Nitrophenols from the Reaction of Cumene Hydroperoxide with Nitric Acid or Dinitrogen Tetroxide

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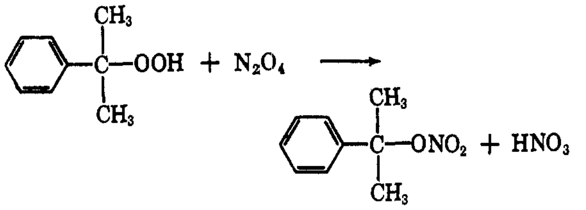
The reaction of cumene hydroperoxide with dinitrogen tetroxide gave mainly a mixture of nitrophenols and acetone; in addition, small amounts of acetophenone and α-methylstyrene were formed. In subsequent nitration of mononitrophenols *p*-nitrophenol was selectively nitrated to 2,4-dinitrophenol leaving the *o*-nitrophenol essentially unchanged.

We were interested in the possibility of *inducing* a free-radical reaction of dinitrogen tetroxide (N_2O_4) by reaction with cumene hydroperoxide (CHP). It was anticipated that CHP would produce alkoxy radicals which would be trapped by NO_2 radicals to produce cumyl nitrate (eq 1). However, no cumyl nitrate was isolated; the major products of the reaction were nitrophenols and acetone (eq 2). Small amounts of acetophenone and α-methylstyrene were also formed. In the course of this work an anomaly in the relative activities of *o*-nitrophenol and *p*-nitrophenol toward subsequent nitration was noted. The formation of nitrophenols by reaction of CHP with N_2O_4 led to an investigation of the reaction of CHP with nitric acid as a preparative method for nitrophenols.[1]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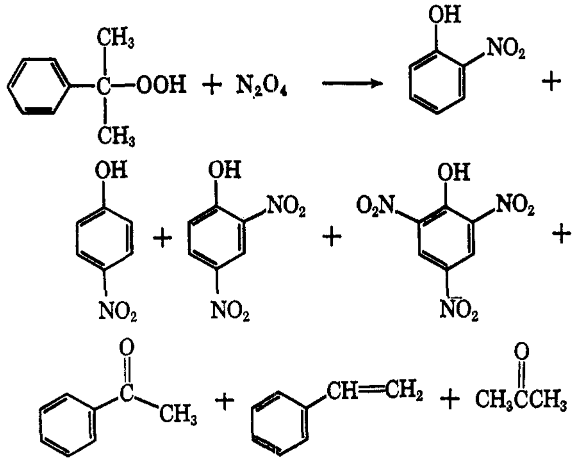
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Results and Discussion

The formation of nitrophenols from the reaction of CHP with N_2O_4 led to an investigation of the reaction of CHP with nitric acid as a preparative method for nitrophenols. As expected, the reaction was quite vigorous and care was exercised to assure that the materials reacted as rapidly as they were mixed; for this purpose a Morton flask and rapid stirring worked quite well.

The results of the reactions of N_2O_4 and nitric acid with CHP are shown in Table I. We were interested primarily in the nitrophenols and, therefore, in most cases did not analyze for acetophenone and α-methylstyrene. The yields of the reactions were quite variable as a result of difficulty in maintaining accurate temperature control. With care the higher yields reported probably represent most accurately the synthetic possibilities of the reaction.

To calculate yields of nitrophenols in the reactions, it was necessary to know the relative amounts of mono-, di-, and trinitrophenols in the products. For this purpose a spectroscopic technique was developed with which it was possible to analyze mixtures of nitrophenols with an accuracy of about 2%. An unexpected anomaly appeared when products were analyzed from reactions in which more than 1 equiv of nitric acid had been used. The spectroscopic analyses are shown in Table II. Two distinct patterns are discernible in the data. In reactions where 1 equiv of nitric acid was used, the products were essentially exclusively mononitrated and the ratio of *ortho* to *para* substitution varied with solvent as expected.[2] In reaction where more than 1 equiv of nitric acid was used, the analyses show a large amount of *o*-nitrophenol remaining and relatively small amounts of *p*-nitrophenol. The same pattern was observed in the nitration of phenol by N_2O_4 as shown in Table III. This result can only be explained by a marked difference in activities of the mononitrophenols toward subsequent nitration. In a competitive nitration experiment, equimolar amounts of *o*-nitrophenol and *p*-nitrophenol were treated with 0.5 equiv of nitric acid. Ninety per cent of the *o*-nitrophenol was recovered unchanged from the reaction, while the *p*-nitrophenol was essentially all converted to dinitrophenol.

A possible explanation for the differences in the relative activities of *o*- and *p*-nitrophenol toward subsequent nitration is offered by the hypothesis of Norman and Radda[3] for low-activity electrophiles. They proposed that charge distribution in the σ complex is important. It has also been suggested that the inductive effect of a group should be strongest at the *ortho* position. These factors would be consistent with the fact that *p*-nitrophenol is readily nitrated. However, the same factors would be operative in *o*-nitrophenol to give 2,6-dinitrophenol. The fact that *o*-nitrophenol is not readily nitrated indicates that although the above

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(1) Several excellent reviews on nitration with HNO_3 or N_2O_4 are available: (a) C. C. Price, *Chem. Rev.*, **29**, 37 (1941); (b) J. L. Riebsomer, *ibid.*, **36**, 157 (1945); (c) P. Gray and A. D. Yoffe, *ibid.*, **55**, 1069 (1955); (d) A. V. Topchiev, "Nitration of Hydrocarbons," Pergamon Press Inc., New York, N. Y., 1959.

(2) J. Podkowka and A. Tarnawski, *Monatsch.*, **90**, 179 (1959).

(3) R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 3610 (1961).

TABLE I

REACTION OF CUMENE HYDROPEROXIDE (15 g) WITH NITRIC ACID OR DINITROGEN TETROXIDE

Expt	Acid	Moles of acid / Moles of CHP	Solvent	Yield: Nitrophenols, g	Yield: Nitrophenols, %	Yield: α-Methylstyrene, g	Yield: Acetophenone, g
A	N_2O_4	1.63	CCl_4	5.6	...	0.478	3.53
B	N_2O_4	2.39	$CHCl_3$	8.1	...	...	2.74
C	HNO_3	1.00	$CHCl_3$	11.8	83.7	a	...
D	HNO_3	1.02	Chlorobenzene	10.0[b]	71.9	a	...
E	HNO_3	0.96	Cumene	6.7	...	a	...
F	HNO_3	1.00	Cumene–chlorobenzene[c]	8.0	...	1.4	3.82
G	HNO_3	1.12	Cumene–chlorobenzene[c]	7.8	56.1	a	...
H	HNO_3	1.43	Cumene	8.1	...	a	...
I	HNO_3	1.43	Cumene	10.4	74.5	a	...
J	HNO_3	1.67	$CHCl_3$	9.1	56.0	0.100	0.476
K	HNO_3	3.00	$CHCl_3$	14.4	78.3	a	...

[a] The solution was not analyzed for α-methylstyrene and acetophenone. [b] Direct distillation of the reaction mixture gave 4.8 g (79% yield) of acetone. [c] A 1:1 mixture by volume was used.

TABLE II

ANALYSIS OF NITROPHENOLS FROM THE REACTION OF CUMENE HYDROPEROXIDE WITH NITRIC ACID

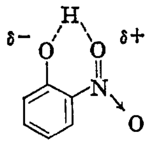
Expt	Moles of HNO_3 / Moles of CHP	Mole % of phenolic product: o-Nitro-	p-Nitro-	2,4-Dinitro-	2,4,6-Trinitro-
C	1.00	36.0	61.3	1.1	1.6
C[a]		9.7	86.5	1.5	2.2
D	1.02	50.0[b]	50.0		
G	1.12	39.8[b]	60.2		
J	1.67	50.4	2.8	40.9	5.9
K	3.00	13.0	1.8	71.6	13.7
I	1.43	53.0	45.8	1.0	0.2

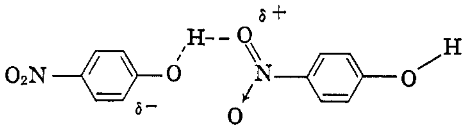
[a] o-Nitrophenol (3.4 g) was removed by steam distillation and the remaining material was analyzed by the spectrophotometric technique. [b] o-Nitrophenol was separated by steam distillation. The nonvolatile nitrophenols were not analyzed by the spectrophotometric technique.

factors may be operating they are not the controlling factors in the nitration.

A second explanation would be that coordination of the nitrating agent with the hydroxyl group would facilitate subsequent nitration to 2,4-dinitrophenol. This mechanism would be analogous to a recent hypothesis by Kovacic and Hiller[4] in which they proposed coordination of the attacking electrophiles with Lewis base substituent groups. Although this hypothesis does not apply to the highly reactive phenol nucleus, it cannot arbitrarily be ruled out for the less reactive p-nitrophenol substitution. Since the hydroxyl group in o-nitrophenol is already intramolecularly hydrogen bonded, the coordination mechanism probably would not be operative. This hypothesis then offers a possible explanation of the differences of activity of o- and p-nitrophenol toward subsequent nitration.

A third explanation for the observed results involves the phenomenon of hydrogen bonding. As mentioned above, o-nitrophenol is hydrogen bonded intramolecularly to the o-nitro group. Any activating effects caused by an increased electron density on oxygen of the hydroxyl group would be negated by increased deactivation by the nitro group as a result of decreased electron density. Therefore, hydrogen bonding would have virtually no effect on the subsequent nitration of o-nitrophenol. In the case of p-nitrophenol, the hydrogen bonding is intermolecular and results in some of the molecules having an increased electron density which facilitates nitration. Hydrogen bonding, therefore, offers a satisfactory explanation of the differences in the relative activities of o-nitrophenol and p-nitrophenol toward electrophilic substitution.





Because acetone forms a constant-boiling mixture with chloroform, we did not attempt isolation of acetone in initial experiments. Acetone was isolated in high yield when the reaction was run in chlorobenzene, the acetone being distilled directly from the reaction mixture. Since acetone was not oxidized by nitric acid in the chlorobenzene reaction, it is reasonable to assume that acetone was not oxidized appreciably in any of the reactions.

In the nitration of phenol by N_2O_4 the product was nitrated to a greater extent than expected. The explanation must be that the nitrous acid produced in the reaction decomposed to N_2O_3 which was then oxidized by air to N_2O_4. The nitrating ability of N_2O_4 was therefore greater than one nitro group per mole.

The formation of nitrophenols as the major product from the reaction of CHP with N_2O_4 was unexpected. As mentioned previously, we believed that reaction of N_2O_4 in the presence of a hydroperoxide would be favorable to achieve predominant reaction by a radical mechanism. Considerable reaction did occur by a radical mechanism as evidenced by the amount of acetophenone and α-methylstyrene formed, these products having been established as free-radical decomposition products of CHP.[5]

The formation of free-radical decomposition products of CHP is evidence that alkoxy radicals were present in the reaction mixtures. The absence of cumyl nitrate in the reaction products can be explained in several ways: (1) NO_2 radicals are poor traps for alkoxy radicals; (2) decomposition of cumyloxy radical to

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(4) P. Kovacic and J. J. Hiller, Jr., *J. Org. Chem.*, **30**, 1581 (1965).

(5) (a) M. S. Kharasch, A. Fono, and W. Nudenberg, *ibid.*, **16**, 1069 (1954); (b) V. A. Belgaev and M. S. Nemtsov, *Zh. Obshch. Khim.*, **32**, 3483 (1962).

Table III

Nitration of Phenol with Nitric Acid or Dinitrogen Tetroxide

				Yield of Nitrophenols		Mole % of phenolic product			
Expt	Acid	Moles of acid / Moles of phenol	Solvent	g	%	*o*-Nitro-	*p*-Nitro-	2,4-Dinitro-	2,4,6-Trinitro-
L	N_2O_4	1.00	$CHCl_3$	9.6	59.0	49.8[a]	1.7	44.2	4.4
M	N_2O_4	1.00	$CHCl_3$	10.6	62.8	36.0	0.4	60.7	2.9
N	HNO_3	1.00	$CHCl_3$	9.6	69.1	36.5[b]	63.5		

[a] Analysis for *o*-nitrophenol by steam distillation gave a value of 52.0%. [b] *o*-Nitrophenol was isolated by steam distillation. The product was not analyzed by spectrophotometric technique.

acetophenone and α-methylstyrene is very rapid; and (3) cumyl nitrate if formed reversed back to alkoxy and NO_2 radicals and the alkoxy radicals then degraded to acetophenone and α-methylstyrene. The ability to dissociate to alkoxy and NO_2 radicals is a general property of nitrate esters.[6] The first two explanations are different only in degree since the ability of NO_2 to act as a radical trap is dependent on the stability of the radical with which it is reacting. The third explanation is least likely since under the mild conditions of the reaction cumyl nitrate should have been stable enough to be isolated.

The formation of nitrophenols resulted from the acid-catalyzed decomposition of CHP to phenol and acetone[7] followed by subsequent nitration of the phenol by N_2O_4. Nitration of CHP followed by subsequent decomposition directly to nitrophenols seems unlikely. It can be stated with certainty that, if nitration of CHP did occur, it was a minor side reaction, since no nitroacetophenone or nitro-α-methylstyrene were detected. The acid-catalyzed decomposition of CHP to phenols was certainly caused by nitrous and nitric acids which were derived by reaction of N_2O_4 with water. The source of water initially would be from the free-radical decomposition of CHP. In addition, it is probable that N_2O_4 acting as a *Lewis* acid catalyzed the decomposition of CHP. The Lewis acid character of N_2O_4 is demonstrated by its ability to form stable complexes with Lewis bases such as ethers,[8] tertiary amines,[9] and nitriles.[10] Sisler proposed that the complexes of ethers with N_2O_4 were of the Lewis acid–Lewis base type.[8] The postulate was based on spectroscopic evidence which showed the absence of NO^+, thereby ruling out a complex based on $NO^+NO_3^-$.

Experimental Section

All experiments were run using 0.10 mole of cumene hydroperoxide.

Reaction of Cumene Hydroperoxide with N_2O_4 in Carbon Tetrachloride.—To a solution of 15 g (0.10 mole) of cumene hydroperoxide (85% solution, technical grade, Matheson Coleman and Bell) in 150 ml of carbon tetrachloride at 5° was added over a 3-hr period 15 g (0.163 mole) of N_2O_4 in 50 ml of carbon tetrachloride. The reaction was stirred for 1 hr, and the nitrogen oxides were removed by passing a stream of dry N_2 through the solution. The yellow solution was extracted with 10% sodium hydroxide solution, which on acidification gave 5.6 g of nitrophenols. The carbon tetrachloride was distilled to give 0.15 g of cumene (solvent for technical cumene hydroperoxide), 0.478 g of α-methylstyrene, 3.53 g of acetophenone, 2.3 g of an unidentified nitro compound, and 1.5 g of pot residue. The acetophenone and α-methylstyrene were identified by infrared spectra and comparison of their gas–liquid partition chromatographic (glpc) retention times with those of authentic samples. The acetophenone was further characterized by its 2,4-dinitrophenylhydrazone derivative, mp 248–249° (uncor).

Reaction of Cumene Hydroperoxide with Nitric Acid in Chloroform.—A solution of 15 g of cumene hydroperoxide in 150 ml of chloroform was cooled to −10° in a Morton flask. To the vigorously stirred solution was slowly added 15 g (0.167 mole) of concentrated nitric acid solution. *The reaction was quite vigorous and care must be exercised not to add the nitric acid too fast.* The reaction was stirred for 1 hr after the nitric acid was added and the solution was extracted with 10% sodium hydroxide solution. Acidification of the base extract yielded 9.1 g of nitrophenols. Distillation of the chloroform solution gave cumene, 0.100 g of α-methylstyrene, and 0.476 g of acetophenone.

Spectrophotometric Analysis of Nitrophenols.—The molar extinction coefficients of *o*-nitrophenol, *p*-nitrophenol, 2,4-dinitrophenol, and picric acid were determined at 294, 272, 253, and 240 mμ in 95% ethanol. The wavelengths were selected by comparing spectra of the nitrophenols on a Cary Model 14M spectrophotometer. The absorbances were measured using a Beckman DU Model 2400 spectrophotometer. Using the molar extinction coefficients of the four nitrophenols at four different wavelengths, a series of simultaneous equations was set up which were used to determine the concentration of the individual components in an unknown mixture

$$A_{294} = 2.975[\mathrm{ONP}] + 7.200[\mathrm{PNP}] + 8.312[\mathrm{DNP}] + 2.070[\mathrm{TNP}]$$

$$A_{272} = 5.985[\mathrm{ONP}] + 2.925[\mathrm{PNP}] + 6.975[\mathrm{DNP}] + 2.225[\mathrm{TNP}]$$

$$A_{253} = 3.390[\mathrm{ONP}] + 1.210[\mathrm{PNP}] + 9.297[\mathrm{DNP}] + 8.269[\mathrm{TNP}]$$

$$A_{240} = 2.960[\mathrm{ONP}] + 3.655[\mathrm{PNP}] + 8.914[\mathrm{DNP}] + 11.722[\mathrm{TNP}]$$

where A is absorbance measured for mixture of nitrophenols in ethanol; [ONP], [PNP], [DNP], and [TNP] are molar concentrations of *o*-nitrophenol, *p*-nitrophenol, 2,4-dinitrophenol, and picric acid, respectively.

The equations were put into a computer program for solution. Analysis of synthetic mixtures of nitrophenols by the above equations gave errors of ±2%. Experimental solutions were made up to give total concentrations of nitrophenols in the range of 10^{-5} M in 95% ethanol. The absorbances due to ethanol were determined and all measurements were run using ethanol from the same container.

Purification of N_2O_4.—Dinitrogen tetroxide (Matheson Co.) was passed through a drying tower of P_2O_5 and collected in a cold trap. The dry, impure N_2O_4 was distilled in a stream of dry oxygen into a second trap where it froze out as a pure white solid. The N_2O_4 was kept frozen until used and transferred directly to the reaction vessel.

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(6) L. Phillips, *Nature*, **165**, 564 (1954).

(7) (a) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **15**, 748 (1954); (b) D. E. Blissing, C. A. Matuzak, and W. E. McEwen, *Tetrahedron Letters*, 763 (1962); (c) W. Pritzkow and R. Hoffman, *J. Prakt. Chem.*, **14**, 131 (1961).

(8) (a) B. Rubin, H. H. Sisler, and H. Schecter, *J. Am. Chem. Soc.*, **74**, 877 (1952); (b) J. G. Whanger and H. H. Sisler, *ibid.*, **75**, 5158 (1958).

(9) (a) D. A. Davenport, H. J. Burkhardt, and H. H. Sisler, *ibid.*, **75**, 4175 (1953); (b) A. E. Comyns, *J. Chem. Soc.*, 1557 (1955).

(10) C. C. Addison, N. Hodge, and J. C. Sheldon, *Chem. Ind.* (London), 1338 (1953).