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REACTION AT C-9 OF ACRIDINE DERIVATIVES. PART XVI[1]. KINETICS OF CONDENSATION OF 9-CHLOROACRIDINE WITH SOME PHENOLS

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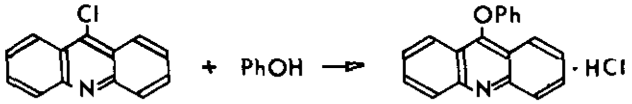
Abstract - The kinetics of reactions of 9-chloroacridine with p-chlorophenol, phenol and p-cresol in CCl_4 at 25 - 60°C was found to be approximate to the second order equation under the conditions used. The most reactive was p-chlorophenol, less phenol and even a little less p-cresol. The reaction occurs through the intermediate, i.e., a hydrogen bonded complex, 9-chloroacridine.phenol, formed in the first reversible reaction step (equations (3) and (4)). The different reactivities observed for variously substituted phenols are due to different strengths of hydrogen bonds formed by them with the acridine nucleus decreasing in this way the electron density at C-9 atom.

The condensation reaction of 9-chloroacridine with phenol is used as the first step of synthesis of 9-aminoacridine derivatives among which numerous are biologically active[2].



(1)

9-Phenoxyacridine may be subsequently condensed with the appropriate amine hydrochloride. Some authors[3,4] suggest that 9-phenoxyacridine is also present in the reaction mixture when 9-chloroacridine is directly condensed with amines in phenol as a solvent.

The intermediate product of reaction (1) was isolated and assumed to be 9,9-diphenoxyacridan hydrochloride. More recently, however, the reinvestigation has proved it to be 9-phenoxyacridine hydrochloride complexed with phenol[5].

The aim of our studies was to examine kinetics of the reaction (1) with particular emphasis put on the influence of substituents in the phenol nucleus on the reaction rate. The reaction was carried out in the carbon tetrachloride as a solvent at 25 - 60°C. The concentration changes were determinated by titration of chloride anions liberated in the reaction course according to Mohr. Gramstad[6] and Aarna[7] suggested that a very weak hydrogen bond was formed between phenol and carbon tetrachloride moieties. On the other hand, other authors[8] were of opinion that the previous statement was not convincing because of the lack of confirmation. Therefore, we assumed that the influence of the solvent on the kinetic parameters of this reaction was minor and might be neglected.

Table 1

Second order rate constants for the reaction of 9-chloroacridine with phenol in carbon tetrachloride at 45°C.

9-Chloroacridine mole . dm^{-3}	Phenol mole . dm^{-3}	$10^4 \times k_{II}$ dm^3. $mole^{-1}$. s^{-1}
0.111	0.888	1.94 (0.07)
0.116	0.646	1.94 (0.20)
0.058	0.469	1.93 (0.19)
0.200	1.595	2.03 (0.16)
0.102	1.630	1.88 (0.16)
0.056	0.896	1.93 (0.07)

Table 2

Second order rate constants for the reaction of 9-chloroacridine with various phenols: 9-chloroacridine concentration 0.06 mole.dm^{-3}, phenol - 0.47 mole.dm^{-3}.

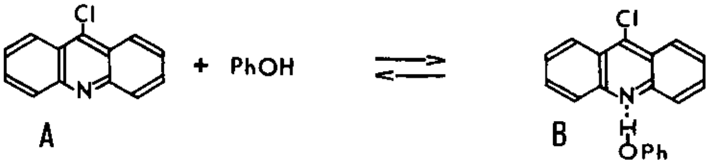
	$10^4 \times k_{II}$ dm^3.$mole^{-1}$.s^{-1}								E_a	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$
	25°	30°	35°	40°	45°	50°	55°	60°			
Phenol		0.85	1.20	1.68	1.94	3.05			50	99	-170
p-Cresol				1.30	1.80	2.40	3.01	3.95	46	100	-180
p-Chlorophenol	2.30	3.15	3.61	5.8	9.9				54	97	-140

E_a, $\Delta G^{\ddagger}$ - kJ.$mole^{-1}$.deg^{-1} $\Delta S^{\ddagger}$ - J.$mole^{-1}$.deg^{-1}

The reaction rate constants of 9-chloroacridine with phenol calculated according to the second order equation, are summarized in Table 1. Standard deviations in rate constants are given in parantheses.

A comparision of rate constants of the reactions with various phenols, given in Table 2, shows the following order of reactivity: p-chlorophenol > phenol ⩾ p-cresol, but the difference between rate constants of reactions involving phenol and p-cresol is very small and nears experimental error.

The observed reactivity order might be due to the different strengths of hydrogen bonds formed between phenols and 9-chloroacridine.



(2)

The formation of strong hydrogen bonds by phenols with both aliphatic and aromatic amines has been confirmed by spectrophotometric and calorimetric methods[9-15].
On the basis of spectrophotometrical investigation of equilibrium of reaction (2) involving corresponding phenol, 9-chloroacridine and a solvent we calculated equilibrium constants K and approximate ΔH values for the hydrogen bond complexes formed (Table 3).

Table 3

Equilibrium constants $K = [B]/[A][PhOH]$ for the reaction (2) and ΔH of hydrogen bond, calculated from absorption changes at 396 nm.

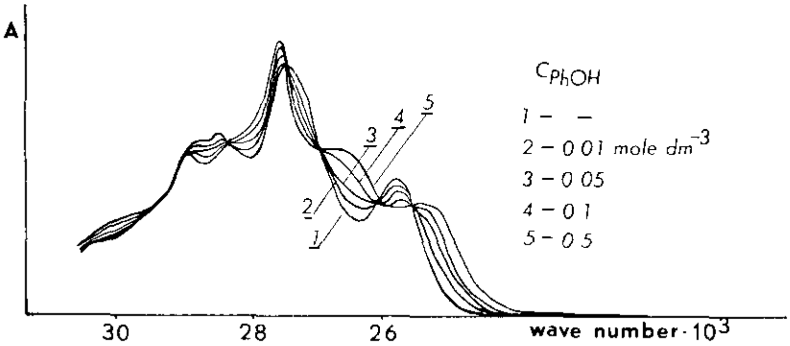
	25°	40°	55°	ΔH kJ . mole^{-1}
Phenol	36	22	12	-29
p-Cresol	29	17	10	-29
p-Chlorophenol	62	31	17	-34

The values of K and ΔH must be considered with some caution because the molar absorptions of the compounds A and B at 396 nm only slightly differ from one another (cf: Fig.1).

Our results can be compared with those reported by Lutskii and Klepanda[14] for acridine complexes with phenol and p-nitrophenol (ΔH's equal -6.7 kcal . mole^{-1}

and -7.9 kcal . mole^{-1}, respectively) and with ΔH values for methyl acetate complexes with phenol and p-chlorophenol (-5.4 and -6.7 kcal . mole^{-1}, respectively).

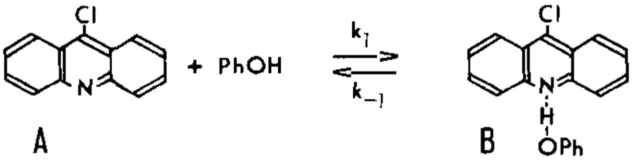
Fig. 1. Spectra of mixtures of 9-chloroacridine (concentration 2.10^{-5}mole.dm^{-3}) with various quantities of phenol in carbon tetrachloride at 25°C.



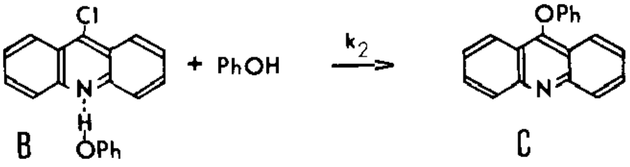
In spite of low accuracy of ΔH determination the observed differences between ΔH's values of hydrogen bonds of phenols examined are in agreement with the order of their acidity.

The formation of acridine - phenol hydrogen bond results in decrease of electron density at C-9 atom of the acridine ring proportionally to the hydrogen bond strength. In this way the highest reactivity of p-chlorophenol and the lowest that of p-cresol can be explained (the dependence of nucleophilic substitution rate at C-9 atom on the electron density at this atom was demonstrated in previous papers of this cycle[16,17]).

The reaction proceeds most likely according to the following scheme :



(3)



(4)

A contribution of the reaction A + PhOH —> C may be excluded on the basis of kinetic data for the reaction of 9-phenoxyacridine with amines[18]. This condensation was found to proceed many times faster in the presence of phenol and, on the other hand, phenol was reported to form a hydrogen bonded complex 9-phenoxyacridine.phenol which was susceptible to nucleophilic attack at 9 position. According to the equilibrium constants of reaction (2) (Table 3) and as we used phenol in excess $[PhOH] > [A] + [B]$, 9-chloroacridine was almost quantitatively bound with phenol to form complex B ($[B] > [A]$). In view of the above we could neglect the contribution of direct reaction.

The equations (3) and (4) form the consecutive reaction system with first equilibrium stage. The possibility of kinetic equation simplifications for the similar reaction schema depending upon the relative values of rate constants and concentrations used is described in the literature[19]. In this case, since the equilibrium reactions similar to (3) are very fast, we can write $k_{-1} \gg k_2 \cdot [PhOH]$. This results in the approximation of the second reaction step to be rate determining and the reaction (3) to be preequilibrium. So the kinetic equation can be simplified to give : $dC/dt = k_2 . [B] . [PhOH] = k_1 . k_2 / k_{-1} . [A] . [PhOH]^2$. However, as it was said above, in fact 9-chloroacridine is almost completely bound to form complex B, and hance we have $B \neq f([PhOH])$. Therefore, the reaction follows the second order kinetics, $dC/dt = k_2 [B] . [PhOH]$, what is in agreement with the first order of reaction with respect to phenol observed in the experiments.

Formal activation parameters listed in Table 2 are burdened with errors, resulting from (i) the experimental errors, (ii) the reduction of kinetic equation to a second order one.

Our results are proof that condensation of 9-chloroacridine with phenols proceeds under the conditions used approximately according to a second order equation mainly through the intermediate product, i.e. 9-chloroacridine - phenol hydrogen bond complex. **The reaction rate** is proportional to the strength of hydrogen bond formed in the complex, that is to the acidity of phenols.

ACKNOWLEDGEMENTS

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