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REDUCTION OF 1-BENZYL-3-CYANOQUINOLINIUM ION BY PHOSPHONATE: SOLVENT EFFECTS IN PROPAN-2-OL–WATER MIXED SOLVENTS

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Rate constants (k_2) were determined for the reduction of 1-benzyl-3-cyanoquinolinium ion by phosphonate dianion in mixed solvents consisting of propan-2-ol and water. The reduction product was mostly 1-benzyl-3-cyano-1,4-dihydroquinoline with a trace of the 1,2-isomer. The solvent properties were varied by increasing the fraction of water in the mixed solvent, which increases the polarity of the solvent. Increasing the proportion of alcohol makes the solvent a better electron pair donor. The higher fraction of propan-2-ol in the mixed solvent gives rise to a substantial increase in k_2. A quantitative comparison of the solvent effect on this reaction with the solvent effects on related reactions suggests a solvent Brønsted α value of 0·45. This suggests that the PO_3^- unit of the transition state interacts only weakly with the solvent although the final oxidized product is phosphate.

INTRODUCTION

Because of the importance of nicotinamide adenine dinucleotide (NAD$^+$) in biochemical reduction and oxidation transformations, the mechanisms of these reactions has generated a great deal of interest and debate.[1,2] Such reactions formally involve transfer of a hydride equivalent from a hydride donor (NADH) to a substrate which is a hydride acceptor, or the chemical reverse of this process. The mechanism of these reactions is thought to be a direct hydride transfer (one-step reaction)[3–6] without high-energy intermediates, although the transfer of the proton and the two electrons may not be perfectly coordinated.[7,8]

A large number of studies, using a variety of structural analogues of NAD$^+$, have been carried out to explore various aspects of the mechanism. The most widely studied NAD$^+$ models are quaternary nitrogen heterocyclics such as quinolinium ions,[9–15] acridinium ions[9–13,15] and phenanthridinium ions,[10–13,15] in addition to pyridinium ions.[9–15] Among these, quinolinium compounds and pyridinium ions have been explored in greatest detail. When quinolinium ions are reduced, they produce either 1,2-dihydroquinoline or 1,4-dihydroquinoline, or both.[11] Bunting and Fitzgerald[16] reported that 1,4-dihydroquinoline is the thermodynamically controlled product in the reaction of C-3-substituted 1-methylquinolinium cations with OH^- when the substituents are $CONH_2$, $COOCH_3$, CN and NO_2, whereas 1,2-dihydroquinoline is the kinetically controlled product (Scheme 1).

This is also true of the hydride-transfer reactions. The first-formed 1,2-dihydroquinoline isomerizes to 1,4-dihydroquinoline in the presence of the corresponding cation by hydride transfer.[14] In general, 3-substituted quinolinium cations produce exclusively 1,4-dihydroquinolines when they react with NADH analogues,[9–13,15] but 1,2-dihydro- and 1,4-dihydroquinoline derivatives are produced by OH^-[17–19] BH_4^-[14,19] and BH_3CN^-.[20]

The effect of the solvent on the rate constant can help in elucidating the reaction mechanism. In fact, it has been very useful for some nucleophilic substitution

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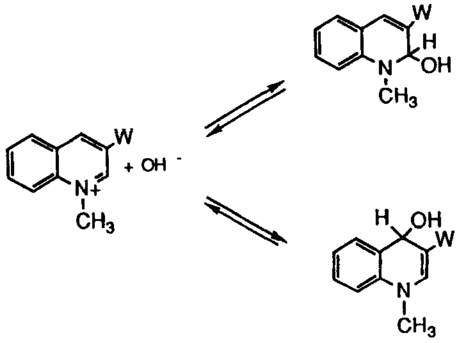
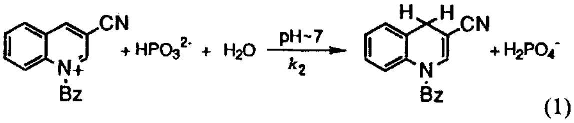


Scheme 1

reactions.[21–25] In this paper we describe the reduction of 1-benzyl-3-cyanoquinolinium cation (Q^+) by phosphonate in mixed solvents consisting of propan-2-ol and water [equation (1)]. The rate constant for this reaction is designated k_2. We examine the solvent effect on k_2 by varying the ratio of propan-2-ol to water from 1 : 1 by volume to pure water.



(1)

For this study the acid dissociation constants of H_3PO_3, K_{a_1} and K_{a_2}, were needed in each of the solvent mixtures, and they were measured [equations (3) and (4)]. The K_{R^+} of the quinolinium ion [equation (5)] was also measured in each solvent. The equilibrium constant for the reduction of the quinolinium ion, K_{eq}, could not be measured for the reaction shown in equation (2), K_2 can be equated to K_{R^+}/K_{a_2}.

$$Q^+ + HPO_3^{2-} + H_2O \overset{K_2}{\rightleftharpoons} QOH + H_2PO_3^- \quad (2)$$

The reaction shown in equation (2) resembles that shown in equation (1) in many respects. The solvent effect on k_2 will be compared with that on K_2.

RESULTS

Reduction of 1-benzyl-3-cyanoquinolinium cation (Q^+) by phosphonate in a propan-2-ol–water mixture gives phosphate and 1-benzyl-3-cyano-1,4-dihydroquinoline with a trace (< 1%) of the 1,2-isomer. The identity of the main product was easily determined from its characteristic electronic spectrum, which has the maximum absorbance at 329 nm.[9] The rate of the reaction was measured spectrophotometrically by observing the growth of product absorption at 340 nm in the propan-2-ol–water solvent system at 25°C. The interpretation of the results was complicated by the fact that both reactants are involved in acid–base reactions.

Phosphonic acid is a diprotic acid. When phosphonic acid dissociates, it loses a proton from one of the hydroxyl groups with the first dissociation constant, K_{a_1}. Then the resulting conjugate base loses the second proton from the other hydroxyl group with the second dissociation constant, K_{a_2}, as shown in equations (3) and (4).

$$HPO(OH)_2 \overset{K_{a_1}}{\rightleftharpoons} HPO_2(OH)^- + H^+ \quad (3)$$

$$HPO_2(OH)^- \overset{K_{a_2}}{\rightleftharpoons} HPO_3^{2-} + H^+ \quad (4)$$

The two pK_a values of phosphonic acid in aqueous propan-2-ol solution are listed in Table 1. The K_a values are expected to increase as the water content of the solvent increases owing to the increase in the dielectric constant and solvation of the ions by water. This expectation was realized. For both K_{a_1} and K_{a_2} there is a good linear correlation of pK_a with the percentage (by volume) of propan-2-ol in the mixed solvents, as shown in Figure 1. We know of no theoretical reason why these plots should be linear, but their linearity is very useful for interpolation and comparison. As expected,

Table 1. Dissociation constants of phosphonic acid in various propan-2-ol–water mixed solvents

Propan-2-ol:water (v/v)	pK_{a_1}[a]	pK_{a_2}[a]
50:50	2·35	7·45
40:60	2·27	7·27
30:70	2·21	7·19
20:80	2·09	6·97
10:90	2·04	6·75
0:100	1·98 (2·00)[b]	6·57 (6·59)[b]

[a] The scatter of replicate measurements is *ca* ±0·01.

[b] At 18°C; from R. C. Weast (ed.), *CRC Handbook of Chemistry and Physics*, 61st ed., p. D-167. CRC Press, Cleveland, OH (1980–81).

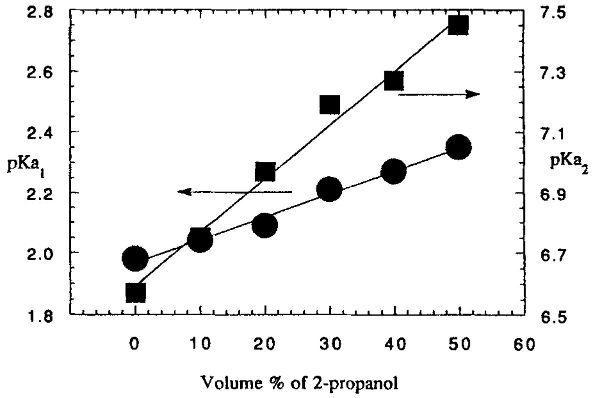


Figure 1. Correlation of pK_{a_1} and pK_{a_2} with volume percentage of propan-2-ol in the mixed solvents

the slope is much larger for K_{a_2} than for K_{a_1} ($1\cdot75\times10^{-2}$ for pK_{a_2}, $7\cdot6\times10^{-3}$ for pK_{a_1}). Each value shown is the average of 2–4 determinations. The average deviation from the mean pK_a is less than 0·01. The measurement of the reaction rates was carried out in the solution of pH 7·0–8·7. In this pH range phosphonic acid is almost entirely in the form of the mono- or dianion. On the other hand, the oxidant, Q^+, is a pseudo-acid. Its reaction with water and propan-2-ol is represented in equation (5). The equilibrium constant for the reaction is designated K_{R^+}.

$$Q^+ + ROH \xrightleftharpoons{K_{R^+}} QOR + H^+ \tag{5}$$

In the present system, R may be either H or isopropyl. We believe, however, that for the most part, R is likely to be H owing to the bulk of the isopropyl group. The acidity of Q^+ is also solvent dependent. In contrast to phosphonic acid, the K_{R^+} value is expected to decrease as the solvent is made more aqueous, because there is no change in charge type and the alcohol, which has two unshared pairs of electrons and only one hydroxylic proton, is a better solvent for H^+ than water.[26]

The values of pK_{R^+} of Q^+ in the various solvents are listed in Table 2. They change in the expected way. Like the pK_a values, pK_{R^+} correlates linearly with the percentage of propan-2-ol the mixed solvent, as shown in Figure 2. The pK_{R^+} values are the averages of two sets of experiments which produced 16–20 pK_{R^+} values from 5–6 buffer solutions. The absorbance was measured at two wavelengths for each solvent (305 and 330 nm). The average deviation from the mean value did not exceed 0·04. In the pH range for the measurement of the rate of reduction, the oxidant, Q^+, is significantly hydroxylated. At pH > 7 the first ionization of phosphonic acid is complete, but the second is not. Taking all the foregoing into account, the kinetics were assumed to be described by Scheme 2.

Following this scheme, the rate constant k_2, can be obtained from the equation

$$k_2 = \frac{k_{obs}(K_{R^+}r_{\pm} + a_H)(K_{a_2}(r_-/r_{2-}) + a_H)}{[H_3PO_3]K_{a_2}a_Hr_{\pm}^2} \tag{6}$$

Table 2. Pseudo-acidity of Q^+ in various propan-2-ol–water mixed solvents

Propan-2-ol : water (v/v)	pK_{R^+}[a]
80 : 20	5·11
50 : 50	5·81
33 : 67	6·55
25 : 75	7·08
20 : 80	7·41
0 : 100	7·82

[a] The scatter of replicate measurements is *ca* ±0·04.

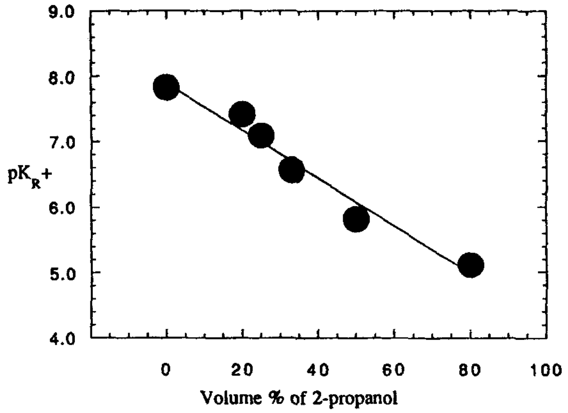


Figure 2. Correlation of pK_{R^+} of Q^+ with volume percentage of propan-2-ol

$$H_2PO_3 \rightleftharpoons HPO_3^{2-} + H^+$$
$$Q^+ + H_2O \rightleftharpoons QOH + H^+$$
$$Q^+ + HPO_3^{2-} + H_2O \rightleftharpoons QH + H_2PO_4^- + H^+$$

Scheme 2

where a_H is the activity of H^+, $r_{\pm}$ is the mean activity coefficient of the solution described under Experimental and r_- and r_{2-} are the activity coefficients of the mono- and dianion of phosphonate. The values for K_{R^+} and K_{a_2} which were not determined experimentally but were needed for calculation of k_2 were obtained from interpolations using the plots shown in Figures 1 and 2. The values of k_2 which were calculated using equation (6) are given in Table 3. The kinetic measurements were repeated at least four times for each solvent. The average deviation from the mean is less than 1% of the value in each case. The plot of k_2 as a function of phosphonate concentration over a factor of 4 showed a slope for unity. As with the equilibrium constants,

Table 3. Rate constant for the reduction of Q^+ by phosphonate in various propan-2-ol–water mixed solvents

Propan-2-ol : water (v/v)	10^3k_2(dm^3 mol^{-1} s^{-1})[a]
50 : 50	63·02
33 : 67	21·84
25 : 75	12·06
20 : 80	7·84
17 : 83	6·81
14 : 86	6·31
13 : 87	5·82
11 : 89	5·56
10 : 90	5·07
0 : 100	3·43

[a] The scatter of replicate measurements is *ca* ±1%.

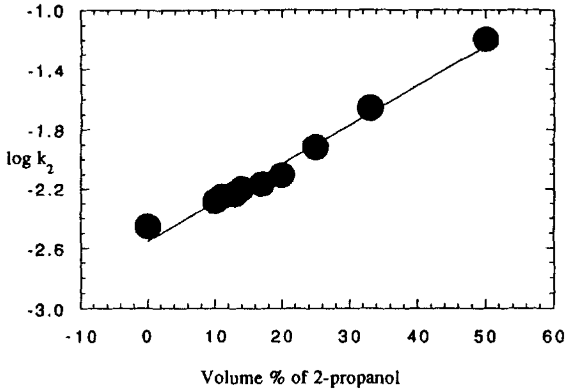


Figure 3. Correlation of log k_2 with volume percentage of propan-2-ol

log k_2 was found to be a linear function of the volume percentage of propan-2-ol from 0 to 50%. The plot is shown in Figure 3.

EXPERIMENTAL

Materials. Q^+ was prepared from the reaction of 3-cyanoquinoline with a two- to threefold excess of benzyl bromide by heating at 120°C for 30 min with stirring. The crude product was recystallized from absolute ethanol to give a >70% yield. This is an improvement on the high-temperature, solvent-free method described previously.[13] A stock solution of phosphonate of pH ≈ 7 was prepared from aqueous phosphonic acid solution by adding a small, predetermined volume of 5 M NaOH. The concentration of the phosphonic acid was determined by titration with standard NaOH solution. Propan-2-ol (commercially purchased, spectroscopic grade) was distilled from 97% H_2SO_4 (*ca* 0·2% by volume) to remove any basic impurities which might be present in the alcohol. Water was distilled once and then redistilled from a small amount of 97% H_2SO_4.

Measurements. Rate constants were determined spectrophotometrically. The temperature of the reacting solution was maintained at 25·0 ± 0·1°C by the temperature-regulated cell compartment in the spectrophotometer. All rate constants were measured with the reducing agent in at least 500-fold excess. Pseudo-first-order rate constants, k_{obs}, were obtained from the equation.[27]

$$k_{\mathrm{obs}} = t^{-1} \ln[A_0 - A_\infty)]/(A_t - A_\infty)] \qquad (7)$$

where A_t is the absorbance at time t of 1,4-dihydroquinoline at 340 nm, which increases as the reaction proceeds; it was monitored for at least four half-lives. Rate constants and A_∞ values were obtained from the experimental data by a program which minimizes the sums of the squares of the differences between measured and recalculated A_t values. The pK_a values of phosphonic acid were determined electrometrically in various combinations of propan-2-ol and water by using an automated potentiometric titrimeter with a glass electrode and a saturated calomel electrode as reference. The phosphonic acid was 0·05 M at the beginning of the titration and the titrant was 0·1 M NaOH in the same solvent.

Assuming that the activity coefficients of ions are given by the Debye–Hückel equation and the activity coefficient of H_3PO_3 is unity, $K_{a_1} = a_H r_\pm^2$ and $K_{a_2} = a_H r_{2-}/r_- = a_H \exp(3 \ln r_\pm)$ at the end-points.[28] The required $r_\pm$ values were obtained from equation (8).[29] The solvent correction of the pH for each mixed solvent was determined by measuring the pH values of four standard solutions of $HClO_4$ whose concentrations were between 10^{-2} and 10^{-4} M in each solvent. The activity coefficients in those solutions were assumed to be unity. The correction was obtained by averaging the difference between measured and theoretical pH values. The equilibrium constants, K_{R^+}, for the reaction of Q^+ with the mixed solvents were determined from the spectra of the Q^+ in a series of buffer solution with pH values between 4 and 10 and, in most cases, in 5×10^{-3} M NaOH. The K_{R^+} values were obtained from equation (9) in which $r_\pm$ is the activity coefficient obtained from the Debye–Hückel equation as given in equation (8).[29]

$$\log r_\pm = \frac{-AZ^2I^{1/2}}{1 + BaI^{1/2}} \qquad (8)$$

$$K_{R^+} = \frac{[Q^+] \times 10^{-pH}}{[QOH]r_\pm} \qquad (9)$$

Parameters A and B were calculated by taking the dielectric constant for each solvent, which was obtained by linear interpolation of known values of the dielectric constant for pure solvents,[30] Z is the ionic charge, a is related to ion size or hydrated diameter and a value of 8·5 Å was used[31] and I is the ionic strength.

DISCUSSION

In the kinetic scheme, phosphonate dianion is represented as the only reducing agent for simplicity. We believe that phosphonic acid does not act as a reductant of quinolinium ion. Phosphonate monoanion does reduce quinolinium ion, but we do not believe that it is an important reactant under the present conditions. It has been reported that the dianion and monoanion of phosphonic acid have the rate constants of $9{\cdot}6 \times 10^7$ and 25·3, respectively, for the reduction of halogens.[32] This indicates that the dianion is more reactive than the monoanion by a factor of $>10^6$. If this factor is maintained for the reduction of quinolinium ion, the rate constant contributed by the monoanion would be negligible since the concentrations of monoanion and dianion are comparable at our operating pH values. We measured the rate constants of the two reactions in a solvent consisting of propan-2-ol–water (1 : 4, v/v). The rate constant for the dianion is much larger than that for the monoanion by a factor of $>10^6$.[33] Thus, at the lowest pH used in this work, the monoanion accounts for much less than 1% of the total rate. We therefore neglected it.

The reaction rate constant is increased when the percentage of propan-2-ol in the mixed solvent is increased. It is about 20 times larger in propan-2-ol–water (1:1, v/v) than in pure water. As noted above, the reaction shown in equation (2) is very similar to that shown in equation (1). It has the same reactants; the products are of the same charge type and similar structure. As shown in Figure 4, $\log K_2$ is a substantially linear function of the volume percentage propan-2-ol in our mixed solvents, from 0 to 50%, with a slope of $5{\cdot}74\times10^{-2}$, because $\log K_{R^+}$ and $\log K_{a_2}$ are both linear with respect to the volume percentage of propan-2-ol, with slopes of $3{\cdot}64\times10^{-2}$ and $-1{\cdot}74\times10^{-2}$, and $K_2 = K_{R^+}/K_{a_2}$. We assume that $\log K_{eq}$ would be also linear with respect to the percentage of propan-2-ol, with the same slope as $\log K_2$, $5{\cdot}74\times10^{-2}$. Since $\log k_2$ is linear with respect to the percentage of propan-2-ol, with a slope of $2{\cdot}61\times10^{-2}$, the Brønsted equation,[34,35]

$$\log k = \alpha \log K + C \tag{10}$$

can be applied. A value of 0·45 is obtained for α. This is in contrast with the Brønstad α value of 0·63 obtained by introducing substituents into the benzyl group.[33] Possible reaction mechanisms are shown in Scheme 3.

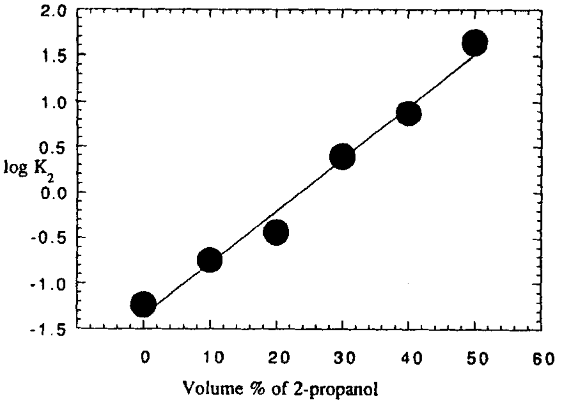
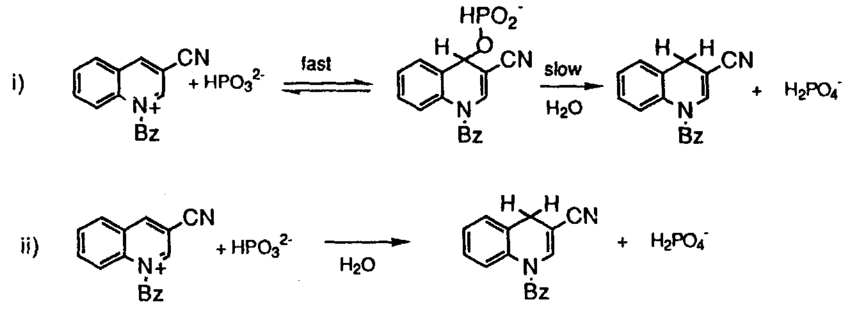


Figure 4. Correlation of $\log K_2$ with volume percentage of propan-2-ol

In both of these mechanisms hydride is transferred from P to C in the rate-limiting step, and the PO_3^- unit is interacting with water. Metaphosphate ion, PO_3^-, is a known species in the gas phase.[36] In hydroxylic solvents, the incipient metaphosphate ion is apparently trapped before it is fully formed.[37,38] Nevertheless, as seems to be common in reactions where a metaphosphate unit is transferred, the total transition state binding of the metaphosphate unit is weak.[37,38] We believe that such circumstances are responsible for the present observations. The two protons of $H_2PO_4^-$ are much more acidic than the two protons of H_2O. The interaction of $H_2PO_4^-$ with solvent makes a larger negative contribution to the system free energy as the alcohol content of the solvent becomes larger. However, the conversion of the H_2O portions to $H_2PO_4^-$ portions is very incomplete at the transition state, so the solvent effect is incompletely realized, leading to a low Brønsted α value. The metaphosphate unit is not thought to be an intermediate in this reaction, but its interaction with the solvent is thought to be weak at the transition state. Both mechanisms in Scheme 3 are consistent with this suggestion. Each would produce metaphosphate in the rate-limiting step if water were omitted. We conclude, therefore, that the metaphosphate unit is weakly bound in the transition state, but we cannot distinguish between mechanisms (i) and (ii) in Scheme 3.



Scheme 3

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APPENDIX

Derivation of equation (6) from Scheme 2 is as follows:

$$\text{rate} = k_2[\mathrm{Q}^+][\mathrm{HPO}_3^{2-}]r_+r_{2-} \qquad \text{(A-1)}$$

From equation (5),

$$K_{\mathrm{R}^+} = ([\mathrm{Q}^+]_{\mathrm{st}} - [\mathrm{Q}^+])a_{\mathrm{H}}/[\mathrm{Q}^+]r_+ \qquad \text{(A-2)}$$

where $a_{\mathrm{H}} = [\mathrm{H}^+]r_+$ and $[\mathrm{QOR}] = [\mathrm{Q}^+]_{\mathrm{st}} - [\mathrm{Q}^+]$. From equation (A-2),

$$[\mathrm{Q}^+] = [\mathrm{Q}^+]_{\mathrm{st}}a_{\mathrm{H}}/(K_{\mathrm{R}^+}r_+ + a_{\mathrm{H}}) \qquad \text{(A-3)}$$

From equation (4),

$$K_{\mathrm{a2}} = [\mathrm{HPO}_3^{2-}]r_{2-}a_{\mathrm{H}}/([\mathrm{H}_3\mathrm{PO}_3]_{\mathrm{st}} - [\mathrm{HPO}_3^{2-}])r_- \qquad \text{(A-4)}$$

where $[\mathrm{H}_2\mathrm{PO}_3^-] = [\mathrm{H}_3\mathrm{PO}_3]_{\mathrm{st}} - [\mathrm{HPO}_3^{2-}]$.
From equation (A-4),

$$[\mathrm{HPO}_3^{2-}] = K_{\mathrm{a}_2}[\mathrm{H}_3\mathrm{PO}_3]_{\mathrm{st}}/(K_{\mathrm{a}_2} + a_{\mathrm{H}}r_{2-}/r_-) \qquad \text{(A-5)}$$

Substitution of equations (A-3) and (A-5) into equation (A-1) gives

$$k_{\mathrm{obs}} = k_2\{a_{\mathrm{H}}/(K_{\mathrm{R}^+}r_+ + a_{\mathrm{H}})\}\{K_{\mathrm{a2}}[\mathrm{H}_3\mathrm{PO}_3]_{\mathrm{st}} r_+r_{2-}/(K_{\mathrm{a}_2} + a_{\mathrm{H}}r_{2-}/r_-)\} \qquad \text{(A-6)}$$

From equation (A-6),

$$k_2 = k_{\mathrm{obs}}\{(K_{\mathrm{R}^+}r_+ + a_{\mathrm{H}})(K_{\mathrm{a}_2} + a_{\mathrm{H}}r_{2-}/r_-)\}/[\mathrm{H}_3\mathrm{PO}_3]_{\mathrm{st}}K_{\mathrm{a}_2}a_{\mathrm{H}}r_+r_{2-} \qquad \text{(A-7)}$$

When both the numerator and denominator in equation (A-7) are multiplied by r_-/r_{2-}, equation (6) can be obtained.