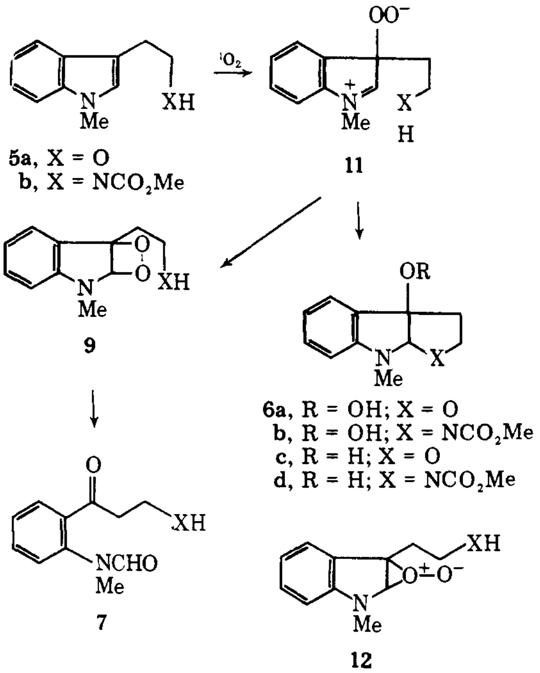

in terms of a stepwise mechanism involving a zwitterion (**10** or **11**), not by a concerted mechanism.[20] Thus the zwitterions (**10, 11**) are intercepted by the nucleophiles at low temperatures to give the hydroperoxides (**3, 6**) or rearrange to the dioxetanes (**8, 9**) at ordinary temperature.[22] According to the MINDO/3 calculations, the zwitterion, an initial intermediate in enamine-singlet oxygen reaction, has been predicted to undergo rearrangement to a dioxetane with a relatively high activation energy compared to that for other processes such as rearrangement to a perepoxide.[6a] If so, it seems very likely that the lifetime of the zwitterions (**10, 11**) will be longer at lower temperature, permitting the trapping reactions more efficiently. The product ratio (**6**/**7**) is also solvent dependent. Polar solvents appear to increase the ratio of the dioxetane mode products (**7**) to the trapping reaction at least at 20 °C (Table I), although the solvent effect is still obscure. It is known that polar solvents increase the ratio of dioxetane formation to ene reaction.[21a,d,23]

In order to get the spectroscopic evidence for the initial intermediate, we carried out the photooxygenation of **5a** at −70 °C in an NMR cell. The NMR spectrum (−70 °C) of the reaction mixture in CD_3OD or $CDCl_3$ had only the resonances of **6a**. Neither zwitterion **11** nor dioxetane **9** could be detected at the temperature.[24] The spectroscopic studies at −70 °C provided no direct evidence in support of the zwitterions; however, we believe that the results described here may represent chemical evidence for the intermediacy of the zwitterionic peroxides.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan and the Japan Society for the Promotion of Science.

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(9) Irradiation was made with a tungsten-bromine lamp through an aqueous $CuCl_2$–$CaCl_2$ filter solution.
(10) The hydroperoxide **3a** readily decomposed in methanol with $\tau_{1/2}$ of ca. 15 min at 30 °C to give a complex mixture of products including **2** (30%) and polymeric materials.
(11) All new compounds gave satisfactory elemental analyses and mass spectral data.
(12) Viscous oil: starch-KI test positive; UV (EtOH) 245, 294 nm; NMR ($CDCl_3$) δ 1.58 (s, 3 H, Me), 2.90 (s, 3 H, NMe), 3.58 (s, 3 H, OMe), 4.45 (s, 1 H, NCHO), 6.30–7.40 (m, 4 H, arom H), 9.70 (s, OOH).
(13) Bp 110 °C/1 mmHg; UV (EtOH) 241 (log ϵ 3.57), 285 nm (log ϵ 3.20); NMR ($CDCl_3$) δ 1.60 (s, 3 , Me), 3.18 (s, 3 H, NMe), 3.23 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 4.28 (s, 1 H, NCHO), 6.50–7.10 (m, 4 H, arom H).
(14) Viscous oil: starch-KI test positive; UV (EtOH) 247, 295 nm; NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.55 (s, 3 H, Me), 2.88 (s, 3 H, NMe), 3.80 (q, 2 H, J = 7 Hz, CH_2CH_3), 4.50 (s, 1 H, NCHO), 6.30–7.40 (m, 4 H, arom H), 9.65 (s, OOH).
(15) Brief refluxing or standing (1 h) at room temperature of the solutions of **6a** and **6b** gave **6c** and **6d**, respectively, in quantitative yield.
(16) Recently, Nakagawa et al.[17] have reported the formation of **6b**, **6d**, and **7b** in the photooxygenation of **5b** in pyridine–methanol. The spectral data of **6b**, **6d**, and **7b** were identical with those obtained by the authors. We are indebted to Professors T. Hino and M. Nakagawa for disclosure of their results prior to publication.
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(19) The possibility that **3** and **6** are formed from the dioxetane **8** and **9**, respectively, cannot be ruled out completely, since the chemistry of indole dioxetanes has never been known. However, the temperature dependency and the solvent effect on the formation of **6** are not satisfactorily explained by the dioxetane mechanism, whereas the MINDO/3 calculations[6a] have predicted that polar solvents increase the ratio of the rearrangement of zwitterion (11) to dioxetane (**9**) in accordance with the experimental results.
(20) Perepoxide such as **12** might also be proposed to explain the formation of **6a,b**. While perepoxides have been proposed to rearrange to ene products and/or dioxetanes,[6a,21] there is no precedent in which perepoxides have been considered to react with alcohols or amines. Note that the compounds (**1**, **5**) having allylic hydrogens do not yield the ene products.
(21) (a) N. M. Hasty and D. R. Kearns, *J. Am. Chem. Soc.*, **95**, 3380 (1973); (b) A. P. Schaap and G. R. Faler, *ibid.*, **95**, 3381 (1973); (c) L. M. Stephenson, D. E. McClure, and P. K. Sysak, *ibid.*, **95**, 7888 (1973); (d) W. Ando, K. Watanabe, J. Suzuki, and T. Migita, *ibid.*, **96**, 6766 (1974).
(22) Analogy for this process has been suggested in the reaction of hydroperoxides of pyrroles and imidazoles with base: (a) G. Rio, A. Ranjon, O. Pouchot, and M-J. Scholl, *Bull. Soc. Chim. Fr.*, 1667 (1969); (b) E. H. White and M. J. C. Harding, *Photochem. Photobiol.*, **4**, 1129 (1965).
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(24) The NMR spectrum (−70 °C) of the reaction mixture resulting from the photooxygenation of 1 (CD_3OD, −70 °C) also showed the presence of **3c** as a sole product.

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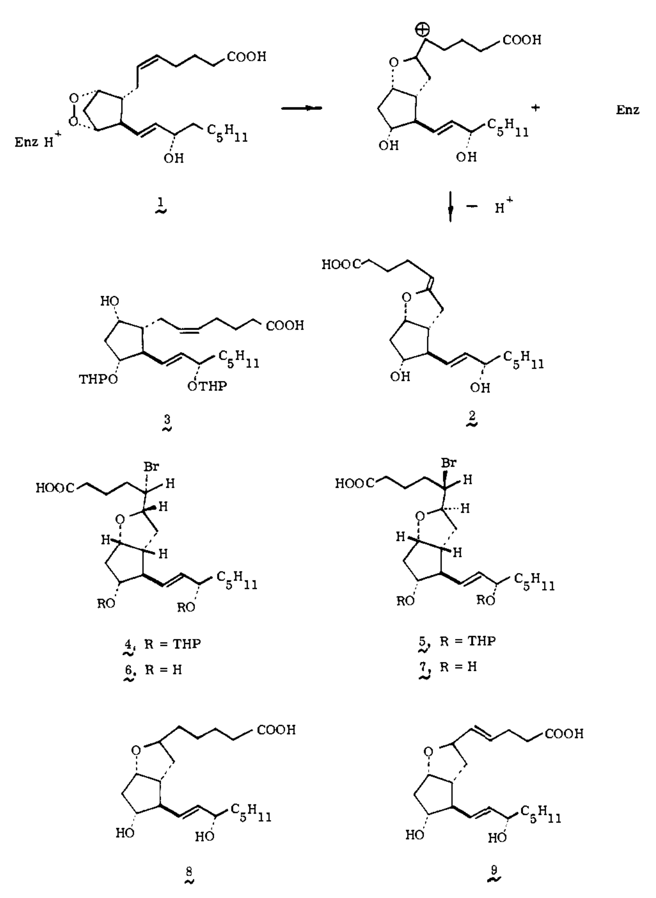
Synthesis of Vane's Prostaglandin X, 6,9α-Oxido-9α,15α-dihydroxyprosta-(*Z*)5,(*E*)13-dienoic Acid

Sir:

Vane and co-workers have recently obtained evidence for the formation of a new and remarkably active prostaglandin, termed PGX, from the prostaglandin endoperoxides PGG_2 or PGH_2 and microsomal fractions of certain tissues, especially aorta, arterial wall, and fundus of stomach.[1,2] Vane's PGX inhibits platelet aggregation as do PGE_1 and PGD_2, but is several times more potent; it also causes relaxation of arterial smooth muscle. Although no structure was proposed for PGX,



the genesis from the PG-endoperoxides (e.g., PGH_2, **1**), the sensitivity to acid in aqueous solutions (rapidly increasing below pH 7), and its probable intermediacy in the formation of 6-oxo-$PGF_{1\alpha}$,[1-3] all suggest that PGX is an internal enol ether of the latter, most likely a 6,9-enol ether **2**, which can arise as shown. This possibility has now been confirmed by an unambiguous synthesis of PGX from $PGF_{2\alpha}$ of natural configuration which also permits the assignment of the *Z* geometry to the 5,6-double bond of PGX as in **2**.

Reaction of the 11,15-bistetrahydropyranyl ether of prostaglandin $F_{2\alpha}$[4] (**3**) in THF-chloroform (25 mL/g of **3**) with 1.1 equiv of *N*-bromosuccinimide at 23 °C for 1 h afforded the diastereomeric bromo ethers **4** and **5**.[5] Although these ethers were not readily separable by thin layer chromatography (TLC), depyranylation (acetic acid-water-tetrahydrofuran 3:1:1 at 45 °C for 4 h) afforded the easily separable dihydroxy bromo ethers **6** and **7** in a ratio of ca. 3:1 (81% yield overall from **3**; observed R_f values on silica gel TLC plates with benzene-dioxane-acetic acid 20:10:1 as solvent, 0.23 for **6** and 0.28 for **7**).[5] The NMR and infrared spectra of **6** and **7** clearly indicate the absence of the *cis*-5,6-olefinic unit and the retention of the trans-13,14-double bond.

Treatment of the major bromo ether **6** with excess potassium *tert*-butoxide in *tert*-butyl alcohol at 45 °C for 1.5 h to effect elimination of hydrogen bromide, concentration, *rapid* extraction of product with ether from a pH 5 aqueous layer cooled to 0 °C, and treatment with diazomethane afforded the acid sensitive methyl ester of **2**.[5,6] In contrast the stereoisomeric bromo ether **7** was recovered virtually unchanged after exposure to potassium *tert*-butoxide under the conditions outlined above. These results indicate that the proton attached to C-6 in the bromo ethers **6** and **7** are exo and endo (i.e., less sterically hindered and more hindered), respectively, relative to the bicyclic nucleus, and together with the well-known trans addition pathway for bromo ether formation allow designation of the stereochemistry of **6** and **7**. Further, the trans-coplanar course of E_2 elimination from **6** (which clearly would be followed here) must produce the *Z* geometry of the 5,6-double bond as shown in formula **2**. Thus, the prostanoid **2** is readily available from **3** by an unambiguous and stereocontrolled synthetic route.

Independent evidence for structure **2** was obtained by the extremely facile and clean hydrolysis of the methyl ester of **2** (in THF-0.01 M hydrochloric acid 3:1 at 23 °C for 10 min) to a more polar substance of R_f 0.17 in ether-acetone (3:1), which was characterized as 6-keto-$PGF_{1\alpha}$ methyl ester by conversion to the known[5] *O*-benzyloxime derivative.[3d,7]

Samples of **2** were obtained for bioassay as the pyrrolidine salt by prompt treatment of the cold ethereal extract (described above) with 2–3 equiv of pyrrolidine, rapid concentration <0 °C under vacuum and storage at −78 °C in the presence of a little potassium carbonate. Solutions for biological testing were prepared by addition of cold (−78 °C) ethanol to the pyrrolidine salt and then adding an aliquot of this standard ethanolic solution (kept at −78 °C) to cold (0 °C) aqueous bicarbonate solution (pH 8.5–9) or pH 9 Tris buffer.

Bioassays of synthetic **2** in two different laboratories demonstrated all the biological properties previously described for Vane's PGX.[1,2,8]

The ease of deactivation of PGX (**2**) by spontaneous hydrolysis to 6-keto-$PGF_{1\alpha}$ places limits on the kinds of experiments which can be performed with this substance and it is obviously desirable to synthesize close structural analogues of PGX which lack the labile enol ether function of **2**. Toward this end we have synthesized both of the 6-epimeric 5,6-dihydro derivatives (**8**) of PGX and both of the 6-epimeric E-$\Delta^{4,5}$ isomers (**9**). The two C-6 epimers of **8**[5] were obtained from **3** (90% overall yield) by the sequence: (a) reaction with 1.2 equiv of mercuric trifluoroacetate in THF-$CaCO_3$ at 23 °C for 1 h, (b) treatment of the 5-mercuri-6,9-ether with excess sodium borohydride in ethanol at −20 °C for 1 h, and (c) depyranylation (acetic acid-THF-water 3:1:1 at 45 °C for 4 h). Chromatographic separation afforded a major and a minor product (ratio 3.8:1) having R_f values of 0.21 and 0.23 (silica gel plates, benzene-dioxane-acetic acid 20:10:1). By analogy with bromo ether formation from **3**, the major isomer of **8** is expected to have the appendage at C-6 in the endo orientation.

The two C-6 epimers of **9** were synthesized from **3** by the sequence (a) reaction with 1.2 equiv of benzeneselenenyl bromide and 1 equiv of calcium carbonate in THF at −20 °C for 10 min and 0 °C for 1 h, (b) depyranylation, as described above, and (c) reaction with 10 equiv of hydrogen peroxide in THF at 0 °C for 16 h. The two epimers of **9**[5] (ratio 1:1, 69% overall from **3**) could be separated chromatographically (R_f values 0.21 and 0.26 in benzene-dioxane-acetic acid 20:10:1 solvent system on silica gel plates).

The results of biological studies with the PGX analogues **8** and **9** will be reported later.[9,10]

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(5) Satisfactory spectral data were obtained on chromatographically homogeneous material.
(6) The infrared spectrum of the methyl ester of **2** revealed in addition to the ester carbonyl at 1730 cm^{-1} a C=C stretching band indicative of enol ether at 1675 cm^{-1}. The ^1H NMR spectrum of this methyl ester exhibited peaks due to vinyl protons at δ 5.45 (2 H, H-13 and H-14) and 4.55 (1 H, H-5), the latter agreeing with expectations for the enol ether unit. The mass spectrum of the bisdimethylsilyl derivative showed the molecular ion (*m/e* 510) as

the strongest peak and the expected fragmentation peaks. Thin layer chromatographic analysis of the methyl ester of 2 using silica gel plates freshly treated with ethereal ammonia revealed a single spot of R_f 0.51 (ether-acetone 3:1). Full spectral details on 2 and intermediates are available from the authors. An unambiguous synthesis of the biologically less active 5,6-(*E*)-isomer of 2 (methyl ester of which shows pmr peak for H-5 at δ 4.77) will be described elsewhere.

(7) Excess pyridine and *O*-benzylhydroxylamine hydrochloride were added directly to the hydrolysis mixture and after 3 h at 60 °C the O-benzyl oxime of 6-keto-PGF$_{1\alpha}$ was isolated. Silylation was accomplished by treatment with *N*-trimethylsilylimidazole in THF at 23 °C for 1 h. The mass spectrum showed in addition to the molecular ion at *m/e* 705 all the expected fragments (see ref 3d).

(8) These tests were kindly carried out by Dr. Babette Weksler, Cornell University Medical College, and Dr. Peter Ramwell and associates, Georgetown University School of Medicine (see *Clin. Res.*, in press; *Prostaglandins*, in press).

(9) This research was assisted financially by a grant from the National Science Foundation and also the award of an IREX Fellowship to Istvan Székely.

(10) Note Added in Proof: Subsequent to the submission of this manuscript for publication a report has appeared (*Chem. Eng. News*, Dec 20, 1976) indicating that Vane and co-workers also assign structure 2 to PGX.

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Mixed Charge Exchange-Chemical Ionization Mass Spectrometry of Polycyclic Aromatic Hydrocarbons

Sir:

The exact structural identification of polycyclic aromatic hydrocarbons (PAH) and their alkylated derivatives is a difficult problem, particularly when they are encountered as complex mixtures. The analytical power of mass spectrometry, which has had wide application in this field,[1-4] has been limited because electron impact mass spectra of isomeric PAH are almost identical. The purpose of this note is to report that charge exchange-chemical ionization mass spectrometry, using an argon-methane reagent gas,[5] easily differentiates PAH isomers.

The mass spectra of a series of PAH were measured with a Hewlett-Packard 5982A gas chromatographic-mass spectrometer system by injecting approximately 200 ng of each compound (dissolved in methylene chloride) on a 180 × 0.32 cm o.d. stainless steel column packed with 3% Dexsil 300 on 80/100 mesh Chromosorb W. The reagent gas mixture (10% methane in argon) served as the carrier gas for the gas chromatographic column which was held isothermally at a temperature appropriate to each sample being analyzed. The mass spectrometer was continuously scanned from 50 to 350 amu at 81.2 amu/s. The ion source pressure was 0.8 Torr and its temperature was 170 °C. Data were collected and processed by a HP 5933A data system. Precautions were taken to assure the absence of water vapor in the ion source, since water is an excellent proton donor and can greatly increase the abundance of the protonated molecular ion. In these experiments, there were no observable traces of water vapor (*m/e* 18 or 19).

The resulting mass spectra showed considerable differences in the relative abundances of the molecular (M^+) and protonated molecular ($M + 1^+$) ions when different PAH isomers were analyzed. Table I lists the compounds analyzed in this study, the resulting ratio of the abundance of the protonated molecular to molecular ion ((M + 1)/M), and the first ionization potential of each compound. It is obvious from this table that the (M + 1)/M ratio has a high positive correlation with ionization potential ($r = 0.877$, $P \ll 0.01$). This trend is consistent with the expectation that as the ionization potential increases, charge transfer processes will be less effective for electron extraction while at the same time protonation becomes more favorable.

Table I. Abundance Ratios for Selected PAH Obtained by CH_4-Ar Chemical Ionization Mass Spectrometry

Compound	Formula	First ionization potential (eV)[a]	Abundance ratio, (M + 1)/M[b]
Pentacene	$C_{22}H_{14}$	6.42	0.32
Tetracene	$C_{18}H_{12}$	6.88	0.45
Anthanthrene	$C_{22}H_{12}$	7.02	0.38
Perylene	$C_{20}H_{12}$	7.03	0.32
Benzo[*a*]pyrene	$C_{20}H_{12}$	7.17	0.73
Anthracene	$C_{14}H_{10}$	7.42	0.82
Benz[*a*]anthracene	$C_{18}H_{12}$	7.47	0.83
Dibenz[*a,h*]anthracene	$C_{22}H_{14}$	7.55	0.95
Pyrene	$C_{16}H_{10}$	7.56	0.73
Coronene	$C_{24}H_{12}$	7.58	0.66
Benzo[*e*]pyrene	$C_{20}H_{12}$	7.58	0.82
Acenaphthene	$C_{12}H_{10}$	7.70	1.00
Chrysene	$C_{18}H_{12}$	7.74	1.26
Fluoranthene	$C_{16}H_{10}$	7.76	1.57
Fluorene	$C_{13}H_{10}$	7.86	1.66
Acenaphthylene	$C_{12}H_8$	8.02	1.34
Phenanthrene	$C_{14}H_{10}$	8.02	1.59
Triphenylene	$C_{18}H_{12}$	8.11	1.73
Naphthalene	$C_{10}H_8$	8.14	1.68
Benzene	C_6H_6	9.29	5.79

[a] Values were averaged from experimental data found in ref 6-8; their variability was usually less than ±0.1 eV. [b] The reproducibility of these measurements was ±4% over a 3-month period. The ratios have been corrected for the natural abundance of ^{13}C.

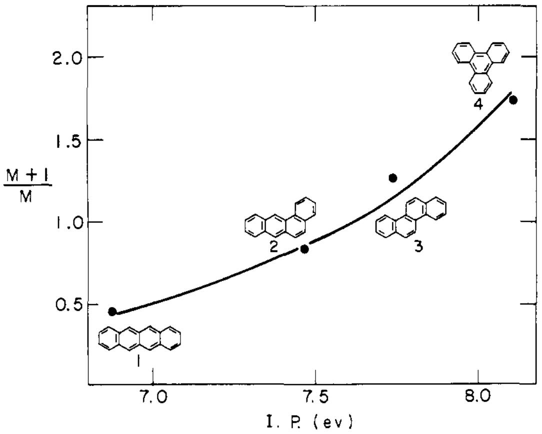

Figure 1. Plot of the abundance ratio ((M + 1)/M) obtained by CH_4-Ar chemical ionization mass spectrometry as a function of ionization potential (IP) for a series of four tetracyclic polycyclic aromatic hydrocarbons: 1, tetracene; 2, benz[*a*]anthracene; 3, chrysene; 4, triphenylene.

This technique should be quite useful for the elucidation of specific isomeric structures of PAH. By using a mixed charge exchange-chemical ionization reagent gas, such as described here, different mass spectra can be obtained for most PAH isomers while conventional mass spectral techniques provide little differentiation. This fact is demonstrated by the series of tetracyclic compounds shown in Figure 1. The (M + 1)/M ratio of each compound is plotted as a function of its first ionization potential. It is interesting to note that this abundance ratio increases from 0.45 to 1.73 as the isomer becomes more nonlinear, making differentiation quite easy. If a standard PAH compound were not available, it seems probable that the mass spectrum of that compound could be predicted from its ionization potential. The ability to calculate ionization potentials from molecular orbital theory[7,8] offers considerable promise for the future identification of presently unknown PAH.