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Conformational Analysis of a Diene Analog of Isocarbacyclin and Prostacyclin

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A diene analog (**2**) of isocarbacyclin has been found to be a potent inhibitor of platelet aggregation. A molecular mechanics calculation study on model compounds of both prostacyclin (**1**) and **2** was undertaken in an attempt to elucidate the stereochemical properties and to find the active conformers. At first the ring structures were investigated, then the directions of the α -chain and finally the entire model compounds were studied. A working hypothesis that four functional groups, consisting of a carboxyl group of the α -chain, a hydroxyl group at position 11, another hydroxyl group of the ω -chain and a π -electron system at the 5, 6 and 6a positions, play an important role in binding with a receptor to elicit activities is presented. Three-dimensional arrangements of these essential functional groups in stable conformations were examined by superimposing the coordinates of the four groups of **2** on those of **1**, because these moieties in the receptor-bound conformations should be identically located in both molecules. Three candidates for the active conformers are presented as a basis for a rational approach to the design of prostacyclin agonists.

Keywords—prostacyclin; isocarbacyclin; π -electron system; conformational analysis; molecular mechanics; MMPI; MM2'; active conformation

Prostacyclin (PGI₂) (**1**) (Chart 1) is a potent, naturally occurring inhibitor of platelet aggregation and a powerful vasodilator.¹⁾ The pharmacological properties of PGI₂ gave rise to numerous expectations as to its therapeutic potential. These ranged from more realistic prospects such as prevention of platelet loss during extracorporeal circulation or hemodialysis to recanalization of occluded arteries and the vague hope of preventing stroke and myocardial infarction.²⁾ From a pharmacotherapeutic point of view, PGI₂ is an unfavorable candidate for drug development. Due to the presence of an enol-ether group that is susceptible to hydrolysis, PGI₂ has a very short half-life of only 3–4 min under physiological conditions.³⁾ Because of this instability and the extreme biological importance of PGI₂, a variety of analogs have been prepared.⁴⁾

Synthetic studies of chemically stable derivatives with functional groups which are considered to be bioisosters of or pharmacologically similar to the enol-ether group have proceeded in our laboratories. Recently, a diene analog (**2**) (Chart 1) was shown to be a potent inhibitor of platelet aggregation with 50% inhibition concentration of 1 ng/ml.⁵⁾ Among the many factors related to the pharmacological activities of a compound, one of the most important is its conformation. Therefore, we have undertaken a conformational analysis of **1** and **2** to identify the 3-dimensional structures responsible for their activities, that is, the active conformations.

It is generally accepted that the carboxyl group of the α -chain, the 11 (*R*) hydroxyl group and the 15 (*S*) hydroxyl group of **1** and related compounds are essential for optimal activity.⁶⁾ We proposed as a working hypothesis that a π -electron system forming a vinyl ether in addition to the hydrophilic groups would serve as another essential functional group. In other

Chart 1

words, we postulated that these four moieties play a significant role in binding with a target receptor to elicit activities. Therefore, active conformations were evaluated in terms of the 3-dimensional arrangements of these moieties in stable conformations.

Molecules such as **1** and **2** consist of too many atoms for molecular mechanics calculations on the whole molecules to be feasible from the viewpoint of computing time. These compounds also have so many rotatable bonds that a tremendous number of initial structures would have to be taken into account. It would be reasonable, therefore, to employ model compounds of **1** and **2** instead. Since **1** and **2** have an identical ω -chain structure, we decided to ignore it. As a result, model compounds **3** and **4** having the carboxyl group of the α -chain, a hydroxyl group at position 11 and a π -electron system were to be analyzed; C12 in place of the ω -chain, including the hydroxyl group at C15, was taken as a dummy essential moiety.

Methods

Generation of Starting Structures—A model builder program named MBCS with a conformational search function was developed and used in order to generate the coordinates of a series of conformers, which were employed as the starting structures for geometry optimizations. The MBCS program uses standard bond lengths and bond angles⁷⁾ to calculate Cartesian and/or internal coordinates of conformers by varying any specified torsional angles automatically at given increments (ex. initial value = 60° and incremental value = 120° for a single bond between an sp^3 carbon atom and another sp^3 carbon atom). During the systematic scans of conformational space, structures with short contacts of atoms are excluded on the basis of van der Waals radii.⁸⁾ Here it is defined that a conformer is judged to have a short contact if the following equation is satisfied.

$$\overline{AB} < (r_A + r_B) \times R_f$$

where $\overline{AB}$ is the distance between nonbonded or nongeminal atoms A and B, r_A and r_B are the van der Waals radii of atoms A and B, respectively and R_f is a reducing factor with a general value of 0.7. As for conformers with a ring structure, any bonds can be rotated systematically (pseudorotation) and the resulting conformations are examined to exclude the structures for which ring formation is impossible. This function is convenient for obtaining a series of starting structures with various kinds of ring puckerings.

Geometry Optimization—Geometry optimizations were performed using the molecular mechanics method because of its relatively short computation time. Calculations of molecules containing a delocalized π -electron system were performed with the MMPI program⁹⁾ and those of other molecules with the MM2' program.¹⁰⁾ In fact, the following approach was adopted to make the calculations more manageable: a stable conformation of a smaller structure or substructure was used as a basic skeleton for construction of starting geometries of a larger structure or parent structure, as shown in Fig. 1. In other words, first the ring structure was investigated, then the direc-

Fig. 1. Schemes to Build up the Model Compounds with Their Substructures, Showing Atom Numbering and Torsional Angles

Based on the stable conformations of **5** and **7**, starting structures of **6** and **8**, respectively, were obtained. Generation of initial structures of **3** and **4** was done using the preferred conformations of **6** and **8**. Torsional angles used are as follows: τ_1 : H-O-C1-C2, τ_2 : O=C1-C2-C3, τ_3 : C1-C2-C3-C4, τ_4 : C2-C3-C4-C5, τ_5 : C3-C4-C5-C6, τ_6 : C4-C5-C6-C7, τ_7 : C5-C6-C7-C8, τ_8 : C6-C7-C8-C9, τ_9 : C7-C8-C9-C6a, τ_{10} : C8-C9-C10-C11, τ_{11} : C9-C10-C11-O, τ_{12} : C10-C11-O-H, τ : A-B-C-D is the angle between the planes A-B-C and B-C-D, with the eclipse form being defined as 0°. Looking along A-B-C-D, a clockwise rotation of the plane B-C-D is considered positive.

tion of the α -chain and finally the entire model compound including the carboxyl group were studied.

Results and Discussion

Stable Conformations

Analysis of 5—The results of a preliminary calculation on cyclopentane with MM2' were used in combination with the MBCS program in order to effectively generate ring structures having diverse puckerings. The bond lengths and angles shown explicitly in Fig. 2 (A) were derived from the results mentioned above and were used instead of standard values. τ_{10} was changed to -25° , 0° and 25° based on the same results. On the other hand, τ_8 and τ_9 were varied to -30° , 0° and 30° , τ_{12} was incremented systematically by -60° , 60° and 180° , and τ_5 and τ_6 were set to 0° and 180° , respectively. τ_5 was defined to be the torsional angle involving one of the three hydrogens at C4 instead of the removed C3. As the coordinates of C5 and C12 were determined spontaneously by the above assignments, τ_7 and τ_{11} did not need to be specified.

Geometry optimization with MM2' was performed on the 46 starting conformers thus obtained to afford 18 independent stable conformers, all conformers having almost constant values for τ_5 and τ_6 , *i.e.*, $-2 < \tau_5 < 2^\circ$ and $174 < \tau_6 < 185^\circ$. Among the 10 lowest energy conformers shown in Table I, the most stable two conformers 5-1 and 5-2 have almost identical 3D-structures except for τ_{12} . Features of the ring structure of these two conformers are as follows. One five-membered ring consisting of C6-C7-C8-C9-O6a has a twist conformation with C7 over the plane (when C8, C9 and O6a are placed on the plane) and C6 slightly under it. The other five-membered ring consisting of C8-C9-C10-C11-C12 also has a twist conformation with C11 over the plane (C11-up) and C12 slightly under it. As described in Table I, conformers with $\tau_{12} = 60^\circ$ are less stable than those with $\tau_{12} = -60^\circ$ and 180° , and

Fig. 2. Geometrical Parameters Derived from Preliminary Calculations and Used by the MBCS Program Instead of Standard Values
(A) 5; (B) 7.

TABLE I. Relative Energies and Torsional Angles of 5 with the Minimum Energies

Conformer No.	$\Delta E^a)$ (kcal/mol)	Torsional angles ($^\circ$)					
		τ_7	τ_8	τ_9	τ_{10}	τ_{11}	τ_{12}
5-1	0	-146	-22	11	16	-156	-67
5-2	0.2	-146	-23	12	16	-156	-176
5-3	0.2	-144	-26	17	-31	-81	-58
5-4	0.3	-157	-7	-5	-17	-84	-68
5-5	0.4	180	-18	26	2	-147	-66
5-6	0.4	180	-18	26	2	-147	-176
5-7	0.5	-148	-19	8	-26	-81	-170
5-8	0.6	150	15	-3	-18	-83	-67
5-9	0.6	150	29	-25	40	-159	-66
5-10	0.6	-146	-23	13	14	-156	57

a) Difference from the lowest energy.

TABLE II. Relative Energies and Torsional Angles of 6 with the Minimum Energies

Conformer No.	$\Delta E^a)$ (kcal/mol)	Torsional angles ($^\circ$)		
		τ_4	τ_5	τ_6
6-1	0	63	-112	175
6-2	0.5	180	-98	174
6-3	0.7	180	120	176
6-4	0.9	-63	119	176
6-5	1.0	-62	-92	174
6-6	1.5	63	93	176

a) Difference from the lowest energy.

structures with $\tau_{12} = -60^\circ$ have slightly lower energies than those with $\tau_{12} = 180^\circ$.

Analysis of 6—Based on the most stable conformer, 5-1, starting conformations of 6 were built using MBCS by increasing τ_5 by 30° , changing τ_4 to $-60, 60$ and 180° , and setting τ_3 to 60° . The resulting structures were subjected to geometry optimizations to find that the stable conformations of 6 can be divided into two major classes with respect to the value of τ_5 . One class includes conformations with $\tau_5 = 80\text{--}130^\circ$ (the conformation is called C3-up because C3 comes over the plane when C4, C5 and C6 are placed on the plane) and the other class contains those with $\tau_5 = -80\text{--}120^\circ$ (C3-down). In each class τ_4 has a preference for $-60, 60$ and 180° as expected, as a result of which there emerge six groups of stable structures of 6. The most stable conformations of each group are reported in Table II. The largest factor

dominating C3-up or C3-down conformations seems to be the steric repulsion between the methylene group at C3 and the lone pairs of oxygen atom (O6a) or the hydrogen atom at C5. A close inspection of Table II indicates that C3-down conformers are a little more stable than C3-up ones.

Analysis of 3—As there are two classes of conformations (C3-up and C3-down) for stable structures of **6**, conformational search was done using both conformers 6-1 and 6-3 to generate starting structures of **3**. τ_5 was changed to -112 and 120° and τ_4 to 63 , 180 and -63° (-62° was used in place of -63° at $\tau_5 = -112^\circ$). Since conformational analysis of carboxylic acids by Allinger and Chang¹¹⁾ showed that τ_2 has a preference for -120 , 0 and 120° and that τ_3 has a preference for -60 , 60 and 180° , these respective values for τ_2 and τ_3 were taken into account at the time of conformational search. τ_1 was set to 180° (O-H being eclipsed against C=O) since conformers of this geometry were considered to have the lowest energies.

Energy calculations were carried out on the 43 starting conformers which were generated by MBCS under the above conditions. Parameters for a carboxylic acid derived by Allinger and Chang¹¹⁾ were employed for computations. Table III summarizes the energies and torsional angles of the conformers with ΔE (difference from the lowest energy) less than 2.0 kcal/mol. The conformations with C3-down are slightly more stable than those with C3-up. There are three favored values for each τ_2 , τ_3 and τ_4 which give the minimum energy structures. This means that the α -chain has considerable conformational flexibility.

Analysis of 7—First, a preliminary calculation on cyclopentene was done with MM2'. The resulting data on the most stable envelope conformation were then employed to generate initial structures of **7**; bond lengths and angles derived from the above calculation are explicitly shown in Fig. 2 (B) and were used with the MBCS instead of standard values. τ_8 and τ_9 had two combinations of angle values, namely, -24 and 24° , and 24 and -24° . On the other hand, τ_{10} was changed to -30 , 0 and 30° and τ_{12} to -60 , 60 and 180° .

After geometry optimizations were performed on the 14 starting conformers generated, 9

TABLE III. Energies and Torsional Angles of **3** with $\Delta E < 2.0$ kcal/mol

Conformation ^{a)} class	Conformer No.	Energy (kcal/mol)	$\Delta E^b)$ (kcal/mol)	Torsional angles ($^\circ$)			
				τ_2	τ_3	τ_4	τ_5
C3-up	3-1	20.1	1.1	0	180	180	118
	3-2	20.2	1.2	-1	-179	-63	121
	3-3	20.6	1.6	-15	-66	-61	114
	3-4	20.8	1.8	-8	-70	179	120
	3-5	20.9	1.9	-1	177	62	94
C3-down	3-6	19.0	0	0	178	62	-112
	3-7	19.6	0.6	-1	71	66	-109
	3-8	19.9	0.9	-118	176	62	-114
	3-9	19.9	0.9	-1	179	180	-112
	3-10	20.2	1.2	114	-179	63	-114
	3-11	20.5	1.5	10	68	178	-109
	3-12	20.6	1.6	-1	-176	-64	-108
	3-13	20.7	1.7	-119	-176	178	-111
	3-14	20.7	1.7	-10	-71	179	-112
	3-15	20.8	1.8	117	-177	-179	-111
	3-16	20.9	1.9	120	-60	179	-110

a) Conformations are divided into two major classes with respect to the τ_5 value. One class has a C3-up conformation (C3 comes over the paper when C4, C5 and C6 are placed on the paper) and the other one has a C3-down conformation. b) Difference from the lowest energy.

independent stable conformers were obtained (Table IV). The cyclopentene ring consisting of C6, C7, C8, C9 and C6a has some geometrical features. In all conformations, torsional angle ϕ (C7–C6–C6a–C9) falls into the range of $0 \pm 1^\circ$, indicating a good planarity of the double bond. As shown in Table IV, each of the conformers 7-1, 7-2 and 7-8 has an envelope conformation with C8-down and each of 7-6 and 7-7 also has an envelope conformation with C8-up, whereas the cyclopentene ring of 7-4 is almost planar. The cyclopentane rings including C8, C9, C10, C11 and C12, on the other hand, have deformed envelope conformations as a whole. Generally speaking, conformers 7-3, 7-4 and 7-5 have C11 under the plane (C11-down) and the rest have C11 over it. More precisely, C12 of conformers 7-1, 7-2 and 7-8 is located downward while C10 of 7-6 and 7-7 is upward. The steric interaction between the hydrogen of OH at position 11 and hydrogens of positions 10 and 12 is considered to disfavor the conformation with $\tau_{12} = 60^\circ$ compared with that with $\tau_{12} = -60$ or 180° . As can be seen from the data in Tables I and IV, the cyclopentane ring (including OH) in the most stable conformer 7-1 has nearly the same 3-dimensional structure as that of 5-1, the most stable conformer of **5**.

Analysis of 8—From the nuclear magnetic resonance (NMR) data obtained for **2** by using the nuclear Overhauser effect technique, the diene (C5a–C5–C6–C6a) moiety is considered to have *s-trans* conformation,¹²⁾ although both *s-trans* and *s-cis* stable conformations are conceivable for it. Since planarity might be deformed in highly substituted dienes, τ_6 was changed to 150 , 180 and 210° . τ_5 was increased by 30° and τ_4 (defined to be the torsional angle involving one of the three hydrogens at position 4 instead of C3) was set to 60° in order to create a series of starting structures of **8** based on the conformer 7-1. Only initial conformational energies were calculated on the structures thus obtained to afford a simple

TABLE IV. Relative Energies and Torsional Angles of **7** with the Minimum Energies

Conformer No.	ΔE^a (kcal/mol)	Torsional angles ($^\circ$)					
		ϕ^b	τ_8	τ_9	τ_{10}	τ_{11}	τ_{12}
7-1	0	-7	-11	11	18	-157	-69
7-2	0	-7	-12	11	17	-158	-177
7-3	0.1	2	3	-3	-19	-82	-71
7-4	0.2	0	0	0	-21	-81	-175
7-5	0.2	-4	-6	6	-25	-80	74
7-6	0.3	7	13	-13	36	-164	-177
7-7	0.4	9	16	-16	37	-163	-68
7-8	0.7	-7	-13	12	17	-158	58
7-9	0.8	-1	-2	2	26	-162	57

a) Difference from the lowest energy. b) ϕ : C6–C6a–C9–C8.

TABLE V. Relative Energies and Torsional Angles of **8** with the Minimum Energies

Conformer No.	Initial structure		Optimized structure				
	Torsional angles ($^\circ$)		ΔE^a (kcal/mol)	Torsional angles ($^\circ$)			
	τ_5	τ_6		τ_5	τ_6	$\tau_6'^b$	τ_7
8-1	90	180	0	90	172	168	-169
8-2	-90	180	0.4	-82	-179	180	-173

a) Difference from the lowest energy. b) τ_6' : C5a–C5–C6–C6a.

TABLE VI. Energies and Torsional Angles of **4** with $\Delta E < 2.0$ kcal/mol

Conformation ^{a)} class	Conformer No.	Energy (kcal/mol)	$\Delta E^b)$ (kcal/mol)	Torsional angles (°)			
				τ_2	τ_3	τ_4	τ_5
C3-up	4-1	17.1	0.3	−116	55	−176	90
	4-2	17.5	0.7	110	−174	−176	90
	4-3	17.5	0.7	−110	174	177	91
	4-4	17.5	0.7	114	−56	178	91
	4-5	17.6	0.8	−109	173	63	84
	4-6	17.7	0.9	108	−178	63	84
	4-7	17.8	1.0	108	−177	−67	106
	4-8	17.8	1.0	−110	173	−62	105
	4-9	18.0	1.2	−125	55	66	84
	4-10	18.0	1.2	86	64	−178	90
	4-11	18.0	1.2	1	−178	180	91
	4-12	18.1	1.3	−88	−65	−178	94
	4-13	18.3	1.5	2	179	61	86
	4-14	18.4	1.6	9	71	−178	92
	4-15	18.5	1.7	17	66	64	88
	4-16	18.5	1.7	−12	−70	177	91
C3-down	4-17	16.8	0	−128	62	−61	−73
	4-18	17.5	0.7	115	−55	176	−81
	4-19	17.7	0.9	109	−174	−61	−78
	4-20	17.8	1.0	−110	175	176	−81
	4-21	17.8	1.0	110	−174	−176	−83
	4-22	17.9	1.1	−114	57	−178	−83
	4-23	18.0	1.2	−109	174	69	−97
	4-24	18.0	1.2	−108	177	−62	−78
	4-25	18.1	1.3	1	179	60	−87
	4-26	18.1	1.3	123	−55	−65	−78
	4-27	18.2	1.4	108	−175	64	−98
	4-28	18.3	1.5	0	−179	−60	−79
	4-29	18.4	1.6	−87	−64	179	−81
	4-30	18.5	1.7	88	65	178	−86
	4-31	18.5	1.7	0	−177	179	−81
	4-32	18.5	1.7	−17	−66	−63	−80

^{a)} Conformations are divided into two major classes with respect to the τ_5 value. One class has a C3-up conformation (C3 comes over the paper when C4, C5 and C6 are placed on the paper) and the other one has a C3-down conformation. ^{b)} Difference from the lowest energy.

energy map for rotations τ_5 and τ_6 . Four conformations with lower energies were selected and subjected to energy optimizations. Two stable conformers 8-1 and 8-2 were obtained as listed in Table V. τ_5 has a preference for $\pm 90^\circ$, showing that C3 is positioned in the perpendicular plane to the paper plane including the diene moiety. This feature of the C3 position is similar to that of **6**.

Analysis of 4—Using the conformers 8-1 and 8-2 in Table V, starting structures were generated by varying τ_3 and τ_4 to -60 , 60 and 180° , and τ_2 to -120 , 0 and 120° , while τ_1 was set to 180° in the same manner as for **3**. The selected 37 initial structures were minimized with respect to energy using MMPI. The energies and torsional angles of conformers with $\Delta E < 2.0$ kcal/mol are described in Table VI. As can be seen in Table VI, there seem to be no significant differences between C3-up and C3-down conformations with regard to energies. The minimum energy structures are obtained with three preferred angle values for each of τ_2 , τ_3 and τ_4 . This indicates that the α -chain has some conformational flexibility.

When the stable conformations of **3** and **4** were elucidated according to the scheme shown in Fig. 1, only the most stable one or two conformations of a substructure were taken into account to estimate the parent structure. The conformers listed in Tables III and IV, therefore, do not represent all of the stable 3-dimensional structures of **3** and **4**, but most of them. Although it would be more sophisticated to consider several stable conformations of a substructure, it takes too much calculation time to do so. In the current state of the energy calculation study the pragmatic strategy employed here^{13,14} was considered to be reasonable for the present purpose.

Active Conformations

Because of the flexibility of the α -chain, it was difficult to predict the active 3-dimensional structures by examining the stable conformations of **3** and **4** separately. It seems to be reasonable that the four essential functional groups consisting of the carboxyl group, the hydroxyl group at C11, C12 in place of the hydroxyl group at C15 and the π -electron system over positions of 5, 6 and 6a are similarly located in the active conformations of **3** and **4**. The positions of COOH of the α -chain, OH at position 11, OH at position 15 and the π -electron system in **3** and **4** were represented by either of the two oxygen atoms, the oxygen atom, the carbon atom at position 12 and the carbon (or oxygen) atoms at positions 5, 6 and 6a, respectively. The conformers listed in Tables III and VI were compared to see if they had similar spatial arrangements of the six atoms by superimposing these atoms with a least-

Fig. 3. Stereoscopic Views of Superposition of **3** (Thick Bonds) and **4** (Thin Bonds)

(A) Conformers 3-3 and 4-13; (B) conformers 3-4 and 4-3; (C) conformers 3-15 and 4-8. Atoms used for superimposition are one of the O atoms of the carboxylic group, C5, C6, O6a (C6a), O11 and C12. Solid circles represent oxygen atoms.

TABLE VII. Geometrical Parameters of the Superimpositions of **3** and **4**

Run	Conformer No.		Atom used for superposition of COOH ^{a)}		Displacement (Å)						
	3	4	3	4	Average	O ^{a)}	C5	C6	O6a (C6a)	O ^{b)}	C12
1	3-3	4-13	O(-H)	O(=C)	0.36	0.50	0.47	0.25	0.47	0.42	0.09
2	3-4	4-3	O(-H)	O(-H)	0.33	0.47	0.38	0.11	0.38	0.43	0.17
3	3-7	4-18	O(=C)	O(=C)	0.36	0.35	0.50	0.21	0.39	0.47	0.22
4	3-7	4-29	O(=C)	O(-H)	0.38	0.47	0.48	0.24	0.44	0.46	0.21
5	3-15	4-8	O(=C)	O(=C)	0.24	0.08	0.46	0.09	0.28	0.37	0.14
6	3-16	4-19	O(=C)	O(-H)	0.37	0.47	0.48	0.21	0.48	0.37	0.18

a) Either of the two oxygen atoms of the carboxyl group of the α -chain. b) The oxygen atom of the hydroxyl group at position 11.

squares fitting.

Table VII summarizes combinations of the conformers with each displacement of the corresponding atoms less than 0.5 Å. As (6 β)-PGI₁, which is formed by hydrogenation of the enol-ether double bond in PGI₂, has higher activity than (6 α)-PGI₁,¹⁵⁾ one of the superimpositions of runs 1, 2 and 5 with C3-up conformation should represent the active conformations. Figure 3 illustrates those superimposed structures, showing that the corresponding atoms discussed above fitted well. From the present analysis the π -electron system seems to play an important role in fixing the C3 position, that is, in regulating the direction of the α -chain. Further speculation is beyond the scope of this paper. The relationship between negative charges at the π -electron system and activities is to be discussed in another paper.

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