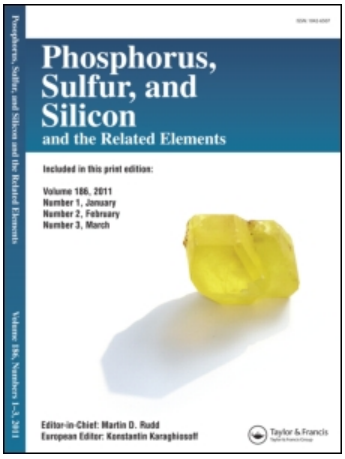

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NEW CRYSTALLINE POLYMORPHIC FORM OF GLYPHOSATE: SYNTHESIS, CRYSTAL AND MOLECULAR STRUCTURES OF *N*-(PHOSPHONOMETHYL)GLYCINE

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NEW CRYSTALLINE POLYMORPHIC FORM OF GLYPHOSATE: SYNTHESIS, CRYSTAL AND MOLECULAR STRUCTURES OF *N*-(PHOSPHONOMETHYL)GLYCINE

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Synthesis of the herbicide glyphosate, *N*-(phosphonomethyl)glycine has been modified by using MnO_2 in the presence of H_2SO_4 for the oxidation of substrate, i.e., *N*-(phosphonomethyl)iminodiacetic acid. The obtained solid appeared to be a new, crystalline polymorphic form of glyphosate. The x-ray structure of the compound has shown that the crystals are monoclinic with $P2_1$ space group, a = 7.1190(5), b = 5.428(1), c = 9.1225(5) Å, β = 105.043(6)°, V = 340.41(7) Å^3, Z = 2. The solution by direct methods and refinement gave final residuals of R = 0.0318, wR = 0.0395 and s = 0.78. The crystal structure of commercial glyphosate which was solved previously by three independent groups, was solved again for comparison. This determination is the most accurate so far. The bond lengths and angles are practically identical in both crystalline forms of glyphosate. The conformation of the molecule's backbone is however different as the torsion angles in Table IV show.

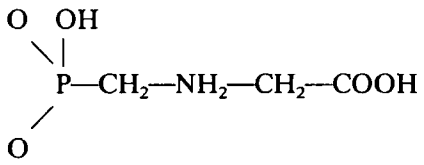
Key words: Glyphosate; *N*-(phosphonomethyl)glycine; herbicide; x-ray crystallography; polymorph.

INTRODUCTION

N-(phosphonomethyl)glycine $^-HO_3PCH_2NH_2^+CH_2COOH$ (trivial name: glyphosate), **1** has become widely used as a commercial herbicide since its discovery in the 1970s by J. E. Franz.[1–5] It is sold as Roundup® and it was introduced in Europe in 1974 by Monsanto Agricultural Products Co., St. Louis, U.S.A. It is now being marketed in over 120 countries and is labelled for use in more than 50 agricultural crops and in industrial sites. Here, we report the crystal structure of a new, polymorphic form of glyphosate, **3** discovered by us when applying a new synthetic route, *vide infra*. **1** is a highly effective phytotoxicant useful in controlling a large variety of weeds. It is applied to the foliage of a very broad spectrum of annual and perennial grasses and broad leaf plants. The introduction of **1** as a commercial herbicide has been described as a revolutionary advance in agriculture.[6] The utility and great commercial success of this compound is based on its unique properties: (1) It is absorbed by all green plant material, is translocated throughout the plant, and then kills the entire plant, including roots and rhizomes. (2) It inhibits a specific plant enzyme and as a result is not toxic to animals. (3) On contact with soil, it is immobilized and inactivated, so that it only affects plant material it immediately contacts. (4) It is safe for the environment as in the soil it is degraded within a period of days by soil organisms to CO_2, PO_4^{-3} and NH_3. Pure **1** is a zwitterionic neutral molecule that is only slightly soluble in water, what significantly limits its

range of applications. The salts of the monoanion of **1**, however, are readily soluble in water, and the commercial products are prepared as such.[7] The crystal structure of the zwitterionic free acid $HO_2CCH_2NH_2^+CH_2PO_3H^-$, **1** has been determined three times.[8-10] Metal ions play a role in the soil immobilization of the herbicide, and therefore the complexation properties of glyphosate have been the subject of particular interest.[11,12] The crystal structures of Ca(II) salts,[11] *i*-Pr-ammonium and trimethylsulfonium salts of glyphosate[12] and Cu(II) salt of *N*-(benzenesulfonyl)glycine[13] have been solved and described.

Usually, glyphosate is prepared by the conversion of *N*-(phosphonomethyl)glycine, **1** using peroxides.[1]



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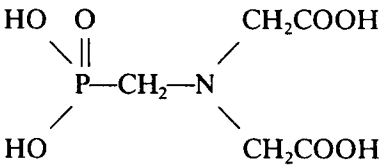

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However, all the methods of preparation suffer from one or more disadvantages, such as the use of excessive amounts of peroxide, the use of strong mineral acids and/or reaction at elevated temperatures and pressures. Thus, there is a need for a process which provides **1** in high yields at atmospheric pressure using substantially stoichiometric amounts of peroxide to oxidize the acid **2** to the desired **1** without using strong mineral acids such as HCl or H_2SO_4. This need is satisfied and other advantages are achieved in a process for producing **1** by the oxidation of acid **2** with a peroxide to form an intermediate *N*-(phosphonomethyl)iminodiacetic acid-*N*-oxide. The improvement comprises adding a catalytic amount of a metabisulfite compound in the presence of a catalytic amount of a water soluble molybdenum compound to convert the intermediate to **1**.[14] In the present work oxidation of amine **2** into **1** was conveniently performed with MnO_2 in water in the presence of H_2SO_4. During attempts to isolate an expected Mn complex salt of **1**, a new solid, **3** was obtained which did not contain Mn(II), however. This compound was subjected to x-ray crystallographic analysis.

EXPERIMENTAL

Synthesis. *N*-(phosphonomethyl)iminodiacetic acid, **2** was obtained according to the literature procedure.[5]

N-(phosphonomethyl)glycine, **3**: To **2** (4.54 g, 20 mmole) suspended in a solution of water (100 ml) and concentrated H_2SO_4 (1 ml), MnO_2 (1.91 g, 22 mmole) was added at room temperature. The mixture was stirred at this temp. for 3 h. Then, after filtration, the filtrate was concentrated on a rotary evaporator to half of a volume and left overnight for crystallization. The crystals were collected by filtration. The crude product was recrystallized from water. Yield 2.2 g (65%), m.p. 220–225° (decomp.). ^{1}H-NMR (DCl): δ 3.71 (2H, d, J_{HP} 14 Hz, CH_2P), 4.35 (2H, s, CH_2CO_2). IR (KBr): 1732(s), 1564(m), 1484(m), 1244(s), 1166(s) cm^{-1}.

Elemental analysis for $C_3H_8NO_5P$. Required: C, 21.31; H, 4.76; N, 8.28%. Found: C, 21.35; H, 4.75; N, 8.25%.

Structure determination and refinement. The crystal structure of **3** was solved by direct methods.[15] All non-hydrogen atoms in the asymmetric unit were subjected to anisotropic refinement. All hydrogen atoms were located easily in a difference Fourier map and refined isotropically except H(4) and H(5).

TABLE I

The comparison of crystallographic parameters from five independent crystal structure determinations of *N*-(phosphonomethyl)glycine

	A	*B*	*C*	*D*	*E*
Space group:	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1$	$P2_1/c$
Lattice constants in Å:					
a	8.682(5)	8.673(2)	8.681[a)]	7.1190(5)	8.687(1)
b	7.973(8)	7.977(3)	7.981	5.428(1)	7.989(1)
c	9.875(5)	9.889(3)	9.893	9.1225(5)	9.893(2)
β (deg.)	105.74(4)	105.67(3)	105.77	105.043(6)	105.75(1)
Z	4	4	4	2	4
R	0.030	0.057	0.035	0.034	0.032
R_w	-	0.058	0.050	0.034	0.049

A: ref. 8; *B*: ref. 9; *C*: ref. 10, [a)] No esd's are given;

D: this work, compound **3**, new crystalline polymorph of **1**;

E: this work, the redetermination of the crystal structure of commercial **1**.

The computations were performed on a personal computer with the SHELXTL system.[15] Full matrix least-squares refinements converged to the *R* and R_w indices listed in Table I. At this point, the crystal structure of the commercial **1** (recrystallized from hot water) has been solved for the comparison (see Table I). This is the most precise determination of the lattice parameters of *N*-(phosphonomethyl)glycine, **1** so far as the esd's present about three to eight-fold decrease as compared with the previous determinations[8,9] (Table I). The lattice constants of the new polymorph **3** of the **1** determined in this work present a ten-fold increase in accuracy.

Experimental data for the crystallographic analyses are reported in Table II (new polymorph of glyphosate, **3** and commercial glyphosate, **1**).

RESULTS AND DISCUSSION

Figures 1 and 2 show the molecules of new polymorphic form **3** of the glyphosate and of the commercial glyphosate **1**, respectively with the numbering scheme adopted which is consistent with that one in Reference 8. The bond lengths and angles are almost identical within the 3σ range. However, the conformation of the backbone

TABLE II

Structure determination summary
for new polymorph of glyphosate, **3** and commercial glyphosate, **1**

	1	3
Crystal Data		
Empirical Formula	$C_3H_8NO_5P$	
Color; Habit	colourless prisms	
Crystal size (mm)	0.64x0.64x0.72	0.28x0.28x0.14
Crystal System	monoclinic	
Space Group	$P2_1$	$P2_1/c$
Unit Cell Dimensions	a = 7.1190(5)	a = 8.6870(10)
	b = 5.4276(10)	b = 7.9890(10)
	c = 9.1225(5)	c = 9.893(2) Å
	β = 105.043(6)°	β = 105.75(1)°
Volume, V	340.41(7)	660.8(2) Å^3
Formula weight	M_r = 169.1	
Density(calc.)	1.650	1.699 Mg/m^3
Absorption Coeff.	0.360	0.371 mm^{-1}
F(000)	176	352
Data Collection		
Diffractometer Used	CAD4/V	Siemens R3m/V
Radiation	MoKα (λ = 0.71073 Å)	
Temperature (K)	293	
Monochromator	Highly oriented graphite crystal	
2θ Range	2.0 to 52.8°	3.5 to 53.0°
Scan Type	ω	2θ - θ
Scan Speed: variable;	1.37 to 5.50°/min. in ω	4.19 to 29.30° in ω
Scan Range (ω)	0.78°	1.10° plus $K\alpha$ sepn.
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time	
Standard Reflections	2 measured every 60 minutes	2 every 48 refls.
Index Ranges	$0 \le h \le 8$, $0 \le k \le 6$, $-11 \le l \le 11$	$0 \le h \le 10$, $0 \le k \le 10$, $-12 \le l \le 11$
Refls. Collected	834	1458
Independent Refls.	774 (R_{int} = 3.51%)	1370 (R_{int} = 1.39%)
Observed Refls.	769	1329 [$F > 3.0\sigma(F)$]
Absorption Correction	n/a	semi-empirical
Min./Max. transmission		0.8045/0.9240
Solution and Refinement		
System Used	Siemens SHELXTL PLUS (PC Version)	
Solution	Direct Methods	
Refinement Method	Full-Matrix Least-Squares	

TABLE II (*Continued*)

	1	3
Quantity Minimized	$\sum\omega(F_o-F_c)^2$	
Extinction Correction	χ= 0.51(3), where $F^* = F\,[1 + 0.002\chi F^2/\sin(2\theta)\,]^{-1/4}$	χ = 0.0085(14), where $F^* = F\,[\,1\;0.002\chi F^2/\sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Riding model, fixed isotropic U	
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0030F^2$	$w^{-1} = \sigma^2(F) + 0.0006F^2$
Number of Parameters Ref.	122	122
Final *R* Indices (obs. data)	*R* = 3.18, *wR* = 3.95,	*R* = 3.16, *wR* = 4.94%
R Indices (all data)	*R*= 3.27, *wR* = 4.32	*R* = 3.39, *wR* = 4.17%
Goodness-of-Fit	0.78	1.80
Largest and Mean Δ/σ	0.941, 0.190	0.432, 0.139
Data-to-Parameter Ratio	6.3 :1	10.7 : 1
Largest Difference Peak	0.50	0.42 $e\text{Å}^{-3}$
Largest Difference Hole	-0.41	-0.30 $e\text{Å}^{-3}$

TABLE III

The comparison of torsion angles

Torsion angle	New polymorphic form of glyphosate, 3	Commercial glyphosate, 1
H(1)-O(1) - P -C(1)	60.1(3.6)	46.2(2.6)
O(1)- P -C(1)- N	-79.8(2)	75.3(1)
O(2)- P -C(1)- N	162.6(1)	-166.6(1)
O(3)- P -C(1)- N	33.9(2)	-37.6(1)
P - C(1)- N -C(2)	-85.7(2)	-174.6(1)
C(1)- N -C(2)-C(3)	-79.1(3)	74.4(2)
N - C(2)-C(3)-O(4)	-8.8(4)	2.0(2)
N - C(2)-C(3)-O(5)	171.2(2)	-177.5(1)

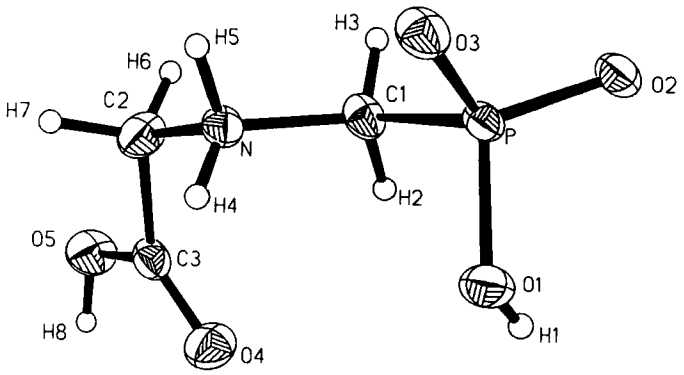

FIGURE 1 The structure of the new polymorphic form of *N*-(phosphonomethyl)glycine, **3** in the crystal.

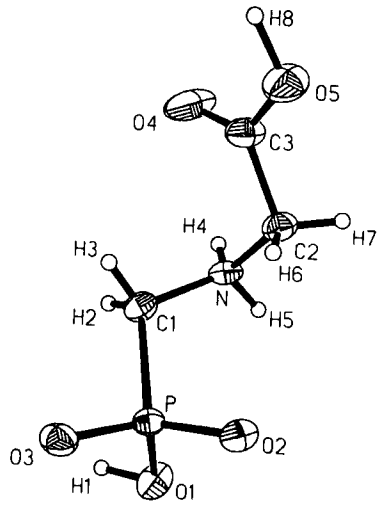

FIGURE 2 The structure of the commercial *N*-(phosphonomethyl)glycine, **1** in the crystal. The numbering scheme is that one adopted in Figure 1.

in both molecules is different as the comparison of the torsion angles in Table III show. Figure 3 shows the fitting of the two molecules. The packing of the molecules in the crystal structure of **3** is determined, as it is in the structure of **1**, by the extensive system of hydrogen bonds. This packing in the crystal structure of **3** is slightly less dense (density 1.650 Mg m^{-3}) as compared with **1** (density 1.699 Mg m^{-3}); decrease ca. 3%. Fractional atomic coordinates of the new polymorph of glyphosate, **3** are given in Table IV; selected bond lengths and angles are listed in Table V.

Note. The tables of experimental data for the crystallographic analyses, of bond lengths and angles, of coordinates for the hydrogen atoms, of anisotropic or isotropic thermal parameters were deposited with the Cambridge Crystallographic Data Center (CCDC) U.K.

TABLE IV

Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^4$) of new crystalline polymorph of *N*-(phosphonomethyl)glycine, **3**

	x	y	z	U(eq)
P	75366(5)	50000	90097(4)	181(2)
O(1)	83216(22)	57961(53)	107116(16)	297(5)
O(2)	58813(20)	32678(48)	89717(17)	246(5)
O(3)	91610(22)	41303(54)	83547(17)	288(5)
C(1)	66321(31)	77898(48)	79656(25)	222(6)
N	46616(26)	84819(54)	81096(21)	206(5)
C(2)	30389(32)	72658(64)	69996(26)	272(7)
C(3)	26798(33)	85428(67)	54851(26)	308(7)
O(4)	34616(33)	104457(60)	53204(22)	497(7)
O(5)	14438(28)	73372(65)	44142(19)	441(7)

• Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

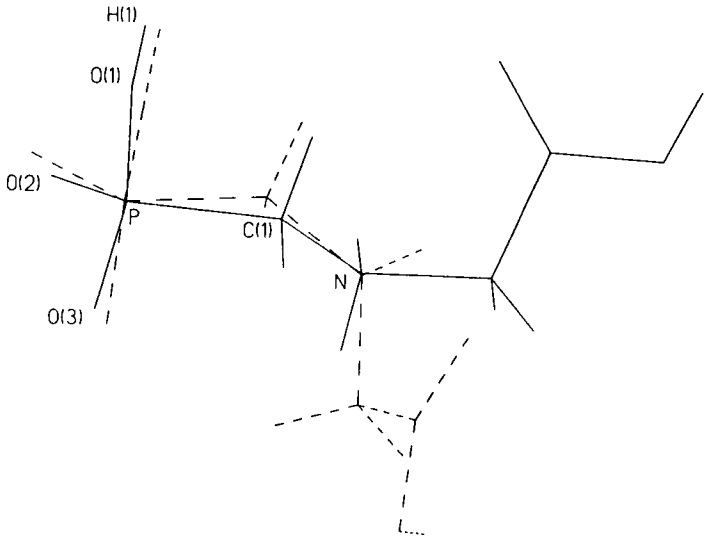

FIGURE 3 The fitting of the two molecules showing the different conformations of the chain. —— **3**, the new polymorphic form of **1**; - - - - the molecule of **1**.

ACKNOWLEDGEMENTS

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TABLE V

Selected bond lengths (Å) and angles (°) with esd's in parentheses for new crystalline polymorph of *N*-(phosphonomethyl)glycine, **3**

		Bonds	
P-O(1)	1.568 (2)	P-O(2)	1.501 (2)
P-O(3)	1.509 (2)	P-C(1)	1.816 (2)
O(1)-H(1)	1.021 (56)	C(1)-H(2)	0.903 (32)
C(1)-H(3)	0.936 (39)	C(1)-N	1.491 (3)
N-H(4)	0.698 (48)	N-H(5)	0.899 (33)
N-C(2)	1.479 (3)	C(2)-H(6)	0.957 (47)
C(2)-H(7)	1.015 (37)	C(2)-C(3)	1.507 (4)
C(3)-O(4)	1.201 (5)	C(3)-O(5)	1.308 (3)
O(5)-H(8)	1.038 (64)		
		Angles	
O(1)-P-O(2)	105.7(1)	O(1)-P-O(3)	111.4(1)
O(2)-P-O(3)	118.2(1)	O(1)-P-C(1)	106.0(1)
O(2)-P-C(1)	109.9(1)	O(3)-P-C(1)	104.9(1)
P-O(1)-H(1)	105.9(26)	P-C(1)-N	112.2(2)
H(4)-N-H(5)	99.1(40)	C(1)-N-C(2)	114.4(2)
H(6)-C(2)-H(7)	116.0(37)	N-C(2)-C(3)	109.8(2)
C(2)-C(3)-O(4)	122.4(2)	C(2)-C(3)-O(5)	112.1(3)
O(4)-C(3)-O(5)	125.5(3)	C(3)-O(5)-H(8)	114.8(42)

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