

1 Introduction

1.1 THE IMPORTANCE OF NITRATION

Nitration is important for two reasons: firstly, because it is the most general process for the preparation of aromatic nitro compounds; secondly, because of the part which it has played in the development of theoretical organic chemistry. It is of interest because of its own characteristics as an electrophilic substitution.

The first nitration to be reported was that of benzene itself. Mitscherlich in 1834 prepared nitrobenzene by treating benzene with fuming nitric acid.¹ Not long afterwards the important method of effecting nitration with a mixture of nitric and sulphuric acids ('mixed acid') was introduced, evidently in a patent by Mansfield;² the poor quality of early nitric acid was probably the reason why the method was developed. Since these beginnings, nitration has been the subject of continuous study.

1.2 NITRATING AGENTS

The means which have been used for effecting nitration are numerous,³ but not all of the methods are in common use. Dilute nitric acid is useful for nitrating reactive substances such as phenol, but the oxidising properties of more concentrated nitric acid can be disadvantageous. Solutions of nitric acid or nitrates in sulphuric acid of various concentrations, or in oleum, provide reagents of a wide range of vigour. They have the additional property, often useful, that some organic compounds are appreciably soluble in them, and the disadvantage of being able to sulphonate some aromatic compounds. The disadvantage is rarely serious, for nitration is generally a more rapid process than sulphonation. Nitric acid in organic solvents also provides reagents in which aromatic compounds are usefully soluble, but these solutions are milder nitrating agents than those in mineral acids. In preparative nitration, acetic acid is probably the most frequently used of organic solvents. Solutions of nitric acid in organic solvents are less acidic than solutions in mineral acids, a virtue when compounds sensitive to acids are being nitrated, and one which is shared by solutions of nitric acid in acetic anhydride (these reactants react together fairly rapidly to give acetyl nitrate;

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§ 5.3). Even less dangerous in this respect are the nitrating systems using alkyl nitrates and sodium ethoxide. Noteworthy examples of the use of these less acidic or basic nitrating systems are found in the pyrrole series.^{4a}

Nitronium salts in solution in inert organic solvents have been used in recent years to nitrate a wide range of aromatic compounds. Yields are generally good, but in preparative work the method is advantageous only in special cases, notably where the aromatic contains a hydrolysable substituent (§ 4.4).

In recent years the analogy between the Friedel–Crafts acylation reaction and various nitrating systems, particularly those in which Lewis acids act as catalysts, has been stressed,^{3c} but this classification adds nothing new in principle.

Our special concern is with those nitrating systems for which mechanistic studies have established, or made probable, the identity of the electrophile through which they effect nitration. In most cases, though not quite all, this has proved to be the nitronium ion. The important nitrating systems formed by mixing nitric acid with acetic anhydride stand out in having so far resisted attempts to identify beyond reasonable doubt the electrophile or electrophiles through which they operate (§ 5.3).

These systems nitrate aromatic compounds by a process of electrophilic substitution, the character of which is now understood in some detail (§ 6.1). It should be noted, however, that some of them can cause nitration and various other reactions by less well understood processes. Among such nitrations that of nitration *via* nitrosation is especially important when the aromatic substrate is a reactive one (§ 4.3). In reaction with lithium nitrate in acetic anhydride, or with fuming nitric acid, quinoline gives a small yield of 3-nitroquinoline; this untypical orientation (cf. § 10.4.2^{4b}) may be a consequence of nitration following nucleophilic addition.⁵

As regards reactions other than nitration brought about by some of these systems, especially noteworthy are the addition processes undergone by certain indole derivatives when treated with solutions of nitric acid in acetic acid. Products include glycols, nitro-alcohols, and nitro-alcohol acetates.^{4b} Such additions might well be encountered with some polynuclear aromatic compounds, and with such compounds the possibility of nitration by addition–elimination must always be borne in mind.

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1.2]

Nitrating agents

Benzene and some of its derivatives react with solutions of mercuric nitrate in concentrated nitric acid to give nitrophenols. These reactions, known as oxynitrations may proceed by mercuriation followed by nitroso-demercuration; the resulting nitroso compound becomes a diazonium compound and then a phenol, which is nitrated.⁶

1.3 NITRATION AND THE DEVELOPMENT OF THEORETICAL ORGANIC CHEMISTRY

The development of theoretical organic chemistry was intimately entwined with the development of that particular aspect of it concerned with aromatic substitution; the history of this twin growth has been authoritatively traced.⁷ Only the main developments, particularly as they affect nitration, will be noted here.

With the establishment of structural organic chemistry in the nineteenth century, the first major landmark in its development to include reactivity was the publication by Holleman in 1910 of his studies on orientation in aromatic substitution.^{8a} The reactions considered by Holleman were those which we now recognise as electrophilic substitutions, and by far the most extensive data were those relating to nitration. Thus, the reaction played a major role in the recognition of the main generalisations which can be made about orientation: the classification of orienting substituents as *o*:*p*- or *m*-directing (already recognised by earlier workers); the frequent association of *o*- with dominant *m*-substitution; the product rule describing further substitution into di-substituted benzenes.⁸ Of the greatest importance was Holleman's recognition of the connection between orientation and activation; *o*:*p*-orienting substituents commonly activate the aromatic nucleus, whilst *m*-orienting substituents de-activate it.

It is interesting to recognise why nitration was so pre-eminently useful a reaction for these purposes. First, it is very generally applicable because of the variety of conditions under which it can be carried out; second, it can usually be stopped cleanly after the first stage, because the nitro group introduced in the first stage is so powerfully deactivating; and third, because despite the wide range of conditions which may be used, nitration most commonly proceeds through the agency of the nitronium ion.

For the electronic theory of organic chemistry 1926 was the *annus mirabilis*, and, particularly, as they applied to aromatic substitution, the

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ideas of Lapworth, Robinson, and Ingold⁹ approached their definitive form,¹⁰ mainly through studies of nitration. Especially important in the refinement and critical testing of these ideas was the combination of data on orientation with data on rate; the definition of partial rate factors, originally called coefficients of activation,¹¹ required the theory to give an account of the state of activation of each individual position in an aromatic molecule.¹¹ As will be seen, nitration continues to be a testing ground of theoretical ideas, as in clarifying the nature of the inductive effect (§9.1.2), and in further defining the notion of aromatic reactivity (§7.1.2).

The electronic theory of organic chemistry, and other developments such as resonance theory, and parallel developments in molecular orbital theory relating to aromatic reactivity have been described frequently. A general discussion here would be superfluous; at the appropriate point a brief summary of the ideas used in this book will be given (§7.11).

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[More information](#)1.3] *Nitration and theoretical organic chemistry*

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2 Nitrating systems:

A. Mineral acids

2.1 INTRODUCTION

Nitration can be effected under a wide variety of conditions, as already indicated. The characteristics and kinetics exhibited by the reactions depend on the reagents used, but, as the mechanisms have been elucidated, the surprising fact has emerged that the nitronium ion is pre-eminently effective as the electrophilic species. The evidence for the operation of other electrophiles will be discussed, but it can be said that the supremacy of one electrophile is uncharacteristic of electrophilic substitutions, and bestows on nitration great utility as a model reaction.

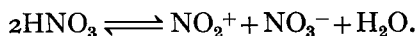
Euler¹ first suggested that the nitronium ion was the active species, but proof of this did not come for many years. Investigations of the mechanisms have been chiefly concerned with the physical examination of the media used, and with the kinetics of the reactions.

2.2 NITRATION IN CONCENTRATED AND AQUEOUS NITRIC ACID

2.2.1 *The state of concentrated nitric acid*

Molecular nitric acid is the main species present in this medium, but physical measurements demonstrate the existence of significant concentrations of other species.

By studying the variation of the freezing point of mixtures of dinitrogen pentoxide and water, over a range of concentration encompassing the formation of pure nitric acid, it was shown² that appreciable self-dehydration was occurring according to the following scheme:

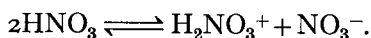


At the freezing point of nitric acid (-42°C), the concentrations of water, nitronium ion, and nitrate ion were found² to be 0.41 mol l^{-1} , but more recent work³ suggests the value 0.69 mol l^{-1} . Measurements of the electrical conductivity of nitric acid at -10°C give a value of 0.51 mol l^{-1} , and at -20°C of 0.61 mol l^{-1} for the concentrations of the three species.⁴

2.2]

Concentrated and aqueous nitric acid

The Raman spectrum of nitric acid shows⁵ two weak bands at 1050 and 1400 cm⁻¹. By comparison with the spectra of isolated nitronium salts⁶ (§2.3.1), these bands were attributed to the nitrate and nitronium ion respectively. Solutions of dinitrogen pentoxide in nitric acid show these bands⁷, but not those characteristic of the covalent anhydride⁸, indicating that the self-dehydration of nitric acid does not lead to molecular dinitrogen pentoxide. Later work on the Raman spectrum indicates that at -15 °C the concentrations of nitrate and nitronium ion are 0.37 mol l⁻¹ and 0.34 mol l⁻¹, respectively.⁹ The infra-red spectrum of nitric acid shows absorption bands characteristic of the nitronium ion.¹⁰ The equivalence of the concentrations of nitronium and nitrate ions argues against the importance of the following equilibrium:

**2.2.2.** *The state of aqueous solutions of nitric acid*

In strongly acidic solutions water is a weaker base than its behaviour in dilute solutions would predict, for it is almost unprotonated in concentrated nitric acid,⁹ and only partially protonated in concentrated sulphuric acid.^{11a} The addition of water to nitric acid affects the equilibrium leading to the formation of the nitronium and nitrate ions (§2.2.1). The intensity of the peak in the Raman spectrum associated with the nitronium ion decreases with the progressive addition of water, and the peak is absent from the spectrum of solutions containing more than about 5% of water;^{5a} a similar effect has been observed in the infra-red spectrum.¹⁰

Because water is not protonated in these solutions, its addition reduces the concentration of ions, and therefore the electrical conductivity. The conductivity reaches a minimum in solutions containing 97% of acid, but rises on further dilution as a result of the formation of nitrate and hydroxonium ions.⁴

The infra-red absorption bands of molecular nitric acid do not change as the medium is varied between 100% and 70% of acid; on further dilution the nitrate ion becomes the dominant species.¹⁰

In equimolar mixtures of nitric acid and water a monohydrate is formed whose Raman spectrum has been observed.¹² There is no evidence for the existence of appreciable concentrations of the nitric acidium ion in aqueous nitric acid.

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[More information](#)*Nitrating systems, A***2.2.3** *Nitration in concentrated nitric acid*

Our knowledge of the mechanism of the reaction in this medium comes from an investigation of the nitration of nitrobenzene, *p*-chloronitrobenzene and 1-nitroanthraquinone.¹³ These compounds underwent reaction according to the following rate law:

$$\text{rate} = k_1[\text{ArH}]$$

Nitric acid being the solvent, terms involving its concentration cannot enter the rate equation. This form of the rate equation is consistent with reaction *via* molecular nitric acid, or any species whose concentration throughout the reaction bears a constant ratio to the stoichiometric concentration of nitric acid. In the latter case the nitrating agent may account for any fraction of the total concentration of acid, provided that it is formed quickly relative to the speed of nitration. More detailed information about the mechanism was obtained from the effects of certain added species on the rate of reaction.

Sulphuric acid catalysed nitration in concentrated nitric acid, but the effect was much weaker than that observed in nitration in organic solvents (§ 3.2.3). The concentration of sulphuric acid required to double the rate of nitration of 1-nitroanthraquinone was about 0.23 mol l⁻¹, whereas typically, a concentration of 10⁻³ mol l⁻¹ will effect the same change in nitration in mixtures of nitric acid and organic solvents. The acceleration in the rate was not linear in the concentration of catalyst, for the sensitivity to catalysis was small with low concentrations of sulphuric acid, but increased with the progressive addition of more catalyst and eventually approached a linear acceleration.

Potassium nitrate anticatalysed nitration in nitric acid (the solutions used also contained 2.5 mol l⁻¹ of water) but the effect was small in comparison with the corresponding effect in nitration in organic solvents (§ 3.2.3 & 4), for the rate was only halved by the addition of 0.31 mol l⁻¹ of the salt. As in the case of the addition of sulphuric acid, the effect was not linear in the concentration of the additive, and the variation of k^{-1}/s with $[\text{KNO}_3]/\text{mol l}^{-1}$ was similar to that of k_1/s^{-1} with $[\text{H}_2\text{SO}_4]/\text{mol l}^{-1}$.

The relative weakness of the two effects, and the adoption of the kinetic form of the catalysis to the linear law only when the concentration of the additive was greater than *c.* 0.2 mol l⁻¹, results from the equilibria existing in anhydrous nitric acid. In the absence of catalyst,

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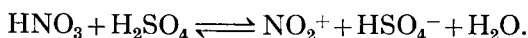
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2.2] *Concentrated and aqueous nitric acid*

nitric acid undergoes appreciable self-dehydration to yield nitronium ions, nitrate ions and water. The addition of sulphuric acid allows the operation of another mode of ionization:



The nitronium ions produced in this way tend to repress the self-dehydration of the nitric acid and therefore the net concentration of nitronium ions is not proportional to the concentration of the catalyst. When sufficient sulphuric acid has been added to make the self-ionization of nitric acid relatively unimportant, the nitronium ions will be produced predominantly from the above ionization, and the acceleration will follow a linear law.

The effect of potassium nitrate on the rate arises in a similar way. The concentration of nitrate ions in concentrated nitric acid is appreciable, and addition of small quantities of nitrate will have relatively little effect. Only when the concentration of added nitrate exceeds that of the nitrate present in pure nitric acid will the anticatalysis become proportional to the concentration of added salt.

Therefore, in the cases of both additives, the kinetic law for the catalysis will assume a linear form when the concentration of the added species, or, in the case of sulphuric acid, the nitronium ion generated by its action, is comparable with the concentration of the species already present. This effect was observed to occur when the concentration of additive was about 0.2 mol l^{-1} , a value in fair agreement with the estimated degree of dissociation of nitric acid (§ 2.2.1).

2.2.4 *Nitration in aqueous solutions of nitric acid*

Added water retards nitration in concentrated nitric acid without disturbing the kinetic order of the reaction.¹³ The rate of nitration of nitrobenzene was depressed sixfold by the addition of 5% of water, (*c.* 3.2 mol l^{-1}), but because of the complexity of the equilibria involving water, which exist in these media, no simple relationship could be found between the concentration of water and its effect on the rate.

In more dilute solutions the concentration of the nitronium ion falls below the level of spectroscopic detection, and the nature of the electrophilic species has been the subject of conjecture.

The nitration of 2-phenylethanesulphonate anion (I) and toluene-*o*-sulphonate anion (II) in aqueous nitric acid containing some added perchloric or sulphuric acid has been studied.¹⁴ When the medium was

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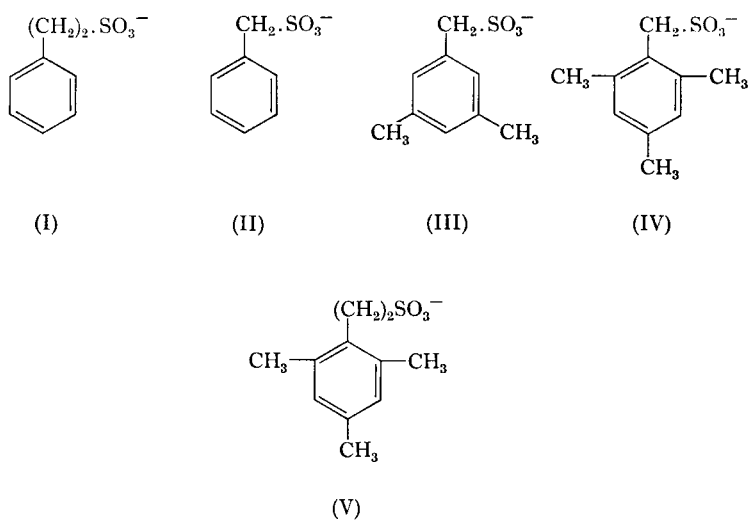
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[More information](#)*Nitrating systems, A*

varied the rate of reaction did not change according to the concentration of molecular nitric acid, which could not therefore be the active species. The distinction between the operation of the nitronium ion and the nitric acidium ion H_2NO_3^+ was less easy to make. The authors of the above work preferred the claims of the latter but could not exclude reaction *via* the small concentration of nitronium ions.



The operation of the nitronium ion in these media was later proved conclusively.^{15a-c} The rates of nitration of 2-phenylethanesulphonate anion ($[\text{Aromatic}] < c. 0.5 \text{ mol l}^{-1}$), toluene-*o*-sulphonate anion, *p*-nitrophenol, *N*-methyl-2,4-dinitroaniline and *N*-methyl-*N*,2,4-trinitroaniline in aqueous solutions of nitric acid depend on the first power of the concentration of the aromatic.^{15b} The dependence on acidity of the rate of ¹⁸O-exchange between nitric acid and water was measured,^{15a} and formal first-order rate constants for oxygen exchange were defined by dividing the rates of exchange by the concentration of water.^{15b} Comparison of these constants with the corresponding results for the reactions of the aromatic compounds yielded the scale of relative reactivities shown in table 2.1.

When the concentration of 2-phenylethanesulphonate anion was $> 0.5 \text{ mol l}^{-1}$, or when 2-mesitylethanesulphonate anion (v),^{15c} mesitylene- α -sulphonate anion, or iso-durene- α^2 -sulphonate anion^{15b} were nitrated, the initial part of the reaction deviated from a first-order dependence on the concentration of the aromatic towards a zeroth-order dependence.