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Jefferson Adcock Selott

ENTITLED Structure-Activity Relationships for a Series of Heteroatom-

Substituted Phenylpropanoid Analogs, Kairomonal Attractants for Northern Corn

Rootworms.

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemistry

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Instructor in Charge

APPROVED: Steven S. Zumdahl 6/6/90

HEAD OF DEPARTMENT OF Chemistry

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Structure-Activity Relationships for a Series of Heteroatom-Substituted Phenylpropanoid Analogs, Kairomonal Attractants for Northern Corn Rootworms (Coleoptera: Chrysomelidae. Diabrotica barberi)

By

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in
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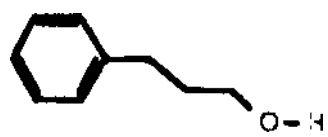
INTRODUCTION

Knowledge of the olfactory responses of adult corn rootworms (Coleoptera: Chrysomelidae) suggests that these insects detect volatile chemical cues for host plant selection. Several studies demonstrated that various phenylpropanoids (C_6C_3 compounds) induce specific olfactory responses from several *Diabrotica* spp. Eugenol, isoeugenol, and 2-methoxy-4-propylphenol specifically attracted adults of northern corn rootworm (NCR), *Diabrotica barberi* Smith and Lawrence (Ladd, 1984). The structurally analogous compounds, estragole (4-methoxy-1-allylbenzene) and trans-anethole (4-methoxy-1-propenylbenzene), attracted western corn rootworm adults (WCR), *Diabrotica virgifera virgifera* LeConte (Lampman et al., 1987).

An understanding of the complementarity between insect sensory receptor and plant kairomone may reveal response specificity of these olfactory receptors and other properties of chemoreception. Relating molecular parameters to kairomone activity provides a method to qualitatively determine the degree of receptor-kairomone complementarity of a series of analogous compounds. Although this technique has not been applied to the phenylpropanoids and *Diabrotica* response, it has been in other substrate-receptor systems. The phenyl substituent constants σ_m and σ_p, the hydrophobic parameter π, and substituent volume MR (molar refractivity) on a variety of substituted 3,4-dimethoxybenzenes were compared to the response of the oriental fruit fly *Dacus dorsalis* (Metcalf et al., 1981). Another investigation related the conformational energies of a series of chain-shortened analogs of (Z)-5-decenyl acetate, a pheromone component of the turnip moth, *Agrotis segetum* (Bengtsson et al., 1990). All of these molecular parameters help to characterize the receptor molecule in terms of the shape of the active site cavity and perhaps the requirements of the substrate to activate, or depolarize the receptor.

In order to develop a structure-activity model for the phenylpropanoid receptors of *Diabrotica barberi* and *D. virgifera virgifera* I have studied 3-phenylpropanol, 3-(p-methoxyphenyl)propanol, and a series of heteroatom-substituted analogs, compounds 2 - 4 and 6 - 8, respectively (Figure 1). The atoms nitrogen, oxygen, and sulfur were substituted for the gamma-carbon on the propanol side chain in each series. Recent data indicate that the position of

the terminal hydroxy group relative to the ring in the phenylpropanoids affects biological response and may interact with an important group in the receptor cleft (Metcalf and Lampman, unpublished data). Through its size and bonding properties within molecules, each heteroatom may alter the orientation and position of the terminal hydroxy sufficiently to affect receptor binding or activation. In this study I report the syntheses of these compounds and their activity measurements and discuss the relationship of various molecular parameters to their activity. The molecular parameters tested were heteroatom



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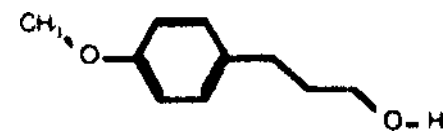
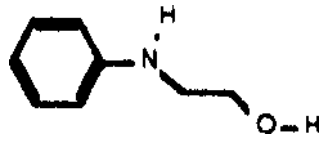
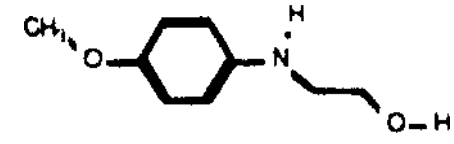


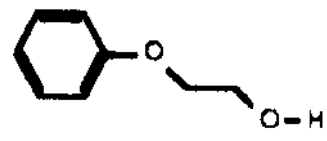
5. 3-(p-methoxyphenyl)propanol



2. phenylaminoethanol



6. p-methoxyphenylaminoethanol



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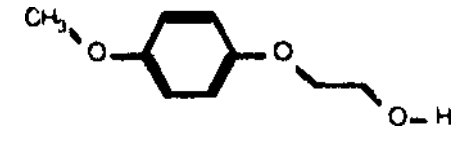
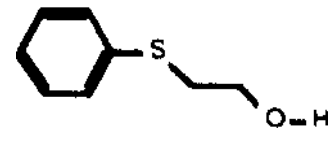
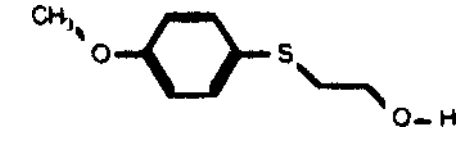


7. 2-(p-methoxyphenoxy)ethanol



4. 2-(phenylthio)ethanol



8. 2-(p-methoxyphenylthio)ethanol

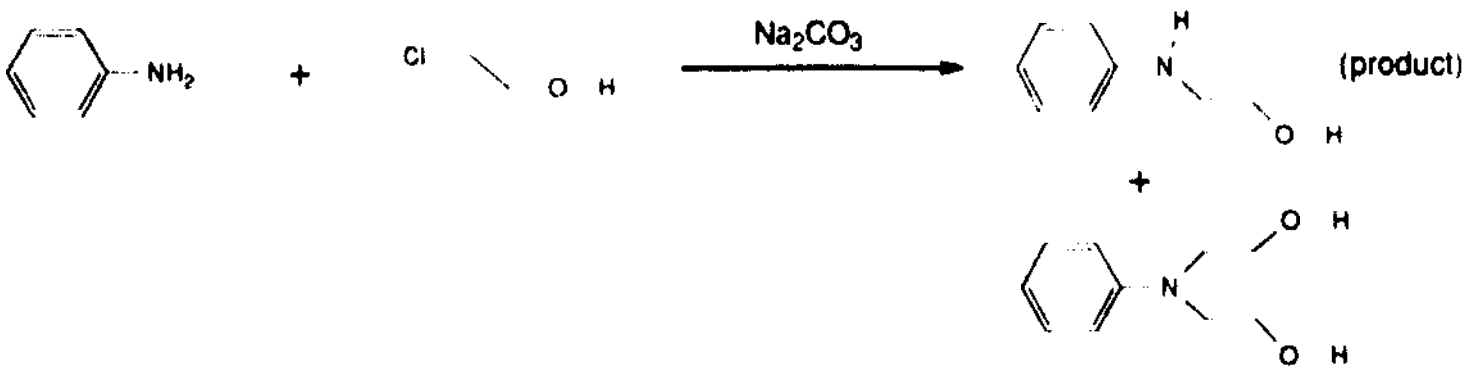
Figure 1 Compounds studied.

charge, propanol side chain length, side chain angle with respect to the ring, molecular dipole moment, and terminal O-H dipole moment. Also, the conformational energies of the compounds were calculated and helped to develop a substrate interaction model based on spatial relationships between groups within each compound. The molecular constants o and π are not available for the particular side chains in this study and were not investigated. The techniques applied in this study may set the foundation for analysis of a wider range of kairomone analogs which may further refine the substrate interaction model.

METHODS AND MATERIALS

Chemicals. 3-phenylpropanol (1), 2-phenoxyethanol (3), and 3-(p-methoxyphenyl)propanol (5) were purchased from Aldrich Chemicals at least 98% pure. The rest of the compounds were synthesized and purified through either recrystallization or distillation.

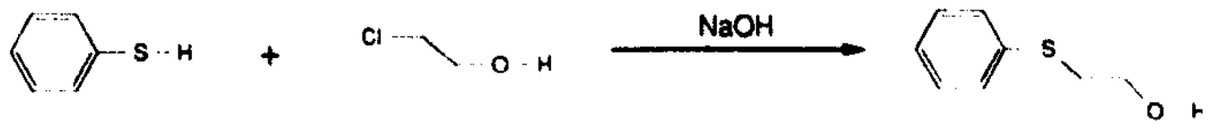
Phenylaminoethanol (2) was prepared according to the procedure by Rindfusz (1920):



In a 50 mL round-bottomed flask, aniline (10.2 g, 0.109 mol), 2-chloroethanol (9.3 g, 0.115 mol), and sodium carbonate (10.9 g, 0.103 mol) were mixed and refluxed for 4 hr. The mixture was cooled and then filtered, washing the solids with diethyl ether. After removing the ether under vacuum, the filtrate was concentrated under vacuum to yield 9.0 g of crude product, a brown liquid.

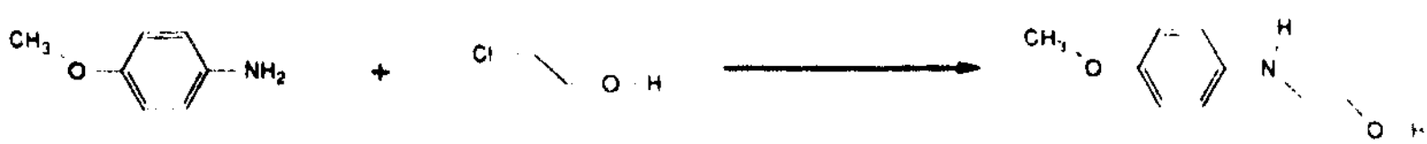
Under high vacuum three fractions were taken at 42 °C/0.3 mm Hg,104-111 °C/0.3 mm Hg, and 165 °C/0.3 mm Hg. The second was a transparent yellow liquid, the desired product 2 (7.5 g, 50%). *m/z*: 137 (M^+; 17%), 106(100), 79(17), 77(26), 51(12), 39(6).

2-(phenylthio) (4) ethanol was prepared according to Kirner (1929):



Thiophenol (8.6 g, 0.078 mol) was dissolved in 10% aqueous sodium hydroxide (40 ml) in a 100 ml round-bottomed flask. While adding 2-chloroethanol (6.4 g, 0.080 mol) to this solution the mixture became cloudy white and noticeably exothermic. It refluxed for 30 min and formed two liquid phases: an upper, cloudy aqueous layer and a more dense yellow oil. The aqueous layer was extracted two times with 10 ml portions of diethyl ether. The oil and ether were combined, washed with 10-15 ml of water, and dried over sodium sulfate. A crude yellow liquid (9.5 g, 79%) was obtained by concentrating under vacuum. Low pressure distillation yielded a clear, pale-yellow liquid, compound 4, at 110 °C/0.3 mm Hg (8.6 g, 72%). *m/z*: 154 (M^+; 58%), 123(94), 110(42), 77(24), 65(20), 51(30), 45(100), 39(15).

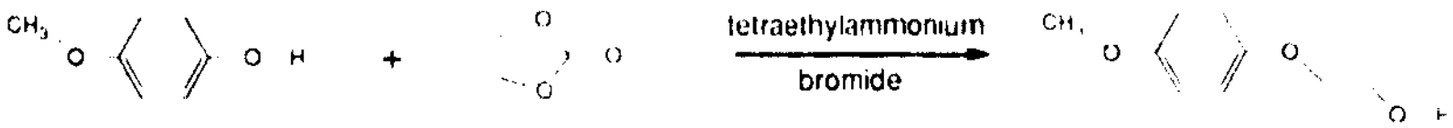
p-methoxyphenylaminoethanol (6) was prepared according to Jacobs (1915):



In a 100 ml round-bottomed flask p-anisidine (14.7 g, 0.119 mol), 2-chloroethanol (4.7 g, 0.058 mol), and water (40 ml) were mixed and refluxed 2 hr. The resulting mixture was made alkaline with 10% aqueous sodium hydroxide (4 ml) and extracted three times with 15 ml portions of diethyl ether.

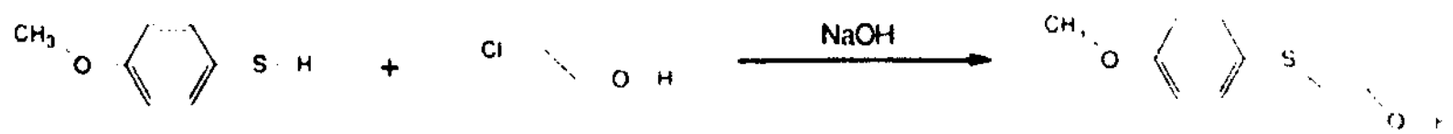
The combined ether extracts were dried over sodium sulfate quickly and concentrated under aspirator vacuum to yield a crude product (5.9 g, 61%). Two fractions were distilled under high vacuum at 79 °C/0.4 mm Hg and 145 °C/0.4 mm Hg. The second was the desired product 6, a clear, yellow liquid (1.5 g, 15%). *m/z*: 167 (M^+; 25%), 136(100), 123(60), 108(100), 80(59), 53(29), 39(14).

2-(p-methoxyphenoxy)ethanol (7) was prepared according to Yoshino et. al. (1973):



A mixture of p-methoxyphenol (3.7 g, 0.030 mol), ethylene carbonate (2.7 g, 0.033 mol), and tetraethylammonium bromide (2.1 g, 0.010 mol) were heated together in a 50 ml round-bottomed flask at 155-160 °C for 2.5 hr. The reaction mixture was dissolved in benzene (50 ml) to precipitate the tetraethylammonium bromide catalyst and filtered. The filtrate was evaporated in vacuo until dry, yielding a crude solid. Recrystallization in ethanol gave the desired compound 7: white crystals that melted at 66-68 °C (4.03 g, 98%). *m/z*: 137 (M^+; 1%), 124(100), 109(88), 81(13), 63(8), 45(13).

2-(p-methoxyphenylthio)ethanol (8) was prepared according to Drain et al. (1963):



In a 50 ml round-bottomed flask 2-chloroethanol (2.0 g, 0.025 mol) was added to a solution of p-methoxythiophenol (2.5 g, 0.018 mol) in 7% aqueous sodium hydroxide (12.5 ml). The mixture immediately turned cloudy-white and was noticeable exothermic, although apparently less than with thiophenol in the

synthesis of 4. This solution was boiled under reflux for 1 hr. After the mixture cooled it was extracted two times with 10 ml portions of diethyl ether. The combined ether extracts were dried over sodium sulfate and then concentrated under aspirator vacuum. A pale yellow solid remained (1.8 g, 54%). The compound could not be recrystallized from light petroleum as directed in the literature, but was obtained through ethanol. The yellow crystals melted at 36-38 °C. *m/z*: 184 (M^+; 100%), 153(88), 140(25), 125(25), 109(37), 45(50).

Trapping. Field activity data of these compounds was collected along 400 meters of fence on a cornfield of the University of Illinois South Farms at Urbana, Ill., in September, 1989. This field testing coincided with the end of the peak silk-feeding and oviposition period of corn rootworm adults in central Illinois (Lampman, 1987).

The activities of these volatile compounds toward each of the *Diabrotica* spp. were measured by the average number of beetles caught on each trap. Beetle counts were recorded at 24, 48, or 72 hr depending on weather conditions following trap setup. Traps were 1.0 liter cylindrical paper cartons evenly coated on the outer curved surface with a clear insect adhesive, TangleTrap (Tanglefoot Co., Grand Rapids, Mich.). Cotton dental wicks (about 13 mm long, 6 mm diameter) were attached to the bottom exterior of the carton with the same adhesive and received the appropriate attractant applied by capillary micropipettes. All compounds, solid and liquid, were prepared as standard solutions of 200 mg per ml in acetone. All treatments were made at the dosage of 100 mg per trap and controls were prepared with untreated wicks. Four replicates of treated and control traps were placed randomly 10 m apart with each carton inverted on a wooden post 1 m tall.

The significance of the field data was determined by analysis of variance and the individual means were separated by Duncan's multiple range test (Nie et al. 1975). For statistical analysis the data were logarithmically transformed but means and standard errors were derived from the untransformed data. Significance levels were set at $P = 0.05$ for all statistical analyses.

Calculations. These molecules were modelled and thermodynamically optimized using the QUANTA Software (Polygen.Corporation; © 1986,1987,1988,1989) and its associated application packages ChemNote, AMPAC, and CHARMm (Polygen Corp.). To roughly estimate energies of structures and generate conformational energy maps I used the CHARMm application. The AMPAC application (Clark, 1985) optimized the geometries of specified molecular conformations and provided information on enthalpy of formation, dipole moments, atomic point charges, and ionization potentials. AMPAC was particularly useful because its molecular input files can be modified directly to fix certain intermolecular distances and angles and prevent them from minimizing with the rest of the molecule. Of the three Hamiltonians provided for calculations in AMPAC, AM1, MNDO, and MINDO^3, I used only MNDO because by default all sulfur-containing molecules (such as compounds 4 and 8) entered this option. Original starting structures for the energy minimization programs were constructed using the two-dimensional molecular construction application, ChemNote. In some cases, starting structures were generated from the output files of optimized geometry and had appropriate parameters manually adjusted before a second series of calculations was performed.

SUBSTRATE-RECEPTOR INTERACTION MODEL

An indirect technique to characterize the olfactory receptor correlates the variations in molecular geometry, or spatial relationships between critical interacting groups, with biological activity of the compound. Conformational energies provide an effective measure of the molecular strain necessary for the stimulant to interact with the active groups in the receptor cavity which are probably in fixed positions defined by the folding of the receptor protein. In other words, a less specific substrate must undergo bond angle adjustments toward a non-preferred or high energy conformation in order to activate the receptor.

The most active of the attractants, 3-phenylpropanol (1), was used as the 'natural compound', or template to define the spatial relationships of certain atoms within each molecule which complement parts of the receptor active site. These atoms are chosen from the molecular groups believed to be most crucial

for biological activity: the aromatic ring and the terminal hydroxy group (in particular the position of the oxygen atom). The orientation of the methoxy group was determined from 3-(p-methoxyphenyl)propanol (4), the most active of the methoxy attractants. It was assumed that the four molecules without methoxy groups interact with the same active site as those with methoxy groups, but only at the aromatic ring and hydroxy positions. An additional assumption is that the stable conformation of compound 1 corresponds to biologically relevant structure of this compound, to which the receptor protein had evolved to interact specifically. The other attractants have varying conformations of their alkyl chains as a result of different heteroatoms and in order to activate the receptor they must have their rings and terminal hydroxyl groups fixed to remain in the space locations defined by the most active compound.

These conformational rearrangements increase steric interactions and raise the energy of the molecule, or its heat of formation. This energy change defines the conformational energy. It is a measure of thermodynamic stability and may correlate with biological activity and receptor affinity.

At present, this model is not sufficient to study those molecules that either lack or are unable to arrange the necessary groups, as defined above, in the appropriate positions. In addition, we do not know the details of the transduction process in the receptor-substrate interaction which may involve one or many steps.

Conformational analysis. To determine the most stable conformation of the receptor-defining attractant, compound 1, several of its bonds were rotated to determine the number of possible low-energy conformations and the energy barriers between them. The spatial relationships of the most stable conformation were used as input parameters for compounds 2 - 4 before minimizing their energy. The low-energy geometry of compound 5 was determined by using the minimized geometry of 1, building a methoxy group on to it, and determining the its lowest-energy orientation through a full rotation. This process maintained consistent, standardized shapes between molecules and prevented the same bonds within different molecules from occupying different conformationally degenerate levels. Energies of the same molecule under the spatial restrictions of the receptor active site may differ markedly in different degenerate geometries.

Computational procedure. The direction of the terminal hydroxy group on 1 was changed through a rotation of the dihedral angle defined by C8-C9-O-H (Figure 2). See Figure 3 to view these atom positions. The dihedral angle of this bond was rotated from 180 (trans- configuration) to 0 (cis-) in 20 increments while calculating minimized energies at each step. The desired dihedral angle was entered in each input file and not allowed to minimize. The resulting data from the lowest-energy geometry of this desired conformation were used as the input file for compounds 2 - 4 and all parameters were allowed to change to

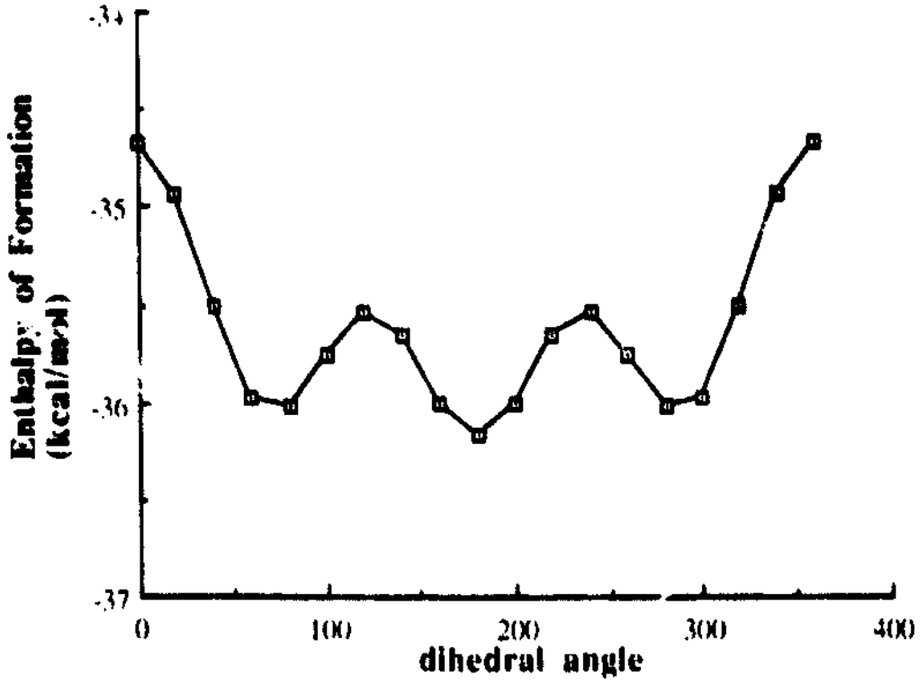


Figure 2. Enthalpy of formation of 1 through rotation of the hydroxy group by the dihedral angle defined by C8-C9-O-H.

optimize individual geometries. The inputs were altered slightly to accommodate the type of heteroatom and to add or remove hydrogens where necessary. In addition, the C-N-H bond angle of compounds 2 and 6 was adjusted to 120 before geometry optimization. A two-dimension conformational

energy map of 5 was generated by rotating the side chain and the methoxy groups through the dihedral angles defined by C4-C5-C7-C8 and C3-C2-O11-C12 (see Figure 3). This procedure was done as a *custom search* under the *conformational search and analysis* application. The resulting lowest energy conformation was used as an input parameter for compounds 6 - 8. At this stage all compounds were standardized and ready for energy minimization calculations with all molecular parameters free to optimize. Thus, each of compounds 1 - 8 was optimized individually while maintaining a similar overall geometry. The heat of formation of each of these structures represents the lowest energy state of the free molecule.

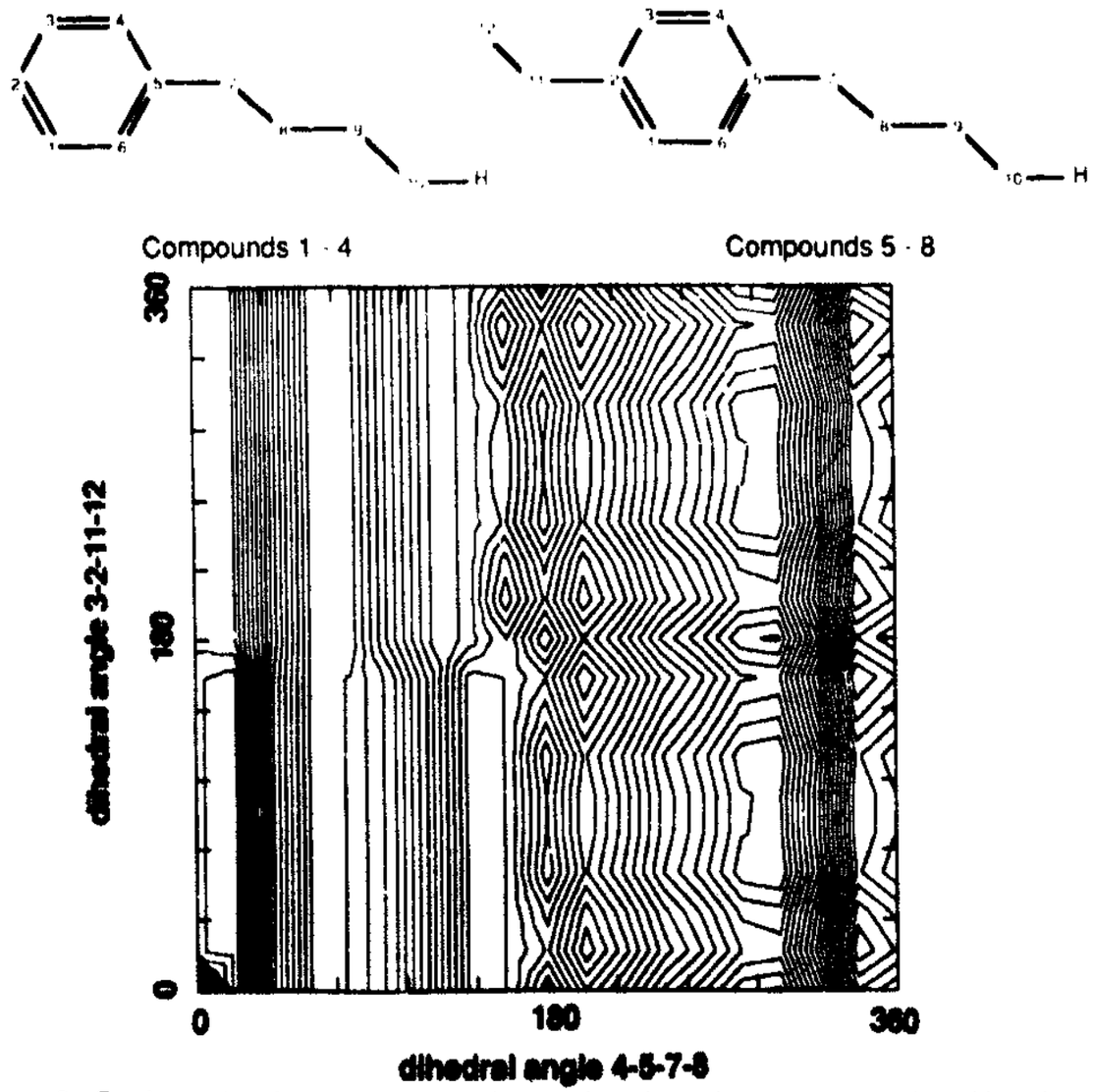


Figure 3. Conformational energy map for the rotation about the substituent-phenyl bonds.

Using the geometry of 1, the following parameters were calculated and entered as fixed values (not allowed to minimize) in the input files for each compound: 1) C5-O10 distance = 5.04 angstroms; 2) C6-C5-O10 angle = 95.45, and 3) C1-C6-C5-O10 dihedral angle = 180. For compounds 4 - 8 the C3-C2-O11-C12 dihedral angle was set at 0 to fix the methoxy group. The energy of each of these 'biologically active' conformations was then minimized and recorded. The difference between these values and those of the minimized, free molecules is a measure of their conformational strain.

RESULTS AND DISCUSSION

The responses of NCR and WCR in corn to 3-phenylpropanol (1), 3-(p-methoxyphenyl)propanol (5), and their heteroatom-substituted analogs are shown in Figure 3. The field data on beetle counts are reported as the average percent activities of one or more trials with the most active molecule defined as 100 % (Figure 4). Compound 1 was most active for NCR while 7 was most active for WCR. These compounds were also grouped according to significant differences through Duncan's (1955) multiple range test on logarithmically transformed data. This result showed that according to WCR response, the activities of all the compounds other than 7 were not significantly distinct. Figure 5 illustrates the activity data with standard error.

Attractant[a]	NCR	WCR	NCR No. of Trials	WCR No. of Trials
control (untreated)	3.8 ± 2.0	1.1 ± 0.7	3	2
1 C_6H_5CEt	100.0 ± 32.9	10.5 ± 3.5	3	2
2 C_6H_5NEt	4.8 ± 3.2	1.3 ± 0.4	3	2
3 C_6H_5OEt	45.6 ± 9.1	3.0 ± 1.1	3	2
4 C_6H_5SEt	34.3 ± 9.8	2.9 ± 1.1	3	2
5 MeC_6H_5CEt	42.4 ± 14.7	3.8 ± 1.3	2	2
6 MeC_6H_5NEt	0.0	5.1 ± 1.8	2	2
7 MeC_6H_5OEt	6.8 ± 4.4	100.0 ± 39.4	2	2
8 MeC_6H_5SEt	19.4 ± 5.3	8.8 ± 4.3	1	1

Figure 4. Percent activity of NCR and WCR adults (± standard error)

[a]Each attractant was tested at 100 mg per trap; n = 4.

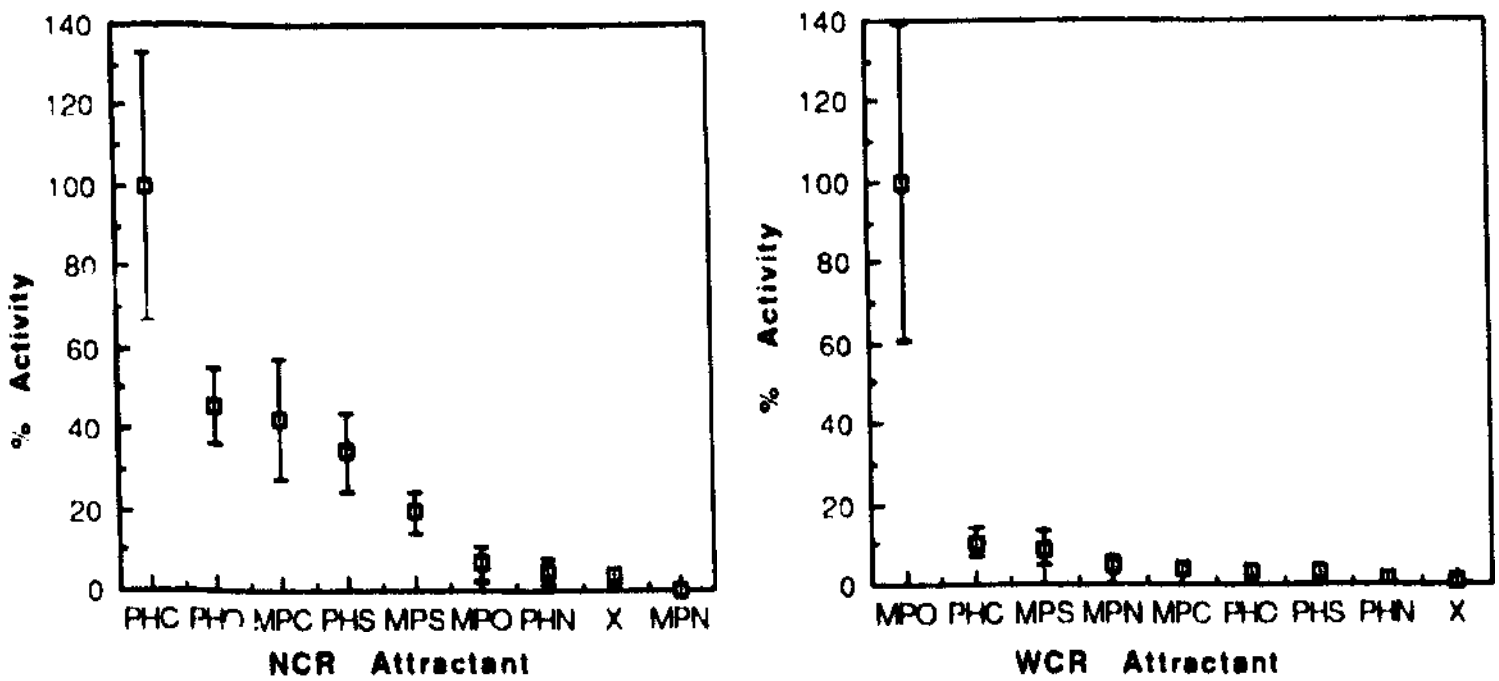


Figure 5. Relative activity of NCR and WCR attractants with standard error.

From these data it appears that the heteroatom influences NCR activity but its function in WCR activity is less defined. Carbon at the gamma position is the most active in both sets of compounds and nitrogen is the least active. Oxygen and sulfur are intermediate and not distinctly different. For each heteroatom, the non-methoxy compound is more active toward NCR than the methoxy version suggesting that the methoxy group may sterically interfere slightly in the active site. WCR responded strongly to 7 but not to any of the other compounds. In fact, the data do not distinguish the activities of the other compounds significantly. It appears that the methoxy group is more significant in WCR activity than the heteroatom considering that substituted carbon produces the most active non-methoxy compound and the least active methoxy compound. Considering that the biological responses of WCR to most of the attractants are not significantly distinct, molecular properties dependent on the heteroatom and conformational studies will not be discussed in relation to this species until more precise data are collected.

Data on the molecular parameters are listed in Figure 6. The heteroatom charge reflects its electronegativity, and would significantly affect biological activity if the atom of the gamma position interacted directly with a group in the

receptor active site. No significant correlations between charge and activity can be drawn from these data. Neither the molecular dipole moment nor the dipole moment of the terminal hydroxy group correlate with activity well.

Attractant	Heteroatom Charge	Molecular DipoleMoment (debye)	Hydroxyl Dipole Moment (debye)	Side Chain Length (angstroms)	Side Chain Angle
1 C_6H_5CEt	0.042	1.32	3.11	5.04	95.5
2 C_6H_5NEt	-0.304	1.25	3.10	4.90	102.1
3 C_6H_5OEt	-0.293	0.62	3.12	4.82	102.4
4 C_6H_5SEt	0.106	0.14	3.05	5.24	93.6
5 MeC_6H_5CEt	0.049	2.33	3.12	5.03	95.8
6 MeC_6H_5NEt	-0.298	0.98	3.08	4.91	99.9
7 MeC_6H_5OEt	-0.290	1.44	3.13	4.82	102.9
8 MeC_6H_5SEt	0.108	1.15	3.06	5.24	93.6

Figure 6. Calculated molecular parameters from molecular modelling and energy minimization studies.

Calculated Structures and Conformational Energies. The geometries of the calculated energy minima for this series of compounds have been examined. The side chains of all of the molecules prefer the all-*anti*-conformation and are aligned with the plane defined by the phenyl group except for 2 and 6 which have skewed side chains, a geometry imposed by the nitrogen substituent. This result agrees with the geometry calculated by the CHARMm conformational search illustrated in the conformational energy map generated from compound 5 (see Figure 3). Also, this map reveals the degenerate low-energy geometries of the methoxy group.

The calculated differences in conformational energies between the lowest energy structures suitable for receptor interaction, according to this model, and the lowest energy of the free molecules are shown in Figure 7 for compounds 1 - 4. These energies correspond to the enthalpies required to bring the molecules from their preferred conformations to their biologically active conformations.

Compound	Hf of the free molecule (kcal/mol)	Hf of biologically active molecule (kcal/mol)	Conformational energy of active form (kcal/mol)
1	-36.168	----	0.000
2	-23.868	-20.358	3.510
3	-65.844	-58.338	7.506
4	-32.498	-32.503	2.276

Figure 7. Enthalpies of formation of the energy-minimized geometries of the free molecules and of the molecules restricted to receptor geometry. The receptor geometry was defined by fixing the position of the oxygen of the terminal hydroxy with respect to the ring. This position was the one given by the lowest energy conformation of the most active attractant, compound 1.

A test of the validity of the molecular modelling and energy calculations in this substrate-receptor model is the plot of conformational energy against the side chain length (Figure 8). It is expected that as chain length either lengthens or shortens for different molecules in comparison with the standard distance in 1, the minimized conformational energies would tend to increase as steric interactions become stronger. This graph demonstrates that the energy calculations correctly predict the expected trends.

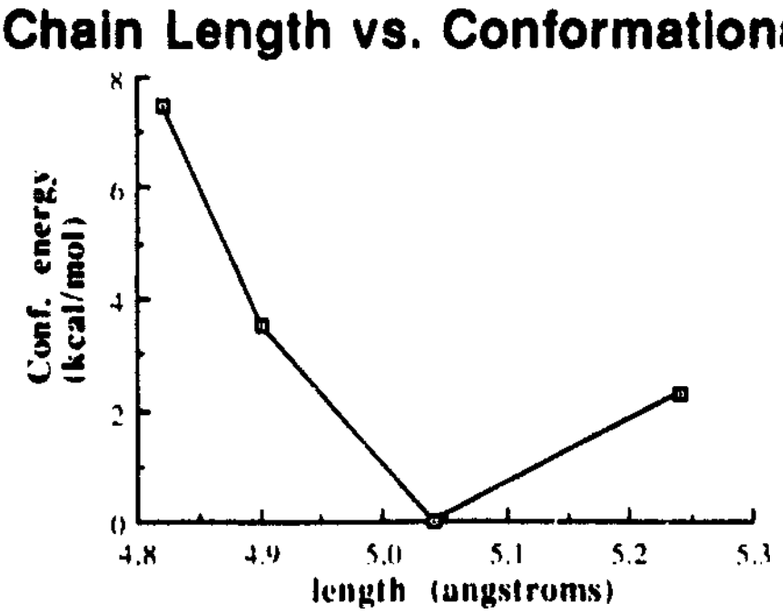


Figure 8

The results of activity as a function of biologically active conformational energy for each molecule are shown in Figure 9. A least squares analysis of the data indicates the expected negative correlation, but the points are variable enough to make the degree of correlation uncertain. In fact, the high conformational energy of compound 3 was unexpected considering its high activity level.

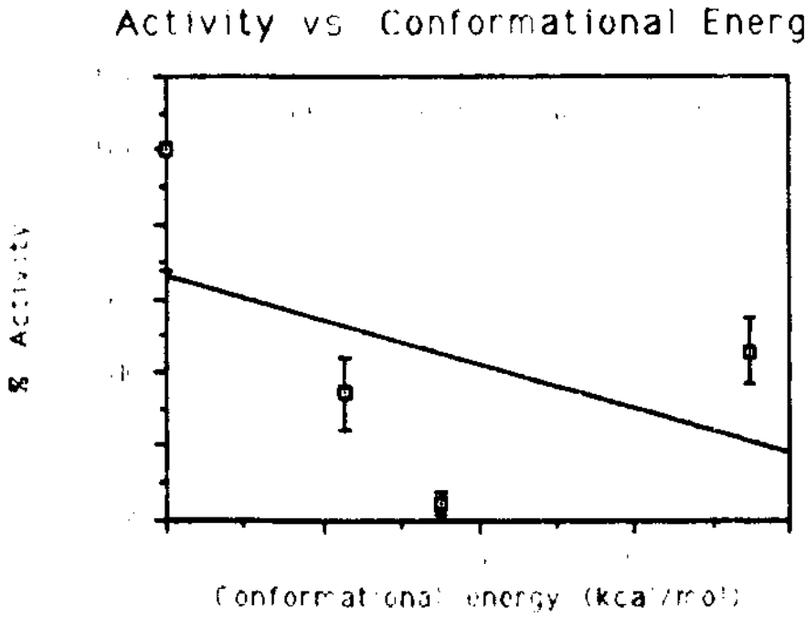


Figure 9

CONCLUSIONS

The molecular parameters of the heteroatom-substituted molecules determined in this study did not correlate well enough with the biological activity data to characterize properties of the receptor reliably. Although some of the molecular parameters studied may not physically influence the activity of the compounds, it is likely that errors in the biological data contribute more toward the lack of correlations. Probably the most significant error in this data is the volatility of the compounds which was not corrected for. More precise data will be necessary to determine the effects of certain molecular properties.

A receptor-interaction model was developed for the study response of *D. barberi* to the series of substituted phenylpropanoids. The flexibility of the propanol side chain made it possible to restrict the phenyl and hydroxy groups to positions occupied by the same groups in the most active parent molecule. Biological activities of the phenylpropanoids may be determined in part by the energy required for these conformational rearrangements to occur. The results of this model indicate that the conformational energies are probably inversely related to activity but the data are not accurate enough to determine a quantitative correlation. If this structure-activity relation holds, the receptor domain that binds the substrate must have spatial restrictions complementary to those on the natural stimulant. With more complete data it will be interesting to apply this modelling technique to several related species that have specific responses for different analogs of the phenylpropanoids. It would be exciting if subtle evolutionary modifications of the substrate-binding domain in the olfactory receptor could be quantitatively determined from this type of study.

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