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A Probable Hydrogen-Bonded Meisenheimer Complex: An Unusually High S_NAr Reactivity of Nitroaniline Derivatives with Hydroxide Ion in Aqueous Media

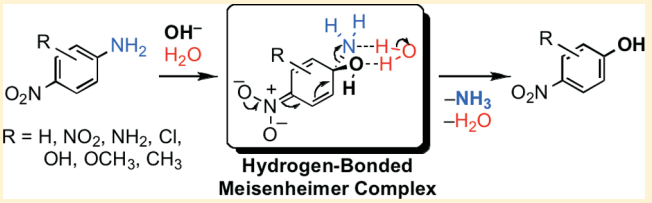
Mitsutaka Imoto,[†] Yasunori Matsui,[‡] Motonori Takeda,[†] Akihiro Tamaki,[†] Hisaji Taniguchi,[†,‡] Kazuhiko Mizuno,[*,‡,§] and Hiroshi Ikeda[*,‡,§]

[†]Seika Corporation, 1-1-82 Kozaika, Wakayama 641-0007, Japan

[‡]Department of Applied Chemistry, Graduate School of Engineering, and [§]The Research Institute for Molecular Electronic Devices (RIMED), Osaka Prefecture University, 1-1 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8531, Japan

Supporting Information

ABSTRACT: Observations show that nitroanilines exhibit an unusually high S_NAr reactivity with OH^- in aqueous media in reactions that produce nitrophenols. S_NAr reaction of 4-nitroaniline (**2a**) in aqueous NaOH for 16 h yields 4-nitrophenol (**4a**) quantitatively, whereas a similar reaction of 4-nitrochlorobenzene (**1a**) gave **4a** in 2% yield together with recovered **1a** in 97%, suggesting that the leaving ability of the NH_2 group far surpasses that of Cl under these conditions. An essential feature of S_NAr reactions of nitroanilines is probably that the NH_2 leaving group participates in a hydrogen-bonding interaction with H_2O. Density functional theory (DFT) calculations for a set of 4-nitroaniline, OH^-, and H_2O suggest a possible formation of a Meisenheimer complex stabilized by hydrogen-bonding interactions and a six-membered ring structure. The results obtained here contrast with conventional S_NAr reactivity profiles in which nitroanilines are nearly unreactive with nucleophiles in organic solvents.

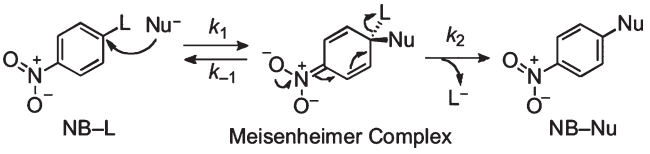


Aromatic nucleophilic substitution (S_NAr) reactions are one family of the transformations that interchange functional groups on aromatic rings containing strong electron-withdrawing groups.[1−3] A typical example of this process is shown in Scheme 1 for nitrobenzene derivative (NB−L) possessing leaving groups (L). In the pathway, nucleophiles (Nu^-) add to NB−L to generate Meisenheimer complexes (k_1) that undergo elimination of L^- to produce substituted nitrobenzenes (NB−Nu).

Organic solvents, especially those that are polar and aprotic such as *N*,*N*-dimethylformamide and sulfolane, are generally used in S_NAr reactions to facilitate efficient addition of Nu^- to NB−L and generation of the Meisenheimer complex. Generally, the formation of the Meisenheimer complex accompanied with dearomatization is considered to be a rate-determining step. When the C−L bond in the complex cleaves more rapidly than the C−Nu bond, the substitution product NB−Nu forms. Thus, for S_NAr reaction to proceed efficiently, the rate constant for elimination from the intermediate complex (k_2) must be larger than that of reversal of the addition process (k_{-1}). This is the reason why good leaving groups L are normally required in substrates that participate in S_NAr reaction.

The general order of the leaving group abilities observed in S_NAr reactions is F > NO_2 > OSO_2Ar > Cl, Br > I > OAr > OH ≫ NH_2.[1] Typically, readily available 4-nitrochlorobenzene and its derivatives (L = Cl, **1**, Scheme 2) that contain Cl with a moderately high leaving ability are used as substrates for S_NAr reactions.[2] On the other hand, as depicted even in textbooks,[4]

Scheme 1. Mechanism for S_NAr Reactions of Nitrobenzenes (NB−L) with Nu^- to Produce Substituted Nitrobenzenes (NB−Nu)



derivatives of 4-nitroaniline (L = NH_2, **2**) only reluctantly undergo S_NAr reactions in which the poor leaving group (NH_2) is eliminated.[5−7]

Rossi and co-workers have described an interesting observation that hydrolysis reaction of *N*-picrylimidazole in aqueous NaOH provides picric acid (Scheme 3)[8] in a process where the rate constant for generation of the Meisenheimer complex is 20 times larger than that of the Meisenheimer complex formed by the addition of OH^- to 2,4,6-trinitrochlorobenzene.

In the current investigation, we have compared S_NAr reactivities of various 4-nitrochlorobenzene derivatives (**1**, Scheme 2) with OH^- in aqueous media with those of the corresponding 4-nitroanilines (**2**). In contrast to predictions based on leaving group abilities, we observed that the nitroaniline derivatives **2**

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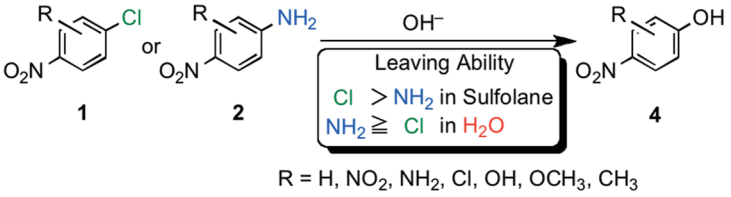
Scheme 2. S_NAr Reactions of 4-Nitrochlorobenzenes (1) and 4-Nitroanilines (2) with OH^-



Scheme 3. Hydrolysis of *N*-Picrylimidazole and 2,4,6-Trinitrochlorobenzene[8]

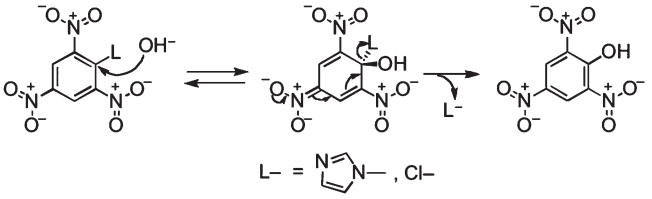
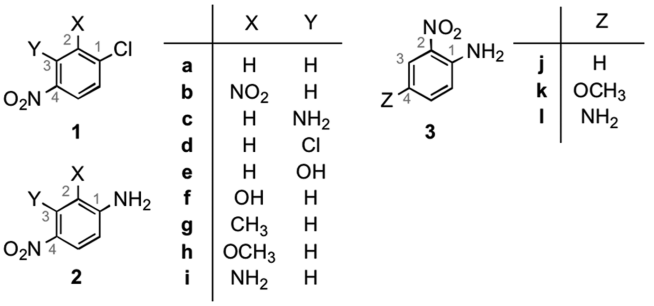


Chart 1. List of 4-Nitrochlorobenzenes (1), 4-Nitroanilines (2), and 2-Nitroanilines (3)[a]



	X	Y
a	H	H
b	NO_2	H
c	H	NH_2
d	H	Cl
e	H	OH
f	OH	H
g	CH_3	H
h	OCH_3	H
i	NH_2	H

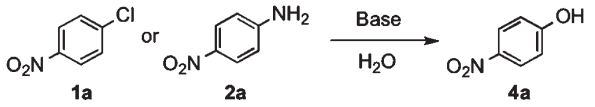
	Z
j	H
k	OCH_3
l	NH_2

[a]Regarding nomenclature, see ref 9.

display unexpectedly high S_NAr reactivities (Chart 1). The source of this reactivity is attributed to hydrogen-bonding interactions between the NH_2 group and H_2O that lead to formation of a six-membered hydrogen-bonded Meisenheimer complex. These findings, which provide a new perspective to S_NAr chemistry, are described below.

S_NAr reactivities of 4-nitrochlorobenzene (**1a**) and 4-nitroaniline (**2a**) in 1.5 M aqueous tetra-*n*-butylammonium hydroxide ($^nBu_4NOH$) or NaOH were determined (Table 1). In this process, **1a** reacts completely in aqueous $^nBu_4NOH$ at 100 °C after 4 h to provide 4-nitrophenol (**4a**) in 96% yield (entry 1). In addition, **2a** reacts under these conditions to produce **4a** in 32% yield (entry 2). When NaOH is used in place of $^nBu_4NOH$, **1a** is unreactive (entry 3). A longer reaction time (entry 4) and the addition of $^nBu_4NCl$ (entry 5) lead to only low conversion reactions of **1a** to **4a**. In contrast, the reaction of **2a** with OH^- readily provides **4a** (entry 6) despite low solubility of **2a** (24 mmol L^{-1} at 100 °C) in aqueous NaOH, as compared with that (almost miscible at 100 °C) in aqueous $^nBu_4NOH$. In addition, prolonged reaction time provides **4a** quantitatively (entry 7).

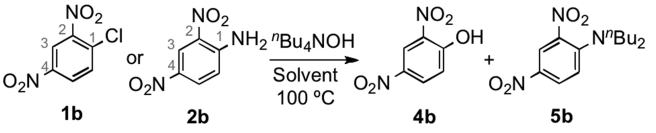
Table 1. S_NAr Reactions of 1a and 2a in Aqueous $^nBu_4NOH$ or NaOH



entry	sub	base[a]	temp, °C	time, h	rec, %	yield, %
1[b]	**1a**	$^nBu_4NOH$	100	4	0	96
2[b]	**2a**	$^nBu_4NOH$	100	4	60	32
3	**1a**	NaOH	100	4	100	0
4	**1a**	NaOH	100	16	97	2
5	**1a**	NaOH + $^nBu_4NCl$[c]	100	4	93	5
6	**2a**	NaOH	100	4	60	40
7	**2a**	NaOH	100	16	0	100
8[d]	**2a**	NaOH	150	0.1	0	100
9[d]	**1a**	NaOH	150	0.1	78	18

[a] 1.5 M. [b] The detailed procedure is given in the Experimental Section. [c] 10 mol %. [d] Carried out in an autoclave.

Table 2. S_NAr Reactions of 1b and 2b with $^nBu_4NOH$[a] in Sulfolane or Aqueous Media



					yield, %	
entry	sub	solvent	time, h	rec, %	**4b**	**5b**
1	**1b**	sulfolane	16	0	39	25
2	**2b**	sulfolane	16	93	0	0
3	**2b**	sulfolane + H_2O (10 equiv)	16	95	0	0
4	**2b**	H_2O	2	0	95	0

[a] 1.5 M.

These findings demonstrate that the leaving ability of the NH_2 group was unusually enhanced in reactions carried out in aqueous media, as compared to those in sulfolane (Table 2, entry 2). Also, in the reaction in aqueous $^nBu_4NOH$, which provides a more hydrophobic environment, the leaving ability of the NH_2 group does not surpass that of Cl (Cl > NH_2, Table 1, entries 1 and 2). On the other hand, the results suggest that the NH_2 group possesses an unusually high leaving ability beyond that of Cl (NH_2 > Cl, entries 4 and 7) in aqueous NaOH, where

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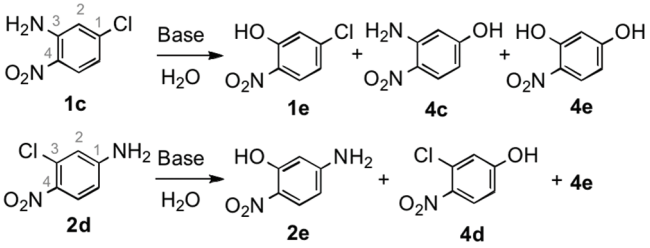
Table 3. S_NAr Reactions of 1c and 2d in Aqueous $^nBu_4NOH$ or NaOH



entry	sub	base[a]	time,[b] h	products; yields, %		
1	**1c**	$^nBu_4NOH$	16	**1e**; 32	**4c**; 57	**4e**; 1
2	**1c**	NaOH	50	**1e**; 68	**4c**; 25	**4e**; 7
3	**2d**	NaOH	50	**2e**; 22	**4d**; 72	**4e**; 5

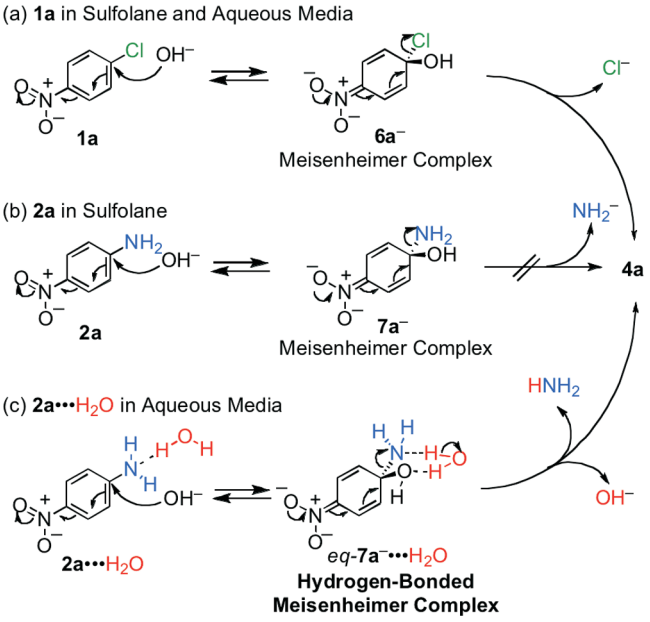
[a] 1.5 M. [b] The reactions were carried out at 100 °C until **1c** or **2d** disappeared completely (TLC analysis).

2a is more hydrated than in the reaction that takes place in a hydrophobic environment provided by $^nBu_4NOH$. This phenomenon is more dramatic when reactions were conducted at 150 °C (entries 8 and 9), where nitroaniline derivative **2a** is transformed quantitatively to **4a** in 0.1 h, whereas **1a** forms **4a** in only 18% yield.

More critical differences in S_NAr reactivities were observed in reactions of 2,4-dinitrochlorobenzene (**1b**) and 2,4-dinitroaniline (**2b**). S_NAr reaction of **1b** takes place completely to generate 2,4-dinitrophenol (**4b**) in 39% yield when 1.5 M $^nBu_4NOH$ is used as the OH^- source and sulfolane as the solvent (100 °C, 16 h) (Table 2, entry 1). In addition, *N*,*N*-di-*n*-butyl-2,4-dinitroaniline (**5b**) is observed as a product in the reaction of **1b** as a likely consequence of the formation and addition of $^nBu_3N$ or $^nBu_2NH$ generated by the Hofmann elimination of $^nBu_4N^+$. In contrast to these observations, **2b** is nearly unreactive when treated with $^nBu_4NOH$ under similar conditions (entry 2). These findings demonstrate that NH_2 is a much poorer leaving group than Cl as traditionally seen in S_NAr chemistry. Similar S_NAr reaction of **2b** in sulfolane containing 10 equiv of H_2O resulted in the recovery of the starting material (95%, entry 3), suggesting that the rate enhancement is related to the bulk properties of H_2O. Surprisingly, when H_2O is used in place of sulfolane as the solvent, **2b** is completely consumed after only 2 h and **4b** is produced in 95% yield (entry 4). This result clearly shows that **2b** possesses unusually high S_NAr reactivity with OH^- in aqueous media.

Reaction of 3-amino-4-nitrochlorobenzene (**1c**) in aqueous $^nBu_4NOH$ preferentially yields 3-amino-4-nitrophenol (**4c**) in 57% yield through a pathway involving substitution of Cl with OH^- at C-1. This process also affords 3-hydroxy-4-nitrochlorobenzene (**1e**) in 32% yield, which would have been generated by OH^- substitution for NH_2 at C-3 (Table 3, entry 1). In addition, a small amount of 3-hydroxy-4-nitrophenol (4-nitroresorcinol, **4e**) is obtained in this process through bis-substitution reactions at C-1 and C-3. In contrast, **1c** preferentially reacts in aqueous NaOH to form **1e** in 68% yield through OH^- substitution of NH_2 at C-3 rather than Cl at C-1 (entry 2). To gain insight into difference in leaving abilities associated with the groups at the C-1 and C-3 positions of **1c**, reaction of 3-chloro-4-nitroaniline (**2d**) was performed in aqueous NaOH (entry 3). The results show that the NH_2 group of **2d** is still preferentially

Scheme 4. Proposed Mechanisms for S_NAr Reactions of 1a and 2a with OH^- in Sulfolane and Aqueous Media



replaced by OH^- to provide 3-chloro-4-nitrophenol (**4d**) in 72% yield together with 3-hydroxy-4-nitroaniline (**2e**) in 22% yield. The combined observations clearly demonstrate that NH_2 group exhibits an unusually high leaving ability that exceeds that of Cl in S_NAr reaction with OH^- in aqueous NaOH.

The mechanisms that explain the contrasting S_NAr reactivities of **1a** and **2a** with OH^- in sulfolane and aqueous media are displayed in Scheme 4. In the conventional manner,[1−3] nucleophilic addition of OH^- to chlorobenzene gives the Meisenheimer complex **6a**$^-$, which then eliminates Cl^- to form **4a** (Scheme 4a). Even if the Meisenheimer complex **7a**$^-$ is formed in the S_NAr reaction between **2a** and OH^- in sulfolane, the poor NH_2 leaving group resists elimination (Scheme 4b) and the better leaving group OH departs. It is clear that these conventional leaving group properties do not govern S_NAr reactions of nitroanilines in aqueous media. To explain this phenomenon, we propose that special hydrogen-bonding interactions take place in the Meisenheimer complex **7a**$^-$ to enhance the leaving ability of NH_2 group.

Three hydrogen-bonding-derived factors could serve as the driving force for this unusual effect. In aqueous media,[10] hydrogen bonding between H_2O and the NH_2 group in **2a** should take place. This interaction, which leads to an increase in electrophilicity at the NH_2-connected C-1 of **2a** should enhance addition of OH^- (Scheme 4c).[11]

As one of the simplest models, hydrogen bonding between one H_2O molecule and the Meisenheimer complex formed by reaction of **2a** with OH^- could generate a six-membered ring structure like *eq*-**7a**$^-$···H_2O shown in Scheme 4c. To gain further insight into the reaction intermediate, density functional theory (DFT) calculations were performed on models where the effects of surrounding H_2O molecules and Na^+ are disregarded. Optimizations of geometries for 14 possible hydrogen-bonded Meisenheimer complexes **7a**$^-$···H_2O[12] were carried out using the B3LYP method[13,14] and a cc-pVDZ basis set[15] with the Gaussian 98 program.[16] The most stable geometry among

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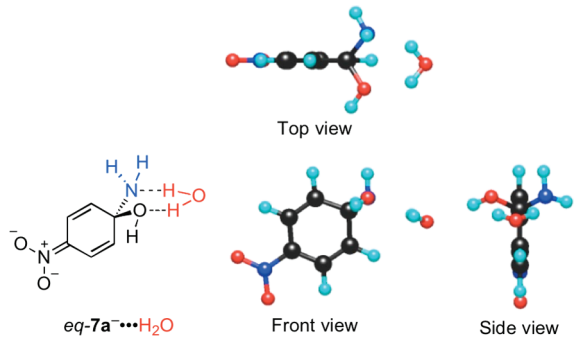
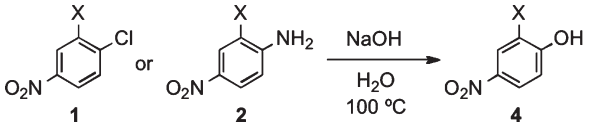


Figure 1. Optimized geometry of the hydrogen-bonded Meisenheimer complex *eq*-7a$^-\cdots H_2O$ (B3LYP/cc-pVDZ).

Table 4. S_NAr Reactions of 1 and 2 in Aqueous NaOH[a]



entry	sub	X	time, h	rec, %	product; yield, %
1	**1b**	NO_2	1.5	0	**4b**; 100
2	**2b**	NO_2	1.5	0	**4b**; 98
3	**1f**	OH	4	93	**4f**; 0
4	**2f**	OH	4	0	**4f**; 95
5	**1g**	CH_3	4	96	**4g**; 0
6	**2g**	CH_3	4	70	**4g**; 29
7	**1h**	OCH_3	4	92	**4h**; 5
8	**2h**	OCH_3	4	33	**4h**; 64
9	**1i**	NH_2	4	95	**4i**; 0
10	**2i**	NH_2	4	25	**4i**; 65

[a] 1.5 M.

these is shown in *eq*-7a$^-\cdots H_2O$ in Figure 1.[17] The results of the calculations show that *eq*-7a$^-\cdots H_2O$ would be a major intermediate in the S_NAr reaction of **2a** with OH^- in aqueous media.

As a consequence of the hydrogen-bonding interactions in the Meisenheimer complex *eq*-7a$^-\cdots H_2O$, elimination of ammonia NH_3 rather than the amide anion NH_2^- can take place to give **4a**.

The observations made in this effort are applicable to S_NAr reactions of a variety of nitroaniline derivatives. Reactions of substrates in 1.5 M aqueous NaOH at 100 °C were compared to those of the corresponding chlorobenzenes (Table 4). In all cases, the nitroanilines were found to be more reactive than the corresponding chlorobenzenes (entries 3−10), except for the highly activated derivatives **1b** and **2b** (entries 1 and 2). In comparison to the reactivities of the mononitro derivatives **1a** and **2a** (see Table 1), reactions of the dinitro analogues **1b** and **2b** with OH^- are exceedingly rapid, providing **4b** quantitatively. 2-Hydroxy-4-nitrochlorobenzene (**1f**) does not undergo S_NAr reaction to yield 2-hydroxy-4-nitrophenol (4-nitrocatechol, **4f**) under these conditions despite its high solubility in aqueous NaOH (entry 3). In contrast, the nitroaniline derivative **2f** readily reacts with OH^- to provide **4f** in 95% yield (entry 4). Also, when a methyl group is present (X = CH_3, **2g**), reaction proceeds under similar conditions to provide **4g** in 29% yield (entry 6). Interestingly, when X is OCH_3 or NH_2 [2-methoxy-4-nitroaniline (**2h**), 2-amino-4-nitroaniline (**2i**)], the reactivity of compounds is enhanced compared with that of **2a** (compare entry 6 in Table 1 with entries 8 and 10 in Table 4). S_NAr reactions of these substances provide **4h** and **4i** in 64% and 65% yields (entries 8 and 10), though an electron-donating OCH_3 or NH_2 group is expected to lower electrophilicities of **2h** and **2i**. The unexpected enhancement of S_NAr reactivity of **2h** and **2i** might be the result of resonance stabilization shown in Scheme 5. This electron-donating substituent effect also operates when the reactivities of 4-methoxy-2-nitroaniline (**3k**, Table 5) and 4-amino-2-nitroaniline (**3l**) are compared with that of 2-nitroaniline (**3j**), probably due to resonance stabilization.

Scheme 5. Resonance Stabilization of the Hydrogen-Bonded Meisenheimer Complex *eq*-7h$^-\cdots H_2O$ Formed in S_NAr Reaction of 2h with OH^- in Aqueous Media

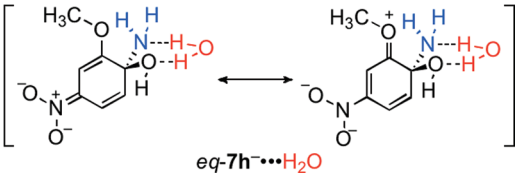
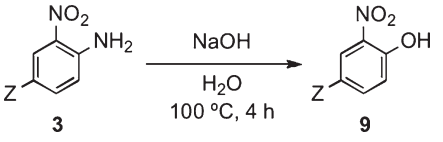


Table 5. S_NAr Reactions of 3 in Aqueous NaOH[a]



entry	sub	Z	rec, %	product; yield, %
1	**3j**	H	86	**9j**; 14
2	**3k**	OCH_3	31	**9k**; 63
3	**3l**	NH_2	5	**9l**; 79

[a] 1.5 M.

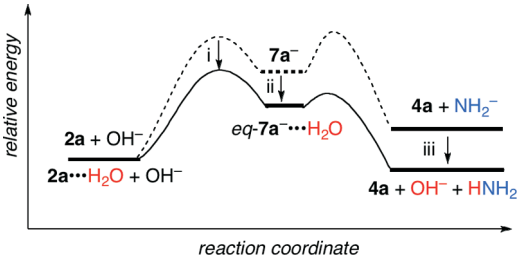


Figure 2. Imaginal energy diagrams for a putative S_NAr reaction of **2a** with OH^- in organic solvent (dotted line) and for an actual S_NAr reaction of **2a** with OH^- in aqueous media (solid line).[18]

In the investigation described above, we discovered that nitroaniline derivatives exhibit unusually high S_NAr reactivities with OH^- in aqueous NaOH that far exceed those of the chlorobenzene analogues. Features governing the unusually high reactivity of these systems, in which NH_2 serves as a leaving group, appear to be associated with hydrogen-bonding interactions with H_2O. These interactions can increase the electrophilicity of the nitroaniline substrate (Figure 2, i), stabilize the Meisenheimer intermediate via

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a six-membered structure (ii), and enable elimination of ammonia rather than an amide anion (iii). The six-membered hydrogen-bonded Meisenheimer complex *eq*-7a$^-$···H_2O are suggested by DFT calculations for a set of **2a**, OH^-, and H_2O.[18] The results contrast with those emanating from studies of conventional S_NAr chemistry that show the nitroanilines have low S_NAr reactivities in organic solvents. This rule is generally applicable for various nitroanilines. As a result, the present findings add a new insight into the long history of the S_NAr chemistry.

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. All melting points were measured on a melting point apparatus and are reported uncorrected.

Typical Procedure for S_NAr Reactions of Nitroanilines in Aqueous NaOH. A mixture of 4-nitroaniline (**2a**, 4.4 g, 32 mmol) and 1.5 M aqueous NaOH (110 mL, containing 165 mmol of NaOH) was stirred for 4 h at 100 °C. The smell of ammonia showed progress of the reaction. The mixture was cooled to room temperature, 200 mL of H_2O was added before extracting twice with EtOAc, and the combined organic layers were washed with dilute aqueous NaOH and H_2O, dried over Na_2SO_4, and concentrated in vacuo giving 2.7 g of yellow solid of recovered **2a** (60%). The aqueous alkali layer obtained from the extractions was neutralized by addition of 17 g of acetic acid and the resulting solution was extracted twice with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo giving 1.7 g of yellowish solid of 4-nitrophenol (**4a**) (40%).

Typical Procedure of S_NAr Reaction of 2,4-Dinitroanilines in Aqueous $^nBu_4NOH$ (Table 2, entries 1 and 2). A solution of sulfolane (65 mL), 40 wt % (1.5 M) aqueous $^nBu_4NOH$ (112 mL, containing 168 mmol of $^nBu_4NOH$), and toluene (60 mL) was distilled under atmospheric pressure to remove 66 mL of H_2O and 60 mL of toluene before the addition of **1b** or **2b** (32 mmol). The resulting solutions were stirred for 16 h at 100 °C and then subjected to the workup procedure described above.

4-Nitrophenol (4a). Mp 113−114 °C (lit. 114 °C[19]); ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 6.96 (AA′XX′, J = 8 Hz, 2H), 8.14 (AA′XX′, J = 8 Hz, 2H), 11.10 (br s, 1H).

2,4-Dinitrophenol (4b). Mp 112−113 °C (lit. 108−112 °C[20]); ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 7.35 (d, J = 8 Hz, 1H), 8.48 (dd, J = 8, 2 Hz, 1H), 9.08 (d, J = 2 Hz, 1H, Ph), 10.97 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 121.3, 121.9, 131.7, 132.6, 140.3, 159.1; ESI-MS m/z 183 [(M − H)$^-$].

***N,N*-Di-*n*-butyl-2,4-dinitroaniline (5b).** ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} 0.90 (t, 6H, CH_3), 1.27 (sex, 4H, CH_2), 1.59 (f, 4H, CH_2), 3.28 (t, 4H, CH_2), 7.07 (d, J = 8 Hz, 1H), 8.19 (dd, J = 8, 2 Hz, 1H), 8.64 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm} 13.7, 20.0, 29.4, 52.0, 118.8, 124.0, 127.6, 136.7, 137.6, 148.7; EI-MS m/z 295 (M^+).

3-Hydroxy-4-nitrochlorobenzene (1e). ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 7.05 (dd, J = 8, 2 Hz, 1H), 7.19 (d, J = 2 Hz, 1H), 7.94 (d, J = 8 Hz, 1H), 11.50 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 118.6, 119.4, 127.0, 135.9, 139.1, 153.0; ESI-MS m/z 172 [(M − H)$^-$].

3-Amino-4-nitrophenol (4c). Mp 183−184 °C (lit. 185−186 °C[21]); ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 6.13 (dd, J = 8, 2 Hz, 1H), 6.29 (d, J = 2 Hz, 1H, Ph), 7.40 (br s, 2H, NH_2), 7.88 (d, J = 8 Hz, 1H), 11.60 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 100.8, 107.1, 124.6, 128.0, 148.8, 164.0; ESI-MS m/z 153 [(M − H)$^-$].

3-Hydroxy-4-nitrophenol (4-Nitroresorcinol, 4e). Mp 121−122 °C (lit. 121−122 °C[22]); ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 3.51 (br s, 1H), 6.43 (dd, J = 8, 2 Hz, 1H), 6.46 (d, J = 2 Hz, 1H), 7.92 (d, J = 8 Hz, 1H), 10.88 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 103.6, 108.8, 127.7, 128.0, 156.0, 165.0; ESI-MS m/z 154 [(M − H)$^-$].

3-Hydroxy-4-nitroaniline (2e). ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 6.11 (dd, J = 8, 2 Hz, 1H), 6.27 (d, J = 2 Hz, 1H), 7.38 (br s, 2H), 7.86 (d, J = 8 Hz, 1H), 10.62 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 100.8, 107.1, 124.5, 128.0, 148.8, 164.0; ESI-MS m/z 153 [(M − H)$^-$].

3-Chloro-4-nitrophenol (4d). ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 7.05 (dd, J = 8, 2 Hz, 1H), 7.18 (d, J = 2 Hz, 1H), 7.94 (d, J = 8 Hz, 1H), 11.50 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 118.5, 119.3, 127.0, 135.9, 139.0, 152.9; ESI-MS m/z 173 [(M − H)$^-$].

2-Hydroxy-4-nitrophenol (4-Nitrocatechol, 4f). ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 6.93 (d, J = 8 Hz, 1H), 7.64 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 10.30 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 110.5, 115.0, 116.5, 139.6, 145.5, 152.9; EI-MS m/z 155 (M^+).

2-Methyl-4-nitrophenol (4-Nitro-2-cresol, 4g). Mp 96−97 °C (lit. 93−98 °C[23]); ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} 2.32 (s, 3H), 5.87 (s, 1H), 6.87 (d, J = 9 Hz, 1H), 8.01 (dd, J = 9, 3 Hz, 1H), 8.07 (d, J = 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm} 15.8, 114.9, 123.7, 125.2, 126.9, 141.3, 159.7; EI-MS m/z 153 (M^+).

2-Methoxy-4-nitrophenol (4h). Mp 103−104 °C (lit. 103−104 °C[20]); ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} 4.00 (s, 3H), 6.21 (s, 1H), 6.99 (d, J = 9 Hz, 1H), 7.77 (d, J = 2 Hz, 1H), 7.89 (dd, J = 9, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm} 56.4, 106.3, 113.9, 118.6, 141.2, 146.1, 151.6; EI-MS m/z 169 (M^+).

2-Amino-4-nitrophenol (4i). Mp 141−142 °C (lit. 140−143 °C[23]); ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 5.17 (br s, 2H), 6.75 (d, J = 9 Hz, 1H), 7.37 (dd, J = 9, 3 Hz, 1H), 7.44 (d, J = 3 Hz, 1H), 10.53 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 107.7, 113.0, 113.1, 137.6, 140.2, 150.6; EI-MS m/z 154 (M^+).

2-Nitrophenol (9j). ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} 7.00 (t, J = 8 Hz, 1H), 7.16 (d, J = 8 Hz, 1H), 7.58 (t, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 10.57 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm} 120.0, 120.2, 125.1, 133.8, 137.6, 155.2; EI-MS m/z 139 (M^+).

4-Methoxy-2-nitrophenol (9k). Mp 79−80 °C (lit. 78−80 °C[23]); ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} 3.83 (s, 3H), 7.09 (d, J = 9 Hz, 1H), 7.22 (dd, J = 9, 3 Hz, 1H), 7.51 (d, J = 3 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm} 56.0, 105.7, 120.8, 127.2, 133.0, 150.0, 152.6; EI-MS m/z 169 (M^+).

4-Amino-2-nitrophenol (9l). Mp 125−126 °C (lit. 125−127 °C[23]); ^1H NMR (400 MHz, DMSO-d_6) δ_{ppm} 5.10 (br s, 2H), 6.87 (br s, 1H), 6.87 (br s, 1H), 7.09 (br s, 1H), 9.80 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm} 107.0, 119.9, 123.5, 135.6, 141.7, 143.8; EI-MS m/z 154 (M^+).

ASSOCIATED CONTENT

Supporting Information. The DFT calculations for 7a$^-$···H_2O and for Figure 2 and the complete ref 16. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: mizuno@chem.osakafu-u.ac.jp; ikeda@chem.osakafu-u.ac.jp.

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(5) It has been reported that highly activated anilines react with OH^- in aqueous media or organic solvents.[6] Very recently, we have also reported an efficient direct conversion of bis(nitroaniline) derivatives into bis(nitrophenol) derivatives under mild conditions.[7]
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(9) To clarify, compounds **1**, **2** and **3**, and **4** are named as derivatives of chlorobenzene, aniline, and phenol, respectively.
(10) Similar S_NAr reaction of **2a** in D_2O resulted in no remarkable kinetic isotope effects.
(11) Leaving groups with high electron-withdrawing capabilities generally facilitate the nucleophilic attack.
(12) Note that 14 conformers are possible for **7a**$^-\cdots H_2O$. Geometry optimizations of seven conformers including *eq*-**7a**$^-\cdots H_2O$ were performed successfully, and the results suggest that *eq*-**7a**$^-\cdots H_2O$ is the most stable among the seven conformers. For details of the calculation results, see the Supporting Information.
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(17) Figure 1 was drawn by using *WinMOPAC ver 3.9*; Stewart, J. J. P; Fujitsu Ltd.: Japan, 2004.
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