

Flazasulfuron: Alcoholysis, Chemical Hydrolysis, and Degradation on Various Minerals

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The herbicide flazasulfuron undergoes rapid alcoholysis. High yields of the corresponding carbamate and aminopyrimidine are obtained after the alcoholysis process (methanol or ethanol) at 30 °C, in the course of which the concomitant rearrangement reaction remains minor. Hydrolysis (pH ranging from 5 to 11) of flazasulfuron at 30 °C principally involves the rearrangement into urea after elimination of SO₂ and can lead, in a small proportion, to both aminopyrimidine and pyridinesulfonamide. First-order kinetics correctly describes the rates of alcoholysis and hydrolysis. The sulfonylurea-bridge contraction and final transformation into the correspondent amine were evaluated with a first-order kinetics hypothesis. Transformations in amine and urea in aqueous medium are pH dependent. The chemical degradation of flazasulfuron on various dry minerals (calcium bentonite, kaolinite, silica, montmorillonite, and alumina) was investigated at 30 °C. The rearrangement reaction is the only one observed in the presence of kaolinite and alumina. However, hydrolysis and rearrangement have the same reaction rate in the presence of silica. The hydrolysis paths of flazasulfuron are comparable to the ones described for rimsulfuron.

KEYWORDS: Flazasulfuron; alcoholysis; hydrolysis; degradation

INTRODUCTION

Sulfonylureas are a relatively recent group of herbicides used essentially in cereal crops. Because of their low application rates (10–50 g ha⁻¹), low mammalian toxicity, and high herbicidal activity, they are of high interest worldwide. Sulfonylureas are based on the general structure R₁–SO₂–NH–CO–NH–R₂, where the R₁ group can be either an aliphatic chain, an aromatic, or a heterocyclic moiety connected by the sulfonylurea bridge to a pyrimidine or triazine heterocycle (the R₂ moiety) (1).

Approximately 25 sulfonylurea herbicides are already developed, and 4 pyridylsulfonylureas (R₁ = pyridine; R₂ = pyrimidine) have been commercialized (Figure 1).

An original hydrolysis process (SO₂ elimination and rearrangement into an asymmetric urea) has been described for rimsulfuron (2–6) and for flupyrsulfuron-methyl (7–9). This reaction is not observed for the nicosulfuron, where, in this case, hydrolysis of the sulfonylurea bridge is predominant (10).

Flazasulfuron, the fourth of this group, *N*-[[[4,6-dimethoxy-2-pyrimidinyl]amino]carbonyl]-3-(trifluoromethyl)-2-pyridine-sulfonamide, was initially developed for the control of several grasses in pasture (11). It is, actually, the only sulfonylurea herbicide authorized in France for use in vineyards. It is applied on vineyards >4 years old, postwinter, at the rate of 50 g ha⁻¹ (12).

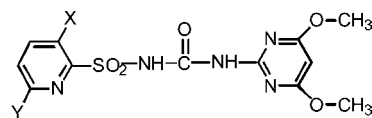


Figure 1. Structure of some pyridylsulfonylureas.

The aim of this study is to determine the major degradation pathway after the investigation of the alcoholysis, chemical hydrolysis, and behavior on minerals of flazasulfuron. The results are compared with those described for other pyridylsulfonylureas.

MATERIALS AND METHODS

Chemicals. For each compound, mass spectrometric data and melting points are shown in Table 1.

Flazasulfuron (1) was isolated from the herbicide formulation AÏKIDO (water dispersible granules, 25% ai). An aliquot of 2 g of AÏKIDO was gently shaken with 40 mL of CHCl₃ for 3 h and filtered on clarsol. CHCl₃ was evaporated to dryness under vacuum. Recrystallization was carried out in CHCl₃, and a high-purity, white crystalline powder was obtained (yield = 80%).

2-Amino-4,6-dimethoxypyrimidine (2) was obtained from Sigma-Aldrich, St. Quentin, France.

3-(Trifluoromethyl)-2-pyridylsulfonylmethylcarbamate (4a) and 3-(trifluoromethyl)-2-pyridylsulfonylethylcarbamate (4b) were prepared as follows: Flazasulfuron (500 mg) was dissolved in 100 mL of dry alcohol (CH₃OH or C₂H₅OH) and maintained at 60 °C for 12 h. The solution was evaporated to dryness under vacuum, and the residues

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Table 1. Mass Spectrometry Data (Direct Injection, EI/70 eV), Melting Point (mp), and Relative HPLC Retention Times (t_R)

compd	mp (°C)	mass spectrometric fragments (ions m/z , relative intensity)	t_R
1 ^a	172	407 [M ₁ ⁺ , 54], 300 [CF ₃ - C ₅ H ₃ N - NH - C ₄ HN ₂ (OCH ₃) ₂ ⁺ , 45], 231 [C ₅ H ₃ N - NH - C ₄ HN ₂ (OCH ₃) ₂ ⁺ , 60], 155 [NH ₂ - C ₄ HN ₂ (OCH ₃) ₂ ⁺ , 95], 146 [CF ₃ - C ₅ H ₃ N ⁺ , 100]	1.00
2		commercial compound	0.61
3	147	227 [M ₃ ⁺ , 9], 162 [CF ₃ - C ₅ H ₃ N - NH ₂ ⁺ , 100], 146 [CF ₃ - C ₅ H ₃ N ⁺ , 94], 126 [CF ₂ - C ₅ H ₃ N ⁺ , 57], 69 [CF ₃ ⁺ , 48]	1.41
4a		284 [M _{4a} ⁺ , 58], 253 [CF ₃ - C ₅ H ₃ N - SO ₂ - NH - CO ⁺ , 44], 146 [CF ₃ - C ₅ H ₃ N ⁺ , 100], 126 [CF ₂ - C ₅ H ₃ N ⁺ , 49], 69 [CF ₃ ⁺ , 15]	1.30
4b		298 [M _{4b} ⁺ , 60], 253 [CF ₃ - C ₅ H ₃ N - SO ₂ - NH - CO ⁺ , 47], 227 [CF ₃ - C ₅ H ₃ N - SO ₂ - NH ⁺ , 36], 146 [CF ₃ - C ₅ H ₃ N ⁺ , 100], 126 [CF ₂ - C ₅ H ₃ N ⁺ , 60]	1.05
5	141	343 [M ₅ ⁺ , 3], 300 [CF ₃ - C ₅ H ₃ N - NH - C ₄ HN ₂ (OCH ₃) ₂ ⁺ , 27], 231 [C ₅ H ₃ N - NH - C ₄ HN ₂ (OCH ₃) ₂ ⁺ , 100], 146 [CF ₃ - C ₅ H ₃ N ⁺ , 56], 126 [CF ₂ - C ₅ H ₃ N ⁺ , 29]	1.15
6	87	300 [M ₆ ⁺ , 90], 281 [CF ₂ - C ₅ H ₃ N - NH - C ₄ HN ₂ (OCH ₃) ₂ ⁺ , 20], 231 [C ₅ H ₃ N - NH - C ₄ HN ₂ (OCH ₃) ₂ ⁺ , 100], 188 [?, 45], 146 [CF ₃ - C ₅ H ₃ N ⁺ , 24]	0.52

^a Retention time = 6.5 min.

were dispersed in Na₂CO₃ aqueous solution (0.2 M, 40 mL) and then extracted by diethyl ether (4 × 20 mL), giving extract E_A.

The aqueous layer is then acidified with hydrochloric acid (HCl) to pH 2 and extracted by diethyl ether (4 × 10 mL). The organic phases were dried and partially evaporated, giving the corresponding carbamate (4a or 4b) as crystals, which are filtered and dried.

Extract E_A was washed with aqueous 0.2 M HCl solution (to eliminate product 2) and dried. The pure urea 5 [N-(4,6-dimethoxy-pyrimidin-2-yl)-N-[3-(trifluoromethyl)-2-pyridinyl]urea] crystals, produced after partial evaporation of diethyl ether, were collected by filtration and vacuum-dried (20 mg).

Sulfonamide (3) [3-(trifluoromethyl)-2-pyridinesulfonamide] was prepared from a methanolic solution of carbamate 4a (15 mL, 170 mg), 10 mL of water and 200 mg of dry Na₂CO₃ were added, and the mixture was heated at 100 °C for 2 h; after cooling, the solution was extracted by diethyl ether (4 × 10 mL). Colorless needles (90 mg) of sulfonamide 3 were obtained by crystallization and filtration.

Amine (6) [N-(3-Trifluoromethyl)-2-pyridinyl]-4,6-dimethoxy-2-pyrimidineamine]. Flazasulfuron (500 mg) dissolved in 100 mL of aqueous 0.2 M Na₂CO₃ was heated at 40 °C for 50 h. After cooling, the formed amine was extracted with diethyl ether (5 × 10 mL). After evaporation of the solvent, recrystallization was carried out in diethyl ether (320 mg).

Minerals. Commercially obtained kaolinite and calcium bentonite (Prolabo), silica gel (Kieselgel 60, Merck), montmorillonite K 10 (Fluka), and alumina (aluminum oxide 90 active neutral, Merck), were oven-dried (100 h at 100 °C) before use.

Experimental Conditions for Alcoholysis and Hydrolysis. All experiments were kept in a thermoregulated water bath at 30 °C using an initial flazasulfuron concentration of ~0.12 mmol L⁻¹. Dry alcohol (CH₃OH or C₂H₅OH) was used for alcoholysis studies. Hydrolysis experiments were conducted using a pH ranging from 5 to 11 for flazasulfuron (1). The pH of the unsterilized aqueous solutions was controlled by the appropriate buffer system: phosphate 1/15 M (pH 5, 6, 7, or 8); sodium carbonate/sodium bicarbonate 0.2 M (pH 9 or 10); sodium bicarbonate/sodium hydroxide 0.2 M (pH 11). Each test was carried out twice.

Herbicide Deposition. Deposition on minerals (typically 10⁻⁵ mol g⁻¹) was performed using either a dry method (thorough crushing of the powder mixture) or a liquid method (herbicide dissolution into acetone, addition of the mineral, and then evaporation to dryness under vacuum at room temperature for 60 min). The herbicide-permeated powder (typically 3 g) was enclosed in 5-mL glass tubes that were sealed and kept at 30 °C, under continuous rotation-stirring. Each experiment was run in duplicate.

Preparation of Analytical Samples. Alcoholysis samples (2 mL) were evaporated to dryness under vacuum and stirred for 30 min with 5 mL of water/chloroform/acetic acid (2:3:0.1). Hydrolysis analytical samples (2 mL) underwent similar extraction stirring for 30 min in 3 mL of chloroform/acetic acid (3:0.1). Analytical mineral samples (typically 30 mg) were stirred for 30 min with 5 mL of chloroform/water/acetic acid (3:2:0.05).

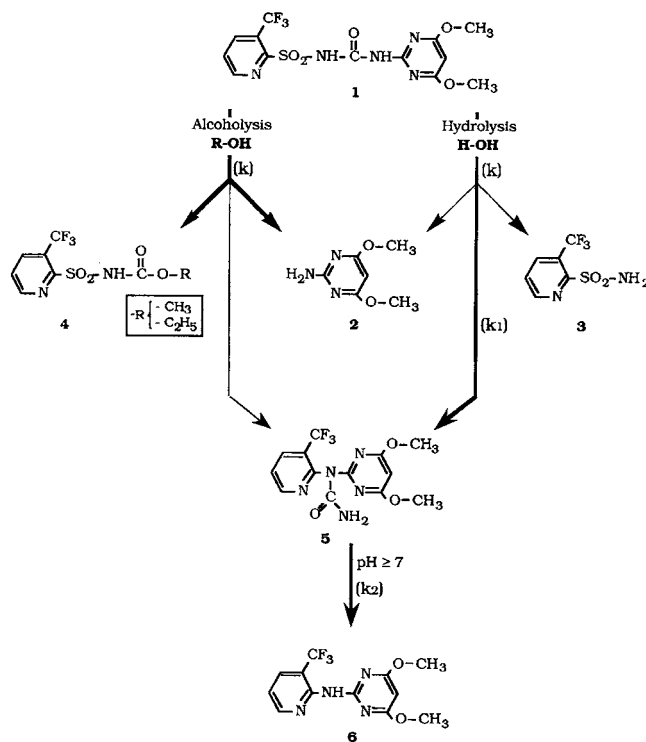


Figure 2. Proposed pathways of alcoholysis and chemical hydrolysis of flazasulfuron (1) at 30 °C.

Analytical Technique. The organic solutions were analyzed in duplicate with a high-performance liquid chromatograph using a normal phase column (Lichrosorb, reference no. 5 m-L5-25F, 25 cm), UV detector system (245 nm), and a mobile phase of isooctane/absolute ethanol/acetic acid (80:20:0.3) at a flow rate of 1.5 mL min⁻¹. Dosage accuracy was satisfactory for compounds 1, 2, 4, 5, and 6 (±2%). Pyridylsulfonamide 3, although detected, was generally not quantified. Retention times are described in Table 1.

RESULTS AND DISCUSSION

Alcoholysis. Flazasulfuron (1) undergoes a rapid alcoholysis (Figure 2) when dissolved in dry methyl alcohol (CH₃OH) or ethyl alcohol (C₂H₅OH) at 30 °C (Table 2). The flazasulfuron degradation rate can be described satisfactorily by first-order kinetics, and the rate constant ($k = 0.40 \text{ day}^{-1}$; Figure 3) is comparable to the one previously described for nicosulfuron (10).

The carbamate 4 (Figure 2) is the major alcoholysis product (respectively, 88 and 91%) as already described for most of

Table 2. Alcoholysis and Hydrolysis of Flazasulfuron at 30 °C

		alcoholysis		hydrolysis							
		CH ₃ OH	C ₂ H ₅ OH	pH 5	pH 6	pH 7	pH 8	pH 9	pH 10	pH 11	
activity	half-life (days)	1.7	2.5	1.3	4.0	5.7	5.6	4.1	1.3	0.19	
relative selectivity ^a (%)	rearrangement	12	9	90	95	97	98	99	100	100	
	hydrolysis			10	5	3	2	1	0	0	
	alcoholysis	88	91								

^a Relative selectivity measured the percentage of each observed transformation.

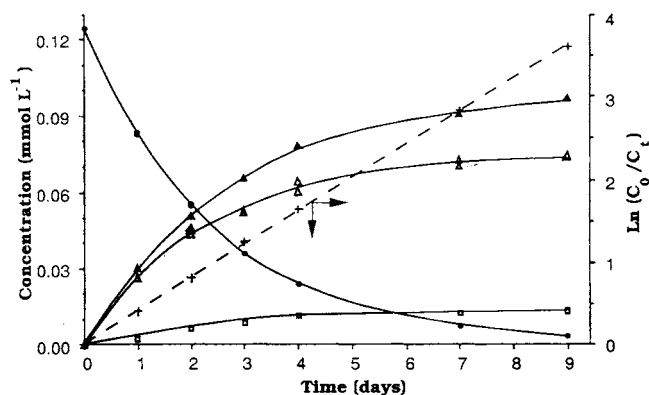


Figure 3. Alcoholysis of flazasulfuron-methyl alcohol at 30 °C: concentration of flazasulfuron (1) (●), ethylcarbamate 4 (▲), aminopyrimidine 2 (△), and urea 5 (□) as a function of time. First-order kinetics line was established from the loss of flazasulfuron (-+-).

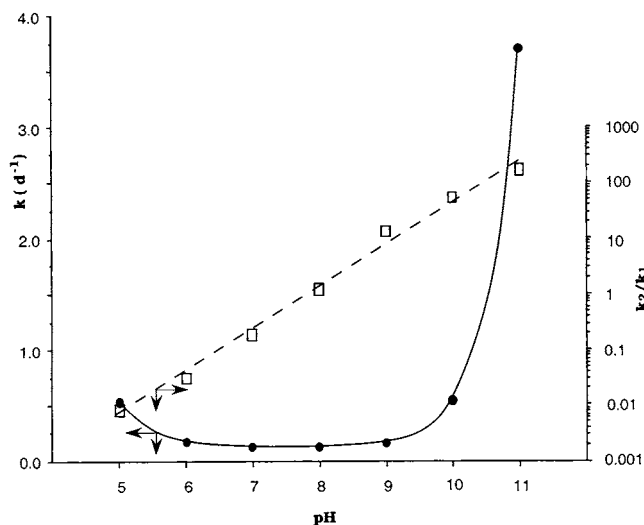


Figure 4. Hydrolysis at 30 °C of flazasulfuron (1) as a function of pH. Rate constant k (day^{-1}) (●) and reaction rate ratios k_2/k_1 (□) were established from the maximum measured for intermediate urea 5 (first-order kinetic hypothesis).

the sulfonylurea herbicides (10, 13, 14). The yield for the aminopyrimidine 2 formation is a little lower than the carbamate (Figure 3), certainly due to analytical losses.

Concomitant rearrangement reaction remains minor and leads to urea 5, the conversion of which into amine 6 is not observed.

No concomitant hydrolysis reaction is observed as shown by the absence of sulfonamide in such conditions.

Hydrolysis. Flazasulfuron is relatively unstable in aqueous solution at 30 °C. As for all sulfonylureas, there is a relationship between the degradation rate and the pH. This effect is illustrated in Figure 4. Under the same pH conditions, flazasulfuron hydrolysis is faster than nicosulfuron hydrolysis (10), but

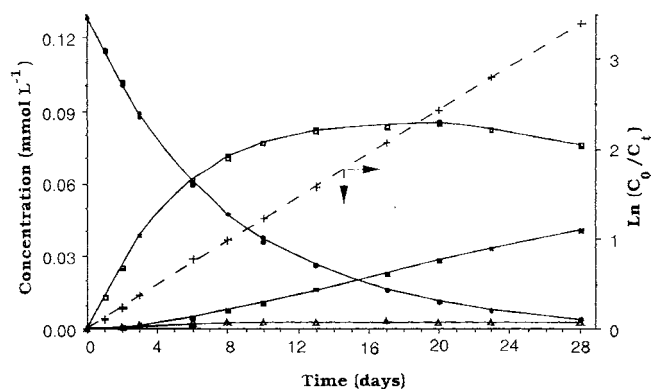


Figure 5. Hydrolysis of flazasulfuron at 30 °C and pH 7: concentration of flazasulfuron (1) (●), aminopyrimidine 2 (△), and urea 5 (□) as a function of time. First-order kinetics line was established from the loss of flazasulfuron (-+-).

comparable rates have been reported for rimsulfuron (3). As an example, rate constants k (day^{-1}) at pH 7 and 30 °C are about 0.002, 0.25, and 0.25 for nicosulfuron, flazasulfuron, and rimsulfuron, respectively. The flazasulfuron degradation rate reaches a minimum for pH 6–9. The degradation is quicker under acidic condition ($\text{pH} \leq 6$) and mainly in alkaline medium ($\text{pH} \geq 9$). Anyway, the reaction rates can be described with first-order kinetics (Figure 5).

The sulfonylurea classical hydrolysis pathway (formation of compounds 2 and 3) is minor: it represents only 10% under acidic conditions and is not observed at $\text{pH} \geq 10$ (Table 2).

The sulfonyl-bridge contraction and the rearrangement in urea 5 are the major modes of degradation (>90%) (Figure 2). The ratio k_2/k_1 corresponding to the kinetics of urea 5 transformation into amine 6 (Figures 2 and 4) was evaluated, with a first-order kinetics hypothesis. Figure 4 shows the important relationship between the successive transformations $1 \rightarrow 5 \rightarrow 6$ and pH. The formation of compound 6 was weak under acidic conditions; under neutral conditions (pH 7 or 8), the urea 5 reaches a maximum and is converted into amine 6 (Figure 5); at $\text{pH} \geq 8$, the urea 5 appears to be very reactive and is quickly transformed into the more stable amine 6. This reaction pathway has already been described for rimsulfuron (3).

Degradation on Various Minerals. The minerals used in this study are selected to represent a wide range of surface properties. The sulfonylurea is deposited, either by the dry method (thorough crushing of the powder mixture) or by the liquid method (herbicide dissolution in acetone, then evaporation to dryness of the mineral suspension). The liquid method gives a homogeneous layer of herbicide on the mineral surface that promoted its adsorption but reduces its extraction rate and the half-life of the herbicide. Finally, this method gives an acceptable correlation with pseudo-first-order kinetics. All of the results are shown in Table 3. Calcium bentonite (Ca^{2+}) remains completely inactive, as already observed for nicosul-

Table 3. Degradation of Flazasulfuron after Deposition on Various Dry Minerals at 30 °C

	dry deposition method				liquid deposition method			
	flazasulfuron (1)		selectivity		flazasulfuron (1)		selectivity	
	initial recovery (%)	half-life (days)	re/hy ^a	k ₂ /k ₁ ^b	initial recovery (%)	half-life (days)	re/hy ^a	k ₂ /k ₁ ^b
calcium bentonite	100	∞ ^c			97	∞ ^c		
kaolinite	90	60 ^b	100/0	45	85	2.4	100/0	3
silica	97	9.7	57/43	0.25	81	10.7	45/55	0.25
alumina	97	3.6	100/0	0.15	93	0.43	100/0	0.01
montmorillonite	86	3.5			73	1.3		

^a Rearrangement/hydrolysis. ^b Approximate value. ^c Inactive mineral.

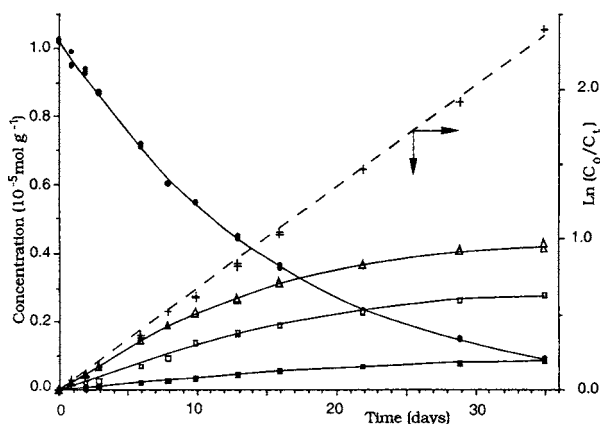


Figure 6. Degradation of flazasulfuron after liquid deposition on silica gel powder at 30 °C: concentration of flazasulfuron (1) (●), aminopyrimidine 2 (Δ), urea 5 (□), and amine (■) as function of time. First-order kinetics line was established from the loss of flazasulfuron (- - -)

flazasulfuron (10). On the other hand, the degradation rates of the flazasulfuron in the presence of the other minerals appear to be relatively quick. However, in the presence of kaolinite or alumina, the rearrangement process is the only one observed, but the urea 5 transformation into amine 6 is not promoted by this last mineral. On silica, the hydrolysis rate of the sulfonylurea bridge and rearrangement reaction rate are comparable (Figure 6).

Montmorillonite K10 offers a very high affinity to several compounds (essentially 2 and 6), which does not allow any accurate interpretation.

Conclusion. The alcoholysis reaction gives high yields of the corresponding sulfonylcarbamate, as already observed for another pyridylsulfonylurea, nicosulfuron (10). This reaction previously described for arylsulfonylurea (13, 14) appears to be a characteristic of all sulfonylurea herbicides.

Hydrolysis of the flazasulfuron at 30 °C is in accordance with first-order kinetics. The reaction rate reaches a minimum at pH 6–9 and increases in acidic or mainly in alkaline conditions. Hydrolysis of the sulfonylurea bridge is a minor pathway, whereas the rearrangement into urea after elimination of SO₂ is prevalent. The urea 5 can generally give the corresponding more stable amine. This uncommon hydrolysis pathway (15) has already been described for rimsulfuron (3, 4).

This hydrolysis and the urea transformation into amine were pH dependent. Under acidic conditions the urea is the major product (compounds 2, 3, and 6 appear slightly), whereas under alkaline conditions the more stable amine 6 is largely prevalent.

In the presence of several minerals the results are variable. The rearrangement reaction is the only one observed in the

presence of kaolinite and alumina. However, hydrolysis and rearrangement have the same reaction rates in the presence of silica.

All of these results lead us to envisage numerous degradation pathways in soils and consequently the eventual presence of several transformation products.

As the active function of these herbicides is known to be the sulfonylurea bridge, it seems unlikely that the degradation products identified in this study are able to present any phytotoxic activity.

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