A QUANTUM MECHANICAL STUDY OF THE GEOMETRY OF TWO MOLECULES RELATED TO VITAMIN A

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ABSTRACT

With the help of the PCILO method (Perturbative Configuration Interaction Method using Localized Orbitals) some conformational energy calculations upon C_9 acid (1,1,4-trimethyl-5-carboxy-cyclopentene-4) and C_{15} acid (retro-β-ionylidene-acetic acid) were made. The results correlate quite well with the experimental R-X data.

INTRODUCTION

In the last fifteen years crystal structures of some compounds related to vitamin A and of carotenoids have been determined in the Laboratory for Crystallography, University of Amsterdam, and elsewhere, namely:

(1) *all-trans-β*-Ionylidene-crotonic acid[1]
(2) *cis-β*-Ionylidene-crotonic acid[2]
(3) Vitamin A acid[3]
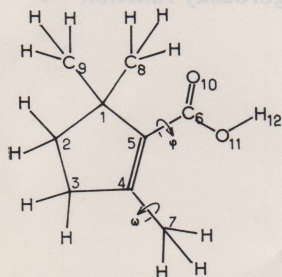(4) 15,15'-Dihydro-β-carotene[4].

Fig. 1. C_9 acid showing the numbering of the atoms and the rotation axes.
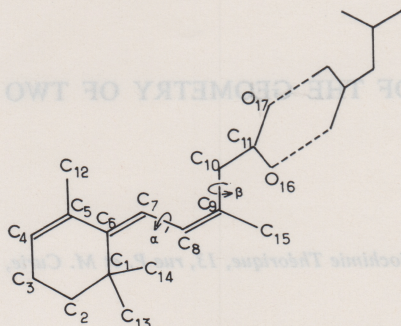
Fig. 2. Retro-β-ionylidene-acetic acid showing the numbering of the atoms and the rotation axes.

With the help of the PCILO method (Perturbative Configuration Interaction Method using localized Orbitals)[5,6] satisfactory results have been obtained from calculations on retinal and β-ionylidene-crotonic acid[7]. In this paper calculations on 1,1,4-trimethyl-5-carboxy-cyclopentene-4 (Fig. 1) and retro-β-ionylidene-acetic acid (an intermediate compound in the vitamin A synthesis of Huisman, Smit, Van Leeuwen and Van Rij[12]) (Fig. 2), and referred to as C_9 acid and retro C_{15} acid, respectively, are given.

METHOD

The PCILO method was used, the calculations being carried through to the third order.

The C_9 acid and C_{15} acid have two methyl groups (C_8, C_9 and C_{13}, C_{14}, respectively) attached to atom C_1. Before each conformation calculation, the positions of the hydrogen atoms of these two methyl groups are found by the minimization method of Powell[8] using a version of the program of Hilleay[9].

In order to minimize a function of several variables with or without constraints and avoiding the calculation of partial derivatives, an aleatory grid of points on the hypersurface $y = f(x_1 \cdots x_n)$ is generated. This grid is modified in an iterative way by continuous deformation until the minimum is reached.

The function used in this minimization is the Kitaygorodsky function

$$v = 3.5 \frac{a}{\left(\dfrac{r}{r_0}\right)^6} - c_2 \exp\left(-\alpha \frac{r}{r_0}\right)$$

with $a = \left(\frac{13}{11}\right)^6 \times 0.04 \times 3.5$ kcal/mole

$\alpha = 11$

$c_2 = 3 \times 10^4$ kcal/mole

$r_0 = \sqrt{r_1 r_2}$ where r_1 and r_2 are the Van der Waals radii.

GEOMETRY

The geometries as given by the X-ray studies of Schenk[10] were used for these two compounds.

C_9 ACID

Three interesting results of Schenk's experimental data were used:

(a) A 21° rotation of the COOH group about the C_5–C_6 bond because of steric interaction of O_{10} with the methyl groups C_8 and C_9.

(b) A 20° deviation of H_2 of methyl group C_7 from the eclipsed conformation.

(c) An opening of the angle $\widehat{C_5-C_4-C_7}$ due to the steric interaction between O_{11} and methyl group C_7.
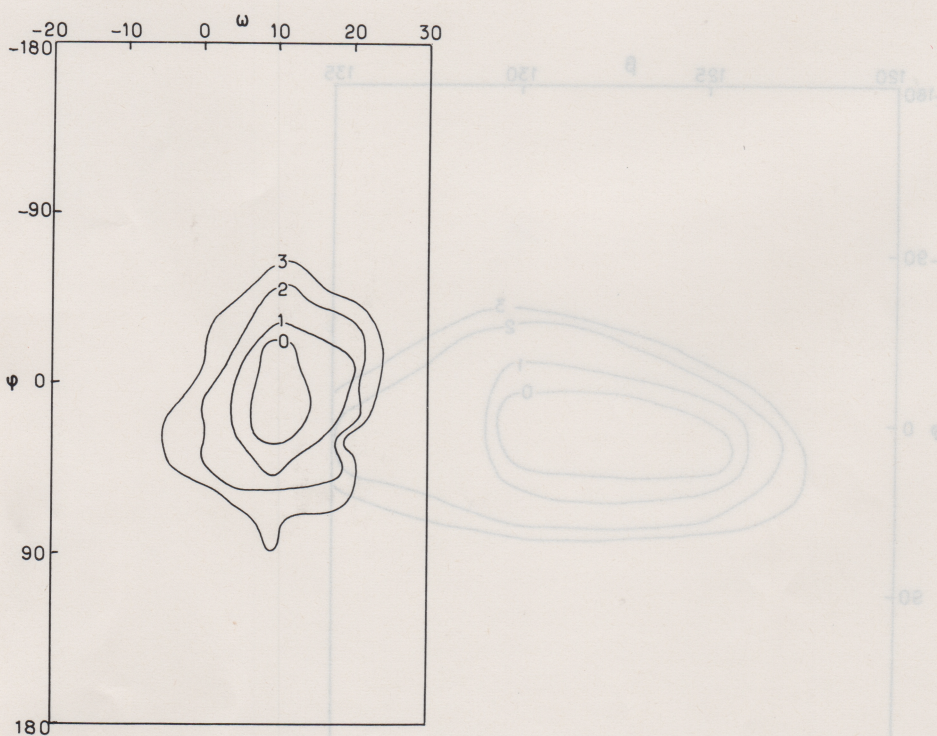
Fig. 3. Evolution of the energy of C_9 acid as a function of the angles φ and ω (for $\beta = 130°8$). φ and ω refer to rotation around the C_5–C_6 and C_4–C_7 axes, respectively; β is the bond angle $\widehat{C_7-C_4-C_5}$.

So we have:

(a) rotated the $C_6 \overset{O_{10}}{\underset{O_{11}-H}{}}$ group about C_5-C_6 as axis (angle φ),

(b) rotated the three hydrogen atoms of methyl group C_7 about the C_4-C_7 bond (angle ω),

(c) varied the bond angle $\widehat{C_7-C_4-C_5}$ (angle β).

We calculated the evolution of energy as a function of the angles φ and ω (Fig. 3), as a first step, keeping the experimental value of $130.8°$ for the $\widehat{C_7-C_4-C_5}$ bond angle. The minimum is attained for values of φ ranging from $-16°$ to $+24°$, and for $\omega = +10°$.

We next varied the three angles φ, ω and β. The minimum of the curve $E(\varphi, \beta) = f(\omega)$ was used for the φ and β values. Thus, each point of the map representing evolution of energy with φ and β angle values represents a minimum of the curve $E(\varphi, \beta) = f(\omega)$ (Fig. 4). An increase in the angle $\widehat{C_7-C_4-C_5}$ by $6–11°$
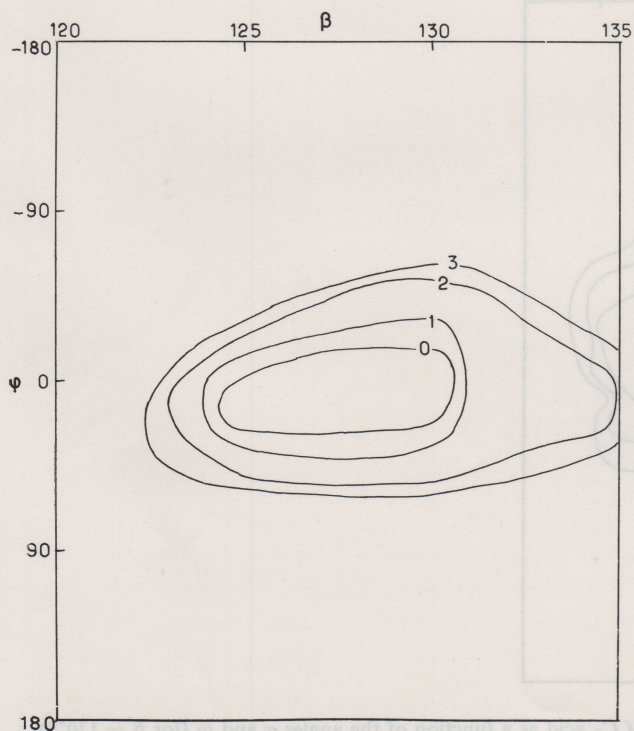

Fig. 4. Evolution of the energy of C_9 acid as a function of the angles φ and β. Each point of this map represents a minimum of the curve $E(\varphi, \beta) = f(\omega)$.

is indicated. Our results correlate with experiment, the region of minimum energy occurs for values from $-16°$ to $+24°$ for φ, from $125°5$ to $131°$ for β, and $+10°$ for ω.

C_{15} ACID

The experimental crystallographic data[10] show that the conjugated system is not planar. Schenk calculated the torsions about the individual bonds and found small torsional angles of $3°$ to $7°$ around $C_4–C_5$, $C_5–C_6$, $C_6–C_7$, $C_8–C_9$, but a more important torsional angle value of $20°$ around $C_7–C_8$. The geometry of ring and chain is nearly the same in retro Vitamin A acid; here this angle is $11°$, indicating that packing considerations account for a spread of $10°$. This torsion
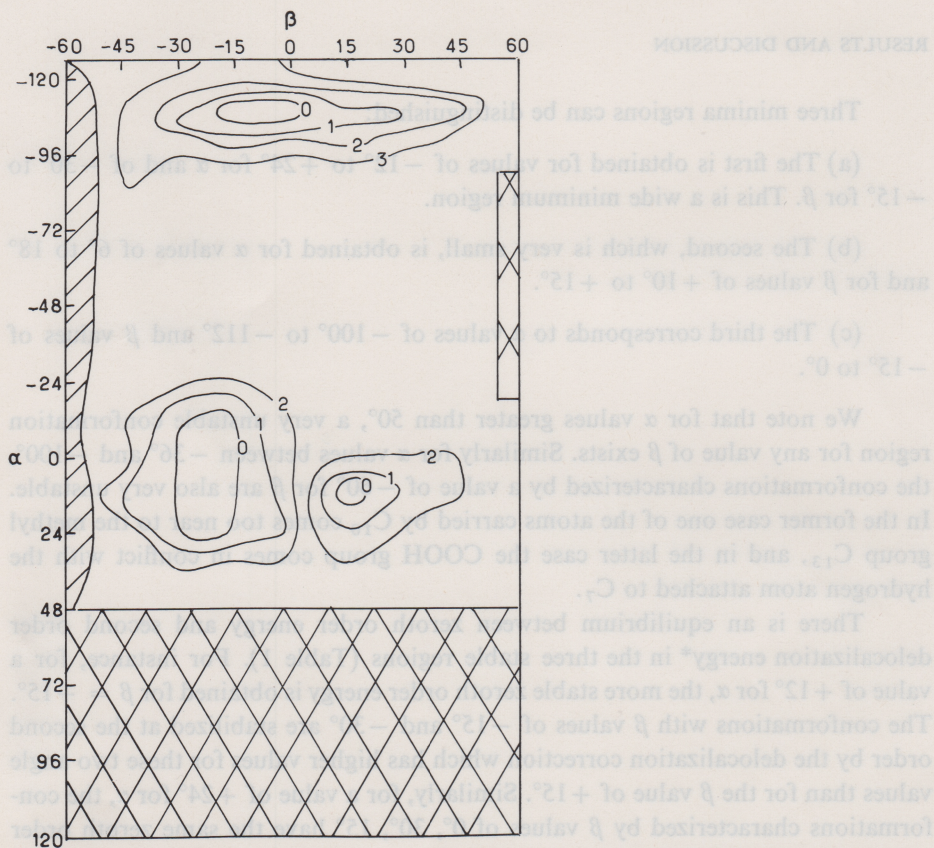
Fig. 5. Evolution of the energy of the retro-acid as a function of the angles α and β. α and β refer to rotation around the $C_7–C_8$ and $C_{10}–C_9$ axes, respectively. The shaded area (////) indicates the region where the difference from the region of minimum energy is 4 to 10 kcal/mole. The cross-hatched areas indicate regions where this difference is more than 10 kcal/mole.

about C_7–C_8 is due to steric hindrance between C_{13} and C_{14} methyl group hydrogens and the hydrogen atom bound to C_8. It is energetically more favourable to rotate about the C_7–C_8 single bond, than about the C_6–C_7 double bond.

Similarly, the hydrogens of the methylene group $C_{10} \overset{\diagup H}{\diagdown H}$ rotated by $15°$ about C_9–C_{10} out of the eclipsed position with respect to the double bond C_8–C_9, because of steric interaction of one hydrogen of this methylene group with the hydrogen of C_7.

We calculated the energy evolution as a function of variation of both rotation angles, i.e. the rotation angle around C_7–C_8 (angle α), and the rotation angle around C_9–C_{10} (angle β). The energetic map as a function of α and β is pictured in Fig. 5.

RESULTS AND DISCUSSION

Three minima regions can be distinguished:

(a) The first is obtained for values of $-12°$ to $+24°$ for α and of $-30°$ to $-15°$ for β. This is a wide minimum region.

(b) The second, which is very small, is obtained for α values of $6°$ to $18°$ and for β values of $+10°$ to $+15°$.

(c) The third corresponds to α values of $-100°$ to $-112°$ and β values of $-15°$ to $0°$.

We note that for α values greater than $50°$, a very unstable conformation region for any value of β exists. Similarly for α values between $-36°$ and $-100°$, the conformations characterized by a value of $-60°$ for β are also very unstable. In the former case one of the atoms carried by C_{10} comes too near to the methyl group C_{13}, and in the latter case the COOH group comes in conflict with the hydrogen atom attached to C_7.

There is an equilibrium between zeroth order energy and second order delocalization energy* in the three stable regions (Table 1). For instance, for a value of $+12°$ for α, the more stable zeroth order energy is obtained for $\beta = +15°$. The conformations with β values of $-15°$ and $-30°$ are stabilized at the second order by the delocalization correction which has higher values for these two angle values than for the β value of $+15°$. Similarly, for a value of $+24°$ for α, the conformations characterized by β values of $0°$, $30°$, $15°$ have the same zeroth order energy but the delocalization correction is weaker for $\beta = +15°$. For $\alpha = 12°$

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* Delocalization energy is the interaction of Φ_0 (the zeroth order determinant) with $\Phi(j*/i)$ (the determinant obtained from Φ_0 when i is replaced by $j*$).

TABLE 1

DELOCALIZATION ENERGY, CORRELATION INTERBOND ENERGY, DELOCALIZATION–DELOCALIZATION ENERGY AND CORR-2-BOND–CORR-2-BOND ENERGY, ZEROTH ORDER ENERGY, SECOND ORDER ENERGY, AND THIRD ORDER ENERGY, AS A FUNCTION OF α AND β

(All values are in kcal/mole)

α	β	Delocalization energy	Correlation interbond energy	Delocalization–delocalization energy	Corr-2-bond–corr-2-bond energy	Zeroth order energy	Second order energy	Third order energy
+12	0	−602.7	−191.5	+40.8	+45.0	−99623.8	−100703.69	−100511.94
	−60	−605.4	−192.0	+41.6	+45.1	−99618.7	−100701.94	−100509.69
	−45	−604.7	−191.8	+41.7	+45.0	−99622.3	−100704.44	−100512.31
	−30	−604.4	−191.6	+41.7	+44.9	−99623.7	−100705.44	−100513.31
	−15	−604.4	−191.5	+41.3	+44.9	−99623.7	−100705.31	−100513.31
	+15	−603.0	−191.6	+40.1	+45.1	−99624.4	−100704.75	−100513.31
	+30	−602.4	−191.8	+40.0	+45.2	−99623.7	−100704.56	−100512.94
	+45	−603.6	−192.0	+40.8	+45.4	−99623.4	−100704.69	−100511.88
	+60	−610.4	−192.6	+43.0	+45.9	−99620.1	−100708.81	−100513.06
+24	0	−602.0	−191.4	+40.4	+44.9	−99624.9	−100704.06	−100512.63
	−60	−604.6	−191.9	+41.1	+45.1	−99619.1	−100701.31	−100509.56
	−45	−603.9	−191.6	+41.3	+44.9	−99621.6	−100702.75	−100511.13
	−30	−603.7	−191.4	+41.3	+44.8	−99624.3	−100705.06	−100513.38
	−15	−603.7	−191.3	+41.0	+44.9	−99624.2	−100704.94	−100513.31
	+15	−602.8	−191.6	+39.8	+45.0	−99624.5	−100704.06	−100512.94
	+30	−601.8	−191.8	+39.6	+45.2	−99624.0	−100703.31	−100511.94
	+45	−602.8	−192.1	+40.3	+45.5	−99623.9	−100704.44	−100511.81
	+60	−609.1	−192.6	+42.3	+45.9	−99620.4	−100707.69	−100512.38
−108	0	−600.2	−191.1	+38.9	+45.0	−99626.2	−100703.38	−100513.38
	−60	−602.8	−191.9	+39.7	+45.1	−99619.4	−100700.00	−100509.50
	−45	−602.1	−191.6	+39.8	+45.0	−99621.9	−100701.44	−100511.00
	−30	−601.9	−191.3	+39.9	+44.9	−99624.4	−100703.44	−100512.94
	−15	−601.9	−191.2	+39.6	+44.9	−99625.2	−100704.06	−100513.63
	+15	−600.4	−191.3	+38.4	+45.1	−99624.8	−100702.31	−100512.68
	+30	−599.8	−191.6	+38.1	+45.3	−99625.7	−100702.31	−100512.69
	+45	−600.9	−192.3	+38.8	+45.7	−99623.4	−100702.31	−100510.50
	+60	−607.5	−193.4	+40.9	+46.5	−99616.1	−100702.75	−100508.75

and $\alpha = 24°$, at the second order, the most stable conformation is obtained for $\beta = +60°$ (because of the high value of the delocalization energy). But, at the third order, it can be seen that for $\beta = +60°$ the positive corrections delocalization–delocalization* and corr-2-bond–corr-2-bond** have very high values so these conformations characterized by $\beta = 60°$ are not favoured.

* Delocalization–delocalization correction represents the third order interaction between monoexcited states $I = (j*/i)$ and $J = (l*/k)$. These configurations only interact if $i = k$ or $j = l$.
** Corr-2-bond–corr-2-bond correction represents the third order interaction between two bond diexcitations.

For all values of α ranging from $+48°$ to $-120°$, the conformations with a value of $-60°$ for β, are not very stable; they give a 5 or 8 kcal/mole energy difference with the stable conformation. These conformations have a very weak zeroth order energy. The unstability is due to the proximity of oxygen O_{17} to one hydrogen of the C_{15} methyl group (the distance is 1.87 Å).

For α angle values from $-12°$ to $-120°$, the conformations characterized by a β angle value of $+60°$ are very unstable, due to the proximity of oxygen O_{17} to the hydrogen of carbon C_7. So the very high repulsion energy leads to a very low zeroth order energy and high delocalization energy, e.g. for $\alpha = -36°$ and $\beta = +60°$, the zeroth order and delocalization energies are 99595.25 and 613.08 kcal/mole, respectively. An important charge-transfer between the $C_{11}=O_{17}$ double bond, and the C_7-H_{24} bond occurs. But the positive third order corrections (delo–delo, corr-2-bond–corr-2-bond) contribute to the destablization of these conformations.

The unstability of the conformations obtained for α angle values from $+60°$ to $120°$ arises from the steric interaction between the hydrogens of the C_{13} methyl group with oxygen O_{17}, and hydrogens of C_{10}.

This steric interaction leads to a very weak zeroth order energy (98.927 kcal/mole) and a very high delocalization correction (224.47 kcal/mole) due to the important charge transfer from the C=O double bond to the C_2-H and $C_{13}-H$ bonds. The third order correction also contributes to the destabilization of these conformations: this positive correction value is very important because of the high positive value of the delocalization–delocalization and polarization–delocalization terms[6].

The second minimum region is in quite good agreement with the experimental conformation.

The third minimum region does not correspond to an experimental conformation. But our calculations are made with an isolated molecule, and related to the crystalline structure, they would be correct only if the intermolecular forces were very weak. As we have said elsewhere[7], Bart and MacGillavry[11] showed the importance of the intermolecular forces which operate in the crystal in the choice of a stable conformation. So, among several conformations which are stable when a molecule is isolated, one can find in the crystal the only one which allows a good packing of the molecules in the crystal. We note here that the molecules form dimers by pairing their –COOH groups over an inversion centre and the angle β then determines how the ring systems pack.

In the conformations characterized by angle α values from $-100°$ to $-112°$ the double bonds $C_6=C_7$ and $C_8=C_9$ are s-cis related to the single bond C_7-C_8, and the molecular structure is very compact. This is a characteristic of the PCILO method to favour the compact conformations when the Van der Waals distances are considered.

ACKNOWLEDGEMENTS

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