Reactions of Tetranitromethane. II. The Kinetics and Products for the Reactions of Tetranitromethane with Inorganic Ions and Alcohols

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Abstract: The reaction of tetranitromethane (**4NM**) with a series of alcohols [CH_3OH, C_2H_5OH, *n*-C_3H_7OH, *i*-C_3H_7OH, *tert*-C_4H_9OH, $CH_3OCH_2CH_2OH$, $HOCH_2CH_2OH$, $C(CH_2OH)_4$, *N*-acetylserinamide, CF_3CH_2OH] and inorganic ions [HO^-, I^-, CN^-, SCN^-, NO_2^-, N_3^-, $S_2O_3^{2-}$] has been investigated. Both quantitative product analysis (where allowed) and determination of rate equations were carried out as were esr spectral studies for selected reactions [**4NM** with CH_3OH, C_2H_5OH, CF_3CH_2OH, *tert*-C_4H_9OH, $CH_3OCH_2CH_2OH$, and *N*-acetylserinamide]. In the reaction of C_2H_5OH, *n*-C_3H_7OH, *i*-C_3H_7OH, *tert*-C_4H_9OH, $CH_3OCH_2CH_2OH$, and $HOCH_2CH_2OH$ with **4NM** the following rate law pertained: $k_{obsd} = k_{OH}[OH^-] + k_1[RO^-] + k_2[ROH][RO^-]$ (eq a). For reaction of **4NM** with CH_3OH and $C(CH_2OH)_4$ the term $k_2[ROH][RO^-]$ was not discernible while k_{obsd} was found to be independent of $[CF_3CH_2OH + CF_3CH_2O^-]$. Product analysis establishes that trinitromethane anion (**3NM**) but not nitrite ion, plus alkyl nitrate, arise from the reaction paths associated with both k_1 and k_2 (eq a) for all reactive alcohols except *tert*-butyl alcohol. For the *tert*-C_4H_9OH 60–70% of starting **4NM** appears as $\times 4\ NO_2^-$. Spectral (esr) studies did not detect stable free radical intermediates in the reactions of the alcohols with **4NM**. The reaction of **4NM** with *N*-acetylserinamide (NASA) appears highly complex, and was not comparable to the other alcohols; esr evidence indicates considerable radical formation in the reaction of NASA with **4NM**. The rate constants k_1 and k_2 (eq a) were found to be linear functions of the pK_a of the alcohol involved. Of the various mechanisms considered the one suggested as possibly the most reasonable involves the reaction of RO^- with **4NM** to provide an anion–cation radical pair species followed by spontaneous electron transfer (k_1) or hydrogen atom abstraction from ROH (k_2) to yield $RONO_2$ as product. To account for altered products in the case of *tert*-C_4H_9OH it has been suggested that RO^- attack at an oxygen of **4NM** yields a cation–anion pair which then undergoes spontaneous electron transfer (k_1) or hydrogen atom abstraction (k_2) from *tert*-C_4H_9OH. Reaction of *p*-cresol with **4NM** under conditions of [**4NM**] $\gg$ [phenol + phenolate] yields only 10–20% *o*-nitrocresol which is in accord with earlier results obtained under conditions of [phenol + phenolate] $\gg$ **4NM**. The reaction of the inorganic ions with **4NM** were found to be first order in **4NM** and first order in anion (k_{A^-}). For the inorganic anions (excluding $I^- + S_2O_3^{2-}$) a plot of log k_{A^-} *vs.* pK_a of the conjugate acids of the anion is linear and of slope 0.27 ± 0.02. A mechanism involving anion attack on a nitrogen of **4NM** to provide **3NM** plus nitrated anion is suggested for these anions. The small value of β suggests little bond formation in the transition state and the correlation of log k_{A^-} with Edward's H_n rather than E_n values is in accord with initial anion attack upon sp^2 hybridized nitrogen. For I^- and $S_2O_3^{2-}$, reduction of **4NM** is suggested as a plausible mechanism; in the case of I^-, I_2 is formed. These species exhibit a positive deviation (*ca.* 10^3) from the Brønsted plot for the other anions. The reaction with the inorganic anions was found to give **3NM** as a major product; nitrite ion (determined where feasible) was also found to be a product of the reaction, the yields varying 30–140% depending upon the anion. Nitrate ion was not determined. Esr studies for I^-, $S_2O_3^{2-}$, and OH^- indicated that no radical species are formed during the reaction.

This study is a continuation of our investigation of the reactions of tetranitromethane (**4NM**). In the previous[3] paper in this series, we describe the reactions of phenol with **4NM**. The electron transfer process that occurs as a mechanism in the reactions of **4NM** with the phenolate ions suggested that perhaps other anions might also be capable of reacting with **4NM** in a similar electron transfer process. This paper is mainly concerned with the reactions of a series of alkoxide ions and several inorganic anions with **4NM**. We have also reinvestigated the nitration process that occurs in the reaction of **4NM** with phenols employing conditions more closely related to those of the protein chemist. The quantitative nitration of tyrosyl side chains in proteins[4] seems to disagree with our present and past findings that nitration of phenols alone in aqueous solution occurs only to 20–30%. The mechanism of nitration of tyrosyl side chains in proteins is discussed in light of the spacial constraint that the tertiary structure of the protein imposes on the amino acid side chains.

Experimental Section

Materials. Absolute methanol and *n*-propyl alcohol (Baker Reagents), pentaerythritol (PEN, Eastman Organic Chemicals), sulfanilic acid (Mallinckrodt), trinitromethane (K & K Laboratories), *N*-acetylglycinamide (NAGA, Cyclo Chemical Co), and all reagent quality inorganic salts were used without further purification. α-Naphthylamine (Baker Reagent) was recrystallized from water. Isopropyl alcohol (Baker Reagent) was distilled over CaO after several hours reflux over $SnCl_2$, bp 82.5°. *tert*-Butyl alcohol (Baker Reagent) was distilled over anhydrous Na_2CO_3, bp 82°. 2-Methoxyethanol (MOE, Matheson) was distilled over Na_2CO_3 and redistilled over magnesium, bp 200°. Trifluoroethanol (TFE, Matheson) was distilled over molecular sieves, bp 73°. *N*-Acetylserinamide (NASA), a product prepared in this laboratory by Fife according to the procedure of Rothstein,[5] was

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[1] Earle C. Anthony Fellowship Award, 1969–1970. A portion of the material submitted by S. L. W. for the Ph.D. in Chemistry, University of California at Santa Barbara.

[2] To whom inquiries should be addressed.

[3] T. C. Bruice, M. J. Gregory, and S. L. Walters, *J. Amer. Chem. Soc.*, **90**, 1612 (1968).

[4] M. Sokolovsky, J. F. Riordan, and B. L. Vallee, *Biochemistry*, **5**, 3582 (1966).

[5] E. Rothstein, *J. Chem. Soc.*, 1968 (1949).

recrystallized from absolute ethanol, mp 137.5–139°. *p*-Cresol (Redistilled, Matheson Coleman and Bell) was distilled, bp 70° (3 mm). 2-Nitro-4-methylphenol (Aldrich) was recrystallized from low boiling petroleum ether. Spectroquality dimethyl sulfoxide (DMSO, Matheson) was used without further purification. Ethyl nitrate (Eastman Organic Chemicals) was also used without purification. Vpc analysis showed no impurities in the $EtONO_2$ except ethanol, 1.3%. *tert*-Butyl hydroperoxide (Matheson) was used without purification. Tetranitromethane (**4NM**, Aldrich) was distilled at room temperature by nitrogen bubbling through a solution of 0.05 M bicarbonate above the **4NM**. The vapors then were passed through $CaCl_2$ (fine mesh) to remove water. The **4NM** was collected at liquid nitrogen temperature.[6] An additional purification procedure for **4NM** also was employed. **4NM** was washed with water three or four times, the **4NM** being frozen at 0° in an ice bath after each washing before decanting off the water. The liquid, immiscible in large quantities with water, was shaken with about 50 ml of water, after which the water was decanted and assayed for **4NM** according to the procedure of Glover and Landsman.[7] This procedure gave solutions of **4NM** from $1 \times 10^{-3}\ M$ to $1 \times 10^{-2}\ M$. A solution of potassium ethoxide was prepared by adding *ca.* 1 g-atom of potassium metal, cleaned by quick submersion in absolute ethanol, to absolute ethanol. The ethanol was dried by distilling over magnesium in a nitrogen atmosphere. In order to determine the ethoxide concentration, a portion of this solution was diluted to 10 ml with water and titrated with standard hydrochloric acid.

Apparatus. Absorbance measurements were made on a Zeiss PMQ II spectrophotometer equipped with a Zieler automatic cell positioner, or a Gilford Model 220 recording spectrophotometer. Kinetic solutions were maintained at 30 ± 0.1° by circulating water at this temperature through the cuvette holder (Zeiss) or Beckman double thermospacers (Gilford). pH measurements were made with a Radiometer Model 22 pH meter with a PHA 630 scale expander using a combined glass–calomel electrode (Radiometer G. K. 2021C). The electrode was thermostated at the temperature of the kinetic runs. pH-Stat measurements were carried out with the aid of a Radiometer TTT 1b autotitrator equipped with a Radiometer PHA 630 scale expander and a Radiometer SBR 2c titrigraph. The water-jacketed titration cell had 35 ml volume with ports for N_2 inlet and outlet, thermometer, salt bridge for the calomel electrode, and a Metrohm EA 115X glass electrode. A Haake circulating water bath maintained the cell at 30 ± 0.1° The solutions were purged with N_2 for 15 min, **4NM** was added, and the cell was sealed for the course of the determination. Purging during the hydrolytic reaction was found to sweep much of the **4NM** from the solution.

Polarographic analyses were made with a dropping mercury electrode and a Sargent Model XU recording polarograph. The water jacket of the cell was maintained at 30 ± 0.1° by means of a Haake circulating water bath. Electron spin resonance spectra were taken on a Varian V-4502 X band epr spectrometer equipped with a Varian V-4560 100-Hz field modulation and control unit.

Kinetics. The rate of disappearance of **4NM** in solutions of the various anions was followed spectrophotometrically by measuring the increase in absorbance at 350 mμ. One or two drops of a stock solution of **4NM** ($\sim 1.0 \times 10^{-3}\ M$ in doubly distilled water) was added to 3 ml of the appropriate reagent solution in cuvettes. The reactions were followed to completion. Pseudo-first-order rates were obtained from the slopes of plots of $-\ln [(OD_\infty - OD_t)/(OD_\infty - OD_0)]$ *vs.* t with the actual calculations performed on an Olivetti-Underwood Programma 101 computer.[8] Pseudo-first-order plots were discarded unless linear to 2.5 or 3 half-lives.

Stock solutions of 1.0 M were prepared for azide, iodide, thiocyanate, and 0.333 M for thiosulfate. Potassium thiocyanate was standardized by the Volhard method.[9] Kinetic solutions of azide, iodide, thiocyanate (0.1–1.0 M), and thiosulfate (0.027–0.24 M) were prepared in 0.067 M Tris buffer, pH 7.00–7.10, neutralized with 1.05 N H_2SO_4. The ionic strength was maintained at 1.0 by addition of 0.333 M K_2SO_4. At this pH there is a negligible amount of the conjugate acid of these anions; furthermore, the pH drift was but ±0.02 pH unit. The absorbance at 350 mμ of a solution of **3NM** ($1.04 \times 10^{-4}\ M$) in 0.03 M thiosulfate, 0.064 M Tris, pH 7.08, μ = 1.0, was observed for 12 hr. No change in absorbance was seen during this time. The decomposition of **4NM** in 0.064 M Tris buffer, pH 7.0, μ = 1.0, K_2SO_4, was also investigated. The reaction of **4NM** with nitrite ion was studied in the Tris buffer over a concentration range of 0.05–0.1 M nitrite ion. A stock solution of cyanide ion (1.0 M) was prepared in 0.01 M KOH, pH 11.59. Dilutions were carried out with 0.01 M KOH, μ = 1.0 K_2SO_4. The pH drift after reaction was less than 0.02 pH unit. Hydroxide rates were obtained for concentrations of 0.005 to 0.5 M, in K_2SO_4, μ = 1.0, or in KCl, μ = 0.5, and for 0.166 M carbonate buffers, pH 9.69, 10.00, 10.31, μ = 0.5. The second-order rate constant for the reaction with hydroxide was found not to depend upon chloride ion or sulfate ion, both being employed to maintain constant ionic strength. Since chloride ion was found to give irreproducible rates in the reaction of **4NM** with iodide, sulfate was employed and extended to the reactions of the other anions.

Kinetic solutions of TFE at pH 12.3, μ = 0.5, were prepared by diluting a 1.0 M stock solution of TFE which was half-neutralized with 1.0 M KOH, μ = 0.5, with 0.5 M KCl. Kinetic solutions for NASA, concentrations ranging from 0.01 to 0.1 M, were prepared in 0.166 M carbonate buffer, μ = 0.5, pH's 9.69, 10.00, and 10.31. NAGA was studied at 0.02 M in the carbonate buffer, pH 10.00, μ = 0.5. Kinetic solutions for the reaction of **4NM** with the alkoxide ions were prepared as follows: a stock solution for each was made by weighing out an appropriate amount of absolute alcohol and diluting to 50 ml with water. At constant hydroxide concentrations of 0.02, 0.01, and 0.005 M, serial dilutions in the alcohols were carried out, the alcohol concentrations ranging from 0.1 to 4.0 M. The ionic strength was maintained at 0.5 with KCl. The maximum pH drift of these solutions was −0.04 pH unit.

Product Analyses. Product analyses were performed on solutions which had been deoxygenated by bubbling nitrogen through the solutions. While the rates were not effected by the presence of oxygen, the product yields, particularly the nitrite ion yields, varied if the solutions were not deoxygenated in this manner. Trinitromethane (**3NM**), nitrite, as well as triiodide were analyzed spectrophotometrically (see Table I for spectral data). The simultaneous determination of both **3NM** and triiodide involved the solution of two simultaneous equations describing the absorbances of both species at two different wavelengths, 350 and 286 mμ.[10] The extinction coefficients of **3NM** at 350 and 286 mμ were determined in 0.067 M Tris buffer pH 7.1, μ = 1.0 with K_2SO_4. The extinction coefficients of triiodide at these wavelengths were determined in 1.0 M KI. Dilutions in I_3^- were made from a stock solution of triiodide ($\sim 9 \times 10^{-3}\ M$, in 1.0 M KI) which was standardized against standard sodium thiosulfate. Nitrite ion concentrations were determined according to the procedure of Kolthoff and Elving.[11] Nitrite analysis was possible only in the presence of the alcohols, NAGA, and the anions cyanide, hydroxide, and thiocyanate. At the acidity employed for the assay of nitrite ion, erroneous results are obtained if iodide or thiosulfate are present. Furthermore, since azide reacts directly with nitrite ion, product analysis for the latter was not feasible when azide was present.

Table I. Spectral Data

Species	λ_{max}, mμ	$\epsilon_{350\ m\mu}$, M^{-1} cm^{-1}	$\epsilon_{286\ m\mu}$, M^{-1} cm^{-1}
3NM	350	13,400	1,450
I_3^-	350	27,300	
	286		36,700
$EtONO_2$	262 (CCl_4)	$\epsilon_{262\ m\mu}$ = 14 M^{-1} cm^{-1}	

Before the nitrite ion yields for the reaction of **4NM** with hydroxide ion in 0.166 M carbonate buffers, pH's 9.69, 10.00, 10.3, were determined spectrophotometrically, a portion of the solution was adjusted to pH 1–2. The evolution of CO_2 takes place removing the buffer which would interfere with the optimum pH for the nitrite test. The pH was then readjusted to 6.5–7.5, appropriate dilutions were made, and the test was begun. Using the same pro-

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[6] J. Rabani, W. A. Mulac, and M. S. Matheson, *J. Phys. Chem.*, **69**, 53 (1965).

[7] D. J. Glover and S. G. Landsman, *Anal. Chem.*, **36**, 1960 (1964).

[8] Programs were written by D. W. Tanner, Ph.D. Thesis, 1967, Cornell University, Ithaca, N. Y.

[9] D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1963, p 262.

[10] See ref 3 for a discussion of the solution of the simultaneous equations.

[11] I. M. Kolthoff, P. J. Elving, and F. J. Welcher, Ed., "Standard Methods of Chemical Analyses," 6th ed, Vol. II, Part B, Van Nostrand, Princeton, N. J., 1962, p 2448.

cedure with standard solutions of nitrite ion in these buffers, it was found that the acidification of the solution to pH 1-2 and the evolution of CO_2 did not lead to the decomposition of nitrite ion >5%.

Ethyl nitrate was definitely established as a major product of the reaction of **4NM** with ethoxide ion. Though quantitative polarographic determinations of ethyl nitrate were not reproducible, the polarograms at neutral pH in the absence of uranyl acetate, where there is no interference from nitrite, nitrate, or **3NM**, definitely indicate the presence of the nitrated alcohol.[12] Semiquantitative reproducible determinations were carried out in the following manner: 5.8×10^{-2} M **4NM** in absolute ethanol was added to 10-ml solutions of varying ethanol concentrations in constant hydroxide concentrations of 0.1 and 0.2 M. The reaction was stirred overnight until reaction was completed. The reaction mixtures were extracted with two 5-ml portions of CCl_4 and dried with $MgSO_4$, The optical density at 262 mμ was taken and the ethyl nitrate concentration calculated from a standard plot of authentic ethyl nitrate in CCl_4, $\epsilon_{262\ m\mu} = 14\ M^{-1}\ cm^{-1}$ (see Table I).

The extraction procedure was carried out with known ethyl nitrate concentrations; the procedure was found to extract out 94 ± 2%. The ethyl nitrate yields are corrected for this small experimental error. In addition the liquid ir of the CCl_4 extract showed a spectrum identical with the authentic ethyl nitrate. The remaining water portion of the reaction mixture was diluted appropriately to obtain **3NM** and nitrite analyses, in order to verify that the product distributions were not changing due to the larger initial **4NM** concentration.

For the specific base-catalyzed reaction of the alcohols with **4NM**, the yields of **3NM** and nitrite ion due only to the alcohol reaction can be obtained from the total yields after subtraction of the products due to hydroxide catalysis alone. The following example for ethyl alcohol illustrates the calculations involved and is valid for all alcohols and concentrations employed. From the rate equation ($k_{obsd} = k_{OH^-}[OH^-] + k_1'[OH^-][ROH]_T + k_2'[OH^-][ROH]_T^2$, see Results) can be calculated the relative proportion of the total reaction that involves each rate term. Choosing $[ROH]_T = 1.7\ M$ and knowing k_{OH^-} and k_1 and k_2 for EtOH (Tables V and VII), we calculate the per cent contribution to the total reaction: $k_{OH^-} \cdot [OH^-] = 13\%$; $k_1'[OH^-][EtOH]_T = 56\%$; $k_2'[OH^-][EtOH]_T^2 = 31\%$. The hydroxide reaction (13%) is assumed to give **3NM** (8.7%) and nitrite (17%) according to the eq 6a. Since the total **3NM** yield found experimentally is 92-95%, both rate terms in alcohol must be leading to **3NM**, hence the total **3NM** yields at $[EtOH] = 1.7\ M$ can be calculated as follows: 8.7% due to $k_{OH^-} \cdot [OH]^- +$ 56% due to $k_1'[OH^-][EtOH]_T +$ 31% due to $k_2'[OH^-] \cdot [EtOH]_T^2 = 96\%$. Similarly the experimental nitrite yield (17%) is found to be the same as that per cent calculated to be due to the hydroxide reaction alone (17%).

Polarographic analysis was employed for the determination of nitrate in the reaction solutions of **4NM** with hydroxide alone. After adjusting the pH from 6.8 to 7.4, an appropriate amount of the reaction mixture (8-10 ml) was added to 12.5 ml of 4×10^{-4} M $UO(CH_3CO_2)_2$, 0.02 M HCl, 0.2 M KCl, in 0.01% gelatin, and the solution diluted to 25 ml, the final pH 1.98. Polarograms were run from +0.1 to −1.2 V *vs.* sce. For quantitative purposes standard plots of diffusion current *vs.* concentration at −1.2 V were obtained for nitrite and nitrate in the uranyl acetate stock solution (Table II). Since nitrous acid is removed from solution during the deaeration process, it is necessary to conduct the reactions in a closed cell, all solutions being deaerated before reaction and with careful transfer to the polarographic cell to avoid oxygen contamination. Since the species, nitrate and nitrite, reduce at −1.2 V in the uranyl solution, the contributions from each are sorted out as follows: the diffusion current contribution, i_d, at −1.2 V due to nitrite ion is calculated from the spectrophotometrically determined concentration of NO_2^- and the diffusion current constant, D μA M^{-1}, calculated from the standard plots of diffusion current *vs.* concentration $\{[NO_2^-]\ M \times 19{,}000\ \mu A\ M^{-1} = i_d(NO_2^-)$ at $-1.2\ V\}$. After this contribution as well as that from uranyl ion are subtracted from the total diffusion current at −1.2 V, the remaining current is attributed to nitrate ion; the nitrate concentration is calculated from this i_d and the nitrate ion diffusion current constant at $-1.2\ V\ [i_d(\text{total}) - i_d(UO^{2+}) - i_d(NO_2^-) = i_d(NO_3^-)$; $i_d(NO_3^-)/35{,}000\ \mu A\ M^{-1} = (NO_3^-)\ M]$. All dilutions are taken into account in these calculations.

Table II. Polarographic Data *vs.* Sce for the Product Analyses in the Reaction of **4NM** with Hydroxide Ion

Species	$-E_{1/2}$,[a] V	D,[b] μA M^{-1}	e^- transferred[c]
NO_3^-	0.9-1.0	35,000	5[d]
NO_2^-	0.9-1.0	19,000	3-3.4[d]
$C(NO_2)_3^-$	0.15	54,000[f]	12[e]

[a] Half-wave potentials. [b] Diffusion current constant (D) [i_d in μA]/concn, where i_d is the diffusion current at −1.2 V *vs.* sce. [c] The number of electrons in the reduction of each species. [d] See ref 12. [e] P. Noble, Jr., F. G. Borgardt, and W. L. Reed, *Chem. Rev.*, **64**, 19 (1964). [f] Diffusion current constant for **3NM** at −0.3 V.

Attempts to generate radicals in the base-catalyzed reaction of alcohols with **4NM** were performed in the following manner. To 1 ml of the alcohol was added 0.1 ml of **4NM** followed by 1 ml of O_2-free 6 N KOH. The following alcohols were used: TFE, MOE, MeOH, EtOH, *tert*-ButOH, and *ca.* 1 mg of NASA in 1 ml of DMSO. Only one phase remained with all alcohols except *tert*-butyl alcohol, TFE, and the NASA in DMSO. These conditions are comparable to those used by Lagercrantz to generate trinitromethane dianion radical [$C(NO_2)_3\cdot^{2-}$, **3NM**$\cdot^{2-}$] in the aqueous phase after addition of strong KOH to mixtures of 1,3-dicarbonyl compounds with **4NM**.[13] In the case of the dicarbonyl compounds, two phases separated; the aqueous phase exhibited a seven-line esr spectrum consistent with the interaction of an unpaired electron with three equivalent nitrogen nuclei. This spectrum was assigned to **3NM**$\cdot^{2+}$. For the reaction of the alcohols with **4NM**, spectra were scanned ±50 G about the center of the spectrum of **3NM**$\cdot^{2-}$; a sample of the radical was generated by the addition of 1 ml of 6 N KOH to 0.1 ml of **4NM** in 1 ml of acetylacetone. Samples were scanned at room temperature only for the presence of the **3NM**$\cdot^{2-}$; no g values were measured. In addition to the alcohols, ethyl nitrate and *tert*-butyl hydroperoxide were incubated with **4NM** in the following manner: to 0.1 ml of $EtONO_2$ and to 0.1 ml of *tert*-ButOOH near 0° was added 10 μl of **4NM** followed by 1 ml of 6 N KOH near 0°. No spectra appeared until the samples had warmed to room temperature. **4NM** (0.1 ml) was also added to 1 ml of 6 N KOH, 5 ml of 1.0 M KI, and 5 ml of 0.333 M $Na_2S_2O_3$, and the spectra of each solution were scanned for the presence of **3NM**$\cdot^{2-}$.

Stoichiometry of the Reaction of Hydroxide Ion with 4NM. The number of moles of hydroxide reacted per mole of **4NM** was determined by the volume of 7.07×10^{-3} M KOH required to maintain a constant pH of 11.3 during the hydrolysis of 5.8×10^{-6} mol of **4NM** in a sealed cell on the pH stat. The total number of moles of base taken up afforded a stoichiometry of 2.75 ml of KOH to 1.0 mol of **4NM**.

Product Analyses of the Reaction of *p*-Cresol with Excess 4NM. To solutions of *p*-cresol (1×10^{-2} to 10×10^{-2} M, one-eighth to one-half neutralized) was added 20-60 molar excess **4NM**. Because of the limited solubility of the reagent in water the reactions were stirred vigorously overnight. No difference in product yields was found when the reaction was carried out in the presence of fully dissolved **4NM**. The 2-nitro-4-methylphenol was extracted from the acidified solution with CCl_4 and these extracts were re-extracted with bicarbonate buffer pH 9.69. Both extractions were analyzed spectrophotometrically for 2-nitro-4-methylphenol [λ_{max} 365 mμ (ϵ 3300 M^{-1} cm^{-1}) (CCl_4), λ_{max} 435 mμ (ϵ 4,300 M^{-1} cm^{-1}, pH 9.69) (H_2O)]. The same extraction procedure repeated on a sample of authentic nitrophenol indicated that with due care this extraction can be quantitative. Product analyses were carried out with solutions containing from 0 to 75% ethanol. Experiments using these concentrations of ethanol were also carried out with phenol, instead of **4NM** in excess. Table III contains the results of these experiments.

Results

Reactions of 4NM with Alkoxide Ions. The experimental conditions employed for the reaction of the alkoxide ions are given in Table IV. The rate constants for the reaction of **4NM** with the alkoxide ions are provided in Table V. Plots of k_{obsd} *vs.* alcohol con-

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(12) F. Kaufman, H. J. Cook, and S. M. Davis, *J. Amer. Chem. Soc.*, **74**, 4997 (1952).

(13) C. Lagercrantz, *Acta Chem. Scand.*, **18**, 382 (1964).

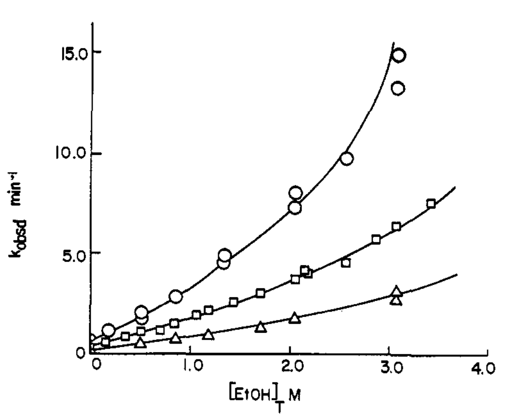


Figure 1. Plots of k_{obsd} vs. total ethanol concentration at hydroxide concentrations of 0.02 M, ○; 0.01 M, □; and 0.005 M, △; 30°, μ = 0.5.

centration for all alcohols except MeOH, PEN, TFE, NASA (see Figure 1) at various constant hydroxide concentrations were found to obey the expression

$$k_{obsd} = k_{OH^-}[OH^-] + k_1'[OH^-][ROH]_T + k_2'[OH^-][ROH]_T^2 \quad (1)$$

A plot of $(k_{obsd}/[OH^-] - k_{OH^-})/[ROH]_T$ vs. $[ROH]_T$ (Figure 2) is linear, least squares analysis giving the slopes and intercepts k_2' and k_1', respectively. The rate expression 1 can be written in the manner

Table III. Reaction of p-Cresol in the Presence of Excess **4NM**

p-Cresol, M	% EtOH	% 2-nitro-4-methylphenol	Molar excess **4NM**
0.01	0	16 ± 1[a]	b
0.01	20–50	40 ± 5	b
0.01	0–5	12 ± 2	60
0.01	75	19 ± 2	20

[a] See ref 3 in which experiments were carried out with **4NM** dissolved in 95% ethanol: per cent nitrophenol = 29 ± 2. [b] Repeat experiments using molar excess phenol.

Table IV. The Reactions of **4NM** with Nine Alkoxide Ions, μ = 0,5, 30°

Alcohol	pH	OH$^-$, M	Concn range $[ROH]_T$	No. of k_{obsd} values detd
tert-ButOH		0.02–0.1	0.52–2.7	30
n-PrOH		0.005–0.02	0.49–3.9	41
i-PrOH		0.005–0.02	0.5–4.0	31
EtOH		0.005–0.02	0.14–5.0	37
MeOH		0.005–0.02	0.46–2.3	25
Glycol		0.005–0.02	0.5–2.5	30
PEN		0.005–0.02	0.04–0.34	30
NASA	9.69–10.31		0.012–0.10	15
TFE	12.3		0.1–1.0	10
NAGA	10.00		0.02	1

$$k_{obsd} = k_{OH^-}[OH^-] + k_1[RO^-] + k_2[ROH][RO^-] \quad (2)$$

or

$$k_{obsd} = k_{OH^-}[OH^-] + k_1[ROH]_T[OH^-][K_a/K_w] + k_2[OH^-][ROH]_T^2[K_a/K_w] \quad (3)$$

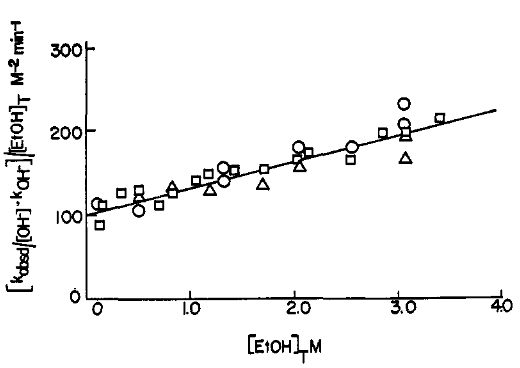


Figure 2. Plot of $[k_{obsd}/[OH^-] - k_{OH^-}]/[EtOH]_T$ vs. $[EtOH]_T$ for hydroxide concentrations of 0.02 M, ○; 0.01 M, □; and 0.005 M, △; 30°, μ = 0.5.

where $[ROH] \simeq [ROH]_T$, $[RO^-] = [ROH]_T[K_a/(K_a + a_H)]$ or $[ROH]_T[OH^-][K_a/K_w]$ since $a_H \gg K_a$. Hence we can obtain the constants k_1 and k_2 by the relationships

$$k_1'K_w/K_a = k_1 \quad (4a)$$

$$k_2'K_w/K_a = k_2 \quad (4b)$$

Plots of k_{obsd} vs. total methanol and pentaerythritol concentration were linear with intercept equal to the hydroxide rate at the given hydroxide concentration. The observed data for these alcohols fit the rate expression

$$k_{obsd} = k_{OH^-}[OH^-] + k_1'[ROH]_T[OH^-] \quad (5)$$

Table V. Rate Constants for the Reaction of **4NM** with Alkoxide Ions at 30°, μ = 0.5, KCl

Alcohol	pK_a	$10^{-4}k_1$, M^{-2} min^{-1}	$10^{-4}k_2$, M^{-3} min^{-1}
tert-BuOH	19.2[a]	145 ± 12	58.6 ± 4.6
i-PrOH	17.5[b]	1.39 ± 1.49	11.2 ± 3.5
n-PrOH	16.4[b]	2.76 ± 0.18	2.15 ± 0.11
EtOH	16.0[c]	1.46 ± 0.015	0.46 ± 0.015
MeOH	15.54[c]	1.57 ± 0.01	
MOE	14.8[c]	0.032 ± 0.0018	0.053 ± 0.0025
Glycol	14.77[c]	0.0936 ± 0.0022[f]	0.0226 ± 0.0003[f]
PEN	14.0[c]	0.0730 ± 0.001[f]	
NASA	13.6[d]	(0.14 ± 0.02[g])	
TFE	12.36[e]	No reaction	
NAGA		No reaction	

[a] J. Murto, *Acta. Chem. Scand.*, **18,** 1043 (1964). [b] Calculated from data of J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74,** 5266 (1952). [c] P. Ballinger and F. A. Long, *ibid.*, **82,** 795 (1960). [d] T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, **1,** 7 (1962). [e] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **81,** 1050 (1959). [f] Since there are two (four) possible sites for reaction on one molecule, the rate constant is divided by a statistical correction 2 (4) before compared to the rates of the other alcohols. [g] Bimolecular, pH independent rate constant (M^{-1} min^{-1}) for the reaction of NASA with **4NM**.

Plots of $(k_{obsd}/[OH^-] - k_{OH^-})$ vs. $[ROH]_T$ are linear, with slopes k_1' intercepts zero. These rate constants can also be expressed according to eq 4a. Table VI contains the product yields for the reactions of **4NM** with the alkoxide ions.

The reaction of **4NM** with hydroxide ion follows second-order kinetics from pH 9.69 to 0.5 M hydroxide (Figure 3). The stoichiometry and product distribution for the reaction are consistent with two mechanistic paths (6a) (Table VII). No rate enhancement over

Table VI. Product Analyses for the Reaction of **4NM** with Nine Alkoxide Ions at 30°, $\mu = 0.5$

ROH	OH^-, *M*	ROH, *M*	Determined[a] % 3NM	Determined[a] % NO_2^-	Calcd from rate eq[b] % 3NM	Calcd from rate eq[b] % NO_2^-
tert-BuOH	0.1	2.11	58 ± 2	162 ± 12	55[c]	188[c]
	0.1	3.16	48 ± 2	199 ± 10	50	209
	0.1	5.26	44 ± 2	220 ± 1	44	223
i-PrOH	0.005–0.02	1.0	86 ± 2	68 ± 4	81	77
	0.005–0.02	2.0	92 ± 2	45 ± 8	91	36
	0.005–0.02	4.0	97 ± 4	22 ± 6	97	12
n-PrOH	0.005–0.02	0.54	87 ± 4	40 ± 2	87	53
	0.005–0.02	1.6	95 ± 1	15 ± 1	96	16
	0.005–0.02	3.2	98 ± 2	6 ± 1	99	6
EtOH	0.01	0.84	89 ± 1	34 ± 3	91	35
	0.01	1.7	92 ± 1	17 ± 2	96	17
	0.01	3.4	94 ± 1	22 ± 1	98	7
		100% 0.01 *M* EtO^-	98	15	100	1
	0.1	0.684	89 (87[d])	36	90	43
	0.1	1.69	95 (96[d])	22	96	17
	0.1	3.3	91 (104[d])	14	98	7
	0.2	0.853	102 (105[d])	13	98	7
MeOH	0.005–0.02	0.98	96 ± 1	18 ± 1	96	15
	0.005–0.02	1.97	99 ± 1	13 ± 2	98	7
	0.005–0.02	3.94	101 ± 2	10 ± 2	99	4
MOE	0.005–0.02	1.0	88 ± 2	52 ± 1	90	39
	0.005–0.02	2.0	92 ± 1	35 ± 1	96	15
	0.005–0.02	3.0	95 ± 2	28 ± 1	98	8
Glycol	0.005–0.02	1.0	91 ± 1	38 ± 1	90	39
	0.005–0.02	2.0	95 ± 1	35 ± 1	96	15
	0.005–0.02	3.0	96 ± 2	33 ± 2	98	8
PEN	0.005–0.02	0.04	80 ± 1	74 ± 3	78	87
	0.005–0.02	0.12	88 ± 1	49 ± 1	87	52
	0.005–0.02	0.24	93 ± 1	36 ± 1	92	34
NASA	pH 9.69	0.012	75	98	75	114[e]
	pH 9.69	0.038	79	97	85	100
	pH 9.69	0.062	84	93	89	93
	pH 10.00	0.02	74	113	73	111[e]
	pH 10.00	0.06	78	88	78	93
	pH 10.00	0.10	83	79	81	84
TFE	pH 12.3	0.1	71	123		116[f]
	pH 12.3	0.5	73	114		108
	pH 12.3	1.0	75	107		99
NAGA	pH 10.00	0.02	64 ± 4	108 ± 6[g]		

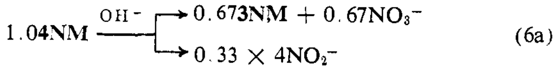
[a] Experimentally determined product yields. All percentages of products are calculated on the basis that the initial **4NM** concentration is equal to 100%, therefore making the total N or NO_2 available from the starting material, 400%. [b] Product yields calculated according to the method discussed in the Experimental Section. [c] Calculated assuming that the reaction with *tert*-butoxide ion gives 36 ± 6% **3NM** and (64 ± 7) × 4% nitrite ion and that products from the hydroxide pathway arise according to eq 6a. [d] Experimentally determined ethyl nitrate yields. [e] Calculated yields assuming that the reaction gives *ca.* 90 ± 10% nitrite at pH 9.69 and *ca.* 70 ± 10% nitrite at pH 10.00. Products from hydroxide rate are assumed to arise according to eq 6a. [f] This number represents the predicted nitrite yield calculated according to eq 6a in the following manner: (100% − % **3NM**) × 4 = % predicted NO_2^-. [g] See Table VII for the product yields found in the reaction of **4NM** with hydroxide ion in 0.166 *M* carbonate buffer, pH 10.00.

Table VII. Product Analyses for the Reaction of **4NM** with Hydroxide Ion, $\mu = 1.0$, 30° [a]

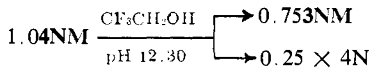
Concn, *M*	% 3NM	% NO_2^-	% NO_3^-
0.01	67	128 (132[b])	70 ± 3[c]
0.005	67	140 (132[b])	64 ± 3[c]
pH 9.69	68	109 (128[b])	
pH 9.69	64	109 (144[b])	
pH 10.00	64	119 (144[b])	
pH 10.00	64	109 (144[b])	
pH 10.30	64	110 (144[b])	71 ± 6[c]

[a] All percentages of products are calculated on the basis that the initial **4NM** concentration is equal to 100%, therefore making the total N or NO_2 available from the starting material 400%. [b] This number represents the predicted nitrite yield calculated in the following manner: (100% − % **3NM**) × 4 = predicted NO_2^-. [c] Polarographic analysis.

that of hydroxide was found in aqueous trifluoroethanol, but the product ratios for the paths were redistributed according to (6b) (NO_3^- analysis not performed).



$$1.04\text{NM} \xrightarrow{OH^-} \begin{cases} 0.673\text{NM} + 0.67NO_3^- \\ 0.33 \times 4NO_2^- \end{cases} \qquad (6a)$$



$$1.04\text{NM} \xrightarrow[\text{pH } 12.30]{CF_3CH_2OH} \begin{cases} 0.753\text{NM} \\ 0.25 \times 4NO_2^- \end{cases} \qquad (6b)$$

The reaction of **4NM** with 0.506 *M* EtOH in varying amounts of TFE, 0.7–3.5 *M*, pH 11.36 (*ca.* 0.005 *M* OH^-), showed no rate enhancement due to the TFE over the rate for the ethanol at the same hydroxide concentration. The deviation of these rate constants in the presence of TFE was random, and equal to ±15%.

For the specific base catalyzed reaction of the alcohols with **4NM**, the yields of **3NM** and nitrite ion due only to the alcohol reaction can be obtained from the total yields after subtraction of the products due to hydroxide catalysis alone. From the rate equations (1 or 5) can be calculated the relative proportion of the total reaction that involves each rate term. This method indicates that the product of **4NM** associated with the reaction paths of k_1 and k_2 is **3NM** and not nitrite ion

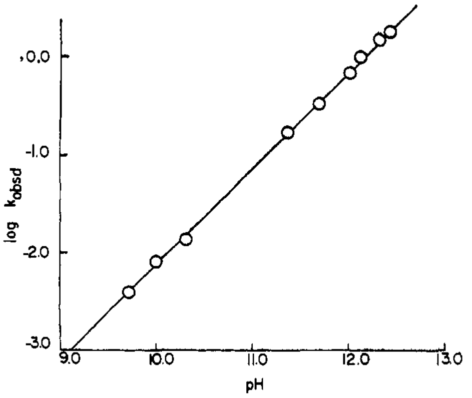


Figure 3. Log k_{obsd} *vs.* pH for the reaction of **4NM** with hydroxide ion; 30°, $\mu = 0.5$ or 1.0.

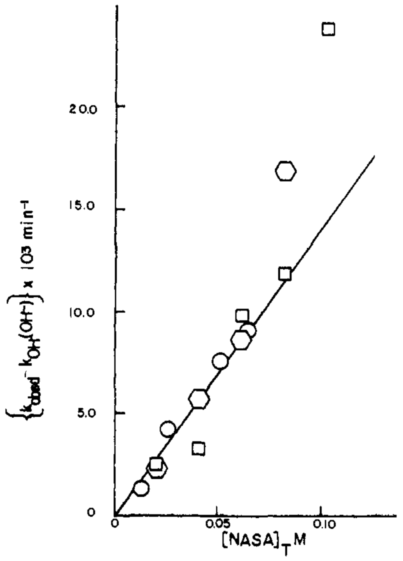


Figure 4. Plot of $[k_{obsd} - k_{OH^-}[OH^-]]$ *vs.* $[NASA]_T$ indicating lack of pH dependence in the reaction with **4NM**: pH 9.69, ○; 10.00, ⬡; and 10.31, □; 30°, $\mu = 0.5$.

(see Experimental Section for an example calculation) for all alcohols except methoxyethanol, glycol, and *tert*-butyl alcohol. For methoxyethanol and glycol, the nitrite yields are only 10–20% higher than predicted from the hydroxide pathway alone. This 10–20% is probably not significant for these two alcohols since small variations in the determined **3NM** yields may be magnified ×4 in the calculated nitrite yields. Ethyl nitrate yields indicate that both rate terms in alcohol lead to 100% ethyl nitrate. Since the nitrite yields in general appear to be due to hydroxide catalysis alone, it seems, therefore, highly likely that the alcohol nitrate is formed in the reactions of the other alcohols. Alkaline decomposition of the nitrate esters may arise after they are formed, but since these decompositions are relatively slow,[14] except for *tert*-butyl nitrate, the decomposition should not be appreciable in the course of the product analyses. For *tert*-butyl alcohol, however, it appears that 60–70% of the initial **4NM** is ending up as 240–280% nitrite ion. The calculated and experimentally determined yields of products are provided in Table VI. The hydroxide catalysis is assumed to give **3NM** and nitrite according to eq 6a. All percentages of products are calculated on the basis that the initial **4NM** concentration is equal to 100%, therefore making the total N or NO_2 available from the starting material 400%.

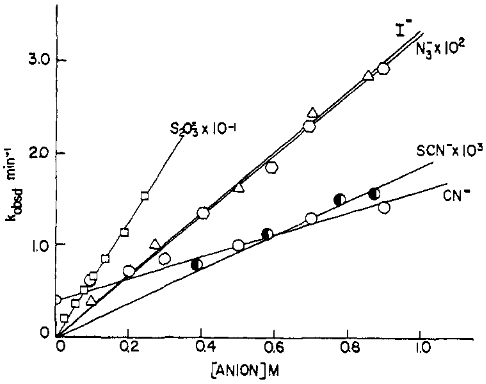


Figure 5. Plot of k_{obsd} *vs.* anion concentration in the reactions with **4NM**, 30°, $\mu = 1.0$: CN^-, ○; $N_3^- \times 10^2$, ⬡; $S_2O_3^{2-} \times 10^{-1}$, □; I^-, △; $SCN^- \times 10^3$, ◐.

Electron spin resonance spectra for the base-catalyzed reaction of the alcohols, TFE, MOE, MeOH, and EtOH, with **4NM** exhibited no signals that could be attributed to the presence of $\mathbf{3NM}\cdot^{2-}$, either under kinetic conditions or under the conditions discussed in the Experimental Section. However, it was observed that a weak seven-line spectrum appeared in the presence of 6 *N* KOH only. The spectrum was also observed after 15 hr at which time the signal was seen to increase (×10–×50). Similarly, the weak seven-line spectrum was initially present for *tert*-butyl alcohol in 6 *N* KOH; however, after 15 hr, the signal was seen to increase only slightly. The reaction mixture containing EtOH was observed also after 15 hr and no signal appeared at all, even to the level of the signal in the 6 *N* KOH solution. The product of the reaction of EtOH with **4NM**, $EtONO_2$, when incubated with **4NM** and KOH at room temperature gave a strong signal in the aqueous phase due to $\mathbf{3NM}\cdot^{2-}$. This signal was comparable to the signal obtained from acetylacetone under similar conditions.

N-Acetylserinamide (NASA) was found to react with **4NM**, the rate constant being independent of pH (see Figure 4). For NASA concentrations below 0.06 *M* the plot of k_{obsd} *vs.* NASA concentration appears first order in NASA, while at concentrations above this the profile curves up in an irreproducible manner. The low solubility of NASA in water prevented rate studies at higher concentrations. The product analyses indicate that 88 ± 3% **3NM** and 60–100% nitrite are formed in the reaction with NASA. In order to ascertain whether

Table VIII. The Reactions of **4NM** with Seven Anions, $\mu = 1.0$, 30°

Anion	pH	Concn range, *M*	No. of k_{obsd} values detd
OH^-	9.69–0.5 *M*		20
I^-	7.14	0.1–0.85	11
CN^-	11.60	0.1–0.9	5
N_3^-	7.12	0.1–0.9	11
$S_2O_3^{2-}$	7.05	0.027–0.24	15
SCN^-	7.00	0.1–0.9	6
NO_2^-	11.59	0.59–0.1	7

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[14] J. W. Baker and D. M. Easty, *J. Chem. Soc.*, 1193, 1208 (1952).

Table IX. Second-Order Rate Constants, pK_a, H_n, and E_n Values for the Reaction of **4NM** with Seven Anions at 30°, μ = 1.0

Anion	k_2, M^{-1} min^{-1}	pK_a	H_n	E_n	E_0
$S_2O_3^{2-}$	62.9 ± 3.7	0.6, 1.72[a]	3.60[b]	2.52[b]	−0.08
OH^-	38.8 ± 2.9	15.7	17.48[b]	1.65[b]	−0.88
I^-	3.38 ± 0.08	−9.5	−7.76[c]	2.06[b]	−0.535
CN^-	1.21 ± 0.12	9.17[e]	10.91	2.23[d]	−0.37
N_3^-	$3.33 \pm 0.13 \times 10^{-2}$	4.72[a]	6.46[b]	1.95[c]	(6.0)
NO_2^-	$3.6 \pm 0.39 \times 10^{-2}$	3.35	5.09[b]	1.97[c]	
SCN^-	$1.87 \pm 0.13 \times 10^{-3}$	0.85[a]	1.00[b]	1.83[d]	−0.77

[a] J. Bjerrum, G. Schwarzenbach, and L. G. Sillén, Ed., "Stability Constants of Metal-ion Complexes; Part II: Inorganic Ligands," The Chemical Society, London, 1958. [b] H_n and E_n values were taken from J. O. Edwards, *J. Amer. Chem. Soc.*, **76,** 1540 (1954). [c] H_n value for I^- and the E_n values for N_3^- and NO_2^- were taken from R. E. Davis, R. Nehring, W. J. Blume, and C. R. Chuang, *ibid.*, **91,** 91 (1969). [d] E_n values were calculated from E_0 values given by W. M. Latimer, "Oxidation Potentials," 2nd ed, Prentice-Hall, Englewood Cliffs, N. J., 1952. [e] T. Maugh and T. C. Bruice, *Chem. Commun.*, 1056 (1969).

or not the amide or acetamido group is reacting with **4NM**, the reaction of *N*-acetylglycinamide with **4NM** was carried out under the same conditions. No rate enhancement over the hydroxide rate was observed. Furthermore, the product distributions remained identical with that of the reaction in the carbonate buffer alone. The addition of base to NASA and **4NM** in DMSO immediately gave rise in the aqueous phase to the seven-line spectra due to **3NM**$\cdot^{2-}$. Furthermore, the organic phase contained radicals also; however, the rather complicated spectrum was weak and no attempt was made to analyze it. The addition of **4NM** to DMSO gave a dark yellow solution which showed no radical species until the addition of KOH. The organic phase then contained no detectable radicals while the aqueous phase showed only a weak spectrum due to **3NM**$\cdot^{2-}$.

Reactions of inorganic anions with 4NM were investigated under conditions of constant pH and ion concentration greatly exceeding that of the substrate (Table VIII). Plots of pseudo-first-order rate constants (k_{obsd}) *vs.* anion concentration were linear (Figure 5) and from the slopes were obtained the second-order rate constants for the various anions (Table IX). In Table X are listed the product yields for the reaction of **4NM** with azide, cyanide, thiocyanate, and thiosulfate. The products for the reaction of **4NM** with iodide ion are found in Table XI, and with hydroxide ion, Table VII. At the pH employed to study the nucleophilicity of cyanide ion, a contribution to the hydrolysis of **4NM** by hydroxide ion was observed; therefore the total product yields have been corrected for hydroxide catalysis.

Table X. Product Analyses for the Reaction of **4NM** with the Anions Thiosulfate, Azide, Cyanide, and Thiocyanate, μ = 1.0, 30° [a]

Anion	Concn, M	% **3NM**	% NO_2^-
$S_2O_3^{2-}$	0.30	82	
	0.17	82	
	0.03	84	
N_3^-	0.9	114	
	0.5	99	
	9.1	95	
CN^-	0.9	99[b]	33
	0.5	96[b]	38
	0.1	96[b]	
SCN^-	0.9	69	71
	0.6	71	74

[a] All percentages of products are calculated on the basis that the initial **4NM** concentration is equal to 100%, therefore making the total N or NO_2 available from the starting material 400%. [b] Corrected for hydroxide rate.

Table XI. Product Analyses for the Reaction of **4NM** with Iodide Ion, μ = 1.0, 30°

Concn, M	% **3NM**	% I_3^-
0.9	104	86
0.5	102	85
0.1	103	84

No radical species (**3NM**$\cdot^{2-}$) were detected in the reactions of KI and $Na_2S_2O_3$ with **4NM**. The **3NM**$\cdot^{2-}$ radical was detected just above noise level in the solutions of KOH and **4NM**. The limit for detection of this radical was estimated to be 10^{-7} to 10^{-9} M. However, it is noted that the purity of the reagent grade KOH is 85% minimum assay; solutions of 6 *N* KOH contain *ca.* 10^{-4} M metal ion species (*e.g.*, Ag, Fe, Ni). The increase after 15 hr of the signal due to this radical in KOH appears not to be sufficient to surpass the concentration of impurities in the sample. Esr spectra were not taken for the reactions of KSCN, KN_3, KNO_2, or KCN with **4NM**.

Reaction of *p*-Cresol in the Presence of Excess 4NM. The results in Table III indicate that, as a function of ethanol and as a result of excess reagent, small changes are occurring in the nitrophenol yields of the reaction of **4NM** with *p*-cresol. The nitrophenol yields appear in general higher in the less polar solvent; however, the excess reagent appears to be decreasing the yield of nitrophenol 20–50%.

Discussion

In summary, the reactions of **4NM** with the alkoxide ions in the pK_a range 14–19 were found to obey the same rate expressions and to yield *ca.* 100% **3NM** and *ca.* 100% nitrate ester. Two exceptions are noted: (1) the reaction with *tert*-butoxide ion gave large nitrite yields and (2) trifluoroethoxide ion was found not to react at all. The reactions of the anions with **4NM** were found to obey simple second-order kinetics, first order in the anion and first order in **4NM**. While **3NM** was found to be a major product in the reactions of the anions with **4NM**, individual variations in nitrite ion yields were found depending on the anion. Any mechanism proposed for the reactions of the alkoxide ions or the anions with **4NM** must be consistent with the rate expressions and product distributions.

Reaction of 4NM with Alkoxide Ions. In Figure 6 is plotted log k_1 and log k_2 *vs.* pK_a for the reactions of

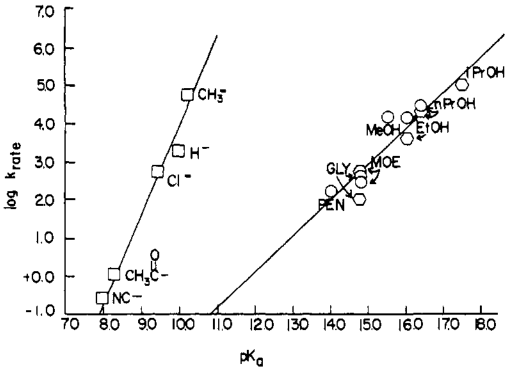


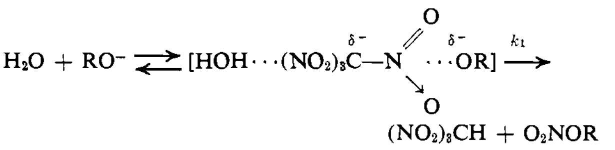
Figure 6. Log k_1 (○) and log k_2 (⬡) *vs.* pK_a for the reaction of seven alcohols with **4NM** and log k_{rate} *vs.* pK_a (□) for the reaction of five para-substituted phenoxide ions with **4NM**.

seven alcohols with **4NM**. Examination of Figure 6 reveals that the reactions associated with k_1 and k_2 are dependent upon the basicity of the alkoxide ion ($\beta = 0.95 \pm 0.15$). Several mechanisms for the reaction have been considered. In most cases the first step is assumed to be the attack in some manner of the alkoxide ion on **4NM**. Even though the second rate term involves a neutral molecule of alcohol, it does not seem reasonable that the neutral molecule is initially leading to the decomposition of **4NM**, particularly since **4NM** does not react with the alcohol in the absence of hydroxide. In addition we have ruled out the possibility that the rate term which is second order in alcohol is arising as a solvent effect on the reaction. The addition of an inert organic solvent, trifluoroethanol, produced no increase in the rate of the reaction of ethoxide ion with **4NM**. Such an increase would have been expected if the presence of the large amount of alcohol was increasing the rate by lowering the activation energy of the reaction. Since the reaction of **4NM** with *tert*-butoxide ion leads to considerable NO_2^- yields, we have considered a different mechanism for this reaction.

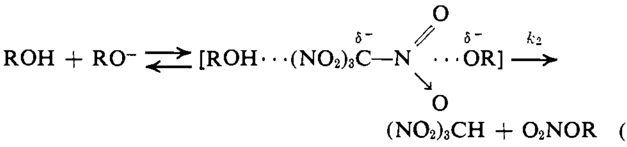
Two general types of mechanisms involve (1) direct ionic attack of the alkoxide ion on **4NM** and (2) formation of radical species as intermediates since **4NM** is known to react with the formation of radical species.[3,13,15–18] If the rate steps k_1 and k_2 exhibited without any reasonable doubt different sensitivities to the basicity of the alcohols, then we might be able to consider two totally different mechanisms for the separate rate terms. However, we do not believe this to be valid. Furthermore since the initial attack appears to be by the alkoxide ion, and since both rate terms lead to alkyl nitrate, it is reasonable to consider similar mechanisms for k_1 and k_2 with the possibility that both rate terms go through a common intermediate or intermediates. Equation 1 can be written as eq 7

$$k_{obsd} = k'_{OH^-}[H_2O][OH^-] + k_1''[H_2O][RO^-] + k_2''[ROH][RO^-] \quad (7)$$

This equation suggests the ionic mechanism



$$H_2O + RO^- \rightleftharpoons [HOH\cdots(NO_2)_3C{-}\overset{\delta^-}{N}(=O)(\rightarrow O)\cdots\overset{\delta^-}{O}R] \xrightarrow{k_1} (NO_2)_3CH + O_2NOR \quad (8)$$



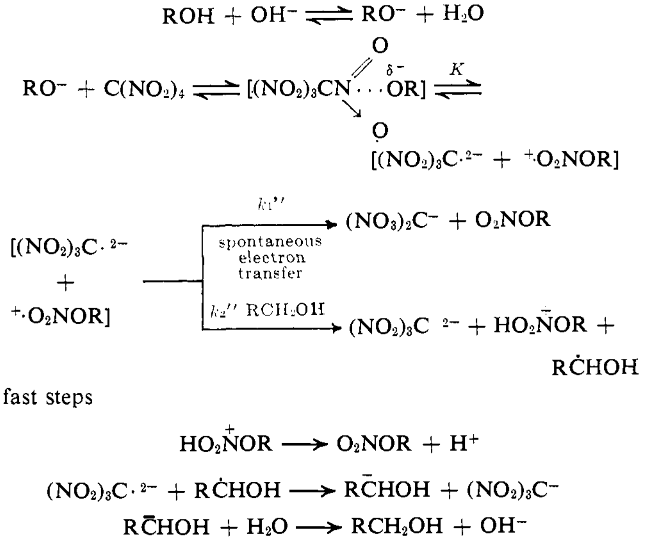
$$ROH + RO^- \rightleftharpoons [ROH\cdots(NO_2)_3C{-}\overset{\delta^-}{N}(=O)(\rightarrow O)\cdots\overset{\delta^-}{O}R] \xrightarrow{k_2} (NO_2)_3CH + O_2NOR \quad (9)$$

$$\underset{\text{or aci form}}{(NO_2)_3CH} \xrightarrow{\text{fast}} (NO_2)_3C^- + H^+$$

While the direct attack of the alkoxide ion as a base (k_1) on **4NM** would be expected to be sensitive to pK_a, we would expect k_2 to be less sensitive to pK_a since for this rate term there appears to be two molecules in the transition state for the reaction, one acting as a base and the other as an acid. Furthermore if protonation were important in a step such as eq 9, the solvent H_2O, in much higher concentration than the alcohol, would be expected to participate as a proton donor for the reactions of alcohols whose acidities are much less than that of water. The fact that the alcohols whose acidities are much less than water exhibit second-order concentration terms in the rate expression would tend to rule out any acid–base pair mechanism suggested by eq 9. The validity of a k_1 step independent of the suggested k_2 step as suggested by eq 9 therefore seems tenuous in view of our discussion that the k_1 and k_2 steps probably proceed through a similar type of mechanism.

The formation of radical species as intermediates along the reaction pathway seems to be the most reasonable suggestion for a mechanism for the reaction of **4NM** with the alcohols. Consider Scheme I. This mechanism reasonably accounts for the overall of the sensitivity of the rate constants k_1 and k_2 to the pK_a alcohols. The first step, the formation of the radical anion–cation pair, would be expected to be sensitive to the electron density on the oxygen of the alkoxide ion,

Scheme I



$$ROH + OH^- \rightleftharpoons RO^- + H_2O$$

$$RO^- + C(NO_2)_4 \rightleftharpoons [(NO_2)_3CN(=O)(\rightarrow O)\cdots\overset{\delta^-}{O}R] \overset{K}{\rightleftharpoons} [(NO_2)_3C\cdot^{2-} + {}^{+}\cdot O_2NOR]$$

$$[(NO_2)_3C\cdot^{2-} + {}^{+}\cdot O_2NOR] \xrightarrow[\text{spontaneous electron transfer}]{k_1''} (NO_3)_2C^- + O_2NOR$$

$$[(NO_2)_3C\cdot^{2-} + {}^{+}\cdot O_2NOR] \xrightarrow{k_2''\ RCH_2OH} (NO_2)_3C^{2-} + HO_2\overset{+}{N}OR + R\dot{C}HOH$$

fast steps

$$HO_2\overset{+}{N}OR \longrightarrow O_2NOR + H^+$$

$$(NO_2)_3C\cdot^{2-} + R\dot{C}HOH \longrightarrow R\bar{C}HOH + (NO_2)_3C^-$$

$$R\bar{C}HOH + H_2O \longrightarrow RCH_2OH + OH^-$$

$$d[3NM]/dt = k_1''K[RO^-][4NM] + k_2''K[ROH][RO^-][4NM]$$

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(15) C. Lagercrantz and M. Yhland, *Acta Chem. Scand.*, **16**, 1807 (1962).

(16) C. Lagercrantz, *ibid.*, **18**, 1384 (1964).

(17) C. Lagercrantz and K. Torssell, *ibid.*, **22**, 1935 (1968).

(18) C. Lagercrantz and K. Torssell, *Ark. Kemi*, **29** (18), 203 (1968).

or in other words to the pK_a of the alkoxide as a reasonable indication of this electron density. Furthermore, the breakup of this ion pair by the spontaneous electron transfer to the cation radical as well as by the hydrogen atom abstraction from another molecule of the alcohol undoubtedly is not a function of the alcohol pK_a. It might be reasoned that the spontaneous electron transfer to the cation radical, as well as the hydrogen abstraction from another neutral molecule, would be increased by the presence of a more electronegative substituent in the alcohol; however, this more electronegative substituent may also decrease the initial rate of formation of the cation–anion pair.[19] These two effects probably cancel each other with the reaction still remaining sensitive to the overall basicity of the alkoxide ion. Participation of the -OH moiety of water or of an alcohol molecule as a hydrogen atom donor in the reaction is ruled out for the following reason. Since C–H bond energies[20] are in general lower than O–H[21] bond energies, it is reasonable to expect that abstraction of hydroxyl hydrogen would take more energy than abstraction of hydrocarbon hydrogen[22] and hence would not occur particularly in the presence of a better H atom donor site on an alcohol molecule.

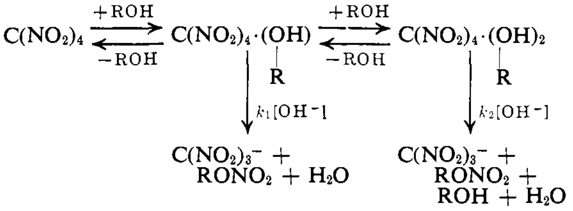
We have suggested the formation of **3NM** dianion radical [$C(NO_2)_3\cdot{}^{2-}$] as an intermediate whose formation can also account for the dependence of the second rate term upon the neutral alcohol molecule. Even though esr experiments have failed to detect it in the reactions of **4NM** with several alcohols, the existence of the radical as an intermediate in Scheme I is still reasonable in view of the following facts. Lagercrantz[13] has found that while the radical is generated in the aqueous phase when mixtures of **4NM** and certain 1,3-dicarbonyl compounds are kept in contact with strongly basic aqueous media, prolonged contact of the organic phase with the alkaline water phase was found to destroy the radical in the aqueous phase. Attempts to generate **3NM**$\cdot{}^{2-}$ radical in the reactions of the alkoxides with **4NM** lead to a single water–alcohol phase for all reactive alcohols studied except *tert*-butyl alcohol. Furthermore several seconds after addition of base to the alcohol–**4NM** mixture, crystals of $KC(NO_2)_3$ precipitated from the mixed solvent. No signal from **3NM**$\cdot{}^{2-}$ radical was detected in these mixed solvents.

Even though we have considered a different mechanism for the reaction of **4NM** with *tert*-butoxide ion, the fact that the *tert*-butyl alcohol–**4NM**–KOH mixtures separated into two phases with the aqueous phase containing a weak signal due to **3NM**$\cdot{}^{2-}$ radical suggests the following possibility: the single phase alcohol–water mixtures do not support the existence of the radical. This possibility is further substantiated when we consider that **3NM**$\cdot{}^{2-}$ radical did appear in **4NM**–KOH mixtures while the presence of EtOH gave rise to no signal due to the radical, even to the level of these **4NM**–KOH mixtures. It is noted that the appearance of no esr signal for **3NM**$\cdot{}^{2-}$ radical in the reactions of the alkoxide ions with **4NM** cannot absolutely rule out the possibility that the radical is a reactive intermediate in low concentration. The detection of this radical may be outside the scope of our simple esr experiments.

In the reactions of **4NM** with 1,3-dicarbonyl compounds, electron transfer from the mononitro derivative of the 1,3-dicarbonyl compounds to the trinitromethane fragment of **4NM** after alkaline cleavage of **4NM** was also proposed by Lagercrantz[16] to account for the observed radical spectra. Our proposal of a anion–cation radical pair is consistent with this suggestion and hence is not unique. Reactions occurring through ion pair formation have been recently reviewed.[23] An example of an ion pair intermediate which is largely undissociated in water was reported by Sneen and Larson.[24] It is interesting to note that the addition of KOH to a mixture of **4NM** and $EtONO_2$ gave rise in the aqueous phase to a strong signal due to **3NM**$\cdot{}^{2-}$ radical. It may be possible to interpret the appearance of the radical under these conditions as arising from **3NM** and $EtONO_2$ after alkaline cleavage of the **4NM**. These conditions, apparently not met by other procedures, ensure large concentrations of **3NM** and $EtONO_2$ as well as separation of the mixture into two phases. The possibility that ethyl nitrate is reacting directly with **4NM** cannot entirely be eliminated. Alkaline hydrolysis of $EtONO_2$[14] would lead mainly to EtOH and NO_3^-, both of which appear to be unlikely candidates for the generation of **3NM**$\cdot{}^{2-}$ radical; however, homolysis of the O–N bond to give EtO· and $NO_2\cdot$ may lead to products capable of reacting with **4NM**.

Mass spectral studies of nitrate esters[25] indicate that a peak corresponding to the parent ion, the radical cation $RONO_2\cdot{}^+$ in Scheme I, is never observed undoubtedly because of the extreme instability of this species. Thus it is apparent that if the formation of this species is to lead to the alkyl nitrate, the cation radical must be trapped in a tight ion pair which does not allow dissociation and hence subsequent fragmentation. The radical pair is not dissociated until either electron transfer occurs or until an encounter with a neutral molecule of alcohol occurs. In addition, the encounter of the dianion radical with the very reactive $R\dot{C}HOH$ radical would be expected to result in immediate electron transfer.

It is possible to consider that complexation of **4NM** and the alcohol molecules occurs along reaction pathway 10. This scheme does not include higher



$$\begin{tikzcd} C(NO_2)_4 \arrow[r, shift left, "+ROH"] & C(NO_2)_4\cdot(\underset{R}{\underset{|}{O}}H) \arrow[l, shift left, "-ROH"] \arrow[r, shift left, "+ROH"] \arrow[d, "k_1[OH^-]"] & C(NO_2)_4\cdot(\underset{R}{\underset{|}{O}}H)_2 \arrow[l, shift left, "-ROH"] \arrow[d, "k_2[OH^-]"] \\ & C(NO_2)_3^- + RONO_2 + H_2O & C(NO_2)_3^- + RONO_2 + ROH + H_2O \end{tikzcd} \qquad (10)$$

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(19) (a) A. F. Gaines and F. M. Page, *Trans. Faraday Soc.*, **62**, 3086 (1966), and references cited therein; (b) E. S. Huyer in "Advances in Free-Radical Chemistry," Vol. I, G. H. Williams, Ed., Academic Press, New York, N. Y., 1966, p 96; (c) G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958). For simplicity we have indicated that the hydrogen abstraction occurs from the position α to the hydroxyl group; however, because of the electrophilic nature of the radical (the presence of the positive charge and the presence of highly electronegative atoms), we would expect hydrogen abstraction from the neutral alcohol molecule to occur also from a more electron-rich center not adjacent to the hydroxyl group.

(20) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 40–53.

(21) P. Gray and A. Williams, *Trans. Faraday Soc.*, **55**, 760 (1959).

(22) A. F. Trotman-Dickenson in "Advances in Free-Radical Chemistry," Vol. I, G. H. Williams, Ed., Academic Press, New York, N. Y., 1965, pp 1–38.

(23) M. Szwarc, *Accounts Chem. Res.*, **2**, 87 (1969).

(24) R. A. Sneen and J. W. Larson, *J. Amer. Chem. Soc.*, **88**, 2593 (1966).

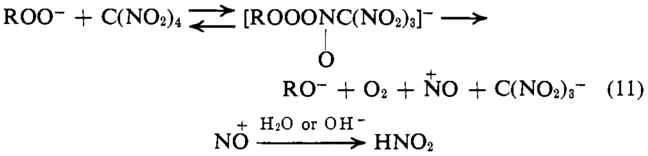
(25) R. T. M. Fraser and N. C. Paul, *J. Chem. Soc. B*, 659 (1968).

order complexation of **4NM** by the alcohol molecules although this could be possible as the water content of the solvent is decreased. Though **4NM** has been shown to form colored complexes with unsaturated compounds,[26] it has been demonstrated[27] that these complexes are generally weak. While the complex itself may not spontaneously decompose to products, the base-catalyzed abstraction of a proton from the alcohol molecule would be expected to result in further reaction perhaps through a stronger **4NM**·⁻OR complex. Furthermore, after formation of the alkoxide ion, the reaction may still proceed through a radical cation–anion pair as was suggested in Scheme I.

The reaction of *tert*-butoxide ion with **4NM** leads to 36 ± 6% **3NM** and [(64 ± 7) × 4%] nitrite ion. The (NO_2) unaccounted for in the reaction appears to be close to the **3NM** yield. The rate expression is the same as for the other alcohols; however, no other alcohol was seen to give NO_2^-. It is apparent that nitrite ion must be arising from full decomposition of **4NM** or, what seems more probable, subsequent attack on **3NM** by an intermediate in the reaction.

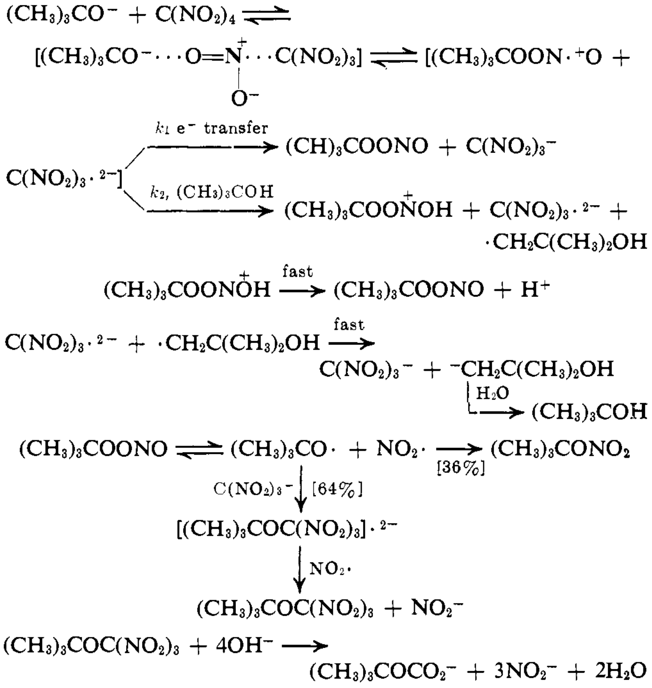
We can rule out the possibility that *tert*-butoxide ion is reacting at the carbon of **4NM** as well as at the nitrogen, thus giving NO_2^- and $(CH_3)_3COC(NO_2)_3$, an undoubtedly unstable intermediate which could quite easily give $3NO_2^-$ by attack of OH^- or H_2O. If the less sterically hindered alkoxide ions do not react with **4NM** in this manner, it seems highly unlikely that *tert*-butoxide ion would be an exception.

A recent study[28] of the reaction of alkyl hydroperoxy anions with **4NM** in aqueous solution indicated that the reaction involves attack at oxygen with the formation of *ca.* 100% **3NM** and 100% NO_2^- (eq 11). If *tert*-butoxide ion reacts with **4NM** by attack at oxygen, a reasonable mechanism can be formulated to account for the large nitrite ion yields as well as the term which is second order in alcohol (Scheme II). Since **3NM** was found to react with OH· formed from the pulsed radiolysis of water,[6] it seems reasonable to suspect that **3NM** would also scavenge the *tert*-butoxyl radical, $(CH_3)_3CO\cdot$



$$ROO^- + C(NO_2)_4 \rightleftharpoons [ROO\underset{\displaystyle O}{N}C(NO_2)_3]^- \longrightarrow RO^- + O_2 + \overset{+}{N}O + C(NO_2)_3^- \quad (11)$$
$$\overset{+}{N}O \xrightarrow{H_2O \text{ or } OH^-} HNO_2$$

Scheme II



$$(CH_3)_3CO^- + C(NO_2)_4 \rightleftharpoons$$
$$[(CH_3)_3CO^-\cdots O{=}\underset{\displaystyle O^-}{\overset{+}{N}}\cdots C(NO_2)_3] \rightleftharpoons [(CH_3)_3COON\cdot{}^+O + C(NO_2)_3\cdot{}^{2-}]$$
$$\xrightarrow{k_1\ e^-\text{ transfer}} (CH)_3COONO + C(NO_2)_3^-$$
$$\xrightarrow{k_2,\ (CH_3)_3COH} (CH_3)_3COO\overset{+}{N}OH + C(NO_2)_3\cdot{}^{2-} + \cdot CH_2C(CH_3)_2OH$$
$$(CH_3)_3COON\overset{+}{O}H \xrightarrow{\text{fast}} (CH_3)_3COONO + H^+$$
$$C(NO_2)_3\cdot{}^{2-} + \cdot CH_2C(CH_3)_2OH \xrightarrow{\text{fast}} C(NO_2)_3^- + {}^-CH_2C(CH_3)_2OH$$
$${}^-CH_2C(CH_3)_2OH \xrightarrow{H_2O} (CH_3)_3COH$$
$$(CH_3)_3COONO \rightleftharpoons (CH_3)_3CO\cdot + NO_2\cdot \xrightarrow[{[36\%]}]{} (CH_3)_3CONO_2$$
$$(CH_3)_3CO\cdot \xrightarrow[{[64\%]}]{C(NO_2)_3^-} [(CH_3)_3COC(NO_2)_3]\cdot{}^{2-} \xrightarrow{NO_2\cdot} (CH_3)_3COC(NO_2)_3 + NO_2^-$$
$$(CH_3)_3COC(NO_2)_3 + 4OH^- \longrightarrow (CH_3)_3COCO_2^- + 3NO_2^- + 2H_2O$$

The decomposition of an intermediate such as *tert*-butyl pernitrite $[(CH_3)_3COONO]$ has not been characterized; however, the decomposition in aqueous solution of pernitrous acid has been studied.[29] The unimolecular decomposition of the acid gives nitrate ion; one mechanism was suggested to be heterolytic cleavage of the O–O bond to OH^- and NO_2^+ which immediately form HNO_3. However, the authors further discuss considerable evidence that homolytic cleavage occurs which can also lead to HNO_3 by recombination of HO· and $NO_2\cdot$ as well as to further reactions of HO· and $NO_2\cdot$. It seems reasonable to consider that $(CH_3)_3$-COONO may decompose homolytically in a fashion similar to HOONO. Homolytic cleavage of this intermediate, if formed, can best account for the large nitrite ion yields in the reaction of *tert*-butoxide ion with **4NM**.

The addition of strong KOH to **4NM** in *tert*-butyl hydroperoxide gave a very complicated esr spectrum that was found to change with time. The seven lines attributed to **3NM**·²⁻ appeared at first along with complicated overlap spectra. No attempt was made to analyze these complicated spectra. The reactions of alkylhydroperoxy anions with **4NM** may also be conceived to react through **3NM**·²⁻ without changing any significant features of the products. The overall radical yield from *tert*-butyl hydroperoxide was again comparable to the radical yield for the reaction of **4NM** with acetylacetone. However, conclusions based on esr experiments about the reaction of **4NM** with practical grade *tert*-butyl hydroperoxide must at this time be tentative.

We have ruled out any mechanism involving a direct one-electron transfer from the alkoxide ion to **4NM** as in eq 12. This scheme cannot explain both the formation of the nitrate ester and the dependence of the rate on a term involving a neutral molecule of the alcohol. We would not expect **4NM** to dissociate into NO_2^- and $\cdot C(NO_2)_3$ after electron transfer since it has been shown that capture by **4NM**[6] of the solvated electron in H_2O leads to fragmentation of **4NM** into $NO_2\cdot$ and $^-C(NO_2)_3$. Even though it is possible to write a mechanism that accounts for both the formation of the nitrate ester and the rate term that involves a neutral molecule of alcohol if $\cdot C(NO_2)_3$ and NO_2^- are formed, this mechanism is not consistent with what is known about the dissociation of **4NM** after electron capture.

$$RO^- + C(NO_2)_4 \longrightarrow RO\cdot + \cdot NO_2 + (NO_2)_3C^- \qquad (12)$$
$$RO\cdot + \cdot NO_2 \xrightarrow{\text{fast}} RONO_2$$

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[26] (a) E. Heilbronner, *Helv. Chim. Acta*, **36**, 1121 (1953); (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 1147–1148; (c) V. A. Gorodyskii, *Zh. Obshch. Khim.*, **36**, 2217 (1966).

[27] P. R. Hammond and L. A. Burkardt, *J. Phys. Chem.*, **74**, 3 (1970).

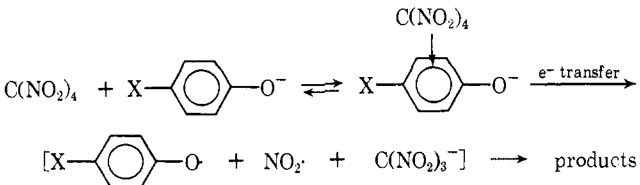
[28] W. F. Sager and J. C. Hoffsommer, *ibid.*, **73**, 4155 (1969).

[29] M. N. Hughes and H. G. Nicklin, *J. Chem. Soc. A*, 450 (1968).

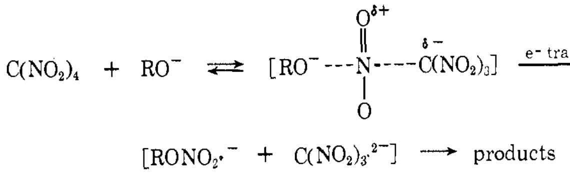
The apparent nonreactivity of trifluoroethoxide ion seems to be inexplicable at this point. The small increases in the **3NM** yields found in the presence of TFE are probably not more than a small solvent effect favoring one pathway of hydroxide attack rather than another. The rather poor correlation with pK_a of all the rate constants for the attack of the alkoxide ions on **4NM** along with the nonreactivity of TFE suggests that the reactions are rather complicated functions not only of basicity, but perhaps of steric hindrance, and even electron availability.

It is instructive to compare this study of the rates of reaction of alkoxide ions with **4NM** to our previous study of the rates of reaction of para-substituted phenoxide ions with **4NM**. It is evident from Figure 6 that the phenoxide ions are probably not reacting by the same mechanism as the alkoxide ions. The log *k vs.* pK_a plot for the phenoxide ions has slope >2 (ρ *vs.* $\sigma^- = -4.25$), while the best slope describing log *k vs.* pK_a for the alkoxide ions is certainly not greater than one. The possibility of rate-determining O nitration followed by an intramolecular rearrangement to the nitrophenol has been ruled out as a possible mechanism for the reaction of the phenoxide ions.[3] Undoubtedly O nitration is occurring in the reactions of the alkoxide ions; however, if such a mechanism were taking place for the phenoxide ions, one would expect to see the rates of the phenoxide ions fall on the same plot of log *k vs.* log pK_a as the alkoxide ions. The rate-determining step for the reactions of the phenoxide ions has been interpreted to be an electron transfer to **4NM** within a charge-transfer complex. On the other hand, the rate-determining step for the reaction of the alkoxide ions appears to be the attack by the oxyanion on **4NM** to form the nitrate ester. This comparison of the rates of the phenoxide ions with the rates of the alkoxide ions also gives further evidence for ruling out a simple one-electron transfer from the alkoxide ion to **4NM** as a plausible mechanism for this reaction. It is undoubtedly the aromatic character of the phenoxide ions which is leading to another mechanism. The relative ease of participation of phenols in radical processes could be well documented by a lengthy list of various experimental conditions and reaction products; hence our proposal of a one-electron transfer process leading to radical intermediates and radical coupling products for the reactions of the phenols with **4NM** is most reasonable.[30]

One serious objection to this comparison of the alkoxide ions and the phenoxide ions does arise. Electron transfer from the oxygen of the alkoxide ion to **4NM** need not be similar to the electron transfer from the phenoxide ion. The transfer from the phenoxide ion undoubtedly does not occur from a localized negative charge on the oxygen of the phenoxy anion. However electron-transfer processes for both types of molecules may still be occurring. The lack of correlation between the two kinds of oxyanions may arise if the oxidations or electron transfers occur from very different molecular orbitals of these two kinds of molecules. A simplified picture of the transition states for the two reactions may be further interpreted as



(13a)

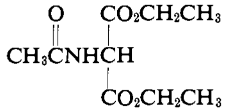


$$C(NO_2)_4 + RO^- \rightleftharpoons [RO^- \text{---} \overset{O^{\delta+}}{\underset{O}{N}} \text{----} \overset{\delta-}{C}(NO_2)_3] \xrightarrow{e^- \text{ transfer}} [RONO_2\cdot^- + C(NO_2)_3\cdot^{2-}] \longrightarrow \text{products}$$

(13b)

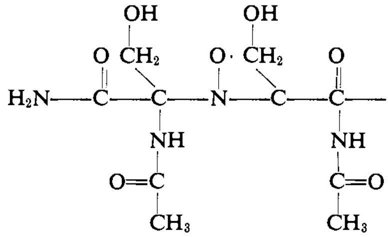
For the reaction of the phenoxide ion the transition state is the electron transfer to **4NM**[3] with subsequent fracture to intermediates and products. However, for the alkoxide ions, the fracture of **4NM** as well as the electron transfer may occur in what amounts to the same step. In this way the electron-transfer processes may be occurring for both types of oxyanions.

The implications of this study of the reactions of alkoxide ions to the use of **4NM** as an agent to modify protein structure is obvious. Does **4NM** also nitrate the serine hydroxyl in proteins? For the reaction of *N*-acetylserinamide (NASA), an obvious model for the serine in proteins, the rate at a given pH was found to increase with increasing NASA concentration. However, a plot of $k_{obsd} - k_{OH}[OH^-]$ *vs.* $[NASA]_T$ yielded a second-order rate constant that was not pH dependent indicating that the alkoxide ion of NASA is probably not the reactive species in the reaction. Higher pH values were not attempted since the decomposition of the amide linkage may complicate the reaction. Further evidence for another mechanism in the reaction of NASA with **4NM** are the high nitrite yields, 60–100%. Lagercrantz and Torssell[17,18] have found imminoxy and nitroxide radicals generated in the reactions of **4NM** with compounds containing hydrogen atoms activated by adjacent carbonyl groups. An example of such a compound is diethyl acetamidomalonate (I). Though the inductive influence of the hydroxymethyl group does not seem large, it may be that NASA is reacting with **4NM** in the same manner as these compounds giving structures such as II. This radical would not be expected to be stable since the most stable radicals were those generated from 1,3-dicarbonyl compounds. Our esr studies have indicated



$$CH_3\overset{\overset{O}{\|}}{C}NH\overset{CO_2CH_2CH_3}{\underset{CO_2CH_2CH_3}{CH}}$$

I



II

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[30] The following references pertain to the electrochemical properties of phenols as an indication of the relative ease with which they are oxidized: (a) B. E. Penketh, *J. Appl. Chem.*, 7, 512 (1957); (b) T. Fueno, T. Ree, and H. Eyring, *J. Phys. Chem.*, 63, 1940 (1959); and (c) R. Glickman, *J. Electrochem. Soc.*, 108, 1 (1961).

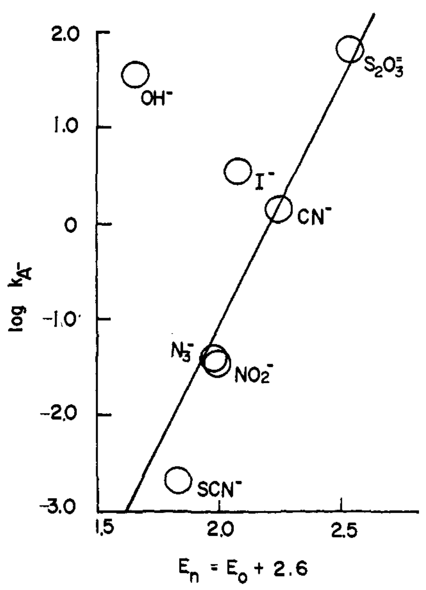

Figure 7. Log k_{A^-} *vs.* E_n for the reactions of seven anions with **4NM** at 30°, $\mu = 1.0$.

that the reaction of **4NM** with NASA is very different from the other alkoxide ions. The appearance of a rather complex radical spectrum in the organic DMSO–NASA phase definitely suggests the possibility of the formation of species such as II. It is interesting to note that no radicals appeared without the addition of KOH while our rate expression suggests no hydroxide dependence for the reaction! It is evident that further investigation is necessary to establish the nature of the reaction of NASA with **4NM**. The possibility that **4NM** may react with the protein backbone under certain circumstances undoubtedly should be investigated.

Reactions of Seven Anions with 4NM. The ability of **4NM** to act as an electron acceptor[3,16,31] suggests that the reactions with the anions might be correlated to the ability of the anion to act a a reducing agent. The logarithm of the second-order rate constant for the reactions of seven anions with **4NM** is plotted in Figure 7 against E_n values (Table IX) suggested by Edwards[32] and derived from the standard electrode potentials compiled by Latimer.[33] E_n is described by eq 14 where E_0 is the standard electrode potential for the dimerization of the anion (eq 15) and 2.6 is the E_0 value for water

$$E_n = E_0 + 2.6 \qquad (14)$$

$$2A^- \longrightarrow A_2 + 2e^- E_0 \qquad (15)$$

used as a reference.[34] The E_n values for N_3^- and NO_2^- were taken from Davis, *et al.*, and are kinetically derived from the reaction of a series of nucleophiles with ethyl tosylate.[35] This plot shows no meaningful correlation with E_n of the rates for all the anions, even if alternate E_n values for N_3^- and NO_2^- are taken from E_0 values suggested by Latimer. A further attempt to correlate these rates is shown in Figure 8 where log k_{rate} is plotted against H_n values defined by Edwards in eq 16 where again 1.74 is a reference correction for

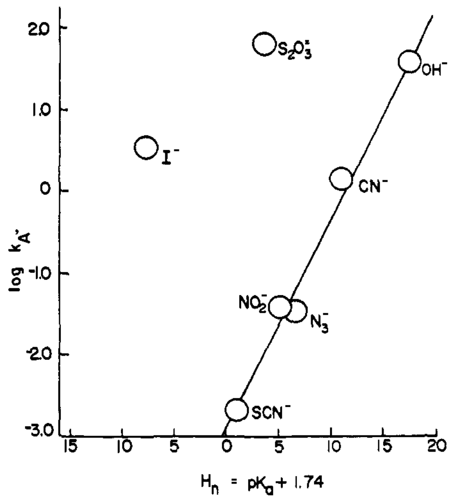

Figure 8. Log k_{A^-} *vs.* H_n for the reactions of seven anions with **4NM** at 30°, $\mu = 1.0$.

$$H_n = pK_a + 1.74 \qquad (16)$$

water. This plot gives the most meaningful correlation of the rates of the anions. Five of the anions, excluding iodide and thiosulfate, fall on a line of slope 0.27 ± 0.02. No better correlation of the rates were found including the use of full form of the Edwards equation (eq 17). Plots of the type log $k_{\text{rate}}/E_n = \alpha + \beta H_n/E_n$

$$\log k_{\text{rate}} = \alpha E_n + \beta H_n \qquad (17)$$

again gave reasonable correlations for the five anions, with iodide and thiosulfate always falling off the plots.

It is apparent then that all the anions may not react with **4NM** by the same mechanism. General mechanisms that we can consider include (1) oxidation of the anion by a electron transfer to **4NM** and (2) nucleophilic attack on **4NM** by the anion. The log k_{A^-} *vs.* H_n profile suggests a reasonable division of the anions into these two general mechanisms.

The ability of iodide and thiosulfate to act as reducing agents is well known; therefore it is reasonable that these two anions are reacting with **4NM** in a one-electron-transfer reaction to form the oxidized reducing agent, **3NM**, and a nitro radical according to Scheme III. The lower **3NM** yields in the reaction of **4NM** with thiosulfate are best explained not by the reduction of **3NM** by thiosulfate since thiosulfate does not react with **3NM** but by the subsequent decomposition of **3NM** as a radical scavenger when it encounters the radical $(S_2O_3)\cdot^-$.[6]

Scheme III

$$C(NO_2)_4 + A^- \xrightarrow{k_{A^-}} A\cdot + C(NO_2)_3^- + NO_2\cdot$$

$$NO_2\cdot + A^- \longrightarrow A\cdot + NO_2^-$$

$$2A\cdot \longrightarrow A_2$$

$$A\cdot + NO_2\cdot \xrightarrow[\text{pathway}]{\text{minor}} ANO_2 \xrightarrow{H_2O} A^- + NO_3^- + 2H^+$$

$$-d[4NM]/dt = k_{A^-}[4NM][A^-]$$

Application of the Brønsted equation has not been limited to reactions involving general acid–base catalysis but has been extended to reactions involving nu-

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(31) C. D. Hall, *Chem. Ind.* (*London*), **9**, 384 (1965).

(32) See Table IX, footnote *b*.

(33) See Table IX, footnote *d*.

(34) The use of the E_0 value for water shifts the plot of log k_{A^-} and does not alter its appearance.

(35) See Table IX, footnote *c*.

cleophilic catalysis as well.[36] The correlation with H_n or pK_a of the reaction of **4NM** with the anions, hydroxide, cyanide, azide, nitrite, and thiocyanate, suggests that the reaction involves nucleophilic attack on sp$_2$ hybridized nitrogen. Furthermore, the β value of 0.27 indicates little bond making in the transition state[37] and is not in accord with the conclusions of Glover[38] about the solvent effects in the reaction of nitrite ion with **4NM**.

The general Scheme IV includes two pathways by which the nucleophilic attack by the anion on **4NM** may occur.[39] Pathway II in Scheme IV cannot be operative

Scheme IV

I $$C(NO_2)_4 + A^- \xrightarrow{k_{A^-}} C(NO_2)_3^- + ANO_2$$

$$A = N_3^-, CN^-, OH^-, SCN^-$$

$$ANO_2 + H_2O \longrightarrow A^- + NO_3^- + 2H^+$$

or

$$ANO_2 + A^- \longrightarrow A_2 + NO_2^-$$

II $$C(NO_2)_4 + A^- \longrightarrow (NO_2)_3CA + NO_2^-$$

$$A = OH^-$$

$$(NO_2)_3CA \longrightarrow \text{further decomposition}$$

$$-d[\mathbf{4NM}]/dt = k_{A^-}[\mathbf{4NM}][A^-]$$

in the reaction of cyanide and azide with **4NM** since 100% **3NM** is formed in the reaction; however, hydroxide may attack **4NM** by this pathway in view of the large nitrite ion yields in the reaction with **4NM**. The nitrite ion yields in the reaction of thiocyanate with **4NM** were seen to increase after *ca.* 10 half-lives, a time during which very little decomposition of **3NM** took place. This suggests that the pathway II in Scheme IV may also be operative for the reaction of thiocyanate with **4NM**, and also suggests that an intermediate is formed which does not immediately decompose. Since thiocyanate anion is known to react either through the sulfur or nitrogen,[40] perhaps this ambient character is leading to the second mode of breakdown of **4NM** (eq 18).

$$\begin{gathered}
C(NO_2)_4 + S{=}C{=}N^- \longrightarrow NO_2^- + (NO_2)_3C\ddot{N}{=}C{=}S \\
(NO_2)_3C\ddot{N}{=}C{=}S \xrightarrow{\text{slow}} NO_2^- + (NO_2)_2C{=}\overset{+}{N}{=}C{=}S \\
(NO_2)_2C{=}\overset{+}{N}{=}C{=}S + H_2O \xrightarrow{\text{fast}} (NO_2)_2C{=}O + {}^-NCS + H^+ \\
(NO_2)_2C{=}O + 2H_2O \xrightarrow{\text{fast}} 2NO_2^- + HCO_3^- + 3H^+
\end{gathered} \tag{18}$$

The reaction of **4NM** with hydroxide ion under various conditions has been studied by several other workers. The ranges of hydroxide concentrations used in this study were well below the range used by Schmidt in 1919.[41] Whereas this worker found increasing nitroform yields in the range 1.0–14.0 *M* hydroxide, we found no trend in nitroform yields from pH 9.69 to 0.02 *M* hydroxide. These studies indicate that while a change in mechanism may well be occurring above 1.0 *M* hydroxide, the mechanism of decomposition of **4NM** in dilute hydroxide solutions does not vary as a function of hydroxide. Our esr work as well as previous esr work by Lagercrantz[17] has indicated that radical species are probably not involved in the alkaline decomposition of **4NM**. For this reason we have not considered any radical mechanism.

Another worker[38] has reported that the decomposition of **4NM** by hydroxide ion in water is an autocatalytic reaction involving the subsequent attack on **4NM** of nitrite ion formed in the reaction. The plot of the formation of **3NM** *vs.* time that was reported appeared to be an S-shaped curve typical of autocatalytic reactions.[42] Under conditions employed in this study for the reaction of hydroxide ion with **4NM** ($[OH^-] \gg [\mathbf{4NM}]$, $[\mathbf{4NM}]_0 = 10^{-4}$ to 10^{-5} *M*), no autocatalysis by nitrite ion was observed. Furthermore, examination of the decomposition of **4NM** in Tris buffer at pH 7.0 indicated no catalysis by the nitrite ion formed in the reaction; hence autocatalysis by nitrite ion does not interfere with the reactions of the other anions at this pH. The rate constant determined by Glover for the reaction of hydroxide ion with **4NM** at 30°, $\mu = 0.1$, is 46 M^{-1} min^{-1} and is comparable to the rate constant determined in this study at 30°, $\mu = 1{,}0$, 39 M^{-1} min^{-1}. Furthermore we have found product distributions identical with those found by this worker. The second-order rate constant we determined at $\mu = 1.0$ for the reaction of nitrite ion with **4NM**, $3.6 \pm 0.39 \times 10^{-2}$ M^{-1} min^{-1}, reasonably agrees with the rate constant determined by Glover at 30°, $\mu = 0.1$, 2.71×10^{-2} M^{-1} min^{-1}. This worker found quantitative production of **3NM** in the reaction of nitrite ion with **4NM**. The mechanism proposed by Glover for the hydroxide and nitrite ion attack on **4NM** is generalized in Scheme IV.

The consistently lower nitrite yields for the reaction of hydroxide ion with **4NM** in carbonate buffers (Table VII) have been explained by one of the referees who indicated his observation that **3NM** reacts with nitrous acid at pH 1–3. It seems reasonable then that nitrite ion is destroyed by this reaction during the initial acidification of the reaction mixture to pH 1–2 (see Experimental Section). The reaction shows no significant trend in nitroform yields over the range of hydroxide studies, pH 9.69 to 0.02 *M;* furthermore the hydroxide rate and nitrite yields determined in these buffers do not depend on the ratio of carbonate to bicarbonate. The product redistribution is shown in reaction 19. It is noted at

$$1.0\mathbf{4NM} \xrightarrow[\text{pH 10.3}]{\text{carbonate buffer}} \left[\begin{array}{l} \longrightarrow 0.64\mathbf{3NM} + 0.71NO_3^- \\ \longrightarrow 0.36 \times 3NO_2^- \end{array}\right. \tag{19}$$

this point that the product redistribution (19) does not effect our conclusions about the reaction of NASA with **4NM** in these buffers.

Reactions of *p*-Cresol with Excess 4NM. Investigations in this laboratory have been concerned with the mechanism of nitration by **4NM** of tyrosyl residues in

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(36) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, pp 37–38.

(37) (a) E. M. Kosower, "Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 18; (b) R. A. Marcus, *J. Phys. Chem.*, **72**, 891 (1968), and *J. Amer. Chem. Soc.*, **91**, 7224 (1969).

(38) D. J. Glover, *J. Phys. Chem.*, **72**, 1402 (1968); **74**, 21 (1970).

(39) Since the reactions of the anions OH^-, CN^-, NO_2^-, N_3^-, and SCN^- were followed by monitoring the formation of **3NM**, the rate constants reported necessarily give the rate of attack at nitrogen only (pathway I in Scheme IV). However, the rate of attack at carbon by hydroxide and thiocyanate must be comparable to the attack at nitrogen since both reaction pathways are observed.

(40) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Wiley, New York, N. Y., 1962, p 467.

(41) E. Schmidt, *Chem. Ber.*, **52**, 400 (1919).

(42) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 19.

proteins. Many earlier studies[4,43–47] have indicated that 100% nitration of all the accessible tyrosine side chains in the proteins can occur under proper conditions. A previous study[3] on the mechanism of the reaction of **4NM** with a series of para-substituted phenoxide ions revealed that the major products consist of nitrite ion and phenol coupling products arising from free-radical oxidation of the phenoxide ion by **4NM**. Nitration of phenol occurs not more than 30%. The question then arises in reference to the modification of proteins by **4NM** as to why 100% nitration of the tyrosine side chains is apparently occurring. Though protein modifiers on the average use 20–60 molar excess of **4NM** in the nitration procedure, our studies have indicated that the use of excess reagent does not lead to 100% nitration. In fact the nitrophenol yields appear lower than expected from our previous study in the presence of excess phenol. Since *m*-nitrophenol was found to react with **4NM**,[3] the 4-methyl-2-nitrophenol derived from *p*-cresol undoubtedly reacts with **4NM** also. Furthermore we have found that the addition of up to 75% ethanol only increases the nitration of *p*-cresol about 20%.

The quantitative nitration of accessible tyrosyl residues in proteins may be rationalized as follows: presumably the major reaction is the formation of the phenoxy radical as was found with the model compounds; however, restriction on the spacial freedom of radical species imposed by the protein tertiary structure may prevent intramolecular coupling of the radical species. Intermolecular cross-linking between protein molecules may be possible if the tyrosyl content on the exterior of the protein is sufficiently high. Once radical coupling is hindered, however, the tyrosyl radical may recombine with a nitro radical generated in the oxidation process to form the nitrated tyrosine. Even though **4NM** is known to cause cross-linking between tyrosyl residues in such biological materials as collagen and γ-globulin,[48] there has been very little evidence reported for any linked tyrosine residues in the enzymes modified so far.[49]

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(43) J. F. Riordan, M. Sokolvsky, and B. L. Vallee, *Biochemistry*, **6**, 3609 (1967).

(44) P. Christen and J. F. Riordan, *ibid.*, **7**, 1525, 1531 (1968).

(45) P. Cautrecasas, S. Fuchs, and C. B. Anfinsen, *J. Biol. Chem.*, **243**, 4787 (1968).

(46) J. A. Verpoorte and C. Lindblow, *ibid.*, **243**, 5993 (1968).

(47) B. Meloun, I. Frič, and F. Šorm, *Eur. J. Biochem.*, **4**, 112 (1968).

(48) R. J. Doyle, J. Bello, and O. A. Roholt, *Biochim. Biophys. Acta*, 274 (1968).

(49) J. Bello, *Biochemistry*, **8**, 4550 (1969).

Optically Active Amines. XI.[1] Optical Rotatory Dispersion and Circular Dichroism Observations on α- and β-Phenylalkylamine Hydrochlorides[2]

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Abstract: Examination of the uv (isotropic absorption), ORD, and CD spectra from about 225 to 300 nm of a number of optically active α- and β-phenylalkylamine hydrochlorides shows that the sign of the Cotton effects in the range 245–270 nm can be predicted using a quadrant sector rule. This rule applies to and is keyed to the $B_2 \leftarrow A_1$ transitions of the phenyl ring chromophore. For open-chain diphenyl-substituted alkylamine hydrochlorides in which the phenyl rings are connected through at least three σ bonds, there is no vicinal interaction between the phenyl groups. The uv, ORD, and CD spectra are the sum of the contributions of each phenyl chromophore. The quadrant sector rule is useful for the interpretation of both the ORD and CD spectra of these compounds. For diphenyl-substituted alkylamine hydrochlorides in which the phenyl rings are connected through two σ bonds, vicinal interaction (homoconjugation) of the phenyl chromophores is reflected in the uv, ORD, and CD spectra. In both the ORD and CD, a large enhancement of the rotational strength of the multiple Cotton effects from 245 to 270 nm is observed. The sign of these Cotton effects is dependent on the preferred orientation of one phenyl group with respect to the other.

Earlier the ORD curves were reported[4] for (*R*)-α-phenylethylamine [(*R*)-**1a**], (*R*)-α-phenyl-*n*-propylamine [(*R*)-**2a**], (*R*)-α-phenylneopentylamine [(*R*)-**3a**], and (*S*)-α-benzylethylamine [(*S*)-**4a**] and their respective hydrochlorides [(*R*)-**1b**–(*R*)-**3b** and (*S*)-**4b**] in methyl alcohol and in isopropyl alcohol from about 225 to 295 nm. As has been noted with similar compounds,[5–13] and in particular with (*R*)-**1a**,[6,7] (*S*)-**1a**,[11]

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(1) Paper X: H. E. Smith and T. C. Willis, *Tetrahedron*, **26**, 107 (1970); erratum: *ibid.*, **26**, 2258 (1970).

(2) Taken from the Ph.D. dissertation of T. C. W., Vanderbilt University, 1969; presented in part at the Combined Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970, Abstract 376.

(3) Tennessee Eastman Fellow, 1966–1967.

(4) H. E. Smith, M. E. Warren, Jr., and L. I. Katzin, *Tetrahedron*, **24**, 1327 (1968); erratum: *ibid.*, **25**, 4648 (1969).

(5) L. Verbit, *J. Amer. Chem. Soc.*, **87**, 1617 (1965).