propane, 108-03-2; 2-nitropropane, 79-46-9; benzene, 71-43-2; α-nitrotoluene, 622-42-4; (1-nitroethyl)benzene, 7214-61-1; (1-nitropropyl)benzene, 5279-14-1; 2-nitroethyl acetate, 18942-89-7; α-nitropropyl acetate, 79101-77-2; toluene, 108-88-3; α-nitro-o-xylene, 38362-89-9; α-nitro-m-xylene, 38362-90-2; α-nitro-p-xylene, 29559-27-1; o-(1-nitroethyl)toluene, 79101-78-3; m-(1-nitroethyl)toluene, 29342-32-3; p-(1-nitroethyl)toluene, 5437-59-2; o-(1-nitropropyl)-toluene, 79101-79-4; m-(1-nitropropyl)toluene, 79101-80-7; p-(1-nitropropyl)toluene, 79101-81-8; $CH_3CH(NO_2)O_2CCH_3$, 24342-21-0; $CH_3CH(NO_2)O_2CC_2H_5$, 79101-82-9; $Mn(OAc)_3$, 993-02-2.

Free-Radical Aromatic Nitromethylation Promoted by Cerium(IV)

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A search for metal salt oxidants, other than manganese(III) acetate, capable of effecting aromatic nitromethylation with nitromethane was undertaken. Of the many screened, cerium(IV) salts showed the most promise. Cerium(IV) ammonium nitrate gave high, though initially erratic, yields (essentially 100% yield of isomeric α-nitroxylenes from toluene and α-nitrotoluene from benzene). However, nitration products and aromatic aldehydes were generated as well. Product formation was followed as a function of time in these reactions, and nitromethylation products were shown to be converted to the corresponding isomeric tolualdehydes or benzaldehyde upon prolonged heating. Cerium(III) nitrate was shown to be primarily responsible for promoting this side reaction. Cerium(IV) acetate, generated in solution by ozonolysis of either cerium(III) nitrate or a mixture of cerium(III) acetate and cerium(III) nitrate in acetic acid, also was shown to promote high yields of nitromethylation products. Furthermore, this reaction was free of side products. Isomer studies and relative rates for nitromethylation were determined for both cerium(IV) salts in comparison with manganese(III) acetate. A Hammett treatment in each case gave similar ρ values (vs. σ^+): −2.3 from manganese(III) acetate, −2.0 from cerium(IV) ammonium nitrate, and −1.9 from cerium(IV) acetate, indicating a common intermediate in each case. The nitromethyl radical, believed to the substituting entity, exhibits marked electrophilic properties.

Recently we reported that aromatic nitromethylation could be accomplished by refluxing a mixture of the aromatic, nitromethane, and manganese (III) acetate in acetic acid.[1] This reaction (eq 1 with $M^nX_n = Mn(OAc)_3$) was

$$ArH + 2M^nX_n + CH_3NO_2 \xrightarrow[HOAc]{} ArCH_2NO_2 + 2M^{n-1}X_{n-1} + 2HX \quad (1)$$

felt to involve the generation of nitromethyl radicals (by oxidative deprotonation of nitromethane) and their subsequent substitution onto the arene.[1,2] While this reaction provides a more direct route to aryl nitromethanes than existing methods,[3,4] it suffers the drawback that the manganese(III) salt must be synthesized by the chemical[5] or electrochemical[6] oxidation of manganese(II) acetate and is not able to be regenerated during the reaction.[1] Consequently, we were interested in finding other oxidants capable of promoting this reaction and herein report on our studies with other metal salt promoters, particularly in comparison to manganese(III) acetate.

Experimental Section

General Methods. IR spectra were obtained with a Perkin-Elmer Model 710B spectrophotometer as thin films or KBr pellets. A 60-MHz Hitachi Perkin-Elmer Model R-24B spectrometer was used to run NMR spectra ($CDCl_3$ solvent containing 1% Me_4Si). GC analyses were made on a Hewlett-Packed Model 5840A gas chromatograph equipped with flame-ionization detectors and a capillary inlet system (split mode). Separations were performed with either a 10 m × 0.22 mm SP2100 glass capillary column or a 15 m × 0.25 mm Carbowax 20M fused silica capillary column. Preparative gas chromatography was done on a GOW MAC Series 150 gas chromatograph equipped with a 4 ft × 0.25 in. SS 15% Carbowax 20M/Chrom P (80/100 mesh) column. Ozonolyses were carried out with the use of a Purification Sciences Inc. Model LOA-1 ozone generator.

Cerium(IV) acetate was synthesized[7] and generally used without isolation. Cobalt(III) acetate was made by the oxidation of cobalt(II) acetate.[8] The remaining metal salts and organic reactants

Table I. Nitromethylation of Benzene and Toluene Promoted by Metal Salts

metal salt	% nitromethylation product[a] benzene	toluene	byproducts
$Ce(NH_4)_2(NO_3)_6$	55	100	many
$Ce(OAc)_4$		58	none
$CeK_2(NO_3)_6$[b]	17	36	some
$CeH_4(SO_4)_4$[b]		23	some
$Ce(NH_4)_4(SO_4)_4 \cdot 2H_2O$[b]		15	some
$Ce(NO_3)_3(OH)$	6	10	some
$Co(OAc)_3$		3	some
$Mn^{III}(C_5H_7O_2)_3$[c]		1	some

[a] Based on 1 mol of product/2 mol of metal salt; average of at least two runs in good agreement. [b] In the presence of $Cu(OAc)_2$. [c] The following metal salts gave no nitromethylation products at all: $Ce(OH)_4$, $Cu(BF_4)_2$, $Cu(NO_3)_2$, $CuCl_2$-LiCl, $Cu(OAc)_2$, $Cu(OAc)_2$-LiCl, $FeCl_3$, $Hg(NO_3)_2$, $Hg(OAc)_2$, $MnCl_3$, MnO_2, NH_4VO_3, $Pb(OAc)_4$, $Tl(OAc)_3$, $UO(OAc)_2 \cdot 2H_2O$.

(1) M. E. Kurz and T. Y. R. Chen, *J. Org. Chem.*, **43**, 239 (1978).
(2) M. E. Kurz, P. Ngoviwatchai, and T. Tantrarant, *J. Org. Chem.*, preceding paper in this issue.
(3) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).
(4) A. P. Black and F. H. Bakers, "Organic Syntheses", Collect. Vol. II, Wiley, New York, 1943, pp 412, 512.
(5) P. J. Andrulis, M. J. S. Dewar, R. Dietz, and R. L. Hunt, *J. Am. Chem. Soc.*, **88**, 5473 (1966).
(6) A. J. Bellamy, *Acta Chem. Scand. B*, **33**, 208 (1979).
(7) R. A. Sheldon and J. K. Kochi, *J. Am. Chem. Soc.*, **90**, 6688 (1968).
(8) J. K. Kochi, R. T. Tang, and T. Bernath, *J. Am. Chem. Soc.*, **95**, 7114 (1973).

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Table II. Aromatic Nitromethylation Promoted by Cerium(IV) Ammonium Nitrate

aromatic	product	byproduct	% yield[a]
benzene	$PhCH_2NO_2$		55
		PhCHO	34
		$PhCH_2OAc$	11
toluene	$CH_3PhCH_2NO_2$		100
		CH_3PhCHO	44
		$PhCH_2OAc$	36
		CH_3PhNO_2	34
		PhCHO	27

[a] Based on 1 mol of product/2 mol of cerium(IV) ammonium nitrate.

were commercially available and used as is. Authentic products not commercially available (isomeric α-nitroxylenes, methoxy-α-nitrotoluenes, chloro-α-nitrotoluenes, and methylbenzyl acetates) were synthesized by literature methods.[1,3,4]

Aromatic Nitromethylation Promoted by Metal Salts. General Procedure. The metal salt (10 mmol), the aromatic (10 mL), nitromethane (25 mL), and acetic acid (25 mL) were refluxed together under nitrogen atmosphere for 24 h or until a color change indicated that the metal ion had been reduced. After cooling, the reaction mixture was poured onto ethyl ether (25 mL) and water (50 mL). The resulting organic layer was separated, washed with water and aqueous sodium carbonate (5%), dried, and concentrated for subsequent analysis by GC. Products were isolated by preparative GC for representative reactions and identified by comparison of their IR and NMR spectra and GC retention times with those of the authentic compounds.

For quantitative analysis, a known amount of an internal standard (usually *p*-nitrotoluene) was added to the reaction mixtures, and product peak areas were compared to that of the internal standard. Yield percentages were based on 1 mol of product/2 mol of metal salt promoter (eq 1), and are the average of two or more runs in good agreement.

A similar procedure was used for the product vs. time studies, except that 1-mL aliquots were withdrawn directly from the reaction mixture at various times and analyzed directly by GC, after addition of an internal standard.

Competition studies with cerium(IV) acetate were carried out in the same manner as above except that two aromatics (10 mL of each) were used.

Results

The search for effective promoting agents for this nitromethylation reaction other than manganese(III) acetate led us to survey many other metal salt oxidants (Table I). The typical reaction procedure involved refluxing the metal salt, toluene or benzene, nitromethane, and acetic acid under nitrogen until the metal salt was reduced.

Cerium(IV) salts were found to be the most effective promoters of those screened; yields for the nitromethylation of toluene of up to 100% for cerium(IV) ammonium nitrate and 58% for cerium(IV) acetate were obtained. Lower yields resulted when cerium(IV) salts containing sulfate were utilized together with copper(II) acetate. Reactions with benzene also gave proportionately lower yields.

Of the other metal salt oxidants, only with cobalt(III) acetate were any nitromethylated toluenes found; various copper(II), mercury(II), and other metal salts were ineffective promoters (Table I).

More detailed investigation of the cerium(IV) ammonium nitrate and cerium(IV) acetate promoted reactions were carried out to determine both the scope and mechanism of these processes.

Nitromethylation Promoted by Cerium(IV) Ammonium Nitrate. Initial studies with this salt gave rather erratic results (widely varying yields and extent of side reactions) which were dependent on the length of reaction reflux. This is due to the difficulty that, unlike the nitromethylation promoted by manganese(III) acetate, there was no clear cut visual indication as to when all the cerium(IV) had been reduced. Along with the nitromethylated products, the byproducts benzaldehyde, methylbenzyl acetate, and isomeric nitrotoluenes and tolualdehydes were found for the reaction with toluene; from the benzene reaction, benzaldehyde and benzyl acetate were also formed in high yield (Table II). In order to follow the formation of the products, time dependent studies were performed. The reaction mixture was analyzed directly by GC at various times during the reaction. The product yields were plotted against time as shown in Figures 1 and 2 for the reaction with benzene and with toluene, respectively. The optimum yield of the desired substituted products required 14 h of refluxing with benzene and 8 h with toluene. After the optimum time, the nitromethylation products decreased upon prolonged heating, and byproducts became more abundant (Figures 1 and 2). It is clearly evident from both figures that the growth of benzaldehyde and tolualdehyde byproducts occurred at the same time as the demise of the nitromethylated products. This suggested that the nitromethylated products underwent conversion to the corresponding aldehydes.

In order to determine which compound in the reaction mixture was responsible for the conversion of the nitroarenes to the aldehydes, we subjected phenylnitromethane to simulated reaction conditions (benzene–nitromethane–acetic acid at reflux) in a series of reactions with each of the following: cerium(IV) ammonium nitrate, cerium(III) nitrate, ammonium nitrate, and acetic acid. Aliquots of each reaction mixture were analyzed at different times, and the ratio of benzaldehyde to phenylnitromethane was

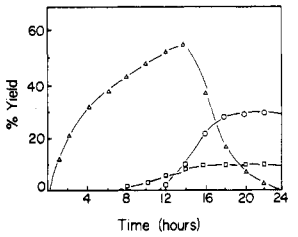

Figure 1. Product formation vs. time for CAN–C_6H_6–CH_3NO_2: △, $C_6H_5CH_2NO_2$; ○, C_6H_5CHO; □, $C_6H_5CH_2OAc$.

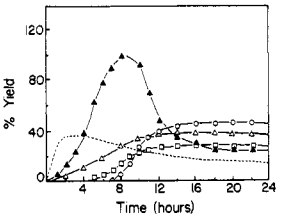

Figure 2. Product formation vs. time for CAN–$C_6H_5CH_3$–CH_3NO_2: ▲, $CH_3C_6H_4CH_2NO_2$; ○, $CH_3C_6H_4CHO$; □, C_6H_5CHO, △, $CH_3C_6H_4NO_2$; - -, $C_6H_5CH_2OAc$.

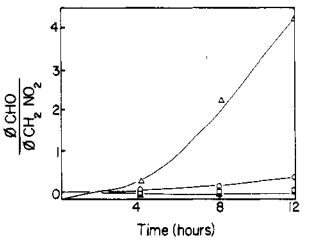

Figure 3. Conversion of α-nitrotoluene to benzaldehyde under simulated reaction conditions: △, with $Ce(NO_3)_3$; ○, with NH_4NO_3; ▲, with HNO_3; □, with CAN.

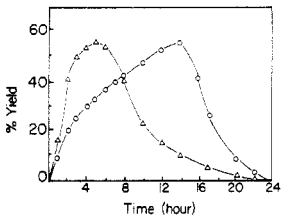

Figure 4. Effect of copper(II) on nitromethylation rate: △, with $Cu(OAc)_2$; ○, without $Cu(OAc)_2$.

$$C_6H_6 + CH_3NO_2 + CAN \xrightarrow{HOAc} C_6H_5CH_2NO_2$$

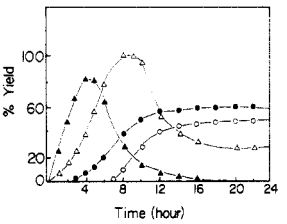

Figure 5. Effect of copper(II) on nitromethylation rate: △, $CH_3C_6H_4CH_2NO_2$ without $Cu(OAc)_2$; ▲, $CH_3C_6H_4CH_2NO_2$ with $Cu(OAc)_2$; ○, $CH_3C_6H_4CHO$ without $Cu(OAc)_2$; ●, $CH_3C_6H_4CHO$ with $Cu(OAc)_2$.

$$C_5H_6CH_3 + CH_3NO_2 + CAN \xrightarrow{HOAc} CH_3C_6H_4CH_2NO_2$$

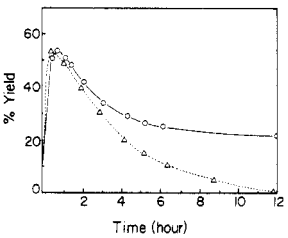

Figure 6. Product formation vs. time and effect of copper(II): ○, without $Cu(OAc)_2$; △, with $Cu(OAc)_2$.

$$C_6H_5CH_3 + CH_3NO_2 \xrightarrow[HOAc]{Mn(OAc)_3} CH_3C_6H_4CH_2NO_2$$

plotted vs. time (Figure 3). Both cerium(III) nitrate and ammonium nitrate were found to convert phenylnitromethane to the aldehyde, the former being more effective.

Previously Heiba[9] had demonstrated that small amounts of copper(II) acetate added to manganese(III) acetate altered aromatic carboxymethylation, a process thought to be mechanistically similar to nitromethylation. When copper(II) acetate was added to a typical benzene–nitromethane–cerium(IV) ammonium nitrate mixture, it had no effect on the product or byproduct yields, but it did increase the rate of formation of the nitromethylation product as shown in Figure 4. Thus a nitromethylation yield maxima was reached in 5 h with the copper salt additive whereas it took 14 h without it. It had little effect on the yield of the product with toluene and also diminished the required time from 8 to about 4 h (Figure 5).

For comparison purposes, the effect of extended exposure of the nitromethylation reaction mixture from manganese(III) acetate was determined by studying the effect of the product yield vs. time. Like the cerium system, the product decomposed to aldehyde (Figure 6) when the manganese(II) reduction product was present in a substantial amount. The introduction of copper(II) acetate into the system was found to slightly speed up the conversion of product to aldehyde (Figure 6). Manganese(II) acetate formed upon reduction was shown to be responsible for the conversion of the product (Figure 7).

(9) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Am. Chem. Soc.*, 91, 138 (1969).

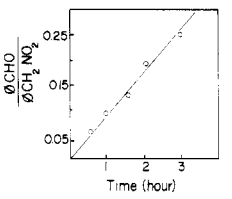

Figure 7. Conversion of α-nitrotoluene to benzaldehyde affected by manganese(II) acetate.

$$C_6H_5CH_2NO_2 \xrightarrow[Mn(OAc)_2]{\Delta} C_6H_5CHO$$

Table III. Toluene Nitromethylation Promoted by $Ce(OAc)_4$

system	$CH_3C_6H_4CH_2NO_2$ % yield[a]	$CH_3C_6H_4CH_2NO_2$ ortho/meta/para ratio
$Ce(OAc)_3$ (4 mmol) + $Ce(NO_3)_3$ (0.4 mmol) + O_3 (excess)	58	54.6/21.6/23.8
$Ce(NO_3)_3$ (4 mmol) + O_3 (excess)	56	56.0/22.7/21.2

[a] Based on 1 mol of product/2 mol of metal salt; average of three runs, ±2%.

Table IV. Nitromethylation of Toluene

metal salt	no. of runs	% isomer distribution[a] ortho	meta	para	rel rate[b] ($k_{C_6H_5CH_3}/k_{C_6H_6}$)
$Mn(OAc)_3$	2	51.7	20.5	27.8	4.4 ± 0.45
$Ce(NH_4)_2(NO_3)_6$	5	56.5	19.1	24.4	3.8 ± 0.23
$Ce(OAc)_4$	2	52.1	22.7	25.2	3.0 ± 0.05

[a] Standard deviation for isomer distributions range from 0.1 to 0.7. [b] Corrected by the molar ratio factor of the aromatics.

Table V. Nitromethylation of Anisole

metal salt	no. of runs	% isomer distribution[a] ortho	meta	para	rel rate[b] ($k_{C_6H_5OCH_3}/k_{C_6H_6}$)
$Mn(OAc)_3$	2	70.3	1.9	27.8	12.9 ± 0.04
$Ce(NH_4)_2(NO_3)_6$	4	68.3	2.1	29.6	11.0 ± 1.14
$Ce(OAc)_4$	2	68.6	3.3	28.1	10.0 ± 0.40

[a] Standard deviation range from 0.2 to 0.9. [b] Corrected by the molar ratio factor of the aromatics.

Table VI. Nitromethylation of Chlorobenzene

metal salt	no. of runs	% isomer distribution[a] ortho	meta	para	rel rate[b] ($k_{C_6H_5Cl}/k_{C_6H_6}$)
$Mn(OAc)_3$	4	63.3	7.7	29.1	0.46 ± 0.03
$Ce(NH_4)_2(NO_3)_6$	4	64.0	11.5	24.5	0.44 ± 0.03
$Ce(OAc)_4$	2	61.5	12.2	26.3	0.46 ± 0.01

[a] Standard deviation range from 0.2 to 2.9. [b] Corrected by the molar ratio factor of the aromatics.

Nitromethylation Promoted by Cerium(IV) Acetate. Cerium(IV) acetate was synthesized,[7] isolated, and then utilized in attempted nitromethylations. However, in these reactions yields of the desired products were low due perhaps to poor solubility and light sensitivity of this salt. Consequently, a method of generating cerium(IV) acetate in acetic acid and using it directly was employed. Using this procedure yields of up to 58% of nitro-

Table VII. Partial Rate Factors[a]

	$Mn(OAc)_3$	$Ce(NH_4)_2(NO_3)_6$	$Ce(OAc)_4$
$M_f^{CH_3}$	2.7	2.2	2.0
$P_f^{CH_3}$	7.3	5.6	4.5
$M_f^{OCH_3}$	0.7	0.7	1.0
$P_f^{OCH_3}$	21.5	19.5	16.9
M_f^{Cl}	0.1	0.2	0.2
P_f^{Cl}	0.8	0.6	0.7

[a] M_f is a meta partial rate factor, and P_f is a para partial rate factor.

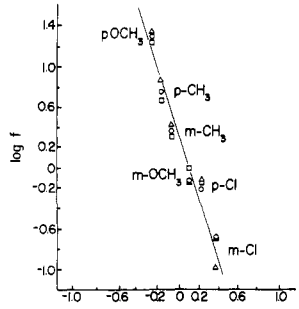

Figure 8. Hammett treatment using σ value.

		ρ	rel error	r
○	$Ce(NH_4)_2(NO_3)_6$	−2.86	±0.26	0.978
□	$Ce(OAc)_4$	−2.65	±0.28	0.974
△	$Mn(OAc)_3$	−3.28	±0.32	0.977

methylation products were obtained (Table III), in a reaction that was complete within 20 min. as indicated by a color change. Unlike the cerium(IV) ammonium nitrate reactions no byproducts were observed.

Relative Rates Studies. In order to help determine mechanistic similarities or differences in the cerium(IV) ammonium nitrate, cerium(IV) acetate, and the earlier studied manganese(III) acetate-promoted reactions, we determined the relative rates for toluene (Table IV), anisole (Table V), and chlorobenzene (Table VI). From these values partial rate factors were determined (Table VII) and the logarithms of these values were plotted against known σ (Figure 8) and σ^+ values (Figure 9). In the former case a reasonably good Hammett correlation was noted in all three cases, and relatively similar values were obtained (ρ = −3.3 for manganese(III) acetate, −2.7 for cerium(IV) acetate and −2.9 for cerium(IV) ammonium nitrate). Relative errors in the slopes ranged from 9–11% and correlation coefficients of 0.974–0.978 were found. The Hammett plots against σ^+ came out even a bit better (relative errors in the slope were 8–10%, and correlation coefficients were in the 0.972–0.985 range). ρ values of −2.3,[10] −1.9, and −2.0 were obtained for the same three salts, respectively.

Isotope Effect Studies. Isotope effect studies were performed with cerium(IV) acetate as the promoter in the same fashion as for manganese(III) acetate.[2] A kinetic isotope effect (k_H/k_D) with nitromethane-d_3 of 4.0 was observed. No isotope effect was found (k_H/k_D = 1.0) with benzene-d_6. These values were very similar to those (k_H/k_D = 4.2 and 1.0, respectively) found for manganese(III) acetate.[2] Neither nitromethane-d_3 nor benzene-d_6 were found to undergo deuterium exchange under simulated reaction conditions.[2]

Discussion

The results of this study showed that cerium(IV) salts, especially cerium(IV) ammonium nitrate and cerium(IV) acetate, are good promoters for the nitromethylation of aromatics, comparing quite favorably with manganese(III) acetate. Each salt has advantages and disadvantages in comparison to the earlier method. Advantages of using cerium(IV) ammonium nitrate include the fact that it is commercially available at reasonable cost and gives very high yields for this reaction. One disadvantage is the many byproducts in this reaction. A number of these (the nitrotoluenes and benzaldehyde) are typical products from the action of either nitric acid or cerium(IV) ammonium nitrate on toluene.[11] Finding benzyl acetate in the toluene case may indicate some oxidation of the aromatic to a radical cation by cerium(IV),[12] while its presence as a benzene byproduct can be accounted for by a cerium(IV)-promoted carboxymethylation of benzene followed by oxidative decarboxylation of the phenylacetic acid produced.[5,9,13]

The aldehyde byproducts shown to be formed from the nitromethyl arene constitute an even more serious problem which is compounded by the long reaction time and visual difficulty in determining when the reaction has been completed. This conversion of nitromethyl arenes to aldehydes, known as the Nef reaction, can be accomplished with a variety of reagents.[14,15] In our reaction mixtures two byproducts of cerium(IV) ammonium nitrate reduction, cerium(III) nitrate and ammonium nitrate, were shown to be primarily responsible for causing the Nef reaction. Manganese(II) also was observed to promote this aldehyde formation. Work is currently underway to determine whether a one-pot method of formylation going through the nitromethylated product (eq 2) might be a potential synthetic method for benzaldehydes.

$$ArH + CH_3NO_2 \xrightarrow{Ce(NH_4)_2(NO_3)_6} (ArCH_2NO_2) \rightarrow ArCHO \quad (2)$$

The use of cerium(IV) acetate as promoter also has its

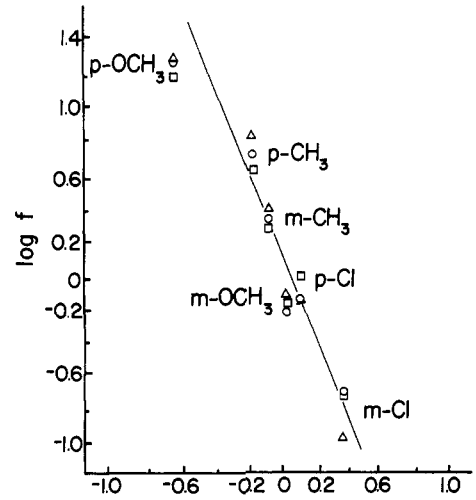

Figure 9. Hammett treatment using σ^+ value.

		ρ	SD	r
○	$Ce(NH_4)_2(NO_3)_6$	−2.02	±0.17	0.985
□	$Ce(OAc)_4$	−1.88	±0.15	0.984
△	$Mn(OAc)_3$	−2.29	±0.25	0.972

(10) This value is more accurate than the earlier value[1] since it is based on more points due to better separation of nitromethylated products by capillary column GC which was not available in the earlier study.

(11) M. E. Kurz, E. M. Steele, and R. L. Vecchio, *J. Org. Chem.*, **39**, 3331 (1974).
(12) W. S. Trahanovsky and L. B. Young, *J. Org. Chem.*, **31**, 2033 (1966).
(13) E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.*, **93**, 995 (1971).
(14) R. Noland, *Chem. Rev.*, **55**, 137 (1955).
(15) N. Kornblum and A. S. Erickson, *J. Org. Chem.*, **46**, 1073 (1981).

pluses and minuses. One advantage is the short reaction time required and the color change occurring upon cerium(IV) reduction which clearly signals the end of the desired reaction. A second important advantage is the complete lack of organic byproducts. Two disadvantages are the need to synthesize cerium(IV) acetate and some difficulty in isolating and keeping this rather light-sensitive salt. However, these problems can be conveniently circumvented by generating cerium(IV) acetate and then using it immediately without isolation.

Product yields and byproduct formation were distinctly affected by the nature of the cerium complex used. Cerium(IV) acetate seemed to be the best in terms of good yield, no byproducts, and the short reaction time required. Some of the other cerium salts investigated (Table I) were much inferior to cerium(IV) acetate due perhaps to solubility problems, low oxidation potentials, or other species released upon solvolysis in acetic acid.

With cerium(IV) ammonium nitrate, the high yield was likely the result of the byproduct, ammonium nitrate, reoxidizing cerium(III) to cerium(IV) during the course of the reaction. This is supported by evidence that ammonium nitrate oxidizes the closely related promoter manganese(II) to manganese(III) which promoted the nitromethylation in the presence of nitromethane and an aromatic.[2,6]

It is interesting to note the relative ease at which cerium(IV) acetate promotes the reaction in comparison to the others. Thus nitromethylation of toluene was complete within 15 min with this salt whereas it took 40 min to complete under the same conditions with manganese(III) acetate.[1] Cerium(IV) acetate has been shown to promote the carboxymethylation of aromatics[13] and the α-ketoalkylation of 1-octene[16] in essentially the same manner as does manganese(III) acetate.[9] In fact, in the latter reaction it was shown to be a power of ten more reactive in oxidizing secondary alkyl radical intermediates than was the manganese(III) species.[16] The relatively sluggish reaction with cerium(IV) ammonium nitrate may be due to some of the side products of its reduction. A similar sluggish behavior was noted for cerium(IV) ammonium nitrate in aromatic oxygenation.[11] The inclusion of copper(II) acetate with cerium(IV) ammonium nitrate speeded up nitroalkylation considerably (Figure 4) due perhaps to the even greater ease of the intermediate aromatic σ-radical oxidation by copper(II).[16,17] However, the nitromethyl radical itself apparently resists oxidation, much like other electron-deficient carbon radicals.[18]

The Hammett treatment with cerium(IV) ammonium nitrate and cerium(IV) acetate gave almost the same ρ values, suggesting that both cerium salts function in the same manner. In addition, this value was virtually the same as that determined for the manganese(III) acetate promoted system under the same conditions (-2.0 vs. -2.3). Similar isotope effects were also noted for cerium(IV) and manganese(III) acetate promoted reactions.[2] Consequently, it seems likely that the mechanism of substitution is the same with both metal ions: generation of nitromethyl radicals by oxidation (eq 3), attack of these radicals

$$CH_3NO_2 \xrightarrow[-Ce(III)]{Ce(IV)} \cdot CH_2NO_2 + H^+ \quad (3)$$

$$\cdot CH_2NO_2 + ArH \longrightarrow Ar(H)CH_2NO \quad (4)$$

I

$$I \xrightarrow[-Ce(III)]{Ce(IV)} ArCH_2NO_2 + H^+ \quad (5)$$

onto the aromatic (eq 4), and oxidative rearomatization (eq 5).[1,2] The initial step probably goes by way of an aci radical cation as shown for manganese(III).[2]

The ρ value of -2 suggests a substantial degree of electrophilic character for the nitromethyl radical, more so than most known carbon radicals[1,19] and in the same range as a number of oxy radicals.[20,21]

(16) E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.*, **93**, 524 (1971).
(17) J. K. Kochi, "Free Radicals", Vol. I, Wiley-Interscience, New York, 1973.
(18) J. K. Kochi and D. M. Mog, *J. Am. Chem. Soc.*, **87**, 522 (1965).
(19) W. A. Pryor, W. H. Davis, Jr., and J. H. Gleaton, *J. Org. Chem.*, **40**, 2099 (1975).
(20) M. E. Kurz and M. Pellegrini, *J. Org. Chem.*, **35**, 990 (1970).
(21) P. Kovacic, C. G. Reid, and M. E. Kurz, *J. Org. Chem.*, **34**, 3302 (1969).

Regeneration of NAD(P)H Using Glucose 6-Sulfate and Glucose-6-phosphate Dehydrogenase

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Glucose 6-sulfate and glucose-6-phosphate dehydrogenase have been used for NAD(P)H cofactor regeneration in preparations of (*S*)-benzyl-α-d_1 alcohol and *threo*-D_s(+)-isocitrate (0.1-mol scale). The reduced nicotinamide cofactors are more stable in solutions of glucose 6-sulfate than in solutions of glucose 6-phosphate and their lifetimes in solution are correspondingly longer. The specific activities of the enzymes are, however, lower with glucose 6-sulfate than with glucose 6-phosphate. Glucose 6-sulfate appears to be a useful and practical reducing agent for NADP; glucose 6-phosphate is clearly superior for NAD. Comparisons of several methods for making glucose 6-phosphate indicate that phosphorylation of glucose with ATP (using ATP cofactor recycling and hexokinase as catalyst) is the most effective method for laboratory-scale syntheses.

The combination of glucose 6-phosphate (G-6-P) and G-6-P dehydrogenase (G-6-PDH from *Leuconostoc mesenteroides*) provides a useful method for large-scale regeneration of NAD(P)H.[2] This procedure has the ad-

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