allowed to run until the pressure became constant (10 half-lives) to provide the infinity pressure. The gas volume change in a typical run was 0.2%; the pressure change was 140 mm. First-order reactions were generally slow the first min., good to ±5% in succeeding 1 min. intervals, reproducible to ±3% average deviation. The second-order runs with amines of the class $ArNH_2$ were carried out under similar conditions with 2.9 mmoles of amine and 0.38 ml. of boronic ester, except that in the run with aniline hydrochloride 2.06 mmoles of aniline, 2.32 mmoles of aniline hydrochloride, and 0.25 ml. of boronic ester were used. Rate constants are summarized in Tables II and III.

Isotope Effects. In 80% ethanol (4:1 by syringe) at 25.0 ± 0.05°, k_1 was 4.22 and 4.12 × 10^{-3}. Substitution of 99.8% deuterium oxide for the water reduced k_1 to 2.26 × 10^{-3}. In 79% ethanol (2 ml. of water and 10 ml. of 95% ethanol, 0.20 ml. of dibutyl 2-bromoethaneboronate) k_1 was 4.29 × 10^{-3}. Substituting deuterium oxide and 95% O-deuterioethanol (98 atom % of D, Merck Sharpe and Dohme of Canada) reduced k_1 to 2.53 × 10^{-3}. For second-order runs, the solvent and reactants were weighed to 0.1% in syringes and injected into the closed, nitrogen-filled apparatus. In 12 ml. of absolute ethanol, 0.20 ml. (0.83 mmole) of dibutyl 2-bromoethaneboronate and 0.20 ml. (1.54 mmole) of dimethylaniline yielded k_2 = 0.0138 and 0.0141 (calculated assuming initial volumes additive). In absolute O-deuterioethanol, 98 atom % of D, k_2 = 0.0133 and 0.0129.

Mechanisms of Cleavage of Heteroaromatic Ethers. II. The Acid-Catalyzed Cleavage of 2-Methoxypyrimidine-O^{18} [1,2]

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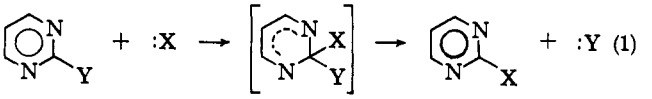
Cleavage of 2-methoxypyrimidine-O^{18} in an aqueous acid medium has been determined as proceeding predominantly via an aromatic nucleophilic substitution (SNAr) reaction. In addition, it has been shown that an SN2 mechanism makes a minor contribution to the overall cleavage of 2-methoxypyrimidine in an aqueous acid medium.

It is well known that the cleavage of a typical alkyl aryl ether proceeds with great difficulty and requires the use of a concentrated mineral acid or a strong Lewis acid; by contrast, certain alkyl heteroaromatic ethers may be cleaved under relatively milder conditions such as dilute aqueous acids.[4] The experiments described in this paper represent part of a study designed to elucidate the mechanisms by which alkyl heteroaromatic ethers were cleaved.

It has been long assumed[5-7] that the facile, acid-catalyzed cleavage of α- and γ-alkoxypyrimidines proceeds *via* a mechanism closely related to the nucleophilic displacement of other functional groups attached to *suitably substituted* aromatic or heteroaromatic rings. Such displacement reactions involve an attack by a nucleophile X at the carbon atom bearing the functional group Y; an intermediate is formed which undergoes loss of Y to afford the substitution product (eq. 1).



However, for the cleavage of heteroaromatic ethers, at least three general mechanisms may be written. Chart I depicts these mechanisms portraying as the substrate the 2-alkoxypyrimidinium cation **1**, the subject of this research.

Mechanism A. Nucleophilic attack of a water molecule at the *aromatic* carbon atom carrying the ether linkage would lead to the formation of an SNAr intermediate (**2**) of the type described above. Subsequently this intermediate would decompose to form an alcohol (**3**) and the 2-hydroxypyrimidinium cation **4**.

Mechanism B. Conversely, an SN2 attack of a water molecule at the *aliphatic* carbon atom of the ether linkage would lead to the same products (**3** and **4**) but these would proceed through a transition state (**5**) rather than an intermediate–complex (**2**).

Mechanism C. These same products could arise *via* an SN1 mechanism involving prior, unimolecular cleavage of the alkyl-to-oxygen bond of the cation **1** to produce a carbonium ion intermediate **7**, which among other reactions could react with water to form the alcohol **3** and a proton. The 2-hydroxypyrimidinium cation **4** would then arise by protonation of the 2-pyrimidone **6** formed by the original cleavage reaction.

(1) This research was supported by National Science Foundation, Cooperative Graduate Fellowship, Oct. 1, 1959–Sept. 30, 1961, and by the Research Board of the Graduate College of the University of Illinois, Grant No. 56-92-62.

(2) A preliminary account of part of this work has been published: R. Daniels, L. T. Grady, and L. Bauer, *J. Org. Chem.*, 27, 4710 (1962).

(3) This paper is abstracted from the thesis submitted by L. T. Grady to the Graduate College of the University of Illinois at the Medical Center, 1963, in partial fulfillment of the requirements for the Ph.D. Degree.

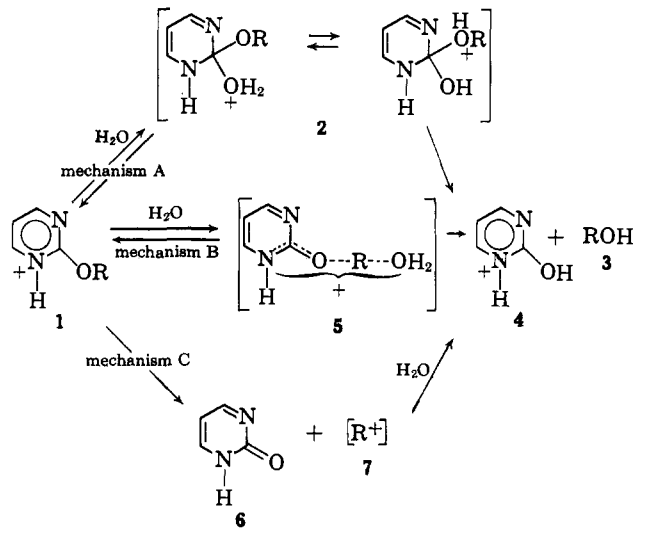
(4) J. Sauer and R. Huisgen, *Angew. Chem.*, 72, 294 (1960).

(5) B. Lythgoe, *Quart. Rev.* (London), 3, 181 (1949).

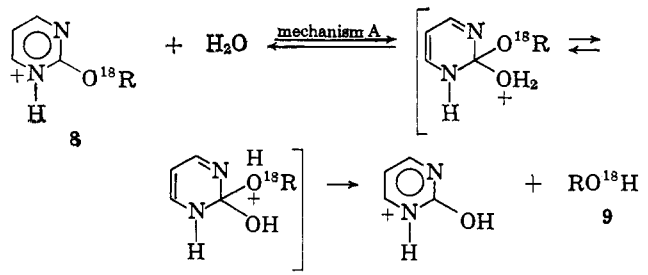
(6) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 49, 273 (1951).

(7) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, 384 ff.

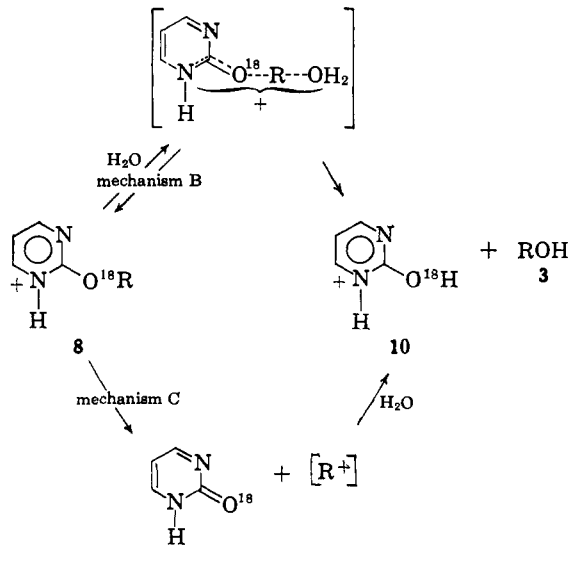
Chart I



These mechanisms may be distinguished by isotopic labeling of the ethereal oxygen atom. Cleavage of a 2-alkoxypyrimidinium-O^{18} cation (**8**) according to mechanism A would produce an alcohol (**9**) containing that isotope.

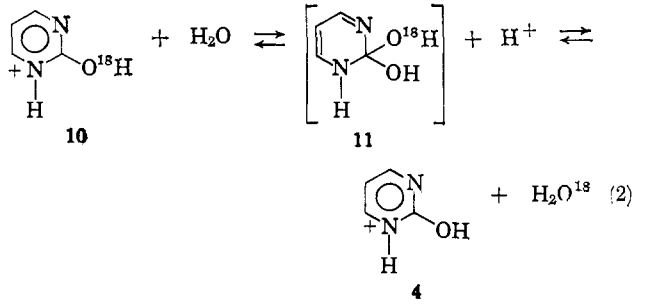


On the other hand, a cleavage of **8** which proceeds by either mechanism B or C would provide an alcohol (**3**) devoid of O^{18}[8]; rather, this isotope would be found initially in the cationic product **10**.



(8) It is of interest to note that intrusion of some labeled oxygen into the alcohol **3** might be anticipated because the O^{18} in 2-hydroxypyrimidinium cation **10** will equilibrate with the oxygen in water *via* intermediate **11** (see eq. 2). To the extent that the water is thereby enriched, mechanisms B and C could produce labeled alcohol; but even assuming a statistical distribution for the case at hand, the amount of spuriously labeled alcohol would be less than the experimental error in the mass spectrographic analysis.

For the solution of the problem at hand, alcohol rather than 2-pyrimidone was selected as the product for mass spectrographic analysis since the latter (**10**) will undergo facile equilibration with water in the aqueous acid medium (eq. 2). Such equilibration would vitiate data that support either mechanism B or C.[9]



Results and Discussion

Redistilled 2-methoxypyrimidine-O^{18} was allowed to undergo cleavage in hot, dilute, aqueous sulfuric acid, and the methanol produced during the hydrolysis was isolated. This methanol (sample 1) along with stock reagent methanol (sample 2), original O^{18}-labeled methanol (sample 3), and labeled methanol from a control experiment (sample 4) were subjected to mass spectrographic analysis. The apparent mass data are recorded in Table I.

Table I. Peak Heights in mm.

	Sample 1 (product)	Sample 2 (stock)	Sample 3 (original)	Sample 4 (control)
Apparent mass 34	10.0	0.0	12.3	14.5
Apparent mass 32	159	182.5	177	211
Ratio 32/34	15.9	...	14.4	14.6
Inlet pressure (in μ)	33.82	34.09	34.36	38.49

The ratio of mass 32/34 for samples 1, 3, and 4 are quite similar; but, as expected, stock reagent methanol (sample 2) exhibits no 34-apparent mass peak under the conditions chosen for the analyses.

By comparing the 32/34 ratio of control (14.6) to that given by the original labeled methanol (14.4) it is calculated that under the conditions chosen for the cleavage of labeled 2-methoxypyrimidine methanol retains 98.6% of the original labeling. Because this is within the experimental error for mass spectrographic data (about 2%) it is concluded that under the conditions employed in the cleavage experiment the control methanol does not exchange its oxygen with that of water.

This is consistent with the results of other workers who also found that methanol does not exchange its oxygen in dilute aqueous mineral acid.[10,11] The

(9) See J. F. Bunnett, E. Buncel, and K. V. Nahabedian, *J. Am. Chem. Soc.*, 84, 4136 (1962), for an account of a study in which exactly this difficulty did arise.

(10) I. Roberts, *J. Chem. Phys.*, 6, 294 (1938).

(11) S. C. Datta, J. N. E. Day, and C. K. Ingold, *J. Chem. Soc.*, 838 (1939).

significance of these data is that the isotopic content of the methanol produced during the cleavage of 2-methoxypyrimidine under these conditions is determined solely by the mechanism by which that cleavage occurs.

Comparison of the 32/34 apparent mass ratios of the control (14.6) and the hydrolysis sample (15.9) reveals that the methanol produced during the cleavage of labeled 2-methoxypyrimidine contains 91.8% of the starting isotopic labeling. This demonstrates that mechanism A which involves an SNAr intermediate complex represents the major pathway for the cleavage of 2-methoxypyrimidinium cation.

However, a small part (8.2%) of the O^{18} content was not contained in the methanol produced during the cleavage. Because formation of a methyl carbonium ion is unlikely under such conditions, it is probable that mechanism B (SN2) also participates in this cleavage. It is believed that the carbon-to-oxygen bond of the methyl group is highly polarized in 2-methoxypyrimidinium cation and thus is susceptible to an SN2 reaction by a nucleophile. To support this thesis, cleavage of 2-methoxypyrimidine in dilute aqueous hydrochloric acid has been found to give rise to methyl chloride in addition to methanol. Since methyl chloride is not liberated from solutions of 6 *N* hydrochloric acid and methanol under these conditions, the methyl chloride results from a nucleophilic attack by chloride ion on the polarized methyl group of the ether cation. This supports the mechanism proposed by Ulbricht[12] for the cleavage of 2-methoxypyrimidine by solutions of sodium iodide in acetic acid.

Conclusion

The evidence presented herein indicates that at least two mechanisms exist for the aqueous acid cleavage of alkyl heteroaromatic ethers: nucleophilic addition of water at the aromatic carbon atom (mechanism A) and attack of water at the aliphatic carbon (mechanism B) of the ether linkage.

Experimental

Materials. 2-Chloropyrimidine was prepared by the usual methods from 2-pyrimidinol.[13,14] Samples prepared by an alternate method from 2-aminopyrimidine[15] were found to be contaminated with the starting material when analyzed by infrared spectrophotometry. Phenyl ether was purified by distillation, b.p. 138–140° at 20 torr. Sodium hydride dispersion (53.2% in mineral oil) was purchased from Metal Hydrides, Inc. Methanol labeled with O^{18} (10.8% stated value) was obtained from Yeda, Rehovoth, Israel.

Mass Spectrographic Data. These data were obtained using a Consolidated Electrodynamics Corporation mass spectrograph No. 21–130 at 40 μa. emission current and 7.0 v. ionizing potential. The authors are indebted to Mr. Robert Sherrill of Northwestern University for performing the analyses.

2-Methoxypyrimidine-O^{18}. Sodium hydride dispersion (4.51 g., 0.10 mole) was added to 50 ml. of dry phenyl ether. With constant stirring and cooling, labeled methanol (4.2 ml., 0.10 mole) was added and the mixture was allowed to stand at room temperature for 1.5 hr. A solution of 2-chloropyrimidine (11.45 g., 0.10 mole, m.p. 63–65°, freshly recrystallized from isopentane) in phenyl ether (50 ml.) was added dropwise with constant stirring and occasional cooling. The mixture was heated in an oil bath at 100° for 2 hr. and then the material distilling below 65° at 0.4 torr was collected (16.9 g.). Redistillation yielded 9.78 g. (88.8%) of 2-methoxypyrimidine-O^{18}, b.p. 96–98° at 33–34 torr.

Cleavage of 2-Methoxypyrimidine-O^{18}. A portion of the above ether (8.80 g., 0.080 mole) was dissolved in a mixture of concentrated sulfuric acid (4.5 ml., 0.081 mole) and water (final volume 40 ml.) and the solution was heated in a distilling flask in an oil bath at 105° for 5.5 hr. (final pH 0.10). Distillation of this reaction mixture provided a 13.5-ml. sample which was treated as outlined below in the methanol isolation procedure. Finally the methanol was distilled at 66–68°, and provided 1.66 g. (64.4%) of hydrolysis product. This sample was dried overnight in contact with 1.0 g. of Drierite, distilled *in vacuo* through a gas manifold, and subjected to mass spectrographic analysis.

Control Experiment. A sample (2.28 g.) of labeled methanol was dissolved in a solution of sulfuric acid (5 ml., 0.09 mole), 2-pyrimidinol (8.52 g., 0.089 mole), and water (final volume 40 ml.). This solution was treated in a fashion identical with the above procedure. The recovered methanol, 1.72 g. (75.4%), was dried over Drierite (1.0 g.), distilled as above, and subjected to mass spectrographic analysis.

Methanol Isolation Procedure. At the termination of the cleavage or control experiment, approximately 15 ml. was collected as distillate. This sample was neutralized by 10% aqueous sodium hydroxide and saturated with anhydrous potassium carbonate (*ca.* 19 g.). After maintaining the carbonate solution at reflux for 10–15 min. without distillation, methanol was collected over another 15-min. period. This methanol was dried overnight by an equal weight of Drierite and collected by distillation through a gas manifold. Gas–liquid chromatographic analysis (carbowax 4000 on Chromosorb P; 70°, 47 p.s.i. of helium) showed samples of methanol prepared in this fashion to be free (less than 0.5%) of water.

Hydrolysis of 2-Methoxypyrimidine in Hydrochloric Acid. 2-Methoxypyrimidine (11.01 g., 0.10 mole) was dissolved in a mixture of water (25 ml.) and concentrated hydrochloric acid (10 ml., 0.12 mole) and the solution was heated in a distilling flask in an oil bath at 100° for 1.5 hr. Distillation provided a 15-ml. sample which was treated according to the methanol isolation procedure outlined above, and yielded methanol, 1.28 g. (40%). The gas which formed during the hydrolysis was collected over

(12) T. L. V. Ulbricht, *J. Chem. Soc.*, 3345 (1961).
(13) J. W. Copenhaver and R. F. Kleinschmidt, *British Patent* 663, 302 (Dec. 19, 1951); *Chem. Abstr.*, **46**, 10212a (1952).
(14) T. Matsukawa and B. Ohta, *J. Pharm. Soc. Japan*, **69**, 489 (1949); *Chem. Abstr.*, **44**, 3456 (1950).
(15) I. C. Kogon, R. Minin, and C. G. Overberger, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 182.

saturated aqueous potassium carbonate in a graduated cylinder and was identified as methyl chloride by infrared spectrophotometry.[16]

(16) R. H. Pierson, A. N. Fletcher, and E. St. Clair Gantz, *Anal. Chem.*, 28, 1218 (1956).

In a separate experiment 2-methoxypyrimidine (5.51 g., 0.050 mole) was dissolved in 2 *N* hydrochloric acid (30 ml., 0.060 mole) and hydrolyzed as above. The volume of methyl chloride collected (230 ml. at STP) represented a 21% yield based on 2-methoxypyrimidine.

The Mechanism of the Diels–Alder Reaction of 2-Methylfuran with Maleic Anhydride[1,2]

Stanley Seltzer

Contribution from the Chemistry Department, Brookhaven National Laboratory, Upton, New York. *Received May 23, 1964*

Five different deuterated isomers of the exo adduct (I) formed from 2-methylfuran and maleic anhydride were synthesized and their rates for retro Diels–Alder reaction in isooctane at about 50° were determined. From the nature of these secondary α- and β-deuterium isotope effects, we conclude that the two bonds formed between diene and dieneophille are ruptured in a concerted process in the reverse Diels–Alder reaction. The n.m.r. spectra of these compounds are discussed.

Introduction

The question of the detailed mechanism of the Diels–Alder reaction[3] still commands attention.[2,4,5] Whether the two new bonds are formed in two separate steps or in one concerted step with equal or unequal bond making is of primary importance. Several new approaches have been used to distinguish between these possibilities but disagreement still exists.[4,5] A new method which appears to be well suited for the study of the relative timing of the formation of two bonds is the secondary α-deuterium isotope effect. The subject of this paper deals with the α- and β-deuterium effects in the decomposition of the Diels–Alder adduct derived from 2-methylfuran and maleic anhydride. From the results, we conclude that the two new bonds must form simultaneously.

Experimental

2-Methylfuran, supplied by Eastman Kodak, was redistilled before use, b.p. 64°, n^{25}D 1.4300.

Maleic anhydride, supplied by Pfanstiehl was sublimed before use.

2-Methylfuran-5-d. 2-Methylfuran was converted to 2-chloromercuri-5-methylfuran.[6] The 2-chloromercuri-5-methylfuran, 47.5 g., was suspended in a 50–50 mixture (w./w.) of EtOD–D_2O (*vide infra*) which was approximately 1 *M* in D_2SO_4. An amount of NaCl, equivalent to the quantity of sulfuric acid, was added and the mixture was refluxed for 0.5 hr. The fraction boiling up to 70° was collected, dissolved in ether, and dried over $MgSO_4$. The ether was fractionated through a 12-in. platinum spiral column until about 25% of the original volume remained. This was chromatographed, in 3–4-ml. portions, on a 12-ft. Ucon column at 70° to yield 4.5 g. of 2-methylfuran-5-*d*.

EtOD–D_2O solution was prepared by refluxing 177 g. (1.5 moles) of E.K.C. diethyl carbonate in 140 ml. of D_2O plus 11 ml. of approximately 19 *N* D_2SO_4. After 72 hr. only one phase was visible; after another 24 hr. only 3% of the original ester was unhydrolyzed as determined by infrared.[7]

Maleic anhydride-d_2 was prepared as described previously.[8]

Maleic Anhydride-d_1. Bromomaleic anhydride, prepared according to previously published methods,[9] was dissolved in ethyl ether to which a slight excess of D_2O was added. The ether was evaporated off and the bromomaleic acid-d_2 was recrystallized from nitromethane, m.p. 127–128° (lit.[9b] m.p. 128°). *Anal.* Calcd. for Br: 40.32. Found: 39.53. The electrolysis was carried out with a preconditioned lead cathode (175 cm.^{2}) and a wire mesh platinum anode. The anode compartment was essentially a fine fritted cylinder that was suspended inside the main cylindrical compartment. A typical reduction was carried out with the catholyte containing 17.3 g. (0.088 mole) of bromomaleic acid-d_2, 100 ml. of D_2O, and 15 ml. of 10.7 *M* NaOD. The anolyte consisted of 20 ml. of 10.7 *M* NaOD. The main compartment was stirred while

(1) (a) Research performed under the auspices of the U. S. Atomic Energy Commission. (b) The majority of the work described herein was presented at the Gordon Conference on "The Chemistry and Physics of Isotopes," New Hampton, N. H., July 1962.

(2) For preliminary reports of this work see (a) S. Seltzer, *Tetrahedron Letters*, No. 11, 457 (1962); (b) *J. Am. Chem. Soc.*, **85**, 1360 (1963).

(3) M. C. Kloetzel, *Org. Reactions*, **4**, 1 (1948).

(4) For pertinent literature references see (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 711–721; (b) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(5) (a) C. Walling and J. Peisach, *J. Am. Chem. Soc.*, 80, 5819 (1958); (b) J. A. Berson, R. D. Reynolds, and W. M. Jones, *ibid.*, 78, 6049 (1956); (c) J. A. Berson, A. Remanick, and W. A. Mueller, *ibid.*, 82, 5501 (1960); (d) J. A. Berson and W. A. Mueller, *ibid.*, 83, 4940 (1961); 83, 4947 (1961); (e) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem.*, 74, 352 (1962); (f) R. P. Lutz and J. D. Roberts, *J. Am. Chem. Soc.*, 83, 2198 (1961); (g) M. J. Goldstein and G. L. Thayer, Jr., *ibid.*, 85, 2673 (1963).

(6) H. Gilman and G. F. Wright, *ibid.*, **55**, 3302 (1933).

(7) R. N. Jones, D. A. Ramsay, D. S. Keir, and K. Dobriner, *ibid.*, 74, 80 (1952).

(8) S. Seltzer, *ibid.*, 83, 1861 (1961).

(9) (a) A. Michael, *J. prakt. Chem.*, 52, 289 (1895); (b) C. K. Ingold, *J. Chem. Soc.*, 121, 1306 (1922); (c) S. Cristol, *J. Am. Chem. Soc.*, 74, 5025 (1952).