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Conformational Analysis of Prostaglandins F_1 Based on Proton Nuclear Magnetic Resonance Spectral Data

Pierre De Clercq,[1] Marc Samson, Dirk Tavernier, Dirk Van Haver, and Maurits Vandewalle*

Department of Organic Chemistry, State University of Ghent, Laboratory for Organic Synthesis, Krijgslaan, 271 (S.4), B-9000 Gent, Belgium

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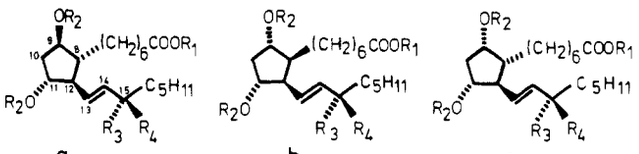
The ^1H NMR spectral parameters of prostaglandin $F_{1\alpha}$ (**5c**), prostaglandin $F_{1\beta}$ (**5a**), 8-*epi*-prostaglandin $F_{1\alpha}$ (**5b**), and derivatives are discussed. Evidence is presented for the occurrence of a restricted number of conformations in the three series. The solvent-dependent variation of the ^1H NMR spectral parameters of prostaglandin $F_{1\alpha}$ is interpreted on the basis of intramolecular hydrogen bonding between the 9- and 11-hydroxyl groups.

Studies of the conformational behavior of prostaglandins are important since it has been shown that there exist strict stereostructural requirements for certain characteristic actions[2a] and for substrate suitability with prostaglandin-metabolizing enzymes.[2b] The restraints applied to the prostaglandin molecule to fix a preexisting receptor site[2c,d] as a stable conformational isomer, or conformer, are so far little understood. Especially x-ray analysis[3] and theoretical calculations[4] have brought some knowledge about the conformation of prostaglandin $F_{1\beta}$ and of prostaglandins of the E series. The results of these studies are generally interpreted on the basis of a conformation (designated "hairpin" [5]) in which the two side chains are closely aligned. In these studies abstraction is made of the molecular environment, as no solvent effects are taken into account. In a series of refined experiments using different techniques Andersen[6] has investigated the occurrence of the "hairpin" conformation in solvated prostaglandins. While a lot of work is done in understanding the relation of the side chains, little attention has been paid to the conformational behavior of the five-membered ring in this molecule.[7] Accurate ^1H NMR spectral data of prostaglandins are scarcely found in the literature (see, however, ref 8). These data should be suited for the study of the conformation of the cyclopentane part of the prostaglandin molecule. We will discuss the ^1H NMR spectral data of the prostaglandins $F_{1\alpha}$, $F_{1\beta}$, and 8-epi-$F_{1\alpha}$ in chloroform-d_1 and methanol-d_4, and we will present evidence for the occurrence of a restricted number of conformations. Hydrogen bonding in aprotic medium, between the 9- and 11-hydroxyl groups of prostaglandin $F_{1\alpha}$ will be proven. The latter fact may be of crucial importance in understanding the ability of prostaglandins to pass through discrete conformational states as the environment changes.

Results and Discussion

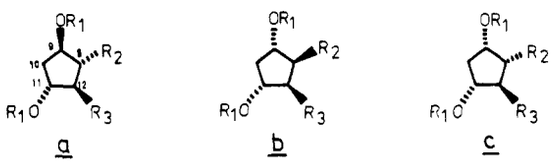
In Tables I–III the relevant ^1H NMR spectral parameters are found for products with three different configurations, **a** (as found in prostaglandin $F_{1\beta}$), **b** (as found in 8-epiprostaglandin $F_{1\alpha}$), and **c** (as found in prostaglandin $F_{1\alpha}$; Scheme I). Whereas products **1–6** are prostaglandins,[9] compounds **7–10** are used as references.[10] Comparison of the ^1H NMR spectral parameters of a large number of differently functionalized 1,4-dihydroxy- (and diacetoxy-) 2,3-dialkylcyclopentanes[11] indicates comparable pseudorotational itinerary energetics

Scheme I



a **b** **c**

1 ; $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
2 ; $R_1 = CH_3$, $R_2 = COCH_3$, $R_3 = H$, $R_4 = OH$
3 ; $R_1 = CH_3$, $R_2 = COCH_3$, $R_3 = OH$, $R_4 = H$
4 ; $R_1 = R_2 = R_3 = H$, $R_4 = OH$
5 ; $R_1 = R_2 = R_4 = H$, $R_3 = OH$
6 ; $R_1 = CH_3$, $R_2 = R_4 = H$, $R_3 = OH$



a **b** **c**

7 ; $R_1 = COCH_3$, $R_2 = R_3 = CH_3$
8 ; $R_1 = H$, $R_2 = R_3 = CH_3$
9 ; $R_1 = COCH_3$, $R_2 = -(CH_2)_6CH{=}C(CH_3)_2$, $R_3 = -CH_2CH{=}C(CH_3)_2$
10 ; $R_1 = H$, $R_2 = -(CH_2)_6CH{=}C(CH_3)_2$, $R_3 = -CH_2CH{=}C(CH_3)_2$

for products with the same configuration. We will therefore assume throughout the discussion that the conformational behavior of prostaglandins is similar to that of the model compounds **7** and **8** as far as the cyclopentane is concerned. Although only sums of vicinal coupling constants are available to substantiate this assumption in the case of prostaglandins with **a** and **b** configurations, individual coupling constants will be used for prostaglandins with the "natural" **c** configuration.

One can expect that the conformational behavior of products with the **a** configuration will be dictated by the requirement of the two trans alkyl side chains to be diequatorial[12] on the base of torsional strain. Calculations[13] of the potential energy of the ten twist and the ten envelope conformations encountered during the itinerary of pseudorotation[14,15] of **7a** show that the C_2 conformation with the methyl groups in the most puckered part of the molecule ($^8_{12}T$; Scheme II) is the minimal-energy form. This conformation is, however, only

Scheme II. Conformations for 1,4-Dihydroxy- (or diacetoxy-) 2,3-dialkylcyclopentanes

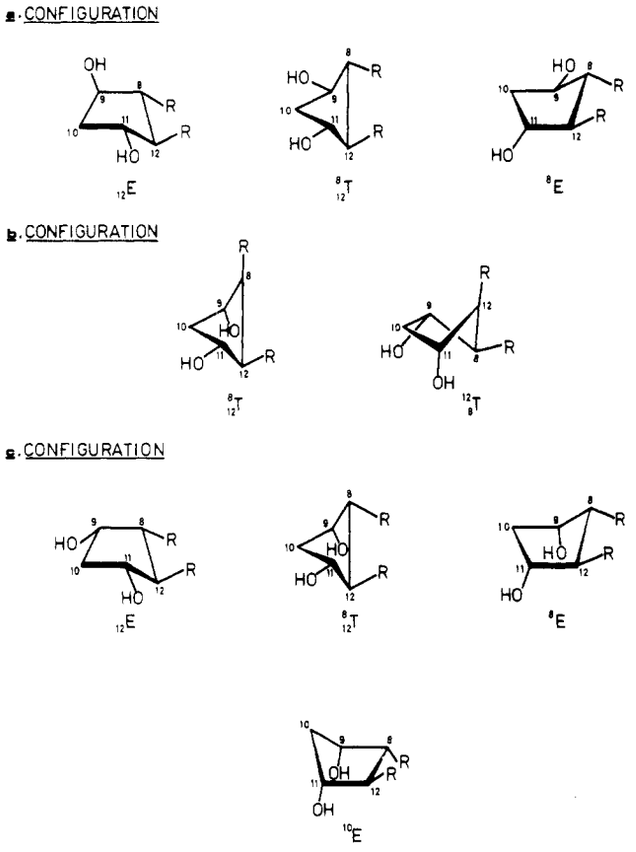


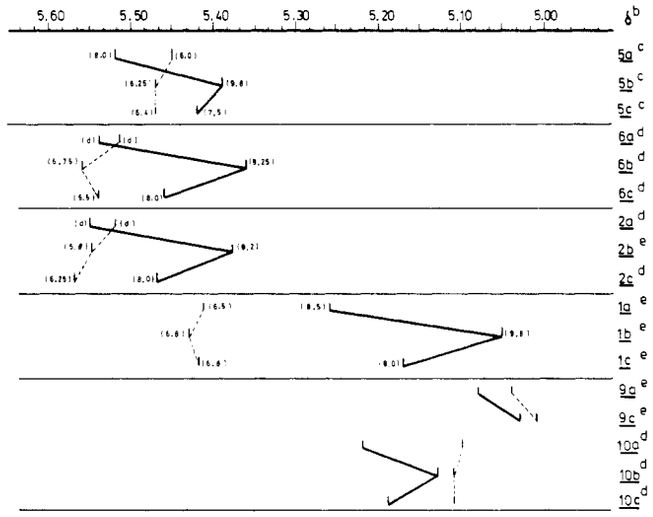
Table I. ^{1}H NMR Spectral Parameters of *a* Series (Prostaglandin $F_{1\beta}$ Analogues)[a]

Product	1a[h]	2a[i]	4a[j]	5a[k]	6a[l]	7a[m]
Solvent	CCl_4	$CDCl_3$	CD_3OD	CD_3OD	$CDCl_3$	CCl_4
δH-10[b,f]	*c*	2.00	1.85	1.90	1.99	1.97
δH-10′[b,f]	1.76	2.00	1.85	1.80	1.95	1.97
δH-9[g]	3.88	4.97	3.95	3.95	4.07	4.67
δH-11[g]	3.83	4.89	3.88	3.87	3.98	4.67
δH-8	*c*	*c*	*c*	*c*	*c*	1.49
δH-12	*c*	2.18	*c*	1.90	1.95	1.49
$\Sigma^e J$ 10[f]	*d*	*d*	*d*	14.0	11	14.2
ΣJ 10′[f]	15.0	*d*	*d*	14.0	*d*	14.2
ΣJ 9[g]	22.0	23.5	23.0	21.6	*d*	21.8
ΣJ 11[g]	17.0	17.5	17.0	18.5	18	21.8

[a] Obtained at 300 MHz at room temperature; chemical shifts are given in parts per million (δ scale) relative to Me_4Si as internal standard; coupling constants are given in hertz. [b] H-10 cis with OH-9 or Ac-9; H-10′ trans with OH-9 or Ac-9. [c] Could not be located. [d] Could not be measured. [e] Sum of vicinal coupling constants given in hertz. [f,g] The values superscripted by *f* or *g* have not been unambiguously assigned and can be pairwise permuted; e.g., in **1a** δH-9 can be either 3.88 or 3.83, but then the tied value of ΣJ 9 must also be exchanged with ΣJ 11. [h] Registry no., 61557-24-2. [i] Registry no., 61557-35-5. [j] Registry no., 62860-86-0. [k] Registry no., 10164-73-5. [l] Registry no., 21562-49-2. [m] Registry no., 62860-87-1.

slightly more stable than the two nearest envelope conformations ^8E and $_{12}E$. Restricted pseudorotation, designated pseudolibration by Altona,[15e] may occur around the minimal-energy form. Important coupling constants of **7a** are $^3J_{8,12}$ = 10.4 and $^3J_{8,9} = {}^3J_{11,12}$ = 7.6 Hz.[10a] The former value clearly locates the maximum pucker of the ring in the C_8–C_{12} bond; the latter relatively small coupling constant can be interpreted

Scheme III. Chemical Shift Values for Olefinic Hydrogen Atoms[a]



[a] For products **1**, **2**, **5**, and **6**, the straight lines correspond to the chemical shift values of H-13 (values in parentheses are for $^3J_{12,13}$) and the dotted lines to the corresponding values of H-14 (values in parentheses are for $^3J_{14,15}$); $^3J_{13,14}$ are comprised between 15.0 and 15.5 Hz; straight lines for H-2′ of the 3-methyl-2-butenyl side chain, dotted lines for H-7′ of the 8-methyl-7-nonenyl side chain (products **9** and **10**). [b] Chemical shifts are given in parts per million relative to Me_4Si as internal standard. [c] Methanol-d_4 solution. [d] Chloroform-d_1 solution. [e] Carbon tetrachloride solution.

as well by a single $^8_{12}T$ form as by a rapidly interconverting pair of ^8E and $_{12}E$ conformations, or a combination of both possibilities. Anyhow, in the simple model compound **7a** calculation and experiment point in the same direction. We assume that in the prostaglandins **1a–6a** the maximum pucker will also be in the C_8–C_{12} bond. The value of ΣJ_{11} is here systematically somewhat smaller, that of ΣJ_9 somewhat larger than the unique value found in **7a.** This is precisely what would be expected for the predominant occurrence of one *E* form. The ring conformation observed by Abrahamsson[3a] for the tri-*p*-bromobenzoylated prostaglandin $F_{1\beta}$ methyl ester is also an envelope conformation with C_{12} at the flap position. While it is satisfactory to find the same basic conformation in the solid state and in solution, we are not able to assign H-9 and H-11 unambiguously and hence cannot tell which atom, C_8 or C_{12}, occupies the flap position preferentially. It has been suggested[7a] on the basis of ^{13}C NMR data that there exists in solution a hydrogen bond between the 9-hydroxyl group and the 5,6 double bond and between the 11-hydroxyl group and the 13,14 double bond in prostaglandin $F_{2\beta}$, among other prostaglandins. The possible occurrence of a weak hydrogen bond between a hydroxyl function and a π-electron cloud is a well-known phenomenon;[16] it has been shown[17] that this results in a downfield shift (e.g., 0.1 ppm) of the vinylic hydrogen atoms. Our data, however, do not support the existence of such a hydrogen bond in the prostaglandins **5a** and **6a** since the chemical shifts of the olefinic hydrogen atoms 13 and 14 in prostaglandin $F_{1\beta}$ methyl ester (**6a**) and the corresponding diacetoxy derivative **2a** are nearly identical (Scheme III).

Analogous calculations[13] of the potential energy during pseudorotation for **7b** indicate the presence of two distinct minima of equal energy in the potential energy curve, coinciding with the two twist conformations $^8_{12}T$ and $^{12}_8T$ (Scheme II). Comparison of the values for the sum of coupling constants of the hydrogen atoms 9 and 11 obtained for the dimethyl derivative **7b** and the prostaglandins (e.g., **5b**) indicates that in the latter products one twist conformation should be more

Table II. ^{1}H NMR Spectral Parameters of *b* Series (8-Epiprostaglandin $F_{1\alpha}$ Analogues)[a]

Product Solvent	**1b**[g] CCl_4	**2b**[h] CCl_4	**3b**[i] CCl_4	**4b**[j] CD_3OD	**5b**[k] CD_3OD	**6b**[l] $CDCl_3$	**7b**[m] CCl_4
δH-10[b]	1.55	*c*	*c*	*c*	*c*	*c*	1.50
δH-10′[b]	2.32	2.68	2.68	2.47	2.46	2.41	2.66
δH-9	3.80	4.78	4.77	3.84	3.81	3.9	4.68
δH-11[f]	3.85	4.81	4.82	3.92	3.90	4.0	4.68
δH-8	1.97	2.12	2.11	2.04	*c*	*c*	2.17
δH-12	2.59	2.73	2.72	2.67	2.62	2.73	2.17
Σ[e]*J* 10	8	*d*	*d*	*d*	*d*	*d*	8.0
Σ*J* 10′	14	14.5	16	*d*	15	14.5	15.4
Σ*J* 9	19	*d*	19	*d*	21	*d*	16.2
Σ*J* 11	12	*d*	14	*d*	14	*d*	16.2

[a] Obtained at 300 MHz at room temperature; chemical shifts are given in parts per million (δ scale) relative to Me_4Si as internal standard; coupling constants are given in hertz. [b] H-10 cis with OH-9 or Ac-9; H-10′ trans with OH-9 or Ac-9. [c] Could not be located. [d] Could not be measured. [e] Sum of vicinal coupling constants given in hertz. [f] The assignment of the H-9 and H-11 resonances is based on the downfield β effect of the C13–C14 double bond. [g] Registry no., 61507-23-1. [h] Registry no., 61557-37-7. [i] Registry no., 61557-36-6. [j] Registry no., 61557-40-2. [k] Registry no., 26771-96-0. [l] Registry no., 21562-59-4. [m] Registry no., 53099-13-1.

Table III. ^{1}H NMR Spectral Parameters of *c* Series (Prostaglandin $F_{1\alpha}$ Analogues)[a]

Product Solvent	**1c**[h] CCl_4	**2c**[i] $CDCl_3$ (CCl_4)	**3c**[j] $CDCl_3$ (CCl_4)	**5c**[k] CD_3OD	**6c**[l] $CDCl_3$	**7c**[m] CCl_4	**8c**[n] CCl_4
δH-10[b]	1.70	*c*	*c*	1.57	1.77	1.53	1.66
δH-10′[b]	2.00	2.55	2.50	2.36	2.16	2.51	2.02
δH-9	4.06	5.15	5.13	4.10	4.19	5.03	3.92
δH-11	3.80	4.87	4.90	3.81	3.95	4.57	3.67
δH-8	*c*	*c*	*c*	*c*	*c*	1.52	1.29
δH-12	*c*	2.55	2.50	2.21	2.27	1.79	1.59
J 10,10′	−14.5	*d* (−15.5)	*d* (−15.5)	−14.5	−15.0	−15.7	−14.8
J 9,10	*d*	*d* (*d*)	*d* (*d*)	2.0	1.0	1.8	1.3
J 10,11	*d*	*d* (*d*)	*d* (*d*)	5.5	2.5	5.0	2.7
J 9,10′	*d*	5.5[f] (6.0[g])	*d* (5.5[f])	6.2	5	6.2	4.7
J 10′,11	*d*	8.5[f] (9.5[g])	*d* (9.0[f])	8.75	7.5	8.8	7.4
J 8,9	*d*	*d* (*d*)	*d* (*d*)	6	*d*	4.9	3.8
J 11,12	*d*	*d* (7.75)	*d* (8.75)	7	*d*	7.8	4.7
J 8,12	*d*	*d* (12.0)	*d* (12.0)	11	*d*	11.8	10.4
Σ[e]*J* 10	5.0	*d* (*d*)	*d* (*d*)	5.0	3.5	6.8	4.0
Σ*J* 10′	*d*	*d* (15.5)	*d* (14.5)	15.0	12.5	15.0	12
Σ*J* 9	9.5	11 (11)	11 (10)	14.0	12.0	12.9	10
Σ*J* 11	14.5	*d* (22.5)	20 (22)	22.0	16.0	21.6	16

[a] Obtained at 300 MHz at room temperature; chemical shifts are given in parts per million (δ scale) relative to Me_4Si as internal standard; coupling constants are given in hertz. [b] H-10 cis with OH-9 or Ac-9; H-10′ trans with OH-9 or Ac-9. [c] Could not be located. [d] Could not be measured. [e] Sum of coupling constants given in hertz. [f,g] Values superscripted by *f* or *g* can be pairwise permuted. [h] Registry no., 61557-25-3. [i] Registry no., 62860-88-2. [j] Registry no., 62860-89-3. [k] Registry no., 745-62-0. [l] Registry no., 13227-94-6. [m] Registry no., 62860-90-6. [n] Registry no., 62928-69-2.

stabilized than the other one. Indeed Table II indicates a somewhat smaller value for the sum of coupling constants of hydrogen atom 11 and a larger value for hydrogen atom 9 in the prostaglandins (**1b–6b**), compared to product **7b**; this suggests a more axial position of H-9—and a more equatorial position of H-11—thus designating $^{12}_{8}T$ as the preferred conformation. The location of the alkyl group (C_7 of the acid side chain) in the equatorial position and the alkenyl group (C_{13}) in the axial position is in accordance with the large $^3J_{12,13}$ value and with a x-ray study.[18] A hydrogen bridge is geometrically not possible between the axial alkenyl side chain and the roughly antiperiplanar OH-11.

Since the values for the sums of coupling constants of respectively H-9 and H-11 in the diacetoxy derivatives with **c** configuration (**2c, 3c, 7c**; Table III) are nearly equal, we believe that these products have the same conformation or conformations. Again, the $J_{8,12}$ of **7c** discloses the most puckered part of the ring. This leaves only three possibilities, $^{8}_{12}T$, $_{12}E$, and ^{8}E, but in view of the magnitude of $J_{11,12}$ and $J_{8,9}$ only the envelope conformation with C_8 at the flap has to be

retained. As mentioned above, this conclusion based on **7c** would also be valid for the diacetoxy prostaglandins. However, the diols in this series (**1c, 6c, 8c**) show a much smaller sum of coupling constants for H-11 and, but to a lesser extent, for H-9. These data are easily rationalized by accepting the existence of an intramolecular hydrogen bond between the cis 1,3-hydroxyl groups. This hydrogen bond demands an ^{10}E conformation, resulting in a smaller value for ΣJ_{11}. The occurrence of this hydrogen bond is independently proven by IR spectroscopy for **8c** and **6c** (methyl ester of prostaglandin $F_{1\alpha}$) for which respectively hydrogen bonded hydroxylic absorptions at 73 and 60 cm^{-1} lower frequencies (CCl_4) are observed. The similarity in conformational behavior of products **6c** and **8c** is further displayed by four individual coupling constants comparable in magnitude. The ^1H NMR spectrum of prostaglandin $F_{1\alpha}$ itself could only be recorded in methanol-d_4 solvent; this solvent, however, interacts with the hydroxyl groups and destroys the intramolecular hydrogen bond. A great similarity is indeed observed between the individual coupling constant values of **5c** and **7c.** It has already been suggested that the side chain alignment in prostaglandins is more favorable in aqueous media than in less polar solvents;[6a] this is in complete agreement with our observations. No intramolecular hydrogen bond in prostaglandin $F_{1\alpha}$ (**5c**) in a polar solvent (methanol-d_4) is observed and the minimal-energy conformation ^8E has the two side chains in the most puckered part of the molecule, with a torsional angle around 73°, thus allowing alignment of the side chains. However, considering prostaglandin $F_{1\alpha}$ methyl ester (**6c**) in an apolar solvent (chloroform-d_1) one has to consider also conformation ^{10}E on the basis of intramolecular hydrogen bonding; the very large torsional angle (around 120°) clearly does not allow side chain alignment in this envelope conformation. It cannot a priori be predicted if the conformation of the five-membered ring actually induces the alignment of the side chains in prostaglandins in a certain medium or if the reverse situation is correct. Considering the magnitude of the different energy values, which have to be accounted for, we advise the latter possibility.[19]

Practical information can be learned from the ^1H NMR data of the olefinic hydrogen atoms of the 13,14 double bond. Theoretical calculations have shown that the most favorable position of the 13,14 double bond is an eclipsed one with H-12 and H-15;[4a] this is in accordance with the absence of a homoallylic coupling between hydrogen atoms 12 and 15 in products **5** and **6.** The chemical shift values for the hydrogen atoms located on the 13,14 double bond of 15(R)-prostaglandins (e.g., **2** and **4**) are situated at lower field compared to the values of the corresponding 15(S) products.[20] A remarkable regularity is observed when considering the chemical shift values of H-13 as a function of the configuration: the magnitude of the δ value increases when considering consecutively the **b, c,** and **a** configuration. The influence of the steric position of the vicinal alkyl side chain and the hydroxyl (or acetoxy) groups on the chemical shift of an H-1′ atom of a side chain has already been observed.[21] As already mentioned, our results do not concord with the occurrence of an intramolecular hydrogen bond between the 11-hydroxyl group and the 13,14 double bond. However, we have evidence that a hydrogen bond between the OH-9 group and the 5,6 double bond in prostaglandins of the 2 series could exist in an apolar solvent.[7a] Products **9** and **10** have two side chains containing a trisubstituted double bond in the 2′ position (for the 3-methyl-2-butenyl side chain) and in the 7′ position (for the 8-methyl-7-nonenyl side chain);[10b] the presence of the 7′ double bond is very convenient since the H-7′ is far removed from the cyclopentane, thus allowing the chemical shift of this hydrogen atom to serve as an internal standard value. Considering the diacetoxy derivatives **9a** and **9c** we may conclude that the steric position of the substituents on the five-membered ring does not influence the shift value of the vinylic proton in the 2′ position. The corresponding diols (**10**), however, exhibit a fairly large downfield effect—relative to the shift value of H-7′—for this hydrogen atom dependent on the configuration (Scheme III); thus, we assume that in **10a** and **10c** (in chloroform-d_1 solution) an intramolecular hydrogen bond occurs between the 11-OH group and the double bond in the 2′ position of the ring.

Careful analysis of the magnitude of the ^1H NMR spectral data of prostaglandins allows easy configurational assignment within the set of the three configurations **a, b,** and **c.** A tentative assignment of the most stabilized conformations of prostaglandins with **a, b,** or **c** configuration can be performed on the basis of ^1H NMR spectral data. It has been proven that those conformations for prostaglandin $F_{1\alpha}$ (**5c** and **6c**) are strongly influenced by the molecular environment. Our results suggest that prostaglandins are able to pass through discrete conformational states as the environment changes. This could bring some light about the still unresolved problem of the mode of action of prostaglandins in the cell membrane.

Experimental Section

The ^1H NMR spectra were recorded in CCl_4, $CHCl_3$-d_1, or CH_3OH-d_4 and the δ values were measured with Me_4Si as internal standard on a Varian HR-300 MHz spectrometer. Double irradiations experiments were done on this apparatus equipped with a Varian SC 8525-2 decoupler unit. IR spectra for the determination of intramolecular hydrogen bonding were recorded on a Perkin-Elmer 337 apparatus in CCl_4 solution. Concentration was 5×10^{-3} mol L^{-1}.

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Registry No.—**9a,** 62842-22-2; **9c,** 62860-91-7; **10a,** 62860-92-8; **10b,** 62860-93-9; **10c,** 62860-94-0.

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(5) The hairpin conformation, also designated the U type or aligned conformation, in contrast with the L-shaped or extended conformation with chains being close to 90° apart, as postulated by Smythies, has been suggested as a result of molecular dynamics calculations of conformations of prostaglandin E_1[3b] and from extended Hückel MO theory.[4a] These calculations suggest a stabilization of 4.9 kcal/mol associated with $\sigma\sigma$ dispersion attractive forces between opposed parallel chains.[3b] Whereas this conformation is closely related to that observed for a heavy-atom derivative of prostaglandin $F_{1\beta}$ in the crystalline state,[3a] some authors[3c] suggest, as a result of x-ray diffraction studies of prostaglindin E_2, that molecular packing, more than any other phenomenon, dictates the interactions between chains observed in these experiments.
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(7) (a) G. Lukacs, F. Piriou, S. D. Gero, D. A. Van Dorp, E. W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, 515 (1973); (b) J. F. Bagli and T. Bogri, *ibid.*, 5 (1967); (c) G. L. Bundy, *ibid.*, 1957 (1975).
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(9) All these prostaglandins were synthesized in our laboratory: F. Vanhulle, V. Sipido, and M. Vandewalle, *Tetrahedron Lett.*, 2213 (1973); F. Vanhulle, M. De Smet, K. Legein, P. De Clercq, and M. Vandewalle, *Bull. Soc. Chim. Belg.*, **85,** 503 (1976); P. De Clercq and M. Vandewalle, *ibid.*, **83,** 305 (1974).

(10) (a) For the dimethyl analogues **7** and **8** see D. Van Haver, D. Tavernier, M. Anteunis, and M. Vandewalle, *Tetrahedron*, **30**, 105 (1974). (b) Compounds **9** and **10** were synthesized in our laboratory: W. Van Brussel, Ph.D. Thesis, Ghent, Belgium, 1975.
(11) P. De Clercq and M. Samson, *Org. Magn. Reson.*, in press; *Bull. Soc. Chim. Belg.*, **85**, 872 (1976).
(12) The "axial–equatorial" terminology used in cyclohexane has been retained, although in cyclopentanes the dihedral angles will not generally equal those in cyclohexane. If ψ is the dihedral angle between cis vicinal bonds, and if there is no angular deformation, then $\psi_{ea} = \psi$; $\psi_{aa} = 120° + \psi_{ea}$; $\psi_{ee} = 120° - \psi_{ea}$. Considering the most puckered part of the molecule we used $\psi = 48.1°$ for the twist conformation and $\psi = 46.1°$ for the envelope conformation.[15d]
(13) These calculations will be discussed in detail elsewhere. The method used was derived from the work of Ouannes[15d] and Altona.[15e] The shape of the potential barrier restricting pseudorotation was calculated from torsional barriers only; nonbonded interactions and dipole–dipole interactions were not calculated but were considered during the study of Dreiding models. The method consists basically in calculating the torsional strain around each carbon–carbon bond of the ring from the rotational barrier of known acyclic compounds and summation of these values for each of the 20 basic conformations met along the itinerary of pseudorotation.
(14) Although the concept of pseudorotation was first introduced[15f] in relation with the conformation of unsubstituted cyclopentane, we will use the same term in the discussion of the conformational behavior of 2,3-dialkyl-1,4-cyclopentanediols.
(15) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morisson, "Conformational Analysis", Wiley, New York, N.Y., 1965; (b) C. Altona, H. R. Buys, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 973 (1966); (c) D. Korver, *ibid.*, **88**, 1070 (1969); (d) C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 3603 (1965); (e) ref 15b; C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967); (f) J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2483 (1947); (g) C. Altona and M. Sundaralingam, *ibid.*, **94**, 8205 (1972).
(16) See, e.g., P. v. R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Am. Chem. Soc.*, **80**, 6691 (1958); M. Oke and H. Iwamura, *Bull. Chem. Soc. Jpn.*, **32**, 306 (1959).
(17) F. De Pessemier, Ph.D. Thesis, Gent, Belgium, 1976.
(18) G. Germain, J. P. De Clercq, and M. Van Meerssche, *Bull. Soc. Chim. Belg.*, **85**, 557 (1976).
(19) The ^{10}E form is a high-energy conformation, whereas an approximate value for the hydrogen bond is 1.5 kcal/mol. Thus the stabilization of the hairpin conformation (4.9 kcal/mol)[5] would normally be the leading factor in the determination of the composition of the conformational equilibrium for prostaglandin $F_{1\alpha}$ methyl ester in an apolar solvent. Since this is not the case (at least not exclusively) we assume that the nature of the solvent will in great part determine if the aligned conformation is indeed a preferred one.
(20) So far, the difference between prostaglandins with 15(*R*) or 15(*S*) configuration has been made only on the base of their TLC behavior; e.g., J. Ide and K. Sakai, *Tetrahedron Lett.*, 1367 (1976).
(21) The chemical shift values of the methyl groups in 2,3-dimethyl-1,4-diacetoxycyclopentane (**7**) are greatly influenced by the considered configuration: M. Samson, Ph.D. Thesis, Ghent, Belgium, 1976.

Synthesis of Deoxyribooligonucleotides by Means of Cyclic Enediol Pyrophosphates

Fausto Ramirez,*[1] Eleftheria Evangelidou-Tsolis, Aleksander Jankowski, and James F. Marecek

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

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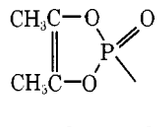
A new method of synthesis of deoxyribooligonucleotides by means of di(1,2-dimethylethenylene) pyrophosphate is described. Reaction of 5′-*O*-*p*-methoxytritylthymidine with the pyrophosphate in dichloromethane (triethylamine as proton acceptor) gives a cyclic enediol phosphate derivative, which is allowed to couple in dimethylformamide (triethylamine as catalyst) with unprotected thymidine to yield the 1-methylacetonyl ester of (5′-*O*-*p*-methoxytrityl)thymidylyl-(3′ → 5′)-thymidine. This protected dinucleotide triester is converted first into the deprotected triester by trifluoroacetic acid in dichloromethane solution, and then into $TpT^-(C_2H_5)_3NH^+$ by triethylamine in aqueous acetonitrile. The protected dinucleotide triester is converted into the protected tri- and tetranucleotide triesters by repetition of the reaction with pyrophosphate and the coupling with thymidine. The tetranucleotide, $TpTpTpT^{3-}[(C_2H_5)_3NH^+]_3$, is obtained after removal of the *p*-methoxytrityl 5′-OH protecting group, and the 1-methylacetonyl phosphate blocking group, from the protected triester. The di- and tetranucleotides are isolated as hydrated triethylammonium salts after DEAE–cellulose chromatography.

One of the strategies employed in the nonenzymatic synthesis of deoxyribooligonucleotides involves the establishment of the 3′ → 5′ internucleotide bond as a phosphotriester, $(R^IO)(R^{II}O)(BLO)PO$, where BL represents the phosphate blocking group, which must eventually be removed to produce the desired phosphodiester, $(R^IO)(R^{II}O)P(O)OH$. This approach, introduced by Todd[2] and explored initially by Letsinger,[3] by Reese,[4] and by Cramer and Eckstein,[5] has been used by many investigators,[6-14] sometimes in conjunction with a search for new reagents to convert the two nucleosides into the triester intermediate. Intensive research effort during the past four years[15-28] discloses a continuing interest in deoxyribooligonucleotide syntheses, in spite of the solution by Khorana and his co-workers[29] of the problem of constructing genes by a combination of nonenzymatic and enzymatic techniques.[30]

The synthesis of ribooligonucleotides is also receiving much attention, in particular by Ikehara, Ohtsuka, and their coworkers, who have developed methods to produce segments suitable for conversion into larger units with amino acid acceptor activity.[31-34] The construction of tRNA's by a combination of nonenzymatic and enzymatic procedures seems possible based on these results.

Work in this Laboratory[35-39] has focused on the development of phosphorylating reagents capable of being applied



by standard procedures to the synthesis of complex phosphodiesters, such as the phospholipids of biological membranes,[40] and both types of oligonucleotides. Previous papers have described the preparation of several derivatives of the 1,2-dimethylethenylenedioxyphosphoryl group, abbreviated X=P(O)–, which are useful for this purpose.[35-37] The conversion of the alcohols R^IOH and $R^{II}OH$ into the phosphodiester can be achieved as "three-, two-, or one-flask" syntheses, according to the number of intermediates isolated and purified:

$$R^IOH + X{=}P(O)Y + B \rightarrow X{=}P(O)OR^I + Y^-BH^+ \quad (1)$$