PYRIDAZINES

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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.

In order to continue to make heterocyclic chemistry as readily accessible as possible, new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

This book attempts to cover all the literature references on pyridazines from the earliest references through those references appearing in *Chemical Abstracts* to mid-1971. There is some deviation in individual chapters by the different authors. Some authors have added selected references past mid-1971. We have attempted at least to list in the tables all the pyridazines known during the period covered. There are some differences in style in the different chapters, reflecting different approaches taken by the individual authors.

We trust that this volume will prove readable and useful to those engaged in research or development on the many phases of pyridazine chemistry. We also are hopeful that reading this volume may stimulate additional research in this simple heterocyclic ring system. Reference is made in this volume to very few condensed pyridazines. This forms the basis for a companion volume in this series, namely, *Condensed Pyridazines Including Cinnolines and Phthalazines*. We hope that these two volumes will be used together and serve as a starting point for research in these areas.

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Provo, Utah
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CHAPTER I

Physical Properties of Pyridazines

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I. Introduction

A. Historical

The pyridazine ring system is a 1,2-diazine or *o*-diazabenzene. The name pyridazine was suggested by Knorr (1), however, the first substituted pyridazines were prepared in 1886 by Fischer (2), and pyridazine itself was prepared by Taüber (3) in 1895.

Pyridazines have not been investigated as thoroughly as the other isomeric diazines because they are not known to occur in nature and are not easily produced by nitrogen biochemical transformations. Since some pyridazines have been found useful as growth inhibitors or as medicinals, the literature is expanding. For additional general information and recent reviews, see Tišler and Stanovnik (4), Ramage and Landquist (5), Druey (6), Jacobs (7), and Albert (8).

B. Structure

Pyridazine has been assumed to be a planar molecule for which two Kekulé structures (**1** and **2**) may be written.

1

2

These Kekulé forms have been shown to be nonequivalent (9, 10). In fact, the crystalline structures of several substituted pyridazines (11, 12) have been determined experimentally by x-ray crystallography, and these results indicate that the bond between the two nitrogen atoms possesses mostly single-bond character. The N—N bond distances were given as 1.3539 ± 0.0068 (11) and 1.346 ± 0.007 Å (12).

Numerous reports have been made on the various methods of calculating the N—N bond distance and bond angles in pyridazine (13–19), and most are in fair agreement with the experimental data. For example, Lofthus (14) obtained a value of 1.285 Å for the N—N bond distance in pyridazine using

the semiempirical linear combination atomic orbitals (LCAO) molecular orbital method.

Since structures **1** and **2** are not equivalent, one may consider pyridazine a resonance hybrid in which the greater contribution is made by the structure containing the =N—N= configuration. The resonance energy for the more stable form has been theoretically calculated as 22 kcal/mole by Maccole (10) and between 36.8 and 39.9 kcal/mole by Davis (20).

The conjugation energy has been experimentally determined by taking the difference between the value calculated for the heat of formation or heat of combustion of pyridazine (**1**) and the experimental value. Tjebbes (21) reported a value of 12.3 kcal/mole, and Cox (22) reported a value of $\approx$10 kcal/mole. These experimental values for the conjugation energy cannot be compared with the theoretical calculations as the amounts differ by an unknown compression energy.

An interesting note is that the calculated heat of combustion of the form **1** (N—N) was given as 1038.8 kcal/mole, whereas the less favored form **2** (N=N) had a value of 1014.6 kcal/mole (21).

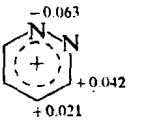
Albert (8) has suggested a framework in which the many heterocyclic compounds can be classed. First, the heterocycles are divided into heteroparaffinic, heteroethylenic, and heteroaromatic substances. The heteroaromatic substances are then subdivided on the basis of π-electron content into π-deficient heteroaromatics and π-excessive heteroaromatics. This division has been most useful in predicting reactivity of the general types.

Pyridazine is a representative of the π-deficient heteroaromatic class and has been derived from benzene by the replacement of two adjacent —CH= groups by two —N= groups. The hetero atoms attract π electrons from the ring and thus cause the other ring atoms to have partial positive charges. The nitrogen atoms are comparable to nitro groups attached to a benzene ring. In later sections the activity and properties are explained by this deficiency of π electrons. Pfleiderer (23) has also discussed the heteroaromatic character of six-membered nitrogen heterocycles in this light.

C. Theoretical Contributions to Structure

The distribution of the electrons in pyridazine has been calculated by several different methods and with various degrees of precision (8, 20, 25–55, 129).

Albert (8) has published a convenient electron distribution diagram (**3**) of pyridazine. The model was constructed from molecular orbital calculations by Brown and Coller (24) using the variable electronegativity self-consistent field (VESCF) method and uniform parameters.



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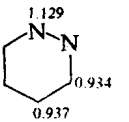
Earlier, Davies (20) had calculated charge densities in pyridazine using LCAO approximations of the molecular orbital theory. He reported two sets of values: one involving the overlap between adjacent atomic orbitals (**4**) and one without atomic orbital overlap (**5**). Good agreement with experimental data was observed. The values with overlap were similar to those reported by Chalvet and Sandorfy (25).



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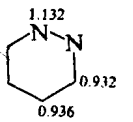

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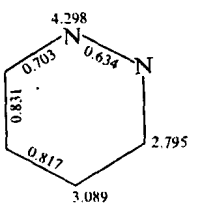
The magnitude of the charges varies somewhat with the method and parameters used. Thus the values of Brown (24) are smaller than those of Davies (20) or Chalvet and Sandorfy (25).

Other values for overpopulation and charge densities have been given by Pugmire and Grant (129) for unprotonated structure **6** and protonated structures **7** and **8**. The following diagrams give the overpopulations inside and the external charge densities (σ values).



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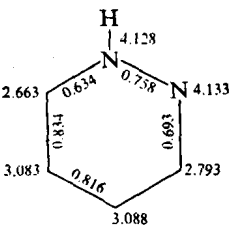

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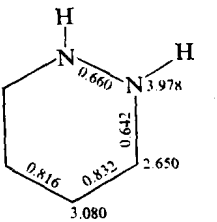

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Pyridazine has been extensively studied with respect to its electronic states, as have the other azines. A critical review has been presented by Innes, Byrne, and Ross (26). Considerable additional work has been done involving molecular orbital calculations for pyridazine using methods such as the Hückel method, EHT, CNDO, LCAO, LCAO-FE, SCMO, and so on. Yonezawa, Yamabe, and Kato (55) found that the Hückel method, which does not include direct interactions, gives an incorrect prediction for the symmetry of the energy levels of pyridazine. After comparative discussion it is concluded that the lone pairs couple with each other directly through space

as well as through bond. Many recent articles which have been often referred to and which are not discussed in other sections of this chapter are also available (27–55).

The calculation of electric dipole moments has been a problem in theoretical chemistry for a considerable period of time. Schneider (56) calculated the dipole moment for pyridazine by the vectorial sum method. Many molecular orbital calculations have also been used to determine the electric dipole moment (13, 20, 56–59). These calculated values have been shown to be in good agreement with the experimental value of 3.97 D. (62, 63).

Brown and Coller (24) made a survey of the computation of electric dipole moments of conjugated systems by the VESCF molecular orbital method. The theoretical and experimental values agreed within 0.4 D, which is notably better than most other procedures.

II. Physical Properties

A. Melting Point, Boiling Point, Density

Pyridazine, being a π-deficient heteroaromatic compound, can be compared with pyridine. At room temperature it is a colorless liquid with a pyridine-like odor and a melting point of $-8°$ C.

The boiling point has been reported as: 208° (760 mm) (3), 207.4° (762.5 mm) (20), 87° (14 mm), and 48° C (1 mm) (60). This unusually high boiling point compared to benzene (bp 80°) indicates the involvement of some type of intermolecular association. A similar situation was noted, to a lesser extent, in a comparison of benzene (bp 80°) with pyridine (bp 115°). Hückel and Jahnentz (60), using ebuliometric methods, reported that the association was due to the formation of a pyridazine dimer, while Coad, Coad, and Wilkins (61), using spectral data from ultraviolet (uv), visible, near infrared (ir), and nuclear magnetic resonance (nmr), showed a discrete dimer did not exist and concluded that the intermolecular attraction was not specific in nature and was due to the classic electrostatic forces arising from the high permanent dipole caused by the adjacent nitrogen atoms.

Some of the other physical properties of pyridazine are listed in Table I.

B. Solubility

π-Deficient nitrogen aromatic heterocycles are more readily soluble in water than their corresponding hydrocarbons because of the availability of

TABLE I. Physical Properties of Pyridazine

Density: $d_4^{20} = 1.1054$, $d_4^{22.5} = 1.1035$, $d_4^{18} = 1.107$
Index of refraction: $n_D^{22.5} = 1.52311$
Surface tension: 50.15 dynes/cm^2 at 0° C
Viscosity: $\lambda_{Abs}\ 10^5 = 2049 \pm 1.8$ at 20°C
Salts:
Hydrochloride, yellow solid, mp 161–163°C
Monopicrate, yellow solid, dec. 170–175° C
Chloroaurate, yellow solid, dec. ~110° C

the lone-pair electrons on the double-bonded nitrogen atoms to form hydrogen bonds with water. Thus pyridazine is completely miscible with water and alcohol. It is also soluble in benzene and ether but insoluble in ligroin and cyclohexane.

The solubility of pyridazines containing substituents with bondable hydrogens (i.e. —OH, —SH, —NH_2) is decreased, and it appears that this increased insolubility is caused by intermolecular hydrogen bonding between the pyridazine molecules in preference to hydrogen bonding with water or a similar solvent. Blocking of the hydrogen atoms by using methyl groups causes an increase in solubility, thus supporting the above explanation.

C. Dipole Moments

Calculations of the dipole moments have been discussed in a previous section. Dipole moments have also been determined experimentally for pyridazine and many pyridazine derivatives containing chloro, methyl, carbethoxy, acetyl, and styryl groups in different positions (56, 62, 63). The magnitudes of the dipole moments showed that the two adjacent sp^2-hybridized nitrogen atoms in the pyridazine molecule possess an electron acceptor activity greater than the nitrogen in pyridine. This is reflected in the reactivity, for example, 3-chloropyridazine is easily decomposed (64), whereas 2-chloropyridine is quite stable.

The dipole moments of 3-acetylpyridazine and 3-carbethoxypyridazine indicated the predominance of the trans configuration in which the charges on the N and O atoms are furthest removed.

D. Molecular Optical Anisotropy

Bothorel et al. (65) examined the molecular optical anisotropy (γ^2) by Rayleigh depolarization diffusion for a series of heterocycles and compared

TABLE II (62, 63) Dipole Moments

Compound	μ(D)	
	Experimental	Calculated
Pyridazine	3.95	4.00
3-Methylpyridazine	3.86	3.96
4-Methylpyridazine	4.34	4.29
3-Chloropyridazine	4.42	4.24
3,6-Dichloropyridazine	4.11	3.94
3-Styrylpyridazine	5.82	
3-Acetylpyridazine	2.48	4.89[a]
		2.19[b]
3-Carbethoxypyridazine	3.33	4.34[a]
		2.30[b]

[a] Calculated allowing for free rotation
[b] Calculated trans configuration.

it to the carcinogenic activity of the compound. The introduction of a nitrogen atom into an aromatic skeleton generally decreased the molecular optical anisotropy; benzene had a higher value than pyridine. The value was higher for pyridazine (Table III). Craig and Bothorel (66) also observed this high value.

TABLE III (65, 66) Molecular Optical Anisotropy

Compound	$\gamma^2 =$ Å6	Water solution (conc. M) γ^2	CCl_4 solution (conc. M) γ^2
Benzene	36.0	—	—
Pyridine	34.0	44 ± 1 (0.5–1)	34 ± 1 (0.5–1)
Pyridazine	38.0	46.5 ± 2 (0.15–0.35)	38 ± 1.5 (0.15–0.35)

E. Polarography

The polarographic reduction behavior of pyridazine has been reported by Vander Meer and Feil (67). According to their preliminary experimental results, pyridazine gave only one reduction wave. The addition of water caused the diffusion current to be increased. The $E_{1/2}$ values for the first wave were shown to correlate with the energy calculated for the lowest vacant π-molecular orbital by the Hückel molecular orbital approximation.

Millefiori (68) studied the polarographic reduction of pyridazine at different pH values and found that $E_{1/2}$ was pH-dependent. At pH 0–2.5 one

reduction curve was found, however, at pH 2.5–5.5 a second wave was present, and then at pH 8 the second wave disappeared. At pH 9.5 an interesting phenomenon was noted; the first wave split into two waves, which suggested that the reduction at this pH was occurring by a free-radical mechanism. The two earlier waves corresponded to an irreversible two-electron process.

$E_{1/2}$ values had been reported for pyridazine by Stone and Maki (141) and for pyridazine derivatives by Rogers et al. (150).

F. Gamma Radiolysis

Lahmani and Ivanoff (69) reported on the products obtained when pyridazine was irradiated in the liquid state at 25° C with a cobalt-60 γ-radiation source. The products, hydrogen, nitrogen, acetylene, and a polymer, indicated that the introduction of nitrogen into an aromatic ring increases the sensitivity toward ionizing radiation and that ring opening plays an important role in this irradiation. Photolysis (69) studies showed that pyridazine gives very different products compared with those obtained by γ irradiation. Lemal et al. (69a) found that 2,5-difluoro-3,6-dichloropyrazine was obtained by irradiation rearrangement of 3,6-difluoro-4,5-dichloropyridazine. The origin of the rearrangement is in the n, π^* singlet state.

III. Spectroscopic Properties

A. Ultraviolet Spectra

The theoretically calculated electronic spectra of pyridazine have been reported by many research groups using different methods and modifications (10, 29, 32, 83–93).

Experimentally determined ultraviolet spectra of pyridazine and many pyridazine derivatives have been reviewed and compared with benzene and the azabenzenes (70–73, 154). The electronic spectra of pyridazine in the vapor phase (74) or in solution (9, 61, 75) showed two bands: one strong band near 2460 Å (40,000 cm^{-1}) (ϵ_{max} 1300) composed of a series of rather widely spaced diffuse bands, and a weaker band, comparably sharp, near 3400 Å ($\sim$30,000 cm^{-1}) (ϵ_{max} 315). The difference in appearance of the two bands diminished when a solution was used. The long-wavelength absorption band (near 3400 Å) has been assigned to transitions due to the promotion of the nonbonding lone-pair electrons to an antibonding π orbital ($n \rightarrow \pi^*$). The band near 2500 Å has been assigned to transitions from the promotion of

a π-bonding electron to an antibonding π orbital ($\pi \rightarrow \pi^*$) (75, 76). The $n \rightarrow \pi^*$ transition is the better understood and the most extensively studied absorption band in heterocycles.

Pyridazine absorbs at longer wavelengths than its isomers. The reason appears to be that the lone-pair orbitals on the adjacent nitrogen atoms overlap appreciably, giving rise to a bonding and an antibonding lone-pair molecular orbital separated by approximately 12,000 cm^{-1}. The lowest energy transition ($n \rightarrow \pi^*$) takes place from the antibonding lone-pair molecular orbital.

A change in the solvent can cause a shift in the spectrum. In the pyridazine series the position of the $n \rightarrow \pi^*$ transition bands was shifted to shorter wavelengths on changing from a hydrocarbon to a hydroxylic solvent (77–80), which is referred to as a blue shift. This shift appeared to be due mainly to hydrogen bonding between the lone-pair nitrogen electrons and the hydroxylic solvent, which caused a greater stabilization of the ground state compared with the excited state of the molecule. This blue shift phenomenon has also been used to characterize the $n \rightarrow \pi^*$ transition from the $\pi \rightarrow \pi^*$ transition (77), as suggested by Kasha (81) and McConnell (82).

An association constant for hydrogen bonding has been obtained from uv data, and it has been shown to be in good agreement with the hydrogen association constant found by ir studies of pyridazine in ethanol (77). Launary and Wojtkowiak (80), by applying MacRae's theory, have used these frequency shifts due to solvent effects to obtain quantitatively a value for the excited-state dipole moment of pyridazine, 2.73 D.

The uv spectra of the sodium salt of the pyridazine anion in tetrahydrofuran has been reported to have two bands appearing at 28,450 cm^{-1} and 41,390 cm^{-1} (94).

The vacuum uv spectra of pyridazine vapors between 1550 and 2000 Å gave two strong diffuse systems and were correlated with the two $\pi \rightarrow \pi^*$ transitions of benzene observed in this spectral region (95).

Hochstrasser and Marzzacco (96, 97) reported the low-temperature electronic spectra of pyridazine at 4.2° K to have a relatively sharp band at 24,251 cm^{-1}, corresponding to the $3n\pi^* \leftarrow S_0$ transition. The higher-energy singlet–triplet transition was broadened to where it could not be identified. They also noted that pyridazine did not phosphoresce in spite of the short radiative half-times of their lowest triplet states.

Loustauneau and Nouchi (98) reported the absorption spectra of pyridazine in a crystalline solution at 77° K to have a primary band at 26,738 cm^{-1}.

The proton addition effect on the near uv and visible spectra was reported (99). The absorption spectra of the three diazines showed a two-step change owing to protonation, however, in the case of pyridazine the L_f bands were not shifted to longer wavelength.