Analysis of Sulfonylurea Herbicides by Gas-Liquid Chromatography. 1. Formation of Thermostable Derivatives of Chlorsulfuron and Metsulfuron-methyl

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A method is described to overcome the thermal instability of sulfonylurea herbicides and thus enable their analysis by gas chromatography (GC). Methylation of chlorsulfuron by diazomethane in a variety of solvents usually yielded *N*-methylchlorsulfuron as the predominant product. This derivative was not stable to GC conditions, forming the *N*-methylsulfonamide. With diazomethane in either acetone or ethyl acetate and with longer reaction times substantial quantities of the *N,N'*-dimethyl derivatives of chlorsulfuron and metsulfuron-methyl were formed, which were characterized by GC-MS (EI and CI). These derivatives were thermostable and gave symmetrical GC peaks with good responses to both electron capture and nitrogen-phosphorus detectors. Reaction conditions were optimized in ethyl acetate to maximize yields of the *N,N'*-dimethyl derivatives. Formation of the derivatives was shown to be linear over the range 0.1-10 μg, and they were suitable for determination at residue levels.

INTRODUCTION

Chlorsulfuron and metsulfuron-methyl are two of the most important sulfonylurea herbicides. They are in widespread use for controlling many grasses and broadleaf and brush weeds in crops, rangeland, and forests. One of the most important features of the sulfonylurea herbicides is their very high herbicidal activity, which results in extremely low application rates of 10-40 g/ha (Blair and Martin, 1988). Depending on the characteristics of the particular soil, sulfonylurea herbicides can persist in the soil for more than 1 year. Residues of chlorsulfuron at ≤0.3 μg/kg can significantly influence the growth rates of some crops, and consequently carry-over from previous crops can be a problem (Rahman, 1989; Brown, 1990).

Standard chemical methods for the analysis of chlorsulfuron and metsulfuron-methyl residues use high-performance liquid chromatography (HPLC) with photoconductivity detection (Zahnow, 1982a,b; Hershberger and Brennan, 1988; Slates and Watson, 1988). Methods for the determination of chlorsulfuron using immunoassay (Kelley et al., 1985) and HPLC with UV detection (Walker and Brown, 1983; Wells and Michael, 1987) have been developed. However, suitable confirmatory techniques for the above methods are lacking. Although HPLC coupled to mass spectrometry (MS) has been used to detect some sulfonylureas at sub parts per million (ppm) levels (Shalaby and George, 1990, 1992), HPLC-MS is a relatively new technique and not available in most analytical laboratories.

Direct determination of sulfonylurea herbicides by gas chromatography (GC) has not been possible due to their thermal instability. Chlorsulfuron, for example, decomposes in the hot injector, forming 2-amino-4-methoxy-6-methyl-1,3,5-triazine (AMMT) which can be determined by GC using nitrogen-phosphorus detection (NPD) (Long et al., 1989, 1990).

Chemical derivatives have not been able to overcome the problem of thermal instability. Methylation using diazomethane in dichloromethane resulted mainly in the replacement of only one of the two imino protons of the sulfonylurea moiety (Ahmad, 1987; Ahmad and Crawford, 1990). The *N*-monomethyl derivatives formed by this reaction are also known to be thermally unstable (Braselton et al., 1976; Maeda et al., 1981). Attempts to form more thermostable *N,N'*-dimethyl derivatives in high yield have failed (Ahmad, 1987; Ahmad and Crawford, 1990).

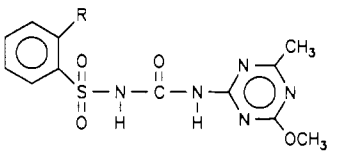

Figure 1. Structure of the herbicides under investigation.

Reaction of chlorsulfuron with pentafluorobenzyl bromide principally formed the bis-PFB derivative of the sulfonamide hydrolysis product (Cotterill, 1992). This product could be detected with high sensitivity by GC-ECD.

Methods based on breakdown products (thermal or reagent) are inherently unsatisfactory due to the possibilities for multiple sources of the fragments including parents, hydrolysis products, or metabolites with a common moiety.

The objective of this study was to investigate chemical derivatization reactions suitable for the formation of thermostable derivatives of chlorsulfuron and metsulfuron-methyl. The resulting products should be useful for the development of residue determination and confirmation methods based on gas chromatography.

EXPERIMENTAL PROCEDURES

Instrumentation. The HPLC system consisted of a Waters M-45 solvent delivery system, a Tracor 970A variable-wavelength detector, a Rheodyne injection valve with a 25-μL sample loop, and a Waters Nova-Pak C-18 column (3.9 × 150 mm). The detector wavelength was set to 235 nm. The mobile phase used for all HPLC measurements was methanol plus 1% acetic acid in water (48:52). A diode array detector (Linear Instruments) with data handling facilities was available for multiple-wavelength acquisition runs.

GC was carried out using a Varian 3500 gas chromatograph equipped with a Varian 8100 autosampler, a split/splitless

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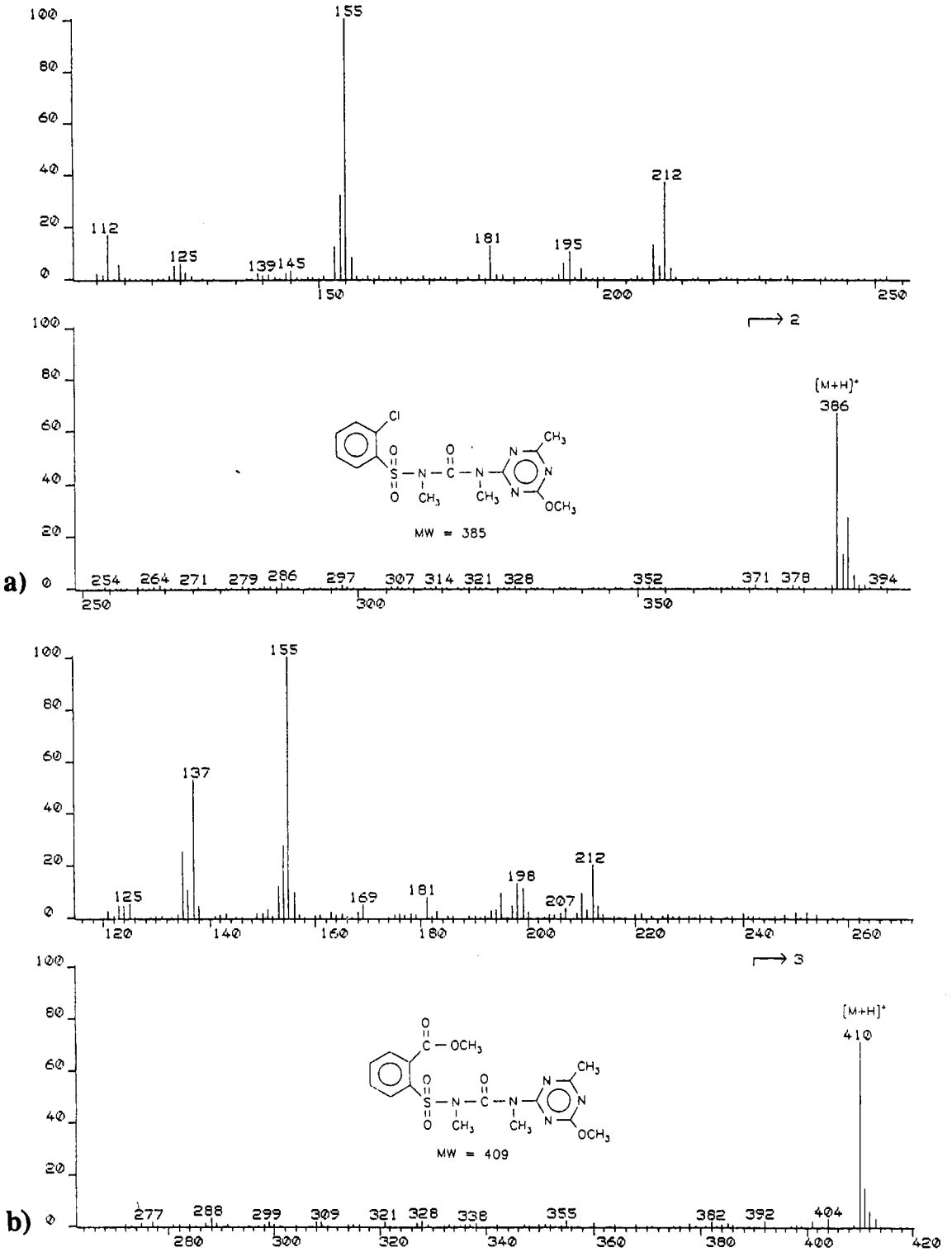

Figure 2. Isobutane PCI mass spectra of (a) *N,N'*-dimethylchlorsulfuron and (b) *N,N'*-dimethylmetsulfuron-methyl.

injector, a ^{63}Ni electron capture detector (ECD), and a nitrogen–phosphorus detector (NPD). A Hewlett-Packard HP-5 capillary column (25 m × 0.2 mm i.d., 0.33-μm film) was used. The column was temperature programmed: 85 °C, 1 min, 40 °C/min to 150 °C, 2 min, 5 °C/min to 250 °C, 20 min. One microliter of the sample solutions was injected in splitless mode, injector temperature 220 °C. A postcolumn fused silica split system led the effluent to the detectors, which were operated at 300 °C.

Peak identifications were confirmed using a Kratos MS80 RFA mass spectrometer directly interfaced to a Carlo Erba Mega Series GC. A DB-5 [15 m × 0.32 mm i.d., 1-μm film (J&W Scientific)] was used. The temperature program was 100 °C initial temperature held for 1 min, raised at 20 °C/min to 280 °C. The final temperature was maintained for 10 min. The split/splitless injector and transfer oven were operated at 220 and 250 °C, respectively. One microliter of the sample solutions was injected in splitless mode. Electron impact ionization parameters used were electron energy 30 eV, source temperature 200 °C, full scan 50–500 amu, and scan rate 1 scan/s. Chemical ionization parameters were reagent gas isobutane, source temperature 190 °C, reagent gas source pressure 0.95 Torr, full scan 100–550 amu, and scan rate 1 scan/s. Helium was used as carrier gas in all GC experiments.

Chemicals. All solvents were of pesticide grade purchased from Mallinckrodt, Paris, KY. *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide (diazald), used for preparation of diazomethane, was obtained from Sigma Chemical Co., St. Louis, MO. Sodium sulfate obtained from Mallinckrodt was heated at 600 °C for 6

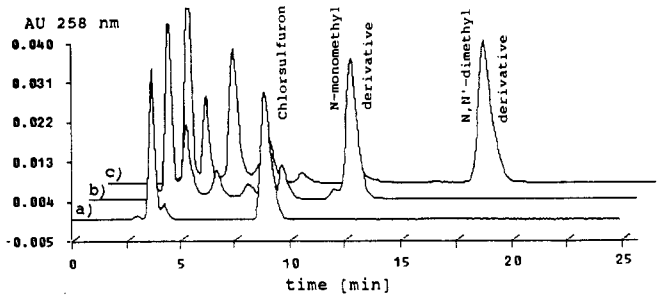

Figure 3. HPLC chromatograms of chlorsulfuron (a) without derivatization, (b) after methylation in dichloromethane, and (c) after methylation in ethyl acetate. UV detection was at 258 nm.

h. Chlorsulfuron, 1-[(2-chlorophenyl)sulfonyl]-3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)urea, CAS number 64902-72-3, purity 95.0%, was obtained from Chem Service, West Chester, PA. Metsulfuron-methyl, methyl 2-(4-methoxy-6-methyl-1,3,5-triazin-2-yl-carbamoylsulfamoyl)benzoate, CAS number 74223-64-6, purity 99.3%, was purchased from Dr. Ehrenstorfer, Augsburg, Germany. The structures of the two herbicides are shown in Figure 1.

Diazomethane Generation. To diazald (1 g), placed in a diazomethane development apparatus (Cohen, 1984), were added diethylene glycol monoethyl ether (3 mL) and diethyl ether (2 mL). The apparatus was purged by a gentle stream of nitrogen. Diazomethane generation was started by adding 40% aqueous potassium hydroxide solution (2 mL).

Safety Precautions. Diazomethane is explosive and toxic and a suspected carcinogen. It should be prepared and used in a fume hood behind a safety shield. Ground joints and sharp surfaces should be avoided. However, the device used for preparation and the small amount of material used minimized the hazard.

Derivatization Reactions. *(1) Alkylation Using Potassium tert-Butoxide/Methyl Iodide (De Leenheer and Gelijkens, 1976).* To a solution of chlorsulfuron in DMSO (1 mL, 100 μg/mL) was added 50 μL of a solution of potassium *tert*-butoxide (1.4% in DMSO). After 1 min, 100 μL of methyl iodide was added, and the mixture was allowed to stand at room temperature for 1 h. The reaction was stopped by adding 5 mL of water, and the mixture was extracted using 5 mL of chloroform. The organic phase was washed, dried, and evaporated. The residue was dissolved in 0.5 mL of methanol/water (55:45) for analysis by HPLC.

(2) Alkylation Using Dimethyl Sulfate (Prescott and Redman, 1972). Chlorsulfuron was extracted from a solution made up in toluene (1 mL), 100 μg/mL) into a solution of 10% potassium carbonate in water. The aqueous phase was separated, and 1 mL of methanol and 100 μL of dimethyl sulfate were added. The mixture was heated at 60 °C for 10 min. After cooling, the mixture was neutralized and extracted with 5 mL of *n*-hexane. The organic phase was evaporated and the residue dissolved in 0.5 mL of methanol/water (55:45) for HPLC analysis.

(3) Methylation Using Diazomethane. Diazomethane, generated as described above, was bubbled through 1 mL of a solution of chlorsulfuron in dichloromethane. After 5 min, the diazomethane bubbling was stopped and the solvent and excess reagent were evaporated by using a gentle stream of nitrogen. The residue was dissolved in 1 mL of methanol/water (55:45) for analysis by HPLC.

(4) Perfluoroacylation of Chlorsulfuron (Gyllenhaal and Ehrsson, 1975). Twenty-five microliters of the anhydride (TFAA, PFPA, or HFBA) and 100 μL of trimethylamine were added to 0.5 mL of a solution of chlorsulfuron in toluene. After 20 min at room temperature, the excess reagent was removed by evaporating the solution to dryness using a stream of nitrogen. The residue was dissolved in 0.5 mL of methanol/water (55:45) for analysis by HPLC.

(5) Perfluoroacylation of N-Monomethyl Derivatives (Braselton et al., 1976). To a solution of chlorsulfuron-*N*-monomethyl, prepared by methylation using diazomethane, dissolved in 50 μL of ethyl acetate/pyridine (9:1), was added 50 μL of the perfluoroanhydride. The mixture was heated at 65 °C for 30 min. The excess reagent was removed by evaporation with nitrogen. The residue was dissolved in 0.5 mL of methanol/water (55:45) for analysis by HPLC.

Optimization of the Methylation Using Diazomethane. *(1) Bubbling Procedure.* An aliquot (1 mL) of the chlorsulfuron standard solution (100 μg/mL in solvent of choice) was derivatized by bubbling diazomethane generated as described through the solution. After a predetermined reaction time, the diazomethane input was stopped and the solvent was evaporated under a gentle stream of nitrogen. The residue was dissolved in 1 mL of methanol/water (55:45) for analysis by HPLC.

(2) Bulk Procedure. The diazomethane generated from 1 g of diazald as described was bubbled into 10 mL of ethyl acetate for 1 h. Portions of the solution were diluted 1:10 or 1:5 using ethyl acetate. These reagent solutions (0.5 mL) were added to aliquots (1 mL) of chlorsulfuron in ethyl acetate (100 μg/mL). After varying reaction times (10 s–120 min), the solvent was evaporated using a gentle stream of nitrogen. The residue was dissolved in 1 mL of methanol/water (55:45) for analysis by HPLC.

Methylation for Residue Analysis by GC. Undiluted diazomethane/ethyl acetate (0.5 mL) was added to the sample dissolved in ethyl acetate (1 mL) in an autosampler vial (1.8 mL). The vial was sealed, and the mixture was kept at room temperature for 30 min. The reaction was stopped by evaporating the solvent using a gentle stream of nitrogen. The residue was dissolved in 1 mL of toluene prior to analysis by GC.

RESULTS AND DISCUSSION

Several established derivatization methods were tested for their suitability to form derivatives of intact sulfonylureas using chlorsulfuron as a modeling substance. These included various methylation procedures and perfluoroacylations. The results of the reactions were monitored by HPLC. This analytical technique allowed the simultaneous detection of the derivatives as well as the unchanged parent compound and breakdown products. To assist in identification of the products of derivatization, a sample of chlorsulfuron was acid hydrolyzed [10 μg in 1 mL of methanol/water (55:45) plus 0.1 mL of 5 M HCL overnight at room temperature]. HPLC conditions were established that eluted the compounds in the order 2-amino-4-methoxy-6-methyl-1,3,5-triazine (AMMT), 2-chlorobenzenesulfonamide (CS-SA), and chlorsulfuron. It was expected that derivatization of chlorsulfuron or its hydrolysis products would produce a shift to longer HPLC rentention times on the reversed-phase system. Derivatization products were also examined by GC–MS.

Of the methods tested in this study only the methylation with diazomethane resulted in derivatives of the intact chlorsulfuron. All other methods resulted in the formation of hydrolysis products or derivatized hydrolysis products. Dimethyl sulfate produced mainly CS-SA and *N*-monomethyl CS-SA (CS-SA-monomethyl). Alkylation using potassium *tert*-butoxide/methyl iodide also resulted in derivatized hydrolysis products only. The reaction of chlorsulfuron as well as *N*-monomethyl chlorsulfuron with perfluoroanhydrides resulted in formation of *N,N*-bis-(perfluoroacyl)-CS-SAs. Pentafluorobenzylation is known to produce *N,N*-bis(PFB)-CS-SA (Cotteril, 1992).

The major product of diazomethane methylation of chlorsulfuron in dichloromethane was the *N*-monomethyl derivative of chlorosulfuron (HPLC t_r 7.1 min) with small amounts of the *N,N'*-dimethyl derivative (HPLC t_r 10.9 min). GC–MS of the reaction mixture revealed four principal components: AMMT, CS-SA-monomethyl (CI-MS, $[M + H]^+$ 206 Da), *N,N*-dimethyl-CS-SA (CS-SA-dimethyl), and *N,N'*-dimethylchlorsulfuron. No peak corresponding to intact *N*-monomethylchlorsulfuron was observed in the GC or GC–MS experiments. This product appears to be thermally unstable, producing CS-SA-

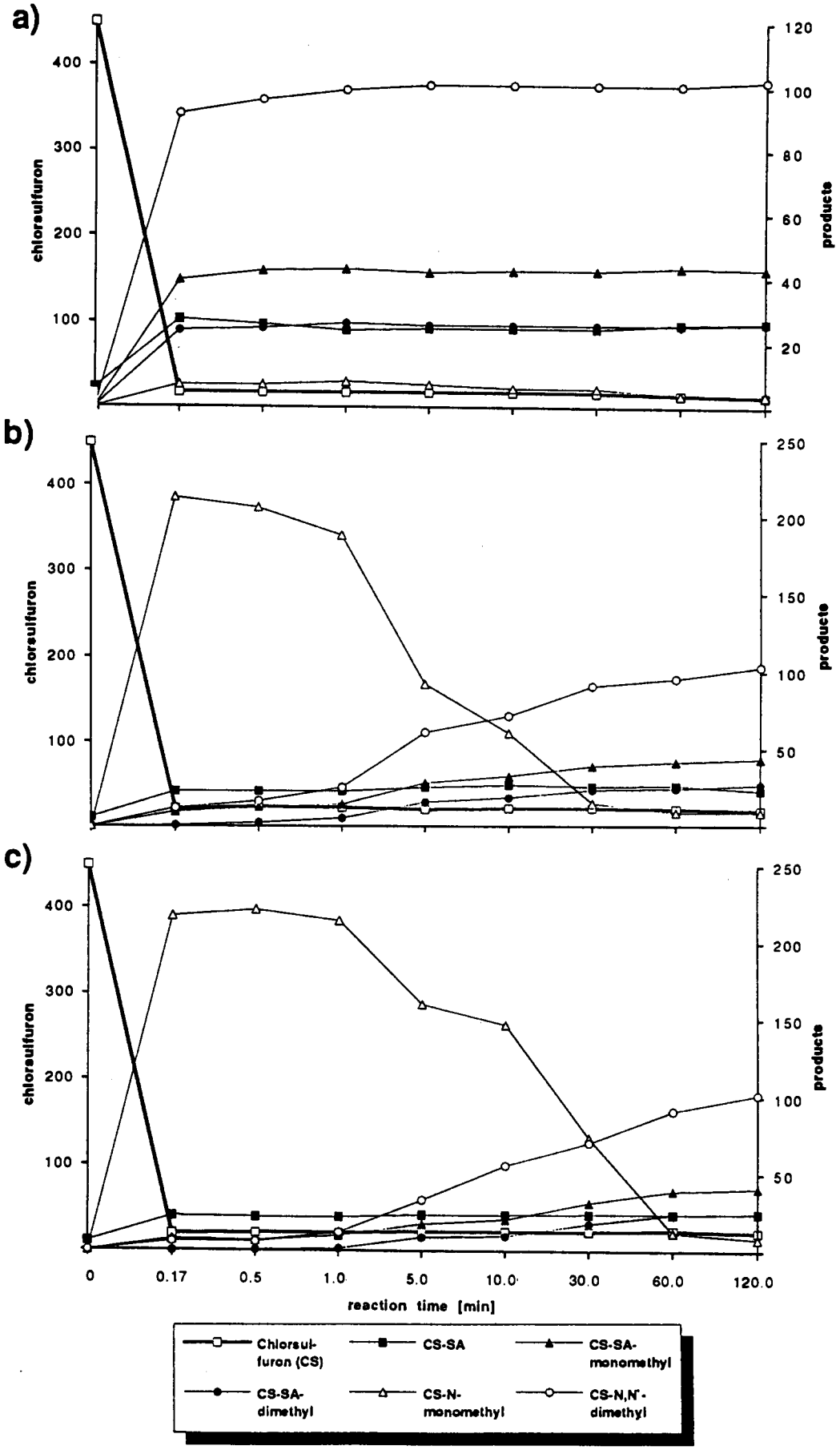

Figure 4. Time course of the methylation of chlorsulfuron in ethyl acetate using (a) undiluted, (b) 1:5 diluted, and (c) 1:10 diluted diazomethane solutions. HPLC peak areas (arbitrary units) are at 235 nm.

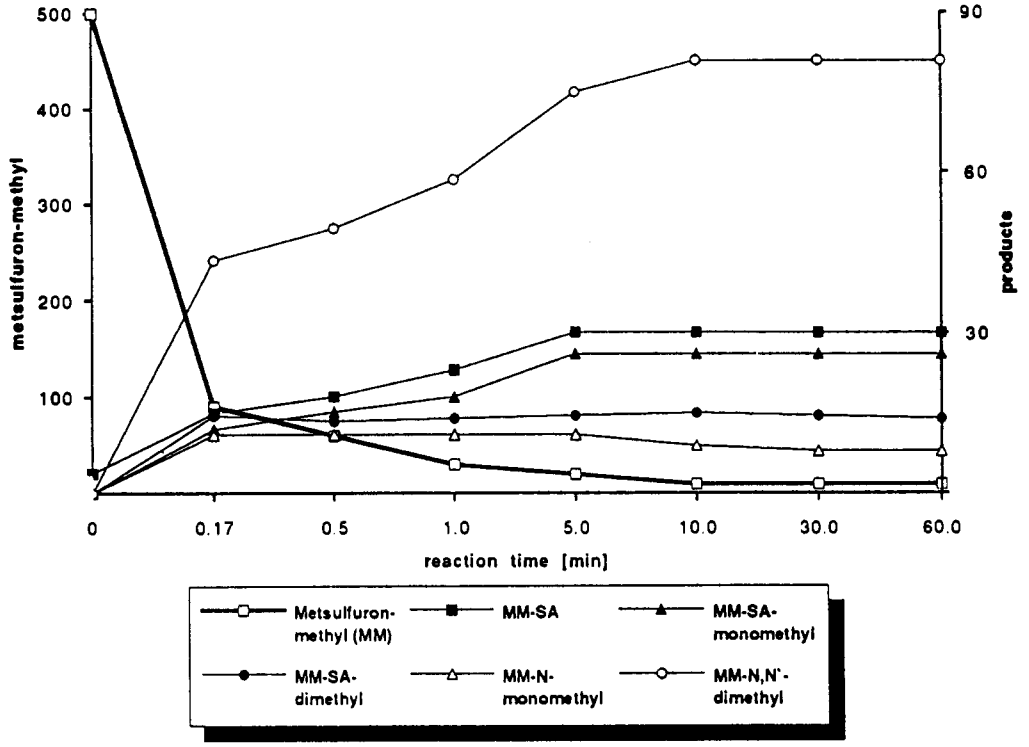

Figure 5. Time course of the reaction of metsulfuron-methyl with diazomethane in ethyl acetate (undiluted reagent). HPLC peak areas (arbitrary units) are at 235 nm.

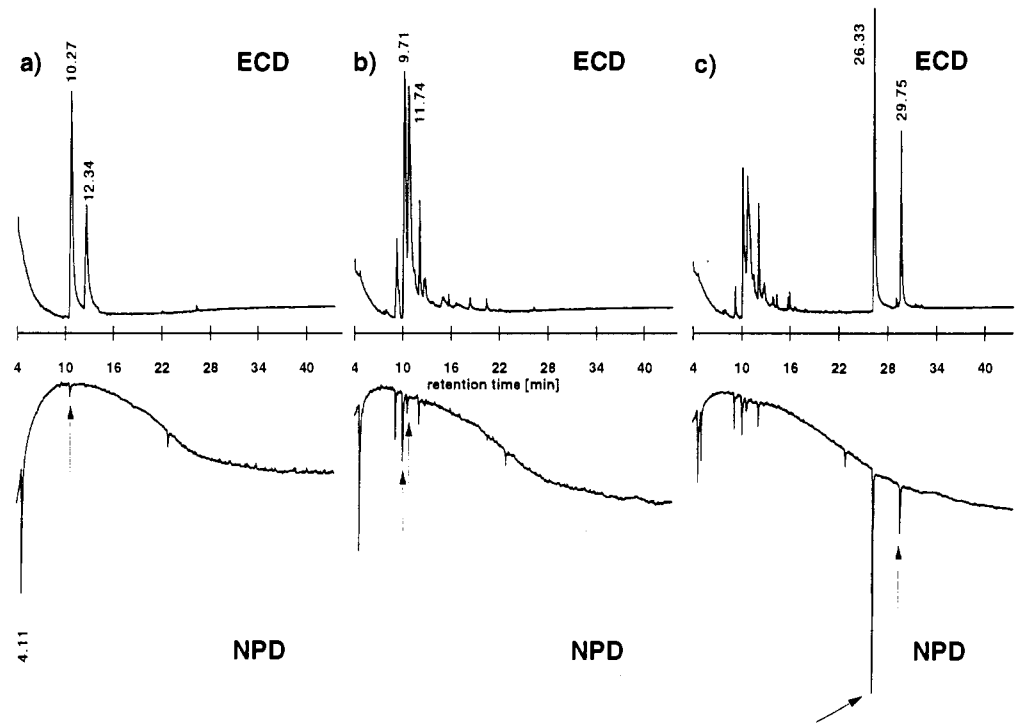

Figure 6. GC-ECD/NPD chromatograms of chlorsulfuron and metsulfuron-methyl (a) without derivatization (t_r 4.11 min, 2-amino-4-methoxy-6-methyl-1,3,5-triazine; t_r 10.27 min, chlorsulfuron sulfonamide; t_r 12.34 min, metsulfuron-methyl sulfonamide), after (b) methylation in dichloromethane (t_r 9.71 min, *N*-monomethylchlorsulfuron sulfonamide; t_r 11.74 min, *N*-monomethylmetsulfuron-methyl sulfonamide), and after (c) methylation in ethyl acetate (t_r 26.33 min, *N,N'*-dimethylchlorsulfuron; t_r 29.75 min, *N,N'*-dimethylmetsulfuron-methyl).

monomethyl in the injector. Thermal decomposition under split/splitless injection conditions has been reported for the *N*-monomethyl derivatives of sulfonylurea drugs (Braselton et al., 1976; Maeda et al., 1981). The EI spectrum of the CS-SA-monomethyl derivative matches that reported by Ahmad and Crawford (1990) from GC–MS of *N*-monomethylchlorsulfuron. It is probable their published method for chlorsulfuron residues is based on the detection of the sulfonamide thermal degradation product rather than the intact *N*-monomethyl derivative of chlorsulfuron.

N,N'-dimethylchlorsulfuron gave a single sharp GC peak with a mass spectrum characteristic for the intact derivative (EI 350 (8%), 286 (50%), 229 (60%), 210 (100%), 194 (95%), 181 (100%), 111 (90%), 113 (30%)]. The CI

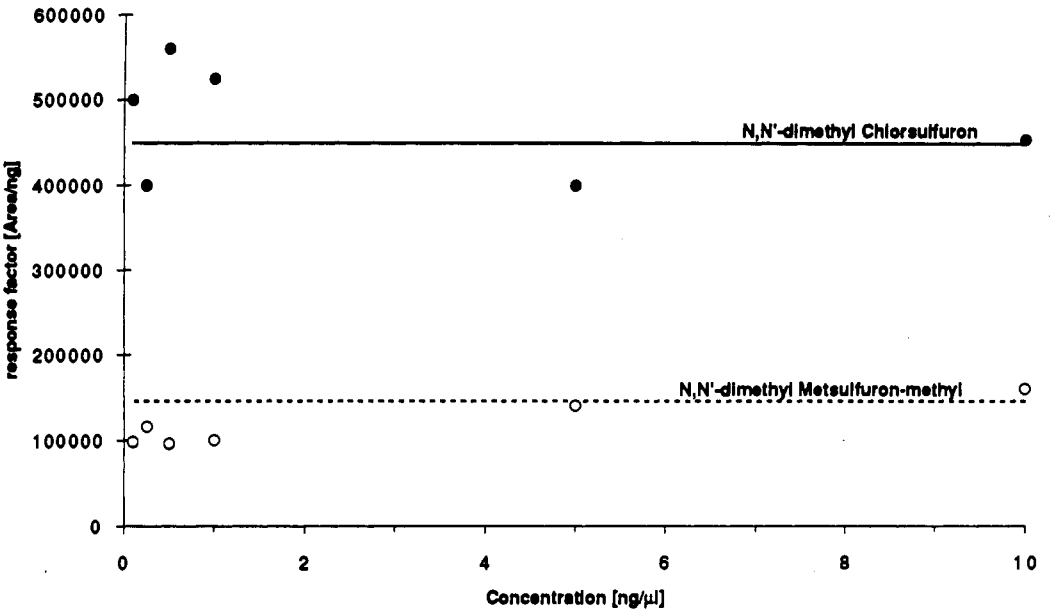

Figure 7. ECD response factors of the *N,N'*-dimethyl derivatives of chlorsulfuron and metsulfuron-methyl at different concentration levels.

Table I. Relative Peak Area (Percent of the Total Peak Area) of the Different Reaction Products after a Reaction Time of 30 min[a]

	relative peak area, %				
solvent	CS-SA	CS-SA-monomethyl	CS-SA-dimethyl	CS-monomethyl	CS-dimethyl
n-hexane	8.3	8.3	4.1	49.8	5.5
toluene	12.8	20.9	6.3	34.1	10.4
diethyl ether	14.8	13.4	9.1	26.7	18.2
dichloromethane	17.5	17.0	19.4	19.8	14.2
2-butanol	19.7	24.1	11.0	3.8	28.3
ether/ethanol (1:1)	11.6	22.9	4.3	2.6	25.3
ethyl acetate	12.6	18.8	11.9	3.9	44.5
acetone	13.4	29.9	12.2	3.7	30.9
methanol	7.8	14.5	9.3	1.4	15.2

[a] CS, chlorsulfuron; CS-SA, 2-chlorobenzenesulfonamide.

mass spectrum exhibited a $[M + H]^+$ ion at m/e 386 (see Figure 2a).

We therefore investigated several parameters of importance for the methylation of sulfonylureas using diazomethane to maximize formation of the *N,N'*-dimethyl derivative.

A number of different solvents were tested to evaluate their effectiveness in the methylation of chlorsulfuron by diazomethane. Chlorsulfuron was dissolved in the solvent tested and diluted to give a concentration of 100 µg/mL. Aliquots (1 mL) of the solutions were derivatized with diazomethane using the bubbling method. The reaction time was varied from 10 s to 60 min. The results of these experiments for a reaction time of 30 min are shown in Table I. In the table the HPLC peak areas of the different reaction products are given relative to the total peak area. Use of a multiple-wavelength detector showed that methylation of the intact compounds resulted in a shift of the absorption maximum to higher wavelengths. The response of the *N,N'*-dimethyl derivative at 235 nm was considerably lower than that of the monomethyl derivative, the unchanged chlorsulfuron, or the breakdown products. However, the relative peak areas at 235 nm are suitable to demonstrate the significant influence of the solvent on the yields of reaction products. The reaction in relatively nonpolar solvents resulted preferentially in the formation of *N*-monomethyl chlorsulfuron (Table I). This reaction was comparatively fast and was completed after 1–5 min. The peak area was found to decrease at longer reaction times. Methylation in more polar solvents resulted in the formation of *N,N'*-dimethylchlorsulfuron as the main product. Of the solvents tested, ethyl acetate was found to give the highest yield of the dimethyl derivative.

Figure 3 shows the HPLC chromatograms of a chlorsulfuron sample without derivatization, after a 10-min reaction with diazomethane in dichloromethane and after a 30-min reaction with diazomethane in ethyl acetate. The detector wavelength was set to 258 nm. At this wavelength the UV absorptions of the unchanged chlorsulfuron and both derivatives were nearly equal.

The conditions resulting in the formation of the *N,N'*-dimethyl derivative also result in the formation of a higher proportion of breakdown products (Table I; Figure 3).

The formation of the monomethyl derivative was usually maximal after 5 min. After this time, the peak area (HPLC) decreased while the peak area of the dimethyl derivative and the methylated hydrolysis products increased. The kinetics for the reaction in acetone were similar to those in ethyl acetate. In both solvents the conversion of the monomethyl derivative was much faster than in the other solvents tested.

A series of experiments using varying concentrations of diazomethane in ethyl acetate was carried out to establish the effect this had on the formation of the *N,N'*-dimethyl derivative of chlorsulfuron and the breakdown products. The time course of the reaction when using different concentrations of diazomethane is shown in Figure 4. Diluted reagent solution resulted in slower methylation, but the maximum peak area reached by the dimethyl derivative was nearly the same. On the other hand, after the reaction was completed, the amount of breakdown products formed was also similar. Therefore, concentrated diazomethane solutions gave the highest possible yield of *N,N'*-dimethylchlorsulfuron in the shortest reaction time.

There was no significant influence of temperature on the formation of the different reaction products. The peak areas of the dimethyl derivative and the breakdown products were unchanged when performing the methylation at −15, 0, or 25 °C.

It has been reported that formation of *N*-monomethylchlorsulfuron in toluene using diazomethane was en-

hanced by pretreatment of the sample with acetic acid (Ahmad, 1987; Ahmad and Crawford, 1990). This effect was explained by the shift in the equilibrium between enolic and ketonic form to the ketonic form. We have found that addition of acetic acid did not enhance formation of *N,N'*-dimethylchlorsulfuron in ethyl acetate.

Methylation with concentrated diazomethane in ethyl acetate was also found to be optimal for the derivatization of metsulfuron-methyl (Figure 5). Metsulfuron-methyl reacted more slowly than chlorsulfuron, but once the reaction was completed, the resulting type and distribution pattern of the products formed were very similar to those observed for chlorsulfuron. Again, the products were identified by HPLC and GC–MS, except for the monomethyl derivative which gave the corresponding *N*-monomethylsulfonamide on GC. The EI mass spectrum of the *N,N'*-dimethyl derivative exhibited prominent ions at *m/z* (relative intensity) 345 (2), 288 (30), 210 (100), 199 (90), and 181 (100). The molecular weight was confirmed by CI-MS with an intense $[M + H]^+$ ion at *m/z* 410 (see Figure 2b).

To demonstrate the suitability of the derivatization reaction for gas chromatographic residue analysis, both substances were analyzed at nanogram to microgram levels. Figure 6 shows the ECD and NPD chromatograms of a standard mixture of chlorsulfuron and metsulfuron-methyl (10 μg/mL) without derivatization, as monomethyl derivatives and as dimethyl derivatives. The underivatized substances decomposed in the GC (Figure 6a). Both herbicides were thermally degraded to the same aminotriazine, AMMT, which responded only on the NPD. Both substances also formed sulfonamides, eluting with strong peak tailing. The peak tailing is reduced but not eliminated in the chromatograms of the monomethyl derivatives (methylation in dichloromethane, Figure 6b). These derivatives were also not thermostable and decomposed forming the corresponding *N*-methylsulfonamides, which eluted with improved peak shape and response on the NPD. The application of the optimized derivatization procedure resulted in a much better response (see Figure 6c). *N,N'*-Dimethylchlorsulfuron and *N,N'*-dimethylmetsulfuron-methyl eluted as single peaks with very symmetrical peak profiles.

Reproducibility of the reaction was tested by derivatizing an aliquot of a standard solution of chlorsulfuron (10 μg/mL) using the described diazomethane method for residue analysis. The derivatization was performed with five repetitions. Each solution was injected three times using the autosampler (1 μL, 10 ng of chlorsulfuron equivalent). The relative standard deviation of all analyses was ±3% at ECD and NPD, while the average standard deviation of three injections of the same sample solution was ±1% at both detectors.

To verify the linearity of the derivatization, standard solutions containing different concentrations of chlorsulfuron and metsulfuron-methyl were derivatized using the described diazomethane method for residue analysis. The concentrations of the original compounds were varied from 0.1 to 10 μg/mL. Analysis was performed using the GC-ECD/NPD system, injecting 1 μL of each solution. The calibration curves of both dimethyl derivatives on both detectors were linear (r = 0.994/0.997 and 0.998/0.999 for chlorsulfuron and metsulfuron-methyl, respectively, for ECD and NPD). Figure 7 plots the electron capture detector response factors against concentration, illustrating the linearity of derivatization and GC to low concentration levels. From the signal to noise ratio of the lowest standard (0.1 μg/mL) the instrumental detection limits on the ECD on the effluent split GC system used for chlosulfuron and metsulfuron-methyl can be estimated as 50 and 100 pg, respectively, which should be adequate as a basis for methods for residues of these herbicides.

CONCLUSION

Methylation of chlorsulfuron and metsulfuron-methyl by diazomethane in ethyl acetate solution produced the *N,N'*-dimethyl derivatives in high yield. Ethyl acetate was preferred over other solvents. The derivatives were found to be volatile and stable under the conditions used in gas chromatography with hot splitless injection and eluted with symmetrical peak profiles. The derivatization reaction was reproducible and linear over the concentration range 0.1–10 μg/mL.

ACKNOWLEDGMENT

Colin P. Malcom and Donald E. McNaughton provided valuable assistance with gas chromatography and mass spectrometry.

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Received for review September 4, 1992. Accepted December 14, 1992.