Relative Reactivity in Piperidino-Dechlorination of 2,4-Diamino-6-chloropyrimidine, 2,4-Diamino-6-chloropyrimidine *N*(3)-Oxide, and Their Acetylamino Analogues

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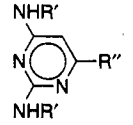
Received June 13, 1994[⊗]

The second-order rate constants k_A for the piperidino-dechlorination of 2,4-diamino-6-chloropyrimidine (**1a**), 2,4-bis(acetylamino)-6-chloropyrimidine (**1b**), 2,4-diamino-6-chloropyrimidine *N*(3)-oxide (**2a**), and 2,4-bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide (**2b**) have been determined from the corresponding pseudo-first-order rate constants, $k\psi$, measured in DMSO at 21.0 °C by the UV spectrophotometric procedure. The second-order rate coefficients of the less reactive substrates **1a** and **2a** at 21 °C have been obtained as extrapolated values from Arrhenius plots of k_A values, calculated through the pseudo-first-order-type relationship, $k\psi = k_A[P]$ (where [P] is the amine concentration), from the $k\psi$ measured at higher temperatures (k_A(**1a**) = 1.36×10^{-5} and k_A(**2a**) = 3.44×10^{-5} L mol^{-1} min^{-1}). The reactivities of the acetyl derivatives **1b** and **2b** are remarkably higher than that of the parent compounds **1a** and **2a**. The pseudo-first-order rate constants of the more reactive substrates **1b** and **2b**, measured as a function of piperidine concentration, increase linearly for **1b**, with a decreasing curvilinear slope only in the higher concentration region of base; in contrast, the reactivity of **2b** remains almost constant and lower than that of **1b** for most of the employed base concentrations. This behavior is due to the acidic character of compound **2b**, which is almost totally transformed by excess piperidine into an anionic form, much less reactive than the protonated one toward the nucleophilic attack, even at relatively low base concentrations. Compound **1b** is much less acidic than **2b** and shows deviations from the second-order-type linear behavior only for the higher base concentrations. The equilibrium constant for the acid–base reaction of **2b** with piperidine has been obtained spectrophotometrically ($K = 0.007 \pm 0.001$), and the second-order rate coefficient k_A has been calculated from the constant apparent reactivity $k\psi$ by means of the formula $k_A = k\psi[PH^+]/K$ (where [PH$^+$] is the piperidinium ion concentration) (k_A(**2b**) = 2.7 L mol^{-1} min^{-1}). That of **1b** is given by the slope of the experimental curve $k\psi$ vs [P] in the proximity of the origin (k_A(**1b**) = 0.15 L mol^{-1} min^{-1}). The results indicate that both the acetylation of the exocyclic $-NH_2$ groups and the oxidation of the cyclic N(3)-atom increase the reactivity of the parent compounds toward piperidinolysis, but that the first modification is much more effective than the second one. The dependence of $k\psi$ of **1b** and **2b** on the amine concentration does not give any evidence for base catalysis, as expected in the model of the intermediate complex mechanism when the leaving group is fast to separate (as the −Cl group is) and/or the complex formation is rate-limiting.

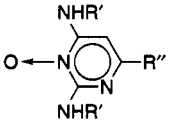
Introduction

Halogenopyrimidines are precursors of a vast number of substituted pyrimidines, such as amino- and alkoxypyrimidines.[1] The conditions under which the halogen displacement reactions take place, depend, among other factors, on the electronic effects exhibited by the other nuclear substituents. Electron-donating groups, such as alkoxy and amino groups, are expected to deactivate the chloroheterocyclic compounds toward nucleophilic substitution, and this is actually observed in aminolysis and alcoholysis of monochloro compounds and in successive aminolysis[2] and alcoholysis[3] of polyhalogenopyrimidines.

A reduction of the electron-releasing power exerted by the amino groups in aminohalogenopyrimidines is expected to increase the chlorine mobility. In the class of pyridine derivatives, this effect has been observed in the aminolysis of 2,6-bis[(ethoxycarbonyl)amino]-4-chloropyridine *N*-oxide, where the chlorine reactivity is enhanced with respect to the parent compound 2,6-diamino-4-chloropyridine by the introduction of the strong electron-withdrawing ethoxycarbonyl groups on the two exocyclic amino groups.[4]



1a: R′ = H, R″ = Cl
1b: R′ = CH_3CO, R″ = Cl
1a′: R′ = H, R″ = $C_5H_{10}N$
1b′: R′ = CH_3CO, R″ = $C_5H_{10}N$



2a: R′ = H, R″ = Cl
2b: R′ = CH_3CO, R″ = Cl
2a′: R′ = H, R″ = $C_5H_{10}N$
2b′: R′ = CH_3CO, R″ = $C_5H_{10}N$

With the aim of throwing more light on this aspect of the chemistry of pyrimidines, we have focused our attention on 2,4-diamino-6-chloropyrimidine (heretofore **1a**), a crucial intermediate in the synthesis of important chemotherapeutic antibacterials.[5] This compound is reported to give nucleophilic chlorine substitution only

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1995.

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(2) Reference 1, p 98.
(3) Reference 1, p 100.
(4) Lawson, J. E.; Dennis, R. D. U.S. Patent 4.021.562, 1977.
(5) Hood, K.; Roberts, G. C. *Biochem. J.* **1978**, *171*, 357.

0022-3263/95/1960-2436$09.00/0

under quite drastic conditions: as an example, the displacement by pure piperidine requires 3 h at 100 °C.[6] We have found that the acetylation of both amino groups in **1a** increases the rate of the chlorine substitution so drastically to allow room-temperature piperidinolysis in few minutes. In contrast, under the same conditions, the parent compound gives scarce evidence for reaction even after many days. Since the amino group acetylation, the amino-dechlorination, and the final hydrolysis of the acetylamino groups are easy, high-yield reactions, the method appears to be a convenient route in the synthesis of 2,4-diamino-6-(substituted amino)pyrimidines from the corresponding diaminochloropyrimidines. More generally, it can be applied to molecules in which primary and/or secondary amino groups, susceptible to be substituted by electron-withdrawing groups, lower the mobility of halogen atoms, or other suitable leaving groups, toward nucleophilic displacements, through releasing of electronic charge to the heterocyclic ring. The higher mobility of the leaving group reduces the importance of secondary reactions, if any, and favors displacements by bases of poor nucleophilicity.

N-Oxidation is reported to activate chloropyridines and -pyrimidines toward chlorine replacement, as a consequence of the electron-withdrawing effect of the N-oxygen atom.[7] However, the room-temperature prolonged treatment of 2,4-diamino-6-chloropyrimidine *N*(3)-oxide (heretofore **2a**) with piperidine is scarcely effective in the chlorine substitution. In fact, the product, 2,4-diamino-6-(piperidin-1′-yl)pyrimidine *N*(3)-oxide, is usually obtained by prolonged warming of pure piperidine with the substrate **2a**.[8] The conclusion which can be drawn from these qualitative results is that the rate of chlorine displacement in **2a** is not very different than in **1a** and that, in contrast, bisacetylation of the amino groups of **1a** increases this rate in a much more significant way.

In order to put the aforementioned observations on a quantitative basis, we have planned to measure the second-order kinetic coefficients for the piperidino-dechlorination of the title compounds **1a** and **2a**, along with the 2,4-bis(acetylamino)-6-chloropyrimidine (**1b**). For the sake of completeness, and in order to establish the degree of cooperation, in increasing the chlorine mobility with respect to substrate **1a**, among the amino group acetylation and the N(3)-oxidation, we have attempted to measure the second-order rate coefficient of the 2,4-bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide (**2b**). This compound has an apparent reactivity lower than that of compound **1b**, pointing to an effect of the N(3)-oxidation essentially opposite to the expectations. As will be evident from the discussion below, **2b**, owing to its acidic character, in presence of piperidine, partly transforms in a much less reactive anionic form, with a reduction in the pseudo-first-order rate coefficients essentially due to lowering of the effective concentration of neutral **2b** in the reaction mixture.

Among dipolar aprotic solvents, DMSO was chosen since rate constants for piperidinolysis in this solvent are expected to be relatively greater[9] and the expected mechanism of S_NAr reactions is the specific base–general acid (SB–GA) mechanism.[10]

Experimental Section

General Remarks. The purity and identity of substrates and products were verified by elemental analysis, TLC, melting points, and ^{1}H-NMR spectra. TLC were performed on precoated silica gel plates (F254 Merck). Melting points were determined on a Kofler microscope and are uncorrected. The ^{1}H-NMR data were obtained in DMSO-d_6 on Varian XL-200 and XL-300 instruments, and the chemical shifts reported below are given in ppm relative to DMSO as an internal standard.

In order to remove from piperidine the 1,2,5,6-tetrahydropyridine, a common impurity of this amine,[11] responsible for an intense absorption at 260 nm, we have employed the procedure of Bunnett and Cartano,[12] modified as follows. Commercial piperidine hydrochloride (Merck) was crystallized from absolute ethanol. To 1 mol of the resulting solid in 300 mL of water was added 4 mol of NaOH in pellets cautiously at room temperature. The final suspension was filtered off, and the supernatant organic layer was isolated from the two-phase filtrate, distilled on NaOH pellets, and fractionated on Na metal. The resulting anhydrous piperidine was stored in the dark, kept in a desiccator over KOH, and withdrawn by means of microsyringes in an atmosphere of dry nitrogen.

DMSO employed in the kinetics and acid–base equilibrium measurements for substrate **2b** was commercial DMSO (Erba, RPE) distilled under vacuum on calcium hydride and kept and withdrawn in a nitrogen atmosphere.

Preparation and Purification of Substrates and Products. Brief remarks on synthetic and purification methods for the substrates and products which this work deals with will precede the individual syntheses. The diacetyl derivatives **1b** and **2b** have been obtained by treatment of corresponding **1a** and **2a** with excess acetic anhydride. The reactivity of substrates **1a** ands **2a** in the acetylation reaction is remarkably different. In fact, in 2,4-diamino-6-chloropyrimidine *N*(3)-oxide, as in other analogous cases,[13,14] the oxygen atom has such strong nucleophilic power that the reaction goes to completeness in few minutes at room temperature, while acetylation of the unoxidized parent compound **1a** requires prolonged heating above 100 °C.

The products were prepared chiefly by piperidino-dechlorination of the corresponding chlorides. However, some of them have been synthesized through other routes and the resulting solids found identical with those prepared with the principal method. Authentic 2,4-diamino-6-(piperidin-1′-yl)pyrimidine *N*(3)-oxide (**2a′**) was reacted with excess acetic anhydride to the bis(acetylamino) derivative **2b′** according to McCall *et al.*[13] and the product was identical to that obtained from the reaction of piperidine on **2b**. Analogously, the product of acetylation of 2,4-diamino-6-(piperidin-1′-yl)pyrimidine (**1a′**) is identical to the solid obtained by piperidino-dechlorination of 2,4-bis(acetylamino)-6-chloropyrimidine (**1b**). The oxidation of **1a′** into **2a′** and **1b′** into **2b′** with peracetic acid did not give any result, in line with previous observations on the behavior of other 2,4,6-triaminopyrimidines toward N-oxidation.[15]

1a. 2,4-Diamino-6-chloropyrimidine (Aldrich) was purified by double sublimation, mp 202 °C. ^{1}H-NMR: 6.59, 6.35 ($2NH_2$), 5.69 (CH).

1b. 2,4-Bis(acetylamino)-6-chloropyrimidine was synthesized as follows: a mixture of 0.5 g (0.002 mol) of **1a** and 2.5 mL of acetic anhydride (0.027 mol) was warmed at 130 °C under vigorous stirring. After 30 min, the dense paste was

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distilled off under vacuum and the yellowish solid residue was mixed and stirred at room temperature with 10 mL of CH_3OH. After 1 h, the liquid was distilled off and 10 mL of water was added. The stirred suspension was made alkaline to pH 8 in 1 h on cooling and filtered, and the microcrystalline solid was washed with cold water and dried. This final solid (0.78 g, th. 0.79 g, 99%) is chromatographically pure and can be crystallized from ethanol to give yellowish crystals with mp 244–46 °C. Anal. Calcd for $C_8H_9N_4O_2Cl$ (228.64): C, 42.02; H, 3.98; N, 24.51. Found: C, 42.13; H, 3.75; N, 23.87. ^{1}H-NMR: 10.82, 10.84 (2NH); 7.72 (CH); 2.20, 2.15 ($2CH_3$).

2a. 2,4-Diamino-6-chloropyrimidine *N*(3)-oxide has been prepared according to a method reported in the literature,[14] crystallized from EtOH and dried under vacuum, mp 193 °C (as in the lit.[14]). Anal. Calcd for $C_4H_5N_4OCl$ (160.57): C, 29.92; H, 3.15; N, 34.90. Found: C, 29.61; H, 3.30; N, 34.76. ^{1}H-NMR: 7.56 ($2NH_2$); 6.09 (CH).

2b. 2,4-Bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide: a suspension of 0.92 g (0.006 mol) of **2a** in 10 mL of acetic anhydride was stirred at room temperature for 45 min. The liquid was distilled off under vacuum, and the solid residue, suspended in 10 mL of MeOH, was stirred at room temperature for 30 min. After distillation of the liquid under vacuum, the solid was suspended in 5 mL of water and the suspension alkalinized to pH 8 with 5% KOH. Compound **2b** is obtained by filtration as a white chromatographically pure solid (0.96 g, th. 1.40 g, 69%). Crystallizes from 2-methyl-2-propanol, mp 234–35 °C, with partial dec. Anal. Calcd for $C_8H_9N_4O_3Cl$ (244.65): C, 39.28; H, 3.71; N, 22.91. Found: C, 38.93; H, 3.73; N, 23.18. ^{1}H-NMR: 10.99, 10.48 (2NH), 7.98 (CH), 2.33, 2.32 ($2CH_3$).

1a′. 2,4-Diamino-6-(piperidin-1′-yl)pyrimidine has been prepared by piperidino-dechlorination of **1a**, after the method of Roth et al.,[6] and crystallized from EtAc/cyclohexane, mp 135–136 °C. Anal. Calcd for $C_9H_{16}N_5$ (194.26): C, 55.64; H, 8.30; N, 36.06. Found: C, 55.03; H, 7.98; N, 36.51. ^{1}H-NMR: 5.62, 5.43 ($2NH_2$), 5.02 (CH), 1.44 (6H of −P). Peaks due to 4H of −P are superimposed to resonances of H_2O, present in traces in DMSO-d_6, at 3.35 ppm. The same solid has been prepared by reduction of **2a′** with $TiCl_3$, according to McCall et al.[16]

1b′. 2,4-Bis(acetylamino)-6-(piperidin-1′-yl)pyrimidine has been obtained by room temperature stirring of 2.0 g of **1b** (0.009 mol) with 2.2 mL of P in 50 mL of DMF. After 3 h, the solution was diluted with water 1:4 on cooling and the precipitated solid filtered and washed with water (1.6 g, th. 2.5 g, 64%). This final white product is chromatographically pure and can be crystallized from EtOH, mp 302–303 °C. Anal. Calcd for $C_{13}H_{19}N_5O_2$ (277.32): C, 56.30; H, 6.91; N, 25.26. Found: C, 56.93; H, 6.78; N, 24.96. ^{1}H-NMR: 10.14, 9.64 (2NH), 7.11 (CH), 3.53 (4H of −P), 2.20, 2.07 ($2CH_3$), 1.52 (6H of −P).

2a′. 2,4-Diamino-6-(piperidin-1′-yl)pyrimidine *N*(3)-oxide has been prepared from piperidino-dechlorination of **2a** according to a literature method.[8] Anal. Calcd for $C_9H_{16}N_5O$ (210.26): C, 51.41; H, 7.67; N, 33.31. Found: C, 51.93; H, 7.24; N, 32.98. ^{1}H-NMR: 6.82 ($2NH_2$), 5.35 (CH), 3.35 (see above, for **1a′**), 1.56 (6H of −P).

2b′. 2,4-Bis(acetylamino)-6-(piperidin-1′-yl)pyrimidine *N*(3)-oxide has been prepared by stirring for 3 h 2.1 g of **2a′** (0.01 mol) in 10 mL of acetic anhydride at room temperature. The final paste was added in small portions to 20 mL of water, kept under stirring and cooling, and the obtained suspension was alkalinized to pH 8 with aqueous ammonia. The filtered solid has been washed with water and EtOH (1.8 g, th. 2.93 g, 62.1%). Microcrystals have been obtained by crystallization from EtOH, mp 218-20 °C, with dec (lit.[13] mp 217–217.5 °C). Anal. Calcd for $C_{13}H_{19}N_5O_3$ (293.33): C, 53.23; H, 6.53; N, 23.88. Found: C, 53.68; H, 6.40; N 24.05. ^{1}H-NMR: 10.50, 9.94 (2NH); 7.31 (CH); 3.52 (4H of −P), 2.39, 2.26 ($2CH_3$); 1.56 (6 H of −P).

Structure of the Substrates in DMSO Solution. The amino- and (acetylamino)pyrimidines employed as substrates in the present work are all capable of tautomerism, and in addition to the amino form, they can also exist in some of the imino forms deriving from the rapid proton transfer from one of the exocyclic amino groups to one of the cyclic N-atoms. In the corresponding *N*-oxides, the proton transfer can involve also the oxygen atom, giving rise to *N*-hydroxy forms. Furthermore, in 2,4-bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide, one of the acetyl residues can slowly migrate to the oxygen atom, giving acetoxy structures.[13] Each of the resulting isomers of each substrate, with its own electronic density on C(6), should have in principle characteristic rate coefficients toward piperidino-substitution of its chlorine atom. Thus, the problem arises, with respect to the rate coefficients determined in this work, about the presence and importance of these equilibria in the reaction mixture.

A description of the situation can be obtained from the aforelisted ^{1}H-NMR spectral results, relative to solutions in pure DMSO. The aminopyrimidine **1a** and its corresponding **2a** both show only shifts and intensities due to two primary amino groups in the molecule. Broadening of signals due to protons bound to N-atoms comes from nitrogen–proton coupling.[17] The spectra taken at higher temperature, in the range 80–130 °C, in which rate measurements have been performed, do not indicate the appearance of new peaks, with respect to those observed at 21 °C, thus excluding both the presence of tautomeric forms and any decomposition reaction. The present structural indication is in agreement with previous ^{1}H-NMR observations on 2- and 4-aminopyrimidines[18] and on aminopyridines[19] and confirms the tendency of these compounds to prefer the primary amine form in the DMSO solution. Accordingly, 2- and 4-amino N-oxides in the pyridine series exist predominantly as such.[20,21]

In compound **1b** the two NH resonances of the acetylamino groups are downfield shifted to around 10 ppm, and this was generally found in all the acetylated substrates and products investigated here. Furthermore, the absence in the spectrum of any $-NH_2$ resonance excludes bisacetylation of only one amino group, and the downfield shift of the "aromatic" CH from 5.69, in the parent compound **1a**, to 7.72 ppm points to the presence of an acetyl on C(4), in analogy with the behavior of **2a**, reported as follows. Hence, here, as well, the ^{1}H-NMR data point to the amino tautomer as the prevalent form present in solution.

This result confirms early observations on 2- and 4-(acetylamino)pyrimidines,[22] the imino form prevailing only in the [(trifluoroacetyl)amino]pyrimidines[11] and in the sulfonyl analogues.[22] In the ^{1}H-NMR spectra of **2b**, the acetylation on C(4) is indicated by the downfield shift of the peak due to the "aromatic" CH to 7.98 ppm, from 6.09 ppm in the unacetylated parent compound.[11,14b] The remaining acetyl group can be bound to the same amino group, giving a *gem*-bis(acetylamino) derivative, to the oxygen, giving rise to a *O,N*-diacetyl derivative (as observed in the pyridine series[23]) or to the other exocyclic amino group. The first possibility is ruled out by the absence of any resonance due to free $-NH_2$ or −OH groups. In the second instance, the expected peak due to one imino group was not observed (the broad =NH resonance has been observed at 7.60 ppm, superimposed to that of C(5)H in 6-amino-1,2-dihydro-1-(propionyloxy)-2-imino-4-chloropyrimidine;[24] however, our intensity values exclude any ambiguity). In conclusion, the spectral evidence points to the presence of one acetyl on each of the two exocyclic nitrogens. Here, as well, the result is in agreement with previous observations on

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Table 1. Wavelength and Molar Absorptivity of the UV Absorptions of the Substrates and Products Studied in This Work (in DMSO, 21 °C)

substance	wavelength (nm)	molar absorptivity ($\times 10^{-3}$ M^{-1} cm^{-1})
1a	285	7.8
1b	258	7.5
	283	9.0
2a	296	5.1
2b	258 (290)	33.0 (10.0)
	326	7.3
1a'	285	15.3
1b'	263	13.2
	295	7.0
2a'	264 (300)	11.7 (7.6)
2b'	260	11.5
	299	11.2
	348	3.0

2- and 4-(acetylamino)pyridine *N*-oxides, which have been found to exist predominantly as such.[25]

UV Spectra of Substrates and Products. All the spectra were taken, against pure DMSO, in the range 240–400 nm with a Perkin-Elmer Model 555 spectrophotometer, equipped with a thermostated cell compartment, using matched 10 mm stoppered quartz cuvettes. The wavelengths of the absorptions of the substrates and products investigated in the present work are listed in Table 1. Beer's law plots were determined at the absorption maxima of each compound in DMSO: straight lines passing through the origin were obtained in all cases, whose slopes have given the molar absorptivity reported on Table 1.

Rate Measurements. In case of substrates **1a**, **1b**, and **2a**, the reaction kinetics were followed by measuring the change in absorption of the solution containing the reactants at the wavelength where the largest difference between the initial and the final spectrum was measured,[26] *i.e.*, 285 nm (**1a**), 283 nm (**1b**), and 295 nm (**2a**). In the case of **2b**, owing to the acidity of this substrate, the initial spectrum changes with the chosen base concentration. As a consequence, the wavelength was chosen accordingly in the range 296–318 nm.

In the case of rapid reactions at 21.0 °C (substrates **1b** and **2b**), to 3 mL of a mother solution of the substrate, kept in a 10 mm stoppered quartz cuvette, directly in the thermostated spectrophotometer cell compartment, a total of 300 μL of a mixture of DMSO and piperidine was added, the volume of base ranging from 0.5 to 300 μL, giving rise to base concentrations in the reaction mixtures ranging from 0.0061 to 0.9190 M. The initial substrate concentrations are reported in the text below; the kinetic results are listed in Table 4. Mixing was ensured by vigorously shaking the cuvette after the addition of the reagent.

For the slower reactions (substrates **1a** and **2a**), samples of the reaction mixtures were confined into Pyrex tubes, solidified in liquid nitrogen, accurately outgassed under vacuum and sealed. These tubes, kept at the desired temperatures (ranging from 69.0 to 127.0 °C), were cooled to room temperature at successive time intervals, and 50 μL of their content was diluted to 10 mL for **1a** and to 25 mL for **2a** and transferred into a 1 mm cuvette for the spectral analysis. For practical reasons, substrates and piperidine concentrations (reported in Table 2) higher than those used for the more reactive substrates **1b** and **2b** have been employed; the dependence of the pseudo-first-order rate constants on the amine concentration has not been investigated. As indicated by the concentration values on Table 2, the [amine]/[substrate] ratio is about 8, which is very much lower than those employed for substrates **1b** and **2b**. In spite of this fact, the kinetic plots were always linear, indicating that the reactions proceed essentially in pseudo-first-order conditions.

In both rapid and slow displacement reactions, pseudo-first-order kinetics were obeyed: in fact, plots of ln $ID - D_\infty I$ vs time were linear. The pseudo-first-order coefficients $k\psi$[27] have been obtained directly from the slope of the foregoing plots.

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Table 2. Reaction of 2,4-Diamino-6-chloropyrimidine (1a) and 2,4-Diamino-6-chloropyrimidine *N*(3)-oxide (2a) with Piperidine in DMSO. Temperature Dependence of Reaction Rates

substrate	temp, °C	$10^3 k\psi$, min^{-1}	$10^3 k_A$, M^{-1} min^{-1}
1a[a]	80.0	1.11	0.50
	95.0	2.30	1.04
	112.0	4.90	2.20
	127.0	9.30	4.21
2a[b]	69.0	1.10	0.91
	82.0	1.86	1.80
	89.5	3.55	2.93
	115.5	11.15	9.95

[a] Initial concentrations: **1a**, 0.26 M; piperidine, 2.21 M. [b] Initial concentrations: **2a**, 0.13 M; piperidine, 1.21 M.

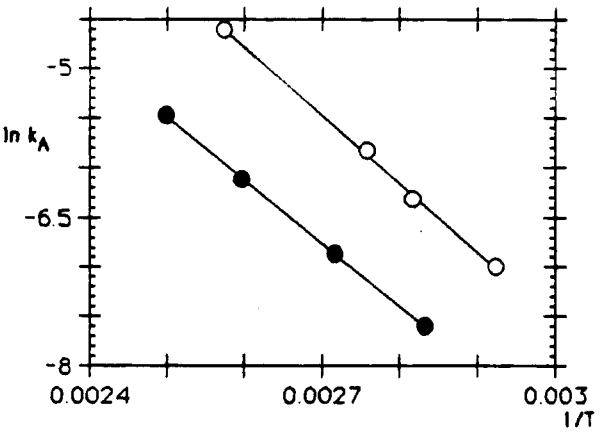

Figure 1. Reaction of 2,4-diamino-6-chloropyrimidine (**1a**, filled circles) and of 2,4-diamino-6-chloropyrimidine *N*(3)-oxide (**2a**, open circles) with piperidine. Arrhenius plots (data from Table 2).

Results and Discussion

As previously mentioned, the reactions of substrates **1a** and **2a** are exceedingly slow at 21.0 °C. For this reason, the second-order-type rate constants at this temperature have been extrapolated from measurements at higher temperatures, assuming the reactivity at higher temperatures as being due to the same amino forms predominant in solution at 21 °C, as revealed by ^{1}H-NMR spectroscopic results.

The kinetic determinations, at different temperatures, on the less reactive substrates **1a** and **2a** are reported on Table 2, where the pseudo-first-order rate coefficients $k\psi$ are listed in the second column. On grounds of the absence of any acidic character of these compounds and the lack of evidence of any basic catalysis on the chlorine displacement of the corresponding bisacetyl derivatives (see below), as expected for good leaving groups such as chloride ions,[28] the second-order-type coefficients have been confidently calculated through the relation $k_A = k\psi/[P]$ and listed on the third column of Table 2. The Arrhenius plots of the k_A values of **1a** and **2a** are represented in Figure 1, and the extrapolated values at 21 °C are k_A(**1a**) = 1.36×10^{-5} L mol^{-1} min^{-1} and k_A(**2a**) = 3.44×10^{-5} L mol^{-1} min^{-1}. For the reaction of piperidine with **1a**, $\Delta H^* = 11.9 \pm 0.3$ kcal/mol and ΔS^*

(28) Bernasconi, C. F. *MTP Int. Rev. Sci.: Org. Chem Ser. 1*, **1973**, *3*, 33.

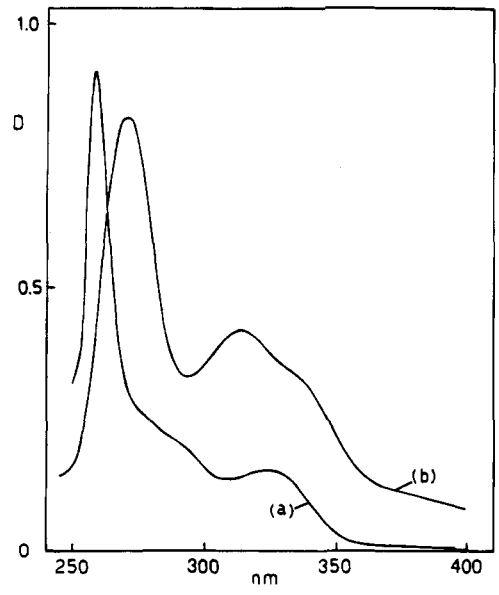

Figure 2. Comparison of the UV spectra of 2,4-bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide (**2b**) (a) in DMSO and (b) in DMSO + piperidine 0.919 M ($c = 2.3 \times 10^{-5}$ M; $d = 1$ cm).

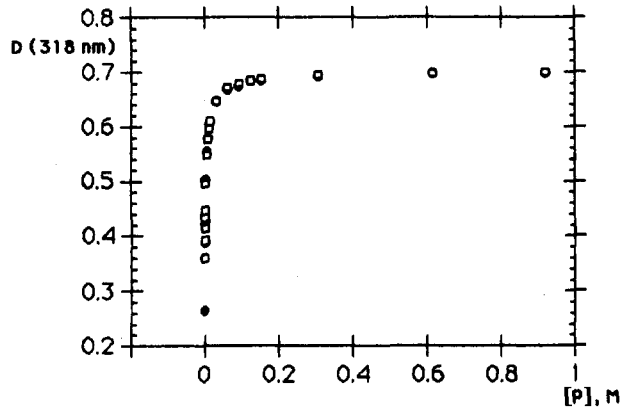

Figure 3. Acid–base equilibrium at 21 °C between 2,4-bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide (**2b**) and piperidine. Plot of D vs [P] for $c = 4.1 \times 10^{-5}$ M (filled circles: experimental values; open squares: calculated values for $K = 0.0078$).

$= -40$ eu, while for **2a** $\Delta H^* = 12.9 \pm 0.4$ kcal/mol and $\Delta S^* = -35$ eu.

For the substrates **1a**, **1b**, and **2a**, the absorption spectrum of the initial reaction mixture is not affected by the presence of piperidine, even at high concentration levels. In contrast, the spectrum of 2,4-bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide (**2b**) changes rapidly with the increasing amine concentration to a final spectrum which becomes constant well within the concentration range investigated in the present work: the band at 326 nm is being flanked by an absorption at 314 nm, with a shoulder at 338 nm, that at 258 nm shifts to 272 nm. The molar absorptivity of these new bands, measured at the highest base concentration employed in this work, are $\epsilon(338) = 12.6 \times 10^3$, $\epsilon(314) = 17.0 \times 10^3$, and $\epsilon(272) = 34.4 \times 10^3$ M^{-1} cm^{-1}. Both the initial and the final spectrum of **2b** are reported in Figure 2. The optical density, at a given wavelength, changes as a function of the base concentration as shown in Figure 3. This spectral behavior and the essential constancy of the rate coefficients $k\psi$ measured for substrate **2b** in almost the same range of initial base concentrations (see below) are due to the acidic character of this substrate, whence the existence of the equilibrium

$$HA + P \rightleftharpoons A^- + PH^+ \quad (1)$$

(where HA represents the undissociated 2,4-bis(acetylamino)-6-chloropyrimidine *N*(3)-oxide, A^- its mononegative anionic form, and PH^+ the piperidinium ion), the acidity of **2b** being due to resonance delocalization of the negative charge of the anion, acquired by the molecule on losing one of the acetylamino protons.

As indicated below, the second-order rate constant for the piperidino-dechlorination of substrate **2b** can be evaluated only if the constant K of the equilibrium (1) is known. This was accomplished here through an extension of the well-known spectrophotometric method,[26] as follows.

At a given wavelength, the optical density of a solution of **2b** in DMSO + piperidine, D_{calc}, is expected to vary as a function of the value of the equilibrium constant K and the piperidine molar concentration [P], according to the formula

$$D_{calc} = (D_0[PH^+] + D_f K[P])/([PH^+] + K[P]) \quad (2)$$

where $[PH^+]$ is the piperidinium ion molar concentration, D_0 is the optical density of the neutral material measured in pure DMSO, and D_f is that measured at base concentrations sufficiently high to ensure the presence in solution of the pure ionized species A^-.

The piperidinium ion concentration can be calculated, for a given K, through straigthforward procedures, remembering that $[PH^+] = [A^-]$ and resolving the quadratic equation coming from the expression of the equilibrium constant

$$[PH^+] = 1/2[(-K[P] + (K^2[P]^2 + 4K[P]c)^{1/2}) \quad (3)$$

(where c is the total concentration of the substrate **2b**).

In four runs on solutions of **2b** with different concentrations, a satisfactory agreement between the experimentally determined optical density D and D_{calc} has been obtained with $K = 0.01$. Further accuracy in the determination of K has been obtained through an iterative procedure on the function obtained from eq 2 with inversion

$$1/(D - D_0) = 1/(D_f - D_0) + (1/(K(D_f - D_0))[PH^+]/[P] \quad (4)$$

where D_0 is the optical density measured at $[P] = 0$. For a given c, the plot $1/(D - D_0)$ vs $[PH^+]/[P]$ is a straight line whose slope gives a new value of K, from which another cycle of calculations can be performed. It has been found that, irrespective of the initial value of K chosen, higher or lower than the final one, there is a rapid convergence to the same value. The inversion plot for $c = 4.1 \times 10^{-5}$ M is reported in Figure 4. The convergence values obtained for four different concentrations of **2b** are as follows: 0.0068 ($c = 5.3 \times 10^{-5}$ M); 0.0078 ($c = 4.1 \times 10^{-5}$ M); 0.0067 ($c = 2.7 \times 10^{-5}$ M); and 0.0056 ($c = 1.8 \times 10^{-5}$ M). The average value of $K = 0.007 \pm 0.001$ has thus been assumed as the equilibrium constant at 21 °C for the acid–base equilibrium (1).

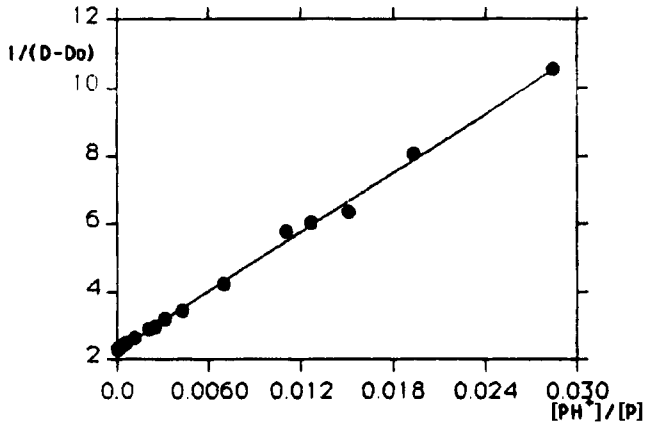

Figure 4. Inversion plot (see eq 4 in the text) of the same experimental data of Figure 3 relative to $c = 4.1 \times 10^{-5}$ M. From the intercept and slope of the line: $K = 0.0078$ and $D_f = 0.702$.

Table 3. Pseudo-First-Order Rate Coefficients for Reactions of Piperidine with 2,4-Bis(acetylamino)-6-chloropyrimidine (1b) and 2,4-Bis(acetylamino)-6-chloropyrimidine *N*(3)-Oxide (2b) in DMSO at 21 °C

[P], M	$k\psi$(**1b**), min^{-1}	$k\psi$(**2b**), min^{-1}
0.0061		0.0070
0.0092		0.0078
0.0123		0.0088
0.0153	0.0015	0.0093
0.0306	0.0035	0.0130
0.0307	0.0052	
0.0613		0.0155
0.0919	0.0130	0.0160
0.1230		0.0160
0.1510		0.0165
0.1530	0.0220	
0.2110	0.0290	
0.2140	0.0270	0.0169
0.2990	0.0440	0.0170
0.3060		0.0170
0.5800	0.0820	0.0176
0.8450	0.0950	0.0180
0.9190	0.0980	

The kinetic determinations on **1b** and **2b** are listed on Table 3 and plotted vs the piperidine concentration [P] in Figure 5. The plot relative to **1b** is almost linear in the region of low base concentrations, but the slope gently decreases as the base concentration becomes higher. In contrast, that of **2b** appears almost unaffected by changes of [P] in most of the range of the amine concentrations, with the exception of the lower employed concentrations. The same difference in reactivity toward alcoholysis has been found among 4-(diethylamino)- and 4-anilino-2,5,6-trichloropyrimidine,[29] the former showing a linear increase of $k\psi$, the latter having a reactivity essentially constant with base concentration. The interpretation was based on the weak acidity of the secondary amino group present in the anilino derivative. Only this molecule, in the presence of the base, transforms in the much less reactive anion. On these grounds, a relationship has been derived[29] among $k\psi$, $k_{A(HA)}$ (the second-order rate coefficient k_A of the undissociated substrate HA), K_{HA} (its ionization constant), and K_w:

$$k = k_{A(HA)}(K_w/(K_{HA} + [H^+]) \quad (5)$$

Equation 5 gives $k\psi = k_{HA}(K_w/K_{HA})$ (an horizontal line)

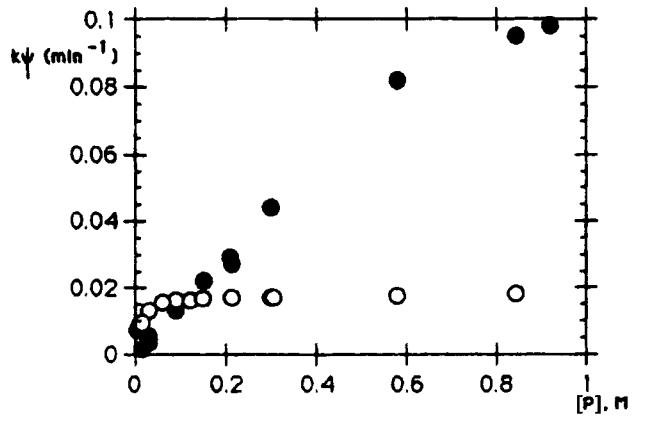

Figure 5. Piperidino-dechlorination of substrates **1b** (filled circles) and **2b** (open circles); effect of the amine concentration on the pseudo-first-order kinetic constants (from data of Table 3).

Table 4. Piperidino-Dechlorination in DMSO at 21 °C of the Title Substrates. Second-Order Rate Coefficients

substrate	$10^3 k_A$, M^{-1} min^{-1}
1a	0.0136
1b	150
2a	0.0344
2b	2680

when $K_{HA} \gg [H^+]$ and $k\psi = k_{HA}[OH^-]$ (a straight line with slope k_{HA}) when $K_{HA} \ll [H^+]$.

In a non aqueous solvent, as is the present case, an analogous relationship can be obtained starting from the equilibrium constant of the reaction (1):

$$k\psi = k_{A(HA)}([PH^+]/(K + [PH^+]/[P])) \quad (6)$$

If $K \gg [PH^+]/[P]$, eq 6 becomes

$$k\psi = k_{A(HA)}([PH^+]/K) \quad (7)$$

while it approximates the equation

$$k\psi = k_{A(HA)}[P] \quad (8)$$

if $K \ll [PH^+]/[P]$. Since in all of our experiments $[PH^+] = [A^-]$ and in the presence of an excess of P (the pseudo-first-order condition), $K \gg [PH^+]/[P]$ and $[PH^+] = c$, eq 7 holds, giving $k\psi$ as a constant, as experimentally found.

From the experimental data reported in Table 3, $k\psi = 0.018$ min^{-1} can be assumed as a reasonable asymptote for $k\psi$, whence, with the previously determined value of $K = 0.007$ and the concentration of the solution employed for kinetic measurements, $c = 4.7 \times 10^{-5}$ M, the second-order-rate coefficient for the undissociated **2b** can be evaluated from eq 7:

$$k_{A(HA)}(\mathbf{2b}) = 2.7 \text{ L mol}^{-1} \text{ min}^{-1}$$

The second-order-rate coefficient for **1b** ($c = 9.61 \times 10^{-5}$ M) can be evaluated from the tendential slope of the line passing through the experimental and the (0,0) points of Figure 5, on going toward the lower values of [P]:

$$k_A(\mathbf{1b}) = 0.15 \text{ L mol}^{-1} \text{ min}^{-1}$$

(29) Ackermann, H.; Dussy, P. *Helv. Chim. Acta* **1962**, *45*, 1683.

By introducing this value in eq 6, along with the aforementioned value of $c = [PH^+]$, a good agreement between the experimental curve $k\psi$ (**1b**) vs [P] and that calculated through eq 6 have been obtained for K(**1b**) = 1×10^{-5}.

The second-order-rate coefficients for the piperidinodechlorination of the substrates investigated in the present work are summarized in Table 4.

In conclusion, the results indicate that in **1a** the monosubstitution of both the amino groups with electron-withdrawing groups, such as acetyls, increases noticeably the reactivity of this substrate, while N(3)-oxidation gives an analogous but feeble effect. In fact, both NH_2-acetylation and N(3)-oxidation cooperate, but the acidity acquired by **2a** on acetylation masks this effect, giving rise to a reactivity in **2b** apparently lower than in the corresponding unoxidized analogue **1b**.

Acknowledgment. I am very grateful to Prof. F. Monacelli for useful suggestions and criticism of the manuscript.

JO940978C