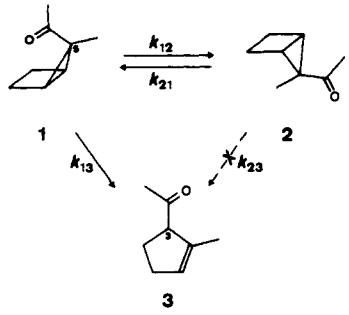
Table I. First-Order Rate Constants at 200° and Activation Parameters of the Thermal Reactions of the 5-Acetyl-5-methylbicyclo[2.1.0]pentanes 1 and 2 in Benzene

Reaction	k,[a] sec^{-1}	$\Delta H^{\ddagger}$,[b] kcal/mol	$\Delta S^{\ddagger}$,[b] eu
1 → 2	(9.30 ± 0.22) × 10^{-2}	33.4 ± 0.8	−1.5 ± 1.7
2 → 1	(2.42 ± 0.15) × 10^{-2}	33.9 ± 0.9	−3.0 ± 2.0
1 → 3	(1.96 ± 0.22) × 10^{-3}	22.2 ± 2.2	−33.0 ± 4.7
2 → 3	<2.96 × 10^{-7}		

[a] Ca. 0.16 M solutions of 1 in sealed glass tubes; VPC analysis on a Carbowax K1540 capillary column at 120° of five samples at each of ten time intervals. For k_{23} see also footnote 6. The rate constants remained the same within experimental error when ~3% pyridine was added to a solution of 1 at 200°. [b] Activation parameters calculated from rate data at 160, 180, 200, and 220°. Errors are standard deviations, and the correlation coefficients are 0.998 (1 → 2), 0.997 (2 → 1), and 0.996 (1 → 3).

of the acetyl group.[3] We now report that the rearrangement to **3** occurs specifically from the *endo*-acetylbicyclopentane (**1**) and that this process and the endo-exo interconversion **1** ⇄ **2** do not involve a common intermediate.



The thermolyses of ketones **1** and **2** were carried out in benzene solution at 160, 180, 200, and 220°, compound **3** remaining unchanged under these conditions.[4] Best-fit rate constants were then calculated using programs designed to handle up to four components linked by equilibria,[5] and these data and associated activation parameters are shown in Table I.

Our kinetic results provide a clear mechanistic differentiation of the two fundamental thermal isomerization processes observed in 5-acetylbicyclo[2.1.0]pentanes. The order in rate constants, $k_{12} > k_{21} > k_{13}$ and $k_{23} \sim 0$,[6] and the significant gap in activation entropies between the stereomutations **1** ⇄ **2** and the rearrangement **1** → **3** strictly preclude that the two types of reaction involve a common intermediate.[7]

The unusually large negative entropy of activation for **1** → **3** indicates that the rearrangement proceeds through a highly ordered transition state and is suggestive of a concerted electrocyclic process involving the four electrons of the internal cyclopropane and the C(5)-acetyl bonds. Disrotatory opening of the former bond would selectively permit the *endo*-acetyl substituent of **1** to transfer by forming a transom of appropriate Möbius topology.[8,9]

A cyclopentane 1,3-biradical path constitutes one possible mechanism for the endo-exo interconversion **1** ⇄ **2**,[11] and indeed cleavage of the central bond has been demonstrated experimentally for 5-benzoyloxybicyclo[2.1.0]pentanes.[12] However, such π-donating substituents on C-5 lower the isomerization barrier[10,13] by enhancing the antibonding character in the central bond,[14] and therefore both an analogous path and the alternative cleavage of an external cyclopropane bond[15] remain possible for the endo-exo stereomutation of **1** and **2**. Work with 5-acetyl-1,5-dimethylbicyclo[2.1.0]pentane to clarify this question is in progress.

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References and Notes

(1) E. Bagglolini, K. Schaffner, and O. Jeger, *Chem. Commun.*, 1103 (1969).
(2) M. J. Jorgenson and A. F. Thacher, *Chem. Commun.*, 1030 (1969).
(3) Cf. K. Schaffner, *Pure Appl. Chem.*, **33**, 329 (1973).
(4) Analytical data for the three ketones including an unambiguous assignment of endo and exo configuration to **1** and **2** will be reported in our full paper.
(5) E. McLaughlin and R. W. Rozett, *J. Chem. Educ.*, **49**, 482 (1972).
(6) The rate constant k_{23} given in Table I is the *maximum* value computed to comply with the other rate data.
(7) A referee has taken the alternate view that there may indeed be a common intermediate by suggesting that the formation of **3** from 1 could also follow the cyclopentane 1,3-biradical path; i.e., **2** could give rise to 1 solely by external bond cleavage whereas 1 could afford **2** by *both* internal and external bond cleavage. This difference in cleavage specificities is to be rationalized in terms of the difference in overlap between the external bond and the π-bond of the carbonyl group in **1** and **2** (which in fact is apparent from the ir spectra of these ketones at room temperature[4]). However, if this were so, the reactions **1** → **2** and **1** → **3** would be expected to have similar $\Delta S^{\ddagger}$ values rather than exhibit a drastic difference in entropy of activation as observed.
(8) C. W. Jefford, *Chimia*, **24**, 357 (1970), and references cited therein.
(9) A concerted mechanism has also been tentatively considered for the facile and similarly endo-selective rearrangement of 5-acetoxybicyclo[2.1.0]pentane[10] and halocyclopropanes.[8]
(10) J. J. Tufariello, A. C. Bayer, and J. J. Spadaro, Jr., *Tetrahedron Lett.*, 363 (1972).
(11) J. P. Chesick, *J. Am. Chem. Soc.*, **84**, 3250 (1962); cf. K. B. Wiberg, *Adv. Alicyclic Chem.* Academic Press, **2**, 208 (1968).
(12) J. J. Tufariello and A. C. Bayer, *Tetrahedron Lett.*, 3551 (1972).
(13) K. Fellenberger, U. Schöllkopf, C. A. Bahn, and P. v. R. Schleyer, *Tetrahedron Lett.*, 359 (1972).
(14) R. Hoffmann, *Tetrahedron Lett.*, 2907 (1970); H. Günther, *ibid.*, 5173 (1970); R. Hoffmann and W. D. Stohrer, *J. Am. Chem. Soc.*, **93**, 6941 (1971); D. B. Chesnut, S. Ferguson, L. D. Smith, and N. A. Porter, *Tetrahedron Lett.*, 3713 (1972).
(15) M. J. Jorgenson, T. J. Clark, and J. Corn, *J. Am. Chem. Soc.*, **90**, 7020 (1968).

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Molecular Basis for Prostaglandin Potency. I. The Case for Biological Significance of Media Dependent Conformational Changes

Sir:

We have for some time been intrigued by the problem of deciphering the stereostructural requirements for pharmacological action[1] of the classical prostaglandins, PGE's and PGF's.[2] Unlike most natural substances of such extraordinary potency the prostaglandins do not present a spatially well-defined skeleton for the contemplation and manipulation of the student of structure-activity relationships (SAR), rather an a priori floppy array in which the several chiral centers can adopt very different relative spatial orientations.[3] As a result of reviewing the SAR data in the open literature,[4] we have proposed, as a working hypothesis, that the ready attainment of a conformation (designated the hairpin[4,5]) in which the two side chains are closely and specifically aligned[5] is a feature of those E- and F-type prostaglandins showing high potency in stimulating contraction of smooth musculature.[9] We now present evidence that $PGF_{2\alpha}$ and the related primary alcohol display media-dependent changes in the CD spectrum in the olefinic span (185–220 nm) which are best rationalized as the result of side-chain alignment in protic media and further that less potent diastereomers do not display these features.

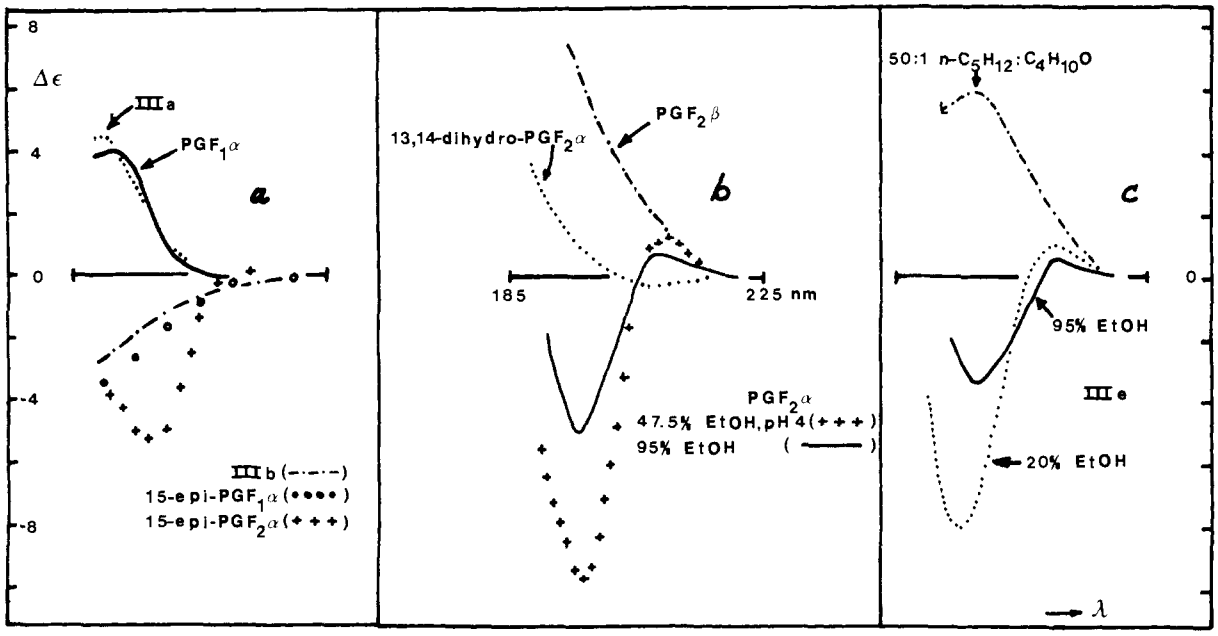
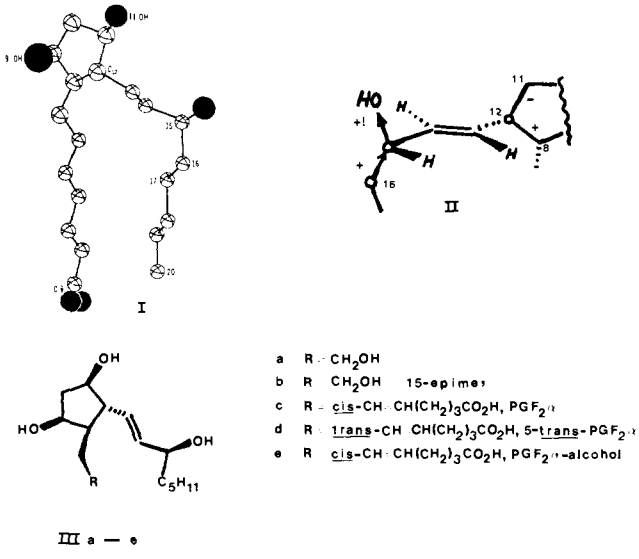


Figure 1. CD spectra of prostaglandins and model compounds. All energy spans, 185–225 nm, are linear in wavelength. Solvent is 95% EtOH unless indicated otherwise.



Recent studies, delineating the effects of local dissymmetry in inducing CD Cotton effects in the olefin transitions,[10] have put us in position to experimentally verify certain features of this conformational model. The local geometry (II) about the $\Delta^{13,14}$ bond in the hairpin conformation (shown for $PGF_{1}\alpha$, I) predicts a positive low energy band due to the chiral disposition of the allyl C–O bond.[10a] In the case of $PGF_{1}\alpha$, which contains only this chromophore, this is observed (Figure 1a). Epimeric model compounds IIIa and IIIb[11] and 15-epi-$PGF_{1}\alpha$ also display consistent CD spectra (Figure 1a): the sense of the Cotton effect being determined by the absolute configuration at C-15; suggesting that the full α side chain is not essential for establishing this stereostructural feature.

However, clear support for close spatial proximity of the two side chains came from studies of the bis unsaturated series. The CD spectrum of $PGF_{2}\alpha$ (IIIc) in 95% ethanol ($\Delta\epsilon_{210} = +0.73$, $\Delta\epsilon_{196} = -4.8$), in contrast to those of the less potent diastereomers, 11-epi-$PGF_{2}\alpha$[11] and $PGF_{2}\beta$,[11] is not the additive sum of the CD spectra of $PGF_{1}\alpha$ ($\Delta\epsilon_{191} = +4.2$) and 13,14-dihydro-$PGF_{2}\alpha$[12] ($\Delta\epsilon_{205} = -0.10 \pm 0.10$, $\Delta\epsilon_{190} = +2.5$!, see Figure 2, supplementary material) but rather the result of through-space coupling[13] of transitions due to the otherwise isolated olefinic bonds (see Figure 1b). In accord with this origin,[14] the couplet amplitude increases on 1:1 dilution with aqueous buffer (pH 4, $\Delta\epsilon_{210} = +1.03$, $\Delta\epsilon_{197} = -9.6$) but decreases in *n*-butyl alcohol ($\Delta\epsilon_{210} = +0.62$, $\Delta\epsilon_{198} = -3.1$) and acetonitrile ($\Delta\epsilon_{210} = +0.50$, $\Delta\epsilon_{200} = -1.28$). Two other potent F-type prostaglandin analogs[12] show similar couplets with comparable media changes (see Table I below). In accord with its significant biological activity (10–50% of $PGF_{2}\alpha$),[4] 11-epi-$PGF_{2}\alpha$ (which shows no couplet in EtOH) shows a developing couplet in aqueous media (evidenced by a growing negative CD band at ca. 195 nm, see Figure 3, supplementary material). Epimerization at either C-9 or C-15 results in loss of 99% of the F-type activity. $PGF_{2}\beta$ (9-epi-$PGF_{2}\alpha$) shows a positive trending CD as expected based on the models for the individual olefin chromophores and displays within experimental error, no media or pH effects.[15] As expected (based on model IIIb and 15-epi-$PGF_{1}\alpha$), 15-epi-$PGF_{2}\alpha$ shows a negative band at 195 nm. On increasing the water content of the media the amplitude of the band *decreases* rather than becoming more negative as in all of the active prostaglandins examined.

Several possible explanations for the unusual media-dependent CD of $PGF_{2}\alpha$ and its active analogs could be constructed which did not implicate side-chain alignment. For one, the degree of association might change with the water content of the media, particularly at acid pH. For this reason we have examined the CD of $PGF_{2}\alpha$ at widely differing concentrations. Neither CD band showed any notable concentration dependence (9–5000 μg/ml) at constant solvent composition.[16] Plots of $\Delta\epsilon_{210}$ vs. concentration in various media appear as Figure 4 in the supplementary material. To eliminate the possibility that the carboxyl chromophore[17] is involved, we have examined the CD spectrum of the primary alcohol analog of $PGF_{2}\alpha$ (IIIe, Figure 1c) in ethanol–water mixtures.[18] The Cotton effect amplitudes are summarized in Table I. The alcohol displays, in detail, the same changes observed for $PGF_{2}\alpha$. In the case of the alcohol a pleasing demonstration of the importance of solvent structure in restricting conformational freedom was possible. The alcohol remains dissolved when a concentrated *n*-butyl alcohol solution is diluted with 50 volumes of pentane; the

Table I

	95% EtOH		25–45% EtOH		0–9% EtOH	
	$\Delta\epsilon_{210}$	$\Delta\epsilon_{195}$	$\Delta\epsilon_{210}$	$\Delta\epsilon_{195}$	$\Delta\epsilon_{210}$	$\Delta\epsilon_{195}$
$PGF_{2}\alpha$ (IIIc)	+0.73	−5.1	+1.03	−9.6[a]	+1.9	−7.4[a]
15(*S*)-15-Me -$PGF_{2}\alpha$	+0.64	−4.6	+1.15	−6.3	+1.35	−5.5
16,16-Me_2-$PGF_{2}\alpha$	+0.75	−2.6	+0.9	−5.65	+1.25	−4.55
$PGF_{2}\alpha$–alcohol (IIIe)	+0.52	−3.4	+0.7	−8.2[a]	+1.06	−5.6[a]
15-epi-$PGF_{2}\alpha$	+0.08	−5.3			+0.25	−3.4
11-epi-$PGF_{2}\alpha$	+2	>+5.5[a]			+2	+1.6
$PGF_{2}\beta$	+1.6	+9[a]			+1.7	+8.2
Typical error	±0.03	±0.4	±0.06	±0.8	±0.10	±0.9

[a] Errors two–three times those indicated apply due to either low optic anisotropy or high noise levels for these samples.

resulting solution displays only a single positive CD band (Figure 1c) as expected for the contribution of isolated olefinic bonds.

Although these spectroscopic studies cannot delineate the detailed conformations of the side chains out beyond C-16 and C-4, they do establish a correlation between biological potency and increasing olefin transition coupling due to side-chain alignment in polar protic media. Chemical and pharmacological tests of the hairpin model, to supplement this spectroscopic study, are in progress.

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Supplementary Material Available. Figures 2–4 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JACS-75-4148.

References and Notes

(1) (a) P. W. Ramwell, J. E. Shaw, E. J. Corey, and N. H. Andersen, *Nature (London)*, **221**, 1241 (1969); (b) H. Shio, P. W. Ramwell, N. H. Andersen, and E. J. Corey, *Experientia*, **26**, 355 (1970); (c) N. H. Andersen, *Ann. N.Y. Acad. Sci.*, **180**, 104 (1971); (d) P. W. Ramwell and I. Rabinowitz in "Effects of Drugs on Cellular Control Mechanisms", Macmillan, New York, N.Y., 1971; (e) E. J. Corey, S. Terashima, P. W. Ramwell, R. Jessup, N. M. Weinshenker, D. M. Floyd, and G. A. Crosby, *J. Org. Chem.*, **37**, 3043 (1972); (f) M. A. Marrazzi and N. H. Andersen in "Prostaglandins", Vol. 2, Plenum Press, New York, N.Y., 1974.

(2) Recent work on the biosynthesis of prostaglandins has revealed that the peroxy and *endo*-peroxide intermediates prior to the classical PG's in the sequence show great potency and may represent the true physiologically important substances: M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 3824 (1974).

(3) Nonetheless the PG's do display, in addition to a notable lack of tissue specificity, very strict stereostructural requirements for certain characteristic actions[1c] and for substrate suitability with PG-metabolizing enzymes.[1f] These have recently been reviewed.[1f,4]

(4) N. H. Andersen and P. W. Ramwell, *Arch. Intern. Med.*, **133**, 30 (1974).

(5) The hairpin conformation, first suggested as a result of molecular dynamics calculations of conformations of PGE_1[6] is closely allied to that observed for a heavy-atom derivative of $PGF_1\beta$ in the crystalline state.[7] Preliminary studies of the crystal structure of PGE_1[6] indicate a morphology similar to that of the $PGF_1\beta$ derivative. The calculations suggest a stabilization of 4.9 kcal/mol associated with $\sigma\sigma$ dispersion attractive forces between opposed parallel chains.[6] Kier and Hoyland arrived at similar conclusions from extended Huckel MO theory.[8]

(6) I. Rabinowitz, P. Ramwell, and P. Davison, *Nature (London), New Biol.*, **233**, 88 (1971).

(7) S. Abrahamsson, *Acta Crystallogr.*, **16**, 409 (1963); D. H. Nugteren, D. A. vanDorp, S. Bergstrom, M. Hambert, and B. Samuelsson, *Nature (London)*, **212**, 38 (1966).

(8) J. R. Hoyland and L. B. Kier, *J. Med. Chem.*, **15**, 84 (1972).

(9) One of the key observations leading us to the hairpin conformation as a working model for SAR correlation is the unusual potency of *ent*-11,15-epi-PGE_1,[1a,c] and the corresponding bis unsaturated analog,[1e] on smooth muscles displaying enhanced sensitivity to F-type prostaglandins.[4] Dr. C. Gandolfi (Milan) indicates that he has also arrived at the conclusion that *ent*-11,15-epi-PGE's are F-type prostaglandins (personal communication).

(10) (a) N. H. Andersen, C. R. Costin, D. D. Syrdal, and D. P. Svedberg, *J. Am. Chem. Soc.*, **95**, 2049 (1973); (b) N. H. Andersen, C. R. Costin, and J. R. Shaw, *ibid.*, **96**, 3692 (1974).

(11) All compounds synthesized for this work display spectra accordant with the assigned structures and purity in excess of 96% by TLC and HPLC. Molecular formulas were confirmed by high resolution exact mass measurements (±0.001 amu). Authentic samples of $PGF_{1\alpha}$ and $PGF_{2\alpha}$ obtained from ALZA Corp. and Upjohn were also examined.

(12) These samples were obtained from J. E. Pike (Upjohn).

(13) Through-space coupling of transition moments yields CD couplets. This effect is the basis of the aromatic exciton method for determining chirality; see N. Harada and K. Nakanishi, *Acc. Chem. Res.*, **5**, 257 (1972). Unfortunately each olefin presents a number of transition moments of unknown orientation relative to the nodal plane, which might couple, and no method for calculating variation in CD spectra with relative orientation is apparent to us.

(14) We assume that restriction of rotation within the α side chain and side chain alignment are in part associated with the disruption of solvent structure inherent in a more random distribution among the conformations possible. Side-chain alignment is thus more favorable in largely aqueous media, less so in less polar solvents.

(15) Models IIIa and IIIb, $PGF_1\alpha$, 15-epi-$PGF_1\alpha$, and 5-*trans*-$PGF_2\alpha$ (IIId) all show no media or pH effects on their CD spectra.

(16) Other studies on $PGF_2\alpha$ indicate solubility without notable association up to the CMC, listed by pH; >3 m*M* (3), >8 m*M* (5), 21 m*M* (6), and 26 m*M* (pH 8): T. J. Roseman and S. H. Yalkowsky, *J. Pharm. Sci.*, **62**, 1680 (1973).

(17) The carboxyl group is reported to show both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ CD transitions in the 190–210-nm energy span: P. Crabbé in "ORD and CD in Chemistry and Biochemistry, an Introduction", Academic Press, New York, N.Y., 1972 pp 50–54.

(18) It should be noted that hydroxyl $n \rightarrow \sigma^*$ CD transitions also occur in this region: D. N. Kirk, W. P. Mose, and P. M. Scopes, *J. Chem. Soc., Chem. Commun.*, 81 (1972). For each olefinic alcohol examined, we have also examined the saturated analogs. In all cases the saturated compounds do not display CD effects of this magnitude. In reviewing the earlier draft of this communication (which did not include the data on 15-epi-PGF's), a referee suggested that the lack of significant $n \rightarrow \sigma^*$ CD activity in the saturated alcohols does not eliminate the possibility that the C-9 and C-11 hydroxyls interact with the double bond at the 5,6 and 13,14 positions and that apparent coupling between the olefinic chromophores is mediated by coupling of the cis-hydroxyl $n \rightarrow \sigma^*$ transitions rather than being a direct through-space interaction. We counter the argument by noting that the models, $PGF_1\alpha$ and 13,14-dihydro-$PGF_2\alpha$, contain each possible hydroxyl–olefin system and the the CD of 15-epi-$PGF_2\alpha$, which retains all the features of the referee's indirect coupling mechanism, does not display a media dependency like that of biologically potent prostaglandins.

(19) Alfred P. Sloan Foundation Fellow, 1972–1974; Camille and Henry Dreyfus Teacher–Scholar, 1974–1979.

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