# PYRIDINE
# and Its Derivatives
## Part One

**Erwin Klingsberg,** *Editor*
*American Cyanamid Company, Bound Brook, New Jersey*

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# PYRIDINE AND ITS DERIVATIVES

In Four Parts

## PART ONE

*This is Part One of the fourteenth volume published in the series*

**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

# THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

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# The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds and accommodate the specific interests of the authors.

*Research Laboratories*
*Eastman Kodak Company*
*Rochester, New York*

ARNOLD WEISSBERGER

# Preface

It is hoped that the organization of this monograph will prove to be self-explanatory, but a few general observations are in order.

Chemical compounds are tabulated exhaustively by the principle of latest position. Thus halogenated pyridinecarboxylic acids are found in Chapter X rather than VI, but hydroxy acids in Chapter XII. The principal exceptions are the quaternary compounds, which proved too numerous to be catalogued, and the N-oxides, which are included in Chapter IV irrespective of nuclear substitution. Other exceptions are explained where they occur.

The principle of latest position does not apply to reactions. All reactions for obtaining pyridine derivatives from non-pyridinoid starting materials are covered in Chapter II irrespective of substitution. If the starting material *is* a pyridine derivative, the reaction is discussed instead in the appropriate later chapter or chapters. Thus the conversion of aminopyridines to pyridinols is discussed in Chapters IX and XII.

Nomenclature follows Chemical Abstracts.

The editor wishes to express his gratitude to Prof. D. S. Tarbell of the University of Rochester for the impetus he gave to this undertaking, to the chemists in many parts of the world who have been so generous with reprints, to the staff of Interscience Publishers for their cooperation, and finally to Dr. R. S. Long and Dr. J. J. Leavitt of American Cyanamid for their patience.

*Bound Brook Laboratories*
*American Cyanamid Co.*
*Bound Brook, N. J.*

ERWIN KLINGSBERG

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## CHAPTER I

# Properties and Reactions of Pyridine and Its Hydrogenated Derivatives

BY R. A. BARNES
*Rutgers, The State University, New Brunswick, New Jersey*

## A. GENERAL ASPECTS

### 1. Introduction

Of all the known heterocyclic systems, pyridine has perhaps the greatest importance, whether judged by the variety and interest of its derivatives and their reactions or simply by the volume of literature devoted to them. Broadly speaking, the chemical properties of the pyridine system may be grouped into three categories:

(*1*) Properties roughly parallel to the benzene system, modified in some degree by the presence of the ring nitrogen. These include the typical electrophilic substitution reactions such as sulfonation and halogenation, which are more difficult than with benzene, and the radical reactions, which are rather similar. The behavior of most ring substituents also follows the pattern in the benzene series, with the greatest divergence observed in 2 and 4 substituted pyridines.

(*2*) Properties unusual for the benzene system. In this group are the various reactions in which the key step involves interaction of the pyridine ring system with a base or nucleophilic reagent, as in the amination by sodamide or the addition of organometallic compounds.

(*3*) Properties associated with the unshared election pair on the ring nitrogen. The formation of salts, quaternary compounds, and *N*-oxides is of major interest, especially in the recent literature. The formation and subsequent transformations of these compounds have, of course, no analogies among benzene derivatives.

In view of this great wealth of chemical reactions, it is not surprising that the pyridine literature in recent years is growing faster than that of many other branches of organic chemistry. While the benzene literature still bulks far larger, the gap may well diminish in the near future.

Although there are a great many similarities between pyridine and benzene, the emphasis, particularly here in the first chapter, is on the differences, that is, the changes in behavior of the aromatic system which result from the presence of the nitrogen atom. In discussing the various reactions, an attempt has been made to formulate reaction mechanisms which are in harmony with the available data and which seem reasonable by analogy or because of similarity to more thoroughly studied examples from other systems. It is clearly recognized that as more experimental data accumulate, some of the generalizations which have been suggested will require revision.

## 2. Historical

Pyridine and its simple alkyl derivatives were undoubtedly obtained in a very impure state from the dry distillation of a variety of animal products as far back as the alchemistic period. However it was not until 1846 that investigations of the components of coal tar, which had been going on for several years, finally led to the isolation of the first pure substance of this series, which was named picoline (from *pix,* Latin for tar or pitch). This discovery was made by Anderson (*1*) in the course of experiments that proved pyrrole to be a constituent of coal tar. The similarity between picoline and some unidentified bases previously obtained from animal oil* led Anderson to extend his investigation to bone oil. From this source, after much laborious work, pyridine was first obtained in pure form (*2*). Its name was based, like "pyrrole," on its preparation by dry distillation (*pyros,* Greek for fire); the ending was chosen in harmony with the other organic bases, aniline and toluidine, which were known at the time.

## 3. Structure

The structure for pyridine was proposed independently by Körner (*3*) and Dewar (*4*) and was apparently made largely by analogy with Kekulé's structure for benzene. Confirmation of this structure was obtained when pyridine was reduced with sodium and absolute ethanol to piperidine; the structure of piperidine in turn had been established by its synthesis from pentamethylenediamine. (*5*). This structure with three double bonds in the ring suffered from the same difficulty as the analogous structure for benzene, namely that it is not compatible with the lack of reactivity which characterizes these aromatic systems. Attempts to modify the structure followed the same lines as for benzene; centric (*6*), Ladenburg (*7*), and diagonal (*8*) structures were suggested and ultimately discarded.

It is impossible to write a "structure" in the classical sense which

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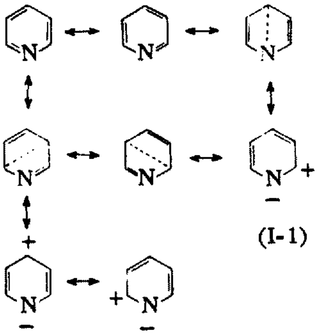
* For a description of the work on crude bases obtained prior to the actual identification of pyridine see Calm and Bucka, *Die Chemie des Pyridins und Seiner Derivate,* Braunschweig, 1889–1891.

adequately characterizes an aromatic molecule, because the "aromatic electrons" ($\pi$ electrons) cannot be localized in the neighborhood of any atoms or pairs of atoms. The most frequently used procedure for describing this situation is the valence bond or resonance approach, in which an aromatic molecule is characterized as a hybrid of various contributing resonance structures. More precisely, the true $\psi$ function which completely describes the behavior of the $\pi$ electrons of the aromatic system is assumed to be adequately approximated as a linear combination of the $\psi$ functions of appropriately chosen contributing structures. Thus for pyridine there are two Kekulé and three Dewar structures, as for benzene, and three charged structures as well (I-1, I-2, I-3).



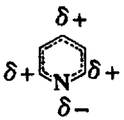
(I-1)

(I-2) (I-3)

An alternate approach is to assume that the $\pi$ electrons of the aromatic system are distributed in various "molecular orbitals" which extend over the whole system. These molecular orbitals have many of the properties of the atomic orbitals. Only two paired electrons can occupy each orbital, and when the lowest energy orbital is filled, the next two electrons are placed in the orbital of next higher energy. The energy of such orbitals could be calculated from the $\psi$ function, which in this approach is usually assumed to be satisfactorily represented by a linear combination of the $\psi$ functions of the atomic orbitals of the atoms of the aromatic system. For pyridine, therefore, the molecular orbitals are formed by a combination of the atomic orbitals of the five carbon atoms and the nitrogen atom of the ring. As in the case of benzene (*9*), the molecular orbitals of pyridine can be visualized as continuous streamers extending around the ring, above and below its plane.

While the reasonance approach is generally satisfactory for a strictly qualitative understanding, it cannot be used for even semi-quantitative estimations of the magnitude of charges, energies, etc., of pyridine or other unsaturated systems containing hetero-atoms. The basic difficulty is that there is no satisfactory method for determining the relative contribution of charged structures such as I-1, I-2, and I-3. This problem does not arise in the case of benzene because it is not necessary to include any charged structures in approximating the true $\psi$ function.

To illustrate, the two approaches can be applied to the question of the electron density at the various positions of the pyridine nucleus. The resonance method predicts from a summation of all contributing structures that there will be a partial positive charge at the 2, 4, and 6 positions of pyridine and a net negative charge on the nitrogen (I-4). However, the magnitude of the charges cannot be estimated because these depend on the relative contributions of the charged structures, which are unknown. The conception that there are molecular orbitals for pyridine does not directly imply that the electrons are unevenly distributed among the atoms; however relatively simple calculations of the charge distributions in pyridine can be carried out (*10*). The magnitude of the charges varies somewhat with the parameters used for the calculations.



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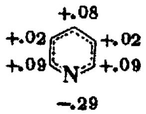
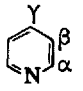
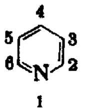


(I-5)

Formula I-5 gives the charges calculated from parameters chosen in such a way as to give reasonable agreement between calculated and observed dipole moments for a series of heterocyclic compounds (*11*).





### 4. Isomerism and Numbering

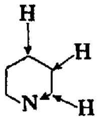
The nitrogen atom introduces an element of asymmetry into the aromatic system and there are, therefore, three possible positions for a single substituent and ten arrangements of two different substituents in the nucleus. For the monosubstituted pyridines the designation of positions by the Greek letters was used almost exclusively in the older literature and is still widely practiced. For di- and polysubstituted pyridines the numbering system with its obvious advantages has been almost universally adopted.

## B. PHYSICAL PROPERTIES

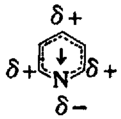
Since pyridine and benzene have essentially the same molecular size, shape, and weight, the differences in physical properties between the two may be attributed largely to the greater polarity of pyridine. This increase in polarity results from the presence of the electronegative nitrogen atom in the ring; the nitrogen atom is the center of negative charge and the positive charge is distributed over the rest of the ring.

### 1. Dipole Moments

The dipole moment, being a function of the magnitude of the charges in a molecule and the distance between them, can give some idea of the electron distribution, particularly in rigid molecules such as pyridine or its simple derivatives. Actually the observed dipole moment for an unsaturated system is the sum of a moment which results from unequal distribution of electrons in the $\sigma$ bonds and a moment arising from unequal distribution of the $\pi$ electrons. Thus the dipole moment of pyridine results from vector addition of the bond moments of the C—H and C—N bonds (I-6) plus a $\pi$ moment (I-7) resulting from the excess of $\pi$ electrons on the nitrogen; the $\sigma$ moment for pyridine is calculated (*11*) to be 0.85 *D* and the observed moment, the sum of $\sigma + \pi$ moment, is 2.23 *D*. In practice it is frequently assumed that $\sigma$ bond moments depend only on the nature of the two atoms and are independent of the $\pi$ electron distribution or of substituents on either atom. Using this assumption it should be possible to calculate the charges produced by the $\pi$ electrons from



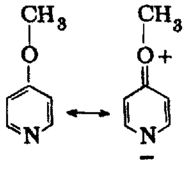
(I-6)



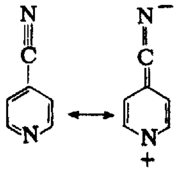
(I-7)

the dipole moment or the reverse. Attempts to correlate dipole moments for a number of heterocycles with charges calculated by the molecular orbital method have met with limited success (*11*).

It should be possible to tell whether a substituent on a pyridine ring interacts with the electrons of the pyridine ring by observing the dipole moment of the substituted pyridine. If there is no interaction, vector addition of the moment of the substituent and of pyridine should give a value identical with that experimentally measured; any electronic interactions will increase or decrease this value depending on the electron accepting or donating properties of the substituent. Comparison of the dipole moments of a series of 4-substituted pyridines with the corresponding benzene derivatives (*98*) indicates that electron-donating substituents interact with the pyridine nucleus (I-8) to a greater extent than with the benzene nucleus. Electron-attracting substituents interact only as much as with benzene if at all. This means that the pyridine nitrogen does not really act as a donor of $\pi$ electrons; that is, structures such as I-9 make little contribution (*99*).



(I-8)



(I-9)

## 2. Melting Points

The melting point of an organic molecule is generally a function of the polarity and symmetry of the molecule. Pyridine is more polar but much less symmetrical than benzene; benzene melts at 5°

while pyridine melts at −38°. Almost all of the alkylpyridines are liquids at room temperature. Exceptions are 2,3,5,6-tetramethylpyridine, m.p. 71° (durene, 1,2,4,5-tetramethylbenzene, melts at 79°) and 3,5-di-*i*-propylpyridine, m.p. 46°. In this latter compound the symmetry is almost the same as in 1,3-di-*i*-propylbenzene (liquid); therefore, the greater polarity of the pyridine derivative is probably responsible for its higher melting point.

An examination of monosubstituted pyridines in which the substituent is amino, hydroxyl, carboxyl, or cyano indicates that for each substituent the melting points decrease in the order, 4-isomer, 3-isomer, and 2-isomer. This further illustrates the importance of the symmetry factor in determining how closely the molecules can pack together in a crystal lattice and hence how effectively the polar groups can interact.

### 3. Boiling Points

Boiling points are largely determined by molecular weight and by association of the molecules in the liquid. The molecular weight of benzene and pyridine are about equal; however, the greater association of pyridine, due to its greater polarity, is responsible for the higher boiling point, 115° (benzene boils at 80°). The presence of alkyl groups increases the boiling point, as in the benzene series. However a striking observation is that the isomers with an alkyl group adjacent to the nitrogen atom always boil lower than those with no substituent at either the 2 or 6 position. For example, 2-methyl- (b.p. 129°) and 2-ethylpyridine (b.p. 149°) both boil about 15° lower than the corresponding 3- or 4-isomer. Similarly, the dimethylpyridines with no $\alpha$- substituent boil at 174 ± 4° and with one $\alpha$-substituent at 159 ± 2° while 2,6-lutidine boils at 144°. The explanation for this phenomenon must be that a large part of the association of pyridine is due to interactions involving the nitrogen atom and that adjacent alkyl groups act as a steric block to such interactions. Thus, for 2,6-lutidine, the nitrogen atom is almost completely blocked and the degree of association of this compound is, therefore, fairly close to that of the corresponding benzene derivative, *m*-xylene (b.p. 139°).

### 4. Solubility

A third property in which pyridine differs from benzene and which is also directly due to the greater polarity of the heterocyclic system is solubility in water. For water solubility the presence of charged centers is not always sufficient, and hydrogen bonding is frequently the most important factor. The complete miscibility of pyridine and water is probably due to the excellent hydrogen bonding between pyridine and water molecules. The difficulty in preparing anhydrous pyridine, the hygroscopic nature of pyridine, and the existence of a constant boiling mixture of the approximate composition $C_5H_5N \cdot 3H_2O$ all attest to the tendency of pyridine to combine with water.

### 5. Spectroscopic Properties

The absorption of light by a pyridine derivative has been used, as for most kinds of organic compounds, to demonstrate the presence of certain structural features in the molecule and also for purposes of analysis and identification. The ultraviolet and infrared have been the most useful regions of the spectrum.

#### *a. Ultraviolet*

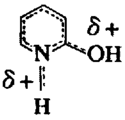
Absorption of a photon of light in the ultraviolet region results in an energy increase sufficient to cause an electronic transition. In a molecule such as pyridine, these transitions involve the shift of a $\pi$ electron to a molecular orbital of higher energy.

The shift of an electron from the highest energy bonding orbital to the lowest energy antibonding orbital is one of the important transitions in aromatic systems. The replacement of —CH— by N in an aromatic system to yield pyridine, quinoline, acridine, etc. does not change the spectrum appreciably from that of the corresponding carbocyclic system *(100)*. This observation is in accord with the molecular orbital calculations which show the energy levels of pyridine and benzene to have similar spacing. The principal maximum for pyridine is at 195 m$\mu$ (benzene 198 m$\mu$) and the center of the fine-structure bands is 250 m$\mu$ (benzene 255 m$\mu$).

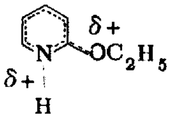
The interactions of functional groups with the pyridine nucleus produces changes in the spectrum which are frequently similar to those for the corresponding benzene derivatives. For example, the spectra of aniline and 3-aminopyridine are very similar (*101*). However, acetophenone and 3-pyridyl methyl ketone differ considerably (*102,103*).

The spectra of pyridines are of course modified by salt formation because the energy levels for the molecular orbitals are changed when the nitrogen atom takes on a positive charge.

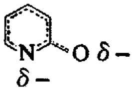
An interesting example is 2(1*H*)-pyridone with three different spectra depending on the pH of the solution (*104*). In acid solution the spectrum resembles that of 2-ethoxypyridine in acid solution. In both of these molecules the aromatic system has an overall positive charge which is mostly at the nitrogen and oxygen atoms (I-10, I-11). In basic solution a proton may be lost to yield a negatively charged system (I-12). In a neutral solution the spectrum of uncharged 2(1*H*)-pyridone is found to be different from either I-10 or I-12.



(I-10)



(I-11)



(I-12)

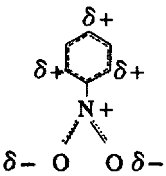
### *b. Infrared*

As yet the published data on the infrared spectra of pyridine derivatives are rather limited and it is difficult to make generalizations. Pyridine itself has been carefully studied (*105–107*) and its vibrational frequencies assigned with some certainty. The C—H stretching frequencies in the range 3020–3070 cm.$^{-1}$ as well as the C=C and C=N stretching frequencies at 1590–1660 cm.$^{-1}$ and near 1500 cm.$^{-1}$ are quite similar to the corresponding vibrations of benzene. The ring vibrations for pyridine are also similar to benzene but there are considerable differences in the C—H deformations, with those of pyridine occurring at lower frequencies. The important regions of the infrared spectrum for the latter two modes of vibration are near 1200 and 710 cm.$^{-1}$ and in the regions 1100–1000 and 900–650 cm.$^{-1}$. Among the stronger absorption bands are the out-of-plane C—H deformations, which depend on the number of adjacent hydrogens, *i.e.*, unsubstituted positions. Thus pyridine with five hydrogens has a band at 750 cm.$^{-1}$ which corresponds to a monosubstituted benzene (730–770 cm.$^{-1}$ and 690–710 cm.$^{-1}$). Similarly 2-, 3- and 4-picolines have bands in this region which parallel those of ortho, meta, and para disubstituted benzenes, respectively (*107*).

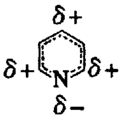
Raman spectral data also give information about the vibrational frequencies in a molecule, and although the technique for observing the weak Raman lines is rather tedious, some of the information obtained in this way cannot be derived from infrared absorption studies. Only a few pyridines have been studied (*125, 126*).

## C. CHEMICAL REACTIVITY

It has been pointed out (*19,20*) that there are many analogies in reactivity between pyridine and nitrobenzene. This parallel behavior results from similarities in electron distribution; in both molecules π electrons are removed primarily from three positions on the ring by electronegative atoms (nitrogen and oxygen). If the extent of electron withdrawal is about equal, it would be anticipated that reactions at the ring carbons of these molecules would be very similar (I-13, I-14).



(I-13)



(I-14)

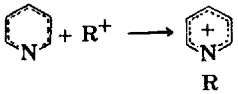
### 1. Theoretical Treatment of Aromatic Substitution Reactions

The replacement of a hydrogen atom by a substituent is the most characteristic and frequently the most important kind of reaction of aromatic systems. The questions as to the position which an entering group will take, if there are several choices, and the relative ease with which different nuclei will react with a given reagent have been fairly well worked out for the benzenoid aromatic systems.

Reagents are classified as electrophilic, nucleophilic, or radical depending on the nature of the fragment which actually attacks the aromatic nucleus. For benzene, electrophilic substitutions are most common, *i.e.*, by a positively charged fragment such as $NO_2^+$. In contrast, nucleophilic reactions of the pyridine nucleus are relatively more important, for example amination by sodamide.

This general difference between pyridine and benzene is caused by the charge distribution in pyridine (I-15); more energy is required to bring the positive reagent within bonding distance of the positively charged carbons of the nucleus. This situation is made even worse by the basic nature of the nitrogen atom. The formation of pyridinium salt by interaction with either $R^+$ or $H^+$ (usually present in electrophilic reactions) means that a full positive charge is now distributed over the atoms of the ring (I-16), making substitution even more difficult.

(I-15)

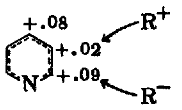


(I-16)

Although the positive charge hinders electrophilic substitution, it must, by the same mechanism, facilitate the approach of a negatively charged fragment in nucleophilic substitutions.

### *a. Static Approach*

In the static approach the aromatic molecule in the ground state is examined and the relative charge at competing positions is estimated. The assumption is made that an electrophilic reagent will attack at the position of greatest electron density and a nucleophilic reagent at the position of lowest electron density (I-17). For free radical attack, the free valence* is calculated (*13*) (I-18), and it is assumed that a free radical will attack at the position of maximum free valence.



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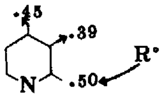


(I-18)

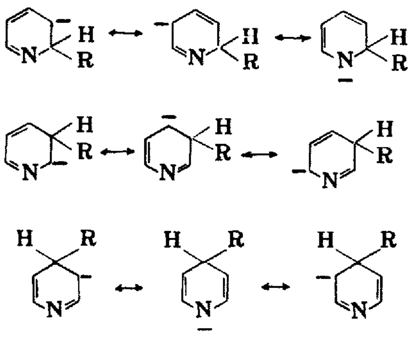
This procedure for predicting substitution frequently gives the correct answer, but in some instances it fails completely. The reason for these failures is that almost all substitutions are kinetically controlled processes in which the energy of activation is the important factor. Therefore the position which an entering substituent most frequently takes will be that one for which the energy requirement, in going from the initial state to the transition state, is the lowest. Thus in the ground state a certain position may have the greatest negative charge, but it does not necessarily follow that partial bond formation with a positive fragment will require the least energy at this position.

### b. *Activation Energy*

While the activation energies may be determined by the usual kinetic studies, generally there are insufficient data available to be of much value for making generalizations or predictions about a given aromatic substitution. When considering the possible positions for attack by a reagent on an aromatic system such as that of pyridine, it is frequently possible to decide which transition state is lowest in energy by considering the important reasonance structures for each state. Formulas I-19 give the important structures for nucleophilic attack at the 2, 3, and 4 positions of pyridine. There are three structures for each transition state; however for the 2 and

---

* Free valence is defined as the difference between the maximum bond number of a carbon atom ($N_{max.} = 3 + \sqrt{3}$) and the actual bond number, which is the sum of the bond orders for all bonds the carbon atom in question makes with other atoms; see reference 9, p. 259.



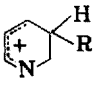
(I-19)

4 positions one structure has the negative charge on the more electronegative nitrogen atom. It may be concluded, therefore, that the transition state for nucleophilic substitution at the 2 and 4 positions is somewhat lower in energy than for the 3 position.

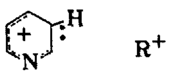
This method is useful only for comparing substitutions at different positions in the same molecule and also is of little value when there are stabilizing and destabilizing factors of uncertain magnitude in opposition.

### *c. Atom Localization Energy*

Even with detailed knowledge of the structure of a transition state, calculation of energies of activation would be difficult. However an energy described as the "atom localization energy" (*14*) can be calculated rather easily by the molecular orbital method. This quantity, as the name suggests, is the amount of energy required to localize either zero, one, or two electrons (depending on the nature of the attacking reagent) at a given position. In effect, it is the energy required to go from the initial state to a sort of a "pseudotransition state" in which the aromatic molecule is prepared to receive the reagent but yet is kept completely insulated from any interactions with the approaching reagent. A comparison of the true transition state (I-20) with the "localized state" (I-21) clearly



(I-20)



(I-21)

shows that in both there are the same number of $\pi$ electrons distributed over the same atoms. A reasonable assumption, therefore, is that the atom localization energy differs from the true energy of activation by a constant factor for a given reaction. A comparison of these energy values should accurately predict the position of substitution in a given nucleus and even allow a comparison of reactivity of different heterocyclic systems as long as the same reaction is being considered for both systems and entropy effects are reasonably constant.

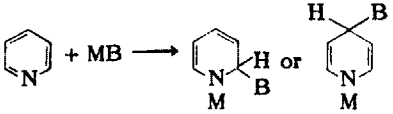
TABLE I-1. Atom Localization Energies

| Position | Pyridine | | | Pyridinium ion | | |
|---|---|---|---|---|---|---|
| | $A_e$ | $A_r$ | $A_n$ | $A_e$ | $A_r$ | $A_n$ |
| 2 | 2.62 | 2.51 | 2.40 | 2.85 | 2.53 | 2.21 |
| 3 | 2.57 | 2.54 | 2.51 | 2.62 | 2.55 | 2.48 |
| 4 | 2.69 | 2.53 | 2.36 | 2.84 | 2.55 | 2.25 |

In Table I-1 are given the values (in terms of $-\beta$ which is about 17 kcal.) calculated (*16*) for the atomic localization energies $A_e$, $A_r$, and $A_n$ for the three kinds of reagents. From this table it would be predicted that the activation energies would be lowest and hence substitution most rapid by electrophilic reagents at the 3 position, radical reagents at the 2 position, and nucleophilic reagents at the 4 position. In most electrophilic substitutions the pyridine molecule is probably present almost entirely as a pyridinium ion. To take this into account it is necessary only to recalculate the atomic localization energy, increasing the electronegativity of the nitrogen atom to account for the fact that it bears a positive charge. The last three columns in Table I-1 give values which have been calculated (*16*) in this way.

Table I-1 indicates that for radical substitution there would be little difference between the three positions and also that the value of $A_r$ is very close to that of benzene ($A_e = A_r = A_n = 2.54$).

The atomic localization energies also predict that the 4 position will be most rapidly substituted by nucleophilic reagents but that the difference between the 2 and 4 positions is rather slight. In comparing experimental results with theory, a statistical factor of two must be used to account for the fact that there are two α-positions and a single γ-position. Another complicating factor in nucleophilic substitutions is that a stable intermediate may be formed in the reaction (I-22). If this were the case, then the yield of a given product may depend on the rate at which the intermediate can decompose to yield a substituted pyridine rather than on the energy of activation for formation of the intermediate.

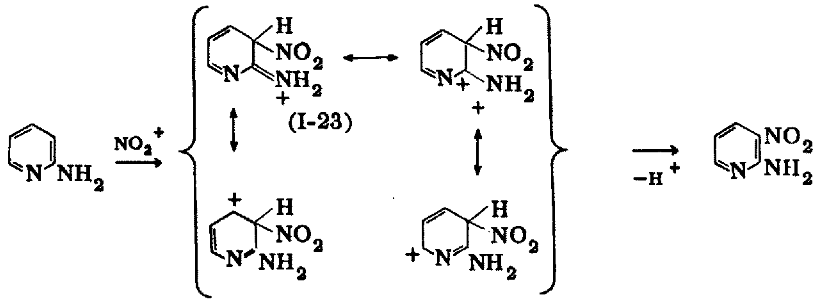


(I-22)

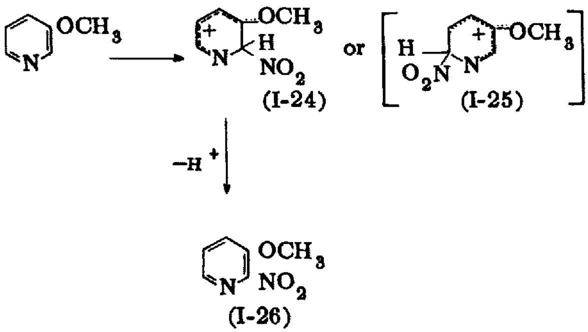
### d. *Effect of Substituents*

In the pyridine series as in other aromatic systems, the course of substitution reactions can be greatly modified by substituents already present. Substituents are classified either as electron acceptors or electron donors, and in general the former are meta directing and the latter ortho-para directing. Some substituents, such as halogens and the nitroso group, are electron acceptors in the ground state of the molecule, but in the transition state can be electron donors and hence are ortho-para directing. The basic principle previously formulated (p. 14) that the position for which the transition state is lowest in energy is the one taken predominantly by the entering group, also applies to this situation provided that the reaction is not reversible.

**(a) Electron-Donating Substituents.** An electron-donating group such as hydroxyl or amino activates the positions ortho and para to it. The extra stability of the transition state for substitution at these positions may be visualized as resulting from the contribution of resonance structures such as I-23 which are not possible if the reagent were to enter a meta position. Since the 3 and 5 positions of pyridine itself are most readily attacked by electrophilic reagents, the effect of the amino group at the 2 position is to further activate these same positions. This same situation prevails when a hydroxyl or other electron-donating group is at the 4 position; that is, the 3 and 5 positions are activated toward electrophilic substitution.



When the substituent is at the 3 position the orienting effect of the pyridine molecule and the substituent are in opposition. However, the major product is usually the one in which the new group enters position 2, indicating the predominating influence of the substituent already present. Qualitative inspection of the transition state reveals no reason why transition state I-24 should be lower in energy than I-25; molecular orbital calculations have not been applied to this situation. It is noteworthy that the electrophilic reagent does not react at the 4 position, which, although activated by the group at 3, is the least active position for pyridine itself (Table I-1); a second nitro group may be introduced at the 6 position of I-26.



**(b) Pyridine 1-Oxides.** Since the introduction of an electron-donating atom at one of the carbons of the pyridine nucleus activates certain positions to electrophilic substitution, it is not surprising that a similar effect should be observed when an oxygen atom is joined to the nitrogen atom. Pyridine 1-oxide reacts fairly