THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DIVISION OF ARTS AND HUMANITIES

UNPRECEDENTED AZINE FORMATION VIA PROTON TAUTOMERISM OF ISOQUINOLYL-1-HYDRAZONES

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ABSTRACT

Previously reported structures of isoquinolyl-1-hydrazones were subjected to electronic structure calculations using density functional theory (DFT). For six targeted compounds, calculations were applied to multiple conformations for both azine and hydrazone tautomers in order to determine the relative energies of the possible conformations. Then calculations were performed using the hybrid functional B3LYP and a 6-31G**++ basis set using the program Jaguar. The lowest gas phase Gibbs free energy conformation was a function of substitution. In some instances, an azine tautomer was the lowest energy conformation, and in others it was a hydrazone. Compounds which showed a significant calculated preference for either the azine or hydrazone tautomer were synthesized and characterized by x-ray crystallography. All compounds synthesized thus far demonstrate a preference for the azine tautomer, showing mixed agreement with the calculated preference.

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Chapter 1

Introduction to Azines and Hydrazones

Potential Use of Hydrazones as Reported by Francis H. Case

In a previous investigation conducted by Francis H. Case of Temple University, a series of isoquinolyl-1-hydrazones were synthesized to investigate their potential use as spectrophotometric reagents for trace metal determination of transition-metal ions.[1] These hydrazone derivatives all formed colored chelates, a coordination compound in which a metal atom or ion is bound to a ligand at two or more points on the ligand, resulting in the formation of a heterocyclic ring containing the metal atom. The hydrazone derivatives formed metal chelates with iron (II), cobalt (II), nickel (II), and copper (II). Depending on the ligation between compound and metal ion, different color chelates were formed. However, the colors of the chelates were similar to those of their free ligands. Case also reported that the hydrazones, in their uncomplexed form, undergo a pronounced color change from intense yellow to red upon acidification. These isoquinolyl-1-hydrazones derivatives are proposed to have a potential use as indicators for pH and pKa measurements of strong acids.[1]

As part of a Case's study of the chelation properties of chromogenic groups, the hydrazone derivatives were prepared via the condensation of isoquinolyl-1-hydrazone with several heterocyclic 2-carboxaldehydes (Figure 1-1).[1] Although heterocyclic aldehydes typically show an overwhelming preference for *E*-hydrazone stereoisomers, both *Z*- and *E*-stereoisomers once formed are capable of isolation. However, no structural analyses for the isoquinolyl-1-hydrazones despite being reported as *Z*- stereoisomers.

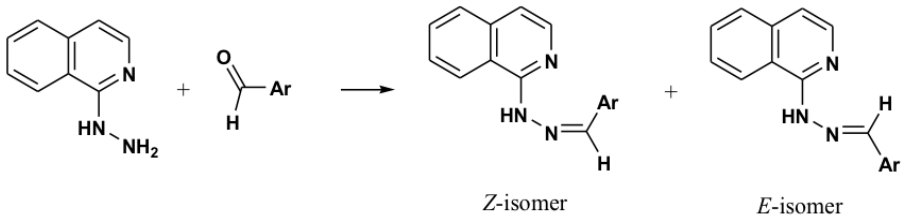


Figure 1-1. Structure of *E* and *Z* Hydrazone Stereoisomers

Richard Butler and Seán Johnston have investigated heterocyclic hydrazone isomers and their isomerization to either the *E* or *Z* configuration. Their results do not support Case's reported *Z*-hydrazone structures. Butler and Johnston demonstrated by analysis of the N-H signal in the ^{1}H NMR spectra that when the acyl substituent R was small (H or Me), the hydrazone heavily favored the *E*-stereoisomer. It was also noted that the *Z*-stereoisomer could not be isolated, but it was detected through thin layer chromatography and ^{1}H NMR.[2] Butler and Johnson also reported that when the R substituent was large (Ph), the hydrazone predominantly favored the *Z*-stereoisomer. The N-H signal in the ^{1}H NMR spectra also indicated intramolecular hydrogen bonding was present in the *Z*-isomer.[2] It was hypothesized that these intramolecular hydrogen bonds stabilized *Z*-stereoisomers since such hydrogen bonds were not detected in any of the *E*-stereoisomers formed.

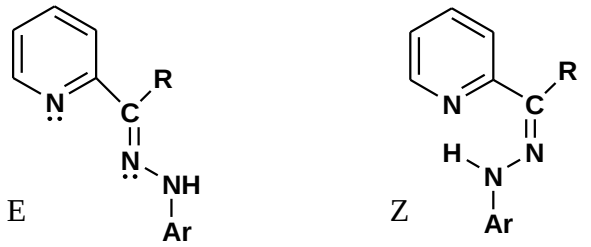
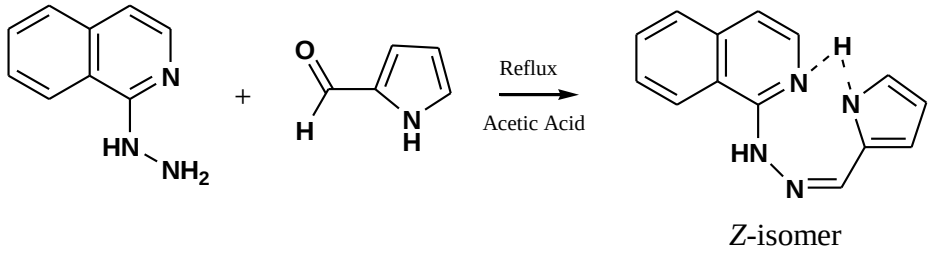


Figure 1-2. *E* and *Z* Hydrazone Derivatives Characterized by Butler and Johnston

Further Investigation into the Chemical Properties of the Hydrazone Derivatives

An investigation of the structural possibilities of the isoquinolyl-1-hydrazones originally

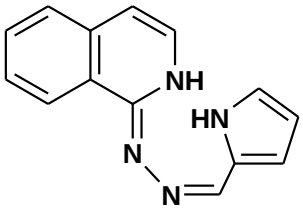
synthesized by Case was initiated by Grant Krow of Temple University. The 2-pyrryl-isoquinolyl-1-hydrazone was targeted for synthesis and characterization because it seemed possible that the hydrogen bonding might lead to a preference for the *Z*-hydrazone.



Z-isomer

Figure 1-3. Synthesis of *Z*-Hydrazone Stereoisomer

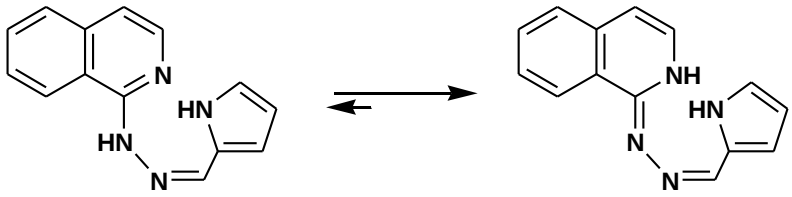
The synthesis of the 2-pyrryl-isoquinolyl-1-hydrazone was repeated according to Case's procedure, and a crystalline solid with a melting point of 200-201^{o}C was similarly produced in reasonable yield (63 %). However, preliminary x-ray analysis suggested that the product was not a hydrazone, but was a *Z*-amidrazoneazine, from this point on simply referred to as "azine."



Z-amidrazoneazine

Figure 1-4. Structure of *Z*-Hydrazone, or Azine

If correct, this structure requires an unprecedented proton tautomerism of the initially formed *Z*-hydrazone to the azine. This tautomerism suggests a potential equilibrium between these two structures that significantly favors the azine isomer in the solid structure.



Z-hydrazone *Z*-amidrazoneazine

Figure 1-5. Potential Equilibrium Between Azine and Hydrazone

Introduction to Azines and Hydrazones

While azines and hydrazones are related tautomerically to one another, they differ significantly in chemical behavior. To directly synthesize azines, typically a condensation reaction between two equivalents of either aldehyde or ketone with one equivalent of hydrazone is required.[16] Azines have often been used as precursor molecules when synthesizing hydrazones and diazo compounds.[12] This family of compounds has received increasing attention in recent years because of their potential use as antibacterial, antifungal, and antitumor agents.[9, 10] Azines are also highly reactive because of the pseudo-diene structure present in their structure. The diene part of azines is in fact a hetero-diene, and behaves much differently than ordinary dienes. The high electronegativity of nitrogen to carbon results in higher electron density around the nitrogen than around the carbon. Therefore, the lone pair of electrons on the nitrogen can act as a sigma donor.[5]

Hydrazones have been known to exist in equilibrium with numerous molecules. For example, hydrazones are able to tautomerize with azo and azoenamine compounds.[6, 11] For example, in the azo-hydrazone equilibrium shown below (Figure 1-6), the compound predominantly exists as the hydrazone isomer.

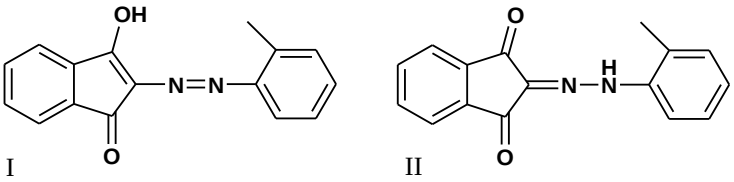


Figure 1-6. Azo (**I**) and Hydrazone (**II**) Tautomers

The process of shifting from azo **I** to hydrazone **II** is exothermic, indicating a highly favorable reaction.[13] This preference was determined by analyzing the products obtained from a Japp-Kligemann coupling reaction, a reaction used to synthesize hydrazones from either β-keto-acids, β-keto-esters, or aryl diazonium salts. The experimental and spectra data from the coupling reaction indicates that the hydrazone form is more stable than the azotautomeric form.[7]

A previous study investigating the tautomerism of a series of 1,3,4-thiadiazolylhydrazones, using ultraviolet spectroscopy, concluded that two types of compounds were formed from this isomerization: hydrazones and thiadiazolinone azines. In this example, the compounds formed have been shown to exist as true hydrazones (structure **I**, Figure 1-7), rather than the thiadiazolinone azines (**II**).[14] However, there was no insight provided as to why the hydrazone isomer **I** was favored. There was also no indication that the hydrazone and azine compounds could be in equilibrium with one another; rather, they were simply two different, stable products of a tautomeric reaction.

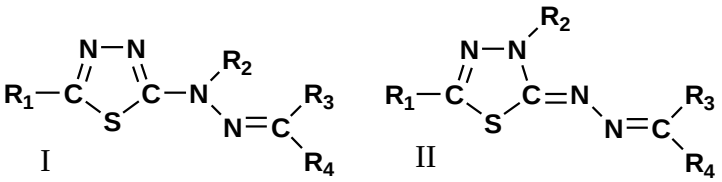


Figure 1-7. 1,3,4,-Thiadiazolylhydrazone (**I**) and Thiadiazolinone azine (**II**)

Additionally, some compounds have been reported to undergo prototropic tautomerism, forming either an azine or hydrazone derivative. More specifically, quantum chemical calculations supported by ^{1}H NMR, ^{13}C NMR, and X-ray studies, show that 4-(1-alkylbenzimidazol-2-ylazo)-2-pyrazoline-5-ones (Figure 1-8) mainly exist in the condensed phase as unusual ketoazine tautomers **I** of high polarity, while the ketohydrazone tautomer **II**, stabilized by intramolecular hydrogen bonds, predomiantes in the gas phase.[15] Again, there was no indication that the azine and hydrazone existed in equilibrium with one another in a given phase.

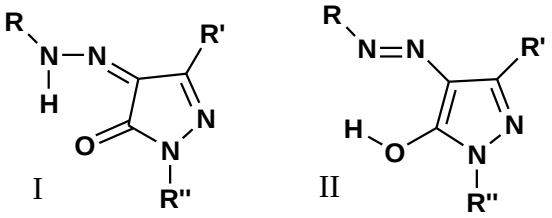


Figure 1-8. Ketohydrazone (**I**) and Ketoazine (**II**) Tautomers

While multiple studies report hydrazones as the favorable isomer in tautomeric reactions, further investigation of the reported isoquinolyl-1-hydrazone derivatives introduced by Case was pursued in order to investigate the existence of a potential azine-hydrazone equilibrium and the role of intramolecular hydrogen bonding using electronic structure calculations for gas phase structures and x-ray crystallographic analysis of the solid state structures.

Density Functional Theory Gas Phase Calculations

Electronic structure calculations using density functional theory (DFT) were applied to six compounds originally reported to be hydrazones shown below. All DFT calculations were completed by Dr. Ann Schmiedekamp and her research assistant, Clayton Wang.

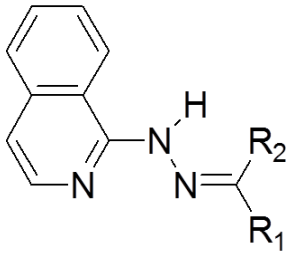


Figure 1-9. General Structure of Isoquinolyl-1-Hydrazone Derivatives

Compound	R_1	R_2
I	H	2-pyridyl
II	H	1-isoquinolyl
III	H	3-isoquinolyl
IV	H	2-pyrryl
V	phenyl	2-pyridyl
VI	methyl	2-pyridyl

Table 1-1. Substituents on Each Isoquinolyl-1-Hydrazone Derivative

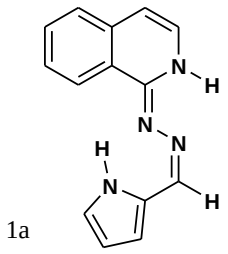
For each compound, calculations were applied to multiple conformations (typically five) for both the azine and hydrazone tautomers in order to determine the relative energies of the possible conformations. The calculations were performed using the hybrid functional B3LYP and a 6-31G**++ basis set using the program Jaguar.[3] The diffuse functions on the basis set were chosen to provide better modeling of the hydrogen bonding interactions.[4]

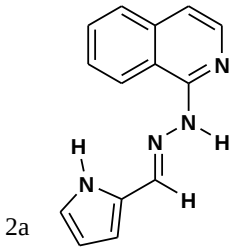
The structures of each conformation were geometrically optimized until the forces on all the atoms were minimized. The frequencies of the normal modes of vibration were calculated with the available Hessian matrix, and all frequencies were positive which showed a minimum stationary (optimized) state. From this, the relative Gibbs free energy in kcal of each conformation was computed at T = 298 K. These energies are given Table 1-2 below. The electronic energy of this optimized conformation was then compared among the possible

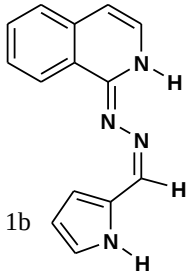
conformations, and it allowed a ranking of the structures according to energy. The lowest Gibbs free energy conformation should be the favored structure in the gas phase. The lowest energy conformation was assigned a value of 0 kcal (highlighted in **red**). Any energy difference less than 2 kcal (highlighted in **blue**) should be considered equivalent due to the accuracy of the calculation. All "1" structures are azines and all "2" structures are hydrazones. All calculations shown in Table 1-2 were completed by Schmiedekamp and Wang.

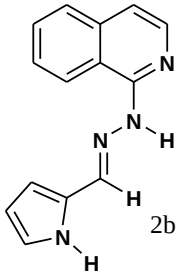
	Azines					Hydrazones				
	1a	**1b**	**1c**	**1d**	**1e**	**2a**	**2b**	**2c**	**2d**	**2e**
I	3.09	11.00	**0.00**	7.34	8.47	13.46	9.26	5.95	3.34	4.23
II	9.60	14.15	**1.74**	6.70	na	2.44	9.51	**0.00**	3.76	na
III	7.97	12.61	**0.00**	7.19	7.45	2.05	3.79	2.87	8.86	2.87
IV	5.40	**0.08**	**0.00**	6.78	7.31	8.57	4.77	4.34	5.94	9.21
V	**1.86**	8.38	**1.98**	7.86	2.12	2.29	**0.00**	2.73	**1.04**	**0.97**
VI	3.74	10.01	**0.00**	6.26	3.06	9.42	5.42	3.57	**0.35**	3.71

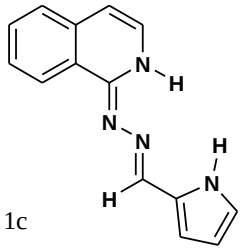
Table 1-2. Calculated Gibbs Free Energy for each Compound Conformation

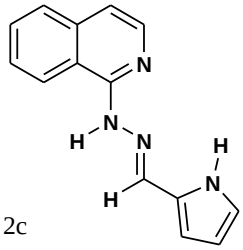


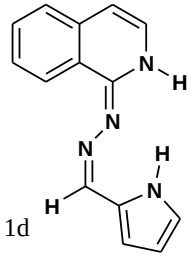


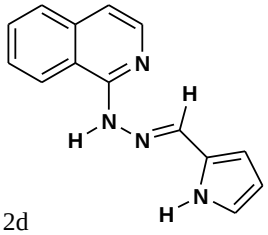


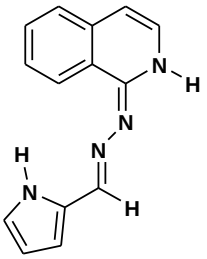












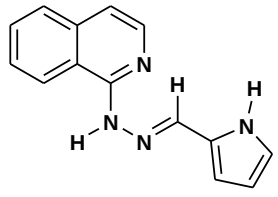


Figure 1-10. Compound Configurations for Compound **IV**

As shown in Table 1-2, the calculated Gibbs free energies for the azine and hydrazone conformations predict that compounds **I, III**, and **IV** are significantly favored as the azine tautomers. Calculations for **IV** show two azine conformations to be nearly identical. Conversely, calculations for compounds **II** and **V** suggest that they slightly favor the hydrazone tautomers. Although calculations for both compounds show a hydrazone tautomer as a minimum energy conformation, at least one azine conformation is within 2 kcal for each. Compound **VI** shows that the azine hydrazone tautomers are essentially the same energy.

Based on the calculated energies, compounds **I**, **IV**, and **V** were initially targeted for synthesis to evaluate if gas phase calculations correctly predict solid state structures.

Chapter 2

Experimental Procedure and Results

General Synthesis of Compounds

The synthesis of compounds **I**, **II**, **IV**, and **V** was accomplished using the identical procedure previously reported by Case, in order to reduce variability between the results.[1] Compounds were synthesized by reacting 0.003 M quantities of aldehyde or ketone and 1-hydrazino-isoquinoline in 20 mL of ethanol at reflux for 3 hours in the presence of three drops of acetic acid. The solvent was then removed by evaporation and the residue crystallized from the appropriate reported solvent. Results are summarized below in Table 2.1.

Compound	Yield	mp, °C	Lit. mp	Crystallization solvent
I	63.8%	176-180	180	benzene
II	86.0%	194-195	195	methanol
IV	67.4%	200-202	200	ethanol
V	38.6%	167-170	172	ethanol

Table 2-1. Summary of Results from Synthesized Compounds

X-Ray Crystallographic Structures and Experimental Bond Lengths

Solid state structures can be inferred by the location of the N-H bond. The azine tautomer may show a hydrogen bonded to the isoquinolyl nitrogen; for the hydrazone, the hydrogen is bonded to the nitrogen adjacent to the quinoline ring. Additionally, C-N bond lengths in these two structures should vary. Pi bonds between carbon and nitrogen should result in significantly shorter bond lengths compared to carbon-nitrogen single bonds.

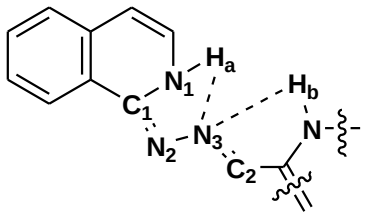


Figure 2-1. Intramolecular Hydrogen Bonding for Compounds **I**, **IV**, and **V**

	Compound I	**Compound IV**	**Compound V**
N_1-C_1	1.366	1.370	1.364
C_1-N_2	1.322	1.324	1.315
N_3-C_2	1.284	1.285	1.296
N_3-H_a	2.270	2.109	2.210
N_3-H_b	na	2.673	na

Table 2-2. Summary of Experimental Bond Lengths (Å)

Compound I

As seen in Table 2-2, compound **I** is exhibiting characteristics that would only be seen in the azine tautomer. The bond length between N_1-C_1 is 1.366 Å, which indicates a single bond. The bond between C_1-N_2, 1.322 Å, indicates that this bond has pi character. The bond between N_3-C_2, 1.284 Å, also shows pi bond character. The bonds between both C_1-N_2 and N_3-C_2 are much shorter than the bond seen in N_1-C_1, which supports the bond pattern expected for the azine tautomer.

From Table 2-2, it is also seen that there is a hydrogen bonded to the isoquinolyl nitrogen N_1. The distance between N_3-H_a is 2.270 Å, indicating only a weak interaction. No hydrogen is bonded to N_2 as expected in a hydrazone tautomer. These observations are all consistent to the assignment of the azine tautomer.

As seen in Table 1-2, the lowest energy conformation for compound **I** indicates a preference for the azine tautomer, in the **lc** configuration. Fortunately, the solid state structure of compound **I** agrees with the predicted structure of azine conformer, validating the gas phase DFT calculation methods applied in this case.

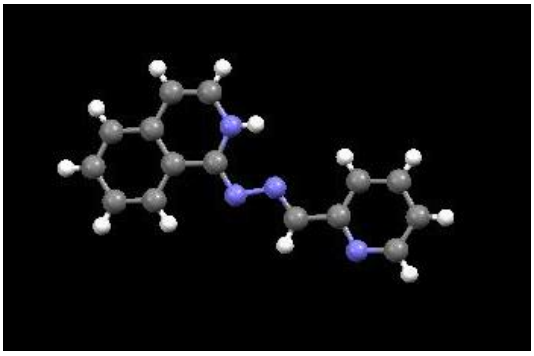


Figure 2-2. X-ray Crystallographic Structure of Compound **I**

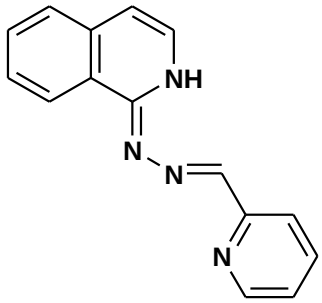


Figure 2-3. Structure of Compound **I**

Compound IV

Similar to compound **I**, compound **IV** exhibited characteristics predicted for the azine tautomer. As seen in Table 2-2, the bond length between N_1-C_1 is 1.370 Å, which indicates a single bond. The bond between C_1-N_2, 1.324 Å, indicates that this bond has pi character. The bond between N_3-C_2, 1.285 Å, also suggests pi bond character. The bonds between both C_1-N_2

and N_3-C_2 are much shorter than the bond seen in N_1-C_1, which supports the bond expected for the azine tautomer.

From Table 2-2, it is also seen that there is a hydrogen bonded to the isoquinolyl nitrogen (N_1). The bond between N_3-H_a is 2.109 Å. This hydrogen bonding pattern is only seen in the azine tautomer.

The solid state structure of compound **IV** also agrees with the predicted structure of azine conformer **1c**, validating the gas phase DFT calculation methods applied in this case.

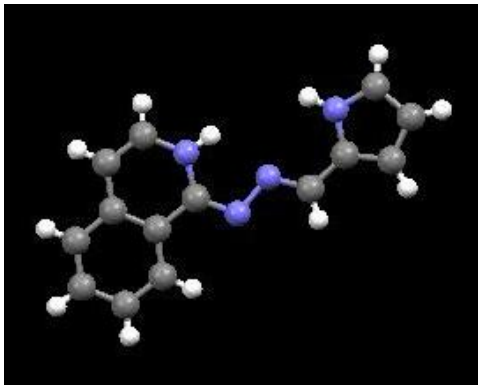


Figure 2-4. X-ray Crystallographic Structure of Compound **IV**

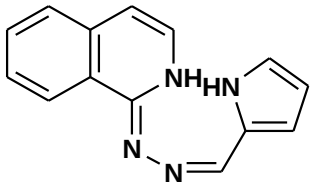


Figure 2-5. Structure of Compound **IV**

Compound V

The same patterns seen in compounds **I** and **IV** are seen in compound **V**. As evidenced in Table 2-2, compound **V** exhibits bonding predicted for the azine tautomer. The bond length between N_1-C_1 is 1.364 Å, which indicates a single bond. The bond between C_1-N_2, 1.315 Å,

suggests that this bond has pi character. The bond between N_3-C_2, 1.296 Å, also shows pi bond character. The bonds between both C_1-N_2 and N_3-C_2 are much shorter than the bond seen in N_1-C_1, which supports the bond patterning expected for the azine tautomer

From Table 2-2, it is also seen that there is a hydrogen bonded to the isoquinolyl nitrogen. The bond between N_3-H_a is 2.210 Å. This hydrogen bonding pattern is only seen in the azine tautomer.

Unlike compounds **I** and **IV**, the experimental results did not agree for compound **V** with the solid state structures predicted by gas phase DFT calculations performed by Schmiedekamp and Wang. Calculations predicted compound **V** to favor the hydrazone tautomer. Upon X-ray crystallographic analysis, compound **V** favors the azine tautomer. Although the calculations did not correctly predict the solid state structure, the X-ray structure was calculated to be less than 2 kcal/mole higher than the hydrazone tautomer which is within the standard error limits of the calculation.

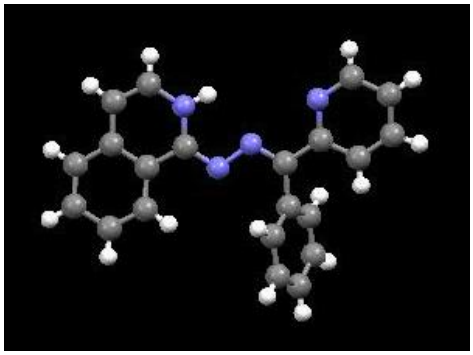


Figure 2-6. X-ray Crystallographic Structure of Compound **V**

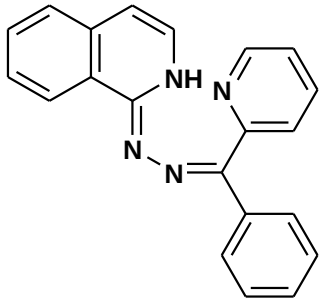


Figure 2-7. Structure of Compound **V**

Compound II

Preliminary X-ray data for compound **II** suggests that it favors the azine tautomer, the **1c** conformation. Files are not yet available to determine bond lengths. According to the DFT calculations, compound **II** was predicted to favor the hydrazone tautomer. However, the **1c** azine tautomer is possible within the 2 kcal/mol standard error limits of the calculation. The bond lengths within this molecule will be further investigated in subsequent experiments, once the files are available.

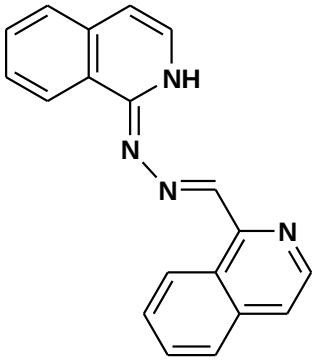


Figure 2-8. Preliminary Structure of Compound **II**

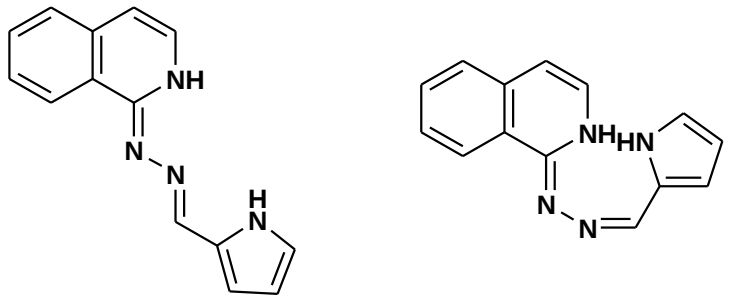
Chapter 3

Discussion

Significance of Results

All synthesized compounds (**I**, **IV**, and **V**) exhibit similar bond lengths that are indicative of the azine tautomer. The bond between N_1-C_1 in all compounds is a single bond; whereas, the bonds in C_1-N_2 and N_2-C_2 are double bonds. Additionally, there is a hydrogen (H_a) that is bonded to the isoquinolyl nitrogen (N_1), which clearly discredits the hydrazone tautomer. If any of these compounds favored the hydrazone tautomer, the bonding patterns would be significantly different. The bonds between N_1-C_1 and N_3-C_2 would both be double bonds, which would be evidenced by much smaller bond lengths. Furthermore, the bond between C_1-N_2 would not exhibit pi bond character. As for intramolecular hydrogen bonding in the hydrazone, the hydrogen would be bonded to the nitrogen adjacent to the quinoline ring (N_2).

While many sources report hydrazones to be the favored tautomer in an equilibrium, data for the Case compounds contradicts these results stated in previous publications; in this hydrazone-azine equilibrium, the azine is the favored tautomer. X-ray data clearly shows that the initial *Z*-hydrazone structure reported by Case was incorrect. Additionally, the isoquinolyl-1-hydrazone derivatives exhibited intramolecular hydrogen bonding (N_1-H-N_3), similar to that reported by Butler and Johnston. However, the isoquinolyl-1-hydrazone derivatives all favored the azine regardless of substituent size. Interestingly, all four azines synthesized favor the S-Cis conformation over the S-Trans in the solid state. All four of the synthesized azines are non-planar molecules, a topic that will be further investigated in subsequent experiments.



S-Trans S-Cis

Figure 3-1. S-Trans and S-Cis configuration of Compound **IV**

One might expect that the azine would not be the favored isomer because the aromaticity has been disrupted. However, the intramolecular hydrogen bonding within the molecule may be responsible for stabilizing the azine tautomer.

Compound **V** was the only synthesized compound whose structure did not agreed with the DFT calculations. The DFT calculations predicted that compounds **II** and **V** would favor the hydrazone tautomer, although for Compounds **II** and **V** an azine tautomer was possible within the limits of the calculations. It may be that the calculations for the azine tautomer did not consider that the S-Cis conformation may have been more stable than the S-Trans. Since all calculations for the azine structures were performed only using S-Trans conformations, this may account for the lack of consistent predictability.

Future Plans

To further test both the preference of these compounds for azine structures and the reliability of the DFT calculation results, an additional compound (**III**) has been synthesized and characterized by NMR.

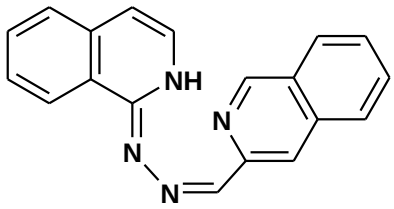


Figure 3-2. Compound **III** (structure not known)

Efforts to produce an x-ray-compatible crystal for Compound **III** are on-going.

In addition to Compound **III**, Compound **VI** (Figure 3-2) has been targeted for synthesis and characterization. This compound was initially passed over for evaluation since the calculations predicted the azine and hydrazone structures to be energetically equivalent. However, **VI** will provide an additional data point as to the preference of the azine or hydrazone structure in this series.

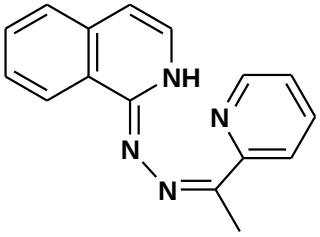


Figure 3-3. Compound **VI** (structure not known)

Chapter 4

Experimental

Instrumentations

For all compounds, ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 Spectrometer or Bruker Avance III 500 spectrometer at Temple University. Chemical shifts were measured relative to the residual solvent resonance for ^{1}H and ^{13}C NMR. X-ray crystallographic data was obtained from the Department of Chemistry, Temple University. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected.

1-Hydrazinoisoquinoline

A mixture of 2.4 g of isocarbostyryl and 12 mL of phosphorous oxychloride was heated at reflux for 2 hours. The excess of oxychloride was then removed by an aspirator on the steam bath. The residue was treated with an excess of a cold aqueous solution of sodium carbonate and extracted with ether. The residue, after removal of the dried ether (Na_2SO_4) was heated at reflux for 2 hours with a mixture of 10 mL of hydrazine (95%) and 15 mL of absolute ethanol. On standing over night, the 1-hydrazinoisoquinoline separated in large crystals. Crystallization from benzene yielded approximately 1.6 g (61%) of product melting at 179 °C.

Isoquinolyl-1-azine

Mixtures of 0.003 M quantities of aldehyde or ketone and 1-hydrazinoisoquinoline in 20 mL of absolute ethanol were refluxed for 3 hours in the presence of 3 drops of acetic acid. The

solvent was then removed by evaporation and the residue crystallized from the solvent indicated in Table 4-1.

Compound	Yield	mp, °C	Lit. mp	Crystallization solvent
I	63.8%	176-180	180	benzene
II	86.0%	194-195	195	methanol
IV	67.4%	200-202	200	ethanol
V	38.6%	167-170	172	ethanol

Table 4-1. Summary of Results

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- Studied the chemical properties of the ortho-substituted 3-Cyclohexyl-2-aryl-1,3-thiazolindin-4-ones derivatives.
- Analyzed the experiments of various gases pertaining to reactions with finery cinders (partially oxidized iron) in order to provide an in-depth comparison of the contributions from Joseph Priestley, William Cruickshank, and James Woodhouse to the discovery of carbon monoxide.

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- Phi Kappa Phi Honors Society

Professional Presentations

13th Annual Younger Chemists Committee Poster Session, February 2013
Abington College Undergraduate Research Activities Fall Colloquium, October 2012
244th American Chemical Society National Meeting and Exposition, August 2012
43rd Mid-Atlantic Regional Meeting, June 2012
Abington College Undergraduate Research Activities Poster Fair, April 2011 and 2012

Scholarships and Awards

Taub Family Endowment, 2012
A.M. Kulp Elementary School Scholarship Fund, 2010
Dean's List, Academic Year 2010, 2011, 2012, and Fall 2013