to participation of mechanism III already presented for amides or to salt effects. All other acids studied yield greater rates than equivalent concentrations of $HClO_4$.

A plot of log $k' - H_0$ *versus* log a_{H_2O} yields a curve which exhibits a negative w decreasing in magnitude as acidity increases. A straight line is not expected at low acidities where, according to the above analysis, $h_0 \simeq k_3/k_2$. At higher acidities the method of analysis overcompensates, due to an additional mode of hydrolysis or salt effects as mentioned before. The effect of salts may be operative through the part they play in B and HB. The variation in effects of salts observed in acetylimidazole hydrolysis may be a more general phenomenon unappreciated because few studies exist of comparable scope on other compounds. Qualitatively the high $w = 19.6$ value of acetylimidazole hydrolysis in perchloric acid is accounted for by mechanism IV. This mechanism predicts the occurrence of oxygen isotope exchange with acetylimidazole at high acidities.

A reaction scheme similar to mechanism IV was used to account for acid inhibition in thiazoline[26a,b] and oxazoline[26c] compounds. In the case of some of the thiazoline compounds such as 2-methylthiazoline where the value of $k_3/k_2 = 0.1$ is small, extraordinary powers of the activity of water would be required to account for the decrease in hydrolysis rate by the decrease in water activity. For 2-(1-acetamino-2-methylpropyl)-thiazoline[26b] and 2-methyloxazoline a value of $k_3/k_2 = 1.2$ was obtained, the same as that for acetylimidazole. The identical value for these three compounds is probably coincidental but is nevertheless suspicious and indicates that some common factor, such as a decrease in the activity of water, might account for the results. In such borderline cases it is difficult to assign with certainty the mode of decomposition. By analogy with other thiazoline derivatives[26b] where $k_3/k_2 = 0.1$ to 0.3, the first compound probably decomposes according to mechanism IV. This conclusion is less certain for 2-methyloxazoline. More studies are required on both compounds with a greater variety of acids and salts. Least certain is the mechanism of hydrolysis of acetylimidazole. Even for this compound we favor mechanism IV with the reservations already discussed.

$$TH^+ + H_2O + B \rightleftharpoons D + HB$$

$$D + HB \rightleftharpoons NH^+ + B$$

$$D \rightleftharpoons S$$

Acknowledgments.—The author is indebted to Dr. W. P. Jencks for transmission of data on the hydrolysis of acetylimidazole in perchloric acid. Thanks are also due to Dr. R. J. P. Williams and the Division of General Medical Sciences for their forbearance while this work was performed on a fellowship granted for another pursuit.

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[26] (a) R. B. Martin, S. Lowey, E. L. Elson and J. T. Edsall, *J. Am. Chem. Soc.*, 81, 5089 (1959). R. B. Martin and A. Parcell, *ibid.*, 83, (a) 4830, (b) 4835 (1961). A complete mechanism proposed for thiazoline hydrolysis and acetyl transfer in ref. 27 is unsatisfactory. In designations similar to those of ref. 27 we show in a forthcoming publication that a mechanism of the following kind is a better representation of all the data.

[27] R. B. Martin and R. I. Hedrick, *J. Am. Chem. Soc.*, 84, 106 (1962).

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N. C., AND THE METCALF CHEMICAL LABORATORY, BROWN UNIVERSITY, PROVIDENCE, R. I.]

The Mechanism of Acid-catalyzed Hydrolysis of Azoaryl Ethers[1]

BY J. F. BUNNETT,[2] ERWIN BUNCEL AND K. V. NAHABEDIAN

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The phenolic products of hydrolysis of 4-(*p*-sulfophenylazo)-1-naphthyl methyl ether (Ic) and 4-(*p*-sulfophenylazo)-anisole (II) in oxygen-18-labeled water carry the oxygen-18 label in the phenolic hydroxy group. However, 4-(*p*-sulfophenylazo)-phenol (IV) exchanges oxygen with the medium under the same conditions. Etherification of 4-phenylazo-1-naphthol (IIIa) and transetherification of 4-phenylazo-1-naphthyl methyl ether (Ia) are accomplished by refluxing with ethanol under acid catalysis. The kinetics of hydrolysis of II in 1–6 M $HClO_4$ solutions have been determined, and w and w^* values computed. For several of these reactions a mechanism of nucleophilic displacement at aromatic carbon is required, and for the rest it seems very likely. The protonated azo linkage is a strong activating group for aromatic nucleophilic substitution.

4-(Phenylazo)-1-naphthyl methyl ether (Ia) and related ethers are exceptionally sensitive to acid-catalyzed hydrolytic cleavage, as represented in eq. 1. Hydrolysis is quite rapid, for example, in 0.1 M hydrochloric acid at 46°. Witt and Schmidt,[3] who discovered this phenomenon in 1892, describe it as "gewiss bemerkenswerth." Although several other chemists took note of this phenomenon,[4–8] it escaped general recognition. Recent studies[9,10] have dealt with the conditions, kinetics and mechanism of such cleavages.

Several features of this reaction suggest that it differs in kind from ordinary ether cleavage as commonly effected by hydrobromic or hydroiodic acid. The reaction occurs readily in dilute acid, it does not require highly nucleophilic anions such

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[1] This research was supported by the National Science Foundation (Grants G-2359 and G-6210).

[2] Department of Chemistry, Brown University, Providence, R. I.

[3] O. N. Witt and C. Schmidt, *Ber.*, **25**, 1013 (1892).

[4] K. H. Meyer, A. Irschick and H. Schlösser, *ibid.*, **47**, 1741 (1914).

[5] W. Borsche, W. Müller and C. A. Bodenstein, *Ann.*, **472**, 201 (1929).

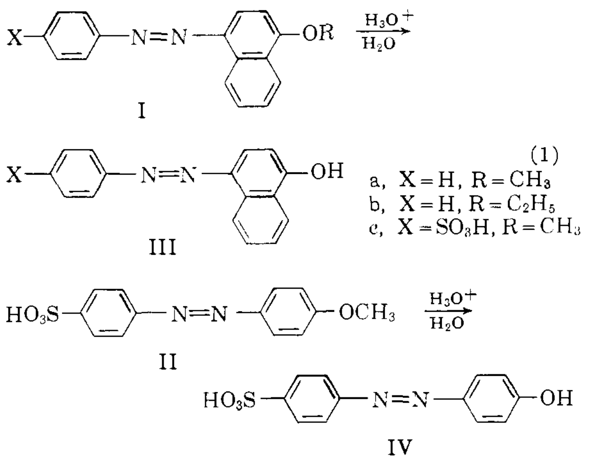
[6] K. H. T. Pfister, *J. Am. Chem. Soc.*, **54**, 1521 (1932).

[7] J. B. Müller, L. Blangey and H. E. Fierz-David, *Helv. Chim. Acta*, **35**, 2579 (1952).

[8] V. Ettel, J. Weichet and J. Spacil, *Coll. Czech Chem. Comm.*, **15**, 204 (1950).

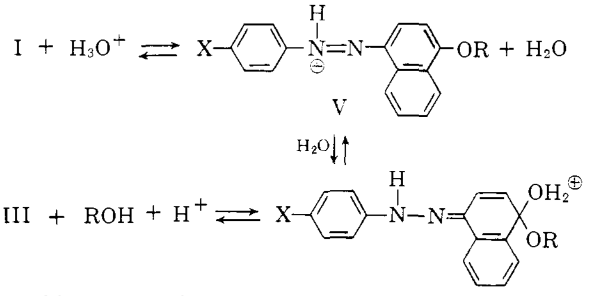
[9] J. F. Bunnett and G. B. Hoey, *J. Am. Chem. Soc.*, **80**, 3142 (1958).

[10] J. F. Bunnett and E. Buncel, *ibid.*, **83**, 1117 (1961),



as bromide or iodide, and it apparently occurs as easily with phenyl ethers as with alkyl ethers of azophenols.[4,11] In consideration of these facts and the observation that in acetic acid solution the azoether scission is vitally dependent on the presence of *water*, Bunnett and Hoey[9] proposed the mechanism of Chart I, in which the actual cleavage is brought about by nucleophilic attack of water on the *aromatic* carbon atom.

CHART I



This mechanism predicts the following consequences: (1) hydrolysis of azonaphthyl ethers I in oxygen-18 labeled water should yield the corresponding naphthols III containing the oxygen label; (2) azonaphthols III should be transformed into azonaphthyl ethers I by treatment with acidified alcohols; (3) in aqueous alcoholic media of appropriate composition, states of equilibrium should prevail between I and III. The present paper describes such observations.

The recent kinetic study[10] of the hydrolysis of 4-(*p*-sulfophenylazo)-1-naphthyl methyl ether (Ic) and of 4-(*p*-sulfophenylazo)-anisole (II) is now extended to include the perchloric acid-catalyzed hydrolysis of II.

Results and Discussion

Oxygen Exchange Studies.—For the oxygen-18 tracer experiments, the hydrolysis of Ic in oxygen-18 labeled 2 *M* hydrochloric acid and of II in labeled 4 *M* hydrochloric acid were carried out. The results of these experiments are shown in the first three rows of Table I. The last row of Table I shows the result obtained when 4-(*p*-sulfophenylazo)-phenol (IV) was subjected to the same hydrolytic conditions as was II.

TABLE I

OXYGEN-18 TRACER EXPERIMENTS

	Atom % oxygen-18		
Substrate	In the hydrol. medium	Calcd. for aryl-oxygen lab. prod.	Found in the product
Ic	1.39	0.50	0.47, 0.47
II[a]	1.20	.45	.45, .44
II[b]	1.20	.45	.40
IV[b]	1.20	.45	.40, .44

[a] The product was recrystallized from 1.57% oxygen-18 enriched water. [b] The product was recrystallized from ordinary water.

It should be noted that all the substrates contain sulfo groups. Therefore the average oxygen-18 content expected for complete exchange at aromatic carbon is, on the assumption that the sulfo oxygens do not exchange, less than the oxygen-18 content of the solvent water. The assumption that sulfo oxygens do not exchange was verified by subjecting azobenzene-4-sulfonic acid to the same hydrolytic medium as used with II and IV. The material isolated after two hours of reflux contained 0.24% oxygen-18. This is the normal abundance (0.20%) within experimental error.

The results in Table I demonstrate that an oxygen atom from water of the medium becomes attached to aromatic carbon, as called for by the mechanism of Chart I. However, the fact that azophenol IV exchanges makes these experiments indecisive as to whether it is the aryl–oxygen or the alkyl–oxygen bond which is ruptured during the actual ether cleavage reaction. Nevertheless the results are fully in accord with the mechanism of Chart I.

Etherification and Transetherification Studies.—The mechanism of Chart I implies that the hydroxy group in azonaphthol III should be replaced by an alkoxy group on reaction with an alcohol under mineral acid catalysis. Such a conversion was in fact described by Witt and von Helmolt[12] in 1894. Treatment of 4-(*p*-tolylazo)-1-naphthol with zinc chloride and hydrochloric acid in ethanol afforded 4-(*p*-tolylazo)-1-naphthyl ethyl ether in 80% yield. This method was reported to be superior to conventional alkylation under alkaline conditions as a preparative method.

We found that reaction of 4-phenylazo-1-naphthol (IIIa·HCl) with refluxing methanol for four hours produced the corresponding methyl ether Ia in 81% yield. From a similar experiment in ethanol solvent, the ethyl ether Ib was isolated in 76% yield.

It was also shown that hydrolysis of azonaphthyl ether Ia in *ca.* 10% water:90% methanol proceeds only to a state of equilibrium and not to completion. The hydrochloric acid concentration was 1.04 *M* and the temperature 46°. The reaction was followed by photometric measurements. Hydrolysis was initially rapid, some 5% of IIIa being produced in the first five minutes, but it slowed to a halt at about 10% total hydrolysis. The plateau was attained in 110 minutes; no further hydrolysis occurred in the next 66 hours.

Transetherification was also demonstrated to occur. Azonaphthyl methyl ether Ia was trans-

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(11) J. Haginiwa and I. Murakoshi, *J. Pharm. Soc. Japan*, **73**, 287 (1953); J. Haginiwa, I. Murakoshi, K. Yokota, H. Takayama and T. Tsuchiya, *ibid.*, **78**, 232 (1958).

(12) O. N. Witt and H. von Helmolt, *Ber.*, **27**, 2351 (1894).

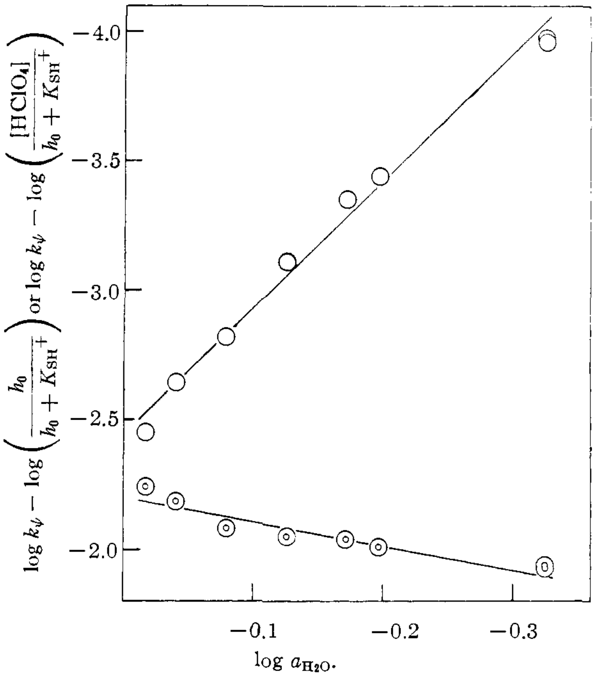

Fig. 1.—Plots for determination of w and w^* for hydrolysis of II: ○ (for w), $\log k_\psi - \log\left(\frac{h_0}{h_0 + K_{SH^+}}\right)$; ⊙ (for w^*), $\log k_\psi - \log\left(\frac{[HClO_4]}{h_0 + K_{SH^+}}\right)$. The slopes are: w, +4.90; w^*, −0.93.

formed into ethyl ether Ib in 75% yield by heating it at reflux in ethanol for 1.5 hr. with a catalytic amount of hydrochloric acid.[13]

Kinetic Studies.—From the rate coefficients for hydrolysis of Ic in moderately concentrated hydrochloric and perchloric acid solutions at 46°, w-values[15] of +4.5 and +8.2, respectively (w^* −0.9 and + 0.9), were reckoned.[10] With reference to an empirical criterion of mechanism,[15] these were taken to indicate a mechanism, an elaboration of that of Chart I, in which water acts as a proton transfer agent in the rate-determining step.

From rate coefficients for hydrolysis of II in hydrochloric acid solutions at 97°, w and w^* of, respectively, +2.8 and −2.2 were computed.[16] The empirical criterion[15] suggested that this reaction involved water acting simply as a nucleophile in the slow step. It was suggested that the conjugate acid of II suffered nucleophilic attack of water, in the S_N2 manner, on its *methyl* carbon with rupture of the alkyl–oxygen bond.

As mentioned above, our oxygen-18 studies do not exclude such a mechanism. On the other hand, the fact that IV exchanges oxygen-18 with a typical hydrolysis medium shows there is no great barrier to nucleophilic displacement on aromatic carbon in 4-phenylazophenyl derivatives. If hydroxydehydroxylation occurs, hydroxydemethoxylation *via* displacement at aromatic carbon seems likely also to take place under the same conditions.

A conceivable alternative explanation for the low w-value in the hydrochloric acid-catalyzed hydrolysis of II is that, at 97°, chloride ion effects a significant fraction of cleavage *via* nucleophilic displacement on methyl carbon. However, this mechanism should not be significant for hydrolysis in perchloric acid, since perchlorate ion is a poor nucleophile.

The rate of hydrolysis of II was therefore determined at several perchloric acid concentrations in the range 1–6 M. Results are presented in Table II.

TABLE II

RATES OF HYDROLYSIS OF II IN PERCHLORIC ACID SOLUTIONS AT 95.1°

$[HClO_4]$,[a] M	$10^4 k_\psi$,[b] sec.$^{-1}$	$-\log a_{H_2O}$[c]	$\log k_\psi - \log\left(\frac{h_0}{h_0 + 40}\right)$[d]	$\log k_\psi - \log\left(\frac{[HClO_4]}{h_0 + 40}\right)$[d]
1.00	1.38	0.018	−2.45	−2.24
1.94	2.83	.041	−2.64	−2.18
2.96	4.32	.079	−2.82	−2.08
3.85	4.10	.126	−3.11	−2.05
4.49	3.06	.171	−3.35	−2.04
4.80	2.76	.197	−3.44	−2.01
5.95	1.03	.325	−3.96	−1.93
5.95	1.00	.325	−3.97	−1.94

[a] Corrected for 95° with use of the thermal expansion coefficient for pure water. [b] k_ψ is the experimental pseudo first-order rate coefficient. [c] From ref. 15. [e] Based on H_0 values of M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957); K_{SH^+} is 40.[10]

A rate maximum, this time at about 3 M mineral acid, is again observed. It has been shown[10,15] that this is a consequence of the substrate having sufficient basicity so that its degree of protonation changes from very low to very high within the range of acid concentrations studied. When the degree of protonation is high, further increase in acid concentration brings about little increase in protonation but diminishes the activity of water in the medium, causing an actual decrease in rate when water is required in the rate-determining step.

In such a case, w and w^* are determined from the slopes of plots of, respectively, $\{\log k_\psi - \log [h_0/(h_0 + K_{SH^+})]\}$ and $\{\log k_\psi - \log [[HX]/(h_0 + K_{SH^+})]\}$ against $\log a_{H_2O}$. The plots are shown in Fig. 1. Both plots are approximately linear though not exactly linear. The slopes are: w, +4.90; w^*, −0.93.[17] By the empirical criterion of mechanism, these w and w^* values indicate a mechanism in which water acts as a proton trans-

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[13] We first encountered the transetherification reaction by accident. A preparation of 4-(p-nitrophenylazo)-1-naphthyl methyl ether (by diazo coupling[9]) was recrystallized from ethanol. The product's m.p. was 154–156° and was not raised by further recrystallization. Since the authentic methyl ether melts at 169° and the ethyl ether at 154–156°,[9] we surmise that the original methyl ether product was transformed into the ethyl ether during recrystallization from ethanol, under catalysis by traces of acid present. The literature reports, in several instances, methyl and ethyl ethers of azonaphthols to have virtually identical melting points.[14] We suspect that transetherification during recrystallization may have occurred in other cases, but gone unrecognized.

(14) T. Zincke and F. Rathgen, *Ber.*, **19**, 2482 (1886); R. Kuhn and F. Bär, *Ann.*, **516**, 143 (1934) (*cf.* T. Zincke and H. Bindewald, *Ber.*, **17**, 3026 (1884)); G. Charrier and L. Casale, *Gazz. chim. ital.*, **441**, 607 (1914).

(15) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

(16) The values of $\{\log k_\psi - \log [h_0/(K_{SH^+} + h_0)]\}$ in Table IV of reference 10 are uniformly low by one logarithm unit. This mistake does not, however, affect the w and w^* values.

(17) For the w plot, σ_w is 0.78, σ_y is 0.20 and r is 0.993. For the w^* plot, σ_w is 0.15, σ_y is 0.04 and r is 0.938.

fer agent in the slow step, just as indicated for hydrolysis of Ic in either HCl or $HClO_4$. The hypothesis that chloride ion participates as a nucleophile in the HCl-catalyzed hydrolysis of II gains support. The *hydrolysis* of II, as contrasted to chloride-induced cleavage, appears to occur by the same mechanism as for Ic, as detailed in Chart I of a previous paper.[10]

Some doubts remain, however. The difference in w^* values for the two acids, $w^*_{HClO_4} - w^*_{HCl}$, is 1.9 for Ic and 1.3 for II. Were nucleophilic attack by chloride ion important only for the HCl hydrolysis of II, this difference would be expected to be larger for II than for Ic, not smaller as observed. Because the reason w^* (or w) values for the same reaction differ from one mineral acid to another is not well understood, this question of chloride involvement in the cleavage of II (or even of Ic) is left somewhat indeterminate.

Another source of doubt, mentioned earlier,[10] is whether the sulfonate group of the sodium salt of II is protonated within the range of acid concentrations studied kinetically and, if it is, what effect that has on the plots from which w and w^* values are derived. If the sulfonate group is protonated *before* the azo linkage, it would seem reasonable for protonation of the azo linkage to be correlated with H_0 and for mechanisms to be inferred from w and w^* values. Sulfonate protonation *within* the range studied possibly would disturb the w and w^* plots because it might (a) change the substrate activity coefficient and (b) alter the polar effect of the sulfonic acid function.

The Mechanism of Hydrolysis.—We summarize arguments presented above. Several items of evidence indicate that azoethers of types I and II undergo hydrolysis by substitution at aromatic carbon with scission of an aryl-oxygen linkage: (1) Cleavage is effected by acids ($HClO_4$ and H_2SO_4) whose anions are poor nucleophiles.[9] (2) Azonaphthyl *phenyl* ethers are readily cleaved.[4,11] (3) Transetherification of azoethers and etherification of azonaphthols occur readily on treatment with alcohols under acid catalysis. (4) Hydrolysis in oxygen-18 labeled water affords azophenols containing oxygen-18 bound to aromatic carbon. (5) Azophenol IV undergoes oxygen exchange with aqueous acid.

It is exasperating that observation 4, which would seem most definitive, is deprived of significance by observation 5. On the other hand, observation 5, by demonstrating a closely similar reaction to occur, re-enforces the proposition that hydrolysis occurs with scission of the aryl-oxygen bond.

The kinetics of hydrolysis of II, as discussed above, suggest that a fraction of cleavage in hydrochloric acid may occur *via* S_N2 attack of chloride ion on the methyl carbon of VI, with alkyl-oxygen scission. The evidence is, however, not compelling.

The kinetics of hydrolysis of Ic in moderately concentrated HCl and $HClO_4$ and of II in $HClO_4$ indicate, when interpreted through w and w^* values with respect to an empirical criterion of mechanism, that water acts as a proton transfer agent in the rate-determining step. Chart I of the paper of Bunnett and Buncel[10] suggests how this may occur.

NOTE ADDED IN PROOF.—Prof. W. M. Schubert and coworkers (personal communication) have shown recently that methanol of normal isotopic composition is produced by cleavage of II in 5 M hydrochloric acid containing 1.7 atom per cent. excess oxygen-18. This confirms that the aryl-oxygen bond is the one ruptured in hydrolysis.

The Protonated Azo Linkage as an Activating Group.—Since most aryl alkyl ethers resist hydrolysis, the sensitivity of azo-protonated ethers of types I and II to nucleophilic attack by water reveals the protonated azo linkage to be a strong activating group for aromatic nucleophilic substitution. Its character is similar to that of the diazo group ($-N_2^+$) and of the protonated hetero nitrogen atom. One knows that alkoxy groups are sometimes hydrolytically cleaved from the *o*- and *p*-positions of diazonium salts,[18] forming diazo oxides, and that 2- and 4-alkoxyquinazolines undergo facile acid-catalyzed hydrolysis.[19]

The protonated azo linkage, the protonated hetero nitrogen and the diazo group have these features in common: a positive charge located on nitrogen, and a capacity to accept through mesomeric shift the pair of electrons that must be accommodated somewhere in the unsaturated system during bimolecular nucleophilic substitution at unsaturated carbon.[20] They are virtually ideal activating groups.[21]

The acid-catalyzed reactions of 4-phenylazo-1-naphthol and related compounds may be likened to those of carboxylic acid derivatives. Ester hydrolysis, esterification and transesterification are analogous to the ether cleavage, etherification and transetherification reactions described above. Carboxylic amide hydrolysis finds its analogy in the facile hydrolysis of 4-arylazo-1-naphthylamines to 4-arylazo-1-naphthols, a reaction described by Allan and Podstata.[22]

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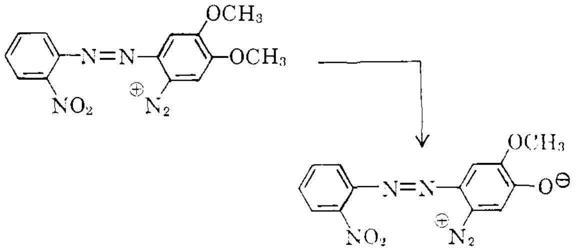
[18] R. Meldola and F. G. C. Stephens, *J. Chem. Soc.*, **87**, 1199 (1905).

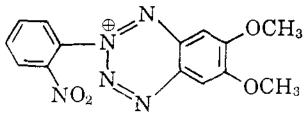
[19] A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.*, **67**, 2112 (1945).

[20] J. F. Bunnett, in "Theoretical Organic Chemistry; Proceedings of the Kekulé Symposium," Butterworths, London, 1959, p. 144.

[21] J. Ribka, *Angew. Chem.*, **70**, 241 (1958), describes the hydrolytic decomposition of some arylazoalkoxydiazonium ions such as



The fact that the methoxy group *meta* to the diazo group and *para* to the azo linkage was lost suggests that the azo linkage is the principal activating group for this reaction. It may be protonated by acids present, or it may be activated by interaction with the diazo group



[22] Z. J. Allan and J. Podstata, *Chem. Listy*, **41**, 1142 (1957); **52**, 290 (1958); *Coll. Czech. Chem. Comm.*, **23**, 725 (1958).

Experimental

The preparations and properties of 4-(*p*-sulfophenylazo)-1-naphthol (IIIc), its methyl ether Ic, 4-(*p*-sulfophenylazo)-phenol (IV), and its methyl ether II, have been described.[10]

4-(Phenylazo)-1-naphthol hydrochloride, IIIa·HCl, was prepared (by coupling in ethanolic hydrochloric acid) according to Witt and Dedichen.[23]

Methylation of 4-(Phenylazo)-1-naphthol.—Twenty-five grams of 4-(phenylazo)-1-naphthol hydrochloride was suspended in 500 ml. of methanol and the system was refluxed for 4 hours. To the system was added 100 ml. of 10% aqueous sodium hydroxide and 200 ml. of water. The insoluble material was removed by filtration, washed with water, and found to weigh 18.8 g. (81%). Recrystallization from methanol gave a solid (Ia) which melted at 79–80° (lit.[24] 83°).

Ethylation of 4-(Phenylazo)-1-naphthol.—Five grams of 4-(phenylazo)-1-naphthol hydrochloride was suspended in 100 ml. of absolute ethanol and the system was stirred and refluxed for 3.5 hours. To the system was added 20 ml. of 10% aqueous sodium hydroxide and 80 ml. of water. The yellow-orange solid was removed by filtration, washed with water, and found to weigh 3.7 g. (76%). With no further purification this material (Ib) melted at 92–95° (lit.[24] 99–100°).

Ethylation of 4-(Phenylazo)-1-naphthyl Methyl Ether (Ia).—One gram of Ia was added to a solution of 1 ml. of concentrated hydrochloric acid in 20 ml. of absolute ethanol. The system was refluxed for 90 minutes. Addition of 10 ml. of 10% aqueous sodium hydroxide and 10 ml. of water yielded 0.8 g. (75%) of 4-(phenylazo)-1-naphthyl ethyl ether (Ib), m.p. 92–95°.

Hydrolysis of 4-(*p*-Sulfophenylazo)-1-naphthyl Methyl Ether (Ic) in Oxygen-18 Labeled Hydrochloric Acid.—Into a 100-ml. r.b. flask equipped with a reflux condenser and a heating mantle, and protected from atmospheric moisture by anhydrous calcium chloride, was placed 16.7 ml. of 1.57% oxygen-18 enriched water, 3.3 ml. of concentrated hydrochloric acid (assumed to be 12 *M*) and 0.20 g. of the sodium salt of Ic. The system was refluxed for 35 minutes and then cooled. The yellow-green solid was removed by filtration and immediately dried in an Abderhalden drying apparatus charged with phosphorus pentoxide by heating at 110° under 0.05 mm. pressure for 4 hours. This material was stored over anhydrous calcium chloride until analyzed for oxygen-18 content; see Table I.

Anal. Calcd. for $C_{16}H_{12}O_4N_2S$: C, 58.54; H, 3.69. Found[25]: C, 58.46; H, 3.67.

Hydrolysis of 4-(*p*-Sulfophenylazo)-anisole (II) in Oxygen-18 Labeled Hydrochloric Acid.—Into a 100-ml. r.b. flask equipped with a reflux condenser and a heating mantle, and protected from atmospheric moisture by a calcium chloride drying tube, were placed 13.3 ml. of 1.57% oxygen-18 enriched water (Stuart Oxygen Co., San Francisco, Cal.), 6.7 ml. of concentrated hydrochloric acid (assumed to be 12 *M*) and 0.20 g. of the sodium salt of II. The system was refluxed for 2.5 hours and then 7.5 g. of anhydrous sodium acetate was added. The solid which crystallized on cooling the system was removed by filtration.

Two separate experiments were executed. In the first, the reaction product was recrystallized from 1.57% oxygen-18 enriched water; in the second, ordinary water was used in the recrystallization. In both cases the recrystallized material was dried by heating at 110° under 0.04 mm. pressure for 4 hours in an Abderhalden drying apparatus charged with phosphorus pentoxide. The material was stored over anhydrous calcium chloride until analyzed for oxygen-18 content.

A sample recrystallized from oxygen-18 enriched water was submitted for elementary analysis.

Anal. Calcd. for $C_{12}H_9O_4NSNa\cdot 0.5\ H_2O$: C, 46.61; H, 3.26. Found[25]: C, 46.50; H, 3.19.

The carbon-hydrogen analysis indicates the sample to be a hemihydrate. The "calcd." oxygen-18 contents for aryl-oxygen labeled IV in Table I are, however, computed for the anhydrous salt. The fact that virtually identical oxygen-18 contents were determined for IV recrystallized from ordinary or from oxygen-18-enriched water supports the view that the material submitted to oxygen-18 analysis was the anhydrous salt.

The explanation of this seeming inconsistency probably lies in the differing histories of the samples submitted to the two kinds of analysis. Those for oxygen-18 analysis were analyzed directly on removal from the desiccator, while those for carbon-hydrogen analysis were several days in transit to the analytical laboratory.[25] During that time, water from the atmosphere was probably incorporated to form the hemihydrate.

Oxygen-18 Exchange between 4-(*p*-Sulfophenylazo)-phenol (IV) and Aqueous Hydrochloric Acid.—The preceding experiment was repeated using the sodium salt of IV in place of the corresponding salt of the methyl ether II. The product was recrystallized from ordinary water.

Oxygen-18 Analyses.—The oxygen-18 content of the enriched water was determined according to the method of Anbar and Guttman.[26] The oxygen-18 contents in the samples of IIIc, the sodium salt of IV and sodium azobenzene-4-sulfonate were determined by the method of Rittenberg and Ponticorvo.[27] The carbon dioxide samples thus obtained were analyzed on the Consolidated Engineering Corporation model 21-103C mass spectrometer at Harvard University. The results of these analyses are either shown in Table I or stated in the text above.

The procedures employed for the rate measurements have been previously described.[10]

Acknowledgments.—We wish to express our thanks to Dr. C. A. Bunton of University College, London, for some earlier oxygen-18 determinations, to Professor F. H. Westheimer for use of the mass spectrometer at Harvard University and for advice on methods of oxygen-18 analysis, to Dr. G. Dudek of Harvard University for guidance in the oxygen-18 analyses, and to Dr. G. B. Hoey for preliminary experiments in this area. We are also grateful for stimulating conversations with Dr. H. Zollinger (ETH, Zurich) and Dr. J. J. Leavitt (American Cyanamid Co., Bound Brook, N. J.).

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[23] O. N. Witt and J. Dedichen, *Ber.*, **30**, 2655 (1897).

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