Piperidino Dechlorination in Chloroquinoline Series. Solvent Effects on Reaction Selectivity[1]

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Abstract: The *meta*-substituent effects on the rate of piperidino dechlorination of 2- and 4-chloroquinoline derivatives in three different solvents have been determined and compared. The reactions in DMSO and piperidine have closely similar selectivities in both series, whereas selectivity drops are observed in methanol which are attributed to H-bond interaction of this solvent with the aza group of the substrate. Unless specific solvation effects of this kind are at work, the α-chloro series is decidedly less selective than the γ-chloro series. A number of $\alpha:\gamma$ reactivity ratios for isomeric pairs and their dependence on solvent are given.

The relative reactivities of the positions α and γ to the aza group in a six-membered heteroaromatic ring have been shown to depend on the solvent in several ways. Characteristic features for these substrates are a rate-enhancing H-bond interaction especially important at the γ position and a reduced sensitivity to the solvent at the α position (α-aza effect).[2]

Reaction selectivities at the α- and γ-reactive centers as measured by the Hammett reaction constants have also been indicated as characteristic differential properties of these heteroaromatic substrates. Thus, piperidino dechlorination in piperidine[3] and methoxy dechlorination in methanol[4] have been found to be less selective at the α than at the γ-reactive center. Also, there was noticed a greater selectivity change at the latter than at the former center on going from one reaction to another.

Obviously, a comparison between the above reactions involves a change in reagent and solvent as well. In order to disentangle some of the factors responsible for the relative sensitivity to substituent effects under diverse experimental conditions, the present paper reports a study of the influence of the solvent on the structure–reactivity correlations in the piperidino dechlorination reaction.

Results and Discussion

It has been shown that the reaction constants, ρ, of Hammett-type free-energy relationships for use in nucleophilic heteroaromatic substitutions are most reliably evaluated when an appropriately selected group of substituents including electron-withdrawing substituents and the mildly electron-releasing alkyl groups is used.[4] Although the ρ–σ relationship for the piperidino dechlorination reaction will not be considered here, and only relative selectivities are needed for the present purposes, the substituents were selected according to the criterion stated above. The second-order rate constants of the reaction in three different solvents, piperidine, DMSO, and methanol, at 86.5° are reported in Table I. The influence of the substituents on the autocatalytic course of the reaction and the procedures for the evaluation of the uncatalytic rate constants have been discussed in the preceding paper.[2] Data for the reaction of 2-cyano and 2-acetyl-4-chloro members in methanol have not been collected because preliminary experiments showed anomalous kinetic behavior. This is probably due to the occurrence of some reversible addition reactions involving the unsaturated CN and CH_3CO groups in this solvent.[4,5] As in methoxy dechlorination,[4] the 2-chloro-4-R isomers instead behaved normally.

Table I. Rate Constants for the Piperidino Dechlorination of Substituted 2- and 4-Chloroquinolines in Piperidine, Dimethyl Sulfoxide, and Methanol at 86.5° [a]

Subst	Piperidine,[b] $10^5 \times k$	DMSO, $10^5 \times k$	MeOH, $10^5 \times k$
	2-Chloroquinolines		
H	3.11	22.1[c]	2.44[c]
4-Me	1.46	9.59	1.30
4-COMe	19.1	139[d]	8.41
4-CO_2Et	15.1	241[d]	13.6
4-CF_3	78.9	1420[d]	67.1
4-CN	211	1800[d]	111
	4-Chloroquinolines		
H	0.0878	8.84[c]	2.35[c]
2-Me	0.0244	2.86	1.52
2-COMe	0.831	70.9[d]	...
2-CO_2Et	0.970	125[d]	14.3
2-CF_3	11.1	1650[d]	62.3
2-CN	63.5	5070[d]	...

[a] k values in l. mole^{-1} sec^{-1}. [b] Data from ref 3. Some of the values therein reported have been revised slightly on duplicating the experiment. [c] Reference 2. [d] Calculated from the Arrhenius equation. The experimental 10^5k values in DMSO at diverse temperatures (°C given in parentheses) for the more reactive compounds are as follows: 2-chloro-4-acetyl 8.21 (40.0), 29.9 (60.0), 75.4 (75.2); 2-chloro-4-carbethoxy 15.4 (40.0), 56.1 (60.0), 132 (75.2); 2-chloro-4-trifluoromethyl 44.9 (25.0), 65.8 (30.0), 125 (40.0), 211 (50.0); 2-chloro-4-cyano 51.1 (20.0), 67.5 (25.0), 174 (40.0); 2-chloro-2-acetyl 6.45 (40.0), 18.7 (60.0), 42.9 (75.2); 4-chloro-2-carbethoxy 9.52 (40.0), 32.1 (60.0), 70.8 (75.2); 4-chloro-2-trifluoromethyl 66.7 (20.0), 85.5 (25.0), 115 (30.0), 215 (40.0), 320 (50.0); and 4-chloro-2-cyano 225 (20.0), 389 (30.0), 661 (40.0).

The reaction selectivities in DMSO and in methanol relative to those in piperidine[6] for both 2-chloro- and

(1) Nucleophilic Heteroaromatic Substitution. XXVI. Work carried out under a CNR (Rome) research contract at the Universities of Rome (G. I.) and Trieste (F. G. and G. M.) on the basis of a conjoint program. Presented by G. I. at the Gordon Conference on the Chemistry of Heterocyclic Compounds (New Hampton, N. H., July 4–8, 1966).

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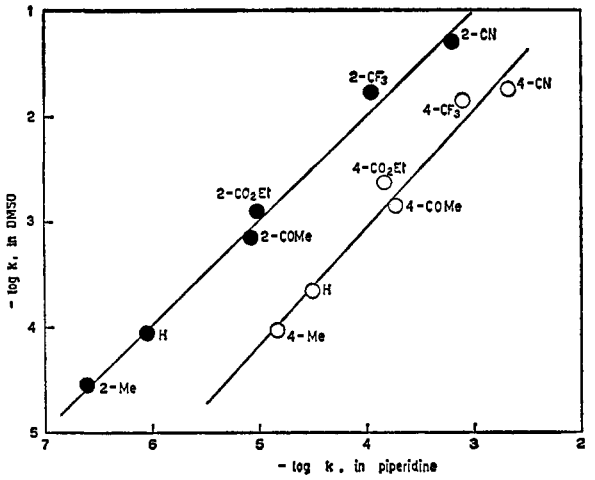

Figure 1. Free-energy correlations in the piperidino dechlorination of 2-chloroquinolines, O, and 4-chloroquinolines, ●; reaction selectivities in DMSO relative to piperidine (slopes, 1.12 and 0.99, respectively).

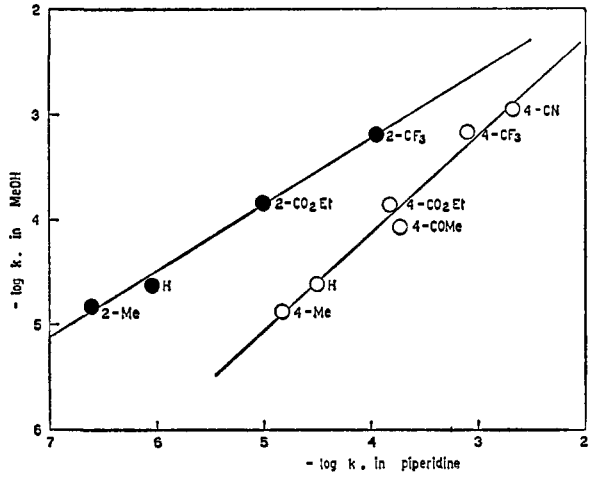

Figure 2. Free-energy correlations in the piperidino dechlorination of 2-chloroquinolines, O, and 4-chloroquinolines, ●; reaction selectivities in methanol relative to piperidine (slopes, 0.93 and 0.63, respectively).

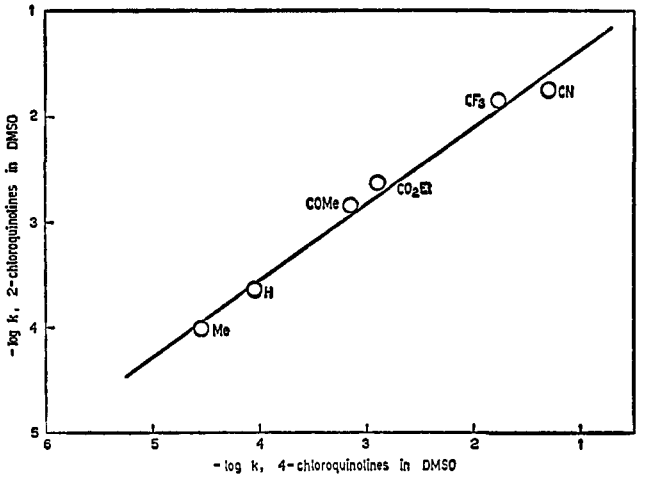

Figure 3. Free-energy correlation in the piperidino dechlorination of 2- and 4-chloroquinolines; reaction selectivity at the α position relative to that at the γ position in DMSO solution (slope, 0.73).

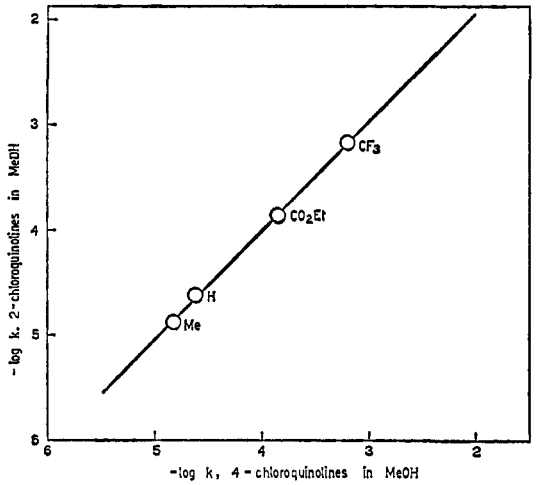

Figure 4. Free-energy correlation in the piperidino dechlorination of 2- and 4-chloroquinolines; reaction selectivity at the α position relative to that at the γ position in methanol solution (slope, 1.04).

4-chloroquinoline series can be deduced from Figures 1 and 2. Despite the different polar character, DMSO has a surprisingly small effect on the intensity of transmission of the substituent effects when the reactive center is at position 4, the slope of the line being in this case 0.99. When the reactive center is at position 2, the reactivities in this solvent are slightly more spaced than in piperidine, the slope of the corresponding line being 1.12. The influence of methanol is in the opposite direction, since for both series the selectivity tends to decrease. The effect is slight in the 2-chloroquinoline series; however, it becomes fairly large in the 4-chloroquinoline series. In the latter series the reaction selectivity is appreciably smaller in methanol than in piperidine solution, the slope of the line being 0.63.

We attribute this selectivity drop in alcohol to H-bond interaction with the aza group of the substrate. Since this interaction has been shown[2] to be more important in the reaction of 4-chloroquinoline relative to that of the 2-chloro isomer, the selectivity drop should be larger in the 4-chloroquinoline series, as is indeed observed. Why a selectivity drop should result from solvent–substrate H bonding can be rationalized in terms of the influence of the substituents along the series. As the substituents become more electron releasing, and the corresponding σ constants change toward more negative values, the electron-donor ability of the substrate increases, and so also does the contribution of the rate-enhancing H-bonding effect. This gradual change will lower the slope of the line for the reaction in alcohol relative to that, say, in piperidine where this H-bonding effect is not important.

As a result of the influence of the solvent and other reaction conditions on reaction selectivity, there are observed changes in the selectivity of one reaction series relative to the other as well as changes in the dependence of the α:γ reactivity ratios on the substituents located *meta* to the reactive center. With the data at hand, the following generalizations are possible. In the reaction with piperidine the 2-chloroquinoline series is less selective than the 4-chloroquinoline series

(6) Piperidine is used as a reference solvent on an arbitrary basis. The reactions in this solvent are susceptible to base catalysis, even though this effect is small in the case of the type of substrates under examination.[2]

Table II. $\alpha:\gamma$ Reactivity Ratios[a]

meta Subst	k_α/k_γ at 86.5°: Piperidine	DMSO	MeOH
Me	59.8	3.35	0.855
H	35.4	2.51	1.03
COMe	22.9	1.96	...
CO_2Et	15.6	1.92	0.949
CF_3	7.13	0.866	1.08
CN	3.32	0.355	...

[a] Rate of a given *meta*-substituted 2-chloroquinoline relative to a similarly *meta*-substituted 4-chloro isomer.

if there are no important solvent–substrate specific interactions. This is the case when piperidine[3] and DMSO (Figure 3, slope, 0.73) are used as solvents. In methanol, where solvent–substrate H bonding occurs, the two series display nearly the same selectivity (Figure 4, slope, 1.04).

The $\alpha:\gamma$ reactivity ratios for a number of isomeric pairs (2-Cl-4-R and 4-Cl-2-R derivatives) are reported in Table II.

When reactions of different charge types are compared (see introductory section) obviously the effect of the negative charge of the nucleophile in the former reaction is superimposed on that of the solvent. However, also in this case change from the nonhydroxylic solvent (amine) to methanol reflects the characteristic effect of solvent–substrate H bonding because the selectivity of the methoxy dechlorination reaction (in MeOH) relative to the piperidino dechlorination (in piperidine) is smaller with the 4-chloro- (1/0.95) than with the 2-chloroquinoline (1/0.67) series,[3,7] a result which is analogous to that illustrated in Figure 2 as discussed above.

Experimental Section

Materials. Methanol,[8] piperidine,[3] and dimethyl sulfoxide[2] have been purified as described in the given references.

All the chloroquinolines examined were available from previous studies.[3,4,8]

Kinetic Procedure. The kinetic experiments were carried out using the same procedure described previously.[1,2] For the treatment of the rate data for the reactions subject to autocatalysis, see the preceding paper.[2]

(7) We must note that in ref 3 the slopes of the lines of Figure 2 thereof are in reciprocal order with respect to those herein reported where piperidine is used as the reference solvent.

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The Piperidino Dechlorination and Methoxy Dechlorination of 6- and 8-Alkyl-4-chloroquinolines. Steric Hindrance to Specific Solvation[1]

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Abstract: Kinetic data for the reaction of 6- and 8-alkyl-substituted 4-chloroquinolines with piperidine in four different solvents and with sodium methoxide in methanol have been obtained and compared. The *t*-butyl group located at the position *peri* to the aza group is found to cause rate-depressing effects and significant increases in the energy and entropy of activation when the solvent is hydroxylic (methanol) whereas only minor changes are observed in aprotic or poor proton-donor solvents (toluene, DMSO, and piperidine). The results are interpreted in terms of steric inhibition of specific solvation (H bonding).

The reactivity in chloroquinoline, especially when the reactive center is at the γ position, is specifically affected by hydroxylic solvents. Hydrogen-bond interaction of these solvents with the aza group has been held responsible for a rate-enhancing effect[2] and for a change in sensitivity to substituent effects.[3]

Specific solvation can be hindered by the proximity of bulky groups.[4,5] In particular, steric hindrance to solvation may play a role in the base-weakening effect of pyridine in water[6] by two *t*-butyl groups located in the α positions. Likewise, H-bond interaction with the aza group of the quinoline ring is expected to suffer from steric hindrance when bulky groups occupy positions adjacent to it, either α or *peri*. Evidence for rate-depressing effects caused by steric hindrance of solvation has recently been found in the methoxy dechlorination of *peri*-substituted 2-chloroquinolines[7] and in the piperidino dechlorination in methanol of α-alkyl-substituted 4-chloropyrimidines.[8]

Since the 4-chloroquinoline series is particularly sensitive to H-bonding effects,[2] in order to obtain further

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