Effective Charge on Oxygen in Phosphoryl ($-PO_3^{2-}$) Group Transfer from an Oxygen Donor

Nicholas Bourne and Andrew Williams*

University Chemical Laboratories, Canterbury, England

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The substituent dependencies of the first ($\beta = -0.09 \pm 0.02$) and second ($\beta_{EQ} = -0.38 \pm 0.03$) ionization constants have been measured for some aryl monophosphate esters at 25 °C and 1 M ionic strength. The Brønsted selectivity ($\beta_{EQ} = -1.35 \pm 0.06$) has been deduced from the literature data for the equilibrium constants for the hydrolysis of monophosphate dianions covering a wide range of oxygen donor acidity. Assuming that the Brønsted values for ionization follow similar selectivities as in the aryl esters we may deduce the β_{EQ} exponents for transfer of phosphoryl (phosphonate, $-PO_3^{2-}$), phosphono monoanion ($-PO_3H^-$), and phosphono ($-PO_3H_2$) groups of -1.36, -1.74, and -1.83, respectively. The Brønsted selectivity data indicate that the phosphono ($-PO_3H_2$) group has approximately the same electropositivity as the acetyl function; successive ionization reduces the electropositivity of the phosphyl group. Knowledge of the β_{EQ} values provides standards with which to compare the effective charge changes on the oxygen donor in monophosphate dianion and monoanion hydrolyses.

Introduction

We are interested in the effect of substituent change on the equilibrium constant for transfer from an oxygen donor of the phosphoryl ($-PO_3^{2-}$)[1f] group (eq 1), the phosphono monoanion ($-PO_3H^-$), and the phosphono ($-PO_3H_2$) group (eq 2 and 3, respectively). Knowledge of the substituent

$$XO\text{-}PO_3^{2-} + Nu \rightleftarrows XO^- + Nu\text{-}PO_3^{2-} \quad (1)$$

$$XO\text{-}PO_3H^- + Nu \rightleftarrows XO^- + Nu\text{-}PO_3H^- \quad (2)$$

$$XO\text{-}PO_3H_2 + Nu \rightleftarrows XO^- + Nu\text{-}PO_3H_2 \quad (3)$$

effect (β_{EQ}) on the phosphoryl group transfer equilibrium (eq 1) will enable the estimation of effective charge[1] distribution (compared with the standard—the ionization of phenols) on the oxygen of the donor throughout the reaction path for all phosphorylation reactions by monophosphate esters. The nature of the nucleophile (Nu) in eq 1, 2, and 3 will have no effect on the β_{EQ} values.[1d]

The equilibrium of eq 1 is in principle difficult to measure for aqueous solutions because transfer of the phosphate to water is a very favorable reaction particularly for esters with a wide range of donor pK (of XOH) values less than 10. Data exist, however, which refer to the hydrolysis of a large number of biological phosphates ($XO\text{-}PO_3^{2-}$) where the equilibrium constants have been measured by coupling the reactions enzymatically with forcing equilibria such as the hydrolysis of ATP. We show in this work that the literature values of equilibrium constants for these reactions fit an excellent linear Brønsted correlation with the pK of the donor group. This work further examines the Brønsted selectivities for the first and second ionisations of aryl monophosphates because these can be used in conjunction with the β_{EQ} of eq 1 to obtain β_{EQ} values for the equilibria of eq 2 and 3.

Table I. Ionization Constants for Aryl Monophosphate Esters[a,f]

substituent	λ_1[c]	pK_1	pK_2	pK^{ArOH}
parent	265	0.48	5.70	9.95
3-Cl	275	0.40	5.42	9.02
4-NO_2	325	0.30[e]	4.96[e]	8.18[b]
4-MeO	285	0.48	5.88	10.20
3,4,5-Cl_3	245	0.32	5.00	7.84
4-Me	277.5	0.56	5.80	10.19
3-NO_3[d]			5.14	8.35

[a] Ionic strength maintained at 1 M with KCl, 25 °C; errors in the pK values are less than ±0.02 pK units. [b] Value of the pK for 4-nitrophenol calculated as shown in the text for the absence of resonance interactions. [c] Wavelength for the determination of the first ionization constant. [d] This ester did not have a UV absorption change suitable for measuring pK_1. [e] Desjobert, A. (*Bull. Soc. Chim. Fr.* 1963, 683) finds pK_1 and pK_2 are respectively 0.21 and 5.18. [f] Satisfactory analytical data were obtained for the cyclohexylamine salts of these esters; see text for details.

Early work on the determination of β_{EQ} values for phosphyl group transfer equilibria is that of Benkovic and Schray[2] who collected rate data from a variety of laboratories to obtain limits for the Brønsted selectivity. Guthrie[3] assumed that the β_{EQ} for transfer of the phosphono ($-PO_3H_2$) group is the same as that for the transfer of the acetyl group (1.7) in his calculation of equilibrium constants for the hydrolysis of monophosphate esters. A previous estimate of the substituent effect on the equilibrium transfer of an *O*-phosphate diester moiety ($-PO(O)R)_2$) between phenolic oxygens ($\beta_{EQ} = 1.2$)[2] seems rather low when compared with an estimate of the β_{EQ} for transfer of the phosphoryl group ($-PO_3^{2-}$).[2] The present communication shows that the phosphono group transfer has a high β_{EQ} in accord with Guthrie's assumption.[3]

(1) (a) Deacon, T.; Farrar, C. R.; Sikkel, B. J.; Williams, A. *J. Am. Chem. Soc.* **1978**, *100*, 2525. (b) Al-Rawi, H.; Williams, A. *Ibid.* **1977**, *99*, 2671. (c) Curran, T. C.; Farrar, C. R.; Niazy, O.; Williams, A. *Ibid.* **1980**, *102*, 6828. (d) Jencks, W. P. *Cold Spring Harbor Symp. Quant. Biol.* **1971**, *36*, 1. (e) Hill, S. V; Thea, S.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 437. (f) The I.U.P.A.C. System[4] names the $-PO_3^{2-}$ group "phosphonato" and the $-PO_3H_2$ "phosphono" independent of the adjacent atom. The former group is generally known as the "phosphoryl"[2] group throughout biochemistry and we therefore propose to use this nomenclature.[5] For the purposes of data retrieval we have included both names and formula in the abstract. A similar nomenclature problem occurs in the naming of transfer reactions of the $-SO_3^-$ group.[6] The correct I.U.P.A.C. name for the $-SO_3^-$ group (independent of the adjacent atom) is "sulfonato" with "sulfono" for the neutral species. We shall use "sulfate" for the $-SO_3^-$ group as this is the term generally used by biochemists. In general discussion of the transfer of an acidic group from donor to acceptor we refer to those acids from phosphorus and sulfur as phosphyl[7] and sulfyl, respectively. The term acyl refers to carboxylic acid groups in particular but it can apply to acid groups in general.

(2) Benkovic, S. J.; Schray, K. J. "The Enzymes"; Boyer, P. D., Ed.; Academic Press: New York, 1973; Vol 8, p 201.
(3) Guthrie, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 3991.
(4) Rigaudy, J.; Klesney, S. P. "I.U.P.A.C. Nomenclature of Organic Chemistry"; Pergamon Press: Oxford, 1979.
(5) (a) Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 3357. (b) Skoog, M. T.; Jencks, W. P. *Ibid.* **1983**, *105*, 3356.
(6) (a) Hopkins, A. R.; Bourne, N.; Williams, A. *J. Am. Chem.* **1983**, *105*, 3358. (b) Hopkins, A. R.; Day, R. A.; Williams, A. *Ibid.* **1983**, *105*, 6062.
(7) Hudson, R. F.; Woodcock, R. C. *Liebigs Ann. Chem.* **1978**, *1*, 176.

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Experimental Section

Materials. Aryl monophosphate esters were prepared as their cyclohexylammonium salts by the following general procedure. The phenol (0.2 mol) in pyridine (100 mL, dried over KOH pellets) was added dropwise to a well-stirred solution of phosphoryl chloride (0.2 mol) in dry pyridine (200 mL) protected against atmospheric moisture. The solution became warm and a fine precipitate slowly separated. The solution was stirred for a further 45 min after which it was filtered, poured into stirred ice (400 g), and allowed to attain room temperature. The product mixture was treated with cyclohexylamine till pH 9 had been reached and the precipitated dicyclohexylamine salt recrystallized from ethanol. The materials had infrared (Perkin-Elmer 297 instrument) and NMR spectra consistent with the proposed structure. We are grateful to Dr. D. O. Smith who recorded the NMR data by using a Jeol 100 MHz instrument. Melting points were indeterminate and microanalyses gave poor values for carbon, hydrogen, and nitrogen; difficulties with the analysis of phosphate salts are well-known[8] but the ratio of carbon to nitrogen gives good agrement with the theoretical. Phosphorus analysis was used to confirm the composition of the parent ester. Potentiometric titration gave equivalent weights which agree with the theoretical values. Proton integration in the NMR spectra was in agreement with the proposed structures; no water peaks, which might have come from water of crystallization, were observed.

Methods. Measurements of the first ionization constant were carried out by using a spectrophotometric titration method (wavelength given in Table I) as potentiometric titration is inaccurate for pK measurements in the region of pH employed. The second ionization constants were measured by pH titration using a Radiometer (Copenhagen) titration set comprising a pH meter PHM 26 (calibrated with E.I.L. standard buffer to ±0.01 units), REC 61 Servograph, REA Titratigraph, TTT 60 Titrator, and ABU 11 autoburette. The data from both methods were fitted to eq 4 to obtain pK values which are recorded in Table I. [A]

$$pK - pH = \log ([A]/[B]) \quad (4)$$

is the concentration of free acid and [B] is that for the free base at pH in question.

Results

The pK values for first and second ionization constants for aryl monophosphates (Table I) obey excellent Brønsted correlations vs. the pK of the appropriate phenol (eq 5 and 6). Since there is a substantial resonance contribution to

$$pK_1 = (0.09 \pm 0.15)pK^{ArOH} - (0.43 \pm 0.14) \quad (r = 0.952) \quad (5)$$

$$pK_2 = (0.38 \pm 0.03)pK^{ArOH} - (1.96 \pm 0.24) \quad (r = 0.988) \quad (6)$$

the ionization of 4-nitrophenol not present in the ionization of the 4-nitrophenyl monophosphate we employ a pK^{ArOH} calculated from the equation $pK = 9.92 - 2.23\,\sigma$[9] with a σ value of 0.78. The equations of the linear Brønsted plots are recorded in Table I.

Data for the equilibrium constant (K') for the eq 7 are

$$X\text{-}O\text{-}PO_3^{2-} + H_2O \rightleftharpoons X\text{-}O^- + H\text{-}O\text{-}PO_3^{2-} + H^+ \quad (7)$$

taken from the literature (Table II). Most of the data refer to 25 °C; the difference in temperature for the other data is not considered to alter the equilibrium constants significantly. Magnesium ions were known to affect the equilibrium constants for some phosphate equilibria and values measured under these conditions were not used in the correlation. It was not possible to obtain a set of equilibrium values at a constant ionic strength. The correlation between log K' and the pK of the hydroxyl species XOH is remarkably linear over a wide range of acidities; random deviations occur from the line (eq 8) up

$$\log K' = \log ([a_H][HOPO_3^{2-}][XO^-]/[XOPO_3^{2-}]) = -1.35 \pm 0.06\ pK^{XOH} + 7.50 \pm 0.76 \quad (8)$$

to about one log unit and these are believed to be caused by the variations in conditions as enumerated above. The fit of the correlation to the experimentally obtained values is illustrated in Figure 1. It is believed that the goodness of fit to the linear equation indicates that the difference in conditions have little effect on the equilibria.

The data in the literature do not directly yield equilibrium constants for eq 7. The values quoted in the litera-

Table II. Equilibrium Constants for the Hydrolysis of Monophosphates[a]

X-O-PO_3^{2-}	log K^y	log $(K'/M)^k$	pK^{XOH}
β-aspartyl-P_i^{2-}	9.45[d,u]	1.41	3.86
acetyl-P_i^{2-}	7.45[d,16a]	0.45	4.76
ATP^{4-}	6.95[e]	−0.45	7.2[n]
P_i-O-PO_3H^{3-}	5.79[v,f]	−1.21	7.2[n]
glucose-6-P_i^{2-}	2.39[w,g]	−12.31	14.7
glucose-1-P_i^{2-}	3.62[w,g]	−8.78	12.4
AcNH-CH_2CH_2-O-P_i^{2-}	2.1[h,g]	−12.85	14.95
phosphoenolpyruvate^{3-}	10.71[v,j]	−7.05[s]	11.1[r]
glycerol-1-P_i^{2-}	1.59[x,g]	−12.81	14.4
HO-P_i^{2-}	1.74[i]	−14.00[n]	16.4[t]
Et-O-P_i^{2-}	2.08[b]	−15.17[m]	16.0
$\overset{+}{N}H_3$-CH_2CH_2-O-P_i^{2-}	−0.31[c,z]	−11.22	12.65[q]
3-phosphorylglyceric acid^{3-}	2.17[g,p]	−13.37	15.54[q]
2-phosphorylglyceric acid^{3-}	2.97[g,p]	−13.58	16.55[q]

[a] Temperature and pH kept at 25 °C and 7.0, respectively, unless otherwise stated; $P_i^{2-} = PO_3^{2-}$. [b] [EtOH]-[H_3PO_4]/[$EtOPO_3H_2$]^3. [c] [$\overset{+}{N}H_3CH_2CH_2OH$][$HPO_4^{2-}$]/[$^+NH_3CH_2CH_2OP_i^{2-}$]. [d] [$XO^-$][$HOP_i^{2-}$]/[X-O-$P_i^{2-}$]. [e] [$ADP^{3-}$][HO-$P_i^{2-}$]/[$ATP^{4-}$] pH 7.4; data from Jencks, W. P. in the "Handbook of Biochemistry", 2nd ed; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; Section J 144. [f] [HO-Pi^{2-}][HO-Pi^{2-}]/[Pi-O-PO_3H^{3-}]. [g] [X-O-H][HO-Pi^{2-}]/[X-O-Pi^{2-}]. [h] Dayan, J.; Wilson, I. B. *Biochim. Biophys. Acta* **1963**, *77*, 446. [i] [H_2O][HO-Pi^{2-}]/[HO-Pi^{2-}]. The equilibrium constant for this reaction equals the concentration of water (if the numerator water activity is defined as unity). [j] [CH_3CO-CO_2^-][HO-Pi^{2-}]/[CH_2=C(CO_2^-)O-Pi^{2-}]. [k] K' = [HO-Pi^{2-}][XO^-][H^+]/[XO-Pi^{2-}]. [m] pK_1 and pK_2 for EtO-PO_3H_2[3] 1.5 and 6.58. [n] pK_1 and pK_2 for H_3PO_4[3] 2.12 and 7.21. [p] Atkinson, M. R.; Morton, R. K. "Comprehensive Biochemistry"; Florkin, M., Mason, H. S., Ed.; Academic Press: New York, 1960; Vol 2, Chapter 1. [q] pK's of XOH calculated from Hall's equation (Hall, H. K. *J. Am. Chem. Soc.* **1957**, *79*, 5441) using the method of Fox, J. P. and Jencks, W. P. (*Ibid.* **1974**, *96*, 1436), the pK of methanol as the standard, and σ_I values from Charton, M. (*J. Org. Chem.* **1964**, *29*, 1222). [r] The pK of "enol pyruvate" assumed to be equal to that of hydroxyethylene (Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1979**, *57*, 240. Guthrie, J. P. *Ibid.* **1979**, *57*, 797). [s] [HO-Pi^{2-}][CH_2=C(CO_2^-)O^-][H^+]/[CH_2=C(CO_2^-)O-Pi^{2-}]. Data for K_T from footnote *r* and Capon, B.; Zucco, C. *J. Am. Chem. Soc.* **1982**, *104*, 7567. [t] The pK of water taken from Sauers, C, K.; Jencks, W. P.; Groh, S. *J. Am. Chem. Soc.* **1975**, *97*, 5546. [u] Black, S.; Wright, N. G. *J. Biol. Chem.* **1955**, *213*, 27. pH 8.0 and 15 °C. [v] Wood, H. G.; Davis, J. J.; Lochmuller, H. *J. Biol. Chem.* **1966**, *241*, 5692. [w] Atkinson, M. R.; Johnson, E.; Morton, R. K. *Biochem. J.* **1961**, *79*, 12. [x] Meyerhof, O.; Green, H. J. *J. Biol. Ch em.* **1947**, *178*, 655. [y] Units of K are as defined in the equation for the reaction given in the appropriate footnote. Water activity is taken as unity. [z] Wilson, I. B.; Dayan, J. *Biochemistry* **1965**, *4*, 645.

(8) (a) Williams, A.; Naylor, R. A. *J. Chem. Soc. B* **1971**, 1973. (b) Cramer, F. *Chem. Ind. (London)* **1960**, 45. (c) Cramer, F.; Rittersdorf, W.; Bohm, W. *Liebigs Ann. Chem.* **1962**, *654*, 180. (d) Kugel, L.; Halmann, M. *J. Org. Chem.* **1967**, *32*, 642.

(9) Barlin, G. B.; Perrin, D. D. *Q. Rev. Chem. Soc.* **1966**, *20*, 75.

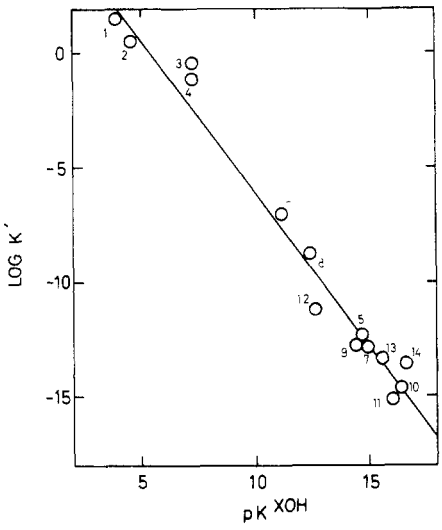


Figure 1. Equilibrium constant for the hydrolysis of phosphate monoesters ($X-O-PO_3^{2-}$ according to eq 7 as a function of the pK of the oxygen donor (XOH). The activity of water is taken as unity and the line is calculated from eq 8; the data are from Table II. Identification of points as given in Table II.

ture are recorded in Table II and are converted into K' by using the known pH and the pK values of the various acidic species as indicated in the footnotes to Table II. The activity of water is arbitrarily defined as unity.

Discussion

Application of Brønsted Parameters to the Elucidation of Mechanisms. The Brønsted relationship has been throughly investigated with regard to its application in the elucidation of organic reaction mechanisms.[10] Bordwell[10a] and Kresge[10b] have shown that the apparently anomalous Brønsted behavior in the ionization of nitro alkanes can be explained if it is assumed that the change in charge monitored by the substituent effect results from a change in bonding *and* in hybridization at the carbon. We have demonstrated experimentally,[11] as has Lewis and his co-workers,[12] that an essentially *single* change in bonding monitored by a substituent effect gives a regular Brønsted relationship for the addition of phenolate ions to isothiocyanate[11] and of aryl diazonium ions to aryl sulphinate ions.[12] In the examples which follow the bonding change "seen" by the substituent is essentially the P–O bond fission. The effective charge is defined as the hypothetical charge required to produce the observed substituent effect relative to that in the standard equilibrium (usually an ionization) where the effective charge is set at unity. The relationship between the change in effective charge (given in parenthesis in the examples) in the transition state of a reaction and the state of bonding requires that the effective charge change be known from reactant to product (the "calibrating" equilibrium). Another way of expressing this is to determine the Leffler parameter ($\alpha = d \log k/d \log K = \beta_F/\beta_{EQ}$).[13] Effective charge can only be interpreted in a straightforward way when the substituents interact with *only one bond undergoing a major electronic change.* The effective charge change will only apply to the electronic state of that bond, in the transition state, interacting with the substituent. The effective charge at an atom in a transition state cannot be directly related to bond order because it could be the net result of more than one bond or hybridization change and solvent interaction. Substituents in the aryl group of phosphate esters will only have a substituent interaction with the oxygen atom; the effective charge thus derived will be useful in monitoring the electronic nature of the P–O bond and to a much smaller extent the change in hybridization at phosphorus. A similar argument indicates that the leaving group substituents are straightforward indices of C–O bond fission in phenyl esters of carboxylic acids.[14] Substituents in the acyl function however see changes in two bonding interactions (forming and breaking) and a hybridization; such resultant substituent effects are not interpretable in a simple way.[15]

Effective Charge for Phosphoryl ($-PO_3^{2-}$), Phosphono Monoanion, and Phosphono Group Transfer from Oxygen Donors. There is an excellent Brønsted correlation between the equilibrium constant for monophosphate hydrolysis (eq 1) and the pK of the donor oxygen group for different structural types. This observation is in accord with the observed linear correlations of other equilibria involving oxygen donors with a multiplicity of structural types (acetate[16] group and carbamoyl[17] group transfer). We are therefore justified in combining the equilibrium data with that for the ionization of the aryl monophosphates. The Brønsted β_{EQ} obtained for eq 7, coupled with those for the first and second ionisations (Table I) of the aryl monophosphates yields β_{EQ} values for eq 2 and 3. The derived values, illustrated in eq 9, indicate

$$\underset{(+0.82)}{X-O-PO_3H_2} \overset{\beta_{EQ}\ -0.09}{\rightleftharpoons} \underset{(+0.73)}{X-O-PO_3H^-} \overset{\beta_{EQ}\ -0.38}{\rightleftharpoons}$$

$$\underset{(+0.35)}{X-O-PO_3^{2-}} \overset{\beta_{EQ}\ -1.35}{\rightleftharpoons} HOPO_3^{2-} + \underset{(-1.0)}{X-O^-} \quad (9)$$

that the effective charges as defined earlier[1] are 0.82, 0.73, and 0.35 on the oxygen adjacent to phosphono, phosphono monoanion, and phosphoryl (phosphonato) groups. These charges are relative to unit charge on the ionized phenol oxygen and zero charge on the unionized phenol. The steady decrease in effective charge as the phosphyl group is ionized is consistent with the results of previous work and would be predicted from the increase in formal negative charge. A carbamoyl group induces +0.8 units of effective charge on an adjacent oxygen whereas the ionized carbamoyl function induces only +0.3 units.[1b] A similar change is seen in the effective charge induced on adjacent oxygen by the thiocarbamoyl group and its conjugate base.[1e] The phosphoryl group, even with two formal negative charges, is still more electropositive than hydrogen. Benkovic and Schray[2] using a β_{EQ} determined from kinetic parameters came to the conclusion that the ($-PO_3^{2-}$) group approximates the electropositive character of hydrogen. The sulfate (sulfonato) group with one less formal negative charge than the phosphoryl group induces an effective charge of +0.7 units on an adjacent oxygen similar to that induced by the phosphono monoanion.

Observations from this laboratory[5a] indicate that the effective charge on the nitrogen of phosphoryl pyridines

(10) (a) Bordwell, F. G.; Boyle, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 3907. (b) See: Lin, A. C.; Chiang, Y.; Dahlberg, D. B.; Kresge, A. J. *Ibid.* **1983**, *105*, 5380 and the references therein. (c) Lewis, E. S. In "The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives"; Patai, S., Ed.; Wiley: New York, 1982; p 715.

(11) Hill, S. V.; Thea, S.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 437.

(12) Ritchie, C. D.; Saltiel, J. D.; Lewis, E. S. *J. Am. Chem. Soc.* **1961**, *83*, 4601.

(13) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963; pp 156–161.

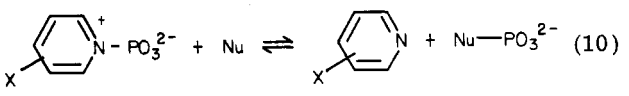
(14) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

(15) Shames, S. L.; Byers, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 6170.

(16) (a) Gerstein, J.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 4655. (b) Jencks, W. P.; Gilchrist, M. *Ibid.* **1964**, *86*, 4651.

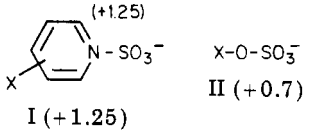
(17) Williams, A. *J. Chem. Soc. Perkin Trans. 2* **1973**, 1244.

is close to unity (+1.07) obtained from studies on the equilibrium transfer of the phosphoryl ($-PO_3^{2-}$ group (eq 10). This result seems anomalous in view of the electro-



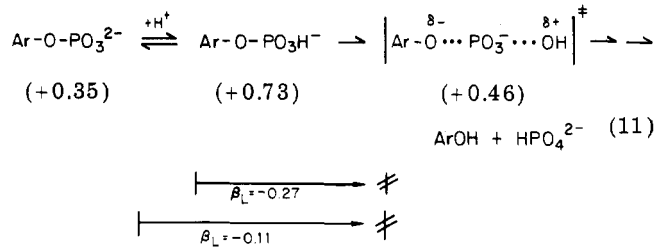
(10)

positivity of the phosphoryl group adjacent to oxygen atoms. The acetyl function induces an effective charge on an adjacent oxygen of +0.7 units and +0.6 units on an adjacent pyridine nitrogen in excess of the existing unit positive formal charge in acetylpyridines. Recent work has shown that the sulfate group ($-SO_3^-$) also induces less positive charge on the nitrogen of pyridine (I) than on an adjacent oxygen (II). This effect seen with the sulfate and



phosphoryl groups may be due to electrostatic interaction between the formal positive charge on the pyridine and the formal negative charges on the sulfate or phosphoryl oxygens.

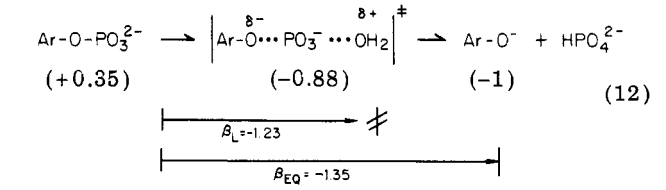
Application to Phosphoryl Group Transfer. Aryl Monophosphate Monoanion Hydrolysis. The hydrolysis of aryl monophosphate monoanions exhibits a Brønsted β_L of –0.27[18] against the pK of the phenol leaving group; this indicates an effective charge change of +0.11 from ground-state dianion (eq 11) to the transition state



(11)

of the rate-limiting step. This change in effective charge compared with an overall change of –0.35 units from dianion to unionized phenol product is consistent with the proposed mechanism[18] where complete proton transfer occurs prior to the rate-controlling step. The change in effective charge is not consistent with complete P–O fission in the transition state.

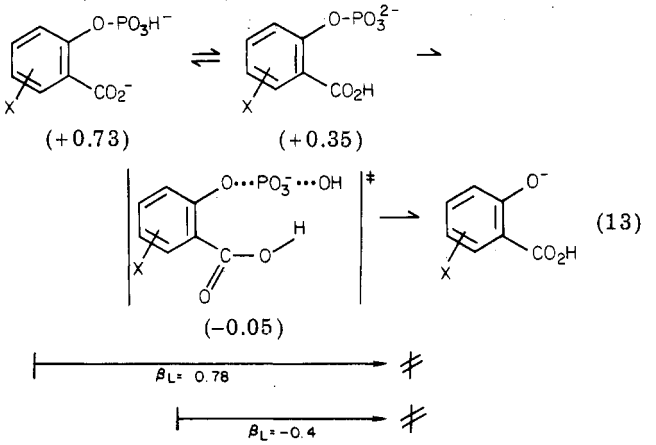
Aryl Monophosphate Dianion Hydrolysis. The uncatalyzed hydrolysis of aryl monophosphate dianion exhibits a very large negative β_L of –1.23.[18,19] The overall change in effective charge in the equilibrium transfer of –1.35 indicates that the effective charge on the oxygen in the transition state (–0.88) is close to that of the product phenolate (eq 12). Both mono and dianion hydrolyses are



(12)

consistent with advanced P–O bond cleavage in the transition state. We have recently shown that phosphoryl ($-PO_3^{2-}$) group transfer between pyridine donors and acceptors is a concerted process not involving the PO_3^- intermediate either as a discrete species or free in an encounter complex with donor and acceptor.[5] The same mechanisms probably applies to transfer between oxygen donor and acceptor in water.

Salicyl Phosphate Hydrolysis. Bender and Lawlor[20] found that the carboxylic acid group was involved in catalyzing the decomposition of the salicyl monophosphate; Kirby and Bromilow[21] further demonstrated that the proton was not transferred from the carboxyl group in the transition state of the rate-limiting step (eq 13). The value



(13)

of β_L for variation in the phenol substituent may be separated from the effect of substituents on the carboxyl group participation by Jaffe plot analysis[21] from which it is obtained by division of ρ_{phenol} by 2.23. The resulting changes in effective charges are –0.78 from the phosphate monoanion to the transition state and –0.4 from the dianion.

The effective charge on the transition-state oxygen becomes more negative as the catalytic effect is reduced from proton-catalyzed hydrolysis of dianion (+0.46) through intramolecular carboxylic acid catalysis (–0.05) to spontaneous hydrolysis of the dianion (–0.88). The gradation in effective charge reflects the relative participation of a proton in the catalysis. There is a close similarity to the corresponding sulfate hydrolyses where decreasingly positive effective charge is caused by decreasing involvement of an electrophilic catalyst.[22] Thus the effective charge on oxygen in the transition state for aryl sulfate hydrolysis changes from proton catalysis (+0.48) through intramolecular carboxylic acid catalysis (+0.06) to spontaneous hydrolysis of the monoanion (–0.46).[22]

In the above examples the changes in effective charge on the leaving aryl oxygen indicate that there is still some bonding between P and O atoms in the rate-limiting transition state involving nucleophile. This implies that the PO_3 group of atoms is never "free" as the metaphosphate ion in these reactions. The metaphosphate ion has been demonstrated in gas-phase reactions by use of negative ion chemical ionization mass spectrometry.[23] There have been many excellent reports of intermediates in phosphoryl-transfer reactions in nonaqueous solvents[24] but there remains the suspicion that these species are

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solvent–metaphosphate complexes ($O(CH_2CH_2)_2O^+-PO_3^{2-}$ and $CH_3C{\equiv}N^+-PO_3^{2-}$) analogous with the known sulfonato species. The metaphosphate ion is of course likely to be highly reactive (by analogy with its isoelectronic sulfur analogue) and will therefore complex with even weakly nucleophilic agents. The mechanisms which could involve such an intermediate must therefore be very close to a borderline where the intermediate does not exist (concerted transfer of the $-PO_3^{2-}$ group)[5,25] or exists only in an encounter complex (preassociation stepwise mechanism).[5,25] Kirby and Varvoglis[26] showed that pyridine attack on 2,4-dinitrophenyl phosphate dianion is independent of the pyridine structure although the reaction is second order. The β_L for pyridine attack on the dianion of aryl phosphates is −1.03[26] and this agrees with almost (but not complete) fission of the P–O bond, when compared with a β_{EQ} of −1.35, in the rate-controlling transition state. These results are consistent with the preassociation stepwise mechanism where a metaphosphate ion, formed in an encounter complex with pyridine and aryl oxide ion, is too unstable to exist as a free species.

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Registry No. Phenyl phosphate, 701-64-4; phenyl phosphate bis(cyclohexylamine) salt, 13798-39-5; 3-chlorophenyl phosphate, 77368-40-2; 3-chlorophenyl phosphate bis(cyclohexylamine) salt, 88766-69-2; 4-nitrophenyl phosphate, 330-13-2; 4-nitrophenyl phosphate bis(cyclohexylamine) salt, 52483-84-8; 4-methoxyphenyl phosphate, 27856-12-8; 4-methoxyphenyl phosphate bis(cyclohexylamine) salt, 75378-48-2; 3,4,5-trichlorophenyl phosphate, 88766-68-1; 3,4,5-trichlorophenyl phosphate bis(cyclohexylamine) salt, 88766-70-5; 4-methylphenyl phosphate, 6729-45-9; 4-methylphenyl phosphate bis(cyclohexylamine) salt, 88766-71-6; 3-nitrophenyl phosphate, 13388-91-5; 3-nitrophenyl phosphate bis(cyclohexylamine) salt, 14545-82-5.

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A Facile Synthesis of 3,4-Dienamides by the Reaction of Propargyl Alcohols with Cyclic Amide Acetals and Their Stereoselective Rearrangement to 2(*E*),4(*Z*)-Dienamides Promoted with Alumina. Total Synthesis of Isochavicine

Sadao Tsuboi, Yuji Nooda, and Akira Takeda*

Department of Synthetic Chemistry, School of Engineering, Okayama University, Tsushima, Okayama 700, Japan

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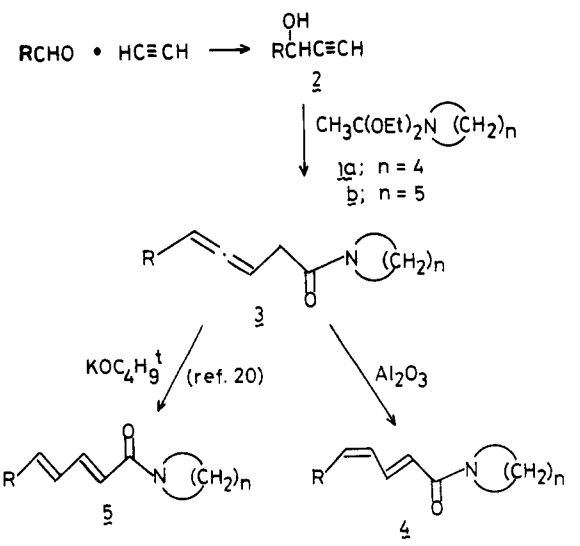
Thermal condensation of propargyl alcohols with acetals of 1-acetylpyrrolidine and 1-acetylpiperidine gave 3,4-dienamides in good yields. Alumina promoted the rearrangement of β-allenic amides to 2(*E*),4(*Z*)-dienamides stereoselectively. Its application to the synthesis of isochavicine of pepper components is described. Carbon-13 NMR data of these dienamides were obtained.

The dienamide is an important structural feature of a number of natural products, which have been reported to be active both physiologically and insecticidally. Examples of piperidine and pyrrolidine dienamides are piperine,[1] chavicine,[1] and isochavicine[1] of peper components, trichostachine,[2] trichonine,[3] and piperstachine,[4] which were isolated from the stem of piper *trichostachyon C. DC.* (family Piperacease). Representative, classical synthesis of the conjugated dienamide involves successive Knovenagel condensations.[2,5,6] The dienoic acid as a key intermediate can be prepared also by the combination of Wittig reaction and hydrogenation of acetylenic compounds.[7]

Scheme I



Since Meerwein[8] reported the preparation of the acetals of *N,N*-dialkylamides, their reactions with allylic[9-14] and

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