a situation is not to be considered impossible since silicon is capable of expending its valence shell and the Si–O bond is a very stable linkage. The possibility of this chelation is now under investigation.

LAFAYETTE, IND. RECEIVED APRIL 24, 1951

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER LABORATORY, LEHIGH UNIVERSITY]

Halogen Reactivities. Certain Heterocyclic Iminohalide Systems[1]

BY THOMAS E. YOUNG[2] AND E. D. AMSTUTZ

Pseudo-first order rate constants have been determined for the reactions of 2-bromopyridine (I), 2-bromoquinoline (II), 2-chloroquinoline (III) and 2-chlorothiazole (IV) with piperidine at various temperatures in the range between 40.00 and 90.00°. The activation energies of these processes have been calculated. The reactions of 2-chloropyrimidine (V) and 2-chlorobenzothiazole (VI) with piperidine have been shown to proceed much more rapidly than the reactions of compounds I to IV, too rapidly, in fact, to permit quantitative rate measurements under similar temperature conditions. Comparison of rate constants calculated at a common temperature of 50.00° establishes the following order of decreasing activity: II > III > IV > I.

Introduction

The present work originated in a desire to discover, if possible some important common basis for the comparison of the various heterocycle systems. After critically surveying the many possible reactions which might be carried out on the various heterocycles for comparative purposes we felt that the most significant results might be obtained by determining the ease of replacement of nuclear halogen by nucleophilic reagents. It was felt that in this way evidence might be obtained as to the relative charge density on the various carbon atoms of the rings.[3]

The reaction rates of the halides of aliphatic and aromatic compounds with nucleophilic halogen–substituting reagents such as hydroxides, alkoxides, ammonia and amines have been widely studied.[4] Analogous kinetic studies of heterocyclic halogen compounds have been just as widely ignored. With the exception of rate constants and activation energy for the ammonolysis of 2-chlorobenzothiazole with liquid ammonia[5] there are no accurate quantitative measurements in this field.

It is the purpose of this paper to present the results of an investigation of the pseudo-unimolecular reaction rates of 2-bromopyridine (I), 2-bromoquinoline (II), 2-chloroquinoline (III) and 2-chlorothiazole (IV) with piperidine. Preliminary experiments have also been made with 2-chloropyrimidine (V) and 2-chlorobenzothiazole (VI), though their reaction rates with piperidine proved to be too rapid for accurate determination.

(1) Taken from the M.S. Thesis of T. E. Young, June, 1950.

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(3) It might appear at first that a study of hydrogen replacement by electrophilic reagents would yield information of a more practical nature. Electrophilic reagents are much more limited in their application however since they frequently add to heterocyclic systems of lower aromaticity, sometimes bring about ring opening and generally are ineffective in attacking certain ring positions. It is true however that the results of such a study could be stated in terms of relative electron density and it is possible that the relative densities so determined would not, in all cases, parallel those determined by the nucleophilic reagent method.

(4) For a most recent example see Berliner, Quinn and Edgerton, THIS JOURNAL, **72**, 5305 (1950).

(5) Lemons, Anderson and Watt, *ibid.*, **63**, 1953 (1941); **64**, 467 (1942).

Experimental

Preparation of Reagents.—Piperidine (VII) was obtained as 98% piperidine from Monsanto Chemical Co.[6] Specifications indicated a maximum of 1% pyridine. Purification was accomplished as follows: one liter of 98% piperidine was refluxed over three successive 100-g. portions of potassium hydroxide pellets for 2 hours for each portion. This partially dried product was made anhydrous and most of the pyridine removed by refluxing with excess sodium metal until the mixture became black with polypyridyls. The product was then distilled through a 50-cm. Widmer column, the fraction boiling at 105.5–105.8° at 760 mm. being collected. This material was stored over sodium wire and redistilled from sodium just prior to use.

2-Bromopyridine (I) was prepared in 60% yield by diazotization of 2-aminopyridine (Reilly Coal Tar product) using the method of Craig.[7] Purified 2-bromopyridine had b.p. 98.2–99.0° at 27.5 mm., $n^{20}D$ 1.5704 (lit.[8] b.p. 91–92° at 24 mm., $n^{20}D$ 1.5713).

2-Bromoquinoline (II).—Five grams of carbostyril (m.p. 199–200°, Eastman Kodak Co.) was placed in a 50-ml. standard taper flask fitted with an air condenser protected by a calcium chloride tube. Twenty-two grams of phosphorus oxybromide was added and the mixture heated on an oil-bath at 150–155° for four hours. The solution was cooled to room temperature, and 25 ml. of water added to decompose the excess phosphorus oxybromide. The resulting clear red solution was neutralized by addition of solid sodium bicarbonate, then made definitely basic by the addition of 10 ml. of 10% sodium hydroxide. The rose colored solid which separated was filtered off, dissolved in 50 ml. of ether, treated with one gram of Darco, and filtered. The resulting solution was evaporated leaving a residue of 5.80 g. (80.9%) of crude 2-bromoquinoline m.p. 42–44°. This material was distilled at 163–163°/16.5 mm. to yield a white product m.p. 47.0–49.0° (lit.[9] m.p. 48.4–48.8°).

2-Chloroquinoline (III) (Eastman Kodak, "White Label" product) was distilled at 90.0–91.4° (2 mm.), m.p. 35.2–36.4° (lit.[10] m.p. 37–38°).

2-Chlorothiazole (IV) was obtained in 66.4% yield from 2-aminothiazole (Matheson Co.) using the diazotization procedure of Ganapathi and Venkataraman.[11] This material had b.p. 34.0–34.5° (10 mm.), $n^{20}D$ 1.5503.

2-Chlorobenzothiazole (VI) (Eastman Kodak product) was purified by distillation, b.p. 90.0–91.5° at 4 mm.; $n^{20}D$ 1.6398.

2-Chloropyrimidine (V).—This material was prepared from 2-pyrimidone and 2-pyrimidone hydrochloride by pro-

(6) We gratefully acknowledge the kindness of the Monsanto Chemical Co. in supplying us with large quantities of piperidine.

(7) Craig, THIS JOURNAL, **56**, 231 (1934).

(8) den Hertog and Wibaut, *Rec. trav. chim.*, **51**, 381 (1932).

(9) Jansen and Wibaut, *ibid.*, **56**, 699 (1937).

(10) Friedlander and Ostermaier, *Ber.*, **15**, 333 (1882).

(11) Ganapathi and Venkataraman, *Proc. Ind. Acad. Sci.*, **22A**, 343 (1945); *C.A.*, **40**, 4059 (1946).

TABLE I

EXPERIMENTAL SPECIFIC REACTION RATE AND ACTIVATION ENERGIES

Compound reacted with piperidine	Temperature of reaction, °C.	Unimolecular rate k, (hr.$^{-1}$)[13]	Activation energy E (kcal./mole)[14]
2-Bromopyridine	90.00 ± 0.08	0.200 ± 0.003	16.4 ± 0.4
	80.00 ± .08	.108 ± .002	
	70.00 ± .10	.053 ± .001	
2-Bromoquinoline	50.00 ± .10	.978	13.8[15]
	40.10 ± .14	.497	
2-Chlorothiazole	69.98 ± .10	.216 ± .001	13.8 ± 0.3
	65.25 ± .11	.164 ± .001	
	60.04 ± .12	.1179 ± .0004	
2-Chloroquinoline	69.98 ± .10	.432 ± .003	13.8 ± 0.4
	65.25 ± .11	.332 ± .002	
	60.04 ± .12	.239 ± .002	
	55.05 ± .10	.176 ± .001	

cedures to be published later. The colorless product distilled at 78–80° at 21 mm. and melted at 65.0–67.0°.

Reaction of the halogen compounds produced the 2-piperidino derivatives. Besides the previously known materials which were isolated the following substances were obtained: 2-piperidinothiazole, b.p. 130–131° at 13 mm.; picrate, m.p. 142.0–143.2°. *Anal.* Calcd. for $C_{14}H_{15}O_7N_5S$: N, 17.63. Found: N, 17.60. 2-Piperidinobenzothiazole picrate, m.p. 174.8–176.4°. *Anal.* Calcd. for $C_{18}H_{17}O_7N_5S$: N, 15.65. Found: N, 15.64.

Typical Rate Run Procedure.—A sample of the halogen compound (0.01500 mole) was weighed in a weighing bottle on an analytical balance, then transferred to a 125-ml. erlenmeyer flask containing 70 ml. of piperidine previously cooled in an ice-bath. The flask was shaken thoroughly for several minutes to insure complete solution of the reactants. By means of a 5-ml. volumetric pipet coupled to a vacuum line through a two-way stopcock (one outlet was open to the atmosphere) a series of twelve 5-ml. samples of the reaction solution was pipetted into individual reaction tubes. These tubes, made by sealing off the ends of $^{19}/_{38}$ standard taper interjoints supplied with hooks, were sealed by applying silicone grease at the joint and secured by attaching a pair of springs to the hooks. The tops of these tubes were then fitted into specially drilled corks, which supported the samples from a thermostat cover containing holes for suspending each tube in the constant temperature medium.

On simultaneously immersing the twelve samples in the thermostat, there was an initial temperature drop which was overcome in about 10 minutes. The first sample was analyzed within a few minutes after thermostatic control was regained. Nine subsequent samples were taken at measured intervals corresponding to about one-tenth of the half-life period (as estimated by crude preliminary measurements). The two remaining samples were titrated after the elapsed time exceeded ten times the half-life period.

Analytical Procedure.—A reaction tube was removed from the thermostat, chilled by stirring rapidly for one minute in an ice-bath, then opened. The contents were rinsed into a 250-ml. erlenmeyer flask using one rinse with 5 ml. of water, one with 12 ml. of 6 *N* nitric acid to form water soluble salts of the amines present, and finally two 10-ml. rinses with water. The resulting acidic solution was titrated for ionic halogen using 0.02500 *N* silver nitrate and 0.02500 *N* potassium thiocyanate solutions. In cases where bromides were determined the familiar Volhard titration using 5 ml. of saturated solution of ferric alum as indicator gave reproducible end points. Where chlorides were involved, 4 ml. of nitrobenzene was added before the back titration with thiocyanate according to the recommendations of Caldwell and Moyer.[12]

(12) Caldwell and Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

(13) The pseudo-unimolecular rate constants were calculated from the equation $\log (a - x) = (-K/2.303)\, t + \log a$.

(14) The activation energies were calculated from the linear form of the Arrhenius equation $\log K = (-E/2.303\, RT) + C$.

(15) Since only two rate constants were evaluated, the limits of validity of the results could not be calculated. However, such limits should be of the same order of magnitude as those indicated for the other tabulated constants.

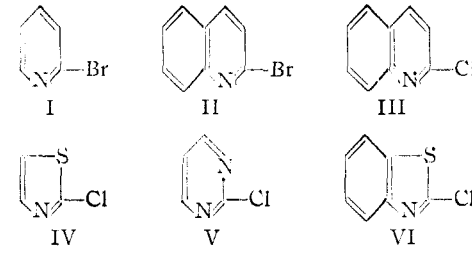
TABLE II

RATE CONSTANTS AND REDUCED RATES[16] AT 50.00°

Compound	$k_{50.00}$ hr.$^{-1}$	Reduced rate
2-Bromopyridine	0.0122	1.00
2-Chlorothiazole	.0620	5.08
2-Chloroquinoline	.1266	10.4
2-Bromoquinoline	.9780	80.2
2-Chloropyrimidine	Not determined, but very much larger than the above values.	
2-Chlorobenzothiazole		

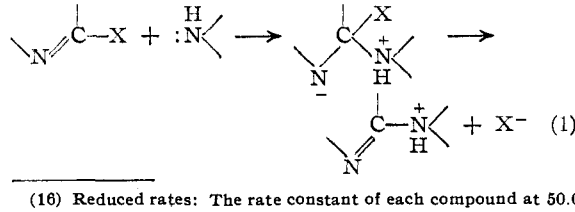
Discussion

A comparison of the structures of the halogen compounds under consideration (I to VI)



I II III IV V VI

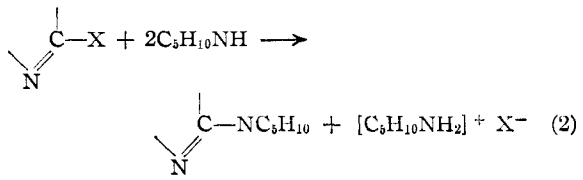
shows that in at least one of the possible resonance forms of each compound, the common grouping —N=C—X, the iminohalide structure, occurs. This system, being the nitrogen analog of an acid halide function, would be expected to be easily attacked by nucleophilic reagents with replacement of the halogen atom. The reaction of this functional unit with piperidine is represented by the mechanism shown below, the product being the hydrohalide salt of the 2-piperidino substituted compound. In the presence of excess[17] piperidine, which is more



(16) Reduced rates: The rate constant of each compound at 50.00° was divided by the value of 2-bromopyridine.

(17) We recognize that the anionic charge in the activated complex may be distributed over a number of ring positions and that the structure is thereby stabilized. While such concepts are extremely useful we also find it convenient to consider that such charge distributions result in an increase in the acid nature (electrophilic character) of the carbon bearing the halogen.

basic than the 2-piperidinoheterocyclic product, the proton is exchanged from one base to the other. The over-all reaction is therefore



Since the main electrical effect activating the α-carbon to nucleophilic attack is the +E effect of imine nitrogen, all of the compounds (I to VI) would be expected to behave similarly, the extent to which halogen activation occurs in any particular case depending on the amount of imine character of the C=N bond, and on the electrical effects of the halogen substituent and of the other ring atoms.

It is clear that the reactivity of the halogen in replacement with piperidine is proportional to the magnitude of the positive charge which can be generated on the substituted ring carbon at the moment of attack. This implies, of course, that the slow, rate-determining step is the coördination of the piperidine nitrogen to the acid carbon and the establishment of the activated complex. Hence, any factors which increase this positive charge would be expected to increase the rate of reaction. This implies that the reaction should be of the S_N2 type, which is entirely reasonable. The same conclusion is also indicated by the "aromatic nature" of the nuclear bound halogen.[18]

While we wish to postpone a thorough discussion of the present results until data on further related structures can be included, we think it is interesting to point out that halogen attached to the 2-position of quinoline is more easily replaced by nucleophilic reagents than that attached to the 2-position of pyridine. One might expect therefore that hydrogen situated on the 2-position of pyridine would more easily be replaced by electrophilic reagents than the 2-hydrogen of quinoline. So far as is known, the above conclusion cannot be proved nor disproved empirically because typical electrophilic reagents never substitute either of those positions preferentially under comparable conditions. It is interesting to discover, however, that qualitatively the same result has been calculated by Longuet-Higgins and Coulson[19] by the method of molecular orbitals. In the same way we might conclude that the effective electron density at the 2-position of thiazole is greater than that at the 2-position of benzothiazole. This conclusion is consistent with the calculated relative electron densities at those positions as published by Pullman and Metzger.[20]

(18) That there is basis for an alternative conception is proposed by Berliner, Quinn and Edgarton (ref. 4).

(19) Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

(20) Pullman and Metzger, *Bull. soc. chim. France*, 1021 (1948).

BETHLEHEM, PA. RECEIVED MARCH 21, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF RADIATION BIOLOGY, SCHOOL OF MEDICINE AND DENTISTRY, UNIVERSITY OF ROCHESTER]

The Beryllium: Citrate System. I. Dialysis Studies in Alkaline Solution[1]

BY ISAAC FELDMAN, W. F. NEUMAN, ROBERT A. DANLEY AND JEAN R. HAVILL

Dialysis–equilibrium studies of the beryllium: citrate system in bicarbonate buffer showed that the maximum molar ratio in which beryllium and citrate ions combine to form a stable, soluble complex at *p*H 8.25 μ equaling 0.1, and at about 10^{-3} *M* deryllium is two. The effect of *p*H and of the order in which citrate and bicarbonate are added to beryllium is discussed.

To aid in the elucidation of the toxicology of beryllium,[2] it is desirable to study the reaction of beryllium with biologically important substances in aqueous medium, particularly in slightly alkaline solution. It has been shown[3,4] that the reaction of beryllium with citrate ions may be of prime importance.

Information in the literature concerning the complexing of beryllium by citrate is of a qualitative nature only. Thomas and Miller,[5] by investigating the effect of various potassium salts on the *p*H and conductance of beryllium hydrosols, concluded that citrate ions have a greater tendency to coördinate with beryllium than do the conjugate bases of dicarboxylic acids, of monocarboxylic acids, or of mineral acids other than phosphoric. This conclusion was confirmed by Kosel and Neuman[4] who carried out potentiometric titrations of equimolar mixtures of beryllium sulfate and various organic acids.

In this paper we have applied the method of continuous variations[6,7] to the dialysis–equilibrium technique of Klotz[8] to show that in alkaline solution the maximum molar ratio in which beryllium and citrate ions combine to form a slightly dissociated, soluble complex ion is two.

Experimental

Materials.—The beryllium chloride stock solution was prepared from pure beryllium metal and standardized according to the directions of Underwood and Neuman[9] with

(1) This paper is based on work performed under contract with the United States Atomic Energy Commission at the University of Rochester Atomic Energy Project, Rochester, New York. Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at Chicago, September, 1950.

(2) J. K. Scott, W. F. Neuman and R. Allen, *J. Biol. Chem.*, **182**, 291 (1950).

(3) I. Feldman, W. F. Neuman, R. A. Danley and J. R. Havill, Univ. of Rochester Atomic Energy Project Report No. UR-59 (1949).

(4) G. E. Kosel and W. F. Neuman, *ibid.*, Report No. UR-106 (1950).

(5) A. W. Thomas and H. S. Miller, THIS JOURNAL, **58**, 2526 (1936).

(6) P. Job, *Ann. Chim.*, **11**, 97 (1936).

(7) W. C. Vosburgh and G. R. Cooper, THIS JOURNAL, **63**, 436 (1941).

(8) I. M. Klotz, F. M. Walker and R. B. Pivan, *ibid.*, **68**, 1486 (1946).

(9) A. L. Underwood and W. F. Neuman, *Anal. Chem.*, **21**, 1345 (1949).