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THE REACTIVITIES OF 2- AND 4-CHLOROQUINOLINES WITH METHOXIDE, ARYLSULFIDE AND PHENOXIDE IONS IN METHANOL

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AMONG charged nucleophilic reagents, methoxide and thiophenoxide ions are of special interest since their relative reactivities in aromatic substitution usually are in the reverse order with basicities (1). With the exception of one substrate, p-nitrofluorobenzene (2), toward which the two reagents are equally reactive, the thiophenoxide ion is generally the much more reactive with nitro-activated halobenzenes (3). Furthermore, both reagents have been found to react faster with p-chloronitrobenzene than with the ortho isomer (4). In the course of our current studies (5) on nucleophilic substitutions, corresponding reactivity relationships have now been investigated with aza-activated six-membered ring substrates.

Second-order rate constants for the reaction of 2- and 4-chloroquinolines with sodium p-thiocresoxide in methanol at 86.5° are reported in Table I and compared with previously reported (5) methoxydechlorination data. The p-thiocresoxide reagent was prepared by mixing a weighed sample of the free thiol with nearly an equivalent amount of sodium methoxide; the reaction was followed by Vohlard analysis of the released chloride ion. Unlike nitro-activated halobenzenes, the reaction of chloroquinolines with the

p-thiocresoxide reagent is vulnerable to two kinds of complications arising from the equilibrium :

$$ArS^- + MeOH \rightleftharpoons ArSH + MeO^-$$

TABLE I

A Comparison of the Reactivities of Chloroquinolines with Methoxide and Arylsulfide Reagents[a]

Substrate	CH_3O^-	p-$MeC_6H_4S^-$	k_{RS^-}/k_{RO^-}
2-Chloro	6.73	1.68	0.24
4-Chloro	6.30	16.04	2.50

a $10^4 k$ (l x $mole^{-1}$ x sec^{-1}), reactions in methanol at 86.5°. Reactant concentrations were 0.04 M in chloroquinoline and 0.08 M in nucleophile.

These are the sensitivity to autocatalysis promoted by ArSH and related to the presence of the basic ring-nitrogen and the competition by MeO^- due to the relatively high reactivity of this reagent in the present substrates. The importance of autocatalysis in the case of 4-chloroquinoline is shown by the fact that in the absence of any added sodium methoxide, free thiol uses up 94% of the chloroheterocycle in 22 mins. at room temperature (initial concentrations : 0.055 M in 4-chloroquinoline and 0.130 M in free thiol). The less basic 2-chloroquinoline is much less sensitive to autocatalysis, in accordance to what is found in aprotic solvents (6). Although the above equilibrium is strongly shifted to the right (2), the effects of traces of free thiol have been ascertained; they have been kept to a

minimum in the presence of 0.14 M 4-picoline as a base of low nucleophilicity but still capable to compete effectively for the proton with the aza-substrate. Use of slight excesses (5%) of sodium methoxide as a stronger base resulted in partial methoxydechlorination; this was shown by V.P. Chromatography and attributed to the second complication referred to above.

Table I shows that, like the chloronitrobenzenes, a chloroquinoline reacts faster with sodium p-thiocresoxide when the chloro group is para to the aza-group than when it is ortho, the factor involved being about 10. However, a striking different behavior is noted in the much lower k_{RS^-}/k_{RO^-} ratio which is 2.5 for 4-chloroquinoline and 0.24 for 2-chloroquinoline. In p-chloronitrobenzene this ratio is 38 and in 2,4-dinitrochlorobenzene is 1950. In no case the reaction of a chloronitrobenzene derivative with sodium methoxide has so far been found to be faster than that with sodium thiophenoxide.

From the above data, it is apparent that the k_{RS^-}/k_{RO^-} ratio depends to a large extent on the nature of the aromatic substrate. In particular, it depends not only on the degree of activation of the substrate and on the displaced group (3) but probably on the type of activation as well.

On both experimental (3,7) and theoretical (8) grounds there is little doubt about the importance of polarizability as a major factor in determining the commonly encountered, though variable, high k_{RS^-}/k_{RO^-} ratios. Were thermodynamic carbon affinities mainly responsible (9) for the usual reactivity order $RS^- > RO^-$ the peculiar behavior of chloroquinolines would be difficult to understand. There is some indication, however, that carbon affinities roughly parallel basicities (hydrogen affinities) (10). In the latter

case, lower k_{RS^-}/k_{RO^-} ratios could be explained in terms of the intermediate complex mechanism (10 a).

Preliminary data have shown that, despite the above peculiarities concerning the k_{RS^-}/k_{RO^-} ratios in the present systems, phenoxide ion reacts in the order $MeO^- > PhO^-$ as previously found with halogenonitrobenzenes (11). This follows from the fact that the apparent 2nd-order rate constants (as observed with a reaction solution made up as follows : chloroquinoline, 0.04 M; phenol, 0.08 M; sodium methoxide, 0.08 M) were found to be in the order of 1×10^{-4} l x $mole^{-1}$ x sec^{-1} at 86.5°, i.e., smaller than those corresponding to methoxydechlorination ($\sim 6.5 \times 10^{-4}$, see Table I) with either 2- or 4-chloroquinoline; furthermore, product analysis by V.P.Chromatography showed that practically no phenoxy derivative was formed and only methoxydechlorination had occurred. Since the equilibrium :

$$PhO^- + MeOH \rightleftharpoons PhOH + MeO^-$$

in the used concentrations is nearly half-way shifted toward the right (12) and a substantial concentration of PhO^- must be present in the solution, we conclude that the phenoxide ion is markedly less reactive than the methoxide ion. It is of interest to note that in the absence of sodium methoxide, free phenol, like p-thiocresol, also reacts with 4-chloroquinoline by a supposedly autocatalytic course. The effect with this reagent is, however, markedly less pronounced since 90% reaction was attained only in 4,600 mins. at 86.5°.

A full account of this work will be published in due course.

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