Above m/e 40 the mass spectra are identical whether the compounds are introduced into the mass spectrometer as hydrochlorides or free bases, indicating dissociation before electron bombardment.

α^4,3-O-Isopropylidene-d_6-pyridoxol (III). Pyridoxol hydrochloride (72 mg), suspended in acetone-d_6 (6 ml), was cooled in ice, and hydrogen chloride gas was passed in for 45 min. The reaction mixture was shaken for 2 hr at room temperature. The resulting isopropylidene derivative was precipitated with ether, and was washed with ether, mp 210° dec, undepressed by addition of undeuterated material (lit.[13] mp 212°, dec). The hydrochloride was converted to the free base with $NaHCO_3$. The free base was recrystallized from water, mp 112-114° (lit.[13] mp 111-112°).

Other Compounds. The syntheses of the undeuterated cyclic ketals of pyridoxol (II and IX) have been reported.[13,14] Also, the preparation and characterization of the deuterated compounds IV, VI, and VII have been described in the preceding paper of this series.[1] The chemistry of α^4,3-O-isopropylideneisopyridoxal (X),[15] and of the other compounds in Table II (2,[16] 3-5,[15] 6[17]), has been described. ω-Methylpyridoxol (VIII) hydrochloride was kindly provided by Dr. S. A. Harris of Merck and Co., Inc.

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(13) W. Korytnyk and W. Wiedeman, *J. Chem. Soc.*, 2531 (1962).

(14) W. Korytnyk, *J. Org. Chem.*, **27**, 3724 (1962).

(15) W. Korytnyk, E. J. Kris, and R. P. Singh, *ibid.*, **29**, 574 (1964).

(16) W. Korytnyk, B. Paul, and B. Garrecht, Abstracts, 148th National Meeting of the American Chemical Society, 1964, p 12P.

(17) W. Korytnyk and B. Paul, *J. Heterocyclic Chem.*, **2**, 144 (1965).

Symmetrical Exchange Reactions at an Aromatic Carbon Atom[1]

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Contribution from the School of Chemistry of the Leicester College of Technology, Leicester, England.[2] *Received November 4, 1965*

Abstract: The order of reactivities of aromatic ethers with sodium methoxide is *p*-nitroanisole < 4-methoxypyridine 1-oxide < 2,4-dinitroanisole < 2,4,6-trinitroanisole. 2,4,6-Trinitroanisole (methyl-^{14}C) undergoes "methanolysis" and forms a red complex with sodium methoxide in methanol which is insoluble in toluene. Subsequent decomposition of the complex with dilute acid results in a nearly 50% decrease in the initial activity of the labeled aromatic compound. The rate of methoxyl exchange for this compound is increased with increasing methoxide ion concentration and reaches a maximum when the reactants have an equal concentration. No "methanolysis" or complex formation is observed between sodium methoxide and 2,4-dinitroanisole or 4-methoxypyridine 1-oxide in methanol. The second-order rate coefficient for methoxyl exchange for 2,4-dinitroanisole is independent of methoxide ion concentration. The mechanism of the methoxyl exchange reactions for the compounds studied in this work is discussed in terms of an intermediate complex formation which is fast for 2,4,6-trinitroanisole but rate determining for 2,4-dinitroanisole and 4-methoxypyridine 1-oxide. From the energies of activation and the heat of formation of the 2,4,6-trinitroanisole–sodium methoxide complex potential energy diagrams are drawn to support the proposed mechanism.

The mechanism of bimolecular nucleophilic aromatic substitution usually has been considered to involve an intermediate complex, formed by addition of the nucleophile to the aromatic carbon atom undergoing substitution. Evidence in favor of the two-step mechanism has been summarized.[3-6] The intermediate complex formed between 2,4,6-trinitroanisole and potassium methoxide has been shown to have a covalent structure by Gold and Crampton,[7] who found only a single methyl resonance peak in the nmr spectrum of the complex in acetonitrile with intensity twice that observed for the parent ether in the same solvent.[7]

Symmetrical exchange reactions offer simple systems for the study of nucleophilic aromatic substitution due to the identity of the reagent and of the displaced group. For methoxyl exchange a study of the activating effect of the nitro groups and the hetero N→O (in pyridine 1-oxide) is reported here. Additional evidence is also presented in support of the intermediate complex mechanism and for the covalent structure of the complex.

Experimental Section

Methanol (AnalaR) was treated with iodine and aqueous sodium hydroxide to convert acetone and ethanol into iodoform, which was filtered off. The filtrate was refluxed for several days to remove traces of iodoform, and twice fractionated.[8] The water content was determined by the Karl Fischer method[9] to be 0.13%.

Methanol (carbon-14 labeled) was purchased from U.K.A.E.A. in sealed ampoules. Its specific activity was 50 μcuries/ml.

Reagent grade toluene, ethyl acetate, and hydrochloric acid were used without purification.

All the aromatic ethers studied in this work are stable, and since carbon-14 has a long half-life, it was convenient to label the organic compounds rather than the sodium methoxide.

p-Nitroanisole (methyl-^{14}C) was prepared by adding 4 ml of methanol in small portions to 0.7 g of sodium in a well-cooled flask equipped with a reflux condensor and drying tube. After the reaction had subsided, 2 ml of labeled methanol containing 200 μcuries of carbon-14 and 2 ml of inactive methanol were added. The sodium methoxide solution was refluxed for 1 hr and cooled to room temperature, when 4.2 g of *p*-dinitrobenzene and 1 ml of inactive methanol were added. The reaction mixture was gently heated for 10 min. The almost solid mass was diluted with 50 ml of water, acidified with 2 *N* hydrochloric acid, and made slightly

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(1) Preliminary account: J. H. Fendler, *Chem. Ind.* (London), 764, (1965).

(2) Present address: Department of Chemistry, University of California, Santa Barbara, Calif.

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

(4) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958).

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

(6) S. D. Ross, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

(7) M. R. Crampton and V. Gold, *J. Chem. Soc.*, 4293 (1964).

(8) H. H. Bates, J. M. Mullaly, and J. H. Hartley, *ibid.*, 401 (1923).

(9) I. M. Kolthoff and R. Belcher in "Volumetric Analysis," Vol. 3, Interscience Publishers, Inc., New York, N. Y., 1957, p 409.

alkaline again with sodium hydroxide. The solid was filtered and recrystallized from ethanol, mp 53.5° (lit.[10] mp 54.0°), yield 80%.

2,4-Dinitroanisole (methyl-^{14}C) was prepared similarly by using 3.5 g of 2,4-dinitrochlorobenzene, mp 89.5° (lit.[10] mp 90.0°), yield 75%.

2,4,6-Trinitroanisole (methyl-^{14}C) was prepared by refluxing 3 g of the purified unlabeled compound with 8 ml of sodium methoxide in methanol containing 100 μcuries of carbon-14. Upon the addition of the ether to the sodium methoxide, the yellow solution immediately turned to a red mass. When it was poured into 2 N hydrochloric acid, it became yellow. The crystals were filtered, and recrystallized from methanol, mp 59° (lit.[10] mp 59°), yield 70%.

4-Methoxypyridine 1-oxide was prepared by the method of Ochiai.[11,12]

4-Methoxypyridine 1-oxide (methyl-^{14}C) was prepared by exchange of the inactive compound with 10 ml of methanolic sodium methoxide containing 100 μcuries of carbon-14. The excess methanol was distilled off, and the residue was recrystallized from ethyl acetate, mp 80.5° (lit.[12] mp 81°), yield 75%.

A stock solution of sodium methoxide in methanol was prepared by dissolving freshly cut sodium in purified methanol in a flask fitted with a water condensor and a calcium chloride drying tube. A series of dilutions were made with methanol and the alkali concentration was determined by titration with 0.1 N hydrochloric acid using methyl orange–xylene–cyanol FF as indicator.

Kinetic Procedures. Thermostated solutions of the labeled ether and sodium methoxide were mixed in a stoppered volumetric flask to give the required concentrations. At suitable time intervals, 1.0 ml of the reaction mixture was withdrawn for separation of the inorganic methoxide from the aromatic ether. The reactions were followed in all cases by measuring the decrease in the specific activities of the isolated aromatic ethers.

For p-nitroanisole and 2,4-dinitroanisole, the 1.0-ml sample was extracted with 15.0 ml of water and 5.0 ml of toluene, and the toluene layer was washed with 15.0 ml of water. The activity of 2.0 ml of the washed toluene layer was measured.

Samples of the 2,4,6-trinitroanisole runs were water soluble unless they were acidified to decompose the addition compound. Therefore, 2 ml of dilute hydrochloric acid was added to each sample before separation. The procedure thereafter was the same as that for p-nitroanisole and 2,4-dinitroanisole.

4-Methoxypyridine 1-oxide is water soluble, therefore the reaction was stopped by adding 0.5 ml of methanolic hydrochloric acid to the 1.0-ml samples. The solvent was evaporated slowly to dryness under an infrared lamp and the organic solid was dissolved in 3.0 ml of ethyl acetate. When the undissolved sodium chloride settled out, 2.0 ml of the solution was carefully pipetted off, and its activity was measured.

The radioactivity in all cases was measured by internally mixing 3.0 ml of Nuclear Enterprise NE 213 liquid scintillator with the samples in a flat-bottomed container which was placed on the photomultiplyer tube. Good optical contact was maintained by the use of silicone grease. Variations in wall thickness of the container and its position on the photomultiplyer were not critical, but counting was carried out after the samples had remained for at least 15 min inside the photomultiplyer, since immediate counting gave higher and false counting rates. The measured activities were expressed as counts per minute per 2.0-ml sample.

The counting equipment was a scintillation head (I.D.L. Type 653A) with stabilized extra high tension unit (Labgear D 40199) and a wide band amplifier and discriminator (I.D.L. 652) coupled to a fast scaler (I.D.L. 1700). Optimum counting condition was usually determined by the statistical method of Greenfield and Koontz,[13] but in some cases by simply taking the maximum on the plot of S^2/B (S = net sample count rate, B = background count rate) against the applied voltage at different discrimination biases.[14]

The rate of exchange was calculated by using the McKay equation[15] modified as follows. The complete isotopic exchange can be represented by

$$\mathrm{ArO^{14}CH_3 + OCH_3^- \overset{slow}{\rightleftharpoons} ArOCH_3 + O^{14}CH_3^-}$$

$$\mathrm{O^{14}CH_3^- + CH_3OH \overset{fast}{\rightleftharpoons} {}^{14}CH_3OH + OCH_3^-}$$

and letting R = the rate of exchange of $\mathrm{OCH_3^-}$ between $\mathrm{ArOCH_3}$ and $\mathrm{CH_3OH}$ in moles l.$^{-1}$ sec^{-1}; a = concentration of $\mathrm{OCH_3^-}$ + $\mathrm{O^{14}CH_3^-}$ in $\mathrm{CH_3OH}$ form, *i.e.*, concentration of methanol in moles l.$^{-1}$; b = concentration of $\mathrm{OCH_3^-}$ + $\mathrm{O^{14}CH_3^-}$ in $\mathrm{ArOCH_3}$ form in moles l.$^{-1}$; x = concentration of $\mathrm{O^{14}CH_3}$ in $\mathrm{CH_3OH}$ form at time t in moles l.$^{-1}$; y = concentration of $\mathrm{O^{14}CH_3}$ in $\mathrm{ArOCH_3}$ form at time t in moles l.$^{-1}$; y_0 = initial concentration of $\mathrm{O^{14}CH_3}$ in $\mathrm{ArOCH_3}$. The fraction of $\mathrm{ArOCH_3}$ molecules that are radioactive at time t is y/b, and similarly the radioactive fraction of $\mathrm{OCH_3^-}$ is x/a. The rate of decrease of y is given by

$$\frac{-\mathrm{d}y}{\mathrm{d}t} = R\frac{y}{b}\left(1 - \frac{x}{a}\right) - R\frac{x}{a}\left(1 - \frac{y}{b}\right) = \frac{R}{ab}(ay - bx)$$

Since at t = 0, all $\mathrm{O^{14}CH_3^-}$ is in the form of $\mathrm{ArOCH_3}$, $x + y = y_0$, and on integration the above equation becomes

$$-\ln\left[\frac{y}{y_0}\left(1 + \frac{b}{a}\right) - \frac{b}{a}\right] = \frac{a+b}{ab}Rt$$

The fraction y/y_0 is equal to S/S_0, where S is the specific activity expressed in counts per minute per 2.0-ml sample of $\mathrm{ArOCH_3}$ at time t, and S_0 that at time 0. Because of the high concentration of methanol, $b << a$, therefore the above equation simplifies to

$$-\ln\frac{S}{S_0} = \frac{R}{b}t$$

or

$$-\log S = -\log S_0 + \frac{R}{2.303b}t \qquad (1)$$

Plots of log S against time gave good straight lines from which the rates of symmetrical methoxyl exchanges were calculated using eq 1. Typical plots for the exchange reactions of 2,4-dinitroanisole and 2,4,6-trinitroanisole with methoxide ions in methanol are given in Figure 1. No corrections were made for isotope effects. The rate constants for "methanolysis" of 2,4,6-trinitroanisole were calculated from

$$R = k_1[\text{2,4,6-trinitroanisole}] \qquad (2)$$

Good first-order plots were obtained in all cases.

Calorimetric Measurements. Calorimetric measurements were carried out at 25.0° in a precision calorimeter described by Morcom and McGlashan.[16–18] The heat of formation of the complex was expressed in terms of kcal mole^{-1} of complex, on the assumption that the reaction goes to completion. Allowance was made for the heat of dilution of sodium methoxide by methanol.[19]

Results

No side reaction occurred, and the initial aromatic ethers were quantitatively recovered in all cases. Individual rates were reproducible within 3%.

The rates of methoxyl exchange between sodium methoxide and the aromatic ethers in methanol at different temperatures and concentrations are given in Tables I and II. For 2,4-dinitroanisole at 55.0°, the concentration of the ether was kept constant while the sodium methoxide concentration was varied in one set of experiments, and the concentration of sodium methoxide was kept constant with changing ether

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(10) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.

(11) A present of 4-nitropyridine 1-oxide from Dr. A. N. Sharp is gratefully acknowledged.

(12) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(13) M. A. Greenfield and R. L. Koontz, *Intern. J. Appl. Radiation Isotopes*, **8**, 205 (1960).

(14) R. Loevinger and R. Berman, *Nucleonics*, **9**, 26 (1951).

(15) H. McKay, *Nature*, **142**, 997 (1937).

(16) K. W. Morcom, Ph.D. Thesis, University of Reading, England, 1957.

(17) M. L. McGlashan and K. W. Morcom, *Trans. Faraday Soc.*, **57**, 581 (1961).

(18) D. S. Adcock and M. L. McGlashan, *Proc. Roy. Soc.* (London), **A226**, 266 (1954).

(19) D. S. Gilbert, Thesis, Leicester College of Technology, Leicester, England, 1963.

concentrations in another set of experiments. In each case good straight lines, with slope 1.0, were obtained on plotting the logarithm of the rate *vs.* the logarithm of the reactant concentration. Thus, the exchange reaction was found to be first order with respect to each reactant. From the expression

$$R = k_2[\mathrm{ArOCH_3}][\mathrm{NaOCH_3}] \qquad (3)$$

the second-order rate constants were calculated and are given in Table I. The same rate expression was used for the exchange between sodium methoxide and 4-methoxypyridine, and the second-order rate constants for this reaction are also given in Table I. This rate expression is reasonable because the reaction between sodium methoxide and 4-chloropyridine 1-oxide is first order with respect to each reactant.[20] The concentration of the complex formed between 2,4,6-trinitroanisole and sodium methoxide in methanol was estimated from the decrease of specific activity during extraction. By letting the initial specific activity of the aromatic ether be S_i, the fraction of ether which is in the form of the complex be α, and the extrapolated specific activity of the aromatic ether at zero time be S_0 (see Figure 1)

$$S_0 = \frac{S_i}{2} + (1 - \alpha)S_i$$

and

$$\alpha = 2\left(1 - \frac{S_0}{S_i}\right)$$

The concentration of the complex was obtained by multiplying the ether concentration by α. Values of α and the corresponding complex concentrations are given in Table II. The second-order rate constants were obtained by dividing the experimentally obtained rates by the concentration of the reactants using eq 3.

Table I. Methoxyl Exchange

Between *p*-Nitroanisole and Sodium Methoxide (*p*-Nitroanisole Concn, M = 0.025)

NaOCH$_3$ concn, M	Temp, °C	Time	
0.024	55.0	2 weeks	No detectable exchange
0.026 0.045	Refluxed	6 hr	
1.000	55.0	3 months	

Between 2,4-Dinitroanisole and Sodium Methoxide

Temp, °C	Concn, M: 2,4-Dinitroanisole	Concn, M: NaOCH$_3$	$R \times 10^3$ l.$^{-1}$ mole sec^{-1}	$k_2 \times 10^3$ l. mole^{-1} sec$^{-1\,a}$
55.0	0.050	0.0011	9.03	16.5
	0.050	0.0053	43.05	16.3
	0.050	0.0143	111.30	15.7
	0.050	0.0216	167.00	15.5
	0.005	0.0053	4.26	16.1
	0.023	0.0053	16.70	16.1
45.0	0.050	0.0219	68.90	6.17
	0.050	0.0109	37.50	6.77
	0.050	0.0011	4.07	7.36
34.9	0.023	0.0222	14.50	2.86
	0.023	0.0139	9.25	2.91
	0.023	0.0111	7.60	2.99
	0.023	0.0011	0.82	3.24
25.0	0.050	0.0225	12.39	1.06

Between 4-Methoxypyridine 1-Oxide and Sodium Methoxide (Concn, M; 4-Methoxypyridine 1-Oxide = 0.028, NaOCH$_3$ = 0.023)

Temp, °C	$k_2 \times 10^6$ l. mole^{-1} sec$^{-1\,a}$	$R \times 10^{10}$, mole l^{-1} sec^{-1}
55.0	82.7	52.1
45.0	28.2	22.3
34.9	11.0	6.9

[a] Calculated from eq 3.

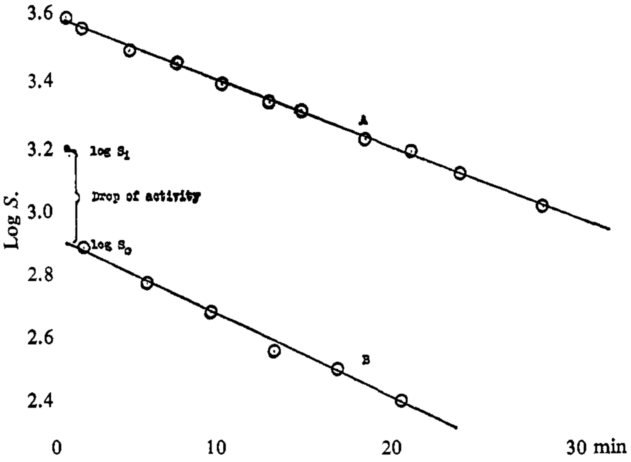

Figure 1. (A) Symmetrical methoxyl exchange between 2,4-dinitroanisole (methyl-^{14}C) and sodium methoxide in methanol at 34.9°: [ArOCH$_3$] = 0.023, [NaOCH$_3$] = 0.022 (time scale is ten times that on figure). (B) Symmetrical methoxyl exchange between 2,4,6-trinitroanisole (methyl-^{14}C) and sodium methoxide in methanol at 34.9°: [ArOCH$_3$] = 0.031, [NaOCH$_3$] = 0.0535.

Using the second-order rate constants obtained at different temperatures, the Arrhenius plots gave good straight lines, from which energies of activation and frequency factors were calculated. (Table III) The energy of activation was not affected by changes in the concentration of the reactants.

When 2,4,6-trinitroanisole (methyl-^{14}C) was dissolved in methanol without the presence of sodium methoxide the activity of the toluene-extracted samples was found to decrease. This process here is termed "methanolysis." The rate of methanolysis was followed at three temperatures. The energy of activation and frequency factor are given in Table III. The product of the reaction was identified spectrocopically as picric acid. The rate of "methanolysis" was, however, considerably slower than the methoxyl exchange; therefore, no allowance for it was made in calculating the latter. No "methanolysis" could be detected at any temperatures for the other compounds studied.

Discussion

For 2,4-dinitroanisole and 4-methoxypyridine oxide, the measured rate of methoxyl exchange was shown to be the product of a second-order rate constant and the concentration of the reactants. A methanolic solution of these compounds did not become red upon the addition of sodium methoxide and the rate coefficient of exchange between the carbon-14 labeled 2,4-dinitroanisole and sodium methoxide did not significantly

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(20) M. Liveris and J. Miller, *J. Chem. Soc.*, 3486 (1963).

Table II

Symmetrical Methoxyl Exchange between 2,4,6-Trinitioanisole and Sodium Methoxide

Temp, °C	Concn, M: 2,4,6-Trinitro-anisole	NaOCH$_3$	Complex	α	$R \times 10^5$ l.$^{-1}$ mole sec^{-1}	$k_1 \times 10^3$ sec^{-1a}	$k_2 \times 10^3$ l. mole^{-1} sec^{-1b}
45	0.024	0.0112	0.008	0.32	2.29	3.0	122.4
34.9	0.031	0.0112	0.007	0.22	1.82	2.7	51.9
	0.031	0.0149	0.011	0.33	2.18	2.0	46.9
	0.031	0.0225	0.017	0.55	2.25	1.3	32.8
	0.031	0.0449	0.028	0.90	3.05	1.1	21.8
	0.031	0.0535	0.029	0.94	2.97	1.0	17.9
	0.024	0.0112	0.008	0.32	1.47	1.9	57.5
25.0	0.024	0.0112	0.007	0.32	0.38	0.5	14.2
15.0	0.024	0.0112	0.007	0.31	0.12	0.2	4.4

Methanolysis of 2,4,6-Trinitroanisole (2,4,6-Trinitroanisole concn (M) = 0.027)

Temp, °C	25.0	34.9	45.0
$k_1 \times 10^7$ sec^{-1c}	22.1	66.7	155.1

[a] Calculated from eq 4. [b] Calculated from eq 3. [c] Calculated from eq 2.

Table III. Arrhenius Parameters

A. Compounds, the Rate-Determining Step Is the Complex Formation

Compd	Concn, M: Ether	NaOCH$_3$	E, kcal mole^{-1}	Log A^a
2,4-Dinitro-anisole	0.050	0.022	16.8	9.4
	0.050	0.011	16.8	9.5
4-Methoxy-pyridine-1-oxide	0.028	0.023	19.8	8.1

B. 2,4,6-Trinitroanisole, Heterolysis of Complex Is Rate Determining

Concn, M: 2,4,6-Tri-nitroanisole	NaOCH$_3$	E, kcal mole^{-1}	Log A^a
0.023	0.011	19.4	12.6

C. 2,4,6-Trinitroanisole, "Methanolysis"

Concn, M, of 2,4,6-trini-troanisole	E, kcal mole^{-1}	Log A^a
0.027	17.5	6.5

Heat of Formation of the 2,4,6-Trinitroanisole Sodium Methoxide Complex at 25.0°

Concn, M $\times 10^6$ of complex	H, kcal mole^{-1}
7.85	−7.1
18.5	−7.2

[a] Calculated at 34.9°.

change with increasing concentration of sodium methoxide (Table I). This implies that the rate-determining step is the formation of the complex.

When a methanolic solution of 2,4,6-trinitroansiole (methyl-^{14}C) was mixed with sodium methoxide, it immediately became red indicating the formation of a Meisenheimer-type complex.[3-6] Due to the ionic nature of this complex,[6] the aromatic ether could only be extracted into toluene after decomposition of the complex by dilute acid. The activity of the extracted aromatic ether (S_0) decreased considerably compared to that of the original labeled ether (S_i) as shown by the α values in Table II, indicating that the methoxyl groups of the complex between methoxide ions and 2,4,6-trinitroanisole are identical and, presumably, are bound covalently.

The rate of exchange between 2,4,6-trinitroanisole (methyl-^{14}C) and sodium methoxide in methanol at 34.9° increased with increasing concentration of methoxide ions until the concentration of the complex was almost equivalent to that of the aromatic ether (Table II). This rate increase is explicable if the rate of exchange is a function of the concentration of the complex, and is substantially independent of the concentrations of the 2,4,6-trinitroanisole and sodium methoxide. As the methoxide ion concentration is increased from small values, the fraction of the complex increases until all of the aromatic ether is in the form of the complex. This implies that the rate-determining step of the exchange between 2,4,6-trinitroanisole and sodium methoxide is the unimolecular heterolysis of the complex, rather than the bimolecular formation of it, and that

$$R = k_1[\text{complex}] \tag{4}$$

First-order rate constants for the heterolysis of the 2,4,6-trinitroanisole–sodium methoxide complex were calculated and are given in Table II. These values are only approximate because they depend on the estimated complex concentration which, in turn, is dependent on the accuracy in the determination of α.

The order of reactivity for the symmetrical methoxyl exchanges is p-nitroanisole < 4-methoxypyridine 1-oxide < 2,4-dinitroanisole < 2,4,6-trinitroanisole. This reflects the electron-withdrawing power of the substituents. The rate enhancement of nucleophilic substitutions by electron-withdrawing groups has been studied, and is demonstrated by the large and positive σ values in the Hammett correlations.[21,22] The order of reactivity of methoxide ion with 1-chloro aromatic systems is chlorobenzene < p-nitrochlorobenzene < 1-chloro-2,4-dinitrobenzene < 2,4,6-trinitrobenzene.[3,23] A single nitro group does not activate

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[21] E. Berliner and L. C. Monarck, *J. Am. Chem. Soc.*, 74, 1574 (1952).

[22] J. F. Bunnett, F. Draper, Jr., P. R. Ryason, P. Noble, Jr., R. G. Tonkyn, and R. E. Zahler, *ibid.*, 75, 642 (1953).

[23] R. C. Farmer, *J. Chem. Soc.*, 3424 (1959).

the *para* position sufficiently for symmetrical methoxyl exchanges under the concentration range studied (Table I). Nevertheles, *p*-nitroanisole was converted into *p*-nitrophenetole by boiling an ethanolic solution of it with caustic soda.[24] The hetero nitrogen atom in pyridine results in a greater electron density on nitrogen and a corresponding reduction on carbon in the 2 and 4 positions. The N-oxide group facilitates the electron withdrawal from the 4 position both by inductive and by mesomeric effects,[25] and Jaffé calculated that the order of nucleophilic reactivity is pyridine N-oxide > pyridine > benzene.[26] Three nitro groups in the 2, 4, and 6 positions activate the methoxyl group in the 1 position so much that an isolable intermediate complex is formed; the rate-determining step then becomes the decomposition of this complex and the aromatic ether itself undergoes "methanolysis."

The energy of activation for the heterolysis of the 2,4,6-trinitroanisole complex is 19.4 kcal mole^{-1} and that for the formation of the 2,4-dinitroanisole sodium methoxide complex 16.8 kcal mole^{-1} (Table III). From these values the potential energy diagrams were constructed (see Figure 2) and an approximate value of 13 kcal mole^{-1} energy of activation was computed for the formation of the 2,4,6-trinitroanisole–sodium methoxide complex. This is a reasonable value because Caldin[27] quotes 13 kcal mole^{-1} energy of activation for the formation of the complex between 2,4,6-trinitroanisole and sodium ethoxide in ethanol.

Kinetics themselves do not distinguish between the one-stage and two-stage mechanisms. If the two-step mechanism for the methoxyl exchange reaction of 2,4,6-trinitroanisole were to change to a synchronous one for 2,4-dinitroanisole, or even for 4-methoxypyridine 1-oxide, then no complex formation would occur and the 19 kcal mole^{-1} activation energy for the heterolysis of the complex (E_2 for A in Figure 2) would necessarily disappear in going from 2,4,6-trinitroanisole to 2,4-dinitroanisole (*i.e.*, the saddle in the potential diagram for B in Figure 2 would disappear completely). The additional nitro group in 2,4,6-trinitroanisole compared to 2,4-dinitroanisole causes an approximate 3–4 kcal mole^{-1} decrease in the activation energy for the formation of the complex (E_1 for A and B in Figure 2). If the assumption is made that the activation energy for the heterolysis of the addition complex (E_2 values) decreases similarly by 3–4 kcal mole^{-1} in going from 2,4,6-trinitroanisole to 2,4-dinitroanisole, then a 15–16 kcal mole^{-1} energy of activation would be expected for the heterolysis of the 2,4-dinitroanisole sodium methoxide complex (*i.e.*, E_2 = 15–16 kcal mole^{-1} for B in Figure 2).

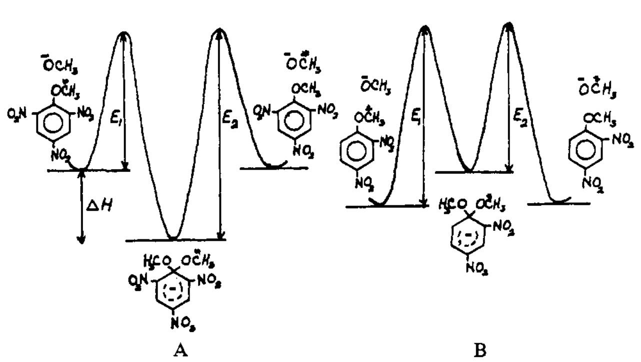

Figure 2. Potential energy diagrams for the symmetrical methoxyl exchange reactions. (A) 2,4,6-Trinitroanisole: ΔH = measured heat of formation of the 2,4,6-trinitroanisole–sodium methoxide complex, −7.15 kcal mole^{-1}; E_2 = measured activation energy, 19.4 kcal mole^{-1}; (B) 2,4-dinitroanisole: E_1 = measured activation energy, 16.8 kcal mole^{-1}.

The mechanisms for the symmetrical methoxyl exchanges in methanol are, therefore, best described as two-step reactions, with the formation of an intermediate which is fast for 2,4,6-trinitroanisole but rate determining for 2,4-dinitroanisole and 4-methoxypyridine 1-oxide.

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(24) A. Olivero, *Atti Congr. Intern. Chim. Rome* 10, 3, 258 (1939); *Chem. Abstr.*, 33, 9302 (1939).

(25) A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1960.

(26) H. H. Jaffé, *J. Am. Chem. Soc.*, 76, 3527 (1954).

(27) J. P. Caldin and E. F. Ainscough, *J. Chem. Soc.*, 2528 (1956).