

Metabolism of Sulfometuron-methyl in Wheat and Its Possible Role in Wheat Intolerance

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[*phenyl*-(U)-¹⁴C]Sulfometuron-methyl was metabolized in excised wheat seedlings (sensitive to sulfometuron-methyl) to [¹⁴C]methyl 2-[[[(4-(hydroxymethyl)-6-methylpyrimidin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate (HM-SM) and its carbohydrate conjugate. This metabolic pathway is consistent with sulfometuron-methyl metabolism in tolerant species such as Bermuda grass. Sulfometuron-methyl was metabolized at a slower rate than metsulfuron-methyl in wheat. When plants were exposed to [¹⁴C]methyl 4-hydroxy-2-[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate (HP-MM) and [¹⁴C]HM-SM (the primary hydroxylated wheat metabolites of metsulfuron-methyl and sulfometuron-methyl, respectively), the rate of glucose conjugation of HP-MM was much faster than the rate of glucose conjugation of HM-SM. Along with their parent compounds, both HM-SM and HP-MM are potent inhibitors of wild mustard acetolactate synthase. These results indicate that wheat intolerance to sulfometuron-methyl (but tolerance to the structurally closely related metsulfuron-methyl) reflects not only a reduced ability to hydroxylate the parent molecule but also a reduced ability to conjugate the primary toxic metabolite to a nontoxic moiety.

INTRODUCTION

Sulfometuron-methyl [methyl 2-[[[(4,6-dimethylpyrimidin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate; SM], the active ingredient of Oust herbicide, is a sulfonylurea herbicide whose target mode of action is to inhibit the plant enzyme acetolactate synthase. Some grasses (such as Bermuda grass) are tolerant of SM. Bermuda grass metabolizes SM readily (G. E. Cadwgan, internal Du Pont Communication), and this metabolic ability is a possible resistance mechanism. This ability of resistant plant species to metabolize sulfonylurea herbicides to nontoxic species is well understood (Beyer et al., 1987). Wheat, for example, is tolerant to metsulfuron-methyl [methyl 2-[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate; MM] because of its ability to catalyze hydroxylation of the phenyl ring, followed by conjugation to glucose (Beyer et al., 1987; Anderson et al., 1989).

The focus of the current work was to utilize excised wheat (a sensitive species) seedlings as a tool to explore the metabolism of SM in wheat and investigate the differential tolerance of wheat to SM and its close analog, MM.

EXPERIMENTAL PROCEDURES

Materials. [*phenyl*-U-¹⁴C]Sulfometuron-methyl (specific activity 5.90 μ Ci/mg) and [*phenyl*-U-¹⁴C]metsulfuron-methyl (specific activity 8.62 μ Ci/mg), both obtained from Du Pont NEN Products, Boston, MA, were used in these studies. Analytical standard grade SM, MM, and their primary plant metabolites were synthesized at Du Pont Agricultural Products, Wilmington, DE. Other chemicals and solvents were of reagent grade or better.

Methods. Quantitation of Radioactivity. Quantitation of radioactivity by combustion analysis has been previously described (Anderson et al., 1989). High-performance liquid chromatography (HPLC), radiochemical detection, and quantitation utilized a Ramona LS radiochemical detector (Raytest, Pittsburgh, PA). Alternatively, HPLC eluants were collected on a Foxy fraction collector (ISCO, Lincoln, NE), and radioactivity was quantitated by direct liquid scintillation counting (LSC). Radioactive components on thin-layer chromatography (TLC)

plates were located and quantitated using an Ambis plate scanner (Ambis Systems, San Diego, CA).

Growth of Wheat. Guard or Anza wheat was grown under greenhouse conditions in Metromix 350 growing medium (E. C. Geiger, Inc., Harleysville, PA).

Treatment of Wheat. Excised wheat seedlings were exposed to [¹⁴C]SM, [¹⁴C]MM, [¹⁴C]HM-SM, or [¹⁴C]HP-MM in dilute phosphate buffer (pH 7) as described in Anderson et al. (1989). Wheat seedlings were excised 7–11 days after planting, when each seedling still consisted of a single leaf blade. Seedlings were excised by cutting close to ground level with a clean razor blade and then cut again under distilled water to minimize air penetration into vascular tissue prior to placement into the uptake solution. For all experiments comparing the metabolism of SM and MM, or HM-SM and HP-MM, wheat seedlings from the same pot of wheat were used.

For metabolite generation purposes, seedlings were left in the solution for up to 1 week. Typically, the concentration of the test compound in the uptake solutions was 5 ppm. For metabolic rate comparisons, seedlings were "pulsed" with the radiolabeled test compound for 3–4 h, after which time they were placed into fresh phosphate buffer and allowed to metabolize the pulsed material for up to 5 h.

Extraction of Treated Wheat. Treated wheat seedlings were extracted using a modified Bligh–Dyer procedure (Bligh and Dyer, 1959). Typically, wheat tissue was extracted with methylene chloride/methanol (2/1 v/v) using a Tekmar Tissuemizer (Tekmar Co., Cincinnati, OH). After each of three sequential extractions, extracted wheat straw was separated from the extract by vacuum filtration; all filtrates were combined. After the extraction, 0.2-sample volumes of methylene chloride and 0.3-sample volumes of 0.1 M (NH₄)₂CO₃ were added to the combined extracts to effect phase separation. The majority of the green plant pigments partitioned into the methylene chloride phase, and the majority of the radioactivity partitioned into the alkaline aqueous/methanol phase. The aqueous phase was concentrated by rotary evaporation (50 °C) until essentially all methanol was removed and then adjusted to pH 3 with phosphoric or formic acid. Immediately, the acidified solution was applied to a C₁₈ solid-phase extraction column (SPE) (Analytichem International, Harbor City, CA). Once the entire solution had been applied and the initial filtrate collected, the column was washed with approximately 1 bed volume of distilled water (combined with

Table I. Chromatographic Behavior of Sulfometuron-methyl, Metsulfuron-methyl, and Selected Wheat Metabolites

A. Thin-Layer Chromatographic Behavior (R_f)		
compound	TLC system I ^a	TLC system II ^b
sulfometuron-methyl	0.65	0.65
HM-SM	0.32	0.51
glucose-HM-SM	—	0.18
metsulfuron-methyl	0.63	—
HP-SM	0.17	—
methyl 2-(aminosulfonyl)-benzoate	0.90	0.65
B. High-Performance Liquid Chromatographic Behavior (HPLC System 1 ^c)		
compound	retention time, min	
sulfometuron-methyl	19.4	
HM-SM	10.5	
glucose-HM-SM	5.9	
metsulfuron-methyl	18.2	
HP-SM	14.5	
glucose-HP-MM	6.6	
methyl 2-(aminosulfonyl)benzoate	4.6 ^d	

^a TLC system 1: silica gel thin-layer chromatography plates with fluorescent indicator (Merck) developed in methylene chloride/methanol/NH₄OH (28%) (144/50/6 v/v/v). ^b TLC system 2: silica gel thin-layer chromatography plates with fluorescent indicator (Merck) developed in methylene chloride/methanol/formic acid (85/15/1 v/v/v). ^c HPLC analyses were conducted on a Hewlett-Packard 1090 liquid chromatograph (Hewlett-Packard) using a 25 cm × 4.6 mm i.d. Zorbax ODS chromatographic column at a flow rate of 2 mL/min and at 40 °C. The mobile phase consisted of a linear gradient from 20% acetonitrile (A)/80% pH 2.3 water (formic acid, B) to 30% A over 20 min, followed by a 5-min wash with 90% A. ^d The retention time of methyl 2-(aminosulfonyl)benzoate was determined using the UV detector; the retention times of all other components were determined using the radiochemical detector.

first filtrate), followed by an acetonitrile wash (collected separately). This acetonitrile wash contained the majority of radioactivity.

Analysis of Wheat Extracts. After the exposure phases for both metabolite generation and pulse studies, seedlings were extracted as described above. Typically, both the methylene chloride phase and the SPE acetonitrile wash were analyzed (in TLC system 1 and in HPLC system 1, respectively; see Table I for chromatographic conditions). All HPLC analyses were carried out on a Hewlett-Packard 1090 HPLC with work station (Hewlett-Packard, Valley Forge, PA). Only the SPE acetonitrile wash was analyzed (by HPLC) in extracts of wheat from the pulse exposure experiment with [¹⁴C]HM-SM and [¹⁴C]HP-MM.

Purification of the Carbohydrate Conjugate of [¹⁴C]HM-SM. The carbohydrate conjugate of [¹⁴C]HM-SM was isolated from excised Guard wheat that had been exposed to a 5 ppm solution of [¹⁴C]SM for 7 days. One hundred and four grams of the wheat was extracted and partitioned as previously described. After the alkaline methylene chloride extraction, the aqueous phase was concentrated by rotary evaporation to remove any remaining methanol, acidified to pH 3, and extracted once with methylene chloride. Radioactive components in the remaining aqueous phase were concentrated by solid-phase extraction as described above. After concentration of the acetonitrile wash to dryness, it was resuspended in acetonitrile/pH 2.3 water (trifluoroacetic acid, TFAA) (15/85 v/v, HPLC mobile phase) and subjected to chromatography on a 25 cm × 4.6 mm i.d. Zorbax ODS column (35 °C, 2 mL/min). Thirteen repeat injections were required to run the entire sample. The fraction eluting from 15 to 17 min was collected into 100 mL of 0.1 M phosphate buffer, pH 7.4, during these repeat injections to prevent decomposition. After acidification to pH 3, SPE was used to concentrate this collected peak. The acetonitrile wash of the SPE column was reduced by rotary evaporation and N₂ evaporation and applied as a band to 500- μ m-thickness silica TLC plate with preadsorbent layer (E. Merck, Darmstadt, Germany) and developed in TLC system 2 (see Table I). Radioactive material at R_f 0.18 (the primary radiolabeled band containing around 80% of the total radioac-

tivity) was scraped, eluted with acetonitrile (plus a few milliliters of water acidified with TFAA), and again purified by HPLC in the system described above (two injections were needed). The peak eluting between 14.7 and 16.3 min was collected, diluted 3-fold with pH 2.3 water, and concentrated by SPE. After removal of the acetonitrile, the purified carbohydrate conjugate of HM-SM was analyzed by mass spectral means.

Mass Spectral Analysis. Purified Glu-HM-SM was analyzed by LC/MS-FAB on a Finnigan 8230 mass spectrometer. Mass spectral experiments were conducted essentially as described in Reiser et al. (1991).

Time Study Metabolism of SM. Excised Guard wheat was placed in a 5 ppm solution of both SM and MM. Approximately equal amounts of plant tissue were removed after 5 h and 1, 2, 3, and 4 days. Tissues were stored frozen at about -20 °C until they were analyzed.

Hydrolysis of [¹⁴C]HM-SM Isolated from Wheat. The acetonitrile wash of the SPE for the 3-day SM sample of the time study was used as a source of [¹⁴C]HM-SM. [¹⁴C]HM-SM (about 10⁵ dpm) was isolated from the acetonitrile wash by TLC. A portion of this [¹⁴C]HM-SM was applied to a silica gel TLC plate. The remainder was dissolved in 2.1 mL of water, combined with 18 μ L of 12 M HCl, and placed in a hot water bath (70 °C) for 30 min. After incubation, this hydrolysis reaction mixture was extracted with 1 volume of methylene chloride. A portion of the methylene chloride extract was applied to the same TLC plate as the "before" sample and analyzed in TLC system I.

Analysis of Treatment Solution. Remaining treatment solution (remaining when Guard wheat was left in the uptake solution for 7 days) was acidified to pH 3 by addition of HCl and immediately applied to a SPE column. The acetonitrile wash from the SPE was reduced in volume by rotary evaporation and analyzed in TLC systems 1 and 2.

Comparison of the Rates of Metabolism of SM and MM. Excised Anza wheat was placed in beakers containing uptake solutions of, respectively, [¹⁴C]SM or [¹⁴C]MM. After 3 h, the wheat was removed from these solutions, rinsed with distilled water, and placed in beakers containing fresh 0.01 M phosphate buffer, pH 7. A sample of wheat from each uptake solution was retained for analysis as the zero time sample. Thereafter, at 1, 2, 3, and 5 h, approximately equal amounts of wheat were removed from each beaker, weighed, immediately frozen on dry ice, and stored in a freezer (at about -20 °C) until they were analyzed.

Comparison of the Rates of Metabolism of HM-SM and HP-MM. [¹⁴C]HP-MM and [¹⁴C]HM-SM were isolated (after β -glucosidase treatment of wheat extracts) from, respectively, [¹⁴C]MM- or [¹⁴C]SM-treated excised wheat. Equivalent amounts of [¹⁴C]HP-MM and [¹⁴C]HM-SM were pulsed into Anza wheat (for 3 h) before transfer to fresh phosphate buffer. For this pulse study, 44.2 g of excised seedlings was pulsed with 89 μ g (MM equivalents) of [¹⁴C]HP-MM in 50 mL of 0.01 M, pH 7.0, phosphate buffer; 42.6 g of seedlings was pulsed likewise with 127 μ g (SM equivalent) of [¹⁴C]HM-SM. After pulsing, the seedlings were then allowed to further metabolize [¹⁴C]HP-MM and [¹⁴C]HM-SM for an additional 3 h.

Determination of Inhibition of Wild Mustard Acetolactate Synthase. Determination of the inhibition of wild mustard acetolactate synthase by HM-SM, HP-MM, and chlorsulfuron was conducted essentially as described in Saari et al. (1990). In these experiments, chlorsulfuron was included as a positive control.

RESULTS

Metabolic Pathway of Sulfometuron-methyl in Wheat. Excised Guard wheat seedlings metabolized SM to more polar (as determined by their shorter retention time in reversed-phase HPLC analysis) components. Figure 1 provides a sample chromatogram of an extract of Guard wheat where the wheat had been allowed to continuously absorb SM from solution for 2 days. The two major peaks formed from SM (eluting at 19.4 min) elute at 5.9 and 10.5 min in HPLC system 1. Cochromatography (in TLC systems 1 and 2 and HPLC system 1) with an authentic standard indicated that the peak

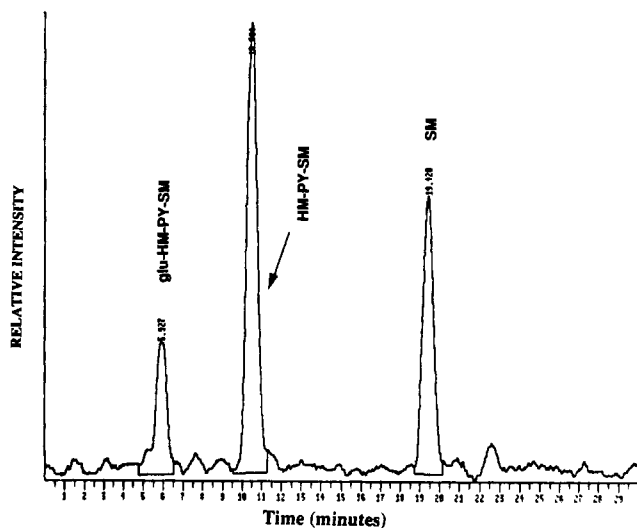


Figure 1. HPLC analysis of a wheat extract from Guard wheat exposed to sulfometuron-methyl for 2 days.

eluting at 10.5 min was methyl 2-[[[(4-(hydroxymethyl)-6-methylpyrimidin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate (HM-SM). The metabolite peak eluting in 5.9 min was hydrolyzed to HM-SM upon enzymatic treatment (with β -glucosidase type I, Sigma Chemical Co., St. Louis, MO). Purification of the 5.9-min peak and mass spectral characterization (Figure 2) confirmed it as the carbohydrate (glucose) conjugate of HM-SM (Glu-HM-SM).

Further evidence that the position of hydroxylation of SM was on a pyrimidine methyl was by hydrolysis of purified HM-SM. Acidic hydrolysis of the parent compound, SM, results in formation of methyl 2-(aminosulfonyl)benzoate (Harvey et al., 1985). Hydrolysis of [*phenyl*- ^{14}C]HM-SM should also yield methyl 2-(aminosulfonyl)benzoate. Acidic hydrolysis of [^{14}C]HM-SM isolated from wheat resulted in quantitative formation of methyl 2-(aminosulfonyl)benzoate (results not shown).

Over a 4-day uptake period, seedlings continued to absorb and metabolize SM to HM-SM and Glu-HM-SM

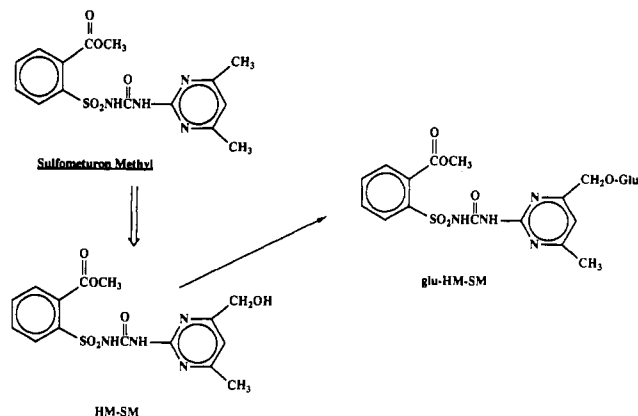


Figure 3. Metabolic pathway of sulfometuron-methyl in wheat.

Table II. Total Radioactivity in Excised Guard Wheat, and the Composition of the Total Radioactivity, as a Function of Time

time, days	total ^{14}C , ppm	% of total ^{14}C		
		SM	HM-SM	Glu-HM-SM
0.2	2.1	74	8	2
1	5.2	40	21	32
2	11.2	29	45	22
3	13.2	23	49	26
4	16.4	17	33	49

(Table II). After 4 days, HM-SM and Glu-HM-SM accounted for 82% of the radioactivity in the wheat seedlings. In a separate 7-day uptake and metabolism experiment, HM-SM was not only present in the plant tissue but also was released into the phosphate buffer uptake solution. This release of HM-SM into the uptake solution may have been a result of senescence and loss of tissue integrity in the seedlings. Figure 3 shows the metabolic pathway of sulfometuron-methyl in wheat.

Comparative Rates of Metabolism of Sulfometuron-methyl and Metsulfuron-methyl in Wheat. Anza wheat seedlings that were pulsed with [^{14}C]SM and [^{14}C]MM metabolized MM more rapidly than SM (Figure 4).

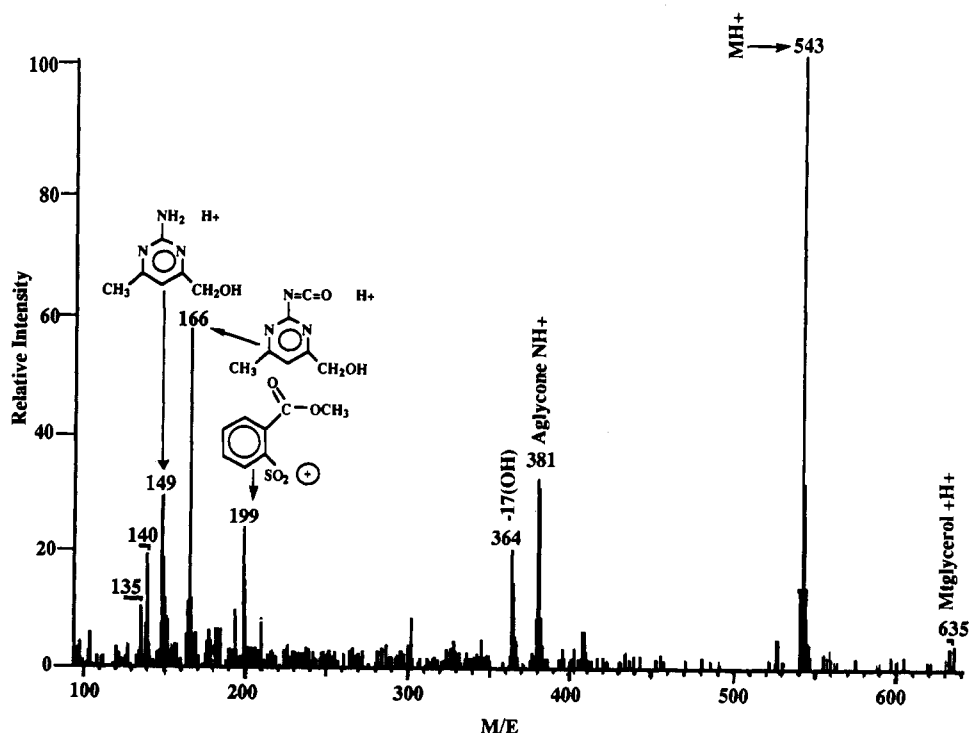


Figure 2. Mass spectrum of the major wheat metabolite of sulfometuron-methyl.

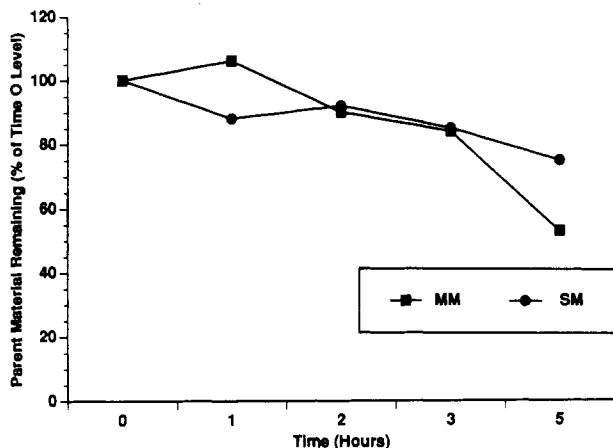


Figure 4. Comparison of rate of wheat metabolism of sulfometuron-methyl (SM) and metsulfuron-methyl (MM).

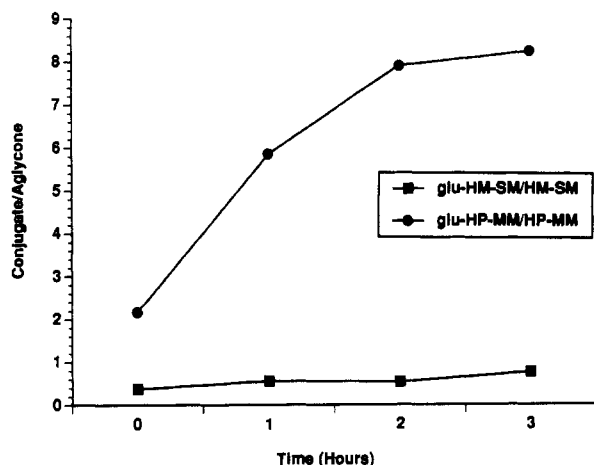


Figure 5. Ratio of the level of glucose conjugate to aglycon for the conjugation of HM-SM and HP-MM in Anza wheat, as a function of time.

Five hours after receiving the pulse, 47% of the MM present at time zero had been metabolized, as compared to 25% of the SM.

Comparative Rates of Metabolism of HM-SM and HP-MM in Wheat. Immediately after the initial 3-h pulse phase, 50% of the total radioactivity in HM-SM-treated wheat was present as HM-SM and 25% of the total radioactivity in HP-MM treated wheat seedlings remained as HP-MM. From these starting levels, the progress of the conjugation reaction was followed for an additional 3 h. After these 3 h, the level of HM-SM had decreased from 50 to 37% and the level of HP-MM had decreased from 25 to 9% of the total radioactivity present in the seedlings. This difference in the ability of the wheat seedlings to conjugate the supplied aglycons can be seen in Figure 5, where the ratio of conjugate/aglycon is plotted vs time for both HM-SM and HP-MM.

Inhibition of Wild Mustard Acetolactate Synthase by HM-SM and HP-MM. The herbicidal properties of HM-SM and HP-MM were evaluated to determine their ability to inhibit the activity of wild mustard acetolactate synthase (ALS; the sulfonylurea herbicide target site). Chlorsulfuron was included in these determinations as a positive control. The respective I_{50} values determined for HM-SM, HP-MM, and chlorsulfuron in this system were 5.0, 1.5, and 4.5 ppb. Therefore, HM-SM and HP-MM are equal to or better than chlorsulfuron in inhibiting ALS.

DISCUSSION

SM and MM are two closely related sulfonylurea herbicides that differ only in the nature of their heterocyclic ring. Both compounds contain the same substituted methyl benzoate moiety. In wheat, MM is metabolized primarily by oxidation of the phenyl ring to HP-MM (Anderson et al., 1989), whereas SM is metabolized by oxidation of the pyrimidine methyl to HM-SM. Both initial oxidations are followed by conjugation with a carbohydrate (presumably glucose). At this time we cannot rule out that a small amount of 4-(hydroxyphenyl)-SM was formed as a minor metabolic product, but it is evident that the heterocyclic derivative predominates in these excised plants. It is not clear to us why the position of oxidation changes so dramatically between SM (methyl) and MM (phenyl ring), and we hypothesize that they are oxidized by two different oxidative enzyme systems (presumably P_{450} -type systems). Such a hypothesis is not unreasonable because multiple P_{450} monooxygenases have been implicated in the metabolism of other agrochemicals in wheat (Moughin et al., 1991).

Excised wheat seedlings may not be physiologically identical to intact seedlings but are a useful tool in understanding differences in plant susceptibility to sulfonylurea herbicides. MM was metabolized more rapidly by the excised wheat seedlings than was SM. This difference in the rate of metabolism probably accounts for the differential response of wheat to SM and MM. This involvement of metabolism in the detoxification of sulfonylurea herbicides is already well documented (Beyer et al., 1987).

Accompanying the slower rate of primary metabolism of the respective parent compound, there was also a much slower conjugation of the aglycon HM-SM, as compared to that for HP-MM. This reduced rate of conjugation of a hydroxylated metabolite by a nontolerant plant has recently been reported for another sulfonylurea herbicide (chlorsulfuron-ethyl) in corn (Lamoureaux et al., 1991). For chlorsulfuron-ethyl metabolism in corn, the authors suggested that the unexpectedly low amount of conjugation was due to either a decreased ability to conjugate the hydroxylated species or an increased level of glucosidases such that the conjugate, if formed, was rapidly hydrolyzed back to the primary metabolite. For the metabolism of SM in wheat, the reduced ability to conjugate HM-SM is possibly the primary reason for its relative persistence in the wheat tissue. If there was an active glucosidase operating, it would also have resulted in hydrolysis of Glu-HP-MM. Such evidence was not observed.

Herbicide tolerance in plants can be due to a number of factors, one of which is selective metabolic detoxification. The extent to which a plant is tolerant to a given xenobiotic may be a function of how rapidly the xenobiotic can be metabolized (Hatzios and Penner, 1982). However, this generalization has its exceptions because metabolism itself can lead to phytotoxic products. For example, in vitro oxidative metabolism of the herbicide chlorsulfuron resulted in a phenolic metabolite that was at least as phytotoxic by several criteria as the parent compound (Lamoureaux and Rusness, 1986). However, the *O*-glucoside was not biologically active. Similarly, when both HM-SM and HP-MM were subjected to the wild mustard ALS screen, the oxidized metabolites had equivalent (HM-SM) or lower (HP-MM) I_{50} values than the positive control chlorsulfuron. Thus, the differential susceptibility of wheat to SM and MM may be due to both a slower ability to hydroxylate the parent compound and a reduced ability to detoxify a phytotoxic metabolite through conjugation.

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