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(32) We believe that this loss of absorbance at 300 nm in more concentrated (0.02–0.08 M) mercaptoethanol solution is due to Michael reaction of RSH with $RSCH{=}CHCOCH_3$ to give $(RS)_2CHCH_2COCH_3$.

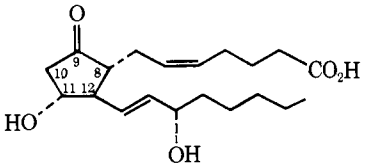
Acid- and Base-Catalyzed Dehydration of Prostaglandin E_2 to Prostaglandin A_2 and General-Base-Catalyzed Isomerization of Prostaglandin A_2 to Prostaglandin B_2

S. K. Perera and L. R. Fedor*

Contribution from the Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260. *Received June 29, 1979*

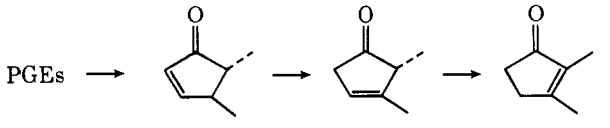
Abstract: Dehydration of prostaglandin E_2 (PGE_2) to prostaglandin A_2 (PGA_2) in aqueous solution is catalyzed by hydrogen ion (k^d_H), hydroxide ion (k^d_{OH}), and quinuclidine (k^d_A). The values of k^d_H and k^d_{OH} are very similar to those for various known enolization reactions and $k^d_H(H_2O)/k^d_H(D_2O) = 0.6$, results that support a mechanism involving rate-determining enolization of PGE_2 during dehydration. Isomerization of PGA_2 to prostaglandin B_2 (PGB_2) is general base catalyzed by tertiary amines with $k^i_A(H_2O)/k^i_A(D_2O) = 1.1$. The rate constants k^i_A and k^i_{OH} for loss of PGA_2 are equal to those for formation of PGB_2 and it is suggested that C-12 proton abstraction is rate determining in the reaction sequence $PGA_2 \rightarrow PGC_2 \rightarrow PGB_2$.

The clinical usefulness of prostaglandin E_2 (PGE_2) in



PGE_2

human reproduction[1-5] coupled with its chemical instability in aqueous solution[6-13] has prompted a research activity directed toward preparation of PGE_2 prodrugs and pharmaceutical formulations[14-17] that retain biological activity and possess greater stability. The chemical instability of E and A series prostaglandins was shown[6-13] to involve dehydration of the 9,11-ketol to PGAs in acidic and alkaline solution (eq 1), isomerization of PGAs to PGCs in alkaline solution (eq 1), isomerization of PGCs to PGBs in alkaline solution (eq 1),



PGAs PGCs PGBs (1)

epimerization of PGE_1 to 8-iso-PGE_1 in ethanolic potassium acetate, epimerization of prostaglandins to 15-epiprostaglandins in dilute acid, and allylic rearrangement of 15-epi-PGA_2 to the 13-hydroxy diastereomers of PGA_2. Biochemical transformations of prostaglandins catalyzed by enzymes include dehydration of PGE_2 to PGA_2,[18-20] isomerization of PGAs to PGCs,[21-23] isomerization of PGCs to PGBs,[20] reduction of the 9-keto group to the carbinol,[24,25] oxidation of the C-15 carbinol to the ketone,[26,27] and reduction of the Δ^{13} double bond.[28,29] Little is known of the chemistry of the dehydratase and isomerase enzymes except that they are inhibited by sulfhydryl reagents and they likely do not require cofactors.[18-21,23]

This study was undertaken to probe the nature of the acid-base-catalyzed dehydration-isomerization sequence $PGE_2 \rightarrow PGA_2 \rightarrow PGC_2 \rightarrow PGB_2$ depicted in eq 1 with a view to contributing to a better understanding of the mechanisms of these transformations. Owing to the variety of prostaglandin chemistry that takes place simultaneously in aqueous solution at any pH, the rate constants reported in this kinetics study do not strictly represent the chemistry of eq 1: 8- and 15-epi-PGE_2 and PGA_2 should be formed during dehydration. However, these epimers are expected to have similar reactivities to PGE_2 and PGA_2 with respect to ring dehydration-isomerization and we suggest that our conclusions of mechanism are little affected by these extraneous events.

Experimental Section

Apparatus. Gilford Model 2400, Beckman Model DBG, and Cary Model 118 spectrophotometers were used. Temperature was maintained with a Tamson T9 circulating water bath connected to thermospacers in the Gilford spectrophotometer. pH measurements were made with a Radiometer PHM 26 meter with GK2321B or GK2321C electrodes.

Reagents. PGE_2 was a gift from Upjohn Co. All reagents were Fisher certified ACS grade except quinuclidine, quinuclidinol (Aldrich), triethylamine (Eastman), D_2O, DCl (99.9% D) (Stohler Isotope Chemicals), K_2HPO_4, and K_3PO_4 (Sigma). Line distilled water was redistilled through a Corning AGla still before use.

Kinetics. All solutions had a calculated ionic strength of 0.5 M (KCl) unless otherwise stated. The temperature of reactions was 30 ± 0.1 °C. The pHs of reactant solutions were measured and found to be constant (±0.04 pH) for all serial dilutions except HCl/KCl and KOH/KCl. Reactions were run under pseudo-first-order conditions and were initiated by addition of PGE_2 in absolute ethanol to aqueous solutions of reactants. The concentration of ethanol was ca. 1% and that of PGE_2 ca. 10^{-4}–10^{-5} M in the 3-mL cuvettes. pK_a values were determined by the method of fractional neutralization. pD was determined from the pH meter reading by adding 0.4 to it.[30] Hydroxide ion activity was determined from K_w/a_H where $pK_w = 13.83$ at 30 °C[31] and deuterioxide ion activity was determined from K_D/a_D where $pK_D = 14.65$ at 30 °C.[32]

Reaction of PGE_2 with hydroxide solution is characterized by an initial increase in optical density (OD) followed by a slower decrease at 224 nm. This decrease is accompanied by an increase in OD at 280

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Table I. Rate Data for Dehydration of PGE_2 to PGA_2 in Aqueous Solution[a]

catalyst	k^d_2, M^{-1} min^{-1} [c]	fraction of base	concn range of catalyst, M	no. of k_{obsd}
Q[b]	1.48 ± 0.07	0.4	0.002-0.02	16
Q	1.60 ± 0.03	0.5	0.001-0.02	15
Q	2.23 ± 0.03	0.6	0.002-0.02	8
OH^-	16.0 ± 0.7		0.01-0.1	23
HCl[d]	0.004 31 ± 0.000 02		0.05-1.0	13
DCl[d]	0.006 97 ± 0.000 54		0.5-1.0	6

[a] $t = 30 \pm 0.1$ °C, $\mu = 0.5$ (KCl), reactions monitored at 224 nm. [b] All Q's are quinuclidine in 0.01 M phosphate buffer, $pK_a(Q) = 11.25$. [c] k^d_2 is a general expression for the second-order rate constant for dehydration of PGE_2 catalyzed by Q (k^d_A), OH^- (k^d_{OH}), and HCl, DCl (k^d_H, k^d_D). [d] $\mu = 1.0$ (KCl).

nm. The OD increase at 224 nm is due to formation of the conjugated ketone system in PGA_2 by dehydration of PGE_2.[33] The subsequent decrease in OD at 224 nm is due to loss of PGA_2 by isomerization and the corresponding increase in OD at 280 nm is due to the formation of another conjugated ketone, PGB_2 (eq 1).[33] Kinetically these reactions are

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

reactions,[34] and k_1 and k_2 are pseudo-first-order rate constants. The concentration of B (PGA_2) at any time is given by $[B] = A_0k_1/(k_2 - k_1)\{(e^{-k_1t} - e^{-k_2t})\}$ where A_0 is the concentration of PGE_2 at zero time. For large values of t, k_2 was determined from the slopes of plots of $\ln (OD_t - OD_\infty)$ vs. t. The constant k_1 was determined from slopes of plots of $\ln \{e^{-k_2t} - [(OD_t - OD_\infty)/C]\}$ vs. t. C is a constant and is the y intercept of those plots used to determine k_2. Plots were linear to 75% reaction or beyond.

Reactions of PGE_2 with hydroxide ion, triethylamine, quinuclidine, and quinuclidinol solutions were studied at 280 nm and were characterized by an initial lag period followed by a usual rectangular hyperbolic OD increase vs. t due to the formation of PGB_2. No Michael addition of hydroxide ions to PGB_2 was detected as evidenced by stable OD_∞ values for these reactions under the conditions of the study. Pseudo-first-order rate constants were obtained from slopes of plots of $\ln \{(OD_\infty - OD_0)/(OD_\infty - OD_t)\}$ vs. t. Plots were linear to 75% reaction or beyond when arbitrary $t = 0$ was taken beyond the initial lag period.

Reactions of PGE_2 with quinuclidine solutions, monitored at 224 nm, are experimentally complicated by the virtually instantaneous reaction of the product PGA_2 with the amine as well as by the poor transparency of amine solutions at this wavelength. The reaction results in decreased absorption at 224 nm and this decrease is a function of amine concentration. We ascribe this to addition of quinuclidine and a proton across the 10,11-olefin bond of PGA_2.[15] However, dehydration of PGE_2 and isomerization of PGA_2 catalyzed by dilute quinuclidine solutions in 0.01 M phosphate buffer to maintain constant pH were studied at 224 nm. No catalysis by the phosphate buffer was detected, although no systematic study of phosphate buffer catalysis was made. Pseudo-first-order rate constants were calculated for an $A \rightarrow B \rightarrow C$ sequence as described above.

Optical density increase at 224 nm vs. time was recorded to follow the dehydration of PGE_2 to PGA_2 in aqueous HCl. Pseudo-first-order rate constants were obtained from the slopes of plots of $\ln \{(OD_\infty - OD_0)/(OD_\infty - OD_t)\}$ vs. t and they were linear to 75% reaction or beyond. The OD_∞ value decreased with time for reactions run in HCl solutions more concentrated than 3 M. The equilibrium constant $K_e = [PGA_2]/[PGE_2] = 161$ was calculated from ϵ_{224} 595 M^{-1} cm^{-1} (five measurements) for PGE_2, ϵ_{224} 10 715 M^{-1} cm^{-1} for PGA_2,[35] the concentration of added PGE_2 (=PGE_2 + PGA_2), and OD at equilibrium.

Results

Dehydration of PGE_2. Dehydration of PGE_2 to PGA_2 in dilute potassium hydroxide solution obeys the rate law

$$d[PGA_2]/dt[PGE_2] = k_{obsd} = k^d_{OH}a_{OH} \quad (2)$$

where a_{OH} is the activity of hydroxide ion determined from the pH of reactant solutions and pK_w. The constant k^d_{OH} (Table I) was evaluated by dividing k_{obsd} by a_{OH} for unbuffered runs at pH >11. The equilibrium dehydration of PGE_2 to PGA_2 in dilute acid solution obeys the rate law

$$d[PGA_2]/dt[PGE_2] = k_{obsd} = k^d_H a_H \quad (3)$$

where a_H is the activity of the hydrogen ion. The constant k^d_H (Table I) was obtained by dividing k_{obsd} by a_H for runs in dilute HCl/KCl solutions. From $K_e = 161$, the rate constant for dehydration is 4.28×10^{-3} M^{-1} min^{-1} and that for hydration is 2.66×10^{-5} M^{-1} min^{-1}. The deuterium solvent kinetic isotope effect (KIE), H_2O/D_2O, is 0.62 (Table I).

Dehydration of PGE_2 to PGA_2 catalyzed by dilute quinuclidine (Q) solutions buffered with 0.01 M phosphate follows the rate law[57]

$$d[PGA_2]/dt[PGE_2] = k_{obsd} = k^d_A f_B[Q_t] + k^d_{OH}a_{OH} \quad (4)$$

The constant k^d_A (Table I) was obtained by dividing the slopes of plots of k_{obsd} vs. $[Q_t]$, where $[Q_t] = [Q] + [QH]$, by f_B, the fraction of base form of Q present in the Q/QH buffer solution.

Isomerization of PGA_2. In dilute potassium hydroxide solution, isomerization of PGA_2 followed at 224 and 280 nm obeys the rate law

$$-d[PGA_2]/dt[PGA_2] = d[PGB_2]/dt[PGA_2] = k_{obsd} = k^i_{OH}a_{OH} + k_0 \quad (5)$$

The rate constant k^i_{OH} (Table II) was evaluated for each wavelength as the slope of a plot of k_{obsd} vs. a_{OH} and the two constants are identical within the limits of experimental error. The intercept k_0 has the value 0.001 ± 0.0019 min^{-1}. We believe that k_0 is real, although its value is uncertain, because plots of k_{obsd} vs. concentration of amine for isomerization reactions run in aqueous amine solutions (vide infra) consistently gave intercepts at a variety of pHs that were larger than those computed from $k^i_{OH}a_{OH}$ by ca. 1.5×10^{-3} min^{-1}.[58]

Isomerization of PGA_2 to PGB_2 in very dilute quinuclidine (Q) solutions buffered with 0.01 M phosphate and monitored at 224 nm obeys the rate law

$$-d[PGA_2]/dt[PGA_2] = k_{obsd} = k^i_A f_B[Q_t] + k^i_{OH}a_{OH} + k_0 \quad (6)$$

Table II. Rate Data for Isomerization of PGA_2 to PGB_2 in Aqueous Solution[a]

catalyst[b]	k^i_2, M^{-1} min^{-1} [e]	fraction of base	concn range of catalyst, M	no. of k_{obsd}
Q[c]	1.13 ± 0.26	0.4	0.002-0.02	20
Q[c]	0.92 ± 0.06	0.5	0.001-0.02	16
Q[c]	0.73 ± 0.07	0.6	0.002-0.02	9
Q	1.43 ± 0.08	0.5	0.02-0.2	9
Q	1.09 ± 0.07	0.6	0.02-0.2	9
Qol	0.005 48 ± 0.000 04	0.5	0.04-0.2	6
TEA	0.0235 ± 0.0012	0.4	0.05-0.5	10
TEA	0.0324 ± 0.0016	0.5	0.05-0.5	10
TEA	0.0327 ± 0.0017	0.6	0.05-0.5	10
TEA (D_2O)[f]	0.0266 ± 0.000 44	0.5	0.1-0.5	6
OH^-[d]	1.59 ± 0.05		0.01-0.1	20
OH^-	1.69 ± 0.19		0.01-0.1	20

[a] $t = 30 \pm 0.1$ °C; $\mu = 0.5$ (KCl); reactions monitored at 280 nm unless otherwise stated. [b] Quinuclidine (Q), $pK_a = 11.25$; quinuclidinol (Qol), pK_a 9.95; triethylamine (TEA), $pK_a = 10.84$. [c] Quinuclidine in 0.01 M phosphate buffer; reactions monitored at 224 nm. [d] Reactions monitored at 224 nm. [e] k^i_2 is a general expression for the second-order rate constant for isomerization of PGA_2 catalyzed by amines (k^i_A) and hydroxide ion (k^i_{OH}). [f] pK_a (D_2O) = 11.47.

where f_B and Q_t are previously identified symbols (vide supra). The rate constant k^i_A (Table II) was obtained by dividing the slopes of plots of k_{obsd} vs. $[Q_t]$ at constant buffer ratio by f_B. The rate law of eq 6 also holds for isomerization of PGA_2 to PGB_2 catalyzed by triethylamine (TEA) and quinuclidinol (Qol) monitored at 280 nm. For the TEA-catalyzed reaction the deuterium solvent KIE, H_2O/D_2O, is 1.1. Isomerization of PGA_2 to PGB_2 followed at 280 nm and catalyzed by higher concentrations of Q than were used to monitor the same reaction at 224 nm obeyed the rate law

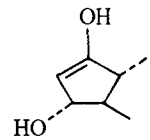
$$d[PGB_2]/dt[PGA_{2_t}] = k^{cor}_{obsd} = k^i_A f_B[Q_t]/(Kf_B[Q_t][H^+] + 1) \quad (7)$$

where $[PGA_{2_t}] = [PGA_2] + [PGA_2\text{-Q adduct}]$ (Experimental Section), $k^{cor}_{obsd} = k_{obsd} - (k^i_{OH}a_{OH} + k_0)$, f_B and Q_t are as previously defined (vide supra), and $K = [PGA_2\text{-Q adduct}]/[PGA_2][Q_t]f_B[H^+]$. The constants k^i_A (Table II) and K were evaluated by plotting $1/k^{cor}_{obsd}$ vs. $1/[Q_t]$, which gave $k^i_A = 1/(\text{slope} \times f_B)$ and $K = k^i_A\,(\text{intercept})/[H^+]$. The values of K at pH 11.24 and 11.57 are 5.9×10^{12} and 4.6×10^{12} M^2, respectively. Equation 7 reduces to eq 6 when very low concentrations of Q, such as were used in the isomerization of PGA_2 to PGB_2 followed at 224 nm, are used.

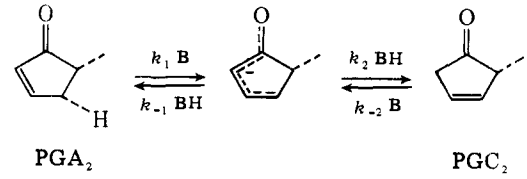
Discussion

Dehydration of PGE_2. Hydroxide ion catalyzed dehydration of PGE_2 to PGA_2 is the fastest detectable reaction on the path to PGB_2 (eq 1). The reactivity of PGE_2 is virtually identical with that of 9-hydroxy-10-methyl-*cis*-decalone-2,[36] also a cyclic β-ketol, that has been shown to undergo dehydration to 10-methyl-$\Delta^{1,9}$-octalone-2 via the enolate anion formed by deprotonation of C-1. Following this work of Spencer et al.,[36] we anticipated at the beginning of our work that analogous kinetics evidence for the formation of the PGE_2 enolate anion in aqueous amine solutions could be obtained. However, the high absorbance of amine solutions at the analytical wavelength and the tendency of amines to add in Michael fashion to C-11 of the dehydration product PGA_2 prevented the attainment of this goal. Nevertheless, general base catalysis of dehydration by quinuclidine buffered with phosphate was established and this result is consistent with rate-determining enolate anion formation at low amine concentrations or a concerted dehydration reaction. In the light of Spencer's work and structure analogy, we favor the E1cB mechanism with enolate anion formation rate determining. We offer the opinion that even with low pK_a amines that favor partitioning of the enolate anion to PGE_2 the experimental problems will frustrate attempts to kinetically detect that intermediate.

Acid-catalyzed dehydration of PGE_2 to PGA_2 probably occurs via the enolization mechanism established by Noyce and Reed[37] for dehydration of the β-ketol 4-phenyl-4-hydroxy-2-butanone to 4-phenyl-2-butenone and supported by results of Bell et al.,[38] who studied the kinetics of hydration of mesityl oxide and crotonaldehyde. Three results obtained from the present study, in addition to structure analogy, support this view. The first is that the values of the rate constants for acid-catalyzed dehydration of PGE_2, 9-hydroxy-10-methyl-*cis*-decalone-2,[36] and 4-phenyl-4-hydroxy-2-butanone[37] and for enolization of acetone[39] are virtually the same, a result that seems unlikely to be fortuitous, so that acid-catalyzed dehydration of PGE_2 probably proceeds via rapid equilibrium protonation of C-9 oxygen followed by rate-determining proton transfer from C-10 to give the enol-allyl alcohol shown. An



Scheme I



PGA_2 PGC_2

easy pathway from this intermediate to PGA_2 could be via the fast-formed C-11 protonated allylic alcohol that could decompose to stabilized carbonium ion-C-9 oxygen-protonated PGA_2. With regard to this latter speculation, Stiles and Longroy[40,41] showed that acid-catalyzed hydrolysis of 3-ethoxy-2-cyclohexenol to cyclohexenone is a rapid process ($k_H = 3.3 \times 10^5$ M^{-1} min^{-1}). In a related study we[42] examined the reaction of 3-methoxy-2-butenol in dilute acid solution to give butenone, also a facile reaction with $k_H = 10^4$ M^{-1} min^{-1}. Both reactions are specific acid catalyzed, although the reactants are vinyl ethers, and most likely occur via protonation of the allyl alcohol group followed by rate-determining carbonium ion formation-rearrangement, hydration, and decomposition of the hemiacetal. Without speaking to the reliability of log k vs. $-H_0$ plots as a criterion of mechanism,[43] we note as a second result in favor of the enolization mechanism that a plot (not shown) of log k_{obsd} vs. $-H_0$ (maximum concentration of HCl 3 M) for dehydration of PGE_2 is curved and shows that log k_{obsd} increases less rapidly than $-H_0$ as was observed for analogous reactions proceeding via the enolization mechanism.[37,38] Lastly, the deuterium solvent KIE, H_2O/D_2O, is 0.62 and this compares favorably with the values 0.54,[44] 0.48,[45] and 0.6[46] obtained for the enolization of acetone.

Isomerization of PGA_2 to PGB_2. PGA_2 is relatively stable in dilute acid solution[47] but it readily undergoes isomerization in dilute hydroxide ion solutions[6-13] (eq 1) to give PGB_2. Isomerization appears to be driven toward PGB_2 by the presumed greater stability of this conjugated and highly substituted dienone.[48] No evidence for the existence of PGC_2 (eq 1) on the path from PGE_2 to PGB_2 was obtained in this study. However, on chemical grounds it is sensible to propose its formation and isomerization. Its chemical instability was noted by Corey et al.,[49] who synthesized it from PGA_2 only under very carefully controlled isomerization conditions. Jones[33] succeeded in isolating and characterizing PGC_1 as the product from enzyme-catalyzed isomerization of PGA_1. An indication of the instability of PGC_1 in solution is provided by his report that its reactivity at pH 7 is comparable to that of PGA_1 at pH 11.5-12. From these data and k^i_{OH} (Table II) for isomerization of PGA_2 it can be estimated that k^i_{OH} for isomerization of PGC_2 is 10^4-10^5 M^{-1} min^{-1}. Our inability to detect PGC_2 spectroscopically is consistent with its estimated reactivity and with the result that the rate constant k^i_{OH} for loss of PGA_2 (224 nm) is equal to that for formation of PGB_2 (280 nm) within experimental error (Table II). Thus isomerization of PGA_2 to PGC_2 is rate determining in the sequence $PGA_2 \rightarrow PGC_2 \rightarrow PGB_2$ (eq 1).

Conversion of PGA_2 to PGC_2 involves removal of the C-12 proton and transfer of a proton to C-10 of the dienolate anion, Scheme I. These reactions should be general base-general acid catalyzed,[50-53] although the kinetics of the isomerization are uninformative respecting the nature of the rate-determining step of Scheme I. The mechanism of Scheme I gives the steady-state rate law

$$-d[PGA_2]/dt[PGA_2] = k_{obsd} = k_1k_2(1 + 1/K_{ei})[B]/(k_{-1} + k_2) \quad (8)$$

where $K_{ei} = k_1k_2/k_{-1}k_{-2}$, and regardless of which step, if either, is rate determining in Scheme I the rate of isomerization appears to be general base catalyzed. However, we[54] have found deuterium solvent KIEs of 6-8 for related amine-cata-

lyzed isomerization of $\Delta^{5,10}$-3-keto steroids and $\Delta^{5,6}$-3-keto steroids and others[50-52] have obtained similar results for related systems, all of which involve isomerization of β,γ-unsaturated carbonyls to α,β-unsaturated carbonyls. This result has been interpreted to mean that in such isomerizations k_{-1} (Scheme I) is rate determining, which requires that k_1 be rate determining in the reverse isomerization of the conjugated ketone to the unconjugated ketone (Scheme I). This conclusion is not firm in those cases where conjugated-unconjugated isomers are approaching equilibrium, however, since the measured general base rate constant is a composite constant that contains all the rate constants of Scheme I and regardless of what step is rate determining a deuterium solvent KIE is expected. For isomerization of PGA_2 to PGC_2, a reaction we view as unidirectional (Scheme I, $k_{-2} = 0$), it is expected that partitioning of the dienolate anion toward PGC_2 will be favorable[50,55] and that general-base-catalyzed C-12 proton transfer from PGA_2 will be rate determining. In fact isomerization of PGA_2 to PGC_2 is general base catalyzed by quinuclidine, quinuclidinol, and triethylamine. This result coupled with the negligible deuterium solvent KIE, 1.1, for isomerization of PGA_2 catalyzed by triethylamine and the essentially identical rate constants for the quinuclidine-catalyzed isomerization of PGA_2 (224 nm) and formation of PGB_2 (280 nm) supports the mechanism of Scheme I, k_1 rate determining, in the overall isomerization of PGA_2 to PGB_2.

Summarized, our results show that dehydration of PGE_2 to PGA_2 is general base catalyzed, that acid- and base-catalyzed dehydrations of PGE_2 are probably typical enolization reactions, that general-base-catalyzed isomerization of PGA_2 to PGC_2 is rate determining in the reaction sequence $PGE_2 \rightarrow PGA_2 \rightarrow PGC_2 \rightarrow PGB_2$ (eq 1), and that for this sequence of reactions C-12 proton abstraction from PGA_2 is probably rate determining.

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(57) The log k_{obsd}–pH profile[11] for dehydration of PGE_2 and the greater reactivity at pH 6 of PGE_2 than PGE_2 carbamoyl methyl ester[17] support intramolecular carboxylate group participation in dehydration of PGE_2. Under the conditions of this study we were unable to detect such participation; intercepts of plots of k_{obsd} vs. $[Q_t]$ were accounted for by the calculated $k^d_{OH}a_{OH}$ values. However, carboxylate group catalysis as reported[11] would contribute only ca. 0.005–0.2% to the value of the calculated intercepts (eq 4) and our analytical method is not sufficiently sensitive to measure that contribution.
(58) The value of k_0 (eq 6) for isomerization of PGA_2 in aqueous amine solutions contributes ca. 20–40% of the intercept values of plots of k_{obsd} vs. concentration of amine (eq 6) and this could be due in part to intramolecular carboxylate group catalysis. A case, albeit a weak one, based on the reported[10] log k_{obsd}–pH profile for PGA_2 isomerization could be made for such catalysis. If k_0 does represent some contribution to the reactivity of PGA_2 via carboxylate group participation, the question arises, why should k_0 for isomerization of PGA_2 be greater than $k^d_{COO^-}$ for dehydration of PGE^2? The data of Tables I and II for hydroxide ion catalysis suggest that the converse should be true, although different Brønsted β's could account for this. Also, comparison of log k_{obsd}–pH profiles for isomerization of PGA_2 and dehydration of PGE_2 at pH ca. 6[10] shows that dehydration proceeds faster than isomerization. In the light of the uncertain values of k_0 and its breakdown, the absence of sufficient low pH rate data, and the unknown preferred conformations of prostaglandins in aqueous solution,[10,59] we defer further comment on this point at this time.
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