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HALOGEN REACTIVITIES. V. KINETIC STUDY OF DISPLACEMENT REACTIONS OF VARIOUS HETEROCYCLIC CHLORIDES WITH PIPERIDINE

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Previous papers in this series have discussed the kinetics of displacement by piperidine of halogen attached to pyridine (1), naphthalene (2), quinoline (3), and thianaphthene (4). The investigation has now been extended to chlorides of thiazole, benzothiazole, pyrimidine, quinazoline, pyrazine, quinoxaline, isoquinoline, and acridine. One of the principal objects of this work has been the elucidation of the effect of fusion of a benzene ring to another nucleus bearing a halogen substituent and one or more activating groups. Since the formation of the quinonoid transition state for a polycyclic nucleus should be accompanied by a relatively smaller decrease in aromaticity than in the parent monocycle, it is to be expected that the activation energy should be lowered by the addition of the fused benzene ring. This qualitative prediction is supported by the molecular orbital calculations of Dewar (5).

How well the prediction is fulfilled may be seen by examination of the activation energies listed in Table III. The following comparisons may be drawn: 2-chloropyridine *vs.* 2-chloroquinoline, 4-chloroquinoline *vs.* 5-chloroacridine, and 2-chloropyrazine *vs.* 2-chloroquinoxaline. In every case the fused benzene ring lowers the activation energy, and the average amount of lowering is roughly 3–4 kcal. with an average maximum possible deviation in the neighborhood of 1.5 kcal.

In the preceding paper of this series it was promised that additional evidence would be adduced in support of the contention that an important part of the activating influence of the aza group is inductive in nature. This may best be shown by comparison of 2-chloropyridine with 2-chloropyrazine and of 2-chloroquinoline with 2-chloroquinazoline. The addition of the "*meta*" aza group lowers the activation energies by 3.9 and 2.4 kcal. respectively.

One of the compounds treated here, 1-chloroisoquinoline, provides a means of testing the "strain" hypothesis which was tentatively advanced as an explanation of the equal reactivities of α- and β-bromonaphthalene (2). Since the polarizabilities of the 1–2 bonds in quinoline and isoquinoline should be very nearly equal, steric interference by the *peri*-CH group of the α-activated complex should cause the activation energy of 1-chloroisoquinoline to exceed that of 2-chloroquinoline. It has now been found however, that these two compounds have almost identical thermodynamic constants of activation and the strain hypothesis is therefore probably not applicable.

[1] Taken, in part, from the Ph.D. Thesis of K.R. Brower (June 1953).

[2] Taken, in part, from the M.S. Theses of John W. Way (June 1951) and William P. Samuels (June 1952).

TABLE I

SECOND ORDER RATE CONSTANTS

Compound	Solvent	Temp., °C.	k(l/mole-hr)
2-Chloroquinoxaline	Toluene	54.8	0.173 ± 0.002
		64.9	.281 ± .002
		77.8	.526 ± .014
		87.7	.852 ± .011
2-Chloropyrazine	Toluene	64.5	.0195 ± .0002
		75.0	.0359 ± .0004
		88.0	.0723 ± .0007
		92.0	.0858 ± .0008
		93.7	.0945 ± .0009
2-Chloropyrimidine	Pet. ether	50.2	1.30 ± .036
		58.5	1.79 ± .024
		64.1	2.55 ± .08
		77.8	4.67 ± .14
2-Chloropyrimidine	Alcohol	45.9	7.01 ± .12
		49.9	8.76 ± .09
		55.8	12.3 ± .3
		69.1	23.5 ± .3
4-Chloroquinazoline	Alcohol	0.0	992 ± 30
		−18.0	385 ± 12
		−30.0	198 ± 6
2-Chlorobenzothiazole	Toluene	45.7	.330 ± .006
		50.1	.431 ± .009
		55.0	.539 ± .011
9-Chloroacridine	Toluene	57.0	.0303 ± .0007
		80.0	.132 ± .003
		90.2	.223 ± .005

PSEUDO-UNIMOLECULAR RATE CONSTANTS

COMPOUND	TEMP.,°C.	k(hr^{-1})
2-Chlorothiazole	60.0	0.118 + .002
	65.2	.164 ± .003
	70.0	.216 ± .004
2-Chloropyridine	91.6	.0246 ± .0005
	96.1	.0334 ± .0006
	121.6	.144 ± .003
1-Chloroisoquinoline	20.8	.0098 ± .0003
	24.1	.0117 ± .0004
	50 1	.0806 ± .002
	69.0	.261 ± .007

It will have been noticed that comparisons have been drawn between compounds whose activation energies have been calculated from pseudo-unimolecular rate constants in some cases and bimolecular rate constants in others. This license is partially justified by the fact that 2-chloroquinoline was found to have the same activation energy (within the limits of experimental error) under both conditions (3). In order to determine the effect of changing the dielectric constant

TABLE II

4-CHLOROPYRIDINE

t(hrs.)	$\ln \frac{a}{a-x}$	k
	T° = 157.7°	
0	0.0030	
0.25	.0639	0.2436
.50	.1432	.2804
.70	.2135	.301
.90	.304	.335
1.10	.404	.364
1.30	.504	.364
1.50	.621	.394
	T° = 138.5°	
0	.0070	
.25	.0286	.0864
.50	.0592	.1044
.75	.0925	.1165
1.0	.1266	.1194
1.25	.1638	.1255
1.50	.2054	.1323
1.75	.248	.1375
2.0	.292	.1425
2.25	.341	.1840
	T° = 125.3°	
0	.0060	
1.0	.0714	.0654
1.5	.1071	.0674
2.0	.1424	.0682
2.5	.1840	.0712
3.0	.2263	.0734
3.5	.269	.0751
4.0	.305	.0747

of the medium more drastically than had been done before, rate constants and activation energies for 2-chloropyrimidine were measured in petroleum ether and in absolute ethanol solutions. Again it was found that no significant difference in activation energy exists, although the reaction in alcohol has an entropy of activation which is seven units above that for petroleum ether solution. This result is not surprising in view of the well-recognized influence of the dielectric constant on the rates of reactions which involve the formation of a polar activated complex from relatively non-polar reactants. Furthermore, Pearson (6) has shown that the entropy of activation should be more sensitive to variation of the dielectric constant than is the heat of activation.

TABLE III

ENERGIES AND ENTROPIES OF ACTIVATION

Compound	$\Delta E_{act.}$	$-\Delta S_{act.}$
2-Chlorothiazole (1)	13.8 ± 1.0	44.5
2-Chlorobenzothiazole in toluene	11.0 ± 1.0	44.6
2-Chloropyridine (1)	17.1 ± .8	42.2
2-Chloroquinoline (2)	13.8 ± .4	43.5
2-Chloropyrimidine in alcohol	10.6 ± .7	37.2
2-Chloropyrimidine in pet. ether	11.5 ± .6	44.4
4-Chloroquinazoline in alcohol	7.0 ± .5	37.2
4-Chloroquinoline (2)	16.1 ± 1.0	44.5
9-Chloroacridine in toluene	14.5 ± 1.0	40.5
1-Chloroisoquinoline	13.5 ± .3	44.7
2-Chloropyrazine in toluene	13.2 ± .3	50.4
2-Chloroquinoxaline in toluene	11.4 ± .5	46.2

In the preceding paper of this series (4) it was found by a comparison of β-bromonaphthalene with 2-bromothianaphthene that substitution of the —CH=CH— group by the isosteric sulfur atom lowers the $E_{act.}$ in the reaction with piperidine by almost 5 kcal. or 19.2%. Comparison of 2-chloropyridine with 2-chlorothiazole now reveals that the same substitution lowers the $E_{act.}$ by 3.3 kcal. or 19.3%, whereas in the benzo-compounds (2-chloroquinoline *vs.* 2-chlorobenzothiazole) the lowering is 2.8 kcal. or 20.3%. It would thus appear that the activating influence of sulfur substitution is a fairly constant fraction of the $E_{act.}$ of the parent cycle.

The behavior of 4-chloropyridine in its pseudo-unimolecular first order reaction with piperidine is worthy of special mention. In typical rate runs with this pair of reactants it was found that the reaction rate constant was continually increasing with time, as shown in Table II. After a short initial time when the rate is increasing rapidly the plot is linear up to about 60–70% reaction after which the increase in k gradually falls off. The reaction does not appear to be purely autocatalytic however, since the rate constant is not proportional to the first power of the salt concentration. It is thought to be significant in this connection that 4-chloropyridine exhibits other properties which are unique among the compounds examined. For example, it readily dimerizes to form 4-chloro-N-(4-pyridyl)pyridinium chloride and, from observations made during the isolation of 4-chloropyridine, this reaction also appears to be somewhat autocatalytic.

EXPERIMENTAL

Preparation of reagents. Piperidine was purified in the manner described previously (2). *2-Chloropyrazine* obtained from American Cyanamid Company was purified by distillation, $b.p._{.17}$ 50–52°. *2-Chloroquinoxaline* obtained from Merck and Co., Inc., was used without further purification, m.p. 46.3–47.9°. *2-Chlorobenzothiazole* obtained from Eastman Kodak Company was purified by distillation, $b.p._{.28}$ 135–136°. *2-Chloropyrimidine* prepared by T. E. Young (1) was purified by distillation, m.p. 65–67°. *4-Chloroquinazoline*, m.p. 93–95° was

prepared from 4-hydroxyquinazoline by the method of Bogert and May (7). *9-Chloroacridine*, m.p. 117–119°, was prepared from acridone by the method of Albert and Ritchie (8). *1-Chloroisoquinoline*, b.p.$_{14}$ 149–152° was prepared by the method of Elkson and Hamilton (9).

Pseudo-unimolecular rate determination procedure. See reference (2).

Second order rate determination procedure. Except for variations in concentration and solvent all but one of the compounds were treated by the method described previously (3). The exception is 4-chloroquinazoline which reacts with piperidine at a rate which is greater by several orders of magnitude than any previously encountered in this investigation. In order to make the analyses as nearly instantaneous as possible, the reaction was carried out in a conductance cell having a cell constant of approximately 0.1, and the concentration of piperidine hydrochloride was obtained by measurement of the conductance of the solution. Absolute alcohol was used as the solvent, and since the activity coefficients were found to deviate appreciably from unity even at concentrations below 0.005 *M* it was necessary to construct calibration plots of conductance *vs.* concentration for each temperature used. The data obtained in a typical rate determination appear below:

Initial concentrations: 4-Chloroquinazoline, 5×10^{-3}M; Piperidine, 10^{-1}M

t[a] (min.)	Conductance (mho × 10^4)	Concentration of piperidine hydrochloride × 10^3	k (l./mol. min)
0	1.895	1.20	—
0.5	2.025	1.32	8.0
1.0	2.140	1.38	6.5
1.5	2.245	1.47	6.7
2.0	2.365	1.57	7.0
3.0	2.545	1.69	6.5
4.0	2.710	1.83	6.7
5.0	2.880	1.97	6.7
6.0	3.030	2.07	6.5
7.0	3.165	2.18	6.5
8.0	3.290	2.28	6.5
9.0	3.410	2.37	6.5
10.0	3.495	2.44	6.4
12.0	3.665	2.58	6.3
14.0	3.850	2.72	6.3
16.0	3.990	2.83	6.2
20.0	4.230	3.05	6.2
24.0	4.420	3.22	6.2
28.0	4.550	3.35	6.1

[a] Measured from time of practical attainment of thermal equilibrium.

$k_{av.}$ = 6.4 l./mol. min.

mean dev. = 0.2

Estimation of precision of activation energies. The method previously described was used without modification.

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