this solution was added 4-phenyl-1,2,4-triazoline-3,5-dione (0.110 g, 0.630 mmol) and the mixture was stirred for 3 h at room temperature. The reaction was chromatographed directly through a column of 230–400-mesh silica gel (30% ethyl acetate in hexanes) at -16 °C to yield **25** and **26** (0.020 g, 0.026 g, respectively, combined yield of 93%) as yellow oils.

exo-5-(3-Oxooct-1-enyl)-2,3-dioxabicyclo[2.2.1]heptane (25): IR (CHCl$_3$) 3010, 1760, 1210 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.89 (t, J = 6.6 Hz, 3 H), 1.20–1.40 (m, 4 H), 1.55–1.70 (m, 4 H), 2.21 (d, J = 11.1 Hz, 1 H), 2.28 (cd, J = 9.6 Hz, 1 H), 2.51 (t, J =7.4 Hz, 2 H), 2.96 (m, 1 H), 4.59 (s, 1 H), 4.79 (s, 1 H), 6.13 (dd, J = 1.5, 15.6 Hz, 1 H), 6.59 (dd, J = 7.8, 15.9 Hz, 1 H); MS (M$^+$) calcd for C$_{13}$H$_{20}$O$_3$ 224.1412, found 224.1457.

endo-5-(3-Oxooct-1-enyl)-2,3-dioxabicyclo[2.2.1]heptane

(26): IR (CHCl$_3$) 3010, 2920, 1740, 1260 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.80 (t, J = 6.7, 3 H), 1.20–1.40 (m, 5 H), 1.50–1.70 (m, 2 H), 2.04 (cdd, J = 11.4, 11.4 Hz, 1 H), 2.31 (d, J = 10.5 Hz, 1 H), 2.42 (ddd, J = 10.2, 4.5, 2.1 Hz, 1 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.74 (m, 1 H), 4.64 (s, 1 H), 4.77 (s, 1 H), 6.11 (d, J = 15.6 Hz, 1 H), 6.98 (dd, J = 15.9, 9.0 Hz, 1 H); MS (M$^+$) calcd for C$_{13}$H$_{20}$O$_3$ 224.1412, found 224.1433.

Catalysis by Undissociated H$_3$PO$_4$ in Aqueous H$_2$PO$_4$$^-$/HPO$_4$$^{2-}$ Buffer Solutions: Dependence on the Magnitude of the Brønsted Exponent

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An expression is derived which relates catalysis by undissociated H$_3$PO$_4$ in aqueous H$_2$PO$_4$$^-$/HPO$_4$$^{2-}$ buffer solutions of pH ~7 to buffer ratio and the Brønsted exponent α for the system. This expression predicts that H$_3$PO$_4$ catalysis will be significant when α is near unity but will have reached negligible proportions by the time α has dropped to 0.6–0.7. These predictions are borne out by experimental data for the hydrolysis of several 2-alkoxy-2-phenyl-1,3-dioxolanes.

Aqueous biphosphate buffer solutions of pH ~7 are frequently used in studies of acid–base catalysis and chemical and biological reaction mechanisms. The principal catalytically active acidic species present in such buffers, in addition to the hydronium ion, is H$_2$PO$_4$$^-$. These solutions, however, also contain very small amounts of undissociated phosphoric acid, H$_3$PO$_4$, which, because it is a much stronger acid, may compete effectively with H$_2$PO$_4$$^-$ as a general acid catalyst. Catalysis by undissociated phosphoric acid in biphosphate buffers has in fact already been detected in at least one typical acid-catalyzed reaction.[1] We present here a general analysis of this phenomenon, which allows prediction of the conditions under which it will be important, plus the results of an empirical test of that prediction.

Consider a general acid catalyzed reaction taking place in biphosphate buffers. The rate law for this process, eq 1, consists of terms for catalysis by each of the four acidic

$$k_{\text{obsd}} = k_0 + k_{\text{H}^+}[\text{H}^+] + k_{\text{H}_3\text{PO}_4}[\text{H}_3\text{PO}_4] + k_{\text{H}_2\text{PO}_4^-}[\text{H}_2\text{PO}_4^-] \quad (1)$$

species H$_2$O (k_0), H$_3$O$^+$ (k_{H^+}), H$_3$PO$_4$ ($k_{\text{H}_3\text{PO}_4}$), and H$_2PO_4$$^-$ ($k_{\text{H}_2\text{PO}_4^-}$). The concentration of H$_3$PO$_4$ may be related to those of H$_2$PO$_4$$^-$ and H$_3$O$^+$ through the equilibrium expression for the first ionization of phosphoric acid, eq 2, and combination of eq 1 and 2 leads to eq 3. This ex-

$$K_1 = [\text{H}_2\text{PO}_4^-][\text{H}^+]/[\text{H}_3\text{PO}_4] \quad (2)$$

$$k_{\text{obsd}} = k_0 + k_{\text{H}^+}[\text{H}^+] + (k_{\text{H}_2\text{PO}_4^-} + k_{\text{H}_3\text{PO}_4}[\text{H}^+]/K_1)[\text{H}_2\text{PO}_4^-] \quad (3)$$

Table I. Evaluation of the Term of Equation 8 Representing Catalysis by H$_3$PO$_4$ for Aqueous H$_2$PO$_4$$^-$/HPO$_4$$^{2-}$ Buffer Solutions with Buffer Ratio = 1.00

α	$(K_1/K_2)^{\alpha-1\,a}$	α	$(K_1/K_2)^{\alpha-1\,a}$
1.0	1.00	0.7	0.031
0.9	0.31	0.6	0.0095
0.8	0.098	0.5	0.0030

$^a K_1 = 7.14 \times 10^{-3}$ M (ref 2) and $K_2 = 6.31 \times 10^{-8}$ M (ref 3).

pression shows that observed rate constants will be linear functions of the concentration of H$_2$PO$_4$$^-$, but the gradient of k_{obsd} upon [H$_2$PO$_4$$^-$] will be equal to $k_{\text{H}_2\text{PO}_4^-}$ only when catalysis by undissociated H$_3$PO$_4$ makes an insignificant contribution, i.e., only when the second term of eq 4 is negligible.

$$(\Delta k_{\text{obsd}}/\Delta[\text{H}_2\text{PO}_4^-])_{[\text{H}^+]} = k_{\text{H}_2\text{PO}_4^-} + k_{\text{H}_3\text{PO}_4}[\text{H}^+]/K_1 \quad (4)$$

Insight into the circumstances under which this might be so may be gained by expressing $k_{\text{H}_3\text{PO}_4}$ in terms of $k_{\text{H}_2\text{PO}_4^-}$ and the first (K_1) and second (K_2) dissociation constants of H$_3$PO$_4$ through use of the Brønsted relation, as in eq 5.

$$k_{\text{H}_3\text{PO}_4} = k_{\text{H}_2\text{PO}_4^-}(K_1/K_2)^\alpha \quad (5)$$

Substitution of eq 5 into eq 4 then gives eq 6. It is con-

$$(\Delta k_{\text{obsd}}/\Delta[\text{H}_2\text{PO}_4^-])_{[\text{H}^+]} = k_{\text{H}_2\text{PO}_4^-}(1 + [\text{H}^+]K_1^{\alpha-1}/K_2^\alpha) \quad (6)$$

venient also to express [H$^+$] in terms of the buffer ratio,

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(1) Loudon, G. M.; Ryono, D. E. *J. Org. Chem.* **1975**, *40*, 3574–3577.
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BR ($=[H_2PO_4^-]/[HPO_4^{2-}]$), and K_2 as in eq 7. This leads to eq 8.

$$[H^+] = K_2[H_2PO_4^-]/[HPO_4^{2-}] = K_2BR \qquad (7)$$

$$(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]} = k_{H_2PO_4^-}(1 + BR(K_1/K_2)^{\alpha-1}) \qquad (8)$$

This expression shows that catalysis by undissociated H_3PO_4, which is represented by the second term of eq 8, will be more prominent the higher the buffer ratio. This is reasonable, for solutions of high buffer ratio will be more acidic and the concentrations of H_3PO_4 will consequently be greater, and more of the reaction will then be able to occur through this species. Equation 8 also predicts that catalysis by H_3PO_4 will depend as well on the value of the Brønsted exponent for the system. Evaluation of the quantity $(K_1/K_2)^{\alpha-1}$ (Table I) shows that this dependence is quite sharp and is such as to make catalysis by H_3PO_4 prominent when α is large but weak when α is small. This again is reasonable, for $k_{H_3PO_4}$ will be greater relative to $k_{H_2PO_4^-}$ the greater the value of α, and catalysis by H_3PO_4 will then be correspondingly stronger.

We have tested these predictions by examining the hydrolysis of three 2-alkoxy-2-phenyl-1,3-dioxolanes, eq 9, in $H_2PO_4^-/HPO_4^{2-}$ buffers. This reaction is known to be

$$\text{diagram} \qquad (9)$$
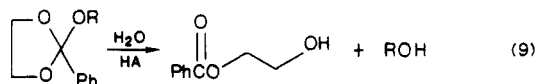
a general acid catalyzed process[4] whose Brønsted exponent depends upon the nature of the alkoxy group.[5] For the examples we have chosen, α lies in the range 0.7–0.9.
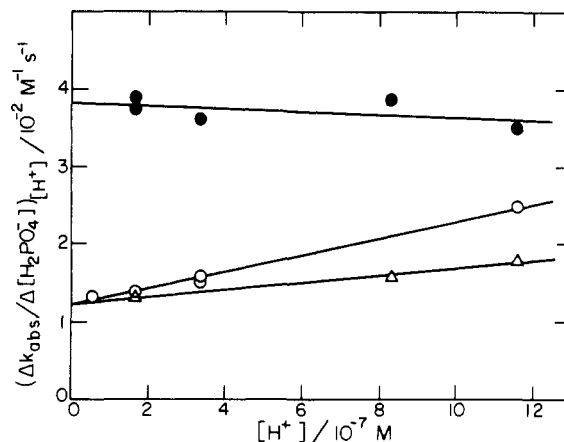
Experimental Section

Materials. The 2-alkoxy-2-phenyl-1,3-dioxolanes were prepared by transetherification as described before,[5] and samples for kinetic measurements were purified by gas chromatography. All other materials were best available commercial grades. Buffer solutions were prepared by using deionized water that had been purified further by distillation.

Kinetics. Rates of hydrolysis were determined spectrophotometrically by following the appearance of benzoate ester absorbance at 230 nm. Measurements were made with a Cary Model 118 spectrometer whose cell compartment was thermostated at 25.0 ± 0.05 °C. Runs were initiated by adding a few microliters of ethanolic stock solution of substrate to 3-mL aliquots of buffer contained in quartz cuvettes, which had previously been allowed to come to temperature equilibrium with the spectrometer cell compartment. Reactions were followed to completion, and first-order rate constants were evaluated either as slopes of plots of $\ln (A_\infty - A)$ vs. time or by computer fitting to an exponential function.

Results and Discussion

Rates of hydrolysis of the three dioxolanes were each measured in several series of $H_2PO_4^-/H_2PO_4^{2-}$ buffer solutions of constant buffer ratio and constant ionic strength ($\mu = 0.10$ M). For each solution series, five buffer concentrations varying by a factor of five were generally used, and duplicate or triplicate measurements were usually

(4) Chiang, Y.; Kresge, A. J.; Salomaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494–4499. Ahmad, M.; Bergstrom, R. G.; Cahsen, M. J.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1977**, *99*, 4827–4829. Chiang, Y.; Kresge, A. J.; Young, C. F. *J. Org. Chem.* **1979**, *44*, 619–622.
(5) Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J. *J. Org. Chem.* **1979**, *44*, 1639–1642.

Figure 1. Relationship between $(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]}$ and $[H^+]$ for the hydrolysis of 2-alkoxy-2-phenyl-1,3-dioxolanes in aqueous $H_2PO_4^-/HPO_4^{2-}$ buffer solutions at 25 °C and ionic strength = 0.10 M: (O) alkoxy group = OCH_3; (△) alkoxy group = OCH_2CH_2Cl; (●) alkoxy group = OCH_2CHCl_2.

Table II. Summary of Rate Data for the Hydrolysis of 2-Alkoxy-2-phenyl-1,3-dioxolanes in Aqueous Biphosphate Buffer Solutions at 25 °C[a]

$[H_2PO_4^-]/[HPO_4^{2-}]$	$10^7[H^+]$, M	$10^2(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]}$, $M^{-1}s^{-1}$
2-Methoxy-2-phenyl-1,3-dioxolane ($\alpha = 0.90^b$)		
0.3	0.549	1.31
1.0	1.66	1.38
2.0	3.32	1.57,[b] 1.52[c]
7.0	11.6	2.48
$(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]} = ((1.21 \pm 0.02) \times 10^{-2}) + ((1.09 \pm 0.04) \times 10^4)[H^+]$		
2-(2-Chloroethoxy)-2-phenyl-1,3-dioxolane ($\alpha = 0.80^b$)		
1.0	1.66	1.32
5.0	8.30	1.61
7.0	11.6	1.79[b]
$(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]} = ((1.23 \pm 0.02) \times 10^{-2}) + ((4.71 \pm 0.23) \times 10^3)[H^+]$		
2-(2,2-Dichloroethoxy)-2-phenyl-1,3-dioxolane ($\alpha = 0.69^b$)		
1.0	1.66	3.90, 3.72[b]
2.0	3.32	3.60
5.0	8.30	3.88
7.0	11.6	3.50
$(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]} = ((3.81 \pm 0.14) \times 10^{-2}) + ((1.68 \pm 2.04) \times 10^3)[H^+]$		

[a] Ionic strength = 0.10 M (NaCl). [b] Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J. *J. Org. Chem.* **1979**, *44*, 1639–1642. [c] Chiang, Y.; Kresge, A. J.; Salomaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494–4499.

made in each solution. The data are summarized in Table S1.[6]

Observed first-order rate constants obtained in this way were accurately proportional to $[H_2PO_4^-]$. Slopes of plots of k_{obsd} vs. $[H_2PO_4^-]$ were therefore evaluated by linear least-squares analysis; the results are listed in Table II.

Hydronium ion concentrations of the buffers employed were determined by calculation, using $pK_a = 7.20^3$ and activity coefficients recommended by Bates.[7] These values are also listed in Table II.

The occurrence of catalysis by H_3PO_4 in $H_2PO_4^-/HPO_4^{2-}$ buffer solutions causes slopes of k_{obsd} vs. $[H_2PO_4^-]$ to increase with increasing $[H^+]$ (see eq 4). This was found to

(6) Supplementary material; see paragraph at end of paper regarding availability.
(7) Bates, R. G. *Determination of pH. Theory and Practice*; Wiley: New York, 1973; p 49.

be the case for two of the dioxolane hydrolysis reactions investigated here, but not for the third: Figure 1 shows that $(\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]}$ increases with increasing $[H^+]$ for 2-methoxy-2-phenyl-1,3-dioxolane and 2-(2-chloroethoxy)-2-phenyl-1,3-dioxolane, but there is no systematic change of slope with $[H^+]$ for 2-(2,2-dichloroethoxy)-2-phenyl-1,3-dioxolane. The latter substrate with $\alpha = 0.69$ has the lowest Brønsted exponent of the three substances examined. Moreover, of the two substrates which do give slopes that increase with increasing $[H^+]$, the dependence of slope on $[H^+]$ is stronger, and catalysis by H_3PO_4 is thus more prominent, for the methoxydioxolane, with $\alpha = 0.90$, than for the chloroethoxydioxolane, with $\alpha = 0.80$. This is exactly the behavior predicted by eq 8. It indicates that catalysis by undissociated H_3PO_4 in $H_2PO_4^-/HPO_4^{2-}$ buffers is significant for reactions with Brønsted exponents near unity but that its importance drops sharply with decreasing α, and, for anything but unusually acidic biphosphate buffers, it will have reached negligible proportions by the time $\alpha = 0.6$–0.7.

Failure to include catalysis by H_3PO_4 in the analysis of kinetic data obtained under conditions where it is significant will of course lead to estimates of catalytic coefficients for $H_2PO_4^-$ which are in error, sometimes by considerable amounts. In the present case, for example, neglect of catalysis by H_3PO_4 in the hydrolysis of the 2-methoxydioxolane in the buffer solutions of BR = 7 would have led to the assignment $k_{H_2PO_4^-} = (2.48 \pm 0.16) \times 10^{-2}$ M^{-1} s^{-1} (the value of $\Delta k_{obsd}/\Delta[H_2PO_4^-])_{[H^+]}$ for this solution series),

whereas the true value obtained by full analysis of all of the data is $k_{H_2PO_4^-} = (1.21 \pm 0.02) \times 10^{-2}$ M^{-1} s^{-1}.

Catalytic coefficients for H_3PO_4 sometimes lie above Brønsted relations based upon other acids[8] (this adds to the prominence of catalysis by this species). This was the case here for hydrolysis of the 2-(2-chloroethoxy)dioxolane: the data of Table II lead to $k_{H_3PO_4} = 52.3 \pm 2.5$ M^{-1} s^{-1}, whereas a Brønsted relation based upon monohydrogenphosphonate ion catalysts $(RPO_3H^-)[5]$ predicts $k_{H_3PO_4} = 33$ M^{-1} s^{-1}. For the 2-methoxydioxolane, on the other hand, observed $(121 \pm 6$ M^{-1} $s^{-1})$ and similarly predicted[5] $(120$ M^{-1} $s^{-1})$ values of $k_{H_3PO_4}$ are concordant.

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Mechanisms of Heterocyclic Ring Formations. 4.[1] A ^{13}C NMR Study of the Reaction of β-Keto Esters with Hydroxylamine

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The reactions of aceto- and benzoylacetic acid esters and of α-acetyl- and α-benzoylpropionic acid esters with hydroxylamine at pH 10–12 give as the first products detected mixtures of the corresponding isoxazolin-5-ones and 5-hydroxyisoxazolidin-3-ones. The latter species predominate, and on rapid acidification they yield the 3-hydroxyisoxazoles by dehydration. If the pH is reduced more slowly the hydroxyisoxazolidin-3-one rings open and reclose to form the isomeric isoxazolin-5-ones. Reactions are followed by ^{13}C NMR, intermediates are identified, and the reaction pathways are rationalized.

The condensation of β-keto ester with hydroxylamine could occur in two directions: to give (i) an isoxazolin-3-one or (ii) an isoxazolin-5-one. Historically, this reaction has been confusing: originally a single product was isolated from each reaction, and all such products were first thought to be isoxazolin-5-ones. Then it was shown[2] that this structure assignment was correct for those products isolated from 2-unsubstituted β-keto esters, but those from 2-substituted analogues were isoxazolin-3-ones (which exist predominantly as 3-hydroxyisoxazoles). Finally, it was demonstrated that both types of products could be produced from both types of keto esters under different conditions.[3] Some of the rather large number of possible

pathways leading from a β-keto ester **3** to an isoxazolin-5-one **14** or a 3-isoxazolol **16** are shown in Scheme I. A satisfactory comprehensive interpretation for the product variation has not been presented previously.

Prior work from our laboratories[2] has showed that the β-keto esters **3a** and **3b** (Scheme I) reacted with hydroxylamine under basic conditions to produce the 3-substituted isoxazolin-5-ones **14a** and **14b**, respectively, in agreement with the earlier work of Claisen,[4a] Hantzsch,[4b] and others.[5] Our early work[2d] also established that under similar conditions the 2-substituted esters **3c** and **3d** (Scheme I) yielded the respective isoxazolin-3-ones **15c** and

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