Molecular Comparisons of Selected Herbicides and Their Safeners by Computer-Aided Molecular Modeling[†]

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The chemical structures of selected herbicides and their respective safeners were modeled by means of the computer-aided molecular modeling program XICAMM and compared to determine the molecular similarities of these agrochemicals. The particular safener/herbicide combinations that were evaluated included dichlormid/EPTC, fenclorim/pretilachlor, flurazole/alachlor, oxime ether safeners (cyometrinil, oxabetrinil, and CGA-133205)/metolachlor, naphthalic anhydride/EPTC or metolachlor, and CGA-154281/metolachlor. Comparisons were based on calculated parameters including connectivity indices, charge distribution, and molecular volume as well as visual evaluations of the modeled structures. The results obtained from these comparisons indicate that the chemical components of the most successful safener/herbicide combinations are quite similar at the molecular level. Evaluations of the oxime ether analogues cyometrinil, oxabetrinil, and CGA-133205 which protect grain sorghum [*Sorghum bicolor* (L.) Moench] against the chloroacetamide herbicide, metalachlor, revealed that as the effectiveness of the safener increases, so does its molecular similarity to metolachlor. Calculated parameters and visual evaluations of the modeled structures showed that CGA-132205, the most effective of the oxime ether safeners is also the most similar to the herbicide at the molecular level.

INTRODUCTION

Herbicide safeners, also known as antidotes, antagonists, and protectants, are used to protect crop plants from the applied herbicide, thus allowing for the control of closely related weed species or hard-to-control weed species without crop injury (Hatzios and Hoagland, 1989). The safener may be applied in one of two ways, depending on the basis of its selectivity. If the safener is selective only for the crop, then the safener can be applied as a tank mixture with the herbicide. This is the case of the dichloroacetamide safener dichlormid (Figure 1), which is used extensively in corn as a formulated mixture with the carbamothioate herbicide EPTC. If the safener is nonselective, it must be applied only to the crop. This specificity is usually achieved by treating the crop seed before planting. The oxime ether safeners (Figure 2) and the thiazole carboxylate safener flurazole (Figure 3) are applied in this manner when used in combination with the chloroacetamide herbicides metolachlor (Figure 4) and alachlor (Figure 3), respectively, on grain sorghum.

The exact mechanism by which these safeners protect grass crops against herbicide injury is not known. Hatzios (1983) has summarized four general mechanisms of action for herbicide safeners. First, the safener may interfere with herbicide uptake and/or translocation; second, the safener may compete with the herbicide at a common site of action within the protected plant (competitive antagonism); third, the safener may stimulate herbicide degradation within the plant (enhanced
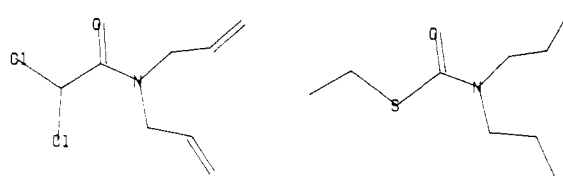
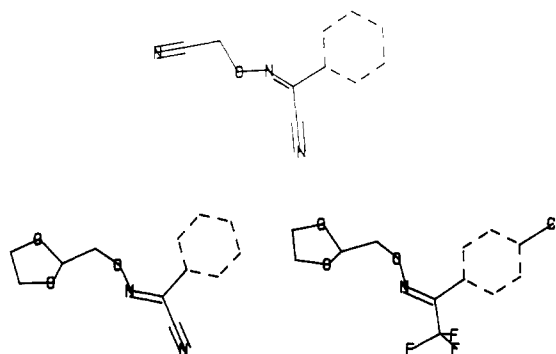Figure 1. Molecular structures of dichlormid (left) and EPTC (right).

Figure 2. Molecular structures of the oxime ether safeners cyometrinil (top), oxabetrinil (bottom left), and CGA-133205 (bottom right). Rings with broken lines are aromatic.

degradation); and fourth, the safener may act through a combination of the above processes.

The "competitive antagonism theory" and the "enhanced degradation theory" proposed for explaining the mechanism of the protective action of herbicide safeners imply that the molecules of safeners and herbicides may share some common molecular characteristics. In some cases, the structural similarity of herbicide and safener molecules is apparent (Figure 1). However, in other cases, the similarities between herbicides and safeners are not so obvious (Figures 2–4).

Computer-aided molecular modeling (CAMM) is now recognized by chemists as a powerful tool for the design

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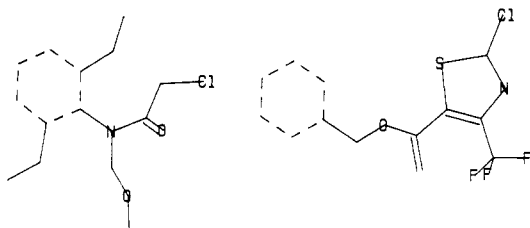

Figure 3. Molecular structures of alachlor (left) and flurazole (right). Rings with broken lines are aromatic.
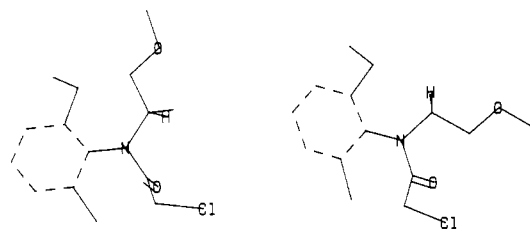

Figure 4. Molecular structures of the less active isomer of metolachlor (left) and the active isomer of metolachlor (right). Rings with broken lines are aromatic.

and development of new chemicals such as pharmaceuticals and pesticides (Davies, 1986; Seiter and Cohan, 1986). CAMM allows chemists to compare three-dimensional (3-D) spatial and electronic properties of hypothetical compounds to those of compounds with known activity, providing a rational basis for selecting new molecules to be synthesized in the laboratory (Davies, 1986). Besides the obvious applications of this technology in chemical synthesis, CAMM is also useful to weed scientists and plant physiologists for comparing compounds with a known mechanism of action to compounds with an unknown mechanism of action. When two compounds have similar chemical structures and properties, then it is quite likely that these chemicals will have similar mechanisms of action. Until recently, the use of CAMM was limited because of lack of the powerful computer equipment needed to run the CAMM programs. With rapid advances in computer technology, CAMM analysis can now be conducted with personal computers (Davies, 1986; Rodgers, 1987).

Therefore, the objective of this study was to use CAMM analysis for modeling the chemical structures of selected herbicides and their respective safeners and then to make molecular comparisons for determining the structural similarities of these molecules. The particular herbicide/safener combinations that were analyzed included EPTC/dichlormid, pretilachlor/fenclorim, alachlor/flurazole, metolachlor/oxime ether safeners (cyometrinil, oxabetrinil, and CGA-133205), and metolachlor plus the safeners naphthalic anhydride and CGA-154281. Molecular comparisons of the structures of herbicides and safeners would provide evidence for or against the proposed hypothesis suggesting that safeners serve either as substrates for inducible enzymes that degrade herbicides or as competitive antagonists of herbicides at a common target site.

MATERIALS AND METHODS

Apparatus. XICAMM (XIRIS Corp., P.O. Box 787, New Monmouth, NJ 07748), a molecular modeling program for personal computers, was used for these studies. Special computer needs to operate this program are a math coprocessor chip (8087) and 640K RAM memory. XICAMM was chosen over other programs because this program provided the best combination of graphics and molecular information that could be obtained from a CAMM program developed for a personal computer. Advantages of this program include the ability to view modeled structures in stick, stick and ball, and space-filled models and the

generation of detailed information about each atom within a molecule. Limitations of this program include the extensive time needed to model a structure and the inability to rotate molecules on screen without redrawing them.

Description of XICAMM. The first step in using this program is to enter the molecule of interest. Entering the molecule can be accomplished by drawing the molecule on the screen by use of the cursor keys to position the cursor, the letter keys to designate the atom after the cursor is positioned, and the number keys to designate the bond type. Another method is to enter fragments such as rings, by use of the function keys, and then to fuse these with side chains or other rings that were entered by use of either the function keys or letter, number, and cursor keys. When one is working with a series of related molecules that have the same general structure, an easier and faster method is to enter the general structure, model the general structure, and then edit this general structure using the methods mentioned above. Following this method of entering and modeling molecules reduces the amount of time needed to model the molecules and also ensures that the core of the molecules is in the same configuration.

After the molecule is entered, the next step is to model it. Molecular modeling consists of a series of algorithms to minimize the internal molecular energy associated with bonding and nonbonding interactions. The algorithms used may vary with the molecular modeling program that is being used; therefore, one should use caution when comparing results obtained from different programs. Even though different algorithms are used to obtain the final results, the same basic parameters are used in each algorithm. In some cases the program may locate a local energy minimum that is not the true minimum for the molecule. To correct for this, one must examine the bond and atom strains along with the 3-D structure, and if the strains appear high or if an atom appears to be trapped, then the atom must be moved and the molecule remodeled.

Information Obtained. The first information obtained from XICAMM are data concerning each atom in the molecule. These data consist of the atomic number, atomic weight, valence, hybrid (sp^1, sp^2, or sp^3), number of implied hydrogens associated with the atom, cyclic or acyclic, and bond data such as the atoms involved in each bond, the bond length, the bond angle, the dihedral angle, and the amount of energy associated with the angle strain, chiral strain, and nonbonding strain. After this information is obtained and evaluated by the researcher to determine if the molecule is modeled correctly, other parameters about the molecule are calculated. The first of these calculated parameters are the connectivity indices described later. Other calculated parameters are the principal moments and the molecular volume.

The final molecular comparison is a visual comparison that includes superimposing one molecule over the other for a geometric evaluation of one molecule relative to the other. The superimposing of these two molecules is accomplished by designating at least three strategic atom pairs between both molecules, and then the distance between the atom pairs is minimized without altering the molecular configuration of either molecule. After the distance between the two molecules is minimized, the structures are redrawn on the screen, one in red, one in green, and the area of exact overlap in yellow. Also, these two molecules can be rotated in space as one unit so that they can be observed from any angle.

Calculation of Parameters. Our molecular comparisons included size, shape, principal moments, molecular volume, and connectivity indices. To make these comparisons, the molecules must first be modeled; i.e., their most stable configuration is calculated by CAMM. When conducting this type of research, one must remember that the most stable configuration may not be the most active configuration. But even if the most stable configuration is not the most active configuration, it is a good starting point for CAMM and for the molecular comparisons.

From the modeled structure of the most stable configuration of a molecule, principal moments and the molecular volume are calculated. Principal moments describe the charge distribution along the x, y, and z axes. They are calculated from the center of mass of the molecule by using the symmetrical ten-

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$$(1.0*3.0)^{-0.5}+(1.0*3.0)^{-0.5}+(3.0*2.0)^{-0.5}+(2.0*1.0)^{-0.5}=2.270$$
(normal connectivity index)

$$(1.0*4.0)^{-0.5}+(1.0*4.0)^{-0.5}+(4.0*3.0)^{-0.5}+(3.0*1.0)^{-0.5}=1.866$$
(bond connectivity index)

$$(1.0*4.0)^{-0.5}+(1.0*4.0)^{-0.5}+(4.0*3.0)^{-0.5}+(3.0*5.0)^{-0.5}=2.270$$
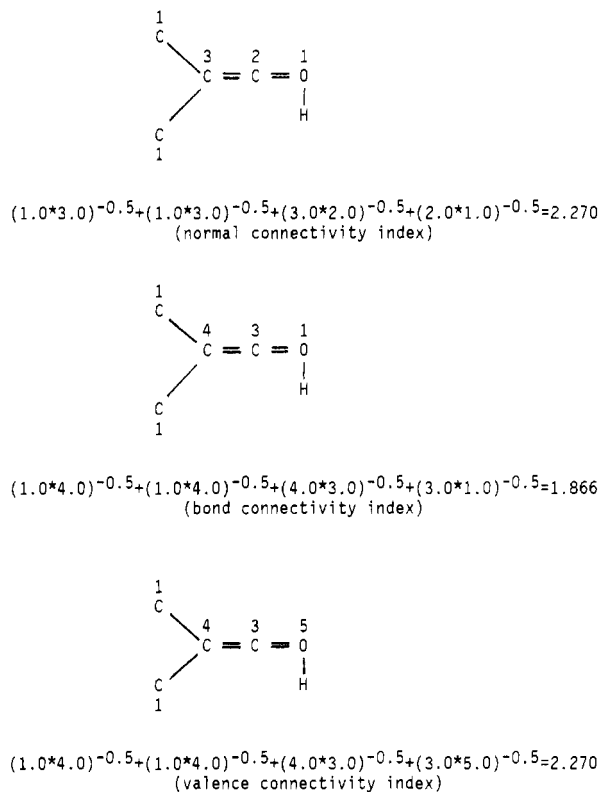(valence connectivity index)

Figure 5. Sample calculations of connectivity indices. Numbers next to atoms represent the number of bonded non-hydrogen atoms (normal connectivity index) and are adjusted for multiple bonds (bonds connectivity index) and for the valence electrons (valence connectivity index). Indices are then calculated by taking the reciprocal square root of all possible combinations and summing them.

sor of gyration matrix from which eigenvalues and eigenvectors are obtained (*XICAMM Users Manual*, 1986). Principal moments are sorted from largest to smallest. The molecule is then rotated to align the largest with the x axis and the smallest with the z axis. Finally, the molecular volume is calculated by using the van der Waals radius for each atom minus the amount of overlap from adjacent atoms (*XICAMM Users Manual*, 1986). The amount of overlap is determined from bond lengths obtained from the modeled bond distances. The calculated volume for each atom is summed, and the total volume is reported as cm³/mol. Modeled strain is the sum of the calculated internal molecular energy associated with bonding and nonbonding interactions.

Connectivity indices are a numerical descriptor of the number of atoms and the amount of branching in a molecule (Randic, 1975). These numerical descriptors can be used in quantitative structure–activity relationship (QSAR) studies. Connectivity indices have also been used to predict the adsorption of pesticides by soils with limited success (Gerstl and Helling, 1987) and to predict the protein binding and cellular uptake of pesticides in cultured human cells with good success (Murakami and Fukami, 1985). For a complete review of connectivity indices including the methodology for their calculation and their potential uses, see Kier and Hall (1986).

Three different connectivity indices are calculated by xicamm: the "normal connectivity index", the "bonds connectivity index", and the "valence connectivity index". These different connectivity indices differ in their consideration of multiple bonds and charged atoms within the molecule. To calculate a normal connectivity index, each non-hydrogen atom is assigned a number corresponding to the number of non-hydrogen atoms to which it is bound (Figure 5). Next, the values for adjacent atoms are multiplied, the reciprocal square root of each product is calculated, and these results are summed (Figure 5) to give the normal connectivity index. The bonds connectivity index makes an adjustment for multiple bonds, and then the bonds connectivity index is calculated as above. Valence connectivity indi-

Table I. Comparison of the Calculated Molecular Parameters of the Herbicide EPTC and the Safener Dichlormid

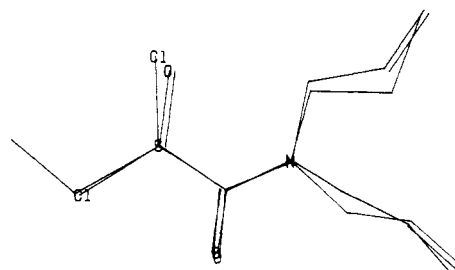| calcd parameters	EPTC	EPTC sulfoxide	dichlormid
connectivity indices			
normal	5.757	6.167	5.629
bonds	5.434	5.537	4.535
valence	5.740	5.998	4.362
principal moments			
x axis	6.055	5.591	5.501
y axis	1.809	1.924	1.865
z axis	0.055	0.071	0.056
modeled strain	2.727	1.352	3.510
molecular vol, cm³/mol	144.768	123.152	138.793

Figure 6. Structure of EPTC sulfoxide superimposed over the structure of the safener dichlormid.

ces take into account valence electrons associated with heteroatoms (non-carbon atoms) and are calculated as described above (Figure 5) (Kier and Hall, 1986).

RESULTS

Molecular Comparison of EPTC and Dichlormid by CAMM Analysis. Comparison of the calculated parameters of EPTC and dichlormid indicate that these two molecules have almost the same number of atoms (normal connectivity index, Table I). However, evaluation of the bonds connectivity index reveals that dichlormid contains more multiple bonds than does EPTC (Table I), and this is also illustrated in Figure 1. Evaluation of the principal moments revealed that the charge associated with EPTC is spread over a slightly longer distance along the x axis, but the charge distribution along the y and z axes is almost identical for EPTC and dichlormid. The molecular volumes of these two chemicals are almost identical (Table I).

Superimposing of the structures of these two molecules, following an alignment of their carbamate moiety, revealed that these two molecules are in fact similar. The only major difference is that the two chlorine atoms of dichlormid do not superimpose over any functional group of EPTC. However, Gronwald (1989) has reported that the sulfur atom of EPTC undergoes an oxidation reaction, generating the herbicidal EPTC sulfoxide. Now if EPTC sulfoxide and dichlormid structures are superimposed, the two compounds are similar with functional groups in the same location on both molecules (Figure 6).

These conclusions are supported by quantitative structure–activity relationship (QSAR) studies conducted by Stephenson et al. (1978, 1979). They showed that dichloroacetamide derivatives most similar to carbamotioate herbicides with respect to the N,N-disubstituted alkyl groups were the most active safeners of corn against these herbicides. In addition, it has been established that dichloroacetamide safeners were more biologically active as corn safeners than their monochloro or trichloro analogues (Dutka et al., 1979; Pallos et al., 1975; Stephenson et al., 1978).

Molecular Comparison of Pretilachlor and Fenclorim by CAMM Analysis. Comparison of the normal

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Table II. Calculated Parameters for the Herbicide Pretilachlor and the Safener Fenclorim

| calcd parameters	pretilachlor	fenclorim
connectivity indices		
normal	9.775	6.315
bonds	8.682	4.589
valence	8.025	4.546
principal moments		
x axis	6.920	6.463
y axis	4.362	2.949
z axis	0.434	0.000
modeled strain	8.801	3.698
molecular vol, cm³/mol	198.956	135.792
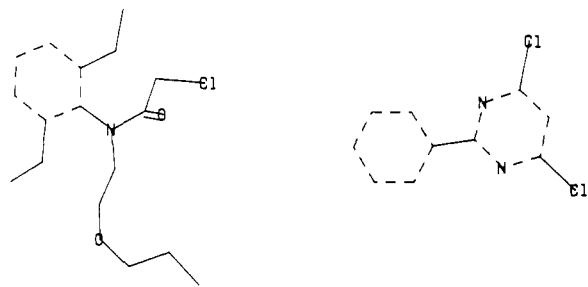
Figure 7. Structure of the herbicide pretilachlor (left) and the safener fenclorim (right). Rings with broken lines are aromatic.
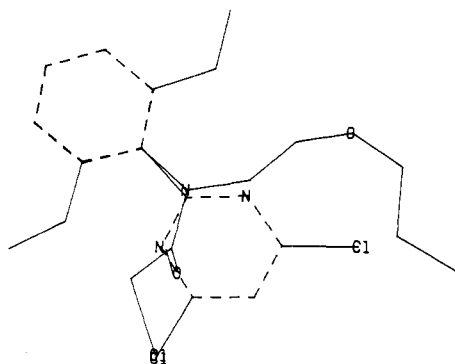
Figure 8. Structure of the herbicide pretilachlor and the safener fenclorim superimposed. Rings with broken lines are aromatic.

connectivity indices for pretilachlor and fenclorim indicates that pretilachlor is a larger molecule containing more atoms than fenclorim (Table II; Figures 7 and 8). The bonds connectivity index indicates that fenclorim contains more multiple bonds than pretilachlor, while the valence connectivity index indicates that pretilachlor contains more valence electrons than fenclorim (Table II; Figures 7 and 8). Evaluation of the principal moments indicates that the charge distributions along the x axis of both compounds are similar (Table II). However, the charge distribution along the y and x axes is greater in pretilachlor than in fenclorim (Table II). In fact, fenclorim does not have any charge distributed along the z axis (Table II), indicating that this molecule is flat. Since pretilachlor contains more atoms and has a larger charge distribution along all axes, its molecular volume is also greater than that of fenclorim (Table II). When these two compounds are superimposed with an alignment of their phenyl rings, most of the functional groups of both compounds lie in the same proximity (Figure 8).

Molecular Comparison of Alachlor and Flurazole by CAMM Analysis. Comparison of the herbicide alachlor with the safener flurazole reveals that most of the calculated parameters are similar except for the principal moment along the x axis and the molecular volume (Table III). Figures 3 and 9 show that flurazole is a larger molecule than alachlor; therefore, these differences are not

Table III. Comparison of the Calculated Molecular Parameters of the Herbicide Alachlor and the Safener Flurazole

calcd parameters	alachlor	flurazole
connectivity indices		
normal	8.275	8.941
bonds	7.182	7.487
valence	6.438	6.675
principal moments		
x axis	5.474	10.158
y axis	3.158	3.422
z axis	0.171	0.200
modeled strain	2.547	10.130
molecular vol, cm³/mol	168.297	225.940
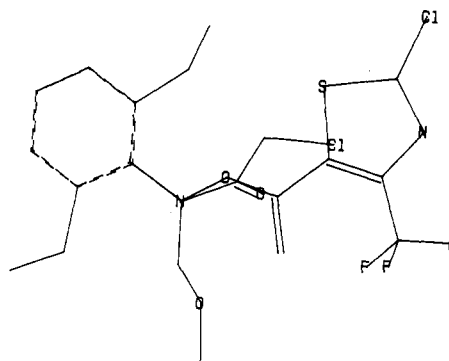
Figure 9. Structure of the herbicide alachlor and the safener flurazole superimposed. Rings with broken lines are aromatic.

surprising. However, all three connectivity indices are similar, indicating that the numbers of atoms, bonds, types of bonds, and valence electrons contained in alachlor and flurazole are similar (Table III).

When the alachlor structure is superimposed over the flurazole structure (Figure 9), the phenyl rings superimpose almost directly, while the acyl side chain of alachlor superimposes over the side chain of flurazole with the chlorine atom being near the trifluoromethyl group; the alkyl side chain does not superimpose directly over the flurazole molecule. However, the end of the alkyl side chain of alachlor is located near the heterocyclic ring of flurazole (Figure 9).

QSAR studies on the biological activity of selected 2,4-disubstituted 5-thiazolecarboxylate safeners have been reported by Howe and Lee (1980). The alkyl esters of the thiazolecarboxylic acids that had a chlorine atom at the 2-position and a trifluoromethyl group at the 4-position of the thiazole ring were found to possess the best activity as sorghum safeners against alachlor or other chloroacetamide herbicides (Howe and Lee, 1980; Sacher et al., 1983).

Molecular Comparison of Metolachlor Stereoisomers by CAMM Analysis. The commercial formulation of metolachlor, DUAL, contains four stereoisomers (Moser et al., 1985). Two of these isomers exist because two different ortho substituents hinder rotation around the N-aromatic bond, giving rise to a chiral axis (Figure 4). The other two isomers arise from the chiral C atom (C-1'), giving rise to an S and an R enantiomer. If the four stereoisomers are separated only by the chiral C, ignoring the isomers originating from the chiral axis, and then evaluated for herbicidal activity, the R enantiomer is inactive while the S enantiomer is very active against three broadleaf and seven grass weeds (LeBaron et al., 1988; Moser et al., 1985). It is interesting to note that while the S enantiomer at the chiral C atom has high herbicidal activity, it has virtually no fungicidal activity, but the R enantiomer has high fungicidal activity and very little herbicidal activity (Moser et al., 1985).

Comparison of the calculated parameters and the visual

Table IV. Comparison of the Calculated Molecular Parameters for the Least and Most Active Isomers of the Herbicide Metolachlor and the Oxime Ether Safeners Cyometrinil, Oxabetrinil, and CGA-133205

calcd parameters	cyo-metrinil	oxa-betrinil	CGA-133205	metolachlor active	metolachlor inactive
connectivity indices					
normal	6.411	7.932	9.015	8.647	8.647
bonds	4.220	6.237	7.867	7.532	7.532
valence	3.588	4.972	5.831	6.805	6.805
principal moments					
x axis	8.586	11.969	11.403	5.712	5.802
y axis	1.390	1.331	3.398	2.911	3.147
z axis	0.002	0.024	0.282	0.690	0.666
modeled strain	0.422	4.090	10.026	6.135	5.747
molecular vol, cm³/mol	134.031	159.316	209.727	180.885	181.215

features of the inactive versus active enantiomers of metolachlor did not reveal any major molecular differences (Table IV; Figure 4). Connectivity indices will not change because they are based on the number of atoms, bonds, and types of atoms and bonds, which are the same in all isomers. When the principal moments for the two enantiomers of metolachlor are compared, there exists a difference in the numerical value of the charge distribution along each axis (Table IV). This difference is explained by the placement of the methyl group and the hydrogen atom on the chiral C and their influence on the molecular configuration and charge distribution of the metolachlor isomers. Analysis of the principal moments reveals that the charge distribution is slightly more compact along the x and y axes in the active isomer than in the inactive isomer, but the visual evaluation of the two isomers revealed no major differences in the location of the functional groups.

Molecular Comparison of Metolachlor and Oxime Ether Safeners by CAMM Analysis. The first commercial oxime ether safener, cyometrinil, contains two nitrile groups (Figure 2). Oxabetrinil, the second oxime ether safener in this series, has only one nitrile group and a 1,3-dioxolane ring (Figure 2). CGA-133205, the third analogue in this series, does not contain any nitrile groups (Figure 2). It has a trifluoromethyl group and a 1,3-dioxolane ring (Figure 2). Molecular comparisons of the oxime ether safener analogues revealed that chemical modifications of cyometrinil and oxabetrinil to yield CGA-133205 resulted in a molecule that is a better safener of grain sorghum and whose calculated parameters are similar to those calculated for metolachlor (Table IV). Therefore, the comparison of the most effective safener, CGA-133205, with metolachlor will be emphasized.

Almost identical comparisons can be made with metolachlor and CGA-133205 as made for alachlor and flurazole. The connectivity indices, the principal moments along the y and z axes, and the molecular volumes are similar for metolachlor and CGA-133205. Normal connectivity indices indicate that both molecules contain about the same number of atoms (Table IV). Bond connectivity indices indicate that both compounds contain about the same number of multiple bonds, while the valence connectivity index indicates that CGA-133205 contains more valence electrons than does metolachlor (Table IV). The only parameter that is not very similar is the principal moment along the x axis, indicating that the charge associated with CGA-133205 is spread over a longer distance along the x axis (Table IV). Further analysis of the principal moments and a visual analysis
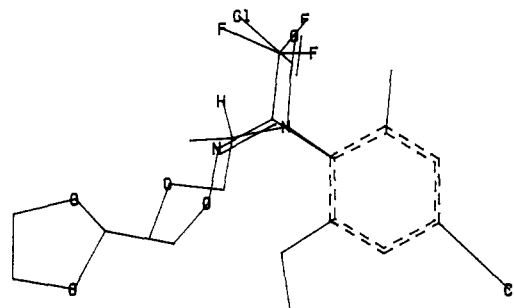

Figure 10. Herbicidally active S enantiomer of metolachlor superimposed over CGA-133205. Rings with broken lines are aromatic.
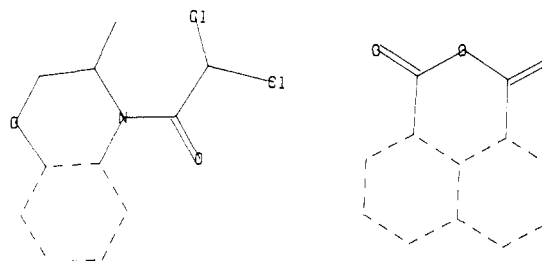

Figure 11. Structures of the safeners CGA-154281 (left) and naphthalic anhydride (right) used to protect grain sorghum or corn from injury caused by chloroacetamide herbicides. Rings with broken lines are aromatic.

of the modeled structures indicate that both of these molecules are long and flat with very little penetration into the z plane (Figures 2 and 4).

When the structures of the active isomer of metolachlor and CGA-133205 are superimposed with their phenyl rings being aligned, the trifluoromethyl group of CGA-133205 is aligned over the alkyl side chain of the metolachlor (Figure 10). The 1,3-dioxolane ring of the CGA-133205 molecule and the acyl side chain of metolachlor do not align well, but they do orient themselves in the same general direction (Figure 10). The comparison of metolachlor with CGA-133205 (Figure 10) is similar to the comparison of alachlor and flurazole (Figure 9). In Figure 10 it is easy to see the similarities between metolachlor and CGA-133205 and that these two molecules could very easily fit into the same binding site on a protein.

During the development of the chloroacetamide herbicides and the acylaniline fungicides, many quantitative structure–activity relationship (QSAR) experiments were conducted to determine the most active substituents (LeBaron et al., 1988). McFarland and Hess (1985) reported that nonhalogenated acetamides were less active in an oat (*Avena sativa* L.) root growth bioassay than were the halogenated derivatives and that an analogue with fluorine was not inhibitory to oat root growth. However, if the α-halogen is replaced by a methoxyacetyl moiety, then this acetamide becomes fungicidal and not herbicidal (McFarland and Hess, 1985). Given the similarities of CGA-133205 and metolachlor, one would suspect that if the trifluoromethyl group of CGA-133205 was substituted with a halogen such as chlorine or bromine, then possibly this compound would have herbicidal activity. Alternatively, if the trifluoromethyl group was substituted with a methoxyacetyl moiety, then this compound might have fungicidal activity.

Molecular Analysis of CGA-154281 and Naphthalic Anhydride and Comparison to Herbicides and Other Safeners. NA (Figure 11) was one of the first safeners developed and has been used to protect corn from injury caused by EPTC but will also protect corn from

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Table V. Calculated Parameters of the Safeners Naphthalic Anhydride and CGA-154281

calcd parameters	naphthalic anhydride	CGA-154281
connectivity indices		
normal	6.863	7.188
bonds	4.856	6.037
valence	4.278	5.592
principal moments		
x axis	3.235	6.092
y axis	2.857	2.105
z axis	0.000	0.128
modeled strain	1.688	3.821
molecular vol, cm^3/mol	116.852	167.679
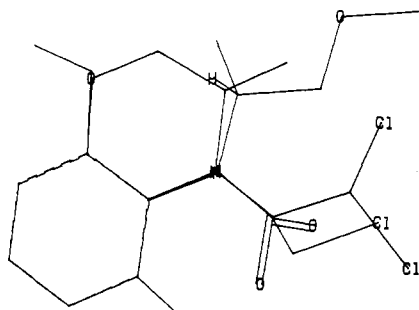
Figure 12. Structure of metolachlor superimposed over CGA-154281. Rings with broken lines are aromatic.

injury caused by metolachlor and alachlor (Hoffman, 1978). Comparison of the calculated parameters of NA with dichlormid reveals that these two safeners are somewhat similar (Tables I and V). Similarities include the bonds and valence connectivity indices, principal moments along the y and z axes, and the molecular volumes (Tables I and V).

Comparison of the calculated parameters of NA with the herbicide, EPTC, revealed few similarities (Tables I and V). These similarities include the charge distribution along the y and z axes and the molecular volume (Tables I and V). Comparison of the calculated parameters of NA with metolachlor did not reveal many similarities (Tables IV and V).

CGA-154281 (Figure 11) was recently introduced by Ciba–Geigy Corp. to protect corn from metolachlor. Unlike the oxime ether safeners, this safener is applied as a prepackaged mix with metolachlor at a ratio of 30 parts metolachlor to 1 part CGA-154281 (Peek et al., 1988). CGA-154281 contains fewer atoms and/or less branching than metolachlor as indicated by the smaller normal connectivity index (Tables IV and V). Both compounds contain about the same amount of multiple bonds and valence electrons as indicated by the bonds and valence connectivity indices (Tables IV and V). Comparison of the principal moments indicates that the charge distributions for both of these compounds are quite similar along the x, y, and z axes and that the molecular volumes are also similar (Tables IV and V). Superimposing these two compounds also reveals a high degree of similarity (Figure 12).

Molecular comparison of all safeners used with chloroacetamide herbicides (fenclorim, flurazole, CGA-154281, and oxime ether safeners) revealed that each safener contained a phenyl ring with one branched side chain, and this branched side chain contained either a chlorine atom or a functional group (trifluoromethyl) on one branch and an alkyl branch with or without functional groups. Molecular volumes of these safeners ranged from 135.792 to 225.940 cm^3/mol. The variation of the molecular volumes was related to differences in the alkyl branch of the side chain or in ring substituents. The alkyl branch

is also responsible for the majority of the differences observed in the connectivity indices and the principal moments.

DISCUSSION

The results of the molecular comparisons conducted in this study indicate that in most of the successful and commercial herbicide/safener combinations the chemical structures of safeners and herbicides are similar at the molecular level. These similarities include the size (volume and physical dimensions), shape, charge distribution, and connectivity indices. Most safeners contain either a chlorine atom or another functional group (trifluoromethyl) that superimposes near the chlorine atom of the chloroacetamide herbicides. This may indicate that these functional groups are important for the binding and/or positioning of these compounds at the target site(s) but not for the phytotoxicity that is associated with these herbicides since safeners are nonphytotoxic.

CAMM programs available for use with personal computers have some limitations. The major ones are related to the size of molecules that can be modeled, the graphic display of the modeled compound, and the lack of computational ability for some of the more complex quantum mechanical calculations (Davies, 1986). However, even with these limitations, the information that can be generated about a series of molecules is quite useful to chemists and plant physiologists. Programs available for use on the personal computer can provide scientists with enough information to compare the size, shape, and charge distribution of molecules containing up to 100 atoms.

Molecular comparisons of compounds possessing biological activity can be also evaluated by the use of QSAR studies. Such studies provide information about the identity and location of functional groups on a general structure required for biological activity. Some of the more common parameters used in QSAR studies include the octanol/water partition coefficient, steric properties (usually determined by the Hansch equations), and inductive constants (Hansch and Leo, 1979). QSAR methods are useful in describing the importance of the functional groups when molecules with the same general structure are compared, but these methods do not allow the comparison of molecules that have different general structures. The major disadvantages of QSAR are (a) biological response data must be generated for each analogue that is to be evaluated and (b) many analogues must be evaluated for statistical purposes. Generation of such biological data may be time-consuming and expensive.

From the results presented in this paper, it can be speculated that a herbicide and its respective safeners may compete for binding to the same active site of the target protein(s) and/or they may serve as substrates of inducible metabolic enzymes which detoxify herbicides in protected plants. The interactions of selected safeners and herbicides at the target site or metabolism levels have been investigated by a number of researchers and reviewed by Hatzios and Hoagland (1989). A follow-up study (Yenne et al., 1990) examines selected aspects of the enhanced detoxication theory as related to oxime ether safeners and the herbicide metolachlor in grain sorghum. The interactions of oxime ether safeners and metolachlor on target sites such as lipid synthesis and acetyl-CoA carboxylase activity have been examined by Yenne and Hatzios (1989).

ABBREVIATIONS USED

Alachlor, 2-chloro-N-(2,6-diethylphenyl)-N-(methoxymethyl)acetamide; CAMM, computer-aided molecular

modeling; CGA-133205, 2,2,2-trifluoro-4'-chloroacetophenone O-(1,3-dioxolan-2-ylmethyl)oxime; cyometrinil, (Z)-α-[(cyanomethoxy)benzeneacetonitrile; CGA-154281, 4-(dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine; dichlormid, 2,2-dichloro-N,N-di-2-propenylacetamide; EPTC, S-ethyl dipropylcarbamothioate; fenclorim, 4,6-dichloro-2-phenylpyrimidine; flurazole, phenylmethyl 2-chloro-4-(trifluoromethyl)-5-thiazolecarboxylate; metolachlor, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide; naphthalic anhydride (NA), naphthalene-1,8-dicarboxylic acid anhydride; oxabetrinil, α-[(1,3-dioxolan-2-ylmethoxy)imino]benzeneacetonitrile; pretilachlor, 2-chloro-2',6'-diethyl-N-(2-propoxyethyl)acetanilide; QSAR, quantitative structure–activity relationship; 3-D, three-dimensional.

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