Preferred Conformation of Prostaglandin E_1

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Calculations on the conformational preference of prostaglandin E_1 (PGE_1) have been made using extended Hückel theory and interaction energy calculations, including dispersion bonding. The results predict the energetic preference for a few conformations in which the two side chains are intimately associated, in contrast to random chain arrangements. These results support the previously invoked conformation of PGE_1 used to compare structural features in the potent β-adrenergic agents. It would appear that if structural modification is to be made on these molecules, retaining the basic prostaglandin structure, then the retention of major portions of both chains is essential for the interchain stabilization and presentation of structurally active features.

The prostaglandins are known to be widely distributed in the body, of very high potency, and responsible for a wide variety of pharmacological actions.[1,2] The present state of our knowledge of mechanisms of action of the various prostaglandins does not permit detailed conclusions. It is known with some certainty, however, that prostaglandins have an intimate relationship with catecholamines and the adrenergic system, adenyl cyclase and cyclic AMP, and that they play a hormonal role in some processes such as reproduction.[3]

In a series of studies[4,5] culminating in some theoretical considerations of α- and β-adrenergic activity,[6] we invoked a possible structural relationship between β-adrenergic agents and prostaglandin E_1 to support our hypothesis of structure-activity relationships influencing β-adrenergic activity. We noted that if prostaglandin E_1 was assigned a "reasonable" conformation in regard to the hydroxylated side chain, then a definite similarity of functional group positions with *N*-*n*-propylnorepinephrine, in its calculated preferred conformation, was evident. This relationship was based on the hypothesis that an onium group is nonessential for β-adrenergic activity.[6]

In spite of the large numbers of studies regularly appearing on the prostaglandins, very little attention has been devoted to their structure. Abrahamsson has reported on the conformation of prostaglandin $F_{2\alpha}$.[7] They analyzed the tri-*p*-bromobenzoate methyl ester crystal using X-ray analysis. The proximity of the faces of two of the benzene rings is such that the side-chain conformations observed are likely a function of benzene-benzene interaction and not necessarily the conformation to be found in the natural prostaglandin.

The conformation prediction of prostaglandin E_1 was undertaken in this study to attempt to support our previously hypothesized relationship with β-adrenergic agonists and to provide structural information from which relationships with presently known and future biological activity data may be correlated.

Experimental Data

A number of assumptions must necessarily be made in a calculation of this kind. We have attempted to utilize existing experimental data as intelligently as possible in order to keep such assumptions to a minimum.

We have assumed, first, on the basis of experimental investigations by Brutcher, *et al.*,[8] that the cyclopentanone ring is maintained in either of the 2 possible half-chair conformations. Extended Hückel (EHT) calcns using truncated side chains of 2-C atoms each were next carried out to determine conformational preferences of atoms close to the ring. These calcns indicated that the second side chain comes off the cyclopentanone ring such that the H at C_{12} eclipses the C_{13}–C_{14} double bond, as expected. It was also predicted that the first, or carboxyl-contg, side chain shows no preference between coming off the ring trans to the C_8–C_9 bond or trans to the C_8–C_{12} bond. This result was assumed thereafter.

The total relative energy of a given conformation can now be assumed to be a sum of 2 parts: first, a conformational energy arising from the twisting of either side chain into a gauche conformation, and secondly, the interaction energy between the 2 chains through long-range forces. It was assumed that an energy increment of 0.6 kcal/mole[9] is associated with the formation of a gauche conformation about a CH_2CH_2 fragment.

Since no experimental information is available concerning internal rotation about the C_{14}–C_{15} and C_{15}–C_{16} bonds, extended Hückel calcns were carried out on isolated chains. These calcns indicated that the C_{15}–H bond eclipses the double bond. Although no good estimate of the energy of the other conformations involving the C_{15}–O or C_{15}–C_{16} bonds eclipsing the double bond can be made since the EHT calcns exaggerate steric effects, these lie significantly higher in energy and also lead to decreased chain-chain interaction energy. For this reason, the C_{15}–H bond was held eclipsed to the C_{13}–C_{14} bond in all calcns. Finally, the EHT results, coupled with studies on 2-BuOH (for which some experimental conformational data are known[10]) predict that the C_{15}–C_{16} bond will prefer a trans orientation to the C_{14}–C_{15} bond, and that C_{15}–C_{16} trans to the C_{15}–O or C_{15}–H bonds will result in approximate energy increments of 0.4 and 0.8 kcal/mole, respectively. It should be emphasized that all EHT calcns described in this paragraph were carried out on isolated chain fragments so that no perturbation by the second chain has been included.

The interaction energy between the 2 chains can be written approximately as a sum of first- and second-order perturbation terms. The monopole-bond polarizabilities method of Claverie and Rein,[11] elaborated by Huron and Claverie,[12] was utilized for the actual numerical calculations. Within this approximation, the interaction energy can be written in terms of the charge distributions of the 2 chains approximated by point charges centered at the nuclei and the polarizabilities of the bonds, together with an algorithm for computing the repulsive energy component as the charge distribution begin to overlap. The actual working equations are given below.

For convenience we designate the 2 chains by subscripts 1 and 2 and let N_i and B_i be the number of atoms and bonds, respectively, in chain i. Then the long-range interaction energy can be written as a sum of electrostatic (E_e), polarization (E_p), and a dispersion (E_d) components. The explicit formulas are as follows.

$$E_e = \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} \frac{q_i q_j}{R_{ij}} \tag{1}$$

$$E_p = -\frac{1}{2} \sum_{k=1}^{B_1} \mathcal{E}_k \bar{\bar{A}}_k \mathcal{E}_k - \frac{1}{2} \sum_{l=1}^{B_2} \mathcal{E}_l \bar{\bar{A}}_l \mathcal{E}_l \tag{2}$$

$$E_d = -\frac{1}{4} \times \frac{I_1 I_2}{I_1 + I_2} \sum_{k=1}^{B_1} \sum_{l=1}^{B_2} R_{kl}^{-6}\, Tr[\bar{\bar{T}}_{kl} \bar{\bar{A}}_k \bar{\bar{T}}_{kl} \bar{\bar{A}}_l] \tag{3}$$

In eq 1, q_i is the charge at nucleus i and R_{ij} is the distance between the nuclei i and j. The quantity $\mathcal{E}_k$ in eq 2 is the electric field at the center of bond k (in chain 1) due to the monopole charges q_j of molecule 2

$$\mathcal{E}_k = \sum_{j=1}^{N_2} q_j \mathbf{R}_{jk} R_{jk}^{-3} \quad (4)$$

where R_{jk} is the distance from nucleus j to the midpoint of bond k, and $\mathbf{R}_{jk}$ is the vector of magnitude R_{jk} pointing from center j to the bond midpoint k. The quantity $\bar{\bar{A}}_k$ is the polarizability tensor for bond k.

The dispersion equation, eq 3, contains the average excitation energies, I_1 and I_2 approximated by the ionization potentials and a factor x which corrects for the fact that the usual London equation ($x = 1$) gives a result which is too small. The quantity R_{kl} is the distance between the midpoints of bonds k and l, and the tensor $\bar{\bar{T}}_{kl}$ is defined as

$$\bar{\bar{T}}_{kl} = 3\frac{\mathbf{R}_{kl} \cdot \mathbf{R}_{kl}}{R_{kl}^2} - 1 \quad (5)$$

where 1 is the unit matrix. The symbol *Tr* in eq 3 indicates the trace of the quantity in parenthesis.

The final contribution which must be considered is the repulsion resulting from overlap of the charge distributions of the 2 chains, which we designate as E_r. We use the Kitaygorodsky repulsion[13] derived empirically from crystal energies of hydrocarbons, but slightly modified by Huron and Claverie. This relation is

$$E_r = 30{,}000 \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} \exp[-5.5\, R_{ij}(V_i V_j)^{-1/2}] \quad (6)$$

where V_i is the van der Waals radius of atom i.

Standard bond lengths and angles are assumed for the 2 side chains. The ionization potentials in eq 3 are taken as 0.4 and 0.37 atomic units, the bond polarizabilities are taken from Denbigh[14] or le Fevre[15] and the van der Waals radii are 1.1, 1.6, and 1.4 Å, respectively, for H, C, and O. The monopole charge distribution is derived from iterative extended Hückel calcns[16] on isolated chains followed by a Mulliken population analysis.[17] The IEHT method was not utilized for conformational calcns since it requires a good deal more computer time with no promise of producing significantly better results. The charges are given in Table I.

Results

The results of the numerical calculations are given in Table II. The notations utilized are summarized below.

The 2 possible half-chair conformations of the cyclopentanone ring are denoted by D and U, the former indicating the conformation in which the angle between the bond vectors C_8-C_7 and C_{12}-C_{13} is a maximum. This angle is a minimum for the conformations labeled U.

The basic conformation to which all others are referred is that for which the alkyl parts of the side chains are in an all-trans configuration, with the carboxyl chain trans to the C_8-C_9 bond. The C_{13}-C_{14} double bond eclipses the C_{12}-H and C_{15}-H bonds, and the pentyl group (C_{16}-C_{20}) is taken to be trans to the C_{14}-C_{15} bond. Gauche conformations arising from this basic structure are listed in Table I by clockwise or counterclockwise (c or cc), indicating rotation about the denoted bond. To carry out these rotations properly, the molecule is assumed oriented such that the cyclopentanone ring is at a maximum distance from an observer, and the side chains are directed toward him, with the carboxyl chain on the left, as shown in Figure 1.

The energies E_e, E_p, E_d, and E_r are the components of the chain-chain interaction energy as discussed in the previous section, E_c is the conformational correction due to formation of gauche structures, and E_t is the total of these five values. All results are given in kilocalories per mole.

The values given in Table II are the predicted results for the lowest lying 12 conformations. These were selected from a study in which over 400 conformations were examined. It is felt that this table includes all the low lying configurations for prostaglandin E_1. It should be noted that we have not found any conformation lying within at least 3 kcal/mole of the preferred mode in which there is any evidence of H bonding.

It is evident from the results that the role of intramolecular forces is a very important one in determining the favorable conformations. This is strikingly illustrated by considering the basic structure and the two gauche configurations arising from clockwise or counterclockwise rotation about the C_{17}-C_{18} bond. Clockwise rotation leads to a much more favorable positioning of the chains which is manifested by a large increase (in absolute magnitude) in dispersion energy. This is partially compensated by a concomitant increase in the repulsion, the net effect being a more favorable chain-chain interaction energy of 1.55 kcal/mole. Subtracting 0.6 kcal/mole due to the formation of a gauche structure leads to a net gain of 0.95 kcal/mole, making this conformation the most favorable of all those examined. Counterclockwise rotation, on the other hand, leads to a net gain in chain-chain interaction energy of only 0.30 kcal/mole, so that this configuration is actually less favorable than the basic one when the conformational component is added. These two gauche conformations are essentially degenerate in the absence of chain-chain interactions, so that the latter effect has led to a splitting of 1.25 kcal/mole.

Table I. Calculated Side Chain Atomic Charges

Atom	q	Atom	q
C_1	0.254	C_{13}	−0.031
Carbonyl O	−0.274	H	0.045
Hydroxyl O	−0.399	C_{14}	−0.035
Hydroxyl H	0.215	H	0.045
C_2	0.018	C_{15}	0.048
H's	0.067	H	0.059
C_3	−0.030	Hydroxyl O	−0.382
H's	0.034	Hydroxyl H	0.158
C_4	−0.054	C_{16}	−0.031
H's	0.027	H's	0.036
C_5	−0.054	C_{17}	−0.054
H's	0.027	H's	0.027
C_6	−0.054	C_{18}	−0.054
H's	0.027	H's	0.027
C_7	−0.054	C_{19}	−0.054
H's	0.027	H's	0.027
		C_{20}	−0.071
		H's	0.024

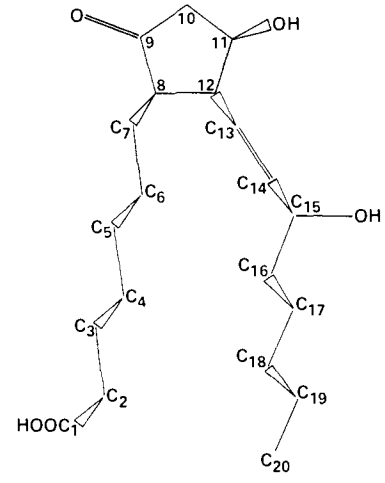

Figure 1. The prostaglandin E_1 molecule.

Table II. Conformational Energy Results[a]

Ring	Chains	E_e	E_p	E_d	E_r	E_c	E_t
U	C_{17}-C_{18}^{c}	0.06	−0.08	−7.37	4.77	0.60	−2.02
D	C_6-C_7^{cc}; C_{15}-C_{16}^{c}	0.01	−0.09	−3.16	0.74	1.00	−1.50
U	C_7-C_8^{c}; C_{15}-C_{16}^{c}	0.00	0.00	−2.52	0.77	0.40	−1.35
U	C_7-C_8^{c}	0.00	0.00	−1.81	0.68	0.00	−1.13
U	Basic	0.08	−0.03	−4.91	3.79	0.00	−1.07
U	C_4-C_5^{c}	0.11	−0.05	−5.62	4.13	0.60	−0.83
U	C_4-C_5^{c}; C_5-C_6^{c}	−0.13	−0.18	−6.50	4.51	1.50[b]	−0.80
U	C_{17}-C_{18}^{cc}	0.07	−0.03	−5.23	3.82	0.60	−0.77
U	C_7-C_8^{c}; C_{15}-C_{16}^{cc}	0.00	−0.01	−2.23	0.68	0.80	−0.76
U	C_{15}-C_{16}^{cc}	0.08	−0.05	−6.69	5.12	0.80	−0.74
D	C_4-C_5^{cc}; C_6-C_7^{cc}	−0.11	−0.07	−1.77	0.11	1.20	−0.64
D	C_7-C_8^{c}	−0.03	−0.01	−0.58	0.07	0.00	−0.55

[a] See text for a discussion of terminology; c indicates clockwise rotation; cc, counterclockwise. Values given in kilocalories per mole. [b] This conformation involves gauche configurations in two consecutive C–C bonds and is considered less favorable than a random double gauche configuration. We have arbitrarily assigned a conformational contribution of 1.5 kcal/mole to this configuration.

Discussion

In carrying out the calculations described in this paper, we have attempted to make use of available experimental data and to make all assumptions as reasonable as possible. This does not leave the present study free of criticism. It is unfortunate that the number of assumptions made must necessarily be so large, but if the results reported here are viewed as preliminary and suggestive only, we feel they should be of significant aid in interpreting the pharmacological properties of prostaglandin E_1.

It should be pointed out at this time that one assumption which has been made is considerably less valid than the others. This is the assumption that the 2 possible half-chair conformations of the cyclopentanone ring have equal energies, aside from chain-chain interaction. It is probable that the U conformations are somewhat more favored in that such configurations bring C_7 more closely into a cis-type arrangement with respect to the carbonyl group. The cis conformation of propionaldehyde is more stabile than the gauche by about 0.9 kcal/mole,[18] so that the U conformations may be further favored in this study by perhaps 0.2-0.3 kcal/mole. Therefore, the exact nature of the second lowest lying conformation may be somewhat doubtful.

The results of this study indicate that the U-type conformations of prostaglandin E_1 show a distance between the ring and unsaturated chain hydroxyl oxygen atoms of about 5.1 Å, which is the same as the O–O separation in active β-adrenergic agonists. These 2 O's are considered vital in binding the β-adrenergic agent to the receptor site, so that the activity of prostaglandin E_1 is not surprising, in that we have previously speculated that the presence of an onium group does not appear to be essential for efficacious β-adrenergic agents.[6] These results then support our hypothesis concerning β-adrenergic activity.

The calculations indicate that a definite pattern or patterns of atoms involving the chains and the rings prevails by virtue of the dispersion interactions between chains, molding each other into a few fairly rigid arrangements. If dispersion bonding between chains was not significant, then the chains would assume isolated independent arrangements. In this case the energetic ease of formation of gauche conformations of each chain would not permit either chain to present to a receptor a prominent or dependable pattern of atoms. The molecule would likely resemble a fatty acid or long-chain alcohol as far as nonspecific biological activity. It is also possible now to explain why chain modifications found in the prostaglandin series can have such a profound effect on activities. These changes likely influence interchain dispersion, hence conformation.

Two observations can be made upon consideration of these results. First, in addition to defining what we have predicted to be the β-adrenergic pattern in the ring and alcohol side chain, another pattern emerges involving the ring and carboxyl side chain. In most of the prominent conformers predicted, the distance separating the ring carbonyl O atom and an O atom of CO_2H is about 10.5 Å. This is identical with the interoxygen distance previously predicted for several active 3,20-keto steroids.[19] The significance of this predicted congruence and possible common biological activities remains to be demonstrated.

The second observation concerns a rationale for the design of compounds with PGE_1 activity of a more potent or more selective nature. It is proposed from these studies that the 2 chains stabilize each other through dispersion interaction. Therefore, if the features of the ring and the alcohol chain are presumed essential for the β-adrenergic-like activity, molecular refinements of the molecule must retain enough of the other chain to permit the interchain conformation stabilizing influence. It might be possible, however, to remove or modify CO_2H, thereby removing an alternate receptor feature and eliminating a particular biological response. It would appear, however, that significant portions of each chain are necessary in minor modifications of PGE_1 in order to retain any of the existing activities.

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