However, cysteine inactivated the enzyme more potently under an aerobic condition than under an anaerobic condition (Fig. 3). If the inactivation was caused only by the chelation, the enzyme had to be inactivated to the same extent under both conditions. Additional factor(s) must be considered. As one of the factor(s) we presume a contribution of certain reactive species which are produced from cysteine under an aerobic condition. In fact, Misra reported that superoxide radical, hydroxyl radical and thiyl radical, which were very reactive species, were generated during autoxidation of sulfhydryl compounds in alkaline solution.[7]

The inhibitory effect of cysteine to metalloenzyme is generally recognized as chelation with essential metal of enzyme. However, the results obtained in this study may suggest that the inhibitory effect of cysteine must be also discussed by considering additional factor(s) other than the chelating effect. Further studies to elucidate the additional factor(s) is necessary.

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7) H.P. Misra, *J. Biol. Chem.*, **249**, 2151 (1974).

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Conformational Analysis of Prostaglandins. IV.[1] Relationship between Melting Point and Calculated Conformational Energy of Prostaglandins[2]

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A conformational energy calculation was carried out on nine prostaglandins; PGE_1, 11-epi PGE_1, 15-epi PGE_1, 11,15-epi PGE_1, PGA_1, 15-epi PGA_1, $PGF_{1\alpha}$, $PGF_{1\beta}$, and PGB_1. The number of sterically allowed backbone conformations obtained by the computer experiment is related to the state of prostaglandins. The prostaglandin having a large number of sterically allowed backbone conformations (more than 70) was in an oily state, and the prostaglandin which had a small number of sterically allowed backbone conformations was in a crystalline state. Melting point of prostaglandin is related to conformational energy difference between the mean conformational energy and the lowest conformational energy of all sterically allowed conformations calculated by the computer experiment.

Keywords——computer experiment; melting point; prostaglandins; PGA; PGB; PGE; PGF

Introduction

A relationship between melting point and conformational energies of prostaglandins calculated by the computer experiment was studied, and relationship between states of prostaglandins and number of sterically allowed conformations was also examined. Crystalline state is the state in which exists only one conformer possesing the lowest conformational energy. Oily state is the state including not only one but many conformers. Populations of the conformers are given by statistical mechanics.

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1) Part III: A. Murakami and Y. Akahori, *Chem. Pharm. Bull.* (Tokyo), **25**, 3155 (1977).
2) A part of this work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976.
3) Location: *2-1, Oshika 2-chome, Shizuoka 422, Japan.*

When compounds melt, a state of the compound changes from a crystalline state to an oily state, so that the following relation is established:

$$\varDelta E = E_{\text{oil}} - E_{\text{cry}} \qquad (1)$$

where $\varDelta E$ is the energy required for melting of a compound, E_{oil} is the energy of a compound in an oily state, and E_{cry} is the energy of a compound in a crystalline state. By using the relationship between energy and the state of a compound, E_{oil} and E_{cry} are rewritten in the following form

$$E_{\text{oil}} = \sum p_i E_i = E_{\text{mean}} \qquad (\sum p_i = 1) \qquad (2)$$

$$E_{\text{cry}} = \text{Min}\,(E_i) = E_{\text{lowest}} \qquad (3)$$

where E_i is the energy of the i th conformer and p_i is the probability of the i th conformer. Min(E_i) is the lowest energy in all of sterically allowed conformers. Therefore, Eq. (1) is rewritten using these descriptions.

$$\varDelta E = E_{\text{mean}} - E_{\text{lowest}} \qquad (4)$$

Energy difference $\varDelta E$ is the energy required for melting of a compound. Accordingly, there might be a correlation between the melting point and $\varDelta E$.

Experimental

The computer experiment was carried out on nine prostaglandins; PGE_1, 11-epi PGE_1, 15-epi PGE_1, 11,15-epi PGE_1, PGA_1, 15-epi PGA_1, $PGF_{1\alpha}$, $PGF_{1\beta}$, and PGB_1. All the conformations were systematically generated and coordinates of all atoms comprising prostaglandins were calculated. Sterically allowed conformations which had no or small steric hindrance was selected from generated conformations, and the conformational energies were calculated using coordinates of atoms on sterically allowed conformations. The method of the computer experiment, the equation, and the values of parameters used in this study were all the same as in our previous paper.[4] The van der Waals radii of parameters used in the calculation were H=1.30, C=1.85, and O=1.55. These values are larger than the values reported by Bondi,[5] and the suitable values to explain properties of molecule in a solid state.[4] A backbone conformation is a conformation neglected the orientation of hydroxyl groups of prostaglandins.

The computation was programed in FORTRAN for use with electronic computers, NEAC 2200-375 (Nippon Denki, Tokyo), FACOM 230-60, and FACOM 230-75 (Fujitsu, Tokyo). Melting points of prostaglandins were cited from previous papers (by Corey *et al.*[6] and Krabisch *et al.*[7]).

Result and Discussion

The number of sterically allowed conformations, the number of backbone conformations, conformational energies, and the melting point for each prostaglandin are listed in Table I, which shows that the number of sterically allowed backbone conformations strongly correlates with the state of prostaglandin. The prostaglandin having a larger number of sterically allowed backbone conformations is in an oily state, and the prostaglandin which has a small number (not more than 70) of sterically allowed backbone conformations is in a crystalline state, except 15-epi PGE_1.

A correlation between calculated conformational energies and melting point of prostaglandins are illustrated in Fig. 1. Fig. 1 shows that the calculated energy difference between the mean conformational energy and the lowest conformational energy of prostaglandins is correlated with their melting point. Therefore, the assumption stated in the Introduction seems to be supported.

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4) A. Murakami and Y. Akahori, *Chem. Pharm. Bull.* (Tokyo), **22**, 1133 (1974).
5) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).
6) E.J. Corey, N.H. Andersen, R.M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R.E.K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).
7) S.L. Krabisch, B. Samuelsson, and J. Sjovall, *Acta Chem. Scand.*, **16**, 970 (1962).

TABLE I. Number of Sterically Allowed Conformations, Number of Sterically Allowed Backbone conformations, Conformational Energies, State, and Melting Point of Prostaglandins

Prostaglandins	Number		Energy (kcal/mol)		State	Melting point (°C)
	Sterically allowed conformation	Backbone conformation	Lowest	Mean		
PGE$_1$	210	70	−15.98	−15.43	Crystal	112.8—113.3a)
15-Epi PGE$_1$	210	70	−15.00	−14.41	Oil	—
11-Epi PGE$_1$	70	70	−13.96	−13.55	Crystal	92.5— 93.0a)
11,15-Epi PGE$_1$	70	70	−13.12	−12.69	Crystal	88.6— 89.3a)
PGA$_1$	140	140	−14.03	−13.50	Oil	—
15-Epi PGA$_1$	140	140	−15.00	−12.86	Oil	—
PGF$_{1\alpha}$	105	35	−9.28	−8.75	Crystal	101b)
PGF$_{1\beta}$	315	35	−11.61	−10.92	Crystal	128b)
PGB$_1$	628	628	−14.77	−13.31	Oil	—

a) E.J. Corey, N.H. Andersen, R.M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R.E.K. Winter, *J. Am. Chem. Soc.*, **90**,. 3245 (1968).
b) S.L. Krabisch, B. Samuelsson, and J. Sjovall, *Acta Chem. Scand.*, **16**, 970 (1962).

A similar correlation will be obtained in other homologs, but not with compounds belonging to different homologs because of their different electronic structure and electronic energy.

Rabinowitz *et al.* studied the relationship between melting point and calculated energies of 2 kinds of prostaglandins and some kinds of fatty acids.8) In our study, the calculation of energy was carried out and a correlation was studied on larger number of prostaglandins than did Rabinowitz *et al.*

Different melting point was reported for PGF$_{1\beta}$ (116.4—116.8°) by Corey *et al.*6) and this melting point was not explained by the relationship described in this paper.

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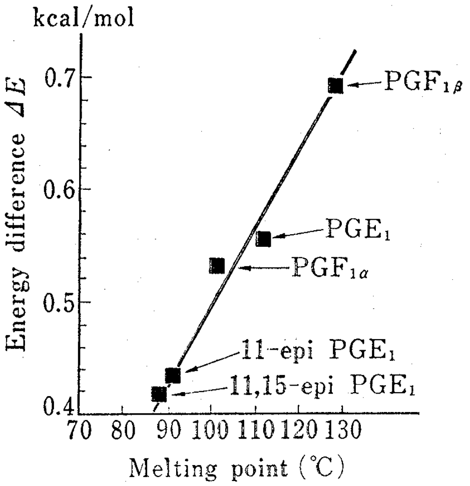

Fig. 1. Correlation between Energy Difference ΔE Calculated by the Computer Experiment and Melting Point of Prostagladins

$\Delta E = E_{\text{mean}} - E_{\text{lowest}}$

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8) I. Rabinowitz, P. Ramwell, and P. Davison, *Nature*, **233**, 88 (1971).