfuron-methyl, the presence of a parallel degradation route which involves the substitution of the methoxy group of the triazine ring by a hydroxide group, followed by the opening of the ring leading to an unidentified product.

Degradation of the triazine ring is considered to be the result of microbial activity.[13]

A comprehensive study is required to investigate the disappearance of chlorsulfuron and metsulfuron-methyl (Fig. 1) and the formation of degradation products, so

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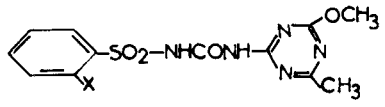

Fig. 1. Structure of chlorsulfuron (X = Cl) and metsulfuron-methyl (X = CO_2CH_3).

that the mechanism of the hydrolytic degradation can be better understood. The present study describes the kinetics of hydrolysis of chlorsulfuron and metsulfuron-methyl in several aqueous buffers in the pH ranges 0–5, 10–14 and temperature range 15–45°C; on the basis of these data a degradation pathway is proposed.

2 EXPERIMENTAL

2.1 Materials

Chlorsulfuron was a commercial sample (Dr Ehrenstorfer GmbH); *o*-chlorobenzenesulfonamide was obtained by macroscopic hydrolysis of chlorsulfuron in methanolic solution in the presence of hydrochloric acid (1 M) at 50°C over 4 h. 4-Methoxy-6-methyl-1,3,5-triazine-2-amine was a generous gift of G.E.R.A.P., Perpignan. Metsulfuron-methyl was extracted with dichloromethane from a commercial formulation (Allie 200 g kg^{-1} WG). Methyl *o*-sulfamoylbenzoate and saccharin were obtained from Aldrich. *o*-Sulfamoylbenzoic acid was obtained by heating a basic saccharin solution at 100°C for 7 h.[14] The progress of the reaction was monitored by thin layer chromatography. The solution was cooled, acidified with hydrochloric acid and left to stand for 12 h. The crystals formed were washed with light-petroleum distilled, dried, and recrystallized from anhydrous ether.

2.2 Hydrolysis of chlorsulfuron and metsulfluron-methyl

All solutions were prepared in deionised water distilled from alkaline potassium permanganate. Aqueous solutions of chlorsulfuron and metsulfuron-methyl, of initial concentration 6×10^{-5} M, were prepared at the required pH, using hydrochloric acid, sodium hydroxide, or an appropriate buffer: sodium monochloroacetate, sodium formate, sodium acetate, borax and sodium hydrogen phosphate. Ionic strength was maintained at 1·0 by addition of potassium chloride.

The process of reaction was monitored by recording the variation of UV absorbance vs time. This absorbance corresponds to the disappearance of the substrate or the formation of the products. HPLC analysis of samples (20 μl) at determined times was carried out on acidic ($[H_3PO_4] = 10^{-3}$ M) and basic ($[NaOH] = 10^{-2}$ M) solutions of chlorsulfuron or metsulfuron-methyl which were maintained at 25°C. A 250 mm × 4 mm i.d. Hamilton PRP-1 polystyrene-divinylbenzene column fitted with UV detectors was used. The mobile phase was acetonitrile + phosphoric acid (10^{-3} M) (60 + 40 by volume) at a flow-rate of 1 ml min^{-1}.

TABLE 1
Retention Time of Chlorsulfuron, Metsulfuron-Methyl and Their Degradation Products

Products	*R.T. (min)*
Chlorsulfuron	11·7
4-Methoxy-6-methyl-1,3,5-triazine-2-amine	2·3
o-Chlorophenylsulfonylcarbamic acid	6·3
o-Chlorobenzenesulfonamide	5·1
Metsulfuron-methyl	9·7
Methyl *o*-sulfamoylbenzoate	5·5
o-sulfamoylbenzoic acid	3·5
Saccharin	3·1
o-Methoxycarbonylphenylsulfonylcarbamic acid	6·8

UV detection: 220 nm·

3 RESULTS

3.1 Rate-constants measurements

At acidic pH values, the change with time of the ultraviolet spectra of solutions of chlorsulfuron and metsulfuron-methyl exhibited two consecutive reactions. The pseudo-first-order rate constants were measured at 266 nm for the first reaction and, for the second one, at 253 nm, the isobestic point of the first reaction.

In basic media, the change with time of the UV spectra showed a single reaction whose rate constant was determined at 270 nm.

3.2 pH-rate profile

At acidic pH values, the pH rate profile involved two linear parts for each reaction (Fig. 2); their slopes are

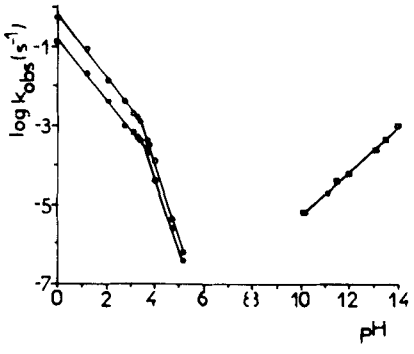

Fig. 2. pH-log rate profile for the hydrolysis of chlorsulfuron at 25°C and at ionic strength μ = 1 (potassium chloride). (○) First reaction; (●) second reaction.

TABLE 2
Rate Constants at 25°C in Acidic Hydrolysis of Metsulfuron-Methyl

pH	$\log k^1_{obs}$ (s^{-1})	$\log k^2_{obs}$ (s^{-1})
1·21	−1·21	−1·87
2·10	−1·80	−2·64
2·80	−2·20	−3·30
3·12	−2·40	−3·52
3·30	−2·80	−3·63
3·40	−3·00	−3·74
3·74	−3·74	−3·96
3·78	−4·00	−3·70
4·03	−4·40	−4·40
4·75	−5·50	−5·60
5·20	−6·30	−6·40

respectively: for the disappearance of chlorsulfuron −0.78 ($r = 0{\cdot}99$) and −1·91 ($r = 0{\cdot}98$); for the cleavage of the intermediate −0·81 ($r = 0{\cdot}98$) and −1·70 ($r = 0{\cdot}99$). For metsulfuron-methyl the results are reported in Table 2. The experimental profile is similar to that obtained with chlorsulfuron.

In basic media, the pH-rate profile is a straight line of slope 0·60 for chlorsulfuron and 0·57 for metsulfuron-methyl (Fig. 2).

3.3 Investigation of a general acid-base catalysis

The acidic hydrolysis of chlorsulfuron and metsulfuron-methyl is not subject to a general acid-base catalysis since the rate constants are independent of the concentrations of the buffers used (chloroacetate, formate or acetate) at constant pH (Table 3).

Similarly, the basic hydrolysis of the two herbicides does not involve a general catalysis, since their rate constants in phosphate buffer at pH 12 are close to that obtained in sodium hydroxide at the same pH (5×10^{-5} and 6×10^{-5} s^{-1}).

3.4 Entropy of activation and deuterium solvent isotope effect

The rate constants in hydrochloric acid (1 M) have been measured at four temperatures (15°, 25°, 35°, 45°C), from which the energy and the entropy of activation have been determined.

For chlorsulfuron:

$E_a = 57$ KJ mole^{-1}, $\Delta S^{\neq} = -130$ J mole^{-1} K^{-1} (first reaction)

$E_a = 65$ KJ mole^{-1}, $\Delta S^{\neq} = -88$ J mole^{-1} K^{-1} (second reaction)

TABLE 3
General Acid-Base Catalysis for Chlorsulfuron at 25°C in Sodium Chloroacetate, Sodium Formate and Sodium Acetate

Buffers	*pH*	[*B*] (*mol litre*$^{-1}$)	k^1_{obs} (10^6 s^{-1})	k^2_{obs} (10^6 s^{-1})
Chloroacetate	2·80	0·50	6300	500
		0·25	6320	510
		0·10	6290	513
		0·05	6340	520
	3·78	0·50	100	200
		0·25	98	205
		0·10	97	210
		0·05	99	212
Formate	3·40	0·50	2000	180
		0·25	2040	183
		0·10	5060	188
		0·05	2030	180
	4·03	0·50	42	42
		0·25	41	44
		0·10	45	41
		0·05	43	43
Acetate	4·75	0·50	3·09	2·50
		0·25	3·16	2·55
		0·10	3·37	2·36
		0·05	3·30	2·67
	5·20	0·50	0·56	0·42
		0·25	0·52	0·43
		0·10	0·50	0·44
		0·05	0·53	0·42

for metsulfuron-methyl:

$E_a = 58$ KJ mole^{-1}, $\Delta S^{\neq} = -134$ J mole^{-1} K^{-1} (first reaction)

$E_a = 66$ KJ mole^{-1}, $\Delta S^{\neq} = -92$ J mole^{-1} K^{-1} (second reaction)

The solvent isotope effects k_{H_2O}/k_{D_2O} measured in hydrochloric acid (10^{-2} M) are: for chlorsulfuron $k_{H_2O}/k_{D_2O} = 0.70$ (first reaction), $k_{H_2O}/k_{D_2O} = 0.76$ (second reaction) and for metsulfuron-methyl $k_{H_2O}/k_{D_2O} = 0.8$ (first reaction), $k_{H_2O}/k_{D_2O} = 0.85$ (second reaction).

3.5 Identification of the end products of hydrolysis

To identify the products of acidic hydrolysis, the changes of solutions of chlorsulfuron and metsulfuron-methyl in phosphoric acid (10^{-3} M) at 25°C were followed by HPLC fitted with a UV detector. A decrease in chlorsulfuron or metsulfuron-methyl until complete disappearance was observed at 220 nm. Simultaneously, two products appeared, an *s*-triazine derivative and an intermediate which was hydrolysed afterwards to give a final stable product whose retention time was identical to that of sulfonamide. This derivative was identified as *o*-chlorobenzenesulfonamide for chlorsulfuron and methyl *o*-sulfamoylbenzoate for metsulfuron-methyl (Figs 3 and 4).

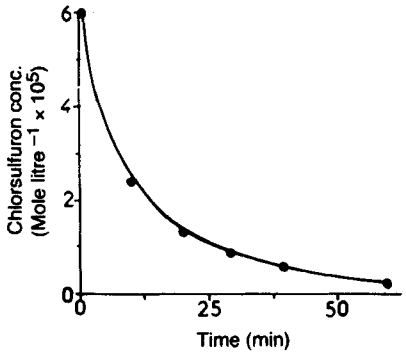

Fig. 3. Acidic hydrolysis of chlorsulfuron. T = 25°C; $[H_3PO_4] = 10^{-3}$ M.

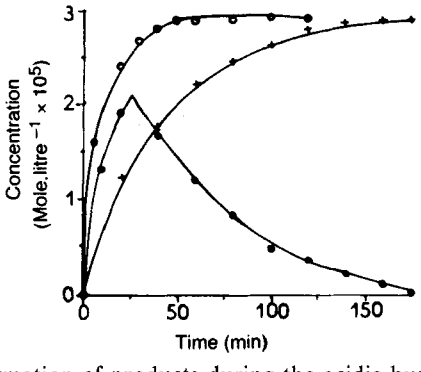

Fig. 4. Formation of products during the acidic hydrolysis of chlorsulfuron. T = 25°C; $[H_3PO_4] = 10^{-3}$ M; (○) 4-methoxy-6-methyl-1,3,5-triazine-2-amine. (+) *o*-chlorobenzenesulfonamide; (●) *o*-chlorophenylsulfonylcarbamate.

The rate constants of the formation of the two end-products of hydrolysis (*s*-triazine and sulfonamide) were calculated from HPLC experiments and were close to those measured by UV spectrophotometry for the first and the second reaction. For example, at pH 3 and 25°C, the rate constants of the formation of 4-methoxy-6-methyl-1,3,5-triazine-2-amine and of *o*-chlorobenzenesulfonamide were respectively $2{\cdot}3 \times 10^{-3}$ and $1{\cdot}5 \times 10^{-3}$ s^{-1} by HPLC and 2×10^{-3} and 10^{-3} s^{-1} for the first and the second reaction by spectrophotometry.

Therefore, under the experimental conditions used, chlorsulfuron and metsulfuron-methyl were converted quantitatively and irreversibly to sulfonamide and *s*-triazine derivatives.

Moreover, it was confirmed that the *s*-triazine and the sulfonamide were stable in acidic media and that the ultraviolet specrum obtained at the completion of a kinetic experiment was identical to that of an authentic sample of a mixture of the two products.

To identify the end products of hydrolysis in basic media, the changes of solutions of the two herbicides in sodium hydroxide (10^{-2} M) were followed by HPLC. Complete disappearance of chlorsulfuron and of metsulfuron-methyl was observed with the simultaneous appearance of a stable end product (Fig. 5). The reaction seems to be a nucleophilic substitution of the methoxy group of the *s*-triazine ring, in agreement with the results of Sabadie.[12]

As a proof, the solution of the end products was acidified to pH 1 and its change with time was examined. Two consecutive reactions were observed, with rate constants close to those of the acid hydrolysis of the two herbicides. Moreover, the UV spectrum at the end of the reaction was similar to that of the end products of the acidic hydrolysis. Thus, the acidification of the end products of the basic hydrolysis led to the 4-hydroxy-6-methyl-1,3,5-triazine-2-amine and the *o*-chlorophenylsulfonylcarbamic acid for chlorsulfuron or *o*-methoxycarbonylphenulsulfonylcarbamic acid for metsulfuron-methyl. Afterwards the two carbamic acids were hydrolysed to sulfonamide derivatives and carbon dioxide.

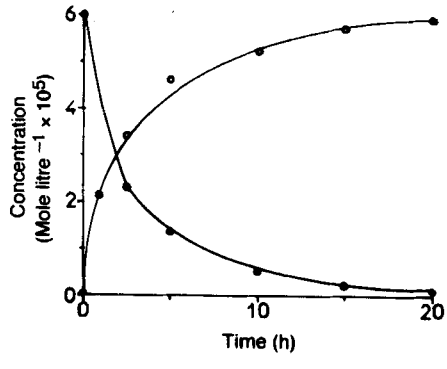

Fig. 5. Basic hydrolysis of chlorsulfuron. T = 25°C; [NaOH] = 10^{-2} M; (●) chlorosulfuron; (○) 1-(2-chlorophenylsulfonyl)-3-(4-hydroxy-6-methyl-1,3,5-triazin-2-yl) urea.

4 DISCUSSION AND MECHANISM

4.1 Acidic hydrolysis

4.1.1 First reaction

The mechanism should be consistent with:

- a pH-rate profile that shows a change of slope from 1 to 2 as the pH increases
- a lack of general acid-base catalysis
- a deuterium solvent isotope effect less than unity

The mechanism of Fig. 6 is expected. The first reaction leads to the carbamic acids and the *s*-triazine derivatives. The pKa_1 of the NH group being in the range of the pH measurements, the substrate exists in the two forms, neutral and anionic. The attack of water on the carbonyl group of the neutral reactant is made easier by protonation of the oxygen. If the various proton transfer equilibria in this mechanism are established rapidly relative to the rate of the other reactions and if we assume that the attack of water is the rate-determining step, the following equation may be derived for the observed rate constant:

$$k^1_{obs} = \frac{k_2/K_{a_2}[H_3O^+]^2}{[H_3O^+] + K_{a_1}}$$

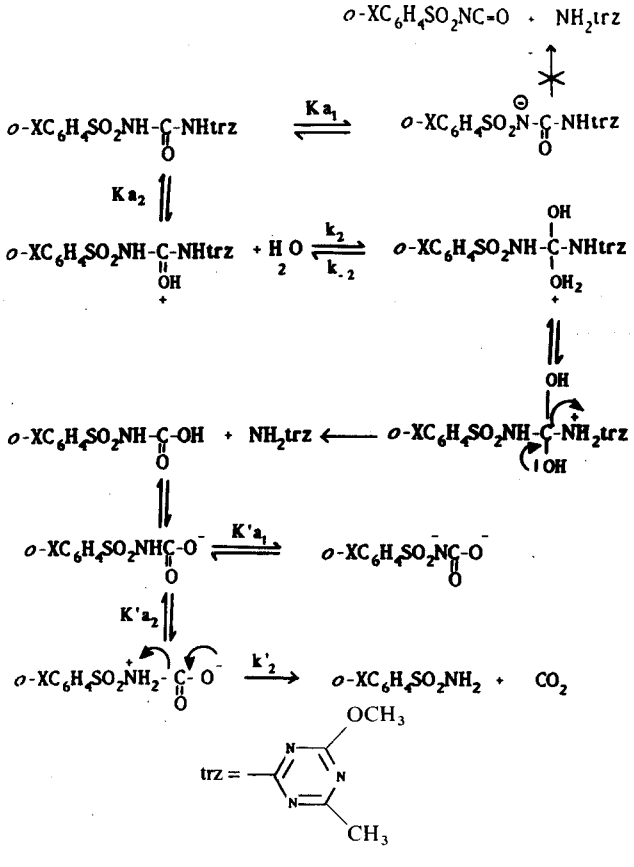

Fig. 6. Mechanism of acidic hydrolysis of chlorsulfuron and metsulfuron-methyl.

This is in agreement with the pH-rate profile since:

- if $[H_3O^+] \gg K_{a_1}$, $\log k^1_{obs} = -pH + \log k_2/K_{a_2}$: line of slope $= -1$
- if $[H_3O^+] \ll K_{a_1}$, $\log k^1_{obs} = -2\,pH + \log k_2/K_{a_2} \cdot K_{a_1}$: line of slope $= -2$.

For chlorsulfuron: $k_2/K_{a_2} = 9{\cdot}7 \times 10^{-3}$

$$K_{a_1} = 1{\cdot}6 \times 10^{-4}$$

The value of 3·6 for pK_{a_1} calculated from the kinetics is close to values in the literature.[3,15]

The line in Fig. 2 was drawn from this equation and these values.

For metsulfuron-methyl: $k_2/K_{a_2} = 6{\cdot}6 \times 10^{-3}$

$$K_{a_1} = 4{\cdot}9 \times 10^{-4}$$

The calculated value of 3.2 for pK_{a_1} is close to that determined by spectrophotometry ($pK_{a_1} = 3{\cdot}1$).

The pH-profile shows that the neutral form of the substrate is the reactant: formation of *o*-chlorophenylsulfonylisocyanate from the anion does not occur.

The proton transfers being established before the rate-determining step, the deuterium solvent isotope effect is less than 1 and the reaction is not subject to general acid-base catalysis.

4.1.2 Second reaction

As for the first reaction, the pH-profile involves two straight lines of slopes close to -1 and -2. The mechanism may again be consistent with a solvent isotope effect less than 1 and with the lack of general acid-base catalysis. The mechanisms of Fig. 6, from the carbamate anion to the end products is expected.

The carbamate anion is in equilibrium with a dianion after ionization of the NH group. The loss of carbon dioxide is made easier by protonation of the NH group. If the rate-determining step is the formation of the sulfonamide, the following equation may be derived for the disappearance of the carbamate anion:

$$k^2_{obs} = \frac{k'_2/K'_{a_2}[H_3O^+]^2}{[H_3O^+] + K'_{a_1}}$$

For chlorsulfuron: $k'_2/K'_{a_2} = 4 \times 10^{-3}$

$$K'_{a_1} = 7 \times 10^{-5}$$

This equation being similar to that of the first reaction, is consistent with the pH-rate profile. Since no proton transfer occurs in the rate-determining step, the solvent isotope effect is less than 1 and the reaction is not subject to general catalysis.

The pKa of the NH group is less by 8 to 9 units than the pKa of this group in *N*-phenylcarbamates,[16] due to the high withdrawing power of the SO_2 group. For the same reason, the pKa of the carboxyl group is much less than the pKa of phenyl carbamic acids (pKa = 4·2 for

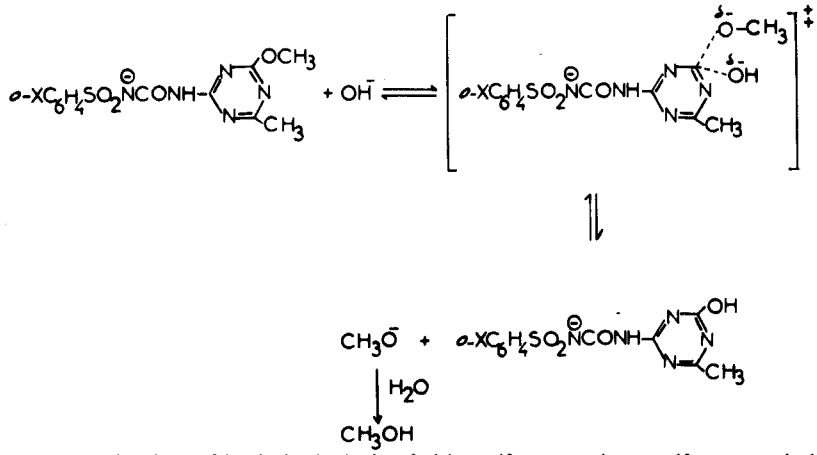

Fig. 7. Mechanism of basic hydrolysis of chlorsulfuron and metsulfuron-methyl.

N-*p*-nitrophenylcarbamic acid)[17] and thus the reactant is the carboxylate anion, even in the acidic media used.

4.2 Basic hydrolysis

The lack of *o*-sulfamoylbenzoic acid and saccharin at the end of the hydrolysis under either acid or basic conditions for either herbicide proves that the ester function of the methoxycarbonyl group of metsulfuron-methyl is stable and thus that the herbicides undergo the same chemical hydrolysis process.

The pH-rate profile is a straight line of slope about 0·6. Then the rate constant increases with the concentration of hydroxide ion and a S_N2 mechanism is proposed (Fig. 7).

5 CONCLUSION

The rate of acidic hydrolysis of chlorsulfuron and metsulfuron-methyl is highly pH- and temperature-dependent. Highly acidic pH values increase the rate of hydrolysis, the neutral form of the substrate being the active one. The acidic hydrolysis of the two herbicides involves two successive reactions. The first one involves the breakdown of the sulfonylurea bridge and leads to 4-methoxy-6-methyl-1,3,5-triazin-2-amine and *o*-chlorophenylsulfonylcarbamic acid for chlorsulfuron or *o*-carboxymethylphenylsulfonylcarbamic acid for metsulfuron-methyl. The second one involves the degradation of the carbamate derivatives to yield, respectively, *o*-chlorophenylsulfonamide and methyl *o*-sulfamoylbenzoate. The absence of *o*-sulfamoylbenzoic acid and saccharin proves that the ester function of the *o*-carboxymethyl group of metsulfuron-methyl is stable.

At pH values > 10, the hydrolysis of the two herbicides shows the occurrence of only one reaction, the nucleophilic substitution of the methoxy group of the *s*-triazine by a hydroxide group. Acidification of the end-solution of basic hydrolysis of each herbicide leads to two successive reactions whose rate constants are of the same order of magnitude as those of the acidic hydrolysis.

It is important to stress that under these conditions, *o*-sulfamoylbenzoic acid and saccharin have not been detected, confirming the stability of the ester function of the *o*-carboxymethyl group of metsulfuron-methyl.

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