Crystal Structure and Postemergent Herbicidal Activity of Geometrical Isomers of Methyl [[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetate

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The solid-state structure and conformation of the *E* and *Z* geometrical isomers of a new diphenyl ether herbicide, methyl [[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]-amino]oxy]acetate (AKH-7088), were determined by direct methods and refined by least squares to final residuals of 0.086 for 3425 and 0.058 for 2961 observed reflections, respectively. Greenhouse testing with postemergent application at 0.025–0.2 kg/ha showed no significant difference between the two isomers in herbicidal effect on broadleaf weeds or tolerance by soybean and corn. These results demonstrate that the substituent adjacent to the nitro group of AKH-7088 effectively nullifies receptor selectivity between trans and cis isomer conformations and suggest further that the receptor might exhibit considerable tolerance to the length of the substituent.

INTRODUCTION

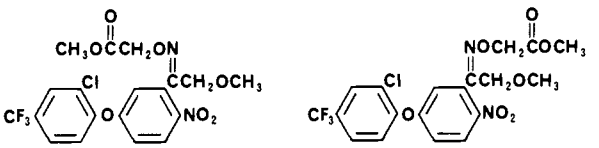
Methyl (*E*,*Z*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)-phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]-oxy]acetate (AKH-7088) is a novel compound (Figure 1) with selective herbicidal effects discovered in 1984 and currently under development as a herbicide by Asahi Chemical Industry Co., Ltd. (Hayashi and Misumi, 1984, 1987). It is a new postemergence herbicide for selective control of a wide spectrum of broadleaf weeds in soybeans. The preceding papers reported the syntheses and herbicidal activities of AKH-7088, a mixture of the *E* and *Z* geometrical isomers (Hayashi, 1990), and the synthesis, NMR analysis, and biological effects of each isomer alone (Hayashi and Kouji, 1990).

Determination of crystal structures by X-ray crystallography has been reported for nitrodiphenyl ether herbicide (Kennard et al., 1987) and phenoxyphenoxy grass herbicides (Smith et al., 1981; Makino et al., 1987), but not for oxime type herbicides consisting of geometrical isomers.

In the present study, we therefore investigated the solid-state structure and conformation of the geometrical *E* and *Z* isomers of AKH-7088 (Figure 1) by X-ray crystallography and further compared their biological activities.

EXPERIMENTAL PROCEDURES

Apparatus. Melting points were determined with a Mettler FP61 melting point apparatus and are uncorrected (degrees Celsius). Refractive index was determined with an Abbe refractometer. Mass spectra were recorded on a JEOL DX-303. NMR spectra were recorded on a JEOL GX-270 and a PMX-60$_{SI}$. Chemical purities were determined on Jasco liquid chromatographs 880-PU and 875-UV. X-ray measurements were performed on a Rigaku AFC-6 four-circle diffractometer at the High Brilliance X-Ray Laboratory of Hokkaido University.



E isomer *Z* isomer

Figure 1. Geometrical isomers of AKH-7088.

Compounds. The *E* and *Z* geometrical isomers of methyl [[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetate (AKH-7088) were synthesized by previously reported procedures (Hayashi and Kouji, 1990). Structural identification of the *E* and *Z* isomers was made by proton and carbon-13 NMR spectroscopy.

The *E* isomer of AKH-7088 was prepared by methyl esterification of (*E*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic acid, and the X-ray analytical grade crystals were obtained by recrystallization successively from isopropyl ether, ethyl acetate–hexane mixture, and carbon tetrachloride–hexane mixture, mp 57.5–58.5 °C. The *Z* isomer of AKH-7088 was prepared from (*Z*)-2-methoxy-1-[2-nitro-5-[2-chloro-4-(trifluoromethyl)-phenoxy]phenyl]ethanone oxime and methyl bromoacetate, and the analytical grade crystals were obtained by recrystallization from ethyl acetate, mp 99–100 °C. Chemical purity of the *E* and *Z* isomers as determined by HPLC was 99.5% and 99.4%, respectively.

X-ray Structure Determination for the *Z* Isomer of AKH-7088. A single crystal with dimensions of ca. 0.2 × 0.3 × 0.4 mm was used. The crystal data were as follows: $C_{19}H_{16}ClF_3N_2O_7$; M_r = 476.8; monoclinic, space group $P2_1/c$; a = 15.546(3) Å, b = 7.373(1) Å, c = 18.092(4) Å, β = 93.64 (2)°; V = 2069 Å^3; Z = 4; D_{calcd} = 1.530 g cm^{-3}; $F(000)$ = 976; μ (Mo Kα) = 2.51 cm^{-1}. The unit-cell dimensions and reflection intensities were obtained on a four-circle diffractometer (40 kV, 30 mA) using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The θ–2θ scanning mode was employed at a θ scan rate of 2 deg min^{-1}; the background was counted for 15 s at each end of the scan range. Three standard reflections, measured at intervals of every 100 reflections, showed no significant decrease in intensity during the course of data collection. No corrections were made for absorption and extinction effects. In the range of 2θ values up to 52°, 2961 unique structure factors above the 3σ(F) level were selected for the structure determination.

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The structure was solved by the Monte Carlo direct method (Furusaki, 1979) and refined by the block-diagonal least-squares method with anisotropic thermal parameters. After all the hydrogen atoms had been located in a difference Fourier map, further least-squares refinements were carried out including the hydrogen atoms with individual isotropic thermal parameters. For these refinements, the weighting scheme used was $w = 1/\{\sigma(F)^2 \exp(c_1X^2 + c_2Y^2 + c_3XY + c_4X + c_5Y)$, where $X = |F_0|$ and $Y = \sin\theta/\lambda$. The c_1–c_5 coefficients were evaluated from the $(\Delta F)^2$ distribution. The final R value was 0.058. The atomic parameters thus obtained are listed in Tables I and II (supplementary material). The atomic scattering factors and anomalous dispersion corrections were taken from the *International Tables* (Ibers and Hamilton, 1974).

X-ray Structure Determination for the *E* Isomer of AKH-7088. A single crystal with dimensions of ca. 0.2 × 0.4 × 0.4 mm was used. The crystal data were as follows: $C_{19}H_{16}ClF_3N_2O_7$; M_r = 476.8; monoclinic; space group $C2/c$; a = 28.216(9) Å, b = 12.613(4) Å, c = 24.918(11) Å, β = 104.94(3)°; V = 8568 Å^3; Z = 16; D_{calcd} = 1.478 g cm^{-3}; $F(000)$ = 3904; μ (Mo Kα) = 2.42 cm^{-1}. In the range of 2θ values up to 47°, 3425 independent structure factors above the $3\sigma(F)$ level were obtained in much the same way as used for the Z isomer.

The structure containing 64 independent non-hydrogen atoms was solved by the Monte Carlo direct method and refined by the block-diagonal least-squares method with anisotropic thermal parameters. A difference Fourier map revealed 26 hydrogen atoms. Further least-squares refinements including the hydrogen atoms reduced the R value to 0.086. The final atomic coordinates and equivalent isotropic thermal parameters for two independent molecules, A and B, are given in Table III (supplementary material).

Biological Testing. The separate E and Z isomers of AKH-7088 were evaluated for postemergent herbicidal activity in a greenhouse by the method reported previously (Hayashi and Kouji, 1990).

Seeds of four broadleaf species and two crops were planted in pots each filled with a sterilized upland soil having a surface area of 0.24 m^2. The test broadleaf species with velvetleaf (*Abutilon theophrasti*; VL), lambsquarter (*Chenopodium album*; LQ), morningglory (*Ipomoea spp.*; MG), and smartweed (*Polygonum lapathifolium*; SW); the crops were soybean (*Glycine max* var. Williams; SOY) and corn (*Zea mays*; CN).

Postemergence treatment was effected by applying the composition at dosages of 0.025, 0.05, 0.1, and 0.2 kg/ha when the soybean, corn, and weeds were respectively at the 0.8–1.0, 4–4.5, and 1–3.1 leaf stage. All treatments were replicated three times. On day 14, percent weed control was determined by visual estimation of percent plant growth reduction in treated as compared with nontreated weeds. On day 21, percent crop injury was determined in the same manner.

RESULTS AND DISCUSSION

Molecular Structures. The atom numbering scheme and molecular conformations for the E and Z isomers of AKH-7088 are shown in Figure 2. The bond distances and angles are listed in Tables IV and V, respectively (supplementary material), and significant torsion angles are given in Table VI. For both the A and B molecules of the E isomer, the large U_{eq} values [0.136(7)–0.246(12) Å^2] for fluorine atoms (Table III) as well as the short C–F bond distances [1.22(2)–1.29(1) Å] (Table IV) suggest some degree of disorder in the trifluoromethyl groups. Except for these groups, the corresponding bond distances in the E and Z isomers are nearly equal to each other within the range of experimental error. As would be expected from the configurational difference at bond N(2)–O(5), bond angles C(1)–C(14)–N(2) and C(15)–C(14)–N(2) in the E isomer make a marked contrast with those in the Z isomer; in the E isomer, the former angle is significantly larger than the latter and, in the Z isomer, vice versa (Table V).

In both isomers, the conformation of ring X with respect to ring Y is such as to minimize interaction between the two ring-substituent groups. As shown in Table V, the steric repulsion between ring X and ring Y occurs C(6)–C(5)–O(1)›C(4)–C(5)–O(1) and C(12)–C(7)–O(1)›C(8)–C(7)–O(1).

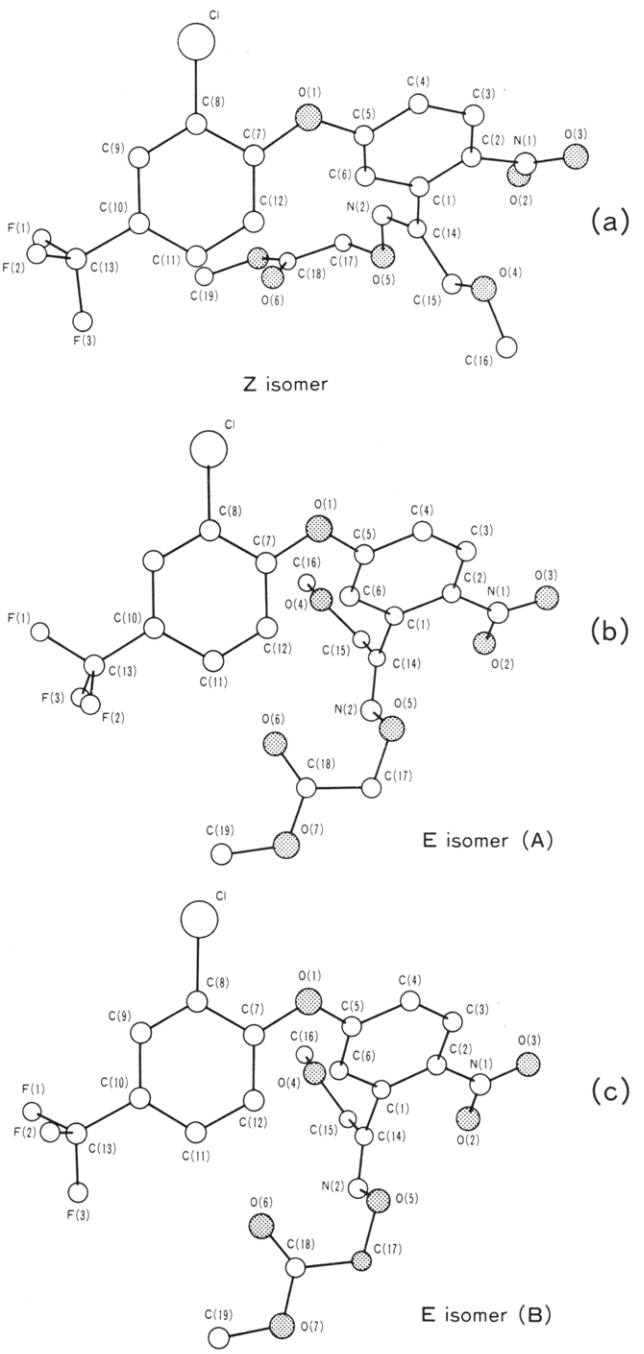

Figure 2. Molecular conformations and atom numbering schemes for (a) the Z isomer and for (b) the A molecule and (c) the B molecule of the E isomer of AKH-7088. View perpendicular to the plane of ring Y.

The nitro group in ring X, which in a benzene ring would generally be coplanar with the ring, is twisted at angles of about 25° and 10° to the phenyl ring in the Z isomer and that in the A molecule of the E isomers, respectively, while the adjacent planar moiety (**1**) containing sp^2-

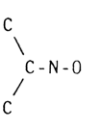

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Table VI. Comparative Torsion Angles (Degrees)

	Z form	E form(A)	E form(B)	acifluorfen[a]
C(5)-O(1)-C(7)-C(8)	-141.4(3)	-147.0 (8)	-143.4 (8)	89.6(8)
C(6)-C(5)-O(1)-C(7)	24.0(5)	33.0(12)	23.5(13)	-162.4(8)
C(1)-C(2)-N(1)-O(3)	-153.6(3)	-169.7 (8)	-177.2 (8)	178.5(6)
C(2)-C(1)-C(14)-N(2)	-125.0(3)	100.1(10)	100.6(11)	-79.6(6)
C(2)-C(1)-C(14)-C(15)	60.6(4)	-85.0(11)	-85.0(11)	
C(1)-C(14)-C(15)-O(4)	1.3(4)	-52.4 (9)	-43.8(10)	
C(14)-C(15)-O(4)-C(16)	164.1(3)	-179.2 (7)	174.6 (7)	
C(1)-C(14)-N(2)-O(5)	-177.5(3)	-8.3(11)	-8.8(11)	
C(15)-C(14)-N(2)-O(5)	-3.5(4)	176.5 (7)	176.7 (7)	
C(14)-N(2)-O(5)-C(17)	176.0(3)	166.1 (8)	169.8 (7)	
N(2)-O(5)-C(17)-C(18)	-81.6(3)	-75.4(10)	-73.6 (9)	
O(5)-C(17)-C(18)-O(7)	-166.6(3)	-179.7 (8)	174.2 (7)	
C(17)-C(18)-O(7)-C(19)	176.7(3)	-177.5(10)	177.3(10)	
C(9)-C(10)-C(13)-F(1)	45.8(5)	-3.3(15)	40.6(13)	

[a] The values for acifluorfen are from Kennard et al. (1987).

Table VII. Greenhouse Postemergent Herbicidal Activities and Selectivities of AKH-7088 *E* and *Z* Isomers Separately, as Percent Inhibition of Untreated Control Growth Determined for Weeds on Day 14 and for Crops on Day 21 after Application

compd	kg/ha	VL	LQ	MG	SW	SOY	CN
E isomer	0.20	100	100	90	100	25	10
	0.10	100	95	75	95	20	5
	0.05	100	90	60	80	15	2
	0.025	100	68	50	75	8	0
Z isomer	0.20	100	100	90	100	25	15
	0.10	100	93	72	92	20	7
	0.05	100	90	65	80	10	2
	0.025	100	65	55	78	5	0
leaf stage		2.2-2.5	2.2-3.0	1.0-1.2	2.5-3.1	0.8-1 trifoliates	4-4.5

carbon and nitrogen is twisted at 55° and 80° to the nitrophenyl ring in the *Z* and *E* isomers, respectively, because of steric and electrostatic repulsion between the nitro group and the substituent. As shown in Tables IV and V, all bond distance and bond angle parameters found for both isomers, except for the substituent adjacent to the nitro group, are similar to those of acifluorfen (Kennard et al., 1987), and as shown in Table VI, both torsion angles C(2)-C(1)-C(14)-N(2) and C(2)-C(1)-C(14)-C(15) define the *E* and *Z* conformations.

Biological Activity. As shown in Table VII, the biological test of the *E* and *Z* isomers of AKH-7088 alone indicates that they are mutually virtually indistinguishable in herbicidal effect and in degree and appearance of crop injury. This similarity of effect may be interpreted as indicating that the two AKH-7088 isomers are recognized as bearing the same substituent at the herbicide-binding site and thus fitting nearly equally and nonselectively to the receptor. That is to say, in the presence of the large substituent group as in AKH-7088, with a characteristic van der Waals volume, the isomeric distinction by the receptor is apparently nullified.

Although the molecular conformation in the crystal is not necessarily the same as that at the active site, it might nevertheless provide important information pertaining to the three-dimensional interaction between the bioactive substance and its receptor site.

As a quantitative approach to expression of the steric characteristics that may be involved, we constructed views of the substituents of the two AKH-7088 isomers, based on three-dimensional projections from the coordinate data obtained X-ray analysis and the van der Waals radii in angstroms (10^{-1} nm) of each atom, and defined the steric parameters L_X, T_{XR}, T_{XL}, W_{XR}, and W_{XL} as shown in Figure 3. As the X-ray analysis showed the moiety 1 in the substituent to be planar, the front view was constructed by projection parallel to this plane and the bond axis through C(1) and C(14) from the direction of nitrophenyl ring, and the top view of projection perpendicular to this plane. L_X is the maximum length of the substituent in the direction of the C(1)-C(14) bond axis. W_{XR} is the maximum width of the right-hand part of the substituent, i.e., the methoxymethyl moiety, as measured from the bond axis when viewed from the connecting end; W_{XL} is that of the left-hand part, i.e., the methoxycarbonylmethoxylimino moiety. T_{XR} and T_{XL} are the maximum thicknesses of the former and the latter moieties, respectively, as measured in an analogous manner. These parameters are similar to width and thickness parameters, different from the original STERIMOL B parameters by Verloop et al. (1976), which have been defined in

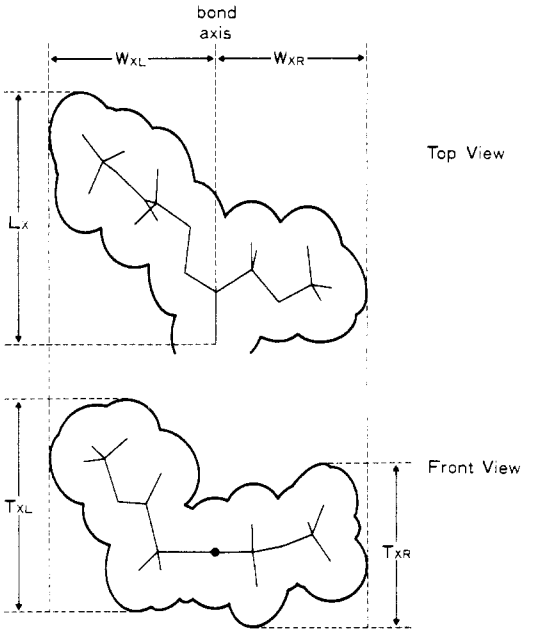

Figure 3. Schematic representation of steric parameters L_X, W_{XR}, W_{XL}, T_{XR}, and T_{XL}.

consideration of the conformational correspondence between substituents, calculated on the basis of the CPK model, and applied to quantitative structure–activity relationship (QSAR) analysis by Iwamura et al. (Iwamura, 1981; Iwamura et al., 1983).

The calculated values of L_X, W_{XR}, W_{XL}, T_{XR}, and T_{XL} are, respectively, 4.822, 4.643, 6.410, 3.971, and 5.319 Å for the substituent of the *E* isomer and 6.828, 4.903, 5.548, 3.600, and 5.258 Å for that of the *Z* isomer. As would be expected from the similarity in activity of the two isomers, the values of W_{XR}, W_{XL}, T_{XR}, and T_{XL} for the two isomers coincide fairly closely, thus indicating a favorable fitting of either compound to the receptor under similar circumstances. On the other hand, the L_X value for the *E* isomer is considerably smaller than that for the *Z* isomer, which may be taken as an indication that the difference in the conformation between the two isomers is revealed only as a difference in substituent length. The exhibition of virtually the same biological activity by the two isomers, in spite of this difference, suggests that the site of action is rather tolerant to the length of the substituents.

Consequently, the results of the present study suggest that the region of the receptor site where the L_X part of the C(1) substituent comes on is sterically flexible.

ACKNOWLEDGMENT

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Supplementary Material Available: Tables I–V, listing atomic coordinates, thermal parameters, bond distances, and bond angles for the *E* and *Z* isomers (14 pages). Ordering information is given on any current masthead page.

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Registry No. (*E*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)-phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]-acetate, 124482-58-2; (*Z*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)-phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]-acetate, 124482-57-1.