A QUANTUM-CHEMICAL STUDY OF PESTICIDAL ACTIVITY OF PHENYLUREA DERIVATIVES. THE EQUILIBRIUM GEOMETRIES

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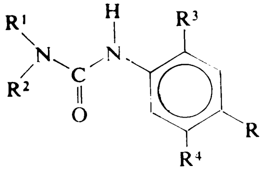
Quantum-chemical methods have been used to study geometry of 13 phenylurea derivatives with respect to their herbicidal activity. From energy hypersurfaces of the equilibrium geometries its was possible to determine the shape and evaluate the fexibility of the molecules. An interdependence is observed between space arrangement and herbidical activity of some derivatives. However, the exceptions found indicate that conformational geometry of the molecules studied does not represent a sufficient condition for their herbicidal activity.

Two phenylurea derivatives with considerable herbicidal activity are known under the names fluometuron (N,N-dimethyl-N'-(3-fluoromethylphenyl)urea) and linuron (N-methyl-N-methoxy-N'(3,4-dichlorophenyl)urea). In our laboratory a number of derivatives were synthetized which showed inhibition ability to the Hill reaction[1]. Out of them only a part show comparable activity to that of the said standards, the other being less active. We found that the parent phenylurea, too, shows activity at high concentrations. It is known[2] that there exists an interdependence between biological activity of compounds and their geometry. Obviously, the nature of substituents and total electronic structure play important roles here. Therefore, in our search for reasons of ability of the phenylurea derivatives to inhibit the Hill reaction we studied first their geometry by the quantum-chemical methods.

THE CALCULATION METHOD AND RESULTS

We used the standard semiempirical PCILO and CNDO/2 methods[3,4]. All the data of bond lengths, valence and dihedral angles were taken from literature[5]. We cal-



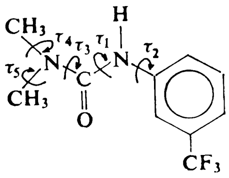
SCHEME 1

culated a series of compounds of the general formula (Scheme 1) with the following substituents:

	R_1	R_2	R_3	R_4	R_5
I	H	H	H	H	H
II	CH_3	CH_3	H	CF_3	H
III	CH_3O	CH_3	H	Cl	Cl
IV	H	H	H	CF_3	H
V	H	H	H	Cl	Cl
VI	H	H	Cl	CF_3	H
VII	H	H	CH_3O	CF_3	H
VIII	H	H	$(CH_3)_2CHO$	CF_3	H
IX	CH_3	H	CH_3O	CF_3	H
X	CH_3	CH_3	CH_3O	CF_3	H
XI	CH_3	H	H	H	H
XII	CH_3	CH_3	H	H	H
XIII	CH_3	H	Cl	CF_3	H

The order of herbicidal activity is $\mathit{II} \approx \mathit{III} \approx \mathit{XI} = \mathit{XII} \approx \mathit{XIII} \gg \mathit{IX} \approx \mathit{X} = \mathit{VII} > > \mathit{I}$.

In the first step we investigated the presumption that the optimum geometry arrangement of the substituents at one side of the carbonyl group of the urea derivative molecule does not depend on the optimum geometry arrangement of the substituents at the other side of the carbonyl group, and *vice versa*. This presumption reduces considerably the number of conformers. To verify corectness of this presumption, we calculated the optimum geometry of the *II* molecule in the following way: First the dihedral angles τ_1, τ_2, τ_3, τ_4 and τ_5 (Scheme 2) were optimized by the PCILO program[6]. Then we optimized separately the geometry of the molecules substituted only at one side of the carbonyl group and obtained the same values of the dihedral angles τ_1 to τ_5. Similar procedure was applied to calculation of the optimum conformational geometry of the molecule *III*, the same results being obtained by the two procedures.



SCHEME 2

Next we investigated the effect on geometry of introduction of individual substituents into various positions of the urea molecule. Figure 1 shows the conformational map of the parent phenylurea. The lowest energy minimum is seen at $\tau_1 = 0°$

and $\tau_2 = 210°$, which agrees with the geometry optimized by the CNDO/2 method[7]. The conformational map in Fig. 2 represents the dependence of E *vs* $f(\tau_1, \tau_2)$ of the molecule *IV*, and its purpose is to determine the geometry change caused by substitution of the *meta*-H in the phenyl group. The lowest minimum is at $\tau_1 = 0°$ and $\tau_2 = 210°$. Fig. 3 shows that introduction of a further substituent into *para* position (*V*) brings no substantial changes in the conformational map, the overall minimum being again at $\tau_1 = 0°$ and $\tau_2 = 210°$. A quite opposite result is observed when introducing a substituent into *ortho* position (*VI*). From the conformational map of compound *VI* (Fig. 4) it is seen that the lowest minimum is shifted to the angles values $\tau_1 = 0°$ and $\tau_2 = 30°$, which is connected with simultaneous disappearance of the isoenergy lines near the angle $\tau_2 = 180°$. Introduction of the R_1 and R_2 substituents into phenylurea (*XII*) is accompanied by disappearance of local minima in the region $\tau_1 = 180°$, the position of the lowest energy minimum at $\tau_1 = 0°$, $\tau_2 = 210°$ (Fig. 5) being unchanged as compared with the parent phenylurea.

In the next step we investigated effect of the R_1 and R_2 substituents on the functions $E = f(\tau_3)$, $E = f(\tau_4)$ and $E = f(\tau_5)$ (Figs 6 and 7).

Fig. 8 gives geometry models of the optimum conformations.

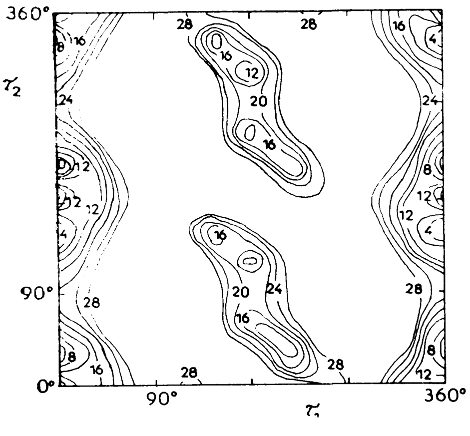


FIG. 1

The conformational map of energy of phenylurea. The isoenergy lines represent values of relative energy in kJ mol^{-1} with respect to the lowest energy minimum which is considered zero

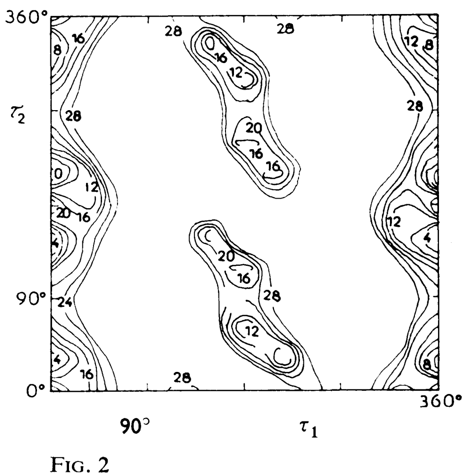


FIG. 2

The energy conformational map of 3-trifluoromethylphenylurea

DISCUSSION

The conformational maps of molecules *I*, *IV*, and *V* show that substitution at *meta*-, and *meta*-, *para*-positions has no significant effect on shape of the energy hypersurface

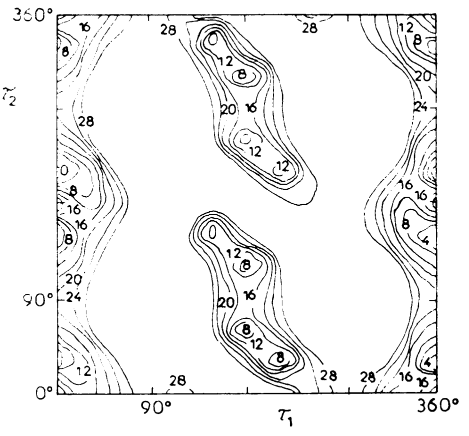


FIG. 3

The energy conformational map of 3,4-dichlorophenylurea

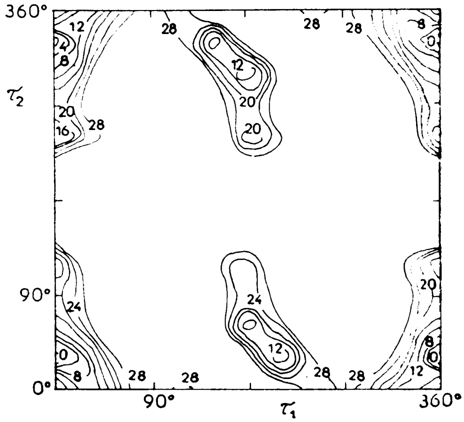


FIG. 4

The energy conformational map of (2-chloro-5-trifluoromethylphenyl)urea

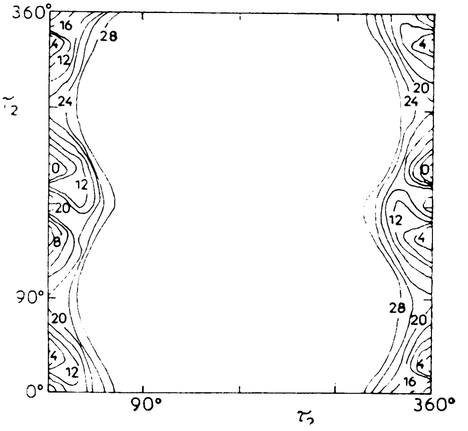


FIG. 5

The energy conformational map of N, N-dimethyl-N'-phenylurea

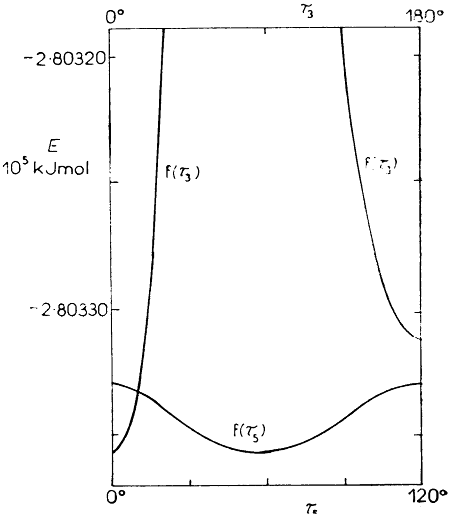
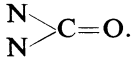


FIG. 6

The dependences $E = f(\tau_3)$ and $E = f(\tau_5)$ for N-methyl-N'-phenylurea and that position of the lowest energy minimum remains unchanged with the angles $\tau_1 = 0°$, $\tau_2 = 210°$. This result follows from the fact that the substituents at *meta*- and *para*-positions of the urea are far away from the remaining atoms and, therefore, the conformation maps are close to that of the parent phenylurea. Introduction of a substituent into *ortho*-position changes the map substantially. At $\tau_2 = 180°$ repulsion interaction between the R_3 substituent and oxygen atom of the carbonyl group makes itself felt, which results in decreased stability of the conformers with this space arrangement, the lowest minimum being shifted to the values $\tau_1 = 0°$, $\tau_2 = 30°$. This position of the lowest energy minimum at the conformational map is the same for all the molecules substituted at *ortho*-position.

The conformational map of the molecule *XII* shows that the isoenergy lines in the region $\tau_1 = 180°$ disappeared, whereas the position of the lowest energy minimum remained the same as in the molecules *I*, *IV*, *V*, *i.e.* $\tau_1 = 0°$ and $\tau_2 = 210°$. This relative instability of the conformations in the region $\tau_1 = 180°$ can be ascribed to repulsion between the methyl group and benzene ring. From the dependences $E = f(\tau_3)$, $E = f(\tau_4)$, and $E = f(\tau_5)$ (Figs 6 and 7) it is seen that the change in τ_3 has the largest influence on the total energy. Obviously, this is due to conjugation disturbance in the system  $^{N}_{N}\!\!>\!C{=}O$. The energy changes caused by changes in τ_4 and τ_5 are negligible with respect to those caused by τ_1, τ_2, and τ_3.

The models (Fig. 8) show that substantial difference between the optimum geometry of the strongly active molecule *II* and the optimum geometries of the *ortho*-substituted derivatives *VI*–*IX*, *XIII* consists in orientation of CF_3 group with respect to carbonyl group. Obviously this fact plays an important role in the inhibition of the Hill reaction, because these compounds (except for *XIII*) show decreased pesticidal activity. However, the exception of the molecule *XIII*, which contains a strongly electronegative substituent at *ortho*-position of the benzene ring, shows

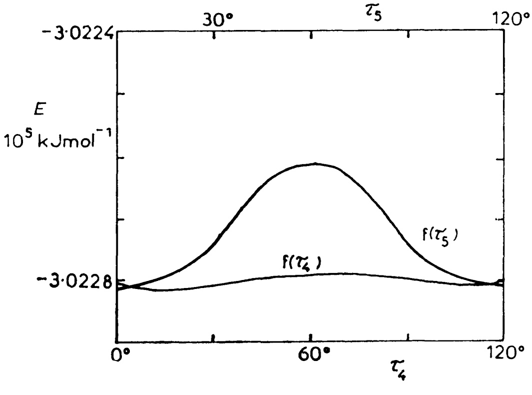
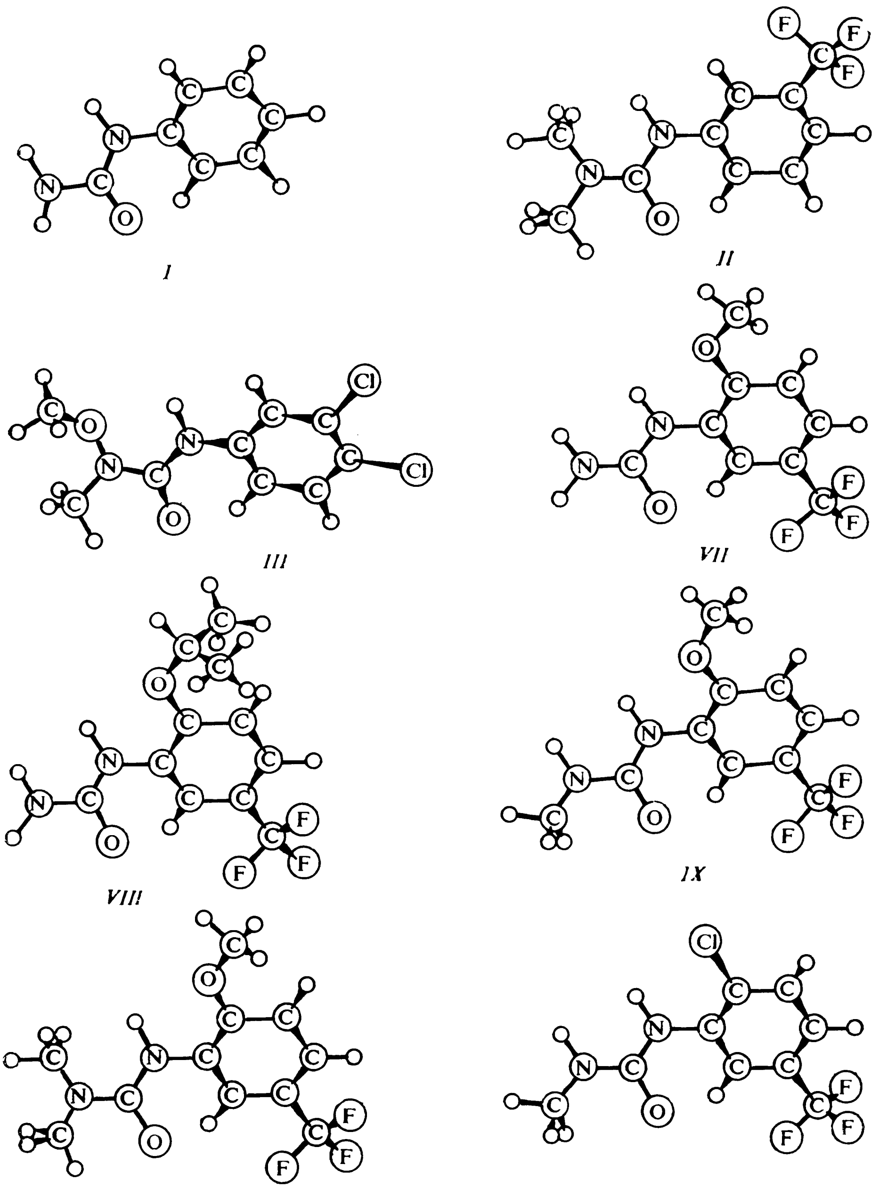


FIG. 7

The dependences $E = f(\tau_4)$ and $E = f(\tau_5)$ for N,N-dimethyl-N'-phenylurea



I

II

III

VII

VIII

IX

X

XIII

FIG. 8

Models of the optimum geometries of the phenylurea derivatives that the conformation geometry does not represent a sufficient condition for pesticidal activity. Therefore, we continue the study of this series of compounds especially with respect to the electron distribution and electrostatic potentials in the vicinity of the molecule.

All the calculations were carried out with a Siemens 4004/150 computer in the computer centre of Comenius University, Bratislava. The biological tests on the Hill reaction by the topical method[8] were realized in Research Institute of Agrochemical Technology, Bratislava.

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