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Reaction of Diphenylphosphine Oxide with a 10-Methylacridinium Salt. Reversible Formation of a P–C Covalent Bond

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ABSTRACT

*Diphenylphosphine oxide (***1′***) reacts reversibly with a 10-methylacridinium salt (***2***) in acetonitrile at 20°C to equilibrate with a new salt* **3** *formed by the addition of* **1′** *to the cation of* **2**. *The forward reaction in this equilibrium proceeds via nucleophilic attack by the phosphorus atom of diphenylphosphinous acid (***1***), the trivalent tautomer of* **1′**, *upon the 9-carbon atom of the cation of* **2**, *forming a phosphorus–carbon covalent bond. The equilibrium constant has been determined by UV-vis and ^{1}H NMR spectroscopy as well as by HPLC analysis. The reaction has been analyzed kinetically, and the results have been compared with those obtained in the similar reaction of an alkyl ester of* **1**, *the diphenylphosphinite (***5***), with* **2** *that gives the phosphonium salt* **6**. *It is suggested that* **6** *is much more stable than* **3**.

The equilibrium constant for the tautomerism between **1′** *and* **1** *has also been estimated. © 1995 John Wiley & Sons, Inc.*

The phosphorus atom in trivalent-phosphorus compounds readily forms a covalent bond with an electrophilic carbon atom to give the corresponding phosphonium salt [1]. This class of reactions is of special importance from the viewpoint of synthetic utility [1,2]. A general feature of these reactions is that the reverse reaction, i.e., breaking of a P–C covalent bond is rarely observed. This is because the formation of the phosphonium salt is usually highly exothermic, and even if it is not, the resulting phosphonium salt decomposes to a four-coordinated pentavalent product very rapidly rather than undergoing P–C bond cleavage to give back the starting materials.

We have now found that diphenylphosphine oxide (**1′**) adds to 10-methylacridinium iodide (**2a**) in acetonitrile at 20°C to give a new salt **3** by forming a covalent bond between the phosphorus atom in **1′** and the 9-carbon atom of the cation of **2a**. The yield of **3** was lower than theoretical, even when **1′** was used in an excess amount, and it was observed that the starting materials remained in significant concentrations. Experiments with varying initial amounts of the starting materials revealed that the less than theoretical yield of **3** is due to the concomitant reverse reaction involving the cleavage of the P–C bond in **3**. The reversibility observed here is of interest when compared with the earlier finding in the similar reaction of an alkyl ester of **1**, the diphenylphosphinite (**5**), with **2a** [3,4], in which phosphonium salt **6** is formed in an es-

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sentially irreversible manner [5]. In this article, we present the results of the product analyses as well as the kinetics of the reaction of **1′** with **2a** in order to be able to discuss the reaction mechanism in a rational manner.

RESULTS AND DISCUSSION

Product Analysis

When **1′** (1.25×10^{-2} M) was reacted with an equimolar amount of **2a** in acetonitrile under an argon atmosphere at 20°C for 60 minutes, (9, 10-dihydro-10-methyl-9-acridinyl)diphenylphosphine oxide (**4**) was detected along with **1′** by HPLC analysis [6]. However, a new signal was detected in the ^{31}P NMR spectrum of the reaction mixture, one that resonated at a significantly lower field (34 ppm from H_3PO_4) than the reported value of the chemical shift for **4** (δ 27 in $CDCl_3$) [3]. The ^{1}H NMR spectrum of the mixture exhibited, in addition to the signals from the starting materials **1′** and **2a**, the identical signals to those observed when **4** was treated with *p*-toluenesulfonic acid in CD_3CN. These observations indicate that a salt **3** is formed from **1′** and **2a** in acetonitrile, and that **3** is deprotonated to **4** during the HPLC analysis in which water-methanol (20/80 (v/v)) is used as an eluent (Scheme 1). The reactions in methanol directly afforded **4** as white precipitates (Table 1, entry 1), which show that the 10-proton in each **3** is so acidic that even methanol serves as an adequate base to remove it. If the reactions in acetonitrile had afforded each **4** as the primary product, a white precipitate should have been obtained in each reaction mixture, since each **4** is sparingly soluble in this solvent. The reaction mixtures, however, remained homogeneous throughout the reaction. However, each reaction in acetonitrile in the presence of an equimolar amount of triethylamine resulted in precipitation of each **4** in a nearly quantitative yield (entry 2) [7]. Thus, the initial product from each reaction in pure acetonitrile is not **4** but **3**.

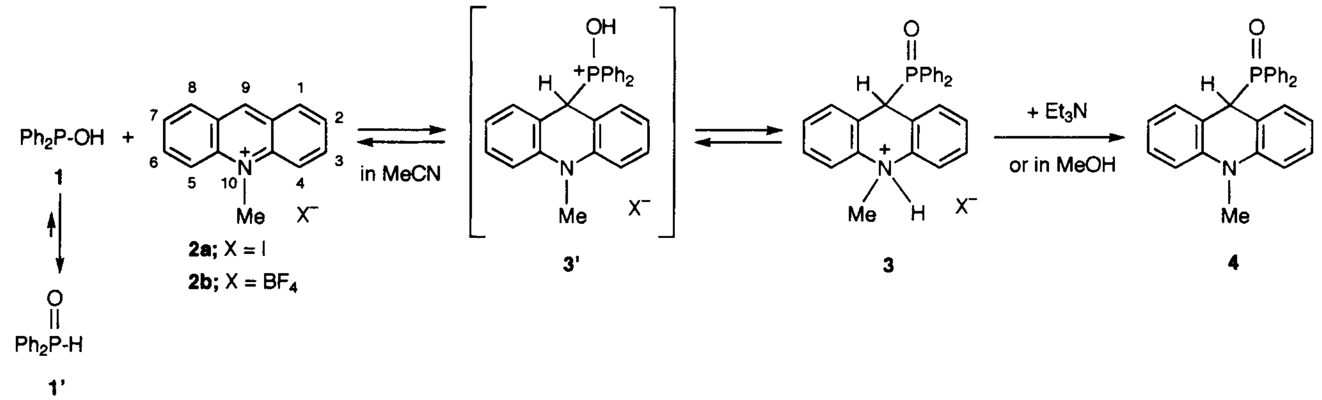
Mechanism for the P–C Bond Formation

Phosphine oxide **1′** has been shown to react with electrophiles in the form of its less stable trivalent-tautomer, diphenylphosphinous acid (**1**), [8,9]. Most likely, the present reaction likewise proceeds via nucleophilic attack by the phosphorus in **1** upon the 9-carbon atom in **2a**, initially giving a phosphonium salt **3′**. The proton on the P–O oxygen in **3′** readily migrates to the more basic 10-nitrogen atom to afford a more stable isomer, the ammonium salt **3** (Scheme 1). In agreement with this ionic mechanism, the employment of aerobic conditions exerted no effect on the reaction (entry 4). In addition, the use of 10-methylacridinium fluoroborate (**2b**) in place of the iodide salt **2a** resulted in nearly identical results (entries 5 and 6).

In the structure **3**, the acidic hydrogen on the 10-nitrogen atom may be hydrogen-bonded to the oxygen in the P=O moiety as suggested by examination with the Corey-Pauling-Koltun atomic models. There is only a small difference between the ^{1}H NMR chemical shift of the methyl protons in **4** (δ 2.68 in $CDCl_3$) and that in **3** (δ 2.71 in CD_3CN), whereas the signal from the methyl protons in methyldiphenylamine, a compound structurally related to **4**, exhibits an appreciably larger downfield shift, from δ 3.27 to δ 3.55, when treated with *p*-toluenesulfonic acid in CD_3CN. The larger difference (0.43 ppm) in the 9-proton resonance of **3** and that of **4** (δ 5.55 and δ 5.12, respectively) than that for the 10-methyl protons also supports this structure.

Equilibrium Constant of the Reaction **1′** + **2** $\rightleftarrows$ **3**

The mixture of **1′** and **2** in equimolar amounts in acetonitrile (initial concentration of each material, 1.25×10^{-2} M) was diluted with a twofold volume of acetonitrile to make the concentration 4.18×10^{-3} M. After a 60 minute reaction period, the yields of **1′** and **3** in the resulting mixture were deter-



SCHEME 1

TABLE 1 Reaction of **1**′ with **2a**[a]

Entry	*Atmosphere*	*Solv.*	*Additive*	*Time (min)*	*X in* **2**	Conc.[b] (10^2 *M*)	*Yield/pct*[c] **1**′[d]	**3**[e]	**4**
1	Ar	MeOH	—	100	I	1.25	18	0	57[f]
2	Ar	MeCN	Et_3N[g]	30	I	1.25	9	0	89[f]
3	Ar	MeCN	—	60	I	1.25	53	38	0
4	air	MeCN	—	60	I	1.25	56	42	0
5	Ar	MeCN	—	60	BF_4	1.25	58	39	0
6	air	MeCN	—	60	BF_4	1.25	58	40	0
7	air	MeCN	—	60	I	0.800	66	34	0
8[h]	air	MeCN	—	60	I	0.418	70	25	0
9[i]	air	MeCN	—	60	I	0.209	83	17	0
10[j]	air	MeCN	—	60	I	0.105	80	17	0

[a] In MeCN at 20°C in the dark.
[b] Initial concentration of the starting materials; $C = [\mathbf{1}']_0 = [\mathbf{2}]_0$.
[c] Based on $[\mathbf{1}']_0$ used; determined by means of HPLC using 1,4-dipentoxybenzene as an internal standard unless otherwise noted.
[d] Recovered.
[e] Detected as **4** on HPLC; for details, see the text, Results and Discussion section.
[f] Isolated yield.
[g] $1.25 \times 10^{\ 2}$ M.
[h] Prepared from the solution employed for the run listed in entry 3 by dilution.
[i] Prepared from the solution employed for the run listed in entry 8 by dilution.
[j] Prepared from the solution employed for the run listed in entry 9 by dilution.

mined by HPLC analysis. As shown in Table 1 (compare entries 3 and 8), the dilution resulted in an increase in the yield of the recovered starting material **1**′ at the expense of the yield of **3**. Further dilution gave similar results (entries 9 and 10). Prolonged reaction brought about hardly any change in the yields of **1**′ and **3** when monitored by HPLC analysis. In addition, ^{1}H NMR spectroscopy showed that the ratio of the molar concentration of **3** to that of **2** in the mixture, determined after a 60 minute reaction period, remained unchanged for more than 24 hours. These observations demonstrate that **3** is in equilibrium with **1**′ and **2** (Equation 1), and that the dilution of the mixture causes a shift of the equilibrium to the starting materials.

If the equilibrium is represented by Equation 1 [10], then the ratio of the concentration of **3** to that of the starting material **1**′ or **2** at the equilibrium state should be related to the apparent association constant K_{app} as shown in Equation 2 in which $C = [\mathbf{1}']_0 = [\mathbf{2}]_0$ [11],

$$\mathbf{1}' + \mathbf{2} \overset{K_{app}}{\rightleftarrows} \mathbf{3} \qquad (1)$$

$$R(R + 1) = C \cdot K_{app} \qquad (2)$$

$$R = [\mathbf{3}]_{eq}/[\mathbf{1}']_{eq} = [\mathbf{3}]_{eq}/[\mathbf{2}]_{eq} \qquad (3)$$

in which the subscript eq denotes the concentration of each component at the equilibrium state. All points of $R(R + 1)$ obtained from ^{1}H NMR and UV-vis spectroscopy, as well as from HPLC analyses, fell approximately on a single line when plotted against C (correlation coefficient $r > 0.99$) (Figure 1). From the slope of the line, K_{app} was estimated to be 1.00×10^2 M^{-1}. The plots deviate from the line at smaller values of C, where the concentration of water contained in the solvent is estimated to be more than 50 times larger than $[\mathbf{1}']_0$ and $[\mathbf{2}]_0$ (see Experimental Section). Hence, the deviation may result from water-mediated decomposition of **3**. In addition, hydration of **2** could take place under the reaction conditions [12], which makes the apparent values of R obtained on a UV-vis spec-

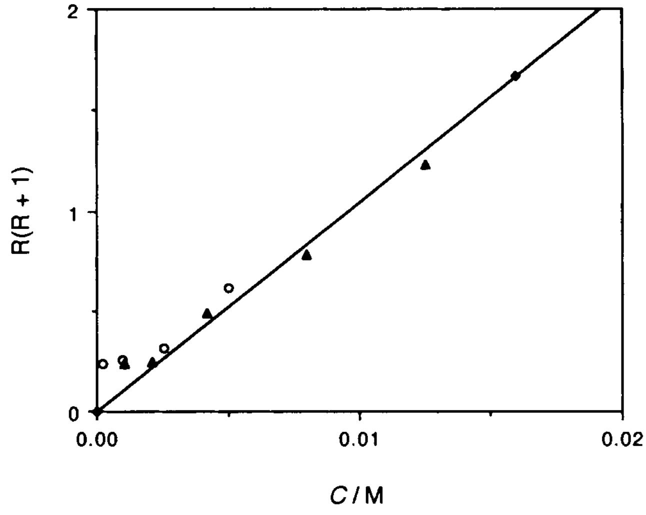
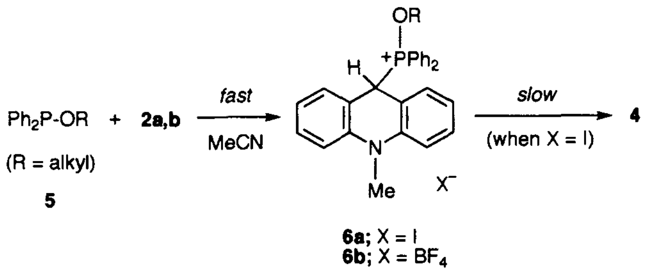


FIGURE 1 Plot of $R(R + 1)$ values against the initial concentrations of the starting materials $C = [\mathbf{1}']_0 = [\mathbf{2}]_0$. Measured on an HPLC (▲), on a ^{1}H NMR (◆), or UV-vis spectrophotometrically (○).



SCHEME 2

trophotometer larger (see Equation 6 in the Experimental Section). Thus, it is concluded that **3** is reversibly formed from **1′** and **2**.

Kinetics

A large molar excess of **1′** was reacted with **2b** (2.00×10^{-4} M), and the decrease in the absorbance by **2** at 357 nm was followed spectrophotometrically. The spectra showed a distinct isosbestic point. If the reaction proceeds according to the reaction scheme represented by Equation 1, the rate expression is given by Equation 4 under the pseudo-first-order conditions where $[\mathbf{1'}] = [\mathbf{1'}]_0 = [\mathbf{1'}]_{eq}$ is assumed.

$$\ln\{([\mathbf{2}]_t - [\mathbf{2}]_{eq})/([\mathbf{2}]_0 - [\mathbf{2}]_{eq})\} = -(k_1[\mathbf{1'}]_0 + k_{-1})t \qquad (4)$$

where subscripts 0, t, and eq denote concentrations of each component at the initial state, at a given time t, and at the equilibrium state, respectively. A plot of $\ln\{([\mathbf{2}]_t - [\mathbf{2}]_{eq})/([\mathbf{2}]_0 - [\mathbf{2}]_{eq})\}$ against t afforded a linear relationship (correlation coefficient $r > 0.9999$) for each reaction, this being consistent with the validity of Equation 4. Thus, the slope of the plot represents the pseudo-first-order rate constant, $k_{obs} = k_1 [\mathbf{1'}]_0 + k_{-1}$, and a plot of k_{obs} against $[\mathbf{1'}]_0$ gave the second-order rate constant $k_1 = 9.0 \times 10^{-2}$ M^{-1} s^{-1} with $r > 0.999$ [13]. By use of this value and the equilibrium constant $K_{app} = 1.00 \times 10^2$ M^{-1}, the first-order rate constant for the reverse reaction was calculated to be 9.0×10^{-4} s^{-1}.

Comparison with the Reaction of an Alkyl Diphenylphosphinite (5)

Reversibility of the reaction of **1′** with **2a** observed here is in sharp contrast with the previous finding that the reaction of an alkyl ester of **1**, the diphenylphosphinite (**5**), with **2a** to form the phosphonium salt **6a** is practically irreversible (Scheme 2) [3,14]. Thus, ^{1}H and ^{31}P NMR and UV-vis spectroscopy have shown that mixing of equimolar amounts of **5** and **2a** results in rapid and complete disappearance of both components with concomitant appearance of **6a**. If decomposition of **6a** to the Arbuzov-type product **4** were rapid, no reverse reaction of the phosphonium-formation step could be observed. However, kinetic investigation of this reaction has indicated that the energy barrier for the phosphonium-decomposition step is much higher than that for the phosphonium-formation step [3]. In other words, the failure to observe the reverse reaction from **6a** to the starting materials **5** and **2** is not because of rapid decomposition of **6a** to **4** but rather it results from the high stability of **6a** relative to the transition states (lines b in Figure 2) for reversal and the Arbuzov-type of reaction. In fact, **5** reacts with the fluoroborate salt **2b** to afford **6b** at the identical rate as observed in the reaction with **2a**, and no reverse reaction is observed in this case, even though **6b** no longer decomposes under the given reaction conditions.

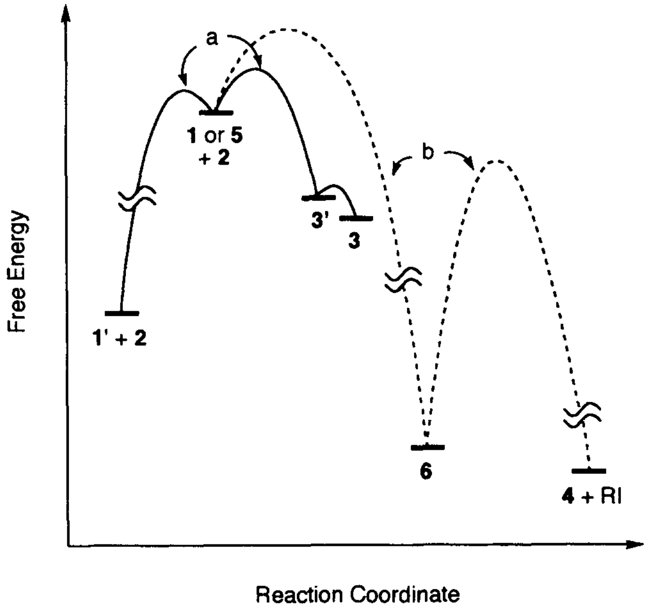


FIGURE 2 Energy diagram for the reaction of **1′** (line a) or **5** (line b) with **2**.

With the energetics for the reaction of **5** with **2** in hand, one can suppose that the reversibility of the reaction with **1′** originates from the poorer stability of the intermediate salt **3** as against that of **6** (lines a in Figure 2). The reason for the greater stability of **6** as against **3** is not clear at the present time. As has been reported [15], the stability of the phosphonium ion of the salt **6** may be enhanced by the presence of the phenyl ligands attached to the phosphorus.

Tautomerism between 1′ *and* 1

The rate constant k_1 is a product of the rate constant for the "actual" reaction of **1** with **2**, k_{act}, and the equilibrium constant for the tautomerism between **1′** and **1**, K_{tau}; that is,

$$k_1 = k_{act} \cdot K_{tau} \quad (5)$$

The rate constant k_{act} would be much less than the diffusion-controlled limit, ca. 10^{10} M^{-1} s^{-1}; therefore, K_{tau} must be much larger than 9×10^{-12}. On the other hand, it has been shown that the rate of reaction of **5** with **2a** increases in the following order with respect to the type of the alkyl substituent: *R* = tertiary < secondary < primary [3]. This means that the second-order rate constants for the reactions of the primary alkyl esters of **5** with **2a**, ca. 1×10^4 M^{-1} s^{-1} (at 25°C), can be a lower limit of k_{act} for the reaction of **1** (*R* = H). Then, $K_{tau} < 10^{-6}$ is predicted. Consequently, the equilibrium constant K_{tau} for the tautomerism between **1′** and **1** is estimated to be $10^{-11} \ll K_{tau} < 10^{-6}$. It has been reported that the equilibrium constants for tautomerism of phosphinic acid, phenylphosphinic acid, and phosphonic acid, the compounds that have one or no phenyl ligands, are in the order of 10^{-12} [9b,16]. The larger K_{tau} for **1′** estimated here suggests the importance of stabilization of a trivalent tautomer through p_π-p_π interaction between aromatic carbons and phosphorus.

EXPERIMENTAL

Instruments

The HPLC analysis was performed with use of a Tosoh CCPD dual pump equipped with a photodiode array UV-visible detector (Shimadzu SPD M6A) on a Cosmosil 5-Ph column (4.6 × 150 mm) with water-methanol (20/80 (v/v)) as the eluent. The ^1H and ^{31}P NMR spectra were obtained on a Varian XL 200 NMR spectrometer. The UV-vis spectra were recorded on a Shimadzu UV-2200A UV-vis Recording Spectrophotometer.

Materials

Diphenylphosphine oxide (**1′**) [17] and 10-methylacridinium salts (**2a** and **2b**) [18] were prepared, respectively, according to procedures described in the literature. Acetonitrile was distilled from calcium hydride prior to its use. The Karl–Fischer analysis showed that this solvent contained about 0.1% (v/v) of water.

Product Analysis

To a solution of **2** in acetonitrile (1.25×10^{-1} M) was added a solution of an equimolar amount of **1′** in acetonitrile. After an appropriate reaction time, the mixture was analyzed by HPLC as well as by ^1H and ^{31}P NMR spectroscopy. The yield of **3** was estimated based on the amount of **4** detected by HPLC analysis. Spectral data were as follows **3**: ^1H NMR (CD_3CN, δ from TMS) 2.71 (3H, s), 5.55 (1H, d, $^2J_{P-H}$ = 17.1 Hz), 6.69–7.48 (18H, m); ^{31}P NMR (CD_3CN, δ from TMS) 34. **4**: ^1H NMR ($CDCl_3$, δ from TMS) 2.74 (3H, s), 5.12 (1H, d; $^2J_{P-H}$ = 16.2 Hz), 6.58–7.59 (18H, m); ^{31}P NMR ($CDCl_3$, δ from TMS) 27.

Determination of Equilibrium Constant K_{app}

Phosphine oxide **1′** was reacted with an equivalent of **2** in acetonitrile at 20°C to allow the equilibrium $\mathbf{1'} + \mathbf{2} \rightleftarrows \mathbf{3}$ to be established (for at least 60 minutes). Then, the yield ratio $R = [\mathbf{3}]_{eq}/([\mathbf{1'}]_{eq}$ or $[\mathbf{2}]_{eq})$ was determined by ^1H NMR or UV-vis spectroscopy or by HPLC analysis. For ^1H NMR spectroscopy, the relative intensity of the signal of the 10-methyl protons in **3** to that in **2** was taken as the *R* value. As for UV-vis spectroscopy, the ratio *R* was determined according to Equation 6.

$$R = (A_0 - A_{eq})/A_{eq} \quad (6)$$

where A_0 and A_{eq} are the absorbances at 357 nm of **2** at the initial and the equilibrium states, respectively. The *R* values based on HPLC analysis were derived from the data listed in Table 1 (entries 3, 7, 8, 9, and 10). Based on the *R* values thus obtained, $R(R + 1)$ was plotted against the initial concentration of the starting material $C = [\mathbf{1'}]_0 = [\mathbf{2}]_0$.

Kinetics

A 30 μL solution of **2** in acetonitrile was added to a 3 mL solution of acetonitrile containing **1′** contained in a UV cell maintained at 20°C (initial concentrations of **1′** and **2** $(1.18–2.32) \times 10^{-2}$ M and 2.00×10^{-4} M, respectively). The decrease in the absorbance at 357 nm was monitored by use of a spectrophotometer.

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[5] Throughout this article, the term "irreversible" is not used for the reaction in which no reverse reaction takes place at any rate, but denotes a circumstance under which the reverse reaction is not observed experimentally.

[6] The other starting material **2a** is undetectable by use of HPLC.

[7] ^{31}P NMR spectroscopy suggested that the deprotonated form of **1'**, $Ph_2P^-{=}O$, hardly exists, if at all, in the presence of an equimolar amount of triethylamine. Therefore, there is little possibility that **4** is formed through nucleophilic addition of $Ph_2P^-{=}O$ to the 9-position of **2**.

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[10] Although this equilibrium is reached via phosphonium salt **3'**, the simplification in Equation 1 does not interfere with the later discussion.

[11] When $[\mathbf{1'}]_0 = [\mathbf{2}]_0 = C$,

$$K_{app} = [\mathbf{3}]_{eq}/(C - [\mathbf{3}]_{eq})^2 \qquad (7)$$

Here, the ratio R is represented by

$$R = [\mathbf{3}]_{eq}/(C - [\mathbf{3}]_{eq}) \qquad (8)$$

which leads to

$$[\mathbf{3}]_{eq} = C \cdot R/(R + 1) \qquad (9)$$

Substitution of Equation 8 with Equation 9 gives Equation 2.

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[13] Since water-mediated decomposition of **3** might occur under these kinetic conditions as mentioned in the Equilibrium Constant of the Reaction section, the rate constants obtained here could have been overestimated. However, the error is still too small to mar the given discussion.

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