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KINETICS OF N-OXIDATION OF COMPOUNDS OF THE QUINOLINE SERIES AND ISOMERIC BENZOQUINOLINES BY PERBENZOIC ACID IN CHLOROFORM AND AQUEOUS DIOXANE

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The kinetics of the N-oxidation with perbenzoic acid of 15 derivatives of quinoline and benzoquinoline in chloroform and 19 compounds in 50% aqueous dioxane at 20, 25, 30, and 35°C were subjected to a comparative study. The rate constants, parameters of the Arrhenius equation, and the activation energies for the N-oxidation of the indicated monoazines were determined. A scale of the reactivities of derivatives of the quinoline series and benzoquinolines was calculated within the framework of general perturbation theory.

The idea that the initial step in many reactions involving electrophilic and nucleophilic substitution in the monoazine series is coordination at the ring nitrogen atom of both a kinetically independent electropositive particle and the electropositive part of an ion pair has become a firmly established principle. It is evident that the reactivity of the monoazine will be determined essentially as a function of the character of such coordination, in the same way as the behavior of the free bases and conjugate acids [1].

For a better understanding of the peculiarities of the behavior of monoazines in the reactions indicated above we needed some kind of model reaction for which at least formal kinetics would be applicable. The N-oxidation of derivatives of the pyridine series is a prime reaction of this sort [2]. In connection with the fact that the literature does not contain kinetic data on N-oxidation and the fact that the nucleophilicities of derivatives of the quinoline series and benzoquinolines have not been calculated, it seemed of interest to investigate the kinetics of oxidation of the indicated monoazines by the method and under the conditions described in [2]. For this, we studied the kinetics of N-oxidation with perbenzoic acid of 15 derivatives of quinoline and benzoquinoline in chloroform and 19 compounds in 50% aqueous dioxane at 20, 25, 30, and 35°C.

It is essential to note that a direct relationship between the consumption of perbenzoic acid and the concentrations of the resulting N-oxides was established in [2-5].

At a molar ratio of the organic base to the peracid of ~1:0.5 the N-oxidation reaction was described satisfactorily by a second-order equation for unequal concentrations. The somewhat arbitrary selection of monoazines for the kinetic measurements was determined by the fact that the principal goal was to develop a general approach to the evaluation of the nucleophilicity of a monoazine with respect to the electron-deficient δ^+ (OH) group of the peracid within the framework of perturbation theory.

In the present research we determined the parameters of the Arrhenius equation and the activation entropies of the indicated heterocycles. We calculated a scale of the nucleo-

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TABLE 1. Rate Constants, Parameters of the Arrhenius Equation, and Activation Entropies for the N-Oxidation of Derivatives of the Quinoline Series in Chloroform

Compound	Substituent in the quinoline ring	pK_a from [13]	$K \cdot 10^3$, liters/mole-sec				E, kcal/mole	lg *pZ*	$-\Delta S^{\neq}$ cal/deg
			20°	25°	30°	35°			
I	4-CH_3	5,20	4,54	5,36	6,38	7,67	6,78	2,70	20,69
II	7-OH	5,48	3,48	4,68	5,97	7,89	10,0	5,00	10,20
III	6-OCH_3	5,06	4,50	5,17	5,89	6,47	4,42	0,96	28,69
IV	3-OCH_3	4,88	4,30	5,01	5,62	—	4,82	1,24	27,41
V	2,7-CH_3	5,02	3,52	4,03	4,52	5,13	3,32	0,04	32,87
VI	3-Br	2,69	4,40	5,49	6,78	8,46	7,92	3,55	16,82
VII	7-CH_3	5,08	1,21	1,48	1,74	2,12	6,78	2,14	23,26
VIII	6-OH	5,17	0,38	1,02	2,10	—	17,70	10,0	−12,60
IX	H	4,94	0,92	0,97	1,012	—	1,77	−1,72	31,84

philicities of the monoazines by means of the fundamental equation of perturbation theory for centers with varying electrophilicity characterized by the energy of the n-th vacant MO of the electrophile (E_n). Although there is no relationship between the basicity of the heterocycle and the rate of its N-oxidation (K), it seems legitimate to ascertain a correlation between K and E_m (the energy of the m-th occupied MO of the nucleophile), since it follows from Pearson's concept of hard and soft acids and bases that the selectivity of the nucelophile varies as a function of the hardness of the electrophilic center [6-8].

Combined data on the reaction rate constants, the parameters of the Arrhenius equation, and the activation entropies are presented in Tables 1-3, nucleophilicity scales are presented in Tables 4 and 5, and the relative reactivities of some of the investigated monoazines are given in Table 6. The reactivities of derivatives of quinoline and benzoquinoline in chloroform and aqueous dioxane are satisfactorily described by the equation

$$\log K_H/K_0 = E_m - 0.168\,H$$

The following conclusions can be drawn from the data presented in the Tables and in Figs. 1-3.

1. The same general kinetic principles that were previously ascertained for the pyridine series [2] are characteristic for the N-oxidation of derivatives of quinoline and banzoquinoline. Except for 4-aminoquinoline and 4-amino-2,3-benzoquinoline, the N-oxidation in chloroform and aqueous dioxane follows second-order kinetics (Fig. 2). The activation energies (E) range from 1 to 11 kcal/mole, while the activation entropies ($-\Delta S^{\neq}$) range from 8 to 42 cal/deg. The $\Delta S^{\neq}$ values overlap the opposed effect of E, and this evidently indicates the bimolecular character of the reaction.

The unexpectedly low reactivities of some of the investigated monoazines in the N-oxidation reaction should be noted. In particular, the annelation of pyridine leads to a decrease in the rate of N-oxidation. The K values for pyridine (pK_a 5.20), quinoline (pK_a 4.94), and 2,3-benzoquinoline (pK_a 5.60) at 25°C in aqueous dioxane are $4.74 \cdot 10^3$, $1.12 \cdot 10^3$, and $0.56 \cdot 10^3$ liters/mole-sec, respectively.

A similar anomalously low reactivity of the monoazine as a function of the character and position of the ring substituent is observed for VII-IX (see Table 1) and VI-IX (see Table 2).

An interesting dependence of K on the solvent polarity is displayed in the case of the highly basic 4-amino-2,3-benzoquinoline (pK_a 9.99). The rate constant changes by almost an entire order of magnitude on passing from chloroform ($K = 0.56 \cdot 10^3$ liters/mole-sec) to aqueous dioxane ($K = 0.062 \cdot 10^3$ liters/mole-sec).

The unexpected activating effect of substituents (bromo, hydroxy, alkoxy, and others) in the 3 position of the quinoline ring in N-oxidation in chloroform should also be noted.

2. The data on the reactivities of the investigated monoazines calculated for centers with variable electrophilicity (see Tables 4 and 5) show relatively good agreement with the order of nucleophilicity corresponding to "hard" center $E_n = +3$ (an orbitally controlled reaction).

As in [2], it is proposed that a δ^+(OH) group is generated from the EDA of the complex in the case of compounds for which good agreement between the experimental and calculated values is observed. Polarization with the formation of δ^-(OH) groups (a charge-controlled

TABLE 2. Rate Constants, Parameters of the Arrhenius Equation, and Activation Entropies for the N-Oxidation of Derivatives of the Quinoline Series (in 50% aqueous dioxane)

Compound	Substituent in the quinoline ring	pK_a from [13]	$K \cdot 10^3$ liters/mole-sec				E, kcal/mole	lg pZ	$-\Delta S^{\neq}$ cal/deg
			20°	25°	30°	35°			
I	H	4,94	1,07	1,12	1,17	1,20	1,62	−1,76	41,11
II	3-Br	2,69	2,40	3,51	4,93	7,50	13,57	7,50	−1,24
III	3-OH	4,30	1,18	1,98	3,14	—	17,96	10,47	−14,84
IV	3-OCH_3	4,88	1,05	1,92	3,35	—	21,81	13,28	−27,70
V	4-CH_3	5,20	3,31	3,80	5,15	6,49	8,23	3,61	16,51
VI	4-COOH	—	0,82	0,91	1,15	1,36	5,85	1,25	16,20
VII	4-CHO	—	1,12	1,23	1,40	1,63	5,08	0,82	29,32
VIII	4-NO_2	—	0,57	0,79	1,01	1,40	10,71	4,74	2,17
IX	4-NH_2*	9,17	0,72	0,93	1,15	1,43	8,60	3,28	8,91
X	6-Br	—	4,18	4,79	5,37	6,13	4,42	0,92	28,82
XI	6-CH_3	4,92	5,04	6,83	8,12	11,62	9,81	5,03	10,10
XII	6-OH	5,17	2,36	3,27	4,52	6,24	11,71	6,29	4,26
XIII	6-OCH_3	5,06	3,62	5,62	8,20	12,37	15,37	8,56	−6,09
XIV	7-OH	5,48	4,26	5,10	6,20	7,47	6,91	2,75	20,48
XV	8-OH	5,13	1,04	2,21	4,11	7,41	23,40	14,40	−33,30

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*Follows first-order kinetics.

TABLE 3. Combined Table of the Rate Constants, Activation Parameters of the Arrhenius Equation, and Activation Entropies for the N-Oxidation of Derivatives of Benzoquinolines in Chloroform and 50% Aqueous Dioxane

Compound	Benzoquinoline	Solvent*	pK_a from [13]	$K \cdot 10^3$ liters/mole-sec				E, cal/mole	lg pZ	$-\Delta S^{\neq}$ cal/deg
				20°	25°	30°	35°			
I	2,3-	chl	5,60	0,546	0,578	0,581	0,600	1192,2	−2,375	34,8
II	2,3-	ad	5,60	0,510	0,562	0,640	0,712	4574,0	1,106	23,43
III	4-Cl-2,3-	chl	—	0,461	0,520	0,609	0,670	5036,2	0,411	22,03
IV	4-Cl-2,3-	ad	—	0,552	0,595	0,668	0,668	2428,8	1,444	30,51
V	4-NH_2-2,3†	chl	9,99	0,505	0,560	0,578	0,580	2472,5	1,440	30,49
VI	4-NH_2-2,3†	ad	9,99	—	0,062	0,071	0,077	4567,5	−0,860	18,68
VII	5,6-	chl	5,15	—	0,609	0,792	1,250	8603,7	3,097	9,746
VIII	5,6-	ad	5,15	0,531	0,550	0,660	0,726	4265,3	−0,0951	24,34
IX	7,8-	chl	4,25	0,550	0,628	0,708	—	4736,4	0,2627	22,66

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*Abbreviations: chl is chloroform, and ad is 50% aqueous dioxane.

†Follows first-order kinetics.

reaction) is possible for compounds that deviate from this sort of dependence, for example VII-IX (see Table 4) and I-IV and XI (Table 5).

The method for the calculation of the nucleophilicities of monoazines relative to N-oxidation composed by means of the general equation of perturbation theory for centers with a variable electrophilicity makes it possible to qualitatively and quantitatively evaluate the relative reactivities of monoazines under conditions similar to those in N-oxidation.

A satisfactory correlation of the activities of heterocycles with respect to the nucleophile from the half-reduction potentials ($-E_{1/2}$, in volts) was established on the basis of the model reaction of S_NH substitution of azinium cations [9] with greater reliability than in [10].

We observed relatively good correlation between the E_m values calculated for the indicated monoazines (relative to pyridine) in N-oxidation and data on the $E_{1/2}$ values (r = 0.97) in the case of a reaction center hardness of $E_n = 0$ in chloroform and $E_n = +3$ in aqueous dioxane (see Table 6). Relatively good agreement between our calculated K and E_m values and the literature data [11], the calculation of the π-electron charge by the Hückel MO method, and the ^{15}N chemical shift determined by the NMR method is observed.

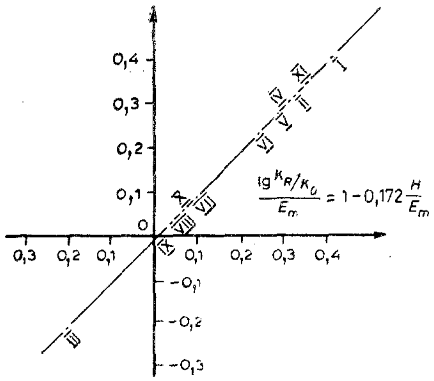

Fig. 1

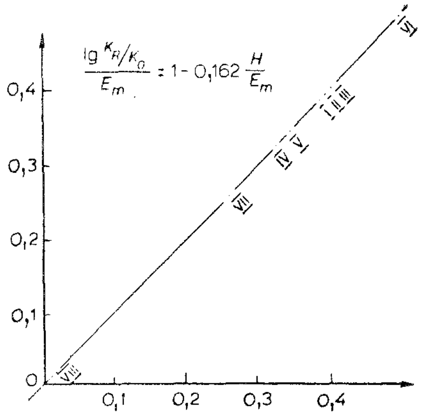

Fig. 2

Fig. 1. Dependence of the relative reactivities of derivatives of the quinoline series in the case of N-oxidation in 50% aqueous dioxane on the parameters of the Edwards equation (the numbering is the same as in Table 5).

Fig. 2. Dependence of the relative reactivities of derivatives of the quinoline series in chloroform on the parameters of the Edwards equation (the numbering is the same as in Table 4).

TABLE 4. Scales of the Reactivities of Quinoline Derivatives Calculated from the Equation for Centers with a Variable Electrophilicity (E_n) (chloroform, 25°C)

Compound	Substituent in the quinoline ring	-2β, eV	E_m	$-\Delta E_p$ ($E_n=0$)	$-\Delta E_p$ ($E_n=+3$)	$K \cdot 10^3$ liters/mole-sec	pK_a
I	4-CH_3	3,369	1,867	−0,24	6,25	5,36	5,20
II	6-OCH_3	3,366	1,828	−0,18	6,15	5,17	5,06
III	3-OCH_3	3,364	1,785	−0,11	6,05	5,00	4,88
IV	7-OH	3,379	1,775	−0,062	6,04	3,91	5,48
V	2,7-CH_3	3,366	1,672	0,109	5,814	3,66	5,02
VI	3-Br	3,329	1,47	0,49	5,46	5,49	2,69
VII	7-CH_3	3,367	1,32	1,01	5,28	1,58	5,08
VIII	6-OH	3,369	1,14	1,69	5,09	1,02	5,17
IX	H	3,367	1,08	1,96	5,03	0,97	4,94

TABLE 5. Scales of the Reactivities of Quinoline Derivatives Calculated for Centers with a Variable Electrophilicity (E_n) (50% aqueous dioxane, 25°C)

Compound	Substituent in the quinoline ring	-2β, eV	E_m	$-\Delta E_p$ ($E_n=0$)	$-\Delta E_p$ ($E_n=+3$)	$K \cdot 10^3$ liters/mole-sec	pK_a
I	6-CH_3	3,365	1,737	3,334	2,59	6,83	4,92
II	7-OH	3,373	1,68	3,461	2,48	4,80	5,48
III	4-NH_2	3,429	1,548	3,872	2,29	0,82	9,17
IV	6-OCH_3	3,366	1,545	3,741	2,24	4,15	5,06
V	4-CH_3	3,369	1,53	3,784	2,22	3,80	5,20
VI	6-OH	3,369	1,46	3,961	2,11	3,27	5,17
VII	8-OH	3,368	1,283	4,495	1,89	2,21	5,13
VIII	3-OCH_3	3,364	1,18	4,869	1,77	1,92	4,88
IX	H	3,365	1,15	5,00	1,74	1,75	4,94
X	3-OH	3,355	1,10	5,19	1,69	1,98	4,30
XI	3-Br	3,329	1,07	5,25	1,65	3,51	2,69

The calculated total energies ($-\Delta E_p$) of the $>N\rightarrow O$ bond for the examined monoazines for $E_n = +3$ in aqueous dioxane (ad) are in good agreement with the available experimental data on the ease of their reduction. In particular [12], the $-E_{1/2}$ values for the $>N\rightarrow O$ group for

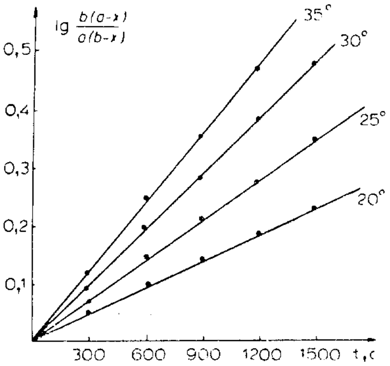

Fig. 3. N-Oxidation of 4-methylquinoline by perbenzoic acid in chloroform at a molar ratio of ~1:0.5.

TABLE 6. Dependence of the Calculated Nucleophilicities E_m and K on the Potentials for Half Reduction of Azinium Cations ($-E_{1/2}$, V), the π-Electron Charges, and the ^{15}N Chemical Shifts of Some π-Deficient Heterocycles

Heterocycle	π-charge [11] (HMO)	δ, ppm [11]	$-E_{1/2}$, V [9]	E_m (chl)	E_m (ad)	K·10^3 liters/mole-sec		$-E_p$	
						(chl)	(ad)	$E_n=0$ (chl)	$E_n=+3$ (ad)
Pyridine	−0,195	+68	1,27	1,20	1,60	1,32	4,74	1,45	1,80
Isoquinoline	−0,198	+68	1,05	1,07	0,80	1,05	1,75	2,02	1,46
Quinoline	−0,216	+78	0,84	0,99	0,50	0,97	1,12	2,72	1,44
2,3-Benzoquinoline	−0,254	+94	0,32	0,87	0,31	0,58	0,56	3,27	1,20
5,6-Benzoquinoline	−0,214	—	—	0,82	0,22	0,61	0,55	3,64	1,14
7,8-Benzoquinoline	−0,209	—	—	0,68	—	0,63	—	5,00	—

*Abbreviations: chi is chloroform, and ad is 50% aqueous dioxane.

pyridine, quinoline, and acridine are −1.364, −1.164, and −0.854 V, respectively. These facts evidently constitute evidence for the small effect on N-oxidation of the electron density on the nitrogen heteroatom and the large role of π conjugation of the substituent with the reaction center as a function of its character and its location in the ring.

EXPERIMENTAL

The low-boiling derivatives of monoazines with stable fractions were subjected to double fractional distillation, while the solid derivatives were recrystallized twice from alcohol. The monitoring of the purity of the compounds, the details of the kinetic measurements, and the method for the determination of the order of nucleophilicity are presented in [2]. The constants of the investigated compounds were in agreement with the literature values.

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