Original Article

Theoretical Studies on the Structure and Reactivity of Insect Juvenile Hormone, JH III

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We estimated lower energy conformers of natural juvenile hormone III (JH III) [methyl-(2*E*,6*E*)-3,7,11-trimethyl-(10*R*,11)-epoxy-dodecadienoate] based on semi-empirical molecular orbital (MO) MNDO calculations. Conformational analysis by PCICO calculations strongly suggested that JH III possesses an extended conformation and that the two methyl groups at the 3- and 7-positions partially restrict the internal rotations along the carbon chain of dodecadienoate. The same extended conformation was also suggested by phase-sensitive NOESY 2D-NMR measurements. The interatomic distance (*L*) between the carbonyl carbon and epoxy oxygen atoms and the molecular dimensions of JH III were estimated to be 11.34 ± 0.36 Å and $18.5 \times 8.2 \times 7.2$ Å, respectively. MNDO calculations, with model enzyme systems, suggested that metabolic oxidation at the (6*E*)-C=C moiety and hydrolysis both at the ester linkage and epoxide moiety are feasible.

INTRODUCTION

Insect juvenile hormones (JH) regulate the life cycle of insects by giving an "status quo" effect on juvenile insects and promoting maturation of reproductive systems in adults.¹⁾ Up to now, natural juvenile hormones, such as JH 0,²⁾ JH I,³⁾ JH II,⁴⁾ and JH III⁵⁾ in Fig. 1, have been successfully isolated and identified to be (2*E*,6*E*)-10,11-epoxy-tridecadienoate or -dodecadienoate derivatives. Recently, another juvenile hormone, 4-Me JH I, has been identified in eggs of *Manduca sexta*.⁶⁾

By modifying chemical structures of natural juvenile hormones, many types of JH mimics have been synthesized with an aim at finding a new insecticide. In such syntheses, relationships between molecular structure and activity have to be taken into consideration from the viewpoints of transport, binding at a receptor site, and metabolism in insects.⁷⁾

Since the nature of a JH receptor still remains obscure, QSAR techniques have been used as receptor mapping procedures in order

to clarify the physicochemical properties of the active sites.⁸⁾ A study suggests that the epoxy or alkoxy group and a π -electron system such as the ester of aryl group at either end of a molecule with an appropriate distance between are prerequisites for optimal JH activity.⁹⁾

Although natural JHs are considered to possess the prerequisite molecular shape for an optimal activity, they are known to show a lower activity as compared with synthetic JH mimics such as methoprene.¹⁰⁾ This is likely to be due to the rapid degradation of natural JHs.¹¹⁾ We therefore chose JH III as a model compound and estimated its molecular shape together with its reactivity in relation to metabolism. We did a theoretical study on lower energy conformers, one of which might possess an active configuration for an effective binding at a receptor site, by means of molecular orbital (MO) calculations, together with 2D-NMR spectroscopic analysis, and by utilizing the optimized geometries of JH III in lower energy states, we estimated

Fig. 1 Chemical structures of juvenile hormones.

their molecular sizes. We also deduced the metabolic sites of JH III in insects from the results of MO calculations.

CALCULATIONS

MNDO (Modified Neglect of Diatomic Overlap) SCF-MO¹²⁾ and PCILO (Perturbative Configuration Interactions using Localized Orbitals)¹³⁾ calculations were executed on an IBM 4381 (MVS) computer. The MNDO method was used with its defect in the core repulsion function in mind. Since the PCILO method is known to be suitable for semiquantitative estimation of molecular geometry in a significantly short computational time,¹⁴⁾ the conformational analysis at each internal rotation was conducted by the PCILO method. A ball-and-stick model of the JH III molecule

and the contours of the molecular orbitals were displayed by using the ACACS system¹⁵⁾ with an NEC ACOS system 430 computer.

1. Initial Geometry of JH III

Since X-ray crystallographic data were not available, the molecular geometry of JH III was constructed by the following procedure: The JH III molecule was divided into the three molecular fragments, methyl (2*E*)-3-methylbutenoate (**I**), (3*E*)-3-methylhexene (**II**) and (1*R*)-1,2,2-trimethylepoxy (**III**), as shown in Fig. 2. The initial geometry of each molecule was derived by using the following values for bond lengths: C-H; 1.08 Å, C=C and C-O; 1.35 Å, C-C; 1.52 Å and C=O; 1.25 Å. The bond angles were: tetrahedral carbon; 109.5°, alkenyl or carbonyl carbons; 120.0° and epoxy ring; 60.0°. The dihedral angles were derived from the following assumptions: (1) The JH III molecule has an extended conformation, (2) the conformation of the methyl and methylene groups is staggered, and (3) the geometry of regions containing the C=C double bond is planar. Under these assumptions, the molecular geometries of (**I**), (**II**) and (**III**) were fully optimized by MNDO. Then, the three fragments were connected to construct the JH III molecule (Fig. 2). The two C-C-C bond

Fig. 2 Procedure to construct the JH III molecule and notation of each atom of JH III.

ϕ_1 : $\text{O}_{15}-\text{C}_1-\text{O}_{13}-\text{C}_{14}$, ϕ_2 : $\text{C}_3-\text{C}_2-\text{C}_1-\text{O}_{13}$, ϕ_3 : $\text{C}_2-\text{C}_3-\text{C}_4-\text{C}_5$, ϕ_4 : $\text{C}_3-\text{C}_4-\text{C}_5-\text{C}_6$, ϕ_5 : $\text{C}_4-\text{C}_5-\text{C}_6-\text{C}_7$,
 ϕ_6 : $\text{C}_6-\text{C}_7-\text{C}_8-\text{C}_9$, ϕ_7 : $\text{C}_7-\text{C}_8-\text{C}_9-\text{C}_{10}$, ϕ_8 : $\text{C}_8-\text{C}_9-\text{C}_{10}-\text{C}_{11}$.

angles at the connected points ($C_4-C_5-C_6$ and $C_8-C_9-C_{10}$) are assumed to be equal to the $C_3-C_4-C_5$ bond angle (113.3°). There are eight internal rotations ($\phi_1-\phi_8$) along the carbon chain of dodecadienoate. Dihedral angles $C_3-C_4-C_5-C_6$ (ϕ_4) and $C_7-C_8-C_9-C_{10}$ (ϕ_7) were fixed at 180.0° where the molecule is fully extended in staggered conformation. The following values were used for the initial dihedral angles; ϕ_3 (270.0°), ϕ_5 (90.0°), ϕ_6 (270.0°), and ϕ_8 (0.0°).

2. Conformational Analysis

The lower energy conformations of the JH III molecule were obtained by conformational analysis with PCILO calculations. The conformation was changed by a step by step rotation of 15° around each of the axes ($\phi_1-\phi_8$) and the total energy of each conformer was calculated under the third-order perturbation. The polarization of each bond was optimized on every rotation. The intrinsic error of total energy by calculation has been reported to be less than 2 kcal/mol (*ca.* 0.001%).¹⁸⁾ The relative total energy to the global minimum was calculated for each conformer and subject to curve fitting with a spline method with an NEC PC micro-RESEARCHER™. The molecular geometries of local minimal energy conformations were then refined by MNDO calculations.

3. Molecular Shape of JH III

Four steric parameters, L , D_x , D_y , and D_z (Fig. 3), were introduced to evaluate the steric dimensions of the JH III molecule, as reported previously.^{8,16)} " L " was the interatomic distance between the carbonyl carbon (C_1) and the epoxy oxygen (O_{12}). To evaluate the steric parameters, the Cartesian coordinates of each atom of the JH III molecule were transformed as follows. The C_1 atom was moved to an origin and the O_{12} atom was placed on the x -axis in the negative direction. The xy -plane was defined by the C_1 , O_{12} and O_{13} atoms. The O_{13} atom was placed on the first quadrant of the xy -plane and a z -axis was chosen perpendicular to this plane. The molecular shape of the JH III molecule was expressed by the steric parameters in consideration of the van der Waals radius of each

Fig. 3 Definition of four steric parameters.

atom, using the following values; hydrogen (1.10 Å), carbon (1.70 Å) and oxygen (1.40 Å).¹⁷⁾ The longest distance of a molecule, measured from the molecular surface along the line parallel to each coordination axis was defined as D_x , D_y or D_z . These steric parameters were computed for all conformers obtained by MNDO calculations.

4. Reactivity of JH III

The enzymatic hydration of the epoxy ring and the hydrolysis of the ester moiety are known to be involved in the metabolic pathways of JH.¹⁸⁾ Since the nucleophilic reaction of JH is expected in both cases, the distribution of the lowest unoccupied MO (LUMO) or the neighboring unoccupied MOs was examined. Degradates via metabolic oxidation catalyzed by oxidases have been also detected *in vivo*. Since this reaction is reported to occur at the electron-sufficient atom of a molecule,¹⁹⁾ the electron distribution of the highest occupied MO (HOMO) or the neighbouring occupied MOs was examined. In order to visualize molecular orbitals of JH III, their contours were calculated and displayed, with the ACACS system.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) analysis was carried out to study the conformation of JH III in solution. Synthetic JH III was purchased from Sigma (St. Louis, U.S.A.) and

purified by silica gel thin-layer chromatography (benzene/ethyl acetate=15/1, R_f =0.4)²⁰⁾ and high-performance liquid chromatography (HPLC)²¹⁾ before NMR measurements. The purity of JH III determined by HPLC was >95%. The ^1H - and ^{13}C -NMR spectra were recorded with a Bruker AM400 NMR spectrometer in 0.5 ml of chloroform- d_1 (CDCl_3 , >99.8%; E. Merck) containing 20 mg and 100 mg of JH III, respectively. CDCl_3 was conveniently utilized as the deuterized solvent to simulate the hydrophobicity at a receptor site due to its low polarity. The spectral peaks of JH III were assigned based on heteronuclear COSY, distortionless enhancement by polarization transfer (DEPT) and long-range ^1H - ^{13}C correlation (COLOC) spectroscopies.²²⁾ Since JH III is a small molecule (mol. wt.=266.4) and the Nuclear Overhauser Effect (NOE) provides information on the spatial proximity of nuclei, phase-sensitive NOE 2D-NMR spectra (PSNOESY)²³⁾ were measured by the use of normal pulse sequence (90° - t_1 - 90° - τ -Acquisition). The τ value was changed stepwise within 3% of τ . For each of the 512 different τ values, consisting of 2048 complex points, 16 scans were collected with the 2 sec of t_1 . The F1 and F2 dimensions were modified with the shifted ($\pi/3$) sine bell squared function before Fourier transforma-

tion.

RESULTS

1. Conformational Analysis

The relative total energy as a function of internal rotation around each of the ϕ_1 - ϕ_8 axes are shown in Figs. 4 and 5. The energy barriers at the ϕ_1 and ϕ_2 rotations were about 5 kcal/mol. The rotation along the ϕ_1 axis by 180.0° increased the total energy by about 3.0 kcal/mol. This is likely to be due to the weak steric hindrance between the ester methyl and 3-methyl groups. Meanwhile, the potential energy curve at the ϕ_2 rotation had two troughs, which showed that two conformers were almost similar in terms of their total energies. The energy barriers at the ϕ_4 and ϕ_7 rotations were almost similar to those appearing in ϕ_1 and ϕ_2 rotations. Since the barrier of the internal rotation around the C-C single bond of alkanes is less than 3-6 kcal/mol,²⁴⁾ these results show that the ϕ_1 , ϕ_2 , ϕ_4 and ϕ_7 rotations are almost free. In contrast, the energy barriers at the other rotations (ϕ_3 , ϕ_5 and ϕ_8) were higher than 10 kcal/mol, as shown in Fig. 5. The steric hindrance between the bulky substituents attached to each of these axes seems to inhibit free rotations. Since the energy barrier was *ca.* 8 kcal/mol, the internal rotation around

Fig. 4 Results of conformational analysis by the PCILO method for ϕ_1 , ϕ_2 , ϕ_4 and ϕ_7 rotations.

Fig. 5 Results of conformational analysis by the PCILO method for ϕ_3 , ϕ_5 , ϕ_6 and ϕ_8 rotations.

ϕ_6 may be less restricted than those around ϕ_3 , ϕ_5 and ϕ_8 . Therefore, two stable conformations could be present around each of the ϕ_3 , ϕ_5 , ϕ_6 and ϕ_8 axes. These results suggest that sixteen lower energy conformers exist even if the ϕ_1 , ϕ_2 , ϕ_4 and ϕ_7 dihedral angles are fixed at their initial values.

2. Optimized Conformations of JH III

MNDO calculation in the case of JH III led to an erroneous estimate of conformation of the ester moiety since its plane was perpendicular to the plane defined by the 2, 3 double bond. Since it is reasonable to assume that the α -alkenyl ester moiety has an approximately planar geometry,²⁵⁾ the ϕ_2 values obtained for the molecular fragment (**I**) ($C_3-C_2-C_1-O_{13}=3.3^\circ$, $C_3-C_2-C_1-O_{15}=183.0^\circ$) were used. For all of the conformers estimated by conformational analysis, the four dihedral angles (ϕ_3 , ϕ_5 , ϕ_6 and ϕ_8) were optimized with MNDO parametrizations as follows; $\phi_3=90.8-91.3^\circ$, $\phi_5=92.3-95.9^\circ$ and $267.4-270.2^\circ$, $\phi_6=85.8-89.1^\circ$ and $272.3-272.7^\circ$ and $\phi_8=158.6-159.3^\circ$ and $268.1-270.6^\circ$. Since all of the conformers were insignificantly different in total energy (less than 0.3 kcal/mol), they could be present in almost equal proportions. The optimized bond angles along the carbon chain of dodecadienoate were in the range from 113.3 to

Fig. 6 The ball-and-stick model of JH III conformer No. 1 by the ACACS system.

130.4°, and the three bond angles forming the epoxy ring were close to 60°. The estimated geometries of the epoxide moiety were in good agreement with the experimental data,²⁶⁾ as shown below: The C-C and C-O bond lengths were calculated to be 1.541 Å (1.470 Å; obs.) and 1.417 Å or 1.423 Å (1.435 Å; obs.), respectively. The ball-and-stick model of one of the JH III conformers (No. 1) is shown in Fig. 6.

3. Molecular Shape of JH III

Distance "L" was in the range of 10.70–11.86 Å for sixteen conformers with the average of 11.34 ± 0.36 Å. The other steric parameters, D_x , D_y and D_z , were calculated to be 18.50 ± 0.40 Å, 8.19 ± 0.65 Å and 7.21 ± 0.52 Å, respectively.

4. Reactivity of JH III

Since the character of molecular orbitals

Table 1 The MNDO SCF-MO results of JH III conformer No. 1.

Molecular orbital	Energy level (eV)	Localization	Electron density (%) ^{a)}
HOMO-3	-11.30	Epoxide	9.1 (C ₁₀), 8.4 (C ₁₁), 42.0 (O ₁₂)
HOMO-2	-11.12	Epoxide	21.8 (C ₁₀), 23.1 (C ₁₁), 28.3 (O ₁₂)
HOMO-1	-10.36	(2E)-C=C	32.7 (C ₈), 41.8 (C ₂)
HOMO	-9.83	(6E)-C=C	37.8 (C ₆), 36.4 (C ₇)
LUMO	-0.22	(2E)-C=C+COO	41.3 (C ₈), 27.0 (C ₂), 13.5 (C ₁), 1.9 (O ₁₃), 10.0 (O ₁₅)
LUMO+1	+0.61	(6E)-C=C	45.2 (C ₆), 42.7 (C ₇)
LUMO+2	+1.74	(2E)-C=C+COO	7.9 (C ₈), 18.3 (C ₂), 47.9 (C ₁), 3.6 (O ₁₃), 19.0 (O ₁₅)
LUMO+3	+2.13	Epoxide	38.8 (C ₁₀), 37.7 (C ₁₁), 6.8 (O ₁₂)

^{a)} Defined as $\sum_i C_{ji}^2 \times 100$, C_{ji} : the eigen vector of the i -th atomic orbital of the j -th molecular orbital.

was not significantly different between each conformer, the result of conformer No. 1 was conveniently used to predict the reactivity of JH III. A large Mulliken charge was observed at either end of the JH III molecule; C₁ (+0.40), C₁₄ (+0.24), O₁₂ (-0.26), O₁₃ (-0.37) and O₁₅ (-0.37). The energy levels and electron distribution of some molecular orbitals are listed in Table 1. The distribution of unoccupied molecular orbitals such as LUMO-LUMO+3 shows that a nucleophilic reaction possibly occurs at the (2E)-C=C+COO and epoxide moieties. In contrast, HOMO-1 and HOMO are localized at the (2E)- and (6E)-C=C double bonds, respectively, where an electrophilic reaction possibly occurs.

5. Spectroscopy

The ¹H- and ¹³C-NMR peak assignments of JH III are listed in Table 2. Although the ¹H-NMR spectrum measured at 90 MHz has been already reported,²⁷⁾ the methylene protons (H₂₇-H₃₀ and H₃₅-H₃₈) have not yet been exactly assigned. In our study almost all protons were assigned by 2D-NMR spectroscopy. The PSNOESY 2D-NMR spectrum of JH III is shown in Fig. 7. Although the resolution of ¹H-NMR spectra at 1.5-1.6 ppm and 1.9-2.2 ppm was poor, a small cross peak observed at 5.60 ppm × 5.10 ppm suggests that the two alkenyl protons (H₂₃ and H₃₁) are oriented in the same direction when viewed from the carbon chain of dodecadienoate. The spatial proximity between the H₂₃ atom and the C₁₄ methyl protons

Table 2 The ¹H- and ¹³C-NMR peak assignments of JH III.

Position	C	H of cross peak ^{a)}	
		Hetero COSY	COLOC
C ₁₇	16.0	1.54	
C ₁₈	18.7	1.17	1.22
C ₁₆	18.8	2.09	2.10, 5.60
C ₁₉	24.8	1.22	1.17
C _{5/4} ^{b)}	25.9	2.10	
C ₉	27.4	1.52	
C ₈	36.3	2.07	1.57
C _{4/5}	40.8	2.09	2.10
C ₁₄	50.7	3.62	3.62
C ₁₁	58.2		1.17, 1.22
C ₁₀	64.1	2.62	1.22
C ₂	115.3	5.60	2.09, 5.60
C ₆	123.5	5.08	1.57
C ₇	135.3		1.57
C ₃	159.8		2.12
C ₁	167.2		2.12, 3.62

^{a)} ppm vs. TMS in CDCl₃.

^{b)} C_{5/4} means that the peak assignment is not clear and the peak is tentatively assigned to C₅.

was deduced from a cross peak at 5.60 ppm × 3.60 ppm.

DISCUSSION

The JH III molecule is likely to possess a flexible structure owing to many possible internal rotations (ϕ_1 - ϕ_8 in Fig. 2). Although the conformation of JH III was not precisely determined, the relative orientations of some

Fig. 7 The PSNOESY spectrum of JH III in chloroform-*d* (ppm vs. TMS).

nuclei could be estimated in part by 2D-PSNOESY NMR spectroscopy. The two alkenyl protons (H_{23} and H_{31}) of the lower energy conformers where (ϕ_3, ϕ_5) are close to $(270^\circ, 270^\circ)$ and $(90^\circ, 90^\circ)$, designated as group (a), were orientated in the opposite direction when viewed from the carbon chain of dodecadienoate, while those of other conformers where (ϕ_3, ϕ_5) are close to $(270^\circ, 90^\circ)$ and $(90^\circ, 270^\circ)$, designated as group (b), were orientated in the same direction. The interatomic distances between the two alkenyl protons were 5.29 Å and 4.41 Å for (a) and (b), respectively. About a threefold increase in the NOE was anticipated for (b) compared with (a), assuming that the dipole-dipole interaction was predominant. It is well known that the NOE is generally observed for interacting proton

nuclei whose interatomic distance is less than 4–5 Å. Since a small cross peak due to H_{23} and H_{31} was observed, the JH III molecule was considered to exist in (b) conformation rather than (a). Moreover, conformers derived from (b) by 180° rotation around the ϕ_2 axis were more likely than (b) itself in consideration of the cross peak between H_{23} and C_{14} methyl protons. However, this change in conformation was not a principle for significant differences in the steric dimensions of JH III and its molecular orbital properties. The results of 2D-NMR spectroscopy and semi-empirical MO calculations, indicating that lower energy conformers existed in the extended conformation.

It is well known that the steric dimensions and hydrophobicity of a molecule are im-

portant factors contributory to biological activity of JH mimics.⁸⁾ Studies on the structure-activity relationship also indicate that the presence of a π -electron system, such as the ester or aryl group and the epoxy or alkoxy oxygen, is essential for activity.⁷⁾ The computed Mulliken charges suggest that although JH III is a hydrophobic molecule, it does possess polar regions due to the epoxy and ester moieties at both ends of the molecule. In the meantime, the O₁₂ atom was estimated to be located 11.34 ± 0.36 Å away from the C₁ (π -center) atom, based on MNDO calculations of the extended JH III conformers. A parameter similar to "L" in this study (Fig. 3) has been used for a series of JH mimics having aryl terpene structures,⁹⁾ to study the relationship between JH activity and molecule length. The distance from the center of the phenyl ring to epoxy oxygen is reported to be 11.5 ± 0.5 Å. Since similar molecular dimensions have been observed for conformationally rigid molecules,²⁸⁾ it seems that the estimated lower energy conformations of JH III are close to an active form at a receptor site.

The active conformation necessary to fit a receptor site was not precisely clarified, but it is possible to deduce some properties of the receptor site. Since the size of the JH III molecule was computed to be $18.5 \times 8.2 \times 7.2$ Å on average, the receptor site is likely to be of similar size, assuming that the conformation of the JH III molecule does not significantly change at the receptor site. Moreover, it is likely that this site consists mainly of hydrophobic regions, and that both ends of the site possess the corresponding opposite charges to those of a JH III molecule.

It appears that the metabolic deactivation of JH III in insects plays an important role in determining its biological activity. Three different types of enzymes, such as epoxide hydrolases, esterases and oxidases, are known to participate in the metabolism of juvenile hormones in insects.¹¹⁾ The major metabolic reaction is hydration of the epoxide and ester cleavage, leading to the formation of JH-diol and JH-acid, respectively. It is expected that a nucleophilic reaction occurs at an atom where the unoccupied molecular orbital at a lower energy level is localized and the larger

Fig. 8 The contours of LUMO+2 (a) and LUMO+3 (b) of JH III conformer No. 1.

positive charge is observed.²⁹⁾ The contour maps of LUMO+2 and LUMO+3 at 0.5 Å and 0 Å above the planes defined by the C₁, O₁₃ and O₁₅ atoms, and C₁₀, C₁₁ and O₁₂ atoms, respectively, are shown in Fig. 8. Since 47.9% of the LUMO+2 molecular orbital was localized on the carbonyl C₁ atom whose Mulliken charge was +0.40, a nucleophilic reaction is likely to proceed at this position, leading to the formation of JH-acid. 38.8% and 37.7% of the LUMO+3 molecular orbital was localized on the C₁₀ and C₁₁ atoms of the epoxide moiety, respectively. A similar nucleophilic reaction would open the epoxide ring by subsequent formation of JH-diol. The other metabolic reaction of JH is oxidation catalyzed by oxidases, *e.g.* cytochrome P-450 enzymes, where the electron-deficient

Fig. 9 The molecular size and the metabolized positions of JH III.

oxene atom is proposed as an active oxygen species.³⁰⁾ A theoretical study on the electrophilic reaction of oxene strongly suggests that the reaction is orbitally controlled.¹⁹⁾ The MNDO calculations showed that the energy level of HOMO of oxene lies at -7.73 eV, which is close to those of HOMO and HOMO+1 of JH III. These results suggest that metabolic oxidation would occur at the (2E)- and (6E)-C=C double bonds, which is in agreement with detection of JH-epoxide and JH-diepoxy *in vivo*.³¹⁾

CONCLUSION

Theoretical and spectroscopic studies on JH III showed that all sixteen of the lower energy conformers could exist. Our study failed in clearly determining the active conformer this time, but it showed that the size of the receptor site is likely to be $18.5 \times 8.2 \times 7.2$ Å, as in Fig. 9. MNDO SCF-MO results were enough to qualitatively predict the reactive sites of JH III.

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要 約

昆虫幼若ホルモン JH III の立体構造と反応性に関する理論的考察

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半経験的分子軌道法 MNDO, PCIO 計算により

dodecadienoate 鎖方向に伸びた構造を有する JH III の安定コンフォーマーを推定し, PSNOESY 2次元 NMR からその構造が支持された. 安定コンフォーマーは, $18.5 \times 8.2 \times 7.2 \text{ \AA}$ の次元を有する形状を示し, 活性発現に関連すると考えられるカルボニル基と末端エポキシ基との距離は, $11.34 \pm 0.36 \text{ \AA}$ であった. さらに, 分子軌道法計算の結果より, (6*E*) 位の二重結合における酸化反応, ならびに, エステル結合部, エポキシサイド部における加水分解反応が, JH III の主代謝経路となることが示唆された.