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Quantitative Structure–Activity Relationship of Photosystem II Inhibitors in Chloroplasts and Its Link to Herbicidal Action

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Inhibition of photosystem II electron transport by anilides, phenylureas, carbamates, and triazines was shown kinetically to be competitive at the site of action. We found that the herbicidal activity of these classes of compounds is directly related in a very similar way for all four to the inhibition of photosystem II. We also analyzed their modes of interaction, finding that various steric parameters are important for their activity in chloroplasts, as well as the hydrophobic and electronic factors already known. The results suggest that the four classes of compounds act at a common site and that steric interaction there is important for inhibition of the photosynthetic electron transport and thus for herbicidal activity.

Several chemically different classes of herbicides such as phenylureas, acylanilides, *N*-phenylcarbamates, uracils, triazines, triazinones, pyridazinones, and benzimidazoles act by interfering with the reducing side of photosystem II (PS II). The results of a number of biochemical and biophysical experiments have been interpreted to indicate that these herbicides bind to a protein with the molecular weight of 32 000–34 000 within the thylakoid membrane: this was reviewed in recent articles (Dodge, 1983; van Rensen, 1982; Pfister and Arntzen, 1979). Strotmann et al. (1973) and Tischer and Strotmann (1977) found that phenylureas, triazines, triazinones, pyridazinones, and bis(carbamates) bind competitively at the same site in the thylakoid membranes.

Studies with weeds resistant to a triazine herbicide atrazine [2-chloro-4-(ethylamino)-6-(isopropylamino)-1,3,5-triazine], on the other hand, showed that photosynthetic electron flow in chloroplasts isolated from a resistant biotype is inhibited by a *N*-phenylurea herbicide DCMU [3-(3,4-dichlorophenyl)-1,1-dimethylurea], suggesting that the resistance is specifically linked with a change in the triazine binding site (Pfister and Arntzen, 1979). However, this view seems to contradict the findings described above of Tischer and Strotmann (1977) that both the triazine and *N*-phenylurea compounds bind competitively to the same site in normal chloroplasts.

To resolve this apparent discrepancy, Pfister and Arntzen (1979) proposed a binding site model where a part of the molecule of each class binds to a common domain but the rest of the molecule binds specifically to its own region. If an alteration occurred in the specific region, the selective resistance is explainable. In this situation, the interaction at the receptive site of PS II inhibitors should have common features at only part of the molecules. Alternatively, Trebst and Draber (1979) suggested that there are multiple binding sites for each class of herbicides and that some of the sites are shared by another class of compounds. Selective resistance can also be explained by this assumption, but in this case the classes of compounds should have very similar or overlapping features in their mode of interaction that involves the whole molecule.

Gressel (1982) showed that chloroplasts from *Spirodela* with most of their 32–34-kDa protein depleted are not more tolerant to atrazine than those containing this protein. Oettmeier et al. (1982) examined in more detail the selective resistance between classes to show that resistance was also developed to various classes of herbicides to some extent. Even for triazines, the resistance varied, with pI_{50} values for several highly lipophilic derivatives in resistant chloroplasts exceeding those in susceptible chloroplasts. Since there are very significant differences in thylakoid lipid composition between resistant and susceptible biotypes (Pillai and John, 1981; Blein, 1980), it was suspected that penetration of a herbicide into the membranes to reach the binding site may be different in susceptible and resistant chloroplasts (Gressel, 1982; Oettmeier et al., 1982).

One way to examine these hypotheses might be to establish the identity or nonidentity of the functional binding that leads to inhibition of electron flow and the similarity or dissimilarity of the mode of interaction of each class of compounds at the receptive site. Thus, we first examined kinetically the binding nature of classes of herbicides shown in Figure 1 in terms of biological activity, applying the method of Lineweaver and Burk (1934). The results with the structurally congeneric anilides, ureas, and carbamates and chemically different triazines suggested that their binding to spinach chloroplasts that was responsible for the shielding of electron transport is competitive at a common site. We then found that their herbicidal activity is directly related to the inhibition of the PS II electron flow. On the basis of these results, we examined by regression analysis the similarity or dissimilarity of the modes of action, especially the steric ones, at the site of action of the four classes of compounds. The results indicated that the structure–activity profiles of anilides, ureas, and carbamates are identical or at least very similar on the basis of whole molecule. It seems that the acyl moiety of these anilide compounds corresponds to the

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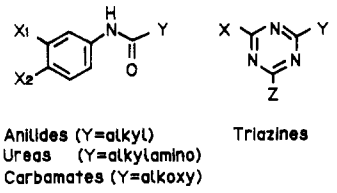

Figure 1. Generic formulas of the compounds studied.

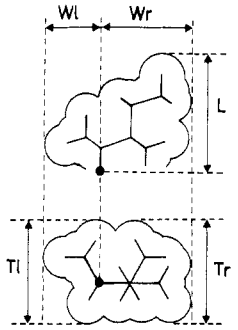

Figure 2. Schematic representation of the steric parameters. The substituent used as the model is 1,2-dimethylbutyl.

shorter one of the two amine substituents of triazines at the interaction site.

MATERIALS AND METHODS

Chemicals. Compounds **A20–A24** were reported by Yamagami et al. (1984); those we used were her gift. Compounds **A2**, **A3**, **A6–A16**, **A19**, **A25**, and **A26** were prepared previously in our laboratory (Hayashi and Fujita, 1983), as were compounds **C1** and **C2** (Kawata et al., 1972), **U1–U5** (Fujita et al., 1969), and **T1** (Nishimura and Nakajima, 1975). Compounds **A1**, **A5**, **A17**, **A18**, **C3**, **C6**, **T3**, **T7**, and **T8** were provided by the Idemitsu Kosan Co., Ltd., **U11–U13**, **U18**, **U17**, and **U19** by Sumitomo Chemical Industries Co., Ltd., and **T2**, **T4**, and **T6** by the Nippon Kayaku Co., Ltd. Compounds **U9** and **U10** were purchased from Chem Service Inc., **U14**, **U15**, and **U20** from National Physical Laboratory, and **U16** from the Tokyo Kasei Kogyo Co., Ltd. The other compounds were synthesized for this study: anilides by addition of an acid chloride in dry benzene to a DMF solution of an appropriately substituted aniline and triethylamine, carbamates in a similar way by reaction of an appropriate phenyl isocyanate with an alcohol in dry benzene, and ureas by the reaction of a phenyl isocyanate with an amine. These reactions were at room temperature. Triazines were prepared by the reaction of 2,6-dichloro-4-(ethylamino)-*s*-triazine (Thurston et al., 1951) with an appropriate amine in the presence of $NaHCO_3$ in water at about 50 °C. The analytical results for C, H, and N of these compounds were within ±0.3% of the theoretical values.

Substituent Parameters. To express the steric features of substituents, we defined the steric parameters L, W_r, W_l, T_r, and T_l as shown by Figure 2 schematically. L is the length of the substituents along the bond axis that connects them to the rest of the molecule. W_r is the maximum width measured from the bond axis (L) in the direction in which the longest chain of the substituents extends in the fully extended (staggered) conformation, and W_l is the width in the opposite direction. T_r expresses the thickness of the right-hand part of the substituents and T_l that of the left-hand part. These steric parameters were calculated by the STERIMOL program developed by Verloop et al. (1976), which gives the coordinates and van der Waals radii in Angstrom units (10^{-1} nm) of a substituent based on the CPK model. The width and thickness parameters are different from the original STERIMOL B parameters in that our definition is made in consideration of the conformational correspondence between substituents (Iwamura, 1980, 1981; Iwamura et al., 1983, 1985: Nakayama et al., 1984).

The partition coefficient P between 1-octanol/water was measured experimentially for the compounds **A1–A3**, **A5**, **A17–A23**, **A25**, **A26**, **C1–C3**, **C6**, **U1–U4**, **U9–U20**, **T1–T3**, **T6–T10**, **T13**, **T17**, and **T19**, and its logarithm, log P, was used as the hydrophobicity parameter. The log P values for the compounds **A6–A16** and **A27** have been previously estimated in our laboratory (Hayashi and Fujita, 1983). The value of **A24** (p-$MeC_6H_5NHCOCH_2C_6H_5$) was calculated by log $P(C_6H_4NHCOCH_2C_6H_5)$ + π(p-CH_3 of anilide) (Fujita, 1983) and that of **U5** (m,p-$Cl_2C_6H_3NHCONHMe$) by log $P(C_6H_5NHCONHMe$, **U1**) + [log P(m,p-$Cl_2C_6H_3NHCONMe_2$, **U16**) − log $P(C_6H_5NHCONMe_2$, **U7**)], the term in the brackets estimating the hydrophobicity difference between m,p-dichloro and unsubstituted analogues. Similarly, the value of ethylthio **T4** was estimated by log P(methylthio **T3**) + [log $P(C_6H_5SEt)$ − log $P(C_6H_5SMe)$]. For compounds having a variation in the Y moiety (Figure 1) from one whose log P value was experimentally measured, the difference in hydrophobicity between the two Y moieties was estimated as that between two YH structures or between π values [$\Delta\pi$(Y)] and was added to the log P values of the parent compound. When fragmental factors were used for the calculation of $\Delta\pi$(Y), the values of 0.54 and −0.13 were adopted for $\pi(CH_3)$ and the branch factor F_{cBr}, respectively (Hansch and Leo, 1979). For cyclopentyl carbamate **C9**, log P = log P(*n*-Bu-**C7**) + $\pi(CH_3)$ + [log P(cyclopentane) − log P(*n*-pentane)] + F_{cBr}. The log P values of the benzanilides **A28–A30** and **A32–A43** were calculated by log P(3,4-$Cl_2C_6H_3NHCOC_6H_4X$) = log P(3,4-$Cl_2C_6H_3NHCOC_6H_5$, **A27**) + π(X), and the π(X) is the π of the benzamide derivatives and was taken from the literature (Fujita, 1983). The value of **A31** was estimated by log P (3,4-$Cl_2C_6H_3NHCOC_6H_4$-m-CF_3) = log P(3,4-$Cl_2C_6H_3NHCOC_6H_5$, **A27**) + [log P(3-$CF_3C_6H_4COOH$) − log $P(C_6H_5COOH)$]. The data necessary for the calculation were taken from the literature (Hansch and Leo, 1979; Pomona College Medicinal Chemistry Data Base).

As the electronic parameter for benzene substituents, the Hammett σ listed by Hansch et al. (1973) was used. For the electronic effect of the Y moiety, σ_I and σ_R were considered and the values were taken from the literature (Charton, 1981). The σ_I values for alkyls higher than *n*-butyl were approximated by that of *n*-butyl, those for branched alkyls at the α position by that of *i*-Pr, and that for 1-methylallyl by allyl. The σ_R values for alkyls that are not available were similarly approximated. For phenyls whose σ_I values are not available, we calculated them from the regression equation formulated in the literature (Iwamura et al., 1985). The σ_R values that are not available were calculated according to the literature (Charton, 1981) from the σ_I values.

Bioassay Procedures. (*A*) *Inhibition of Photosynthetic Electron Flow.* Chloroplasts were isolated from fresh, washed, and depetiolated spinach leaves (120 g) that were homogenized in an ice-cold Waring blender with 200 mL of buffer consisting of tricine (50 mM), NaCl (10 mM), and sucrose (0.4 M) at pH 8.0. The homogenate was filtered through four layers of gauze, and the filtrate was centrifuged at 2000*g* for 10 min. The supernatant was discarded, and the pellets were suspended in homogenizing medium and centrifuged again as above. The chloroplasts were suspended in 25 mL of the buffer, added to the same volume of ethylene glycol, mixed well, and stored at −20

°C until use (Asada and Takahashi, 1971). The amount of chloroplasts was measured by the method of MacKinney (1941).

The reaction mixture consisted of 1.0 mL (15 μg) of chloroplast suspension in a buffer (pH 7.8) of Tris (20 mM), NaCl (10 mM), $MgCl_2 \cdot 6H_2O$ (2 mM), $CH_3NH_2 \cdot HCl$ (10 mM), and sucrose (0.4 M), 1.0 mL of DCIP [(2,6-dichlorophenoxy)indophenol] solution (40 μM) in a buffer (pH 7.2) of Tris-HCl (50 mM) and NaCl (10 mM), and 0.5 mL of a solution of a test compound. Test compounds were dissolved in water containing less than 2% (v/v) of ethanol or methanol or less than 3% (v/v) of Me_2SO, depending on their solubility. The reduction of DCIP was followed at 600 nm by Shimadzu UV-300 spectrophotometer, modified for illumination with red right through a Toshiba R65 filter. The activity was expressed in terms of the logarithm of the reciprocal of the molar concentration at which 50% inhibition of the photosynthetic DCIP reduction is obtained, pI_{50}; the range of the experimental error was within ±0.08.

(B) *Postemergent Herbicidal Activity.* Seeds of Chinese cabbage (*Brassica rapa* L.) were sown on the surface of 2.5 g of absorbent cotton stuffed into a 50-mL beaker and moistened with water containing 0.5 g/L of HYPONEX. The seedlings were grown in a phytotron at 30 °C under daylight conditions and at 25 °C during the night with illumination by fluorescent and tungsten lamps. The seedlings were thinned out to 10 plants per beaker after 2 or 3 days, and the 7–9-day-old plants were sprayed with an emulsified solution of a test compound containing an emulsifier (10%, v/v) prepared with Tween 80, ethylene glycol, and ethanol (1:2:17). The test plants were grown for 7 days after this treatment, derooted, and weighed. The activity was expressed by pLD_{50}, which is the logarithm of the reciprocal of the dose (mol/are) at which is obtained 50% of the fresh weight yield given by the control experiment. The experiments were repeated twice or more, and the average values were reported. The range of the experimental error was within ±0.24.

RESULTS

The inhibition of the PS II electron transport and physicochemical parameters by anilides, carbamates, and ureas are summarized in Table I, and those of triazines, in Table II. The results of herbicidal tests are in Table III.

Competitive Nature of Inhibition of PS II Electron Transport. In Figure 3A, the reciprocal of the percentage inhibition of PS II electron transport by a mixture of DCMU (U16) with an anilide herbicide pentanochlor [A17; *N*-(3-chloro-4-methylphenyl)-2-methylpentanamide] was plotted against the reciprocal of the concentration of DCMU. That the resultant family of straight lines possesses a common intercept fulfills the requisites for competitive inhibition (Lineweaver and Burk, 1934), and this indicates that these two compounds share the same binding site for the expression of biological activity. Similar results were obtained for a carbamate herbicide swep [C1; methyl *N*-(3,4-dichlorophenyl)carbamate] and a triazine herbicide atrazine (T7) (Figure 3B,C), so these compounds also share the binding site with DCMU. Although this treatment was not tried for all compounds, the results strongly suggest the competitive nature of functional binding of each class of compounds with another, providing a basis for investigating the mode of interaction of the different classes of herbicides with a common receptor.

Relationship between the Inhibition of PS II Electron Transport and the Herbicidal Activity. To examine how postemergent herbicidal activity is related

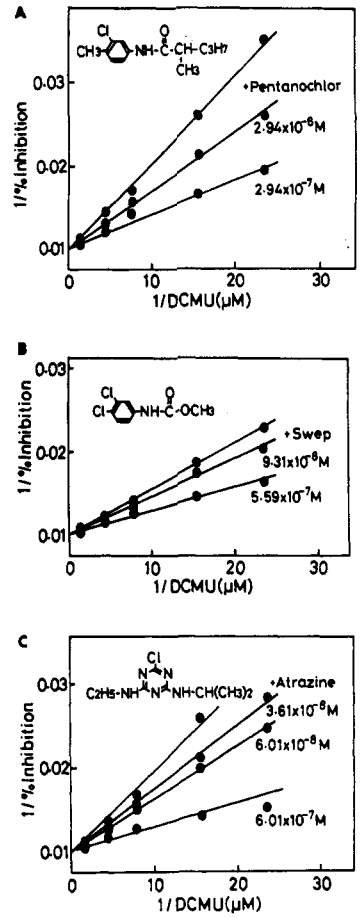

Figure 3. Reciprocal of the percentage of inhibition of PS II electron flow as a function of the reciprocal of the concentration of DCMU (U16), in the presence of (A) pentanochlor (A17) (B) swep (C1), and (C) atrazine (T7).

to the inhibition of PS II electron transport, we analyzed this activity in terms of the inhibition and structural parameters, finally obtaining a single, common equation (1a, 1b) for a set of the four classes of representative com-

$$pLD_{50} = \underset{(0.16)}{0.56}pI_{50} - \underset{(0.96)}{1.79} \quad (1a)$$

$$n = 34,\ s = 0.43,\ r = 0.78,\ F_{1,32} = 50.31$$

$$pLD_{50} = \underset{(0.15)}{0.64}pI_{50} - \underset{(0.15)}{0.26}\ \log P - \underset{(0.83)}{1.53} \quad (1b)$$

$$n = 34,\ s = 0.34,\ r = 0.85,\ F_{1,33} = 12.91$$

pounds. In these and the following equations, n is the number of compounds analyzed, r is the multiple correlation coefficient, and s is the standard deviation. The figures in parentheses are the 95% confidence intervals. The squared correlation coefficient between the pI_{50} and log P was 0.29, and the steric and electronic parameters were not significant over the 95% level. The results show that the essentials of the postemergent herbicidal action of these classes of compounds are the same, the log P term in eq 1b probably reflecting the transport processes.

Quantitative Structure–Activity Relationships in Photosystem II Inhibition. (A) *Anilides, Ureas, and Carbamates.* The inhibition of PS II electron flow by 26 anilides whose Y moiety is alkyl (A1–A26) in Table I was plotted against the log P values, giving Figure 4. The dispersed plots show that the correlation with the hydrophobicity only of the molecules is quite incomplete for this set of compounds where the structure of the acyl moiety is varied as well as the benzene substituents. The data are not shown, but the addition of the electronic parameter

Table I. Inhibition of Photosystem II Electron Transport and Physicochemical Parameters of Anilides, Carbamates, and Ureas

				activity			physicochem param					
				pI_{50}, M								
no.	X_1	X_2	Y	obsd	calcd[a]	ΔpI_{50}	log P	σ	L(Y)	W_l(Y)	T_r(Y)	$W_r(X_1)$
A1	Cl	Cl	Et	6.35	5.86	−0.49	3.38	0.52	4.11	1.52	3.80	1.80
A2	Cl	Cl	*i*-Pr	6.07	6.43	0.36	3.72	0.52	4.11	2.76	3.80	1.80
A3	Cl	Cl	*i*-Bu	4.94	4.88	−0.06	4.11	0.52	4.92	1.52	5.06	1.80
A4	Cl	Cl	*n*-Bu	6.43	5.99	−0.44	4.46	0.52	6.17	1.90	3.80	1.80
A5	Cl	Cl	1-Me-allyl	6.77	6.27	−0.50	3.49	0.52	4.11	3.09	3.80	1.80
A6	H	H	1-Me-c-Pr	5.04	5.11	0.07	2.01	0.00	4.29	2.86	3.80	1.00
A7	Cl	H	1-Me-c-Pr	5.72	5.74	0.02	2.98	0.37	4.29	2.86	3.80	1.80
A8	Br	H	1-Me-c-Pr	5.50	5.85	0.35	3.14	0.39	4.29	2.86	3.80	1.95
A9	NO_2	H	1-Me-c-Pr	4.21	4.63	0.42	2.36	0.71	4.29	2.86	3.80	2.44
A10	OMe	H	1-Me-c-Pr	4.57	4.72	0.15	2.15	0.12	4.29	2.86	3.80	2.86
A11	CF_3	H	1-Me-c-Pr	5.32	5.71	0.39	3.19	0.43	4.29	2.86	3.80	2.61
A12	H	F	1-Me-c-Pr	5.14	5.28	0.14	2.19	0.06	4.29	2.86	3.80	1.00
A13	H	Cl	1-Me-c-Pr	5.80	5.91	0.11	2.86	0.23	4.29	2.86	3.80	1.00
A14	H	OMe	1-Me-c-Pr	4.78	5.00	0.22	1.76	−0.27	4.29	2.86	3.80	1.00
A15	H	CN	1-Me-c-Pr	4.51	4.73	0.22	2.11	0.66	4.29	2.86	3.80	1.00
A16	Cl	Cl	1-Me-c-Pr	6.88	6.28	−0.60	3.63	0.52	4.29	2.86	3.80	1.80
A17	Cl	Me	CH(Me)-*n*-Pr	6.48	6.22	−0.26	4.31	0.20	6.17	2.76	3.80	1.80
A18	H	Cl	$C(Me)_2$-*n*-Pr	5.80	5.97	0.17	3.83	0.23	6.17	2.76	3.80	1.00
A19	Cl	Cl	c-Hx	5.17	5.03	−0.14	4.72	0.52	6.17	2.76	5.06	1.80
A20	H	H	CH_2Ph	4.95	4.93	−0.03	2.72	0.00	5.86	1.52	3.80	1.00
A21	F	H	CH_2Ph	5.73	5.03	−0.70	3.14	0.34	5.86	1.52	3.80	1.35
A22	H	Cl	CH_2Ph	5.75	5.67	−0.08	3.61	0.23	5.86	1.52	3.80	1.00
A23	H	NO_2	CH_2Ph	4.13	4.82	0.69	3.17	0.78	5.86	1.52	3.80	1.00
A24	H	Me	CH_2Ph	5.13	5.45	0.32	3.09	−0.17	5.86	1.52	3.80	1.00
A25	Cl	Cl	CH_2Ph	6.72	6.02	−0.71	4.47	0.52	5.86	1.52	3.80	1.80
A26	Cl	Cl	CH_25CH_2Ph	4.77	5.14	0.37	4.85	0.52	8.33	1.52	3.80	1.80
A27	Cl	Cl	Ph	4.95	4.39	−0.56	4.42	0.52	6.28	3.11	3.40	1.80
A28	Cl	Cl	*m*-FPh	4.76	4.60	−0.16	4.69	0.52	6.28	3.11	3.40	1.80
A29	Cl	Cl	*m*-ClPh	4.99	4.92	−0.07	5.29	0.52	6.28	3.11	3.60	1.80
A30	Cl	Cl	*m*-BrPh	4.98	4.84	−0.14	5.43	0.52	6.41	3.11	3.90	1.80
A31	Cl	Cl	*m*-CF_3Ph	4.00	4.31	0.30	5.50	0.52	6.40	3.11	4.88	1.80
A32	Cl	Cl	*m*-CNPh	4.12	4.29	0.17	4.30	0.52	6.44	3.11	3.40	1.80
A33	Cl	Cl	*m*-MePh	4.74	4.57	−0.17	4.96	0.52	6.28	3.11	3.80	1.80
A34	Cl	Cl	*m*-OMePh	4.66	4.18	−0.49	4.45	0.52	6.28	3.11	3.80	1.80
A35	Cl	Cl	*m*-NMe_2Ph	3.78	3.62	−0.16	4.64	0.52	7.24	3.11	5.00	1.80
A36	Cl	Cl	*m*-NO_2Ph	4.84	4.76	−0.08	4.55	0.52	6.87	3.11	3.40	1.80
A37	Cl	Cl	*p*-FPh	4.56	4.60	0.04	4.69	0.52	6.87	3.11	3.40	1.80
A38	Cl	Cl	*p*-ClPh	4.73	4.95	0.22	5.33	0.52	7.74	3.11	3.40	1.80
A39	Cl	Cl	*p*-BrPh	4.78	4.91	0.13	5.54	0.52	8.04	3.11	3.90	1.80
A40	Cl	Cl	*p*-CNPh	4.02	4.25	0.23	4.26	0.52	8.45	3.11	3.40	1.80
A41	Cl	Cl	*p*-MePh	3.99	4.57	0.58	4.96	0.52	7.09	3.11	3.80	1.80
A42	Cl	Cl	*p*-OMePh	3.98	4.33	0.35	4.64	0.52	8.20	3.11	3.80	1.80
A43	Cl	Cl	*p*-NMe_2Ph	3.82	3.62	−0.20	4.64	0.52	8.24	3.11	3.80	1.80
C1	Cl	Cl	OMe	6.00	6.05	0.05	3.54	0.52	3.98	1.35	3.80	1.80
C2	H	H	O-*i*-Pr	3.63	3.61	−0.02	2.27	0.00	4.80	1.44	5.06	1.00
C3	Cl	H	O-*i*-Pr	4.00	4.46	0.46	3.51	0.37	4.80	1.44	5.06	1.80
C4	Cl	Cl	O-*i*-Pr	5.12	5.34	0.22	4.49	0.52	4.80	1.44	5.06	1.80
C5	Cl	Cl	$OCH_2C{\equiv}CH$	4.82	4.36	−0.46	3.20	0.52	1.35	1.90	3.60	1.80
C6	Cl	H	$OCH(Me)C{\equiv}CH$	3.90	3.63	−0.27	3.53	0.37	6.58	1.35	5.06	1.80
C7	Cl	Cl	O-*n*-Bu	5.74	6.13	0.39	5.16	0.52	6.86	1.35	3.80	1.80
C8	Cl	Cl	O-*i*-Bu	4.97	5.22	0.25	5.03	0.52	6.05	1.35	5.06	1.80
C9	Cl	Cl	O-*c*-pentyl	4.97	4.63	−0.34	5.46	0.52	5.56	1.35	6.00	1.80
C10	Cl	H	$OCH(Me)C{\equiv}CCl$	4.69	4.42	−0.27	3.94	0.37	8.42	1.35	3.80	1.80
U1	H	H	NHMe	4.92	4.79	−0.13	1.11	0.00	4.02	1.49	3.80	1.00
U2	Et	H	NHMe	5.41	5.63	0.22	2.10	−0.70	4.02	1.49	3.80	2.97
U3	OMe	H	NHMe	4.56	4.44	−0.12	1.26	0.12	4.02	1.49	3.80	2.86
U4	H	Cl	NHMe	5.69	6.05	0.36	2.23	0.23	4.02	1.49	3.80	1.00
U5	Cl	Cl	NHMe	6.68	6.43	−0.25	2.99	0.52	4.02	1.49	3.80	1.80
U6	Cl	Cl	NH-*n*-Pr	5.96	6.54	0.58	4.07	0.52	6.07	1.49	3.80	1.80
U7	Cl	Cl	NH-*n*-Bu	6.56	6.64	0.08	4.61	0.52	6.88	1.49	3.80	1.80
U8	Cl	Cl	NH-*s*-Bu	6.27	6.05	−0.22	4.48	0.52	6.07	1.49	5.06	1.80
U9	Cl	Cl	NH-*i*-Bu	5.19	5.72	0.53	4.48	0.52	6.07	1.49	5.06	1.80
U10	H	H	NH-1-Me-c-Hx	4.25	4.17	−0.08	3.60	0.00	6.07	1.49	6.32	1.00
U11	H	H	NMe_2	5.49	4.86	−0.64	0.98	0.00	4.02	2.73	3.80	1.00
U12	*n*-Pr	H	NMe_2	5.72	6.27	0.55	2.55	−0.70	4.02	2.73	3.80	3.49
U13	CH_2Ph	H	NMe_2	5.96	5.96	0.00	2.83	−0.80	4.02	2.73	3.80	6.02
U14	CH_2CH_2Ph	H	NMe_2	7.01	6.71	−0.30	3.21	−0.70	4.02	2.73	3.80	4.56
U15	H	Cl	NMe_2	6.10	6.03	−0.07	2.01	0.23	4.02	2.73	3.80	1.00
U16	Cl	Cl	NMe_2	7.05	6.59	−0.46	2.86	0.52	4.02	2.73	3.80	1.80
U17	Cl	Me	NMe_2	6.47	6.33	−0.14	2.41	0.20	4.02	2.73	3.80	1.80
U18	NO_2	H	N(Me)OMe	4.58	4.62	0.04	1.71	0.71	4.68	2.73	3.80	2.44
U19	H	Cl	N(Me)OMe	5.73	5.97	0.24	2.22	0.23	4.68	2.73	3.80	1.00
U20	H	NO_2	N(Me)OMe	4.81	5.01	0.20	1.78	0.78	4.68	2.73	3.80	1.00
U21	Cl	Cl	N(Me)OMe	6.93	6.54	−0.39	3.11	0.52	4.68	2.73	3.80	1.80

[a] Values were calculated from eq 5.

Table II. Inhibition of Photosystem II Electron Transport and Physicochemical Parameters of Triazines

				activity			physicochem param	
				pI_{50}, M				
no.	CH_2X_1	Y	Z	obsd	calcd[a]	ΔpI_{50}	log P	$T_r(X_1)$
T1	Et	Et	Cl	5.84	5.89	−0.05	2.14	3.80
T2	Et	Et	OMe	5.17	5.58	−0.41	1.82	3.80
T3	Et	Et	SMe	6.89	6.22	0.67	2.54	3.80
T4	Et	Et	SEt	6.89	6.52	0.37	3.00	3.80
T5	*n*-Pr	Et	Cl	6.06	6.37	−0.31	2.75	3.80
T6	allyl	allyl	Cl	5.55	6.17	−0.62	2.75	3.20
T7	*i*-Pr	Et	Cl	6.52	6.27	0.25	2.61	3.80
T8	*i*-Pr	*i*-Pr	SMe	6.85	6.77	0.08	3.51	3.80
T9	c-Pr	Et	Cl	6.17	5.98	0.19	2.13	4.12
T10	CH_2-c-Pr	Et	Cl	6.42	6.66	−0.24	2.85	4.50
T11	*n*-Bu	Et	Cl	6.53	6.66	−0.13	3.25	3.80
T12	*i*-Bu	Et	Cl	6.41	6.59	−0.18	3.12	3.80
T13	c-Bu	Et	Cl	7.01	6.78	0.23	2.77	5.01
T14	*n*-Pentyl	Et	Cl	7.02	6.85	0.17	3.76	3.80
T15	*n*-Hx	Et	Cl	7.28	6.94	0.34	4.33	3.80
T16	2-EtBu	Et	Cl	6.40	6.94	−0.54	4.20	3.80
T17	c-Hx	Et	Cl	6.79	7.22	−0.43	3.63	5.05
T18	CH_2-c-Hx	Et	Cl	7.28	7.35	−0.07	4.17	5.05
T19	CH(Me)-*n*-Pentyl	Et	Cl	7.43	6.96	0.47	4.74	3.80
T20	CH_2Ph	Et	Cl	6.24	6.48	−0.24	3.16	3.40
T21	*n*-Octyl	Et	Cl	6.56	6.89	−0.33	5.27	3.80
T22	CH(Me)-*n*-Hx	Et	Cl	6.78	6.86	−0.08	5.28	3.80
T23	CH_2CH_2Ph	Et	Cl	7.08	6.83	0.25	3.70	3.80
T24	$(CH_2)_3Ph$	Et	Cl	7.54	6.95	0.59	4.24	3.80
T25	$(CH_2)_4Ph$	Et	Cl	6.88	6.95	−0.07	4.78	3.80
T26	CH_2-Tol	Et	Cl	6.71	6.84	−0.13	3.72	3.80
T27	CH_2-Naph	Et	Cl	6.85	6.82	0.03	4.33	3.40
T28	$CH_2CH(OEt)_2$	Et	Cl	5.27	5.08	0.19	1.37	3.12

[a] Values were calculated from eq 7.

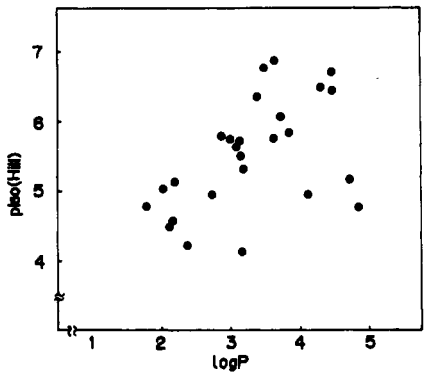

Figure 4. Relationship between the inhibition of PS II electron flow and log P in the anilide compounds **A1–A26**.

σ for benzene substituents did not improve the correlation to our satisfaction. Since the acyl substituents of the set of compounds are alkyl and thus their electronic effect is considered to be nearly constant, it suggests that factors other than hydrophobic and electronic ones, that is, steric factors, are operative in binding to the receptive site. We thus explored correlations in consideration of the steric parameters defined above to obtain eq 2. The positive

$$pI_{50} = \underset{(0.30)}{1.34}\log P - \underset{(0.70)}{1.23}\sigma - \underset{(0.21)}{0.69}L(Y) - \underset{(0.50)}{1.23}T_r(Y) + \underset{(1.96)}{9.79} \quad (2)$$

$$n = 26,\ s = 0.38,\ r = 0.90$$

coefficient of the log P term indicates that the hydrophobicity of the compounds enhances activity, and the negative coefficient of the σ term suggests that electron-donating benzene substituents favor activity. As was expected, the steric parameters for the Y moiety, $L(Y)$ and $T_r(Y)$, were significant, the negative signs indicating that the length toward the L direction and thickness of the right-hand side of the Y moiety interfere with accommodation in the receptor cavity. Any of the steric parameters for the benzene substituents, X_1 and X_2, were not fully significant, probably because of their poorer variation in steric shape.

For the set of 21 urea compounds (U1–U21) in Table I, eq 3 was obtained as the best correlation. The σ term

$$pI_{50} = \underset{(0.30)}{1.15}\log P - \underset{(0.37)}{0.84}L(Y) + \underset{(0.32)}{0.30}W_1(Y) - \underset{(0.35)}{0.68}T_r(Y) - \underset{(0.16)}{0.22}W_r(X_1) + \underset{(1.96)}{9.17} \quad (3)$$

$$n = 21,\ s = 0.37,\ r = 0.93$$

was not meaningful enough over the 95% level, and this appears to be due to the variation of its value not being sufficiently wide in the urea set of compounds, compared to the anilides. Steric features were apparently very similar to those of eq 2, the coefficient values of the $L(Y)$ and $T_r(Y)$ terms overlapping with those of the corresponding terms within the 95% confidence intervals. Furthermore, with ureas, the width in the $W_1(Y)$ direction favored activity. Supposedly reflecting the importance of steric interaction at the receptive site of meta substituents (X_1), the $W_r(X_1)$ term was significant, the X_1 being sterically more variable than those in the anilide set of compounds.

The similarity or correspondence between eq 2 and 3 suggested to us that these two sets of compounds could be combined and analyzed together. Furthermore, examination of the biological and physicochemical data of the carbamate series of compounds suggested that they could be incorporated into eq 2, 3, or both. Thus we explored common correlations for the three sets of compounds, obtaining eq 4. The physicochemical parameters incor-

$$pI_{50} = \underset{(0.17)}{1.09}\log P - \underset{(0.46)}{0.80}\sigma - \underset{(0.14)}{0.51}L(Y) + \underset{(0.19)}{0.20}W_1(Y) - \underset{(0.20)}{1.04}T_r(Y) - \underset{(0.13)}{0.25}W_r(X_1) + \underset{(0.24)}{1.00}IU - \underset{(1.27)}{8.75} \quad (4)$$

$$n = 57,\ s = 0.37,\ r = 0.92$$

Table III. Herbicidal and Hill Inhibitory Activities and Hydrophobicity of Anilides, Carbamates, Ureas, and Triazines Used for the Development of Equation 1[a]

no.	herbicidal act.: pLD_{50}, mol/are obsd	herbicidal act.: pLD_{50}, mol/are calcd[b]	Hill inhib act. pI_{50}, M	log P
A1	0.89	1.68	6.35	3.38
A5	1.28	1.93	6.77	3.49
A6	0.75	1.17	5.04	2.01
A7	1.07	1.37	5.72	2.98
A9	0.72	0.53	4.21	2.36
A13	1.46	1.45	5.80	2.86
A17	1.34	1.53	6.48	4.31
A18	1.08	1.20	5.80	3.83
A23	0.38	0.27	4.13	3.17
A25	1.44	1.64	6.72	4.47
C1	1.04	1.41	6.00	3.54
C6	0.52	0.03	3.90	3.53
C7	0.62	0.82	5.74	5.16
U1	1.32	1.32	4.92	1.11
U3	1.06	1.05	4.56	1.26
U10	0.34	0.24	4.25	3.60
U11	1.04	1.73	5.49	0.98
U14	2.44	2.16	7.01	3.21
U15	1.65	1.87	6.10	2.01
U16	2.72	2.28	7.05	2.86
U17	1.93	2.01	6.47	2.41
U18	0.88	0.95	4.58	1.71
U19	1.91	1.57	5.73	2.22
U21	2.47	2.13	6.93	3.11
T2	1.62	1.31	5.17	1.82
T3	1.61	2.25	6.89	2.54
T5	1.99	1.65	6.06	2.75
T6	1.29	1.32	5.55	2.75
T7	2.54	1.99	6.52	2.61
T8	2.31	1.98	6.85	3.51
T9	2.27	1.88	6.17	2.13
T11	2.01	1.83	6.53	3.25
T13	2.51	2.24	7.01	2.91
T14	2.15	2.02	7.02	3.76

[a] For structures, see Tables I and II. [b] Values were calculated from eq 1.

Table IV. Squared Correlation Matrix of the Variables Used in Equation 4

	log P	σ	L(Y)	W_l(Y)	T_r(Y)	$W_r(X_1)$
σ	0.20					
L(Y)	0.43	0.06				
W_l(Y)	0.16	0.01	0.26			
T_r(Y)	0.19	0.01	0.06	0.16		
$W_r(X_1)$	0.00	0.02	0.04	0.02	0.01	
IU	0.13	0.03	0.08	0.00	0.00	0.06

Table V. Squared Correlation Coefficients between the Variables of Benzanilide Derivatives

	log P	T_r(Y)
T_r(Y)	0.05	
L(Y)	0.01	0.04

porated into eq 2 and 3 were all significant. The IU is an indicator variable term that takes the value of 1 for ureas and 0 for others, the positive coefficient indicating that the urea type of compound is somewhat more active than the other two types. The indicator variable term for the carbamates was not necessary. Through the steps to attain eq 4, none of the steric parameters for the X_2 (para substituents) were significant. This suggests that the region of the receptor surface where the para substituents locate is relatively roomy, although the variation of their structure is somewhat less than that of the meta substituents (X_1). A rather high correlation was found between the steric parameters for X_1 substituents, $W_r(X_1)$ and $L(X_1)$ (data not shown), the r^2 being 0.77. Thus, what we can say safely about the meaning of the $W_r(X_1)$ in eq 4 may be only that bulkiness of the substituents at the meta position is important for activity, in addition to their hydrophobic and electronic properties in relation to the log P and σ terms. The squared correlation matrix of the variables used is shown in Table IV.

To examine the electronic effect of the Y moiety, we prepared substituted benzanilides **A27–A43**. Against our expectation, the inhibition of PS II electron transport by these compounds was unvarying and poor, despite the aromatic substituents on the benzoyl moiety being electronically variable. Because of this poor activity, it was difficult to analyze them quantitatively, but examination of their structure–activity profiles suggested that they could be incorporated into eq 2, 4, or both, giving eq 5 for

$$\begin{aligned} pI_{50} = {} & \underset{(0.43)}{1.55}\log P - \underset{(0.06)}{0.08}(\log P)^2 - \underset{(0.43)}{0.76}\sigma - \underset{(0.12)}{0.48}L(\mathrm{Y})^{\mathrm{R}} - \\ & \underset{(0.19)}{1.01}T_r(\mathrm{Y})^{\mathrm{R}} + \underset{(0.18)}{0.19}W_l(\mathrm{Y})^{\mathrm{R}} - \underset{(0.32)}{0.59}T_r(\mathrm{Y})^{\mathrm{Ph}} - \underset{(1.85)}{5.92}I^{\mathrm{Ph}} - \\ & \underset{(0.18)}{0.19}W_r(\mathrm{X}_1) + \underset{(0.23)}{0.99}\mathrm{IU} + \underset{(1.31)}{7.91} \quad (5) \end{aligned}$$

$$n = 74,\ s = 0.36,\ r = 0.93$$

the whole set of compounds. In this equation, we separated the steric parameters for the Y moiety of alkyls from those of phenyls, and they are indicated by superscripts R and Ph, respectively. By this treatment, it is shown that although the thickness T_r(Y) is always significant, the length along the bond axis is not important for the activity of phenyl derivatives, reflecting somewhat different spatial arrangements of both at the site of action. This seems to arise from their different molecular shape. A similar situation was found in analyses of agonists and antagonists of a class of plant hormones, the cytokinins (Iwamura et al., 1985). The I^{Ph} is the indicator variable that is 1 when Y is phenyl and 0 when Y is alkyl, indicating that the activity of the phenyl derivatives is uniformly lower than that of the alkyl series of compounds, although the physicochemical basis for this is unknown. The significance of the $(\log P)^2$ term in this equation may be that inhibition of PS II is somewhat parabolically related to the hydrophobicity of the molecule. The electronic effect of the Y moiety in terms of σ_I, σ_R, or both was not at all significant. The squared correlation coefficients of the

Table VI. Development of Equation 5

const	$W_l(\mathrm{Y})^{\mathrm{R}}$	log P	$(\log P)^2$	IU	$T_r(\mathrm{Y})^{\mathrm{R}}$	$T_r(\mathrm{Y})^{\mathrm{Ph}}$	$L(\mathrm{Y})^{\mathrm{R}}$	I^{Ph}	$W_r(\mathrm{X}_1)$	σ	r	s	$F_{x,y}$[a]
4.53	0.44										0.52	0.77	$F_{1,72} = 27.26$
2.49	0.60	0.82	−0.08								0.62	0.72	$F_{3,70} = 14.24$
1.68	0.60	1.01	−0.09	0.83							0.72	0.64	$F_{1,69} = 19.50$
1.52	0.73	1.20	−0.12	0.89	−0.12						0.73	0.63	$F_{1,68} = 3.41$
4.38	0.46	1.06	−0.07	0.91	−0.68	−0.86					0.84	0.51	$F_{1,67} = 35.78$
5.12	0.40	1.12	−0.07	0.87	−0.62	−1.16	−0.22				0.86	0.48	$F_{1,66} = 9.82$
7.31	0.16	1.24	−0.06	0.84	−0.91	−0.57	−0.40	−5.19			0.90	0.42	$F_{1,65} = 24.35$
7.69	0.19	1.39	−0.07	0.96	−0.96	−0.58	−0.45	−5.63	−0.20		0.91	0.39	$F_{1,64} = 9.31$
7.91	0.19	1.55	−0.08	0.99	−1.01	−0.59	−0.48	−5.92	−0.25	−0.76	0.93	0.36	$F_{1,63} = 12.43$

[a] F static for the significance of the addition of each variable.

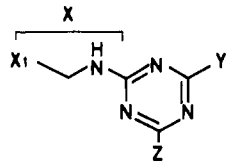

Figure 5. Definition of the substituent X_1 for the triazines.

variables considered for the incorporation of the benzanilide derivatives are listed in Table V, and the development of the inclusive eq 5 is summarized in Table VI.

(*B*) *Triazines.* As the first step of our comparison of the structure vs. activity relationships or the mode of interaction of triazines (Table II) with those of the anilide type of herbicides, we analyzed compounds having various amines at one position (X) and somewhat fixed substituents at two other positions, Y and Z. The correlation was passably good with only log P and its squared term, as shown by eq 6. Examination of the structure–activity

$$\underset{}{pI_{50}} = \underset{(0.91)}{1.75 \log P} - \underset{(0.13)}{0.19(\log P)^2} + \underset{(1.52)}{3.04} \quad (6)$$

$$n = 28,\ s = 0.38,\ r = 0.80,\ F_{2,25} = 21.59$$

profiles in consideration of the steric features suggested, however, that of the two amine substituents (X, Y) one having a larger L value varies the activity and that a branch or a cyclization (or both) at the β or γ position, or both positions, is responsible for activity, while the α position is not much involved. Thus, we defined the longer amine substituent as X and the portion of the X one C–N unit apart from the triazine ring as X_1, as depicted by Figure 5. In consideration of the steric parameters for X_1, the correlation obtained was eq 7. Among the steric pa-

$$\underset{}{pI_{50}} = \underset{(0.92)}{1.64 \log P} - \underset{(0.13)}{0.19(\log P)^2} + \underset{(0.32)}{0.32T_r(X_1)} + \underset{(1.80)}{1.95} \quad (7)$$

$$n = 28,\ s = 0.36\ r = 0.84,\ F_{1,24} = 4.27$$

rameters, only the $T_r(X_1)$ was significant over the 95% level, irrespective of the structure of the X_1 moiety being sterically so varied. The squared correlation cofficient between the log P and $T_r(X_1)$ terms was less than 0.01.

DISCUSSION

The competitive nature of the functional binding and the identity of the receptive site of the four classes of herbicides were indicated directly in terms of the biological activity, I_{50}, by applying the method of Lineweaver and Burk (1934) (Figure 3). This method has been used before to establish the competitive nature of antiauxins (McRae and Bonner, 1953) and that of cytokinin agonistic and antagonistic compounds (Iwamura et al., 1979, 1983). The binding was proved by eq 1a,b to be directly and in a very similar or identical way to be related to their postemergent herbicidal activity.

The modes of the interaction at the common site were quite similar for the rather chemically congeneric anilides, carbamates, and ureas, as revealed by the combined eq 4 and 5, with compounds having sterically varied substituents. As for the steric effect of the Y moiety, the longer and thicker, the lower the activity; width in the W_1 direction favored activity. These results coincide with and provide a physicochemical basis for the fact that many of the potent commercial herbicides possess a relatively short Y having a branch α to the common carbonyl group, such as $N(Me)_2$ and N(Me)OMe in ureas and CH(Me)R and $C(Me)_2R$ in anilides. One cannot introduce the α branch into the Y moiety of the carbamates. This is probably one reason for inhibition of PS II electron transport by carbamates being generally weak, in other words, for this class having less potent intrinsic activity than the others. No steric effect was significant for the para substituents (X_2). With earlier results that only a weak steric effect or none is observed for ureas and anilides having more various para substituents than the set of compounds studied here but a fixed Y moiety (Kakkis et al., 1984; Hayashi and Fujita, 1983), it is suggestive that the site of action is rather tolerant to steric bulkiness of the para substituents. They are thought to be responsible principally for the hydrophobic and electronic effects.

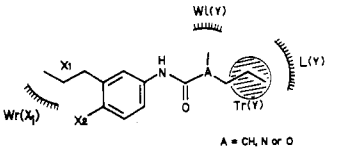

Figure 6. Schematic receptor map for PS II inhibitors. The stippled solid lines show the steric interaction sites or spatial walls, and the striped circle is that located upward (or downward). The affixes indicate the steric parameters incorporated into eq 5.

The significance of the $(\log P)^2$ term in eq 5 may suggest that there is an optimum hydrophobic condition for activity, although the parabolic relation is shallow. In this connection, we examined the bilinear model of Kubinyi (1979), which has been used for the analysis of urea derivatives to interpret optimum hydrophobic conditions (Kakkis et al., 1984). For our set of compounds, the result was as shown in eq 8, which was essentially the same as

$$\underset{}{pI_{50}} = \underset{(0.20)}{1.22 \log P} - \underset{(0.47)}{0.63 \log(\beta 10^{\log P} + 1)} - \underset{(0.42)}{0.78\sigma} - \underset{(0.13)}{0.50L(Y)^R} - \underset{(0.19)}{1.00T_r(Y)^R} + \underset{(0.17)}{0.20W_1(Y)^R} - \underset{(0.32)}{0.45T_r(Y)^{Ph}} - \underset{(1.86)}{7.00I^{Ph}} - \underset{(0.13)}{0.26W_r(X_1)} + \underset{(0.23)}{1.04IU} + 8.21 \quad (8)$$

$$n = 74,\ s = 0.35,\ r = 0.93,\ \beta = 0.000\,067$$

eq 5. The optimum log P value could not be derived, however, from this relationship. To obtain a reliable value, more study is needed along with the synthesis of compounds that are highly hydrophobic and readily soluble in the bioassay medium.

The negative sign of the σ term suggests that electron-donating X_1 and X_2 substituents favor activity. Since the electronic term is not always significant in other studies of PS II inhibitors, Kakkis et al. (1984) have doubted its reality. Within the scope of our results, however, the electron density at the amide portion may participate in the interaction with the receptor site, probably via H bonding. A similar electron-donating effect of aromatic substituents favorable to PS II inhibition has been recorded for the urea series of compounds (Takemoto et al., 1984).

On the basis of the information obtained from eq 5 (and eq 4, or both) for the steric characteristics that are responsible for the binding, we drew the schematic receptor map in Figure 6. The stippled solid lines represent the steric interaction sites or receptor walls located on the plane of the page and the striped circle expresses that located upward (or downward). The affixes $W_r(X_1)$, $L(Y)$, $W_1(Y)$, and $T_r(Y)$ show the corresponding steric parameters incorporated into eq 5. The model drawing suggests that the interaction sites at the Y moiety may be continuous, constituting a cavity. The results may be of help in comparing the mode of interaction of the anilide type of compounds with those of other classes of PS II inhibitors that share the same binding site.

To examine the correspondence of the mode of interaction of the triazines with that of the anilide type of

compound, we prepared compounds in which the amine substituents at one position (X) are sterically varied and longer than those at another position (Y). In eq 7 for this set of compounds, only the thickness parameter $T_r(X_1)$ was significant. Its coefficient was positive whereas that of the $T_r(Y)$ in eq 5 was negative and large. By this and the fact that the steric parameters, L and W_1, significant in eq 5 for the Y moiety were not significant here, it seems that the sterically longer of the two amine substituents of the triazines differs from the acyl Y moiety of the anilide types of compound. We think that the region of the receptive surface where the X_1 or X moiety of the triazines comes on is sterically tolerant. This reminds us of that the steric effect of the X_1 (and/or X_2) moiety of the three other classes of herbicides was also tolerant. More details of the structural correspondence between the two types of herbicides remain for future study, concerning the supposition that one of the N=C moieties of the triazines bound to the exocyclic amines corresponds to the acylamino moiety of the anilide types of compound (Hansch, 1969; Moreland, 1969; Trebst and Harth, 1974; Moreland and Hilton, 1976).

Our results here suggest that the four classes of compounds act at a common site and that the steric interaction there is important for the inhibition of the electron transport and thus for the herbicidal activity. Accordingly, if one assumes that the hereditary mutation leading to herbicide resistance occurred at this site, it must have caused an alteration of the steric shape of the receptor cavity that altered the significance of the steric parameters incorporated into the correlation equations. Thus, it is possible in one class of herbicides and also with different classes that the activity of some compounds varies greatly but that of some others is not affected so much, depending on their structural characteristics. If the mutations alter the transport process(es), this will be reflected as a variation in the significance of the log P and its squared term.

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Registry No. **A1**, 709-98-8; **A2**, 882-14-4; **A3**, 7017-11-0; **A4**, 2150-96-1; **A5**, 74064-59-8; **A6**, 102587-29-1; **A7**, 3022-71-7; **A8**, 102587-30-4; **A9**, 102587-31-5; **A10**, 102587-32-6; **A11**, 102587-33-7; **A12**, 102587-34-8; **A13**, 102587-35-9; **A14**, 102587-36-0; **A15**, 102587-37-1; **A16**, 2790-16-1; **A17**, 2307-68-8; **A18**, 7287-36-7; **A19**, 15907-85-4; **A20**, 621-06-7; **A21**, 5215-27-0; **A22**, 2990-06-9; **A23**, 13140-77-7; **A24**, 6876-65-9; **A25**, 27816-82-6; **A26**, 86886-77-3; **A27**, 10286-75-6; **A28**, 58954-98-6; **A29**, 83426-47-5; **A30**, 10286-90-5; **A31**, 24094-75-5; **A32**, 102587-38-2; **A33**, 102587-39-3; **A34**, 102587-40-6; **A35**, 102587-41-7; **A36**, 62129-26-4; **A37**, 102587-42-8; **A38**, 56661-50-8; **A39**, 56661-53-1; **A40**, 102587-43-9; **A41**, 86886-82-0; **A42**, 102587-44-0; **A43**, 102587-45-1; **C1**, 1918-18-9; **C2**, 122-42-9; **C3**, 101-21-3; **C4**, 2150-28-9; **C5**, 25217-33-8; **C6**, 1967-16-4; **C7**, 63785-38-6; **C8**, 25217-29-2; **C9**, 91393-93-0; **C10**, 102587-46-2; **T1**, 122-34-9; **T2**, 673-04-1; **T3**, 1014-70-6; **T4**, 30360-82-8; **T5**, 90952-64-0; **T6**, 15468-86-7; **T7**, 1912-24-9; **T8**, 7287-19-6; **T9**, 22936-85-2; **T10**, 40533-52-6; **T11**, 49624-63-7; **T12**, 74150-96-2; **T13**, 102587-50-8; **T14**, 102587-51-9; **T15**, 102587-52-0; **T16**, 102587-53-1; **T17**, 84712-77-6; **T18**, 102587-54-2; **T19**, 102587-55-3; **T20**, 102587-56-4; **T21**, 102587-57-5; **T22**, 102587-58-6; **T23**, 102587-59-7; **T24**, 102587-60-0; **T25**, 102587-61-1; **T26**, 102538-65-8; **T27**, 102587-62-2; **T28**, 19916-25-7; **U1**, 1007-36-9; **U2**, 23138-95-6; **U3**, 23138-98-9; **U4**, 5352-88-5; **U5**, 3567-62-2; **U6**, 5006-83-7; **U7**, 5006-89-3; **U8**, 5089-85-0; **U9**, 5006-90-6; **U10**, 1611-63-8; **U11**, 101-42-8; **U12**, 102587-47-3; **U13**, 102587-48-4; **U14**, 102587-49-5; **U15**, 150-68-5; **U16**, 330-54-1; **U17**, 15545-48-9; **U18**, 88132-19-8; **U19**, 1746-81-2; **U20**, 88132-15-4; **U21**, 330-55-2.

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