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Kinetic Study on the Reaction of *p*-Nitrophenyl Acetate with 6-Substituted 2,4-Diamino-1,3,5-triazines

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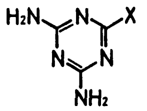
The reactions of *p*-nitrophenyl acetate (**1**) with six 6-substituted 2,4-diamino-1,3,5-triazines, (**2a**—**2f**), were kinetically investigated in aqueous DMSO or in water at 30 °C. It was found that the reaction rate R could be expressed according to the equation $R=(k_0+k_N[\mathbf{2}])[\mathbf{1}]$, and that Brönsted-type plots for the k_N-reaction give a straight line with a slope (β) of 1.05. The solvent deuterium isotope effect was not observed in this reaction $[k_N(H)/k_N(D)=1.0—1.15]$. Furthermore, the isolated reaction product was 2-acetylamino-4-amino-6-methyl-1,3,5-triazine (**4c**), which was formed by a nucleophilic attack of **2c** to **1**. From these results, the mechanism for this nucleophilic reaction is discussed.

The structure-reactivity relationship in acyl transfer reactions has been investigated by many workers.[1] Among these reactions, nucleophilic reactions of tertiary amines, pyridines, or imidazoles are especially useful in the preparation of acylated compounds[2,3] and in the catalytic hydrolyses of esters.[1] Furthermore, nucleophilic catalyses of secondary or primary amines in acyl transfer reactions are important as a model of enzymatic reactions.[1] It is therefore worthwhile studying the reaction of an ambident nucleophile, such as a 2-aminopolyazine, with carbonyl compounds. It has been reported that 2-aminopyridines[4] or 2-aminopolyazines, such as 2-aminopyrimidines[5] and 2-amino-1,3,5-triazines,[6,7] react with formaldehyde to give 2-(hydroxymethylamino)pyridines or 2-(hydroxymethylamino)polyazines. In addition, 2-aminopyridines and/or 2-aminopyrimidines react with picryl chloride and/or fluoride to give 2-picrylamino derivatives by initial formation and subsequent rearrangement of 1-picryl-2-imino-1,2-dihydro derivatives.[8,9] That is to say, the reacting site in the initial step of this reaction is not the amino-nitrogen atom, but the ring-nitrogen atom of this ambident nucleophile. Since we have been investigating kinetics for the reaction of 2,4,6-triamino-1,3,5-triazine (melamine) with formaldehyde,[10] it is very interesting for us to determine the actual nucleophilic site of this ambident nucleophile.

In this paper, we wish to report on the reaction of *p*-nitrophenyl acetate (**1**) with 6-substituted 2,4-diamino-1,3,5-triazines (**2a**—**2f**) in aqueous DMSO or water, as an extension of our above-mentioned study or in connection with an investigation regarding the model of enzymatic reactions. The reaction was kinetically investigated by the aid of Brönsted-type plots, the solvent deuterium isotope effect, and product analyses by HPLC.



2a; X=$N(CH_3)_2$, **b**; X=NH_2, **c**; X=CH_3, **d**; X=H, **e**; X=$OCH(CH_3)_2$, **f**; X=OCH_3

Results and Discussion

Kinetics. When *p*-nitrophenyl acetate (**1**) was treated with the 1,3,5-triazines (**2a**—**2f**) in the presence of phosphate buffers at 30 °C in aqueous DMSO [DMSO : water=3 : 7 (v/v)] or in water, *p*-nitrophenol was generated according to the reaction rate R expressed by Eqs. 1 and 2,

$$R=k_{\mathrm{obsd}}[\mathbf{1}] \tag{1}$$

$$k_{\mathrm{obsd}}=k_0+k_N[\mathbf{2}] \tag{2}$$

where k_0 is a rate constant for a reaction in the absence of **2** in the buffered media, and k_N is a rate constant for a nucleophilic attack of the 1,3,5-triazines (**2**) to the ester (**1**) (described later). The second-order rate constants (k_N) for the reaction were obtained as slopes of plots of $[\mathbf{2}]_0$ against the observed pseudo first-order rate constants, k_{obsd} (Table 1), at constant pH, buffer concentration, and ionic strength (Eq. 2). Typical examples of the plots are shown in Fig. 1; the k_N values, thus obtained, were not affected by the pH in the medium. Therefore, the mean values are shown in Table 2 together with each pK_a of the conjugate acid of **2**.

Mechanism. The rate constants for the formation of *p*-nitrophenol catalyzed by both water (the spontaneous formation) and phosphate buffers are included in the k_0 term. Since the rate constant k_{obsd} is proportional to the concentration of the 1,3,5-triazine (**2**), as shown in Eq. 2, the following three mechanisms, expressed by Schemes 1—3, are conceivable, where HA and A^- are the acid and base components of the phosphate buffer.

The rate laws of all these three mechanisms are given by Eq. 2. Generally, the solvent isotope effects, k_H/k_D, for the first mechanism shown in Scheme 1 is in the range 2 to 4 when a proton is being transferred in the transition state.[11] However, the observed $k_N(H)/k_N(D)$ values for the reactions of **1** with **2a**, **2c**, and **2e** are 1.0—1.15 in aqueous DMSO or in water (Table 3). Therefore, the first mechanism (Scheme 1) would be ruled out; it is expected that the 1,3,5-triazine (**2**)

Table 1. Experimental Conditions for the Determination of the Rate Constants, k_{obsd}, for the Reaction of *p*-Nitrophenyl Acetate (**1**) with the 1,3,5-Triazine (**2a**—**2f**) in Aqueous DMSO in the Presence of Phosphate Buffers at 30 °C, Ionic Strength of 0.3 (KCl)[a)]

2	[**2**]/mol·l^{-1}	*br*[b)]	pH[c)]	k_{obsd}/min^{-1} [d)]	No. of run
a	0—1.00×10^{-3}	0.6	8.13	(7.55—8.33)×10^{-4}	10
		0.4	8.32	(8.13—8.99)×10^{-4}	12
		0.2	8.74	(1.21—8.99)×10^{-3}	12
b	0—1.0 ×10^{-3}	0.6	8.23	(7.58—8.05)×10^{-4}	10
		0.4	8.36	(8.13—8.52)×10^{-4}	12
		0.2	8.73	(1.21—1.26)×10^{-3}	12
c	0—1.00×10^{-2}	0.4	8.29	(8.13—8.99)×10^{-4}	14
		0.2	8.71	(1.23—1.31)×10^{-3}	15
		[0.04	8.46	(3.95—4.09)×10^{-3}	10[e)]]
d	0—2.01×10^{-2}	0.6	8.17	(7.58—8.13)×10^{-4}	12
		0.4	8.34	(8.13—8.71)×10^{-4}	10
		0.2	8.71	(1.21—1.27)×10^{-3}	12
e	0—6.00×10^{-2}	0.6	8.17	(7.58—7.92)×10^{-4}	11
		0.4	8.33	(8.13—8.50)×10^{-4}	11
		0.2	8.66	(1.21—1.25)×10^{-3}	12
f	0—2.00×10^{-2}	0.4	8.34	(8.13—8.23)×10^{-4}	16
		0.2	8.69	(1.21—1.22)×10^{-3}	20

a) DMSO : H_2O=3 : 7 (v/v). b) $br=[H_2PO_4^-]/[HPO_4^{2-}]$; $[HPO_4^{2-}]=1.25\times10^{-2}$ mol·l^{-1}. c) The mean value (standard deviation ≤0.01). d) The observed pseudo-first-order rate constant (correlation coefficients *r* were larger than 0.999 for all runs). In all cases, the initial concentration of **1** was 5×10^{-5} mol·l^{-1}. e) The reaction in water.

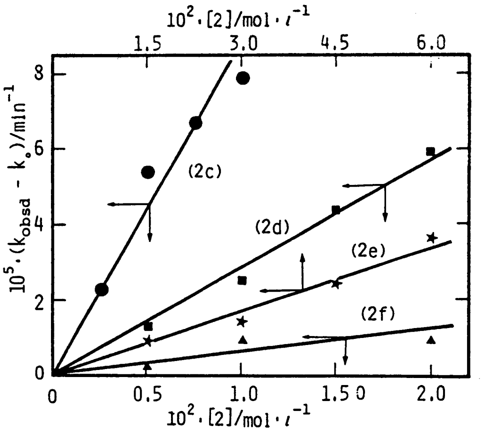


Fig. 1. Plots of (k_{obsd} $-k_0$) against the initial concentration of the 6-substituted 2,4-diamino-1,3,5-triazines (**2**) for the reaction with *p*-nitrophenyl acetate (**1**, 5×10^{-5} mol·l^{-1}) in the presence of phosphate buffers (pH 8.7, *br*=0.2) in aqueous DMSO at 30 °C and ionic strength of 0.3 (KCl).

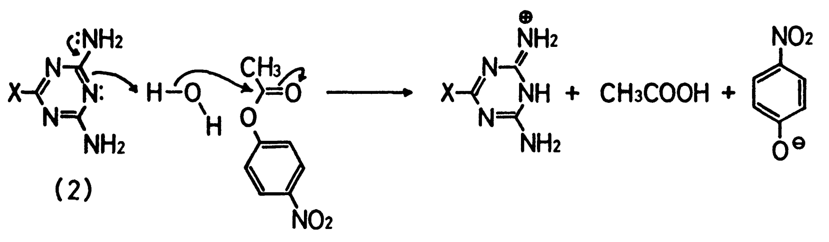
Table 2. Second-Order Rate Constants, k_N, for the Reaction of *p*-Nitrophenyl Acetate (**1**) with the 1,3,5-Triazine (**2a**—**2f**) in Aqueous DMSO in the Presence of Phosphate Buffers at 30 °C, Ionic Strength of 0.3 (KCl)[a)]

2	pK_a[b)]	k_N/l·mol^{-1}·min^{-1} [c)]
a	5.50	(8.2±0.4)×10^{-2}
b	5.15	(4.4±0.3)×10^{-2}
c	4.45	(8.8±0.2)×10^{-3}
d	4.00	(2.84±0.02)×10^{-3}
e	3.87	(5.9±0.2)×10^{-4}
f	3.47	(5.7±0.7)×10^{-4}

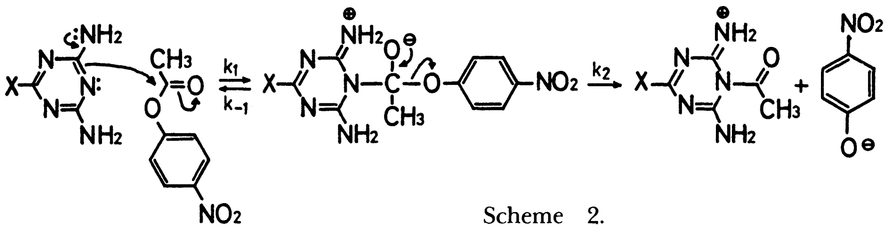
a) DMSO: H_2O=3 : 7 (v/v). b) The value of the conjugate acid of **2** was determined by a titrimetric method in aqueous DMSO at 30 °C and ionic strength of 0.3 with KCl. c) The pH's in the medium did not affect on the k_N values, and the error shown is standard deviation of the slope, by least-squares analysis, for the plots of Eq. 2.

nucleophilically attacks the carbonyl carbon of *p*-nitrophenyl acetate (**1**) to form the acetylated compound[12)] through a tetrahedral intermediate, as shown in Scheme 2 or 3, like a reaction of 2,4-dinitrophenyl acetate with pyridine,[13)] or a reaction of **1** with imidazoles.[14)]

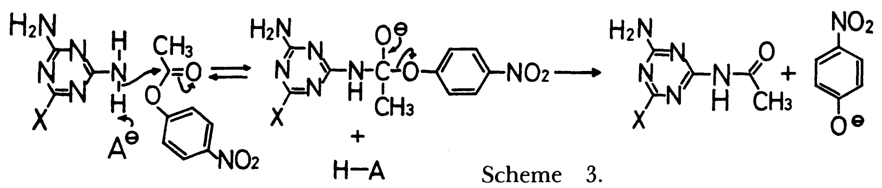
In order to determine the reacting site of this ambident nucleophile **2**, the log k_N's for the reactions of the six 1,3,5-triazines (**2a**—**2f**) in aqueous DMSO were plotted against the pK_a's of their conjugate acids (the Brönsted-type plots). A good linear relationship (the slope, β=1.05) was obtained (Fig. 2). The deviation of **2e** from the line is suggestive that the 1-N atom is the actual nucleophilic site in the reaction of **2e**, because the deviation must result from a steric hindrance by the relatively bulky isopropoxy group adjacent to the 1-N atom[15,16)] (Scheme 2). When the log k_N values were statistically corrected, **2b** also showed a large negative deviation from a line like **2e**. This deviation of **2b** and **2e** from statistically corrected Brönsted-type plots is not explicable by the third mechanism (Scheme 3), in which the substituent X does not sterically hinder a carbonyl attack of the amino group. Furthermore, the 1,3,5-triazine **2** is not protonated at the amino group but at the ring-nitrogen,[16)] and the basicity or electron density (nucleophilicity) of the amino-nitrogen is extremely diminished by the electron-withdrawing 1,3,5-triazine ring[17)] compared



Scheme 1.



Scheme 2.



Scheme 3.

Table 3. Solvent Deuterium Isotope Effect in the Reaction of *p*-Nitrophenyl Acetate (**1**) with 6-Substituted 2,4-Diamino-1,3,5-triazines (**2a**, **c**, and **e**) in the Presence of Phosphate Buffers at 30 °C and Ionic Strength of 0.3 (KCl)

2	Solvent	pH or pD[a)]	k_N / $l \cdot mol^{-1} \cdot min^{-1}$	$k_N(H)$ / $k_N(D)$
a	DMSO-H_2O[b)]	8.34	8.2×10^{-2}	1.0
	DMSO-D_2O[b)]	9.24	8.3×10^{-2}	
c	DMSO-H_2O[b)]	8.71	8.8×10^{-3}	1.1
	DMSO-D_2O[b)]	9.26	8.3×10^{-3}	
c	H_2O	8.46	1.50×10^{-2}	1.15
	D_2O	8.84	1.30×10^{-2}	
e	DMSO-H_2O[b)]	8.66	5.9×10^{-4}	1.1
	DMSO-D_2O[b)]	9.22	5.3×10^{-4}	

a) pD="meter pH"+0.40 (see Ref. 30). b) DMSO: H_2O (or D_2O)=3 : 7 (v/v).

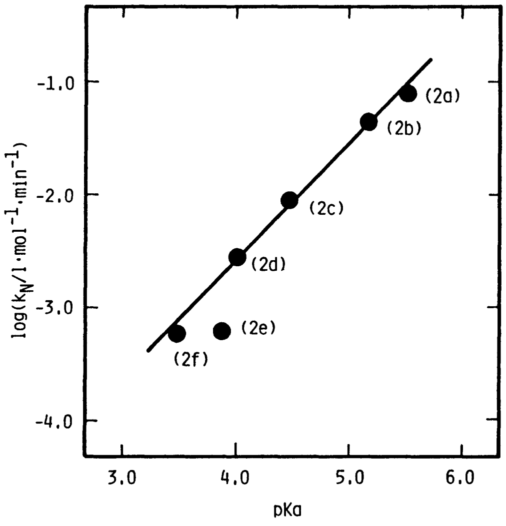
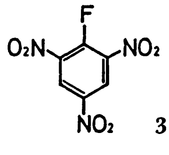


Fig. 2. The Brönsted-type plots for the reaction of *p*-nitrophenyl acetate (**1**, 5×10^{-5} mol·l^{-1}) with the 6-substituted 2,4-diamino-1,3,5-triazines (**2a**—**2f**) in the presence of phosphate buffers (pH 8.7) in aqueous DMSO at 30 °C and ionic strength of 0.3 (KCl); the slope β=1.05 and correlation coefficient r=0.99. When the k_N values were corrected by statistical factors in order to explain the third mechanism in Scheme 3, **2b** showed a large negative deviation from a line like **2e**.

with the amides[18)] or urea (pK_b=13.8).[19)] This low nucleophilicity of the amino-nitrogen of **2** was demonstrated by lack of reactivity of **2c** against picryl fluoride (**3**), as described later. From these results, it is



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inferred that the reaction proceeds through an initially formed unstable acetyl adduct (**6**). In other words, the second mechanism (Scheme 2) is more probable as the main reaction in our system than the third (Scheme 3).

The slope (β=1.05) of the Brönsted-type plots (Fig. 2) is nearly equal to those for aminolysis reactions of activated carbonyl compounds[13)] such as 2,4-dinitrophenyl acetate (β=0.85) and methyl chloroformate (β=0.93). If the result of Castro and Freudenberg[13)] is applicable to our system, the 1,3,5-triazine leaves more easily from the tetrahedral intermediate than the *p*-nitrophenoxy group ($k_{-1} \gg k_2$); that is, the second step (the k_2-reaction) would be rate determining in Scheme 2.

We now give another conceivable mechanism (the fourth mechanism). It has been reported by Okano and Ogata[20] that the hydroxymethylation of melamine (**2b**) with formaldehyde in the presence of a basic catalyst takes place by a consecutive mechanism, including a carbonyl attack by a conjugate base of **2b**, which is generated from **2b** by the action of a basic catalyst. However, an analogous mechanism for the reaction of **2** with **1** (the fourth mechanism) would also be ruled out[17] because the amino-hydrogen of **2** (pK_a of **2b**, 36)[17] is not acidic enough to be abstructed by the basic component of the buffer (hydrogenphosphate, pK_a of the conjugate acid,[21] 7.63).

Reaction of *p*-Nitrophenyl Acetate (1) or Picryl Fluoride (3) with 2,4-Diamino-6-methyl-1,3,5-triazine (2c). In order to determine the structure of the product in the reaction of the ester (**1**) with the 1,3,5-triazine (**2**), **1** or **3** was treated with one of the 1,3,5-triazines, **2c**, in dry DMSO, which was employed as a solvent instead of aqueous DMSO to minimize the hydrolysis of **1** or **3** and to increase the solubility of **2c** in the medium.

First, 2,4-diamino-6-methyl-1,3,5-triazine (**2c**) was heated with *p*-nitrophenyl acetate (**1**) in dry DMSO at 100 °C for 17.5 h to afford 2-acetylamino-4-amino-6-methyl-1,3,5-triazine (**4c**) in 60% yield as colorless crystals. The formation of this compound **4c** looks strange in comparison with the result from the Brönsted-type plots (Fig. 2), which supports the second mechanism illustrated in Scheme 2. This discrepancy may be interpreted by the hypothesis that the 1,3,5-triazine (**2**) attacks the ester (**1**) to afford, ultimately, the acetylamino derivative (**4**) by initial formation and subsequent fast rearrangement of 3-acetyl-4-amino-2-imino-2,3-dihydro-1,3,5-triazine derivatives (**6**) or the corresponding 1-acetyl derivatives[16] (Scheme 4). In fact, it has been reported that 2-aminopyridines analogously react with picryl chloride or **3**.[8,9] Accordingly, the 1,3,5-triazine (**2c**) was treated with **3** in dry DMSO at 80 °C. However, neither the corresponding 3-picryl product nor the 2-picrylamino-6-methyl-1,3,5-triazine obtained, and most of the unreacted **2c** was recovered as the picrate. This result indicates that the sterically crowded ring-nitrogen of **2c** is not able to attack the 1-C atom of **3**, which is more crowded than the carbonyl carbon of **1**, and that the acetylation of **2** with **1** must proceed through the pathway illustrated in Schemes 2 and 4.

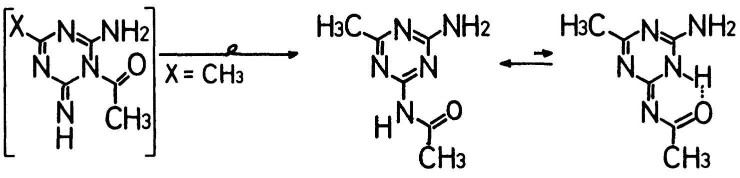
The acetylated product **4c** was considerably stable under the kinetic conditions in this study, and it was identical with the product in the kinetic runs (by HPLC).

The structure of **4c** was determined by its spectroscopic data. The MS of **4c** showed a molecular ion (M^+) peak at *m/z* 167 (molecular weight of **4c**; $C_6H_9N_5O$= 167.18), and the IR spectrum, measured in a KBr disk, suggested that the acetylated product was a tautomeric mixture of **4c** and **5c** (Scheme 4). That is to say, absorption bands assignable to the acetylamino form (**4c**) were observed at 3300 (ν_{NH} of the secondary amide), 1680 ($\nu_{C=O}$, amide I band), 1540 (amide II band), 1315 (amide III band), and 815 cm^{-1} (medium, 1,3,5-triazine ring) in addition to those of acetylimino form **5c** at 3230 (ν_{NH} of the ring), 1615 ($\nu_{C=N}$), 1375 (δ_{NH} of the ring), and 760 cm^{-1} (very weak, 2,3-dihydro-1,3,5-triazine ring).[22] Analogous tautomerization was observed in 2,4-diamino-6-cyanoamino-1,3,5-triazine.[22] However, the equilibrium would lie to the left (as discussed below regarding to UV and ^{1}H and ^{13}C NMR spectra).

Compound **6** is not expected to have a UV absorption maximum in the wavelength region 220 to 280 nm,[23,24] whereas product **4c** shows absorption maxima at 223, 260, and 326 nm. The ^{1}H NMR spectrum of **4c** consists of two methyl protons (δ 2.4 and 2.7) and the NH protons of NH_2 (δ 7.7) and NH groups (δ 7.1), and ^{13}C NMR of **4c** in acetic acid exhibited a signal at δ 166.9 for the ring-carbon 2-C which was attached to the acetylamino group. This low-field shift of 2-C, compared with 4-C (δ 163.1), must result from the acetyl group. If the structure of the acetylated product is **6**, the ring-carbons would resonate at a higher magnetic field than δ 163.1. Signals assignable to the tautomeric isomer (**5c**) were not observed in the spectrum.

Experimental

All melting and boiling points are uncorrected. The UV spectra were recorded on a JASCO UVIDEC-505 spectrophotometer, and the IR spectra on a Hitachi model 260-50 spectrophotometer. The ^{1}H NMR spectra were recorded with a JEOL PMX-60SI spectrometer for solutions in DMSO-d_6 or



(6) (4c) (5c)

Scheme 4.

CF_3COOH, and ^{13}C and ^{19}F NMR spectra with a JEOL FX-90Q spectrometer in acetic acid. The chemical shifts are reported in δ (internal standard Me_4Si or $CFCl_3$). The MS were determined with a Hitachi M-80 double-focusing mass spectrometer at 70 eV. The pH was measured with a Toa model HM-5ES pH meter. The analytical HPLC determination was carried out with a JASCO TWINCLE apparatus equipped with a UV detector.

Materials. Commercially available 2,4,6-triamino-1,3,5-triazine (**2b**) and 2,4-diamino-6-methyl-1,3,5-triazine (**2c**) were recrystallized from water. 2,4-Diamino-1,3,5-triazine (**2d**) was kindly presented by Dr. E. Ichikawa (Tokyo Institute of Technology) and recrystallized from water, mp 322.3—324.0 °C (lit,[25] 329 °C). The other 6-substituted 2,4-diamino-1,3,5-triazines, (**2a**, **e**, and **f**), were prepared by methods in literature,[26,27] and recrystallized from water, **2a**; mp 310—312 °C (lit,[28] 307—308 °C), **2e**; mp 168.5—169.5 °C (lit,[27] 172 °C), **2f**; mp 237—238 °C (lit, [27] 229—230 °C). All the 1,3,5-triazines, (**2a**—**2f**), were dried at 50 °C for one day, and then at room temperature for three days under reduced pressure (5 mmHg; 1 mmHg=133.322 Pa) after recrystallization. ^1H NMR (DMSO-d_6) **2a**, δ=5.97 (4H, s, NH_2), 3.02 (6H, s, CH_3); **2b**, 6.02 (s, NH_2); **2c**, 6.45 (4H, s, NH_2), 1.88 (3H, s, CH_3); **2d**, 6.61 (4H, s, NH_2), 7.91 (1H, s, H); **2e**, 6.63 (4H, s, NH_2), 5.28 (1H, se, J=7 Hz, CH), 1.43 (6H, d, J=7 Hz, CH_3); **2f**, 6.62 (4H, s, NH_2), 3.73 (3H, s, CH_3); ^{13}C NMR (CH_3COOH) **2c**, δ=173.5 (CH_3-$\underline{C}$-ring), 164.0 (C-NH_2), 21.7 (CH_3). Picryl fluoride (**3**) was also prepared by a method in literature[29] and recrystallized from carbon tetrachloride. Yield 60—70%, mp 122—123 °C (lit,[29] 122—123 °C). ^1H NMR ($CDCl_3$) δ=8.95 (d, J=5.6 Hz); ^{19}F NMR (84.31 MHz, $CDCl_3$) δ=−116.36 (t, J=5.49 Hz).

Kinetics. Rates of the reaction of **1** with **2a**—**2f** were followed on a spectrophotometer equipped with an isothermal cell holder (30±0.2 °C) and 1-cm cells by observing the appearance of *p*-nitrophenolate at 408 [in aqueous DMSO, DMSO : H_2O=3 : 7 (v/v)] or 400 nm (in water). The reaction was initiated by stirring the buffer solution with a Teflon rod, on which 30 μl of a stock solution (5.05×10^{-3} mol · l^{-1}) of **1** in DMSO (or in acetonitrile for the reaction in water) was put with a Gilmont micrometer buret. The buffer solution (KH_2PO_4/Na_2HPO_4, $[Na_2HPO_4]=1.25\times10^{-2}$ mol · l^{-1}) contained the 1,3,5-triazine (**2**), and the ionic strength was maintained at 0.3 with potassium chloride. The final concentration of acetonitrile, which was introduced with solutions of **2**, in the reaction mixture did not exceed 1%. The initial rate, R_0, was proportional to $[\mathbf{1}]_0$ at constant $[\mathbf{2}]_0$ (5×10^{-5} mol · l^{-1}) and pH (8.7), and a slope of $\log R_0$ vs. $\log[\mathbf{1}]_0$ plots is 1.0. Furthermore, (R_0-R_{00}) was proportional to $[\mathbf{2}]_0$ at constant $[\mathbf{1}]_0$ (5×10^{-5} mol · l^{-1}) and pH (8.7), and a slope of $\log(R_0-R_{00})$ vs. $\log[\mathbf{2}]_0$ plots was also 1.0, where R_{00} is the initial rate in the absence of **2**.

The observed pseudo first-order rate constants, k_{obsd}, were calculated from the spectrometric data by the use of the usual first-order equation (correlation coefficient r is larger than 0.999 for each run), and are summarized in Table 1 along with the reaction conditions. The concentration of (**1**), 5×10^{-5} mol · l^{-1}, was ordinarily used to determine the rate constants k_N by using Eq. 2. The reaction product in the kinetic run of **2c** was found to be identical to the acetylamino derivative **4c** by means of HPLC [column, 4.6×250 mm, Finepak Sil C_{18}, 5 μm; eluent, 0.02 mol · l^{-1} K_2HPO_4/NaH_2PO_4 buffer (pH 6.8) in 10% (v/v) aqueous MeOH; flow rate, 0.5 ml · min^{-1}; detection, 260 nm; retention time of **2c** and **4c**, 23.5 and 25.6 min].

Solvent isotope effect experiments were performed in DMSO-D_2O for **2a**, **2c**, and **2e** and in D_2O for **2c** in the presence of the deuterated phosphate buffers under a nitrogen atmosphere (over a more restricted pD range). The results are summarized in Table 3. The pD values were calculated by adding 0.4 unit to the pH value obtained by using a conventional pH meter.[30]

Reaction of *p*-Nitrophenyl Acetate (1) with 2,4-Diamino-6-methyl-1,3,5-triazine (2c); Preparation of 2-Acetylamino-4-amino-6-methyl-1,3,5-triazine (4c). The 1,3,5-triazine (**2c**) (1.25 g, 0.01 mol) and **1** (3.6 g, 0.02 mol) were heated in dry DMSO (20 ml) at 100 °C for 17.5 h. After cooling, the reaction mixture was poured into 200 ml of water containing crashed ice to afford a crystalline product, which was washed with carbon tetrachloride to give the pure product **4c** in 60% yield. Its homogeneity was established by HPLC (conditions are shown above). Mp 271.0—272.5 °C; UV(EtOH) λ_{max} 223 (ε 2800), 260 (5500), and 326 nm (850); IR(KBr) 3300, 3230, 3140, 1690, 1680, 1615, 1540, 1375, 1315, 815, and 760 cm^{-1}; ^1H NMR(CF_3COOH) δ=7.7 (2H, b, NH_2), 7.1 (1H, b, NH), 2.7 (3H, s, $COCH_3$), 2.4 (3H, s, ring-CH_3); ^{13}C NMR (CH_3COOH) δ=176.6 (CO), 173.1 (CH_3-$\underline{C}$-ring), 166.9 (N=C-NH-Ac), 163.1 (C-NH_2), 25.2 ($\underline{C}H_3CO$), 22.9 (CH_3-ring); MS m/z (rel intensity in %) 169 (2), 168 (8), 167 (M^+, 80), 139 (19), 126 (10), 125 ($M-CH_2=C=O$, 97), 110 (13), 98 (42), 85 (11), 84 (27), 83 (22), 68 (24), 43 (100), 42 (59).

Found: C, 42.83; H, 5.37; N, 41.61%. Calcd for $C_6H_9N_5O$: C, 43.11; H, 5.43; N, 41.90%.

Reaction of 2c with Picryl Fluoride (3). A mixture of **2c** (1.25 g, 0.01 mol) and **3** (4.6 g, 0.02 mol) was heated in dry DMSO at 80 °C for 48 h. After cooling, the reaction mixture was poured into 200 ml of water containing crashed ice to afford the corresponding crude picrate (99.6% yield), which was recrystallized from tetrahydrofuran (73% yield, Found: C, 34.23; H, 2.92; N, 31.04%), and it was identical to an authentic sample. Mp 277—278 °C (decomp., browned at 259—260 °C; lit,[31] 275 °C). UV(EtOH) λ_{max} 250 (sh), 360 (ε 1400), 410 nm (sh); IR (KBr) 3430, 3340, 3260, 3120, 1700, 1645, 1625, 1600, 1570, 1545, 1360, 1325, and 790 cm^{-1}; MS m/z (rel intensity in %) 229 [27, 228.9962 (+0.9 mu, $C_6H_3N_3O_7$)], 125 [100, 125.0698 (−0.2 mu, $C_4H_7N_5$)], 62 (10), 42 (28).

Stability of 4c. A solution of the compound **4c** (5×10^{-3} mol · l^{-1}) in aqueous DMSO was maintained at 30 °C under the same conditions used in the kinetic runs. Aliquots were periodically removed, and the amount of unreacted **4c** was determined by HPLC (conditions are shown above). After 1 h, compound **4c** was still unchanged but 5—10% of **4c** was decomposed after 2 h.

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