Pyridinolysis of 2,4-Dinitrophenyl Phenyl Thionocarbonate: Effect of Changing Electrophilic Center from C=O to C=S on Reactivity and Mechanism

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Second-order rate constants (k_N) have been measured spectrophotometrically for nucleophilic substitution reactions of 2,4-dinitrophenyl phenyl thionocarbonate **4** with a series of Z-substituted pyridines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 ℃. The Brønsted-type plot for the reactions of **4** exhibits downward curvature (i.e., $\beta_1 = 0.21$ and $\beta_2 = 1.04$), indicating that the reactions proceed through a stepwise mechanism with a change in rate-determining step. It has been found that **4** is less reactive than its oxygen analogue, 2,4-dinitrophenyl phenyl carbonate **3**, although the thionocarbonate is expected to be more electrophilic than its oxygen analogue. The pK_a at the center of the Brønsted curvature, defined as pK_a^o, has been analyzed to be 6.6 for the reactions of **4** and 8.5 for those of **3**. Dissection of k_N into the microscopic rate constants k_1 and k_2/k_{-1} ratio has revealed that the reactions of **4** result in smaller k_1 values but larger k_2/k_{-1} ratios than the corresponding reactions of **3**. The larger k_2/k_{-1} ratios have been concluded to be responsible for the smaller pK_a^o found for the reactions of **4**.

**Key Words :** Electrophilic center, Pyridinolysis, Polarizability, HSAB principle, Rate-determining step

Introduction

Nucleophilic substitution reactions of esters with amines have been intensively investigated due to their importance in biological processes as well as synthetic applications.[1-10] Aminolysis of carboxylic esters has generally been proposed to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$ on the basis of curved Brønsted-type plots reported for reactions of esters possessing a good leaving group (e.g., 2,4-dinitrophenoxide).[1-10] The rate-determining step (RDS) has been suggested to be dependent on the basicity of the incoming amine and the leaving group, i.e., it changes at pK_a^o, defined as the pK_a at the center of the Brønsted curvature,[9,10] from breakdown of $T^{\pm}$ to its formation as the incoming amine becomes more basic than the leaving group by 4 to 5 pK_a units.[1-10]

Aminolysis of thiono esters has been reported to proceed through one or two intermediates (i.e., $T^{\pm}$ and its deprotonated form T^-) depending on the reaction conditions.[5] Castro *et al*. have reported that reactions of 4-nitrophenyl phenyl thionocarbonate with strongly basic amines proceed through $T^{\pm}$ while those with weakly basic amines proceed through $T^{\pm}$ and T^-.[5] However, we have shown that the aminolysis of *O*-4-nitrophenyl thionobenzoate proceeds through $T^{\pm}$ and T^- regardless of amine basicity.[6]

Pyridinolysis of esters is relatively simple since the pyridinium moiety in $T^{\pm}$ has no acidic proton to be removed. Pyridinolyses of 2,4-dinitrophenyl benzoate (**1**) and thionobenzoate (**2**) have been reported to proceed through a stepwise mechanism with a change in RDS on the basis of curved Brønsted-type plots.[7] Interestingly, the pK_a^o has been reported to be strongly dependent on the nature of the electrophilic center, i.e., 9.5 and 7.5 for the reactions of **1** and **2**, respectively.[7]

1: X = O
2: X = S
3: X = O
4: X = S
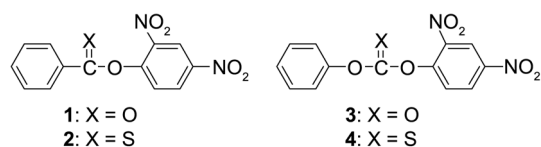
We have recently reported that pyridinolysis of 2,4-dinitrophenyl phenyl carbonate (**3**) proceeds through a stepwise mechanism with a change in RDS at $pK_a^o = 8.5$.[8] Our study has been extended to pyridinolysis of 2,4-dinitrophenyl phenyl thionocarbonate (**4**) to investigate the effect of changing the electrophilic center from C=O to C=S on reactivity and mechanism including pK_a^o.

Results and Discussion

The kinetic study was performed spectrophotometrically

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Z = H, 3-Me, 4-Me, 3,4-Me$_2$, 4-NH$_2$, 4-NMe$_2$, 4-O^{-}.
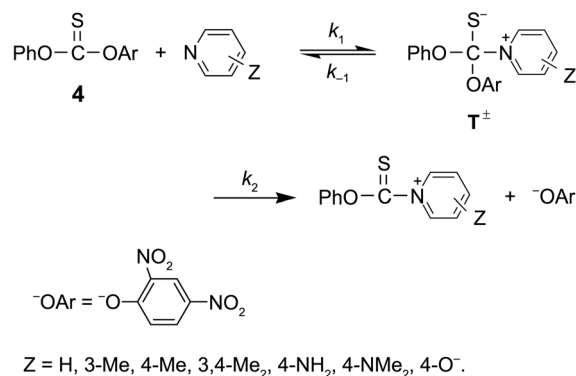
Scheme 1. Pyridinolysis of 2,4-dinitrophenyl phenyl thionocarbonate.

Table 1. Summary of Second-Order Rate Constants (k_N) for Reactions of 2,4-Dinitrophenyl Phenyl Carbonate (**3**) and Thionocarbonate (**4**) with Z-substituted Pyridines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

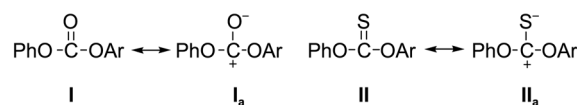| Entry	Z	pK_a	k_N / $M^{-1}s^{-1}$	
			3	**4**
1	4-O$^-$	11.30	8720	513
2	4-NMe$_2$	9.12	2627	169
3	4-NH$_2$	8.93	2520	152
4	3,4-Me$_2$	5.78	17.4	7.07
5	4-Me	5.53	9.11	3.20
6	3-Me	5.09	3.83	1.21
7	H	4.73	2.07	5.29×10^{-1}
8	3-Cl	2.14	1.40×10^{-2}	1.24×10^{-3}

[a]Data for the reactions of **3** were taken from ref. 8.

under pseudo-first-order conditions (i.e., the pyridine concentration was in excess over the substrate concentration). All reactions proceeded with quantitative liberation of 2,4-dinitrophenoxide ion and/or its conjugate acid. The reactions obeyed first-order kinetics and pseudo-first-order rate constants (k_{obsd}) were determined from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The correlation coefficient for the linear regression was usually higher than 0.9995. Plots of k_{obsd} *vs.* [pyridine] were linear and passed through the origin, indicating that contribution of H_2O and/or OH^- from hydrolysis of pyridines to k_{obsd} is negligible. Thus, the second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} *vs.* [pyridine]. The uncertainty in the k_N values is estimated to be less than 3% from replicate runs. The k_N values determined for the reactions of **4** are summarized in Table 1 together with those reported previously for the corresponding reactions of **3** for comparison purpose.

Effect of Changing Electrophilic Center from C=O to C=S on Reactivity. As shown in Table 1, the reactivity of pyridines decreases as the basicity of pyridines decreases, e.g., the k_N value for the reactions of **4** decreases from 513 $M^{-1}s^{-1}$ to 7.07 and 1.24×10^{-3} $M^{-1}s^{-1}$ as the pK_a of the pyridinium decreases from 11.3 to 5.78 and 2.14, in turn. A similar reactivity trend is shown for the corresponding reactions of **3**, although **4** is much less reactive than **3**.

Replacement of the C=O in **3** by a polarizable C=S bond would increase the polarizability of the reaction center, since the overlap between 2p and 3p orbitals in a C=S bond is not as strong as that between 2p orbitals in a C=O bond.[11,12] The enhanced polarizability of thiono esters is also reflected in ^{13}C NMR spectra as well as the difference in bond energy between C=O and C=S bonds. The chemical shifts have been reported to be 163.8 and 209.8 ppm for the carbon atoms of the C=O and C=S bonds in 4-nitrophenyl benzoate and thionobenzoate,[13] respectively, while 155.3 and 193.4 ppm for those in 4-nitrophenyl phenyl carbonate and thionocarbonate,[14] respectively. It is apparent that contribution of II_a to the resonance structures is more significant than that of I_a. Thus, one can expect that **4** is more electrophilc than **3**. In fact, thiono ester **2** has been reported to be 16000 fold more

reactive than its oxygen analogue **1** toward 4-chlorothiophenoxide (4-ClC$_6$H$_4$S$^-$), a highly polarizable nucleophile.[13]

$$\underset{\textbf{I}}{\overset{O}{\underset{\parallel}{PhO\text{-}C\text{-}OAr}}} \longleftrightarrow \underset{\textbf{I}_a}{\overset{O^-}{\underset{\underset{+}{\parallel}}{PhO\text{-}C\text{-}OAr}}} \quad \underset{\textbf{II}}{\overset{S}{\underset{\parallel}{PhO\text{-}C\text{-}OAr}}} \longleftrightarrow \underset{\textbf{II}_a}{\overset{S^-}{\underset{\underset{+}{\parallel}}{PhO\text{-}C\text{-}OAr}}}$$

The fact that **4** is less reactive toward pyridines than **3** appears to be in accord with the HSAB principle since pyridine was classified to be a hard base.[15] This argument can be further supported by the reports that **2** is less reactive than **1** toward hard bases such as HO^- and EtO^-.[13,16] Similarly, Castro *et al.* have reported that 4-nitrophenyl chlorothionoformate and bis-(4-nitrophenyl) thionocarbonate are less reactive than their oxygen analogues toward aryloxides.[17] Thus, one can suggest that reactivity of thiono esters is, at least partly, dependent on the nature of nucleophiles.

Effect of Changing Electrophilic Center from C=O to C=S on Mechanism. The effect of pyridine basicity on reactivity is illustrated in Figure 1 for the reactions of **3** and **4**. The Brønsted-type plots are nonlinear, i.e., a large slope in the low pK_a region and a small one in the high pK_a region. Such curved Brønsted-type plots are typical for reactions reported to proceed through a stepwise mechanism with a change in RDS.[1-10] In fact, the nonlinear Brønsted-type plot for the reaction of **3** has been reported as evidence for a change in RDS.[8] Thus, one can propose that the reactions of **4** proceed also through a stepwise mechanism with a change in RDS as shown in Scheme 1 on the basis of the curved Brønsted-type plot.

The curved Brønsted-type plots shown in Figure 1 have been analyzed on the basis of the mechanism proposed in Scheme 1 using a semiempirical equation Eq. (1).[18] The
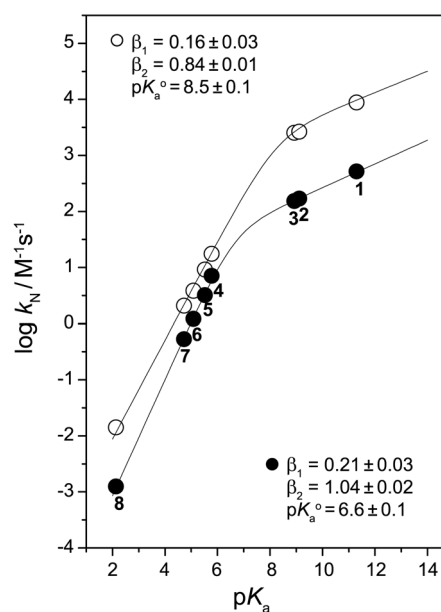
Figure 1. Brønsted-type plots for reactions of 2,4-dinitrophenyl phenyl carbonate **3** (○) and thionocarbonate **4** (●) with Z-substituted pyridines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of numbers is given in Table 1.

parameters β_1 and β_2 represent the slope of the Brønsted-type plots in Figure 1 for the reactions with strongly basic and weakly basic pyridines, respectively, and k_N° refers to the k_N value at pK_a°, where $k_2/k_{-1} = 1$.

$$\log (k_N/k_N^\circ) = \beta_2(pK_a - pK_a^\circ) - \log (1 + \alpha)/2$$
$$\text{where} \quad \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a^\circ) \qquad (1)$$

The parameters β_1, β_2 and pK_a° values determined in this way are shown in Figure 1. One can see that the reactions of **4** result in slightly larger β_1 and β_2 values than those of **3**, i.e., β_1 and β_2 are 0.16 and 0.84 for the reactions of **3** while 0.21 and 1.04 for those of **4**, respectively. However, the pK_a° for the reactions of **4** is 1.9 pK_a units smaller than that for the corresponding reactions of **3**, i.e., $pK_a^\circ = 8.5$ and 6.6 for the reactions of **3** and **4**, respectively. This is consistent with the report that pK_a° for reactions of thiono compounds is *ca.* 2 pK_a units smaller than that for the reactions of their oxygen analogues, i.e., $pK_a^\circ = 9.5$ for the reactions of **1** and $pK_a^\circ = 7.5$ for those of **2**.[7] A similar result has been reported for pyridinolysis of **3** performed in 44 % aqueous ethanol ($pK_a^\circ = 8.0$)[19a] and for those of **4** performed in H_2O ($pK_a^\circ = 7.0$).[19b]

It has generally been understood that RDS changes from expulsion of the leaving group from $T^\pm$ to its formation as the incoming amine becomes more basic than the leaving group by 4 to 5 pK_a units.[1-10] Since the pK_a of 2,4-dinitrophenol, the conjugate acid of the leaving group for substrates **3** and **4** is 4.1, pK_a° of 8.5 for the reactions of **3** is normal. However, pK_a° of 6.6 for the reactions of **4** is unusually small.

Gresser and Jencks have shown that pK_a° for quinuclidinolysis of diaryl carbonates increases as the substituent in the nonleaving group changes from an electron-donating group (EDG) to an electron-withdrawing group (EWG).[9] The explanation given is that an EWG in the nonleaving group retards departure of the leaving group from $T^\pm$ (i.e., a decrease in k_2) but it accelerates expulsion of quinuclidine (i.e., increase in k_{-1}).[9] Accordingly, it has been concluded that an EWG in the nonleaving group decreases the k_2/k_{-1} ratio and the decreased k_2/k_{-1} ratio causes an increase in pK_a°.[9] A similar conclusion has been drawn for pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates and *S*-2,4-dinitrophenyl X-substituted thiobenzoates.[10] However, we have shown that pK_a° and k_2/k_{-1} ratio are independent of the electronic nature of substituent X in the nonleaving group for aminolysis of 2,4-dinitrophenyl X-substituted benzoates[20] and benzenesulfonates.[21]

Dissection of k_N into Microscopic Rate Constants k_1 and k_2/k_{-1} Ratio. To investigate the effect of changing C=O by C=S on the microscopic rate constants, the k_N values have been dissected into k_1 and k_2/k_{-1} ratios associated with the reactions of **4**. The k_2/k_{-1} ratio has been calculated from eq. (2) using the β_1, β_2 and pK_a° values shown in Figure 1. The k_1 values have been calculated from eq. (3) using the k_N values in Table 1 and the k_2/k_{-1} ratios calculated above. The k_1 and k_2/k_{-1} ratios calculated in this way are summarized in Table 2.

Table 2. Summary of Microscopic Rate Constants (k_1 and k_2/k_{-1} ratio) for Reactions of 2,4-Dinitrophenyl Phenyl Carbonate (**3**) and Thionocarbonate (**4**) with Z-Substituted Pyridines in 80 mol % H_2O/20 mol % DMSO at $25.0 \pm 0.1\ ^\circ C^a$

| Z	pK_a	$k_1/M^{-1}s^{-1}$		k_2/k_{-1}	
		3	**4**	**3**	**4**
1. 4-O$^-$	11.30	8830	513	80.0	7960
2. 4-NMe$_2$	9.12	3620	170	2.64	123
3. 4-NH$_2$	8.93	3810	154	1.96	85.9
4. 3,4-Me$_2$	5.78	1250	41.0	1.41×10^{-2}	2.09×10^{-1}
5. 4-Me	5.53	962	27.9	9.56×10^{-3}	1.29×10^{-1}
6. 3-Me	5.09	802	22.9	4.80×10^{-3}	5.58×10^{-2}
7. H	4.73	760	19.4	2.73×10^{-3}	2.80×10^{-2}
8. 3-Cl	2.14	296	6.24	4.73×10^{-5}	1.99×10^{-4}

^{a}Data for the reactions of **3** were taken from ref. 8.

$$(\log k_2/k_{-1}) = (\beta_2 - \beta_1)(pK_a - pK_a^\circ) \qquad (2)$$
$$k_N = k_1 k_2/(k_{-1} + k_2) = k_1/(k_{-1}/k_2 + 1) \qquad (3)$$

As shown in Table 2, k_1 for the reactions of **4** decreases as the pyridine basicity decreases, e.g., it decreases from 513 $M^{-1}s^{-1}$ to 41.0 and 6.24 $M^{-1}s^{-1}$ as the pK_a decreases from 11.3 to 5.78 and 2.14, respectively. A similar result is shown for the reactions of **3**. However, the reactions of **4** result in much smaller k_1 values than those of **3**, although **4** is expected to be more electrophilic than **3** as mentioned in the preceding section.

The effect of pyridine basicity on k_1 is illustrated in Figure 2. The Brønsted-type plots are linear with β_1 values of 0.16 and 0.21 for the reactions of **3** and **4**, respectively, indicating that the k_1 for the reactions of **4** is slightly more sensitive to
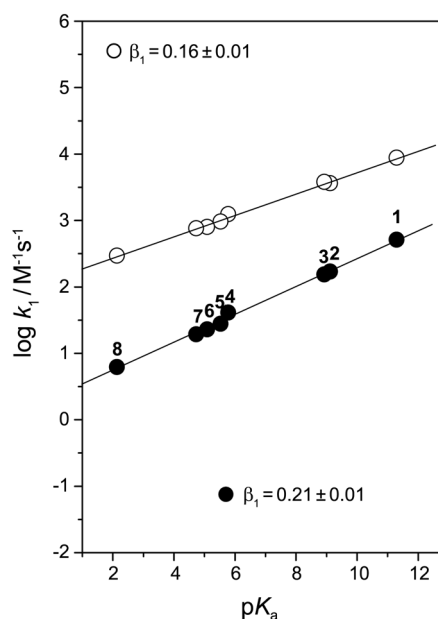
Figure 2. Plots of log k_1 *vs.* pK_a for the pyridinolysis of 2,4-dinitrophenyl phenyl carbonate **3** (○) and thionocarbonate **4** (●) in 80 mol % H_2O/20 mol % DMSO at $25.0 \pm 0.1\ ^\circ C$. The identity of numbers is given in Table 2.
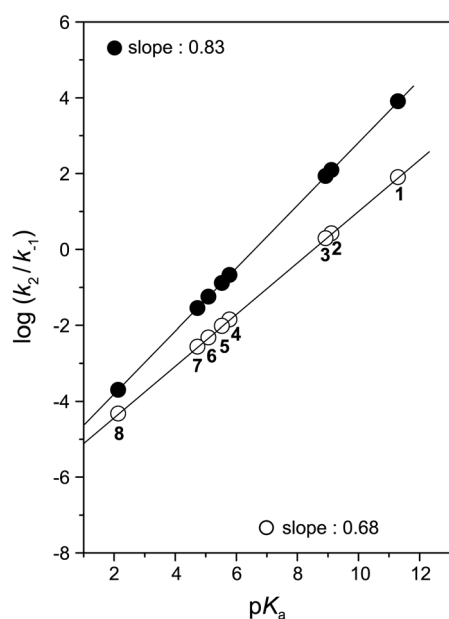
Figure 3. Plots of log k_2/k_{-1} *vs.* pK_a for the pyridinolysis of 2,4-dinitrophenyl phenyl carbonate **3** (○) and thionocarbonate **4** (●) in 80 mol % H$_2$O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of numbers is given in Table 2.

the pyridine basicity than that for the reactions of **3**.

Table 2 shows that the k_2/k_{-1} ratio for the reactions of **4** decreases as the pyridine basicity decreases, e.g., it decreases from 7960 to 0.209 and 1.99 × 10^{-4} as the pK_a decreases from 11.3 to 5.78 and 2.14, in turn. A similar result is shown for the reactions of **3**. However, the k_2/k_{-1} ratio is larger for the reactions of **4** than for those of **3**. The effect of pyridine basicity on the k_2/k_{-1} ratio is illustrated in Figure 3. The plots are linear with slopes of 0.68 and 0.83 for the reactions of **3** and **4**, respectively, indicating that the k_2/k_{-1} ratio for the reactions of **4** is more sensitive to the pyridine basicity than that for the reactions of **3**.

Since the overlap between 2p and 3p orbitals in a C=S bond is not as strong as that between 2p orbitals in a C=O bond,[11,12] the ability of C–S$^-$ moiety in **IV** to form a C=S bond is weaker than that of C–O$^-$ moiety in **III** to form a C=O bond. Thus, one might expect that k_2 and k_{-1} values would be smaller for the reactions of **4** than for those of **3**.
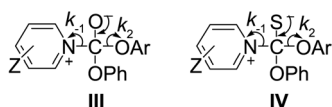
As shown in Table 2 and Figure 3, the k_2/k_{-1} ratio is larger for the reactions of **4** than for those of **3**. A larger k_2/k_{-1} ratio can be obtained by increasing k_2 and/or by decreasing k_{-1}. It is apparent that the reactions of **4** cannot result in a larger k_2 than those of **3** as mentioned above. Thus, one can propose that replacing C=O by C=S decreases k_{-1} more significantly than k_2 on the basis of the fact that the reactions of **4** result in larger k_2/k_{-1} ratios than those of **3**, which is responsible for the smaller pK_a^o found for the reactions of **4**.

Conclusions

The current study has allowed us to conclude the following: (1) Thionocarbonate **4** is less reactive than its oxygen analogue **3**, although **4** is expected to be more electrophilic than **3**. (2) The reactions of **4** proceed through a stepwise mechanism with a change in RDS. (3) The reactions of **4** result in a smaller pK_a^o than the corresponding reactions of **3**. (4) Dissection of k_N into microscopic rate constants k_1 and k_2/k_{-1} ratio has revealed that the reactions of **4** result in smaller k_1 values but larger k_2/k_{-1} ratios than the corresponding reactions of **3**. (5) It is proposed that k_{-1} decreases more significantly than k_2 upon changing the C=O in **3** by C=S, which is responsible for the smaller pK_a^o found for the reactions of **4**.

Experimental Section

Materials. 2,4-Dinitrophenyl phenyl thionocarbonate (**4**) was prepared readily by reaction of phenyl chlorothiono-formate with 2,4-dinitrophenol under presence of triethyl-amine in anhydrous ether. Other chemicals including the pyridines used were of the highest quality available. The reaction medium was H$_2$O containing 20 mol % DMSO due to low solubility of **4** in pure H$_2$O. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed with a UV-vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to maintain the temperature in the reaction cell at 25.0 ± 0.1 °C. The reaction was followed by monitoring the appearance of the leaving 2,4-dinitrophenoxide ion. All the reactions were carried out under pseudo-first-order conditions in which pyridine concentrations were at least 20 times greater than the substrate concentration. The pyridine stock solution of *ca.* 0.2 M (except the most weakly basic 3-chloropyridine) was prepared by dissolving two equiv. of pyridine and one equiv. of standardized HCl solution to keep the pH constant in this self-buffered solution. The stock solution of the most weakly basic 3-chloropyridine was prepared without addition of HCl. All solutions were prepared freshly just before use under nitrogen and transferred by gas-tight syringes. Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of the substrate in CH$_3$CN by a 10 μL syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermo-statted reaction mixture made up of solvent and aliquot of the pyridine stock solution.

Product Analysis. 2,4-Dinitrophenoxide (and/or its conjugate acid) was liberated quantitatively and identified as one of the products by comparison of the UV-vis spectrum at the end of reaction with the authentic sample under the experimental condition.

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