

Electrophilic nitration of alkanes with nitronium hexafluorophosphate

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ABSTRACT Nitration of alkanes such as methane, ethane, propane, *n*-butane, isobutane, neopentane, and cyclohexane was carried out with nitronium hexafluorophosphate in methylene chloride or nitroethane solution. Nitration of methane, albeit in poor yield, required protolytic activation of the nitronium ion. The results indicate direct electrophilic insertion of NO_2^+ into C–H and C–C σ -bonds.

Aromatic electrophilic nitration is a well studied and well understood reaction (1). In contrast, aliphatic nitration is much less investigated. Beilstein and Kurbatov (2) were the first to nitrate “paraffins” from petroleum fractions with nitric acid and obtained minor amounts of nitro compounds besides overwhelming oxidation products. Kononov (3) and Markovnikov (4) carried out a more detailed study of nitration of paraffins. Kononov first showed the nitration of aliphatic hydrocarbon at high temperature using dilute nitric acid. Hass *et al.* (5) have carried out extensive studies of gas-phase nitration of propane, *n*-butane, isobutane, *n*-pentane, and isopentane with nitric acid vapor at 350–400°C under free-radical conditions. Grundmann (6) has extended this reaction for higher molecular weight hydrocarbons at 160–180°C with nitric acid and NO_2 . More recently, it was reported (7, 8) that gas-phase nitration of alkanes higher than methane with NO_2 and O_2 gives nitroalkanes. This procedure also was applied (9–14) for gas-phase nitration of aldehydes, ketones, alcohols, and carboxylic acids to give nitro paraffins. Umstead *et al.* (15) have shown the formation of 2-nitro-2-methylpropane in the laser-induced reaction of isobutane with NO_2 radical. Stanley and Godbey (16–18) have used the laser-induced nitration procedure for other alkanes. Nitration of ethane also has been carried out under free-radical conditions by passing H_2O_2 gas and NO_2 (19) with ethane as the carrier gas. The mechanism of this free-radical reaction involves hydroxyl and ethyl radicals as the chain carriers. NO_2 – N_2O_4 mixture also was used (20) for the nitration of alkanes; for example, propane nitrated by NO_2 – N_2O_4 and Cl catalyst at 180–320°C gave a mixture of CH_3NO_2 , $\text{CH}_3\text{CH}_2\text{NO}_2$, Me_2CHNO_2 , and $\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$. The amount of $\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$ obtained was higher than that of Me_2CHNO_2 . Some nitroalkanes also have been obtained by treating alkanes with HNO_3 over metal nitrates (21).

Aromatic hydrocarbons are readily nitrated with mixed acids ($\text{HNO}_3 + \text{H}_2\text{SO}_4$) in high yields as the resulting aromatic nitro compounds are stable under the acidic reaction conditions. In contrast, tertiary and secondary nitroalkanes are not stable under similar acidic conditions. Even primary nitroalkanes are rapidly hydrolyzed by hot sulfuric acid whereas secondary and tertiary nitroalkanes form tars. Olah and Lin in a preliminary communication first reported (22) aliphatic electrophilic nitration using nitronium salts under mild conditions. More

recently, we also have carried out nitration (23) of adamantane and diamantane using nitronium tetrafluoroborate in nitroethane solvent. Electrophilic nitration of adamantane with $\text{NO}_2^+\text{BF}_4^-$ gave a mixture of 1-nitroadamantane and 1-adamantanol. The reaction with bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane under similar conditions gave only oxidation products, bicyclo[2.2.1]heptan-2-one and bicyclo[2.2.2]octan-1-ol (24). We now report a more detailed study showing that nitronium hexafluorophosphate with its superior solubility over tetrafluoroborate in solvents such as dichloromethane or nitromethane nitrates alkanes to give the corresponding nitroalkanes in useful yields without any accompanying oxidation products.[†]

EXPERIMENTAL PROCEDURE

Dichloromethane (Mallinckrodt) and nitroethane (W. R. Grace, Cambridge, MA) were dried by refluxing over calcium hydride followed by distillation. 1,1,2-Trichlorotrifluoroethane (Freon-113) (Aldrich) was dried over phosphorus pentoxide under dry nitrogen and then distilled. Trifluoromethanesulfonic acid (triflic acid) (3M Co.) was freshly distilled under dry nitrogen before use. Nitronium hexafluorophosphate was prepared from fuming nitric acid, anhydrous HF, HPF_6 (60%), and PCl_5 following a recently developed procedure (G.K.S.P., D.K. Padma, P.R., D. Adamson, and G.A.O., unpublished results). Reference nitro compounds were purchased from Aldrich. All alkanes used were commercial products. GC-MS analyses were carried out on a Hewlett-Packard 5971 (electron impact) or a Finnigan INCOS 50 Mass Spectrometer (chemical ionization). NMR spectra in CDCl_3 with tetramethylsilane as the internal standard was obtained on a 200-MHz spectrometer.

General Procedure for the Nitration of Alkanes with Nitronium Hexafluorophosphate. Nitronium hexafluorophosphate (3.82 g, 20 mmol) was added under dry nitrogen into a flame-dried 50-ml reaction flask equipped with a magnetic stirrer, condenser, nitrogen, and alkane inlet. Dry dichloromethane (20 ml) then was added, and the appropriate gaseous alkane was passed into the suspension at ambient temperature with rapid stirring. The reaction mixture was monitored by GC-MS by taking aliquot samples. Introduction of the alkane was stopped until the yield of nitroalkane did not increase further. The reaction mixture then was quenched with water and extracted with dichloromethane. The organic layer was washed successively with 5% aqueous NaHCO_3 solution and water, dried over MgSO_4 . After evaporation of the solvent, the products were characterized by GC-MS and NMR and compared with those of authentic samples. The nitro product yields reported in Table 1 are based on the amount of $\text{NO}_2^+\text{PF}_6^-$ used.

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[†]This is Paper No. 29 in the series “Reactions at Single Bonds.” For Paper No. 28 see ref. 25.

Table 1. Nitration and nitrolysis of alkanes and cycloalkane with $\text{NO}_2^+\text{PF}_6^-$ in dichloromethane or nitroethane

Hydrocarbon	Time, hr	Nitroalkane products	Mol ratio [‡]	Yield, [§] %
Methane*	96/65°C	CH_3NO_2		<3
Ethane	6	$\text{CH}_3\text{NO}_2 > \text{CH}_3\text{CH}_2\text{NO}_2$	2.5:1	67, 33
Propane	10	$\text{CH}_3\text{NO}_2 > \text{CH}_3\text{CH}_2\text{NO}_2 > 2\text{-NO}_2\text{C}_3\text{H}_7 > 1\text{-NO}_2\text{C}_3\text{H}_7$	3.5:1.3:0.7:0.15	55, 25, 16, 3.5
Isobutane	5	$\text{tert-NO}_2\text{C}_4\text{H}_9 > \text{CH}_3\text{NO}_2$	3.1:1	84, 16
<i>n</i> -Butane	10	$\text{CH}_3\text{NO}_2 > \text{CH}_3\text{CH}_2\text{NO}_2 > 2\text{-NO}_2\text{C}_4\text{H}_9 > 1\text{-NO}_2\text{C}_4\text{H}_9$	5.1:3.8:1.45:0.8	37, 34, 18, 11
Neopentane	10	$\text{CH}_3\text{NO}_2 > \text{tert-C}_4\text{H}_9\text{NO}_2$	2.8:0.8	67, 33
Cyclohexane [†]	3	$\text{C}_6\text{H}_{11}\text{NO}_2$		30 [¶]

*Methane was nitrated with boron tris(triflate) in the presence of triflic acid.

[†]Cyclohexane was nitrated in nitroethane solvent.

[‡]Product analyses carried out by GC-MS and comparison of isolated products with authentic samples.

[§]Based on GC.

[¶]Isolated yield.

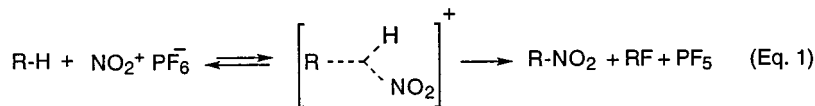
Superacid-Activated Nitration of Methane. A solution of boron tris (triflate) (4.58 g, 10 mmol) (26) in 20 ml of triflic acid was prepared from 9 ml, 0.103 mol boron trichloride and an excess 30 ml triflic acid in 110 ml 1,1,2-trichlorotrifluoroethane. $\text{NO}_2^+\text{PF}_6^-$ was added to the solution, and the resulting suspension was transferred into a 200-ml stainless steel autoclave under dry nitrogen atmosphere. The autoclave was fitted with a magnetic stirrer and placed in a sand bath. The autoclave was charged with methane at a pressure of 1,500–1,600 psi. While the autoclave was kept stirring its temperature was raised to 60°C. Stirring was continued for 4 days at 60°C. After cooling and depressurization the remaining material was extracted with ether and washed with cold 5% aqueous NaHCO_3 solution and water. After separation and drying the solvent was distilled off. The residue was analyzed by GC-MS, and the formation of nitromethane in an amount of $\approx 3\%$ (based on the nitronium salt used) was shown.

Nitration of Cyclohexane. Nitronium hexafluorophosphate (3.8 g, 20 mmol) was placed in a dried three-neck flask under dry nitrogen followed by addition of 10 ml of anhydrous nitrile-free nitroethane. The solution was cooled to 0°C, and 0.84 g, 10 mmol cyclohexane was introduced under rapid stirring. The reaction mixture was stirred at 0°C for 1 hr followed by room temperature for 3 hr. The mixture was

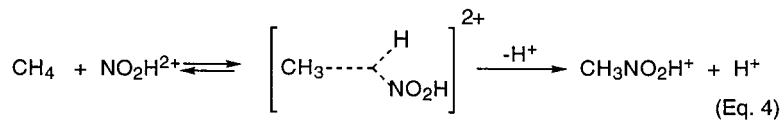
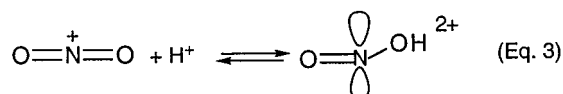
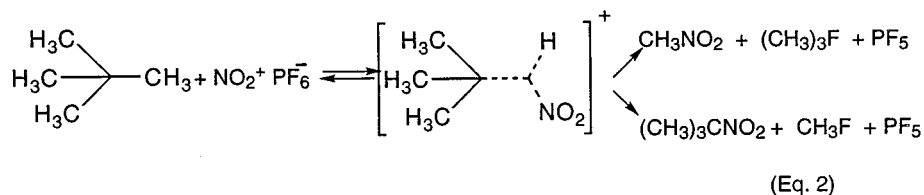
poured into water and extracted with ether. The organic extract was washed with 5% aqueous sodium bicarbonate solution followed by water and dried over MgSO_4 . The solvent was removed by distillation under reduced pressure. The residue was purified by bulb-to-bulb distillation under vacuum to obtain 0.38 g (30%) of pure nitrocyclohexane, b.p. 108°C_(bath)/(30 mm), literature (28) 106–108°C at 40 mm; ^1H NMR δ 1.0–2.5 (broad multiplet, 10 H), 4.27 (sextet 1 H), ^{13}C -NMR δ 84.61, 30.88, 24.70, 24.05; m/z 83 ($M - 46$, 78%).

RESULTS AND DISCUSSION

$\text{NO}_2^+\text{PF}_6^-$ is much preferred over $\text{NO}_2^+\text{BF}_4^-$ as a nitrating agent because it is substantially soluble in dichloromethane (≈ 4 mol%), the latter is practically insoluble in dichloromethane. In nitroethane the solubility of $\text{NO}_2^+\text{PF}_6^-$ is more than 25 mol%. The results of nitration of various alkanes are summarized in Table 1. Methane was nitrated by treating $\text{NO}_2^+\text{PF}_6^-$ in the presence of boron tris (triflate) (26) in triflic acid under pressure of 1,500 psi for 4 days at 65°C in an autoclave. A small amount (1–3%) of nitromethane is formed. In the absence of superacid in either methylene chloride or nitroethane solutions no methane was detected. On the other hand, higher alkanes such as isobutane were readily nitrated with nitronium



R = Et, Pr, *n*-But, *t*-But, cyclohexyl



hexafluorophosphate in methylene chloride solution. Nitration takes place with ethane, propane, *n*-butane, and neopentane in yields up to 70%. Cyclohexane reacts with $\text{NO}_2^+\text{PF}_6^-$ also in nitroethane to provide nitrocyclohexane in 30% isolated yield. Along with nitro products some fluoro products (due to C–C bond cleavage) also were formed (GC-MS analysis of exit gas) (28). No oxidation byproducts were observed under the conditions used. The results indicate that tertiary C–H bonds show highest reactivity followed by C–C bonds, which in turn are more reactive than secondary C–H bonds. However, with cyclohexane only nitrocyclohexane was obtained. With neopentane only C–C bond nitrolysis products, nitromethane, and 2-methyl-2-nitropropane were observed.

The mechanism of the electrophilic aliphatic nitration is similar to that of protolytic and alkylation reactions. The reaction proceeds via two electron three-center bound carbocationic transition states formed by the insertion of the nitronium ion into C–H (Eq. 1) and C–C bonds (Eq. 2). It is thus a front-side $\text{S}_{\text{E}}2$ reaction. Unlike reaction with adamantane and diamantane (23) the absence of oxidation byproducts indicates a straight nitronium ion insertion into C–H and C–C σ -bonds. Because the linear nitronium ion $\text{O}=\text{N}^+=\text{O}$ has no vacant orbital on nitrogen atom the reactions must take place via its polarization. In contrast to π -donor electron-rich aromatics, the σ -bonds of alkanes are poor electron donors and are less capable to bring about such polarization. As long as the nitronium ion remains linear it cannot act as an active nitrating agent for unreactive alkanes such as methane. Once the linear nitronium ion is partially bent, i.e., its nitrogen rehybridizes from *sp* to *sp*², reaction can ensue. Strong acids can activate the nitronium ion by coordination of oxygen nonbonded electron pairs (superelectrophilic activation), resulting in bending (29). In the limiting case fully bent dipositive nitronium ion, NO_2H^{2+} (Eq. 3) (or its Lewis acid-activated counterpart NO_2MX_n^+ is formed with strong Lewis acids) and is reactive as indicated by its reaction with the C–H bond of methane (Eq. 4). The proposed protonitronium dication (NO_2H^{2+}) (30) recently has been observed in the gas phase by electron impact mass spectrometry (31) and is invoked in the ¹⁷O NMR studies of nitronium ion in superacids (32). In the case of alkanes higher than methane additional activation by added protic acid appears unnecessary. Sufficient acid seems to be in the system (some initial moisture and acid formed during the nitration reaction) for the protolytic activation of the nitronium ion.

Tertiary nitroalkanes such as 2-nitro-2-methylpropane formed by C–H insertion of NO_2^+ into isobutane are not stable to more prolonged exposure to acid. It undergoes protolytic cleavage to *tert*-butyl cation and derived products. No protolytic cleavage reactions were observed with the primary and secondary nitro products of methane, ethane, propane, and butane. The corresponding nitro compounds were found to be stable under the reaction conditions. This also was established by treating the authentic samples of nitromethane, nitroethane, 1- and 2-nitropropane, and nitrobutanes with nitronium hexafluorophosphate under similar conditions to those used in nitration.

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