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Conformational Analysis of Prostaglandins. I. Theoretical Calculation on the Conformation of Prostaglandin $F_{1\beta}$ Derivative[1]

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The computer experiment was applied on the calculation of sterically allowed conformations of tri-(*p*-bromobenzoate) of methyl ester of prostaglandin $F_{1\beta}$ in order to accumulate conformational informations of prostaglandins and develop a useful calculation method which could be applied on compounds containing saturated chains. Eighty-four forms of sterically allowed conformations were found.

Calculations on the conformational energies of each of these conformations were carried out in order to find the conformation with the lowest energy and to research the relationships between sterically allowed conformations and their conformational energies. The calculation on the energies were restricted to the nonbonded and electrostatic energies, and the sum of them was approximated as the conformational energy. In this calculation, the values of van der Waals radii were parametrized and the effects on the conformations were discussed in detail.

Different conformations of the lowest energy were given by the different values of van der Waals radii. The geometrical properties of the most stable conformation that were calculated using larger values of van der Waals radii than the usual values were identical with the information from X-ray diffraction study on prostaglandin $F_{1\beta}$ derivative.

Introduction

It is well known that optical isomers of a physiological active compounds sometimes show quite different activities; so that it is necessary to study the interactions between physiological active compounds and their receptors, especially regarding with their conformational relations. Needless to say, studies on their electronic structures are important. But conformational analysis of these compounds is also necessary at the first stage to interpret the principle of physiological activity.

Recently many studies on conformations of some molecules have been carried out by computer experiments. Ramachandran, *et al.* used the hard sphere model for calculating the conformations of peptides and obtained many useful results.[3] By this method, however, it is possible to select the sterically allowed conformations but not to calculate the conformational energies, so that it is difficult to carry out farther discussions. Moreover, the calculation by this method was very sensitive to the values of hard sphere radii.

To overcome these difficulties the method using conformational energies was attempted. Scheraga, *et al.* carried out the calculation on sterically allowed conformations and their energies of the cyclic decapeptide gramicidin-S, and described that the most stable conformation agreed well with the informations from X-ray diffraction studies on gramicidin-S derivatives.[4] It is very difficult, however, to apply the computer experiment on compounds containing saturated chain structures because of a great numbers of sterically allowed conformations

1) A part of this work was presented at the 93 th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973.
2) Location: *2-2-1, Oshika, Shizuoka.*
3) G.N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan, *J. Mol. Biol.*, **7**, 95 (1963).
4) G. Vanderkooi, S.J. Leach, G. Némethy, R.A. Scott, and H.A. Scheraga, *Biochemistry*, **5**, 2991 (1966).

due to their internal rotations about the single bonds. Therefore, it is difficult to search the most stable conformation and to carry on the farther calculation.

The main purpose of this study is to develop the more advanced and useful calculation method which can be applied on compounds containing saturated chains. The second purpose is to accumulate informations which will be required to study the relationships between conformations and physiological activities.

The new calculating method was applied to tri-(*p*-bromobenzoate) of methyl ester of prostaglandin $F_{1\beta}$ ($PGF_{1\beta}$ derivative), illustrating the structural formula in Fig. 1, since the X-ray diffraction study had been carried out by Abrahamsson.[5]

Prostaglandins contain two side chains consisted of 7 and 8 carbon atoms respectively and a five membered ring. Prostaglandins have very strong physiological activities and optical isomers of various kinds of prostaglandins show quite different activities.[6] These properties of prostaglandins are suitable for our purpose.

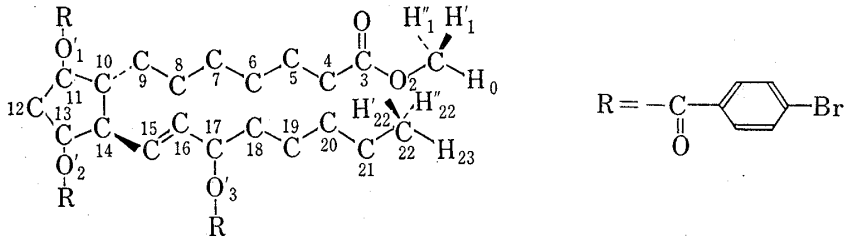

Fig. 1. Structural Formula of Tri-(*p*-bromobenzoate) of Methyl Ester fo Prostaglandin $F_{1\beta}$ and Numbering of Its Atoms

Method

The method used in this study has good points of the two methods[3,4] above described; so that relationships between sterically allowed conformations can be calculated in a short computation time. In our method two kinds of parameters are used; one is the hard sphere radius and the other is van der Waals radius which is greater than the former. Using hard sphere radii all of sterically allowed conformations are found, and their conformational energies are calculated using van der Waals radii.

Some Assumptions——Some assumptions were introduced to simplify the calculations. The first, rotations were only allowed around single bonds, and they were assumed to be restricted free rotations, and three kinds of staggered forms were permissible. About peptides, most of the observed rotational angles around single bonds deviated less than $\pm 12°$ from the staggered forms,[7] showing that the first assumption is reasonable. By this assumption the calculation was very simplified.

The rotational angles around single bonds in the five membered ring were fixed because of their characteristic circumstances of making a ring structure. Concerning the *p*-bromobenzoxyl group in the compounds the rotations around the single bonds were disallowed, because the group was regarded as a plane due to strong double bond character.

As the other assumption, the fixed bond angle and fixed bond length model was introduced to carry

Table I. Bond Lengths

Bond	Length (Å)	Bond	Length (Å)
C–C	1.533[a]	O=C	1.240[a]
H–C (sp^3)	1.095[a]	O–C (sp^2)	1.440[b]
H–C (sp^2)	1.071[a]	O–C (sp^3)	1.490[b]
C=C	1.335[a]	C–Br	1.875[a]
C=C (benz.)	1.390[a]	O–H	0.950[a]

a) from L.N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, 1963
b) S. Abrahamsson, *Acta Cryst.*, **16**, 409 (1963).

5) S. Abrahamsson, *Acta. Cryst.*, **16**, 409 (1963).
6) P.W. Ramwell, J.E. Shaw, E.J. Corey, and N. Andersen, *Nature*, **221**, 1251 (1969).
7) G. Némethy and H.A. Scheraga, *Biopolymer*, **3**, 155 (1965).

TABLE II. Bond Angles

Bond angle	Value	Bond angle	Value
C-C-C	109.467°	C-O-C	120.0°
C-C-C (ring)	108.0°	C-C-O	103.0° a)
C-C-H	109.467°	C-C-Br	120.0°
C=C-C	120.0°	C=C-H	120.0°
O=C-C	120.0°	C-O-H	108.0° b)

a) S. Abrahamsson, *Acta Cryst.*, **16**, 409 (1963)
b) K.K. Knaell and R.A. Scott, *J. Chem. Phys.*, **54**, 566 (1971)

out more simply the calculation, and the dihedral angle of sp^3 type was always fixed to the value of 109° 28′. The calculation was carried out on these assumptions using various values of bond angles and bond lengths, and the values are listed in Table I and II.

Atomic Coordinates and Energy Equations——In the coordinate system centered on carbon atom C_{i-1}, atomic coordinates of atom C_{i+1} are determined by parameters, such as bond lengths l_i and l_{i+1}, bond angle θ_i and rotational angle ω_i. They are illustrated in Fig. 2. The coordinate system is right handed and it is illustrated in Fig. 3. The coordinates of each atoms are calculated using the equation by Scott and Scheraga.[8]

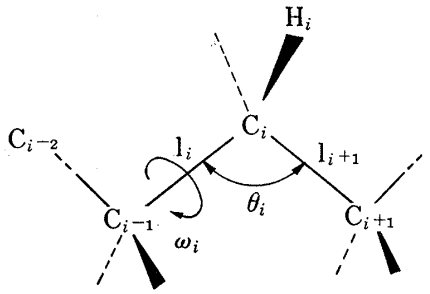

Fig. 2. Various Parameters to determine Coordinates of Atoms

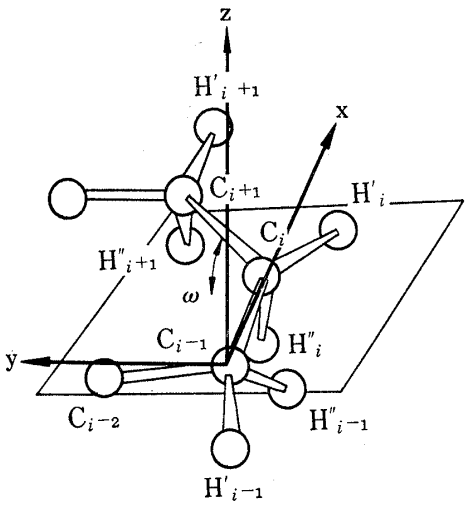

Fig. 3. Coordinate System Centered on C_{i-1}

The intramolecular conformational energy E was given by the following equation.

$$E = E_{ele} + E_{tos} + E_{nonb} + E_{est} + E_{Hb} + E_{st} + E_{be}, \quad (1)$$

where E_{ele}, E_{tos}, E_{nonb}, E_{est}, E_{Hb}, E_{st} and E_{be} represent electronic energy, torsional energy, nonbonded energy, electrostatic energy, hydrogen bonding energy, stretching energy and bending energy, respectively.

In this study some assumptions were introduced for the purpose of rewriting the energy equation in a more simple form. The constant values of the bond lengths and the bond angles lead the following equations.

$$E_{st} = 0, \quad E_{be} = 0. \quad (2)$$

The torsional energy E_{tos} was attributed to the energy barrier of internal rotations around the single bonds due to exchange interactions of electrons in bonds adjacent to the bond about which internal rotation takes place.[9] The equation was

$$E_{tos} = \sum_i U_i, \quad (3)$$

where U_i was given for usual single bonds

8) R.A. Scott and H.A. Scheraga, *J. Chem. Phys.*, **44**, 3054 (1966).
9) L. Pauling, "The Nature of the Chemical Bond," 3rd ed., Cornell University Press, Ithaca, New York, 1960, p. 130.

$$U_i = \frac{1}{2}B_i(1+\cos 3\omega_i), \tag{4}$$

or for the single bonds next to double bond (*i.e.*, C_{14}–C_{15}, C_{16}–C_{17} in Fig. 1)

$$U_i = \frac{1}{2}B_i\left(1+\cos\left(3\omega_i-\frac{\pi}{3}\right)\right), \tag{5}$$

where B_i was the height of the rotational energy barrier and ω_i was the rotational angle about a single carbon-carbon bond. In this study it was assumed that for values of rotational angles about single bonds the three values were only allowed to make the potential barrier minimum. Therefore about all single bonds,

$$U_i = 0 \tag{6}$$

was obtained.

The other two simplifications of the energy equation are the followings. The calculations of the electronic energies for various conformations would need prohibitive amount of computer time. Thus, it was assumed that all sterically allowed conformations had same electronic energies, *i.e.*

$$E_{\text{ele}} = \text{const.} \tag{7}$$

And it seemed that prostaglandin $F_{1\beta}$ derivative had no hydrogen bond, so that it was not necessary to calculate the hydrogen bonding energy. For these reasons the energy equation was simplified to

$$E = E_{\text{nonb}} + E_{\text{est}} + \text{const.}, \tag{8}$$

so that the nonbonded energies and the electrostatic energies were calculated to evaluate the relative intramolecular conformational energies.

In treating the nonbonded interactions between all pairs of nonbonded atoms, the so-called Lennard-Jones "6–12" potential function was used. This potential function between nonbonded i and jth atoms is of the form[10]

$$U_{ij} = \frac{d_{ij}}{r_{ij}^{12}} - \frac{e_{ij}}{r_{ij}^{6}}, \tag{9}$$

where

$$e_{ij} = \frac{\frac{3}{2}e(\hbar/m^{1/2})\alpha_i\alpha_j}{(\alpha_i/N_i)^{1/2}+(\alpha_j/N_j)^{1/2}}, \tag{10}$$

$$d_{ij} = e_{ij}\, r_{\min}/2, \tag{11}$$

and where e is the electronic charge, m the electronic mass. α_i the atomic polarizability of the ith atom. N_i is a parameter for the ith atom which had been discussed by Scott and Scheraga,[11] and $r_{\min}$ the sum of van der Waals radii of atom i and j.

The nonbonded energy is the form

$$E_{\text{nonb}} = \sum_{i,j} U_{ij}, \tag{12}$$

and is a sum over all the pairwise nonbonded interaction in the molecule. But about all conformations the nonbonded interactions between atoms separated by two bonds have same values which generated no difference by the rotation about the single bond. Therefore, nonbonded interactions were calculated between atoms separated by three or more bonds.

As shown in Eqs.(9), (10), (11) the nonbonded energy is affected by the values of van der Waals radii of atoms. In most studies Pauling and Corey's values of van der Waals radii (PC parameters[3]) are used, but there are some studies which pointed out that the PC parameters were too large to explain properties of molecules especially in the liquid state,[12,13] so that it is important to estimate the optimum values of van der Waals radii for various atoms. Therefore the nonbonded energies were calculated by using various sets of values of van der Waals radii in this study.

The equation for the electrostatic energy is

10) R. A. Scott and H.A. Scheraga, *J. Chem. Phys.*, **45**, 2091 (1966).
11) R.A. Scott and H.A. Scheraga, *J. Chem. Phys.*, **42**, 2209 (1965).
12) C.P. Smyth and K.B. McAlpine, *J. Am. Chem. Soc.*, **57**, 979 (1935).
13) E. Heilbronner and R. Gerdil, *Helv. Chim. Acta*, **39**, 1996 (1956).

$$E_{est} = \sum_{i,j} \frac{332.0\, q_i q_j}{D\, r_{ij}} \qquad (13)$$

where D is the dielectric constant and q_i is the partial charge of ith atom. In this study $D=4.0$ was used[10] and partial charges were calculated from bond moments. Various values of parameters used in this study are listed in Table III, IV, and V.

Table III. Parameters for Calculating Nonbonded Potential

Atom	$\alpha \times 10^{24}(cm^3)$[a]	N	Atom	$\alpha \times 10^{24}(cm^3)$[a]	N
C	0.93	5.2	H	0.42	0.9
O	0.84	7.0	Br	3.34	21.8
O (ester)	0.64	7.0			

a) J. Ketelaar, "Chemical Constitution," Elsevier Publ. Co., New York, 1958, p. 91

Table IV. Bond Moments and Partial Charges on Their Bonds

Bond	Bond moment[a]	Charge (in units of "e", the electronic charge)
H-C (sp^3)	0.30	0.057
H-C (sp^2)	0.30	0.058
H-O	1.53	0.335
C-O (sp^3)	0.86	0.120
C-O (sp^2)	0.86	0.122
C=O	2.40	0.403
C-Br	1.38	0.153

a) C.P. Smyth, *J. Phys. Chem.*, **40**, 209 (1937)

Table V. Hard Sphere Radii and van der Waals Radii

Hard sphere radii[a]		C=1.45	O=1.30	H=0.95	Br=1.70
Van der Waals radii	A)	C=1.45	O=1.30	H=0.95	Br=1.70
	B)[b]	C=1.50	O=1.35	H=0.95	Br=1.70
	C)	C=1.60	O=1.41	H=1.10	Br=1.85
	D)[c]	C=1.70	O=1.52	H=1.20	Br=1.95
	E)	C=1.85	O=1.55	H=1.30	Br=2.03

a) K.K. Knaell and R.A. Scott, *J. Chem. Phys.*, **54**, 566 (1971)
b) G.N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan, *J. Mol. Biol.*, **7**, 95 (1963)
c) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964); PC parameter

Result

Eighty-four forms of sterically allowed conformations were found, using the values of the hard sphere radii listed in Table V. The single bonds possible to rotate are only C_3–C_4, C_4–C_5, C_{17}–C_{18}, C_{11}–O'_1, C_{13}–O'_2 (Fig. 1), and other single bonds within the molecule are not allowed to rotate around the bonds because of prohibitive intramolecular steric hindrances. The rotations around the bonds C_1–O_2 and C_{21}–C_{22} are obviously possible but generate no different conformations because they are the terminal bonds in the saturated chains. About rotational angles around the single bonds C_{11}–O'_1 and C_{13}–O'_2 two values are allowed, one is $\omega=180°$ (*trans* conformation) the other is $\omega=60°$ or $\omega=300°$ (*gauche* conformation). About the single bond C_{17}–O'_3 the rotation is not allowed and only allowed is $\omega=60°$ (*gauche* conformation).

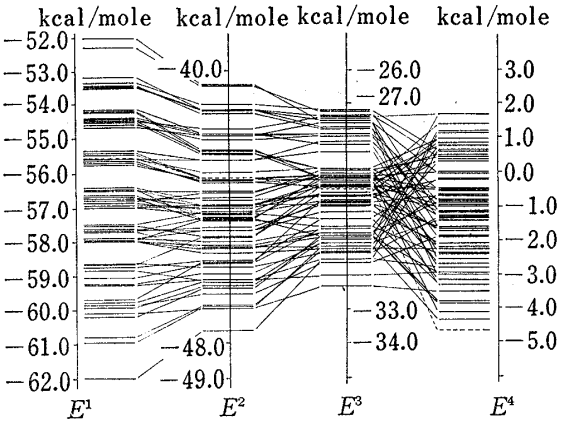

Fig. 4. Energy Diagram of 84 Sterically allowed Conformations

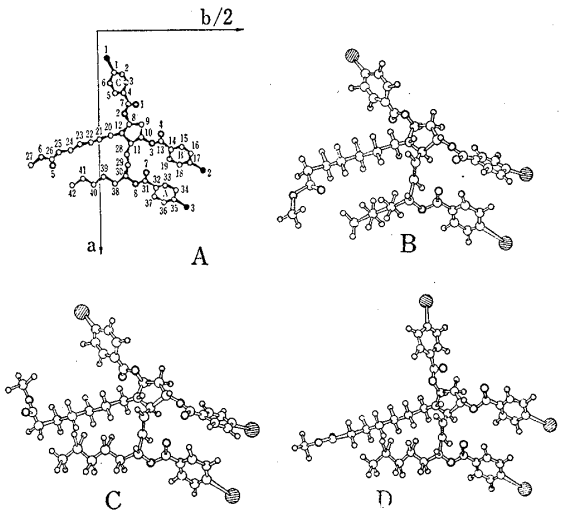

Fig. 5. View of Conformations

A: conformation determined by X-ray diffraction study[a]
○: O, ○: C, ●: Br
B: calculated most stable conformation using smaller van der Waals radii than PC parameters
C: calculated most stable conformation using van der Waals radii equal to PC parameters
D: calculated most stable conformation using larger van der Waals radii than PC parameters
▨: double bond, ◍: Br, ○: C, ○: O, ○: H
a) S. Abrahamsson, *Acta Cryst.*, **16**, 409 (1963)

About the double bond in the side chain of $PGF_{1\beta}$ derivatives ($C_{15}=C_{16}$ of Fig. 1), the calculation was carried out under the condition of $\omega=180°$. The calculation was also carried out under the condition of $\omega=0°$, but sterically allowed conformations were not found in this calculation by using the smaller values of the hard sphere radii of C_{14} and C_{17}.

Calculations on the nonbonded energy and the electrostatic energy were performed for the 84 forms of sterically allowed conformations. The energy diagram calculated by various sets of values of van der Waals radii is shown in Fig. 4, where E^1, E^2, E^3 and E^4 correspond to the values of E in Eq. (8) using the four sets B), C), D) and E) listed in Table V, respectively. The dashed lines of Fig. 4 are the energy levels of the conformation determined from X-ray diffraction study. As shown in Fig. 4 energy levels of the sterically allowed conformations place close to each other, and the calculated most stable conformation is altered by the set of values of van der Waals radii used in the calculation of the nonbonded energy. In general, the electrostatic energy is quite smaller than the nonbonded energy.

The view of conformation determined by the study of X-ray diffraction and three forms of the most stable conformations obtained by this computer experiment were illustrated in Fig. 5. Geometrical properties of the most stable conformation obtained by the calculation using the set E) (Fig. 5,D) agree well with the conformation by the X-ray diffraction study (Fig. 5,A).

The time of computation on the FACOM 230-60 electronic computer at Data Processing Center of Kyoto University was about 15 min, including the time required (about 15 sec) for the compiler to translate the program into machine language from the FORTRAN listing.

Discussion

It was shown that the calculated most stable conformation using the set E) of larger values of van der Waals radii than PC parameters agreed quite well with the conformation determined by the X-ray diffraction study on $PGF_{1\beta}$ derivative. This fact seems to show that the set E) has the suitable value to explain properties of the molecule in the solid state. As described in the previous section, it was shown that the five membered ring in the $PGF_{1\beta}$ derivative was a plane, but it was known that the five membered ring of cyclopentan was

not a complete plane,[14] and according to the X-ray diffraction study one carbon atom in the five membered ring was slightly out of the plane.[5] Modified calculations are now in progress to study the forces and the effects on the bond angles, bond lengths and rotational angles.

It was also shown that the conformational energies of sterically allowed conformations were only slightly different to each other, so that existence of the various conformations may be possible in a solution for the molecules containing the saturated chains. Therefore, it is not enough that only the conformation obtained by X-ray diffraction study was used to study the mechanism of physiological activity.

In a solution, no detail study of the optimum values of van der Waals radii for various atoms has been reported. In our preliminary experiment, the values of the dipole moment and their temperature dependences were calculated using the various sets of the values of van der Waals radii which had the same names and values of this paper, and they were compared with the observed data. As the results, it was suggested that the set C) of the smaller values than PC parameters was suitable to explain their behaviour in the solution. The details of the experiment will be reported in future.

Although, in the study on physiological active compounds, it is very important to know the intermolecular interaction especially between physiological active compounds and their receptors, the calculation of the intermolecular interaction is impossible at the present moment by the following reasons. The calculation containing intermolecular interaction may be theoretically carried out, but actually this calculation needs prohibitive amount of computer time. Moreover, about receptors of physiological active compounds, they have not been isolated and their structures have not been reported.

Prostaglandins show physiological activities at extremely low concentration. Therefore, in the prostaglandin solution system which shows activity, the interaction between prostaglandins may be very small and it may be neglected. About another intermolecular interactions, it seems that they make equal contribution to each prostaglandin molecules. By these reasons described above, in this study all of the intermolecular interactions were neglected.

The results applied this method described in this paper on prostaglandins will be used to calculate "the populations of eath conformations" (*i.e.* the probabilities of existence of each conformation), and their probabilities will be compared with biological experimental data to know the relationships between the conformation and the physiological activity. By this method, without calculating intermolecular interaction, the initial attempt to explain the mechanism of physiological active compounds will be performed. This attempt may have many weak points but may be available to study the mechanism of physiological active compounds because of ignorance for receptors.

To make this method more useful it is suggested that it is necessary to calculate the energies involving the hydrogen bonding energy and determine the optimum values for van der Waals radii. The study along these lines is under development in this labolatory.

Acknowledgements The authors wish to thank the Computing Center of Shizuoka Prefectural Government and Data Processing Center of Kyoto University for performance of our calculations.

14) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," Interscience Publishers, a division of John Wiley Sons, Inc., New York, 1965, p. 201.