GAS PHASE STUDIES OF ORGANIC AND BIOORGANIC SPECIES BY MASS SPECTROMETRY

by

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ABSTRACT OF THE DISSERTATION

Gas Phase Studies of Organic and Bioorganic Species

by Mass Spectrometry

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The research performed in this dissertation involves mass spectrometry method development in studying the kinetic and thermodynamic properties of organic and bioorganic species in the gas phase.

Chapter 2 covers the background of gas phase studies of the Formamidopyrimidine Glycosylase (Fpg) excision mechanism, either by exocyclic cleaving the glycosidic C1-N bond or by endocyclic ring-opening of the ribose or deoxyribose sugar. A brief introduction of Fpg and experimental methods for measuring the gas phase acidities and proton affinities of Fpg substrates are explained. The acidity of Fpg substrates is measured and analyzed if it correlates to the Fpg excision rates. Computational data indicates the weak correlation between substrate acidity and Fpg excision rates, where the results support the endocyclic

mechanism.

In Chapter 3, the measurement of the deprotonation of a series of benzhydryl cations has been completed both experimentally and computationally. These studies provide the experimental basicity values of diarylcarbene for the first attempt. The deprotonation pathways, including whether the singlet or triplet carbene is formed, are examined computationally. Assessment of the protonation energy of these diarylcarbenes is of fundamental importance.

In Chapter 4, a series of silane hydrides' gas phase kinetic hydricity studies are performed. The understanding of hydricity is crucial for a series of silane hydrides in organic synthesis, hydrogen activation, and photoelectrocatalysis because hydride reactions are involved in many of these processes. We find that the gas phase hydricity trends are different from that in the solution, which reveals the solvent effect. H/D studies and calculations are performed. We find that trends of hydricity in the gas phase are different from that in solution, explaining the impact of the solvents. Computational studies and further experiments, including H/D studies, are used to explore the structure and the reactivity of studied substrates. The reported studies in this chapter also help with systematically understanding nucleophilicity and electrophilicity without the effect of the solvent.

In Chapter 5, a series of positive and negative charge-tagged *N*-heterocyclic carbene (NHC) are synthesized to study the NHC catalyzed *Umpolung* reactions, such as the

benzoin condensation and Stetter reaction in the gas phase. A simpler and easier synthetic route is designed to obtain the thiazolylidene catalysts with charge tags, which allows us to monitor NHC-catalyzed reactions by mass spectrometry. Computational studies are performed for choosing the appropriate substrate for NHC catalyzed *Umpolung* reactions.

Last, in Chapter 6, fluorenylidene and diphenyl carbene's proton basicity are computed and measured. According to the bracketing result, the experimental basicity of 2,7-dinitrofluorenylidene shows a discrepancy with DFT calculated basicity. The possible alternative deprotonation pathways of fluorenylidene are computed and analyzed by DFT calculation.

DEDICATION

To my parents and my husband, for their love

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Chapter 1. Introduction

1.1 Overview

Mass spectrometry is a powerful tool in gas phase ion chemistry reactions as well as in molecule identification and quantification coupled with other separation methods[1-5]. Mass spectrometry can also be utilized to monitor the ion-molecule reactions in the gas phase because of the vacuous environment. We investigated the intrinsic properties of both biological molecules such as damaged nucleobase, and organic molecules such as diarylcarbenes in the gas phase.

1.1.1 Damaged nucleobase and DNA repair

The consistency of nucleotides sequence DNA double helix chains is the key to maintain the health of living organisms. DNA is under constant assault by endogenous and exogenous agents. Thus some of the nucleobases may be damaged during the duplication and transcription process [6]. One of the most famous DNA damage is DNA methylation, and the involved damaged base including 5-methylcytosine, 5-hydroxymethylcytosin, 5-formylsytosine, and 5-carboxylsutosine [7]. These damaged bases may cause base pair mismatch that consequently leads to variation in genetic information, which would potentially threaten proper cell function. In order to avoid this mismatch during the duplication and transcription process, living organism has developed a mechanism “base excision repair (BER)” to correct the DNA damage.

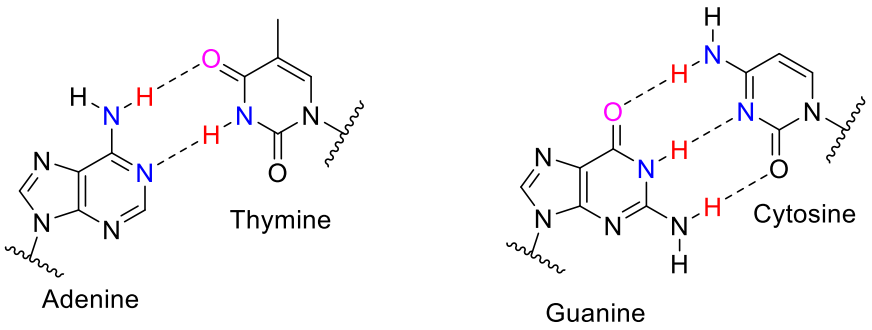

Figure 1-1 Base paired by hydrogen bonds in DNA

The BER was firstly discovered in 1974 by Thomas Lindahl, and BER is the most frequent used DNA repair mechanism[8]. Lindahl found one enzyme called DNA glycosylase which can cleave the glycosidic bond between the nucleobase and deoxyribose. (**Figure 1-2**) Then the AP endonuclease will process the resulting abasic site and cleaves DNA's base-free sugar-phosphate residue. Last, the DNA polymerase will fill the resulting gap by ligase[9].

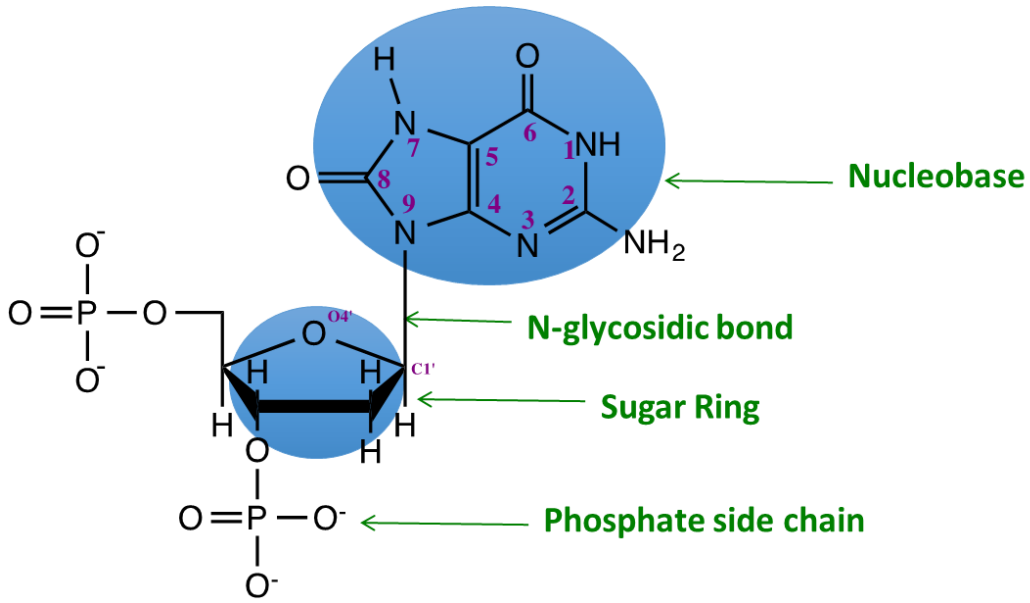

Figure 1-2 Nucleotide structure

As mentioned above, the DNA glycosylases can catalyze the hydrolysis of the N-glycosidic bond; some of the mono-functional DNA glycosylases can only remove the damaged base, other bifunctional DNA glycosylase can also cleave the DNA 3' of the abasic site [10]. Different orgasms have their own set of enzymes; **Table 1-1** shows the common DNA glycosylases found in human and bacterial and their substrates.

Table 1-1. Human and *E. coli* DNA glycosylases and its substrates[10]

DNA Glycoslases	**Substrates**	**Location**
AlkA: 3-Methyladenine-DNA glycosylase II	3- and 7-methylpurines, 7-ethylpurines, 3-meA,O_2-methylpyrimidines	E.coli
MutY: MutY-DNA glycosylase	An opposite 8-oxoG	E.coli
Fpg: FaPy-DNA glycosylase	Oxidized and ring-opened purines (8-oxoG)	E.coli
UNG: Uracil-DNA glycosylase	Uracil	Human
SMUG1: SMUG DNA glycosylase	Uracil, 5-hydroxymethyl-U	Human

Herein, in this paper Chapter 2, the Fpg (FaPy-DNA glycosylase) substrates are studied in the gas phase; both gas phase proton affinities and acidities were measured by FT-ICR bracketing experiment. The experimental results revealed the Fpg excision mechanism.

1.1.2 Diarylcarbenes and its protonation

Carbenes are neutral compounds with a formula of :CXY, the carbon atom is divalent

and consists of six electrons in the valence shell. Thus carbenes are treated as reactive intermediates. Here, the studied reactive carbenes in Chapter 3 are diarylcarbenes; the basic structure of diarylcarbenes is shown in **Figure 1-3**.

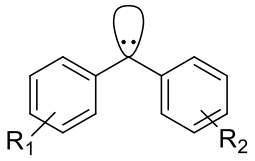

Figure 1-3 The basic structure of diarylcarbenes.

Several scientists studied the actual structure of the simplest diarylcarbene—diphenylcarbene **1-1**. Singlet diphenylcarbene would undergo rearrangement to form a fluorene **1-3**. Rice and Michaelsen proposed a mechanism that the electron would distribute on the phenyl rings and then the fluorene **1-3** will form[11,12]. (**Figure 1-4**)

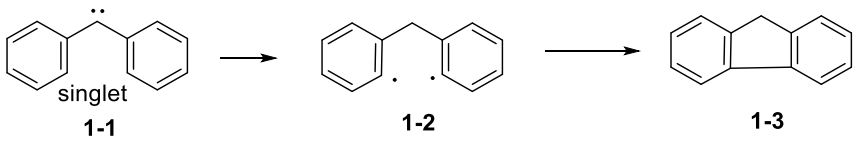

Figure 1-4 Rich and Michaelsen proposed diphenylcarbene rearrangement mechanism

Later in 1970, Myers and Joines proposed the carbon that connects to the phenyl rings would migrate first to form the intermediate **1-4**, then the fluorene **1-3** will form [13]. **(Figure 1-5**)

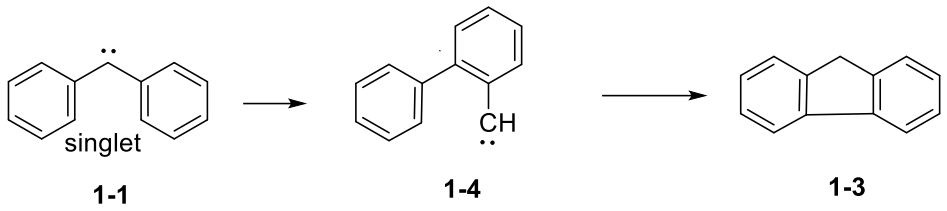

Figure 1-5 Myers and Joines proposed diphenylcarbene rearrangement mechanism

The protonation of the diarylcarbenes is an approach to generate the trivalent carbocations. Kirmse found that the photolysis of diphenyldiazomethane **1-5** in methanol would result in benzhydryl methyl ether **1-7**. (**Figure 1.6**) The reaction pathway proposed the benzhydryl cation **1-6** is an intermediate generated in the reaction of diphenylcarbene **1-1** protonation[14,15].

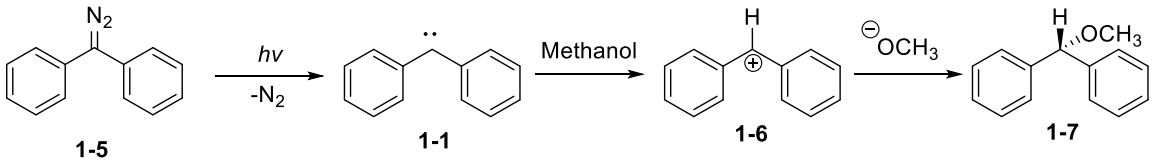

Figure 1-6 Photolysis of diphenyldiazomethane in methanol pathway

In Chapter 3, the protonation process of a series of diarylcarbenes will be studied both experimentally and computationally. Furthermore, in Chapter 4, the kinetic rate constant of reaction between protonated diarylcarbenes— benzhydryl cations and silanes will be measured in the gas phase. The measured rate constants also reveal the hydricity of silane hydrides.

1.1.3 Charge-Handled N-Heterocyclic Carbene and *Umpolung* reactions

Unlike traditional carbenes, N-heterocyclic carbenes (NHC) demonstrated higher

stability[16,17]. Neutral NHC are widely used as organic catalysts[18-27] and ligands of transition metal catalysts such as Grubbs second-generation Ru catalyst[28].

In most cases, the NHC catalyzed reaction involves the step of NHC nucleophilically attacking the carbonyl group. Followed by a proton transfer, the carbon on the carbene center converted to a nucleophilic carbon. This polarity inversion is called *Umpolung*[29]. This NHC catalyzed benzoin condensation reaction is a typical *Umpolung* reaction. In 1958, Breslow firstly proposed the mechanism of benzoin condensation reaction[30]. (**Figure 1-7**)

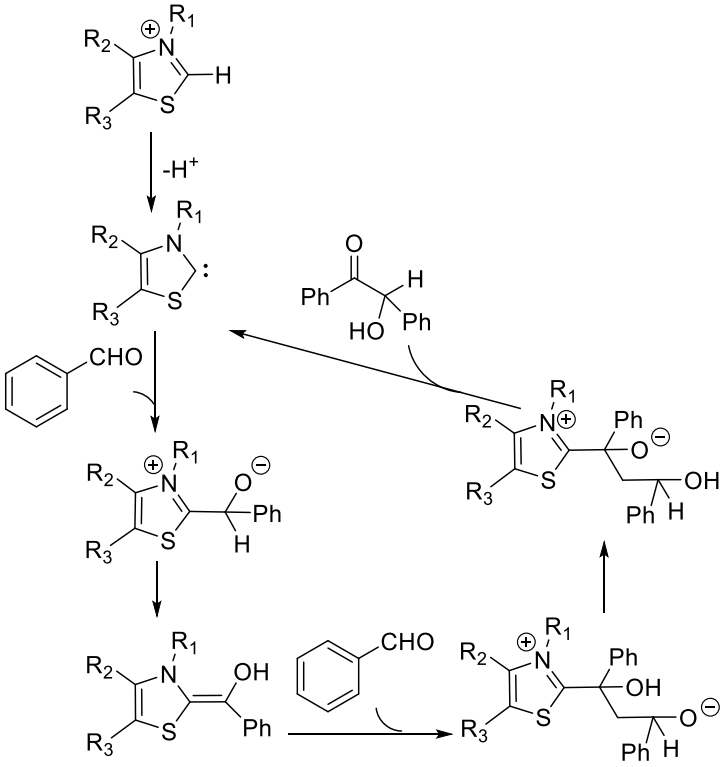

Figure 1-7 Benzoin condensation reaction catalyzed by NHC

The reaction starts with the deprotonation of the thiazolium precatalyst to generate a thiazolyidene, then thiazolyidene attack the benzyl aldehyde to yield a Breslow

intermediate after proton transfer. This Breslow intermediate can either attack another benzyl aldehyde to finish the benzoin condensation reaction or attack a Michael acceptor through a Stetter reaction[31,32].

However, in the scope of Stetter reactions, most of the published work focuses on asymmetric catalysis[33-35]. [36-38] The mechanistic study of the Stetter reaction is limited. In order to study the Stetter reaction in the gas phase by using mass spectrometry, two series of thiazolyidene and triazolylidene catalysts with sulfonate and carboxylate charge tags were used to track the reaction and capture the possible intermediates in the gas phase[36,37].

1.2 Instrumentation

1.2.1 FT-ICR Mass Spectrometry

In 1974, Fourier transform ion cyclotron resonance (FT-ICR) was first invented by Comisarow and Marshall[38,39]. FT-ICR MS features outstanding mass accuracy and resolution among all other mass spectrometry[40].

In order to measure the mass of the ions in the magnetic field, the ion cyclotron resonance was used. The cyclotron motion of charged ions in a homogeneous magnetic field is subject to its Lorentz Force[41]. When an ion has a mass of m, charge q = z * e (e is the charge of an electron/proton, 1.60217662e-19 Coulomb and z is an integer) and velocity v, the magnetic field is B. The Lorentz force can be expressed as:

$$F = zevB \qquad \textbf{Eq. 1.1}$$

The force will serve as the centripetal force that enables the ion move in a circle; if the

angular speed of ion is ω, the centripetal force can be expressed as:

$$F_C = \frac{mv^2}{r} = m\omega v \qquad \textbf{Eq. 1.2}$$

When the Lorentz force F balances the centrifugal force F_c (**Eq. 1.2**).

$$F = F_C \qquad \textbf{Eq. 1.3}$$

$$\omega = \frac{ze}{m} B \qquad \textbf{Eq. 1.4}$$

By substituting $f = 2\pi/\omega$, the cyclotron equation can also be expressed as:

$$f = \frac{ze}{2\pi m} B \qquad \textbf{Eq. 1.5}$$

Therefore, in the ICR cell, the homogeneous magnetic field B is a fixed value. Therefore, the frequency of the cyclotron motion of an ion is directly related to the ion's mass-to-charge ratio. In order to measure the frequency, ions are injected and trapped in the ICR cell; a radio electromagnetic wave will excite the ion resulting in a larger motion trajectory radius. The image current will be altered by the excited ion. Thus the electrically conductive sensor will know this change and interpret it to frequency signals. Last, the frequency signal will be further translated into the mass-to-charge ratio.

Our Finnigan 2001 FT-ICR mass spectrometer is equipped with two cubic ICR cells. The two adjacent 2-inch cubic cells are in the 3.3 T magnetic field. A small hole between the two cells allows ions to transfer between the cells. Substrates can be introduced into the FT-ICR by electrospray ionization (**ESI**) electron ionization (**EI**) and chemical ionization (**CI**).

1.2.2 Electrospray Ionization (ESI)

The electrospray ionization is a "soft" ionization method,[42,43]especially for biomolecules, ESI can help with preserving their native structure[44-46]. Figure 1.8 shows a typical diagram of ESI. The volatile solvents such as methanol, acetonitrile, and water are usually used for ESI. Acids or bases are widely added to the sample solution to promote ionization.

The sample solution flows through a spray needle with 1-6 kV electric potential applied under the atmosphere. A Taylor cone will be formed at the tip of the spray needle under the applied electric field. The flowing solvents will covert to droplets. The charge gathers on the droplets, and when Coulomb repulsion overcomes the surface tension of the droplets, the large droplets break into many smaller droplets [47]. This process repeats until the generation of desolvated ions starts.

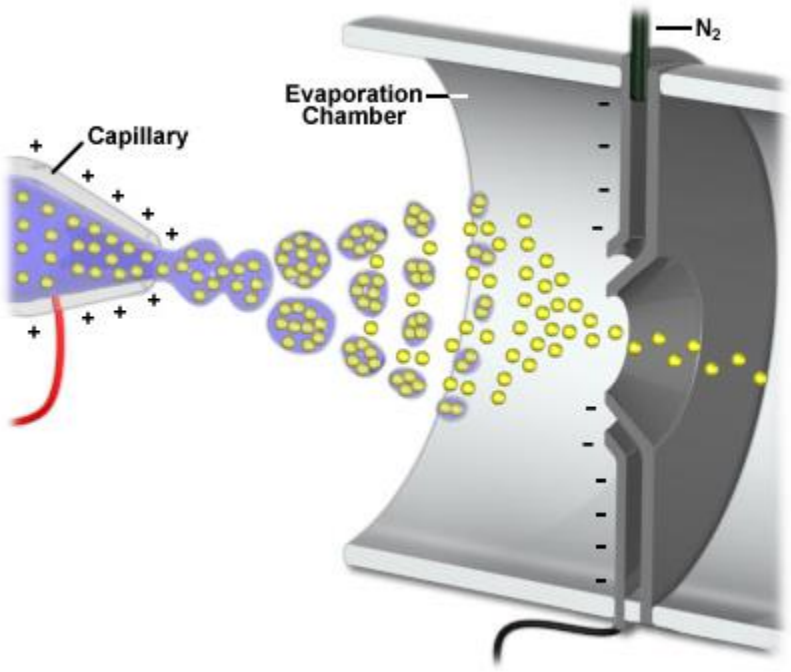

Figure 1-8 Diagram of electrospray ionization, producing cations. Image Source: National High Magnetic Field Laboratory website (nationalmaglab.org/user-facilities/icr/techniques/esi).

Our Thermo Finnigan LCQ DUO mass spectrometer is equipped with an ESI ion source that can be used to introduce molecules that are not volatile without breaking their native structure.

1.2.3 Quadrupole Ion Trap Mass Spectrometer

Invented in 1989 by Hans Dehmelt and Wolfgang Paul, the ion trap technique uses the stability of ions' trajectories to differentiate different mass-to-charge ratios. The quadrupole

ion trap mass spectrometer became popular due to its sensitivity, tandem mass capability as well as relatively low cost[48].

Invented by Wolfgang Paul in 1953, the original quadrupole ion trap is the 3D ion trap consists one ring electrode and two endcap electrodes. In order to trap ions, the quadrupole ion trap utilizes a radio frequency oscillating AC and a constant DC electric field[49,50]. (**Figure 1-9**) During the 1980s, Stafford at Finnigan modified it and applied it to a commercial mass spectrometer[51].

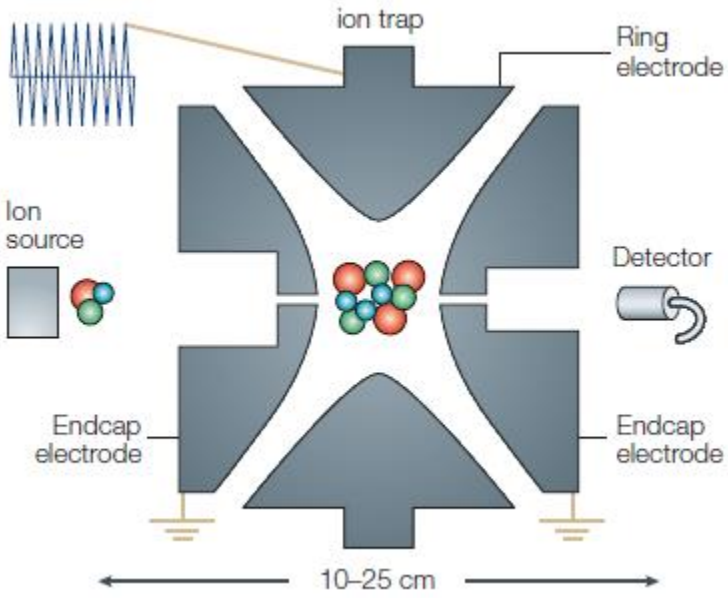

Figure 1-9 Structure of quadrupole ion trap [55]

Herein, we used a Finnigan LCQ DUO (ESI-ion trap) for the gas phase reaction monitoring gas phase kinetic study and gas phase bracketing experiment.

1.2.4 Modified Finnigan LCQ DUO Mass Spectrometer

Our in-house Thermo Finnigan LCQ (ESI-3D quadrupole ion trap) can be used for gas phase bracketing experiments, gas phase reaction monitoring as well as gas-phase reaction

kinetic study. The ion-trap is used as the reaction container as well as the mass spectrometer for gas-phase reactions. ESI can help us to generate the charged species, and the modifirf helium buffer gas line enables us to introduce two additional neutral compounds via two leak valves along with the helium gas flow. Different cryo-bath could be used for different compounds with different volatilities to control the concentration of neutral compounds in the ion trap cell. (**Figure 1-10**)

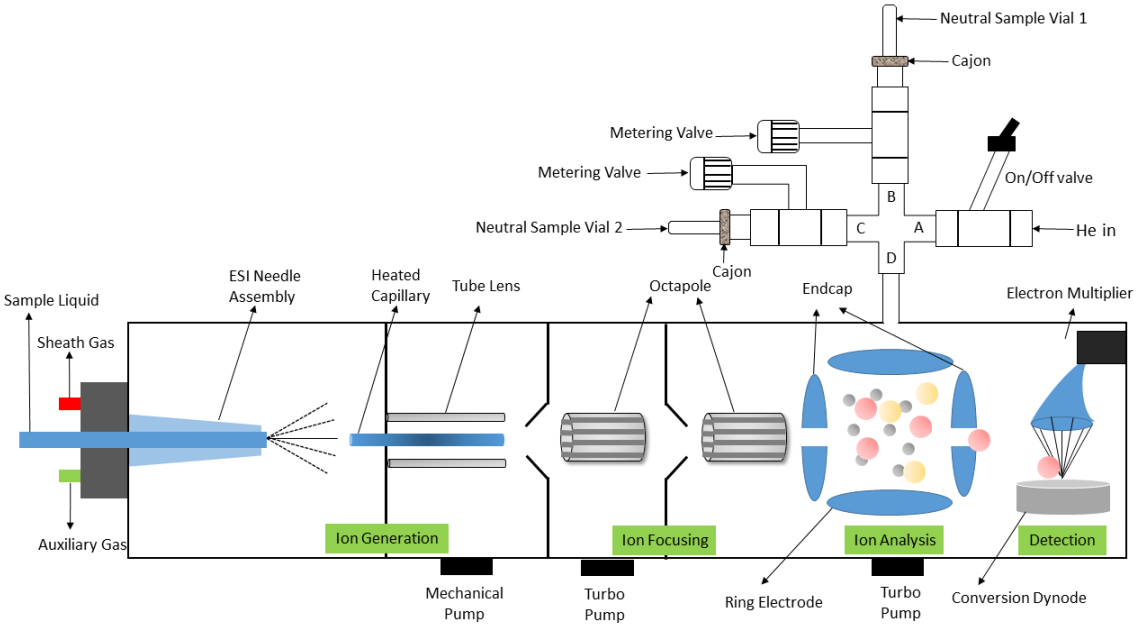

Figure 1-10 Modified Finnigan LCQ DUO Mass Spectrometer[52]

1.3 Methodology

1.3.1 Gas Phase reaction monitoring

The gas phase reaction is conducted using a modified Finnigan LCQ DUO Mass Spectrometer (**Figure 1-10**) by connecting two extra leak valves that introduce neutral compounds into the ion analysis system (ion trap). Solutions of charged handled chemicals

(such as deprotonated carbene) are introduced to the ion trap through electrospray ionization (ESI). Spectra are recorded to track the progress of reactions by giving different reaction times.

1.3.2 Reaction Kinetics Measurement by FT-ICR Mass Spectrometer

The reaction rate constant k can be measured by FT-ICR mass spectrometer. The reaction involves one charged ion reacting with a neutral compound. The charged ion can be generated in one cell in the FT-ICR via chemical ionization or electron ionization. The neutral compound is introduced via a leak valve or batch inlet into the second cell. The generated ions are then transferred to the second cell and allowed to react with the neutral compound. Argon pulsing is used to cool down the ions. Thus, the rate of the reaction can be written as **Eq. 1.6.**

$$\boldsymbol{r} = \boldsymbol{k}\,[Neutral]\,[ion] \qquad \textbf{Eq. 1.6}$$

The concentration of the neutral compound is in excess, thus the reaction can be treated as a pseudo-first-order reaction. **Eq. 1.7** and **1.8**

$$\boldsymbol{k_{obs}} = \boldsymbol{k}\,[Neutral] \qquad \textbf{Eq. 1.7}$$

$$\boldsymbol{r} = \boldsymbol{k_{obs}}[ion] \qquad \textbf{Eq. 1.8}$$

By plotting the relative intensity of ion peaks against reaction time (the rate of ion disappears), we can generate the observed reaction rate constant $\boldsymbol{k}$.

1.3.3 Bracketing method

The bracketing method is used to measure the acidity of the most acidic site of a

designated substrate. Proton transfer between the substrate and references' conjugated base can be monitored by the intensity of the substrate conjugated base's peak. The rapid growth of a substrate conjugated base's peak indicates that the proton transfer reaction occurred. Comparison with different references of variable acidities, the acidity of the substrate is "bracketed" to a narrow range. The more detailed bracketing method using different types of mass spectrometers will be discussed in detail in the following chapters.

1.3.4 Computation method

In order to predict the organic and biological species' thermodynamic properties and the structural information described in this dissertation, theoretical studies were conducted. The gas phase calculations were conducted using Gaussian09[53] and Gaussian 16[54]; all the ground states density functional theory was und the method of B3LYP/6-31+G(d)[55-57]. The geometries were fully optimized, and frequencies were calculated. All optimized ground state structures do not have any negative frequencies. No scaling factor is applied. All the values in the gas phase reported are ΔH at 298K.

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Chapter 2. Gas Phase Studies of Formamidopyrimidine Glycosylase (Fpg) Substrates

2.1 Introduction

The health of living organisms is dependent on the maintenance of DNA integrity, yet DNA is under constant assault by cellular metabolites as well as exogenous agents. Nucleobase damage threatens proper cell function and compromises the correct propagation of the genetic code.[1] Guanine has a low redox potential, making it particularly susceptible to oxidative damage, forming primarily 8-oxoguanine (OG, **2-1**).

One means by which organisms protect the genome is via the base excision repair (BER) pathway, which excises damaged bases. In *Escherichia coli*, Fpg (also called MutM) catalyzes the removal of OG:C base pairs within DNA.[2] Fpg cleaves a wide range of

substrates in addition to OG, including ring-opened structures (derivatives of purines) and other 8-oxo-purines. Several Fpg substrates are shown in Scheme 1: 8-oxoguanine (OG, **2-1**), 8-oxoadenine (OA, **2-2**), 8-oxoinosine (OI, **2-3**), 8-oxonebularine (ON, **2-4**), formamidopyrimidine-guanine (FapyG, **2-5**), 5-hydroxyuracil (OHU, **2-6**), and 5,6-dihydrothymine (DHT, **2-7**).

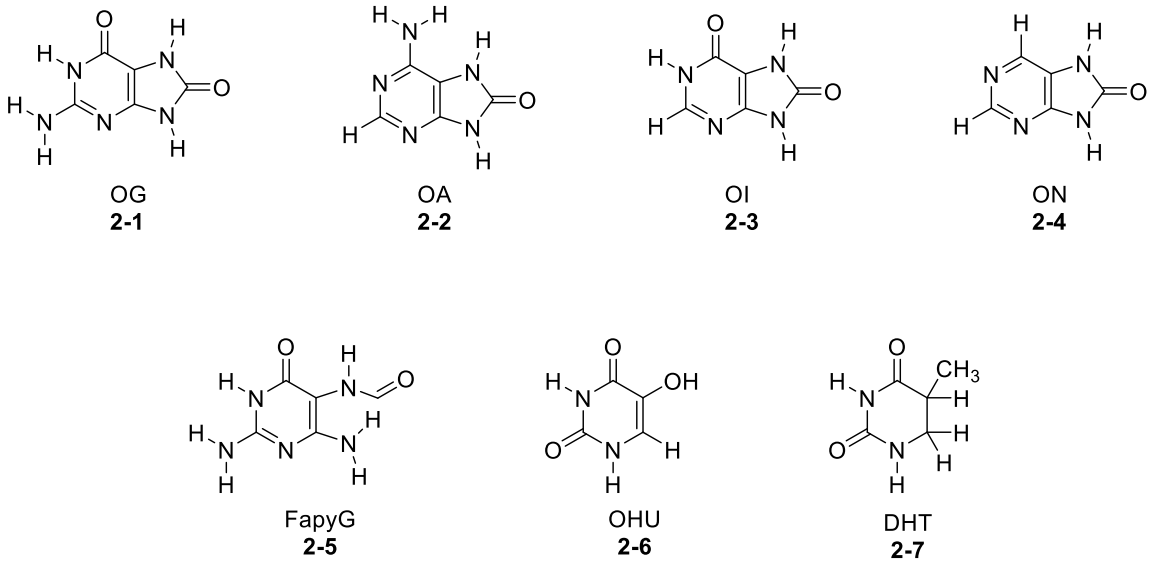

Figure 2-1. Fpg substrates studied herein.

The mechanisms by which glycosylases can recognize, locate, and remove damaged nucleobases are of great interest due to these enzymes' central role in the prevention of mutation and disease.[1,2] The exact mechanism by which Fpg excises the wide range of substrates shown in **Figure 2-1** is still unknown. In particular, the first step in the enzyme mechanism could involve direct base excision ("exocyclic" cleavage, path A, **Figure 2-2**) or ribose ring-opening ("endocyclic" cleavage, path B, **Figure 2-2**). To date, there is no

direct experimental evidence for an endocyclic mechanism, though it has been considered, and one set of recent calculations support it.[2-4] The situation is complicated by the fact that Fpg is a bifunctional enzyme, effecting both glycosylase (base excision) and lyase (DNA backbone cleavage) activity. This means that a Schiff base is formed (**Figure 2-2**) regardless of how the base is excised, followed by beta or delta elimination. Thus ring opening is always observed, but the timing of that step is unknown.

Another mechanistic question is how Fpg cleaves such a diverse set of damaged bases. In prior work, we postulated that other glycosylases which cleave a wide range of bases (MutY, AlkA, AAG) may provide a hydrophobic active site which aids in the discrimination of damaged from normal bases by enhancing the differences in their leaving group ability.[5-7] We hypothesized that Fpg may do the same.

In this chapter, we calculate and measure the gas phase acidities and proton affinities of a series of Fpg substrates (**Figure 2-1**) that have not been heretofore studied *in vacuo*, and discuss the results in the context of the Fpg mechanism. The examination of properties in the gas phase, which provides the "ultimate" nonpolar environment, reveals intrinsic reactivity that can be correlated to activity in other media, such as hydrophobic active sites.[8-14]

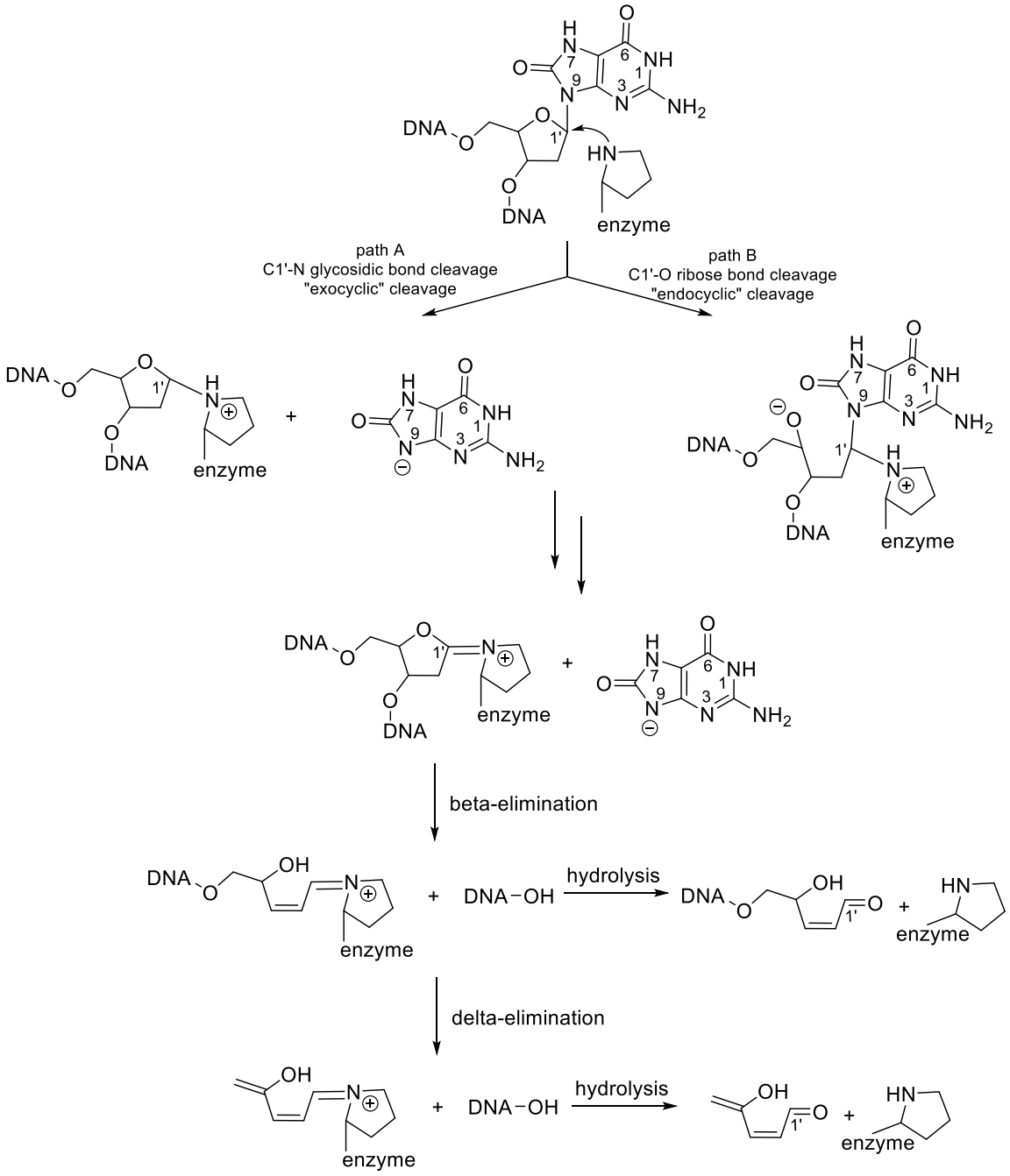

Figure 2-2. Fpg bifunctional activity.

2.2 Experimental

Substrates and reference compounds are commercially available and were used as received.

2.2.1 Bracketing method

Acidity and proton affinity bracketing measurements were conducted using a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FTMS) with a dual cell setup, which has been described previously.[8,9,11-13,15,16] In our FTMS, two adjoining 2-in. cubic cells are positioned collinearly with the magnetic field produced by a 3.3 T superconducting magnet. The pressure of the dual cell is pumped down to less than $1x10^{-9}$ Torr. Solid substrates are introduced into the cell via a heatable solids probe. Hydroxide(OH^-) or hydronium ions(H_3O^+) are generated from water pulsed into the cell, and ionized by an electron beam (typically 6 eV and 8 μA (for OH^-), or 20 eV and 6 μA (for H_3O^+), ionization time 500ms). Liquid reference acids or bases are introduced through the batch inlet system or the leak valve and then allowed to react with either OH^- (for acidity measurement) or H_3O^+ (for proton affinity (PA) measurement).

The typical protocol for bracketing experiments has been described previously by Lee group.[8,9,11-13,15,16] Briefly, ions are generated from a reference compound (acid or base) or the unknown substrate (nucleobase), selected, transferred to another adjoining cell via a 2-mm hole in the center of the central trapping plate, cooled by a pulse of argon (that raises the cell pressure to 10-5 Torr), and allowed to react with a neutral (either a reference compound or nucleobase). Proton transfer reactions are conducted in both directions. The occurrence of proton transfer is regarded as evidence that the reaction is exothermic ("+" in the Tables).

We run bracketing reactions under pseudo-first order conditions, where the amount of the neutral substrate is in excess relative to the reactant ions. Reading the pressure from an ion gauge is often unreliable, both because of the gauge's remote location as well as varying sensitivity for different substrates.[15] We, therefore, "back out" the neutral pressure from a control reaction (described previously). [7,13,16-18]

2.2.2 Computation method

Calculations were conducted at B3LYP/6-31+G(d),[19-21] M06-2X/6-311+G(2df,2p),[22,23], and CBS-QB3[24] levels using Gaussian09;[25] the geometries were fully optimized and frequencies were calculated. All the values reported are enthalpies at 298 K.

2.3 Results and Discussion

2.3.1 Fpg substrate properties: Calculations

5-Hydroxyuracil (OHU, 2-6) Calculations: tautomers, acidity, proton affinity.

5-Hydroxyuracil (OHU, ***2*-6**) has three tautomers that are within roughly 10 kcal/mol of the most stable structure ***2*-6a** (**Figure 2-3**). The most stable structure ***2*-6a** is 7.8 kcal/mol more stable than ***2*-6b**; these two structures are actually rotamers (at the 5-hydroxy position). The third most stable tautomer, ***2*-6c**, is 10.9 kcal/mol less stable than ***2*-6a**. The most stable tautomer ***2*-6a** has an acidity of 330.4 kcal/mol at its most acidic site, which is the N1-H. The PA of ***2*-6a** is 197.8 kcal/mol, at the most basic site, the O4.

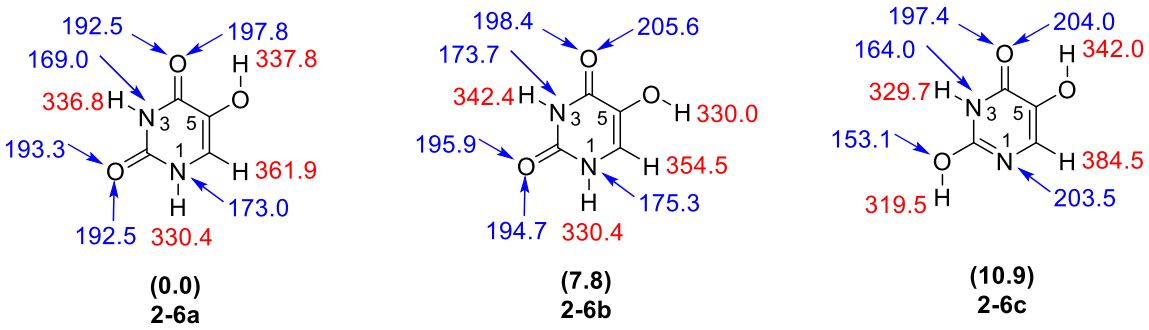

Figure 2-3. Three of the possible tautomeric structures of OHU (***2*-6**). Gas phase acidities are in red; gas phase proton affinities are blue. Relative stabilities are in parentheses. Calculations were conducted at B3LYP/6-31+G(d); reported values are ΔH at 298 K.

Dihydrothymine (DHT, 2-7) Calculations: tautomers, acidity, proton affinity.

Dihydrothymine (DHT, ***2*-7**) has only one stable tautomer (within 10 kcal/mol of the most stable), shown in Figure 7. The next most stable tautomer is 16.7 kcal/mol less so. The most acidic site on DHT is the N3-H, with an acidity of 347.7 kcal/mol. The PA is calculated to be 200.7 kcal/mol at the most basic site, the O2.

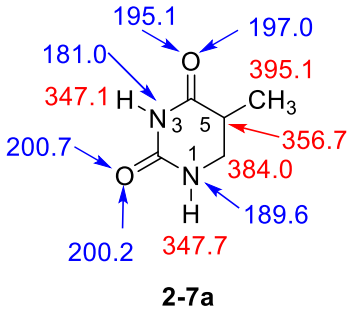

Figure 2-4. The most stable tautomer of DHT (**2-7**). Gas phase acidities are colored in red; gas phase proton affinities are colored in blue. Calculations were conducted at B3LYP/6-31+G(d); reported values are ΔH at 298 K.

2.3.2 Bracketing Experiments

In an effort to benchmark our calculations and also provide new experimental data on these Fpg substrates, we measured the gas phase acidity and proton affinity of 5-hydroxyuracil (OHU, **2-6**) and dihydrothymine (DHT, **2-7**). The purine 8-oxoguanine (OG, **2-1**) proved to be difficult to vaporize due to nonvolatility. Electrospraying the deprotonated or protonated form also proved intractable, as OG is quite insoluble in appropriate solvents such as water and methanol. FapyG and the other purines were not readily accessible commercially or via synthesis and were therefore not studied experimentally.

5-Hydroxyuracil (OHU, 6) Experiments: acidity.

We measured the acidity of 5-hydroxyuracil (OHU, **2-6**) using acidity bracketing (**Table 2-1**, details in the Experimental Section). The conjugate base of OHU does not deprotonate perfluoro-*tert*-butanol (ΔH_{acid} = 331.6 kcal/mol); the reaction in the opposite direction (perfluoro-*tert*-butoxide with OHU) does occur (**Table 2-1**). Pyruvate does not deprotonate OHU, but the conjugate base of OHU does deprotonate pyruvic acid (ΔH_{acid} = 333.5 kcal/mol). We therefore bracket the ΔH_{acid} of OHU as 333 ± 4 kcal/mol.

Table 2-1. Summary of results for acidity bracketing of 5-hydroxyuracil (**2-6**).

Reference compound	*ΔH_{acid}[a]*	*Proton transfer[b]*	
		Ref. acid	*Conj. base*
1,1,1-trifluoro-2,4-pentadione	328.3+2.9	–	+

difluoroacetic acid	331.0±2.2	–	+
perfluoro-*tert*-butanol	331.6±2.2	–	+
pyruvic acid	333.5±2.9	+	–
2-chloropropanoic acid	337.0±2.1	+	–
α,α,α -trifluoro-*m*-cresol	339.2 ± 2.1	+	–

[a]ΔH_{acid} is in kcal/mol.[26] [b]A "+" indicates the occurrence and a "–" indicates the absence of proton transfer

We also measured the acidity of OHU using an additional experimental method, the Cooks kinetic method (details in Experimental section).[27-30] Five reference acids were used: difluoroacetic acid (ΔH_{acid} = 331.0 ± 2.2 kcal/mol), *α,α,α* -trifluoro-*m*-toluic acid (ΔH_{acid} = 332.2 ± 2.2 kcal/mol), pyruvic acid (ΔH_{acid} = 333.5 ± 2.9 kcal/mol), adenine (ΔH_{acid} = 335.1 ± 2.2 kcal/mol), and 2-chlorobenzoic acid (ΔH_{acid} = 335.1 ± 2.1 kcal/mol), yielding a ΔH_{acid} of 333 ± 4 kcal/mol.

5-Hydroxyuracil (OHU, 2-6) Experiments: proton affinity.

In bracketing the PA of OHU, we find that 2,4-dimethyl-3-pentanone (PA = 203.2 kcal/mol) deprotonates protonated OHU; the opposite reaction (OHU deprotonating protonated 2,4-dimethyl-3-pentanone) does not occur (**Table 2-2**). Diethylsulfide (PA = 204.8 kcal/mol) does not deprotonate protonated OHU, but OHU does deprotonate protonated diethyl sulfide. We, therefore, bracket the PA of OHU to be 204 ± 3 kcal/mol.

Table 2-2. Summary of results for gas phase proton affinity bracketing of 5-hydroxyuracil (**2-6**).

Reference compound	*PA*[a]	*Proton transfer*[b]	
		Ref. base	*Conj. acid*
cyclohexanone	201.0±2.0	+	–
4-methylcyclohexanone	201.9±2.0	+	–
2,4-dimethyl-3-pentanone	203.2±2.0	+	–
diethylsulfide	204.8±2.0	–	+
4-fluoroaniline	206.0±2.0	–	+

[a]PA is in kcal/mol.[26] [b]A "+" indicates the occurrence and a "–" indicates the absence of proton transfer

Dihydrothymine (DHT, 2-7) Experiments: acidity.

We measured the acidity of dihydrothymine (DHT, ***2-7***) using acidity bracketing (details in the Experimental Section). The conjugate base of DHT deprotonates *p*-cresol (ΔH_{acid} = 350.2 kcal/mol); the reaction in the opposite direction (the conjugate base of *p*-cresol with DHT) does not occur (**Table 2-3**). Acetate does deprotonate DHT, but deprotonated DHT cannot deprotonate acetic acid (ΔH_{acid} = 348.1 kcal/mol). We, therefore, bracket the ΔH_{acid} of DHT as 349 ± 3 kcal/mol.

Table 2-3. Summary of results for acidity bracketing of dihydrothymine (***2-7***).

Reference compound	*ΔH_{acid}*[a]	*Proton transfer*[b]	
		Ref. acid	*Conj. base*
formic acid	345.3±2.2	–	+
butyric acid	346.5±2.2	–	+
acetic acid	348.1±2.2	–	+
p-cresol	350.2±2.1	+	–
1-pentanethiol	352.5±2.4	+	–
2-propanethiol	353.4±2.2	+	–

[a]ΔH_{acid} is in kcal/mol.[26] [b]A "+" indicates the occurrence and a "–" indicates the absence of proton transfer

We were unable to do a full Cooks kinetic method assessment, because of experimental difficulties, such as low dimer signal. We were, however, able to establish that the acidity of DHT is less than that of acetic acid (ΔH_{acid} = 348.1 kcal/mol), which is consistent with the bracketing results.

Dihydrothymine (DHT, 2-7) Experiments: proton affinity.

In bracketing the PA of dihydrothymine, we find that diethyl sulfide (PA = 204.8 kcal/mol) deprotonates protonated DHT; the opposite reaction (DHT deprotonating protonated diethyl sulfide) also occurs (**Table 2-4**). We, therefore, bracket the PA of DHT to be 205 ± 3 kcal/mol.

Table 2-4. Summary of results for gas phase proton affinity bracketing of dihydrothymine (**2-7**).

Reference compound	*PA*[a]	*Proton transfer*[b]	
		Ref. base	*Conj. acid*
cyclohexanone	201.0±2.0	+	–
2,4-dimethyl-3-pentanone	203.2±2.0	+	–
diethylsulfide	204.8±2.0	+	+
4-fluoroaniline	208.3±2.0	–	+
pyrrole	209.2±2.0	–	+

[a]PA is in kcal/mol.[26] [b]A "+" indicates the occurrence and a "–" indicates the absence of proton transfer

2.3.3 Obtaining "k_2"

Calculated versus experimental values.

The calculated acidity and proton affinity values for OHU (**2-6**) and DHT (**2-7**) are summarized in **Table 2-5**. For acidity, the calculated and experimental values are not too different; for OHU, the experimental value is 2.6 kcal/mol higher than the calculated, while for DHT, the experimental value is 1.3 kcal/mol higher. For proton affinity, the correlation is not as good; OHU has a calculated PA that is 6.2 kcal/mol lower than that of the experimental value. The calculated DHT PA is 4.3 kcal/mol lower.

Table 2-5. Calculated and experimental data for damaged bases.[a] (B3LYP/6-31+G(d); 298 K)

Substrate	Calculated value	Experimental value
ΔH_{acid}[a]		
5-hydroxyuracil (**6**)	330.4	333±4
Dihydrothymine (**7**)	347.7	349±3
PA[a]		
5-hydroxyuracil (**6**)	197.8	204±3
Dihydrothymine (**7**)	200.7	205±3

[a] ΔH_{acid} and PA values are in kcal/mol.

To probe this discrepancy further, we calculated the PAs of **2-6a** and **2-7** using M062X/6-311+G(2df,2p) and CBS-QB3. For **2-6a**, M062X yields a computed PA of 200.9 kcal/mol, while the CBS-QB3 result is 199.9 kcal/mol. Both are still lower than the experimental PA (204 kcal/mol). For DHT (**2-7**), the M062X PA is 204.5 kcal/mol, while

the CBS value is 204.6 kcal/mol, which is both consistent with the experiment (205 kcal/mol). Thus, we can calculate the DHT PA but not the OHU PA accurately. The inability to calculate PAs accurately, even with more computationally intensive methods such as M062X and CBS, has been observed by us before, in the study of two other nucleobases, uracil and xanthine.[6,31] All the nucleobase structures that show this discrepancy between calculated and experimental PAs have a structural element in common: the site being protonated has an NH group to the protonation site, and a double bond in the ring. DHT (**2-7**) does not have the double bond at C4-C5. We are unsure why this particular structural element leads to poorly calculated PAs, but such discrepancies highlight the importance of the gas phase experimental data.

2.4 Conclusions

The acidity and proton affinity for a range of purine, pyrimidine, and ring-opened substrates for the enzyme Fpg were examined experimentally in the gas phase, for the first time. Calculations were also conducted. B3LYP/6-31+G(d) was found to be accurate for the calculation of acidity but yielded inaccurately low values for proton affinity. For proton affinity, M062X and CBS methods gave accurate values for DHT (**2-7**) but not OHU (**2-6a**). Such discrepancies highlight the importance of gas-phase experiments to benchmark computations.

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Chapter 3. Gas Phase Deprotonation of Benzhydryl Cations: Carbene Basicity, Multiplicity, and Rearrangements

3.1 Introduction

Carbenes are molecules with the formula CXY, where the carbon atom is divalent and features two nonbonding electrons. They are key species in many organic reactions, serve as ligands for organometallic catalysts, and function as effective catalysts in their own right.[1-4]

Despite the many applications of carbenes, fundamental properties remain unknown. A key example is the energetics of the protonation of carbenes. It is known that this process should yield the corresponding cation (**Figure 3-1**); however, for many years, there was only indirect evidence to support this.[5,6] Many of the known experimental carbene proton

affinities (PAs) are for *N*-heterocyclic carbenes, while those for the traditional acyclic reactive carbenes are rarer.[5,7-22]

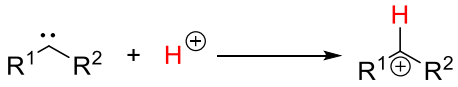

Figure 3-1. Protonation of carbene to yield the corresponding cation.

Another key reaction of carbenes, the insertion of singlet carbenes into O-H bonds, has various possible mechanisms (**Figure 3-2**). In the case of diarylcarbenes, the mechanism for O-H insertion is known to proceed via a proton transfer mechanism, with the diaryl (benzhydryl) carbocation as an intermediate.[6,23-27] Despite this well-established mechanism, the energetics of the protonation are not fully understood, since fundamental properties, such as the experimental proton affinities of carbenes, are unknown.[7] New insights into the energetics of these processes are therefore essential and of major importance for assessing the heats of formation of the corresponding carbenes.[5,7,11,13-16,18] The lack of experimental proton affinities for diarylcarbenes is especially remarkable since they are among the strongest organic bases.[5]

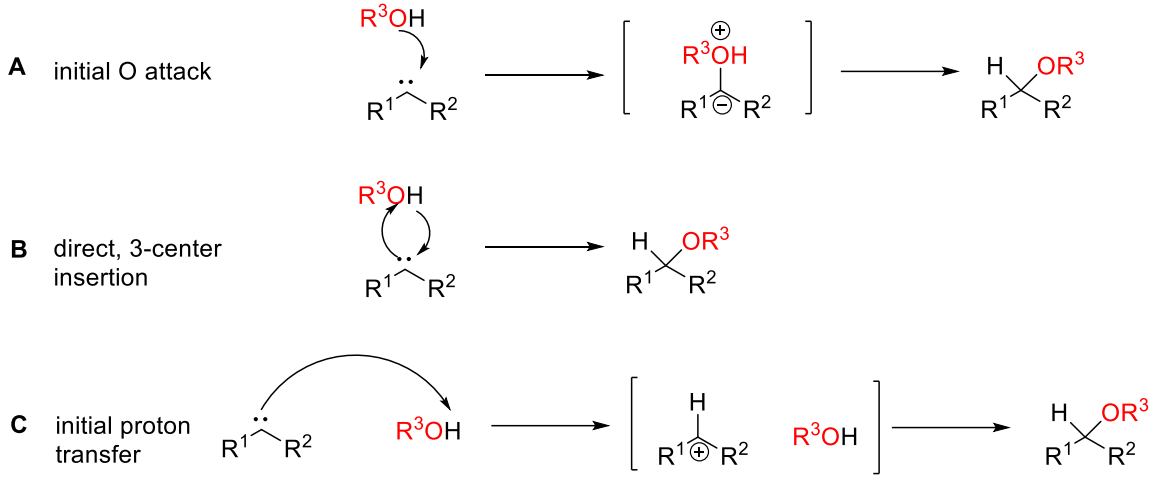

Figure 3-2. Three pathways for O-H insertion.

Herein, for the first time, the gas phase acidity of a series of benzhydryl cations is examined, as a step toward obtaining the corresponding diarylcarbene basicities.

3.2 Experimental

All of the carbene precursors (the benzhydryl alcohols) were commercially available, except for the deuterated substrate described herein, which was synthesized following literature procedure.[28]

3.2.1 FTMS Bracketing experiments

The bracketing method was used to measure the gas phase acidity of the benzhydryl cations. For the FTMS experiments (manuscript section i), a Fourier transform ion cyclotron resonance mass spectrometer with dual cell setup (described previously) was used.[29-33] The magnetic field is 3.3 T; the baseline pressure is 1 x 10^{-9} Torr. The solid benzhydrol carbene precursors were introduced into the cell via a heatable solids probe,

while liquid reference acids bases were introduced via a system of heatable batch inlets. Water was pulsed into the cell, and ionized by an electron beam (typically 8 eV (for HO^-), 20 eV (for H_3O^+), 6 μA (for H_3O^+), 9 μA (for HO^-), 0.5 s) to generate hydronium ions. Protonated carbene ions were generated by reaction of the benzhydrol with the hydronium ions. The protonated carbene ions were then selected, and transferred from one cubic cell to another via a 2-mm hole in the middle trapping plate. Transferred ions were cooled with pulsed argon gas that allowed the pressure to rise to 10^{-5} Torr. Reaction with reference bases was then tracked. Experiments were conducted at ambient temperature. The typical protocol for bracketing experiments has been described previously.[29,30,33-35] The occurrence of proton transfer is regarded as evidence that the reaction is exothermic (denoted as "+" in the tables). Bracketing experiments are run under pseudo-first-order conditions with the neutral reactant in excess, relative to the reactant ions. Obtaining the pressure of the neutral compounds from the ion gauges is always inaccurate; therefore, we "measure (back out)" the neutral substrate pressure from fast control reactions (described previously).[29,35-39]

3.2.1 Quadrupole ion trap bracketing method

We also conducted bracketing experiments in a house-modified quadrupole ion trap (manuscript section ii) mass spectrometer (previously described).[22] To generate the protonated carbene ions via electrospray ionization (ESI), the corresponding benzhydrols were dissolved in methanol. To facilitate ionization, we added 1 μL of a 0.1 *M* HBF_4

solution and 1 μL of 0.1 *M* CF_3SO_3H solution to a 10 mL aliquot of the benzhydrol-methanol solution. Final concentrations of these solutions were ~2 x 10^{-4} *M*. A flow rate of 30 μL/min was used for the electrospray ionization. ESI should vaporize only those ions that already exist in solution; we thus trap and isolate the desired protonated benzhydryl cation reactant.[40]

The capillary temperature was 190°C. Neutral reference bases were introduced into the system with the helium gas flow. The protonated carbene ions (from ESI) were allowed to react with neutral reference bases for 0.03-10,000 ms. The occurrence of proton transfer was regarded as evidence that the reaction was exothermic ("+" in Table); otherwise the reaction was marked as endothermic ("–" in Table). The typical electrospray needle voltage was ~1.80 kV. A total of 10 scans were averaged.

3.2.3 Computation method

Calculations are conducted at B3LYP/6-31+G(d) using Gaussian 09. The geometries are fully optimized, and frequencies are calculated. No scaling factor is applied. All the values reported are ΔH at 298 K.

3.3 Results and Discussion

3.3.1 Experimental acidity of benzhydryl cations.

Five protonated carbenes were examined (**3-1aH$^+$ to 3-1eH$^+$**, **Figure 3-3**). These benzhydryl cations feature different substituents at the phenyl rings directly attached to the

carbene center.

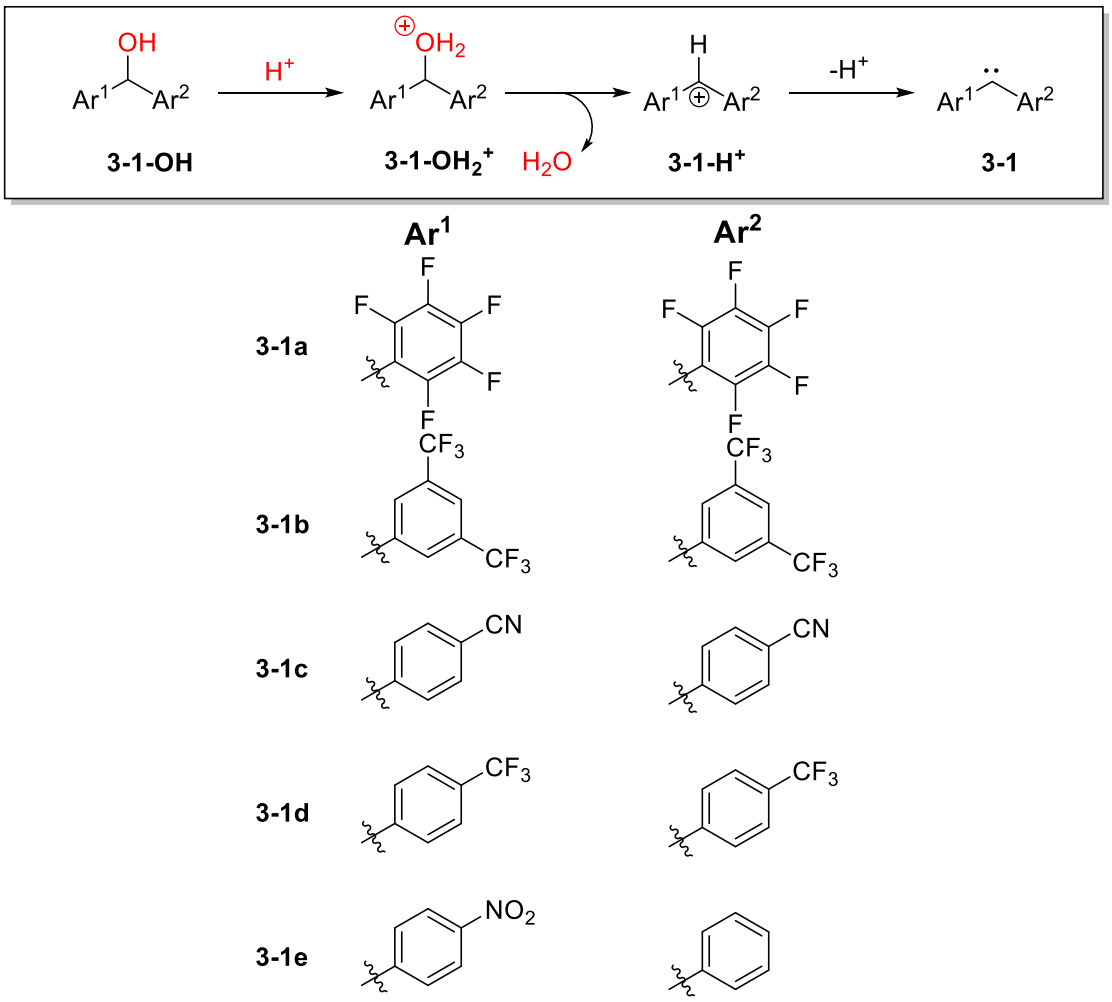

Figure 3-3. Compounds studied.

These acidities have not heretofore been measured; deprotonation of these benzhydryl cations should reflect the basicity of the corresponding diarylcarbene **3-1** (**Figure 3-3**). Therefore, our main goal was to generate the benzhydryl cations and measure the gas phase deprotonation energy. To do this, we used a bracketing method in our mass spectrometers, described in detail in the Experimental section.

3.3.2 Fourier Transform mass spectrometric experiments.

Initially we conducted these experiments in a Fourier Transform ion cyclotron resonance mass spectrometer (FTMS). Vaporization of the benzhydryl alcohol (**3-1-OH**) followed by reaction with hydronium ions (generated from electron ionization of water, see Experimental section for details) yields a *m/z* ratio corresponding to the benzhydryl cation **3-1H**$^+$ (**Figure 3-4**). Reference bases with known proton affinities (PAs) are then allowed to react with **3-1H**$^+$, and the presence (or absence) of proton transfer, as indicated by the formation of **BH**$^+$, allows one to ascertain the acidity of **3-1H**$^+$ (**Figure 3-4**).

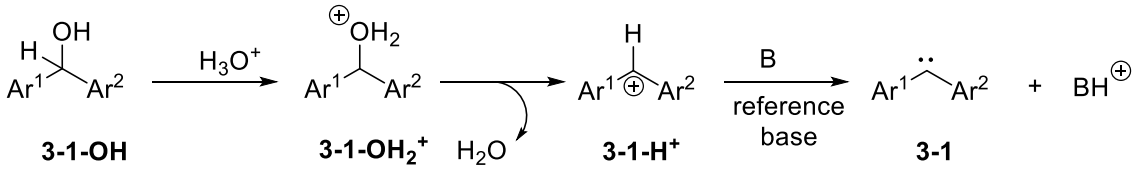

Figure 3-4. Acidity bracketing experiment in FTMS.

We first examined the perfluoro derivative **3-1aH**$^+$. We found that reference bases *N,N′*-dimethylcyclohexylamine (PA = 235.1 kcal/mol), TMEDA (*N,N,N′,N′*-tetramethyl-1,2-ethanediamine, PA = 242.1) and TMPDA (*N,N,N′,N′*-tetramethyl-1,3-propanediamine, PA = 247.4 kcal/mol) all become protonated in the presence of **3-1aH**$^+$. Although the acidity of benzhydryl cations has not been measured before, calculations have been conducted on the parent diphenylcarbene PA, yielding a value of 275 kcal/mol (for the singlet carbene, MP2/DZ//HF/DZ).[41] We note that this is a calculation at a level of theory that is probably

not enough to properly describe the energetics of the carbene, and we also know that perfluorophenyl substitution is sure to lower the PA, but still, the presence of **BH**$^+$ when *N,N′*-dimethylcyclohexylamine is used as the reference base, (implying a PA for **3-1a** under 235 kcal/mol) seemed rather surprising. We thus entertained the possibility that the protonated reference base signal **BH**$^+$ was not arising from **3-1aH**$^+$, but from some other proton source.

To ensure that we are not seeing deprotonation of **3-1aH**$^+$ to form **BH**$^+$, we synthesized the corresponding alcohol of the deutero derivative, **3-1aD-OH**, and allowed it to react with hydronium in the FTMS to generate deuterated **3-1aD**$^+$ (**Figure 3-5**). We then allowed the deuterated perfluoro diarylcarbene **3-1aD**$^+$ to react with both *N,N′*-dimethylcyclohexylamine (PA = 235.1 kcal/mol) and TMPDA (PA = 247.4 kcal/mol), respectively. We see *no deuteron* transfer to either of these reference bases, indicating the acidity of **3-1aD**$^+$ is above 247.4 kcal/mol. **Figure 3-6** shows the mass spectra for the reaction of **3-1aD**$^+$ with *N, N′*-dimethylcyclohexylamine. We still see the protonation of the reference base at *m/z* 128 (whose provenance is unknown to us), but the *m/z* signal corresponding to **BD**$^+$ (*m/z* 129) does not appear. We next allowed **3-1aD**$^+$ to react with DBU (PA = 250.5 kcal/mol); for this reaction, we do see deuteron transfer to form **BD**$^+$, indicating that DBU is basic enough to de-deuterate **3-1aD**$^+$. This places the acidity of **3-1aD**$^+$ between TMPDA (PA = 247.4 kcal/mol) and DBU (PA = 250.5 kcal/mol).

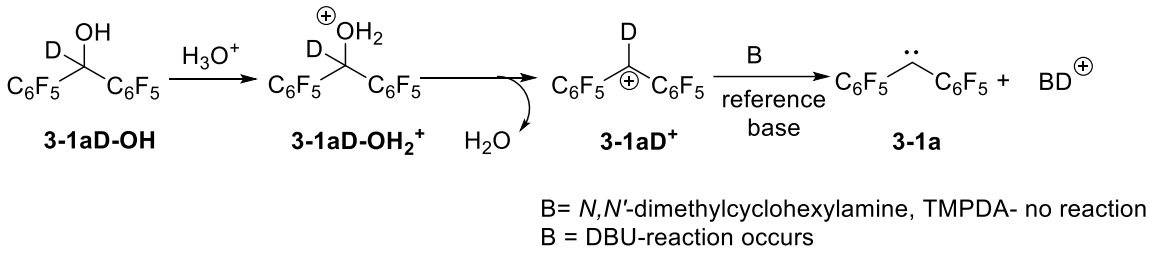

Figure 3-5. Acidity bracketing with deuterated substrate.

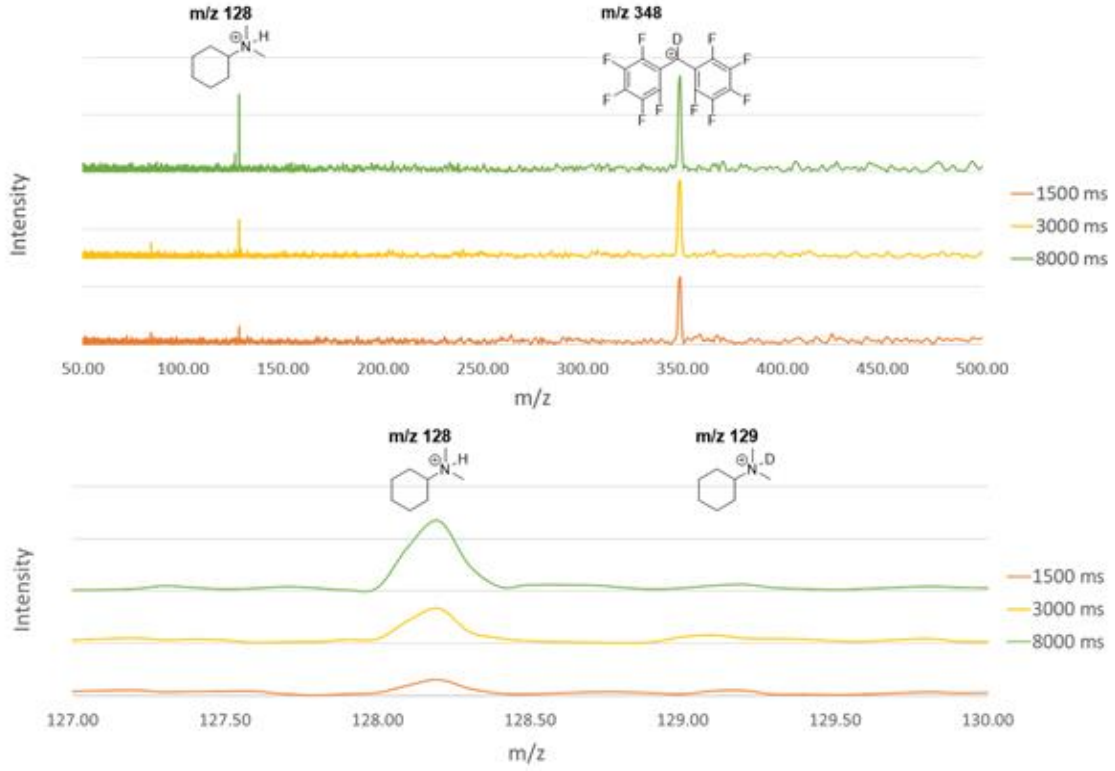

Figure 3-6 (Top) Spectrum showing reaction of *N,N'*-dimethylcyclohexylamine with **3-1a-D$^+$**. (Bottom) Enlarged spectrum showing lack of deuterated *N,N'*-dimethylcyclohexylamine.

Volatility issues precluded the use of reference bases with PAs higher than DBU. However, the results with the deuterated **1aD$^+$** do show that the proton transfer we observed,

to form $\mathbf{BH^+}$, in our initial reactions of $\mathbf{3\text{-}1aH^+}$ with reference bases *N,N′*-dimethylcyclohexylamine and TMPDA, did not result from deprotonation of the $\mathbf{3\text{-}1aH^+}$.

The provenance of the reference base protonation is unknown. We considered the possibility that stray electrons might generate the radical cation of the reference base **B** to form $\mathbf{B^{+\bullet}}$. This radical cation could serve as the acid/proton donor. To exclude this possibility, double resonance experiments with $\mathbf{3\text{-}1aH^+}$ and *N,N′*-dimethylcyclohexylamine ("**B**") were conducted. We irradiated the *m/z* ratio corresponding to the radical cation of *N,N′*-dimethylcyclohexylamine ($\mathbf{B^{+\bullet}}$, *m/z* 127) to ascertain the effect, if any, on the protonated *N,N′*-dimethylcyclohexylamine signal ($\mathbf{BH^+}$). We find that irradiation of the signal at *m/z* 127 does not affect the protonated base signal, indicating that the protonated reference base does not arise from the radical cation. We are still unsure from whence the $\mathbf{BH^+}$ signal arises, but our studies do indicate that neither the $\mathbf{3\text{-}1aH^+}$ nor $\mathbf{B^{+\bullet}}$ appear to be the sources.

3.3.3 Quadrupole ion trap experiments.

The constant presence of proton transfer, regardless of whether the reference base is actually deprotonating the reactant benzhydryl cation, complicates the bracketing of the benzhydryl cation acidities in the FTMS. We thus turned to an alternate instrument, a quadrupole ion trap that we have modified to allow for bracketing experiments.[22] The benzhydryl cations $\mathbf{3\text{-}1H^+}$ are generated from electrospray ionization (ESI) of a solution

containing the corresponding alcohol (**Figure 3-7**, details in Experimental section). The **3-1H**$^+$ cations are then allowed to react with reference bases and the absence or presence of proton transfer is ascertained. We again started with the perfluoro derivative **3-1a** (**Table 3-1**).

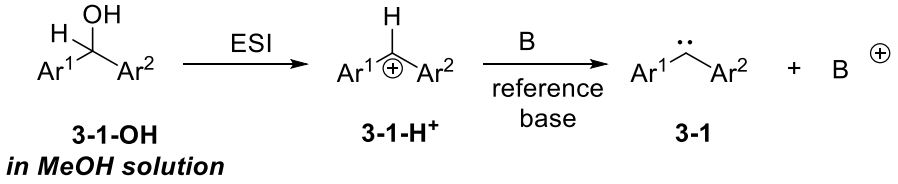

Figure 3-7. Generation of benzhydryl cations via electrospray ionization.

We find that TMEDA (PA = 242.1 kcal/mol), 1-pyrrolidino-1-cyclopentene (PA = 243.6 kcal/mol) and TMPDA (PA = 247.4 kcal/mol) are all unable to deprotonate **3-1aH**$^+$ (Table 1). However, DBN (PA = 248.2 kcal/mol) and DBU (PA = 250.5 kcal/mol) both deprotonate **3-1aH**$^+$. We therefore bracket the acidity of the perfluorobenzhydryl cation derivative **3-1aH**$^+$ to be 248 ± 3 kcal/mol. *We also note that this result is consistent with the bracketing of* ***3-1aD***$^+$ *in the FTMS described above*.

For the tetra-trifluoromethyl derivative **1b**, DBN (PA = 248.2 kcal/mol) and weaker bases cannot deprotonate **3-1bH**$^+$; however, DBU (PA = 250.5 kcal/mol) and MTBD (PA = 254.0) do deprotonate **3-1bH**$^+$ (Table 1). We thus bracket the acidity of **3-1bH**$^+$ to be 249 ± 3 kcal/mol.

For the 4,4'-dicyano derivative **3-1c**, TMPDA (PA = 247.4 kcal/mol) and DBU (PA =

250.5 kcal/mol) are unable to deprotonate **3-1cH**$^+$; however, MTBD (PA = 254.0 kcal/mol) does, placing the acidity of **3-1cH**$^+$ at 252 ± 4 kcal/mol (Table 1).

$tBuP_1$(dma) (PA = 260.6 kcal/mol) is able to deprotonate both the 4,4'-di-trifluoromethyl and 4-nitro benzhydryl cations, while HP_1(dma) (PA = 257.4) is unable to do so, placing the acidity of both **3-1dH**$^+$ and **3-1eH**$^+$ at 259 ± 4 kcal/mol (**Table 3-1**).

Table 3-1. Summary of results for acidity bracketing of benzhydryl cations **3-1aH**$^+$ **to 3-1eH**$^+$.

Reference base[a,b]	*PA (kcal/mol)*[c]	*Proton transfer to reference base*[d]				
		3-1aH$^+$	**3-1bH**$^+$	**3-1cH**$^+$	**3-1dH**$^+$	**3-1eH**$^+$
N,N,N',N'-tetramethylethylenediamine	242.1	–	–			
1-(cyclopent-1-en-1yl)pyrrolidine	243.6	–				
N,N,N',N'-tetramethyl-1,3-propanediamine	247.4	–	–	–		
DBN	248.2	+	–	–		
DBU	250.5	+	+	–		
MTBD	254.0		+	+	–	–
HP_1(dma)	257.4			+	–	–
$tBuP_1$(dma)	260.6			+	+	+
$tOctP_1$(dma)	262.0			+	+	+
BEMP	263.8				+	+

[a]References [8,42,43]; [b]DBN = 1,5-Diazabicyclo[4.3.0]non-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; MTBD = 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene;

HP_1(dma) = Imino-tris(dimethylamino)phosphorane; $tBuP_1$(dma) = *tert*-Butylimino-tris(dimethylamino)phosphorane; $tOctP_1$(dma) = *tert*-Octylimino-tris(dimethylamino)phosphorane; BEMP = 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine. [c]Reference base PAs typically have an error of ±2 kcal/mol. [d]The "+" symbol indicates the occurrence and the "–" symbol indicates the absence of proton transfer.

A summary of our experimental data is shown in **Table 3-2**. At present, we are unable to experimentally ascertain the acidity values for benzhydryl cations with ΔH_{acid} values much higher than **3-1eH**$^+$ due to the low volatility of reference bases, though future plans include instrument modifications that would allow us to explore less acidic benzhydryl cations.

Table 3-2. Experimental ΔH_{acid} for benzhydryl cations **3-1H**$^+$.

Benzhydryl cation	Experimental ΔH for deprotonation (kcal/mol)
3-1aH$^+$	248 ± 3
3-1bH$^+$	249 ± 3
3-1cH$^+$	252 ± 4
3-1dH$^+$	259 ± 4
3-1eH$^+$	259 ± 4

These data represent the first time that the acidity of these benzhydryl cations have been measured. Next, we investigated the chemistry taking place when we deprotonate these benzhydryl cations.

3.3.4 Structures and pathways.

Diphenylcarbene (**DPC**), the parent carbene for **3-1a** - **3-1e**, is known to have a triplet ground state.[4,44] Carbenes **3-1a** - **3-1e** are therefore likely to have triplet ground states as well, since electron withdrawing groups should increase the singlet-triplet gap (ΔE_{S-T}).[45-48] In agreement, the calculated values for the singlet-triplet gap, $\Delta E_{S-T,}$ are larger for **3-1a** - **3-1e** than for **DPC** (**Table 3-3**). For calculating the energetics of reactive carbenes, single point calculations at the CCSD(T) level of theory on structures that have been optimized using a less expensive computational method (typically DFT) are the usual choice.[49] Here, the ΔE_{S-T} values calculated at the CCSD(T)/cc-pvdz//B3LYP-D3/def2-tzvp level of theory are shown in **Table 3-3**. Due to the size of the largest carbene, **3-1b**, the ΔE_{S-T} could only be calculated at the DLPNO-CCSD(T)/cc-pvdz//B3LYP-D3/def2-tzvp level of theory. DLPNO-CCSD(T) has been previously shown as a reliable alternative to CCSD(T) for calculating the ΔE_{S-T} of a series of arylcarbenes, including the parent carbene **DPC**.[50]

Table 3-3. Singlet-triplet gap, ΔE_{S-T}, calculated for **3-1a - 3-1e**.

Diarylcarbene	Substituent	ΔE_{S-T} (kcal/mol)[a]
3-1a	perfluoro	4.9
3-1b	3,3',5,5'-tetra-CF_3	3.7[b]
3-1c	4,4'-di-CN	5.2
3-1d	4,4'-di-CF_3	4.8
3-1e	4-NO_2	4.6
DPC	parent diphenylcarbene	3.3

[a] Calculations were conducted at the CCSD(T)/cc-pvdz//B3LYP-D3/def2-tzvp level of theory; [b] The DLPNO-CCSD(T)/cc-pvdz//B3LYP-D3/def2-tzvp level of theory was used for **3-1b** (see text).

In order to provide further insight into the deprotonation of these species, the enthalpies of deprotonation were calculated at the CBS-QB3 level of theory. Since these are demanding calculations for large systems, we focused on the two smallest species in this study, **3-1c** and **3-1e**. First, we checked whether this method is able to reproduce the ΔE_{S-T} obtained in the CCSD(T) calculations to assess if with CBS-QB3 we can also properly describe the complex electronic structure of these species. The calculated ΔE_{S-T} values for **3-1c** and **3-1e** with the CBS-QB3 method are 4.8 kcal/mol and 3.9 kcal/mol, respectively. These values compare favorably to those calculated using CCSD(T) (5.2

kcal/mol and 4.6 kcal/mol respectively). Also, while the CBS-QB3 ΔE_{S-T} values are somewhat lower than those with CCSD(T) (less than 1 kcal/mol difference), they are consistent with experimental results in that carbenes with electron-withdrawing groups, like **3-1c** and **3-1e**, have larger singlet-triplet gaps than the parent **DPC** (the ΔE_{S-T} value with CBS-QB3 is 2.3 kcal/mol).

In **Table 3-4**, we summarize the calculated and experimental ΔH_{acid} values for the protonated carbenes **3-1cH**$^+$ and **3-1eH**$^+$. For these diarylcarbenes, the experimental enthalpy of deprotonation correlates best to the calculated enthalpy of deprotonation to the singlet carbene. We do know, from other studies of proton transfer in the gas phase, that spin-forbidden proton transfer is possible.[10,51-55] Tian and Kass showed that the methyl cation is deprotonated to yield the more stable triplet carbene, in bracketing experiments in the gas phase.[10] Triplets are more stable for diarylcarbenes **3-1a - 3-1e**, so it is possible that we could also see spin-forbidden proton transfer to yield these triplet ground states, but our calculations imply otherwise, for **3-1c** and **3-1e**. [56]

Table 3-4. Experimental and calculated ΔH_{acid} values for benzhydryl cations **3-1cH**$^+$ and **3-1eH**$^+$ (in kcal/mol)

Benzhydryl cation	Calculated ΔH for deprotonation, to singlet[a]	Calculated ΔH for deprotonation, to triplet[a]	Experimental ΔH for deprotonation
4,4'-di-CN (**3-**	250.3	245.5	252 ± 4

1cH$^+$)			
4-NO_2 (**3-1eH$^+$**)	257.8	253.9	259 ± 4

[a] Calculated values at the CBS/QB3 level of theory

3.3.5 Benzhydryl cation versus tropylium.

We also used computational approaches to probe other mechanistic aspects of this experiment. For these calculations that do not involve carbenes, we used B3LYP/6-31+G(d) since in our experience, this level of theory yields acidities and relative enthalpies that are consistent with gas-phase measurements.[21,22,34,35,37,57]

We considered the possibility that the initial cation formed is not the benzhydryl, but rather, the tropylium, or cycloheptatrienyl, cation (**Figure 3-8**). Calculations of the relative stabilities of the benzhydryl cation and tropylium structures are shown in **Table 3-5**.

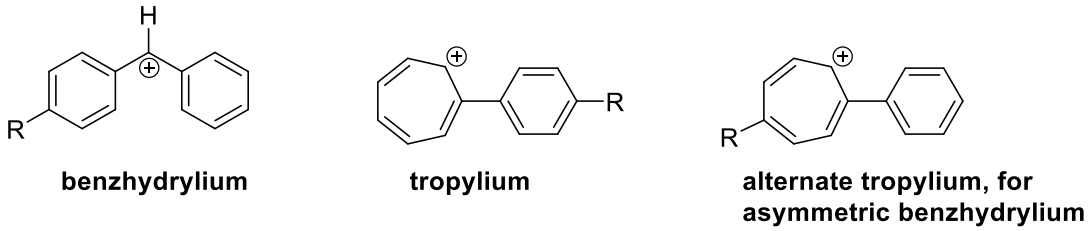

Figure 3-8. Structures of benzhydryl cation and tropylium ions.

Table 3-5. Relative stabilities of benzhydryl cation and tropylium structures for protonated diarylcarbenes.[a,b]

Protonated	Relative enthalpy	Relative enthalpy	Relative enthalpy

substituted diarylcarbene	of benzhydryl cation structure	of tropylium structure,	of alternate tropylium structure, if relevant
3-1aH$^+$	0.0	+0.7	
3-1bH$^+$	0.0	+7.9	
3-1cH$^+$	0.0	+6.8	
3-1dH$^+$	0.0	+5.3	
3-1eH$^+$	0.0	+5.7	+7.5

[a] All values are in kcal/mol. [b] Calculations at B3LYP/6-31+G(d).

For all these cations, the benzhydryl cation appears to be more stable than the tropylium, though for **3-1aH$^+$**, the difference is small (the tropylium is less stable by only 0.7 kcal/mol). For **3-1bH$^+$**, **3-1cH$^+$**, **3-1dH$^+$**, and **3-1eH$^+$**, the tropylium is less stable than the benzhydryl cation by more than 5 kcal/mol. Therefore, if dehydration of the protonated benzhydryl alcohol precursor **3-1-OH** yields the most stable cation, we are likely to produce the benzhydryl cation (as shown in **Figure 3-3**).

In terms of rearrangement, evidence indicates that the barrier for benzyl cation conversion to tropylium is prohibitively high in the gas phase. Calculations by Dewar estimated a barrier of 32.7 kcal/mol, using MINDO/3.[58] Hoppilliard conducted calculations on a dihydroxy benzyl cation derivative and reported rearrangement barriers as "very high in energy."[59] Through experimental gas phase studies, Kebarle concluded

that rearrangement of the ground state benzyl cation to tropylium does not occur in the gas phase.[60-62]

We also believe we most likely have the benzhydryl cation structure because the cations are generated from solution via electrospray. Mayr's work with benzhydryl cation electrophilicity established that the solution-phase ions are *not* tropylium ions.[3] In our work, the benzhydrols **3-1-OH** are dissolved in methanol, with a small amount of acid (see Experimental section), then electrosprayed into the mass spectrometer. Electrospray ionization is widely accepted as a gentle method which captures the ions that already exist in solution.[40] Thus, there is a high probability that the cations generated in solution and electrosprayed are, as in Mayr's studies, benzhydryl cations.

3.3.6 Pathways after deprotonation.

We also need to consider pathways that may occur after deprotonation of the benzhydryl cation, since rearrangements are possible. Pathways for the deprotonation of **3-1H**$^+$ are shown in Scheme 7. We show a general "asymmetric" benzhydryl cation with substitution "R" on just one ring, as this has the most possible pathways. Pathway A is simple deprotonation to yield the diarylcarbene, singlet or triplet. Pathway B involves ring expansion; expansion into the substituted and non-substituted ring are options. Pathway C generates a fluorene; again with this substrate, there are two possibilities since the parent cation is substituted asymmetrically (via **3-2** to form **3-3** and via **3-2'** to form **3-3'**, **Figure 3-9**). Fluorene has been seen as a rearrangement product of diarylcarbene in

the high-intensity excimer laser photolysis of diaryldiazomethane, although it is not observed in the conventional UV lamp photolysis of diaryldiazomethane.[63,64] Wentrup and co-workers hypothesize that any rearrangement from diphenylcarbene to fluorene occurs via hot or more likely higher excited states; our mass spectrometric methods are designed to be under thermally equilibrated conditions, so formation of fluorene should be less likely.[65]

Pathway B involves carbenes; as noted earlier in the manuscript, calculating the enthalpies of reaction for these singlet and triplet paths are computationally prohibitively demanding. The barrier for rearrangement of diphenylcarbene to the ring-expanded phenylcycloheptatetraene was recently calculated by Régimbald-Krnel and Wentrup at B3LYP/6-311+G**//B3LYP/6-31G* to be 19.3 kcal/mol.[65] Substitution by electron-withdrawing groups would most probably lower this barrier, based on studies of phenylcarbene rearrangement.[66-73] If the barrier is indeed less than 20 kcal/mol, then we cannot discount Path B, since formation of the initial ion-molecule complexes between a charged and neutral reactant (in our case, the protonated carbene and reference base) is generally estimated to be about 20 kcal/mol exothermic.[74]

However, we did calculate Pathway C (**Figure 3-9**) for **3-1bH**$^+$ through **3-1eH**$^+$ (**Table 3-6**) at the 6-31+G(d) level of theory. The perfluorobenzhydryl cation **3-1aH**$^+$ is not included, as it is unable to form fluorene due to the lack of a proton beta to the cationic site.

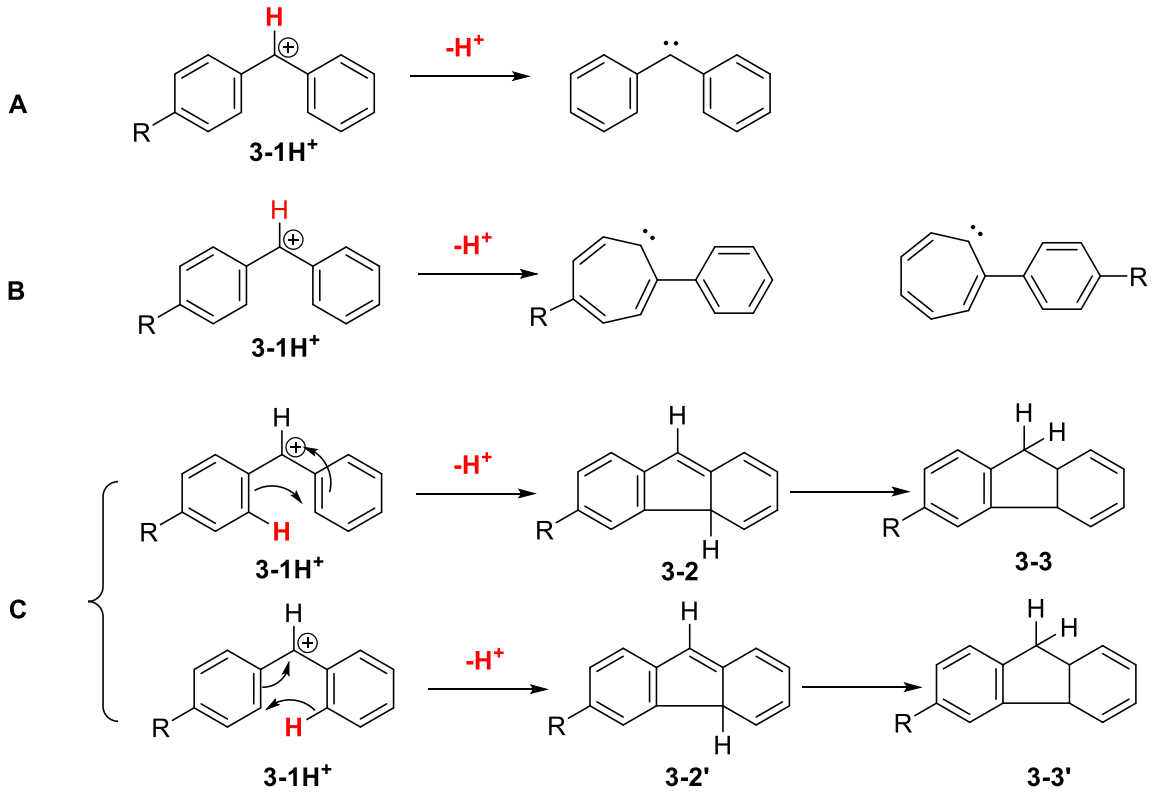

Figure 3-9. Deprotonation pathways.

Table 3-6. Enthalpies for the fluorene path. [a,b,c]

Benzhydryl cation	ΔH from benzhydryl cation to **3-2**	ΔH from benzhydryl cation to fluorene **3-3**	experimental acidity, ΔH
3-1bH$^+$	210.8	186.6	249 ± 3
3-1cH$^+$	212.0	178.0	252 ± 4
3-1dH$^+$	213.8	180.4	259 ± 4
3-1eH$^+$	216.9/218.7	184.0/184.0	259 ± 4

[a] All values are in kcal/mol. [b] Calculations at the B3LYP/6-31+G(d) level of theory. [c] ΔH at 298 K. For **3-1eH$^+$**, the two values represent **3-2/3-2'** and **3-3/3-3'** enthalpies.

Interestingly, the enthalpy to form fluorene from the benzhydryl cations is much lower than our experimental values of deprotonation. For example, we measure the proton affinity of **3-1bH$^+$** to be 249 ± 3 kcal/mol. The computed ΔH to form, say, **3-2** from **3-1bH$^+$** (**Figure 3-9**) is 210.8 kcal/mol (**Table 3-6**). If the formation of **3-2** were taking place, then we would find that all reference bases **B** with PAs of about 211 or higher would produce signal corresponding to protonated reference base, **BH$^+$**. Instead, we find that only reference bases with PAs above DBN (PA = 248.2 kcal/mol) effect reaction. **Table 3-7** shows our experimental results versus that expected if path C were taking place. We are thus reasonably certain that the fluorene path is not at play under our experimental conditions.

Table 3-7. Hypothetical bracketing table if reaction between reference base and **3-1bH$^+$** followed path C (**Figure 3-9**).

Reference base[a,b]	*PA (kcal/mol)*[c]	*Proton transfer to reference base*	
		experimentally observed for **3-1bH$^+$**	hypothetical, if **3-1bH$^+$** formed **3-2** and/or **3-3**
N,N,N',N'-tetramethylethylenediamine	242.1	–	+
N,N,N',N'-tetramethyl-1,3-propanediamine	247.4	–	+
DBN	248.2	–	+
DBU	250.5	+	+
MTBD	254.0	+	+

[a]Reference 29; bDBN = 1,5-Diazabicyclo[4.3.0]non-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; MTBD = 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. cReference base PAs typically have an error of ±2 kcal/mol. dThe "+" symbol indicates the occurrence and the "–" symbol indicates the absence of proton transfer.

3.4 Conclusions

For the first time, the experimental gas phase acidities of a series of benzhydryl cations were measured. There is a dearth of thermochemical data for carbenes, and these measurements represent a first attempt to ascertain values that correspond to carbene

basicity for the diarylcarbene family. Our studies indicate that the benzhydryl cation structure is the most stable and most likely structure generated experimentally. We also determined that reaction with reference bases follows a deprotonation path that is unlikely to involve fluorenes. Quantum chemical calculations suggest that we are measuring deprotonation of the benzhydryl cations to form the corresponding singlet carbenes, for **3-1c** and **3-1e**. This study represents an important step toward understanding the energetics of some of the strongest organic bases known, the diarylcarbenes.

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Chapter 4. Kinetic Hydricity of Silane Hydrides in the Gas Phase

4.1 Introduction

Hydride transfers play an important role in many areas of chemistry.[1] In organic chemistry, hydride transfer is a key step in many invaluable reactions, including the Cannizzaro, the Meerwein-Ponndorf-Verley, and the Tischenko reactions. Furthermore, metal hydrides such as lithium aluminum hydride and sodium borohydride are indispensable in synthetic chemistry for reducing ketones and aldehydes to alcohols.[2] Nicotinamide adenine dinucleotide phosphate (NADPH) and flavin adenine dinucleotide ($FADH_2$) are important enzymatic cofactors that are hydride donors for many biological processes.[3] Recent interest in metal-free hydride donors as catalysts for hydrogen activation further solidifies the importance of hydride transfer reactions.[4-8]

Thermodynamic hydricity is the standard Gibbs free energy change for the dissociation of a hydride donor RH to R^+ and H^-. These values are always positive and therefore, lower values indicate a better hydride donor.[6] Kinetic hydricity is usually expressed in terms of a nucleophilicity factor *N*, which is an empirical value obtained from rate constants for the reaction of hydride donors with reference acceptors.[6,9,10] Stronger hydride donors have a higher *N* value.

The development of the nucleophilicity parameter *N* has been accomplished largely by Mayr and coworkers, who have demonstrated that the rates of reactions of electrophiles and nucleophiles can be described by a linear-free energy relationship (**eq 4-1**).[9-11]

$$\log k = s_N(N + E) \text{ [at 20°C]} \qquad \text{(eq 4-1)}$$

"s_N" is a nucleophile-specific slope parameter, "*N*" is a nucleophilicity parameter and "*E*" is an electrophilicity parameter. *k* is a normalized rate constant for the nucleophile-electrophile reactions. Mayr's studies of hydride donor ability are one type of reaction examined, toward his developing a general nucleophilicity-electrophilicity scale.[12] As Mayr's work has been done in the solution phase, solvent is a potentially complicating factor.

To fill these major gaps in knowledge of general intrinsic nucleophilicity and electrophilicity, as well as specifically, hydricity, we have studied, in the gas phase, the

reactions of a series of silane hydrides with substituted benzhydryl cations. While there have been some prior studies of nucleophilicity and electrophilicity in the gas phase, including a Mayr-like study on the association of benzhydryl cations with amines, the systematic application to hydricity has not heretofore been conducted.[13-26] Knowledge of the intrinsic kinetic hydricities of metal-free hydrides will be useful for understanding the role of solvent in reactivity. These results are of import both for further developing the utility of hydrides for organic and catalytic applications, as well as for generally understanding nucleophilicity and electrophilicity in the absence of solvent.

4.2 Experimental

All of the benzhydryl cation precursors (the benzhydryl alcohols) were commercially available, except for the deuterated substrate described herein, which was synthesized following literature procedure.[27]

4.2.1 FTMS reaction kinetic study

Measurement of rate constants was carried out in a Fourier Transform ion cyclotron resonance mass spectrometer (FTMS). The FTMS has a dual cell setup (described previously).[28-32] The magnetic field is 3.3 T; the baseline pressure is 1 x 10^{-9} Torr. The solid benzhydrol precursors were introduced into the cell via a heatable solids probe, while the silanes were introduced via a system of heatable batch inlets. Water was pulsed into the cell, and ionized by an electron beam (typically 20 eV, 6 μL, 0.5 s) to generate hydronium ions. The benzhydryl cations were generated by reaction of the benzhydrol with the

hydronium ions. The cations were then selected, and transferred from one cubic cell to another via a 2-mm hole in the middle trapping plate. Reaction with silanes was then tracked. Experiments were conducted at ambient temperature. The typical protocol for obtaining gas phase rate constants has been described previously.[28,29,32-34] The experiments are run under pseudo-first-order conditions with the neutral silane hydride reactant in excess, relative to the reactant cations. Reading the pressure of the neutral compounds from the ion gauges is not always accurate; therefore, we "back out" the neutral substrate pressure from fast control reactions (described previously).[28,34-38] Under our conditions, the ionic species are generated, then argon gas is pulsed in, so that the ions are cooled. Thus, only thermoneutral and exergonic reactions are observable.[13,39]

4.2.2 Computational method

All calculations were performed using density functional theory (B3LYP/6-31+G(d)) as implemented in Gaussian 09 and 16.[40-45] All ground state geometries were fully optimized and frequencies were calculated; no scaling factor was applied. The optimized structures had no negative frequencies. The transition structures corresponding to the reaction of toluene with benzyl cation, and toluene with benzhydryl cation, correspond to partially optimized structures in which the distance between carbocation (benzyl/benzhydryl) and carbon atom *para* to the methyl carbon of toluene was constrained to 2.0 A. The partially optimized transition structure resulted in the one imaginary frequency corresponding to the bond formation between the carbocation

(benzyl/benzhydryl) and toluene. The temperature for the calculations was set to be 298 K. Calculations in methylene chloride were also conducted at B3LYP/6-31+G(d), using a polarized continuum model; specifically, we utilized the SMD variation of IEFPCM of Truhlar and co-workers.[46]

4.3 Discussion

4.3.1 Experimental results: hydride abstraction from silanes.

We have examined hydride abstraction from silanes by benzhydryl cations; the general reaction is shown in **Figure 4-1**.

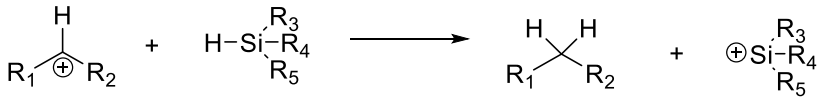

Figure 4-1. General hydride transfer reaction studied herein.

For this model to succeed in the gas phase, the reaction must be exergonic. This poses some challenges in design since the parent benzhydryl cation ($R_1 = R_2 = Ph$) is quite stable. At B3LYP/6-31+G(d), the benzhydryl cation has a calculated hydride affinity (ΔG) of 245 kcal/mol, while a silyl cation with methyl groups ($R_3 = R_4 = R_5 =$ methyl) has a computed hydride affinity of 252 kcal/mol. The reaction between these two species would therefore be endergonic. Although our experiments measure *kinetic*, not thermodynamic, hydricity, our gas phase conditions are such that we do not generally observe endergonic reactions (more details in Experimental section).[13,28,32,47-49]

We first allowed Me_2PhSiH and iPr_3SiH to react with the parent benzhydryl cation, as calculations (**Table 4-1**) indicated that these reactions should be exergonic in the gas phase. These reactions are also known to proceed in solution, which would allow for direct comparison between gas and solution phase reactivity.[10]

Table 4-1. ΔG for reactions shown in Figure 1 (R_1, R_2 = Ph).[a]

Silane substitution (Figure 4-1)			**Calculated ΔG for reaction in Figure 4-1 (kcal/mol)**
R_3	**R_4**	**R_5**	
Me	Me	Ph	–1.6
iPr	iPr	iPr	–1.3

[a] Calculations at B3LYP/6-31+G(d).

Unfortunately, we found that although these reactions are calculated to be slightly exergonic in the gas phase, we do not observe reaction under our experimental conditions. We hypothesize that the reactions may in reality be slightly endergonic. The reactions may also be favored by solvation of the silyl cation, which is not possible *in vacuo*.

To drive these reactions further, we added electron withdrawing groups to the benzhydryl cation. The reactions between a series of fluoride-substituted benzhydryl cations and silanes shown in **Figure 4-2** were examined.

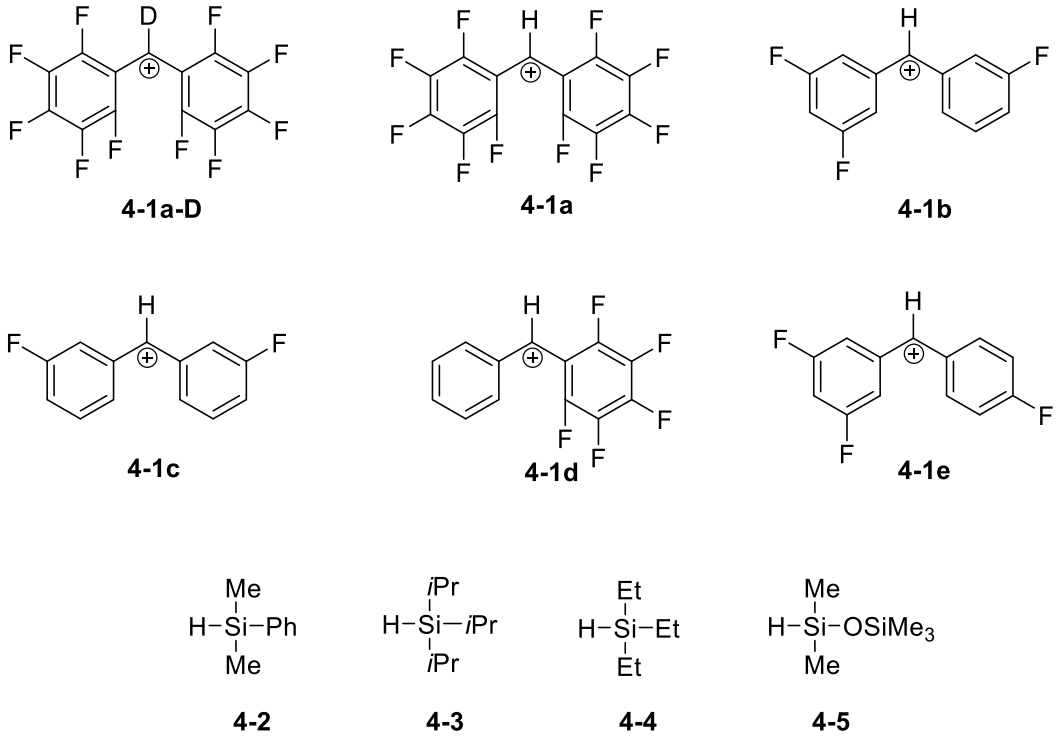

Figure 4-2. Benzhydryl cations and silanes studied herein.

Briefly, to conduct this experiment, we vaporize the alcohol **4-1-OH** into our Fourier Transform mass spectrometer **(Figure 4-3)**. Reaction with hydronium ions should generate the desired benzhydryl cation. We then allow the cation to react with the silane hydrides. The rate constants for the reactions between **4-1** and the various silane hydrides are reported in **Table 4-2**.

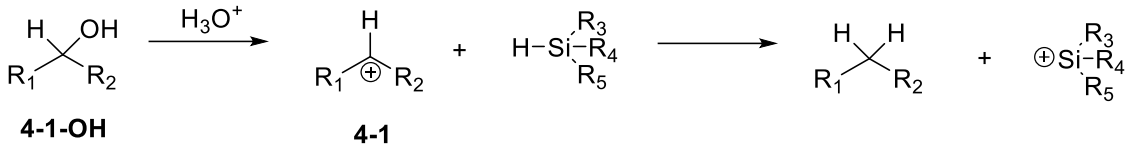

Figure 4-3. Generation of benzhydryl cations and subsequent reaction with silane hydrides.

Table 4-2. Gas phase rate constants k (x 10^{-10} cm^3 $molecule^{-1}$ s^{-1}) for the reaction of **4-1** with silanes **4-2** to **4-5**.

	4-1a-D	**4-1a**	**4-1b**	**4-1c**	**4-1d**	**4-1e**
4-2	5.62±0.17	4.13±0.26	3.47±0.22	3.16±0.27	2.76±0.17	1.69±0.45
4-3	3.31±0.11	2.82±0.12	2.09±0.04	1.90±0.11	1.78±0.05	0.81±0.06
4-4	3.30±0.27	2.60±0.19	1.84±0.09	1.16±0.20	1.27±0.11	0.57±0.09
4-5	0.49±0.07	0.42±0.11	0.14±0.08	0.13±0.01	0.08±0.02	too slow

Further interpretation of these data will follow, in the "Discussion" section. We next describe additional studies delving into reaction mechanisms.

4.3.2 Reaction details: reaction paths.

Two concerns that arose in the course of our studies were whether i) the desired hydride transfer, and not a proton transfer type reaction was taking place; and ii) the structure of the reactant cation was in fact a benzhydryl cation, and not a tropylium.

Hydride transfer versus proton abstraction.

One concern of ours was that the silane hydride might *abstract* a proton from the benzhydryl cation to form a carbene (Path B, **Figure 4-4**), instead of the desired hydride transfer (Path A, **Figure 4-4**). Calculations on various benzhydryl cations and silanes indicate that while hydride transfer (Path A) is very exergonic, proton abstraction (Path B) is extremely (>35 kcal/mol) endergonic, so should not be a competing pathway.

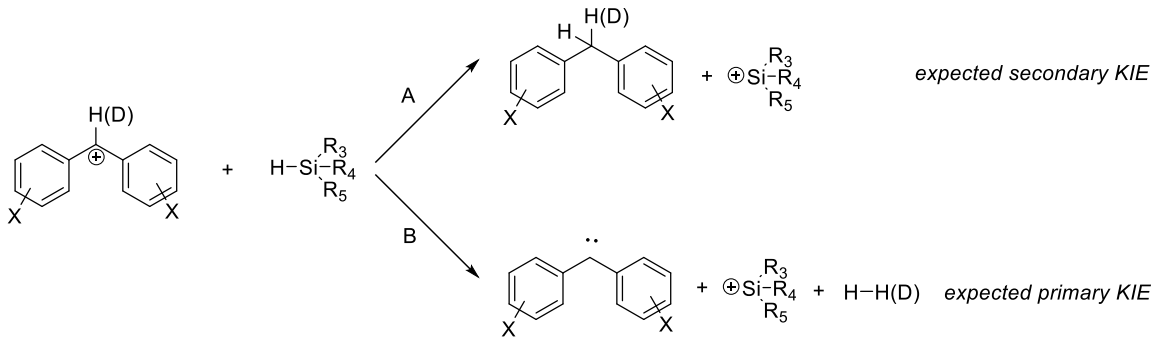

Figure 4-4. Hydride abstraction versus proton abstraction.

To lend further insight into which pathway we see, we compared the rate constant for reaction of the deuterated perfluorobenzhydryl cation **4-1a-D** with that of the undeuterated compound **4-1a**. As shown in Figure 4, if hydride transfer occurs (Path A), the carbon with the H(D) should undergo a hybridization change from sp^2 to sp^3. This should yield a secondary KIE of less than 1. If the H(D) is abstracted (Path B), then the KIE should be normal and primary, a value greater than 1.

Comparison of the rate constants for the reaction of cation **4-1a** versus that of the

deuterated **4-1a-D** (**Table 4-2**) indicate an inverse secondary KIE of ~0.8; we therefore believe hydride abstraction is indeed taking place.

Benzhydryl cation versus tropylium

The second concern is whether, in the mass spectrometer, we are generating the benzhydryl or the tropylium cation (**Figure 4-5**).

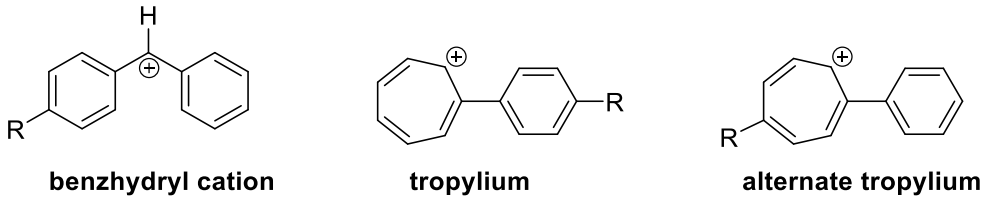

Figure 4-5. Benzhydryl cation versus tropylium structures.

We first calculated the free energy change associated with the isomerization of the benzhydryl cation to the tropylium (**Table 4-3**). In all cases, the isomerization is endergonic (albeit by just 0.5 kcal/mol for **4-1b**).

Table 4-3. ΔG for the rearrangement: benzhydryl cation **4-1** → tropylium (**Figure 4-5**).[a,b]

Cation	Free energy to form tropylium	Free energy to form alternate tropylium structure, if relevant
4-1a	+1.1	
4-1b	+0.5	+0.6
4-1c	+2.1	+2.1

4-1d	+1.9	+4.2
4-1e	+2.4	+4.2

[a] All values are in kcal/mol. [b] Calculations at B3LYP/6-31+G(d).

We also sought to determine structure experimentally, through reactions with toluene. It is known that the benzyl cation reacts with toluene in the gas phase, while the tropylium remains unreactive (**Figure 4-6**).[50-54]

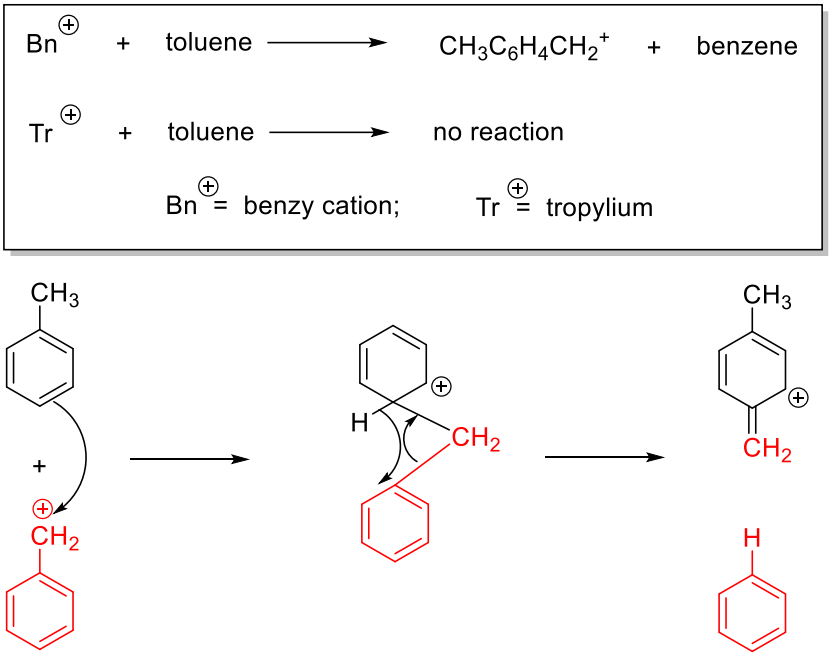

Figure 4-6. Characteristic benzyl cation reaction with toluene in the gas phase.

While benzyl cation and tropylium display the divergent reactivity shown in **Figure 4-6**, to our knowledge, such reactions have not been studied with benzhydryl cations. As a control, we examined the reaction of benzyl cation with toluene under our conditions, and we do produce the expected $CH_3C_6H_4CH_2^+$ cation. However, when we allow the cations

derived from the parent benzhydrol to react with toluene, we observe no reaction. We also tried the cations derived from the perfluorobenzhydrol; these also show no reaction with toluene.

These results could either mean that we have tropylium structures, or that the reactivity of benzhydryl cations with toluene is not the same as that of benzyl cations with toluene. We conducted calculations on the parent benzhydryl cation plus toluene reaction, to ascertain the barriers to reaction. Calculations indicate that the barrier to nucleophilic attack of the benzhydryl cation by toluene is relatively higher, by roughly 20 kcal/mol, than that of the benzyl cation with toluene. Unlike benzyl cation, the benzhydryl cation has a quite sterically hindered center, which might slow down any reaction. Thus, the lack of reaction between toluene and the cations derived from benzhydrol would seem inconclusive; we cannot say that we do not have the benzhydryl cation structure as the reaction with toluene may simply be unfavored.

Overall, we do have reason to believe that our cations are benzhydryl in structure. First, the generation method should favor the benzhydryl cation, not the tropylium. We produce the cation from the corresponding benzhydryl alcohol, via protonation. Seen Sharma and Kebarle established that abstraction of chloride from benzyl chloride in the gas phase yields the benzyl cation, not the tropylium.[51] This reaction is similar to our generation method, which should favor the benzhydryl cation structure. Tropylium is usually produced by direct electron impact, which we are not using.[52-59] Furthermore,

both computational and experimental evidence indicates that under thermoneutral conditions, rearrangement from benzyl cation to tropylium is unlikely. [51,52,59-61]

Second, in work done for an orthogonal project, we find that our measured gas phase acidity of perfluorobenzhydryl cation **4-1a-D** is the same, whether we generate the cation in the gas phase or from solution.[62] That is, if we generate **4-1a-D** as described herein, or from solution (via electrospray), we find that both species have the same acidity. Our calculations indicate that tropylium should be about 15 kcal/mol more acidic than benzhydryl cation. Therefore, the similar acidity for the two differentially generated cations implies both have the same structure.[62] Electrospray ionization (ESI) is widely accepted as a gentle method which captures the ions that already exist in solution.[63] Since in solution, these ions are believed to be benzhydryl cations, it would stand to reason that the ions brought into the mass spectrometer by ESI would also be benzhydryl in structure.[10]

We should also note that ultimately, while the evidence taken together points to a benzhydryl cationic structure, the identity of the structure does not strictly affect the results herein. The rate constants are used to ascertain the silane hydride nucleophilicities, and if the cations are of varying structure, it will not affect those nucleophilicity trends.

With rate constants (**Table 4-2**) in hand, we looked to Mayr equation 1, to ascertain the kinetic hydricity, or nucleophilicity, of the silanes. At this early point in our research, rather than derive any specific parameter values, we instead made a "Mayr-type" graph, plotting the log of the rate constant for the reaction between the series of nucleophiles and

electrophiles (y axis) versus the log of the rate constant of the electrophiles with **4-3** as our reference nucleophile (x axis) (**Figure 4-7**).

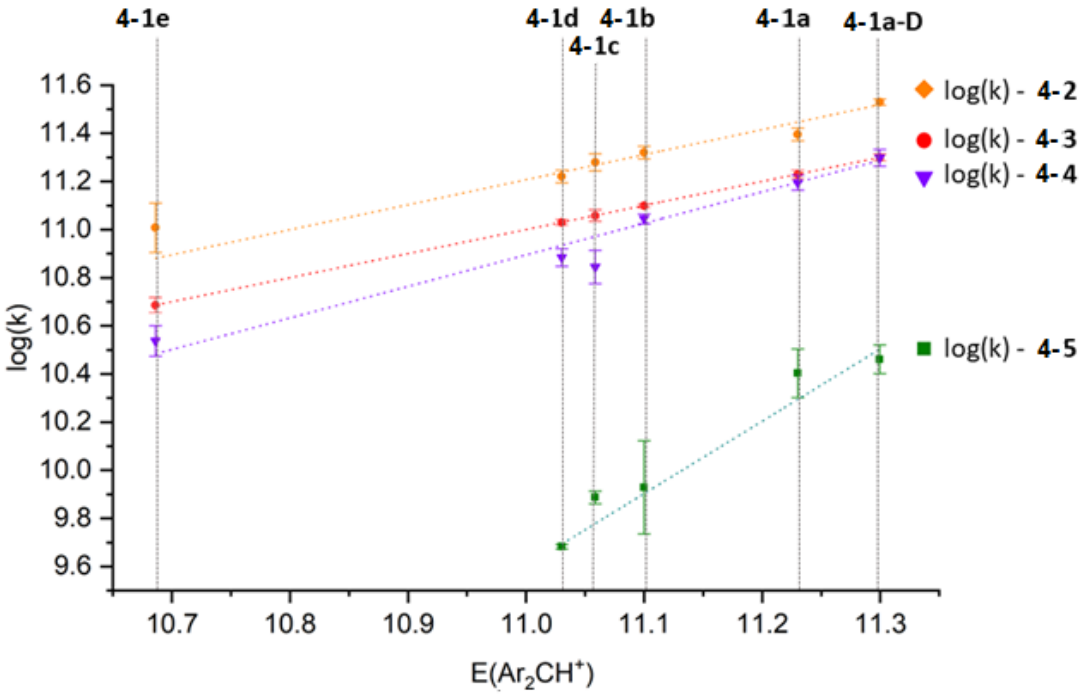

Figure 4-7. Plot of benzhydryl cation and silane data. The y-axis represents the log of the rate constant for the reaction of each electrophile with each nucleophile. The x-axis is the log of the rate constant of each electrophile with **4-3**.

The results show that the trend for silane nucleophilicity in the gas phase is **4-5** < **4-4** < **4-3** < **4-2**. The trend in solution (methylene chloride) is **4-3** < **4-5** < **4-2** < **4-4**.[10] This change in trend between the gas phase and solution is of interest, since such changes usually reveal the role of solvent. One possible reason for the differences between the gas phase

and the solution phase could be solvation of the silyl cation product. In solution, the most nucleophilic silane hydride is Et_3SiH (**4-4**), while the least nucleophilic species is iPr_3SiH (**4-3**). In the gas phase, iPr_3SiH (**4-3**) is more nucleophilic than Et_3SiH (**4-4**). The higher nucleophilicity of iPr_3SiH in the gas phase could be due to the stability that the product iPr_3Si^+ cation gains from the polarizable isopropyl groups. In solution, those bulky isopropyl groups may inhibit solvation of iPr_3Si^+ relative to Et_3Si^+, which results in the reversal of the hydricity of the parent neutral compounds. This is reminiscent of the well-known reversal of acidity of methanol versus *tert*-butanol in solution versus the gas phase.[64] In order to lend insight into this possible explanation, we calculated the free energy of solvation in methylene chloride for the silyl cations. We find that the triethylsilyl cation (generated from **4-4**) has a $\Delta G_{solvation}$ of -52 kcal/mol, while the triisopropyl cation (generated from **4-5**) has a $\Delta G_{solvation}$ of -49 kcal/mol. Therefore, the triethylsilyl cation is slightly better solvated, reflecting the observed trend. The solvation model does not include specific solvation, which would be expected to further enhance the differences between the two cations.[65]

Another possible reason for the differences between the gas phase and solution silane nucleophilicity, suggested by a referee, is that the dichloromethane solvent may form weak Cl-Si interactions, such that a CH_2Cl_2–SiR_3H species might be the true hydride donor in solution.

Hydricity is of importance for understanding reactions in which silane hydrides serve

as hydride sources. One intriguing example is the use of silane hydrides to reduce *N*-heterocyclic carbene (NHC)-activated carbon dioxide.[7,8] Utilization of carbon dioxide has become of paramount importance, given the rising carbon dioxide concentration in our atmosphere. Radian, Zhang and Ying found that CO_2 activated by NHCs (to form an imidazolium carboxylate) will react with silane hydrides to form methanol.[7,8] In terms of substrates that overlap with ours, they found that hydride transfer by Me_2PhSiH (**4-2**) is more effective than Et_3SiH (**4-4**). We find this of interest, as our gas phase nucleophilicity trend is consistent with this result, while the solvent nucleophilicity trend is not. That is, our gas phase results on hydricity may be useful for predictive power in applications utilizing silane hydrides.

Ultimately, the kinetic hydricity of the studied silanes are different in the gas phase and in solution. Such results show the importance of gas phase studies, to establish how solvent is affecting our understanding of reactivity.

In terms of electrophilicity, the gas phase trend for the benzhydryl cations is **4-1e < 4-1d < 4-1c < 4-1b < 4-1a**, with **4-1a** being most electrophilic. Mayr and coworkers have examined **4-1b** and **4-1c** in solution; the electrophilicity trend for these cations is the same as that in the gas phase. This is consistent with the Mayr interpretation that electrophile solvation energies change proportionally with electrophilic reactivities; we see this proportionality in the absence of solvent. Furthermore, a survey of other fluorinated benzhydryl cations studied by Mayr indicates that fluorine substitution on the 3-position

increases electrophilicity the most; F substitution on the 5 position also enhances electrophilicity, but not as much as on the 3-position; and F substitution on the 4-position tends to have a negative effect on electrophilicity.[12] These trends are consistent with that which we see in the gas phase.[11,12,25,66]

In terms of absolute rate constants, the reactions are faster in the gas phase than in solution. For the reaction of cation **4-1b** with Et_3SiH **4-4**, the solution phase rate constant is 6.04 x 10^7 $M^{-1}s^{-1}$. In the gas phase, this reaction rate constant is 1.11 x 10^{11} $M^{-1}s^{-1}$. For the reaction of cation **4-1c** with **4-4**, the solution phase rate constant is 2.51 x 10^7 $M^{-1}s^{-1}$, while the gas phase *k* is 0.70 x 10^{11} $M^{-1}s^{-1}$. Thus, for these reactions, the rates are roughly 2000 times faster in the gas phase.

This work indicates the importance of examining properties in the gas phase; comparison of intrinsic reactivity with solution phase behavior can ferret out the details of media effects.

4.4 Conclusions

This work represents the first attempt toward developing a gas phase hydricity scale. Kinetic hydricity is of import both for general understanding of nucleophilicity and electrophilicity, as well as for improved design of hydrides for energy applications. Our studies indicate that the abstraction of hydride from a series of silane hydrides follows a trend that differs from that in solution, revealing the effect of solvent. Our work also delves into the reactivity and structure of our cations, using H/D studies, calculations, and

further experimentation. Having established that hydricity can be studied as described herein, we are moving toward expanding the cations and silane hydrides studied. Overall, the ability to independently investigate electrophilicity and nucleophilicity in the gas phase would allow us to ascertain the solvent effects by direct comparison to solution phase electrophile and nucleophile data. Such studies would be a breakthrough in the understanding of organic reactivity, because many of the phenomena observed in electrophile-nucleophile studies in solution cannot be adequately interpreted.[67]

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Chapter 5. Gas Phase Studies of N-Heterocyclic Carbene-Catalyzed Stetter Reaction

5.1 Introduction

The mechanism of the N-heterocyclic carbenes (**NHC**) catalyzed Stetter reaction in the gas phase is not known, and determining the detailed mechanism should assist researchers in designing synthetic routes to new drugs in the pharmaceutical industry[1].

Umpolung in organic chemistry is the chemical modification of a functional group with the aim of reversing the polarity of that group. A classic example is the benzoin condensation, which was first reported by Wöhler and Liebig in 1832. In the 1940s, Breslow found that the deprotonated thiazolium (thiazolylidene) can serve as a catalytic species.[2] His version of the mechanism (**Figure 5-1**) involves the deprotonation of thiazolium **5-1,** forming a thiazolylidene **5-2**, which nucleophically adds itself to a benzaldehyde, and then, the Breslow intermediate **5-4** is formed via a proton transfer (**5-3** to **5-4**). The Breslow intermediate possesses *Umpolung* reactivity because it adds to a second benzaldehyde (**5-4** to **5-6'**). This reaction, as well as the Stetter reaction (wherein the second addition, an enone was added) **(5-1** to **5-4** then to **5-6**) became quite popular in recent decades.[3-5]

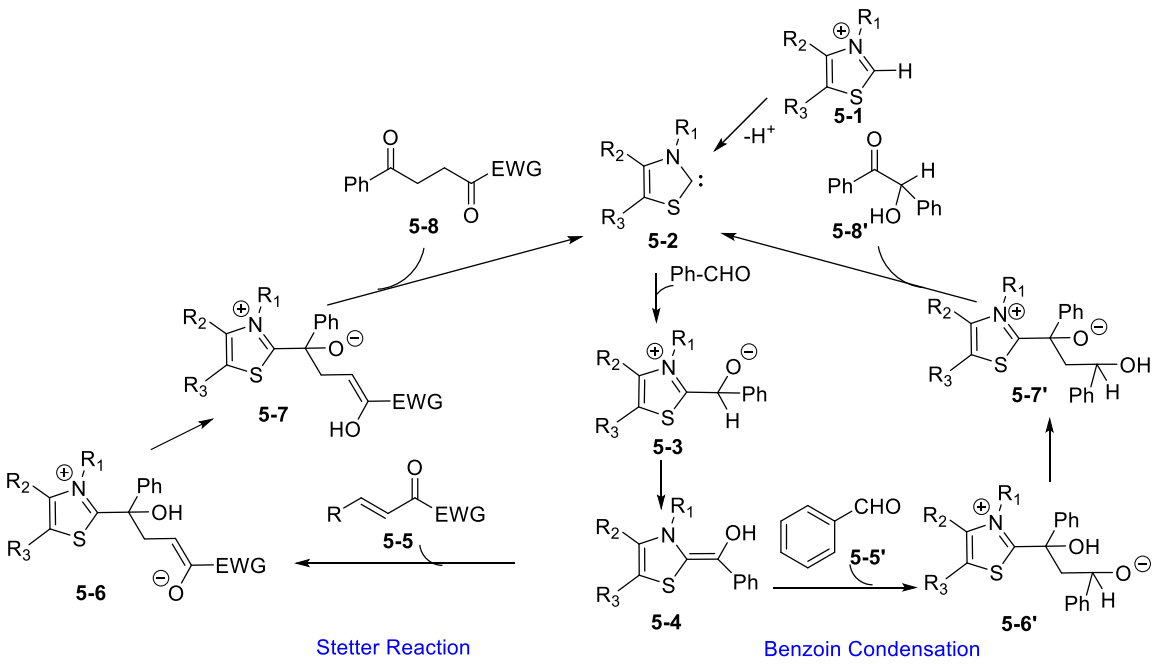

Figure 5-1. Breslow proposed deprotonated thiazolium catalyzed benzoin condensation and Stetter reaction mechanism.

Although popular, the Stetter mechanism has not been demonstrated experimentally in the gas phase. This mechanism is assumed to be similar to the benzoin condensation. However, scant evidence exists for either proposed mechanisms. [1]

In 2015, the Lee Group used a charge-tagged NHC catalyst (**5-9**, **Figure 5-2**) to help monitor the reaction in the gas phase by mass spectrometry. [6]

The results showed that during the first step, the addition of the NHC catalyst **5-9** to a benzaldehyde formed the "Breslow intermediate (**5-12**)," however, the reaction did not proceed because the "Breslow intermediate" or the final product was not detected by the mass spectrometer. The energy barrier for the proton transfer (**4c**) in the gas phase to form the Breslow intermediate **5-12** is quite high when using benzaldehyde as the substrate

(Figure 5-3, TS 1'-H). Specifically, the barrier between the zwitterion and TS1'-H is 39.4 kcal/mol. For this reason, we used benzytrimethylsilane as the substrate, whose barrier is 0.4 kcal/mol that makes reaction easily occur experimentally[7] **(Figure 5-3, TS 2'-Si)**.

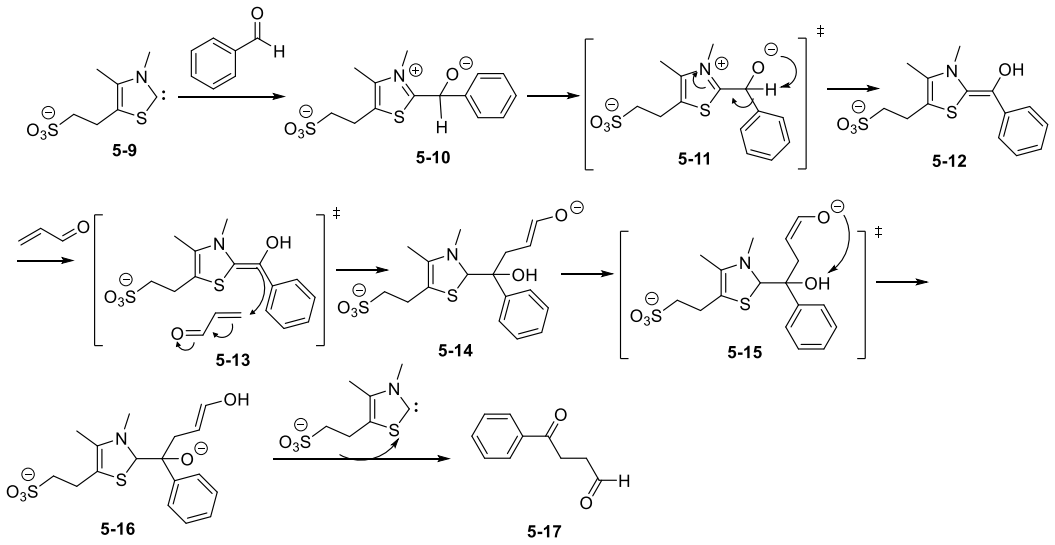

Figure 5-2. The NHC catalyzed the Stetter reaction.

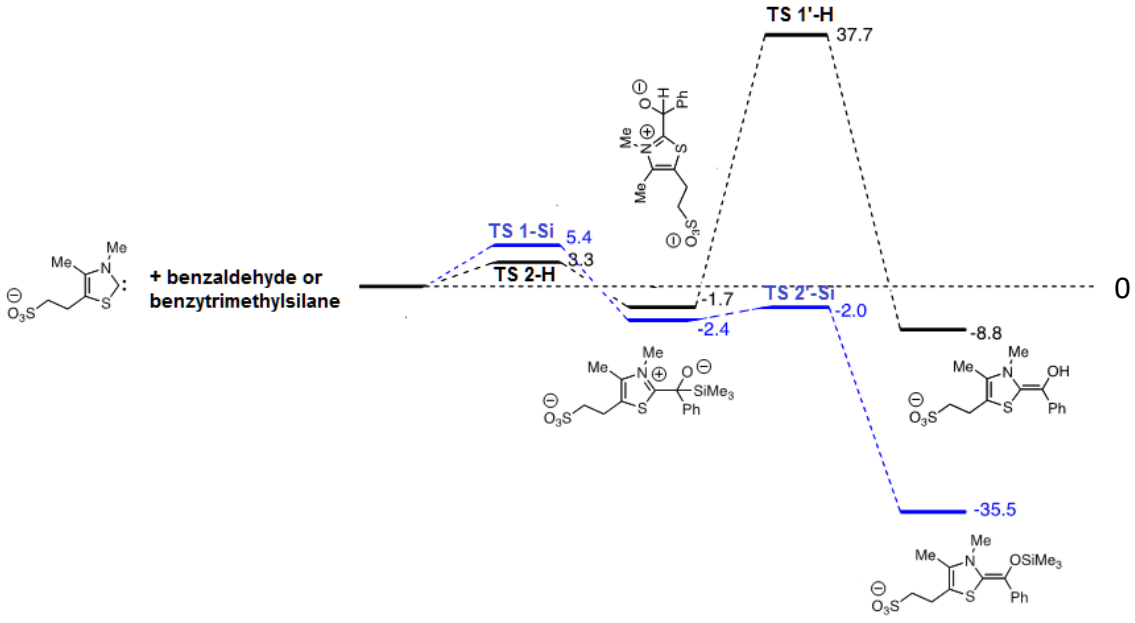

Figure 5-3. Energy barrier diagram for the first addition when using different substrates. Calculations conducted at the B3LYP/6-31+G(d) level of (ΔH, 298 K)[6]

However, the second addition reaction with enone did not easily occur experimentally in the gas phase after "Silyl-Breslow intermediate" **(Figure 5-4, 5-12')** formed, and calculations showed the reaction barrier **5-12' to 5-18'** between "Silyl-Breslow intermediate" **5-12'** and arcolein was high. But, when benzaldehyde was used as a substrate, calculations showed that although the first addition had a high barrier in proton transfer (C to O) **(Figure 5-3,** black diagram**),** the second addition with arcolein **5-12 to 5-18** was favorable.

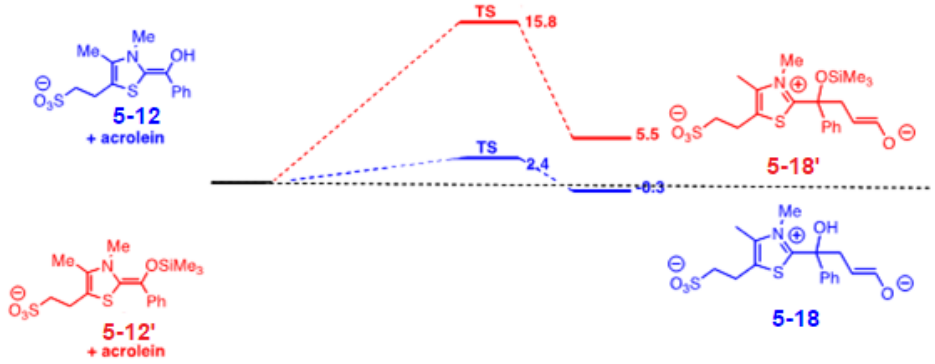

Figure 5-4. Energy barrier diagram for the second addition when using benzoyltrimethylsilane/benzaldehyde as substrate. Calculations conducted at the B3LYP/6-31+G(d) level of (ΔH, 298 K)[6]

5.2 Experimental

5.2.1 Gas phase reaction monitoring

The gas phase reaction is conducted using a modified Finnigan LCQ DUO Mass Spectrometer (**Figure 1-10**) by connecting two extra leak valves that introduce neutral

compounds into the ion analysis system (ion trap). Solutions of charged handled chemicals (such as deprotonated carbene) are introduced to the ion trap through electrospray ionization (ESI). Spectra are recorded to track the progress of reactions by giving different reaction times.

5.2.2 Computation method

Calculations are conducted at B3LYP/6-31+G(d) using Gaussian 09[8]. The geometries are fully optimized, and frequencies are calculated. No scaling factor is applied. All the values reported are ΔH at 298 K.

5.3 Results and Discussion

5.3.1 Synthesis of thiazolium carbenes with a sulfonate charge tag.

To monitor the whole Stetter reaction in the mass spectrometry, we synthesized a thiazolium carbene with a sulfonate charge tag: 3,4-dimethyl-5-(2-sulfoethyl) thiazol-3-ium iodide (**Me-NHC**)

We successfully synthesized Me-NHC by using the new synthetic route. (**Figure 5-5**)

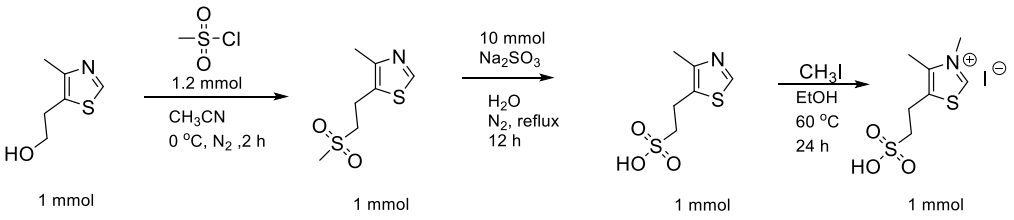

Figure 5-5. Old & New synthetic route for 3,4-dimethyl-5-(2-sulfoethyl) thiazol-3-ium iodide (**5-9**)

(1) 4-Methyl-5-(2-hydroxyethyl) thiazole (1 mmol) and methanesulfonyl chloride (1.2 mmol) was dissolved in acetonitrile under N_2, cooled the to 0 °C in an ice-water bath and 5 mmol of triethylamine was added. After stirred for 2 h, the mixture was purified by a silica gel column (eluent methanol/ethyl acetate 1:1).

(2) 4-Methyl-5-(2-methanesulfonate) thiazole (1 mmol) and sodium sulfite (10 mmol) were dissolved in 5 mL of water, refluxed for 3h, and purified on silica gel column (eluent: methanol).

(3) 4-methyl-5-(2-sulfonyl) thiazole (1 mmol) and ethyl iodide (1.5 mmol) were dissolved in 1.5 mL of ethanol. And stirred at 60 °C for 72 h, the final product was purified by alumina column (eluent: methanol).

The ^{1}H NMR (300 MHz, CD_3OD) spectrum (**Figure 5-6**) was completed: δ 2.56 (s, 3H), 3.15 (t, J = 12 Hz, 2H), 3.40 (t, J = 12 Hz, 2H), 4.18 (s, 3H). The peaks at 2.56 and 4.18 indicated that we obtained the desired structure.

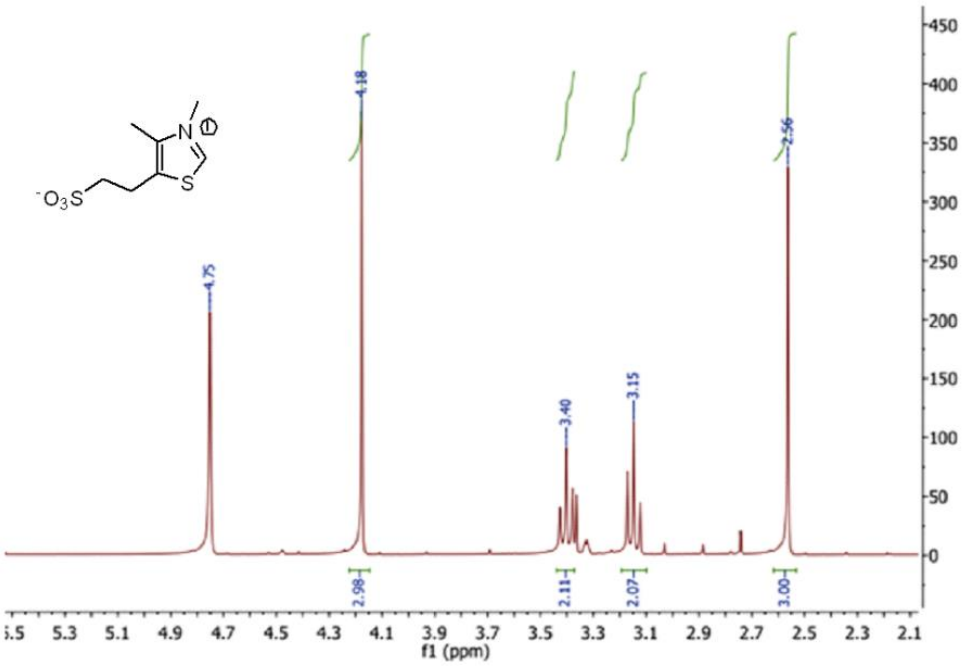

Figure 5-6. H-NMR spectrum of 3,4-dimethyl-5-(2-sulfoethyl)thiazol-3-ium iodide

5.3.2 Synthesis of saturated carbene with a positive charge tag

Meanwhile, we also successfully synthesized another saturated NHC with a positive tag with the synthetic route showing in **Figure 5-7**.

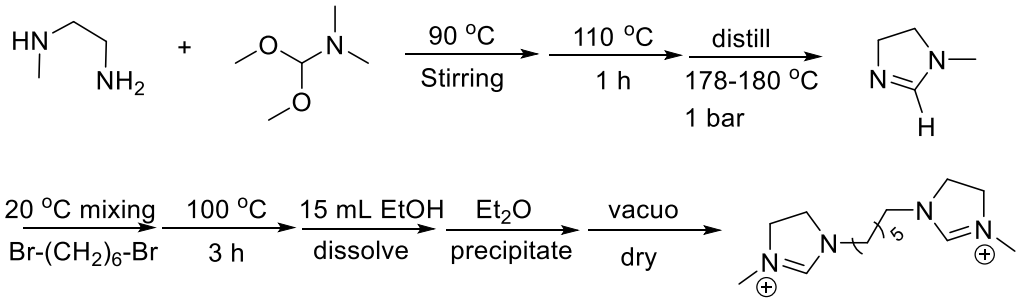

Figure 5-7. Synthetic route for saturated NHC with positive charge tag

The detailed experimental steps are:

(1) In a round-bottomed flask equipped with a 15 cm Vigreux column and distillation

bridge N-methylethylenediamine (1.416g, 19 mmol) was stirred with N,N-dimethylformamide dimethyl acetal (2.05 g,20.5 mmol) at 90 ˚C for 20 min. The mixture was heated to 110 ˚C for 1 h and then distilled to yield the product (178-180 ˚C/1 bar) as a colorless oil; The yield is 85% The product fraction contained up to 15% of DMF and 8% MeOH (determined by ^{1}H NMR spectroscopy) and was used without further purification.

(2) 1-Methyl-4,5-dihydro-1H-imidazole (0.50 g, 5.9 mmol) and 1,6-dibromohexane (0.63 g, 2.6 mmol) were first mixed at room temperature for 20 min and then heated at 100 °C for 3 h. The resulting mixture was cooled to room temperature, dissolved in EtOH (5 mL), precipitated by the addition of Et2O, decanted. Use Et_2O to wash the product 2 times, decated, and dried in vacuo. The desired salt (68%, 0.7 g) was obtained as a sticky yellow solid.

^{1}H NMR (300 MHz, D_2O): δ = 8.03 (s, 2 H, 2 NCHN), 3.95 (s, 8 H, 2 NCH_2CH_2N), 3.47 (t, 4 H, J = 7.1 Hz, 2 NCH_2), 3.15 (s, 6 H, 2 NCH_3), 1.70 (m, 4 H, 2NCH_2CH_2), 1.37 (m, 4 H, 2 $NCH_2CH_2CH_2$). (**Figure 5-8**)

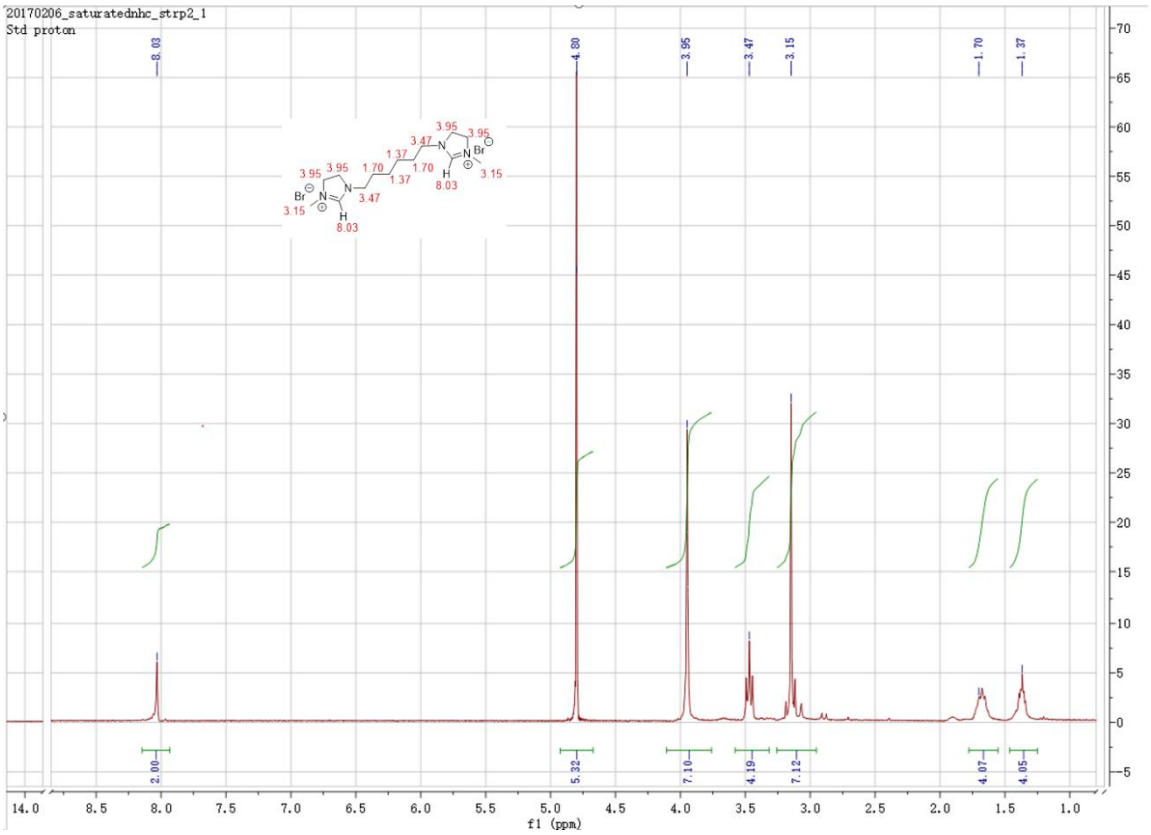

Figure 5-8. H-NMR spectrum of saturated NHC with positive charge tag

5.3.3 Computational Results in the Gas Phase

Although the "Sily-Breslow intermediate" was formed in the 1st addition, the second addition to enone (**Figure 5-4, 5-12' to 5-18'**) has a high barrier.

To decrease the barrier, we proposed to use F-substituted enones (commercially available) in the second addition. F-substituted enones (**Figure 5-9, structure 5-19 to 5-23**) are more electrophilic than enone. Thus the reaction will be easier.

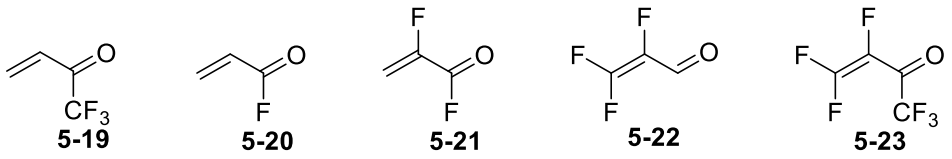

Figure 5-9. A series of F-substituted enone

Before conducting experiments in the gas phase, computations will be carried out to select the most suitable F-substituted enone with the lowest reaction barrier. The instrument set up will be the same as **Figure 1-10** showed.

Computations were conducted at B3LYP/6-31+G (d) by Gaussian09. [22] The geometries were fully optimized, and the frequencies calculated. No scaling factor was applied. All the values reported are enthalpies at 298 K in kcal/mol. The computational energy diagram for the second addition was shown in **Figure 5-10**.

A reaction between all F-substituted enones and "Sily-Breslow intermediate" was studied computationally.

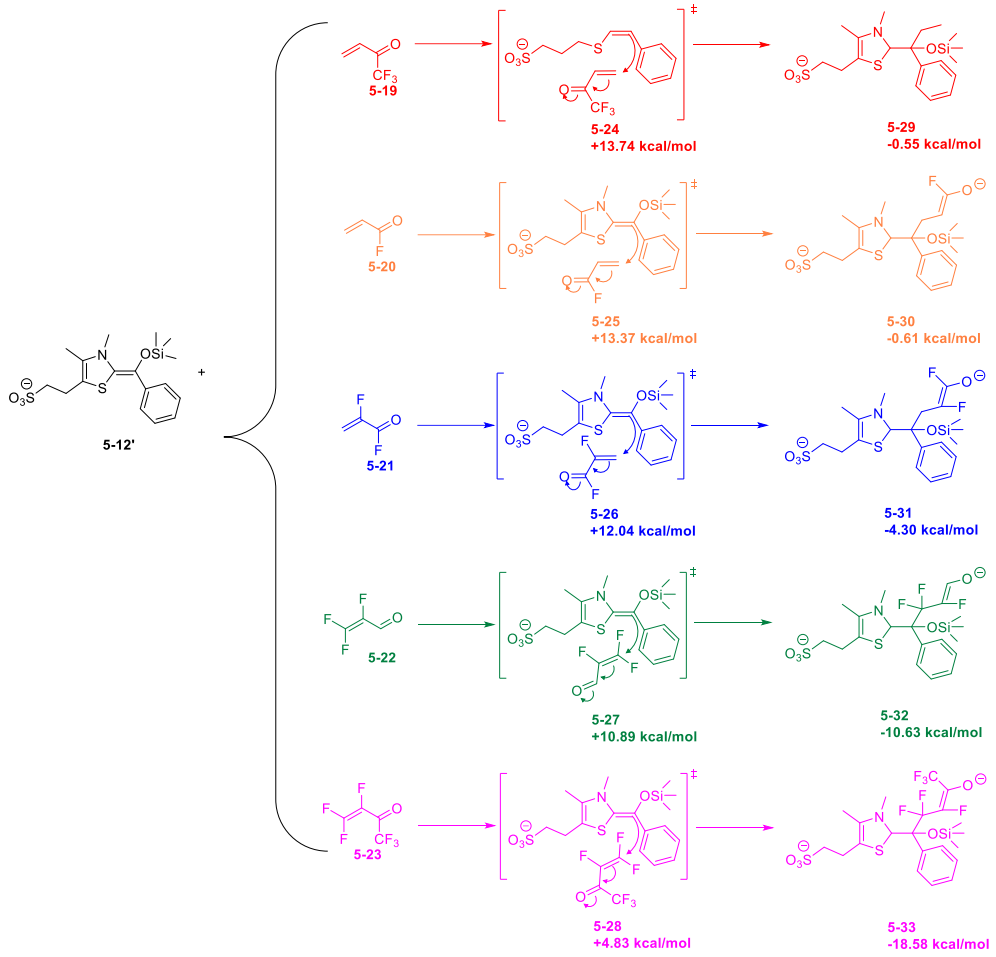

Figure 5-10. Calculated [B3LYP/6-31+G(d)] enthalpies (298 K) for gas phase reaction of catalyst methyl N-substituted carbene with benzoyltrimethylsilane in the first addition and different F-substituted enone in the second addition

From **Figure 5-10**, the second addition's energy differences between starting material Sily-Breslow intermediate and enones) and the transition state differs from each other with the increasing number of substituted F atoms.

We found that the reaction barrier of the second addition step with 1,1,1,3,4,4-hexafluorobut-3-en-2-one (**5-23**) is 4.9 kcal/mol, much lower than with enone (>20

kcal/mol), which indicates that the reaction will occur in the gas phase. In this way, the final product 2,2,3,5,5,5-hexafluoro-1-phenyl-4-((trimethylsilyl)oxy) pent-3-en-1-one **5-33** will be observed if the second addition occurs.

5.3.4 Experimental Results in the Gas Phase

PhCOSiMe$_3$ react with 3,4-dimethyl-5-(2-sulfoethyl)thiazol-3-ium in the LCQ:

The actual experimental result is not as expected. The signal for 3,4-dimethyl-5-(2-sulfoethyl) thiazol-3-ium is in low intensity in the LCQ mass spectrometer due to the low spray voltage we can reach. (**Figure 5-11**) As showing in Figure 5-9, the relative abundance of the m/z 220 is less than 3E03; the subsequential reaction will be affected by this low signal. Thus, we decided not to continue with this molecule.

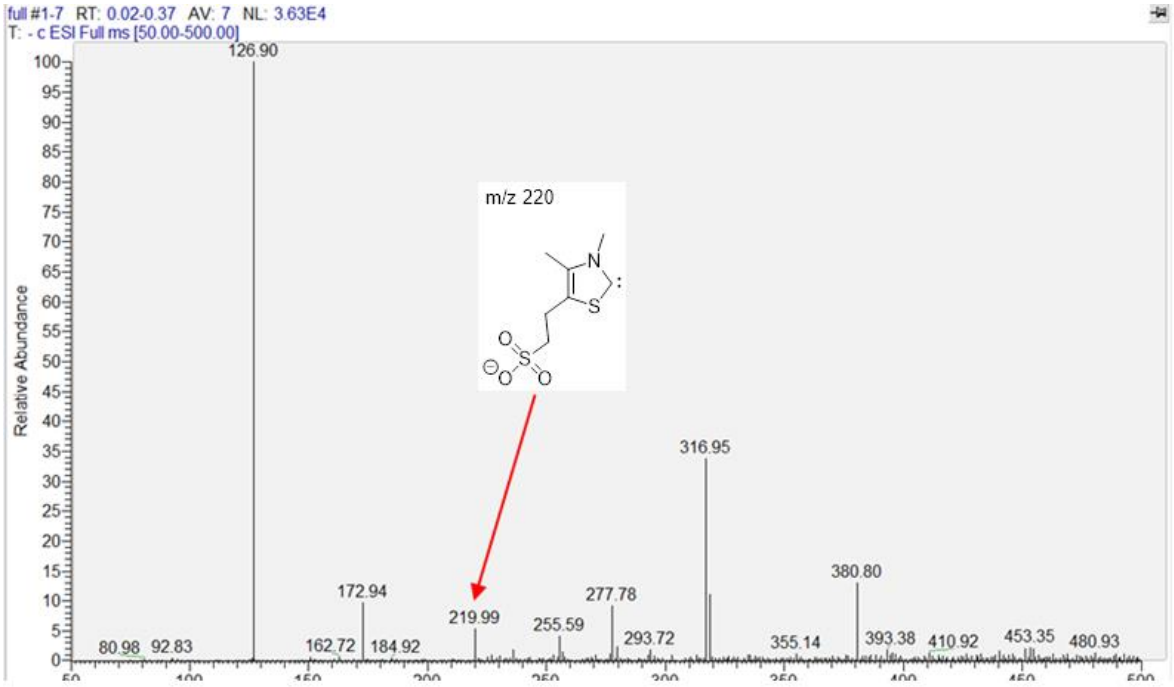

Figure 5-11 Mass spectrum 3,4-dimethyl-5-(2-sulfoethyl)thiazol-3-ium, full scan

2-Br-benzaldehyde, enone react with saturated NHC with positive charge tag in the LCQ:

As **Figure 5-12** shows, the saturated NHC with a positive charge tag gives a better signal in the LCQ than 3,4-dimethyl-5-(2-sulfoethyl)thiazol-3-ium. The overall signal is higher than 10E6. We can proceed to the gas phase reaction stage.

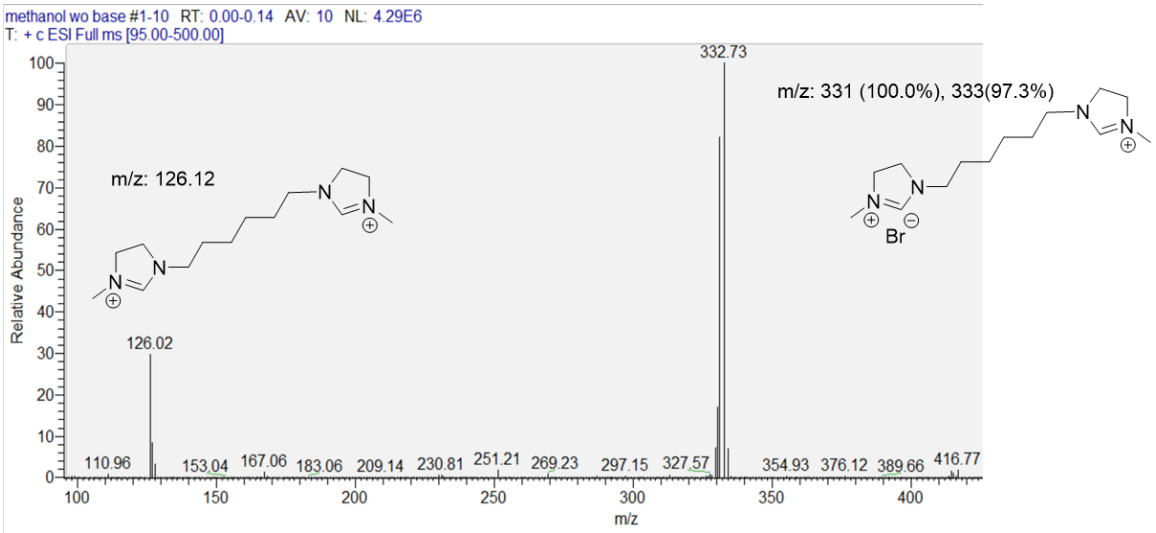

Figure 5-12 Mass spectrum saturated NHC with positive charge tag, full scan

When using the positive charged tag NHC, mix the 2-Br-benzaldehyde in 10^{-4} M MeOH solution, with 1% NH_4OH added. ESI the solution mixture to LCQ. Meanwhile, acrolein was introduced to LCQ by leak valve. The spectrum for the gas phase reaction is showing in **Figure 5-13**.

No peak related to the "Breslow intermediate" (m/z 435 and 437) is observed. But the peak of Breslow intermediate adduct with acrolein was observed. When isolating the peak m/z 491, the CID result cannot be interpreted. The peak of 266 and 320 cannot be

identified.

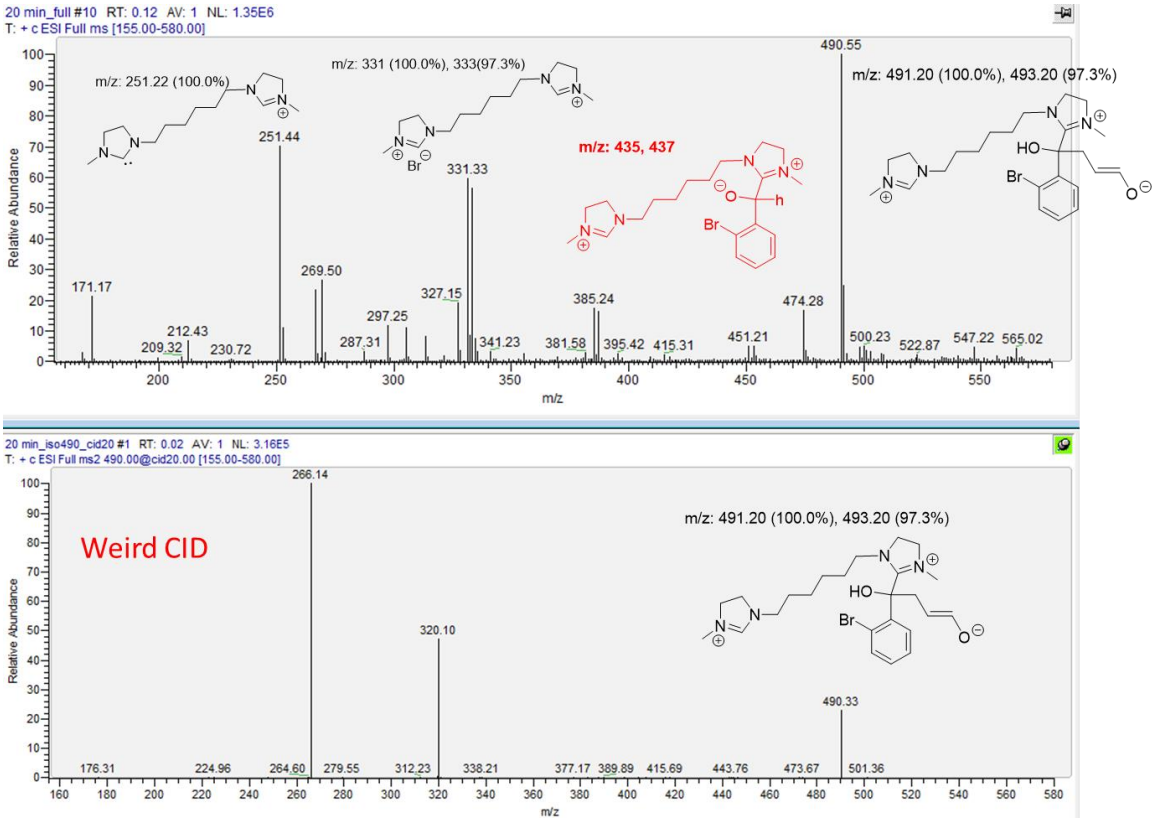

Figure 5-13 Mass spectrum saturated NHC with positive charge tag react with 2-Br-benzaldehyde, enone, full scan

5.4 Conclusions

In this Chapter, the computational and experimental study for N-Heterocyclic Carbene-Catalyzed Stetter Reaction Mechanism was conducted. One negative charged tagged NHC and one positive charged tagged NHC were synthesized and tested in the LCQ. Experimental results indicated that the negative charged tagged NHC 3,4-dimethyl-5-(2-sulfoethyl)thiazol-3-ium's signal in the LCQ is inadequate and too weak for the subsequent

steps. The positive charged tagged NHC gives a better signal in the LCQ mass spectrometer which is a suitable catalyst to study the Stetter reaction in the gas phase. However, the expected reaction intermediate " Breslow Intermediate" was not observed in the gas phase, further consideration in choosing the suitable substrates need to be performed in order to monitor the reaction process and capture the critical reaction intermediates in the gas phase.

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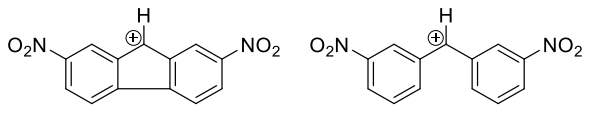
Chapter 6. Gas Phase Studies of Fluorenylidene versus Diphenyl Carbene

6.1 Introduction

Measuring proton affinities (PAs) of carbene in the solution phase by monitoring the exchange of isotopes in water[1-4] or tracking free carbene reacting with hydrocarbon indicators in DMSO or THF [5-7] have been developed over the past years. However, this measurement strategy is highly solvent dependent, that is because carbenes are solvated in the solution. In the gas phase, there is no need for carbene to break the solvation case to get protonated. Thus PA of carbene in the gas phase is intrinsic to the carbene entity. The gas phase of PAs of carbene can be measured by bracketing experiment.[8-10]

The basicity of a series of reactive diarylcarbenes has been studied recently [8]. However, there are still a bunch of interesting potential substrates to be studied. One series of substrates could be 2,7-dinitrofluorenyl cation (**6-1**) and bis(3-nitrophenyl)methylium (**6-2**). By studying and comparing the gas phase proton affinity of **6-1** to **6-2**, we can get a better understanding of how antiaromaticity can affect cations acidities and identify the possible rearrangements of fluorene cations in the gas phase.



6-1 **6-2**

Figure 6-1. Substrates to be studied

6.2 Experimental

6.2.1 Quadrupole ion trap bracketing method

The gas phase reaction is conducted using a modified Finnigan LCQ DUO Mass Spectrometer (**Figure 1.10**) by connecting two extra leak valves that introduce neutral compounds into the ion analysis system (ion trap). Solutions of charged handled chemicals (such as deprotonated carbene) are introduced to the ion trap through electrospray ionization (ESI). Spectra are recorded to track the progress of reactions by giving different reaction times.

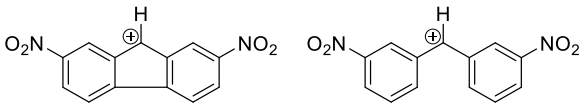
6.2.3 Computation method

Calculations are conducted at B3LYP/6-31+G(d),[11-13] using Gaussian 09[14]. The geometries are fully optimized, and frequencies are calculated. No scaling factor is applied. All the values reported are ΔH at 298 K.

6.3 Results and Discussion

6.3.1 Gas Phase Acidity Computation

The computed gas phase acidity of 7-dinitro-9H-fluorene-9-ylium (**6-1**) is 253.7 kcal/mol and bis(3-nitrophenyl)methylium (**6-2**) is 252.7 kcal/mol under B3LYP/6-31G(d) level of theory. This result could aid us in choosing the proper reference bases for the gas phase bracketing experiments.



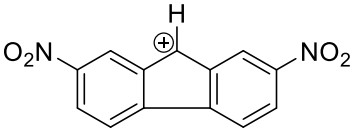
6-1 253.7 kcal/mol **6-2** 252.7 kcal/mol

Figure 6-2 Computed gas phase acidities of 6-1 and 6-2 at B3LYP/6-31+G(d) level of theory.

6.3.2 Gas Phase Bracketing Experiment result

The bracketing experiments were performed by using our in-house Thermo Finnigan LCQ (ESI-3D quadrupole ion trap). The experiment summary is shown in **Table 6-1**.

Table 6-1 Summary of bracketing for 2,7-dinitrofluorenyl cation **6-1**.



Experimental PA: 237 ± 2 kcal/mol
Calculated PA: 251.7 kcal/mol

Ref. Compound	Proton Affinity (kcal/mol)	Proton Transfer
N,N,N',N'- tetramethyl-1,3-propanediamine	247.4	+
N,N,N',N'-tetramethylethylenediamine	242.1	+
Tributylamine	238.6	+
N,N'-dimethylcyclohexylamine	235.1	-
N-methylpiperidine	232.1	-

"+" symbol indicates the occurrence of proton transfer, and the "-" symbol indicates no proton transfer reactions.

We found that reference bases Tributylamine (PA = 238.6 kcal/mol), TMEDA (*N,N,N′,N′*-tetramethyl-1,2-ethanediamine, PA = 242.1) and TMPDA (*N,N,N′,N′*-

tetramethyl-1,3-propanediamine, PA = 247.4 kcal/mol) all become protonated in the presence of **6-1**.

However, *N,N'*-dimethylcyclohexylamine (PA = 235.1 kcal/mol) and *N*-methylpiperidine (PA = 232.1 kcal/mol) were both unable to deprotonate 6-1. We, therefore, bracket the acidity of the 2,7-dinitrofluorenyl cation **6-1** to be 237 ± 3 kcal/mol.

Clearly, there is a discrepancy in the experimental and computational PA of cation **6-1**.

6.3.3 Discussion

We all the discrepancy in the experimental result and calculated result of cation 6-1. The reason is probably due to the high reactivity that destabilized the cation 6-1. One possible reason is the cation **6-1** rearranged in the gas phase before the deprotonation as the cation **6-1** itself is highly reactive. Three possible cationic isomers of cation **6-1** and their deprotonation pathways were computed. (**Figure 6-3**). However, the actual measured gas phase acidity of cation **6-1** can not be achieved with these possibilities.

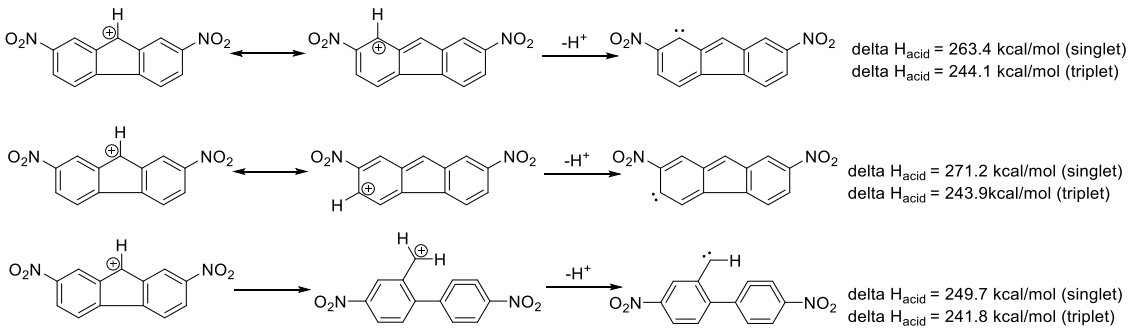


Figure 6-3 Possible deprotonation pathways and the calculated gas phase acidity of cation **6-1**

6.4 Conclusion

In this Chapter, the gas phase acidity of 2,7-dinitrofluorenyl cation and 2,7-dinitrofluorenylidium were computed under the B3LYP/ 6-31+G (d) level of theory. The gas phase acidity of 2,7-dinitrofluorenyl cation was measured by quadrupole ion trap bracketing method. The large discrepancy in the experimental result and calculated results were observed. Further study needs to be performed to investigate how this discrepancy occurs or to validate if the discrepancy is due to the instrumental error or alternative deprotonation pathway.

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