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# Oxidative Formation of Thiolesters in a Model System of the Pyruvate Dehydrogenase Complex†

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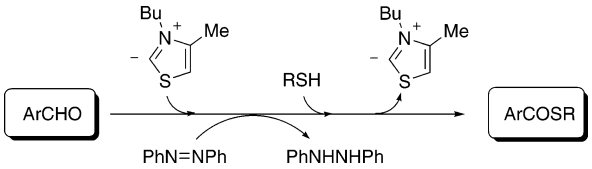
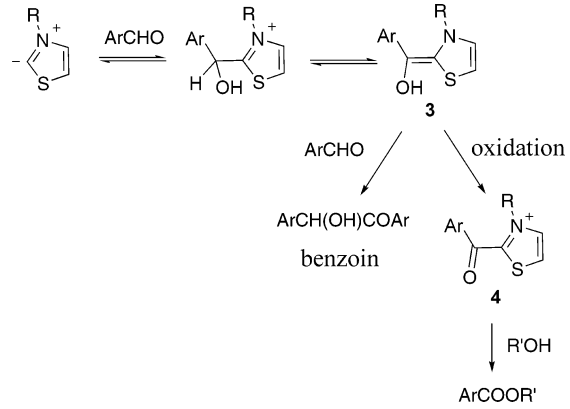



In the presence of a catalytic amount of 3-butyl-4-methylthiazolium bromide, the reaction of benzaldehydes with azobenzene in dichloromethane containing octanethiol and $Et_3N$ gave the corresponding *S*-octyl thiobenzoates in good yields. The thiolesters were produced by trapping of the 2-benzoylthiazolium salts with the thiol, which were generated through the azobenzene oxidation of the active aldehydes. This is the first example for the thiolester formation mimicking the function of the pyruvate dehydrogenase complex. An electron-withdrawing substituent at the 4-position of benzaldehyde enhanced the reaction rate. The effect of benzaldehyde substituents on the reaction rate was examined quantitatively on the basis of kinetic measurements, leading to a nonlinear correlation of $\log(k_{obs})$ with Hammett's substituent constants ($\sigma$). The origin of the nonlinear Hammett plot was interpreted in terms of a shift in the rate-determining step of the multistep reaction with change of the electronic nature of substituent. Further support for this assumption was given by the observation that the reaction constant ($\rho$) of the Hammett plot for the azobenzene substituent effect on the oxidation rate of 4-bromobenzaldehyde was much smaller than that of 4-cyanobenzaldehyde.

## Introduction

Thiamine pyrophosphate (TPP, **1**) serves as a catalytic cofactor of important biochemical reactions catalyzed by a variety of enzymes such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and transketolase.[1] In 1958, Breslow established that the catalytic action of TPP involved a nucleophilic attack of the conjugate base of its thiazolium ring onto the carbonyl group of substrate, and also proposed the mechanism of the benzoin condensation catalyzed by thiazolium salts, e.g. 3-benzyl-4-methylthiazolium bromide (**2**), in the absence of enzyme.[2] It is generally accepted that the thiazolium-catalyzed benzoin condensation proceeds through the acyl carbanion equivalent **3** (known as "an active aldehyde") (Scheme 1), which is considered to be an analogue of the intermediate involved in the enzymatic oxidative decarboxylation of pyruvic acid. Moreover, Breslow's and Ingraham's groups revealed independently that 2-acylthiazolium salts **4**, which were prepared by oxidation of active aldehydes **3** or quaternization of 2-acylthiazoles, were

**SCHEME 1. Mechanism of the Thiazolium-Catalyzed Benzoin Condensation and the Oxidative Formation of Carboxylic Acid Derivatives**




† This paper is dedicated to Professor Michinori Ōki on the occasion of his 77th birthday.

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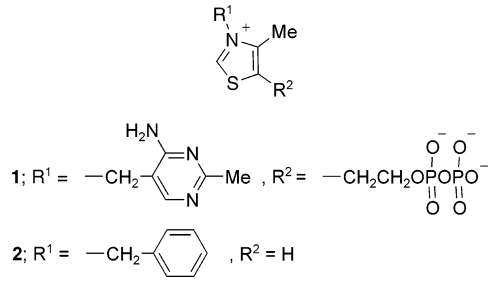


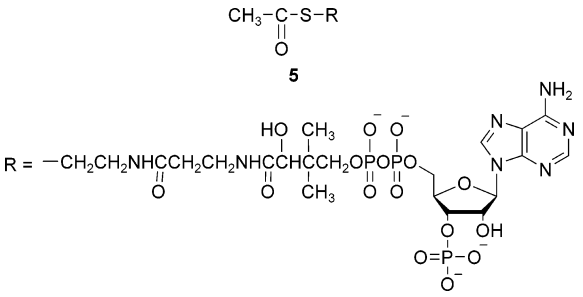


extremely reactive toward water to afford the corresponding carboxylic acids.[3,4] This finding provided not only insight into the mechanism of biochemical reactions involving TPP as the prosthetic group, but also a novel method for mild oxidation of aldehydes to carboxylic acids and esters utilizing thiazolium salts as a catalyst (Scheme 1). Several research groups have developed this catalytic oxidative transformation by employing a variety of oxidizing agents such as nitrobenzene,[5,6] flavins,[7,8] acridine and its analogues,[9] potassium ferricyanide,[10,11] and disulfides.[12,13] Very recently, Chow and Bode applied this method to stereoselective synthesis of $\beta$-hydroxyesters from epoxyaldehydes.[14,15]

Despite great importance in biochemical reactions, the chemistry of thiolesters RC(=O)SR′ has not been thoroughly investigated, compared with that of their oxygen analogues, carboxylate esters. Acetyl coenzyme A (**5**), the energy-rich thiolester of coenzyme A, which is known to participate in a number of important in vivo chemical transformations, is a final product formed by oxidative decarboxylation of pyruvic acid catalyzed by the pyruvate dehydrogenase complex.[1] Therefore, an artificial reaction system that produces thiolesters oxidatively from aldehydes or α-keto acids utilizing thiazolium salts as a catalyst is of particular interest as a model system mimicking the function of the pyruvate dehydrogenase complex. In the course of our studies on biomimetic reactions, we found that benzaldehydes were readily converted to the corresponding thiolesters in organic solvents by employing a thiazolium salt and azobenzene as a catalyst and an oxidizing agent, respectively.[16] In this paper, we report details of these reactions, which are the first example for catalytic thiolester formation in a model system of the pyruvate dehydrogenase complex.

## Results and Discussion

**Oxidative Thiolester Formation from Benzaldehydes.** In principle, thiazolium-catalyzed formation of thiolesters would be achieved by the reaction of thiol with 2-acylthiazolium salt **4** produced by the oxidation of active aldehydes **3** (Scheme 1). Diago and Reed reported that 2-acetyl-3,4-dimethylthiazolium iodide, which was prepared by 2-acetyl-4-methylthiazole with MeI, reacted with butanethiol in DMSO−water in the presence of sodium acetate or NaOH to give *S*-butyl thioacetate in 30−38%.[17] Moreover, Rastetter and Adams obtained thiolesters by the reductive cleavage of the sulfur−sulfur bond of disulfides with the active aldehyde generated by deprotonation of isolable 2-(α-hydroxyethyl)thiazolium salt.[12] However, they failed in catalytic thiolester formation from acetaldehyde and diphenyl disulfide in THF containing the thiazolium salt and base, because of facile sulfenylation of the thiazolium salt with the disulfide. After examination of several oxidizing agents, we found that azobenzene in dichloromethane gave a satisfactory result for the thiazolium-catalyzed thiolester formation. Azobenzene, which was once used as an oxidizing agent in the oxidative formation of esters catalyzed by 3-benzylthiazolium salt,[9] is reduced stoichiometrically to hydrazobenzene during the course of the reaction. This redox behavior of azobenzene is advantageous to reduce the complexity of the reaction system, compared with that where nitrobenzene is used as an oxidizing agent, which gives various kinds of reduction products.[5] Moreover, azobenzene oxidation is favorable for mechanistic studies because its oxidation ability can be readily controlled by introduction of substituent groups into its benzene rings (vide infra).

We used 3-butyl-4-methylthiazolium bromide (**6**) as a catalyst for the reason of solubility in dichloromethane. Under an Ar atmosphere, 4-bromobenzaldehyde (**7**-Br, 1 mmol) was reacted with azobenzene (**8**-H, 1 mmol) in dichloromethane containing octanethiol (**9**, 1.5 mmol), $Et_3N$ (1 mmol), and a catalytic amount of **6** (0.1 mmol) at room temperature. After the starting aldehyde was completely consumed, the reaction mixture was treated with water to yield *S*-octyl 4-bromothiobenzoate (**10**-Br) and *N*,*N*′-diphenyl(4-bromobenzoyl)hydrazide (**11**-Br) in

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(4) (a) White, F. G.; Ingraham, L. L. *J. Am. Chem. Soc.* **1960**, *82*, 4114. (b) White, F. G.; Ingraham, L. L. *J. Am. Chem. Soc*. **1962**, *84*, 3109.
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(14) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126.
(15) The analogous conversion of α-haloaldehydes and α,$\beta$-unsaturated aldehydes into acylating agents catalyzed by nucleophilic carbenes has been reported: (a) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (c) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.
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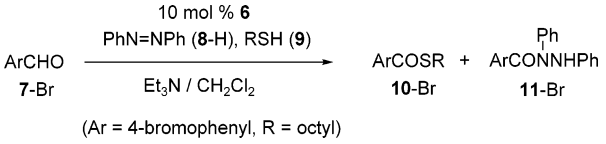
**TABLE 1. Products in the Thiazolium-Catalyzed Azobenzene Oxidation of 4-Bromobenzaldehyde (7-Br)[a]**

| | | yield/% | | | |
|---|---|---|---|---|---|
| [**8**-H]/M | [**9**]/M | **10**-Br | **11**-Br | **13** | others |
| 0.4 | 0.6 | 75 | 19 | 0 | |
| 0 | 0.6 | 12 | | 34 | 42[b] |
| 0.4 | 1.2 | 76 | 19 | 0 | |
| 0.8 | 0.6 | 65 | 29 | 0 | |

[a] [**6**] = 40 mM, [**7**-Br] = [$Et_3N$] = 0.4 M in $CH_2Cl_2$ for 22 h at ca. 25 °C. [b] 4,4′-Dibromobenzil (5%) and 4-bromobenzoic acid (40%).

73% and 22% yields, respectively, along with dioctyl disulfide and hydrazobenzene (**12**). The desired thiolester




**10**-Br was stable under these reaction conditions, and could be fully characterized spectroscopically after isolation with gel permeation liquid chromatography. The byproduct **11**-Br was supposed to be formed through the acylation of hydrazobenzene (**12**) produced in situ by the reduction of azobenzene (**8**-H). The structure of **11**-Br was also determined spectroscopically and confirmed by an independent synthesis from 4-bromobenzoyl chloride and **12**.

The product distributions obtained under various reaction conditions are summarized in Table 1. In the absence of azobenzene (**8**-H), the benzoin ArCH(OH)COAr (Ar = 4-bromophenyl) **13** was obtained as a major product in agreement with the well-known catalytic action of thiazolium salts, together with various oxidation products.[18] However, addition of 1 equiv of **8**-H completely suppressed the formation of **13**, and diverted the reaction to the oxidative thiolester formation. It is noted that the ratio of the desired thiolester **10**-Br to the byproduct **11**-Br was little affected by an increase in the concentration of the thiol **9**. An increase in the concentration of the oxidizing agent **8**-H was also ineffective to enhance the yield of **10**-Br.

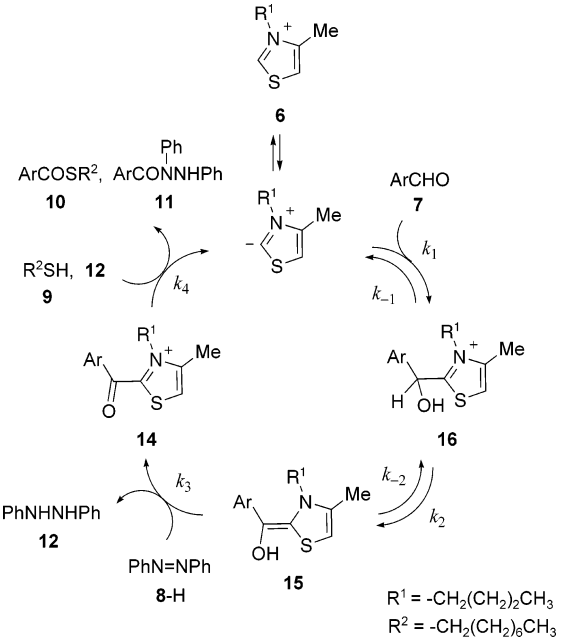
Moreover, we found that this method could be employed to convert benzaldehydes into the corresponding thiolesters having various substituents at the 4-position, except the $NO_2$ group, which would be reduced under these reaction conditions.[5,6,19] The product distributions obtained from the azobenzene oxidation of substituted benzaldehydes are summarized in Table 2. It should be noted that although all substituted benzaldehydes examined were oxidized to give the corresponding thiolesters **10** in good yields along with the hydrazides **11**, the reaction rate was extremely dependent on the electronic effect of substituent; the reaction rate was accelerated with an increase in the electron-withdrawing nature of substituent. The substituent effects in the oxidative thiolester formation are discussed in the following sections.

**TABLE 2. Products and Rate Constants for the Thiazolium-Catalyzed Azobenzene Oxidation of 4-Substituted Benzaldehydes (7-X)**

| | yield/%[a] | | | |
|---|---|---|---|---|
| X | **10** | **11** | $k_{obs}/10^{-4}$ $s^{-1}$ [b] | $\sigma$[c] |
| MeO[d] | 87 | 7 | 0.15(±0.02) | −0.28 |
| Me[d] | 88 | 6 | 0.67(±0.09) | −0.14 |
| H[d] | 75 | 19 | 1.0(±0.1) | 0 |
| Br[e] | 68 | 26 | 1.7(±0.2) | 0.22 |
| COOMe[e] | 76 | 19 | 2.2(±0.2) | 0.44 |
| CN[e] | 77 | 17 | 3.1(±0.2) | 0.71 |

[a] [**6**] = 40 mM, [**7**-X] = [**8**-X] = [$Et_3N$] = 0.4 M in $CH_2Cl_2$ containing 10% of **9** at ca. 25 °C. [b] [**6**] = 2.4 mM, [**7**-X] = 12 mM, [**8**-H] = [**9**] = 30 mM, [$Et_3N$] = 20 mM in $CDCl_3$ at 21.7−22.2 °C. [c] Reference 22. [d] The yields were determined on the basis of the reacted material after 3 d. The consumption of **7**-MeO, **7**-Me, and **7**-H was 25%, 61%, and 97%, respectively. [e] The yields were determined on the basis of the reacted material after 15 min. The consumption of **7**-Br, **7**-COOMe, and **7**-CN was 69%, 84%, and 98%, respectively.

**SCHEME 2. Mechanism of the Thiolester Formation in the Thiazolium-Catalyzed Azobenzene Oxidation of Benzaldehydes**




On the basis of the scheme established for the catalytic action of thiazolium salts (Scheme 1) and the foregoing results, we propose the mechanism for the formation of **10** and **11**, which involves competitive trapping of the 2-benzoylthiazolium ion **14** with the thiol **9** and hydrazobenzene (**12**) (Scheme 2). It appears that the redox reaction between azobenzene (**8**-H) and the active aldehyde **15** to give **12** and **14** proceeds by a mechanism involving the transfer of electrons from **15** to **8**-H. The analogous mechanism was already postulated in the thiazolium-catalyzed oxidative formation of esters by Inoue and Higashiura.[9] Fukuzumi and his colleagues revealed recently that active aldehydes derived from 3-benzylthiazolium ion and various aldehydes were very

(18) We could not identify what acted as an oxidizing agent in this reaction, although it appeared that contaminating molecular oxygen was at least partly responsible for the formation of these oxidation products.

(19) When 3-phenylpropanal was treated under the reaction conditions described in the text, the corresponding hydrazide was predominately obtained (55%), along with small amounts of the thiolester (6%). Thus, some modifications of the reaction conditions are required to employ this method for the synthesis of thiolesters derived from aliphatic aldehydes, which are ongoing in our laboratory.

strong reductants having one-electron oxidation potentials of −0.98 to −0.77 V (vs SCE).[20] On the other hand, **8**-H is known to be a good electron acceptor, the half-wave reduction potential of which was measured to be −1.39 V (vs Ag/AgCl).[21] Thus, a small endothermicity (10−15 kcal mol$^{-1}$) is estimated for the electron transfer from active aldehydes to **8**-H, which supports the mechanism involving the transfer of electrons in the oxidation of the active aldehyde **15** with **8**-H. Subsequently, the resulting 2-benzoylthiazolium ion **14** reacts smoothly with the thiol **9** to yield the desired product **10**. It is thought that **11** is mainly produced by the reaction of **14** with hydrazobenzene (**12**) formed concomitantly by the redox reaction in a solvent cage, while **10** is produced by external trapping of **14**, which escapes from a solvent cage with **9**. This assumption accounts for the observation that increasing the concentration of **9** was not effective in an increase in the ratio of **10**-Br to **11**-Br.

Thus, we have achieved the oxidative conversion of benzaldehydes into the corresponding thiolesters in the pyruvate dehydrogenase model system, in which the thiazolium salt and azobenzene are utilized as a catalyst and an oxidizing agent, respectively.

**Substituent Effects in Oxidative Thiolester Formation**. As mentioned in the previous section, we have found significant substituent effects on the reactivity of benzaldehydes in the thiazolium-catalyzed oxidative thiolester formation, in which a benzaldehyde having an electron-withdrawing substituent at the 4-position reacts more rapidly. Although the same tendency was observed in the thiazolium-catalyzed flavin oxidation of benzaldehydes in the CTAB micelle,[7a] no systematic studies of the substituent effects on the thiazolium-catalyzed oxidative transformation have been reported so far. We have treated the observed substituent effects quantitatively and discussed the origin of the substituent effects on the basis of the reaction mechanism.

**(1) Kinetics of Oxidative Thiolester Formation.** At first, to evaluate the substituent effects quantitatively, kinetic measurements of the thiazolium-catalyzed azobenzene oxidation of 4-bromobenzaldehyde (**7**-Br) were carried out by the use of $^1$H NMR spectroscopy. The reaction was initiated by the addition of a $CDCl_3$ solution containing **7**-Br (12 mM), $Et_3N$ (20 mM), and octanethiol (**9**, 30 mM) into a solution of azobenzene (**8**-H, 30 mM) and 3-butyl-4-methylthiazolium bromide (**6**, 2.4 mM) in $CDCl_3$ under an Ar atmosphere. The reaction was followed by monitoring the decrease in the intensity of the $^1$H NMR signal at $\delta$ 9.98 due to **7**-Br at 22 °C. Unfortunately accurate kinetic data could not be obtained at the very initial stage of the reaction, while we found that the decrease in the concentration of **7**-Br obeyed good first-order kinetics in the range of ca. 15−35% consumption of the starting aldehyde. The apparent first-order rate constant ($k_{obs}$) was evaluated to be $1.7(\pm0.2) \times 10^{-4}$ s$^{-1}$. As the reaction further progressed, the consumption of the material was slowed considerably deviating from the first-order kinetics.

As described in the previous section, it is assumed that the thiazolium-catalyzed azobenzene oxidation of benzaldehyde proceeds by the mechanism depicted in Scheme 2. In the early stage of the reaction where the concentrations of azobenzene and thiol are considered to be unchanged from the initial values, the rate of the decrease in the concentration of benzaldehydes ($v_{obs}$) is expressed by eq 1 by using a steady-state approximation.

$$v_{obs} = -\frac{d[S]}{dt} = \frac{k_1k_2k_3[Az]_0k_4[Th]_0[Tz]_0[S]}{Ak_4[Th]_0 + Bk_1[S]} \quad (1)$$

$$A = k_{-1}k_{-2} + k_3[Az]_0(k_{-1} + k_2)$$

$$B = k_2k_3[Az]_0 + k_2k_4[Th]_0 + k_{-2}k_4[Th]_0 + k_3[Az]_0k_4[Th]_0$$

In this equation, [S] is the concentration of benzaldehyde, and $[Az]_0$, $[Th]_0$, and $[Tz]_0$ are the initial concentrations of azobenzene, thiol, and the thiazolium salt, respectively. When the relation $Ak_4[Th]_0 \gg Bk_1[S]$ is satisfied, eq 1 is rewritten as eq 2, suggesting that the $v_{obs}$ is first order with respect to [S].

$$v_{obs} = -\frac{d[S]}{dt} = \frac{k_1k_2k_3[Az]_0[Th]_0[S]}{k_{-1}k_{-2} + k_3[Az]_0(k_{-1} + k_2)} \quad (2)$$

As mentioned above, the decrease in the concentration of **7**-Br is found to obey the first-order kinetics in the early range of the reaction. Thus, it is supposed that eq 2 can be applied to the kinetics in this range, and that the observed first-order rate constant ($k_{obs}$) is expressed by eq 3.

$$k_{obs} = \frac{k_1k_2k_3[Az]_0[Th]_0}{k_{-1}k_{-2} + k_3[Az]_0(k_{-1} + k_2)} \quad (3)$$

Further support for this assumption was given by the following two kinetic measurements. First, the identical $k_{obs}$ values were obtained within experimental errors in the measurement for different initial concentrations of **7**-Br ranging from 6.0 to 18 mM, indicating that $k_{obs}$ was independent of the initial concentration of the substrate. Second, the $k_{obs}$ values were found to depend linearly on the initial concentration of the thiazolium salt **6**, $[Tz]_0$, in the measurement with the initial concentration of **7**-Br kept constant at 12 mM. These observations are consistent with eq 3.

**(2) Effects of Substituents of Benzaldehyde.** Under the experimental conditions mentioned in the previous section, kinetic measurements were carried out for the thiazolium-catalyzed azobenzene oxidation of benzaldehyde and its five derivatives having various substituents at the 4-position. In all cases the apparent first-order rate constants ($k_{obs}$) could be determined by the kinetic analyses described above, which are also summarized in Table 2 along with Hammett's substituent constants ($\sigma$).[22] The table indicates explicitly that the introduction of an electron-withdrawing group into the benzene ring of benzaldehyde causes an acceleration of the thiazolium-catalyzed azobenzene oxidation. The sub-

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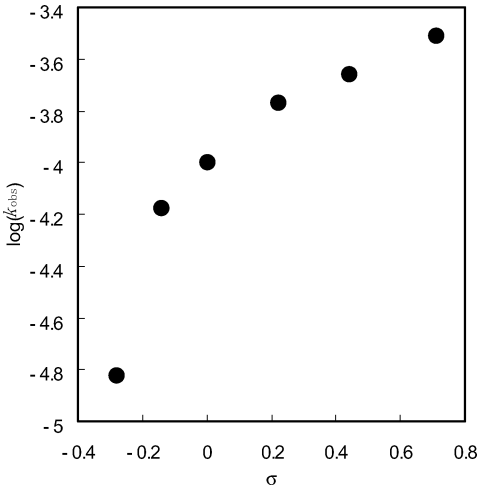
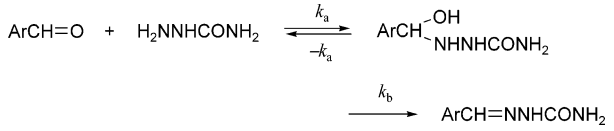



**FIGURE 1.** Plot of $\log(k_{obs})$ for the thiazolium-catalyzed azobenzene oxidation of substituted benzaldehydes against $\sigma$ value.

stituent effect on the reaction rate is graphically demonstrated in Figure 1, which shows that a simple linear relationship between $\log(k_{obs})$ and $\sigma$ is not obtained. The plot appears to be linear in the region of negative $\sigma$ with a reaction constant ($\rho$) of 2.9, while the plot deviates downward from the line in the region of positive $\sigma$.

A number of reactions, the substituent effect of which shows a nonlinear Hammett plot, have been reported so far. It is generally accepted that a nonlinear Hammett plot can be due to the following two factors: a change in the mechanism and a change in the rate-determining step with change in the electronic nature of substituent. In the former case, a Hammett plot is generally concave upward, which has been reported in various reactions such as ethoxidation of benzyl fluorides,[23] the copolymerization of methyl methacrylate with styrenes,[24] and pyridinium chlorochromate oxidation of cinnamic acids.[25] On the other hand, a Hammett plot, which is convex upward like that shown in Figure 1, has been observed when the rate-determining step of a multistep reaction is shifted with change in the electronic nature of the substituent.[26−28] Typically, Anderson and Jencks reported that the rate of semicarbazone formation from substituted benzaldehydes at pH 3.9 (Scheme 3) exhibited a nonlinear Hammett plot that was convex upward.[28] This observation is explained in terms of a shift in the rate-determining step from semicarbazide addition ($k_a$ step) to acid-catalyzed dehydration ($k_b$ step) with an increase in the electron-withdrawing ability of substituent, because an electron-withdrawing substituent accelerates the $k_a$ step but retards the $k_b$ step.

**SCHEME 3. Mechanism of the Semicarbazone Formation from Benzaldehydes**




The origin of the nonlinear Hammett plot observed in the thiazolium-catalyzed azobenzene oxidation of benzaldehydes is analogous basically to that of the semicarbazone formation, although the mechanism is much more complicated (Scheme 2). The active aldehyde **15** is generated through two steps, i.e., nucleophilic attack of thiazolium salt to yield 2-(α-hydroxybenzyl)thiazolium salt **16** ($k_1$ step) and deprotonation of **16** ($k_2$ step). Unfortunately it is difficult to identify which of these steps is rate determining for the active aldehyde formation, because recent mechanistic studies on the thiazolium-catalyzed benzoin condensation reported by White and Leeper revealed that both steps, as well as the benzoin formation step, are partially rate determining for the reaction.[29] However, in analogy with the $k_a$ step in the semicarbazone formation (Scheme 3), an electron-withdrawing substituent accelerates the $k_1$ step in the active aldehyde formation. There are a number of studies demonstrating that the attack of nucleophiles to benzaldehydes or benzoates is accelerated by an electron-withdrawing substituent.[30] Moreover, it appears that an increase in the electron-withdrawing ability of substituent increases the acidity of the benzylic proton of **16** by stabilization of its conjugate base, which is favorable for the deprotonation step ($k_2$ step). Accordingly, it is supposed that the rates of both $k_1$ and $k_2$ steps are favored by electron-withdrawing substituents. However, on the contrary, the rate of azobenzene oxidation of **15** ($k_3$ step) is expected to be accelerated by electron-donating substituents. As mentioned in the previous section, the $k_3$ step is assumed to proceed by a mechanism involving the transfer of electrons from **15** to azobenzene, which could be accelerated by the introduction of an electron-donating group into the benzene ring of **15**. This expectation is supported by the observation that the oxidation potential of the active aldehyde derived from benzaldehyde and 3-benzyl-4-methylthiazolium bromide is reduced considerably by the substitution of methoxy group at the 4-position.[20]

Thus, we propose that the nonlinear Hammett plot observed is derived from a balance of these opposing substituent effects, which causes a shift in the rate-determining step of the reaction from the active aldehyde formation step ($k_1$ and $k_2$ steps) to the oxidation step ($k_3$ step) as the substituent changes from an electron-donating to an electron-withdrawing group. Alternatively, considering that the observed rate constant ($k_{obs}$) is expressed by eq 3, when the relation $k_3[Az]_0 \gg k_{-1}k_{-2}/(k_{-1} + k_2)$ is satisfied, $k_{obs}$ is further simplified to give eq 4, indicating that the $k_1$ and $k_2$ steps are rate determining for the overall reaction. It appears that this is the case of benzaldehydes having an electron-donating

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**TABLE 3. Rate Constants for the Thiazolium-Catalyzed Oxidation of 4-Bromobenzaldehyde (7-Br) and 4-Cyanobenzaldehyde (7-CN) with 4,4′-Disubstituted Azobenzenes (8-X)[a]**

| X | $k_{obs}/10^{-4}$ s$^{-1}$ **7**-Br | **7**-CN | $\sigma^{-}$ [b] |
|---|---|---|---|
| Me | 1.7(±0.2) | 2.1(±0.1) | −0.14 |
| MeO | 1.8(±0.1) | 2.3(±0.1) | −0.12 |
| H | 1.7(±0.2) | 3.1(±0.2) | 0 |
| Br | 1.6(±0.1) | 2.8(±0.1) | 0.26 |
| CN | 2.1(±0.1) | 6.5(±0.3) | 0.99 |

[a] [**6**] = 2.4 mM, [**7**-Br,CN] = 12 mM, [**8**-X] = [**9**] = 30 mM. [$Et_3N$] = 20 mM in $CDCl_3$ at 21.7−22.2 °C. [b] Reference 22.

group, which retards the $k_1$ and $k_2$ steps but accelerates the $k_3$ step.

$$k_{obs} = \frac{k_1 k_2 [Tz]_0}{k_{-1} + k_2} \quad (4)$$

On the other hand, with an increase in the electron-withdrawing ability of the substituent, eq 4 is no longer applied because of retardation of the $k_3$ step, which increases the contribution of the $k_3$ step to the rate-determining step of the overall reaction.

**(3) Effects of Substituents of Azobenzene.** To gain further support for the assumption that the rate-determining step is shifted with change of the benzaldehyde substituent, we examined the effect of substituents introduced into the two benzene rings of azobenzene on the rate of oxidation of 4-bromo- (**7**-Br) and 4-cyanobenzaldehyde (**7**-CN). If the rate-determining step of the reaction is shifted with change of the benzaldehyde substituent from Br to CN, the magnitude of the azobenzene substituent effect on the overall reaction rate for **7**-Br would be different from that for **7**-CN, because the azobenzene substituents influence only the rate of the oxidation step ($k_3$ step).

The apparent first-order rate constants ($k_{obs}$) were measured for the two aldehydes **7**-Br and **7**-CN, using five azobenzenes having various substituents at the 4,4′-positions as an oxidizing agent.[31] The results are summarized in Table 3 and graphically demonstrated in Figure 2, showing a linear correlation of log($k_{obs}$) with Hammett's substituent constant ($\sigma^{-}$)[22] with a positive reaction constant ($\rho$) for both aldehydes. It should be noted, however, that the $k_{obs}$ values for **7**-Br depend only slightly on the azobenzene substituents with a $\rho$ value of 0.07, while a remarkable dependence with a $\rho$ value of 0.40 is observed for **7**-CN.

These results strongly suggest that the contribution of the oxidation step ($k_3$ step) to the rate-determining step of the overall reaction increases largely with change of the benzaldehyde substituent from Br to CN, which is in accord with the expectation based on the nonlinear Hammett plot described in the previous section.

(31) Although the product distributions were not determined in the reactions with substituted azobenzenes **8**-X (X = Me, MeO, Br, and CN) as an oxidizing agent, it was confirmed that in all cases the thiolesters, which were identified by the methylene protons split into a triplet at around $\delta$ 3.1 in the $^1$H NMR spectrum of the reaction mixture, were produced in yields comparable to those in the azobenzene oxidation.

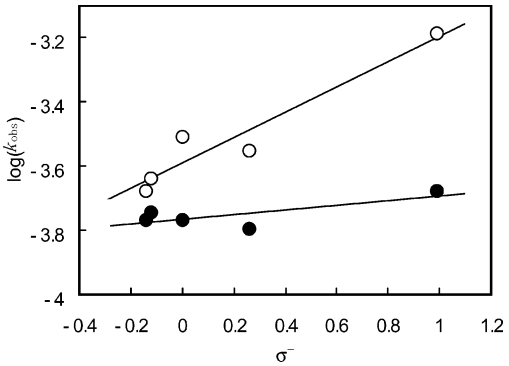


**FIGURE 2.** Plots of log($k_{obs}$) for the thiazolium-catalyzed oxidation of 7-Br (●) and 7-CN (○) with 4,4′-disubstituted azobenzene against $\sigma^{-}$ value.

## Conclusions

We have established the reaction system in which benzaldehydes are converted into the corresponding thiolesters in good yields by utilizing the thiazolium salt and azobenzene as a catalyst and an oxidizing agent, respectively. This is the first example for the thiolester formation mimicking the function of the pyruvate dehydrogenase complex. Moreover, the remarkable rate acceleration is observed in the oxidation of benzaldehydes having an electron-withdrawing substituent. The effect of substituents on the reaction rate ($k_{obs}$) is treated quantitatively to give a nonlinear correlation of log($k_{obs}$) with Hammett's substituent constants ($\sigma$). We propose that the nonlinear Hammett plot is attributed to a shift in the rate-determining step of the multistep reaction with change in the electronic nature of substituent. The finding reported here provides not only a new synthetic procedure of thiolesters, but also a useful insight into the mechanism of biochemical reactions in which TPP serves as a prosthetic group.

## Experimental Section

**3-Butyl-4-methylthiazolium Bromide (6).**[6,13] A mixture of 1-bromobutane (3.0 mL, 28 mmol) and 4-methylthiazole (2.40 mL, 27.1 mmol) was refluxed for 5 h. After cooling, ether was added to the reaction mixture. The precipitate was filtered and dissolved in dichloromethane. To the dichloromethane solution was added ether again to precipitate the product, which was filtered and dried in vacuo to give 5.8 g (90%) of **6** as pale orange powder: mp 45.2−45.8 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.01 (3H, t, $J$ = 7.3 Hz), 1.43−1.57 (2H, m), 1.90−2.02 (2H, m), 2.64 (3H, s), 4.73 (2H, t, $J$ = 7.6 Hz), 7.72 (1H, d, $J$ = 1.1 Hz), 11.56 (1H, d, $J$ = 2.7 Hz).

**4,4′-Dimethoxyazobenzene (8-MeO).**[32] To a solution of $LiAlH_4$ (2.87 g, 75.9 mmol) in THF (30 mL) was added a solution of 4-nitroanisole (3.00 g, 19.6 mmol) in THF (35 mL) at 0 °C under a $N_2$ atmosphere. After refluxing for 4 h, the reaction mixture was cooled, and water (1 mL) was added to the reaction mixture. After the precipitate was filtered off, the filtrate was washed successively with an aqueous solution of $NaHCO_3$, dilute HCl, and water, and dried over $Na_2SO_4$. The solvent was removed to give the crude product, which was purified by recrystallization from hexane−benzene (3:2) to give 1.15 g (48.5%) of **8**-MeO as yellow needles: mp 168.3−169.3 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.89 (6H, s), 7.00 (4H, d, $J$ = 8.9 Hz),

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7.88 (4H, d, $J$ = 8.9 Hz); MS *m/z* (rel intensity) 242 ($M^+$, 73), 135 (47), 107 (100).

**4,4′-Dimethylazobenzene (8-Me).**[32] To a suspension of aluminum powder (1.06 g, 39.3 mmol) in methanol (11 mL) containing 4-nitrotoluene (2.74 g, 20.0 mmol) was added KOH pellets (6.9 g, 107 mmol) under an Ar atmosphere. After vigorous reaction ceased, the reaction mixture was filtered, and the residue was washed with dichloromethane and dilute HCl. The organic layer was separated from the filtrate, washed with dilute HCl and water, and dried over $Na_2SO_4$. The solvent was removed to give the crude product, which was developed on a silica gel column chromatography with hexane−dichloromethane (15:1) eluent to give 0.59 g (28%) of **8**-Me as orange plates: mp 148.1−148.8 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.42 (6H, s), 7.30 (4H, d, $J$ = 7.8 Hz), 7.81 (4H, d, $J$ = 7.8 Hz); MS *m/z* (rel intensity) 210 ($M^+$, 100), 119 (37).

**4,4′-Dibromoazobenzene (8-Br).**[32] This azobenzene was prepared in the procedure described for **8**-Me from 4-bromonitrobenzene in 45% yield. **8**-Br: orange plates; mp 206.7−207.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.65 (4H, d, $J$ = 8.5 Hz), 7.80 (4H, d, $J$ = 8.5 Hz); MS *m/z* (rel intensity) 342 ($M^+$ + 4, 42), 340 ($M^+$ + 2, 82), 338 ($M^+$, 42), 185 (65), 183 (67), 157 (98), 155 (100).

**4,4′-Dicyanoazobenzene (8-CN).**[32] This azobenzene was prepared in the procedure described for **8**-Me from 4-nitrobenzonitrile in 27% yield, except that the KOH pellets were added at −20 °C to avoid the replacement of the cyano group by the methoxy group. **8**-CN: red-orange needles which sublime at 263−267 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.85 (4H, d, $J$ = 8.9 Hz), 8.04 (4H, d, $J$ = 8.9 Hz); MS *m/z* (rel intensity) 232 ($M^+$, 52), 130 (24), 102 (100).

**Thiazolium-Catalyzed Azobenzene Oxidation of Benzaldehyde.** In a typical run, to a solution of 4-bromobenzaldehyde (**7**-Br, 1 mmol), azobenzene (**8**-H, 1 mmol), and 3-butyl-4-methylthiazolium bromide (**6**, 0.1 mmol) in dichloromethane (2.5 mL) containing 10% of octanethiol (**9**, ca. 1.5 mmol) was added $Et_3N$ (1 mmol) under an Ar atmosphere. After stirring for 22 h at room temperature, water was added to the reaction mixture to cease the reaction. The organic layer was separated, washed with water, and dried over $Na_2SO_4$. The solvent was removed to give the residue containing the thiolester **10**-Br and the hydrazide **11**-Br. The consumption of the material and the yields of the products based on the reacted material were determined by the integration of $^1$H NMR in the crude reaction mixture. The residue was separated by GPLC with chloroform eluent to give the products **10**-Br and **11**-Br. Further purification of these products was accomplished by TLC. *S*-Octyl 4-bromothiobenzoate (**10**-Br): pale yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.8 Hz), 1.2−1.5 (10H, m), 1.61−1.72 (2H, m), 3.06 (2H, t, $J$ = 7.3 Hz), 7.58 (2H, t, $J$ = 8.9 Hz), 7.83 (2H, d, $J$ = 8.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 22.6, 28.9, 29.1, 29.1, 29.4, 31.7, 128.1, 128.6, 131.8, 135.9, 191.0; MS *m/z* (rel intensity) 330 ($M^+$ + 2, 9), 328 ($M^+$, 9), 185 (95), 183 (100), 157 (10), 155 (10); HRMS found $M^+$ 328.0504. $C_{15}H_{21}BrOS$ requires $M^+$ 328.0496. *N*,*N*′-Diphenyl(4-bromobenzoyl)hydrazide (**11**-Br): colorless oil; $^1$H NMR (acetone-$d_6$) $\delta$ 6.78 (1H, t, $J$ = 7.3 Hz), 6.91 (2H, d, $J$ = 7.8 Hz), 7.16−7.20 (3H, m), 7.33 (2H, t, $J$ = 8.0 Hz), 7.50−7.56 (6H, m), 8.28 (1H, br s); $^{13}$C NMR ($CDCl_3$) $\delta$ 113.5, 121.6, 124.5, 125.4, 126.6, 129.0, 129.4, 130.3, 131.3, 133.6, 142.8, 146.8, 169.8; MS *m/z* (rel intensity) 368 ($M^+$ + 2, 26), 366 ($M^+$, 21), 183 (100), 157 (5), 155 (5); HRMS found $M^+$ 366.0370. $C_{19}H_{15}BrN_2O$ requires $M^+$ 366.0368. The thiazolium-catalyzed azobenzene oxidation of other benzaldehydes **7** was carried out in a similar manner to afford the corresponding thiolester **10** and hydrazide **11**. In the preparative experiments, the reaction time varied depending upon the substituent of the aldehydes. After stirring for an appropriate time (3 h for **7**-CN, 22 h for **7**-COOMe and **7**-Br, 7 d for **7**-H, and 15 d for **7**-Me), the aldehyde was consumed almost completely, and the thiolester **10** and the hydrazide **11** could be isolated in 46−84% and 4−9% yields, respectively. In the case of **7**-MeO, even after reaction for 19 d, the consumption of the aldehyde was 55%, but the thiolester **10**-MeO could be isolated in 36% yield from the reaction mixture. The characterization of the byproduct **11**-MeO was carried out by using the product obtained by an independent preparation (vide infra). *S*-Octyl 4-cyanothiobenzoate (**10**-CN): pale yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.8 Hz), 1.2−1.5 (10H, m), 1.62−1.74 (2H, m), 3.10 (2H, t, $J$ = 7.4 Hz), 7.75 (2H, t, $J$ = 8.5 Hz), 8.05 (2H, d, $J$ = 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 22.6, 28.9, 29.0, 29.1, 29.3, 29.5, 31.8, 116.4, 117.9, 127.6, 132.4, 140.3, 190.8; MS *m/z* (rel intensity) 275 ($M^+$, 7), 130 (100), 102 (15); HRMS found $M^+$ 275.1342. $C_{16}H_{21}NOS$ requires $M^+$ 275.1344. *N*,*N*′-Diphenyl(4-cyanobenzoyl)hydrazide (**11**-CN): pale yellow oil; $^1$H NMR (acetone-$d_6$) $\delta$ 6.79 (1H, t, $J$ = 7.0 Hz), 6.91 (2H, d, $J$ = 7.0 Hz), 7.18 (1H, t, $J$ = 8.0 Hz), 7.19 (2H, t, $J$ = 8.0 Hz), 7.36 (2H, t, $J$ = 7.8 Hz), 7.61 (2H, br s), 7.75 (2H, d, $J$ = 8.5 Hz), 7.77 (2H, d, $J$ = 8.0 Hz), 8.38 (1H, br s); $^{13}$C NMR ($CDCl_3$) $\delta$ 113.6, 114.1, 118.0, 121.9, 124.4, 127.0, 128.9, 129.2, 129.5, 131.9, 139.4, 141.8, 146.3, 169.2; MS *m/z* (rel intensity) 313 ($M^+$, 25), 183 (100), 130 (14); HRMS found $M^+$ 313.1214. $C_{20}H_{15}N_3O$ requires $M^+$ 313.1215. *S*-Octyl 4-methoxycarbonylthiobenzoate (**10**-COOMe): colorless granules; mp 57.8−58.2 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.6 Hz), 1.2−1.5 (10H, m), 1.62−1.74 (2H, m), 3.09 (2H, t, $J$ = 7.4 Hz), 3.95 (3H, s), 8.01 (2H, t, $J$ = 8.4 Hz), 8.10 (2H, d, $J$ = 8.4 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 22.6, 28.9, 29.0, 29.1, 29.3, 29.4, 31.8, 52.5, 127.1, 129.8, 134.0, 140.5, 166.2, 191.6; MS *m/z* (rel intensity) 308 ($M^+$, 3), 163 (100), 135 (8), 104 (3); HRMS found $M^+$ 308.1438. $C_{17}H_{24}O_3S$ requires $M^+$ 308.1446. *N*,*N*′-Diphenyl-(4-methoxycarbonylbenzoyl)hydrazide (**11**-COOMe): pale yellow oil; $^1$H NMR (acetone-$d_6$) $\delta$ 3.87 (3H, s), 6.78 (1H, t, $J$ = 7.5 Hz), 6.90 (2H, d, $J$ = 7.0 Hz), 7.15−7.20 (3H, m), 7.34 (2H, t, $J$ = 7.8 Hz), 7.58 (2H, d, $J$ = 7.8 Hz), 7.69 (2H, d, $J$ = 8.5 Hz), 7.94 (2H, d, $J$ = 8.5 Hz), 8.29 (1H, br s); $^{13}$C NMR ($CDCl_3$) $\delta$ 52.3, 113.7, 121.7, 124.5, 126.7, 128.4, 129.1, 129.3, 129.4, 131.8, 139.3, 142.5, 146.7, 166.3, 170.0; MS *m/z* (rel intensity) 346 ($M^+$, 40), 183 (100), 163 (18), 135 (3); HRMS found $M^+$ 346.1311. $C_{21}H_{18}N_2O_3$ requires $M^+$ 346.1317. *S*-Octyl thiobenzoate (**10**-H):[33] colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.5 Hz), 1.2−1.5 (10H, m), 1.61−1.73 (2H, m), 3.07 (2H, t, $J$ = 7.3 Hz), 7.44 (2H, t, $J$ = 7.6 Hz), 7.56 (1H, t, $J$ = 7.4 Hz), 7.97 (2H, d, $J$ = 7.4 Hz); MS *m/z* (rel intensity) 250 ($M^+$, 7), 105 (100); HRMS found $M^+$ 250.1389. $C_{15}H_{22}OS$ requires $M^+$ 250.1391. *N*,*N*′-Diphenylbenzoylhydrazide (**11**-H):[34] colorless granules; mp 144−145 °C; $^1$H NMR (acetone-$d_6$) $\delta$ 6.78 (1H, t, $J$ = 7.0 Hz), 6.92 (2H, d, $J$ = 7.5 Hz), 7.14−7.20 (3H, m), 7.3−7.4 (5H, m), 7.51 (2H, d, $J$ = 7.0 Hz), 7.59 (2H, d, $J$ = 7.5 Hz), 8.23 (1H, br s); $^{13}$C NMR (acetone-$d_6$) $\delta$ 113.5, 113.5, 120.7, 120.7, 125.1, 126.5, 128.5, 128.7, 129.3, 129.9, 130.9, 137.3, 171.9; MS *m/z* (rel intensity) 288 ($M^+$, 57), 183 (100), 105 (39); HRMS found $M^+$ 288.1252. $C_{19}H_{16}N_2O$ requires $M^+$ 288.1263. *S*-Octyl 4-methylthiobenzoate (**10**-Me): pale yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.8 Hz), 1.2−1.5 (10H, m), 1.60−1.72 (2H, m), 2.40 (3H, s), 3.05 (2H, t, $J$ = 7.3 Hz), 7.23 (2H, t, $J$ = 8.4 Hz), 7.86 (2H, d, $J$ = 8.4 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 21.6, 22.6, 28.9, 28.9, 29.1, 29.2, 29.6, 31.8, 127.2, 129.2, 134.7, 144.0, 191.8; MS *m/z* (rel intensity) 264 ($M^+$, 5), 119 (100); HRMS found $M^+$ 264.1553. $C_{16}H_{24}OS$ requires $M^+$ 264.1548. *N*,*N*′-Diphenyl(4-methylbenzoyl)hydrazide (**11**-Me): pale yellow oil; $^1$H NMR (acetone-$d_6$) $\delta$ 2.31 (3H, s), 6.78 (1H, t, $J$ = 7.3 Hz), 6.92 (2H, d, $J$ = 7.5 Hz), 7.13 (2H, d, $J$ = 8.0 Hz), 7.17 (1H, t, $J$ = 8.5 Hz), 7.18 (2H, t, $J$ = 8.5 Hz), 7.31 (2H, t, $J$ = 8.0 Hz), 7.48 (2H, d, $J$ = 9.0 Hz), 7.50 (2H, d, $J$ = 8.0 Hz), 8.19 (1H, br s); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.5, 113.6, 121.5, 124.6, 126.2, 128.8, 128.9, 129.4, 131.8, 141.3, 143.7, 147.4, 170.7; MS *m/z* (rel intensity) 302 ($M^+$, 61), 183 (54), 119 (100); HRMS found $M^+$ 302.1418. $C_{20}H_{18}N_2O$ requires $M^+$ 302.1419. *S*-Octyl 4-methoxythiobenzoate (**10**-MeO): pale yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.8 Hz), 1.2−1.5 (10H, m), 1.60−1.72 (2H, m), 3.04 (2H, t, $J$ = 7.4 Hz), 3.86 (3H, s), 6.91 (2H, t, $J$ = 8.9 Hz), 7.95 (2H, d, $J$ = 8.9 Hz); $^{13}$C

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NMR ($CDCl_3$) $\delta$ 14.1, 22.6, 28.9, 29.0, 29.1, 29.2, 29.7, 31.8, 55.5, 113.7, 129.3, 130.1, 163.6, 190.7; MS *m/z* (rel intensity) 280 ($M^+$, 5), 135 (100); HRMS found $M^+$ 280.1478. $C_{16}H_{24}O_2S$ requires $M^+$ 280.1479.

**Independent Preparation of 11-Br.** A mixture of 4-bromobenzoic acid (0.135 g, 0.668 mmol) and $SOCl_2$ (2 mL) was refluxed for 3 h. After removal of an excess of $SOCl_2$ in vacuo, the residual acid chloride was dissolved in $Et_2O$ (8 mL). The ethereal solution was slowly added to a solution of hydrazobenzene (**12**, 0.312 g, 1.70 mmol) in $Et_2O$ (8 mL). After stirring for 6 h at room temperature, water was added to the reaction mixture. The organic layer was separated, washed successively with an aqueous solution of NaOH and water, and dried over $Na_2SO_4$. The solvent was removed to yield the crude product, which was separated by GPLC with chloroform eluent to give **11**-Br in 52% yield. Spectroscopic data were thoroughly consistent with those of the product obtained by the thiazolium-catalyzed azobenzene oxidation of **7**-Br.

**Independent Preparation of 11-MeO.** To a solution of 4-methoxybenzaldehyde (**7**-MeO, 0.5 mmol), azobenzene (**8**-H, 0.5 mmol), hydrazobenzene (**12**, 0.5 mmol), and 3-butyl-4-methylthiazolium bromide (**6**, 0.3 mmol) in dichloromethane (4 mL) was added $Et_3N$ (70 $\mu$L, 0.5 mmol) under an Ar atmosphere. After stirring for 3 d at 60 °C, the reaction mixture was developed on a silica gel column with dichloromethane−hexane (10:1), and separated by TLC with dichloromethane−ether (10:1). Further purification of the product was accomplished by GPLC with chloroform eluent to give *N*,*N*′-diphenyl(4-methoxybenzoyl)hydrazide (**11**-MeO) as a colorless oil (37%): $^1$H NMR (acetone-$d_6$) $\delta$ 3.79 (3H, s), 6.78 (1H, t, $J$ = 7.5 Hz), 6.85 (2H, d, $J$ = 9.0 Hz), 6.93 (2H, d, $J$ = 7.5 Hz), 7.14 (1H, t, $J$ = 7.5 Hz), 7.18 (2H, t, $J$ = 8.0 Hz), 7.30 (2H, t, $J$ = 7.8 Hz), 7.45 (2H, d, $J$ = 8.5 Hz), 7.60 (2H, d, $J$ = 9.0 Hz), 8.20 (1H, br s); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.3, 113.3, 113.6, 121.4, 124.5, 126.0, 126.6, 128.9, 129.3, 131.1, 144.0, 147.5, 161.7, 170.3; MS *m/z* (rel intensity) 318 ($M^+$, 18), 183 (6), 135 (100); HRMS found $M^+$ 318.1359. $C_{20}H_{18}N_2O_2$ requires $M^+$ 318.1368.

**Kinetic Measurements.** The kinetic measurements of the azobenzene oxidation were carried out by the use of $^1$H NMR spectroscopy (500 MHz) at 21.7−22.2 °C. A degassed solution of thiazolium salt **6** and azobenzene **8** in $CDCl_3$ (500 $\mu$L) was placed in a Pyrex NMR tube. To the solution was added a degassed solution of aldehyde **7**, thiol **9**, and $Et_3N$ in $CDCl_3$ (50 $\mu$L) containing phthalide as an internal standard. The initial concentrations of the materials were adjusted as follows: [**6**] = 2.4 mM, [**7**] = 12.0 mM, [**8**] = [**9**] = 30.0 mM, [$Et_3N$] = 20.0 mM. The reaction was followed by monitoring the decrease in the intensity of the $^1$H NMR signal at around $\delta$ 10 due to **7** on the basis of phthalide ($\delta$ 5.33). The apparent first-order rate constants ($k_{obs}$) were calculated from the linear part, where the consumption of **7** was not more than 35%, of the plot of log[**7**] against reaction time. The $k_{obs}$ values obtained for the azobenzene oxidation of various benzaldehydes and the oxidation of **7**-Br and **7**-CN with various azobenzenes are listed in Tables 2 and 3, respectively. When the initial concentration of **6** was adjusted to 1.80, 2.40, and 3.00 mM with the initial concentration of **7**-Br kept constant at 12.0 mM, the values of $1.6(\pm0.3) \times 10^{-4}$, $1.7(\pm0.2) \times 10^{-4}$, and $2.6(\pm0.2) \times 10^{-4}$ $s^{-1}$ were obtained as $k_{obs}$ values, respectively, suggesting that $k_{obs}$ is proportional to the initial concentration of **6**. Furthermore, although five different initial concentrations of **7**-Br (6.0, 9.0, 12.0, 15.0, and 18.0 mM) were employed, identical $k_{obs}$ values of $1.7(\pm0.2) \times 10^{-4}$ $s^{-1}$ were obtained for all concentrations, indicating that $k_{obs}$ is independent of the initial concentration of **7**.

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**Supporting Information Available:** $^1$H NMR spectra for *S*-octyl thiobenzoates **10** and *N*,*N*′-diphenylbenzoylhydrazides **11**; plot of a decrease in the concentration of **7**-Br vs reaction time; and general experimental methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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