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## AM1 Treatment of Some Phenoxyacetic Acid Herbicides

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**Abstract:** AM1-type semiempirical quantum chemical calculations were carried out to explain differences in herbicidal activity between certain phenoxyacetic acid derivatives. It was found that the proper orientation and shape of the COOH group and the phenyl moiety both mutually and individually affected the observed activities.

**Key Words:** Herbicides, phenoxyacetic acid derivatives, 2,4-D, AM1 type calculations, weed killers.

### Bazı Fenoksiasetik Asit Ot Öldürücülerinin AM1 İncelenmesi

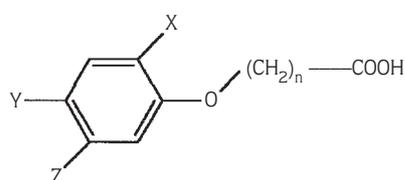
**Özet:** Bazı fenoksiasetik asit türevleri arasındaki ot giderici (herbisit) aktivite farklarını izah için AM1 tipi yarıempirik kuvantum kimyasal hesaplar yapılmıştır. Gözlenen aktiviteler üzerinde, COOH ve fenil gruplarının uygun oryantasyon ve biçimlerinin müştereken veya ayrı ayrı etkili oldukları bulunmuştur.

**Anahtar Sözcükler:** Herbisitler, fenoksiasetik asit türevleri, 2,4-D, AM1 tipi hesaplar, zararlı ot öldürücüler.

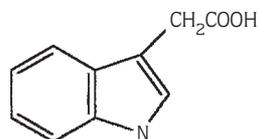
### Introduction

The discovery of the phenoxyacetic acid herbicides was made during the work of Kögl et al. (1), who showed that indole-3-acetic acid (IAA, Auxin) promotes cell elongation in plants. Auxin was isolated from plants and this stimulated the search for other compounds of related structure. 1-Naphthylacetic acid was found to be active, as was 2-naphthoxyacetic acid. This created great interest in aryloxyacetic acids as potential plant growth regulators (2). In 1942, Zimmerman and Hitchcock showed that certain chlorinated phenoxyacetic acids, such as 2,4-dichlorophenoxyacetic acid (2,4-D)(I, X=Y=Cl, Z=H, n=1), were more active than the natural growth hormone IAA (II), and that they were not rapidly metabolized in the plant (3). Consequently, 2,4-D could be externally applied to cause abnormal growth and the death of the plant since it is not internally regulated like IAA. The herbicidal phenoxyacetic acids were found to be much more active against broad-leaved weeds (dicotyledons) than against cereals and grasses (monocotyledons). Despite its vital importance, the selectivity of these compounds is not clearly understood (4-8). However, they came into use at a time when maximum production with much reduced agricultural resources was a vital factor in the war effort (3).

Research by Wain on the herbicidal properties of a series of  $\omega$ -phenoxyalkanecarboxylic acids of type I (X=Y=Cl, Z=H) showed that herbicidal activity alternated along the series,



(I)



(II)

those members possessing an even number of methylene groups being almost inactive (9). The higher homologues were shown not to be herbicidal themselves, but those containing odd numbers of methylene groups owe their herbicidal activity to *in vivo*  $\beta$ -oxidation within the plant by the enzyme  $\beta$ -oxidase to give 2,4-D, which is the active herbicidal entity. It has been established that 2,4-D discontinues oxidizing phosphorylation by inhibiting the esterification of the phosphate, with disruption of the process of formation of compounds rich in energy: ADP and ATP. Consequently, the energy exchange in plants is disrupted. It has also been established that 2,4-D strongly affects the synthesis of RNA. Therefore, it is probable that the herbicides first affect the nucleic acids and then, through these the biosynthesis process. 2,4-D noticeably affects the photosynthesis process; first of all the photolytic activity of chloroplast and photosynthetic phosphorylation (8).

Although, phenoxyacetic acid derivatives have been referred to as herbicides since the Second World War, activity-structure relations and selectivity properties have not yet been rationalized. For example, 2-methyl-4-chlorophenoxyacetic acid (MCPA) used for control of many broad-leaved weeds post-emergence in cereals, grassland and asparagus (10) whereas 2,4,5-trichlorophenoxyacetic acid is employed in the control of woody plants and can be used for selective weed control in conifers (10). It is more persistent in soil than either MCPA or 2,4-D. However, recent research on phenoxyacetic acid and its derivatives has concentrated on their physiological effects (11-16) rather than mechanistic investigations at molecular level. In addition, there have been no, quantum chemical studies of the above-mentioned compounds at any level of sophistication, including the AM1 type reported in the literature.

As for the structure-activity relationship of these structures, only a few have been reported (17,18). These are chemical (complexation behavior and Hammett relationship have been considered) rather than examining the physiological structure-activity relationship.

In the present study, various phenoxyacetic acid derivatives were considered for AM1-type semiempirical quantum-chemical treatment with the aim of clarifying the structure-activity relationship.

## Method

In the present work, the geometry optimizations and molecular orbital calculations were carried out using the AM1 (Austin method-1 (19)) method at the level of a restricted Hartree-

Fock (RHF) approach, and a conjugate gradient minimization, Polak-Ribiere, technique was applied to get the optimized geometries. Throughout the calculations, the convergence limit and gradient values (RMS) were kept below  $10^{-4}$  kcal/mol and  $10^{-3}$  kcal/(Å° mol), respectively. All these calculations were carried out using the Hyperchem (release 5.1) package program. The solvent accessible surfaces of the molecules were obtained using the CS Chem 3D Net program.

## Results and Discussion

Of the various derivatives of phenoxyacetic acids, 2,4-D (salts and esters) and MCPA (salts) are widely used as herbicides. The physiological activity of phenoxyacetic acid increases when a halogen atom such as fluorine or chlorine is introduced into the aromatic part. The position of the halogen is crucial for this activity: for instance, activity decreases between the dichlorosubstituted phenoxyacetic acid derivatives in the order of 2,4-D > 2,5- > 3,4- > 3,5- > 2,6-. When an aliphatic group is substituted for one hydrogen atom on the ring, the activity of the compound increases insignificantly (8). For high activity, the molecule must generally possess either the -COOH group or a group that is easily converted to it within the plant tissues (1,8). In the present study, only the acid form of the phenoxyacetic acid type herbicides were concerned.

As far as the ring substitution-activity relationship is concerned it has been argued that one free ortho position is an essential requirement for activity, but there are some very active compounds, like 2,4-dichloro-6-fluorophenoxyacetic acid, in which all the ortho positions are substituted. There is therefore some uncertainty regarding the importance of specific nuclear positions on growth regulating properties; however, at least one nuclear position must be unsubstituted.

All these observations of herbicides causing contortions of leaf stalks and stems and stumpiness of the roots require some theoretical explanation. Table I shows the herbicides considered in the present study. Some molecular orbital, physicochemical and geometrical properties of these compounds are shown in Table II.

As far as the activity is concerned, there exists no correlation between the properties contained in Table II. The highest occupied and the lowest unoccupied molecular orbital energies ( $E_{\text{HOMO}}$  and  $E_{\text{LUMO}}$ , respectively), interfrontier energy gap ( $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$ ) and activity seem to be irrelevant. In addition, the log P values which measure the lipid/water distribution of the compounds, and the surface area and volume of the compounds do not correlate with activity. All these results imply that activity is dictated mainly by sterical factors and the spatial arrangement of the groups.

It has been reported that the harmful effects of these compounds leading to herbicidal activity arise from the disturbance occurring in various vital biochemical steps in plant tissues (1,8,20). For instance, they prevent normal plant growth, which depends on optimum amounts of auxins being present. There is evidence that sublethal amounts of 2,4-D stimulate the production of ethylene. Because of this multi-targeting behavior, it may be difficult to relate the

Table 1. Phenoxyacetic acid derivatives considered.

Compound	No	Activity	Remarks
2-Chloro	1	Highly active	
4-Chloro	2	Highly active	
2,4-Dichloro	3	Very active	Selective weed killer and defoliant
2-Methyl-4-chloro	4	Very active	Selective for dicotyledons
2,6-Dichloro	5	Poorly active	
3,5-Dichloro	6	Poorly active	
2,4,5-Trichloro	7	Active	Selective weed control in conifers
2,4,6-Trichloro	8	Inactive	
2,4-Dichloro-6-fluoro	9	Very active	Growth regulant and seed preventative

Information excerpted from ref.9.

Table 2. Some quantum chemical, physicochemical and geometrical properties of various phenoxyacetic acid derivatives.

Compound	<sup>a</sup> E <sub>HOMO</sub>	<sup>a</sup> E <sub>LUMO</sub>	<sup>a</sup> ΔE	<sup>b</sup> ΔHf	log P	<sup>a</sup> Volume	<sup>a</sup> Surface Area
2-Chloro	-9.41	-0.05	9.36	-107	1.85	527	352
4-Chloro	-9.28	-0.06	9.22	-108	1.85	537	357
2,4-Dichloro	-9.42	-0.34	9.08	-113	2.37	570	376
2-Methyl-4-chloro	-9.18	-0.01	9.17	-116	2.32	578	377
2,6-Dichloro	-9.90	-0.49	9.4	-109	2.37	571	370
3,5-Dichloro	-9.66	-0.39	9.2	-114	2.57	579	382
2,4,5-Trichloro	-9.67	-0.7	8.96	-119	2.89	605	388
2,4,6-Trichloro	-9.95	-0.79	9.16	-115	2.89	615	394
2,4-Dichloro-6-fluoro	-9.98	-0.84	9.1	-153	2.51	586	382

Energies in <sup>a</sup>ev.; <sup>b</sup>)Kcal/mol; <sup>c</sup>)Å<sup>3</sup>; <sup>d</sup>)Å<sup>2</sup>

activities of series of phenoxyacetic acid derivatives directly with certain structural and steric properties. However, it is possible to gain a much better insight into the mode of action of these compounds. For this purpose, the analysis of shapes was the main aim of the present work. Hence, AM1 geometry optimized structures of the phenoxyacetic acid derivatives listed in Tables I and II were considered. The molecules were oriented in space in parallel alignment and viewed in three different directions using ball models (Figures 1-3). Figure 4 shows the solvent

(water) accessible surfaces of these molecules which more realistically reflect the effective shapes *in vivo*. In Figures 1 and 3 the molecules are projected onto the XY-plane and viewed along the Z-direction in such a way that a substituent (if any exists) at position-2 of the phenyl ring is on the right hand side. The other figures are obtained from Figure 1 by rotating all of the molecules in the same direction.

From Figure 1 it is possible to see that 2-chloro, 2,4-dichloro and 2-methyl-4-chlorophenoxyacetic acids have carboxylic acid groups oriented in space in more or less the same way. Although the 3,5-dichloro derivative is displayed having a quite differently oriented carboxylic acid moiety, rotating the molecule by  $180^\circ$  out of the XY-plane produces an alignment of the acid group similar to 2,4-dichloro or 2-chloro derivatives. However, an inspection of Figure 2 for the 3,5-dichloro derivative reveals that the orientation of the COOH group is not exactly the same as for the 2,4-dichloro derivative (see also figure 3). On the other hand, from Figures 1-3 it is evident that the 2,6-dichloro derivative possesses a very differently orientated COOH moiety. Both of the 2,6- and 3,5-dichloro derivatives exhibit low activity.

When the shapes of the 2,6-dichloro and 2,4,6-trichloro derivatives are compared, one can see that the orientation of the COOH group in these compounds is almost identical. Therefore,

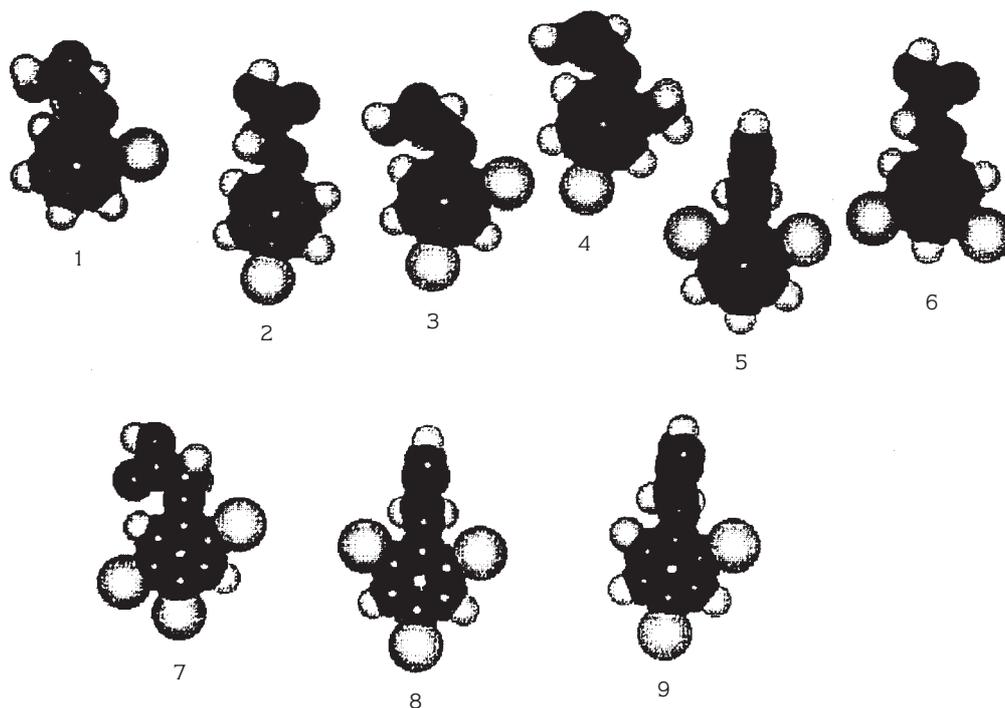


Figure 1. Shapes of the pesticides (1-9) observed in the Z-direction.

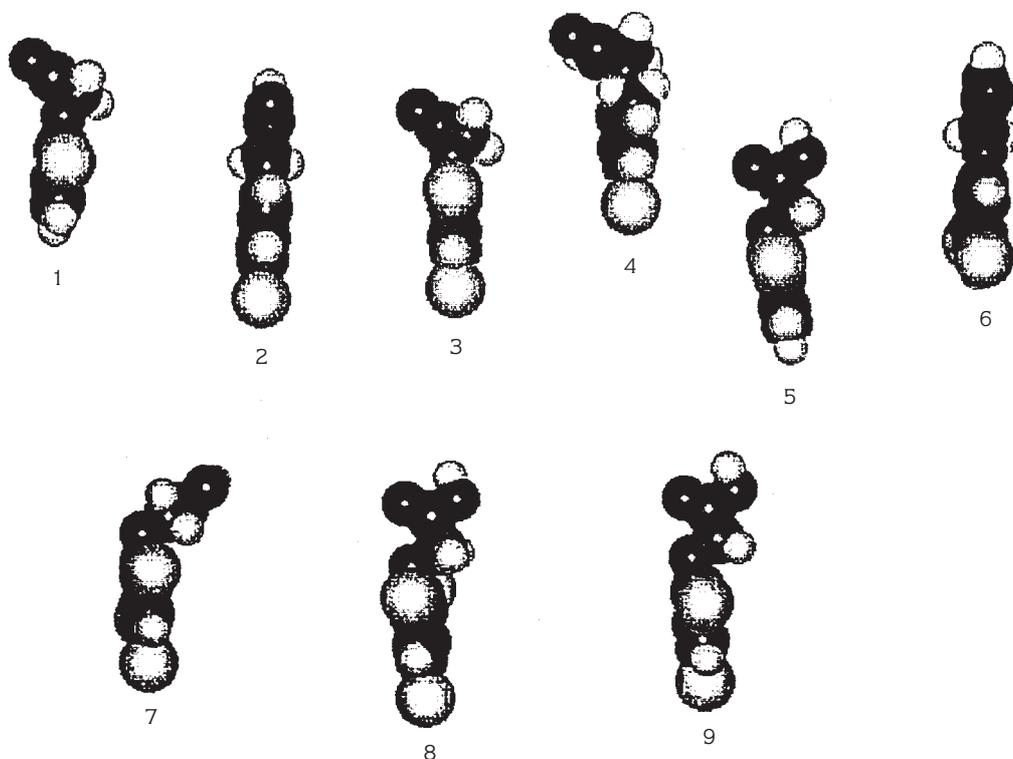


Figure 2. Shapes of the pesticides (1-9) observed in the X-direction.

the fact that there is low activity in one but no activity in the other needs to be explained by the presence of a 4-chloro substituent in the latter case.

As for the 2,4,5-trichloro derivative, Figures 1-3 indicate that the compound is unique, but the reflection through the XY-plane (mirror image) produces a structure in which the COOH group orientation is quite similar to the other highly active compounds. The in terms of 2,4-dichloro-6-fluoro derivative, which is also very active, resembles the 2,6-dichloro and 2,4,6-trichloro derivatives in terms of the COOH group. The enhanced activity for the latter compound cannot be explained by matching the shapes of certain parts of the molecule with the other active structures. This suggests that more than one site in the molecules has an effect on the activity, namely, whenever the COOH group or the substituted phenyl moiety has the proper orientation and shape, the molecule exhibits a herbicidal action. The most likely explanation is that the size of the fluorine atom is not sufficient to disturb the activity although the shape pattern looks like that of the 2,4,6-trichloro derivative.

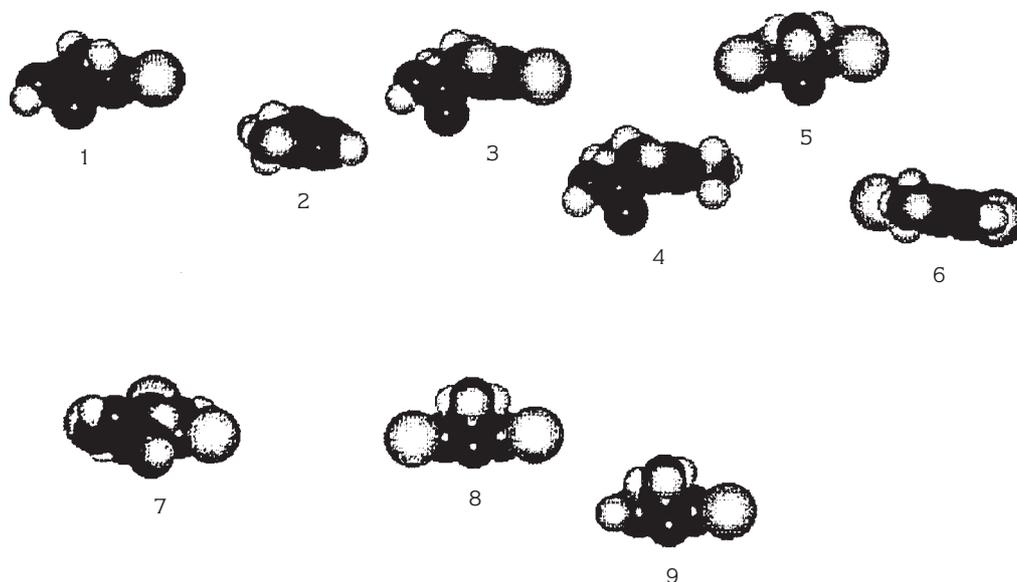


Figure 3. Shapes of the pesticides (1-9) observed in the Y-direction.



Figure 4. Solvent accessible surfaces of the pesticides (1-9) considered.

### Conclusion

The present study reveals that the herbicidal action of phenoxyacetic acid derivatives is mainly dictated by molecular shapes rather than certain quantum chemical and physicochemical properties. Moreover, it has been found that the COOH group and phenyl moiety play an equally important role in the herbicidal action mechanism, mutually as well as individually.

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