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Conformational Analysis of Prostaglandins. II.[1] Most Probable Conformation of Prostaglandin A, B, E, and F[2]

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The computer experiments were carried out on the physiologically active compounds of prostaglandins: PGE_1, 15-*epi* PGE_1, 11-*epi* PGE_1, 11,15-*epi* PGE_1, PGA_1, 15-*epi* PGA_1, $PGF_{1\alpha}$, $PGF_{1\beta}$, and PGB_1. Sterically allowed conformations and their conformational energies were calculated, and correlation between the conformation and biological potencies of the prostaglandins was examined.

The pair of isomers, PGE_1 and 15-*epi* PGE_1, has equal number of sterically allowed conformations and similar range of conformational energies, but the distribution of conformational energies and the conformation near the five-membered ring are quite different. Data on 11-*epi* PGE_1 and 11,15-*epi* PGE_1 or PGA_1 and 15-*epi* PGA_1 were also in the same pattern. The conformation near the five-membered ring are restricted except in PGB_1. Orientation of the hydroxyl group bonded to C_{15} affects orientation of the side chain of prostaglandins. Importance of the orientation of the hydroxyl group and of the conformation near the five-membered ring was suggested.

Keywords——computer experiment; conformation; conformational analysis; conformational energy; structure-activity relationship; prostaglandins

Introduction

The interaction between physiologically active compounds and their receptors may be the first stage of the pharmacological action, so that the compounds should take a suitable conformation when they approach the active site of the receptors. The most probable conformation responsible for physiological activities may be the most stable conformation, and there may be some correlation between the population of the most stable conformer and potency of the physiological action.

Prostaglandins were chosen as the model compounds. Prostaglandins are known to be widely distributed in the animal body, have a very high potency, and are responsible for a wide variety of pharmacological actions.[4] Prostaglandins have various isomers including optical isomers, and these isomers show quite different physiological activities. These properties of prostaglandins are suitable for this study. The computer experiments on some prostaglandins and their optical isomers were carried out, and the relationship between the most probable conformation and physiological activities of prostaglandins was examined. The structural formulae of the prostaglandins studied in the present work are illustrated in Fig. 1, in which the numbering of the prostaglandin molecule is also given.

Experimental

All the conformations were systematically generated for prostaglandin, and coordinates of all atoms comprising of prostaglandin were calculated. The conformational energies containing nonbonded energies and electrostatic energies were calculated using calculated coordinates of atoms on sterically allowed confor-

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[1] Part I: A. Murakami and Y. Akahori, *Chem. Pharm. Bull.* (Tokyo), 22, 1133 (1974).

[2] A part of this work was presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1974.

[3] Location: *2-1, Oshika 2-chome, Shizuoka, 422, Japan.*

[4] E.W. Horton, *Physiol. Rev.*, 49, 122 (1962).

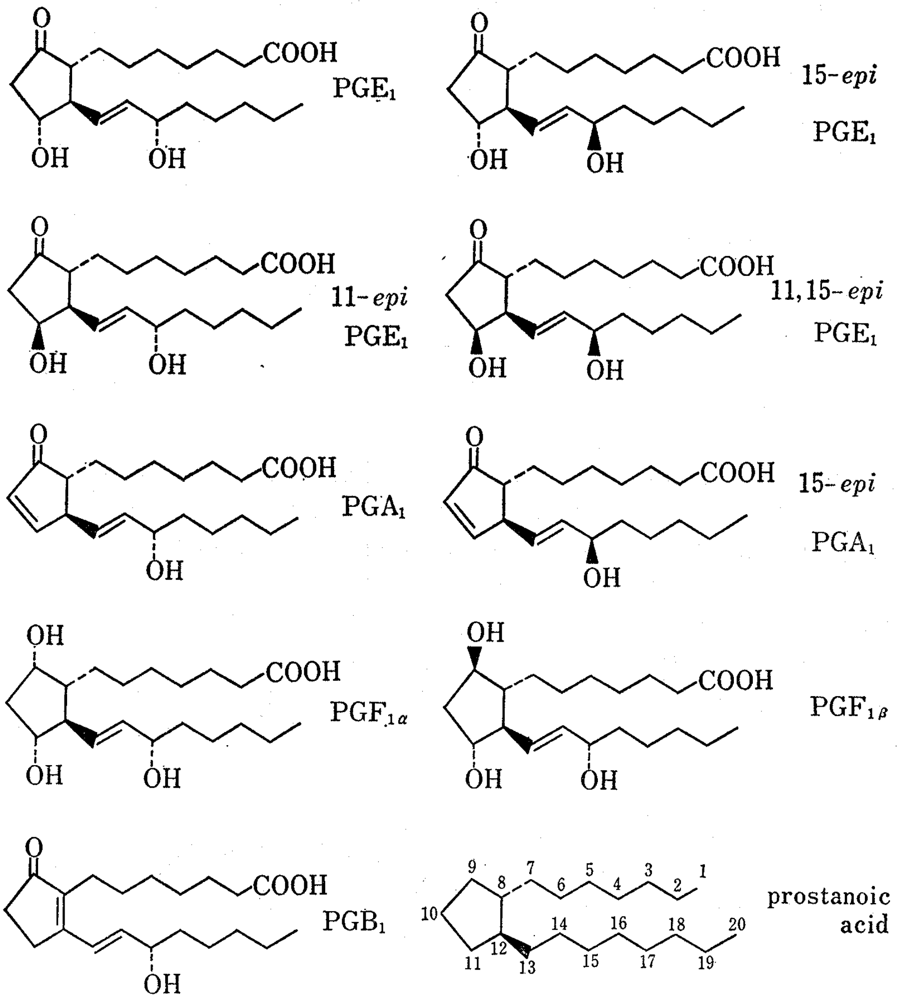

Fig. 1. Structural Formulae and Numbering of Prostaglandins

mations. The equations and the values of parameters used in this study were all the same as in our previous paper.[1] The computation was programed in FORTRAN for use with a NEAC 2200-375 electronic computer (Nihondenki, Tokyo) at Computing Center of Shizuoka Prefectural Government, with a FACOM 230-60 (Fujitsu, Tokyo) at Nagoya University Computation Center, and with a FACOM 230-75 at Data Processing Center of Kyoto University. The time of computation on FACOM 230-60 computer was about 25 min for one run, including the time for compilation.

Result

The number of sterically allowed conformations and the range of conformational energies are listed in Table I, which shows that PGE_1 and 15-*epi* PGE_1 have the same number of sterically allowed conformations, but the range of their conformational energies is slightly different. The results on 11-*epi* PGE_1 and 11,15-*epi* PGE_1 or PGA_1 and 15-*epi* PGA_1 are also in the same pattern.

The sterically allowed conformations were mainly generated by the internal rotation of single bonds within the side chains or of C–OH single bonds. In all prostaglandins, no or small intramolecular steric hindrance was produced by the internal rotation of C_1–C_2, C_2–C_3, C_{15}–C_{16}, C_{19}–C_{20}, and C_{15}–OH single bonds. The internal rotation of the C_7–C_8 single bond within PGE, PGA, and PGB produced no intramolecular steric hindrance but prohibitive intramolecular steric hindrance was produced by the internal rotation of the C_7–C_8 single bond within PGF, because –OH functional group was more bulky than =O functional group. PGB_1

Table I. Number of Sterically Allowed Conformations and Their Energies

Prostaglandins	Number of conformations	Energy (kcal/mol)
PGE_1	210	−41.26—−38.44
15-*epi* PGE_1	210	−41.09—−38.33
11-*epi* PGE_1	70	−40.75—−38.06
11,15-*epi* PGE_1	70	−40.29—−37.96
PGA_1	140	−35.58—−32.97
15-*epi* PGA_1	140	−35.45—−32.92
$PGF_{1\alpha}$	105	−44.16—−40.26
$PGF_{1\beta}$	315	−44.86—−41.07
PGB_1	628	−38.11—−31.96

had two single bonds which did not produce steric hindrance in addition. They were C_6–C_7 and C_{12}–C_{13} single bonds. Other internal rotations produced prohibitive intramolecular steric hindrance, so that only special rotational angles were allowed for these internal rotations. The trans conformations were sterically suitable for the C_{13}–C_{14} double bond in all prostaglandins. These results are summarized in Fig. 2. The single bonds which did not produce steric hindrance are denoted by a curved arrow.

Regarding the conformation near the five-membered ring (from C_7 to C_{15}), only a special kind of conformation was sterically allowed, except in PGB_1. The sterically allowed

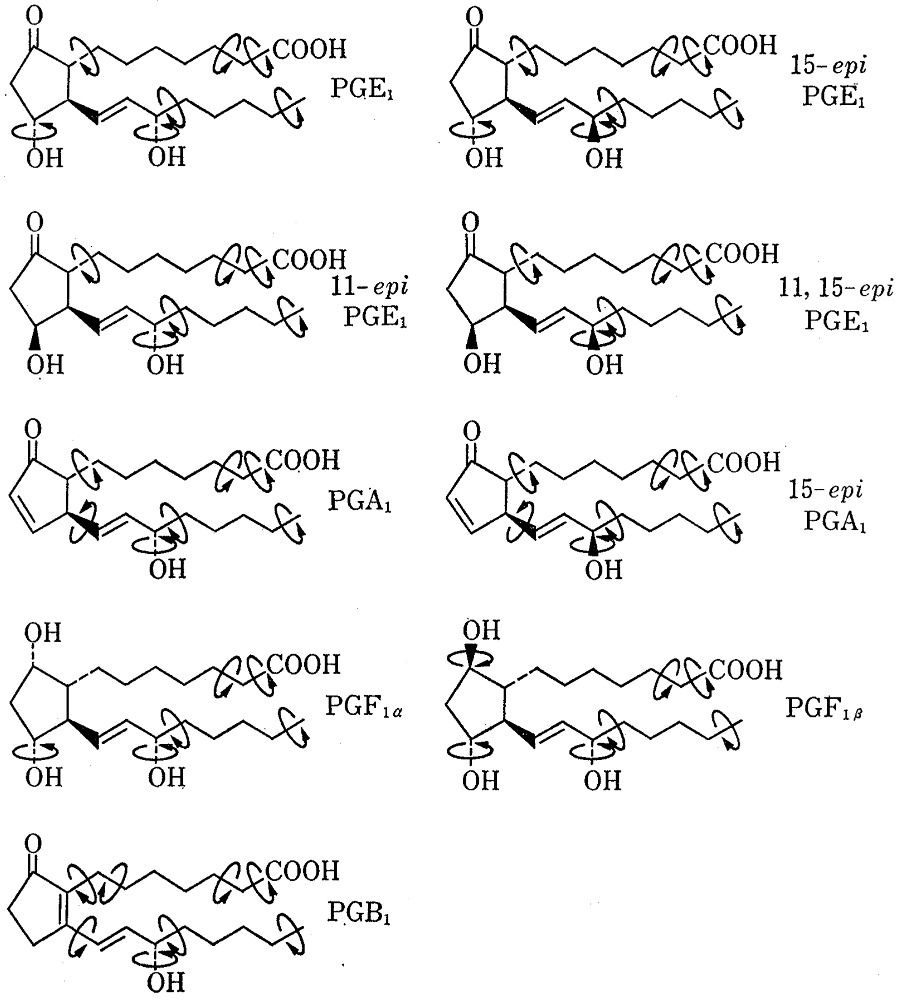

Fig. 2. Internal Rotation which did not Produce Steric Hindrance

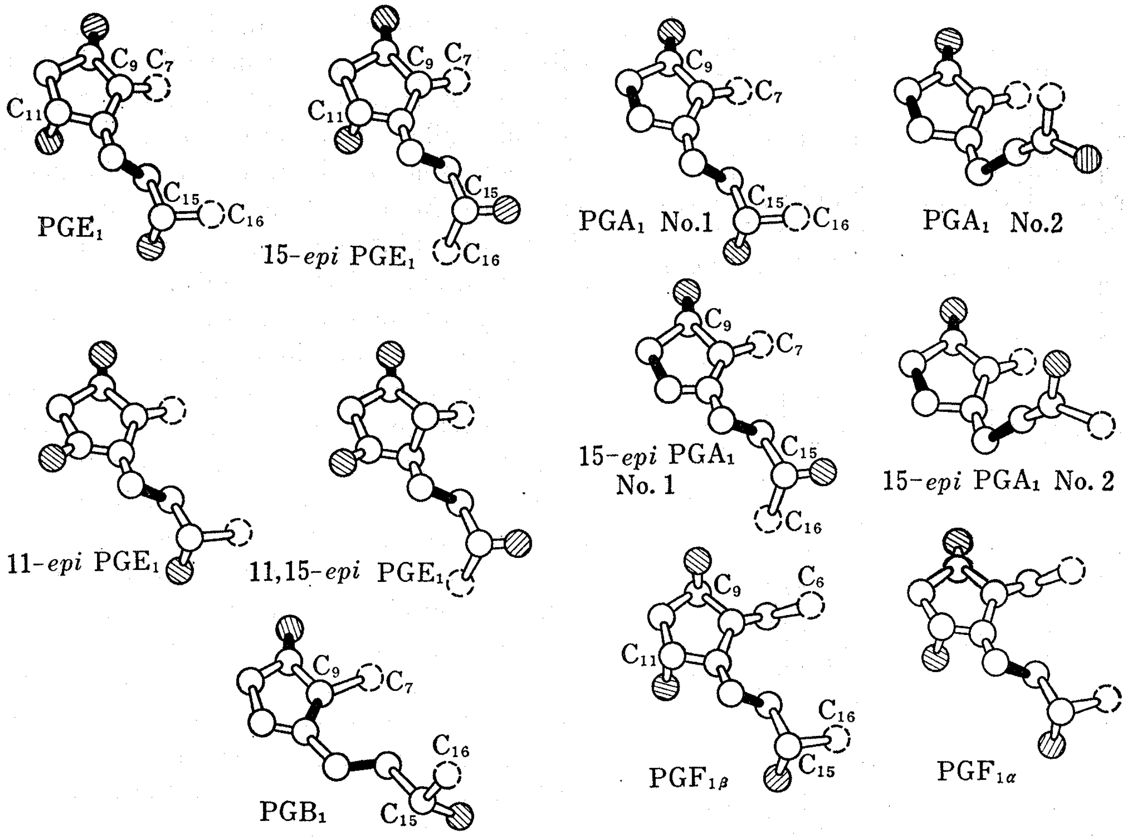

Fig. 3. View of Conformations Near the Five-membered Ring

○ : C atom, ▨ : O atom, // : single bond, / : double bond.

conformations are illustrated in Fig. 3, where only the most stable conformation is illustrated for PGB_1. The two kinds of conformations were sterically allowed for PGA_1 and 15-*epi* PGA_1. Orientation of the hydroxyl group bonded to the C_{15} affected the orientation of the side chain (from the C_{15} to the C_{20}).

The potency of various pharmacological actions of natural and synthetic prostaglandins was reported by Ramwell *et al.*⁵⁾ The conformations of PGB_1 were quite different from the conformations of other prostaglandins, especially near the five-membered ring, and PGB_1 showed no activities in any of biological responses.⁶⁾ In the conformation near the five-membered ring, 15-*epi* PGE_1 is different from PGE_1, and the biological activity of 15-*epi* PGE_1 is less than that of PGE_1. Importance of the orientation of the hydroxyl group bonded to C_{15} may be recognized, but there is poor correlation between the population (probability of presence) of each conformer and biological activities of prostaglandins.

Discussion

Each prostaglandin shows a characteristic distribution of conformational energies. Table I shows that the optical isomers of PGE_1 and 15-*epi* PGE_1 have equal number of sterically allowed conformations and similar ranges of conformational energies, but the distribution of conformational energies of PGE_1 and 15-*epi* PGE_1 was quite different. The data on other pairs of isomers, 11-*epi* PGE_1 and 11,15-*epi* PGE_1 or PGA_1 and 15-*epi* PGA_1, were similar to those for PGE_1 and 15-*epi* PGE_1. The distribution of conformational energies of the prostaglandins is illustrated in Fig. 4.

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6) O. Hayaishi, S. Yamamoto, and T. Miyamoto, *Igaku-no-Ayumi*, **81**, 241 (1972).

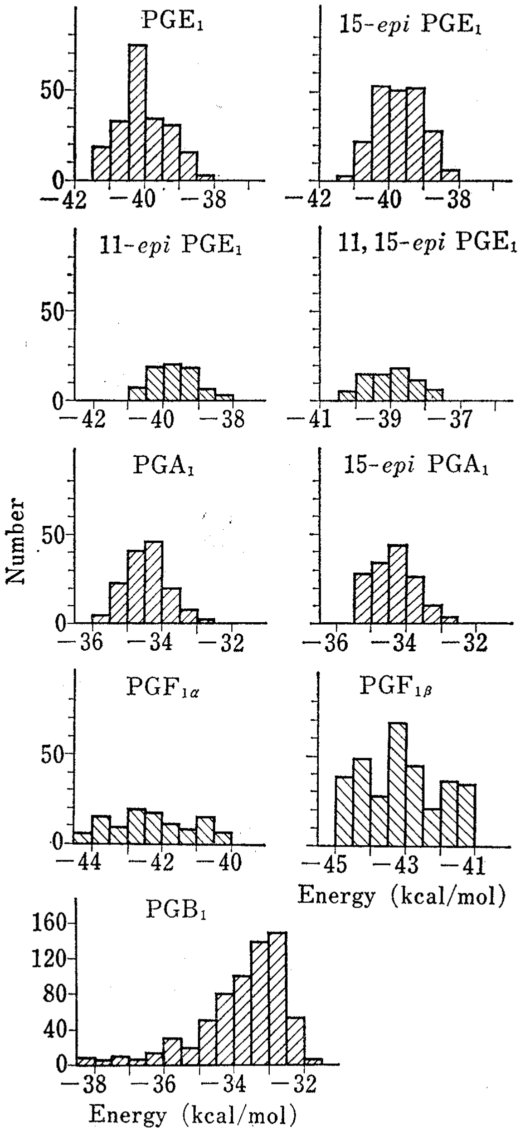

Fig. 4. Distribution of Conformational Energies of Prostaglandins

Many sterically allowed conformations distribute in a narrow range of conformational energies, so that the conformational energy of a sterically allowed conformation is only slightly different (tens or hundreds calories per mol). Therefore, in a solution in which biological activities are exhibited by prostaglandins, not only one conformer but many conformers are present. Not only one conformer but more than two conformers may show biological activities, because there is a poor correlation between the population of each conformer and biological activitites. Importance of the orientation of the hydroxyl group bonded to C_{15} was postulated, and also the importance of the conformation near the five-membered ring, but no quantitative correlation was obtained. It is necessary to give a numerical description on the shapes of a molecule to study the quantitative correlation. These studies are under development in this laboratory.

There is no useful method for studing the conformation in a solution, so that this computer experiment may be a useful method. However, this method has some defects; one is that the intermolecular interactions are neglected. The change of the conformation by the effect of receptors may be important. This conformational change is made by intermolecular interactions. Details were discussed on other intermolecular interactions in our previous paper.[1] The second is that the conformational energy and sterically allowed conformations are influenced by the parameters used for the calculation. Suitable values of van der Waals radii were selected by comparison with the experimental results on dipole moments for some kind of model compounds containing the same functional groups as prostaglandins in a nonpolar solution of carbon tetrachloride, and the aforementioned defect had been overcome using these values. Details will be reported later.

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