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An Acid-catalyzed Aromatic Nucleophilic Substitution Reaction

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The rate of displacement of the halogen in 2-halo-5-nitropyridines by water in 5–10 *M* sulfuric acid, acetic acid–water and dioxane–water has been investigated. The rate decreased with increasing acid concentration in aqueous sulfuric acid and was found to be proportional to the 4th power on a_{HOH} and to the fraction of the halopyridine protonated. The reaction rates were determined in D_2O with D_2SO_4 catalyst and an isotope effect of 2.36 was obtained. The pK_a of the 2-halo-5-nitropyridines were determined. A mechanism for the reaction is suggested.

The nucleophilic substitution of halogen substituents by basic reagents has been known for a long time. However, the fact that protonation of the heterocyclic nitrogen results in an increased rate of substitution only recently has been recognized. Banks[2] showed that the rate of replacement of "active Cl" on heterocyclic bases was increased if acid were present. He used about 10 heterocyclic compounds and 40 aromatic amines to demonstrate the generality of the reaction. Bunnett[3] and Mertel[4] have reviewed the literature and have given a number of examples of the scope and usefulness of this reaction. Chapman and Rees[5] were concerned with the autocatalytic reaction in which the HCl liberated in the reactions of chloronitropyridines with aniline protonated the aromatic substrate. Dummel and Mosher[6] have observed the acid-catalyzed displacement of the nitro group of 2-nitropyridine-5-carboxylic acid by the OH or Cl group.

The present research was initiated in the expectation of obtaining some quantitative data on these acid-catalyzed reactions.

Experimental

Materials.—Sulfuric acid, du Pont reagent grade, was used without further purification. The acid was standardized by a potentiometric titration with NaOH. The density was also determined; the value was within the manufacturer's specifications and corresponded exactly to the composition given in the literature.[7]

Deuterium sulfate was prepared by the method of Schubert and Burkett.[8] The grease on the ₸ joints of the apparatus turned dark on practice runs, but the use of Teflon sleeves eliminated this difficulty. The product was analyzed by titration of a weighed amount of the acid as above.

Deuterium oxide was obtained from Isotopes Specialties Co. of Pasadena, Calif., and was labeled 99.5%.

2-Chloro-5-nitropyridine, hereinafter abbreviated 2C5NP, was obtained from Aldrich Chemical Co., Inc. It was purified by recrystallization from benzene or benzene–petroleum ether and had a melting point of 107–108°, lit.[9] 108°.

2-Iodo-5-nitropyridine, abbreviated 2I5NP, was synthesized by the replacement of Cl by I^- in an acid-catalyzed reaction. One-half mole of NaI was refluxed for 1.5 hr. with 0.1 mole of 2C5NP in 300 ml. of glacial acetic acid. The product was isolated by pouring the reaction mixture on 400 g. of crushed ice and filtering. The crude yield was 23 g., 90%. It was recrystallized from benzene–petroleum ether to give a melting point of 163–164°. The infrared spectra was similar to that of the known 2C5NP. Analysis was for %I of a sample hydrolyzed in acid solution: calcd. 50.78%, found 50.51, 50.58%.

2-Hydroxy-3-bromo-5-nitropyridine was prepared by the diazotization of the corresponding amino compound. The melting point of 204–205° was obtained after recrystallization from acetone.

Dioxane was purified by the method given in Weissberger[10]; *i.e.*, acid hydrolysis followed by reflux over Na metal.

Glacial acetic acid, Fisher reagent grade, was partially frozen and the liquid discarded.

Procedure.—Pipets, burets and thermometers were calibrated. The halopyridine, 0.5–0.6 g., was weighed accurately on a tared aluminum pan and transferred to a volumetric flask. The sample was dissolved in concentrated sulfuric acid, and ice-cold water was added to the flask in an ice-bath to obtain the desired concentration. Final dilution was performed after the solution had warmed to room temperature. Eight samples were pipetted into tubes and these were sealed by fusing their elongated necks. The reactions were run in a bath in which the temperature variation was ±0.1° or less. The reaction was stopped by plunging the sample tube in ice. Immediately after the sample tube was opened and rinsed, the Cl^- or I^- was titrated with $AgNO_3$. The electrode system was Ag-calomel with an ammonium nitrate or KNO_3 salt bridge to eliminate Cl^- leakage from the calomel electrode. A Beckman Zeromatic *p*H meter was used as a potentiometer. Plots of $\log(V_\infty - V)$ *vs.* time were prepared and the pseudo-first-order rate constants determined from the slope. Some oxidation of I^- was observed, so that the reaction mixture was outgassed with nitrogen by means of a sintered glass filter stick. In addition, the sample tubes were flushed with nitrogen before filling. In spite of these precautions, some I_2 color developed in samples removed toward the end of a run. The samples were treated with 5 ml. of water saturated with SO_2 to reduce the I_2. The product of the reaction, 2-hydroxy-5-nitropyridine, 2H5NP, did not iodinate under reaction conditions.

pK_a Values.—The pK_a of 2C5NP, 2I5NP and 2H5NP were determined by the method of David and Geissman.[11] The wave lengths used were 2800 and 2650 Å. for 2C5NP, 3220 and 3030 for 2I5NP, and 2550 and 2400 for 2H5NP. The temperature dependence of the pK_a of 2C5NP was obtained by filling the cells at a given temperature and quickly reading the absorbance before the temperature changed. The uncertainty in the temperature was estimated by placing a thermometer in the cell and timing the operations. This gives an estimate of the temperture change, which is given in the results.

Isolation of the Reaction Products.—Dilution of the dioxane–water reaction mixture with a large amount of water gave a yellow material identical with 2H5NP by its melting point of 182–183°, lit.[12] 184°. Other reaction mixtures were made basic after 10 half-lives and the ultraviolet spectra compared to that of an authentic sample of 2H5NP. Other reaction mixtures were brominated to give a sample melting at 204–205°. The mixed melting point with an authentic

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[1] This research was supported by a grant (No. DA-ORD-1) from the Office of Ordnance Research, U. S. Army.

[2] C. Kenneth Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

[3] J. F. Bunnett and R. Zahler, *Chem. Revs.*, **49**, 331 (1951).

[4] H. E. Mertel. "In the Chemistry of Heterocyclic Compounds," A. Weissberger, Editor, Interscience Publishers, Inc., New York, N. Y., Part II, 1961, Ch. VI.

[5] N. B. Chapman and C. W. Rees, *J. Chem. Soc.*, 1190 (1954).

[6] R. J. Dummel and H. S. Mosher, *J. Org. Chem.*, **24**, 1007 (1959).

[7] "International Critical Tables," Vol. III, p. 57.

[8] W. M. Schubert and H. Burkett, *J. Am. Chem. Soc.*, **78**, 65 (1956).

[9] W. T. Caldwell and E. C. Kornfeld, *ibid.*, **64**, 1696 (1942).

[10] A. Weissberger, "Technique of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 2nd Edition, Vol. VIII, p. 372.

[11] C. Davis and G. Geissman, *J. Am. Chem. Soc.*, **76**, 3507 (1954).

[12] Beilstein's "Handbuch Der Organischen Chemie," Julius Springer, Berlin, 1935, 4th Edition, 1st Supplement, Vol. XXI, p. 202.

sample of 2-hydroxy-3-bromo-5-nitropyridine gave no depression.

Results

The k_ψ, the first-order rate constants, are given in Tables I, V and VI. The activation energies are also given in the same tables, and indicate that the reaction in D_2O has a higher activation energy than the comparable reaction in HOH. The k_ψ were extrapolated to 25° because H_0, pK_a and other data are available at this temperature. In order to validate this extrapolation, a few rate constants were run at 25°. The agreement is satisfactory, and indicates that no unexpected errors are introduced in the extrapolation.

TABLE I

REACTION RATE CONSTANT FOR THE REACTION OF 2-HALO-5-NITROPYRIDINES WITH WATER AND DEUTERIUM OXIDE IN SULFURIC ACID

Sulfuric acid concn., moles/l.[a]	Temp., °C.	$k\psi \times 10^5$ kcal./mole
2-Chloro-5-nitropyridine		
5.38	25.0	0.0799 (calcd.)
	25.0	0.0800
	57.3	2.85, 2.95, 2.95
	76.5	18.9, 18.9
(21.6) ΔE	96.5	105, 97, 99
5.68	25.0	0.0752
	25.0	0.0730 (calcd.)
	60.0	3.70, 3.70
(21.9)	80.5	24.7, 24.5, 24.9
6.04	25.0	0.0747 (calcd.)
	60.0	3.57, 3.71
(21.7)	80.5	24.5, 24.9, 23.1, 27.1
6.39	25.0	0.0612 (calcd.)
	60.0	3.28, 3.46
(22.4)	80.5	23.5, 22.6, 23.7
6.75	25.0	0.0625 (calcd.)
	60.0	3.00, 3.07
(22.0)	80.5	20.8, 20.3, 21.4
7.16	25.0	0.048 (calcd.)
	25.0	0.045
	57.3	1.85, 1.87
	67.4	5.46, 5.56, 5.40, 5.40
	76.5	16.1, 15.0
	86.7	33.0, 32.8
(22.7)	96.5	80.6, 82.2
7.46	25.0	0.0365 (calcd.)
	60.0	2.09, 2.18
(23.0)	80.5	16.3, 16.3
7.99	25.0	0.032 (calcd.)
	60.0	16.2, 12.2
	106.5	95.5
8.99	25.0	0.0187 (calcd.)
	76.5	4.67, 4.51
	96.5	27.8, 27.4
	106.5	61.0
(22.2)	127.0	260, 263
10.79	25.0	0.00379 (calcd.)
	76.5	1.06, 1.02
	96.5	6.73, 6.57
(22.7)	127.0	70.0, 71.5
5.38[b]	25.0	0.0595 (calcd.)
5.38[b]	78.2	23.9
5.68[b]	25.0	0.0560 (calcd.)
	68.0	8.13
	78.2	22.6
(23.7)	90.3	69.5
6.04[b]	25.0	0.0483 (calcd.)
	78.2	19.5
8.99[b]	25.0	0.0084 (calcd.)
	78.2	3.36
2-Iodo-5-nitropyridine		
5.68	25.0	0.0196 (calcd.)
	72.0	3.84, 4.24
	99.1	45.3, 46.4
6.04	25.0	0.0169 (calcd.)
	72.0	3.20
	76.8	4.79
	82.1	8.26
	89.1	14.6
(22.9)	98.0	32.1
6.39	25.0	0.0115 (calcd.)
	72.0	2.55
	76.8	3.91
	82.1	6.46
	89.1	11.8
(23.5)	98.0	27.6
7.16	25.0	0.00700 (calcd.)
	72.0	1.57, 1.78
	99.1	19.7, 21.1
8.99	25.0	0.00370 (calcd.)
	72.0	.417
	76.8	.638
	82.1	1.05
	89.1	1.79

[a] Value in parentheses is Arrhenius activation E, kcal./mole. [b] D_2SO_4.

The pK_a of the 2C5NP and 2I5NP were determined experimentally and also estimated by a Hammett plot. The pK_a for 2-chloropyridine and 2-iodopyridine were taken from the data of McDaniel and Brown and the ρ-value, 5.20, was determined from the plot given by Jaffé and Doak.[13] The σ-values were taken from Jaffé's paper.[14] The calculated value of −3.00 for 2C5NP and −1.87 for 2I5NP compare favorably with the experimental values of −2.97 and −1.70 given in Table II.

TABLE II

pK_a OF 2-SUBSTITUTED-5-NITROPYRIDINES

Substance	Temp., °C.	$-pK_a$
2-Cl	25.0	+3.00
	25.0	+2.65[a]
	20.0	2.90
	37	3.08
	46	3.15
	60	3.30 (calcd.)
2-I	25	1.70
2-OH	25	3.15

[a] In D_2SO_4; see Results.

The temperature dependence of pK_a of 2C5NP is also given in Table II. A plot of pK_a *vs.* $1/T$ gave a straight line from which pK_a at 60° was calculated. The pK_a of a Hammett indicator base is known to change when the solvent is changed to DOD. Bigeleisen's data[15] indicate that the deuter-

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(13) D. H. McDaniel and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 3752 (1955); H. H. Jaffé and G. O. Doak, *ibid.*, **77**, 4441 (1955).

(14) H. H. Jaffé, *Chem. Revs.*, **53**, 522 (1953).

(15) E. Högfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, **82**, 15 (1960).

TABLE III

FRACTION OF 2-HALO-5-NITROPYRIDINE PROTONATED OR DEUTERATED AT 25 AND 60°

HSO$_4$, moles/l.^{e}	HSO$_4^-$, moles/l.^{a}	$-H_0$	h_0	F^b	$k\psi \times 10^{-7}$, sec.$^{-1}$	$k\psi/F \times 10^{-7}$, sec.$^{-1}$	$a_{HOH}{}^c$
5.38	4.57	2.45	282	0.22	7.99	37.3	0.555
5.38^d	..	2.45	282	.387	5.95	15.3	...
5.38^{60}	..	2.42	263	.116	400	3450	.565
5.68	4.78	2.60	398	.285	7.52	27.8	.515
5.68^I	4.78	2.60	398	.884	1.96	2.21	.515
5.68^d	..	2.60	398	.470	5.60	11.9	...
5.68^{60}	..	2.57	372	.156	371	2380	.530
6.04	5.00	2.78	602	.375	7.47	19.8	.470
6.04^I	5.00	2.78	602	.915	1.69	1.85	.470
6.04^d	..	2.78	602	.574	4.83	8.40	...
6.04^{60}	..	2.73	536	.212	364	1720	.490
6.39	5.23	2.96	912	.477	6.12	12.8	.435
6.39^I	5.23	2.96	912	.948	1.15	1.21	.435
6.39^{60}	..	2.90	795	.284	324	1140	.450
6.75	5.48	3.17	1479	.597	6.25	10.5	.395
6.75^{60}	..	3.08	1205	.376	303	804	.412
7.16	5.70	3.38	2390	.705	4.80	5.96	.345
7.16^I	5.70	3.38	2390	.980	0.70	0.71	.345
7.16^{60}	..	3.26	1820	.476	265	556	.368
7.46	5.90	3.55	3550	.780	3.65	4.68	.310
7.46^{60}	..	3.31	2140	.517	213	411	.338
7.99	6.20	3.87	7410	.881	3.22	3.65	.260
7.99^6	..	3.66	4570	.696	116	166	.283
8.99	6.65	4.40	25100	.962	1.87	1.94	.175
8.99^I	6.65	4.40	25100	.998	0.370	0.37	.175
8.99^d	..	4.40	25100	.982	0.83	0.84	...
8.99^{60}	..	4.16	14450	.878	100	113	.195
10.79	6.50	5.30	199500	.995	0.375	0.38	.068
10.79^{60}	..	5.23	170000	.998	24.5	24.7	.079

The temperature is 25.0° unless otherwise designated. The substrate is 2C5NP unless otherwise designated. ^{a} From the data of Young and Blatz, ref. 18. ^{b} Calculated from $F = h_0/(h_0 + K_{SH^+})$; H_0 was obtained from the data compiled by F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 13 (1957); H_0 at 60° from A. I. Gelbshtein, *et al.*, *Zhur. Neorg. Khim.*, **1**, No. 3, 506 (1956). ^{c} Activities of water calculated from vapor pressure data in "International Critical Tables," Vol. III, p. 303. ^{d} DOD for D$_2$SO$_4$ system. ^{e} ^{I} for 2I5NP; ^{60} for temperature is 60°.

TABLE IV

ISOTOPE EFFECT AT 25°

Acid concn., moles/l.	$\frac{(k\psi/F) \text{ for } H_2SO_4}{(k\psi/F) \text{ for } D_2SO_4}$
5.38	2.43
5.68	2.33
6.04	2.35
8.99	2.31
Av.	2.36

TABLE V

REACTION RATE CONSTANT FOR THE REACTION OF 2C5NP IN ACETIC ACID–WATER AT 106.5°

HOH, moles/l.	H$_2$SO$_4$,^{a} moles/l.	$k\psi \times 10^{-5}$, sec.$^{-1}$
None	None	0.87, 0.86
0.663	None	0.94
1.660	None	1.02
2.760	None	1.15
5.527	None	1.30
13.8	None	1.43, 1.44
27.8	None	1.23, 1.27
38.6	None	1.20, 1.17
None	0.176	4.90, 5.25
None	0.92	17.4, 19.3
None	1.94	19.5, 18.9
27.6	0.375	5.06, 5.60
27.6	0.94	16.1, 15.6
27.6	1.88	34.6, 33.6
38.6	0.94	16.4, 16.2
13.8	0.94	18.4, 17.8

^{a} The concentration of the acid solution was measured at 25°.

ated base is a weaker acid than the protonated by about 0.35 *p*K unit for secondary and tertiary anilines. This gives an estimate of −2.65 for the pK_a of 2C5NP in the D$_2$SO$_4$–DOD solvent.

The fraction protonated was calculated on the assumption that the substrates behaved as Hammett bases. These data are collected in Table III and the isotope effect is given in Table IV. Bigeleisen's demonstration that D_0 and H_0 are essentially identical permitted the use of Long and Paul's extensive H_0 tables. The variation of H_0 with temperature as given by Gelbshtein was used to calculate F at 60° (note *c*, Table III).

The reaction was studied in acetic acid–water and in dioxane–water as solvents as well as sulfuric acid–water. The data are given in Tables V and VI. In acetic acid, the rate increases as the concentration of water increases, goes through a maximum at [HOH] = 10 *M*, then decreases to an apparently constant value at 30*M*. If 0.537 *M* sulfuric acid is present in dioxane, the reaction follows the same course, though the data are less complete. In acetic acid, the rate increase is proportional to the concentration of added acid. The numerical values for zero, 13.8, 27.6 and 38.6

TABLE VI

THE REACTION RATE CONSTANT OF 2C5NP IN HOH–DIOXANE AT 106.5°

HOH, moles/l.	H_2SO_4, moles/l.	$k\psi \times 10^{-6}$, sec.$^{-1}$
16.56	None	Zero
16.56	0.089	0.59
16.56	.178	0.81, 0.78
16.56	.537	3.03
16.56	.888	5.43
16.56	1.79	15.8
0.125	0.537	2.88
1.096	.537	5.80
27.03	.537	4.10
28.0	1.79	24.3

M HOH are practically identical if 0.9 *M* sulfuric acid is added. If no water is present, the rate remains the same if the acid concentration is doubled. In dioxane, the rate was *zero* if no acid was present. The rate constant increased with added acid: a plot of rate *vs.* *M* H_2SO_4 indicated that the rate constant rises slightly more rapidly than linearly.

The deuterium isotope effects are assembled in Table IV and were calculated in the following manner. In order to have the same basis for comparison, k_ψ was divided by F for the protonated and deuterated forms. This amounts to comparing the rates at 100% protonation or $F = 1$. This gives a deuterium isotope effect of 2.36 for all 4 runs. To find the contribution of HSO_4^- (as a second nucleophile) to the over-all rate, eq. 1 was utilized. The plot of $k_\psi/F \times (HSO_4^-)$ *vs.* $(a_{HOH})/(HSO_4^-)$ gave an intercept of 1.52×10^{-8}.

The contribution of HSO_4^- to the total rate is quite small, for the term $(HSO_4^-) \times 1.52 \times 10^{-8}$ ranges in value from 0.6 to 0.7×10^{-7} throughout the range of acidities studied. At low acidities k_ψ/F is very large, 37×10^{-7}, so that the term $k_{HOH} \times (a_{HOH})^n$ is 36.3×10^{-7} or larger by a factor of 50. As the total rate decreases, the relative contribution of the bisulfate term increases.

Discussion

The solvents dioxane and acetic acid are somewhat less than ideal for this reaction. In dioxane, though purified, outgassed with nitrogen and sealed in nitrogen flushed tubes, several samples in each run turned dark. While these samples seemed to fit the kinetic plot, some doubt as to the nature of the reaction studied under these conditions persists. In addition, there are little data on H_0 in dioxane–water mixtures available over the whole range of HOH concentrations. Acetic acid presents the difficulty of the second nucleophile, for there is a reaction in pure acetic acid. The facts that no second product of the reaction was isolated does not exclude this, for the acetate so formed would be expected to hydrolyze during the isolation procedure.

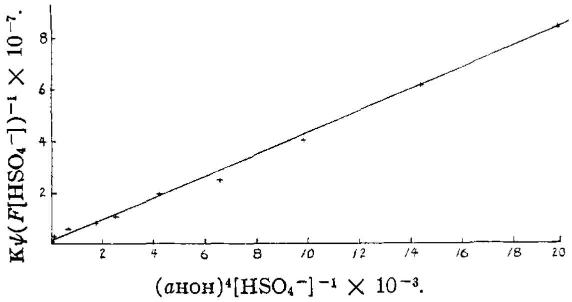

Fig. 1.—$K\psi(F[HSO_4^-])^{-1}$ *vs.* $(a_{HOH})^4[HSO_4^-]$ for 2-chloro-5-nitropyridine at 25°; intercept = 1.5×10^{-8} (least squares).

Some useful conclusions may be drawn from the data in these solvents. The fact that *there is no reaction in dioxane–water when no acid is present* and the almost linear rate increase with added acid indicate acid catalysis. The linear increase in rate constant with added sulfuric acid in acetic acid is additional evidence for this conclusion. Low and variable amounts of water which could be obtained in these solvents indicate that the reaction rate is dependent on water concentration. The rates in aqueous sulfuric acid also provide evidence for the rate's dependence on water activity. If the rate is only proportional to the fraction protonated, it should increase as acid concentration increases until $F = 1.00$. However, the experimental facts are that the rate decreases as the fraction protonated increases. Since the activity of water decreases with increasing acidity, the qualitative dependence of rate on the activity of water follows.

The solvent system sulfuric acid–water is more suitable in that more data are available on its properties. The difficulties with its use are the low solubility of the 2C5NP in low concentrations of sulfuric acid, the fact that acid and water concentrations cannot be independently varied, and the probability that bisulfate is also a nucleophile. The choice of perchloric acid would eliminate the last problem, but attempts to use this acid indicated that oxidation of Cl^- and possibly the reaction product had taken place. The lower limit of (H_2SO_4) that could be used was about 5 *M*, and the rate decreased to an inconveniently low value above 10 *M*. However, the fraction protonated could be varied from 0.22–0.99$^+$ in this range of acidities.

The general rate law presented by Swain[16] appears to be applicable to this reaction.

$$k\psi/F = \frac{k_{HOH}a_{HOH} \times \gamma_{SH^+}}{\gamma^+} + \frac{k_{HSO_4^-}[HSO_4^-]\,\gamma_{HSO_4^-}\gamma_{SH^+}}{\gamma\ddagger} \tag{1}$$

where $k\psi$ = pseudo-first-order rate constant, F = fraction protonated, γ^+ = activity coefficient of transition state for HOH and $\gamma\ddagger$ = activity coefficient for transition state for HSO_4^-.

The known components of this equation are k_ψ, F and a_{HOH} from vapor pressure measurements[17] and HSO_4^- from the Raman spectrographic data of Young.[18] If the activity coefficient ratios are reasonably constant, a plot of $k_\psi/(F \times HSO_4^-)$ *vs.* a_{HOH}/HSO_4^- would be linear and have an intercept of $k_{HSO_4^-} \times$ constant. Information collected at 25 and 60° has been plotted and shows that it is not linear in a_{HOH}. Plots of the 2nd, 3rd, 4th and 5th power of a_{HOH} were prepared, with the result

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[16] C. G. Swain and A. T. Rosenberg, *J. Am. Chem. Soc.*, **83**, 2154 (1961).

[17] "International Critical Tables," Vol. III, p. 303.

[18] T. F. Young and L. A. Blatz, *Chem. Revs.*, **44**, 93 (1949).

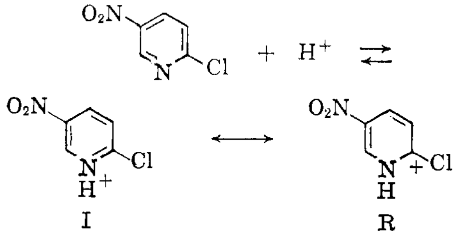
that only the 4th power gave the expected linearity. This holds for both the 2C5NP and 2I5NP. At 60°, the data for the bisulfate concentration are not available, so that k_ψ/F vs. $a_{\mathrm{HOH}}{}^n$ was prepared for 2C5NP. This also gave a linear plot, with n = 3.9. The second term of eq. 1 is so small that the HSO_4^- is regarded as non-reactive. To a first approximation, the system contains one nucleophile, HOH. The total lack of reaction in dioxane when HSO_4^- was the only potential nucleophile supports this argument.

The relative rates of displacement of the Cl and I atoms in 2-halo-5-nitropyridines provide a basis for assigning this reaction the aromatic nucleophilic substitution mechanism. For an SN1 reaction,[19] the I atom is more readily replaced than the Cl, and the same relationship prevails for aliphatic SN2 reactions. However, for an activated aromatic nucleophilic substitution reaction, the Cl and Br are more rapidly replaced than I. With 1-halo-2,4-dinitrobenzenes and piperidine, the relative rate of replacement of Cl was 4.3 times as great as for I.[20] The Cl is displaced more rapidly in these reactions by the ratio of 3.8 to 6.9 at different concentrations of acid and water (Table III). This constitutes strong evidence that the aromatic nucleophilic substitution mechanism applies.

The intermediate complex for this mechanism has been well established[20] and widely accepted by responsible chemists.[21]

Any proposed mechanism must account for the fourth power on the activity of water, acid-catalysis, an intermediate complex and the deuterium isotope effects.

The acid catalysis is relatively easy to explain if the heterocyclic nitrogen is protonated. This positive charge can resonate to provide a positive carbon which will be readily attacked by a nucleophile. This is demonstrated in eq. 2 with resonance form R.



The rates of reaction of an acid-catalyzed reaction in the solvent HOH as compared to DOD are usually explained on the basis of the lower basicity of DOD.[22] The protonated substrate SH^+ is the active species rather than S, according to this analysis. In the less basic solvent DOD the S can compete for the H_+ more effectively, so that the (SH^+) is greater and a higher rate results. This explanation cannot be correct, for the observed rate in HOH is greater than that in DOD.

The problem of degree of protonation or deuteration is also complicated by the fact that the basicity of the substituted pyridine changes with change in solvent. The pK_a of 2C5NP is greater in HOH–H_2SO_4 than in DOD–D_2SO_4. To compare results, it was necessary to compare (k_ψ/F) for water and deuterium oxide. This amounts to comparing the rates at 100% protonation, so that the observed isotope effects cannot be due to fraction protonated. The nucleophilic attack of HOH, or the solvation of the intermediate or the breaking of an OH bond must be the cause of the deuterium isotope effect. An estimate for each of these processes follows: For a nucleophilic attack of HOH and DOD on alkyl halides by either SN1 or SN2 reactions, the isotope effects (k_H/k_D) were 1–1.4.[23] If resonance form R is the species attacked, the lower value seems more likely. The isotope effect on the solvation of II→III and the proton transfer may be estimated from the ion product of HOH and DOD.[22] This shows that the transformation of

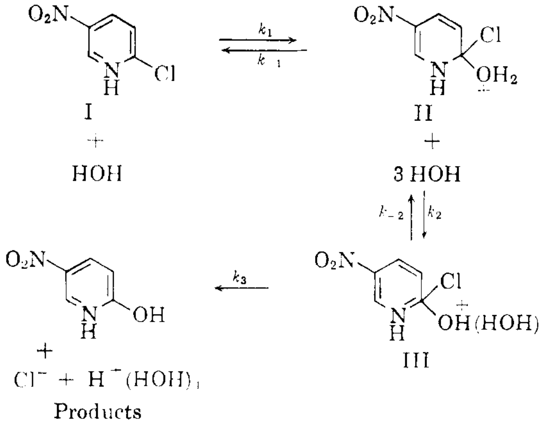
$$(n+4)\mathrm{HOH} + \mathrm{HOH} \rightleftarrows \mathrm{H}^+(\mathrm{HOH})_4 + \mathrm{OH}^-[\mathrm{HOH}]_n$$

$$\frac{[\mathrm{H}^+(\mathrm{HOH})_4][\mathrm{OH}^-[\mathrm{HOH}]_n]}{[\mathrm{D}^+(\mathrm{DOD})_4][\mathrm{OD}^-(\mathrm{DOD})_n]} = 5$$

If $x = [\mathrm{H}^+(\mathrm{HOH})_4]$ and $y = [\mathrm{D}^+(\mathrm{DOD})_4]$

$$x^2/y^2 = 5, \text{ and } x/y = \sqrt{5} = 2.2$$

II to products, if it is regarded as analogous to the proton transfer in water, will have a maximum value of 2.2. Further separation of this effect into the hydration and proton transfer steps is uncertain. The over-all isotope effect would then be estimated as (1–1.4) × 2.2 = 2.2 – 3.1, if we assume the maximum value for the second and third steps. These rough estimates and the observed isotope effects are in reasonable agreement; the mechanism is not incompatible with these results.



The fourth power on a_{HOH} can be obtained if one assumes that $k_3 << k_{-2}$, and uses the steady state approximation on the intermediates II and III. The solvation of III was based on $H^+(HOH)_4$, in which the place of one HOH was taken by II.[24]

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(19) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Edition, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 139.

(20) J. F. Bunnett, E. W. Garbisch and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).

(21) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960, p. 122.

(22) K. Wiberg, *Chem. Revs.*, **55**, 715 (1955).

(23) P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **37**, 1491 (1959).

(24) E. Wicke, M. Eigen and T. Ackerman, *Z. physik. Chem.*, **1**, 340 (1954).

$$\text{Rate} = k_3\text{III}$$

$$\text{dIII}/\text{d}t = 0 = -k_3\text{III} - k_{-2}\text{III} + k_2\text{II}\,(a_{\text{HOH}})^3$$

$$\text{III} = \frac{k_2}{k_{-2} + k_3}\,[\text{II}(a_{\text{HOH}})^3] \quad (1)$$

$$\text{If } k_{-2} \gg k_2,\ \text{III} = (k_2/k_{-2})\text{II}\,(a_{\text{HOH}})^3$$

$$\text{dII}/\text{d}t = k_1\text{I}(a_{\text{HOH}}) - k_{-2}\text{III} + k_2\text{II}(a_{\text{HOH}})^3 - k_{-1}\text{II}$$

$$\text{and II} = (k/k_{-1})\text{I}\,(a_{\text{HOH}}) \quad (2)$$

$$\text{rate} = k,\text{III} = k,\ k_2k_1/k_{-1}\,(a_{\text{HOH}})^4\text{I} = k'\text{I}(a_{\text{HOH}})^4 \quad (3)$$

One further deduction may be made from the mechanism given. If the halogen–carbon bond is broken after the O–H bond is broken, electronegative halogen should weaken this O–H$^+$ and hence increase the reaction rate. This agrument is analogous to the greater acid strength of chloroacetic acid as compared to acetic acid. Further, the more electronegative halogen, Cl, should have a greater effect than I, as is observed.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, IND.]

Thermal Rearrangement of 1,3-Dienes

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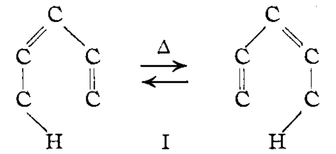
RECEIVED JANUARY 18, 1962

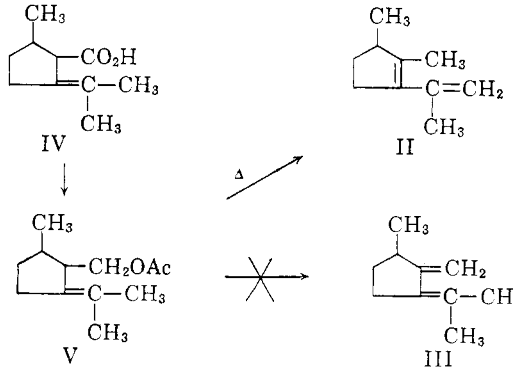
It is demonstrated that 1,3-dienes, in which a vinyl and alkyl group are *cis*, undergo a reversible thermal isomerization involving the over-all 1,5-transfer of a hydrogen with concomitant migration of both carbon–carbon double bonds. At 350–450°, depending on the nature of the dienes on hand, an equilibrium mixture is approached in which the more thermodynamically stable isomer predominates. Dienes in which a vinyl group and alkyl group are *trans* appear to be thermally stable. A means for distinguishing between isomeric *cis*- and *trans*-1,3-dienes is suggested on the basis of this difference in thermal behavior. In this manner, geometric configurations have been assigned to α- and β-ocimene.

Thermal rearrangements of the type described in eq. 1 have occasionally been observed. It is well known that ocimene on being heated above 200° is transformed into alloöcimene.[2,3] Pines[4,5] has shown that the shifting of double bonds in a number of substituted 1,3-cyclohexadiene derivatives occurs at 300–400°. Furthermore, it has been recognized that calciferol (Vit. D) is produced by the thermal isomerization of precalciferol.[6] However, the generality of such thermal isomerizations has not, hereto, been recognized.[7,8] In this communication the generality of the reversible thermal rearrangement of 1,3-dienes according to eq. 1 is demonstrated. Such transformations have considerable synthetic and theoretical application and, in addition, provide an important diagnostic method for distinguishing between isomeric *cis*- and *trans*-dienes.



(1)

This investigation was prompted by the observation that 2-isopropenyl-1,5-dimethyl-1-cyclopentene (II), rather than the expected 3-isopropylidene-2-methylene-1-methylcyclopentane (III), was produced by the pyrolysis of 2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane (V). Acetate V was prepared from pulegone *via* the pulegenic acids (IV) as described in the Experimental section.



The constitution of diene II was indicated by a peak at 11.28 μ which is characteristic of a terminal methylene group, by absorption at 237 and 243 mμ (ε 10,130 and 9,860) in the ultraviolet, by its n.m.r. spectrum, determined at 60 mc. and related to tetramethylsilane, which exhibited signals at −57 and −64 c.p.s. (one methyl group spin coupled with an adjacent proton), −100.6 and −107.6 c.p.s. (two methyl groups attached to unsaturated carbon atoms), and −280.8 and −289.6 c.p.s. (two hydrogens of a terminal methylene group), and *by reductive ozonolysis which afforded formaldehyde and only a trace of acetone.*

The assumption that diene III had formed initially during the pyrolysis of acetate V, but then rearranged to the observed product, diene II, appeared well founded. In order to verify this hypothesis, diene III was prepared from the amine VI by employing the mild elimination procedure

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(1) (a) Participant in the National Science Foundation Undergraduate Research Program, 1960. (b) 1961.

(2) C. J. Enklaar, *Rec. trav. chim.*, **26**, 171 (1907).

(3) J. E. Hawkins and H. G. Hunt, *J. Am. Chem. Soc.*, **73**, 5379 (1951).

(4) H. Pines and R. H. Kozlowski, *ibid.*, **78**, 3776 (1956).

(5) H. Pines and C. T. Chen, *ibid.*, **81**, 928 (1959).

(6) L. Velluz, G. Amiard and B. Goffinet, *Bull. soc. chim. France*, 1341 (1955).

(7) K. Alder and M. Schumacher, *Fort. Chem. Org. Naturf.*, **10**, 8 (1953), have postulated a general reaction in the sense of eq. 1 but their basis for this postulate can hardly be regarded as compelling.

(8) Thermal isomerization of dienes should be distinguished from acid-catalyzed processes which, for example, are known for the abietic acids (N. M. Joye and R. V. Lawrence, *J. Org. Chem.*, **26**, 1024 (1961)) and from rearrangements observed during vigorous Diels–Alder condensations (I. N. Nazarov and M. V. Mavrov, *Proc. Acad. Sci. U.S.S.R.*, **120**, 325 (1958)).