Structure–Activity Relationships in the Hill Inhibitory Activity of Substituted Phenylureas

Patrick Camilleri,* John R. Bowyer, Terence Gilkerson, Barbara Odell, and Roger C. Weaver

The Hill inhibitory activity of a number of phenylureas has been measured. These data have been analyzed by stepwise multiple regression analysis and the results compared to those of other recent structure–activity studies. Although lipophilicity is the most important contributing factor to activity, there seems to be some affinity at the receptor site for halogen substitution in the phenyl ring meta to the urea moiety. Substitution ortho to the urea group decreases activity considerably, probably due to the interference of this group with the orientation of the phenyl ring with respect to the urea moiety. We also present in vivo herbicidal results that again indicate a relationship between lipophilicity and plant phytotoxicity. These in vitro and in vivo data have helped in the design of a novel class of phenylureas, about which we present preliminary findings.

A large majority of the commercially available herbicides act by interfering with photosynthetic electron transport. Photosystem I (PSI) herbicides, such as the bipyridinium salts (Summers, 1980) and the heteropentalenes (Camilleri et al., 1984), "draw off" electrons at the acceptor side of PSI by competing with the natural substrate ferredoxin. Photosystem II (PSII) herbicides, e.g. phenylureas (Hansch and Deutsch, 1966), phenylamides (Hansch, 1969), alkoxyuracils (Brown et al., 1981), and triazines (Gabbott, 1969), inhibit electron flow (the "Hill reaction") at the reducing side of PSII. Such inhibitors are thought (Trebst and Draber, 1979) to suppress the photosynthetic process by binding to a 32-kDa protein of the PSII reaction center complex, thereby inhibiting electron transfer from a bound plastoquinone molecule designated Q_A to a secondary plastoquinone Q_B. It has been postulated (Pfister and Arntzen, 1979) that certain PSII inhibitors such as the phenylureas and the triazines compete directly with the plastoquinone molecule at the Q_B binding site on the 32-kDa protein. However, other lines of evidence (Kyle, 1985) suggest that different classes of PSII inhibitors interact with areas of the receptor site that do not overlap with one another or at the most only partially overlap. The phenylureas are the class of PSII herbicides that have been the most studied and commercially exploited. In fact, the number of patents that have been issued since the discovery of monuron [1,1-dimethyl-3-(*p*-chlorophenyl)urea] exceeds 350, which demonstrates the wide range of structures of phenylureas that can be involved. The utility of quantitative structure–activity relationships (QSAR) for studying the mode of action of this class of compounds was demonstrated as early as 1966 when Hansch and Deutsch investigated the inhibition of the Hill reaction by 12 3- and 4-substituted 1-phenyl-3,3-dimethylureas; using multiple regression analysis these authors derived the relation

$$pI_{50} = 1.29\pi + 0.54\sigma + 4.18 \quad (1)$$

where I_{50} represents the molar concentration giving 50% inhibition of the Hill reaction rate, and π and σ are the hydrophobic and Hammett substituent constants, respectively. While π gives the extent of hydrophobic binding of a molecule at the receptor site, σ expresses the importance of the electronic nature of the phenylurea in determining its biological activity.

Since this original study, several other QSAR studies (Kakkis et al., 1984; van den Berg and Tipker, 1982; Takemoto et al., 1984) have been reported. Hydrophobicity expressed either by π or by the logarithm of the octanol/water partition coefficient (log P) appears as the most significant term to explain the Hill inhibitory activity in all these correlations. On the other hand, the inclusion of a σ term has not been found necessary in two recent QSAR studies carried out by Kakkis et al. (1984) and by van den Berg and Tipker (1982). It is noteworthy that these studies utilized measured values of log P rather than π. Kakkis et al. (1984) have demonstrated that measured log P is related to both calculated log P (and to π) and to σ. They also showed that pI_{50} correlated well to calculated log P and found no evidence for an electronic effect on inhibition. These results are incompatible both with the original results by Hansch and Deutsch (1966) and with a recent publication by Takemoto et al. (1984).

To discover more about the extent to which the electronic nature of substitution on the phenylurea plays a part in determining its biochemical activity, we have undertaken a QSAR study on a series of 20 mono- and disubstituted compounds. The findings of this part of the study were then compared with those of the most recent studies (Kakkis et al., 1984; Takemoto et al., 1984). We also present data that show the effect of substitution ortho to the urea moiety on the Hill inhibitory activity. This information was required as part of our detailed studies of the region in the neighborhood of the phenylurea binding site on the 32-kDa protein. Finally, we have attempted to find a relationship between herbicidal activity of a number of phenylureas and the hydrophobic nature of the substituents on the phenyl ring.

EXPERIMENTAL SECTION

Reagents. The phenylurea derivatives were supplied by the Organic Chemistry Division at Sittingbourne Research Centre.

Hill Reaction. Freshly picked pea leaves (*Pisum sativum*) (20 g) were homogenized in a Waring blender for 20 s at full speed in 100 mL of ice-cold buffer (pH 6.8), consisting of 0.35 M sucrose, 0.01 M magnesium chloride, and 0.1 M potassium phosphate. The remaining operations were performed at 4 °C. The homogenate was filtered through two layers of muslin and a pellet obtained by centrifuging for 7 min at 2000*g*. This pellet was resuspended in 50 mL of homogenizing buffer and re-formed by again centrifuging for 7 min at 2000*g*. The resulting pellet was homogenized for several minutes in 25 mL of dilute salt solution (0.1% sodium chloride and 0.1% magnesium chloride, w/v), using a small Potter–Elvehjem hand homogenizer. The resulting ruptured chloroplasts were finally centrifuged for 10 min at 15000*g*, separated

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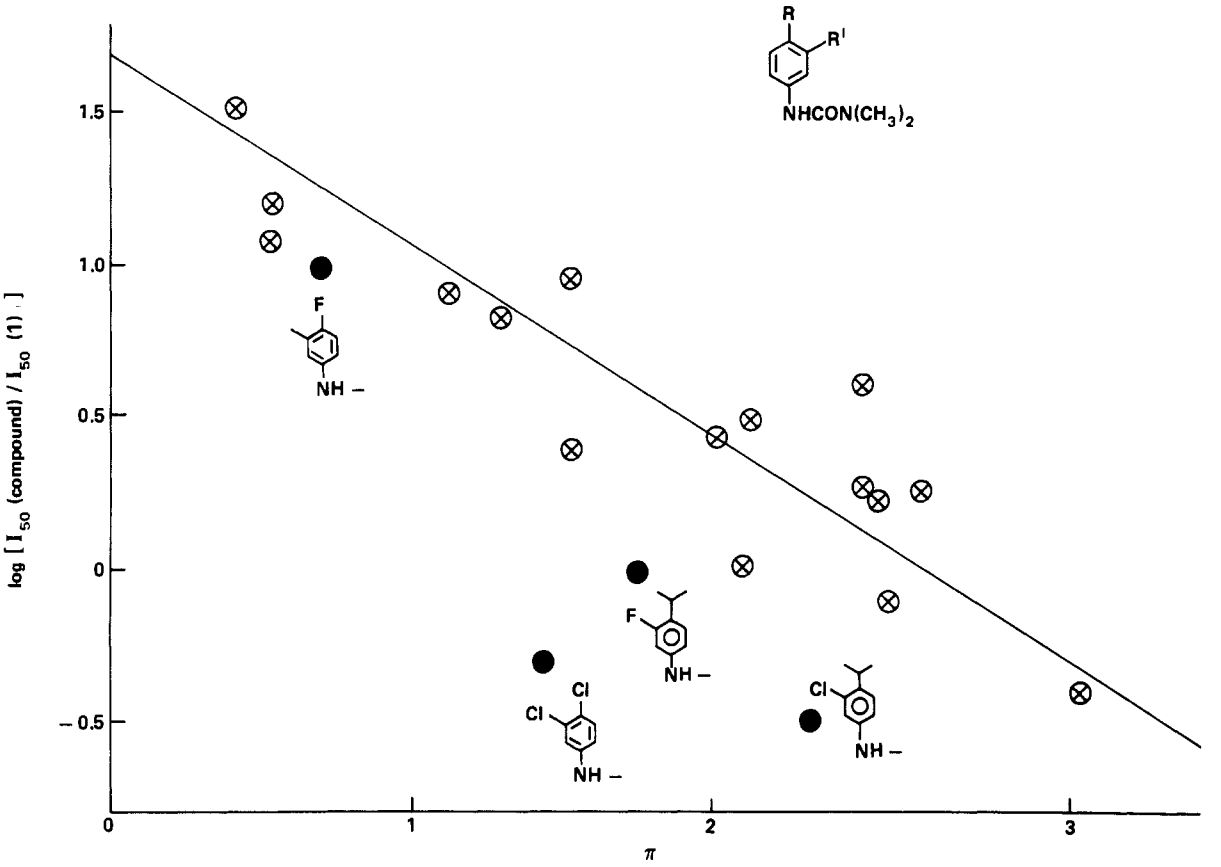
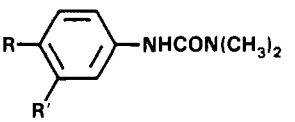


Figure 1. Observed in vitro activity against π for some phenylurea derivatives.

from the solution, gently resuspended in 12 mL of the dilute salt solution, and kept on ice throughout the assay period. The assay medium consisted of 0.75 mL of a 0.1 M tricine buffer (pH 8.0) (containing 0.05 M methylamine as an uncoupler and 0.002 M sodium azide to inhibit catalase activity), about 100 μL of the chloroplast suspension (containing about 100 μg of chlorophyll), 15 μL of a solution of the phenylurea in ethanol, and 15 μL of a 10^{-3} M solution of 2-acetamido-3-(isopropylamino)-1,4-napthoquinone as the electron acceptor. The solution was made up with distilled water to a final volume of 1.5 mL and was then illuminated with red light of saturating intensity (150-W quartz/iodine projector bulb with a red filter). The rate of electron transport was monitored by measuring net oxygen uptake associated with reoxidation of the napthoquinone acceptor using a Hansatech oxygen electrode thermojacketed at 20 °C. The activity of a phenylurea as a Hill inhibitor was estimated by plotting percentage inhibition vs. the logarithm of the concentration of inhibiting compound. The concentration for 50% inhibition (I_{50}) was determined as the molar concentration required to decrease the rate of oxygen uptake to 50% of the value obtained in the absence of the compound. Since measurements were made using different chloroplast preparations, 3-(4-isopropyl-3-methylphenyl)-1,1-dimethylurea (1) was used as the standard Hill inhibitor, and structure–activity analyses were made relative to this compound. The I_{50} of 1 varied between 1.5 and 0.5 × 10^{-7} M.

Substituent Constants and Regression Analysis. The substituent constants used in this study were those compiled by Hansch and Leo (1979). Hill inhibitory activity was analyzed by means of multiple regression analysis. The F test was used to judge the level of significance of each term in a particular correlation. All computations were done on a 4341 IBM computer.

Table I. Hill Inhibitory Data Used in the Derivation of Equations 2 and 3



compd	R	R′	log [I_{50}(compd)/I_{50}(1)] obsd	calcd[a]	Δ
1	$CH(CH_3)_2$	CH_3	0.00	0.42	0.42
2	F	CH_3	0.99	0.99	0.00
3	$CH(CH_3)C_2H_5$	C_2H_5	−0.41	−0.16	−0.25
4	CH_3	CH_3	0.91	1.06	−0.15
5	$CH(CH_3)_2$	OCH_3	0.84	0.64	0.20
6	H	CH_3	1.08	1.16	−0.08
7	$CH(CH_3)_2$	Cl	−0.50	−0.35	−0.15
8	$CH(CH_3)C_2H_5$	CH_3	−0.10	0.07	−0.17
9	$CH(CH_3)_2$	CH_2OH	1.52	1.35	0.17
10	C_2H_5	C_2H_5	0.48	0.46	0.02
11	$CH_2CH(CH_3)_2$	CH_3	0.31	0.13	0.18
12	C_3H_7	CH_3	0.50	0.38	0.12
13	C_4H_9	CH_3	0.29	0.18	0.11
14	C_2H_5	CH_3	0.98	0.74	0.24
15	$CH(CH_3)_2$	C_2H_5	0.28	0.17	0.11
16	$CH(CH_3)_2$	F	−0.01	0.02	−0.03
17	C_2H_5	$CH(CH_3)_2$	0.60	0.14	0.46
18	$CH(CH_3)_2$	H	0.36	0.67	−0.31
19	CH_3	H	1.20	1.29	−0.09
20	Cl	Cl	−0.29	−0.36	0.07

[a] Calculated from eq 3.

RESULTS AND DISCUSSION

Observed I_{50} values relative to the I_{50} for compound 1 are collected in Table I. The more effective Hill inhibitory compounds correspond to the more negative ratios. These data are plotted in Figure 1 against the sum of the substituent constants π. It is apparent from Table I and

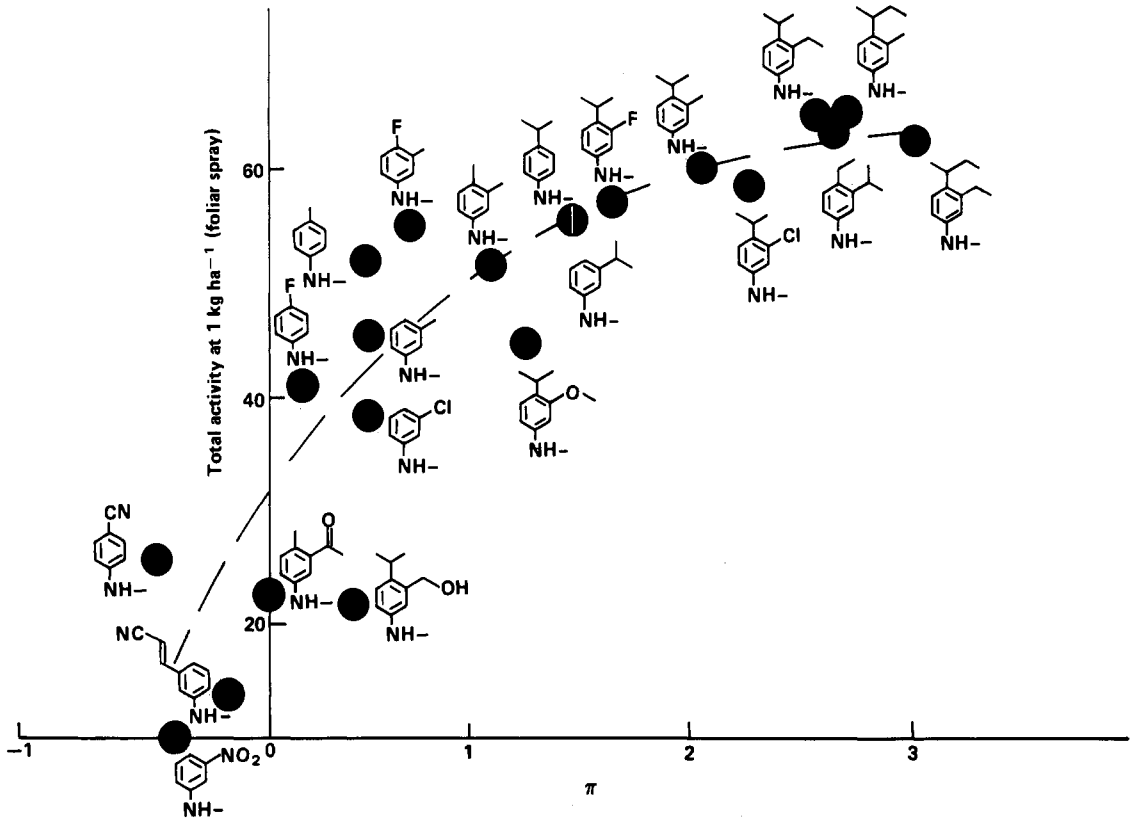


Figure 2. In vivo herbicidal activity as a function of lipophilicity (the urea moiety has been partly omitted).

Figure 1 that increasing the lipophilic nature of the substituents in the 3- and 4-positions of the phenyl ring increases the Hill inhibition potency of a molecule. Activity cannot increase indefinitely with π so that the linear relationship of Figure 1 signifies that optimum lipophilicity has not been reached within the range of π considered. Regression analyses of the data in Table I gave eq 2; where n is the number of compounds, r is the correlation coefficient, and s is the standard deviation. The numbers in brackets are 95% confidence limits.

$$\log [I_{50}(\text{compd})/I_{50}(1)] = 1.4\ (\pm 0.44) - 0.54\ (\pm 0.33)\pi$$
$$n = 20,\ r = 0.76,\ s = 0.38 \qquad (2)$$

Figure 1 shows that a significant deviation from this trend occurs in the case of compounds having a halogen atom meta to the urea moiety. A much improved correlation was obtained by the introduction of a term that takes into account the electronic properties of the molecules under study (eq 3).

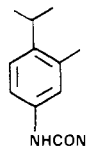
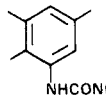
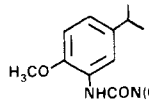
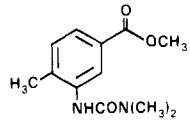
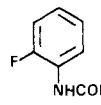
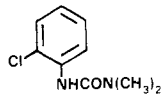
$$\log [I_{50}(\text{compd})/I_{50}(1)] = 1.41\ (\pm 0.26) - 0.63\ (\pm 0.14)\pi - 1.47\ (\pm 0.52)\sigma$$
$$n = 20,\ r = 0.93,\ s = 0.22 \qquad (3)$$

The ratios of the Hill reaction inhibitory activities calculated by eq 3 are included in Table I. The agreement between the observed and calculated values is very good for the majority of compounds. The slightly larger deviation shown by the standard compound 1 may be due to the range of I_{50}'s measured for this compound (see the Experimental Section). Moreover, a comparison of the deviation shown by compound 17 in comparison to that by isomer 15 could be an indication that branching in the 4-position is tolerated more than that in the 3-position.

In order to elucidate further the nature of the environment at the site of inhibition by the phenylureas, we measured the Hill inhibition by five molecules having substituents ortho to the urea moiety. Results are presented in Table II. It is seen that the percentage Hill inhibition of these compounds is very low compared to that of 1. This suggests that ortho substitution has an adverse effect on the affinity of the phenylurea for the site of action. Computer graphic studies show that ortho substitution interferes strongly with the orientation of the planar urea group with respect to the phenyl ring, restricting the latter moiety from taking up a conformation that is most suitable for binding at the Q_B receptor site. This is in agreement with earlier work (Boots et al., 1970, 1972) carried out on conformationally restricted cyclic phenylureas found to be much less active Hill inhibitors compared to the corresponding conformationally nonrestricted linear ureas.

After establishing the in vitro structure–activity relationship for the mono- and disubstituted phenylureas, we attempted to correlate in vivo herbicidal activity with the lipophilic nature of substituents in these positions. The postemergence effect of 18 phenylureas applied at 1 kg ha^{-1} on eight plant species was assessed. The eight plant species submitted to this test were maize (*Zea mays*), rice (*Oryza sativa*), barnyard grass (*Echinochloa crus-galli*), oat (*Avena sativa*), linseed (*Linum sativum*), mustard (*Sinapis alba*), sugar beet (*Beta vulgaris*), and soyabean (*Glycine max*). Plant damage was assessed after 10 days of treatment. A herbicide rating of 9 was given for complete kill and zero for no effect. For the eight species this gave a maximum rating of 72 and a minimum rating of 0. Unfortunately, not all the 20 compounds in Table I were available in the quantities necessary for screening. However, the range of π values for the compounds considered still allowed us to make some conclusions on the effect of lipophilicity on herbicidal activity. Results are presented schematically in Figure 2. As in the case of the Hill inhibition activity, herbicidal activity increased with an increase in π. We have included structures in Figure 2 so that such a trend can be observed clearly. Although our data do not permit us to identify with precision the "real"

Table II. Comparison of the Hill Inhibition Activity of Some Ortho-Substituted Phenylureas to That of Compound 1

compound	% Hill inhibn at 10^{-5} M
	100
	20
	18
	10
	26
	27 (at 10^{-4} M)

position of an optimum herbicidal effect, a flattening of activity at the higher π values most probably signifies that the relationship between herbicidal effectiveness and π is parabolic in form. An optimum in biological activity may mark the achievement of a compromise between the ability of a compound to translocate to the binding site and its affinity for this site on reaching it. Since π for a substituted phenylurea is approximately equal to log P for that compound minus 0.98 (where 0.98 is the log P measured by Kakkis et al. (1984) for the unsubstituted phenylurea) then to a close approximation Figure 2 indicates that compounds for which log $P \approx 4$ are still very active at 1 kg ha^{-1}.

In order to rationalize our in vitro studies with similar studies carried out recently on a variety of other 3- and 4-substituted phenylureas, we attempted a detailed analysis of the Hill inhibitory activity of 44 compounds. We were able to perform this exercise as data have been reported for compounds common in all three studies. Moreover, studies by Takemoto et al. (1984) have suggested that there appears to be no significant difference in Hill inhibition by phenylurea derivatives on chloroplasts derived from different plant species. Data standardized with respect to compound 1 are presented in Table III. For convenience the pI_{50} for this compound was taken as 7. We have omitted the data on the cyclohexane derivative from Kakkis et al. (1984), as the ratio of activity for this compound differed by at least a factor of 10 from that predicted by our analysis (see later text). Kakkis et al. (1984) have introduced a branching term that accounted for such a discrepancy. As the activity of all the other compounds from this study and those from Takemoto et al. (1984) could be accommodated satisfactorily by our QSAR analysis, we decided not to introduce a branching

Table III. Standardized Hill Inhibitory Data from Kakkis et al. (1984) and Takemoto et al. (1984)

			log $[I_{50}(\text{compd})/I_{50}(1)]$		
compd	R[a]	R′	obsd	calcd[b]	Δ
21	H	NO_2	1.91	2.24	0.33
22	H	CF_3	0.98	0.59	0.39
23	H	$COCH_3$	2.50	1.79	0.71
24	COC_6H_5	H	0.31	0.47	−0.16
25	F	H	1.21	1.42	−0.21
26	H	H	1.49	1.58	−0.09
27	H	n-C_4H_9	0.11	0.20	−0.09
28	H	$OCH_2CH_2C_6H_5$	−0.36	−0.04	−0.32
29	t-C_4H_9	H	0.84	0.37	0.47
30	H	OH	2.76	2.09	0.67
31	H	NH_2	2.47	2.84	−0.37
32	H	$OCH_2C_6H_3$-2′,4′-Cl_2	−0.68	−0.69	0.01
33	H	3-Cl-4-CO_2CH-$[CH_2C(CH_3)CH_3]_2$	−0.91	−1.23	0.32
34	4-$O(CH_2)_{11}CH_3$	H	−0.72	−0.59	−0.13
35	H	F	0.97	1.22	−0.25
36	H	Cl	0.75	0.76	−0.01
37	H	OCH_3	1.61	1.51	0.10
38	H	OC_2H_5	1.14	1.20	−0.06
39	Cl	H	0.71	0.86	−0.15
40	Br	H	0.52	0.75	−0.23
41	I	H	0.44	0.61	−0.17
42	OCH_3	H	1.51	1.80	−0.29
43	CN	H	1.79	1.60	0.19
44	NO_2	H	1.32	1.25	0.07

[a] Structure as in Table I. [b] From eq 6; the data from Table I also included to derive eq 6.

term. We shall refer to the cyclohexane derivative in a later part of our discussion. From the data in Tables I and III we have derived eq 4–6.

$$\log [I_{50}(\text{compd})/I_{50}(1)] = 1.40\ (\pm 0.17) - 0.52\ (\pm 0.08)\pi$$
$$n = 44,\ r = 0.88,\ s = 0.41 \quad (4)$$

$$\log [I_{50}(\text{compd})/I_{50}(1)] = 1.49\ (\pm 0.16) - 0.55\ (\pm 0.01)\pi - 0.56\ (\pm 0.39)\sigma$$
$$n = 44,\ r = 0.90,\ s = 0.38 \quad (5)$$

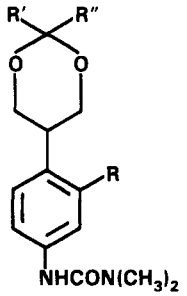
$$\log [I_{50}(\text{compd})/I_{50}(1)] = 1.58\ (\pm 0.13) - 0.84\ (\pm 0.13)\pi + 0.07\ (\pm 0.03)\pi^2 - 0.74\ (\pm 0.31)\sigma$$
$$n = 44,\ r = 0.94,\ s = 0.29 \quad (6)$$

Bearing in mind the method that we have utilized to standardize the data in Table III, the correspondence between our in vitro data and those reported by Kakkis et al. (1984) and by Takemoto et al., (1984) is remarkable. From a comparison of eq 4 and eq 5 and 6 it is clear that the hydrophobicity term is the most significant. The magnitude of the coefficient for π is of the same order as that determined by us for the first 20 compounds (eq 1) and is also very similar to that derived by the other two groups of researchers. The introduction of a term involving σ (eq 5) results in a better correlation, further improved by the inclusion of a π^2 term (eq 6). Although the coefficient for σ is about the same size as that reported for the Hill inhibition by [(phenylmethoxy)methyl]ureas (Kakkis et al., 1984), the error limits derived by us are lower. This coefficient of σ is also smaller than the one we have derived for the first 20 compounds (eq 3), and this is in part due to the larger number of cogeners used to derive eq 5.

Nevertheless from these equations it is apparent that consideration of σ is less important than π in the design of herbicidal phenylureas. However, there remains the possibility that halogen substitution in the 3-position (especially chlorine or fluorine) improves the interaction of the phenylurea at the receptor site of the 32-kDa pro-

tein. We have indicated the possible occurrence of such a phenomenon in Figure 1. Moreover, closer examination of the data of Kakkis et al. (1984) adds further support to this; the observed pI_{50} values for the *m*-halo derivatives **6** and **16** from Table I of this reference and **7**, **31** and **33** from Table II are all lower than the predicted pI_{50} values. A final observation we make in this respect is that the crystal structures of (4-chlorophenyl)dimethylurea (monuron) (Baughman et al., 1980a) and (3,4-dichlorophenyl)dimethylurea (diuron) (Baughman et al., 1980b) show some differences apparently due to the introduction of a halogen atom in the 3-position. The dihedral angle between the plane of the phenyl ring and that of the urea moiety is 33.6° in diuron compared to the significantly larger angle of 53.6° in monuron. Such differences may be very important in any dipole–dipole interactions between the phenylurea and the receptor site.

The foregoing structure–activity analysis has allowed us to design a novel class of active phenylurea herbicides that have **45** as their general structure:



R is either CH_3 or Cl while R′ and R″ are saturated hydrocarbon fragments. We shall present a full report on the physicochemical properties and structure analysis of this class of phenylureas at a later date. However, we can summarize our findings so far as follows: compounds with R = Cl are at least 10 times more active in Hill inhibition than those with R = CH_3; this difference in activity cannot be accounted for simply by the difference in the lipophilicity of the two substituents. An increase in the hydrophobicity of R′ and R″ leads to more potent Hill inhibition; the log *P* for compound **46** (R = CH_3, R′ = R″ = C_2H_5) has been measured as 2.76. Using the log *P* value of 0.98 measured by Kakkis et al. (1984) for the unsubstituted phenylurea, we have estimated π for **46** as 1.78. Inserting this value and $\sigma = -0.25$ in eq 6, we calculate a value of 0.47 for the ratio of activities. This is close to the measured value of 0.30. The total activity of **46** at 1 kg ha^{-1} is 53, which again is in agreement with the in vivo herbicidal activity shown in Figure 2. Correlation of field activity either to in vivo (primary screen) data or to Hill inhibition potency is difficult for phenylureas of general structure **45** because other physicochemical properties such as solubility in water and hydrolytic stability are important under field conditions.

Although the partition coefficient of **46** is about 10 times *lower* than the structurally similar 1-(4-cyclohexylphenyl)-3,3-dimethylurea, which we referred to earlier in our discussion, the pI_{50} for **46** is around 7; i.e., it is about 15 times *more* active than the cyclohexane derivative. We do not as yet understand why the cyclohexane derivative does not fit our analysis in view of the fact that the fit with compound **46** is very good. The branching term introduced by Kakkis et al. (1984) cannot explain the discrepancy since it should be of a similar magnitude for the two compounds.

ACKNOWLEDGMENT

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Registry No. **1**, 79473-12-4; **2**, 107598-60-7; **3**, 107615-83-8; **4**, 29003-72-3; **5**, 107598-61-8; **6**, 28170-41-4; **7**, 34123-51-8; **8**, 107598-62-9; **9**, 107598-63-0; **10**, 107598-64-1; **11**, 107598-65-2; **12**, 107598-66-3; **13**, 107598-67-4; **14**, 107598-68-5; **15**, 107598-69-6; **16**, 107598-70-9; **17**, 107598-71-0; **18**, 34123-59-6; **19**, 7160-01-2; **20**, 330-54-1; **21**, 7159-98-0; **22**, 2164-17-2; **23**, 42865-65-6; **24**, 61706-06-7; **25**, 332-33-2; **26**, 101-42-8; **27**, 88132-40-5; **28**, 70859-35-7; **29**, 32745-69-0; **30**, 4849-46-1; **31**, 39938-79-9; **32**, 88132-42-7; **33**, 107598-72-1; **34**, 88132-44-9; **35**, 330-39-2; **36**, 587-34-8; **37**, 28170-54-9; **38**, 96337-68-7; **39**, 150-68-5; **40**, 3408-97-7; **41**, 92317-98-1; **42**, 7160-02-3; **43**, 82261-41-4; **44**, 7159-97-9.

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