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EFFECTS OF DOUBLE-BOND CONFIGURATION ON INTERACTION BETWEEN A MOTH SEX PHEROMONE COMPONENT AND ITS RECEPTOR: A Receptor–Interaction Model Based on Molecular Mechanics

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Abstract—The dependence of the electrophysiological activity on the change of double-bond configuration of (*Z*)-5-decenyl acetate, a pheromone component of the turnip moth, *Agrotis segetum*, and a dienic analog, (*E*)-2,(*Z*)-5-decadienyl acetate, have been investigated by single-cell measurements and molecular mechanics calculations (MM2). A previously reported model for the interaction between a moth sex pheromone component and its receptor has been refined. This new model gives an essentially quantitative correlation between the measured activities and the calculated conformational energies for a biologically active conformation defined by the model. Previously obtained structure–activity results for chain-elongated analogs of (*Z*)-5-decenyl acetate are significantly improved by the refined model. The effect of a change of the double-bond configuration on the substrate–receptor interaction is not additive but depends on the conformational properties of the entire molecule.

Key Words—Structure–activity, conformational energy, molecular mechanics, double-bond configuration, *Agrotis segetum*, Lepidoptera, Noctuidae, sex pheromone, single-cell recordings, receptor interaction.

INTRODUCTION

Straight chain monoolefinic acetates with a (*Z*) double bond constitute by far the largest class of known pheromone components of noctuid moths (Scheme 1) (Steck et al., 1982).

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SCHEME 1.

Field trapping experiments and electrophysiological measurements on the response of male moth antennae (EAG) or single olfactory receptor cells have revealed that the (*E*) isomer of a pheromone component is significantly less active than the natural (*Z*) isomer. In an EAG screening of a large number of noctuid species, Priesner et al. (1975) reported that the (*E*) isomer is 1.8–5.6 times less active than the (*Z*) isomer. Single-cell measurements, which are better suited for this kind of comparison, show up to 10-fold less activity for the (*E*) isomer in noctuid species (Priesner, 1979). In tortricid species, this difference is usually about 100-fold (Priesner, 1979, 1980, 1983).

However, of all analogs of natural (*Z*) pheromone components so far tested in various studies, the corresponding (*E*) isomer is nevertheless among the most active. For instance, its activity corresponds to, or exceeds, the activity of analogs chain elongated or chain shortened by one methylene unit, which are geometrically more modest perturbations of the natural compound than the (*Z*) to (*E*) configurational change.

Previous structure–activity studies on moth pheromone components strongly indicate that the spatial relationships between the acetate group, the double bond, and the terminal methyl group are crucial for the biological activity (Kafka and Neuwirth, 1975; Kikuchi, 1975; Bestmann and Vostrowsky, 1982; Liljefors et al., 1985). Considering that the three-dimensional shapes of the thermodynamically preferred conformers of the (*Z*)- and (*E*) isomers are significantly different, the relatively high activity of the (*E*) isomer is surprising. However, straight-chain monoolefinic acetates are very flexible molecules. Rotations about single bonds of the (*E*) isomer may make it possible for this isomer to approach the three-dimensional shape of the corresponding (*Z*) isomer. This has previously been suggested by Kafka and Neuwirth (1975) in connection with the development of a receptor interaction model for pheromone components, but no attempts were made to fit (*E*) isomers to this model (Kafka and Neuwirth, 1975; Neuwirth, 1973).

Recently, we reported a new model for the interactions between a monoolefinic pheromone component and its receptor, employing structures and conformational energies calculated by the molecular mechanics method (Liljefors et al., 1985). This model was successfully used to rationalize the effects of chain elongation on observed electrophysiological single-cell activities of homologs of (*Z*)-5-decenyl acetate **(1)**, a pheromone component of the turnip moth, *Agrotis segetum* (Bestmann et al., 1978; Arn et al., 1980; Löfstedt et al., 1982). In the present work, we report an extension of this model to include

the effects of a change of the double-bond configuration as well. This extension made necessary a refinement of the previously reported receptor interaction model (Liljefors et al., 1985). As will be described below, this refinement also significantly improves the quantitative aspects of the previously obtained results for chain-elongated analogs.

In connection with structure–activity studies on dienic analogs of (*Z*)-5-decenyl acetate (Bengtsson et al., 1987), we surprisingly observed that changing the configuration from (*Z*) to (*E*) at position 5 of (*E*)-2,(*Z*)-5-decadienyl acetate (compounds **4** and **5**, respectively) did not produce any significant change in the electrophysiological activity, in contrast to the effect of the corresponding configurational change in (*Z*)-5-decenyl acetate (see above). These observations provide a good test of the performance of the refined receptor interaction model.

We report electrophysiological single-cell measurements and conformational analysis of the compounds shown in Figure 1. Olfactory receptor cells specifically tuned to (*Z*)-5-decenyl acetate (**1**) are present in antennal sensilla type SW1 of the turnip moth, *Agrotis segetum*, and are readily accessible for single-cell recordings (Hallberg, 1981; Löfstedt et al., 1982; van der Pers and Löfstedt, 1983).

METHODS AND MATERIALS

Chemicals. The synthesis of (*Z*)-5-decenyl acetate (Figure 1, **1**), (*E*)-5-decenyl acetate (**2**), and the chain-elongated analogs (**6**)–(**12**) have previously been reported (Olsson et al., 1983; Liljefors et al., 1985). (*E*)-5-Dodecenyl acetate (**3**) was purchased from the Institute for Pesticide Research, Wageningen, The Netherlands. The synthesis of (*E*)-2,(*Z*)-5-decadienyl acetate (**4**) will be reported elsewhere (Bengtsson et al., 1987).

(E)-*2,(E)-5-Decadienyl Acetate (5).* This was prepared according to the method of Ando et al. (1982) from zirkonocene monohydride (2.2 g, 9 mmol) (Schwartz's reagent), 3-(2-tetrahydropyranyloxy)-1-propyne (1.2 g, 9 mmol), 1-bromo-2-heptene (1.5 g, 9 mmol) and $Pd(PPh_3)_4$ (0.26 g) to yield 1.6 g (91%) of crude (**5**). δ_H(300 MHz; $CDCl_3$) 0.89 (3H, t, Me), 1.28–1.36 (4H, m, CH_2CH_2), 1.98–2.04 (2H, m, $CH_2C{=}$), 2.06 (3H, s, $MeC{=}O$), 2.72–2.78 (2H, m, $={CCH_2C}=$), 4.52 (2H, dd, OCH_2), 5.33–5.51 (2H, m, J_{AB} = 15.2 Hz, CH=CH), 5.51–5.62 (1H, m, J_{AB} = 15.2 Hz, C<u>H</u>=CH), 5.72–5.83 (1H, m, J_{AB} = 15.2 Hz, CH=C<u>H</u>), δ_C(15.03 MHz; $CDCl_3$) 14.0, 21.0, 22.2, 31.6, 32.2, 35.2, 65.1, 124.1, 126.9, 132.3, 134.9, 170.9, *m/e*: 136 (M^+-60; 5%), 107 (1), 93 (7), 79 (32), 67 (10), 55 (11), 43 (100).

The compounds were purified by argentation liquid chromatography (Houx et al., 1974) and by preparative GLC (column OV-351, 6 m). All compounds were at least 98.5% isomerically pure as determined by capillary GLC (column Supelcowax 10, 30 m). The double-bond configurations were confirmed by ^1H

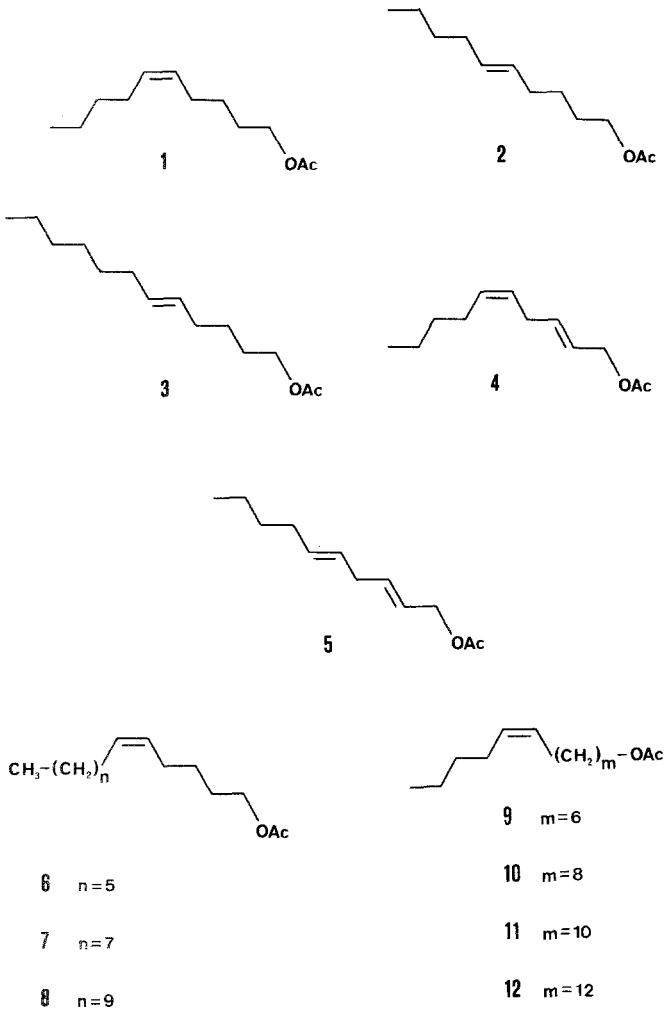

FIG. 1. Compounds studied.

and ^{13}C NMR spectroscopy using a Varian XL-300 or a Nicolet 360 WB spectrometer. Mass spectra were recorded on a Finnigan 4021 mass spectrometer.

Calculations. Energy-minimized geometries and conformational energies were calculated using the molecular mechanics program MM2 developed by Allinger and coworkers (Allinger and Yuh, 1980; Burkert and Allinger, 1982). Starting structures for the energy-minimization program were constructed by the molecular modeling system MIMIC (Liljefors, 1983; von der Lieth et al., 1984). This system was also used in the molecular superimposition studies and in the calculation and plotting of conformational energy maps.

Electrophysiology. The biological activities of the different compounds were established by measuring the electrical responses of receptors selective for (*Z*)-5-decenyl acetate (**1**) on the male *Agrotis segetum* antenna.

The measuring procedure was essentially the same as that described by van der Pers and den Otter (1978). A freshly excised antenna from a 2-day-old moth was placed with the base in a capillary electrode filled with Beadle-Ephrussi Ringer solution and connected to earth by an Ag–AgCl wire. The tip of an olfactory sensillum was cut off by a glass knife, and the recording electrode was placed in contact with the cut surface of the sensillum. The recording electrode was then connected to a high-impedance amplifier by an Ag–AgCl wire.

The stimulus was loaded onto a piece of filter paper and put into a plastic syringe. The amounts used ranged from 10^{-3} to 10^{2} μg. Two milliliters of the gaseous content of the syringe was injected into an airstream flushing the antenna continuously at a linear flow of 0.5 m/sec. Ten replicates were recorded with each different stimulus.

The response of the receptor cell was defined as the number of action potentials (nerve spikes) generated during 1 sec, starting from the onset of the stimulation. Dose–response curves using five different concentrations were made for all compounds tested.

The relative electrophysiological activities of the tested compounds were calculated from the dose-response curves, and expressed as the reciprocal of the relative quantities required to elicit the same response of the receptor cell.

Corrections for differences in vapor pressure were calculated as previously described (Liljefors et al., 1985), using data from Olsson et al. (1983).

Refined Substrate–Receptor Interaction Model

The new features of the refined model are: (1) the use of the entire pheromone component molecule **1** in the construction of the model instead of using only part of the molecule; (2) the use of the complete structure of the analogs in the calculations of conformational energies; and (3) addition of flexibility to the model with respect to the required location of the double bond (see Computational Procedure section below). As in our previously described model, the natural pheromone component **1** is used to define spatial relationships in the cavity of the receptor active site between positions of molecular parts crucial for full biological activity (Liljefors et al., 1985). The corresponding molecular parts in the studied analogs (**2–12**) may, through conformational rearrangements of their alkyl chains, be positioned in these space locations. The conformational energy required for such a rearrangement may then be related to the biological (electrophysiological) activity of the analog. A high conformational energy should correspond to a low biological activity and vice versa. As before, we assume receptor sites complementary to the acetate group, the double bond, and the terminal methyl group (Liljefors et al., 1985).

At the present stage of development our model is only applicable to com-

pounds analogous to the natural pheromone component and which have the ability to position the crucial molecular parts, as defined above, in the required positions. Thus, compounds such as chain-shortened analogs cannot be fitted directly to the model and its assumed interaction sites. It must also be borne in mind that the details of the transduction process are still largely unknown and that the process may be a complex multistep one (Kaissling, 1974, 1976, 1977). Our model is to be understood as a model for an "activated complex" related to the efficacy (intrinsic activity) rather than as model for the initial binding of the substrate.

In our previous model only those parts of the molecules which were changed in the test series were included in the calculations. This simplification facilitated the calculations for the chain-elongated analogs **6–12** in the structure–activity analysis previously reported (Liljefors et al., 1985) but is less satisfactory in the general case. In the present work the complete molecules are used in the calculations. This, however, introduces a complication since we now have to take the conformational properties of the natural pheromone component **1** into account.

Conformational Analysis of Compound 1. Compound **1** is a very flexible molecule with a large number of conformers within 1 kcal/mol of the energy of the thermodynamically most stable one. However, a study of conformationally restricted dienic analogs of compound **1** strongly indicates that the alkyl chains of **1** should have an all-*anti* conformation in the biologically active state (Bengtsson et al., 1987). This reduces the problem to the conformation with respect to the C=C−C−C fragment. It is then implicitly assumed that one of the stable conformers in this respect corresponds to the biologically relevant structure of compound **1.**

A calculated conformational energy map for the rotation about the vinylic bonds in (*Z*)-4-octene, used as a model for the olefinic part of a monoolefinic pheromone component, is shown in Figure 2. It shows a degenerate double-minimum for the *cisoid* conformation (Figure 3) and a single minimum for the *transoid* one with an energy difference of 0.11 kcal/mol, favoring the *transoid* conformation. The populations of the two types of conformations are thus very similar, in agreement with experimental data on other (*Z*)-olefins. An electron diffraction study on (*Z*)-3-hexene indicates the presence of both types of conformations with comparable populations (van Hemelrijk et al., 1981). This has also been concluded from infrared data on liquid (*Z*)-3-hexene (Shimanouchi et al., 1971). Raman spectra of crystals of (*Z*)-monoolefinic fatty acids show the molecules to have either the *cisoid* or the *transoid* conformation depending on the crystalline modification (Koyama and Ikeda, 1980).

The energy barrier between the two *cisoid* conformers in (*Z*)-4-octene is calculated to be very low, 0.12 kcal/mol. The interconversion between the two *cisoid* forms may thus be described as a large amplitude torsional motion. The energy barrier for the *cisoid* to *transoid* interconversion is calculated to be 0.84

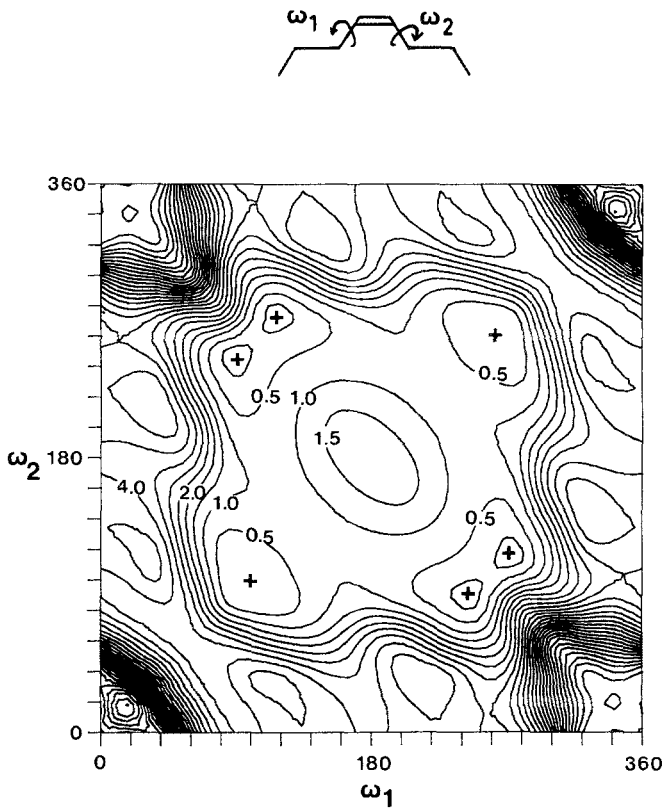

FIG. 2. Conformational energy map for the rotation about the vinylic bonds of (Z)-4-octene. ω_1 and ω_2 are C=C−C−C dihedral angles in degrees. Local minima are denoted by +. Isoenergy contours are shown with an energy difference of 0.5 kcal/mol. At the degenerate minima at ω_1, ω_2 = 90,240 and 120,270 (and the symmetry related pair) the 0.2 kcal/mol level also is shown.

kcal/mol, in good agreement with the experimental value 0.60 ± 0.06 kcal/mol for the analogous barrier in (Z)-2-pentene (van Eijk, 1981). The above analysis of (Z)-4-octene implies that there are three conformers of the natural pheromone component **1** which are candidates for the biologically active structure within the context of our model.

The energy-minimized geometries of these conformers are shown in Figure 4. The *cisoid 1* and *cisoid 2* conformers differ mainly in the torsional angles about the (C=C)-(C−C) bonds. In the *cisoid 1* structure the C=C−C−C dihedral angles are calculated to be 116.1 and −87.2 degrees for the *n* and *m* chains, respectively. The corresponding values for the *cisoid 2* conformer are 88.4 and −114.9 degrees. The difference in calculated conformational energy

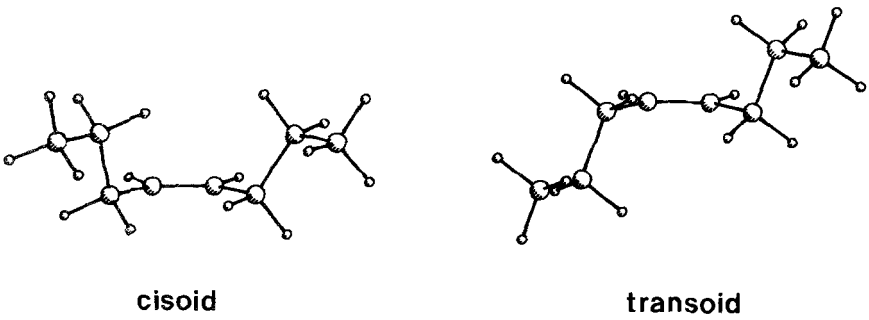

FIG. 3. Energy-minimized *cisoid* and *transoid* conformers of (Z)-4-octene.

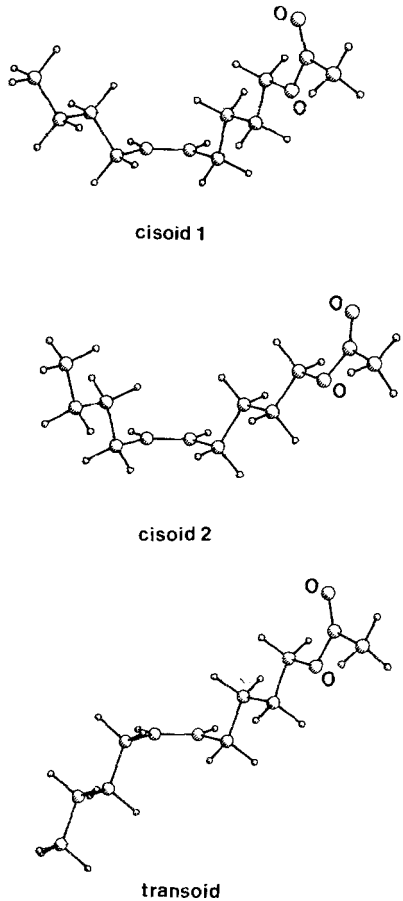

FIG. 4. Energy-minimized geometries of the *cisoid* and *transoid* conformers of (Z)-5-decenyl acetate (**1**) with all-*anti* alkyl chains.

between the three conformers is less than 0.06 kcal/mol. As there are presently no data from which it is a priori possible to choose which of these conformers to use as a model for the biologically active conformation of **1**, all three were used in turn and all calculations were done for each of the three models. These models will, in the following, be denoted *cisoid 1, cisoid 2,* and *transoid* according to Figure 4. The use of all three models in the calculations gives a good check of the sensitivity of the calculated results to the precise geometry of the substrate–receptor interaction model.

Computational Procedure. As in our previous model, the pheromone component analogs studied were assumed to interact with the receptor with the terminal methyl group and the acetate group in the relative positions in space defined by the natural pheromone component. Computationally this is accomplished by restricting the encircled atoms in Figure 5 to these fixed positions during the energy-minimization procedure. In our previous model the double bond and the vinylic carbons were also restricted to fixed positions. However, the results obtained indicated that these constraints are too severe in the general case (Liljefors et al., 1985). To add more flexibility to the model, the double bond and the vinylic carbon atoms were allowed to move during the energy minimization process in the plane defined by the C—C=C—C fragment in the reference molecule **1.** The restriction to a common plane ensures that the pi orbitals have the same direction in all molecules studied, and thus may interact with the corresponding binding site in a similar way. Before energy-minimization, the double bond in the studied analog was placed in a position as close to the double bond in the reference molecule **1** as possible.

With these restrictions, the molecules were energy-minimized with respect to all remaining degrees of freedom. A large number of starting structures was employed, and the lowest energy one after energy-minimization was used in the further analysis. The construction of trial structures for the chain-elongated analogs, employing a diamond lattice, has previously been described (Liljefors et al., 1985). Next, the unconstrained global energy minimum for each molecule was calculated. The conformational energies required by the molecules to acquire their "biologically active conformations" could then be evaluated by

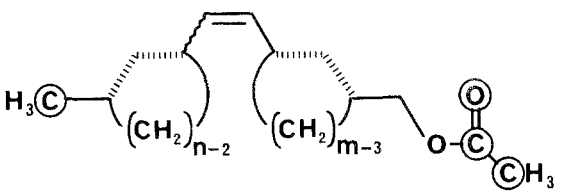

FIG. 5. Encircled atoms are held in fixed positions in the calculations of structures and energies for biologically active conformations. The dashed lines indicate the alkyl chains in the natural pheromone component **1.** For constraints on the double bond, see text.

taking the difference in calculated energy between the lowest energy conformationally rearranged structure that fits the requirements of the receptor–interaction model and the unconstrained global energy minimum. These energies are then compared to the observed electrophysiological activities relative to the reference compound **1.**

Note that in the context of our model the interaction energies between the terminal methyl group, the double bond, and the acetate group and their receptor counterparts are the same or at least very similar for all molecules included in the present study. This is due to the requirement that the three receptor-interacting parts of the substrate molecule are at fixed positions in space or, in the case of the double bond, only allowed a very limited freedom of motion. However, the conformational energy required to attain the biologically active structure is different and depends on the structure of the molecule. Thus, the differences in total receptor–interaction energies along the series of molecules are, according to our model, determined by the different conformational energies. The calculated conformational energies correspond to enthalpies. The entropy terms have not been explicitly considered in the present work, but differences in the conformational entropy contributions for the molecules in the series investigated should largely be compensated by differences in hydrophobic binding (Liljefors et al., 1985).

RESULTS AND DISCUSSION

Chain-Elongated Analogs. The new model described above was first used to recalculate the conformational energies required for the previously studied chain-elongated analogs **6–12** to acquire their "biologically active conformations". For details of the results obtained previously, see Liljefors et al. (1985). The purpose of this recalculation was to study the performance of the refined model in relation to the old one and to investigate if the calculated results are dependent on the choice of biologically relevant conformer for the natural compound **1** (*cisoid 1, cisoid 2* or *transoid*, see Figure 4).

The results are shown in Figure 6. The calculated energies are clearly not very dependent on the conformer assumed to be the biologically active one for the natural pheromone component **1.** The observed minima in activity for compounds **7** and **10** correspond to calculated conformational energy maxima in all three cases, and the results are qualitatively similar to those previously obtained (Liljefors et al., 1985). However, very satisfactorily, the refined model now makes it possible to put the results for chain elongation on either side of the double bond on the same energy scale. Our previous model clearly exaggerated the conformational energies required for the analogs chain-elongated between the double bond and the acetate group, by as much as 8–10 kcal/mol (Liljefors et al., 1985). This was due to the overly severe constraints imposed on the molecule in the previous model.

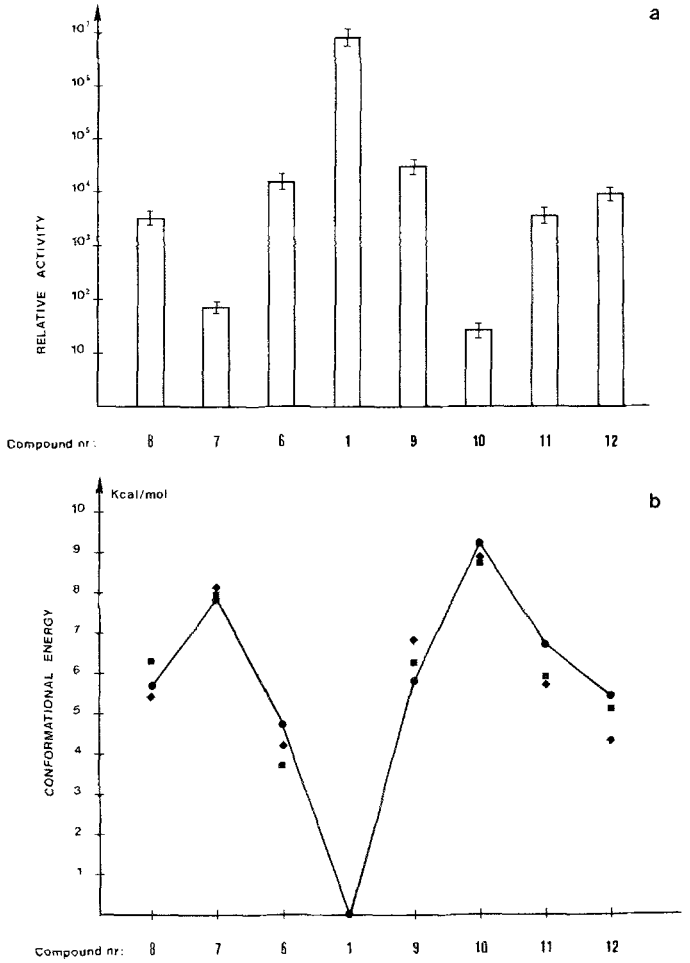

FIG. 6. (a) Experimental single-cell activities (from Liljefors et al., 1985 and (b) calculated conformational energies for the biologically active conformations of chain-elongated analogs of **1.** ♦ *cisoid 1;* ● *cisoid 2;* ■ *transoid* model. The calculated energies for the *cisoid 2* model are connected by a solid line.

From the results in Figure 6 it is possible to calculate the conformational energy corresponding to a decrease of the biological activity by a factor of 10. On average this becomes 1.7, 1.7, and 1.6 kcal/mol for the *cisoid 1, cisoid 2,* and *transoid models*, respectively. For all three models and for all seven analogs the maximum calculated deviation from these numbers is 0.5 kcal/mol. The refined model thus significantly improves the results for the chain-elongated analogs **6–12,** and gives an essentially quantitative relationship between calculated conformational energy and observed biological activity. The similar re-

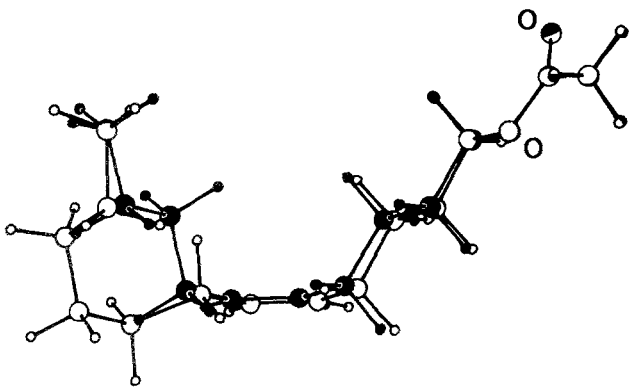

FIG. 7. Superimposition of the *cisoid 2* conformer of **1** (filled atoms) and the calculated biologically active conformation of compound **6.**

sults obtained with this series of compounds for the three different models precludes the possibility of selecting one of them as the most probable biologically active structure of the natural pheromone component **1.**

As an example of the structure of a calculated biologically active conformation, a superimposition of the calculated "active structure" of compound **6** and the natural pheromone component **1** in its *cisoid 2* conformation is shown in Figure 7. To fit the geometrical requirements of the receptor–interaction model, **6** is forced to adopt *gauche* conformations about two adjacent bonds. The difference in double bond positions of **1** and **6** is quite small. The distance between the midpoints of the double bonds in **1** and **6** in the superimposition shown is 0.6 Å. The calculated conformational energy of **6** in this "biologically active" conformation relative to the lowest energy one is 4.7 kcal/mol, which may be compared to the corresponding value using our previous model, 5.8 kcal/mol. For compounds **9–12,** the difference between the calculated energies using the old and new models is even larger, as much as 5–10 kcal/mol. This implies that a substantial reduction of the conformational energy may be achieved with a modest adjustment of the double-bond position in the cavity of the receptor "active site." It should be noted that the calculated biologically active conformations of **6–12** do not correspond to local energy minima of the unconstrained "free" molecules.

Double-Bond Configurational Isomers. The measured electrophysiological single-cell activities for compounds **2–5** relative to the natural pheromone component **1** are shown in Figure 8a. The (*E*) isomer **2** is less active by a factor of 100 than the corresponding natural (*Z*) isomer **1.** Chain elongation by two methylene units (compound **3**) further lowers the activity by about a factor of 100 (including corrections for differences in vapor pressure). This may be compared

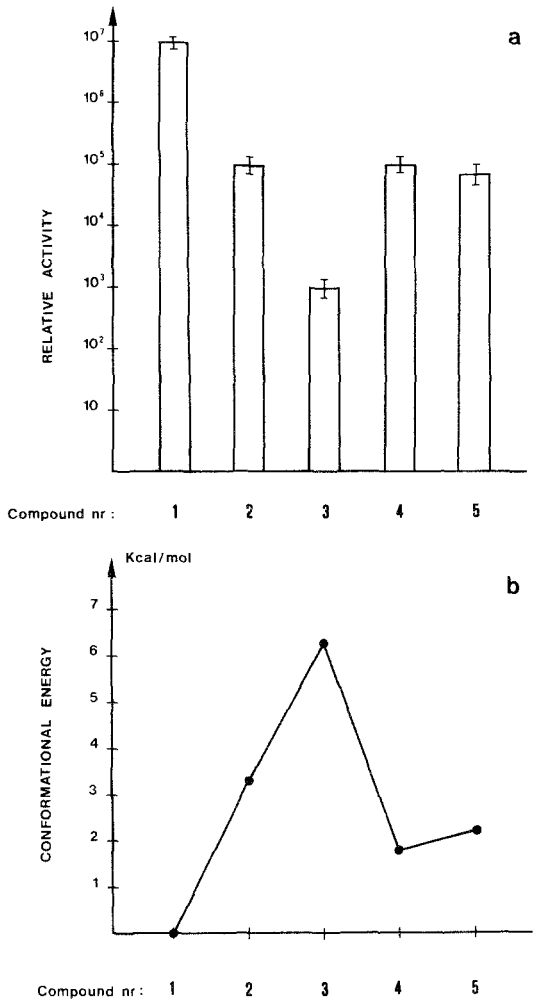

FIG 8. (a) Experimental single-cell activities for compounds **1–5.** (b) Calculated conformational energies for the biologically active conformations (*cisoid* **2** model) of compounds **1–5.**

to the relative activity for **6** with respect to **1,** which is ca. 1000 (Figure 6). The loss of activity due to chain-elongation is thus somewhat less in the (*E*) series than in the corresponding (*Z*) series.

Introduction of an (*E*) double bond in the 2 position of the natural pheromone component (compound **4**) has approximately the same effect as the *Z*/*E* configurational change (Figure 8a); the observed activity is reduced by a factor of ca. 100. Surprisingly, no further significant change in the activity was ob-

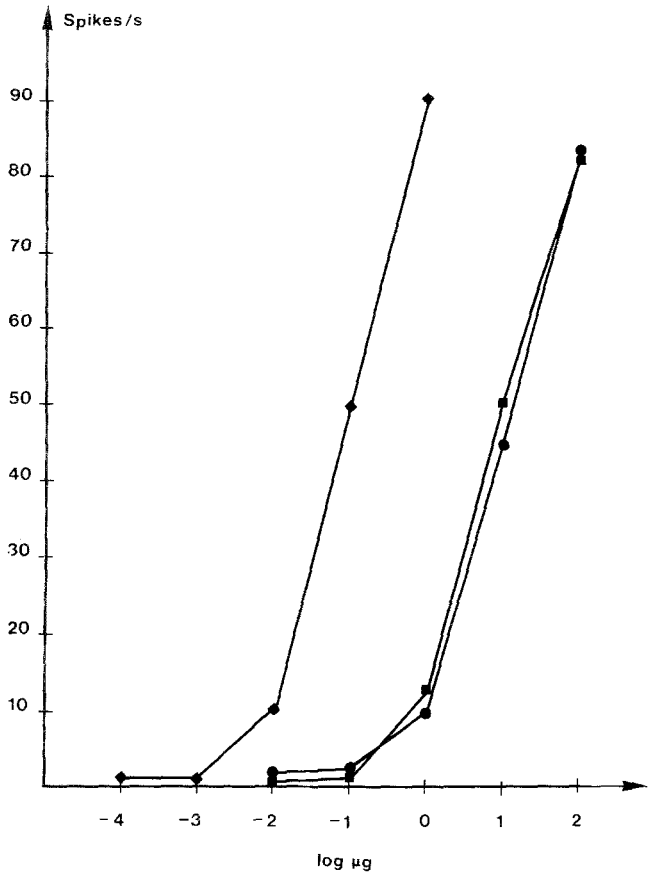

FIG. 9. Dose–response curves for compounds **1**, ♦; **4**, ■; and **5**, ●; obtained by electrophysiologic single-cell recordings.

served for the (*E*)-5 isomer **5** of this diene. The close similarity of the electrophysiological response of the two compounds is demonstrated in Figure 9, which shows the dose–response curves for the natural pheromone component **1** and the two diene analogs **4** and **5**. The effect of configurational change is thus not additive, but depends on the properties of the entire molecule.

The conformational energies required for compounds **2–5** to acquire their biologically active conformations, according to the receptor–interaction model described above was calculated, and the results are shown in Figure 8b. (The results for the *cisoid 2* model according to Figure 4 are shown. The results for the other two models in this series are also very similar).

The calculated conformational energies clearly have a very close correla-

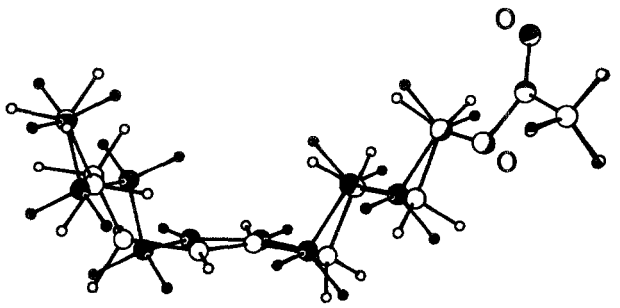

FIG. 10. Superimposition of the *cisoid 2* conformer of **1** (filled atoms) and the calculated biologically active conformation of compound **2.**

tion to the measured electrophysiological activities. The calculated conformational energy for compound **2** is 3.3 kcal/mol, which corresponds to 1.65 kcal/mol for each power of 10 of decrease in activity compared to **1.** This is identical to the number obtained for the chain-elongated analogs. A superimposition of compound **2** in its calculated "biologically active conformation" and compound **1** is shown in Figure 10. The (*E*) isomer is forced to adopt a *gauche-anti* conformation of the alkyl chain connecting the double bond and the methyl group. The position of the (*E*) double bond in **2** is sufficiently close to that of the (*Z*) double bond in **1** to assure similar interactions with the binding site.

The chain-elongated (*E*) isomer **3** is calculated to have a conformational energy requirement of 6.3 kcal/mol to reach its "biologically active conformation." Using the value 1.65 kcal/mol for a 10-fold decrease in activity as obtained above, this should give a reduction of the activity by a factor of ca. 100 compared to that of **2,** which is also observed (Figure 8a). Furthermore, comparing compounds **2** and **3,** the conformational energy for reaching the biologically active conformation is increased by 3.0 kcal/mol due to chain-elongation by two methylene groups in the (*E*) series. This may be compared to the corresponding value of 4.7 kcal/mol in the (*Z*) series (Figure 6, compound **6**). The calculations thus also reproduce the observation that chain elongation in the (*E*) series leads to a smaller decrease of the activity than in the (*Z*) series.

Gratifyingly, the unexpected similarity of the activities of compounds **4** and **5** is also well calculated. After conformational rearrangements which increase the energy by 1.8 kcal/mol (Figure 8) the (*E*)-2, (*Z*)-5 diene **4** becomes an extremely good "mimic" of the natural pheromone component **1,** as is demonstrated by the superimposition of the two molecular structures in Figure 11a. The (*E*) double bond in **4** closely mimics the *anti*-conformation of the corresponding saturated fragment in **1.** The (*E*)-2, (*E*)-5 diene **5** requires a conformational energy of 2.2 kcal/mol, only slightly higher than that for **4,** to mimic the molecular shape of **1,** as can be seen in Figure 11b.

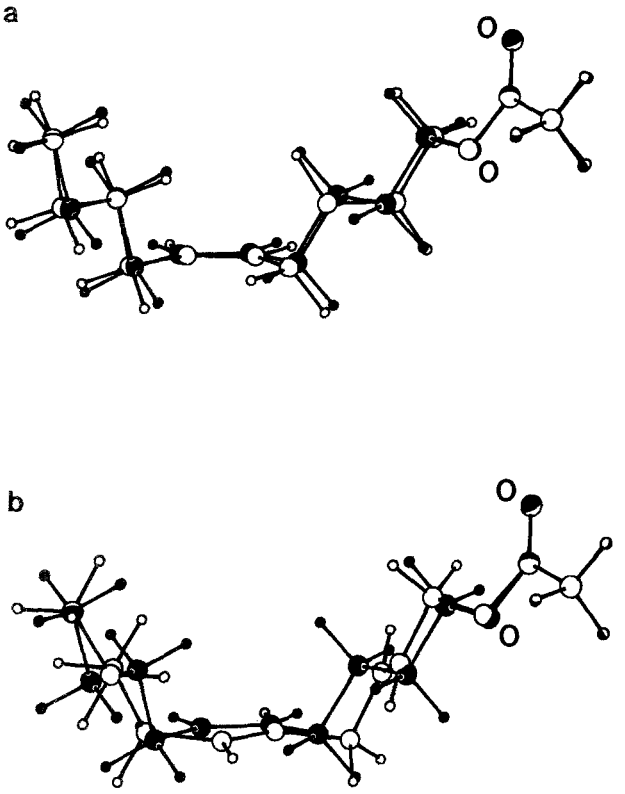

FIG. 11. Superimpositions of the *cisoid 2* conformer of **1** (filled atoms) and the calculated biologically active conformations of (a) compound **4** and (b) compound **5.**

CONCLUSIONS

The model for the interaction between a pheromone component and its receptor presented in this work gives an essentially quantitative correlation between the measured electrophysiological single-cell activities and conformational energies calculated by molecular mechanics. The calculated conformational energies correspond to the energies required for the molecules to acquire a biologically active conformation as defined by the model. It should be noted that the resulting conformations for the analogs of the natural pheromone component are not local energy minima for the "free" molecules.

The effect of a change of double-bond configuration on the biological (electrophysiological) activity is not additive, but depends on the conformational properties of the entire molecule.

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