was identical with a sample of *exo*-norbornanol prepared by hydroboration of norbornene.[8] The low-field proton (<CHOH) in the nmr spectrum of each alcohol appeared at τ 6.38. The minor isomer was a nitrate, ir 6.1 μ (-ONO$_2$).

Silver Nitrate Promoted Hydrolysis of 3.—1,*exo*-2-Dichloronorbornane (**3**) was treated with aqueous silver nitrate as described above. After 8 hr vpc analysis (SE-30, 130°) showed the presence of norcamphor and a small amount of unreacted **3**.

4-Chloronorcamphor (14) from 1-Chloro-3-*endo*-norbornanol (10).[8]—To a solution of 0.21 g of **10** in 0.7 ml of ether was added dropwise a solution of 0.15 g of sodium dichromate dihydrate and 0.11 ml of concentrated sulfuric acid in 0.75 ml of water. After 45 min at room temperature, 10 ml of ether was added. The organic phase was washed successively with aqueous sodium bicarbonate and water and dried over magnesium sulfate, and the solvent was removed at the rotary evaporator. Analysis by vpc showed two products (ratio of *ca.* 95:5). The major product was isolated by preparative vpc; its nmr and ir spectral properties and vpc retention time were identical with those of **14**,[18] except for the slight difference in carbonyl position already noted.

Solvolysis of 2,2-Dichloronorbornane (2).—A solution of 2.8025 g (17.10 mmol) of **2** and 2.3569 g (28.73 mmol) of sodium acetate trihydrate dissolved in 80% ethanol–20% water (v/v) was diluted to 100 ml in a volumetric flask. Aliquots (5 ml) were injected into soft glass ampoules which were then chilled, sealed under vacuum, and immersed in a constant-temperature bath at 70.0 ± 0.1°. Ampoules were titrated with 0.0200 *M* silver nitrate by Fajan's method, using dichlorofluorescein as indicator.[40] Analysis by vpc (SE-30, 125°) showed the products to be **6** (56 ± 1%) and **15** (44 ± 1%); the ratio was constant throughout the reaction.

Attempted Solvolysis of 1,*exo*-2-Dichloronorbornane (3).—A solution of 1.0 g of **3** in 20 ml of 80% ethanol was maintained at 85° for 480 hr. No liberated acid could be detected by titration with base. Analysis by vpc (SE-30, 140°) showed only **3**. Aliquots (5 ml) of a solution of 0.6943 g of **3** in 25 ml of 80% ethanol were sealed in ampoules as above. Titration of the ampoule opened after 795 hr indicated less than 0.2% reaction.

Attempted Solvolysis of 1,*exo*-3-Dichloronorbornane (4).—A solution of 1.6017 g (9.766 mmol) of **4** and 0.8040 g (9.800 mmol) of sodium acetate was diluted to 100 ml in 80% ethanol and sealed in ampoules as above. The contents of the ampoule titrated with 0.0100 *M* silver nitrate after 530.5 hr at 70° required 2.70 ml of titrant. The rate constant based on this titration (*ca.* 5% reaction) was based on the assumption that the impurity (0.4%) (*vide supra*) consisted of 2,2-dichloronorbornane **2**.

Registry No.—**2**, 19916-65-5; **3**, 15019-72-4; **4**, 19916-67-7; **5**, 15019-71-3; **6**, 694-93-9; **11**, 19916-70-2; **12**, 19916-71-3.

Acknowledgments.—Financial support by the National Science Foundation and by the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged. Professors P. von R. Schleyer and J. W. Wilt generously supplied preprints describing their studies, and Professor K. B. Wiberg kindly supplied spectral data for 1-chloro-3-norbornanone. W. B. F. was the recipient of a Wesleyan University 1967 Summer Study Grant. Professor B. Franzus carried out spin-decoupling experiments on **4** and made a number of helpful comments on the manuscript. Kinetic data were subjected to least-squares analysis on a General Electric time-sharing computer; Mr. Lee Riggs performed these analyses.

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[40] H. H. Willard and N. H. Dean, "Elementary Quantitative Analysis," 3rd ed, D. Van Nostrand Co., New York, N. Y., 1940, p 169.

Cleavage of Hindered Aromatic Ethers. Kinetics[1]

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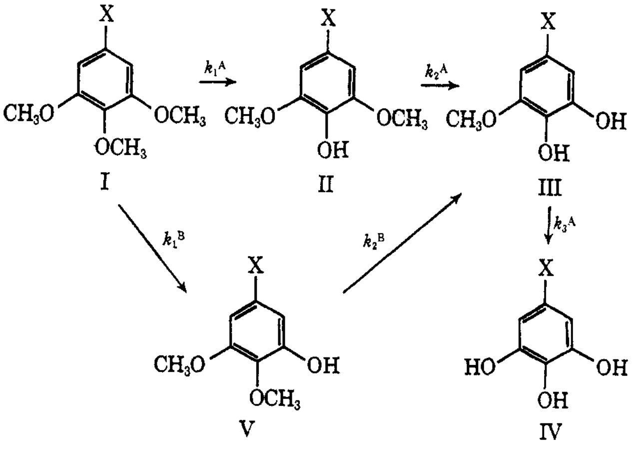
The rates of ether cleavage by HBr in glacial acetic acid at 76° for trisethers and related monoethers are correlated by a $\rho\sigma$ plot. It is concluded that the enhanced rate of cleavage of 1,2,3-trimethoxybenzenes is too large to be accounted for by electrostatic substituent effects and occurs mainly because of the enhanced basicity of the central methoxyl as it is sterically twisted out of the plane of the benzene ring. The role of nonbonded interactions is discussed.

It is well known that trisethers with structure I, where X can be either an electron-attracting or electron-donating group, are cleaved by various acidic reagents to give largely II along with slight amounts of III and IV but little if any V[2-4] (Scheme I). Three different rationalizations can be offered. The generally accepted view[5] is that the middle methoxyl is crowded out of the plane of the benzene ring. This involves an unspecified combination of steric alteration of nonbonded interactions and enhanced basicity of the central methoxyl due to partial loss of conjugation. Brossi, *et al.*,[6] in discussing the ether cleavage of cactus alkaloid isoquinoline analogs of I, emphasized the second component involving enhanced basicity. A third possibility is that the rates are normal and determined solely by the accepted electronic effects of all ring substitutents. Although much qualitative product data are available for this reaction, there are only

SCHEME I



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[1] Taken in part from the M.S. dissertation submitted by M. A. Seager to the Cornell Graduate School, Sept 1966.

[2] W. J. Horton and J. T. Spence, *J. Amer. Chem. Soc.*, **77**, 2894 (1955); P. D. Gardner, W. J. Horton, and R. E. Pincock, *ibid.*, **78**, 2541 (1956).

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[6] A. Brossi, M. Baumann, and R. Borer, *Monatsh. Chem.*, **96**, 25 (1965).

TABLE I

ETHER CLEAVAGE RATES IN HBR AND ACETIC ACID AT 76° OF X-SUBSTITUTED METHOXYBENZENES

Compd[a]	3-R[b]	4-R[b]	5-R[b]	1-X[b]	$\Sigma\sigma$	Rate[c] constant × 10^4
A_1	OCH_3	OCH_3	OCH_3	CH_3	−0.706	30.3
A_2	OCH_3	OH	OCH_3	CH_3	−0.320	2.0[d]
A_3	OH	OH	OCH_3	CH_3	−0.320	0.83
A_x	H	OCH_3	H	CH_3	−0.170	0.67
B_1	OCH_3	OCH_3	OCH_3	H	−0.536	19.6
B_2	OCH_3	OH	OCH_3	H	−0.255	1.33[d]
B_3	OH	OH	OCH_3	H	−0.255	0.55
B_x	H	OCH_3	H	H	0.000	0.38
C_1	OCH_3	OCH_3	OCH_3	$NHCOC_6H_5$	−0.458	19.3
D_1	OCH_3	OCH_3	OCH_3	$CH_2NEt_3^+$	−0.287	9.3
E_1	OCH_3	OCH_3	OCH_3	CHO	−0.320	6.7
F_1	OCH_3	OCH_3	OCH_3	CO_2H	−0.086	7.7
F_x	H	OCH_3	H	CO_2H	0.450	0.10
G_1	OCH_3	OCH_3	OCH_3	CN	0.124	3.3
H_1	OCH_3	OCH_3	OCH_3	NO_2	0.242	2.5
H_2	OCH_3	OH	OCH_3	NO_2	0.460	0.17[d]
H_x	H	OCH_3	H	NO_2	0.778	0.033
I_1	OCH_3	OCH_3	H	H	−0.268	4.0[d]
I_2	OH	OCH_3	H	H	−0.370	1.7

[a] These designations are keyed to Figure 1. [b] Substituents of 1,3,4,5-substituted benzenes; *e.g.*, A_1 is 3,4,5-trimethoxytoluene. [c] Rate constants are in moles per liter second. [d] This rate constant contains a statistical correction of 0.5.

fragmentary quantitative data and these do not permit a distinction between the above possibilities.

In keeping with our general interest in the transmission of substituent effects the present work was undertaken to obtain quantitative data on the rates of cleavage of the three methoxyl groups of trisethers, and to use these data to begin to unravel the factors leading to selective reaction of the central methoxyl. A plot of the kinetic data should give a single line if only electrostatic substituent effects are responsible while the incursion of special steric effects for the central methoxyl should reveal itself by the systematic enhancement of these rates over the "standard" nonaccelerated cleavage rates.

The study included a range of substituents in the simple trisethers of type I, as well as dimethoxybenzene, anisole, three *para*-substituted anisoles, and the three 6,7,8-trimethoxyisoquinolines used by Brossi. The reagent–solvent combination selected was hydrogen bromide in glacial acetic acid since it would give homogeneous reactions, is easily prepared, and cleaves these ethers at convenient rates.

Experimental Section[7]

Materials.—The hydrogen bromide in glacial acetic acid was prepared according to the procedure of Kolthoff and Bruckenstein.[8] The solution was stored at −20° until needed. Solutions of sodium acetate in glacial acetic acid were prepared by dissolving dried (110° for 5 hr) sodium acetate in commercial glacial acetic acid. The acetate solutions were standardized against 0.0977 *M* perchloric acid in acetic acid using *p*-naphtholbenzein as an indicator.[8]

N-Benzoyl-3,4,5-trimethoxyaniline.—To 3.7 g (0.02 mol) of 3,4,5-trimethoxyaniline in 70 ml of dry ethyl acetate was added 3.0 ml of benzoyl chloride and the mixture refluxed for 4 hr. The solvent was removed and the product was recrystallized from dilute ethanol to yield 4.2 g (90% yield) of gray crystals: mp 140°; nmr ($CDCl_3$, TMS), τ 2.72, 3.00, 3.28 (total of 7 H), and 6.46 (9 H).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.90; H, 5.92; N, 4.88. Found: C, 66.84; H, 5.77; N, 4.63.

3,4,5-Trimethoxybenzyltriethylammonium Bromide.—A solution of 5 ml of (0.050 mol) of triethylamine and 1.3 g (0.005 mol) of α-bromo-3,4,5-trimethoxytoluene in 25 ml of dry acetone was refluxed for 5 hr. The crystalline product was collected and washed repeatedly with acetone until it was pure white. From the analysis it appeared to be the monohydrate.

Anal. Calcd for $C_{16}H_{28}O_3NBr \cdot H_2O$: C, 50.53; H, 7.95; N, 3.68; Br, 21.01. Found: C, 50.30, 50.67; H, 7.68, 8.09; N, 3.90, 3.71; Br, 21.41, 21.28.

3,4,5-Trimethoxynitrobenzene was prepared[9] by nitration of pyrogallol trimethyl ether to give pale yellow crystals in 76% yield, mp 97–97.5° (lit.[9] mp 97°).

3,4,5-Trimethoxytoluene was prepared by Wolff–Kishner reduction of the available 3,4,5-trimethoxybenzaldehyde[10] and purified by preparative glpc on a 5% FFAP column.

The 6,7,8-Trimethoxyisoquinolines.—The 1-methyl-6,7,8-trimethoxyisoquinoline, 1-methyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline, and 1-methyl-6,7,8-trimethoxy-1,2,3,4-tetrohydroisoquinoline were experimental compounds from the laboratory of Hofmann-La Roche, Inc., Nutley, N. J.[11]

Other ethers studied in this work were purchased commercially and were repurified before use.

Kinetics and Analysis.—Aliquots (2.5 ml) of an acetic acid solution of an ether and hydrogen bromide were sealed into necked tubes and suspended in a constant-temperature bath at 76.0°. One tube, not placed in the bath, served as an initial point and was titrated immediately. At selected intervals a tube was removed from the bath, quenched in ice water, and a 2-ml aliquot of the contents titrated with sodium acetate in acetic acid using *p*-naphtholbenzein as an indicator.

The kinetic measurements and data analysis for trimethoxybenzene, trimethoxytoluene, and trimethoxynitrobenzene were carried out in two ways. In the first the ether concentration was 0.020 *M* and the HBr concentration was 0.090 *M*. The resulting data were analyzed by the procedure of French and McIntire.[12] This method converts consecutive second-order reactions containing a common order in one component into consecutive first-order reactions by using the time integral of the common component in place of time as the independent variable. The resulting pseudo-first-order data are then analyzed graphically to obtain k_1, k_2, and k_3. In the present situation the actual kinetic scheme is one of parallel consecutive reactions (still reducible to pseudo-first-order reactions). The graphically derived value

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[7] Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were determined on an A-60 Varian spectrometer.

[8] I. M. Kolthoff and S. Bruckenstein, *J. Amer. Chem. Soc.*, **78**, 1 (1956).

[9] R. F. Collins and M. Davis, *J. Chem. Soc.*, 1863 (1961).

[10] Y. Asakina and M. Yasue, *Chem. Ber.*, **69**, 2327 (1936).

[11] We would like to thank Dr. A. Brossi of the Hofmann-La Roche Co. for making these experimental samples available to us.

[12] D. French and R. L. McIntire, *J. Amer. Chem. Soc.*, **72**, 5148 (1950).

of k_1 is the sum of the two rate constants for cleavage of one methoxyl from the trisether. The values of k_2 and k_3 are averages of the cleavage rate constants of bis- and monoethers, respectively, with weighting functions that are approximately the fraction of reaction proceeding by each path. Since both kinetic and product data indicate that cleavage of the central ether dominates the reaction (by a factor estimated to be 30:1), the observed k_1 corresponds fairly closely to k_1^A, the rate constant for the cleavage of the central ether. The precision of each k_1 is about ±2% which means that k_1^A should be about $0.97k_1$ with an uncertainty of no more than ±5%. The value of k_2^A is less certain but is probably equal to about $0.9k_2$ with a combined uncertainty of less than ±10%. The value of k_3^A should be essentially the same as the observed k_3. The measured k_1 and k_3 rate constants are collected in Table I. Also tabulated are the measured values of k_2 divided by a statistical correction factor of 2.

In the second method of obtaining the kinetic rate constants for the trimethoxybenzene, trimethoxytoluene, and trimethoxynitrobenzene the ether and HBr concentrations were both 0.0335 *M*. The data were analyzed for k_1 by the usual procedure for second-order kinetics with equal concentrations. The values of k_2 and k_3 were not obtained. The values of k_1 agreed within 1% of the values obtained by the first method.

The constants for the other trisethers and monoethers listed in Table I were obtained and analyzed by the second method. The constants for dimethoxybenzene were obtained by both methods. In general, duplicate kinetic runs gave rate constants that agreed within ±5%. For 3,4,5-trimethoxybenzaldehyde, the worst case, the agreement was only ±15%.

The French and McIntire kinetic analysis used above was applied to the isoquinoline ethers. Here the cleavage of the second ether group is relatively faster so that k_1^B makes a larger contribution to k_1. Estimates based on the $\rho\sigma$ treatment to be described as well as the product analysis[6] suggest that k_1^A for these ethers is approximately $0.8k_1$ and k_1^B is approximately $0.2k_1$. The derived kinetic constants for these ethers are collected without statistical corrections in Table II.

TABLE II

ETHER CLEAVAGE OF ISOQUINOLINES AT 76° IN EXCESS HBr

Compd	$k_1 \times 10^4$ [a]	$k_2 \times 10^4$ [a]	$k_3 \times 10^4$ [a]
VII	5.3	2.5	0.31
VIII	1.2	0.51	0.051
IX	1.1	0.36	0.039

[a] Units are liters per mole second.

Results and Discussion

It is generally accepted that aromatic ethers are cleaved in acid by equilibrium protonation of the ether oxygen followed by nucleophilic attack on the neighboring alkyl carbon to give methyl bromide and a phenol. Aliphatic ethers cleave similarly except that the resulting alcohol normally reacts further. In accordance with this mechanism, ether cleavage by hydrogen bromide in aqueous acetic acid has been reported[13] to be second order with respect to the halogen acid. However, Mayo, *et al.*,[14] found aliphatic ether cleavage to be first order in glacial acetic acid. As discussed below, the difference is that in this (low dielectric constant and anhydrous) solvent the hydrogen bromide exists as ion pairs which, under the prevailing halogen acid concentrations and ether basicity, effectively cancel a kinetic order in the halogen acid.

Kolthoff and Bruckenstein[8] have investigated the system of hydrogen bromide in acetic acid in its reaction with the weak base indicator, *p*-naphtholbenzein. They give eq 1 where K_i is the equilibrium constant for formation of ion pairs, and K_d is the equilibrium constant for the dissociation to free ions. They concluded that there are few free ions in solution. On this basis the detailed mechanism given by eq 2–5 can be written for the cleavage of the ethers.

$$\mathrm{HBr} \xrightleftharpoons{K_i^{\mathrm{HBr}}} \mathrm{H^+Br^-} \xrightleftharpoons{K_d^{\mathrm{HBr}}} \mathrm{H^+} + \mathrm{Br^-} \qquad (1)$$

$$\text{ether} + \mathrm{H^+Br^-} \xrightleftharpoons{K_i^{\mathrm{IHBr}}} \text{ether } \mathrm{H^+Br^-} \qquad (2)$$

$$\text{ether } \mathrm{H^+Br^-} \xrightleftharpoons{K_d^{\mathrm{IHBr}}} \text{ether } \mathrm{H^+} + \mathrm{Br^-} \qquad (3)$$

$$\text{ether } \mathrm{H^+} + \mathrm{Br^-} \xrightarrow{k_2} \text{products} \qquad (4)$$

$$\frac{\mathrm{d(product)}}{\mathrm{d}t} = k_2[\text{ether } \mathrm{H^+}][\mathrm{Br^-}] \qquad (5)$$

Substitution of eq 1, 2, and 3 into eq 5 yields eq 6. This can be expressed in terms of the experimentally

$$\frac{\mathrm{d(product)}}{\mathrm{d}t} = k_2K_i^{\mathrm{HBr}}K_i^{\mathrm{IHBr}}K_d^{\mathrm{IHBr}}[\text{ether}][\mathrm{HBr}] \qquad (6)$$

observable stoichiometric concentrations by means of eq 7 and 8. In these equations the concentrations of

$$[\text{ether}] = [\text{ether}]_{\mathrm{st}} - [\text{ether } \mathrm{H^+Br^-}] \qquad (7)$$

$$[\mathrm{HBr}] = [\mathrm{HBr}]_{\mathrm{st}} - [\mathrm{H^+Br^-}] \qquad (8)$$

dissociated ions have been neglected relative to the ion pairs and un-ionized species.[8]

The H_0 acidity function[15] for hydrogen bromide in glacial acetic acid, by a short extrapolation of the data reported by Smith and Elliot,[16] is −1.6 for the highest (3×10^{-2} *M*) acid used in this work. Aromatic ethers undergo both ring-carbon and oxygen protonation; Kresge and Hakka[17] have estimated that 1,3,5-trimethoxybenzene has an effective pK_a for C protonation of −3.7. Since this molecule should be a considerably stronger carbon base than the molecules included in this study diversion of ether by C protonation need not be considered here.

The question of oxygen protonation is somewhat more complex. Anisole has a pK_a = −6.5 while 5,5-dimethylhomochroman, in which the ether oxygen is held completely out of the plane of the benzene ring, has a pK_a = −1.9, typical of an aliphatic ether.[18] Since models suggest that the central methoxyl is only partially tipped out of the plane it is reasonable to suppose the parent pK_a for the central methoxy group lies closer to −6.5 than to −1.9. The basicity of the central methoxyl will be enhanced by the neighboring methoxyls but fragmentary data in the literature suggest this is less important than the steric effect.[19] It can be concluded that the trisethers in this study are predominantly in the unprotonated form. This receives partial support from the observation of an unchanged nmr spectrum for 3,4,5-trimethoxytoluene in glacial acetic acid with and without hydrogen bromide present. It is supported further by the relative constancy of the derived kinetic constants since the HBr

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(13) R. L. Burwell, Jr., *Chem. Rev.*, **54**, 615 (1954).

(14) F. R. Mayo, W. B. Hardy, and C. G. Schultz, *J. Amer. Chem. Soc.*, **63**, 426 (1941).

(15) L. P. Hammett and A. J. Deyrup, *ibid.*, **54**, 2721 (1932).

(16) T. L. Smith and J. H. Elliott, *ibid.*, **75**, 3566 (1953).

(17) For an analysis of the protonation data and leading references to earlier work, see A. J. Kresge and L. E. Hakka, *ibid.*, **88**, 3868 (1966).

(18) E. M. Arnett and C. Y. Wu, *Chem. Ind.* (London), 1488 (1959).

(19) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1964).

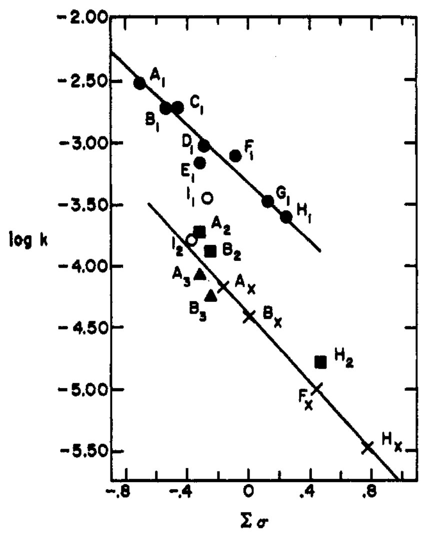


Figure 1.—Plot of log k *vs.* $\Sigma\sigma$ for all ethers in Table I; ●, cleavage of R_1 of trimethoxybenzenes; ■, cleavage of R_2 of trimethoxybenzenes; ▲, cleavage of R_3 of trimethoxybenzenes; ×, cleavage of monomethoxybenzenes; ○, cleavage of Veratrole.

concentration changes markedly during a kinetic run. On this basis eq 6 can be rewritten as eq 9.

$$\frac{d(\text{product})}{dt} = \frac{k_2K_i^{HBr}K_i^{IHBr}K_d^{IHBr}}{1 + K_i^{HBr}}[\text{ether}]_{st}[\text{HBr}]_{st} \quad (9)$$

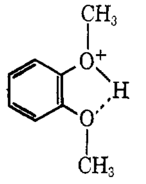
All experimental results were consistent with the cleavage reactions (see Experimental Section) being first order in stoichiometric ether and first order in stoichiometric hydrogen bromide. Consistent with this kinetic scheme, added bromide ion or added tosylic acid had no significant effect.

A $\rho\sigma$ plot of the entire set of data recorded in Table I is shown in Figure 1. Substituent constants[20] were available for all of the *para* substituents except $-CH_2N^+Et_3$ for which a value of $0.35 \times \sigma$ [p-$N^+(CH_3)_3$] was assigned.[21] The o-OCH_3 and o-OH substituents were assigned p-OCH_3 and p-OH σ constant values. As has been pointed out,[22] the few available *ortho* σ^* constants defined by Taft and used to fit ionization of *ortho*-substituted benzoic acids and other similar reactions[23] are nearly the same as the corresponding *para*-substituent constants. While these *ortho* constants may not characterize precisely the electronic effects involved in the ether cleavages, they would appear to be a reasonable approximation to them.

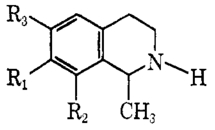
To the extent the σ values are in error, they presumably deviate in the direction of more positive values as a consequence of being closer to the reaction site and having a larger positive inductive component.[24]

In Figure 1 the points marked × are for cleavages of the monomethoxybenzenes. These ethers, uncomplicated by special steric, solvent, or substituent effects, define an excellent regression line, log $k = (-1.36 \pm 0.01)\Sigma\sigma + (-4.41 \pm 0.01)$.[25] Clustered about this line are the rates for cleavage of the second (■) and the third (▲) methoxyls of the trisethers. With these additional values the regression line becomes log $k = (-1.32 \pm 0.05)\Sigma\sigma + (-4.36 \pm 0.07)$. On a regression line distinct from the first but of similar slope (log $k = (-1.13 \pm 0.04)\Sigma\sigma + (-3.33 \pm 0.05)$ are the rates of cleavage of the central methoxyls of the trisethers. The spread between these last two lines corresponds to a factor of 10 in cleavage rate. If the placement of the filled points on the lower line is accepted, Figure 1 represents good evidence that the cleavage of the central methoxyls of the trisethers is sterically enhanced relative to the cleavage rates of the flanking methoxyls. The 0.19 difference in slope between the two lines is statistically significant in the sense that with the observed standard deviations of each set of points there is less than 1% chance that another random sampling of ethers would give identical slopes. On the other hand the difference is so small that it could easily be accommodated by appeal to minor changes in the σ constants in the two sets or to variation in ρ from differences in solvation.

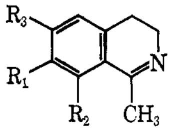
Important evidence for the correctness of this interpretation is provided by the entries (○ in Figure 1) for the cleavage of the first and second methoxyls of dimethoxybenzene. Unlike the trisethers, the methoxyls of dimethoxybenzene can be simultaneously coplanar and it would be expected that dimethoxybenzene should show a significantly enhanced rate by virtue of forming the more stable, internally hydrogen-bonded intermediate (VI). In terms of eq 9 this corresponds to



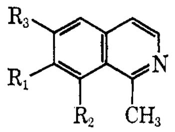
VI



VII



VIII



IX

$R_1 = R_2 = R_3 = OCH_3$

a larger K_i^{IHBr} and K_d^{IHBr}. The cleavage rate of the second methoxyl of dimethoxybenzene has no unique structural feature and should fit on the lower regression line with the other unaccelerated ethers. As Figure 1 shows, these expectations are borne out.

The three cleavage rates of 1-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline, VII, are also consistent with the steric interpretation. Saturated rings fused to aromatic rings have similar effects as two appropriate groups attached to the same points of fusion.[26] In a strongly acidic medium the amine will be protonated so that for it the $-CH_2N^+R_3$ σ is appropri-

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[20] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

[21] G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1941.

[22] J. Hine, "Physical Organic Chemistry," 2nd ed., McGraw-Hill Book Co., Inc., New York, 1962.

[23] See R. W. Taft, Jr. in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, Chapter 13. For a recent evaluation of several *ortho* substituent constants, see G. G. Smith and K. K. Lum, *Chem. Commun.*, 1208 (1968).

[24] G. G. Smith, private communication, has found in several cases of ester pyrolyses that the *ortho* substituent constant for methoxyl is significantly more positive than the *para* constant.

[25] The deviations in the slope and intercept are standard deviations calculated in the conventional way by the unweighted least-squares method.

[26] G. B. Barlin and D. D. Perrin, *Quart. Rev.* (London), **20**, 75 (1966).

ate. An important difference in the isoquinoline series is the presence of the 1-methyl which forces the 8-methoxy out of the plane. This means that appropriate representation of the substituent effect of the 8-methoxyl toward cleavage of the central 7-methoxyl is given by a *meta* σ (OCH_3). Because of these same steric effects, the cleavage rate of the 8-methoxyl of the isoquinoline trisether is much faster than the simpler ethers represented in Table I. Estimates based on σ constants using a *meta* constant for a twisted *ortho* methoxyl, and the same steric acceleration factor of 10, yield a k_1^B that is one-third the value of k_1^A. It can be seen that k_1^A $(= k_1/1.33)$ fits nicely on the upper line with the estimated $\Sigma\sigma = -0.02$.

These identical considerations indicate also that the cleavage rate, k_2, of the second methoxyl of VII should be much faster than the k_2 of the simpler ethers. The estimated value of k_2 of about 1.3×10^{-2} compares extremely well with the observed value of 1.5×10^{-2} and lends further support to the present interpretation.

The three cleavage rates of 1-methyl-6,7,8-trimethoxy-1,2-dihydroisoquinoline, VIII, and of 1-methyl-6,7,8-trimethoxyisoquinoline, IX, were also measured. Unfortunately the uncertainties in the electrostatic influence of the heteroatom do not permit an unambiguous placement of these points on the graph in Figure 1. Examination of the data will show, however, a good fit for any reasonable $\Sigma\sigma$. Furthermore, the k_1/k_2 ratios show the same expected high value as the tetrahydro derivative.

The preceding argument has been concerned with the consistency of the data using conventional *ortho* substituent constants. It is instructive to turn the argument around and consider first what changes in the analysis are required in order to have the points for the cleavages of the central methoxyls fall on the line defined by the *para*-substituted anisoles. The consequences for the placement of the other points must then be considered. Since the central methoxyls are flanked by two methoxyls, denial of the observed 0.8 σ unit spread requires that the *ortho* σ (OCH_3) be *more negative* by about 0.4 units. Such σ values would be exceptional but supporting arguments might be found.[27] The remaining compounds have only one *ortho* substituent and would be displaced by only 0.4 of a unit. Such an assignment happens to place around a single regression line all points of Table I except those for the cleavage of the third methoxyl of the trisethers, which are then in a unique position far below the new line. It might be hypothesized that these third ether groups are unique because of a retardation due to internal hydrogen bonding that is necessarily absent in the trisethers and in the hydroxydimethoxy ethers. However, the second methoxyl of dimethoxybenzene would also be hydrogen bonded; so its cleavage rate would then show an unexplained apparent acceleration. The cleavage rates of the second methoxyls of the isoquinoline ethers would present a further difficulty since with the modified σ constants and no steric acceleration these would also be too fast. Because of the difficulties created by this alternative rationalization we reject it in favor of invoking conventional substituent constants combined with steric acceleration of central methoxyls.

The conclusion that the tenfold rate enhancement of k_1 is primarily steric in origin brings more clearly into focus the question of the source of this steric effect. From the high basicity of 5,5-dimethylhomochroman it might have been expected that the k_1 rates would be enhanced by a factor nearer 10,000. That only a factor of 10 is visible suggests that nonbonded interactions may *increase* in going through the transition state. Since the configuration of the methyl group undergoing cleavage must invert, increased interactions would be expected if bond making to the entering nucleophile were advanced over bond breaking to the ether oxygen. This suggests that poorer nucleophiles, for which bond making would be still more advanced, might show a smaller net steric effect.

Conclusion

The enhanced cleavage rates of the central methoxyl of 1,2,3-trimethoxybenzene derivatives can be explained consistently and reasonably by invoking steric acceleration. It is estimated that the observed rate factor of 30 is composed of a factor of about 10 from steric acceleration and about 3 from substituent effects. An alternative explanation in terms of decreased basicity of the 1- and 3-methoxyls could account for most of the available data but only by postulating unprecedentedly negative *ortho* σ (OCH_3) constants.

Registry No.—N-Benzoyl-3,4,5-trimethoxyaniline, 19987-70-3; A_1, 6443-69-2; A_2, 6638-05-7; A_3, 1125-67-3; A_x, 104-93-8; B_1, 634-36-6; B_2, 91-10-1; B_3, 934-00-9; B_x, 100-66-3; C_1, 19987-70-3; D_1, 19978-23-5; E_1, 86-81-7; F_1, 118-41-2; F_x, 100-09-4; G_1, 1885-35-4; H_1, 6307-90-0; H_2, 19978-25-7; H_x, 100-17-4; I_1, 91-16-7; I_2, 90-05-1; VII, 3881-29-6; VIII, 4838-98-6; IX, 19978-28-0.

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(27) The electrostatic field effect of the methoxyl could be quite dependent on the details of conformational averaging. Bias toward conformations with the lone pair electrons pointing toward the central methoxyl favors more negative σ values.