Kinetic Studies on the Amination of Leucoquinizarin

Masashi KIKUCHI, Takamichi YAMAGISHI, and Mitsuhiko HIDA*

Department of Industrial Chemistry, Faculty of Technology, Tokyo Metropolitan University, Fukazawa, Setagaya-ku, Tokyo 158

(Received September 30, 1981)

Leucoquinizarin reacts with amines to give mono- and diaminoanthraquinones. The amination mechanism of leucoquinizarin was investigated on the basis of the kinetics and structures of leuco compounds. The amination reaction of leucoquinizarin was characterized as follows. This amination proceeded in polar solvent but not in nonpolar solvent at all. The reaction rate was not influenced by the addition of a small amount of water (95% ethanol) but enhanced largely in 80% ethanol. This amination reaction has a low activation energy ($\Delta E^* = 5.7-9.0$ kcal mol^{-1}) and an extraordinarily small pre-exponential term ($A = 10^3-10^5$ l mol^{-1} min^{-1}). Leucoquinizarin was proposed to be aminated by the addition of amine to carbonyl group at its 1,4-position. The oxidation of leuco monoaminohydroxyanthraquinone was also examined.

Leucoquinizarin (**1**) reacts with amines to give mono- and diaminoanthraquinone derivatives, which are among the most important compounds in synthetic dyes. Although many patents[1] and some papers[2] on the amination of **1** have been reported, most of them are nothing but technical reports and no mechanistic investigation has been made. Though some reports concerning the structures of leucoanthraquinones have been published,[3] they have given no convincing data.[4,5] We have recently elucidated the structures of leucoanthraquinones on the basis of ^{13}C-NMR spectra.[6] In this paper we discuss the amination of **1** from the kinetic point of view, and propose that **1** in 1,4-diketo form is the most reactive to amine among the possible tautomeric isomers. The oxidation of leuco monoaminohydroxyanthraquinone was also examined.

Results and Discussion

Kinetics of the Amination of 1 with Butylamine. The reaction of **1** with butylamine in air gave 1-butylamino-4-hydroxyanthraquinone (**2**) and 1,4-bis(butylamino)-anthraquinone (**3**). The reaction under a nitrogen atmosphere gave compounds **2** and **3** in their leuco forms. Since all attempts of quantitative oxidations of these leuco compounds to the anthraquinone derivatives led unsatisfactory results, the amination reaction under a nitrogen atmosphere was followed by taking visible spectra of the amination solution in the presence of citric acid as reducing agent to suppress the oxidations of leuco compounds of **1** and **2**. By using a small amount of butylamine ($C_4H_9NH_2$/**1**=1—5) and by setting the conversion low only leuco compound of **2** was obtained. The reaction was first order on both concentrations of **1** and butylamine and the second order rate constant was independent of these concentrations. The Arrhenius plots showed a good straight line. As shown in Table 1, the reaction proceeded easily in ethanol and DMF, but did not at all in nonpolar solvent such as benzene. These facts show that the polarity of solvent largely enhances the reaction rate and suggest that the reaction intermediate is of ionic character.

If the solvation energy (ΔF_{solv}) of reaction intermediate was approximated by the Born's equation (1), and if the cavity size and the temperature dependency of dielectric constant (D) do not vary with solvent, both values of ΔH^* and ΔS^* will increase with increase in

$$\Delta F_{solv} = C(1-1/D) \quad (1)$$

dielectric constant of the solvent. In accordance with our expectation ΔH^* and ΔS^* have larger values in DMF (D=36.7) than those in ethanol (D=23.2). Since dielectric constant of aqueous ethanol increases in proportion to the amount of water,[7] the reaction rate in aqueous ethanol will increase with increase in water content. But the reaction rate in aqueous ethanol did not increase proportionally to water content and both values of ΔH^* and ΔS^* in 80% ethanol decreased as compared with those in ethanol, though the dielectric constant (D=34) is larger than that of ethanol. Thus the results in aqueous ethanol could not be understood only by the increase in polarity of solvent, but another interaction such as the hydrogen bonding between the reaction intermediate and water should be also assumed.

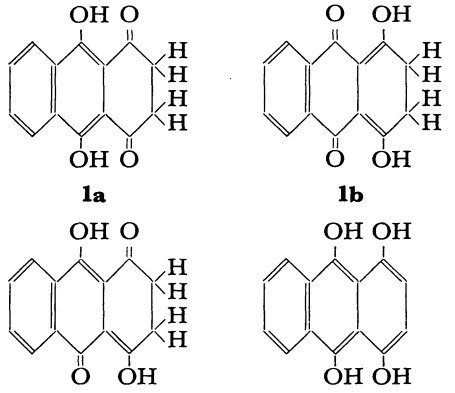
The amination reaction of **1** was characterized by a low activation energy (ΔE^*=5.7—9.0 kcal mol^{-1}) and extraordinarily small pre-exponential term ($A=10^3$—

Table 1. Solvent effects on the amination of leucoquinizarin

Solvents	$k_{60\,°C}$ / l mol^{-1} min^{-1}	ΔE^* / kcal mol^{-1}	A / l mol^{-1} min^{-1}	ΔH^* / kcal mol^{-1}	$\Delta S^{*a)}$ / cal deg^{-1} mol^{-1}
DMF	0.989	9.04	7.51×10^5	8.38	−35.21
C_6H_6	No reaction	—	—	—	—
C_2H_5OH[b)]	0.523	7.02	1.96×10^4	6.36	−41.07
C_2H_5OH/H_2O[c)]	0.532	—	—	—	—
C_2H_5OH/H_2O[d)]	1.014	5.72	5.96×10^3	5.05	−43.44

a) This value is shown by correcting a statistic factor 2. b) These values were reinvestigated (see Ref. 6). c) 95% ethanol. d) 80% ethanol.

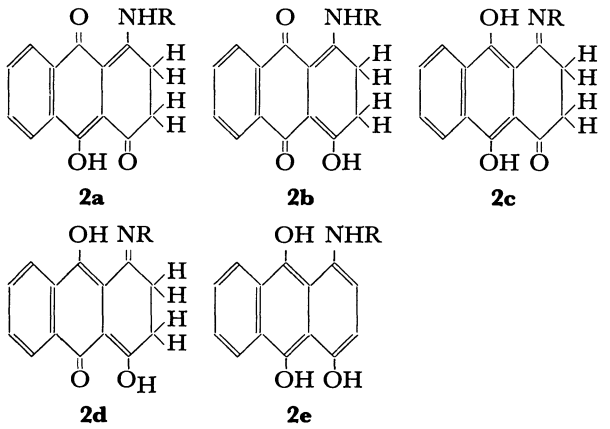
10^5 l mol^{-1} min^{-1}). In many cases the activation energy and pre-exponential term are reported to be 20—30 kcal mol^{-1} and 10^9—10^{11} l mol^{-1} min^{-1}, respectively, while anomalously small activation energy (ΔE^*=10—18 kcal mol^{-1}) and pre-exponential term (A=10^5—10^6 l mol^{-1} min^{-1}) are known in the Menschutkin reaction between pyridine or triethylamine and alkyl iodide[8] and in the semicarbazone formation of acetophenones (ΔE^*=4—11 kcal mol^{-1}, A=0.27—10^5 l mol^{-1} min^{-1}).[9] These reactions are known to proceed through ionic intermediates.



1a **1b** **1c** **1d**

The Structures of ***1*** *and Leuco Compound of* ***2***. The ^{1}H-NMR spectrum of **1** showed methylene protons (4H; singlet, 3.05 ppm), hydroxyl protons (2H; singlet, 13.50 ppm) and aromatic ring protons (4H of A_2B_2 type, 8.42, 7.77 ppm). This result suggests the possibilities of the structures **1a** or **1b**.

With respect to leuco compound of **2**, the five possible structures (**2a**—**e**; R=C_4H_9) can be written as follows.



2a **2b** **2c** **2d** **2e**

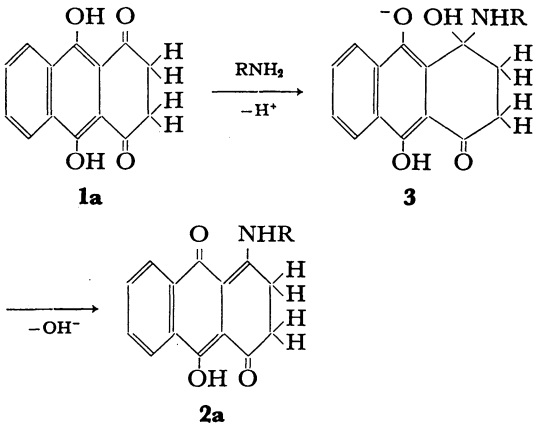
The ^{1}H-NMR spectrum of leuco compound of **2** showed methylene protons (4H; triplet, 2.88 ppm), one hydroxyl proton (1H; singlet, 13.95 ppm), one amino proton (1H; broad, 14.90 ppm) and unsymmetrical ring protons (4H; multiplet, 8.36, 7.62 ppm). This result permits the assignment of leuco compound of **2** to **2a** or **2b**. The presence of the unsymmetrical ring protons seems to demand 4,9-diketo form (**2a**) for leuco compound of **2**.

An examination of ^{13}C-NMR spectra shows that the resonance peaks of carbonyl carbons (C-9, 10) of anthraquinons were characteristically observed at about 180 ppm,[10] but the chemical shifts of carbonyl carbon adjacent to the methylene or methyl carbon are at about 200 ppm.[11] The chemical shift 200.8 ppm of the carbonyl carbon of **1** suggested that **1** may exist in the 1,4-diketo form **1a**. The chemical shifts of the carbonyl carbons of leuco compound of **2** were 199.9 and 172.2 ppm and the latter corresponds to the carbonyl carbon detached from the methylene carbon. These results concluded that the leuco compound of **2** exists predominantly in unsymmetrical 4,9-diketo form **2a** in solution. All ^{1}H-NMR spectra of **1** in $CDCl_3$, DMF-d_7, C_6D_6 and $CDCl_3$–C_2D_5OD (1 : 1) were the same except hydroxyl protons. Also ^{13}C-NMR spectra of **1** in $CDCl_3$, C_6D_6, DMF-d_7 were the same. These spectra showed that **1** retained 1,4-diketo form **1a** predominantly in these solutions. The spectra in C_2D_5OD could not be measured due to low solubility of **1**.

Two possibilities as to the reaction mechanism could be considered as follows.

1. The elementary reaction, which determined the rate of the amination of **1**, has intrinsically a low activation energy and a small pre-exponential term.
2. A very reactive species is one of the tautomers (**1b**—**d**), which exists in a very small amount in the solution.

The compounds of **2a** and 1,4-dimethoxy-9,10-anthracenediol gave no aminated product with butylamine in the same conditions as **1** undergoes amination. This result suggests that **1c** and **1d** are much less reactive than 1,4-diketo form **1a**. Consequently, though the possibility of **1b** to be reactive species cannot be excluded, **1a** could be thought to be the most reactive among tautomeric isomers. The amination of leucoquinizarin seems to proceed by the addition and elimination mechanism as shown in Scheme 1. The addition of amine to carbonyl group of **1a** was led to **2a** *via* an ionic reaction intermediate such as **3**.



1a **3** **2a**

Scheme 1.

Base catalysis by amine can be excluded, because the second order rate constant was independent of amine concentration. The possibility of the reaction intermediate having an ion pair also may be excluded, because the polarity effect of solvent was very large, and then the inner solvation cannot be considered.

Dissociation of ***1*** *in Solution.* The possibility of the dissociation of **1** in the reaction media was examined since the dissociation may be promoted by the presence

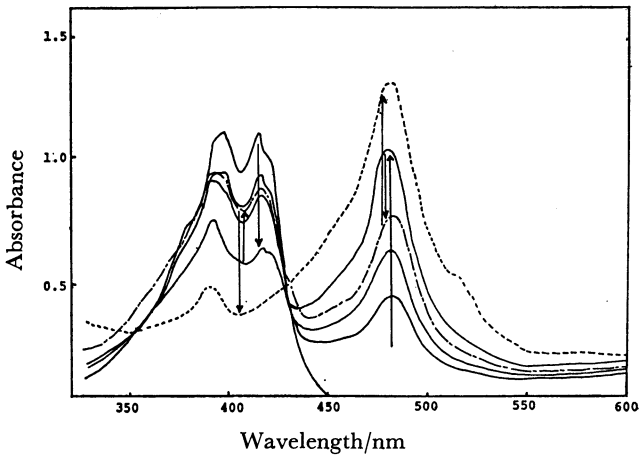


Fig. 1. The visible spectra of leucoquinizarin (**1**) depending on the amount of triethylamine (TEA). [TEA]/mol dm^{-3}: ——; 0—0.358, -·-·-; 0.358—0.574, ------; 0.574—0.717. [**1**]$=8.257\times10^{-5}$ mol dm^{-3}.

of amine. The dissociated **1** may suppress the reactivity of **1** for the nucleophilic attack of amine. Change of the visible spectra of **1** by the presence of triethylamine (inactive for the amination) tells the stepwise dissociation of **1** as shown in Fig. 1. The absorption spectra showed isosbestic points at 353 nm and 429 nm in range of the amine concentration below 0.358 mol dm^{-3}. If a single acid and base equilibrium between **1** and triethylamine can be assumed, the acidity of **1** could be estimated from change of absorbance with the concentration of amine, as shown in Fig. 1, by usual method. But the value of the acid and base equilibrium constant obtained largely depends on wavelength. This means that the single equilibrium cannot be reasonably assumed, but formation of other species, such as radical anion, also should be assumed. Consequently, the amount of dissociated **1** in the amination could not be determined, but it can be considered to be negligible, since the same spectra in the absence and presence of triethylamine were observed in the same conditions as **1** undergoes amination.

The Oxidation of Leuco Compound of **2**. Leuco compounds of aminated product have been oxidized by heating in nitrobenzene,[2a,b] by heating with an excess of amine,[2c] in oleum,[12] or alkaline solution.[1] Currently the heating in nitrobenzene has been reported to be the most plausible method of oxidation of these leuco compounds. As shown in Table 2, the oxidation could not be carried out quantitatively in triethylamine–ethanol solution. The oxidation in nitrobenzene gave **2** in *ca.* 60% at most, accompanied by side reactions such as dealkylation and other reactions. The dealkylated product was confirmed to be 1-amino-4-hydroxyanthraquinone by comparison of its spectra and TLC with those of the authentic sample. The brown product was composed of several compounds and identification of their structures was impossible. It is found that the aminated products are susceptible to dealkylation, while the formation of the brown product is easily formed at lower temperature. Consequently the current method heating in nitrobenzene cannot be approporiate method. The quantitative oxidation method of leuco compounds, which is not accompanied by side reactions, should be investigated.

Table 2. The oxidation of leuco compound of **2**

Solvents	Temp/°C	Time/h	Yield of **2**/%	Conv.
TEA[a]–Ethanol	60	2	72.1	—
Nitrobenzene	160	2	59.6 (4.0)[b]	100
Nitrobenzene	170	2	64.5 (9.2)	100
Nitrobenzene	180	2	61.5 (14.2)	100
Nitrobenzene	Reflux	0.25	62.5 (27.9)	100

a) Triethylamine. b) Parenthesis shows the yield of 1-amino-4-hydroxyanthraquinone.

Experimental

Materials. The leuco compounds and anthraquinone derivatives were prepared and confirmed as reported previously.[6] Leucoquinizarin (**1**): λ_{max} (ethanol) 398 nm (ε; 12700), 415 nm (ε; 12300).[13] Leuco compound of **2**: λ_{max} (ethanol) 432 nm (ε; 17000), 457 nm (ε; 18570).[13] The butylamine was dried by refluxing on sodium metal and distilled under a nitrogen atmosphere. All the solvents were purified by the usual methods, and stored under a nitrogen atmosphere.

Kinetic Measurements. A typical run is as follows. Leucoquinizarin and ethanol were mixed in a flask. After this solution was brought to the reaction temperature, the reaction was initiated by adding butylamine ethanol solution into the leucoquinizarin solution; the concentrations of leucoquinizarin and butylamine were 5 mmol dm^{-3} and 5—25 mmol dm^{-3}, respectively. All above operations were performed under a dry and oxygen-free nitrogen atmosphere. At regular time interval, 0.3 ml portion of reaction solution was withdrawn and diluted to 25 ml with ethanol containing citric acid (0.603 g/250 ml) to suppress the oxidation of leuco compounds. The yield of leuco aminated product **2a** was determined spectrometrically. Visible spectra were measured with Shimazu UV-210 spectrometer.

^{1}H-NMR and ^{13}C-NMR Measurements. ^{1}H-NMR spectrum of leucoquinizarin in $CDCl_3$ was already reported.[6] ^{1}H-NMR spectra in DMF-d_7, C_6D_6, and C_2D_5OD–$CDCl_3$ (1 : 1) were as follows. The parentheses show the chemical shifts (δ, ppm) of α, β protons of aromatic ring, methylene protons and hydroxyl protons, respectively. DMF-d_7: (8.50, 8.00; 3.10; 14.78), C_6D_6: (8.48, 7.36; 2.28; 14.23), C_2D_5OD–$CDCl_3$(1 : 1) : (8.24, 7.64; 2.97; 4.21). The peaks of carbonyl carbons in ^{13}C-NMR were observed at 200.8 ppm ($CDCl_3$),[6] 200.8 ppm (C_6D_6), and 202.6 ppm (DMF-d_7) showing the existence of the carbonyl carbon adjacent to the methylene carbon. In the case of C_2D_5OD solution, the spectrum could not be measured due to low solubility. ^{1}H-NMR spectra were measured using TMS as an internal standard with a Hitachi R-24 spectrometer. ^{13}C-NMR spectra were measured under a nitrogen atmosphere using TMS as an internal standard with a JEOL FX-60 spectrometer.

The Oxidation of Leuco Compound of **2**. A mixture of leuco compound of **2** (20 mg) and nitrobenzene (0.65 ml) was heated in air. The products were separated by column chromatography on silica gel using benzene as eluent and identified to be **2** and 1-amino-4-hydroxyanthraquinone as the dealkylated product by comparison with authentic samples. The yields of products **2** and 1-amino-4-hydroxyanthraquinone were determined spectrometrically.

References

1) M. R. Michael, Brit. Patent 2013701 (Cl C09B1/22) ICI. (1979); *Chem. Abstr.*, **92**, 199751 (1980); J. A. W. George, Brit. Patent 1504137 (Cl D06p1/16) Kodak Ltd. (1978); *Chem. Abstr.*, **89**, 112381u (1978).

2) a) K. Naiki, *Yuki Gosei Kagaku*, **12**, 364 (1954); b) Y. Banshō, *Kogyo Kagaku Zasshi*, **57**, 80 (1954); c) Y. Bansho and K. Kondō, *ibid.*, **57**, 751 (1954); d) M. S. Simon, *J. Am. Chem. Soc.*, **85**, 1974 (1963); M. S. Simon and D. P. Waller, *Tetrahedron Lett.*, **1967**, 1527; e) C. W. Greenhalgh and N. Hughes, *J. Chem. Soc., C*, **1968**, 1284.

3) S. M. Bloom and P. F. Hutton, *Tetrahedron Lett.*, **1963**, 1993.

4) G. S. Egerton, N. E. N. Assaad, and N. D. Uffindell, *J. Soc. Dyers Colour.*, **83**, 45 (1967).

5) C. W. Greenhalgh, *Endeavour*, **35**, 134 (1976).

6) M. Kikuchi, T. Yamagishi, and M. Hida, *Dyes Pigments*, **2**, 143 (1981).

7) E. S. Amis, "Solvent Effects on Reaction Rates and Mechanisms," Academic Press, New York (1966), p. 175.

8) K. J. Laider, "Reaction Kinetics, Vol. II, Reaction in Solution," Pergaman Press, London (1963).

9) R. P. Cross and P. Fugassi, *J. Am. Chem. Soc.*, **71**, 223 (1949).

10) G. Höfle, *Tetrahedron*, **30**, 1963 (1976).

11) M. Kobayashi, Y. Terui, K. Tori, and N. Tsuji, *Tetrahedron Lett.*, **1976**, 619.

12) M. I. Krasnoselśkaya, L. D. Leichenko, N. A. Parfenov, V. I. Kolodyazhnyi, and M. P. Venzelovskii, U. S. S. R. Patent 411077 (Cl C07C, C09b) (1974); *Chem. Abstr.*, **81**, 93052d (1974).

13) These values were determined in ethanol containing citric acid (0.603 g/250 ml) to suppress the oxidation of leuco compounds.