MECHANISMS AND RATES OF THE ELECTROPHILIC SUBSTITUTION REACTIONS OF HETEROCYCLES

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Abstract - The mechanisms and rates of electrophilic substitution reactions, especially acid catalyzed hydrogen exchange and nitration, of heterocycles are discussed.

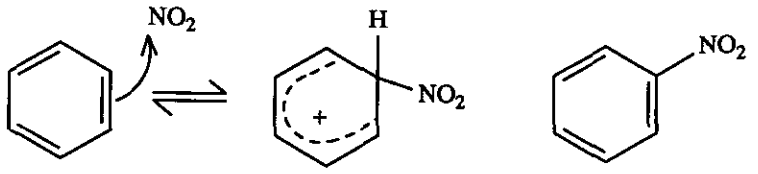
CONTENTS

Introduction

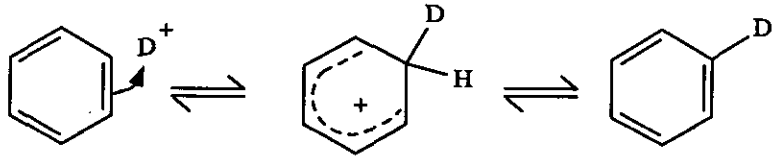
Electrophilic substitution reactions such as nitration and acid catalyzed hydrogen exchange (Scheme 1) are typical of benzene, of substituted benzenes, and of analogous polycyclic compounds.[1]

Scheme 1. Electrophilic Substitution Reactions

Nitration: $2H_2SO_4 + HNO_3 \longrightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$



Acid catalysed hydrogen exchange:



Other Electrophilic Substitutions include:
Halogenation; sulphonation; F/C - reaction; azo-coupling

Electrophilic substitution reactions are also very wide-spread among heteroaromatics.[2-4] The general effects of heteroatom substitution of one or more of the CH groups of benzene to give a heterocycle include changes in mechanism and in rate (see Scheme 2):

Scheme 2. Effects of Hetero-Atoms on Aromatic Reactivity

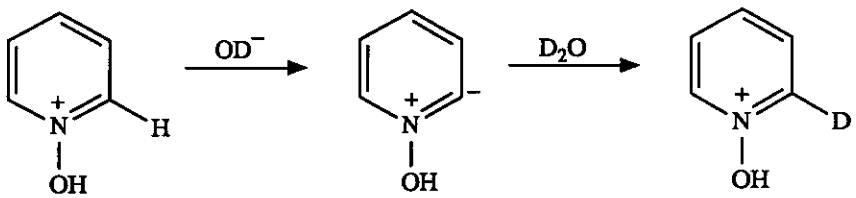
(i) Pyridine-like nitrogen - i.e. substitution of -CH= by -N= or especially $-N^+R=$, $-O^+=$ or $-S^+=$ lessens susceptibility to electrophilic attack.

(ii) Pyrrole-like nitrogen - i.e. substitution of -CH=CH- by -NR-, -O-, -S-, (or especially $-N^-$- enhances attack by electrophiles.

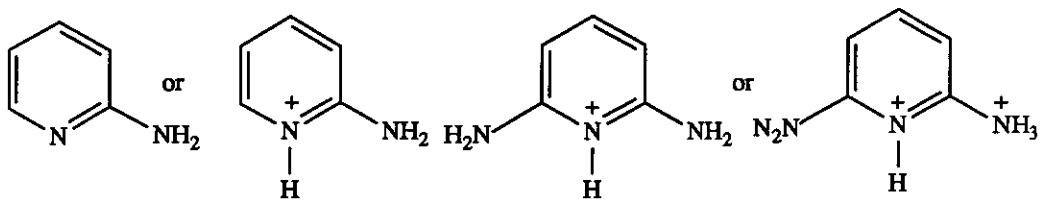
However, the situation in heteroaromatic compounds is complex because of a number of alternative mechanistic pathways (Scheme 3). Thus, instead of reaction with an electrophile followed by a loss of a proton, the proton loss can occur before the reaction with the electrophile. Furthermore, the characteristic electrophilic substitution can also occur on a variety of ionic forms or on covalent hydrates as illustrated in Scheme 3.[5]

Scheme 3. Mechanistic Diversity in Heterocyclic Substitution Reactions

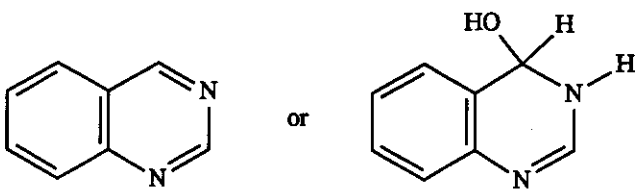
A. Deprotonation Mechanism for Hydrogen Exchange



B. Various Ionic Forms



C. Covalent Hydration



The objectives of the research described in the present report are listed in Scheme 4. They included both the determination of the mechanism under particular sets of conditions and also the determination of the quantitative effects of heteroatoms, the correlation of the rates and the applications of the findings to a better understanding of preparative work.

Scheme 4. Objectives of Research

1. Determination of Reaction Mechanisms
2. Quantitative Effect of Heteroatoms
   Replacement CH in Benzene by: N, NR^+, O^+, S^+, N^+, O^- etc.
   Replacement of CH=CH in Benzene by: NR, O, S, N^- etc.
3. Correlation of Rates with M.O. and Linear Free Energy Relations: Mutual Interactions of Two Substitutions.
4. Better Understanding of Preparative Work, Optimisation of Reaction Conditions and Prediction of New Reactions.

Hydrogen Exchange Reactions as Illustrated by Quinoline and Isoquinoline

Hydrogen exchange is very useful as a quantitative measure of heteroaromatic reactivity for the reasons outlined in Scheme 5.

Scheme 5. Hydrogen Exchange as a Quantitative Measure of Heteroaromatic Reactivity

Deuteration can be used with advantage:

(i) it can be followed rapidly by nmr.
(ii) it gives separate rates for simultaneous reaction in several positions.

Tritiation can be used with advantage:

(i) low concentration of substrate can be used which avoids correction for activity and acidity and allows sparingly soluble substrates to be studied.
(ii) slow reactions can be followed over small proportion of reaction.
(iii) gas phase electrophilic substitution can be studied.[6,7]

Aqueous Media can be used:

acidity function behaviour better understood, range of acidity pH + 14 to H° - 10

Successive Reactions can be followed:

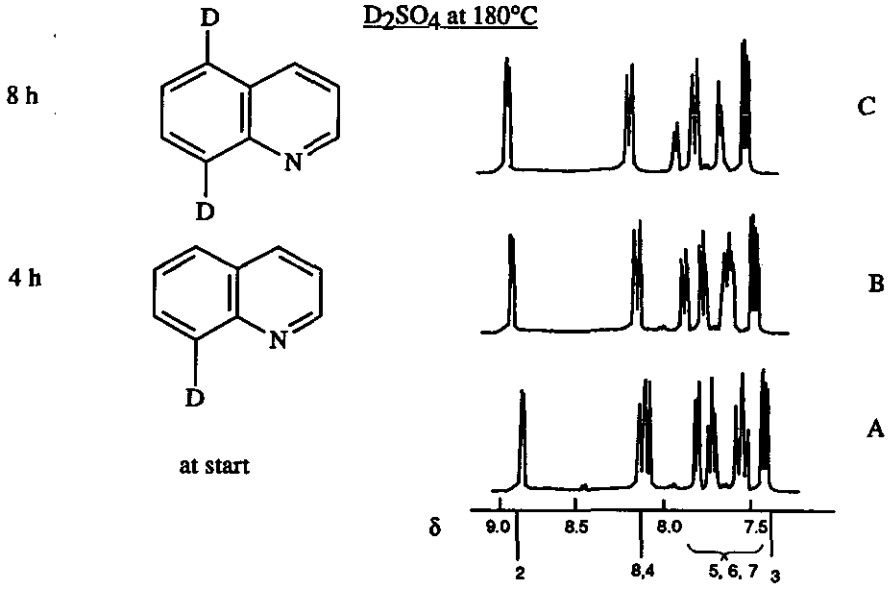
because exchange of one hydrogen atom does not appreciably affect the exchange rates of further hydrogen atoms

Hence - a very wide range of compounds can be measured including heterocyclic annulenes [8,9]

The formation of many heterocyclic cations, such as pyrrolium and indolium cations, occurs only in strongly acid media,[10,11] where the rates for the equilibrium formation of these σ-adducts are generally inaccessible by conventional kinetic techniques.[12,13] Accordingly, data on the protonation of many heterocycles are most often obtainable through tritium or deuterium isotope exchange in acid media.[14 – 16]

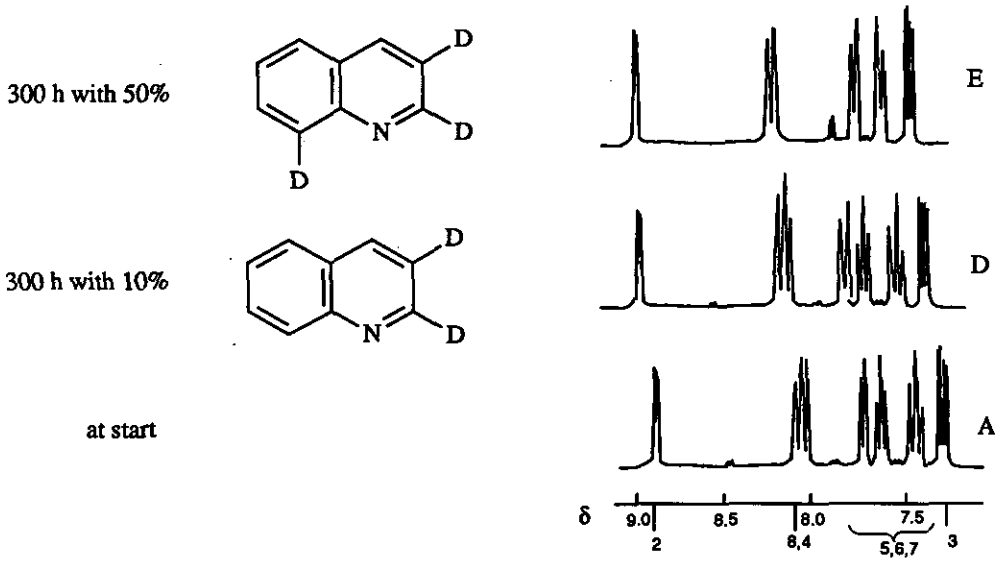
The advantages are illustrated by the spectra shown in Schemes 6 and 7 which record ^1H nmr spectra of quinoline taken after various periods of heating with D_2SO_4. Using 90% D_2SO_4 at 180°C, we find (Scheme 6), that exchange takes place quite rapidly at the 8-position, and then more slowly at the 5- and 7-positions.[17]

Scheme 6. Nmr Spectra of Quinoline In CCl_4 at 300 MHz After Heating With 90% D_2SO_4 at 180°C



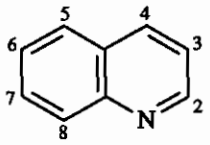
By contrast, on heating at 245°C with more dilute acids, we find that exchange takes place in the 2- and 3-positions preferentially (Scheme 7).

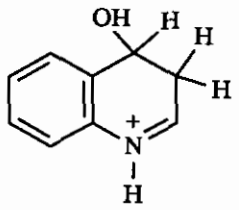
Scheme 7. Nmr Spectra of Quinoline in CCl_4 At 300 MHz After Heating with D_2SO_4 at 245°C



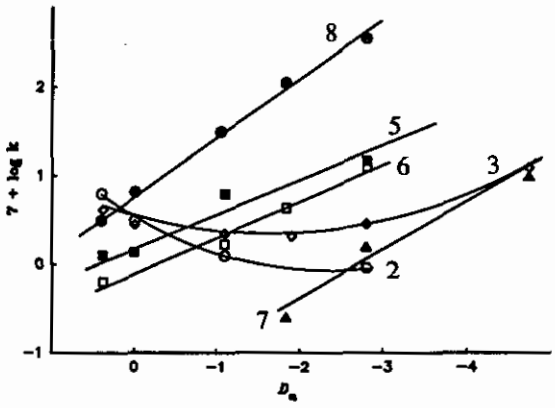
The results of a large number of these experiments are plotted in Scheme 8. The rate profiles for exchange at the positions in the benzenoid ring show that the rate increases continually as the acidity increases, and that the rate is fastest in the 8- followed by the 5-, the 6-, and then the 7-positions. By contrast, exchange at the 2-position shows very little change in the rate over a wide acidity range, whereas exchange at the 3-position shows at first little increase in the rate, but then a significant increase.

Scheme 8. Dependence of the Quinoline Hydrogen Exchange Rate on Acidity of the Medium



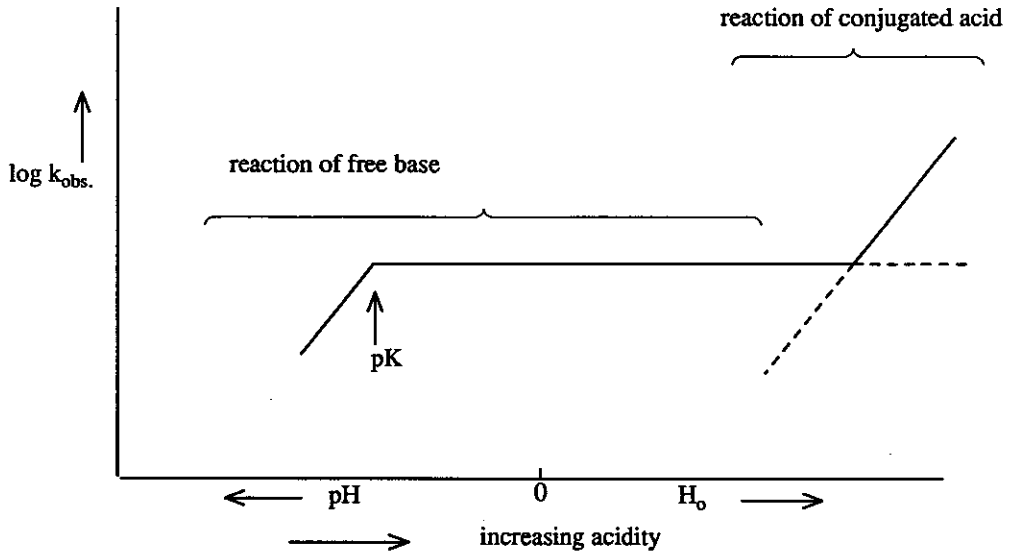


possible covalent hydrate (see text)



The expected form of the rate profile for hydrogen exchange of heteroaromatic compound is shown in Scheme 9.[5,18]

Scheme 9. Expected Rate Profile for Hydrogen Exchange of a Heteroaromatic Compound

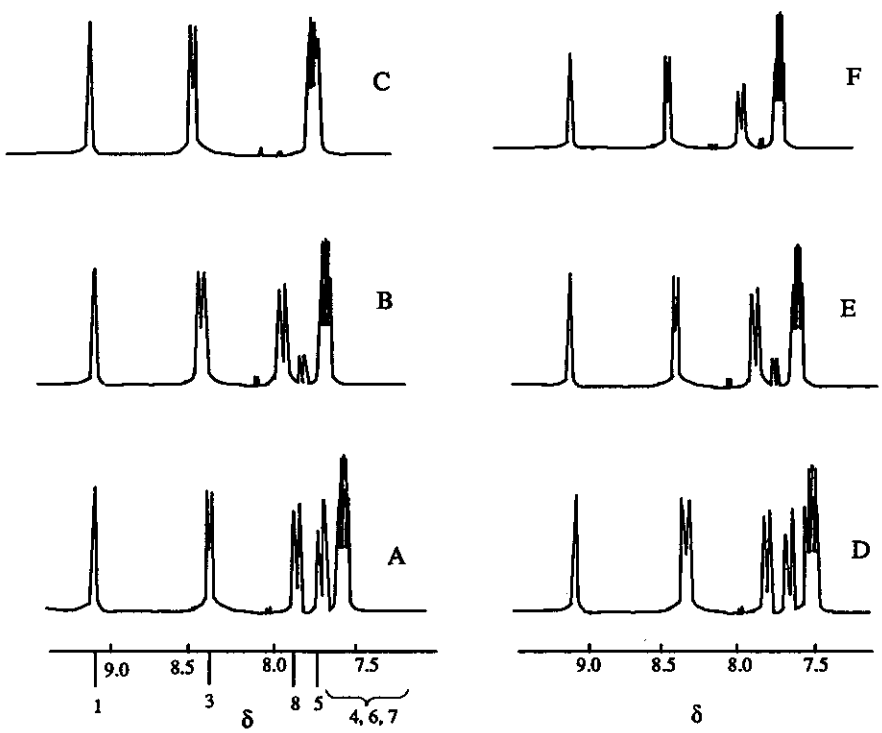


At pH regions above the pK for proton addition to the heteroaromatic ring, exchange will take place on the free base and will increase continually as the acidity increases. However, at pHs below the pK, reaction will still proceed on the free base, but now the increasing activity of hydrogen ion concentration will be cancelled out by the decrease in the concentration of the free base. At very low acidities, reaction on the conjugated acid will take over and the rate will start increasing again.

We can now interpolate the rate profiles for the reactions of quinoline at various positions. In Scheme 8, exchange at the 8-, 5-, 6-, and 7-positions is taking place only on the conjugated acid. However, exchange on the 3-position and the 2-position is taking place on the free base which for the 3-position changes over to exchange on the conjugated acid at very low acidities. In fact, exchange at the 2-position probably occurs on a covalent hydrate of structure shown.

Analogous work for isoquinoline is now discussed. In Scheme 10, the NMR spectra are given which indicate that exchange takes place on the 5- and 8-positions and also on the 1- and 4- positions.[17]

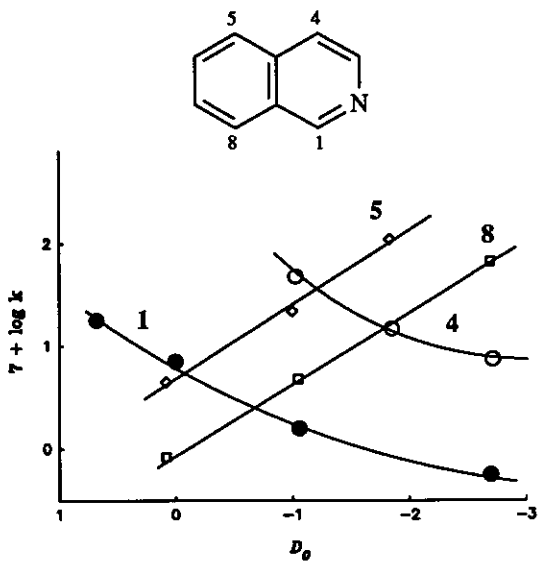
Scheme 10. Nmr Spectrum of Isoquinoline in CCl_4 at 300 MHz after Heating with D_2SO_4



A, before heating; B, 90% D_2SO_4, 180°C, 2 h; C, 90% D_2SO_4, 180°C, 24 h;
D, 20% D_2SO_4, 245°C, 300 h; E, 40% D_2SO_4, 245°C, 300 h; F, 50% D_2SO_4, 245°C, 300 h.

The exchange profiles are shown in Scheme 11.[17] Exchange at the 5- and 8- positions occurs by the normal mechanism on the conjugated acids while that at 4- and 1-positions actually decreases as the acidity increases and probably reflects reaction by the deprotonation mechanism.

Scheme 11. Dependence of the Isoquinoline Hydrogen Exchange Rate on Acidity of the Medium at 245°C



Quantitative Comparison of H-Exchange Rates

Because hydrogen exchange rates are measured under many different conditions, a set of standard conditions must be chosen so that rates can be compared under the same conditions. The standard conditions chosen are described in Scheme 12, and the procedure for making quantitative comparisons in Scheme 13.[19,20a,20b]

Scheme 12. Standard Conditions for Making Quantitative Comparisons

Comparisons must be between rates under same conditions:

(a) Acidity: pH = 0 chosen, as best means of converting pseudo 1st order rate constants into 2nd order rate constant
rate = K_0 [subst] [H^+]

(b) Temperature: 100°C chosen as most rates have been measured in range 20°C - 100°C, to minimise extrapolation.

Scheme 13. Procedure for Making Quantitative Comparisons

Deteermination of k_O (100°C) at pH = 0 requires the following steps:[21]

(i) k (stoich) (T°C) requires: (a) knowledge of acidity function at T°C
(b) effect of dissolved substrate on acidity function
(c) effect of using D_2SO_4 instead of H_2SO_4.

(ii) k (stoich) (T°C) at pH = 0 requires construction of rate profile and extrapolation.

(iii) k (stoich) (100°C) at pH = 0 requires assumption about or measurement of rate variation with temperature.

(iv) k_o (100°C) at pH = 0 requires correction for minority species which needs assumption regarding protonation behaviour of bases and variation of pK with temperature.

The measurement of acidity in a normal pH range is quite straightforward (Scheme 14), but at greater acidities, the situation becomes more difficult and various acidity functions exist which describe the protonation behaviour of various classes of bases, for example the Hammett and Amide Acidity Functions (Scheme 15).

Scheme 14. Measurement of Acidity

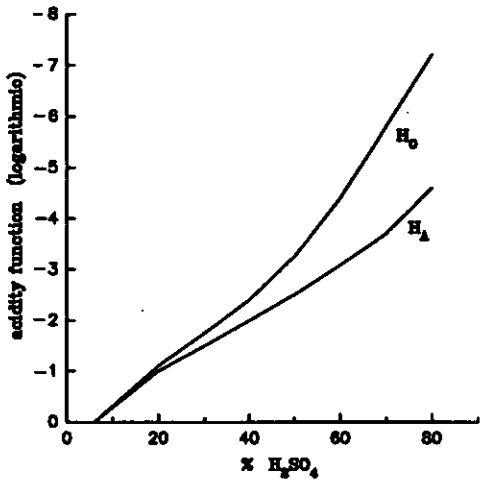
$$\frac{M}{100}\ HCl \equiv pH\ 2$$

for Hammett base $\frac{[B]}{[BH^+]}$ at pH 2 $= \frac{10\,[B]}{[BH]}$ at pH 1 etc.

pD = pH + 0.4 (Glassoe and Long, 1960)

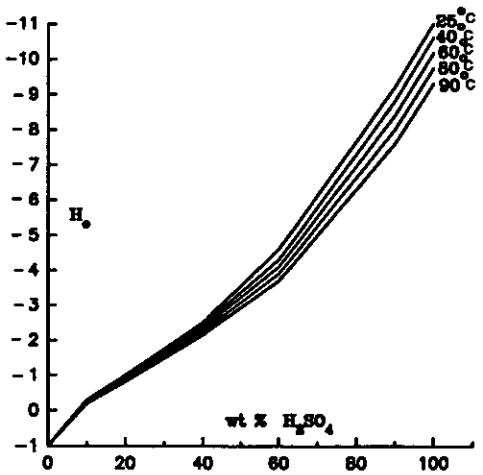
$D_O = H_O$(Hoegfeldt and Bigeleisen, 1960)

Scheme 15. Comparison of Hammett and Amide Acidity Functions



To complicate the matter further, both acidity functions (Scheme 16) and pK_a values (Scheme 17) vary with temperature.[22,23]

Scheme 16. Variation of H_O with Temperature



$$H_0(T) = H_0(25°C) + \frac{K(298-T)}{298T}$$

Scheme 17. Variation of pK with Temperature

for NH_2 protonation

$$pK\,(T) = pK\,(25°C) - \frac{2.303}{298RT}\,(T - 298)\,[1.14\,pK\,(25°C) + 2.28]$$

for pyridine ring nitrogen protonation

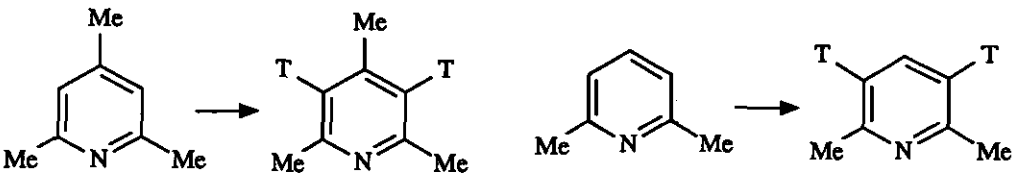
$$pK\,(T) = pK\,(25°C) - \frac{2.303}{298RT}\,(T - 298)\,[1.14\,pK\,(25°C) - 2.85]$$

Because of all these complications, and because considerable extrapolations have sometimes to be made, quantitative comparisons of H- exchange rates are subject to considerable errors. However, interesting deductions can nevertheless be drawn.

Hydrogen Exchange of Pyridine and Substituted Pyridines

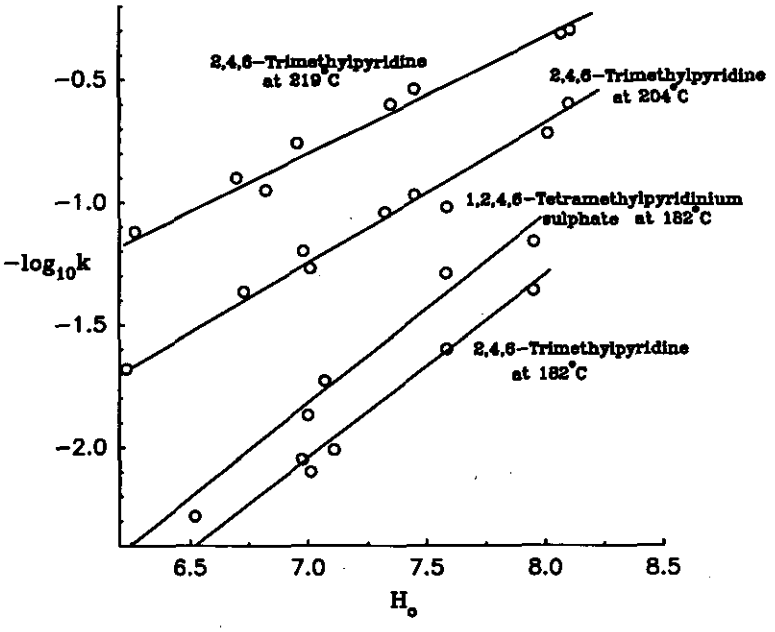
The acid-catalyzed hydrogen exchange of pyridine is extremely slow, but the tritiation of 2,6-dimethyl- and of 2,4,6-trimethylpyridine has been measured (Scheme 18) experimentally.[24,25]

Scheme 18. Tritiation of Methylpyridines



The rate profiles found are shown in Scheme 19.[26]

Scheme 19. Rate Profiles for the Tritium Exchange of Some Heterocycles

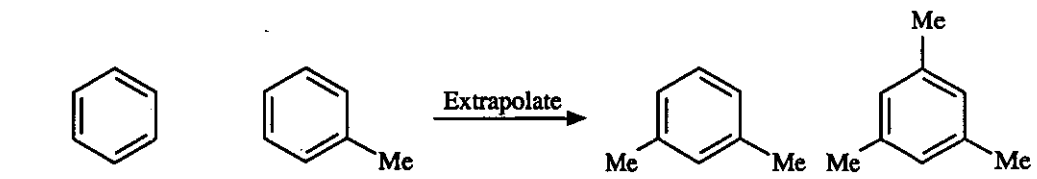


From the way in which these rate profiles vary with temperature, Arrhenius parameters were calculated (Scheme 20) thus enabling a comparison of pyridine and benzene reactivity (Scheme 21).[26] The result of this comparison is a conclusion that the substitution of a positively charged nitrogen for one of the carbon atoms of benzene deactivates the meta-position by a factor of about 10^{19}, the deactivation is still greater at the ortho- and para-positions.

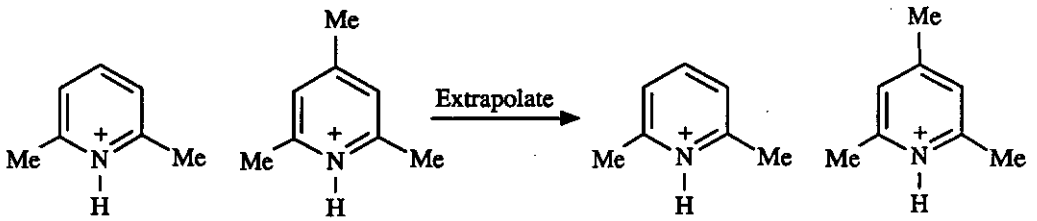
Scheme 20. Arrhenius Parameters for the Hydrogen Exchange Reaction

Compound	H_o	ΔH* (kcal/mole)	ΔS* (at 200°) (e.u.)
2,4,6-Collidine	-6.3	38	-6
	-7.4	31	-16
	-8.4	24	-28
2,6-Lutidine	-8.4	37	-10
	-9.0	33	-16

Scheme 21. Comparison of Pyridine and Benzene Reactivity



(Eaborn and Taylor) at H_o = -6.3, 25°C

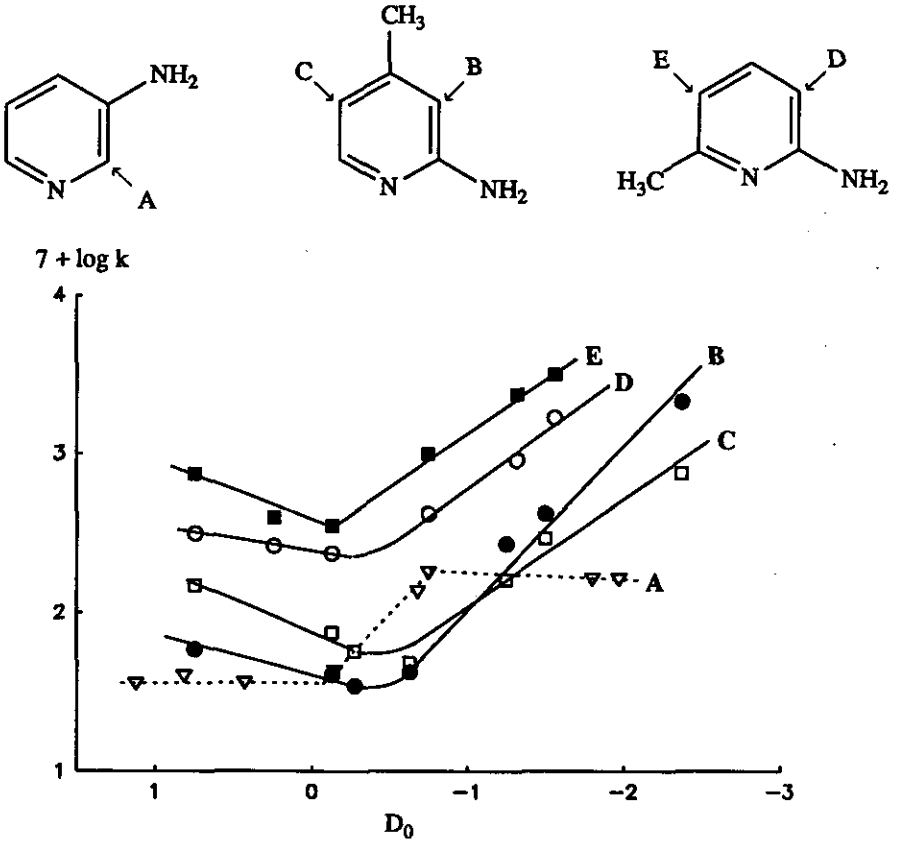


at 180 - 220°C
H_o = -6.3 to -9

at H_o = -6.3, 25°C

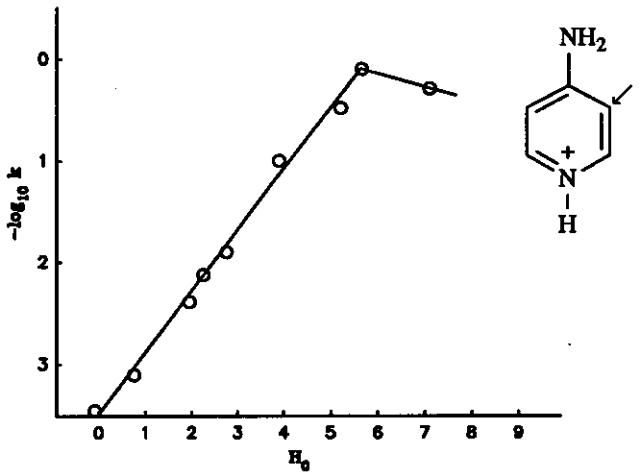
Hydrogen exchange in aminopyridines is much faster and rate profiles are shown for exchange at the 2-position of 3-aminopyridine and at the 3- and 5-positions of 4-methyl-2-amino- and 6-methyl-2-aminopyridine in Scheme 22.[27,28] These rate profiles show that exchange takes place on the neutral forms above at pH > 0. At pH < 0, the exchange switches over to the monocations. In the case of 3-aminopyridine, the second pK_a occurs at H_o=-0.5 and thus the rate profile shows another bend at this place.

Scheme 22. Rate Profiles for H-Exchange at Individual Positions in Aminopyridines



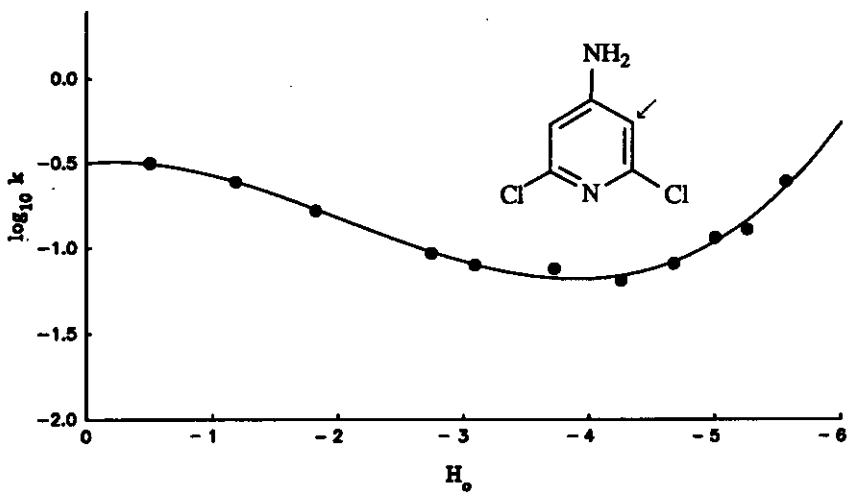
The rate profile for hydrogen exchange in 4-aminopyridine is shown in Scheme 23.[18] Exchange takes place at the 3-position in the monocation over the whole range studied. The second pK_a of 4-aminopyridine occurs at $H_o = 5.5$ and this accounts for the turnover in the rate profile.

Scheme 23. Rate Profile for Exchange in 4-Aminopyridine



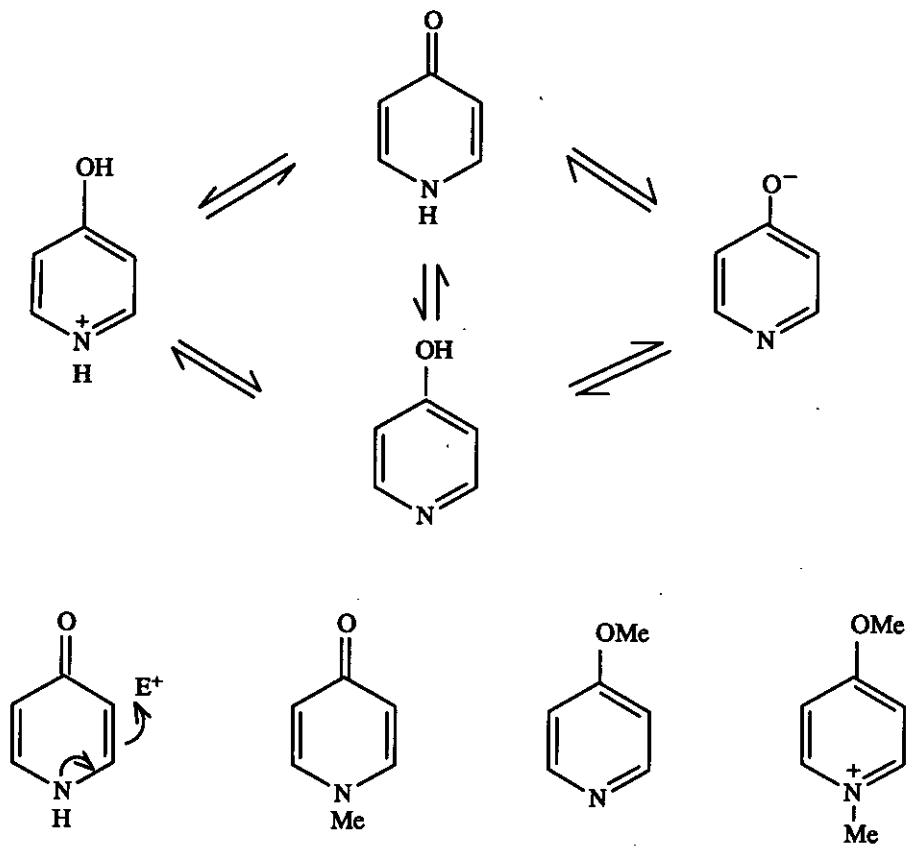
The rate profile for 2,6-dichloro-4-aminopyridine (Scheme 24) shows that exchange takes place in this compound on the free base form down to $H_o = -5$ and above this on the conjugate monocation.[18]

Scheme 24. Rate Profile of Hydrogen Exchange of 2,6-Dichloro-4-Aminopyridine



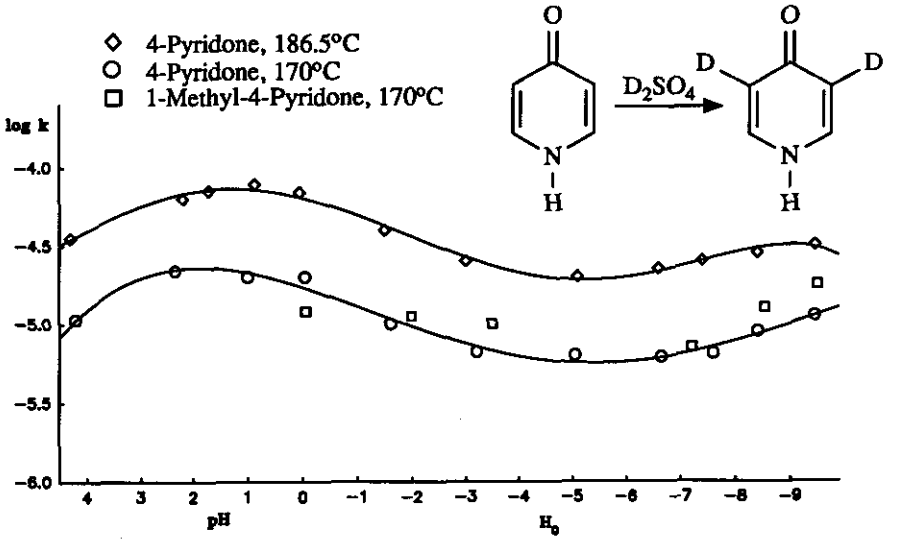
In considering the electrophilic substitution of pyridones, one has to take into account that four possible species could undergo reaction: the cation, the anion, or either of the two tautomeric neutral forms. Which species undergoes reaction can be determined by consideration of the rate profile and by comparison with methylated model compounds. Scheme 25 illustrates this situation for 4-pyridone/4-hydroxypyridine and also shows the methylated models.[19,20,29]

Scheme 25. Electrophilic Substitution of Pyridones



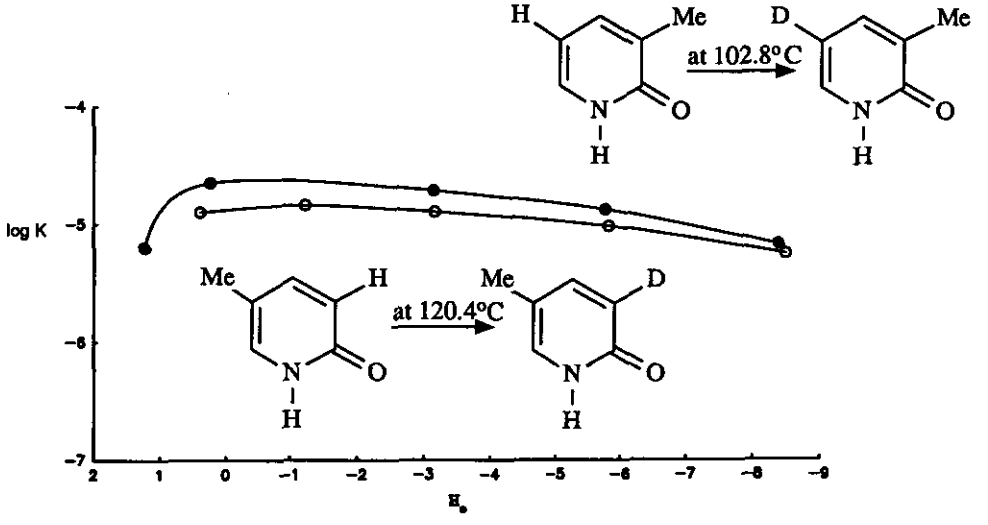
The rate profile for 4-pyridone is shown in Scheme 26. Both 4-pyridone and its 1-methyl derivative exchange at almost the same rate over the whole range with reaction occurring on the free base.[19]

Scheme 26. Hydrogen Exchange of 4-Pyridine



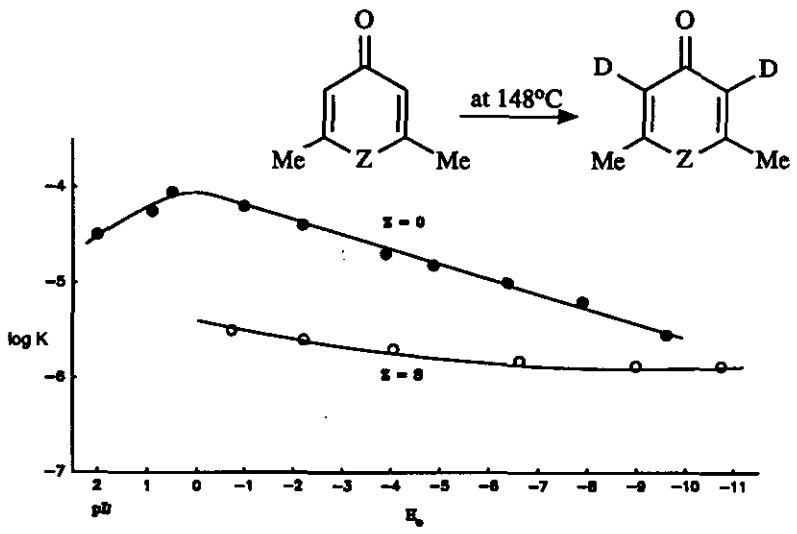
The rate profiles for 3-methyl- and 5-methyl-2-pyridone are shown in Scheme 27.[19] Here again, the exchange takes place on the free bases in a region where the majority species is the monocation and thus, the rate shows little variation with acidity.

Scheme 27. Hydrogen Exchange of 2-Pyridones



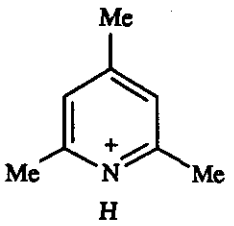
Rate profiles for 2,6-dimethylpyrone and for 2,6-dimethylthiapyrone are shown in Scheme 28 [30] and the corresponding extrapolated exchange rates are compared in Scheme 29 with those for the analogous pyridine and for benzene.

Scheme 28. Rate Profile for Pyrone and Thiapyrone Hydrogen Exchange

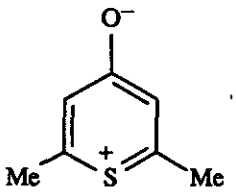


Scheme 29. Exchange Rates (log k in sec $^{-1}$ 100°C and pH = 0)

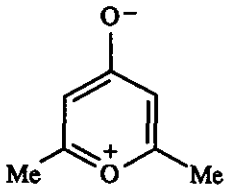
-10.5



-1.8



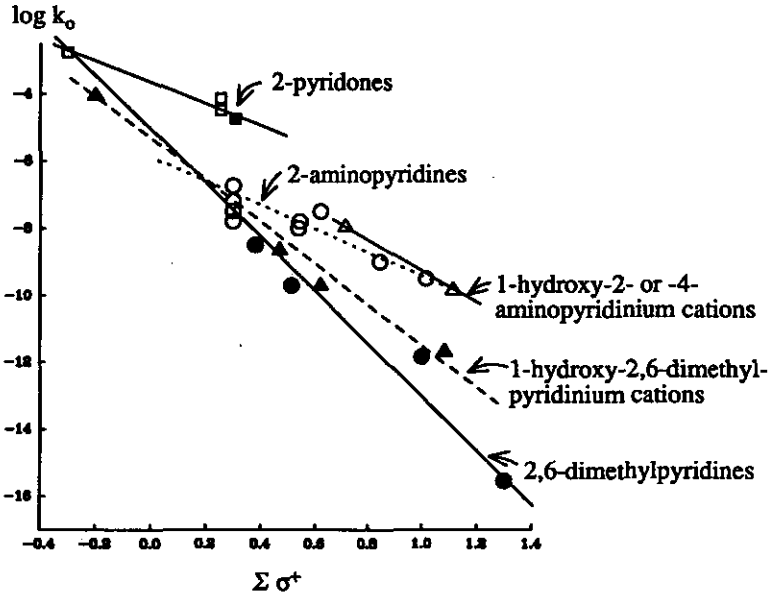
-6.7



-5.9

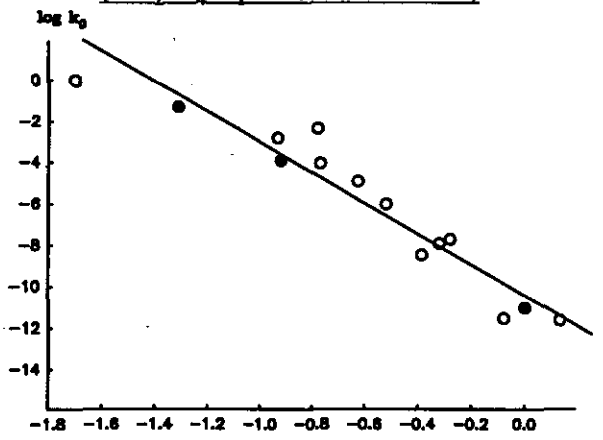
All this work has been combined in Scheme 30 which shows a Hammett treatment for the hydrogen exchange of substituted pyridines[31] compared with the similar plot for the hydrogen exchange of monosubstituted benzenes (Scheme 31).[32] It is seen that no single line accounts for the exchange of all the pyridines, but that compounds of similar types do lie on or near straight lines.

Scheme 30. Hammett Treatment of Hydrogen Exchange of Substituted Pyridines



Scheme 31. Hammett Treatment of Hydrogen Exchange of Monosubstituted Benzenes

(in H_2SO_4 at pH = 0 and T = 100°C)



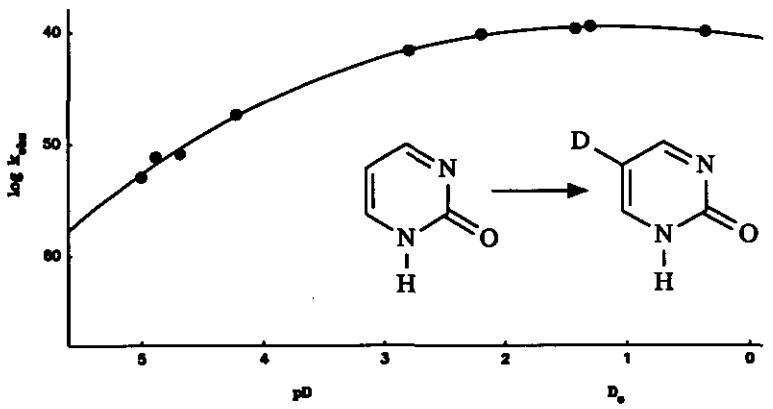
From bromobenzene of log k_o = -11.6 to dimethylaniline of log k_o = 0.1

[ρ = -7.5]

Hydrogen Exchange in Azines

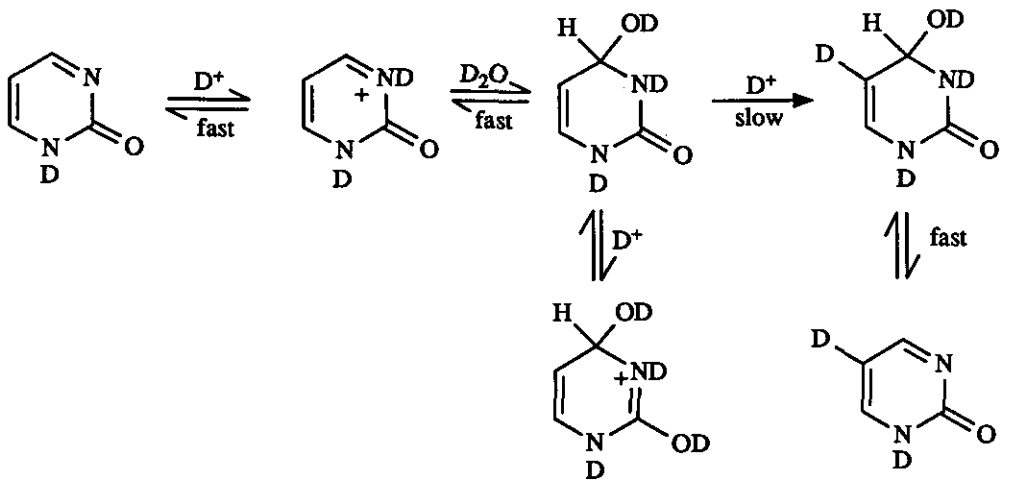
The rate profile for 2-pyrimidinone is shown in Scheme 32.[33,34] However, the exchange rate thus deduced is found to be much too fast, much faster than expected.

Scheme 32. Rate Profile for the Hydrogen Exchange of 2-Pyrimidinone at 107°C



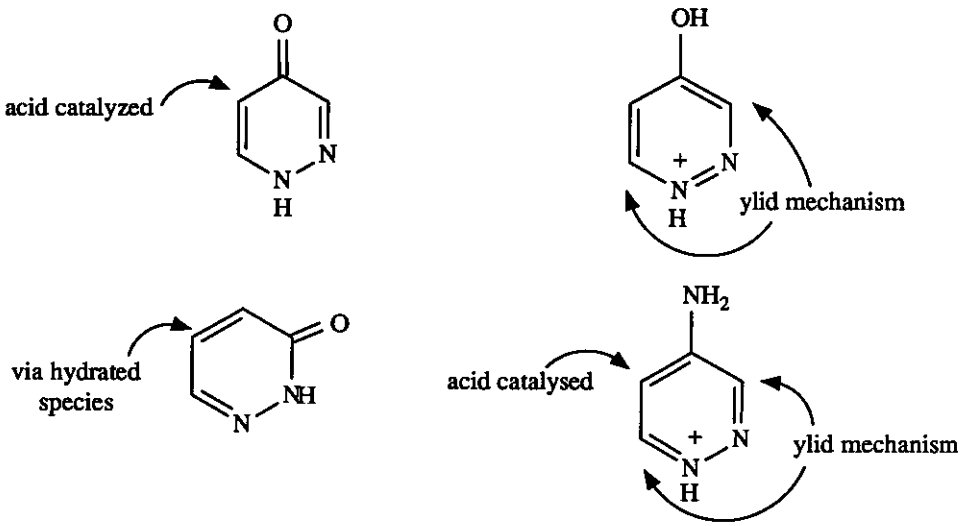
The probable reason for this is shown in Scheme 33. It is postulated that covalent hydration takes place and that the hydrogen exchange which occurs is on the covalent hydrate.[33]

Scheme 33. Covalent Hydration Mechanism of Hydrogen Exchange in 2-Pyrimidinones



A similar situation has been found for other azines as is illustrated for certain pyridazines in Scheme 34.[5,35]

Scheme 34. Hydrogen Exchange of Pyridazine Derivatives



4-Pyridazinone undergoes acid-catalyzed exchange at the 5-position, whereas the protonated species and protonated 4-aminopyridazine undergo base-catalyzed exchange at the 3- and 6-positions,[35] because of the combined effects of the ring nitrogens, one of which is protonated (Scheme 34).

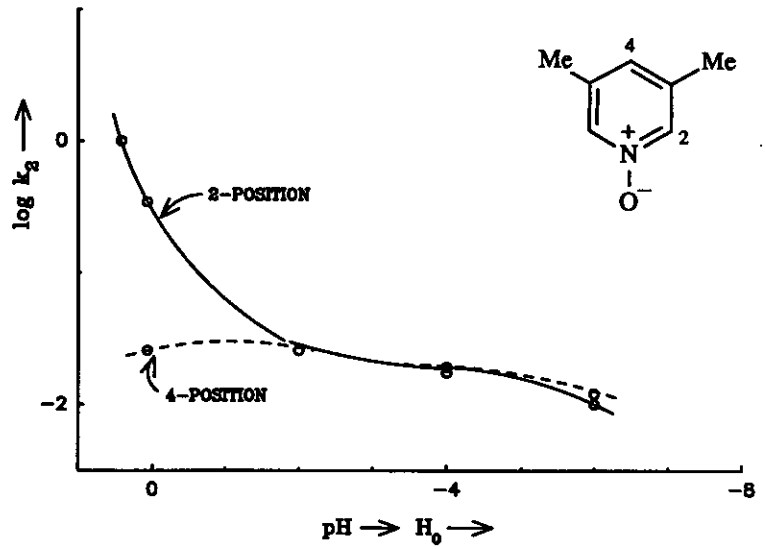
The rate-pH profile for detritiation from the C-2 position of 1-methylimidazole has recently been determined in aqueous solution at 85°C. The profile is consistent with a mechanism involving attack by hydroxide ion on the conjugated acid of the substrate to give an ylid intermediate in the rate-determining step.[36]

Hydrogen Exchange in *N*-Oxides

The rate profiles for hydrogen exchange at the 2,6- and at the 4-position of 3,5-dimethylpyridine 1-oxide are shown in Scheme 35.[37,38,39] At the 4-position, hydrogen exchange takes place over the region investigated exclusively on the free base where the dominant species is the cation. In the 2-position (at higher acidities) exchange occurs on the cation, but at low acidities the exchange rate increases greatly which is undoubtedly

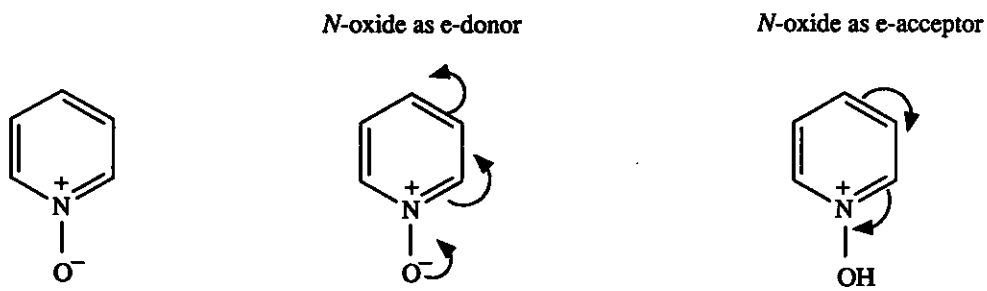
due to exchange occurring by a deprotonation as discussed earlier (Scheme 3).

Scheme 35. Rate Profile for the Hydrogen Exchange of 3,5-Dimethylpyridine 1-Oxide



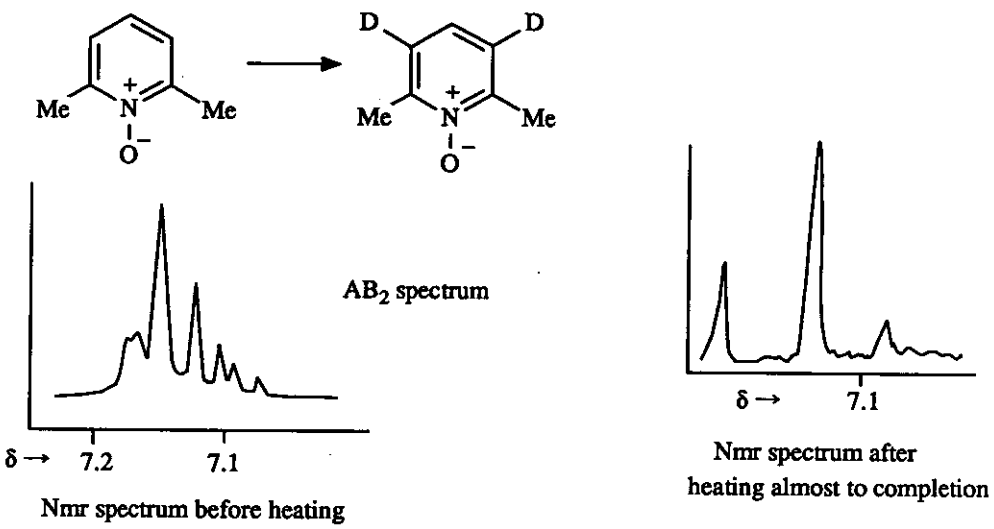
Electrophilic substitution in pyridine 1-oxide is known to be affected by the dominance of the *N*-oxide group in being both an electron donor and an electron acceptor, particularly an electron acceptor in the monocationic form (Scheme 36).

Scheme 36. Electrophilic Substitution in Pyridine 1-Oxide



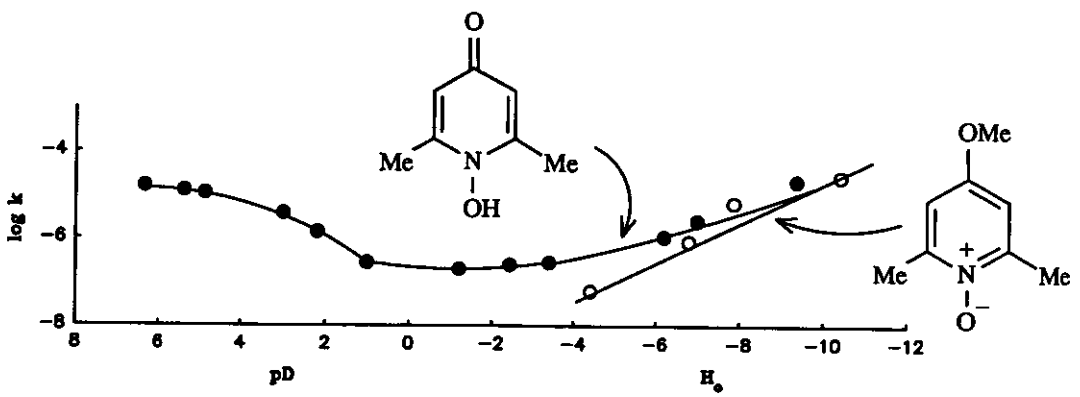
Indeed in 2,6-dimethylpyridine 1-oxide exchange takes place in the 3- and the 5-positions (Scheme 37).[37,38]

Scheme 37. Electrophilic Substitution in 2,6-Dimethylpyridine 1-Oxide



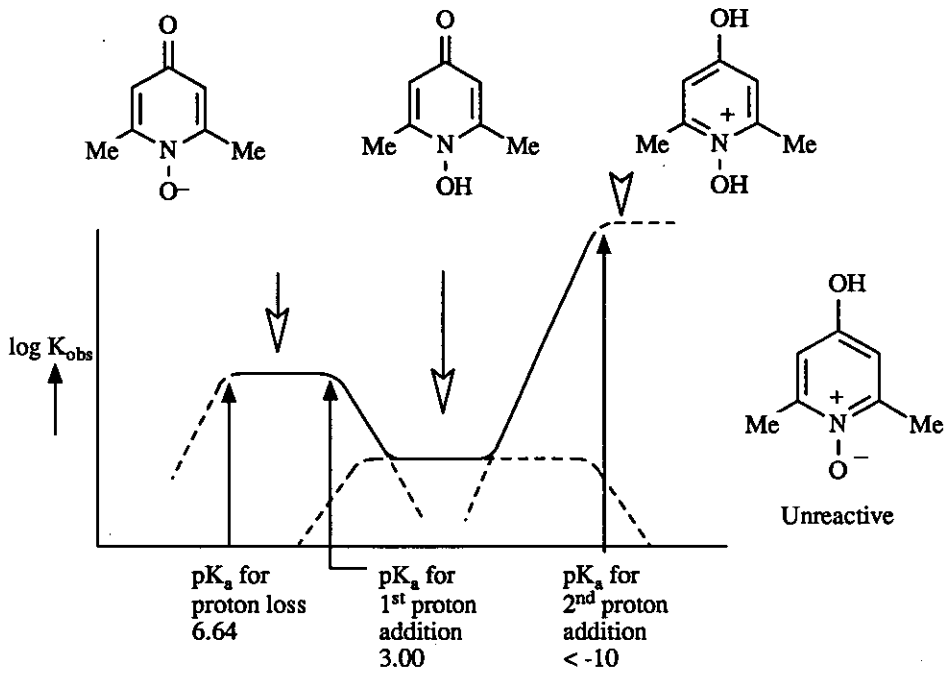
The rate profile for 2,6-dimethyl-1-hydroxy-4-pyridone[26] shows an extraordinary form (Scheme 38).

Scheme 38. Rate Profile at 100°C for Hydrogen Exchange of 1-Hydroxy-2,6-dimethyl-4-pyridone and 4-Methyoxy-2,6-dimethylpyridine 1-Oxide



The idealized version of this rate profile is shown in Scheme 39.[20]

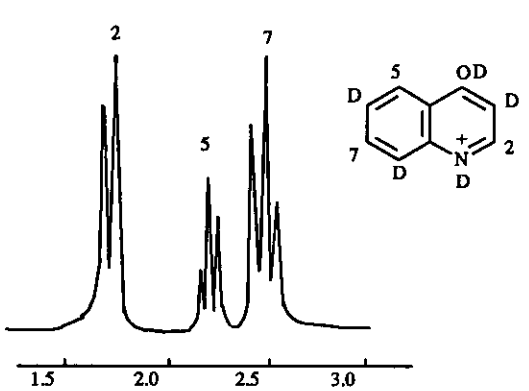
Scheme 39. Idealized Rate Profile for Hydrogen Exchange of 1-Hydroxy-2,6-dimethyl-4-pyridones



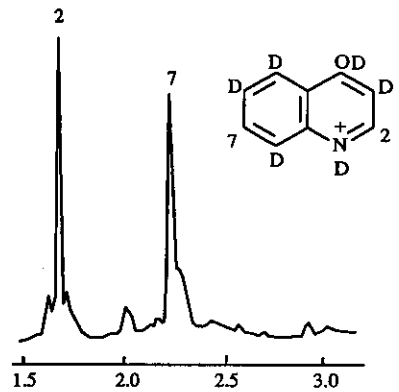
Hydrogen Exchange of 4-Quinolone

Schemes 40 and 41 show nmr spectra which define the positions of hydrogen exchange in 4-quinolone under various conditions.[19]

Scheme 40. ^{1}H Nmr of Hydrogen Exchange of 4-Quinolones at $H_0 = -9.2$

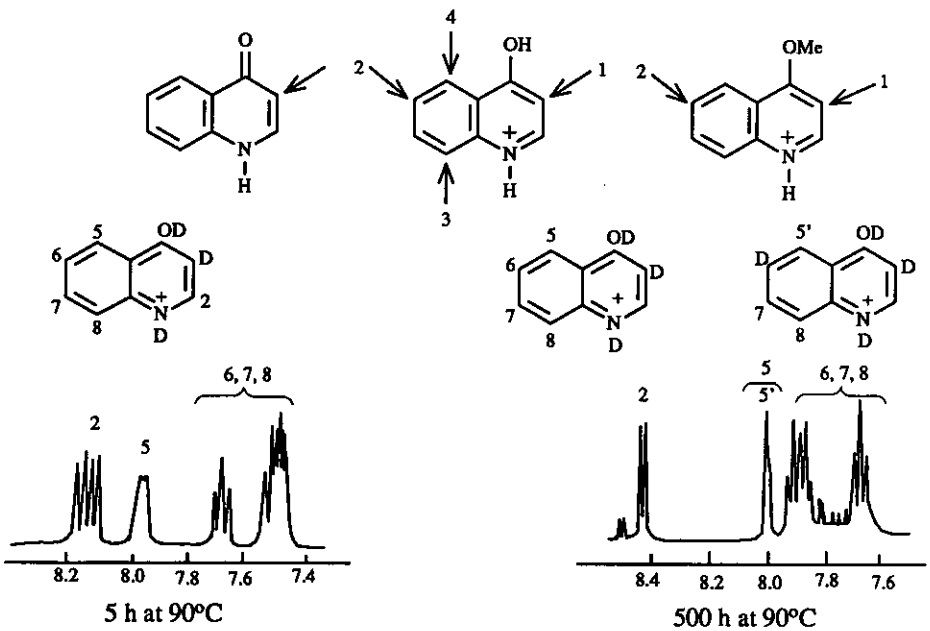


500 h at 90°C and 140 h at 100°C



500 h at 90°C and 1000 h at 140°C

Scheme 41. Hydrogen Exchange of 4-Quinolone at $H_0 = -9.2$



5 h at 90°C

500 h at 90°C

Introduction to Nitration of Heterocycles

Nitration is one of the most studied and best understood of organic reactions.[40,41,42] Various geometric structures in the reaction have been examined by using the MNDO self-consistent field method[43] and ^{15}N nuclear polarization.[44]

To make a quantitative comparison of nitration rates after the position of attack and the species undergoing attack (i.e. free base or conjugate acid) have been determined, it is necessary to select standard conditions and then to extrapolate rates if needed to these conditions. The standard conditions shown in Scheme 42 were chosen.[45]

Scheme 42. Standard Conditions for Nitration of Heterocycles

25°C and H_0 - 6.6 (i.e. 75% H_2SO_4)

A. Determine the Position of Attack and the Species Undergoing Attack (Free Base or Conjugate Acid)

B. Procedure for Quantitative Measurement of Standard Rate

(i) Determine k_2 (obs) at particular T and range of H_o value

(ii) Interpolate or extrapolate rate profile to obtain k_2 (obs) at H_o -6.6

(iii) Using $\Delta H^{\neq}$ 35 kcals extrapolate to get k_2 (obs) at H_o -6.6 and 25°C

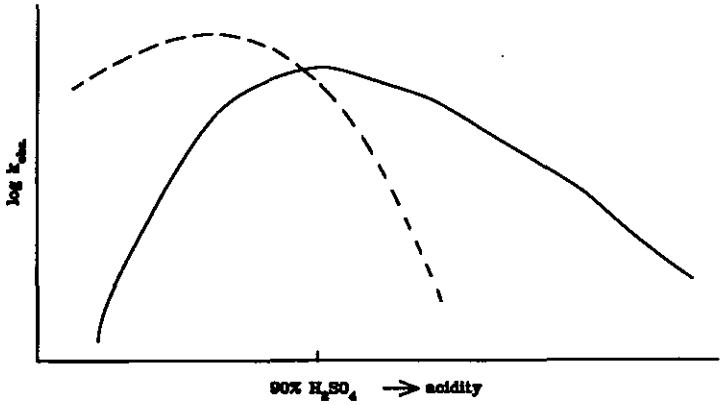
(iv) Correct for minority species if needed

The typical rate profile for nitration, i.e. dependence of rate on the acidity, is shown in Scheme 43 where the solid line is for a majority species and the dotted line for a minority species i.e. for attack on a free base in conditions where most of the compound is present as a conjugate acid.

Scheme 43. Rate Profiles for Nitration Reaction

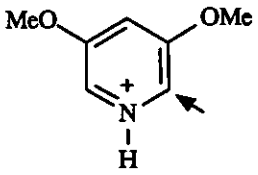
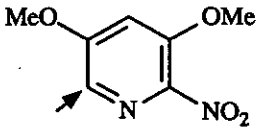
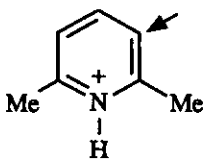
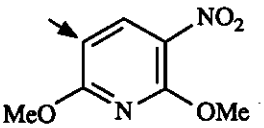
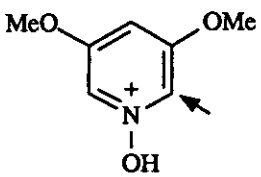
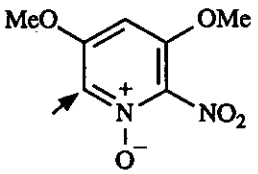
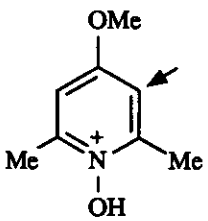
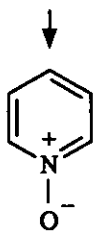
solid line: majority species

dotted line: minority species of which the concentration falls according to H_0 acidity function



A wide variety of orientation and species undergoing nitration is possible,[46] as is illustrated in Scheme 44. Thus, examples are known for the nitration of pyridines, both as free bases and as conjugate acids in both the 2- and 3-positions of the ring (no examples, so far, are known of nitration of pyridines at the 4-position).[47,48] For pyridine oxides, by contrast, examples are known of both nitration as free base and conjugate acid at the 2-position, whereas nitration at the 3-position takes place only on the conjugate acid, and at the 4-position only on the free base.[49] We will now discuss how these conclusion were reached.

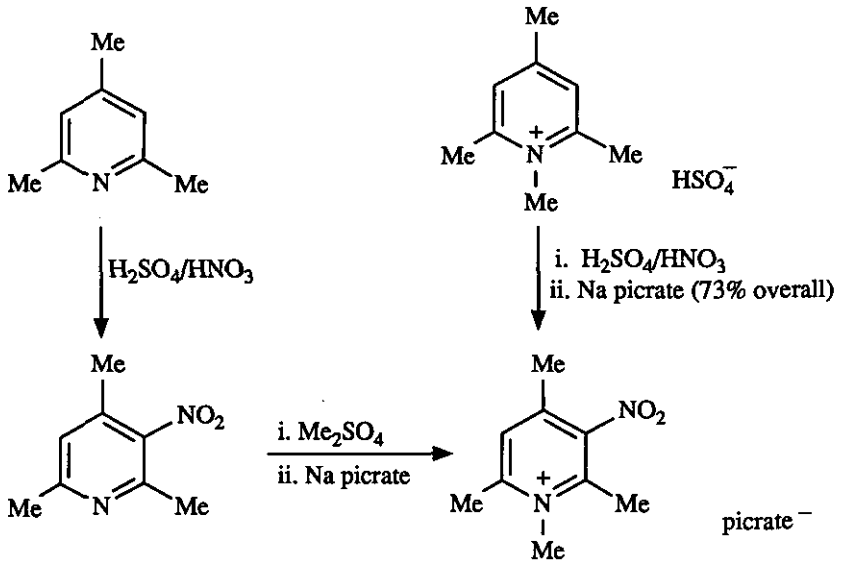
Scheme 44. Species and Orientations Undergoing Nitration in Pyridines and Pyridine 1-Oxides

	Conjugate Acids	Free Bases
Pyridine α-position		
Pyridine β-position		
Pyridine γ-position	not known	not known
Pyridine 1-oxides α-position		
Pyridine 1-oxides β-position		not known
Pyridine 1-oxides γ-position	not known	

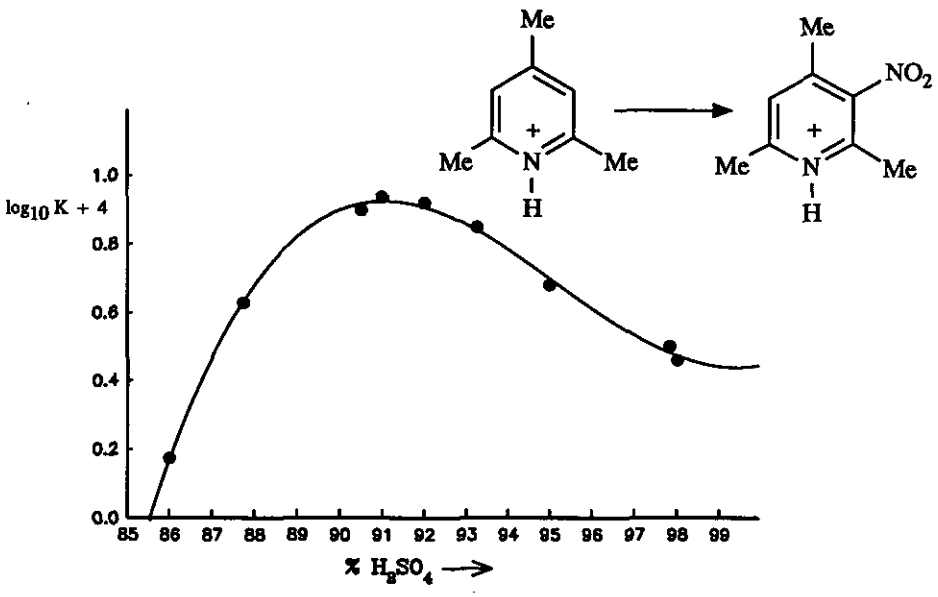
Nitration of Pyridine 1-Oxides at the 3-Position via the Conjugate Acid

While pyridine undergoes preparative nitration in poor yield, 2,4,6-trimethylpyridine can be nitrated reasonably easily to yield the 3-nitro compound.[48,49] Two independent pieces of evidence show that this nitration takes place on the conjugate acid. Firstly, the methosulfate undergoes nitration under comparable conditions (Scheme 45), and secondly, the rate profile for the nitation of 2,4,6-trimethylpyridine (Scheme 46) is a typical majority species shape.

Scheme 45. Preparative Nitration of 2,4,6-Trimethylpyridine and its Methosulphate

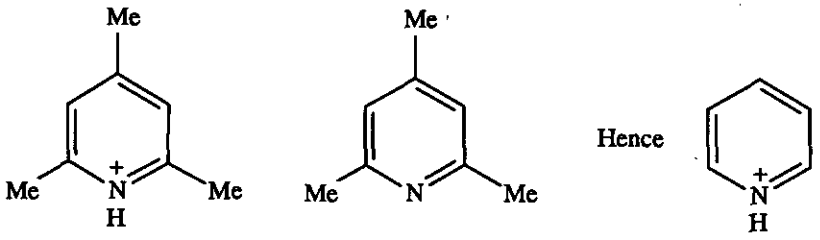


Scheme 46. Rate Profiles for the Nitration of 2,4,6-Trimethylpyridine[48]



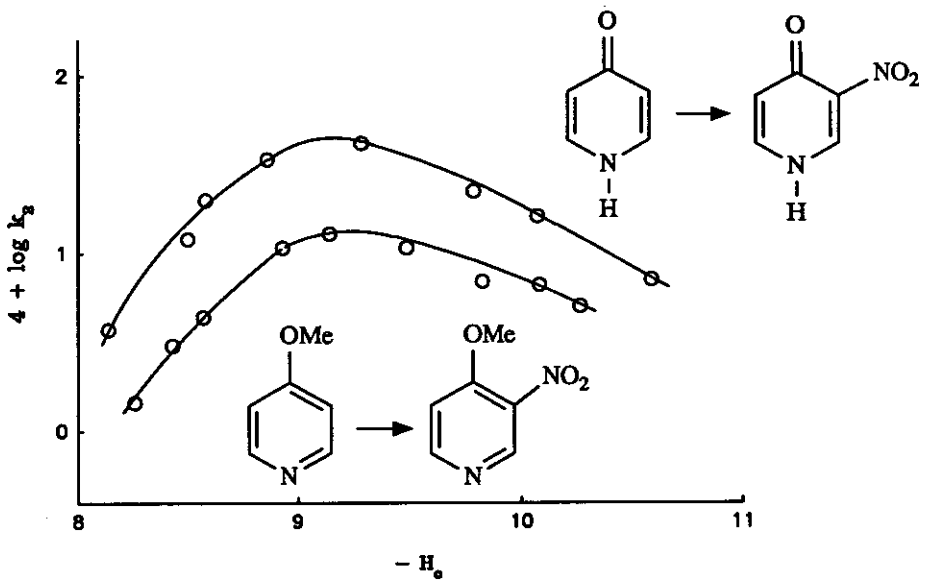
Using the extrapolation procedures mentioned, the tremendous deactivation induced by the positively charged nitrogen atom can be shown to be as in Scheme 47.[48,49]

Scheme 47. Partial Rate Factor for 2,4,6-Trimethylpyridine Nitration



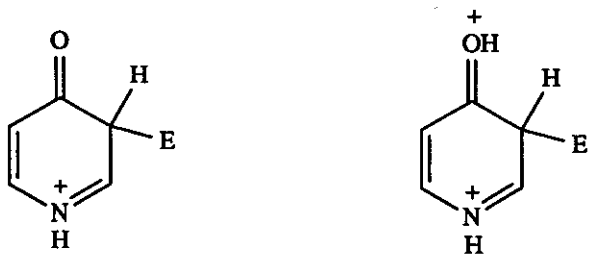
Both 4-pyridone and 4-methyoxypyridine are nitrated as conjugate acids as shown by the rate profiles in Scheme 48.[50] It is of interest that 4-pyridone is nitrated as a conjugate acid whereas it undergoes hydrogen exchange in the free base form as discussed earlier.[19,51]

Scheme 48. Rate Profiles for the Nitration of 4-Pyridone and 4-Methoxypyridine



The reason for this is in part, but only in part, that hydrogen exchange occurs under less acidic conditions than nitration (Scheme 49).

Scheme 49. Mechanism of Electrophilic Substitution in Pyridones



Preferred When $E^+ = H^+$ Preferred when $E^+ = NO_2^+$

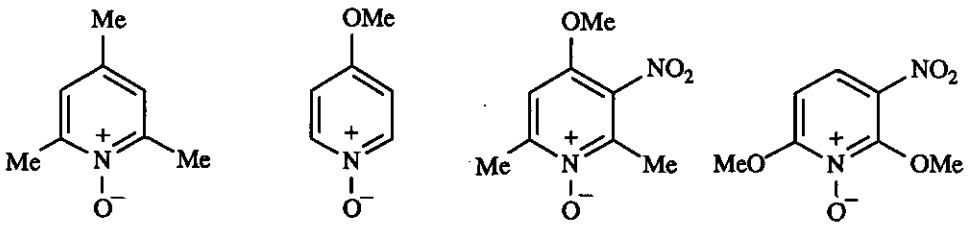
The acidity function followed by pyridines approximates to the Hammett acidity function quite clearly (Scheme 50).

Scheme 50. Acidity Function for Pyridines

	pK_a	Value of n in $pK_a = H_o - n \cdot \log_{10}\frac{[BH^+]}{[B]}$
3,5-Dichloropyridine	+ 0.73	0.80
2,3-Dichloropyridine	- 0.84	1.10
2,3,4-Tribromopyridine	-1.16	0.95
2,6-Dichloropyridine	-2.88	0.99

Pyridine 1-oxides can be nitrated at the 3-position as the conjugate acids, provided a sufficient number of activating groups are present. For this, neither three methyl groups nor a single methoxy group suffices. However, one methoxy and 2 methyl groups, or 2 methoxy groups, are sufficient (Scheme 51).[49]

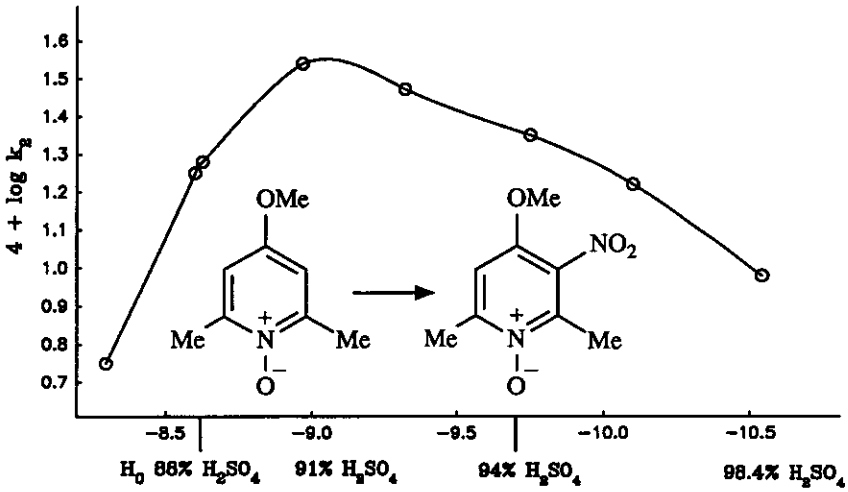
Scheme 51. Nitration of Pyridine 1-Oxides in β-Position



No Reaction Decomposition Good Yield

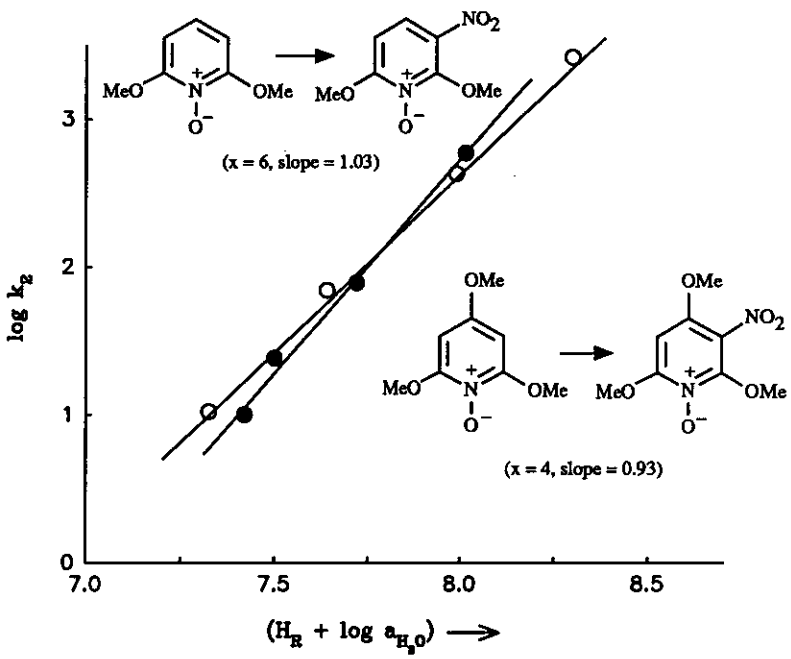
The rate profile (e.g. Scheme 52) is again clearly that of a majority species.

Scheme 52. Rate Profile for Nitration of 4-Methoxy-2,6-Dimethylpyridine-N-Oxide at 33.7°C



An alternative criterion, which is more precise than the normal rate profile, is to use the so-called "Schofield Plot" (Scheme 53). Majority species nitration gives a slope of approximately unity as is shown in the two examples.[49]

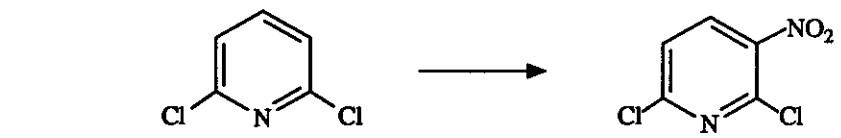
Scheme 53. Schofield Plots for β-Nitration



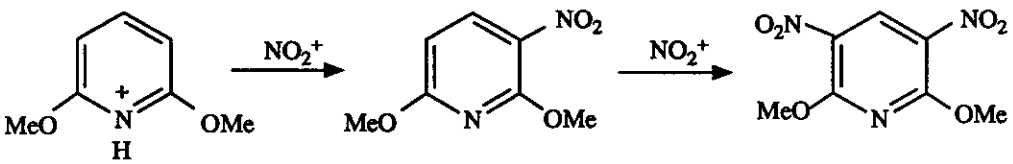
Nitration of Pyridines at the 3-position via the Free Base

It was found preparatively that 2,6-dichloropyridine undergoes nitration at the 3-position quite readily at 100°C i.e. very much more easily than pyridine itself.[48] This is, at first sight, most surprising as the introduction of a chlorine atom normally makes electrophilic substitution much more difficult. Thus, *m*-dichlorobenzene undergoes nitration at a much slower rate than benzene itself. The explanation is that the chlorine atoms reduce the basicity of the pyridine nitrogen atom so much, that there is sufficient free base left for this to undergo the nitration (Scheme 54).

Scheme 54. Pyridine Nitration at the 3-Position Via Free Base



reacts as free base

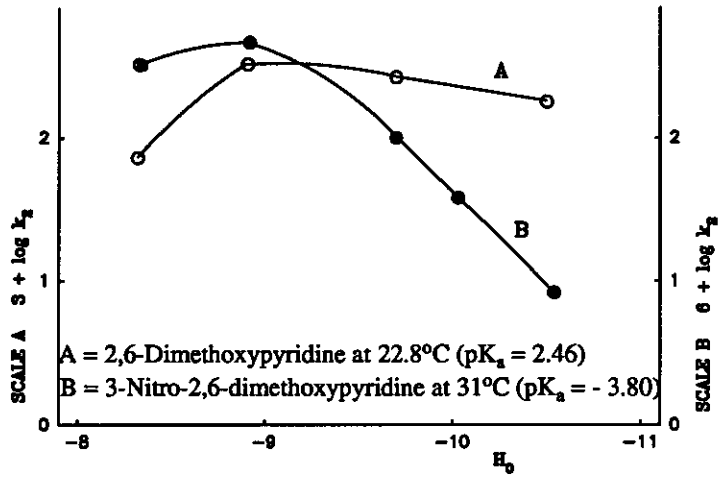


reacts as conjugate acid reacts as free base

Also shown in Scheme 54 is the situation for 2,6-dimethoxypyridine. This can be nitrated twice; first at the 3-position and then at the 5-position. The rate profiles for these two nitrations are shown in Scheme 55,[48] and whereas that for the first nitration is clearly for a majority species, i.e. conjugate acid, by contrast, the rate profile for the second ntration is for the free base nitration. The explanation once again is that the 3 nitro group reduces the basicity of the pyridine nitrogen atom so that the protonated species is not present in sufficient quantity to react.

The nitration of 2-pyridone yields largely the 3-nitro derivative in low acidity media and largely the 5-nitro compound in high acidity media, but both reactions occur in the free base species.[52]

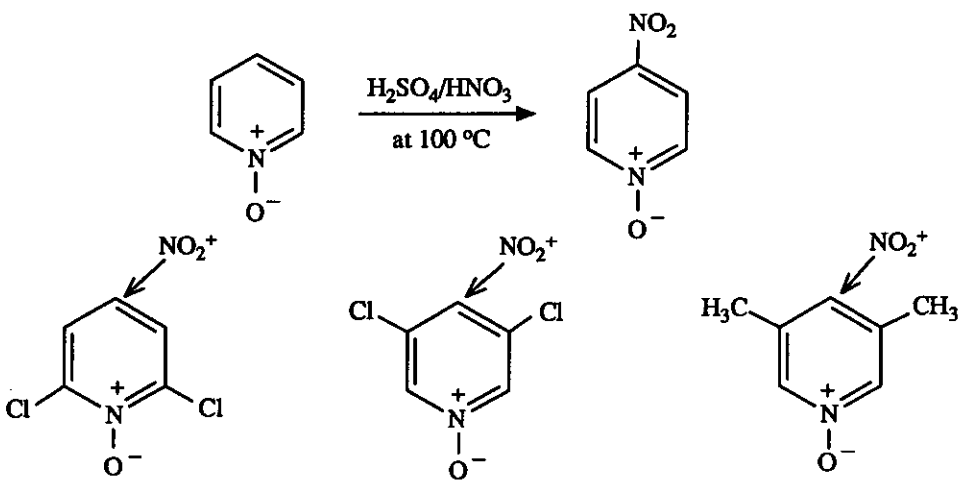
Scheme 55. Rate Profiles for the Nitration of Pyridines at the β-Position



Nitration of Pyridine *N*-Oxides at the 4-Position

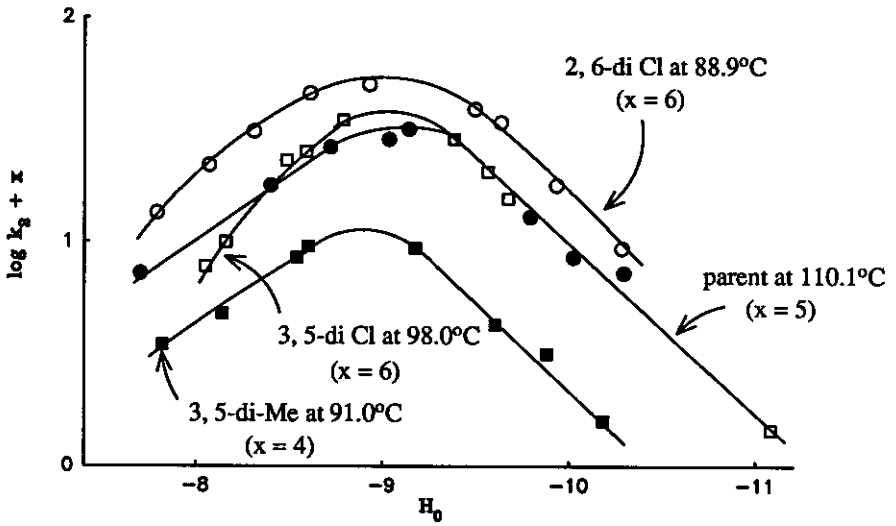
A wide range of pyridine *N*-oxides can be nitrated in good yield at the 4-position.[49] A few examples are shown in Scheme 56.

Scheme 56. γ-Nitration of Pyridine 1-Oxide



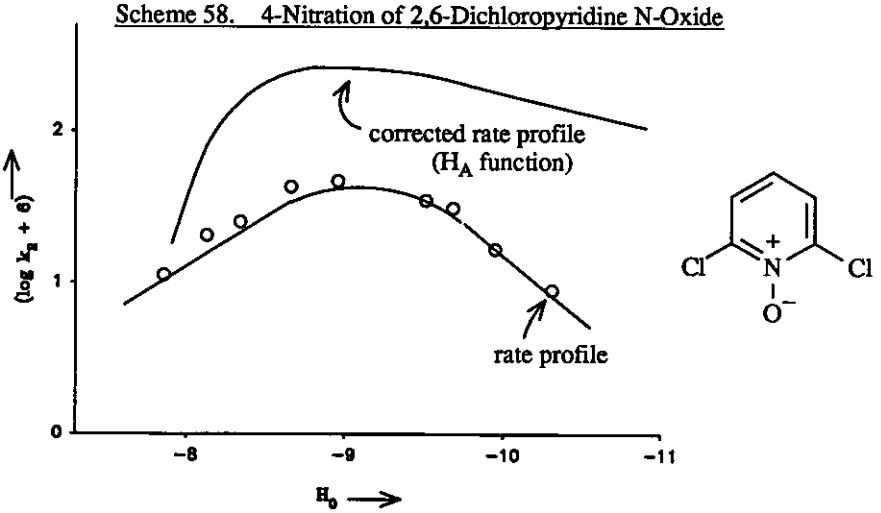
The rate profiles for these four nitrations are at first sight somewhat confusing (Scheme 57). They appear to be rather mid-way between the shape typical for a majority species and for a minority species nitration. An explanation for this is that the protonation of pyridine 1-oxides does not follow the normal Hammett acidity function, but instead follow the H_A amide acidity function.

Scheme 57. Rate Profiles for 4-Nitration of Pyridine N-Oxides



When the rate profile is corrected using the H_A function, then the normal shape for majority species is found as illustrated in Scheme 58.

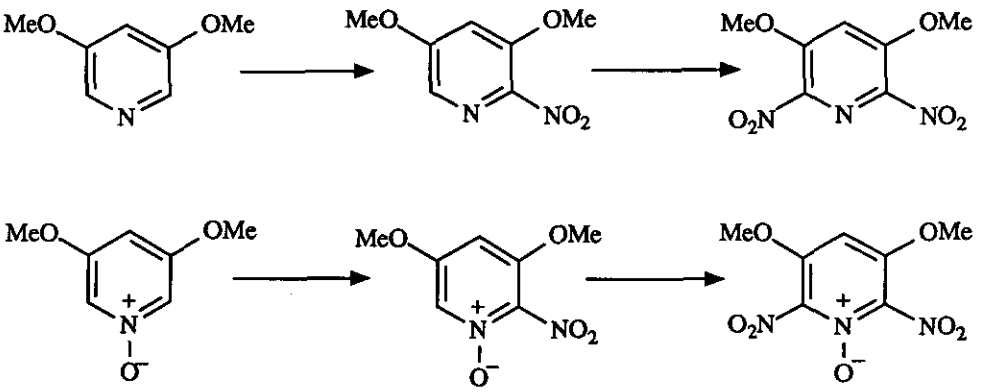
Scheme 58. 4-Nitration of 2,6-Dichloropyridine N-Oxide



Nitration of Pyridines at the 2-Position

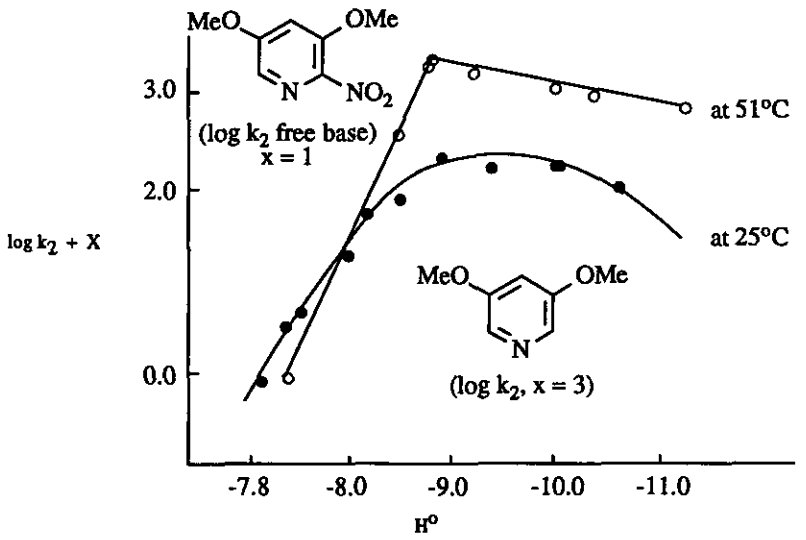
Given sufficient activation, both pyridines and pyridine 1-oxides can be nitrated at the 2- and at the 2,6-positions (Scheme 59).[47,49]

Scheme 59. Pyridine Nitration at 2- and 6-Positions

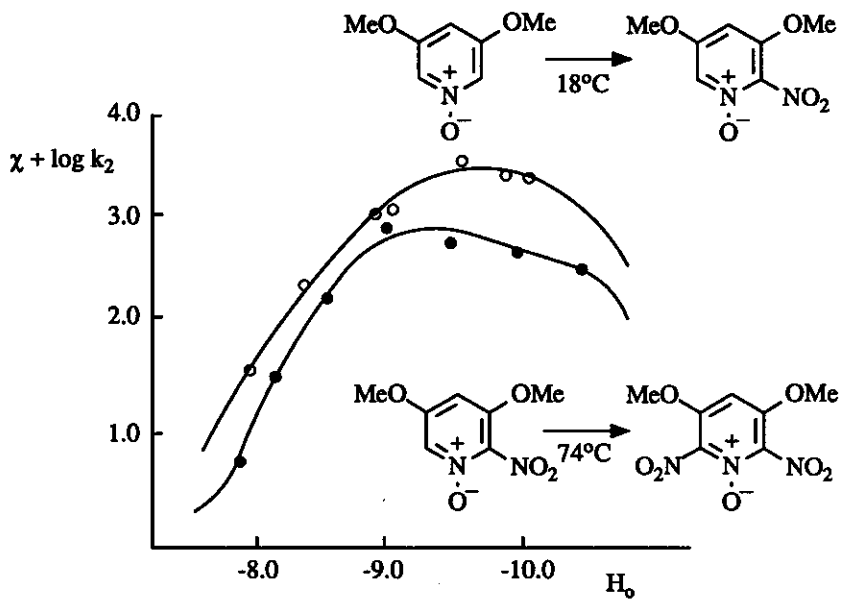


The rate profiles for the reactions are shown in Schemes 60 and 61.

Scheme 60. α-Nitration Rate Profiles



Scheme 61. Rate Profiles for α-Nitration of *N*-Oxides

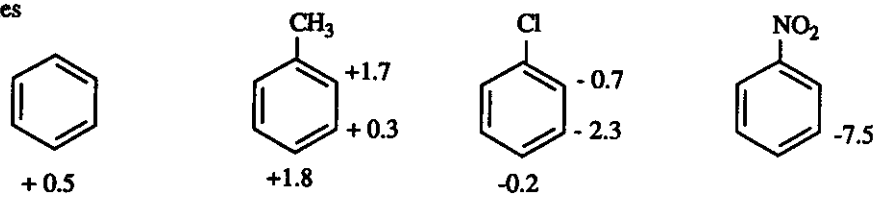


Qualitative Comparisons of Standard Nitration Rates

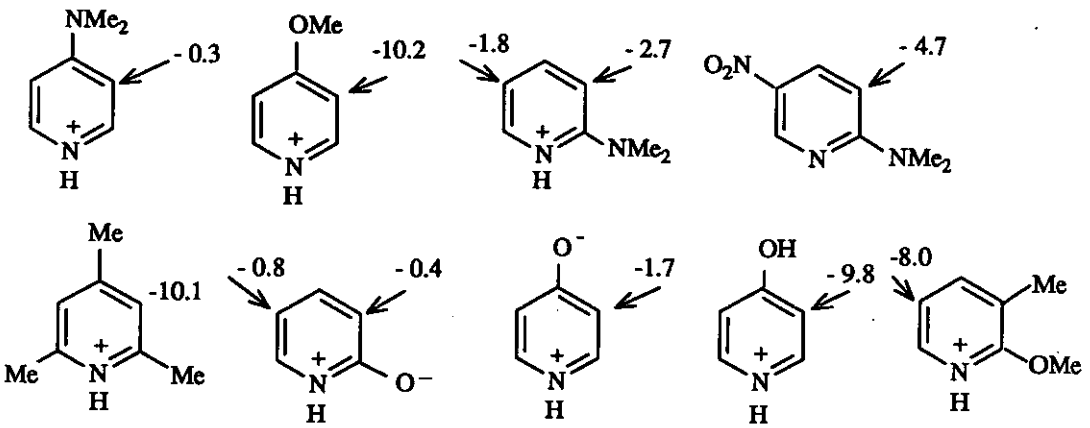
Using the extrapolation procedure mentioned, it has been possible to obtain nitration rates under the standard conditions which are directly comparable with each other.[53,54] Scheme 62 reproduces a number of standardized rates for variously substituted pyridines and pyridine derivatives together with a few substituted benzene rates for comparison. The standard conditions chosen are 25 °C and H_0 -6.6 (*i.e.*, 75% H_2SO_4 at 25 °C).[53] The data available for *ca.* 130 compounds are processed in this way to derive the standard rate coefficients. When nitration occurs at more than one position, the slope of the rate profile refers to the overall reaction. Standard rate coefficients for nitrations at the individual positions are then obtained using the isomer distribution at the measured acidity nearest to 75% H_2SO_4. When nitration occurs at two or more equivalent positions, the calculated log k_o values refer to overall reactivity, and must therefore be statistically corrected.

Scheme 62. Standard Nitration Rates for Pyridines (log k_o Values) [53,54]

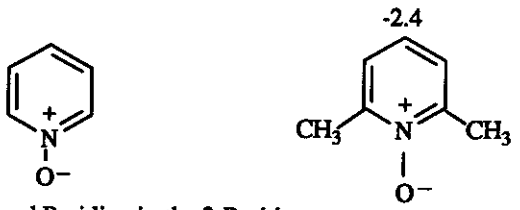
Benzenes



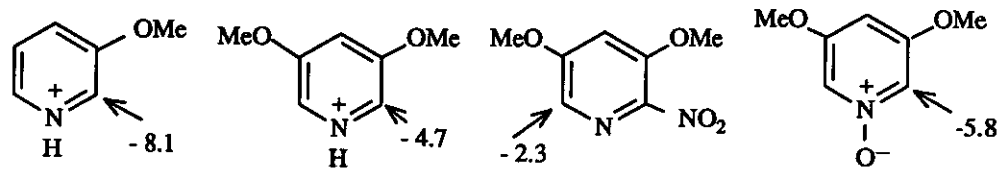
Pyridine and Conjugate Azides in 3-Position [55]



Pyridine 1-Oxides in the 4-Position

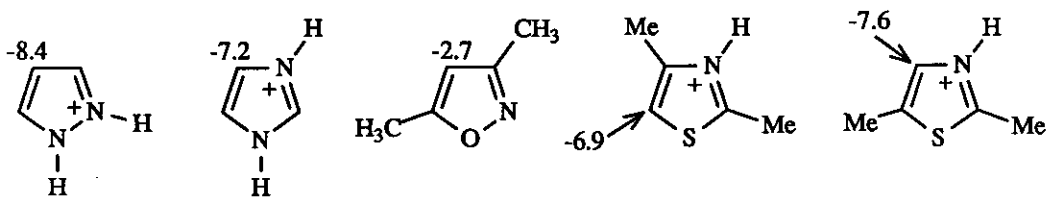


Pyridinium and Pyridine in the 2-Position

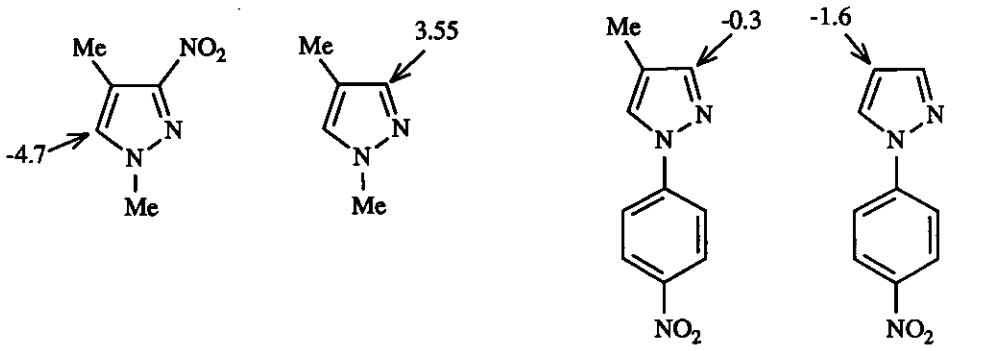


Standard rates for nitration of some azoles are given in Scheme 63.[53,54]

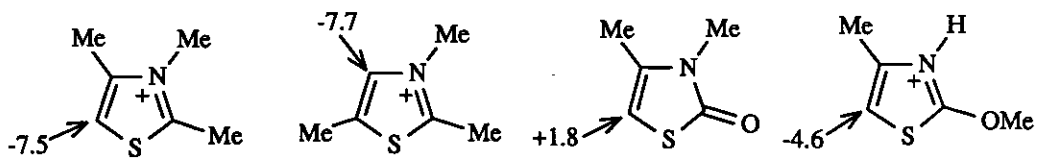
Scheme 63. Standard Nitration Rates for Azoles (log k_0 Values)



Nitration of Pyrazoles[56 – 58]



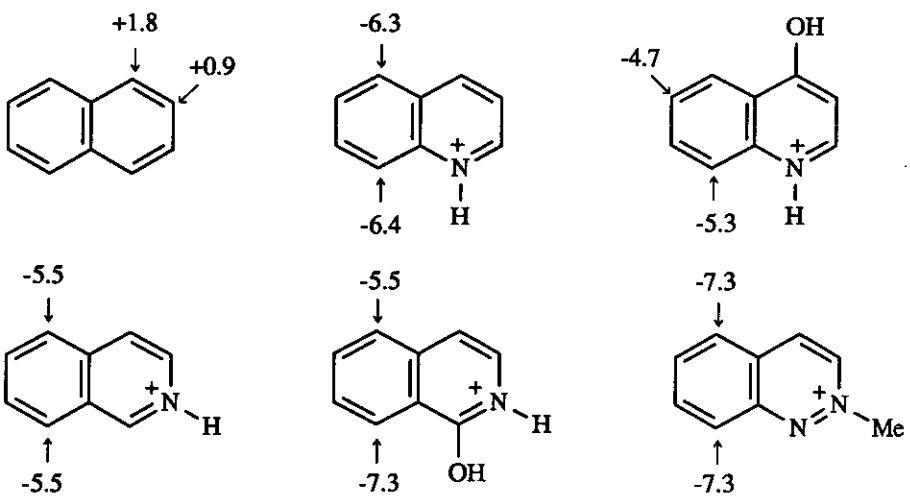
Nitration of Thiazoles[58,59]



Deactivation relative to benzene is still very marked for pyrazole, imidazole, and thiazole which all react as their conjugate acids although these compounds are much more reactive, in turn, than pyridine. In the case of isoxazole, nitration takes place on the free base, and the standard rate is correspondingly less negative. The data given before for the various substituted pyrazoles show that nitration on the pyrazole free bases is now much less deactivated even when a nitro group is present, and also that there is little intrinsic difference in reactivity between the 3-, 4- and 5-positions of the pyrazole free base. Similarly, the data for the thiazoles show little intrinsic difference between the reactivity of the 4- and 5-positions in the thiazole conjugate acid. Also shown is the enormous effect of the anionic oxygen substituent in the 2-thiazolone compound.

Scheme 64 shows standard nitration rates for bicyclic compounds.[53,54] The deactivation in the α-positions of the benzenoid ring in the quinoline and isoquinoline conjugate acids is far less than that which occurs in pyridine.

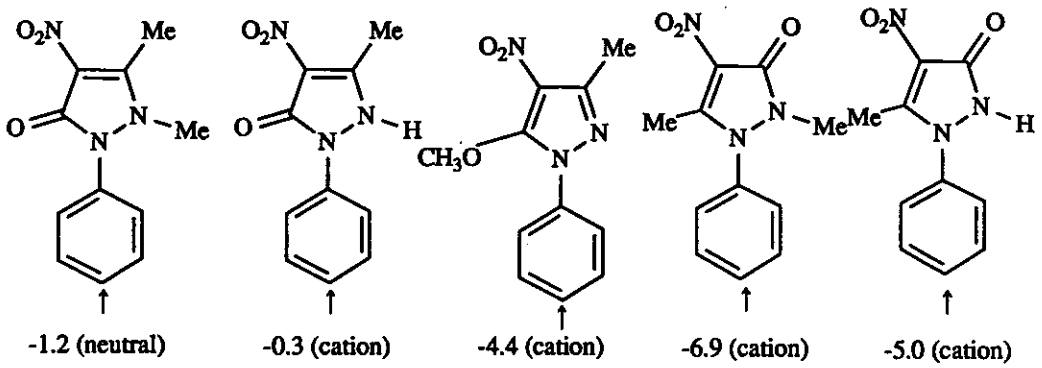
Scheme 64. Standard Nitration Rates for Bicyclic Compounds (log k_0 Values)



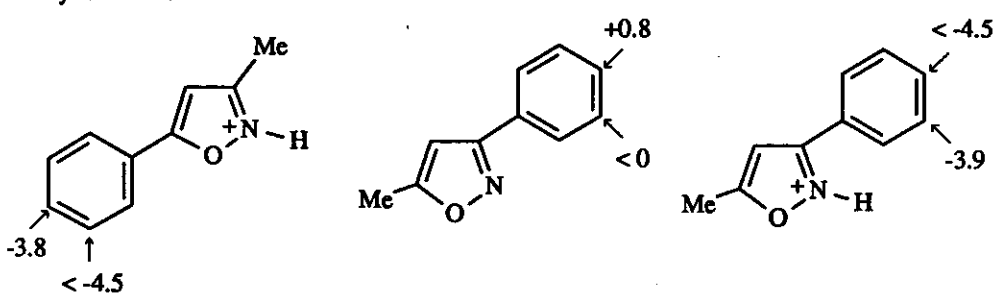
In Scheme 65, the effects of heterocyclic rings as substituents are not exactly in the series of 3- and 5-pyrazolones as shown. Steric effects of substitution look to be important in these series.

Scheme 65. Steric and Electronic Effects on Nitration Rates

a) Phenyl Substituents 3- and 5-Pyrazoles[56,57,60]



b) Phenylisoxazoles [61]

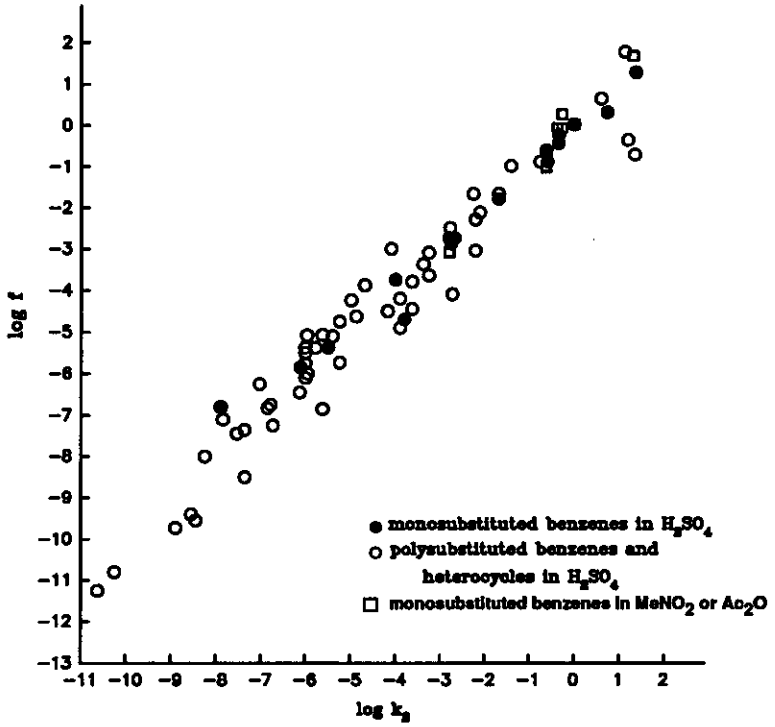


In the phenylisoxazoles, the difference between the conjugate acid and the free base is shown to have a very marked effect on the orientation and the rate of nitration of the phenyl group (Scheme 65).

Quantitative Interpretation of Standard Nitration Rates

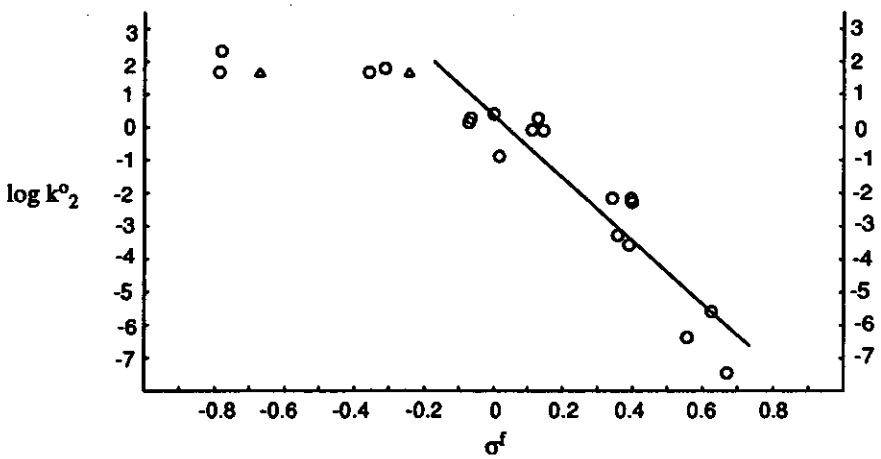
Scheme 66 shows a comparison of literature partial rate factors with standard nitration rates.[54] The correlation is not perfect but the overall trend is given quite distinctly.

Scheme 66. Comparison of Literature p.r.f. with Standard Nitration Rates



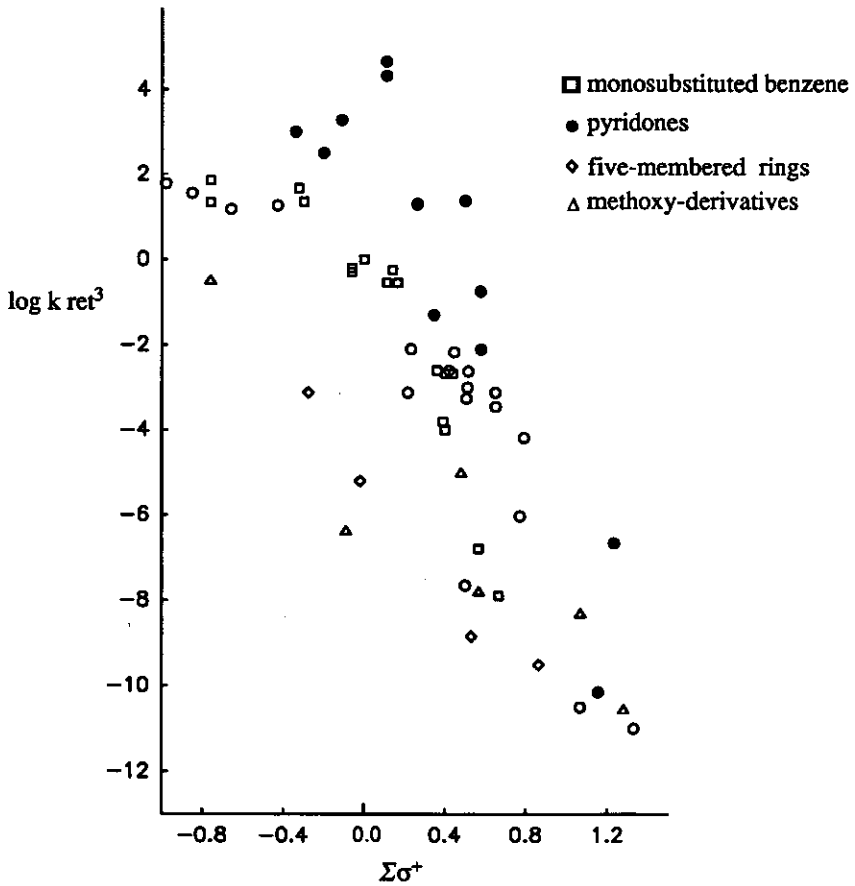
In Scheme 67, a Hammett plot for the nitration of monosubstituted benzenes is shown.[54] This shows clearly that below a Hammett σ^f value of -0.2, all nitrations proceed at essentially the same rate. This is because the encountered rate becomes rate determining.

Scheme 67. Hammett Plot for Nitration of Monosubstituted Benzenes



Scheme 68 shows a plot of nitration rates against the summation of σ+ values for substituents.

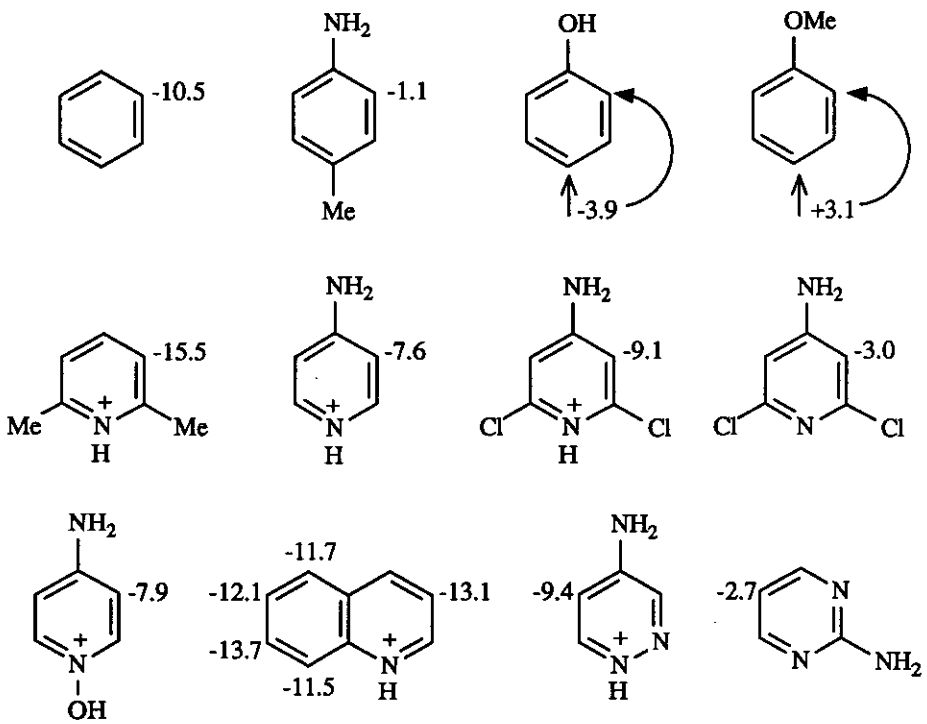
Scheme 68. Plot of Nitration Rates vs. $\Sigma\sigma^+$ of Substituent



Comparison of Hydrogen Exchange Rates with Nitration Rates

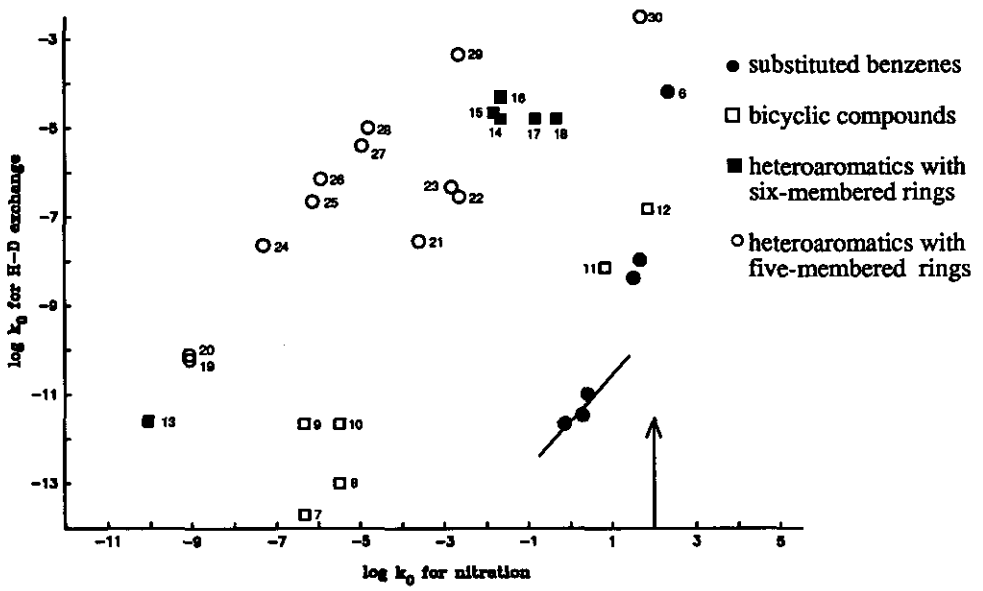
Some examples of hydrogen exchange rates under standard conditions are shown in Scheme 69.

Scheme 69. Examples of Hydrogen Exchange Rates (log k_0 Values)



In Scheme 70, standard rates for hydrogen exchange[21] are plotted against standard rates for nitration.[53,62,63] There is no simple relation between these two measures. Although for both hydrogen exchange[32] and nitration,[54] linear free energy relations hold for limited series of compounds in which only a single structural parameter is changed (e.g. for monosubstituted benzenes), the differences in the effects of the mutual interaction of substituents in poly-substituted and heteroaromatic compounds on hydrogen exchange and on nitration is vividly indicated by the scatter apparent in Scheme 70. It is clear that there is no unique order of the susceptibility of individual ring position towards electrophilic attack and in particular that no single reactivity index can be used as such a measure.

Scheme 70. Plot of Standard Rates of Hydrogen Exchange vs. Nitration



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