14 hr. The crude product remaining on removal of solvent was crystallized with difficulty from methanol. Several recrystallizations from the same solvent gave an analytical sample, mp 140–143°; infrared: 1724 (s), 1651 (m), 1276 (s), 1110 (m), and 774 (ms) cm^{-1} (KBr).

Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.15; H, 4.74. Found: C, 80.98; H, 4.59.

The same compound could be obtained more readily (96%) by diazomethane esterification of the keto acid.

Methyl Pseudo-8-(1′-naphthoyl)-1-naphthoate. A solution of 200 mg of keto acid **19** in 20 ml of methanol was warmed to achieve homogeneous solution, treated with 0.9 ml of acetyl chloride, and then left at room temperature overnight. The crystalline material which had separated was twice recrystallized from methanol to give an analytical sample, mp 204.5–206°; infrared: 1715 (s) and 1290 (ms) cm^{-1} (KBr).

Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.15; H, 4.74. Found: C, 81.10; H, 4.73.

Methyl 8-(2′-Methoxy-1′-naphthoyl)-1-naphthoate. A solution of 200 mg of methoxy keto acid **20** in 15 ml of methanol was esterified with excess diazomethane in ether. After several recrystallizations the product ester showed mp 161°; infrared: 1721 (s), 1651 (m), and 1275 (ms) cm^{-1} (KBr).

Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.82; H, 4.90. Found: C, 77.57; H, 4.86.

3-(2′-Methoxy-1′-naphthyl)naphthalide (23). A solution of 500 mg of methoxy keto acid **20** in 25 ml of acetic acid containing 100 mg of 5% palladium on carbon was shaken under 3 atm of hydrogen for 18 hr at 65°. The yellow glass resulting from removal of solvent and catalyst crystallized readily from ethanol to give 140 mg of product, mp 177–179° (29%). Further crystallization gave an analytical sample, mp 180–181°; infrared: 1721 (s) cm^{-1} (CH_2Cl_2).

Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.15; H, 4.74. Found: C, 80.95; H, 4.98.

Acetonide 24. A solution of 200 mg of **7** in 200 ml of acetone containing 4 ml of 70% perchloric acid was left at room temperature 18 hr. To the resulting clear, dark brown solution was added excess solid sodium bicarbonate and then water and ether. The organic layer was separated, washed, and dried. Removal of solvent left colorless crystals contaminated with yellow oil which was washed away with cyclohexane, yield 180 mg (80%). One recrystallization from benzene gave an analytical sample which did not melt below 355°; infrared: 1092 (s), 1025 (s), 792 (s), and 779 (s) cm^{-1} (KBr); nmr: δ 1.22 (singlet) and 7.2–8.0 (multiplet) ($CDCl_3$).

Anal. Calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.97; H, 5.39.

Carbonate Ester 25. A mixture of 32 mg of **7** and 14 mg of potassium *t*-butoxide in 16 ml of diethyl carbonate (distilled) was heated at reflux under nitrogen for 66 hr. The cooled solution was diluted with ether, washed with water, and dried. Removal of solvent left off-white crystals which were recrystallized from benzene, yield 32 mg (92%). One further recrystallization gave an analytical sample, mp 314–315°; infrared: 1810 (s), 1795 (s), 1050 (ms), and 780 (s) cm^{-1} (KBr).

Anal. Calcd for $C_{23}H_{12}O_3$: C, 82.13; H, 3.60. Found: C, 81.78; H, 3.64.

Attempted chromatography over Woelm neutral alumina (II) resulted in complete hydrolysis; only a small amount of diol could be recovered by elution with methanol.

Acknowledgment. It is a pleasure to acknowledge the kind support and encouragement of Professor Lyman C. Craig. Mr. Laurence Smith provided able technical assistance. This investigation was supported by National Science Foundation Grant GB-137 and National Institutes of Health Grant AM-02493.

The Piperidino Dechlorination of Chloroquinolines. Solvent Effects on the Reaction Kinetics[1]

Gabriello Illuminati, Gianlorenzo Marino, and Giancarlo Sleiter

Contribution from the Departments of Chemistry, University of Rome, Rome, Italy, and University of Trieste, Trieste, Italy. *Received January 21, 1967*

Abstract: The kinetics of the reaction of 2- and 4-chloroquinolines with piperidine have been investigated in five different solvents. With both isomeric substrates, the reactivity order is qualitatively predicted by the dielectric constant in the case of aprotic solvents (toluene, ethyl acetate, DMSO). The so-called α-aza effect of 2-chloroquinoline is also observed with such solvents and is believed to originate from electrostatic effects. The reactivity of a chloroquinoline is exalted by H-bonding interaction with a hydroxylic solvent (methanol) especially for the γ-chloro isomer. Base catalysis is practically absent at low piperidine concentrations in toluene solution. However, it can be detected as a small kinetic factor in neat piperidine; this effect is larger for the α than for the γ isomer. Use of N-*d*-piperidine in toluene solution results in a small *inverse* isotope effect for the γ-chloro isomer and practically no effect for the α-chloro isomer. The present investigation includes a preliminary study on the scope of autocatalytic phenomena with respect to structure of the substrate and to solvent, and on a reliable evaluation of the "uncatalytic" rate constants under several conditions involving the 4 isomer.

Nucleophilic substitution involving six-membered-ring N-heteroaromatic substrates is characterized by the basicity of the aza group. Special features of the reaction include acid catalysis (or autocatalysis), bifunctional catalysis, and specific interactions with the reagent and/or the solvent.[2,3]

Specific interactions involving the aza derivative as the proton acceptor may consist of salt formation or of hydrogen-bond formation and also depend on the proton donor ability of the species present in the medium. The most familiar nucleophiles possibly concerned with such interactions are the primary or secondary amines and the thiols as having an ionizable hydrogen atom bound to the nucleophilic atom; the most familiar solvents are the alcohols because of their hydroxylic character.

(1) Nucleophilic Heteroaromatic Substitution. XXV. Work carried out under a CNR (Rome) research contract at the Universities of Rome (G. I. and G. S.) and Trieste (G. M.) on the basis of a conjoint program. Presented in part by G. I. at the Gordon Conference on the Chemistry of Heterocyclic Compounds (New Hampton, N. H., July 4–8, 1966). For part XXIV, see M. Calligaris, P. Linda, and G. Marino, *Tetrahedron*, **23**, 813 (1967).

(2) G. Illuminati, *Advan. Heterocyclic Chem.*, **3**, 285 (1964).

(3) R. G. Shepherd and J. L. Fedrick, *ibid.*, **4**, 145 (1965).

Table I. Solvent Effects on the Piperidino Dechlorination Reaction[a]

Solvent	$10^5 \times k$ at varying temp, °C 60.0	75.2	86.5	99.5	115.7	E_a	$-\Delta S^{\ddagger}$
			2-Chloroquinoline				
Toluene			0.405	0.901	2.67	18	36
DMSO	4.05	11.6	22.2			15	35
Methanol			2.44	5.46	15.0	17	34
Piperidine	0.603	1.58	3.11		14.1	15	41
Ethyl acetate			1.00				
			4-Chloroquinoline				
Toluene	0.15[b]	0.54[c]	0.0052[d]		0.055	22	39
DMSO	1.7	4.3	8.8			15	38
Methanol			2.4	4.4	10.0	14	44
Piperidine			0.088	0.16	0.375	14	50
Ethyl acetate			0.059				

[a] k in l. mole^{-1} sec^{-1}; E_a in kcal/mole; $\Delta S^{\ddagger}$ in eu. [b] At 130°. [c] At 150°. [d] Calculated from the Arrhenius parameters.

Hydrogen-bond interactions of hydroxylic species with pyridine and other azines closely related to the ones involved in nucleophilic heteroaromatic substitution reactions have been established in several studies by spectral,[4-8] thermochemical,[9] and other methods.[10] They have often been assumed[2,3] to play a role in determining the reactivity of the heterocyclic compound, but a quantitative appraisal of their influence is not available.

Owing to the well-known analogies between nucleophilic aromatic and nucleophilic heteroaromatic substitution, many of the problems concerning the former are also of interest in the latter; one of these is base catalysis, which may become important in the reactions with amines.

The main object of this and the following papers is to provide information on the specific characteristic interactions of the aza group with the reaction medium. The present paper reports on the solvent effects on the kinetics of the reaction of the 2- and 4-chloroquinoline isomers with piperidine. A few substituted derivatives were also investigated in connection with autocatalysis.

It seems apparent that for a genuine interpretation of the fundamental features of aza activation, the aza group should be the only activating group present in the heterocycle, because substrates containing other additional activating groups, such as nitropyridine derivatives, are expected to yield "mixed" behavior. For this reason in our present research we have restricted our attention to substrates containing a single aza group as the activating moiety.

Results

The kinetics of piperidino dechlorination of 2- and 4-chloroquinolines have been studied in five solvents: toluene, methanol, dimethyl sulfoxide (DMSO), ethyl acetate, and piperidine. The reactions in ethyl acetate were followed as long as piperidinolysis of the solvent remained kinetically unimportant.

The reaction is generally susceptible to autocatalysis as it eventually leads to the removal of a proton from the reagent and to a rate-enhancing proton transfer to unreacted substrate molecules.[2] While autocatalysis is well known to occur in these reactions, the present results provide new information as to its scope with regard to solvent as well as substituent effects.

Under second-order conditions (0.1–0.2 M in piperidine, 0.05 M in substrate), the more basic 4-chloroquinoline is subject to strong autocatalysis in such widely different solvents as toluene, ethyl acetate, and methanol. The phenomenon is much less pronounced in DMSO, which indicates more effective competition for the proton by this solvent in agreement with its greater basic character.[11] Under pseudo-first-order conditions, *i.e.*, when the piperidine concentration is substantially increased, autocatalysis tends to vanish; it is still evident in toluene and methanol solutions 1.8 M in piperidine, but is completely absent in neat piperidine (*ca.* 10 M) which is the most basic solvent investigated.

Autocatalysis is also controlled by the presence of substituents acting on the electron-donor ability of the aza group of the substrate. In the 4-chloroquinoline series, electron-withdrawing substituents (2-CF_3, 2-CO_2Et) prevent autocatalysis even at low piperidine concentrations (second-order conditions in DMSO and methanol solutions), whereas electron-releasing substituents, such as 2-CH_3, 2-OR, 2-NH_2, exalt it. 2-Amino-4-chloroquinoline is subject to this phenomenon even in neat piperidine, in agreement with the very powerful electron-releasing ability of the amino group.

In contrast, the less basic 2-chloroquinoline follows second-order kinetics (pseudo first order in piperidine solution) and shows no autocatalysis effect in any solvent. However, electron-releasing substituents (4-OC_2H_5, 4-SCH_3) promote some autocatalysis even in this series.

The above results consistently indicate that the appearance of autocatalysis depends on the inability of the medium to hold the proton efficiently and to prevent its transfer to the substrate, and on the basic character of the latter, as influenced by the position of the leaving group and by the electronic effects of the substituents.

In these reactions autocatalysis is evident from an upward drift eventually appearing in either the second-order or the pseudo-first-order plots. For an accurate

(4) A. R. Katritzky and A. P. Amber in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 282.
(5) P. Chiorboli and A. Bertoluzza, *Ann. Chim.* (Rome), **49**, 245 (1959).
(6) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 363.
(7) E. D. Becker, *Spectrochim. Acta*, 17, 436 (1961).
(8) A. Weller, *Progr. Reaction Kinetics*, **1**, 196 (1961).
(9) D. Neerinck and L. Lamberts, *Bull. Soc. Chim. Belges*, **75**, 473, 484 (1966); see also several references reported therein.
(10) W. Cochran and S. Walker, ref 4, Vol. I, pp 171 and 211 ff.
(11) I. M. Kolthoff and T. B. Reddy, *Inorg. Chem.*, **1**, 189 (1962).

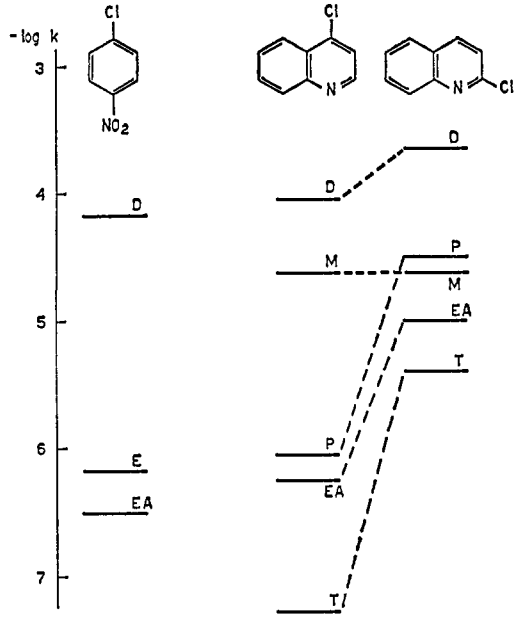


Figure 1. Reactivity levels in the piperidino dechlorination of *p*-chloronitrobenzene (at 50°) and 2- and 4-chloroquinolines (at 86.5°) in diverse solvents (T, toluene; EA, ethyl acetate; E, ethanol; M, methanol; P, piperidine; D, DMSO).

investigation of the solvent and substituent effects to be discussed in this and the following papers, a reliable evaluation of the "uncatalytic" rate constants is required (see Experimental Section).

The rate constants and the activation parameters for the unsubstituted 2- and 4-chloroquinoline isomers are reported in Table I.

Discussion

In order to detect some of the main factors involved in solvent effects on N-heteroaromatic reactivity, we have chosen solvents belonging to different types. With respect to polarity, such solvents (dielectric constants[12,13] at 25° are given in parentheses) range from toluene (2.38) to DMSO (48.5). Piperidine (5.80) is the most basic of the group, although DMSO also possesses some basic character.[11] Ethyl acetate (6.00) is about as polar as piperidine but is much less basic. Finally, methanol (32.6) is taken as a representative polar, hydroxylic solvent. Table II reports the rates in any given solvent relative to the "slowest" solvent, toluene.

Table II. Kinetic Solvent Effects Relative to Toluene at 86.5°[a]

Compound	k_{DMSO}/k_T	k_M/k_T	k_P/k_T	k_{EA}/k_T
2-Chloroquinoline	54.8	6.02	7.68	2.47
4-Chloroquinoline	1700	458	16.9	11.3

[a] The symbols k_T, k_{DMSO}, k_M, k_P, and k_{EA} refer to rate constants for the reactions in toluene, DMSO, MeOH, piperidine, and ethyl acetate, respectively.

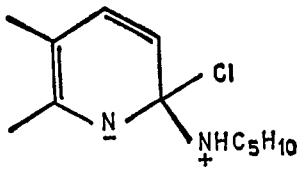
The kinetic solvent effect of DMSO may be quite complex depending on the other components of the medium (hydroxylic solvents) and the nature of the reactants.[14,15] In addition to the dipolar aprotic nature and to the general ability to solvate cations,[16] DMSO may become involved in specific H-bonding interactions as an electron donor. In the reaction under examination, such H-bonding interaction might be considered only in connection with the possible occurrence of base catalysis (assistance of proton abstraction from the amine nitrogen). However, in a subsequent section it will be seen that base catalysis is at best a minor effect in the more basic solvent piperidine and presumably is less important still in DMSO.

For a reaction involving neutral reactants and going through a charged transition state, the influence of the purely electrostatic effect as expressed by the dielectric constant should be important and, according to Hughes and Ingold's theory,[17] responsible for the observed reactivity order as shown by the solvent sequence DMSO >> ethyl acetate > toluene which is found to hold for both isomeric chloroquinolines (Table II). In fact, DMSO is known to deviate toward higher rates from Kirkwood's[18] linear free-energy dependence on the function $(D - 1)/(2D + 1)$ in nucleophilic aromatic substitution reactions.[19] From the data at hand, this effect appears to be present also in the heteroaromatic reactions under examination and is probably related to the ability of this solvent to solvate the cationic part of the reacting system at the point of attack by the amine reagent.

The reactivity order in the two other investigated solvents, piperidine and methanol, although intermediate between those in DMSO and ethyl acetate, cannot be accounted for by the dielectric properties alone even on a qualitative basis and will be discussed in a later section.

The α-Aza Effect. From the rate data at 86.5° reported in Table I a free energy of activation diagram can be set up (Figure 1) to show that 2-chloroquinoline is *less sensitive* to solvent effects than the 4-chloro isomer and that the reactivity range of the former is located on the *high side* of the latter. A similar observation was made in a previous paper[20] as based mainly on the kinetic effect of methanol relative to toluene. In view of the dual role of methanol as a polar as well as hydroxylic solvent, inclusion of DMSO and ethyl acetate in the present study is of interest because it indicates that the dipolar aprotic character of the solvent is indeed a factor in determining a different response of α and γ reactivities to solvent action. For example, the 4-chloro isomer is 11.3 times more reactive in ethyl acetate than in toluene, whereas a rate factor of 2.5 is involved in the 2-chloro isomer (Table II and Figure 1). Attack by the neutral amine reagent on the 2-carbon of the latter isomer results in the development of electrical charges of opposite sign at relatively short distance in a transition state assumed to be close enough to structure I. Consequently, a sort of "built-in" solvation[21,22] may set in whereby less stabilization by an "external" solvent is required.

(12) Landolt-Börnstein, "Zahlenwerte und Funktionen," Vol. II, Part 6, 6th ed, Springer Verlag, Berlin, 1959, p 618 ff.
(13) H. Suhr, *Ber. Bunsenges. Physik. Chem.*, **67**, 893 (1963).
(14) C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).
(15) J. Murto and L. Kääriäinen, *Suomen Kemistilehti*, **B39**, 40 (1966).
(16) A. J. Parker, *Advan. Org. Chem.*, **5**, 1 (1965).
(17) E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 665 (1941).
(18) J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934).
(19) H. Suhr, *Ber.*, **97**, 3277 (1964).
(20) G. Illuminati and G. Marino, *Chem. Ind.* (London), 1287 (1963).
(21) J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, **77**, 5051



I

With an aza-activated substrate the relative insensitiveness of α reactivity to solvent effects may be referred to as the *α-aza effect*.

Beyond the purely electrostatic mechanism of this effect, it was of interest to know whether the relatively high reactivity of 2-chloroquinoline as compared to 4-chloroquinoline even in nonpolar solvents could be possibly due to assistance from a cyclic H-bond formation with participation of a molecule of solvent (in alcohol) or of an extra molecule of amine (in nonhydroxylic solvents) in the transition state.[2,3,20] A test for this hypothesis is provided by the experiments reported in Table III where the second-order rate constant for the reaction of 2-chloroquinoline in toluene is shown to be independent of the concentration of piperidine as well as added methanol. Thus, at least within the scope of the investigated concentration range, this result is in contrast to the idea of the formation of such a particularly stable cyclic H-bonded transition state with the participation of an external proton donor. Although such a participation is thus unlikely, there remains a possibility of an intramolecular hydrogen bonding of the amine hydrogen to the aza group. The resulting four-membered ring, H-bonded cyclic structure would be quite strained, but could gain extra stabilization in a cyclic concerted process.[23] Examination of the kinetic hydrogen isotope effects (Table IV) in the reaction with N-*d*-piperidine again discloses a slight, but significant, difference between α and γ reactivity. While a small inverse effect ($k_H/k_D = 0.75$) is found at the γ position, practically no isotope effect accompanies the reaction at the α position, which is not inconsistent with an intramolecular nitrogen-to-nitrogen hydrogen transfer.

Table III. Effect of Added Methanol on the Rate of Piperidino Dechlorination of 2-Chloroquinoline in Toluene at 115.7°[a]

Piperidine, *M*	Methanol, *M*	$10^5 \times k$
0.0504	...	2.71
0.106	...	2.63
0.166	...	2.67
0.105	0.0500	2.61
0.112	0.100	2.66
0.170	0.100	2.70
		Av 2.66 ± 0.03

[a] Concentration 0.05 *M* in the substrate; *k* values in l. mole^{-1} sec^{-1}.

Table IV. Isotope Effects on the Piperidino Dechlorination Reaction in Toluene at 115.7° [a]

Compound	Piperidine, $10^5 \times k_H$	N-*d*-Piperidine, $10^5 \times k_D$	k_H/k_D
2-Chloroquinoline	2.73	2.80	0.98
4-Chloroquinoline	0.045	0.060	0.75

[a] *k* values in l. mole^{-1} sec^{-1}.

Methanol and Piperidine. A. Role of H Bonding. We have already made reference to the well-established evidence concerning the H-bonding interaction of hydroxylic solvents with heteroaromatic compounds.[4-10] Although both alcohols and amines present association phenomena in their respective gaseous or liquid states through O–H···O and N–H···N hydrogen bonding,[24-26] methanol is by far a better proton donor than piperidine as can be inferred from the $\Delta\nu$ values of the appropriate infrared bands in the H-bonding interaction with pyridine in CCl_4 solution.[27,28] For this reason, in the reaction with a basic N-heteroaromatic substrate, a rate-enhancing effect *via* H-bonding interaction between solvent and aza nitrogen is expected in the sense stated by Palit[29] and to a much greater extent in methanol than in piperidine solution. The significance of the free energy of activation with reference to specific solvation of polar transition states in hydroxylic solvents has been discussed in detail by Hudson.[30]

If we now inspect our results for 4-chloroquinoline as illustrated in the free energy of activation diagram of Figure 1 and compare them with those related to the reaction of *p*-chloronitrobenzene,[19] we note that in the N-heteroaromatic substrate the rate-enhancing effect follows the sequence methanol >> piperidine and that the rate-enhancing influence of the hydroxylic solvent relative to ethyl acetate is much greater with the better proton-acceptor quinoline derivative (in methanol) than with the nitrobenzene derivative (in ethanol).[31] These facts lead us to believe that H-bond interaction with the substrate is a major factor in the reaction of 4-chloroquinoline in methanol and that polarity alone of this solvent is not sufficient to explain all the results. Specific solvation also accounts for the fact that the second-order constant is quite insensitive to the addition of substantial excesses of piperidine (Table V) although on going from methanol to piperidine a fall-off factor of ~27 at 115.7° is observed.

The nucleophilicity of piperidine is decreased in alcoholic solution by hydrogen-bond interaction.[19,32] This effect is obviously present whatever substrate is being attacked, whether a nitro- or an aza-activated one. The relatively low reactivity of *p*-chloronitrobenzene in ethanol (Figure 1) does not necessarily

(1955); J. F. Bunnett, R. J. Morath, and T. Okamoto, *J. Am. Chem. Soc.*, 77, 5055 (1955).
(22) See ref 2, pp 308–310.
(23) W. Luck, *Naturwissenschaften*, **52**, 25, 49 (1965).
(24) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960.
(25) R. F. Hudson and I. Stelzer, *J. Chem. Soc., Sect. B*, 775 (1966); J. Feeney and S. M. Walker, *ibid.*, 1148 (1966).
(26) R. N. Jones and C. Sandorfy in "Chemical Applications of Spectroscopy," W. West, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p 247.
(27) A. M. Dierkx, P. Huyskens, and Th. Zeegers-Huyskens, *J. Chim. Phys.*, **62**, 336 (1965); see also ref 9.
(28) R. E. Dodd and G. W. Stephenson in "Hydrogen Bonding," D. Hadzi, Ed., Pergamon Press Inc., New York, N. Y., 1959, p 177 ff.
(29) S. R. Palit, *J. Org. Chem.*, **12**, 752 (1947).
(30) R. F. Hudson, *J. Chem. Soc., Sect. B*, 761 (1966).
(31) The difference in the alcohols under comparison (methanol and ethanol) does not seem to have any significant effect in this case, since W. Greizerstein and J. A. Brieux [*J. Am. Chem. Soc.*, 84, 1032 (1962)] found similar rate constants for the piperidino dechlorination of *p*-chloronitrobenzene ($10^7 \times k$ at 75°, *k* in l. mole^{-1} sec^{-1}: methanol, 35.8; ethanol, 38.2).
(32) J. Miller and A. J. Parker, *ibid.*, **83**, 117 (1961).

Table V. Piperidino Dechlorination in Toluene–Piperidine and Methanol–Piperidine Mixtures at 115.7° [a]

Solvent other than piperidine	Piperidine, M	$k_\psi \times 10^5$	$k \times 10^5$
	2-Chloroquinoline		
Toluene	0.150	...	2.67
	0.810	2.12	2.94
	1.620	5.36	3.71
	3.442	17.80	5.79
Methanol	0.150	...	15.0
	1.620	19.7	13.9
	2.673	32.1	13.7
	3.442	43.3	14.2
None	10.03	124.7	14.1
	4-Chloroquinoline		
Toluene	0.150	...	0.055
	1.619	0.150	0.103
	3.442	0.445	0.147
Methanol	0.150	...	10.0
	1.214	13.6	11.2
	1.822	17.5	11.0
	3.442	33.9	11.2
None	10.03	3.31	0.375

[a] Concentration 0.05 M in substrate; k_ψ values in sec^{-1}; k values in l. $mole^{-1}$ sec^{-1}.

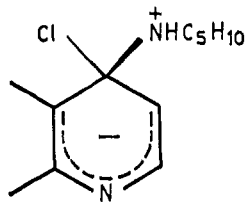
indicate complete absence of specific ethanol–substrate interaction (rate enhancing) because there is a compensating effect due to the ethanol–nucleophile interaction (rate depressing). Therefore what we can say is that the alcohol–substrate interaction is characteristically stronger with the aza-activated substrate.

Going to the 2-chloro isomer, we find that methanol here becomes much less effectively rate enhancing (Figure 1), which is consistent with the fact that 2-chloroquinoline is a weaker base than 4-chloroquinoline.[33] Furthermore, the observed solvent sequence in this case is piperidine $\gtrsim$ methanol and can be explained as a combination of the diminished H-bonding effect of the hydroxylic solvent, of the reactivity range-reducing α-aza effect, and of a small base-catalysis effect in piperidine solution to be discussed further on.

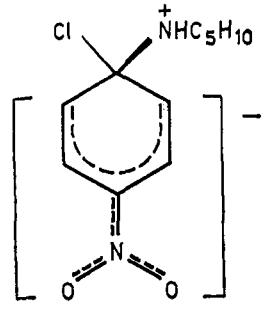
In the above we have assumed that H bonding roughly parallels the basic character of the proton acceptor and noted that the rate-enhancing influence of the hydroxylic solvent by specific solvation can be related to the proton-acceptor ability of the substrate in the ground state. However, we wish to point out that the observed correlation may be somewhat fortuitous since the rate-enhancing effect depends on the difference in the state of specific solvation between transition and ground states. The reactive substrates give rise to different situations in their respective transition states, as shown below.

In the reaction of 4-chloroquinoline the electron delocalization *toward the nitrogen atom* required by a structure of type II can be assisted quite effectively by the solvent according to Palit's concept.[29] This contributes to the observed efficiency of methanol as proton donor with this substrate.

With 2-chloroquinoline, where an α-aza effect is operative as predicted by structure I, the negative charge is partly neutralized "internally" and a weaker interaction with the solvent should result. This is probably an important factor in reducing the efficiency of H bonding with methanol in this case.



II



III

Finally, in the reaction of *p*-chloronitrobenzene the electron charge is delocalized *toward a p-nitro group* (formula III), but is more dispersed than in the case of 4-chloroquinoline. This factor should contribute to the observed apparent lack of rate-enhancing specific solvation in the nitro-activated substrate.

In summary, from the above it appears that the observed reactivities in a hydroxylic solvent are consistent not only with the properties of the substrates in the ground states but also, and more fundamentally, with the expected differences between ground and transition states with respect to specific solvation effects.

B. Role of Base Catalysis. The subject of base catalysis in the reaction of amines with nitro-activated aryl halides has been reviewed recently.[34,35] In general, the chlorides are subject to mild or no catalytic effects as shown in investigations at low or moderately low concentrations in amine.

Our data show that in toluene solution the observed second-order rate constant for the reaction of 2-chloroquinoline is independent of the concentration of piperidine in the range 0.05–0.17 M in this reagent (Table III). This result is also consistent with the absence of positive isotope effects (Table IV). When the concentration is increased more substantially, the observed rate constant also increases. Under pseudo-first-order conditions, the catalytic rate expression can be written in the form

$$k_\psi = k'[\text{amine}] + k''[\text{amine}]^2$$

However, a plot of log k_ψ *vs.* log [piperidine] using the data reported in Table V for toluene solutions failed to yield a straight line, and gave an upward curved line instead, in the whole concentration range up to 10 M (neat piperidine). This is interpreted as a possible combination of a mild base catalysis and a medium effect.

It seemed of interest to have a rough estimate of the kinetic significance of base catalysis in *neat piperidine*. Comparison of piperidine as solvent with ethyl acetate having a closely similar dielectric constant but much less basic character results in rate factors of 1.5 and 3.1 (Table II) for 4-chloro- and 2-chloroquinoline, respectively.

Small factors such as these hardly deserve detailed discussion. We only wish to note that a larger base-catalysis effect for the 2-chloro isomer is not required

(33) See ref 2, p 288.

(34) S. D. Ross, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

(35) J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, **87**, 3875 (1965).

by an intramolecular hydrogen transfer (see above); it probably means that some of the molecules seek assistance to proton abstraction from the solvent in neat piperidine. The purely electrostatic, nonhydrogen-bonded α-aza effect might imply that the N–H bond is less loosened in the rate-determining step and that more molecules obtain assistance from a base than in the case of the 4-chloro isomer. However, there is no firm experimental basis to settle such mechanistic details as yet.

Experimental Section

Materials. Dimethyl sulfoxide (Fluka) was purified by partial freezing; the liquid was decanted off, and the crystalline mass was melted and then fractionated through a 42-plate Todd column under reduced pressure, using a 10:1 reflux ratio. The central fraction boiling at 66–67° (6 mm), $n^{21}D$ 1.4783, was used. The water content, as determined by the Karl Fischer procedure, was 0.00408 g/l.

Ethyl acetate (Erba R.S.) was purified according to the procedure described by Gillo,[36] bp 77.3–77.5°.

Methanol,[37] toluene,[38] and piperidine[39] were purified as described in previous papers.

N-Deuteriopiperidine was prepared as described by Hawthorne[40] and purified by distillation over sodium under dry nitrogen, bp 107–108°. The isotopic purity was at least 95%, as deduced from the nmr spectrum.

Nearly all the chloroquinolines examined, as mentioned in the Results section, were samples available from previous work.[37,39,41] 2-Amino-4-chloroquinoline, mp 134–135°, was prepared as described in the literature[42] and purified first by chromatography through aluminum oxide and then by treatment with 5 *N* hydrochloric acid and subsequent precipitation with a 10% NaOH solution.

Kinetic Measurements. a. The general procedure adopted in this work has been described in previous papers of the series.[37,39] The reaction rates were determined by analyzing for the displaced chloride ion. The titration was carried out either by the Volhard method (indicator: ferric ammonium sulfate) or by the potentiometric method. In the latter case a Radiometer (Copenhagen) Model 22r potentiometer was used (silver indicator electrode, P401, and reference $Hg_2SO_4|K_2SO_4$ electrode, K601). When this method was used, heterogeneous quenched reaction mixtures were treated with sufficient acetone to dissolve any material.

The rate constants for the nonautocatalyzed reactions were obtained graphically from second-order or pseudo-first-order plots. In this case the average deviation from the mean *k* value is 2.5%.

In the case of the autocatalyzed reactions, the rate constants were reliably obtained from the linear portion of the second-order plots if the observed upward drift appears after the reaction has progressed to a good extent, say 30% or so. However, for more precocious effects, the "uncatalytic" rate constants were evaluated either by computation to zero amount of the reacted material[43] or from the initial rate of the reaction.[44] In any case, the resulting rate constants are less precise than those of the noncatalyzed reactions, the average deviation from the mean being 10%. All the rate constants were corrected for the density change of the solvent at the temperature of the experiment. Data for a typical kinetic experiment showing autocatalysis are reported in Table VI. Activation energies and entropies were calculated from the *k* values at three or four temperatures using the least-square method.

Table VI. Typical Kinetic Data for the Reaction of 4-Chloroquinoline with Piperidine in Methanol Solution[a]

Time, min	NH_4CNS, ml	% Reaction	x	log $(0.5a - x)/(b - x)$	$10^4 \times k_2$ (app)
0	5.02	0	0	0.3849	...
30	4.98	2.84	0.0009	0.3923	0.98
45	4.96	4.26	0.0014	0.3961	0.99
60	4.94	5.67	0.0019	0.4000	1.01
75	4.91	7.80	0.0026	0.4060	1.13
90	4.88	9.93	0.0033	0.4122	1.21
110	4.83	13.47	0.0045	0.4229	1.38
140	4.77	17.73	0.0060	0.4367	1.48
200	4.60	29.79	0.0100	0.4816	1.93
240	4.48	38.30	0.0129	0.5200	2.25
280	4.40	43.97	0.0148	0.5497	2.35
320	4.31	50.35	0.0169	0.5879	2.54
360	4.18	59.57	0.0200	0.6560	3.01
400	4.12	63.83	0.0215	0.6940	3.09
435	4.05	68.79	0.0237	0.7648	3.51
490	3.91	78.72	0.0265	0.8866	4.10
560	3.82	85.05	0.0286	1.0244	4.57
∞	(3.61)	(100)	0.0336	...	...

[a] Initial concentrations: 4-chloroquinoline, 0.0336 *M;* piperidine, 0.163 *M;* temperature 115.7°. "Uncatalytic" *k* values (l. mole^{-1} sec^{-1}): 1.08×10^{-4} (by the method of initial rates); 0.984×10^{-4} (by the extrapolation method).

b. Reactions in Ethyl Acetate. The kinetics in this case were complicated by some piperidinolysis of the solvent as a side reaction.[45] Blank experiments showed that appreciable amounts of ethanol were formed after about a week at 86.5°, as revealed by a vpc analysis of the reaction mixture. As a consequence, second-order kinetic plots for the reactions of 2-chloroquinoline showed downward curvatures after 55% reaction, and the rate constants were evaluated from the linear part of the plot. As to the 4-chloro isomer, which is subject to autocatalysis, the uncatalytic rate constant was calculated by the method of initial rates and, therefore, the effect of piperidinolysis could be neglected.

c. Reaction with N-Deuteriopiperidine. The general procedure was slightly modified. The reaction mixture was prepared by weighing out the desired amount of chloroquinoline into a 25-ml volumetric flask, introducing the calculated volume of N-deuteriopiperidine, and adding solvent to the mark. The exact concentration of piperidine in the reaction solution was then determined by titrating a sample of it with a 0.1 N H_2SO_4 solution.

The preparation of the solution and the filling of the tubes were carried out in a dry-nitrogen atmosphere.

Acknowledgment. The Esso Research Engineering at Linden, N. J., is gratefully acknowledged for a grant to G. S.

(36) L. Gillo, *Bull. Soc. Chim. Belges*, **48**, 341 (1939).
(37) G. Illuminati and G. Marino, *J. Am. Chem. Soc.*, **80**, 1421 (1958).
(38) G. Illuminati and G. Marino, *Atti Accad. Naz. Lincei, Rend., Classe Sci. Fis., Mat. Nat.*, [8] **38**, 525 (1965).
(39) G. Illuminati and G. Marino, *Ric. Sci.*, [2A] **35**, 449 (1965).
(40) M. F. Hawthorne, *J. Am. Chem. Soc.*, **76**, 6358 (1954).
(41) M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron*, **19**, 345 (1963).
(42) R. Hardman and M. W. Partridge, *J. Chem. Soc.*, 617 (1958).
(43) N. B. Chapman and C. W. Rees, *ibid.*, 1190 (1954).
(44) R. Livingston, "Investigation of Rates and Mechanisms of Reactions," S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p 122 ff.
(45) See, for instance, E. M. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950).