Supersonic Jet Studies of Alkyl-Substituted Pyrazines and Pyridines. Minimum Energy Conformations and Torsional Motion

Jeffrey I. Seeman, John B. Paine, III, Henry V. Secor, Hoong-Sun Im, and E. R. Bernstein

Contribution from the Philip Morris Research Center, P.O. Box 26583, Richmond, Virginia 23261, and the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. Received December 5, 1990. Revised Manuscript Received April 11, 1991.

Abstract: Conformational preferences for methyl-, ethyl-, propyl-, and isopropyl-substituted pyrazines and pyridines are determined by mass resolved excitation spectroscopy (MRES) and MOPAC 5/PM3 semiempirical calculations. The results of these studies suggest that the conformational behavior of alkyl-substituted pyrazines and pyridines is different from that of alkyl-substituted benzenes. Based on the experimental and semiempirical theoretical results reported herein and published ab initio calculations, this difference can be attributed to a stabilizing interaction between an α-hydrogen atom of the alkyl substituent and the adjacent lone pair nonbonding electrons on the ring nitrogen atom.

I. Introduction

The azines, or azabenzences, are a valuable and fascinating series of compounds which are related to benzene through the substitution of one or more C-H fragments by nitrogen atoms. Azines form the basic structures of innumerable alkaloids and of numerous molecules of both practical and theoretical interest. Various naturally occurring and synthetic pyridines, pyrazines, and related compounds are known to possess unique and intense flavors and fragrances. A continuing, fascinating area of both basic research and practical application is an understanding of the relationship between structure and biological properties for the simple azines. Consequently, studies of the structural and electronic characteristics of azines have great significance.

Many investigations have been reported on σ- and π-electron distributions of azines, on their altered chemical reactivity compared with analogous benzenes, and on their resonance energies. In contrast, the conformational analysis of substituted azines has received scant attention. This is unfortunate, given the effect that conformation has on physical, chemical, and biological properties and processes. A similar situation existed for saturated alicyclic hydrocarbons versus saturated heterocycles; thus conformational analysis for cyclohexanes had a history of over 20 years prior to the emergence of similar systematic studies of, for example, piperidines.

Perhaps most interesting of the substituted azines are those compounds bearing substituents α to the nitrogen atom, e.g., 1.

\[ \text{N} \text{R} \text{Z} \text{CH}_3 \]

\( R = \text{alkyl, halogen, oxygen, heteroalkyl, etc.} \)

Indeed, most of the structural information to date on compounds such as 1 comes from direct comparison with and extrapolation from data on related benzenes. Because empirical force fields for heterocycles have not been available until recently, almost all the theoretical studies to date have been done using semiempirical methods.

In this paper, we report the application of mass resolved excitation spectroscopy (MRES, sometimes referred to as time-of-flight mass spectroscopy) to the conformational analysis of α-alkyl-substituted pyridines and pyrazines. Recently, MRES has been utilized to identify the minimum energy conformations of various alkyl- and hetero-substituted benzenes in the gas phase. Included in the list of substituents studied thus far are methyl, ethyl, propyl, and isopropyl.
ethyl, propyl, isopropyl, tert-butyl, vinyl, allyl, methoxy, ethoxy, hydroxymethyl, aminomethyl, hydroxy, and carboxymethoxy. The work described herein represents one of the few experimental conformational analysis studies of substituted nitrogen heteroaromatic compounds and the first such study of alkyl-substituted heterocyclic systems employing MRES.

This investigation has two goals: (1) the determination of the minimum energy conformation(s) of methyl-, ethyl-, propyl-, and isopropyl-substituted pyrazines and pyridines; (2) the examination of the torsional motion of these substituents. At the initiation of this project, we were not certain that substituted pyridines and pyrazines would possess the requisite photophysical properties (i.e., relative geometries, lifetimes, quantum yields, etc.) necessary for the successful observation of spectra. In fact, the non-rotative (interconversion and significantly crossing) rates for many 3- and 4-substituted pyridines are too fast to allow fluorescence excitation or MRES to be obtained. Mass resolved excitation spectra (MRES) of the S₁ → S₂ transition of 2-9 and a number of deuterated and polysubstituted derivatives are reported herein. In conjunction with these experimental efforts, we employ MOPAC/SPM3 calculations to provide additional information on the conformational properties of some of these molecules. The logic, techniques, and methods for the conformational analysis have been previously outlined in some detail. By using suitably substituted molecules, one can assign the geometry of the stable conformation(s) of a molecule by comparing the number of stable conformations observed with the number of stable conformations predicted for specific "hypothetical energy minima". The MRES technique provides a means to count the number of stable conformations in a manner analogous to that obtained using dynamic NMR experiments. The MRES experiment is performed in the following manner. A sample is irradiated with a laser of energy ω, resulting in the generation of the first excited singlet state (S₁ → S₂). A second photon ω₂ subsequently ionizes those molecules in S₁ (I → S₂). The ions are detected in given mass channels by time-of-flight mass spectroscopy, such that only ion current representing a chosen m/z is recorded. The energy of the ω₁ laser is scanned, and an S₁ → S₂ excitation spectrum of a mass selected species is obtained.

The unique qualities of the MRES technique, based on previous experimental results, are summarized as follows: (1) conformational interconversions of a molecule are halted by the rapid cooling which occurs in a supersonic expansion (within 1-2 mm of the expansion nozzle, the effective internal temperature of the molecules is ca. 10 K); (2) the optical absorption process occurs much more rapidly than nuclear motion; (3) each different conformation of a molecule has its own spectroscopic properties which can be accessed and distinguished through optical (S₁ → S₂) excitation; and (4) the features around the origin (00) transition of the S₁ → S₂ excitation can be analyzed to yield the number of stable conformations of the species under study. The observation of a single origin transition in this work implies that either (a) only one single stable ground state conformation exists, (b) one conformation is significantly more stable than the others, or less likely, but possible, (c) the transition energies for two origin transitions are unresolved. Observation of a number of transitions in the 00 region is a complicating result which requires the distinction between actual origin transitions and low energy vibronic transitions. One strategy which we have used successfully in the past3 has been to obtain MRES of specifically deuterated derivatives of the substrate of interest. In general, the origin

![Figure 1](image-url)
transitions of the various conformers undergo little or no relative shift upon deuteration of the compounds studied, while the various vibronic transitions do evidence much more substantial relative shifts. This difference in behavior of conformer origin transitions and vibronic transitions with respect to deuteration of the substrate arises because the zero point energy of the molecule in the two electronic states involved in the transition is the average of the (positive and negative) individual vibration isotope shifts in each state. These contributions to the isotopic zero point energy of the conformers tend to average to zero in each state as well as between states. The individual vibrational isotope shifts are built upon these averages and can, of course, be much larger. By comparing the MRES of a compound with the MRES of its deuterated derivative, conformer origin transitions can frequently be assigned as the features in the spectrum that do not shift under isotopic substitution of the substrate.

As described above, the deuterated derivatives are used in the MRES experiments to distinguish between origin transitions, which do not show isotope shifts, and vibrational transitions, which do show isotope shifts, relative to the MRES of the parent compound.

II. Results and Discussion

A. Methylpyrazine (2), 2-Methylpyridine (3), and Related Compounds. The MRES of methylpyrazine (2) and methyl-\textsubscript{d\textsubscript{3}}-pyrazine (11) are displayed in Figure 1, a and b, respectively. The origin of the \textsubscript{S\textsubscript{1}} \rightarrow \textsubscript{S\textsubscript{0}} transition of 2 occurs at 30945.3 cm\textsuperscript{-1}. Peak A at 358.2 cm\textsuperscript{-1} to higher energy of the origin is assigned as \nu\textsubscript{10a}\textsuperscript{16}. Between these two peaks (the origin and \nu\textsubscript{10b}), several weak features appear in the absorption spectrum. The MRES of 11 contains a single origin at 30937.7 cm\textsuperscript{-1} and one strong feature (peak A') at 363.0 cm\textsuperscript{-1} to the blue of the origin. The latter feature is assigned as \nu\textsubscript{10b} in this molecule.

Deuteration of the methyl group causes most of the weak features in the MRES to shift to higher energy, although a few do not shift at all. Only the first weak doublet feature (peaks B and C) displays an energy reduction upon methyl deuteration. From an expansion pressure study for both 2 and 11, however, this doublet feature can be assigned as a vibrational hot band (see Figures 2 and 3). Deuteration of the methyl rotor should yield a significant isotope effect for the features associated with this isolated substituent: if the rotor is unhindered by a potential barrier (a "free rotor"), H/D isotope substitution should reduce the level spacings by a factor of \(1/2\); if the methyl motion is both hindered and isolated from the other molecular ring modes (usually a good assumption), H/D isotope substitution should reduce the level spacings by roughly a factor of \(1/4\). As the experimentally observed shifts are so small and not systematic, these features are not associated with pure methyl rotor transitions, either hindered or free.

Deuteration of the methyl group causes most of the weak features in the MRES to shift to higher energy, although a few do not shift at all. Only the first weak doublet feature (peaks B and C) displays an energy reduction upon methyl deuteration. From an expansion pressure study for both 2 and 11, however, this doublet feature can be assigned as a vibrational hot band (see Figures 2 and 3). Deuteration of the methyl rotor should yield a significant isotope effect for the features associated with this isolated substituent: if the rotor is unhindered by a potential barrier (a "free rotor"), H/D isotope substitution should reduce the level spacings by a factor of \(1/2\); if the methyl motion is both hindered and isolated from the other molecular ring modes (usually a good assumption), H/D isotope substitution should reduce the level spacings by roughly a factor of \(1/4\). As the experimentally observed shifts are so small and not systematic, these features are not associated with pure methyl rotor transitions, either hindered or free.

The MRES of 2-methylpyridine (3) shown in Figure 4 is nearly identical with that of methylpyrazine. Neither the MRES of 2

---

(16) Herzberg, G. Molecular Spectra and Molecular Structure; Van Nostrand Reinhold: New York, 1966; Vol III, p 660. Other authors have referred to \(\nu_{10a}\) as \(\nu_1\).
N-heterocycles suggests that this barrier is considerably larger than that found for methyl-substituted benzenes. Three possible mechanisms could be responsible for this increased barrier to internal methyl rotation for 2-methyl-substituted 1,2,3, and 11 must arise from the difference in the elemental composition and symmetry of the aromatic ring and thus the difference in the symmetry and strength of the rotational potential experienced by the methyl group; replacement of a ring C-H group with a nitrogen atom and its nonbonding electrons must change the potential energy barrier for methyl torsion.

Since no methyl torsional transitions are directly observed for 2, 3, and 11, one cannot readily discern (from these data alone) whether the methyl potential barrier has increased or decreased for these heterocycles relative to the methyl potential barrier for toluene. The barrier to internal rotation of the methyl group in toluene has been established to be extremely small (ca. 10 cal/mol) by both experiment and theory.17 For 2-methylpyridine (3), the barrier to rotation has been reported to be 258 cal/mol as measured by microwave spectroscopy18 and 207 cal/mol as calculated by MINDO/3 semiempirical procedures.64 MOPAC 5/PM3 calculations indicate a barrier of 54 cal/mol for 2-methylpyridine and 17 cal/mol for methylpyrazine. The MRES results for 2 are consistent with our calculations for this molecule and with the experimental and theoretical results for 3.

The preponderance of experimental and theoretical data on barriers to internal methyl rotation for 2-methyl-substituted-1,2,3-N-heterocycles suggests that this barrier is considerably larger than that found for methyl-substituted benzenes.13 Three possible mechanisms could be responsible for this increased barrier to rotation: a reduced steric effect for the α-hydrogen(s) of the alkyl substituent when directed toward the nitrogen lone pair electrons; asymmetric π and π* interactions in the ring system;13 and an increased attractive interaction between an α-hydrogen and the nitrogen lone pair (i.e., a "hydrogen bonding" interaction). Ab initio calculations on aldehyde imines suggest that the reason for this increased barrier is an attractive interaction between an alkyl group α-hydrogen and the nitrogen in-plane lone pair electrons. In subsequent discussions of the conformational analysis of 2-alkylpyridines and 2-alkylpyrazines, an attractive interaction between the nitrogen lone pair and an α-hydrogen atom will also be invoked.

### B. Ethylpyrazine (4), 2-Ethylpyridine (5), and Related Ethyl-Substituted Heterocycles.

The MRES about the origin region of the S1 → S0 transition of 2-ethylpyridine (5) and 2-ethyl-d5-pyridine (13) are presented in Figure 5, and that of ethylpyrazine (4) is presented in Figure 6. These spectra, which are strikingly similar, can be interpreted in one of two ways: (a) each spectrum consists of one origin and a series of vibronic features built on it; or (b) each spectrum consists of two origins (the first two peaks A and B) and two series of vibronic features built on them.

We have previously used deuterated substrates to identify the 00 transitions in complex spectra, since the positions of origins do not shift relative to the lowest energy 00 transition while vibrations do have isotope effects (from 3 to 8% typically).9 In order to choose between these two spectroscopic assignments for 5, a comparison can be made between the MRES of 5 and its deuterated analogue 13 (Figure 5). The MRES of 5 and 13 show an origin peak (A) at 34 756.6 and 34 764.2 cm⁻¹, respectively, and that of (a) 2-ethylpyridine 5 and (b) 2-ethyl-d5-pyridine 13 around their 00 transition regions. The origins occur at 34 756.6 cm⁻¹ for 5 and at 34 764.2 cm⁻¹ for 13. Only one origin is observed for each molecule. See Table I for assignments and positions.

Figure 5. MRES of (a) 2-ethylpyridine (5) and (b) 2-ethyl-d5-pyridine (13) around their 00 transition regions. The origins occur at 34 756.6 cm⁻¹ for 5 and at 34 764.2 cm⁻¹ for 13. Only one origin is observed for each molecule. See Table I for assignments and positions.

### Table I. Positions for 2-Ethylpyridine and 2-Ethyl-d5-pyridine Features in the 00 Region of the S1 → S0 Transition (Figure 5)

<table>
<thead>
<tr>
<th>Feature*</th>
<th>ethylpyridine ν - μ(00), cm⁻¹</th>
<th>ethyl-d5-pyridine ν - μ(00), cm⁻¹</th>
<th>Isotope shift, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.0 (34 756.6)</td>
<td>0.0 (34 764.2)</td>
<td>0.0</td>
</tr>
<tr>
<td>B</td>
<td>59.9</td>
<td>53.8</td>
<td>10.0</td>
</tr>
<tr>
<td>C</td>
<td>117.8</td>
<td>101.4</td>
<td>13.9</td>
</tr>
</tbody>
</table>

*a through C are the notation for the observed vibronic features in the absorption spectrum of each molecule as shown in Figure 5.

### Figure 6. MRES of jet cooled ethylpyrazine around its 00 region. The origin occurs at 30 856.8 cm⁻¹ and a torsional progression of the ethyl group is built on it (see Table II for assignments and positions). Only one origin is identified in this spectrum.

![Figure 6](image-url)
ments for the first two peaks in the MRES of ethylpyrazine emission spectra arising from excitation of these features. A planar and anti-planar formation corresponds to the single stable ground state minimum observed (see Figure 6). This observation implies that the peak marked B in Figure 6 is a new origin of a second ethylpyrazine conformation excited at 30856.8 cm⁻¹ (0.0 cm⁻¹), the feature marked A in Figure 6; (b) excitation at 30856.8 cm⁻¹ (0.0 cm⁻¹), the feature marked B in Figure 6.

Additionally, a distinction between these two possible assignments for the first two peaks in the MRES of ethylpyrazine (4) (marked A and B in Figure 6) can be made based on the dispersed emission spectra arising from excitation of these features. In a dispersed emission spectrum, an excited state (S₁) feature (vibrionic or origin) is populated and emission from it is resolved. Figure 7 depicts the dispersed emission spectrum of ethylpyrazine excited at 30856.8 cm⁻¹ (0.0 cm⁻¹ transition, Figure 7a) and at 30918.6 cm⁻¹ (X₂₁ transition, Figure 7b). Both spectra show the same spacing (40 cm⁻¹) of vibrational progressions built on the excitation line. This observation implies that the peak marked B in Figure 6 is a member of the vibrational progression built on the single origin at 30856.8 cm⁻¹ (peak A of Figure 6). If the feature X₂₁ (0.0 cm⁻¹) in Figure 7b were a new origin of a second ethylpyrazine conformation, emission spectra arising from the two excitations (0₂ and X₂₁) would not be so similar. The data and assignments for the absorption spectrum are collected in Table II. Since only one origin is observed, only one stable conformation of ethylpyrazine exists in the ground state.

These results taken together strongly suggest that only a single origin (0₂) transition is observed for 2-ethylpyridine and ethylpyrazine. As shown in Figure 8, several conformations can be considered as the possible stable ground state minimum observed for both ethylpyrazine and 2-ethylpyridine: perpendicular 14, syn-gauche and anti-gauche (15 and 16, respectively), and syn-planar and anti-planar (17 and 18, respectively). For ethylbenzene, C₆ is in a plane perpendicular to the plane of the aromatic ring, i.e., r(C₆-C₅-C₆-C₅) = 90° as in 14. In these heterocycles, unlike ethylbenzene, 15 and 16 are not identical and hence have different energies; similarly, conformers 17 and 18 are not energetically degenerate. To determine which of these five conformations corresponds to the single 0₂ transition observed, we have (a) obtained the MRES of 2,6-diethylpyrazine (19a) and 2,5-diethylpyrazine (20a) and their deuterated analogues 19b and 20b and, (b) performed a series of MOPAC 5/PM3 calculations on ethylpyrazine and 2-ethylpyridine. As described above, the deuterated derivatives are used in the MRES experiments to distinguish between origin transitions, which do not show isotope shifts, and vibrational transitions, which do show isotope shifts, relative to the MRES of the parent compound.

Figure 9 shows the MRES of jet cooled 2,6-diethylpyrazine (19a) and its d₅-analogue 19b about the origin region of the S₁ ← S₀ transition. A comparison of these two spectra demonstrates that two origins are observed for each molecule, at 30949.6 (A) and 30962.6 (B) cm⁻¹ for 19a, and at 30962.6 (A') and 30975.1 (B') cm⁻¹ for 19b. Comparison of Figure 9 with Figures 5 and 6 indicates that many of the single features in the ethylpyrazine and 2-ethylpyridine spectra are doubled in the diethylpyrazine spectra, as would be expected if one conformer were present for ethylpyrazine and two conformers were present for 2,6-diethylpyrazine. The same vibrionic features found in the spectrum of ethylpyrazine also appear to be built on each of these origins. Since two origins are observed for both 19a and 19b, each of these molecules has two stable conformers in the ground state. These results are consistent with a single nonplanar conformation for

**Table II. Positions for Ethylpyrazine Features in the S₁ ← S₀ Region of the Origin (Figure 6)**

<table>
<thead>
<tr>
<th>feature</th>
<th>ν (cm⁻¹)</th>
<th>assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.0 (30856.8)</td>
<td>origin</td>
</tr>
<tr>
<td>B</td>
<td>61.8</td>
<td>T₁</td>
</tr>
<tr>
<td>C</td>
<td>116.2</td>
<td>I</td>
</tr>
<tr>
<td>D</td>
<td>122.7</td>
<td>T₀</td>
</tr>
<tr>
<td>E</td>
<td>176.0</td>
<td>I + T₀</td>
</tr>
<tr>
<td>F</td>
<td>183.1</td>
<td>T₂</td>
</tr>
<tr>
<td>G</td>
<td>207.9</td>
<td>T₁</td>
</tr>
</tbody>
</table>

* A through G are the notations of Figure 6 for the observed vibronic features in the absorption spectrum of ethylpyrazine. I and II are the notation for the undetermined vibrational motion of the molecule, and T is the notation for the torsional vibrational motion of the ethyl group (see Figure 6).

**Figure 8. Possible conformations of ethylpyridine and ethylpyrazine (R = CH₃). The assignments “syn” and “anti” refer to the relative position of the nitrogen atom and the R = CH₃ substituent.**
the ethyl group on these heterocycles; i.e., \( r(N-C_C-C_C) \neq 0 \) or \( 180^\circ \).

The MRES of 2,5-diethylpyrazine (20a) and its deuterated analogue 2,5-diethyl-\( d_2 \)-pyrazine \( 20b \) are shown in Figure 10. Only the first feature in each spectrum can be assigned as an origin transition because all the other peaks show significant relative isotope effects. Nonetheless, from the above discussion concerning the conformation of ethyl groups relative to the plane of the aromatic ring, two origins (as found for 19 and 1,4- and 1,3-diethylbenzenes) are to be expected. Note that the two origins for 2,6-diethylpyrazine (19a) are separated by 13.0 cm\(^{-1}\); this separation can be compared with the smaller separations of 4 and 10 cm\(^{-1}\) found for the two origins of 1,4-diethylbenzene and 1,3-diethylbenzene, respectively. Apparently, the two origins for 20a (and 20b) must be degenerate. The change in the comparable meta/para substitution splitting for the benzene ring system is only ca. a factor of 2.5 (10 versus 4 cm\(^{-1}\)), while it is significantly greater for the pyrazine ring system (13 versus <2 cm\(^{-1}\)). Since the meta splittings for the two ring systems are similar (10 versus 13 cm\(^{-1}\)) while the para splittings are quite different, we suggest that the coupling between the two ethyl groups is an electronic rather than a steric effect and that the ring-mediated substituent coupling in the (para) 2,5-diethylpyrazine is suppressed relative to that for 1,4-diethylbenzene.

Figure 11 illustrates the PM3-derived potential energy function for ethylpyrazine about \( \tau = r(N-C_C-C_C) \). A single energy minimum is observed at ca. \( \tau = 103^\circ \), the anti-gauche conformer. The single energy minimum at ca. 90\(^\circ \) is consistent with the above reported results on 4, 5, 13, 19, and 20. Note that for the ethyl-substituted benzenes, the energy minimum is found to be at \( \tau = 90^\circ \).

We thus conclude that the ethyl group of ethylpyrazine and 2-ethylpyridine is not truly perpendicular to the plane of the ring. The deviation of \( \tau \) by roughly 10\(^\circ\) to 15\(^\circ\) from a true perpendicular conformation (\( \tau = 90^\circ \)) for the \( C_C-C_C \) bond with respect to the plane of the ring is suggested, based on ab initio calculations as discussed above for 2-methylpyridine and methylpyrazine, to be due to a ring nitrogen lone pair electron/\( \alpha \)-hydrogen interaction. This interaction results in an ethyl \( \alpha \)-hydrogen moving toward the ring plane and thereby generating an overall anti-gauche 16 conformation for these molecules.

C. Propylpyrazine (6), 2-Propylpyridine (7), and Related Compounds. The MRES of propylpyrazine (6), its deuterated derivative propyl-\( d_2 \)-pyrazine (21), and 2-propylpyridine (7) are shown in Figures 12a, 12b and 13, respectively. The spectra of 6 and 7 are similar, with that of 7 being much weaker, presumably
due to the reduced lifetime of its $S_1$ state through relatively enhanced nonradiative processes (i.e., intersystem crossing and internal conversion).

To distinguish between origin (0) transitions and vibrations, the isotope shifts are determined in the MRES of 21 relative to 6. Only one of the peaks (marked A') among the features in Figure 12 does not show a relative isotope shift. Other features show approximately a 3% isotope effect (B, C, D, and E) or a 9% isotope effect (B' and C'). These data are collected in Table III. The two peaks A and A' (at 30782.3 and 30852.0 cm$^{-1}$, respectively) in the MRES of propylpyrazine which have no relative isotope effect ($E_A - E_{A'} = 70$ cm$^{-1}$) are assigned as origins. The peaks marked B, C, D, and E are assigned as the torsional mode vibrational progression associated with propyl group motion built on origin A, and those marked B' and C' are assigned as a similar torsional mode vibrational progression built on origin A'. The observations of two origins imply that two stable conformers exist for the ground state of propylpyrazine.

From the MRES of jet cooled 2-propylpyridine (7) (Figure 13), the number of origin transitions is not readily assignable. Since two origins are observed in the MRES of propylpyrazine, by analogy two origins would be predicted in the MRES of 2-propylpyridine. In Figure 13, the peaks at 34665.6 cm$^{-1}$ (A) and at 34703.1 cm$^{-1}$ (A') are assigned as origins for two different conformations. Based on this assignment, other peaks are assigned as shown in Table IV.

To define the conformational properties of propyl-substituted aromatic compounds, e.g., propylpyrazine and 2-propylpyridine, two torsional degrees of freedom must be assigned, $\gamma_1$ and $\gamma_2$ as shown in Figure 14a. By analogy with the benzene $\rightarrow$ toluene $\rightarrow$ ethylbenzene $\rightarrow$ propylbenzene series, and by analogy with the results found for ethylepyrazine and 2-ethylpyridine discussed above, we assign $\gamma_1 = \gamma(N-C_{prop}-C_{prop}) \approx 105^\circ$ for 6, 7, and 21 (cf. 22-24 in Figure 14a). The conformations depicting $\gamma_2$ are 22-24 and are also shown in Figure 14a.

The experimental results for propylpyrazine (6) and 2-propylpyridine (7) should be related to those found for 3-methylpropylbenzene (28); however, two origins are found experimentally in the MRES of 6 and 7 while three origins representing the conformations 25-27 (cf. Figure 14b) are observed for 3-methylpropylbenzene. The situation for 6 and 7 is somewhat different from that for 28 because the asymmetric perturbation of the latter molecule is a methyl substituent while it is the ring nitrogen(s) in the former two substrates.

The following three possibilities arise for the two assigned origins in the spectra of 6 and 7: (a) one gauche (23 or 24) and the anti conformation 22 are observed; (b) anti 22 and both gauche 23 and 24 (coincidentally degenerate in energy) are observed; or (c) only both gauche (23 and 24) conformations are observed.

To aid in the conformational assignments, we examine a substrate having an additional substituent which enhances the ring's asymmetry. For example, while propylbenzene evidences two $\tilde{0}_0^\circ$ transitions (one each for the anti and the gauche conformers), 3-methylpropylbenzene shows three $\tilde{0}_0^\circ$ transitions (one for the anti 25 and one each for the gauche 26 and 27 conformers). Relative to propylpyrazine, 2-methyl-6-propylpyrazine (29) fits this strategy, in that both the methyl group and the ring nitrogens are asymmetrically disposed relative to the propyl group. Hence, 2-methyl-6-propylpyrazine was prepared and its MRES obtained. In principle, the added methyl group should break any degeneracy between the two assigned origins. This is indeed the case as shown in Table IV.
Table IV. Positions for 2-Propylpyridine Features in the 00 Region of the S1 – S0 Transition (Figure 13)

<table>
<thead>
<tr>
<th>Feature</th>
<th>( \nu - \nu(00) )</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.0 (34 665.6)</td>
<td>origin I</td>
</tr>
<tr>
<td>B</td>
<td>52.7</td>
<td>1'</td>
</tr>
<tr>
<td>C</td>
<td>105.6</td>
<td>2'</td>
</tr>
<tr>
<td>D</td>
<td>137.0</td>
<td>3'</td>
</tr>
<tr>
<td>A'</td>
<td>0.0 (34 703.1)</td>
<td>origin II</td>
</tr>
<tr>
<td>B'</td>
<td>51.3</td>
<td>1'</td>
</tr>
<tr>
<td>C'</td>
<td>104.9</td>
<td>2'</td>
</tr>
<tr>
<td>D'</td>
<td>139.4</td>
<td>3'</td>
</tr>
</tbody>
</table>

* A through C and I, II are the notations for the observed vibronic features in one conformer of 2-propylpyridine; A' through C' and I', II' are notations for the observed vibronic features in the other conformer of this molecule (see Figure 13). \(^{1}\) 1 through 3 and \(^{1}\) through 3' are the notations for the undetermined vibrational motion of the molecule for each stable conformation (see Figure 13).

in the energy of the 00 transitions of the gauche conformers.

The origin region of the S1 – S0 of 2-methyl-6-propylpyrazine (29) is shown in Figure 15. The MRES of 6, 7, and 29 are very similar, as indicated by the letters A–D and A'–C' identifying the various transitions shown in Figures 12 and 15. Thus the spectrum of 29 as presented in Figure 15 evidences only two origins, A and B (at 30 984.3 and 31 059.8 cm\(^{-1}\), respectively), with the same vibrational progressions built on them. Several other weak features due to methyl substitution can be observed in the spectrum as well. Since only two origins can be assigned, excluding the possibility of degenerate origin transitions, the data suggest that 29 has only two stable conformers in the ground state.

To distinguish between the two other possibilities given above is not easy, especially as previous results in the benzene series and chemical intuition do not particularly favor either of them over the other. MOPAC 5/PM3 calculations performed on propylpyrazine are summarized in Figure 16. Three energy minima are located, namely, the anti conformation 22 and the syn-gauche 23 and the anti-gauche 24 (Figure 14a, \( Z = N \)). The relative energies of these three conformations are shown in Figure 16 along with the values of \( \tau_1 \) and \( \tau_2 \) for these conformations. The calculations suggest three stable conformations of similar energy, with the anti conformer lower in energy (by about 2 kcal/mol) than the two gauche conformers. Pending additional experimental and/or theoretical studies, we can only speculate as to the conformational preferences of propylpyrazines and 2-propylpyridine;
Alkyl-Substituted Pyrazines and Pyridines

Figure 17. MRES of jet cooled (a) isopropylpyrazine (8) and (b) 2-isopropylpyridine (9) around their origin transition region.

Figure 18. MRES of the 00 region of (S1 → S0) for jet cooled 2-methyl-6-isopropylpyrazine (30). The single intense feature is assigned as the origin and occurs at 31,027.4 cm⁻¹.

however, results for benzene analogues and MOPAC calculations suggest that one of the stable observed conformers should be the anti 22.

D. Isopropylpyrazine (8), 2-Isopropylpyridine (9), and 2-Methyl-6-isopropylpyrazine (30). The MRES of jet cooled isopropylpyrazine (8) and 2-isopropylpyridine (9) are depicted in Figure 17, a and b, respectively. Only one intense origin is observed (at 30,792.7 and 34,757.8 cm⁻¹, respectively) in each spectrum. Thus, only one stable conformer exists for these molecules in the ground state.

To probe the conformations of the isopropylazines further, 2-methyl-6-isopropylpyrazine (30) is examined and Figure 18 displays its MRES around the origin region of the S1 → S0 transition. The MRES of 30 contains only one origin with several weak features to high energy built on it. This observation implies that only one stable conformer exists for 30 in the ground state.

The deformation of isopropylbenzene for which the α-hydrogen is in the plane of the ring has been determined to be the stable minimum energy conformation. From this result, one of the two conformers 31 or 32 can be considered as the single stable conformation of isopropylpyrazine. Because of the demonstrated asymmetric interaction of the substituent with the ring, these two conformers do not have the same conformational energy. Conformer 31 for which the α-hydrogen is toward the nitrogen atom and nearly in the plane of the ring is suggested to be the minimum energy conformer based on the foregoing results for methyl, ethyl, and propyl pyridines and pyrazines and MOPAC 5/PM3 calculations20 for isopropylpyrazine (see Figure 19).

The current literature consensus49,21 for these molecules appears to be that \( \tau = (N-C_{iso}-C_{alpha}-H) \) = 0° or 180°; that is, Hα lies in the plane of the aromatic ring, for a 2-isopropyl-3-unsubstituted pyridine. Note, however, that one report of a gauche (\( \tau = 60° \)) 2-isopropyl-3-unsubstituted pyridine has appeared.22 This latter study employs lanthanide shift reagents and NMR techniques. The relationship between ground state conformation and complexation (which may alter the observed geometry) with a lanthanide shift reagent requires a Curtin-Hammett/Winstein-Holness analysis21,22 not presented for the lanthanide shift studies.22

(20) (a) In contrast to the MOPAC 5/PM3 results, MINDO/3 semi-empirical all-valence electron calculations have indicated20 that the most stable conformation of 2-isopropylpyridine is \( \tau = (N-C_{iso}-C_{alpha}-H) = 180° \). (b) See also: Tower, J. L.; Spangler, L. H.; Pratt, D. W. J. Am. Chem. Soc. 1988, 110, 1615.
III. Summary and Conclusions

This report presents one of the few experimental studies of the conformations of alkyl-substituted pyridines and pyrazines. The effect of the nitrogen atom on the conformational properties of 1-N-2-substituted azines can be evaluated and characterized through comparison with the isostructurally substituted benzene species.

The stable conformations of alkyl-substituted pyrazine and pyridine systems are determined through the use of supersonic jet mass resolved and fluorescence excitation spectroscopies and semiempirical (MOPAC 5/PM3) calculations. Under the conditions of the laser jet experiments, supersonic transitions are observed for the stable ground state conformations of these alkyl-substituted azines. Using specifically (positionally and isotopically) substituted derivatives and structural "logic," one can assign the geometry of these stable conformations. The individual stable conformations of these heterocycles are quite different from those of the comparable alkyl-substituted benzenes. One can draw the following four conclusions from the experimental and theoretical result reported above.

1. The motion of the methyl group in 2-methylpyridine and methylpyrazine is highly hindered in both $S_0$ and $S_1$. Since methyl group behavior for toluene in both electronic states is nearly that of a free rotor, the potential surface for methyl motion in the azines and the benzenes is very different.

2. Spectroscopic studies yield single unique conformations (origins) for both 2-ethylpyridine and ethylpyrazine but yield two conformations (origins) for both 2,6-diethylpyridine and 2,6-diethylpyrazine. Based on semiempirical calculations, the ethyl substituents in these compounds are suggested to be somewhat tilted from the perpendicular with an $\alpha$-hydrogen atom nearly in the plane of the aromatic ring [i.e., $\tau(N-C-C-C-H) = \pm 17^\circ$]. This is to be contrasted with the reported minimum energy structure for ethylbenzene [i.e., $\tau(C(\text{ortho})-C(p)-C-H) = 30^\circ$].

3. Two spectroscopic origins are observed for each propyl-substituted azine studied (2-propylpyridine, propylpyrazine, and the corresponding 2-methyl-6-propylazines). Excluding the possibility of degenerate origin transitions, two conformers are assigned for each of these molecules: one of the possible gauche conformers and the (most stable) anti conformer. For these compounds, a tilted configuration of the propyl group is suggested in which $\tau(N-C-C-C-H) = 17^\circ$. This result is in contrast to those of 3-methyl-1-propylbenzene for which three conformations are assigned: two gauche and one anti.

4. Only a single stable conformation is characterized for the isopropyl group in 2-isopropylpyridine and isopropylpyrazine. The assigned structure has the $\alpha$-hydrogen atom of the isopropyl group lying in the plane of the aromatic ring pointing toward the ring nitrogen atom [i.e., $\tau(N-C-C-C-H) = 0^\circ$]. The combined available experimental and theoretical data for these molecules suggest that a relatively strong and important interaction exists between the $\alpha$-hydrogen of the alkyl substituent and the ring nitrogen lone pair of electrons. This suggest is reasonable: the nitrogen atom has a large negative partial charge, especially on the basis of Bader's integrated populations, and the $\alpha$-hydrogens (i.e., C$_2$H$_5$) have a substantial positive partial charge.

IV. Experimental Procedures

A. Spectroscopy and Calculations. All the spectra were obtained using a two-color, two-photon ionization with time-of-flight mass detection. The MRES chamber is described elsewhere. A pulsed molecular jet was employed using an R.M. Jordan pulsed valve. All the samples were placed inside the valve head and heated to about 60 °C to increase their concentration in the beam. In all cases, helium was used as the carrier gas at roughly 50 psi. Two Nd$^{3+}$/YAG lasers were used to produce excitation and ionization photons. The doubled output of DCM dye was employed for the $\pi^*\rightarrow\pi$ excitation of alkyl-substituted pyrazines, and the doubled output of R610 dye was employed for the $\pi^*\rightarrow\pi$ excitation of alkyl-substituted pyridines. For both systems, the doubled output of R590 dye mixed with the residual 1.064 µm Nd$^{3+}$/YAG beam was used to provide the ionization photon.

Dispersed emission (DE) experiments were performed in a fluorescence excitation (FE) chamber described previously. Expansion of the gas into the chamber was achieved with a CW nozzle with 100 µm pinhole. 7/4 optics were used to collect and focus the emission onto the slits of an f/8 2051 GCA McPherson monochromator. Spectra were recorded with a 1200 groove/mm, 1.0 µm blazed grating in the third order.

Stable geometries of various alkyl-substituted pyrazine and pyridine systems were calculated using the MOPAC 5 programs, which have two Hamiltonians available for structure calculations: PM3 and AM1. The PM3 Hamiltonian has been augmented and improved for heteroatom (N, O, etc.) calculations. All calculational results reported in this work are based on the PM3 Hamiltonian. Input data for the calculations were obtained from the crystal structures of pyrazine$^{28}$ and normal alkanes$^{29}$ and the gas phase structure of pyridine.$^{23}$

2-Methylpyridine, 2-ethylpyridine, 2-propylpyridine, methylpyrazine, and ethylpyrazine were purchased from Aldrich. 2-Isopropylpyridine and isopropylpyrazine were obtained from Wiley Chemical Co. Grignard reagents and diethylzinc were obtained from Aldrich.

B. Synthesis of Substituted Pyridines and Pyrazines. General Approach and Methods. Crucial to the spectroscopic studies which follow is the use of a number of substituted azines chosen to satisfy certain symmetry and conformational requirements. In addition, a number of these compounds had to be prepared having specific isotopic substitution patterns. Because of the essential role of these substrates, and because they are not commercially available, it is useful to discuss the general strategies used to synthesize these compounds. Although several of the required substrates have been previously reported in the literature, in some cases the compounds were not expediently prepared or had been obtained as side products in, for example, mechanistic studies. The following discussion will focus attention on either new synthetic routes or improvements in previously reported methodologies.

Equation 1 illustrates the procedure by which four substrates, meth-
**Scheme I**

\[
\begin{align*}
&\text{Na} \\
&\begin{array}{c}
\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} \\
\end{array}
\end{align*}
\]

**Scheme II**

\[
\begin{align*}
&\text{Na} \\
&\begin{array}{c}
\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} \\
\end{array}
\end{align*}
\]

**Scheme 11**

\[
\begin{align*}
&\text{Na} \\
&\begin{array}{c}
\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} \\
\end{array}
\end{align*}
\]

Wolff–Kishner reduction of 2,5-diacylpyrazine\(^{34,35}\) proceeds without incident to the desired 2,5-diethylypyrazine (20a) as displayed in eq 3. Analogously, 2,5-diethylpyrazine-d\(_2\) (20b) was prepared from 15 using hydrazine, NaOD, diethylene glycol, and D\(_2\)O employing toluene as the azotropic solvent. The reaction is performed in one pot but in multiple steps: the first series served to exchange the solvent and the hydrazine protons; base was then added to effect the exchange of the methyl protons, followed by disproportionation of the fully deuterated hydrazine in the presence of the resulting deuterated solvents after the exchanges with D\(_2\)O were complete, and the toluene had been distilled off. Interestingly, the reaction conditions caused exchange of the ring protons as well.

2-Methyl-6-proplypyrazine (29) can be prepared by two methods (Scheme I), both of which involve tedious workups. 6-Methyl-2-pyrazinylmethy1thiullium (34) reacts with iodoethane to give a complex mixture from which 29 is isolated. Alternatively, 34 is allowed to react with N,N-dimethylacetamide to afford, upon workup, easily purifiable 2-methyl-6-(2-oxopropyl)pyrazine (35). The Wolff–Kishner reduction of 35 could provide 29 directly; however, this strategy is complicated by the accompanying of an unanticipated rearrangement, described in full detail elsewhere,\(^{33}\) in which 29 is formed along with 2-methyl-6-iso-propylpyrazine (30) (see Scheme II). Centrifugal chromatography can be employed to isolate sufficient quantities of 29 for our spectroscopic studies.

2-Methyl-6-isopropylpyrazine (30) can be prepared by a literature procedure\(^{36}\) involving the reaction of acetone with methylpyrazine and sodium metal in absolute diethyl ether as shown in Scheme II. Elaborate workup is needed to remove unreacted starting material, acetone self-condensation products including methyl oxide, and the isomeric 2-methyl-5-isopropylpyrazine (36) which is also formed. Because pyrazine-2,5-diacetylpyrazine\(^{29}\) was prepared from propyl-d\(_2\) bromide (5.0 g, 38.5 mmol) and magnesium in toluene under a balloon of dry hydrogen (1 atm), the dipropyl isomer was prepared in 95% yield with a final product of C-13C NMR (CDCl\(_3\)) \(8 13.76 (C-3'), 22.68 (C-2'), 37.46 (C-1'), 142.11, 111, 54.\)

**Propyl-d\(_2\)-pyrazine (21)**. This preparation was carried out in the same manner as for 6 using chloropyrazine (5.4 g, 38.3 mmol), DpppNiCl\(_2\) (330 mg, 1.16 mmol), methyl-2-dimethyl-ammonium (1.2 g, 18.0 mmol), and ether (150 mmol). The propyl-d\(_2\)-pyrazine \((30\text{ mg})\) was isolated by distillation: \(bp 60\degree C (100\text{ mmHg})\).

**2-Methyl-d\(_2\)-pyrazine (11)**. This preparation was carried out in the same manner as for 6 using chloropyrazine (30.4 g, 38.3 mmol), DpppNiCl\(_2\) (330 mg, 0.61 mmol), methyl-d\(_2\)-ammonium (1.1 g, 31.6 mmol), and ether (150 mmol). The 2-methyl-d\(_2\)-pyrazine \((30\text{ mg})\) was isolated by distillation: \(bp 60\degree C (100\text{ mmHg})\).

**Diethyl-d\(_2\)-pyrazine (20a)**. 5,5-Diethylpyrazine was prepared from ethyldenedipersulfonic acid (mp 199-201\degree C) and anhydrous hydrazine (1 M, 100 mmol) in diethyl ether. The ethereal phases were combined and dried (Na\(_2\)SO\(_4\)), and the aqueous layer was separated and extracted with 6 N HCl (36 mL). The acidic extract was concentrated to a volume of 2 mL, and the mixture was passed through a 3 cm Vigreux column to afford 4.21 g (90.6%).

**2,5-Diethylpyrazine (20b)**. 5,5-Diethylpyrazine \((30\text{ mg})\) was prepared from the bis-hydrazine \((2.82 \text{ g})\) using chloropyrazine (4.40 g, 38.5 mmol) and hydrazine (5.9 mL, 176 mmol) in ethanol (100 mmol). The mixture was stirred for 2.5 h, and then the mixture was diluted slowly by diethyl ether. The resulting clear clear colorless oil (4.21 g) was added through a 5 cm Vigreux column to afford 4.21 g (90.6%); \(bp 35\degree C (0.3 \text{ mmHg})\).

**2,5-Diethylpyrazine (20a)**. 2,5-Diethylpyrazine \((30\text{ mg})\) was prepared from the bis-hydrazine \((2.82 \text{ g})\) using chloropyrazine (9.54 g, 83.1 mmol), DpppNiCl\(_2\) (330 mg, 0.61 mmol), methyl-d\(_2\)-ammonium (1.1 g, 31.6 mmol), and ether (150 mmol). The 2,5-diethyl-d\(_2\)-pyrazine \((30\text{ mg})\) was isolated by distillation: \(bp 60\degree C (100\text{ mmHg})\).
temperature. Water (50 mL) was then added. On being allowed to stand the ether evaporated. The product was extracted with hexane, and the solvent was removed in vacuo to give a crude oil (10.22 g). Upon Kugelrohr distillation, 9.17 g of volatile material was isolated. This was subjected to column chromatography in two lots [Silica Gel 60, 10% (v/v) acetone in n-hexane]. The fractions of appropriate polarity (corresponding to the middle spot of the three principal spots observed by TLC) were combined, and the contained product subjected to spinning-band distillation (water aspirator vacuum). The resulting 29 (the most volatile remaining component) was 100% pure by GC: $^1$H NMR (CDCl$_3$ $\delta$ 0.99 (3 H, t, $J$ = 7.4 Hz), 1.76 (2 H, sextet, $J$ = 7.5 Hz), 2.54 (3 H, s), 2.75 (2 H, t, $J$ = 7.7 Hz), 8.25 (1 H, s), 8.38 (1 H, s); $^{13}$C NMR (CDCl$_3$ at 76.92) $\delta$ 13.79 (CH$_2$CH$_2$CH$_3$), 21.54 (2-CH$_3$), 22.96 (CH$_2$-CH$_2$CH$_3$), 37.48 (CH$_2$CH$_2$CH$_3$), 140.96 (5), 141.48 (3), 152.60 (2), 161.25 (6). This material had the same GC retention time as the byproduct from the Woff–Kishner reduction of 1-(6-methyl-2-pyrazinyl)-2-propanone (35), confirming the relative isomeric structure.

2-Ethyl-d$_5$-pyridine (13). Magnesium turnings (2.31 g, 95 mg-atoms) were warmed with iodine (ca. 1 mg) under N$_2$ in a 50 mL three-necked round bottom flask until purple fumes were visible. The apparatus was then cooled under N$_2$ to room temperature, and anhydrous diethyl ether (20 mL) added. Ethyl-d$_5$-bromide (10 g, 87.7 mmol) was placed in an addition funnel atop the condenser, and ca. 1 g was added to start the reaction. The reaction mixture was warmed gently, and the reaction, once initiated, was maintained by the gradual addition of the remaining halide. After the addition had been completed, the dark cloudy mixture was refluxed an additional 15 min. The resulting Grignard solution was added by syringe to a cooled (–5 OC) solution of 2-bromopyridine (11.55 g, 73.0 mmol) in anhydrous diethyl ether (80 mL) containing Dppp-NiCl$_2$ (0.425 g, 0.78 mmol). An exothermic reaction occurred, and the temperature was brought to and maintained at 30 OC with external cooling. The mixture was stirred at room temperature for 2.5 h, then treated with 5% HCl (75 mL), to give a pH of 1. The aqueous phase was rinsed 3X with ether (discarded), then basified with K$_2$CO$_3$ (7.5 g), then 50% KOH. The product was extracted into ether (3X), dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was distilled through a 5 cm Vigreux column, bp 57 OC (32 Torr), to give 6.60 g (80.6%) of 2-ethyl-d$_5$-pyridine (13).

Registry No. 2, 109-08-0; 3, 109-06-8; 4, 13925-00-3; 5, 100-71-0; 6, 18138-03-9; 7, 622-39-9; 8, 29460-90-0; 9, 644-98-4; 11, 139607-04-8; 13, 139607-05-9; 19a, 13067-27-1; 19b, 139607-06-0; 20a, 13238-84-1; 20b, 139607-07-1; 21, 139607-08-2; 29, 29444-46-0; 30, 25451-74-0; 33, 39248-49-2; 33 dihydrazine, 139607-09-3; D$_2$, 7782-39-0; chloropyrazine, 14508-49-7; 2,6-dichloropyrazine, 4774-13-5; 2,6-dimethylpyrazine, 108-50-9.