Investigations into the H-D Exchange of Malonganenone B

by
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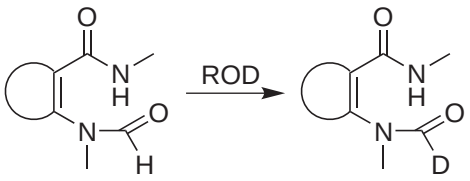
Abstract

H-D exchange at the formyl residue of the natural product malonganenone B was investigated. Models of the system were synthesised and displayed the same exchange. Kinetic studies, performed using NMR spectroscopy, found the exchange was first order with respect to base whilst displaying acid inhibition, in opposition to existing research. Cyclic species, including an N-heterocyclic carbene precursor, were formed that, in conjunction with the previous findings, suggested a carbene-based mechanism was in operation. Further synthetic studies were performed to demonstrate the existence of a carbene. With use of silver oxide, a fulvalene dimer and an organopalladium complex of this carbene were obtained, which provide further support towards a carbene-based mechanism being involved in the H-D exchange of malonganenone B.



Acknowledgements

There's no earthly way of knowing,
Which direction we are going.
There's no knowing where we're rowing
Or which way the river's flowing.

Roald Dahl, *Willy Wonka and the Chocolate Factory*

Thank you to Dr. Rob Keyzers, my long-suffering supervisor. Without the long discussions and guidance I doubt this project would have been anywhere near as fruitful. Also without his humour and our *interesting* supervisor-student relationship this project would have been much more dull.

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Glossary

at	acquisition time
d1	relaxation delay between pulses
DMF	dimethylformamide
DMFDMA	dimethylformamide dimethylacetal
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
min	minute(s)
MS	mass spectroscopy
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
nt	number of transients
pad	pre-acquisition delay
pw	pulse width
R^2	coefficient of determination
RDS	rate-determining step
rt	room temperature
SOMO	singly occupied molecular orbital
$t_{1/2}$	half-life
THF	tetrahydrofuran
UV	ultra-violet

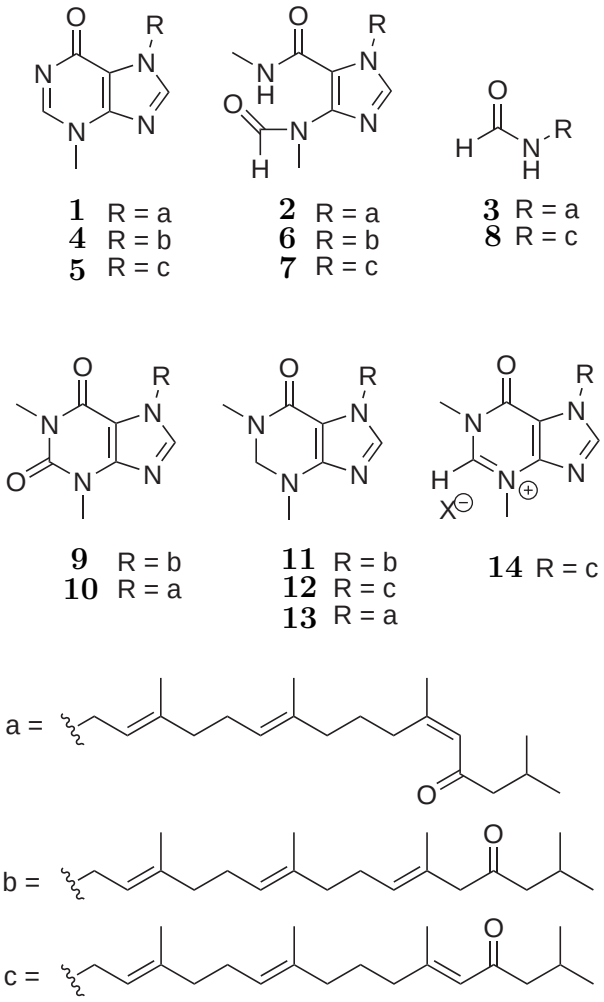
Chapter 1

Introduction

1.1 Malonganenone B and H-D exchange

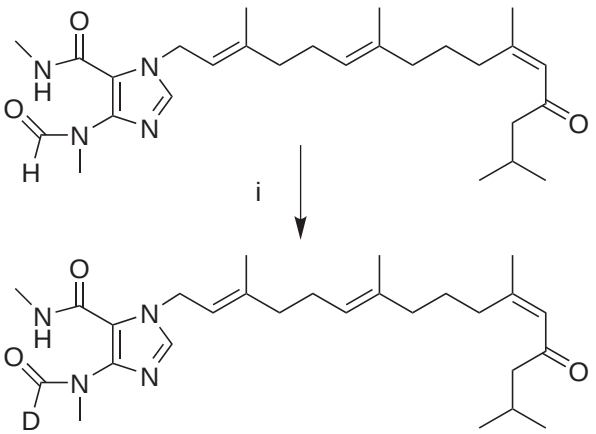
Two related families of natural products have been reported from African gorgonian species. Gorgonians (order Gorgonacea of the phylum Cnidaria) are commonly known as sea fans or sea whips. The gorgonian *Leptogorgia gilchristi*, collected from a reef near Ponto Malongane, Mozambique, yielded three novel prenylated alkaloids, malonganenones A (**1**), B (**2**) and C (**3**).[1] These bear the same tetraprenyl chain, but differ in their head groups; malonganenone A features a hypoxanthine moiety, B a substituted imidazole system and C a simple formamide. These compounds were re-isolated from a different gorgonian, *Euplexaura nuttingi*, from Uvinage, Pemba Island, Tanzania, alongside malonganenones D-H (**4**–**8**) and the nuttingins A-F (**9**–**14**).[2] The later malonganenones differ in their tetraprenyl tail, whereas the nuttingins feature different purine-based alkaloid heads but with the same range of tails. Malonganenones A-C were found to exhibit moderate cytotoxic effects against oesophageal cancer,[1] which is a major health concern in southern Africa.[3] Similarly, malonganenones D-H and the nuttingins were tested for activity against both K56224 and UT725 human leukaemia cell lines, for which they demonstrated moderate inhibitory action on cellular proliferation.[2]

The structural elucidation of malonganenone B was particularly problematic. Mass spectral analysis, which followed NMR acquisition in methanol-d_4, resulted in two strong molecular ion peaks, the difference between which was substitution of a proton for a deuteron (m/z 471.3335 and 472.3398, respectively).[1] Comparison of the 1D and 2D NMR data with malonganenones A and C suggested they share the same tetraprenyl chain but B instead bears an imidazole ring with N-methylamide and N-



methylformamide substituents. The data suggested the presence of two isotopomeric carbonyls at the formamide, which, in addition to the lowered proton integration at this position and the presence of a deuterated analogue as indicated by MS, suggested that the formamide proton, rather than the *N*-H of the methylamide, had exchanged for a deuteron whilst dissolved in methanol-d_4 [Scheme 1.1]. In support of this, a sample exposed to methanol for a number of days showed full return of the proton integration at the formyl position by ^{1}H NMR.

Hydrogen-Deuterium (H-D) exchange is a well known phenomenon, but not with these conditions or functionalities. H-D exchange is an established field utilised in the production of isotopically-labelled standards for use in studies elucidating mechanistic theories or C-H bond activation.[4,5] These studies rely upon establishment of an equilibrium between the carbon-bound protons and the deuterons in the reagents, whereupon there is a drive for preferential formation of a C-D bond over a C-H bond. This is due in part to the increased stability of a C-D bond arising from the greater mass of a deuteron lowering the vibrational frequency and hence lowering the zero point energy. However, the preference in these reactions mainly exists due to the large excess of deuterium from the solvent compared to protons from the reactant driving the equilibrium. These reactions usually involve acid, base or



Scheme 1.1 H-D exchange at the formyl centre of malonganenone B

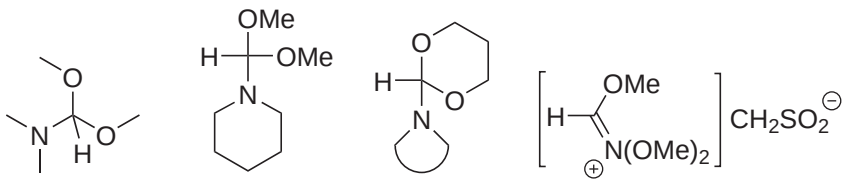
metal catalysis. With malonganenone B, however, this occurs in methanol-d_4 with a notable absence of any of the aforementioned catalytic species. In addition, these exchanges usually occur at positions on π-ring systems or at the α- or β-positions of carbonyl functionalities; however, exchange in species similar to malonganenone B has been reported once before, also in the absence of any notable catalysts, by Simchen & co-workers at the University of Stuttgart.

1.2 Simchen's work on the H-D exchange of *N,N*-dialkylformamide acetals

As with many discoveries in science, this curious H-D exchange was serendipitously found. Following previous findings that chloroform readily exchanges its proton in the presence of a base[6] but that orthoformate esters do not,[7] Simchen and co-workers began investigating electrophilic substitution at the formyl carbon of orthoformamides via the acidity of the formyl proton through base-catalysed H-D exchange.[8] During this work, it was found that *N,N*-dimethylformamide acetals exchanged their formyl protons in deuteroalcohols without *any* catalyst. A correlation was found that increasing the alkyl chain length, and hence acidity, of the deuteroalcohol decreased the rate of exchange.

This initial work was followed with a more comprehensive study, in which Simchen investigated the H-D exchange of a number of derivatives to probe the mechanism in operation. The study was based around the compound dimethylformamide dimethylacetal (DMFDMA, **15**), where it was found that increasing the alkoxy chain length, and hence the pK_a of the resultant alcohol, led to a decrease in H-D exchange, in contrast to an initial increase in rate with increasing length of the nitrogen-alkyl

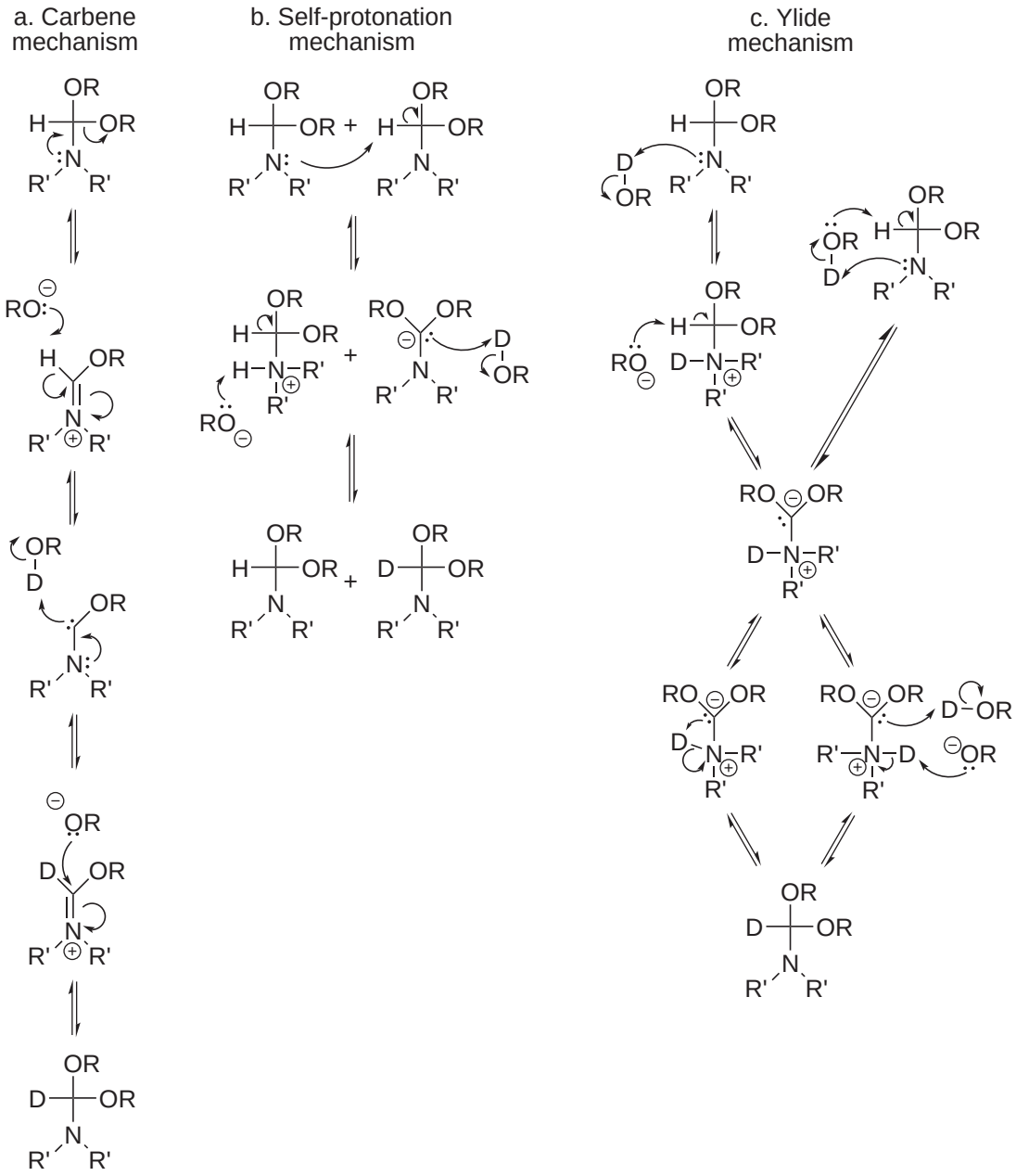
chains. A decrease in rate with larger nitrogen-alkyl chains was attributed to competing steric factors at the nitrogen centre. Derivatives with cyclic-nitrogen substitution were synthesised, for example the piperidine derivative **16**, which showed a decrease in exchange compared to the original methyl model. Cyclic acetals, **17**, were also synthesised, but no H-D exchange occurred provided the ring did not open. To specifically probe a carbene mechanism, carbene-precursor iminium compounds, *e.g.* **18**, were made which also did not exhibit any H-D exchange, even upon heating and addition of base, to facilitate removal of the proton to form the carbene. Due to the fact that protons shift repeatedly in this exchange, kinetic studies in the presence of exogenous bases, such as sodium methoxide and triethylamine, were performed. Addition of an exogenous base was found to inhibit H-D exchange at the formyl centre, which was critical in elucidating the mechanism of this exchange.



15 **16** **17** **18**

Based on these results, Simchen proposed three mechanisms for the H-D exchange.[9] The three proposed were [Scheme 1.2]; a. a carbene mechanism in which nitrogen-assisted elimination of an alkoxy group precedes removal of the formyl proton, generating a carbene that may then extract a deuteron from the solvent; b. a self-protonation mechanism in which the nitrogen of one molecule abstracts the formyl proton of another, similarly followed by deuterium-quenching of the resulting carbanion; c. a mechanism in which deuteration of the nitrogen and solvent abstraction of the formyl proton, concerted or stepwise, generates an ylide, which undergoes either a 1,2-deuterium shift or incorporation of a deuteron from the solvent.

The findings were interpreted by Simchen as disproving two of the suggested mechanisms. In support of a carbene mechanism, the decrease in H-D exchange with increasing size of the N-alkyl groups was reasoned as due to increasing hindrance to co-planarity, and that H-D exchange has been seen for related cyclocarbonium ion species[10] and cyclic nucleophilic carbenes.[11] It was argued that base would not influence the reaction due to a balance between the effects on the dealkoxylation and deprotonation steps, although this assumes an exact balance and one would expect that catalysis in the rate-determining step (RDS) would have a larger effect on the rate. The greatest evidence against this mechanism is that the carbene precursors did not exhibit H-D exchange. In support of the self-protonation mechanism there was a positive correlation between exchange and basicity of the nitrogen, reasoned



Scheme 1.2 Simchen's proposed mechanisms for H-D exchange

as due to an increase in the rate of self-protonation. But, again, inhibition by an exogenous base disfavours this mechanism. Technically, other agents should have no effect as only two acetal molecules are involved in the RDS, however a foreign base could directly deprotonate the acetal leading to an apparent increase in H-D exchange, or act to increase the concentration of the free amine by competing for deuterium ions, which would actually increase the rate.

Simchen concluded from this research that the findings best supported an ylide mechanism, but this author is sceptical about the assignment. An initial increase in nitrogen basicity with increasing size of alkyl chain would act to increase the rate of deuteration, until the size of the alkyl groups became sterically hindering. The carbene-precursor derivatives could not exchange through this mechanism, in

correlation with the observations. Most importantly, however, addition of a foreign base would compete for deuterium with the formyl acetal nitrogen and hence is the only mechanism that accounts for the observed base-inhibition. Why the cyclic acetals and nitrogen substituents did not react was discussed but largely unreasoned. Notwithstanding this, the hypothesis that best fits the available data for the H-D exchange, according to Simchen, is the ylide mechanism; which may be correct, when one neglects the base activation in the proposed RDS of this mechanism. In the opinion of this author, the results of the study were not definative: all the mechanisms were supported by some of the data, but no mechanism was supported by all the data. The most conflicting piece of information is the base inhibition as the two main mechanisms, ylide and carbene, should be base catalysed. Further investigation is therefore required to confirm the mechanism.

1.3 Kinetic studies

To gain insight into the mechanism, an investigation into the kinetics of the exchange was required. Of key importance is ascertaining the species involved in the RDS and their order. This can be done simply by performing kinetic studies and analysing the rate of exchange with respect to concentrations of the different species.[12] For a generic reaction, such as shown in Equation 1.1, the rate is equal to the rate of change of concentation of each species involved proportional to their stoichiometry [Equation 1.2]. This generic reaction would give rise to a rate law of the form such as Equation 1.3, where the rate is dependent on the concentration of each species to the power of its stoichiometry in the RDS. A number of manipulations of these simple equations are available to allow mechanistic data to be found experimentally.

$$nA + mB \rightarrow xX + yY \tag{1.1}$$

$$rate = -\frac{1}{n}\frac{dA}{dt} = -\frac{1}{m}\frac{dB}{dt} = \frac{1}{x}\frac{dX}{dt} = \frac{1}{y}\frac{dY}{dt} \tag{1.2}$$

$$rate = k[A]^n[B]^m \tag{1.3}$$

The order of a species in a reaction can be obtained from analysis of the initial rate of reaction. The Initial-Rate method is based upon the approximation that over

the first 10% of change in a reaction, the rate of change of a species with time can be approximated by the rate of change of concentration of that species [Equation 1.4]. Applying a linear model to the change in concentration with time gives an estimate of the initial rate. If the rate is measured at two different concentrations of a molecule, while other species are held constant, Equations 1.5 and 1.6 can be defined to describe these situations, which can be combined and have common factors eliminated to give Equation 1.7. As can be seen, taking the logarithm of this equation, Equation 1.8, would result in a plot of $\log(r_1/r_2)$ against $\log([A]_1/[A]_2)$ having a straight line of slope n, where n is the order of the species investigated. This method has certain advantages in that complex rate equations can be simplified easily and the orders obtained. However, fitting a linear model to obtain the initial rate is affected hugely by any delay to the acquisition of data. Similarly, the fact that a linear model is being applied to an exponential curve means that the data is not always accurate. Finally, this method only allows two sets of data to be used at any one time and an array must be used to generate enough data points to be confident of any result.

$$-\frac{dA}{dt} \simeq -\frac{\Delta A}{\Delta t} \tag{1.4}$$

$$r_1 \simeq -(\Delta A/\Delta t)_1 = k[A]_1^n[B]^m \tag{1.5}$$

$$r_2 \simeq -(\Delta A/\Delta t)_2 = k[A]_2^n[B]^m \tag{1.6}$$

$$r_1/r_2 = ([A]_1/[A]_2)^n \tag{1.7}$$

$$\log(r_1/r_2) = n\log([A]_1/[A]_2) \tag{1.8}$$

An alternative method to obtain this data is by measuring the half-life. The half-life is the time required for the concentration of a species from any point to decrease by a half. Applying an exponential model to the concentration of species in the reaction with time allows the κ value to be obtained [Equation 1.9]. Taking the logarithm of this equation [Equation 1.10], substituting in [concentration] = 0.5 and $t = t_{1/2}$, and rearranging, the Equation 1.12 can be obtained. Substituting in the κ value

obtained for a particular kinetic experiment allows the half-life to be calculated. The Half-Life method can then be used to investigate the half-life as a function of initial concentrations. If the concentration of all other species are kept constant, then the rate law Equation 1.3 becomes Equation 1.13, with a new k' value that incorporates $[B]^m$. Integrating this equation and substituting in $A = A_o/2$ and $t = t_{1/2}$, the Equation 1.14 can be obtained, the logarithm of which can be rearranged such that plotting $\log t_{1/2}$ against $\log A_o$ should describe a straight line of slope $(1-n)$ [Equation 1.15]. Provided data is collected over a number of half-lives, this provides a more accurate assessment of order than the Initial-Rate method. However, if the H-D exchange for a particular analyte is too long, this method becomes impractical.

$$[concentration] = exp^{-\kappa.t} + c \tag{1.9}$$

$$log([concentration]) = -\kappa.t + c' \tag{1.10}$$

$$log(2) = \kappa.t_{1/2} \tag{1.11}$$

$$t_{1/2} = log(2)/\kappa \tag{1.12}$$

$$-\frac{dA}{dt} = k'[A]^n \tag{1.13}$$

$$t_{1/2} = \frac{2^{n-1} - 1}{(n-1)kA_o^{n-1}} \tag{1.14}$$

$$\log t_{1/2} = (1-n)\log A_o + \mathrm{C} \tag{1.15}$$

1.4 N-heterocyclic carbenes

The area of carbene chemistry has been greatly explored since Simchen's work was completed.[13] The concept of divalent, uncharged carbon atoms, or carbenes (**19**), in

a molecule was first suggested in 1855 by Geuther and Hermann.[14] Their work was carried along over the following century by research into radicals, where carbenes were treated as diradicals, but there was only a true resurgence in the area following Doering's demonstration in 1954 of a dibromomethylene intermediate in the alkaline hydrolysis of bromoform.[15] In this work a carbene was trapped with an alkene in a new cyclopropanation reaction, the first demonstration of a carbene. Much work has gone into their geometric and electronic properties.[16] These can be either triplets or singlets, with a lone pair or two singly-occupied orbitals respectively, which are strongly influenced by any α-substituents. These substituents also dictate whether the carbene is electrophilic or nucleophilic.

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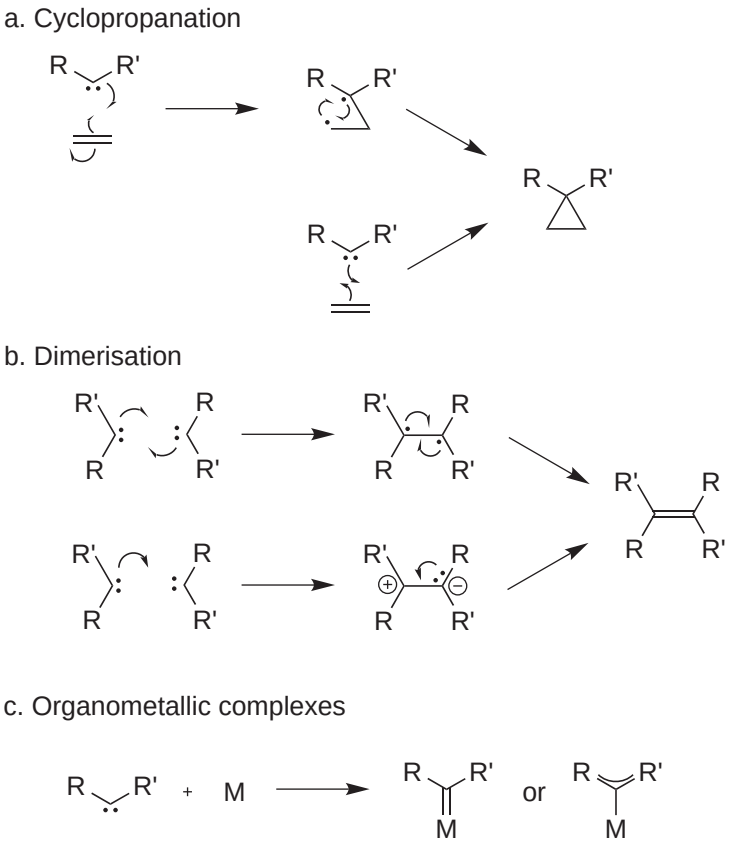
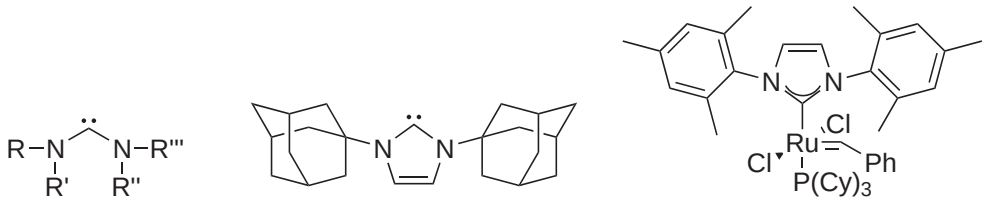
Carbenes can undergo a range of different reactions to generate a number of different species. Cyclopropanation reactions with carbenes are of historical importance as this was used to first prove their existence.[15] The mechanism of this reaction is dependent upon the nature of the carbene; triplet carbenes react through two radical steps and therefore give a mixture of *cis* and *trans* isomers, whereas singlet carbenes react in a single pericyclic step to give only the *cis* product [Scheme 1.3.a]. As with most reactions, matching the energy of the alkene to that of the carbene



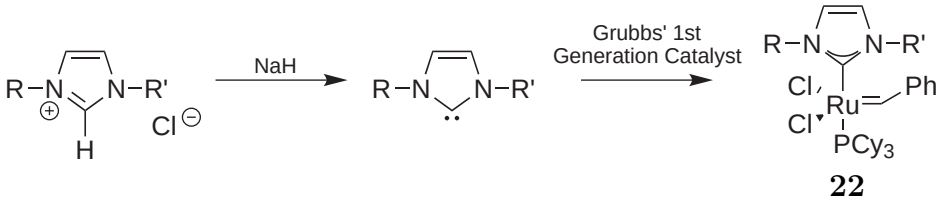
Scheme 1.3 Some general reactions of carbenes

is of crucial importance. Carbenes can alternatively react with themselves to form dimers [Scheme 1.3.b]. Each carbene has an unoccupied orbital, no formal charge to repel the other and have high reactivity, plus strong carbon-carbon double bonds are the outcome of such dimerisation. As they are identical in energy, matching of HOMO and LUMO levels for singlet-carbene dimerisation is not possible; however, the SOMO levels of the diradical triplet carbenes match exactly and have good orbital overlap. As a result, it is expected that triplet carbenes dimerise faster than singlets. The most recent development is the use of carbenes as organometallic ligands [Scheme 1.3.c]. When binding to metals, the carbene centre is stabilised either by back-donation from the metal or by lone pairs of the α-substituents. Historically, these complexes have not been that stable.



20 **21** **22**

This changed with the development of N-heterocyclic carbenes (NHCs) (**20**). Carbenes with two amino substituents were first proposed at the time of Simchen's investigations by Öfele and Wanzlick in 1968.[17,18] The field was largely ignored, however, until Arduengo demonstrated the first instance of a stable free NHC, the diadamantyl-substituted imidazolylidene **21**.[19] NHCs typically form singlet carbenes, due to stabilisation of the empty carbon p-orbital from overlap with the lone pairs of the nitrogen atoms. This intramolecular stabilisation of the carbenic center helps to prolong the lifetime of NHCs. In addition, the two nitrogen substituents, through electron-donation, mean NHCs are quite nucleophilic. Although many methods to prepare these are known,[13] they are most commonly synthesised from the corresponding imidazolium salt that is deprotonated to give the free NHC, as occurs in the synthesis of Grubbs' 2nd generation catalyst (**22**) [Scheme 1.4].[20] This example highlights the main area in which NHCs are employed: as organometallic ligands.



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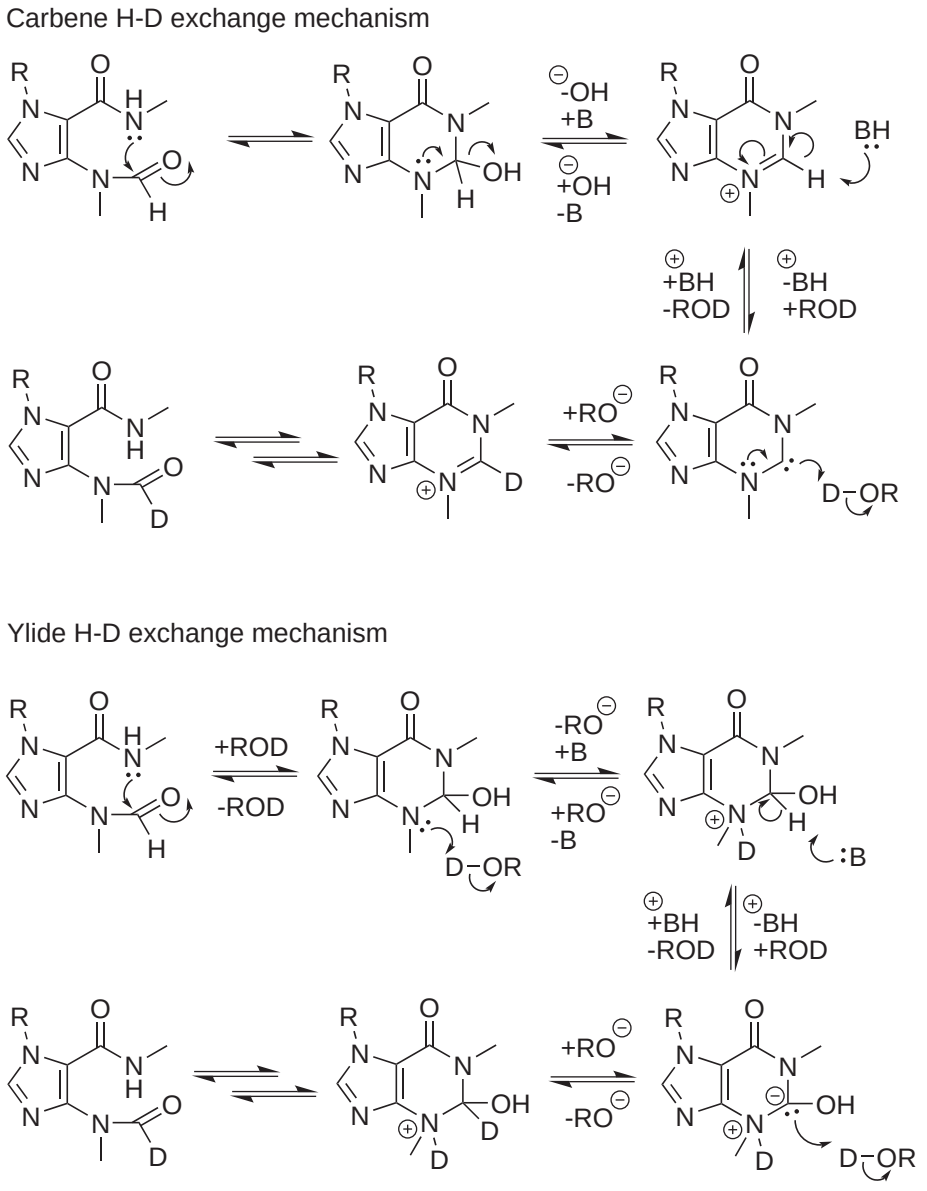
Scheme 1.4 Synthesis of Grubbs' 2nd generation catalyst

NHCs have found large application in organometallic chemistry. They are alternatives to phosphine ligands that can be less sensitive to air, water, silica and oxidation, as well as having stronger binding to metal centers.[21–23] They typically form strong σ-bonds with metals with little back-donation due to the stabilisation of the carbene center by the lone-pairs of the nitrogen atoms.[13] Slight changes to the substituents of the NHC can have notable effects on their electronic and geometric properties, allowing these to be used to tune the properties of the complex. Furthermore, they usually act as spectator ligands, therefore these effects can last throughout a catalytic cycle. Many organometallic complexes with NHC ligands have now been produced and used in catalysis,[24–28] the most note-worthy example of which is Grubbs' second generation catalyst.[20]

1.5 Intended Research

Investigations into the H-D exchange of malonganenone B were based on the mechanisms of Simchen and the more recently acquired knowledge on NHCs. To obtain a species similar to that upon which Simchen's mechanisms were based requires an initial cyclisation event [Scheme 1.5]. This would be expected to result from the attack of the amide nitrogen on the formamide moiety, generating an aminal ester. The nitrogen is expected to attack rather than the oxygen, based on the increased nucleophilicity and by comparison to existing natural compounds such as caffeine. From this point it is expected that the mechanism would proceed either through the ylide or carbene mechanism (the self-protonation mechanism is treated as a variation of the ylide mechanism). To try and probe which mechanism is occuring in the H-D exchange, kinetic and synthetic studies were to be performed. Synthesis of models of malonganenone B were to be conducted and kinetic studies performed on these compounds using NMR spectroscopy. The order of the reaction with respect to all species involved was to be obtained and confirmation of Simchen's base "inhibition" would be sought. Once the mechanism was putatively assigned, conclusive proof was to be sought through the trapping and demonstration of key intermediates.



Scheme 1.5 Proposed mechanisms for H-D exchange of malonganenone B

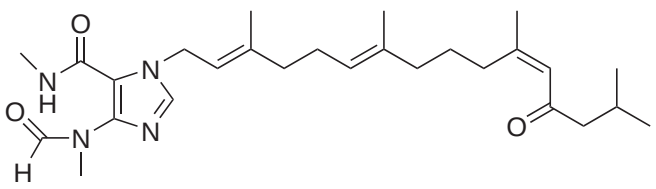
Chapter 2

Synthetic and kinetic investigations

2.1 Imidazole-based models

2.1.1 Synthesis of imidazole-based models

To analyse the H-D exchange of malonganenone B, an analyte was first required. Given that only 14 mg of malonganenone B (**2**) was originally isolated,[1] and lacking the resources to go diving off the coast of Mozambique to collect more, the compounds to be studied were synthesised. Rather than devise and complete the total synthesis of malonganenone B (to date none of the malonganenones or nuttingins have been synthesised), a simpler model was proposed. 4-[Formyl(methyl)amino]-*N*,1-dimethyl-1*H*-imidazole-5-carboxamide, **23**, differs only in that a methyl group replaces the tetraprenyl tail of malonganenone B at the 1-position of the imidazole ring. As the tail was not believed to be involved, but that the unique, substituted imadazole of malonganenone B was accurately replicated, it was expected that this would exhibit the same H-D exchange.



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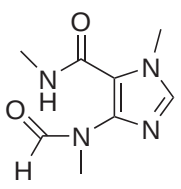

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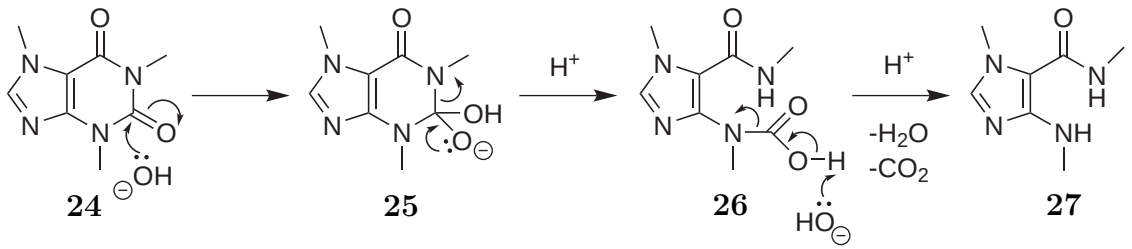
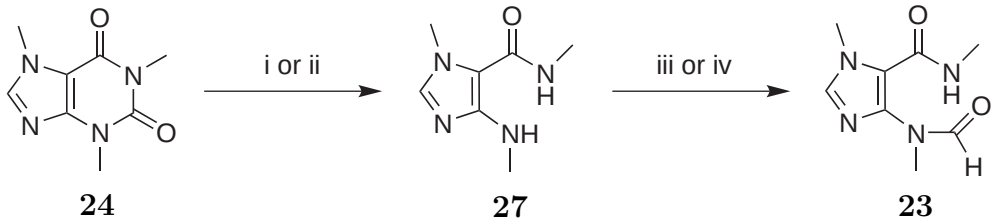


Scheme 2.1 Mechanism of the ring-opening of caffeine

Given the similarities between the target compound and caffeine (**24**), this appeared as the ideal starting material. Hydroxide can be used to attack the carbamide center, which is the most electrophilic carbonyl due to the two electron-withdrawing nitrogen atoms attached [Scheme 2.1].[29] When the carbonyl of species **25** reforms, the bond to the amide breaks selectively because the resultant amide can better stabilise the charge through resonance than the amine if the alternate bond where to break. The resulting carbamate **26** decarboxylates in the presence of base to give **27**. Unfortunately, this reaction is usually performed on substituted purines with alkyl tails that allow a handle for separation. Given the presence of basic functionality in the form of a secondary amine and an imidazole ring, the possibility of hydrogen-bonding between the amine and amide generating a dipole, plus the possibility of a charged resonance form involving the amine, amide and imidazole, it is not surprising that this molecule was too polar for standard organic synthetic purification techniques to be used. Extraction with many organic solvents was unsuccessful, including, but not limited to, liquid/liquid partitions, solid/liquid extractions and continuous liquid/liquid extraction. Eventually a reverse-phase chromatographic method was utilised to yield **27** [Scheme 2.2]. Subjecting this compound to refluxing formic acid led to acid-catalysed formamide formation on the secondary amine to afford **23** as an impure solid.[30] Formylation of the amine had only a limited effect on polarity of the molecule and purification was still problematic. Eventually, it was found that recrystallisation from ethyl acetate, on occassion, afforded small crystals of **23**.

Having laboured to obtain purification methods, further literature searching revealed that this synthetic scheme had been completed previously.[31] Here, the ring-opening



Reagents and Conditions: i. NaOH, EtOH, H_2O, reflux, 3 h, 56%; ii. NaOH, H_2O, reflux, 2 h, 37%; iii. Formic acid, reflux, 30 min, 6%; iv. Formic acetic anhydride, rt, 12 h, 51%.

Scheme 2.2 Synthesis of **23**

was again performed with aqueous sodium hydroxide, but nitric acid was then added to form the nitrate salt, which was empirically found to be insoluble in water. Filtration of the precipitate and equilibration in aqueous potassium carbonate to regenerate the free amine gave **27** with a higher purity and yield than previously. Interestingly, from this source the material is soluble in organic solvents, hence able to be recrystallised, which begs the question of whether it is interactions between **27** and impurities from its synthesis that led to the purification issues. The synthesis was then completed using formic acetic anhydride as formylating agent, rather than formic acid, to give **23** in good yield.

2.1.2 Rotamers of 23

Upon first obtaining the NMR spectrum of **23**, two sets of resonances were observed. Solving each set revealed the same chemical connectivity, which suggested that two conformational isomers were being observed. Given the proximity of the formamide and methylamide substituents, it was hypothesised that steric hindrance between these groups could limit rotation around the bonds connecting these to the imidazole ring. The ratio of the two conformers was found to be solvent dependent [Table 2.1]. Omitting deuterium oxide, it appears there is a relationship between polarity and the ratio of isomers, with one isomer being favoured with increased polarity. There was also a noticeable difference in the resonance of the nitrogen-bound proton of the methylamide substituent, which in chloroform-d was 7.57 ppm for one conformer and 6.02 ppm for the other. Together, this was interpreted as suggesting one of the conformers involved hydrogen-bonding between the substituents, which would be more stabilised and hence favoured by more polar solvents. This is discussed in more detail in Section 2.2.2.

Table 2.1 Solvent-dependance of rotameric ratio of **23**

Solvent	Polarity of solvent	Ratio (A:B)
$CDCl_3$	4.1	1:1.2
CD_3OD	5.1	4.1:1
DMSO	7.2	7.2:1
D_2O	9.0	2:1

2.1.3 Kinetic studies with 23

To be able to perform kinetic studies, methods to follow the H-D exchange are required. Given that it is the replacement of a proton for a deuteron, ^{1}H-NMR spectroscopy appeared as the ideal tool; the resonance for the exchanging proton would decrease with time while the other signals of the molecule would remain unchanged. In ^{1}H-NMR spectroscopy, the area under a peak is proportional to the number of protons contributing to that peak in the molecule- comparing the ratio of the integrals of the signals allows insight into the ratio of protons in the molecule. To follow the decrease in the formyl peak area, a reference is needed, the most obvious of which is the other, non-changing resonances of the molecule. Rather than comparing the formyl integral to a single resonance, the formyl was compared to the total integral of all other resonances in the molecule for accuracy purposes. The total integral for all resonances in the analyte were defined as 100, and the fall in the contribution of the formyl resonance, the formyl integral, was tracked. This value could be manipulated to be expressed as the change in formyl integral compared to the average integral for a proton in the rest of the molecule and potentially normalised to a set value across experiments. However, given that only rates, and not absolute integral values, were to be compared between experiments, this represented unneccessary manipulations and the preferrence was to work with the raw data.

Before **23** could be used as a model for the H-D exchange of malonganenone B, it was neccessary to ensure that H-D exchange occurred. Joyfully, first exposing **23** to methanol-d_4 resulted in the loss of the formyl proton resonance, 8.3 ppm, with time whilst other peaks remained unchanged, proving the validity of our model [Figure 2.1]. The decline in the integral for this proton maps an exponential curve [Figure 2.2]. Only defining the integrals of the analyte could prove problematic if intermediates, with different resonances, were forming, as the ratio of exchange might vary between the equilibrium populations. However, no other resonances were observed, suggesting that these populations are small and make a negligible contribution to the equilibrium distribution. To explore the possible observation of intermediates, as evidence towards which mechanism is occurring, variable temperature ^{1}H-NMR spectroscopic studies were performed. The samples were incubated for five hours in the respective NMR solvents to allow for establishment of the equilibrium populations. However, in both chloroform-d and methanol-d_4, at both ambient temperature and -50 °C, no other species were observed, reiterating again that the intermediates in the exchange are neither formed in high concentration nor have a long lifetime.

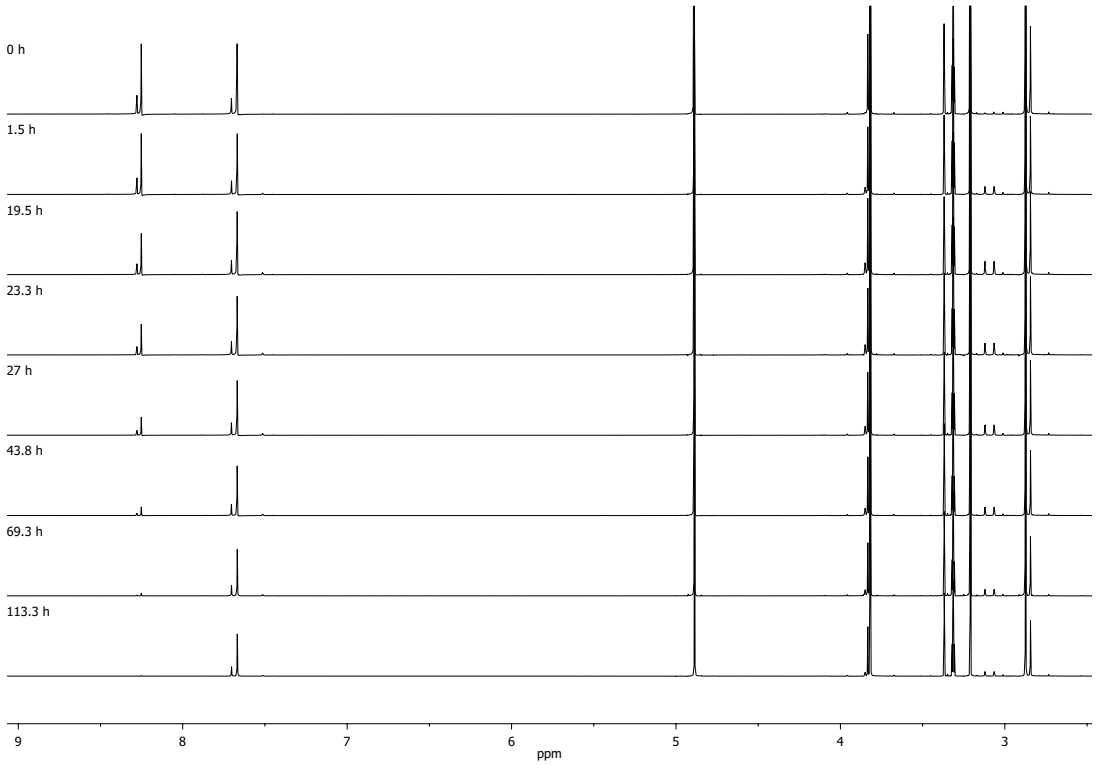


Figure 2.1 ^{1}H NMR spectra of **23** with time in CD_3OD

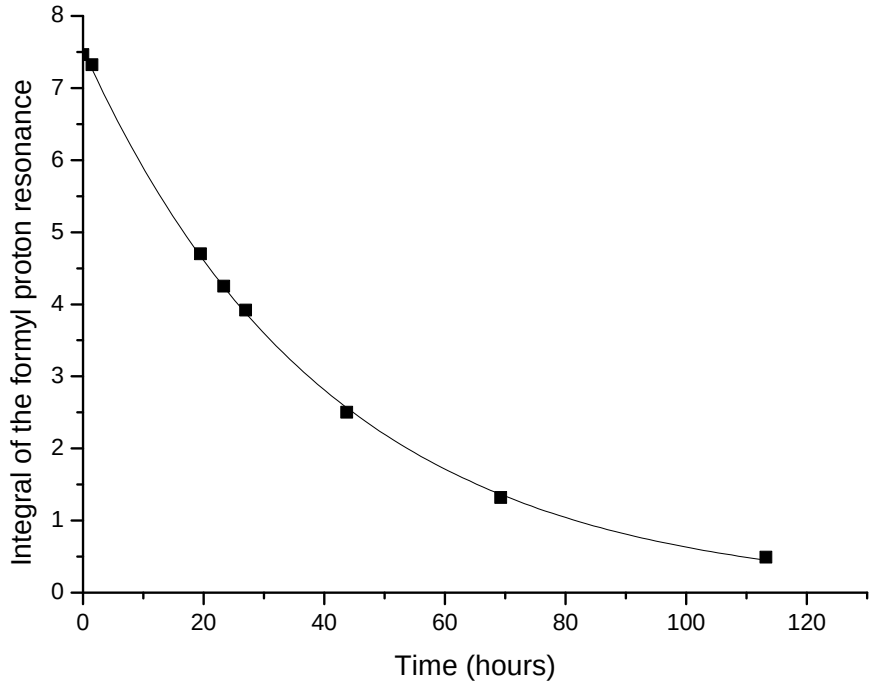


Figure 2.2 Formyl proton resonance with time for **23** in CD_3OD

The H-D exchange was found to be highly dependent on the source of the analyte. Early kinetic studies showed a variation in rate that was not correlated to the changes in concentration. Upon inspection, it was realised that these differences were instead originating from the source crystal. Comparing the half-life of **23** from different sources, or isolation events, huge differences were observed between them [Figure 2.3]. Although all sources of **23** were crystalline and had been recrystallised repeatedly, the level of impurity strongly affected the rate of exchange. Given the mechanisms were believed to be acid-inhibited in the RDS, variation in trace amounts of formic or acetic acid from the final formylation step may strongly hinder, or cease entirely, the exchange. For this reason, only experiments from the same source could be compared.

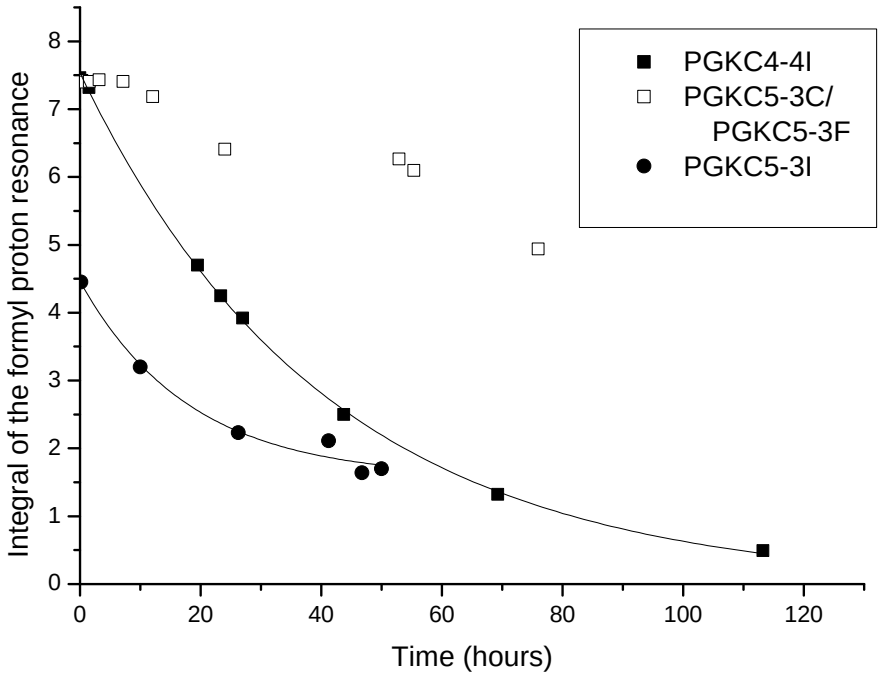


Figure 2.3 Source-dependence of rate of H-D exchange

Kinetic studies investigating the effect of [**23**] on the rate of exchange yielded interesting results. The rate of H-D exchange was measured across a concentration range of 20 - 100 mmol/L for **23** [Figure 2.4, Table 2.2]. Inspection of the data suggested there was a trend towards a faster rate at higher concentrations, but in reality this is a very small change. Applying a linear model to this data, the change in rate with respect to concentration is only -7 nmol/L.min, or approximately zero, suggesting the rate of exchange, and hence RDS, is independent of **23**. Were the RDS the formation of a highly energetic deuterating species that spontaneously forms in methanol-d_4 and only deuterates the molecules studied in this research, then this would be conclusive evidence. Given the alternative, that our molecule is *actually* involved in the RDS and some more normal deuterating agent, such as

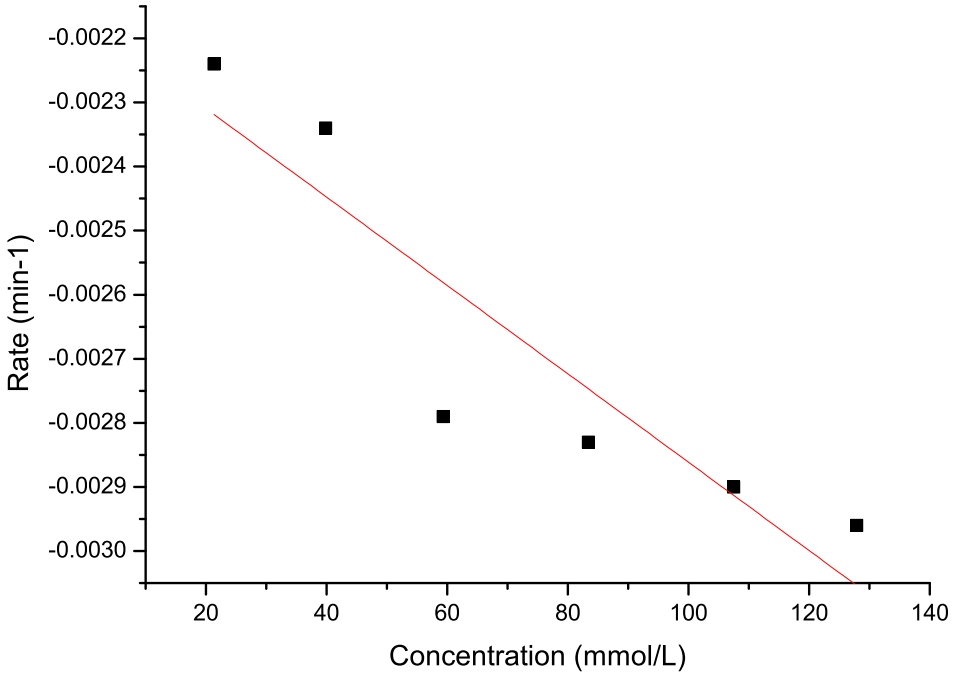


Figure 2.4 Concentration-dependence of rate of H-D exchange of **23**

Table 2.2 Analysis of concentration-dependence of rate of H-D exchange with a linear model

Parameter	Value
Gradient	-0.0000069
R^2	0.79496

methanol-d_4, is used, it was concluded the data was misleading. It is known that for any reaction, there is a concentration above which the reaction rate is constant and becomes limited by other steps or processes. This reflects a saturation of reagents or a maximal concentration of charged intermediates, such that the generation of more is inhibited. The solution to this kinetic problem is to assay at lower concentrations, such that the rate is analysed under unsaturated conditions.

The effect of base on the rate of H-D exchange was investigated with conflicting results. Simchen & co-workers reported that the addition of an exogenous base had the effect of inhibiting H-D exchange, whereas acid appeared to be activating. However, they had a difficult time reconciling this with their proposed mechanisms, as both the ylide and carbene mechanisms would require an equivalent of base in the RDS to remove the exchanging proton (to find it was base inhibited was quite a conundrum). In opposition to Simchen's results, addition of triethylamine was found to *increase* the rate of H-D exchange for **23**, which fits with the deprotonation required in the RDS [Figure 2.5, Table 2.3]. This is discussed in further detail in Section 2.2.3.

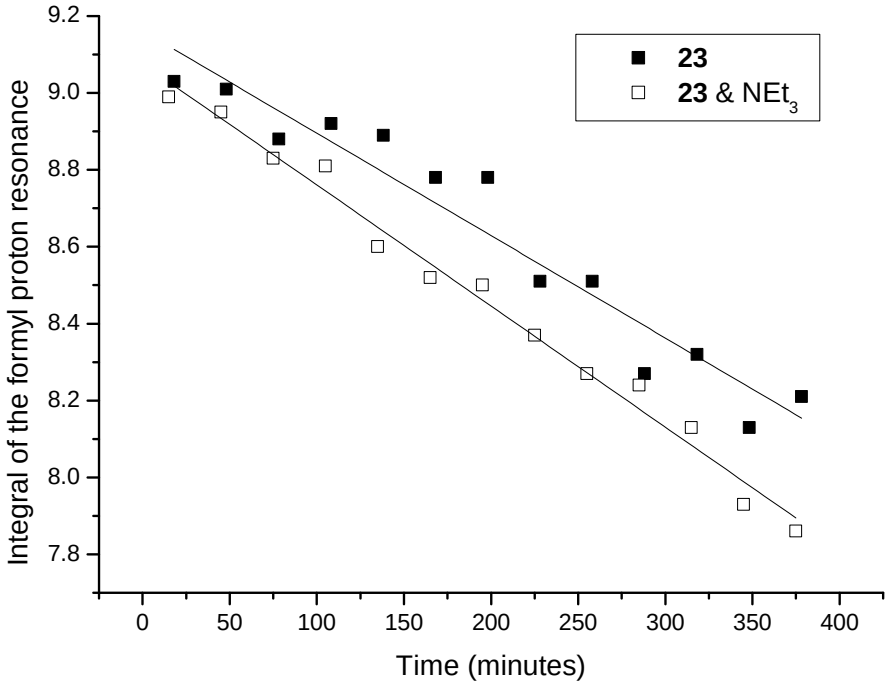


Figure 2.5 Effect of NEt_3 on H-D exchange

Table 2.3 Analysis of effect of NEt_3 on H-D exchange

Components	Parameter	Value
23	Rate	-0.00266
	R^2	0.92749
23 &	Rate	-0.00315
NEt_3	R^2	0.98538

Given that the exchange is dependent only on a solvent with exchangeable deuterons, deuterium oxide was assayed. Performing kinetic studies in deuterium oxide resulted in an increased rate of H-D exchange, an approximately one-fold increase over methanol-d_4 [Figure 2.6, Table 2.4]. There are many potential reasons for this. Deuterium oxide would be better able to stabilise the cationic species in a carbene mechanism that feeds into the RDS, aiding the exchange. The hydroxide ion is also less nucleophilic than methoxide, hence there would be less attack upon the cation and resultant sequestration of the exchanging-species in other forms. Finally, for fiscal purposes, it was decided to complete the remaining kinetic studies in deuterium oxide.

Kinetic studies on **23** were halted, however, when a new model became available for use. It is prudent to point out that model compounds are synthesised and studied to make systems simpler and therefore easier to approach. However, in this case removing the tetraprenyl tail led to more difficulties because of the problem of

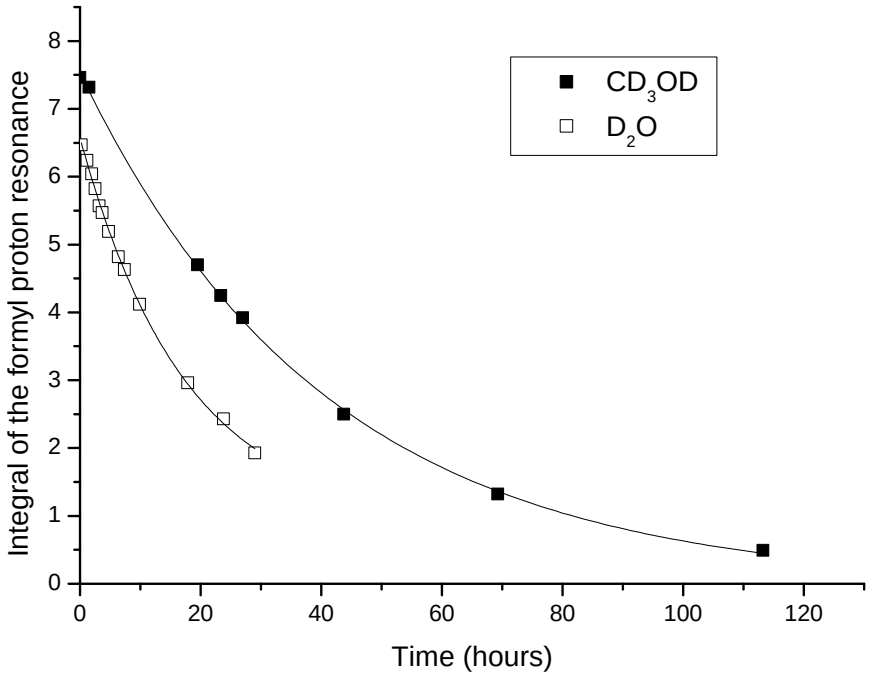


Figure 2.6 H-D exchange of **23** in different solvents

Table 2.4 Half-life of H-D exchange in different solvents

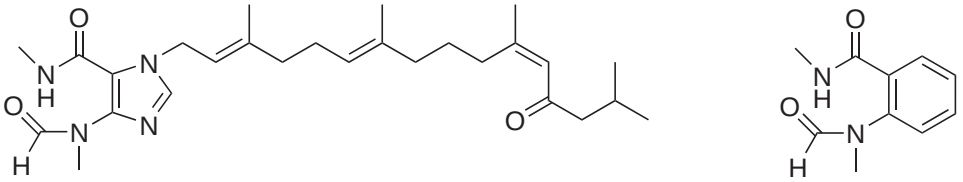
Solvent	Half-life (h)
CD_3OD	28.2
D_2O	12.0

polarity, and therefore subsequent purification. As a result, it could be asked why the model was not altered to solve this. Towards this, methods were explored to attach simple alkyl tails to substituted imidazole rings, with some success. However, this work was ceased with the completed synthesis and observed H-D exchange of a benzene-based model.

2.2 Benzene-based models

2.2.1 Synthesis of benzene-based models

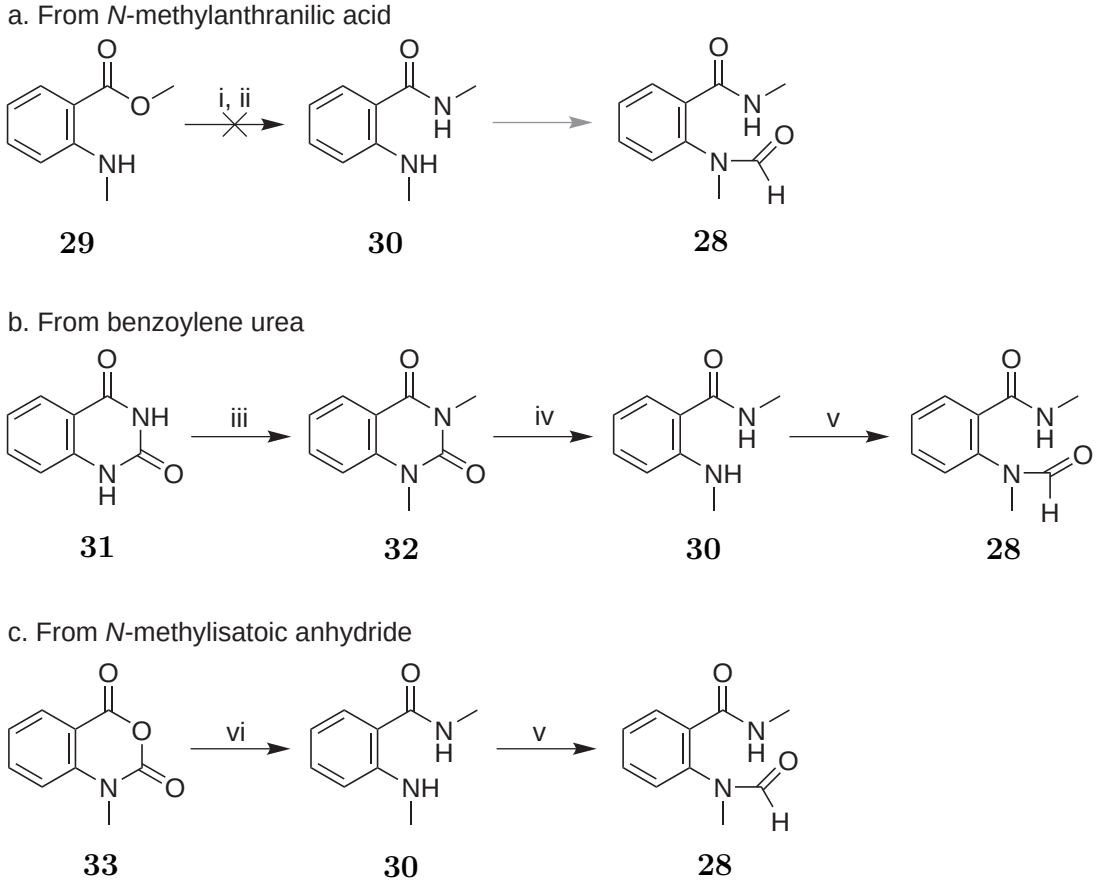
It seemed prudent to investigate other models of malonganenone B, to test the versatility of this exchange. *N*-methyl-2-(*N*-methylformamido)benzamide, **28**, was proposed that features a benzene ring in place of an imidazole ring. This model was expected to benefit from a decreased dipole across the ring and less nitrogen



2 **28**

atoms, enabling easier purification than for **23**. Also, the presence of more bound hydrogens would make spectroscopic analysis of any generated products easier. The bond angles of a benzene ring, however, differ from those of the imidazole ring, and there was a risk that this would make formation of the cyclic species necessary for H-D exchange unfavourable.

Synthesis of this model, as before, was not straight forward. Initially synthesis was attempted from *N*-methylanthranilic acid (**29**), which was converted to the chloroanhydride with thionyl chloride then reacted with methylamine to try and yield the compound **30** [Scheme 2.3.a].[32] Given that a reactive electrophile is being generated in a molecule with an amine, hence the chance for polymerisation, it is not surprising this reaction was unsuccessful. An alternative method started with



Reagents and Conditions: i. $SOCl_2$, reflux, 3 h; ii. *aq.* CH_3NH_2, THF, 12 hr, -%; iii. MeI, K_2CO_3, DMF, 36 h, 63 %; iv. NaOH, H_2O, 36 hr, 92 %; v. formic acetic anhydride, rt, 12 h, 86 %; vi. *aq.* CH_3NH_2, H_2O, 50 °C, 1 hr, 98 %.

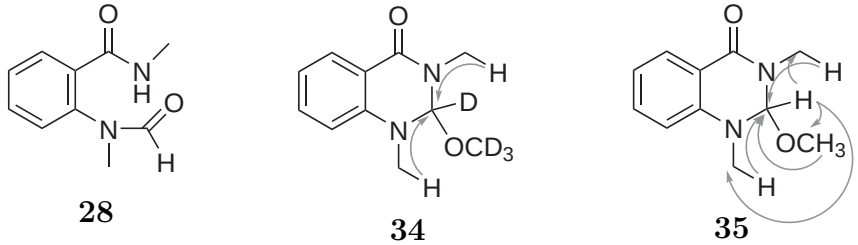
Scheme 2.3 Synthetic routes to **28**

dimethylation of benzoylene urea (**31**) by methyl iodide and potassium carbonate to form **32** [Scheme 2.3.b].[33] This was then ring-opened under the same conditions and mechanism as per **23** to yield **30**, but with the advantage that purification could be achieved by a simple liquid-liquid partition. This was then formylated with mixed formic acetic anhydride and purified by flash chromatography to give **28** as a white crystal in good yield.

As with **23**, it turned out a shorter synthesis to **28** had already been completed. *N*-methylisatoic anhydride (**33**) is attacked by methylamine at the carbonyl closest to the ring, which is less resonance stabilised than the other carbonyl and hence is more electrophilic [Scheme 2.3.c].[34] This generates the desired methylamine and a carbamate that decarboxylates as per the synthesis of **23** to give the free amine in good yield. Given the formylation methodology developed in this research was better than that reported in the paper, this methodology was applied to complete the synthesis of **28** in good yield. It seems prudent to comment that not all old chemistry shows up in new databases.

2.2.2 Rotamers and cyclic species

Testing for H-D exchange in this model resulted in the observation of a new species. Incubation of **28** in methanol-d_4 did result in disappearance of the formyl resonance with time, but all the other peaks of the molecule also disappeared with a new set of resonances appearing [Figure 2.8]. Characterising this species by 2D NMR experiments revealed that protons of both methyl groups exhibited HMBC correlations to a carbon signal at 96.9 ppm [Figure 2.9]. Given that these methyls cannot couple to the same carbon through the existing backbone, this suggested that a cyclisation event had occurred. MS of this species was unsuccessful, with only **28** being observed. Given that all of **28** had been consumed as observed by NMR, it was proposed that this new species was unstable and reverted to **28** under atmospheric conditions. With the evidence available, a putative structure of **34** was proposed, with uncertainty over whether the oxygen-bound substituent at the aminal ester centre was OCD_3 or simply OD.



28 **34** **35**

Figure 2.7 Cyclic species of **28**, with key HMBC correlations shown

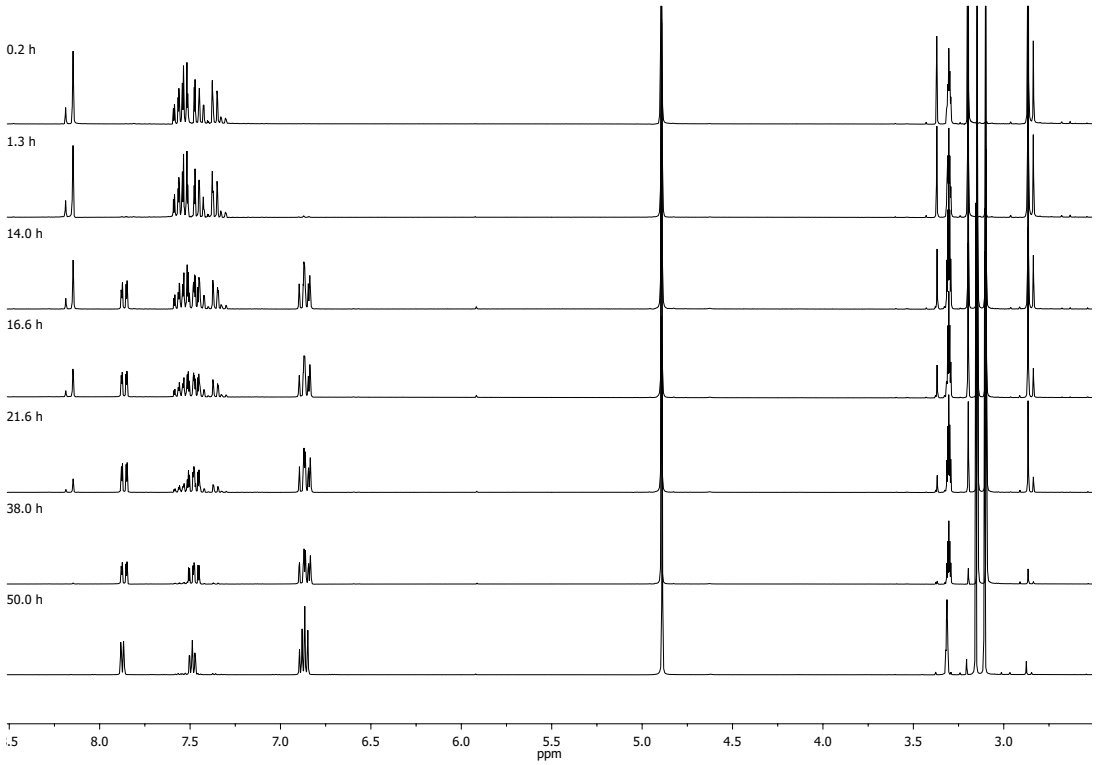


Figure 2.8 ^{1}H NMR spectra of **28** with time in CD_3OD

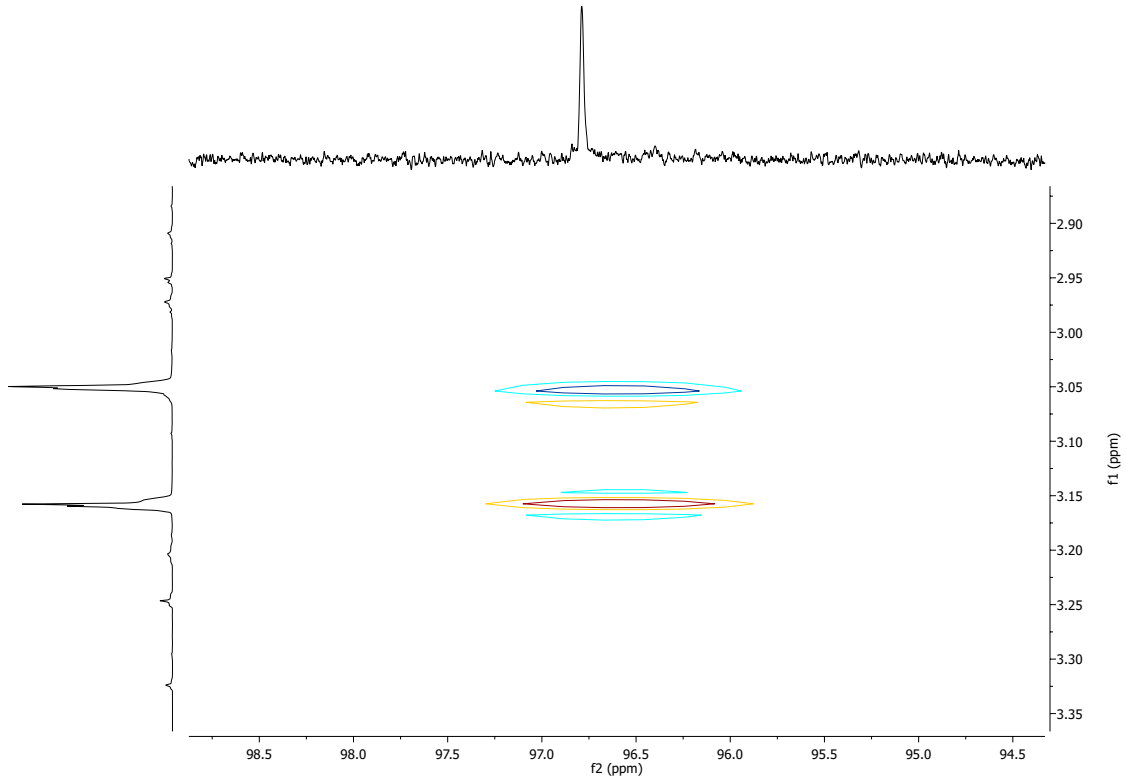
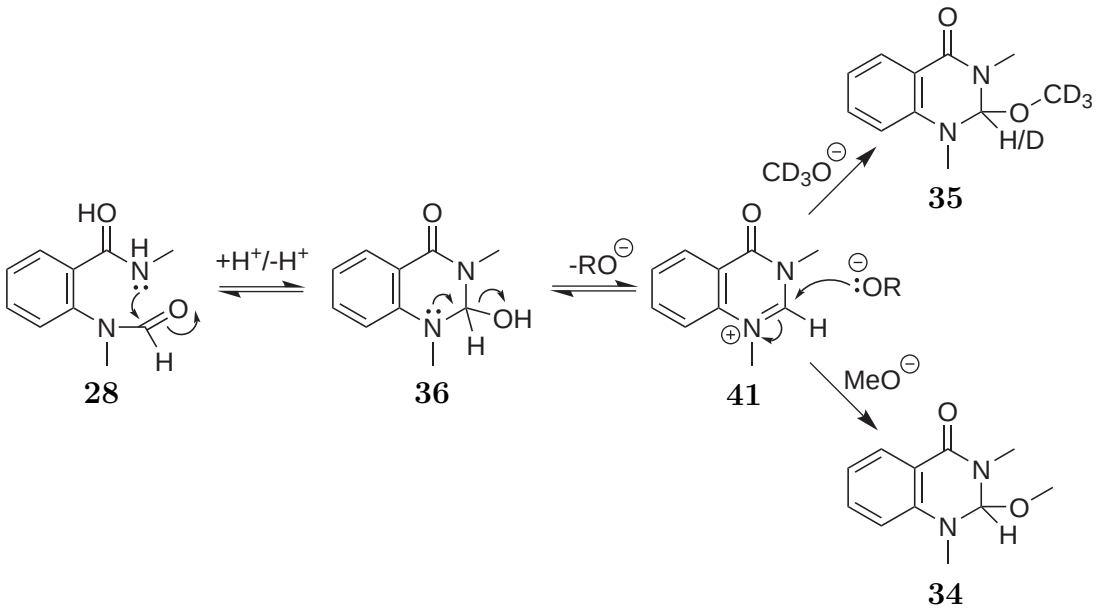


Figure 2.9 Key HMBC correlation of **34**

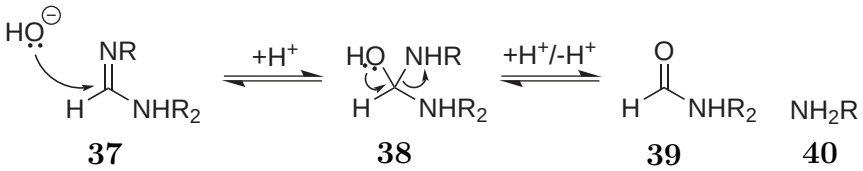
For more conclusive evidence, the protonated form was synthesised. Compound **28** was incubated in methanol for a period of days, quickly concentrated and transferred to chloroform-d to avoid hydrolysis or lose the putative methoxy adduct. As before, MS only revealed the presence of **28**. NMR spectroscopy, however, revealed a set of resonances akin to those found for **34**, with the notable addition of a resonance integrating for a single proton at 5.77 ppm and a resonance integrating for three protons at 2.93 ppm. HSQC correlations demonstrated that the proton with the resonance at 5.77 ppm was attached to a carbon at 96.8 ppm, as for **34**, whereas the resonance at 2.93 ppm is attached to a carbon at 49.3 ppm, which is expected for a methoxy group. As before, protons of both of the nitrogen-bound methyl groups showed HMBC correlations to the 'cyclic' carbon, in addition to the new methyl protons showing correlations to this too. Reciprocated correlations were seen between the proton at the 'cyclic' center and the three methyl carbons. These correlations provide good evidence towards this species having the structure **35**.

Having proposed a structure for this new species, the mechanism of formation was addressed. The cyclisation event is believed to occur according to the mechanism presented earlier, with the amide nitrogen attacking the formyl carbonyl that, following proton transfer, generates aminal ester **36** [Scheme 2.4]. For the alkoxy substituent to be able to bind to the exchanging center, the exisiting hydroxy group must be removed. With the aid of the lone pairs of the two neighbouring nitrogens, hydroxide, or water, could be ejected, generating the charged species **41**. Due to the delocalisation of the charge across both nitrogens, this species is expected to be relatively stable. Nucleophilic attack from the solvent could then generate the desired cyclic species, **34** or **35**.



Scheme 2.4 Proposed mechanism of formation of **34** and **35**

This mechanism is not without precedent and had been confirmed previously. Much work has been done investigating the hydrolysis of amidines.[35,36] In this mechanism, an amidine, **37**, accepts the addition of water at the amidine center to form a hemiaminal ester, **38**, followed by cleavage to yield a formamide (**39**) and an amine (**40**) [Scheme 2.5]. Inspection of this mechanism reveals that this is the opposite sequence of events as occurs in the formation of the cyclic species of **28**, which, given each step is an equilibrium, are applicable in directions. Studies have shown this mechanism is base catalysed and, if the concentration of base is sufficient, cleavage to **30** can be seen. Although this represents the opposite mechanism to that presented, each reaction is an equilibrium and hence the mechanism is valid in both directions. Studies investigating the mechanism of bromination of quinazolinone, in which the perchlorate salt of **41** was studied, found this hydrolysis using the exact compounds being studied in this thesis.[37] Subsequently work was done to demonstrate a tetrahedral intermediate in this hydrolysis reaction.[38] Kinetics for each equilibrium in this reaction were analysed using UV and NMR spectroscopy and the mechanism they propose matches that proposed here.



Scheme 2.5 Mechanism of hydrolysis of amidines

Discovery of this cyclisation and deduction of the mechanism of formation also helped explain the rotamers. Characterisation of each rotamer shows that they are constitutionally identical, with the same bond connectivity, and were believed to differ only in their conformation in space. Given the steric size of each group and their proximity to the benzene ring, it can be concluded that both substituents cannot be planar with the ring at the same time. Instead, each substituent must be twisted out of the plane and, depending on the orientation, different rotameric species can be formed [Figure 2.10]. The change in ratio in different solvents was puzzling, however, until now: interchange between rotamers is possible, but only through the tetrahedral intermediate **36**, which can open to yield either rotamer.[38] Although bond breaking is required to interchange these, and hence they could be

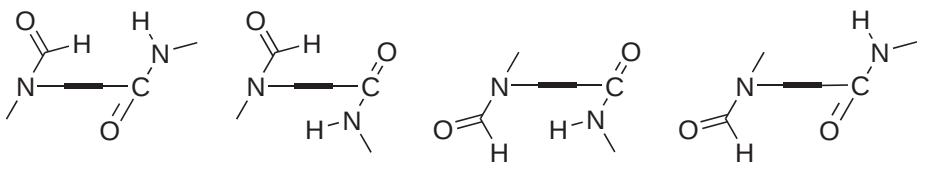


Figure 2.10 Possible distributions of the substituents of **28** in space

argued as configurational isomers, they only differ in rotation about a single bond, which is impeded in this system, hence the "rotamer" nomenclature is valid.

These cyclic species are the first conclusive evidence towards explaining the H-D exchange of malonganenone B. Although the work on amidines has only previously been completed on benzene-based compounds, the same mechanisms can be applied to the imidazole-based systems. The absence of demonstration of an aminal ester for **23** is believed to be due to the cyclic species being less stable. In **28**, cyclisation involves formation of two fused 6-membered rings, which is a wellknown stable system. In **23** however, a fused-5,6-bicyclic system is formed. The geometry of the bridge-head carbons is different in the 5-membered ring, with the substituents being angled further from each other. Formation of the 6-membered ring is likely further hampered by the appearance of an amine and a lactam moiety in the ring, and the possible effect of the lone pair on the nitrogen of the imidazole ring. Although these effects may be only subtle changes in geometry and structure, the effect on population sizes in the equilibrium system could be quite pronounced. Nonetheless, these results suggest that cyclisation is occurring in our system to generate aminal esters, hence the mechanisms proposed by Simchen are applicable here. Further, the implication of the cationic species **41** is very good evidence towards the carbene mechanism being in operation.

2.2.3 Kinetic studies of 28

Amongst the discovery of the new cyclic species forming, the successful demonstration of H-D exchange in another model was overlooked. As noted earlier, there was no equivalent resonance in the species **34** for what was the formyl proton. As has been confirmed by further studies, this is indeed due to H-D exchange occurring with this proton. In methanol-d_4, the half-life of the exchange is 13.5 hours as opposed to 28.3 hours when compared to **23**, meaning the exchange occurs at more than double the rate [Figure 2.11, Table 2.5]. When trialling the exchange in deuterium oxide, the formyl resonance was lost but the other peaks remained the same- the hemiaminal ester is obviously not as stable as the aminal ester [Figure 2.12]. Comparing the

Table 2.5 Half-life of H-D exchange of different models in different solvents

Species	Solvent	Half-life (h)	R^2
23	CD_3OD	28.3	0.999
	D_2O	12.0	0.999
28	CD_3OD	13.5	0.988
	D_2O	1.5	0.999

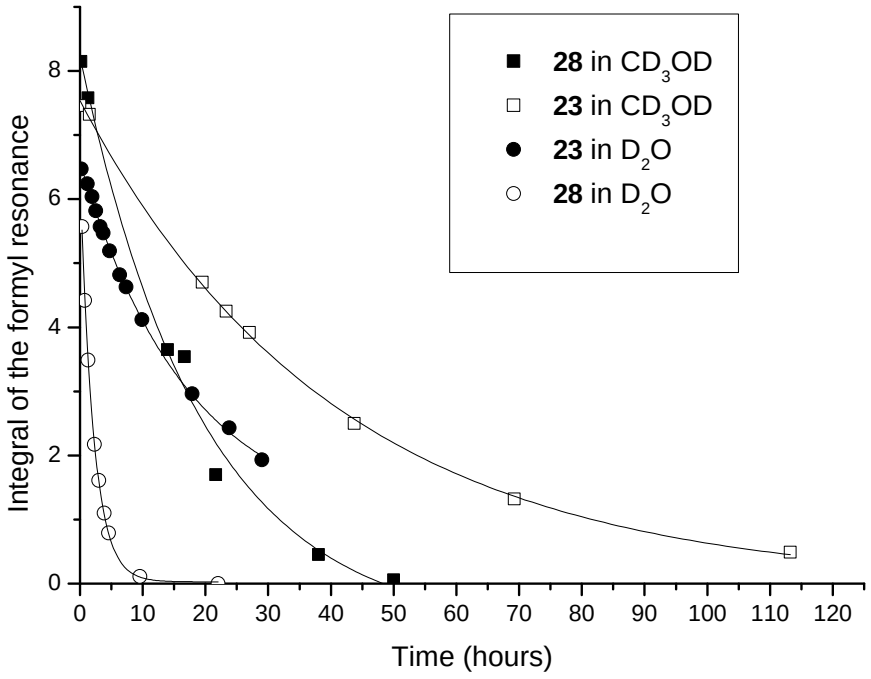


Figure 2.11 H-D exchange of different models in different solvents

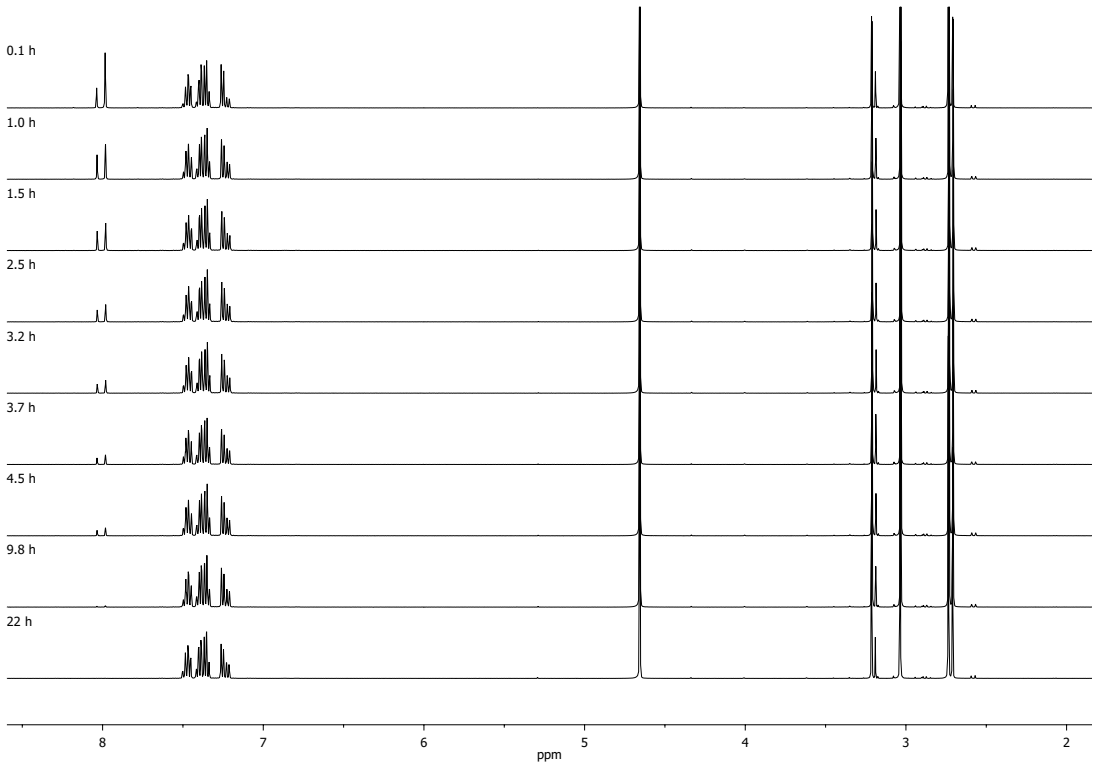


Figure 2.12 ^{1}H NMR spectra of **28** with time in D_2O

rate of exchange in deuterium oxide instead, **28** has a half-life that is 8-times shorter than for **23**, 1.5 and 12 hours respectively. The argument previously supporting the observation of cyclic species for **28** but not for **23** can be applied here. As a result the intermediates and transition states required for the H-D exchange of **28** are more stable and there is less of an energy barrier for molecules to exchange. This idea of stable species can be developed further by the observation that **28** reacts 9-times faster in deuterium oxide than methanol-d_4. It can now be argued that the cyclic species **34** is actually too stable and sequesters some of the exchanging population, meaning that less progresses though the steps of the exchange with methanol-d_4 as the solvent compared to deuterium oxide, ergo the rate in the former solvent is slower. Effects of increased polarity of solvent better stabilising the charged intermediates and the decreased nucleophilicity of hydroxide compared to methoxide also likely influence this.

Before full kinetic studies were completed, the effect of source and analysis method were assessed. Given the difficulties associated with purity of different sources of **23**, the half-life of exchange for each source crystal was assessed before use. Whereas large differences were seen for **23**, the rate of exchange for **28** is largely independent of source [Figure 2.13]. This is a reflection of the better separation and purification that is possible with **28** due to its lower polarity compared to **23**. The benefit of a shorter life-time for the exchange is that the Half-Life method can be used for analysing the rate. Mapping this data over multiple half-lifes gives high accuracy, as compared to approximating a linear model to the start of an exponential curve for the Initial Rate method. Unfortunately, the data could not be collected over multiple

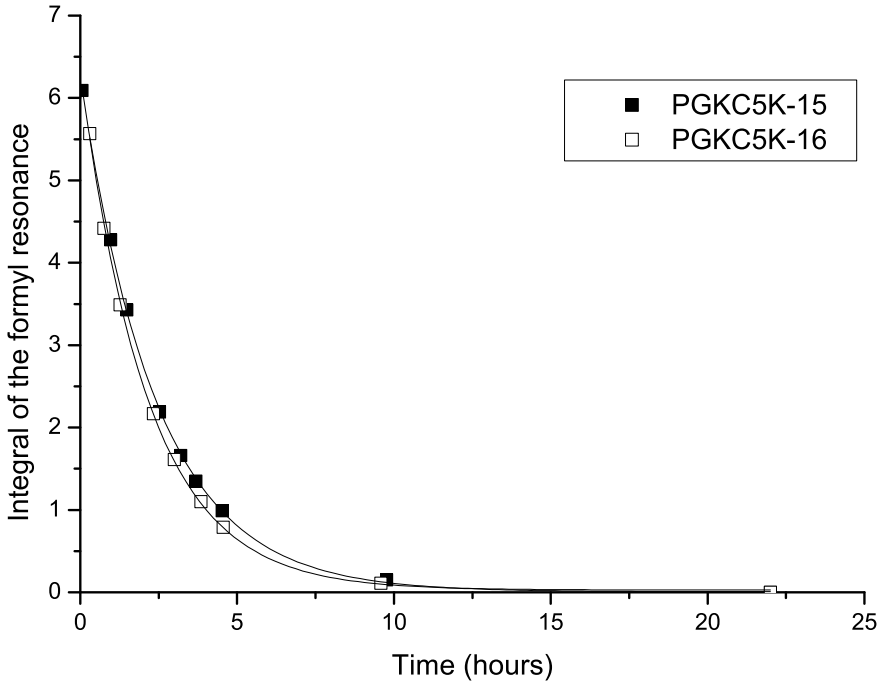


Figure 2.13 Rate of H-D exchange of **28** from different sources in CD_3OD

half-lifes in all cases, due to some long half-lives of the exchange, and hence some of the experiments have less accurate estimates. The other advantage of this model is that it has a shorter relaxation time of the resonances in the molecule meaning that more data can be acquired in a shorter time, allowing for more accurate data. Given the choice of methanol-d_4, in which the disappearance of the two rotamers and appearance of the aminal ester need to be assessed for each spectrum, or deuterium oxide, which is less expensive and involves only following the loss of two peaks relative to two sets that are unchanging, remaining kinetic studies were performed in the later solvent.

The effect of concentration of **28** on the rate of H-D exchange was investigated but with limited success. The half-life of exchange at different concentrations of **28** were assayed [Figure 2.14, Table 2.6]. R^2 values have been omitted from the table as all fits had a value of 0.999. There appeared to be a good relationship between concentration and half-life, but this was complicated by some of the studies that were performed at a later date; the only difference that can be imagined would be in the absorbance of water from the atmosphere or decomposition of the sample. Logarithms of the half-life and concentration were plotted against each other and a linear model applied, which, according to Equation 1.15, would have a gradient equal to one minus the order of the species [Figure 2.15]. Although this gradient suggests it is closest to first order, given the low fit of this data ($R^2 = 0.777$) no

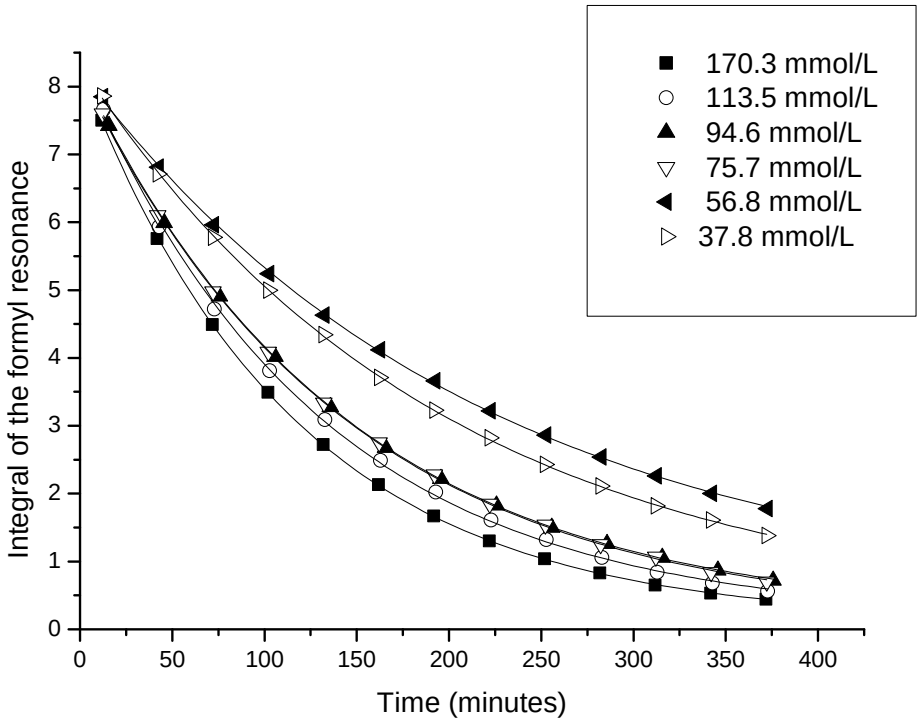


Figure 2.14 Concentration-dependence of H-D exchange of **28**

Table 2.6 Half-life of H-D exchange of **28** at different concentrations

Concentration (mmol/L)	Half-life (min)
37.8	134.9
56.8	148.7
75.7	99.4
94.6	98.9
113.5	88.9
170.3	79.7

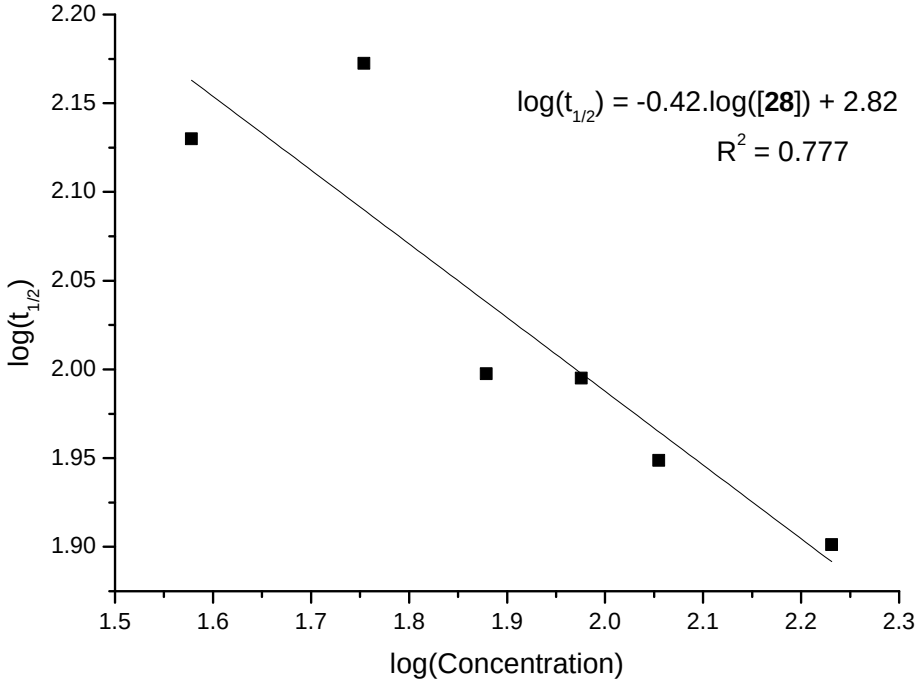


Figure 2.15 $\log(t_{1/2})$-dependence on log(concentration) of **28**

conclusions could be drawn with confidence [Figure 2.15]. Given the number of steps from this analyte to the RDS, it is not surprising that this data is not useful.

As previously, results with regards to acid and base are contrary to those reported by Simchen. Addition of triethylamine resulted in an acceleration of the H-D exchange, as for **23**, but addition of acetic acid-d_4 acted to completely *inhibit* the exchange [Figure 2.16]. Although Simchen originally had problems reconciling his observations, these findings support the possibility of either the ylide or carbene mechanism; both involve deprotonation in the RDS, which exogenous base would aid whilst exogenous acid would inhibit. Exploring this with other bases, namely sodium hydroxide and dimethylaminopyridine, showed similar catalytic activity. Investigating the response of the rate to the concentration of base would allow an exploration of this catalysis.

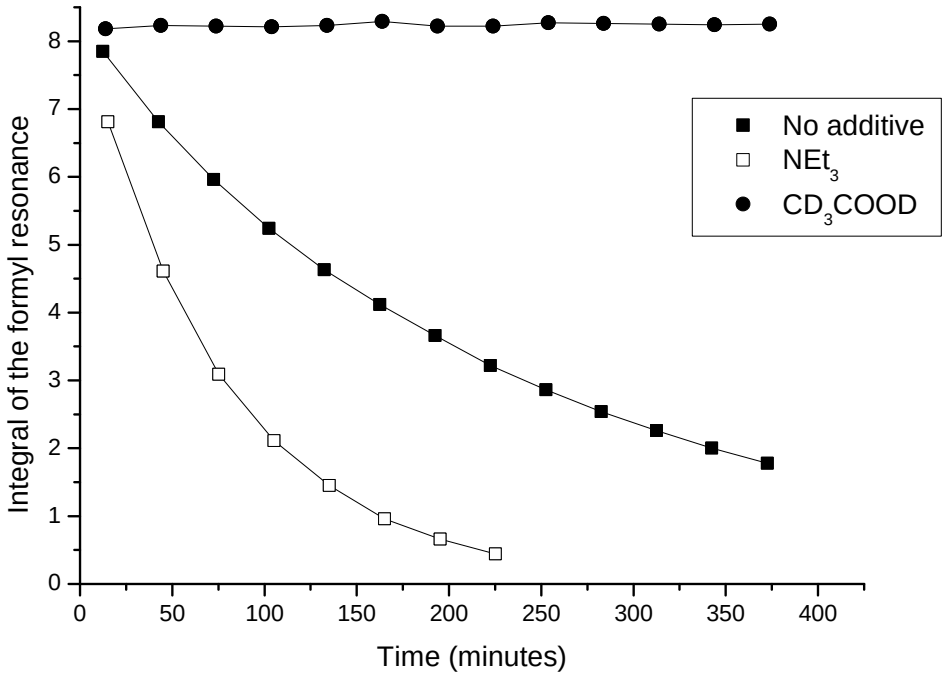


Figure 2.16 Effect of acid and base on rate of H-D exchange of **28**

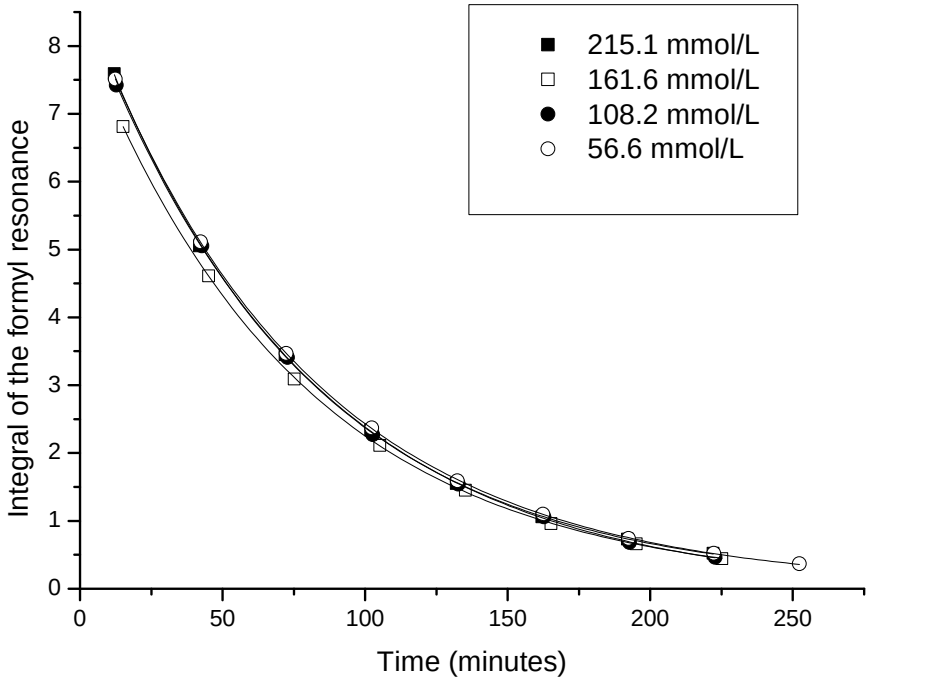


Figure 2.17 Effect of different concentrations of NEt_3 on rate of H-D exchange of **28**

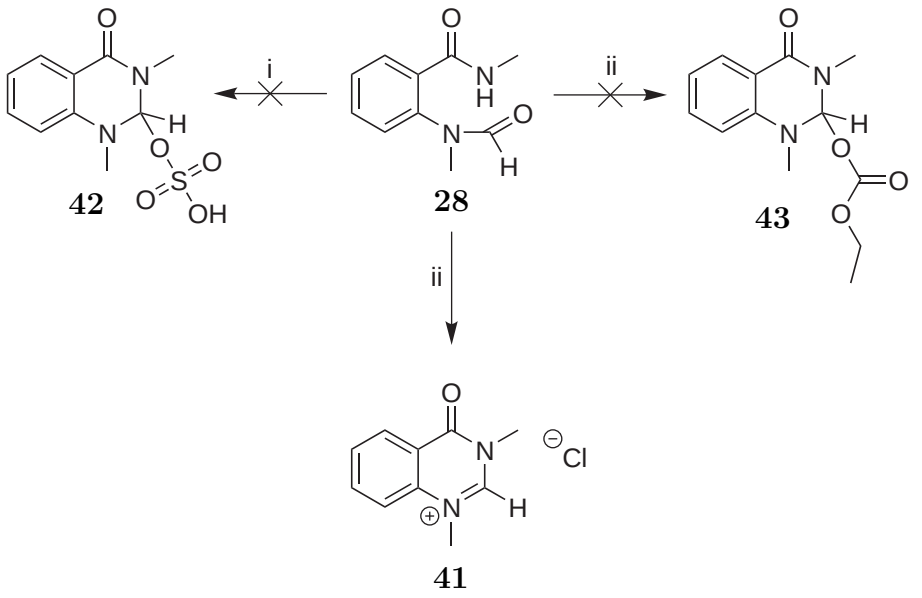
The effect of concentration of triethylamine on the rate of H-D exchange was investigated but also met with limited success. Triethylamine was chosen for concentration studies as it is a stable, non-nucleophilic base, avoiding concerns about side-reactions occurring. Varying the concentration from 56.6 mmol/L, 1 stoichiometric equivalent, to 215.1 mmol/L, 4 equivalents, showed absolutely no change in rate between the different concentrations, such that there was no point in analysing this data further [Figure 2.17]. Although this could be taken as the reaction being independent of the concentration of base, these rates are still faster than **28** alone. The conclusion drawn therefore is simply that the rate is independent of [triethylamine] at *these* concentrations of base. This suggests that the maximal rate of catalysis has been achieved and that the reaction simply can not go any faster. The solution to this is to assay the rate of reaction at substantially lower concentrations, which, since the base is not the analyte and hence needs not be at a concentration that is observable by NMR spectroscopy, is achievable in this experimental setup, as shown in Section 2.3.2.

Kinetic studies on this benzene-based model have progressed the level of knowledge towards solving the question of the mechanism of H-D exchange of malonganenone B. The main advantage this model has over **23** is the ability for it to be suitably purified, using flash chromatography. Demonstration of a cyclic species is important to the cause in that it allows Simchen's mechanisms, which admittedly are the only that have been proposed to date, to be applied to our system. Although kinetic studies assessing the order of the exchange with respect to **28** were unsuccessful, it has demonstrated that the exchange responds in opposition to acid and base as how Simchen originally reported. The major failing point of this model is that it is too many steps from the RDS, such that useful kinetic data may not be obtainable from this system. With the help of a serrendipitous discovery, however, this problem could be overcome.

2.3 Quinazolinium-based models

2.3.1 Synthesis of cationic species

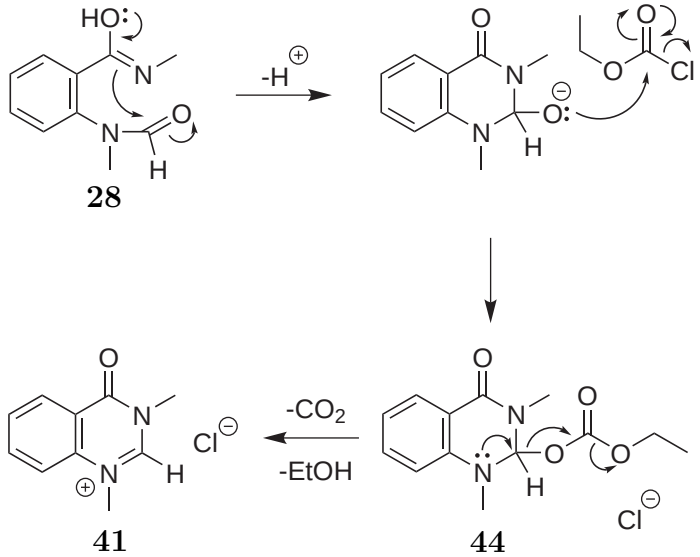
Attempts to trap a cyclic species had a very serendipitous outcome. To demonstrate the existence of an aminal ester resulting from formation of the second ring during H-D exchange in **28**, an attempt was made to trap the resulting oxyanion covalently with compounds that had very labile leaving groups. It was expected that the cyclisation would occur in most solvents, so experiments were run with a



Reagents and Conditions: i. $SO_3 \cdot$ pyridine complex, DMF, rt, 4 d; ii. ethylchloroformate, 50 °C, 12 hr.

Scheme 2.6 Attempts to trap a cyclic intermediate involved in the H-D exchange mechanism

sulfur trioxide-pyridine complex in DMF[39,40] and also in neat ethylchloroformate, to try and form the sulfate (**42**) and carbonate (**43**) respectively [Scheme 2.6].[41,42] Nothing formed in the sulfur reaction, but something new appeared in the reaction with ethylchloroformate that was not the expected product; instead it was found to be the cationic species 1,3-dimethyl-4-oxo-3,4-dihydroquinazolin-1-ium chloride, **41**. Upon cyclisation, the generated oxyanion was expected to attack the carbonyl of the ethylchloroformate with loss of a chloride leaving group to generate **44** [Scheme 2.7]. Instead of this species being stable as expected, it is believed the lone pair of one of

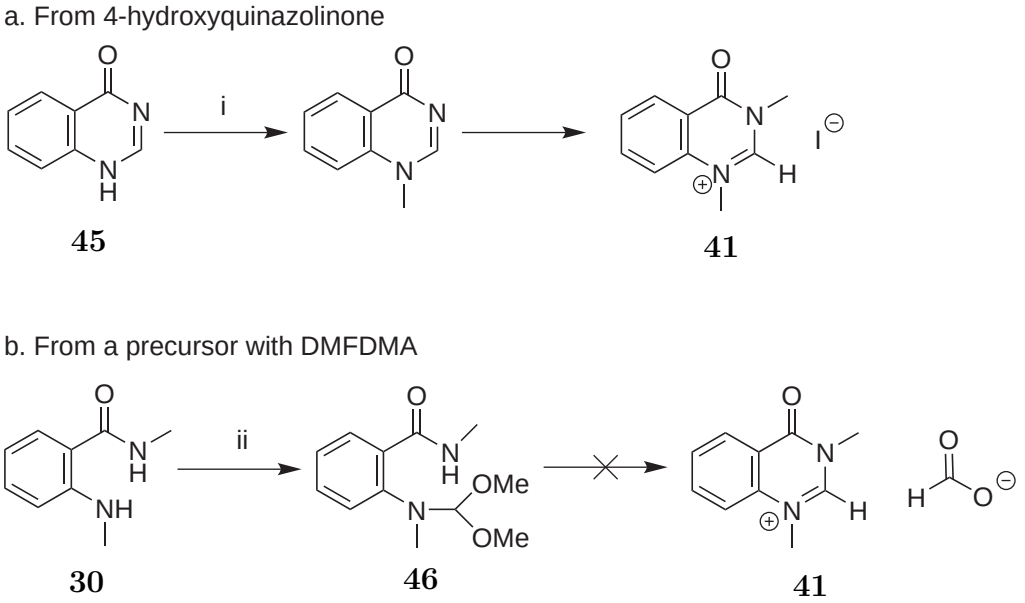


Scheme 2.7 Proposed mechanism of formation of **41**

the flanking nitrogens could donate to the exchanging-centre, with ejection of carbon dioxide and ethanol, generating the cationic species **41** as the chloride salt. In hindsight, with the expulsion of an equivalent of gas it is not surprising the intermediate species **44** was not stable.

This species became of exceptional importance to this research. The existence of this compound in itself is very strong evidence towards the carbene mechanism. Given that this species represents the input molecule for the RDS for the proposed carbene H-D exchange mechanism, the possibility for obtaining useful kinetic data towards the order of the mechanism was possible. The other important role of this molecule is that it represents a carbene precursor as used in synthetic studies to generate N-heterocyclic carbenes, which is addressed in Chapter 3.

In addition to synthesis using ethylchloroformate, other methods were explored. One of these involved starting from 4-hydroxyquinazolinone (**45**), which was heated in a pressure tube with methyl iodide and an equivalent of sodium bicarbonate [Scheme 2.8].[43] This resulted in addition of a methyl group to each of the nitrogens to generate the desired product as the iodide salt. Unfortunately, purification of this from the mono-alkylation product and remaining sodium bicarbonate was unsuccessful. An alternative method involves using the precursor to **28**, **30**, and DMFDMA. In this both nitrogens attack the DMFDMA, with loss of good leaving groups, followed by loss of the final heteroalkane to generate the desired product. Although this is a typical method to generate N-heterocyclic carbenes, it was unsuccessful here as the amide moiety was not sufficiently nucleophilic to complete the

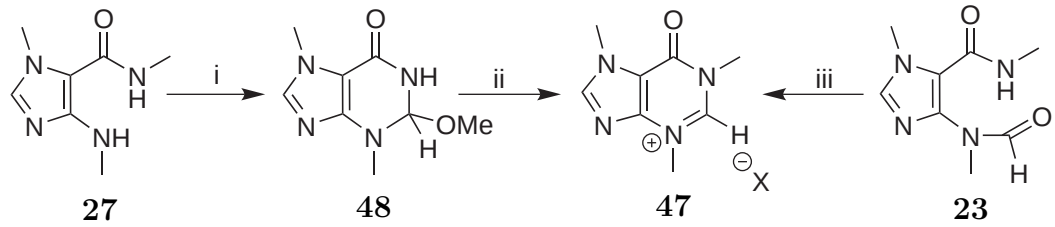


Reagents and Conditions: i. MeI, $NaHCO_3$, 55 °C, 4 d; ii. DMFDMA, CH_3OH, formic acid, rt, 2 d.

Scheme 2.8 Alternative attempts to synthesise **41**

cyclisation of **46**. The ethylchloroformate method was used for all further studies. In this, there is a risk that if any ethylchloroformate has hydrolysed, hydrochloric acid would remain, as the only nonvolatile byproduct of this reaction, which would act to completely inhibit any H-D exchange, as was seen with one sample of **41**. As a result, all sets of studies were performed on the same source of **41** to avoid impurity issues.

Attempts were made to obtain the imidazole-based cation **47** but this was unsuccessful. Synthesis from the precursor **27** with DMFDMA was unsuccessful, despite the beauty of the reaction with all reagents and solvents distilled off to drive the equilibria to completion [Scheme 2.9]. As opposed to the benzene-based model, the cyclisation occurred to form the second ring, with the intermediate **48** being isolated. Upon treatment with methanolic formic acid, this appeared to form **47**, with a resonance above 11 ppm in the ^{1}H-NMR spectrum, but this quickly degraded. Ethylchloroformate was also trialled with apparent success: a similar compound with a peak above 11 ppm in the ^{1}H-NMR spectrum was observed. However, this was not synthesised in high enough yield and was not easily purified. Further, the species again proved to be highly labile and readily hydrolysed. For these reasons, kinetic studies were limited to the benzene-based cation **41**.



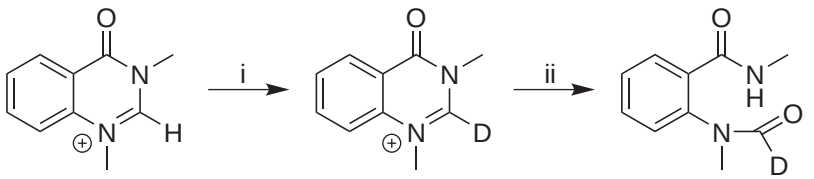
27 **48** **47** **23**

Reagents and Conditions: i. DMFDMA, 50 °C, 3 d; ii. formic acid, CH_3OH, rt, 1 d; iii. ethylchloroformate, 50 °C, 3 hr.

Scheme 2.9 Attempted syntheses of **47**

2.3.2 Kinetic studies of 41

Although it was believed that **41** would be too susceptible to hydrolysis for use in kinetic studies, initial observations were good. In the beginning, there was much hesitation in removing this compound from an inert atmosphere, let alone dissolving it in deuterium oxide. However, **41** showed surprising stability to both atmospheric conditions, where no hydrolysis was seen over a time period of weeks, and aqueous conditions, where no hydrolysis was seen in the timescale of the H-D exchange. Basifying deuterium oxide with potassium carbonate was able to exact the hydrolysis in a shorter timeframe to confirm hydrolysis to **49** [Scheme 2.10]. Meanwhile, H-D



41 **50** **49**

Reagents and Conditions: i. D_2O; ii. K_2CO_3, D_2O.

Scheme 2.10 H-D exchange of **41**

exchange of the amidine proton to **50** was occurring smoothly, as seen by the decrease in the amidine resonance, at approximately 9.5 ppm, with time in deuterium oxide [Figure 2.18].

41 was found to undergo H-D exchange faster than for **28** with the same response to exogenous acid and base. The half-life of the H-D exchange in **41** was found to be shorter than that for **28**, 80 minutes as compared to 149 minutes [Figure 2.19, Table 2.7]. This is not surprising, given that this is the immediate starting material for the RDS, whereas **28** is a number of mechanistic steps away. This means that the majority of the population is closer to the RDS and it is a shorter time for molecules to reach the transition state. However, **41** did respond similarly to **28** with regards to acid and base: addition of acetic acid-d_4 led to a complete inhibition of exchange, whereas triethylamine promoted this [Figure 2.20, Table 2.8]. Although

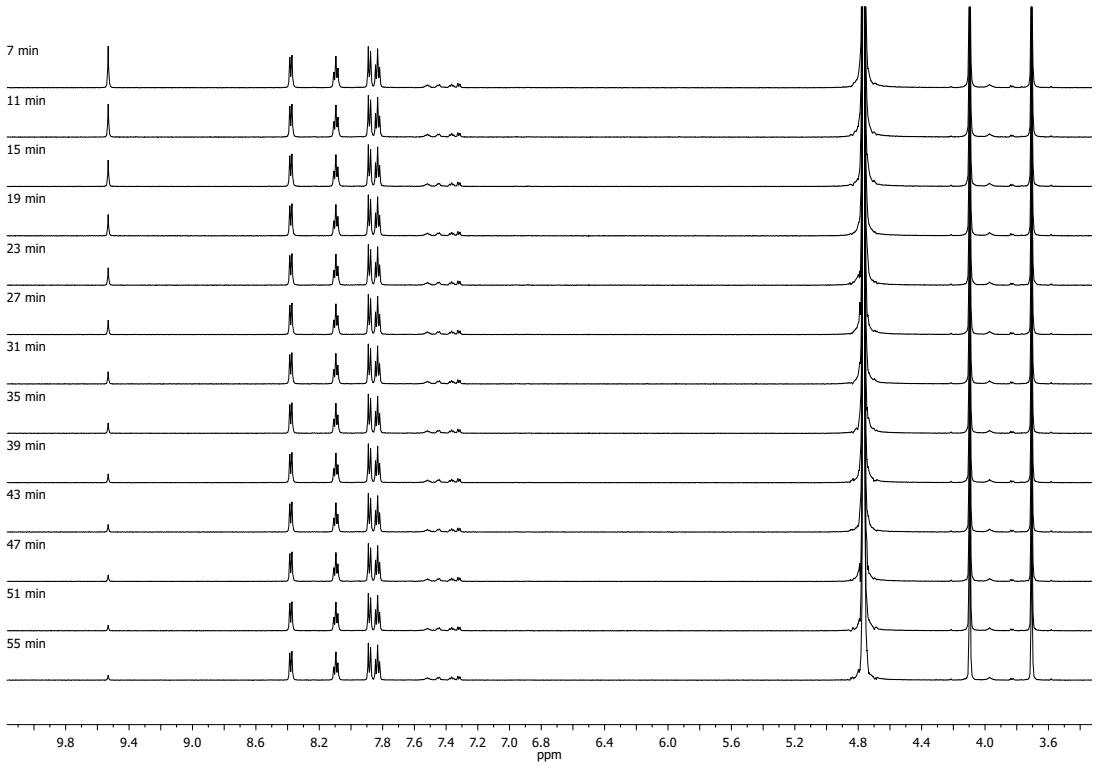


Figure 2.18 ^{1}H NMR spectra of **41** with time in D_2O

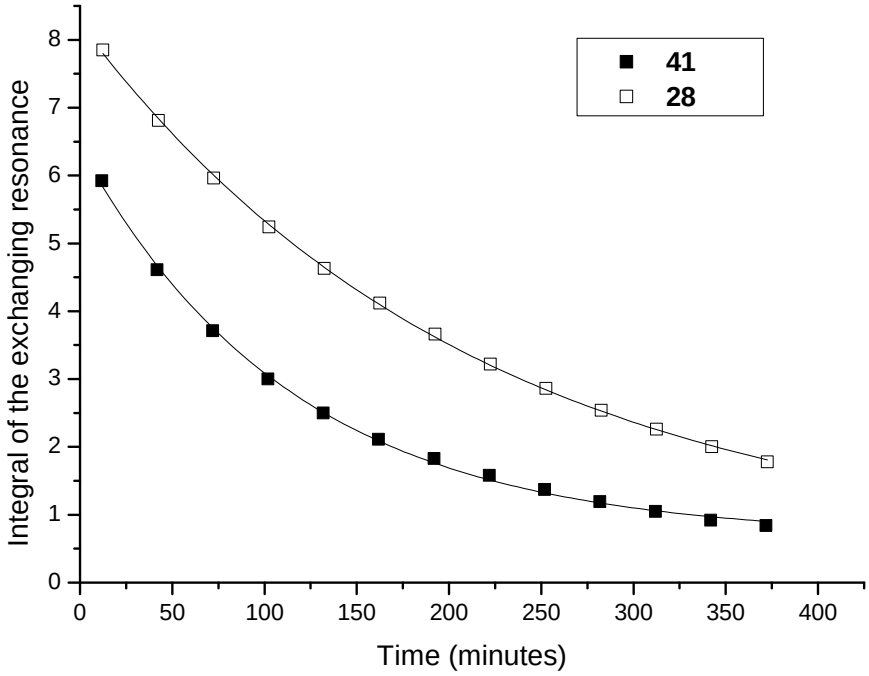


Figure 2.19 H-D exchange of **28** and **41**

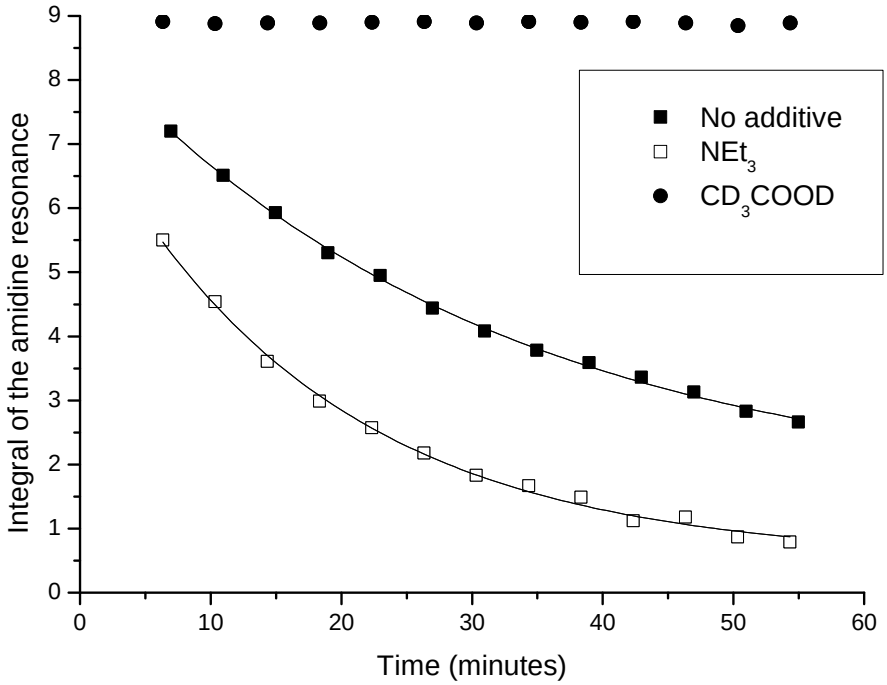


Figure 2.20 Effect of acid and base on the rate of H-D exchange of **41**

Table 2.7 Half-life of H-D exchange of **28** and **41**

Species	Half-life (min)	R^2
28	148.7	0.999
41	80.0	0.999

Table 2.8 Effect of acid and base on the half-life of the H-D exchange of **41**

Additive	Half-life (min)	R^2
No additive	21.4	0.998
NEt_3	12.5	0.996
CD_3COOD	-	-

further [acid] studies could have been performed, the data obtained would not allow much insight into the mechanism of exchange as the RDS dominates the observed rate law. Observation of acid inhibition is sufficient for these studies.

The correlation found between the concentration of **41** and half-life was unexpected, but suggestions can be made towards its origin. Although it would be expected that the rate would increase with an increase in concentration, assaying the H-D exchange at different concentrations of **41** showed the opposite: the lowest concentrations of **41** exchanged the fastest [Figure 2.21, Table 2.9]. This could be rationalised in that **41** is inherently acidic: in formation of the carbene an equivalent of H^+ is liberated. At higher concentrations of **41**, the population of carbene, and hence

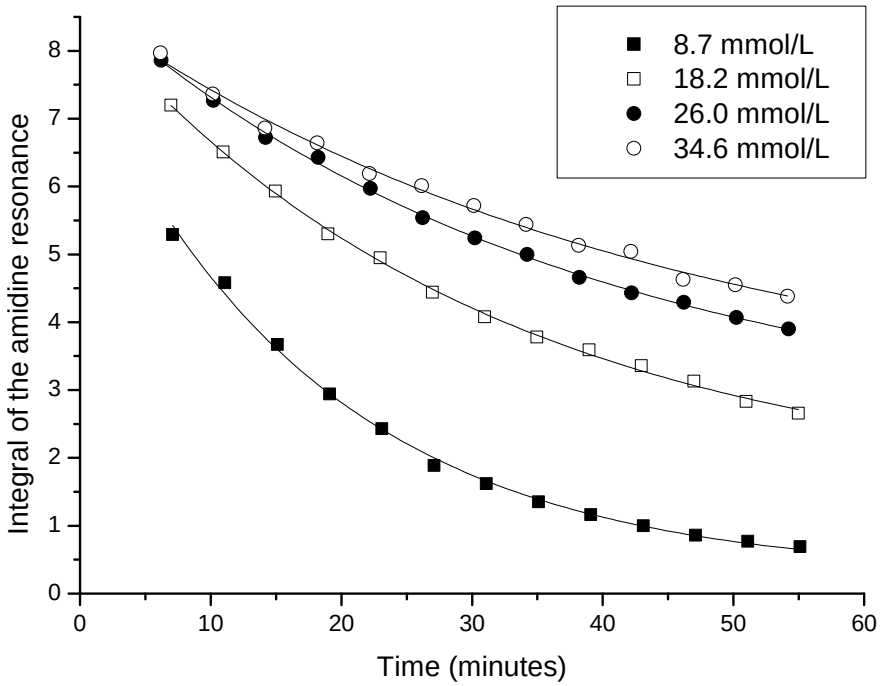


Figure 2.21 Half-life of H-D exchange with respect to concentration of **41**

Table 2.9 Effect of concentration of **41** on half-life of H-D exchange

Concentration (mmol/L)	Half-life (min)	R^2
8.7	12.7	0.997
18.2	21.4	0.998
26.0	25.7	0.999
34.6	30.0	0.995

H^+, is higher and could become self-inhibitory. However, the larger population of carbenes would suggest a higher rate of exchange. A more reasonable rationale is due to residual hydrochloric acid on the surface of the analyte. As more analyte was used, more acid was introduced to the system and the increased acidity would increasingly inhibit the exchange. A solution would be to purify the analyte further, which is problematic, or assay at lower concentrations where this is less significant.

Herein lies the problem with using NMR spectroscopy to follow the kinetics: only a narrow concentration range of the analyte observed can be tolerated. There are difficulties shimming the instrument at high concentrations and at low concentrations it can not accurately observe the signals of the material due to the insensitivity of the technique. Whereas a concentration range of 104,000-fold was possible with triethylamine, which need not be observed, only a 4-fold difference was possible with **41**. A different spectroscopic technique, or a revision of the existing method, would be required to investigate this further.

Kinetic studies investigating the effect of [triethylamine] were not similarly limited, but finding the necessary concentrations to test took much experimentation. For these base-concentration studies, the dissociation of deuterium oxide was ignored; even at the lowest concentration of triethylamine used, the concentration of exogenous base was more than 100 times that of the dissociation of water, so its contribution was assumed to be negligible. A correlation was observed that increasing the concentration of base increased the rate of exchange, as would be expected for a base-catalysed model. Indeed the highest concentration of base, 1042 mmol/L, resulted in an exchange that was too fast to be accurately monitored [Table 2.10,

Table 2.10 Initial studies into the effect of concentration of NEt_3 on half-life of H-D exchange of **41**

Concentration (mmol/L)	Half-life (min)	R^2
1042	-	-
1.055	6.3	0.997
0.844	5.7	0.997
0.633	9.0	0.999
0.422	8.3	0.999
0.211	12.5	0.996

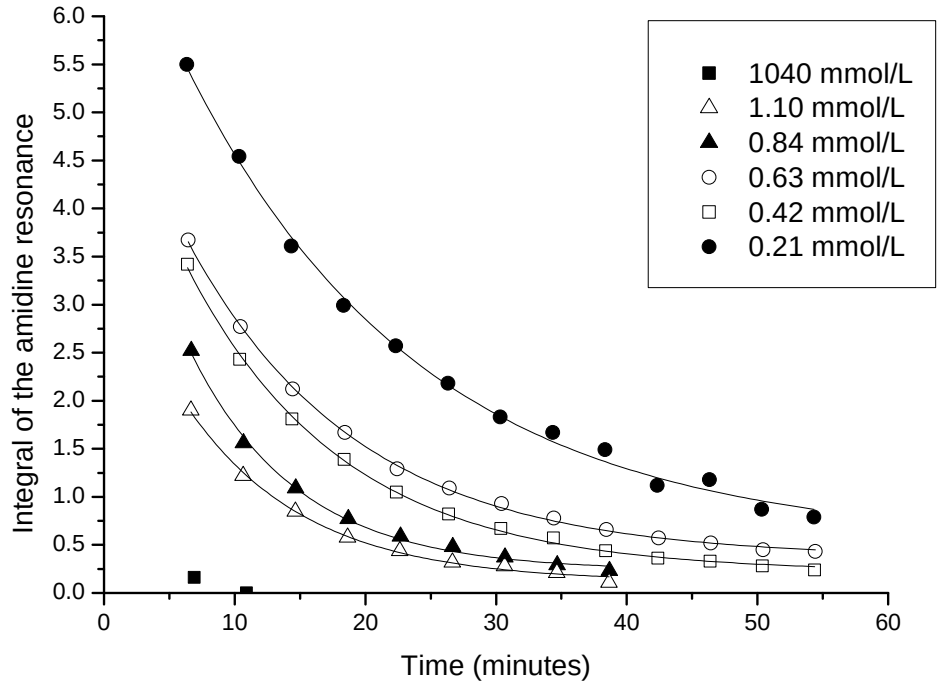


Figure 2.22 Initial studies into the effect of concentration of NEt_3 on rate of H-D exchange of **41**

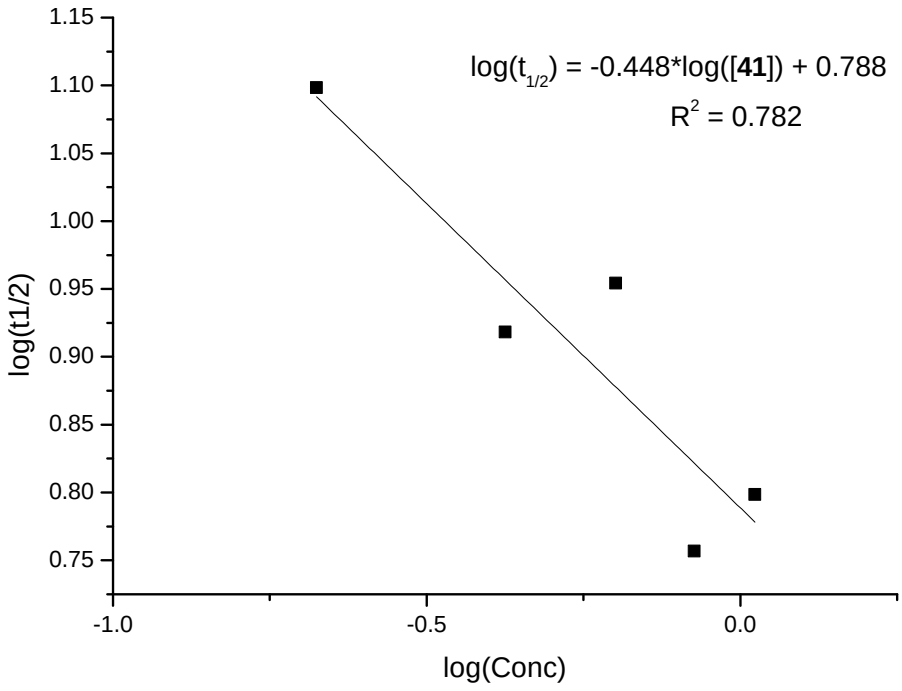


Figure 2.23 $\log(t_{1/2})$-dependence on log(concentration) of NEt_3

Figure 2.22]. Plotting the logarithms of the concentration and half-life against each other gave a linear trend with a gradient of -0.44, which corresponds to an order of 1.44 for base in the RDS [Figure 2.23]. The data was not ideal, as can be seen visually and as shown by the R^2 value of 0.78. More data was needed to be collected to supplement this data set, but due to the requirement of only comparing kinetic experiments run from the same sample, these had to constitute an independent set of data. Also, to allay fears that the concentrations used were approaching a rate-saturation point, much lower concentrations were assayed using dilute standard solutions.

The second study into the effect of base on the H-D exchange justified the need to continually assay lower concentrations. The constant fear that the concentrations investigated were approaching the maximal rate of exchange, and hence displaying a non-linear response between concentration and rate, was warranted when visualising the half-life against the concentration [Figure 2.24, Figure 2.25]. It is apparent that these values describe an exponential curve, with higher concentrations resulting in a half-life that is approaching a minimum value, the maximum rate of exchange, which is approximately 0.5 minute. Having started the first base study with a concentration 1043 mmol/L, this justified the need to go down to a concentration of 0.01 mmol/L, a 104,300-fold decrease in concentration.

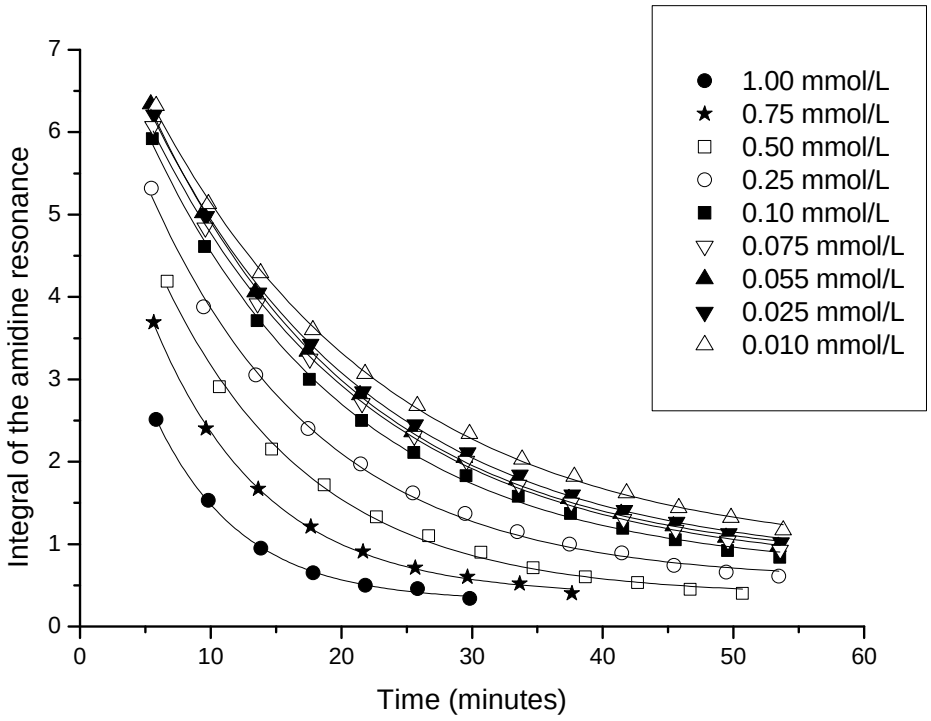


Figure 2.24 Final studies into the effect of concentration of NEt_3 on half-life of H-D exchange of **41**

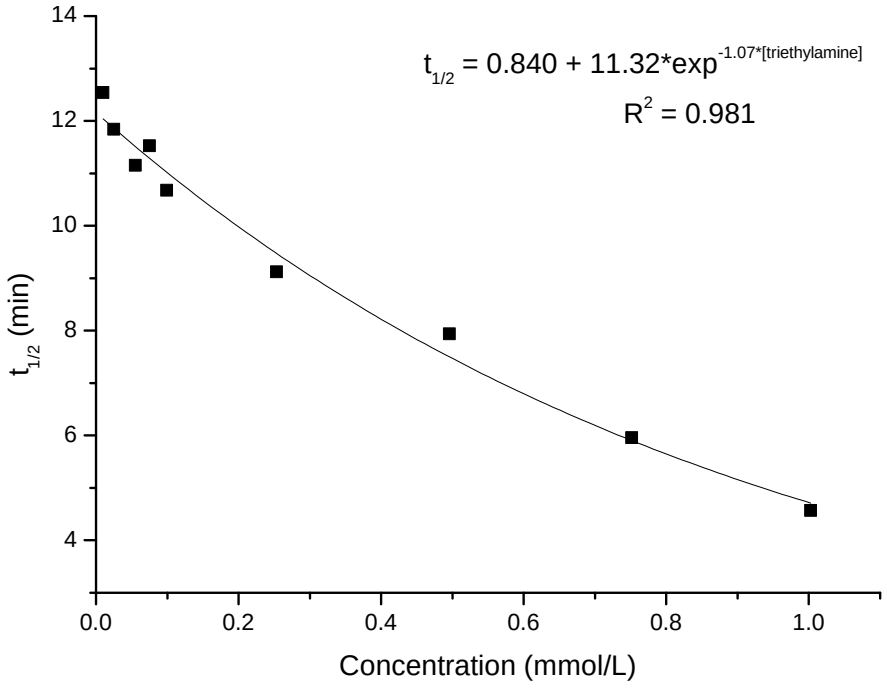


Figure 2.25 Half-life of exchange of **41** with changes in [NEt_3]

The kinetic studies with the lowest concentrations of base gave good evidence towards the order of base in the RDS. Analysing the lowest five sets of data, by plotting the log of $t_{1/2}$ against log(concentration), resulted in a linear model with a gradient of -0.060 and an R^2 value of 0.812 [Figure 2.26]. The fit of the model could be better, but it is apparent one of the data values is slightly erroneous, which, given the concentrations being used, is understandable. Nonetheless, a gradient of -0.060, or approximately 0, means the exchange is, according to Equation 1.15, first order with respect to base. This disproves the self-protonation mechanism, as this would be zero order with respect to base, whilst supporting both the carbene and ylide mechanisms. However, given how close this estimate is to the ideal value for a first order reaction, there is more support for the carbene mechanism over the ylide. From **41** the exchange, according to a carbene mechanism, is one step and first order with respect to base, as these findings suggest. The ylide mechanism, however, involves an additional protonation step that would be disfavoured under basic conditions and should make the observed rate law deviate from an exact first-order value. Given the accuracy of the estimate for the order, the exchange would appear to go through a carbene mechanism.

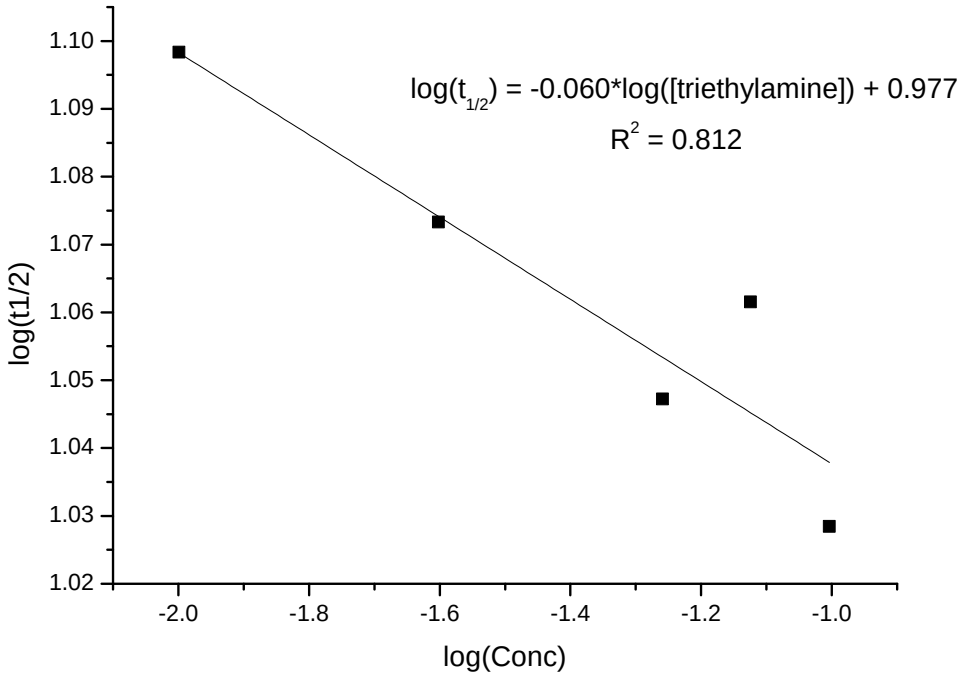


Figure 2.26 $\log(t_{1/2})$-dependence on $\log([NEt_3])$ at low concentrations

2.3.3 Kinetic studies of DMFDMA

To address the contradiction of this data with Simchen's observations, studies on DMFDMA were attempted. Simchen originally found acid catalysis and base inhibition of H-D exchange, but he had difficulty reconciling this with his mechanisms. To attempt to confirm this independently, kinetic studies were performed on DMFDMA. Simchen's original studies were composed of reacting this species neat in a 1:1 stoichiometric ratio with deuterated solvents. Instead of following their original method, it was instead decided to attempt kinetic studies using dilute solutions as have been performed throughout this research. Kinetic studies were run in different solvents and the response to different concentrations of the analyte, as well as changes in concentration of exogenous acid and base were analysed [Figure 2.27]. There appeared to be no effect on the rate of H-D exchange due to the presence or absence of acid or base, which seemed to go against all results to date.

There are certain inherent difficulties in studying DMFDMA, however. Deuterated DMFDMA (**51**) was observed by NMR and MS, confirming exchange occurred. However, DMFDMA is in itself the solvent adduct (methanol) of a solvent (DMF, **52**), which makes following the resonances in NMR spectroscopy, where peaks from residual, non-deuterated solvents are typically ignored but nonetheless present, difficult. As seen in a study in deuterium oxide, DMFDMA (**15**) hydrolysed back to

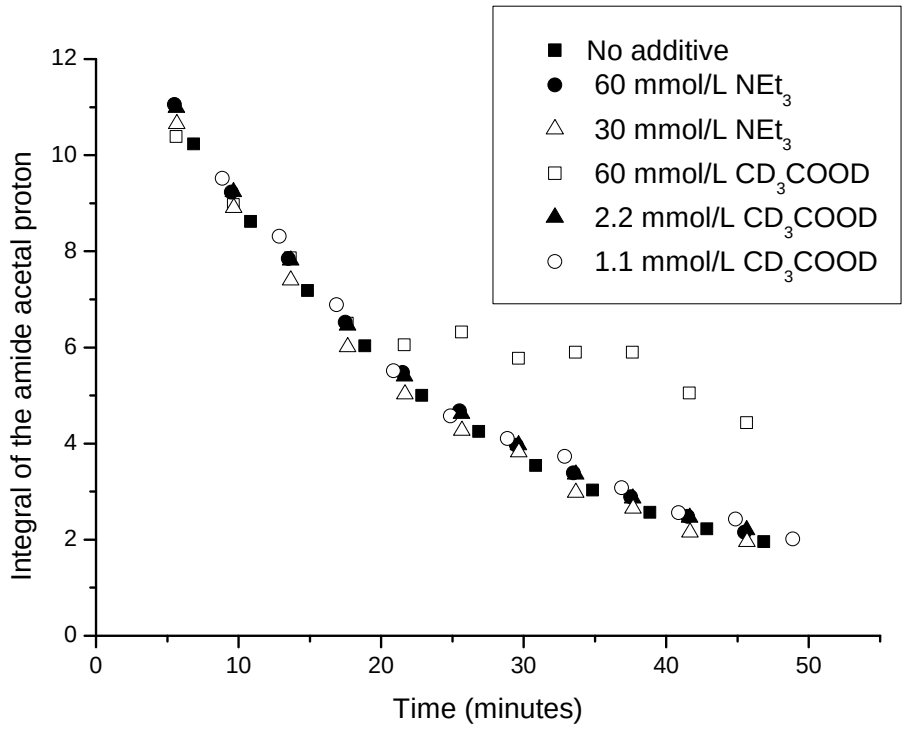
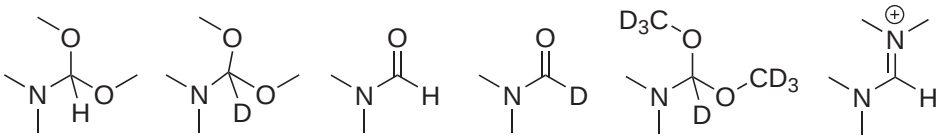


Figure 2.27 H-D exchange of DMFDMA under varied conditions

these base solvents, with some deuterated DMF (**53**) observed. Alternatively, in other solvents, such as methanol-d_4, it can exchange groups for their isotopically-labelled, and NMR-invisible, counterparts (**54**). Given that a deuterated-solvent is required, this is unavoidable. But to monitor the exchange of the amide acetal proton for a deuteron requires comparison to an existing, unchanging peak. Due to ligand exchange, this is limited to the dimethylamine substituent. However, evidence of the iminium compound **55** was observed by MS, suggesting that there is ligand exchange of the dimethylamine substituent as well. Needless to say, with every part of the molecule changing or exchanging, bar the central carbon, kinetic studies on this species are challenging and outside of the scope of this research. Simchen's findings of acid catalysis and base inhibition in the H-D exchange of DMFDMA remain to be confirmed.



15 **51** **52** **53** **54** **55**

Figure 2.28 Species appearing in the DMFDMA kinetic studies

Chapter 3

Trapping a carbene

The research now shifted from trying to understand the H-D exchange phenomenon to trying to prove the mechanism. Although this was a risky gamble, in that if nothing works nothing is learned, it was believed to be known which mechanism was occurring and sought to prove this. The body of evidence from this research, as well as literature work on carbenes and NHCs, led us to believe a carbene was generated in the H-D exchange of malonganenone B. The best evidence for this therefore would be to trap a carbene. The ideal starting point was akin to how carbenes were first demonstrated; by reaction with an alkene to generate a cyclopropane.[15,44] Carbenes, as divalent, neutrally-charged carbon species, also have a tendency to dimerise to form fulvalenes, which can undergo further reactions to generate more stable species.[45,46] Finally, NHCs have had their most important work as ligands in organometallic complexes.[16,21,22] Given that the carbene proposed here is similar to existing NHCs, albeit a new class that has never been reported, following existing methods to generate an organometallic species was the final approach to be explored.

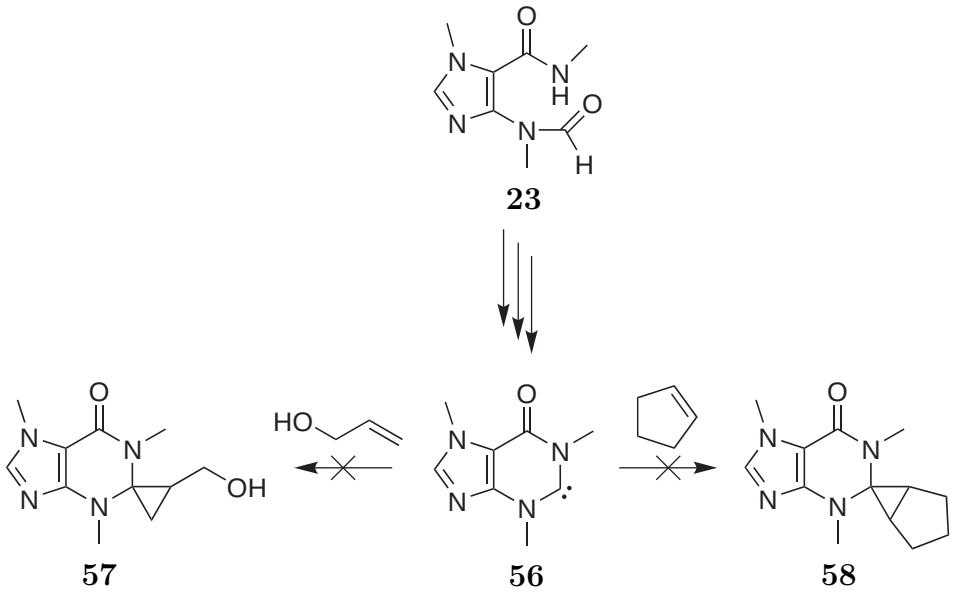
3.1 As a cyclopropane

3.1.1 Intermolecular attempts

Attempts were made to trap the model compounds available with exogenous alkenes. NHCs are highly nucleophilic carbenes, due to the electron-donating properties of the two adjacent nitrogen atoms. With the carbene proposed here, this effect would be lessened by the fact one of the nitrogens is part of an amide, which would draw

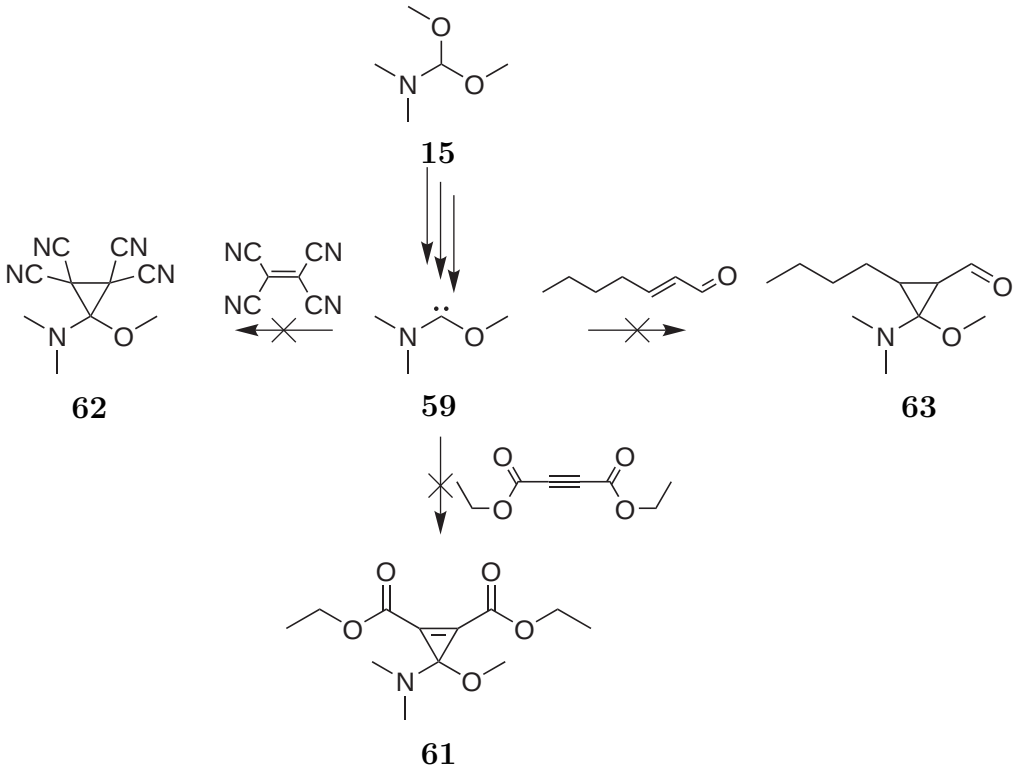
electron density to the carbonyl rather than the carbene. For this reason it would be expected that these carbenes are nucleophilic, but not to the same extent as existing NHCs. As for many chemical reactions, it is important to match the energies of the reagents; in this case, matching the LUMO of an alkene with the high HOMO of the carbene. Towards this end, alkenes with electron-withdrawing groups were investigated to a greater degree. A wide range of alkenes was trialled, however, limited only by what was available.

Initially attempts were made to trap the imidazole-based carbene **56** but these were unsuccessful. 10 equivalents of allyl alcohol or cyclopentene were added to a solution of **23** in methanol in an attempt to form **57** and **58** respectively, but these were unsuccessful [Scheme 3.1].[47] It was hoped that in the dynamic equilibria of the H-D exchange, a trapping event may occur. But, given the number of steps required to reach the carbene and the proposed short half-life of this species, particularly in a nucleophilic solvent, the chance of such an event occurring is very low and it is not surprising that no trapping was observed.

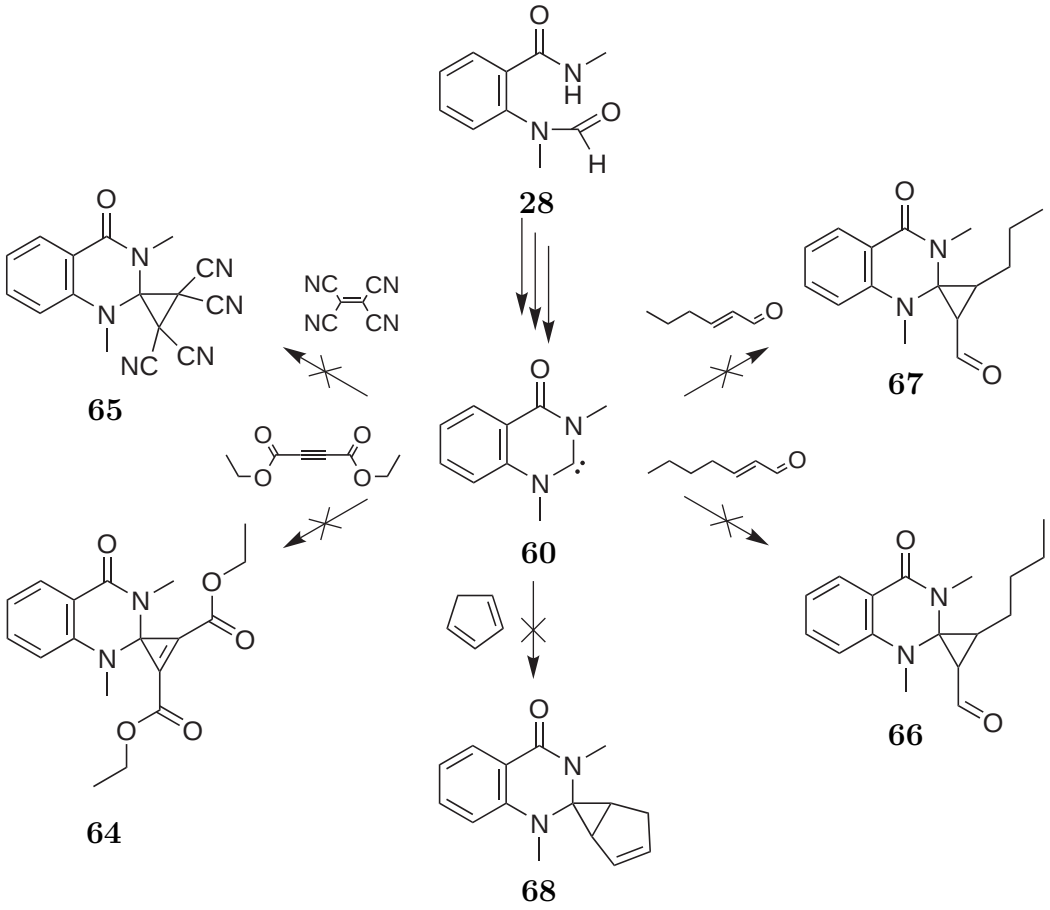


Scheme 3.1 Attempts to trap **47**

Similar attempts were made to trap the carbene resulting from DMFDMA, **59**, and the benzene-based carbene **60** with revised reaction conditions and reagents. To try and prolong the half-life of the carbene, non-nucleophilic solvents were trialled, namely tetrahydrofuran and dichloromethane. It was expected that the largely intramolecular reactions, and hence carbene formation, would still be occurring in these solvents and that leaving the reactions for a prolonged period would increase the probability of a trapping event occurring. To try and match the energy levels of the orbitals, alkenes with electron-withdrawing groups were required: diethy-



Scheme 3.2 Attempts to trap **59** generated from **15**



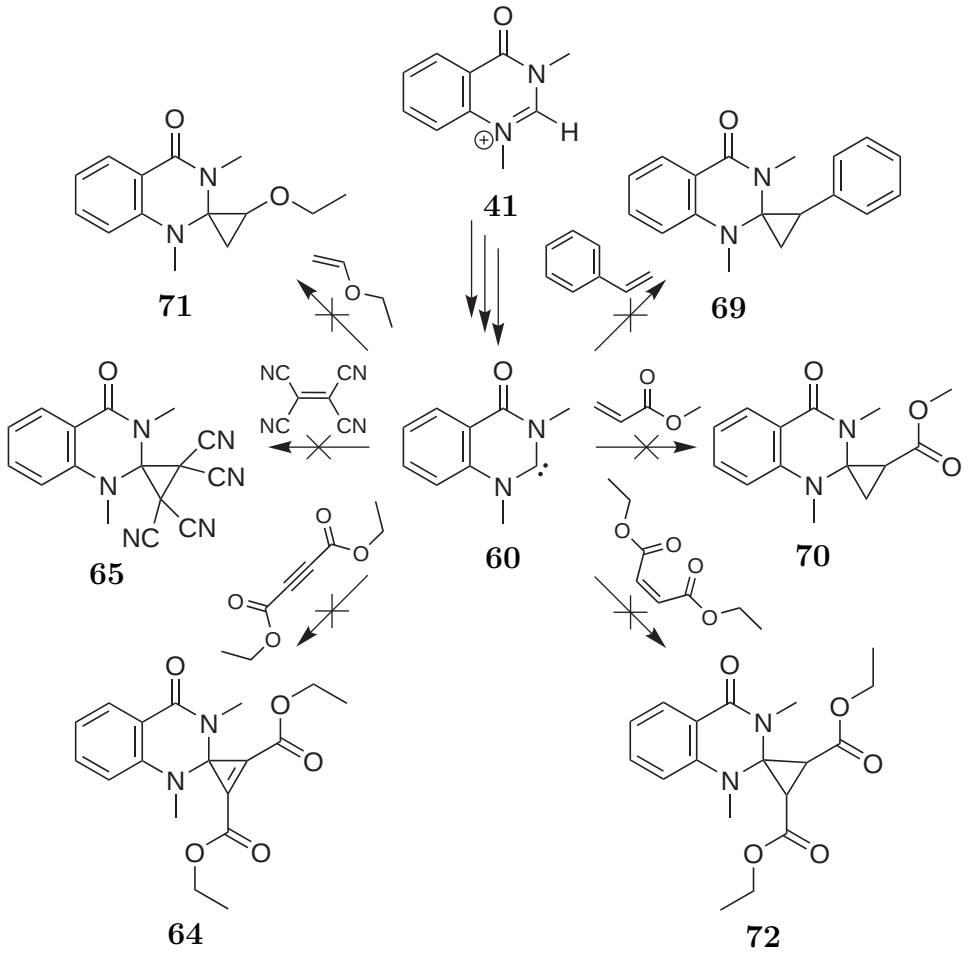
Scheme 3.3 Attempts to trap **60** generated from **28**

lacetylenedicarbonate, tetracyanoethylene and hept-2-en-1-al were trialled in the reactions. Unfortunately, attempts to synthesise **61** to **66** were unsuccessful, even after leaving for three months to react [Scheme 3.2, Scheme 3.3].[48,49] **60** was also attempted to be trapped with 2-hexenal and cyclopentadiene to form **67** and **68** respectively,[48,50] but this met with the same glorious outcome. Reactions were also performed in neat diethylacetylenedicarbonate, but this was similarly unsuccessful. There is a possibility that these solvents were too nonpolar and generation of the charged carbene precursor was disfavoured, inhibiting carbene formation. This represents something of a Catch-22, in that polar solvents may be necessary for formation of the carbene, but these simultaneously decrease its half-life.

Given the number of steps from these models to the carbene, trapping reactions were performed instead on **41** using known carbene-generating methods. In this set of reactions, a base, such as sodium hydride, exacts abstraction of the proton to generate the carbene directly and nonpolar solvents, such as tetrahydrofuran, can be used to solubilise the generated carbene, extending its lifetime and making a trapping event more likely. Using **41**, generated previously or *in situ*, in tetrahydrofuran or dichloromethane, degassed or as was, with sodium hydride or triethylamine for base, a number of trapping reactions were trialled. Renewed attempts to form **64** and **65** were unsuccessful [Scheme 3.4], although the later generated an exciting crimson-red colour which resulted from a single-electron transfer between triethylamine and tetracyanoethylene.[51] Triethylamine was only trialled over concerns that the sodium hydride available was partially hydrolysed, which is discussed later along with the need for the degassing of solvents. To assay a range of alkenes with different energies, styrene,[52] methyl acrylate,[53] ethyl vinyl ether[54] and ethyl maleate[55] were used to try and synthesise **69**, **70**, **71** and **72** respectively. The outcome of these reactions was a mixture of **28**, hydrolysed starting material, and **32**, one of the intermediates in the synthesis of **28** but which also represents the oxidative degradation product of a dimerised carbene species. The formation, and importance, of this species is covered later. In summary, all intermolecular trapping events with alkenes were unsuccessful.

3.1.2 Intramolecular attempts

Intramolecularly-bonded alkenes were next to be trialled. It was expected that tethering the alkene, making it an intramolecular reaction, would boost the chances of a trapping event occurring. The tethered-alkene compounds **73** and **74** were intended to be synthesised, which were expected to lead to the cyclopropanes **75** and **76** respectively. Although the energy levels of the carbene and alkene are

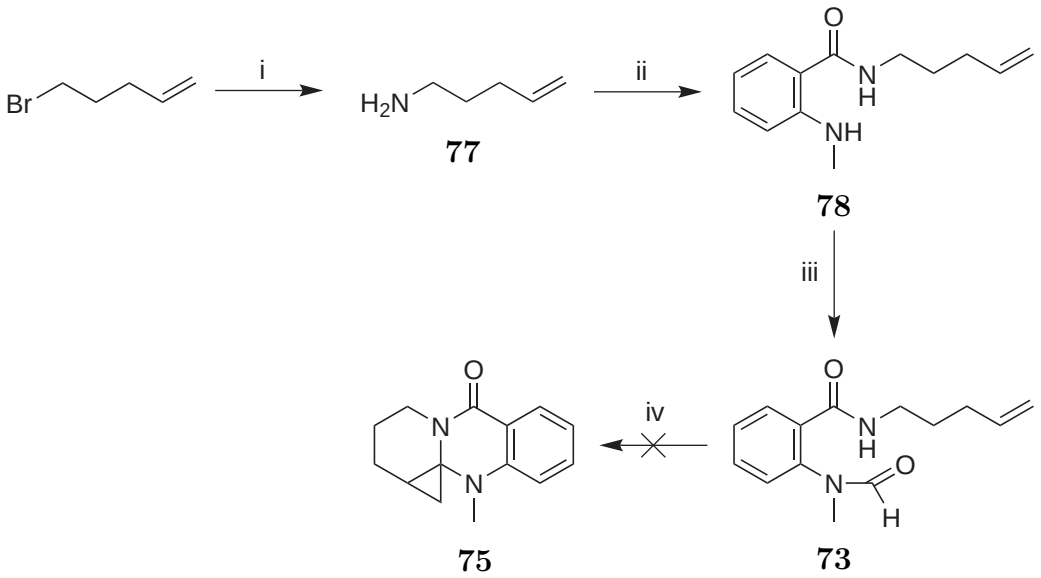


Scheme 3.4 Attempts to trap **60** generated from **41**

not well matched, it was believed the increased proximity would overcome this. These compounds could be easily obtained using the methodology developed in this research by changing the amine used in the ring-opening of *N*-methylisatoic anhydride.

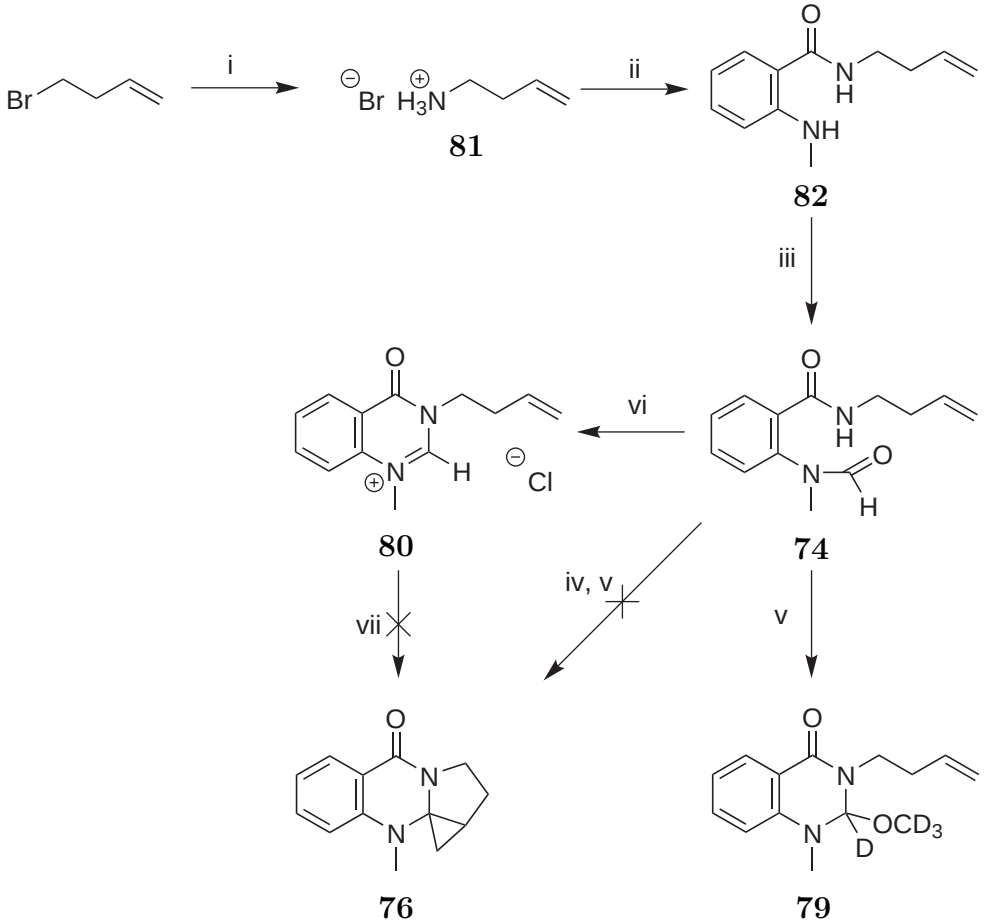
Although **73** was successfully synthesised, no trapping occurred. Pent-4-en-1-amine (**77**) was synthesised from the corresponding bromide in methanolic ammonia and equilibrated in a bicarbonate solution to give the free amine **77** [Scheme 3.5].[56] This was then reacted with *N*-methylisatoic anhydride to give the precursor compound **78**, which was formylated to give the pentene derivative, **73**. After leaving this to exchange, and therefore hopefully to cyclopropanate, in the polar solvent dimethylsulfoxide-d_6 for seven days, no change was observed by NMR spectroscopy. When this was repeated in methanol-d_4, the product underwent solvolysis, with no trapping occurring.

Even though the cationic species **80** was obtained, no trapping was observed. As before, **81** was synthesised from the equivalent bromide but left as the ammonium bromide salt to avoid loss of material [Scheme 3.6]. This was then reacted with



Reagents and Conditions: i. NH_3, MeOH, 90 °C, 24 h, 28%; ii. *N*-methylisatoic anhydride, H_2O, 50 °C, 24 h, 3%; iii. mixed formic acetic anhydride, 55 °C, 2 h, 70%; iv. $(CD_3)_2SO$ or CD_3OD, rt, 7 d.

Scheme 3.5 Attempted synthesis of **75**



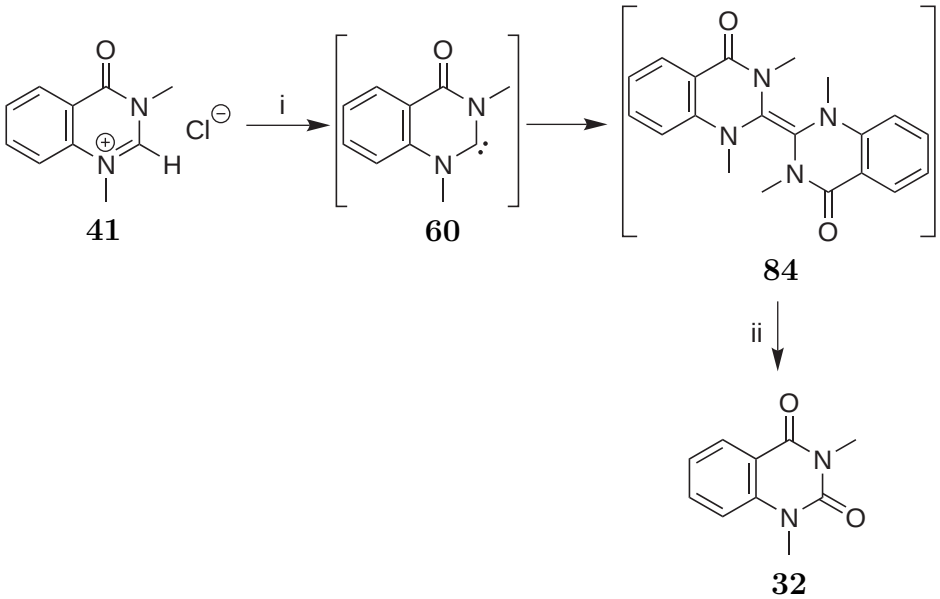
Reagents and Conditions: i. NH_3, CH_3OH, 90 °C, 24 h, 60%; ii. *N*-methylisatoic anhydride, H_2O, 50 °C, 24 h, 8%; iii. mixed formic acetic anhydride, 55 °C, 2 h, 31%; iv. $(CD_3)_2SO$, rt, 7 d; v. CD_3OD, 7 d; vi. ethyl chloroformate, 50 °C, 12 h, quant.; vii. NEt_3, $CDCl_3$, 1 h.

Scheme 3.6 Attempted synthesis of **76**

N-methylisatoic anhydride to form **82** and formylated to give **74**. Incubation in methanol-d_4 led to the methanol-adduct **79** forming, which highlights that **74** is chemically similar to the methylated parent compound, hence it is expected that carbene-formation would be occurring. Using the methodology available from the work with **41**, this was converted into the cationic species **80** using ethylchloroformate. This allowed the carbene to be generated directly and hence increase the chance of trapping. However, reacting this species with triethylamine in degassed chloroform-d gave only the hydrolysed product **74**. As was prewarned in the preface of this section, if nothing worked, as occurred here, nothing was learnt about the H-D exchange, except for ways to *not* demonstrate the existence of a carbene.

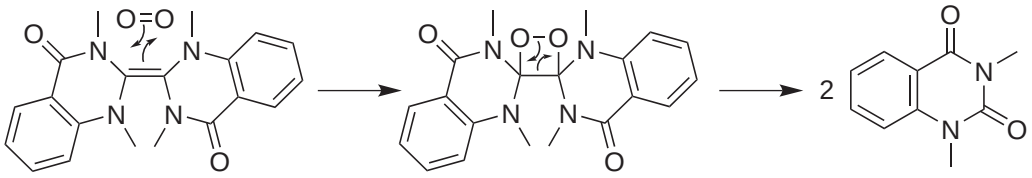
3.2 As a dimer

The ability of carbenes to dimerise was utilised in the next approach towards proving the existance of a carbene in this exchange. Given the successful attainment of **41**, the synthesis of dimeric species **84** was attempted first. Treatment with sodium hydride in tetrahydrofuran resulted in a set of peaks that, at this time, were believed to belong to a previously unseen product in this project [Scheme 3.7]. Through NMR and MS investigations it was found that this species was not **84** but the oxidative degradation product of this, **32**. It is well known that enetetramines undergo oxidative cleavage in the presence of oxygen, forming first the 1,2-dioxirane **85** from a [2+2] cycloaddition with oxygen which then undergoes a pericyclic cleavage to give the urea **32** [Scheme 3.8].[57,58] After realising this structure, it was found that



Reagents and Conditions: i. NaH, THF, 50 °C, 4 h; ii. O_2.

Scheme 3.7 Attempted synthesis of **84**



84 **85** **32**

Scheme 3.8 Oxidative cleavage of **84** to give **32**

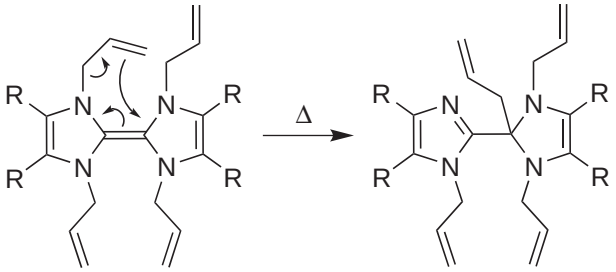
the spectra of this perfectly matched those of one of the intermediates in the initial synthesis of **28** [Scheme 2.3].

Although this is not a direct demonstration of a carbene, it is good indirect evidence towards its existence. There are other possible mechanisms through which the formation of **32** could have occurred, however, these usually require aggresive reagents[59,60] or reactive oxygen species.[61] Given that these conditions were absent, but that the leakage of air into the reaction was possible, this adds support to the theory **32** formed as a result of degradation of **84**. Given the lack of steric bulk around what is an electron-rich, highly-reactive alkene, it is not surprising that the compound decomposes, even if this, as an enediaminediamide, is less electron rich and hence less reactive. Where **32** was observed in some of the previous trapping studies, this is evidence that the carbene was formed, and that trapping, as opposed to generation of the carbene, was unsuccessful. As a side thought, it is disappointing that the equivalent carbene precursor could not be generated from **23**, because it is also known that the oxidative cleavage of enetetramines generates light.[62] One can only imagine the PR campaign possible if an energy drink were to contain the dimer of this, which, when you opened the bottle, emitted light and synthesised caffeine!

Observation of this species was crucial in the drive towards using full Schlenk conditions with the equipment available. A synthetic organic chemist's and an organometallicist's concept of *inert* conditions are somewhat different; the former would exclude air from the reaction itself but perform a work-up under atmosphere, whereas the later would never let the compound come in contact with air. To try and exclude oxygen, and hence cleavage of any dimer, the experimental techniques and methods were continually improved to ensure inert conditions, measured by the presence of **32**. This culminated in reactions performed in NMR tubes under argon with degassed solvents. Many unsuccessful reactions could have been avoided if these conditions were employed at an earlier stage, but the learning process is an integral part of any research.

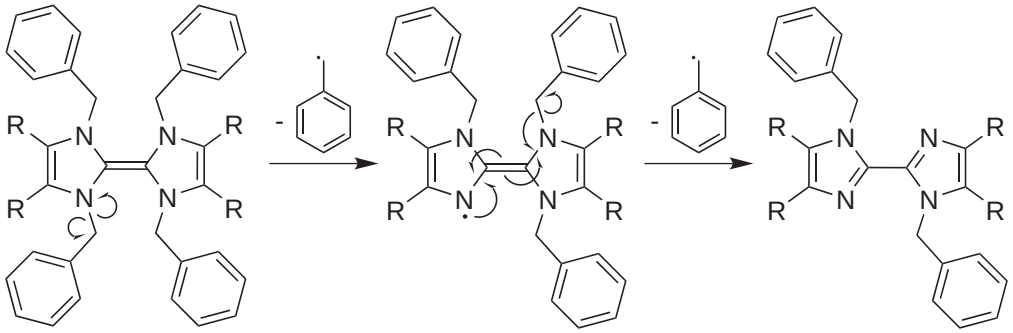
Given the instability of **84**, other dimers that rearrange to stable species were proposed. With allylic or benzylic substituents, the dimer can undergo intramolecular reactions. Allyl-substituted dimers, **86**, undergo a [3,3]-sigmatropic amino-Claisen

a. Tetraallyl enetetramines



86 **87**

b. Tetrabenzyl enetetramines

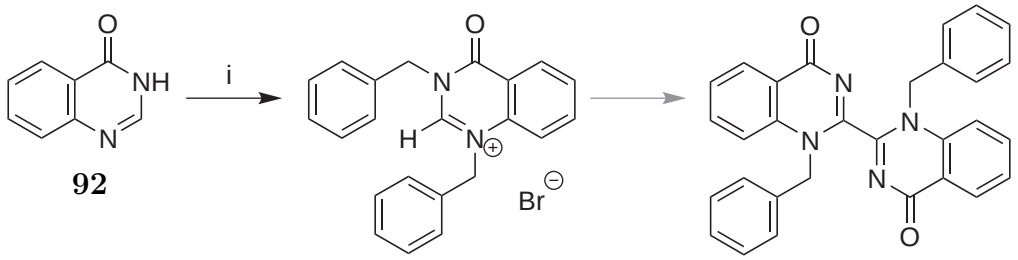


88 **89** **90**

Scheme 3.9 Mechanisms of rearrangement of substituted dimers

reaction to form the stable species **87** [Scheme 3.9.a].[45] It has been suggested, however, that this forms instead through a radical mechanism,[46] which is the mode of degradation for the tetrabenzyl species (**88**). In this, a benzyl radical spontaneously leaves generating the resonance-stabilised radical **89**, which undergoes an intramolecular radical reaction to eject a second benzyl radical and forms the stable biamidine **90** [Scheme 3.9.b].[63] Although the chemistry of our compounds is undoubtedly different, with the presence of an amide which could have serious effects in a radical mechanism, synthesis of the allyl- and benzyl-substituted species was attempted.

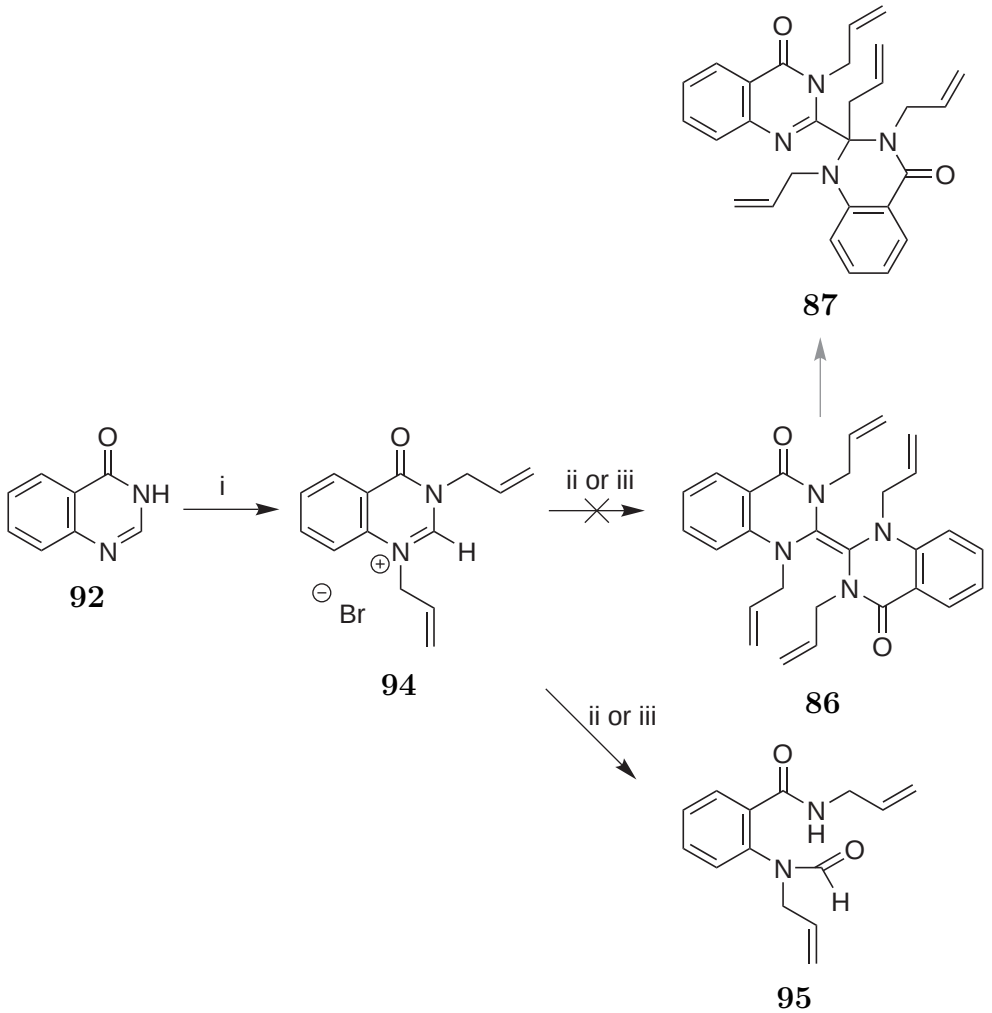
Although the dibenzyl compound **91** was synthesised, lack of purity defeated any attempted use. An exceedingly efficient method to this compound is through the reaction of 4-hydroxyquinazoline (**92**) with benzyl bromide in the presence of an equivalent of sodium bicarbonate [Scheme 3.10].[46] In this the two ring nitrogens attack benzyl bromide leading to alkylation and generation of the carbene-precursor cation **91**, which was successfully obtained according to MS analysis. As one could imagine, purifying a cationic salt, **91**, from the unreacted starting-material salt, sodium bicarbonate, and the ionic byproduct, sodium bromide, might pose difficulties. It did. Despite multiple attempts to extract with organic solvents and flash chromatography, sufficient purity of **93** was never obtained. By the end of the attempted purification process, the major impurity was the hydrolytic degradation



92 **91** **93**

Reagents and Conditions: i. benzyl bromide, sodium bicarbonate, ethanol, reflux, 2 d.

Scheme 3.10 Attempted synthesis of **93**



92 **94** **86** **95**

Reagents and Conditions: i. allyl bromide, $NaHCO_3$, EtOH, reflux, 2 d, 5%; ii. NaH, THF, rt, 12 h; iii. NEt_3, $CDCl_3$, rt, 6 d.

Scheme 3.11 Attempted synthesis of **87**

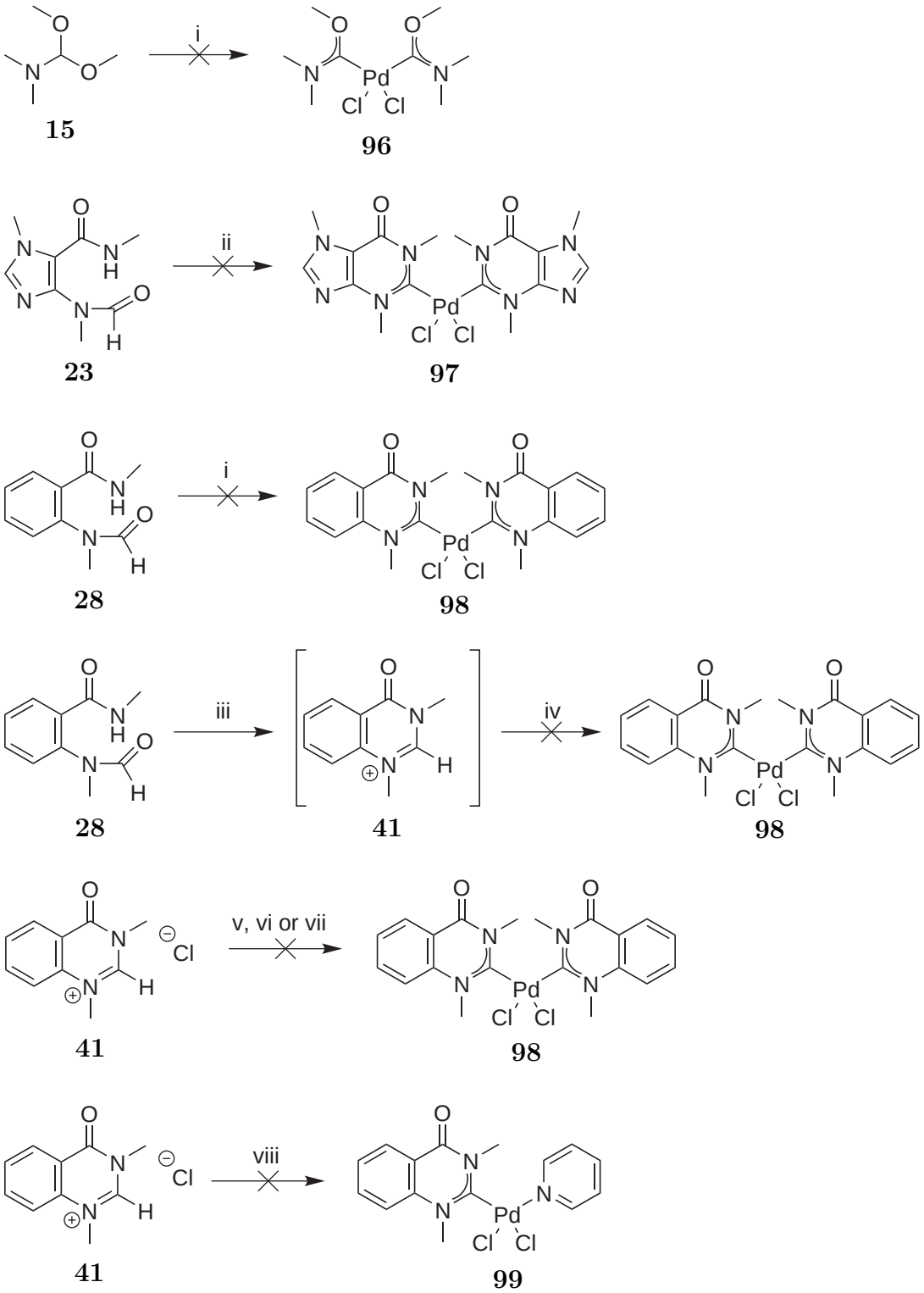
product of **91**, the dibenzyl-equivalent of **28**. Continuous liquid-liquid extraction could be a possible way to purify this in the future, however this usually utilises water as one of the solvents, which may not be ideal. Ion exchange chromatography may be a way forward instead. Given the low purity of this compound, it was not subjected to carbene-generating conditions.

Although the diallyl species was made and purified, formation of the dimeric species was unsuccessful. As before, 4-hydroxyquinazoline was reacted with allyl bromide to give the cation **94**, which, given the knowledge garnered from the synthesis of the benzyl derivative, was able to be sufficiently purified by repeated solvent extraction [Scheme 3.11]. Subjecting this to standard carbene-generating conditions, sodium hydride in degassed tetrahydrofuran, resulted in the hydrolytic product of the starting material, **95**. Repeating this experiment in an NMR tube under argon with degassed chloroform-d and triethylamine resulted in the same product being isolated. As was the case for the imidazole-based cation, this species was highly susceptible to hydrolysis. Although all the dimeric trappings were unsuccessful, the observation of **32** is good evidence towards the existence of a carbene.

3.3 With organometallic compounds

The final method used to demonstrate a carbene involved organometallic species, which, fortunately, was more successful. As mentioned previously, NHCs are good ligands in organometallic chemistry, ergo an attempt was made to demonstrate our novel NHC through one such complex. The acetate anion of palladium acetate has been found to be sufficient to induce deprotonation of NHC precursors, and catalyse formation of organometallic species by itself.[64,65] The first attempt to form a palladium species relied upon the spontaneous, *in situ* generation of the carbene in a range of solvents, which could then dimerise and suffer oxidative addition of palladium into the alkene. Given the number of mechanistic steps involved in this, this approach involved a certain level of optimism.

Attempts to trap a carbene in this way, despite being numerous, were unsuccessful. DMFDMA and the imidazole- and benzene-based models from the kinetic studies were incubated with palladium acetate in various solvents for a period of time in the hope of observing the species **96**, **97** and **98** respectively [Scheme 3.12]. No new species were observed, except for the successful synthesis of palladium mirrors on the inside of the vessels. Subjecting **41**, after its *in situ* formation, to these same conditions was similarly unsuccessful. Using **41** in a method that utilised

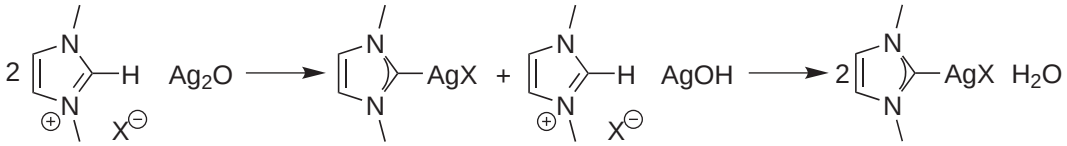


Reagents and Conditions: i. $Pd(OAc)_2$, DCM *OR* THF, rt, 3 months; ii. $Pd(OAc)_2$, CD_3OD, rt, 7 d; iii. ethylchloroformate, 50 °C, 3 h; iv. $Pd(OAc)_2$, NaH, THF, rt, 3 h; v. $Pd(OAc)_2$, 'wet' DMSO, rt, 12 h; vi. $Pd(OAc)_2$, NaOAc, THF, rt, 12 h ; vii. $Pd(OAc)_2$, degassed $CDCl_3$, rt, 4 d; viii. $Pd(OAc)_2$, K_2CO_3, pyridine.

Scheme 3.12 Unsuccessful attempts to form palladium-carbene complexes

'wet' dimethylsulfoxide also failed,[65] as well as attempts with added sodium acetate to help balance abstraction of the proton, with or without degassing of solvents. Finally, attempts to make the mono-NHC palladium complex **99** with palladium acetate, potassium carbonate and pyridine were in accord with previous results. In all cases, either starting material or the oxidative degradation product of the dimer, **32**, resulted, which is evidence that a carbene was at least being generated. As to their accumulative lack of success, substrates other than **41** would suffer from the low concentration of carbene at any one time, whilst all would suffer from being performed without true Schlenck techniques.

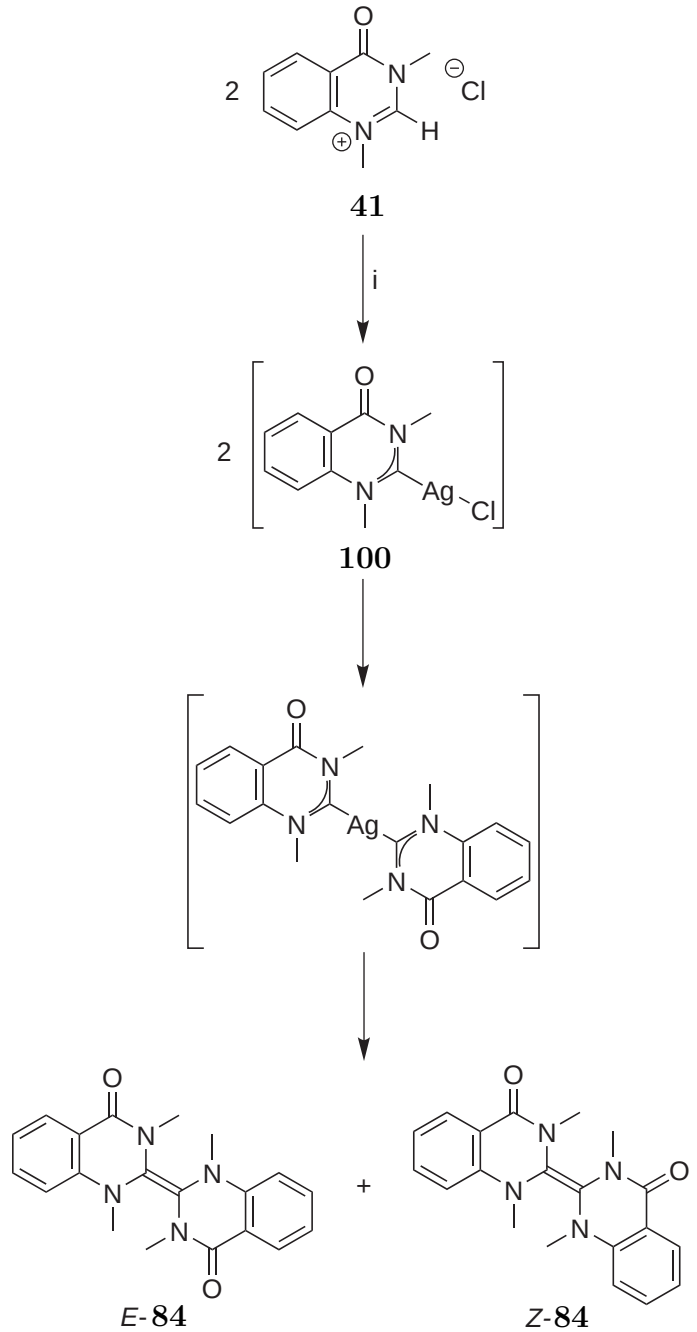
Silver oxide is another reagent used in the generation of NHCs. In this approach, silver oxide reacts with NHC precursors to directly generate silver-bound NHCs.[66] A theoretical study into this reaction suggested that in the first step the oxygen of silver oxide abstracts the proton from one molecule of carbene precursor, which is closely mapped with transfer of a silver atom to generate one equivalent of carbene [Scheme 3.13].[67] The silver hydroxide generated from the first step then abstracts the proton from a second precursor molecule, to generate the second silver-NHC complex and an equivalent of water. Silver-NHC bonds, however, are highly labile and these compounds can rapidly degrade through a number of mechanisms.[68] There is a dynamic equilibrium between silver-NHC complexes such that ligand exchange can occur. Reductive elimination of the silver from such a species would result in formation of an NHC dimer. The main use of silver oxide in NHC chemistry, however, is as a transmetallating agent. Silver is able to transfer NHC ligands to other metals, such as palladium, and is a useful method for forming metal-NHC species that are otherwise difficult to form.[66,69,70]



Scheme 3.13 Synthesis of silver-NHC complexes from Ag_2O

After multiple attempts and slow progress towards true Schlenck conditions, reacting **41** with silver oxide in degassed chloroform-d led to the generation of a new species. By ^{1}H-NMR spectroscopy, this was first noticeable as a new set of methyl peaks appearing at 3.13 and 3.00 ppm. By use of correlations observed in an HMBC experiment, it was found that these methyls were attached to a benzamide framework equivalent to the starting material. The benzyl protons of this species also had distinctly different resonances to the starting material, with two of the proton resonances appearing as far upfield as 6.81 and 6.65 ppm. In addition to this connec-

tivity, the two novel methyl resonances also shared HMBC correlations to another carbon, confirming the second ring from the starting material was still present. This carbon was found to have a shift of 106.8 ppm, a substantial difference to the shift of 153.7 ppm for the starting material. In silver-NHC complexes, the metal-bound carbon usually has a shift of approximately 185-195 ppm,[71–73] whereas enetetramines are somewhat more varied, with reports ranging from 100 ppm up to 125 ppm.[62,74] Given the shift of this novel species falls in the range of the later, this suggests that **84** has been obtained, rather than **100** [Scheme 3.14].

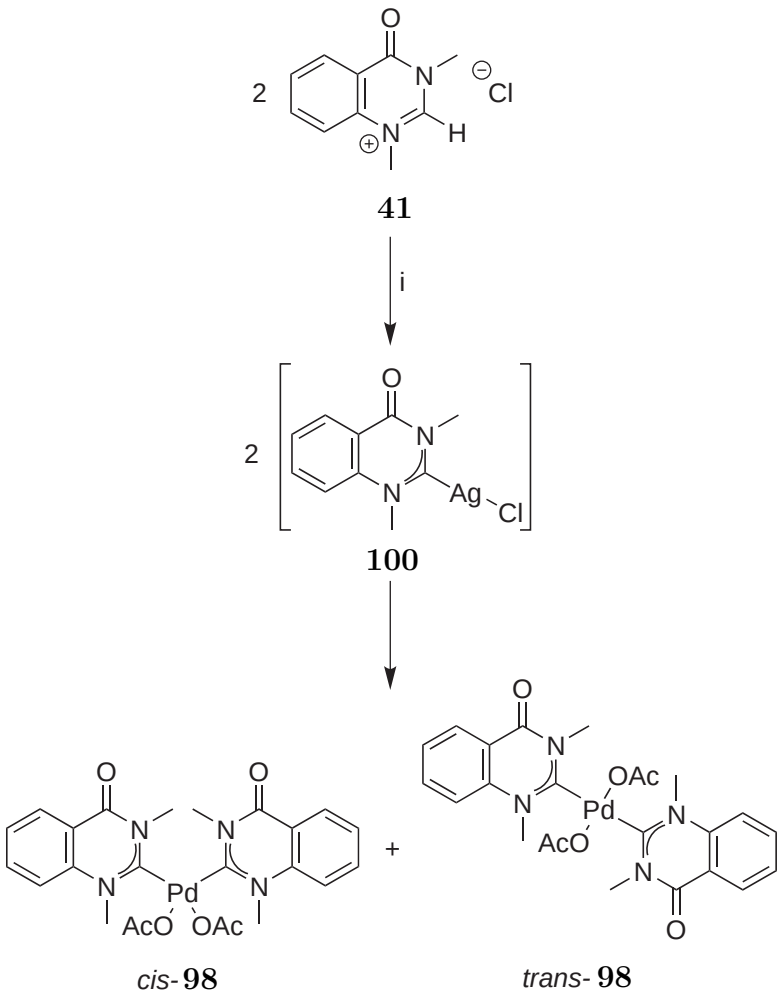


Reagents and Conditions: i. Ag_2O, degassed $CDCl_3$, rt, 2 h.

Scheme 3.14 Successful synthesis of **84**

Although symmetry elements would hinder demonstration of a dimer, MS evidence suggests this species has been successfully synthesised. It is possible that both the *E*- and *Z*-dimer could form, *E*-**84** and *Z*-**84** respectively, although the *E*-alkene would be expected to form preferentially as the thermodynamic product. The nuclear Overhauser effect (NOE) can allow through space correlations to be observed in ^{1}H-NMR spectroscopy, such as might be seen between the methyls of each side of the dimer due to their spatial proximity. Although *Z*-**84** would not show correlations, as the two methyls are equivalent and resonances would be obscured by the excitation pulse of the experiment, it is possible that *E*-**84** would show correlations between the two methyls. Unfortunately, observation of any correlations were obscured by through-bond coupling artifacts and the results were inconclusive. However, MS analysis revealed the presence of a species with the molecular formula $C_{20}H_{20}N_4O_2$, correlating to the dimeric species **84**, as three different adducts. From this NMR and MS data, it was concluded that 2-(1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylidene)-1,3-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one, **84**, had been successfully synthesised, as either the *E*- or *Z*-isomer. Sadly, this compound was unstable and degraded over a period of days, such that x-ray crystallographic analysis could not be performed to confirm this.

When performing this reaction in the additional presence of palladium acetate, a second new species was observed. By ^{1}H-NMR spectroscopy, **84** was observed forming but never reached a significant concentration. Instead, two new sets of resonances were observed forming with time. This was first observed as two new sets of methyl resonances forming at 5.00 & 4.99 ppm, the N-1 methyl group, and at 4.69 & 4.68 ppm, the N-3 methyl group, in addition to new acetate peaks that did not correlate to the palladium acetate starting material. Similarly in the carbon spectrum two new sets of resonances were observed. Again, through HMBC correlations, these were seen to have the same benzamide framework as the starting material and **84**, with noticeable changes to the aromatic region with each species having a proton resonance above 8.2 ppm. The sets of methyl resonances each shared HMBC correlations to another carbon, C-2 for each species, which here had shifts of 199.2 and 199.1 ppm. Although peaks for Pd-NHC carbons appear at around 150 ppm in ligands where the carbene is part of an unsaturated system,[75,76] saturated systems exhibit peaks that are further downfield at approximately 200 ppm.[77] Although technically a π-system exists in our ligand, the exocyclic carbonyl and benzene ring would act to decrease the effect of any delocalisation. Coupled with the increased electron-withdrawing effects of the amide and a shift of 199 ppm for the palladium species, the structure **98** seems reasonable [Scheme 3.15].



Reagents and Conditions: i. $PdOAc_2$, Ag_2O, degassed $CDCl_3$, rt, 6 h.

Scheme 3.15 Successful synthesis of **98**

The two sets of resonances were reasoned as isomers of a palladium complex that was confirmed by MS. Although the two closely related sets of methyl peaks appear as if they result from J-coupling, they are each part of two distinct molecules. In a palladium complex with two acetate and two NHC ligands, two isomers of the expected square planar complex can be expected: *cis*-**98** and *trans*-**98**. Which set of resonances were which species could potentially be assigned on the basis of NOESY correlations, but these were again hampered by intramolecular processes in each monomer. The suggestion of two isomers is supported by the observation of only one signficant species by MS. Here, the species with the molecular formula of $C_{24}H_{26}N_4O_6Pd$ was observed as both the $[M+H]^+$ and the more exotic $[M\text{-}AcOH\text{-}AcO]^+$ and $[M\text{-}AcOH\text{-}AcO+HC(O)OH]^+$ species, the latter two of which result from loss of the acetate ligands. More importantly, the M^+ peak displayed the characteristic palladium-isotope pattern: 3.7 $[M]^+$: 40.8 $[M+2]^+$: 81.7 $[M+3]^+$: 100 $[M+4]^+$: 96.8 $[M+6]^+$:42.9 $[M+8]^+$ [Figure 3.1]. Collectively, this evidence suggests the diacetoxybis(1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylidene) palladium(II) **98** species was successfully obtained. Again, the compound quickly degraded so x-ray crystallographic analysis could not be performed.

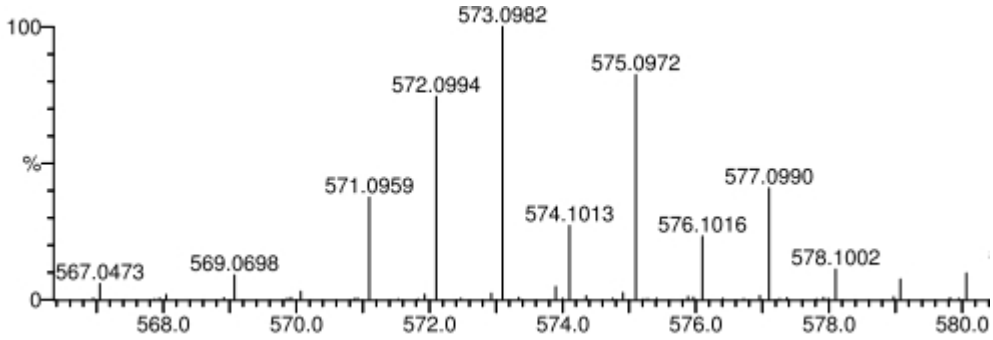
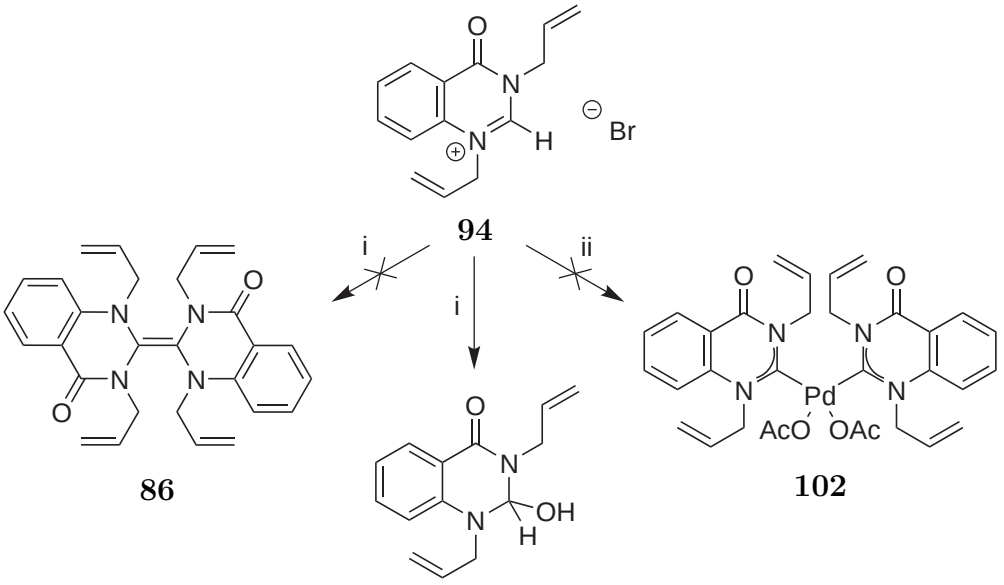


Figure 3.1 The $[M+H]^+$ peak for **98**

Combining all the information gathered suggested that **84** and **98** were successfully synthesised. Neither reaction was clean, with resonances resulting from the starting material (**41**), the two rotomers of the hydrolysis product (**28**) and the oxidative degradation product (**32**) all present and changing in relative amounts throughout the course of the reaction, in addition to those of **84** and **98** which decomposed within two days in an NMR tube under argon. Despite this, we are confident in the assignments. These results represent the successful generation and trapping of a carbene species in a motif that has never been demonstrated before. The ability to generate these species shows that, under the right conditions, a carbene can be formed in this quinazolinium-based compound, which supports the possibility of a carbene-based mechanism occurring in the H-D exchange of these models and the parent natural product malonganenone B. In addition, this is the first demonstration of a new class of NHC ligand: although diamine- and diamide-ligand species have been synthesised and complexed previously,[78] this it the first time an amineamide-ligand has been achieved.

Based on this success, the synthesis of a dimer and a palladium species from the di-allylic compound **94** was attempted. This species has more steric protection around the carbene centre and would be expected to show greater stability. Further, there is the possibility that the allyl group could stabilise the metal through π-interactions with the alkene, acting as a bidentate ligand. Attempts to synthesise the dimer **86** from **94** and silver oxide resulted in generation only of the water adduct of the starting material, **101**, as confirmed by NMR and MS [Scheme 3.16]. Meanwhile, attempted synthesis of the palladium species **102** using palladium acetate and silver oxide resulted in no change. With further experimentation, these species may be obtainable.



Reagents and Conditions: i. Ag_2O, degassed $CDCl_3$, rt, 2 h; ii. $PdOAc_2$, Ag_2O, degassed $CDCl_3$, rt, 6 h.

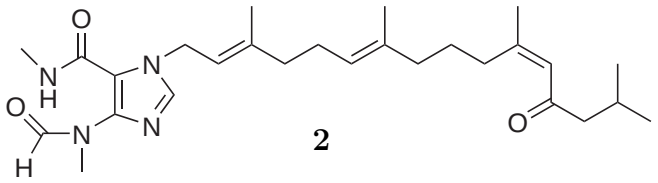
Scheme 3.16 Attempted synthesis of **86** and **102**.

Chapter 4

The H-D exchange of malonganenone B

Kinetic evidence towards the mechanism of H-D exchange of malonganenone B (**2**) was obtained. By use of NMR spectroscopy, the rate of H-D exchange was measured for various models of the exchanging moiety (**23**, **28** and **41**) of this natural product. Eventually, data was obtained that suggests the reaction is first order with respect to base, which supports both a carbene and an ylide mechanism. However, sufficiently low concentrations of the model could not be assayed using this form of spectroscopy to allow establishment of the rate with respect to itself. Acid inhibition was also observed, in contrast to previous investigations into this reaction class. In addition, cyclic species were observed (**34** and **35**), which gave evidence that an initial cyclisation event takes place prior to H-D exchange. Further, the observation of a cationic, carbene-precursor species (**41**) gave more evidence towards a carbene mechanism being in operation.

The assignment of a carbene mechanism makes sense in view of the observations of Simchen & co-workers. Increasing the length of the *N*-alkyl chain would, through electron-donation, increase the electron density of the flanking nitrogens that would hence be better able to stabilise the carbene. Conversely, longer *O*-alkyl chains would destabilise the alkoxide leaving group, inhibiting formation of the cationic amidine. As reported, cyclic acetals would not exchange unless a group was lost: loss of this group is fundamental in the carbene mechanism. On the other hand, cyclic substituents on the nitrogen were found to decrease the H-D exchange, which is reasoned as due to inhibition of the co-planarity required for the amidinyl cation. The carbene precursors trialled by Simchen showed no H-D exchange, but given these had oxygen- and nitrogen-based substituents, perhaps this is evidence that



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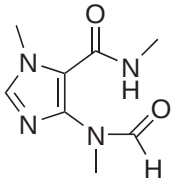

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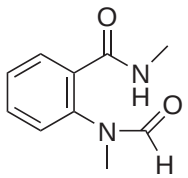

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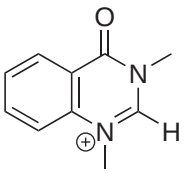

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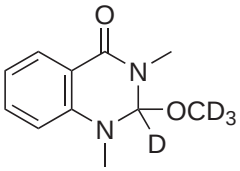

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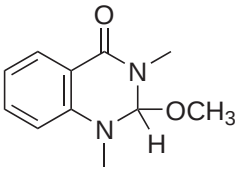

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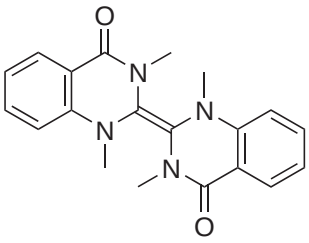
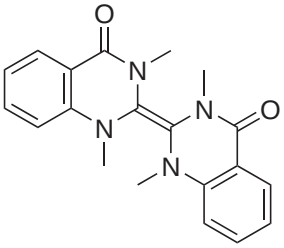
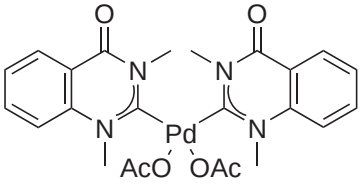


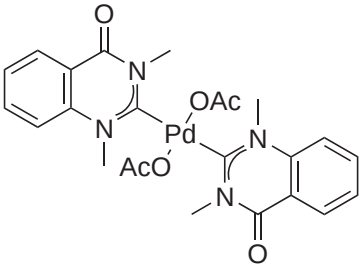
E-**84**



Z-**84**



cis-**98**



trans-**98**

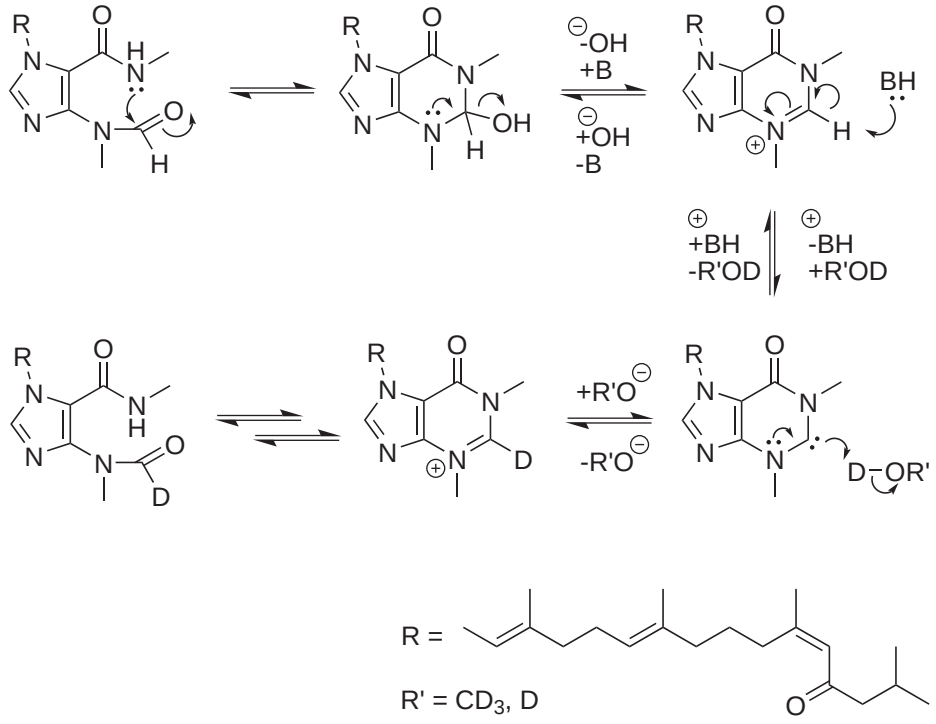
two nitrogens are needed for sufficent stabilisation of the carbene. This concurs with the observation of an amidine species by MS in the H-D exchange of DMFDMA. Simchen's acid and base results, as mentioned previously, make no sense but the results presented here rectify this observation. It is therefore plausible that the carbene mechanism is in operation for both DMFDMA and malonganenone B.

A carbene mechanism also seems more logical when considering other factors. Were an ylide mechanism to be operating, a hemiaminal ester intermediate would result with two nitrogen substituents and a hydroxyl group. In the presence of base, it is likely the hydroxyl proton would be removed preferentially over the carbon-bound aminal ester proton. The resultant charged species would hinder, if not completely inhibit, formation of the proposed ylide; adjacent positive and negative charges stabilise each other, but the same would not be expected for a positive and two negative charges in a row! In comparison, removal of the amidine proton from an NHC precursor would be more facile given the electron density accumulated around the amidine. Further, when considering orbital systems, it could be imagined that the NHC-precursor amidine would have a delocalised π-system composed of p-orbitals, of the nitrogens and carbonyl, and π-bonds, of the amidine and aromatic ring. Although this would not be an aromatic system, due to the attached aromatic ring and the exocyclic carbonyl, the positive charge of this species would still be stabilised through this overlap. In the case of ylide formation, however, one of the nitrogens would be tetrahedral and the delocalised system would be lost. Finally, the mechanisms differ only by an intramolecular elimination for the carbene and an intermolecular protonation for the ylide. It is accepted that intramolecular reactions hold a kinetic advantage, which further supports the carbene mechanism. This can be concluded with the surprising statement that this combination of factors result in breakage of a C–O bond being favoured over formation of an N–H bond.

Synthetic studies were eventually able to provide evidence of the existence of a carbene resulting from these species. After a slow progression of experimental design and practices towards true Schlenck techniques, and after trialling various methods, a fulvalene resulting from the dimerisation of two carbenes was observed (**84**). Repeated observation of the oxidative degradation product of this species was both good indirect evidence towards its existence as well as an indicator of whether carbenes were forming in the experiments. Given that this species was observed in reactions without silver oxide, it can be concluded that spontaneous dimerisation of the carbene was occurring. Through the additional presence of palladium acetate, a palladium-NHC species was also synthesised (**98**). The characteristic palladium-isotope pattern in the mass spectrum is the best evidence of this success. Given the lack of steric protection around the carbenic carbon, it is not surprising that

both the dimer and the palladium species were not particularly stable. In addition, this NHC complex is likely less stable than conventional NHCs, which usually bond strongly with metals because of the degree of electron density around the carbene due to the flanking nitrogens. In this ligand, however, some of this density is pulled towards the carbonyl, weakening the carbon-metal bonding and resulting in these systems being less stable than diamino NHCs. Nonetheless, the amineamide carbene proposed here is a novel class of NHCs, for which this is their first successful synthesis and demonstration. This shows that carbenes can be formed from these species under the right conditions. Hence, if a carbene mechanism were to be involved in the H-D exchange of malonganenone B, this is good evidence to support the feasibility of such a mechanism.

The H-D exchange of malonganenone B has now been addressed. The accumulated evidence suggests this occurs through an N-heterocyclic carbene, representing a new class of NHCs that has never been reported [Scheme 4.1]. Although carbenes are reactive species, it is unlikely that this is related to the biological purpose of the secondary metabolite malonganenone B. As has been seen throughout this research, the carbene is shortlived, particularly in the imidazole species and in nucleophilic solvents, hence deactivation would occur before the carbene could serve any defensive purpose to the organism. It is more likely, given that the head-groups of the malonganenones and nuttingins largely resemble purines, that this is involved in inhibition of binding to the active sites of enzymes or alternatively is involved in signalling pathways. Were a way found to increase the life-time of the carbene



Scheme 4.1 Expected mechanism of H-D exchange of malonganenone B

from this species, the possibility exists that the enone present in the tail of malonganenone B could trap the carbene itself in a cyclopropanation reaction. Finally, previous research was found that examined the instance of rotamers that was so prevalent in these analytes. Although it was observed that all peaks were doubled in the original report of malonganenone B, this was assumed to be the appearance of a degradation product and hindered initial isolation of this species.

Despite much failure along the way, the goal of the project was attained. Although there were many unsuccessful attempts to obtain useful kinetic data or to trap a carbene, this would not be the first research to contain many failures. Thomas Edison, when confronted over his numerous failed attempts at creating the light bulb, replied:

> I have not failed. I have just found 10,000 ways to *not* make the light bulb.

Yet, he needed only one way to illuminate the world. Despite much wasted time, reagents and sanity, proof of the carbene was finally obtained. From a natural product found in the sea off the coast of Africa, through model syntheses, kinetic studies and repeated attempts to trap a species that may not have actually existed, a fulvalene and a new class of organometallic ligands were obtained. Who knows what the next natural product may bring to the world of chemistry?

Chapter 5

Future Work

As with all projects, the more work that *is* done, the more work there is that *needs* to be done. Regarding the initial objectives of the project, more research could be done to finalise the assignment of the carbene mechanism. Chief among these would be confirming those results obtained for the case of the benzene-based model, in the cases of the imidazole-based model and the natural product malonganenone B itself. This could include confirming the exchange is first order with respect to base and finding a spectroscopic technique that would allow low enough concentrations of the analyte to be observed and the order with respect to this species ascertained. Further, a range of other bases could be trialled to try and assay the relationship between catalysis and basicity. Similarly, quantification of acid inhibition could be investigated.

Of more importance is exploration of this new class of NHC ligands. Attempting the synthesis with more sterically-hindered substituents, which should convey greater stability, would be chief among these. In addition, attempts to form alternative metal complexes, for example with ruthenium or gold, would be of interest. Also, copper oxide would be explored as an alternative transmetallating agent to silver oxide. Although there is confidence in the assignment of the dimeric and palladamic species, x-ray crystallography of an amineamide-metal complex would confirm this beyond reasonable doubt. As with all new ligands in organometallic chemistry, the catalytic ability of these species should be measured in a variety of reactions. Finally, forming an organometallic complex with malonganenone B would be the crowning achievement of this project. Given the absence of a synthetic method to malonganenone B, more of the natural product would need to be collected from its source on the reef of Ponto Malongane, Mozambique. Funding is to be sought for this expedition.

Chapter 6

Experimental

6.1 Synthesis

Unless otherwise stated, reactions were performed under air in glassware that was not predried. Inert conditions are defined as reactions performed under argon (zero grade) in vacuum-dried glassware using dry solvents and standard syringe techniques. Tetrahydrofuran was freshly distilled from the sodium benzophenone ketyl radical ion, and triethylamine was freshly distilled from calcium hydride. All other reagents and solvents were used as received from commercial suppliers. Degasification was performed by the standard freeze-pump-thaw technique, with three repetitions. Purification of products *via* flash chromatography was conducted using a column filled with silica gel 60 (220-240 mesh) or DSC-Discovery Diol (Supelco). Purification of products *via* reverse-phase chromatography was conducted using a column filled with Diaion HP-20 (Supelco). ^{1}H-NMR and ^{13}C-NMR spectra for structural eludications were recorded on a Varian Unity Inova 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer. ^{15}N-NMR spectra for structural eludication, NMR-scale reactions and NOESY spectra were recorded on a Varian DirectDrive 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C and 60 MHz for ^{15}N) equipped with a Varian inverse-detected triple-resonance HCN cold probe operating at 25K. High-resolution mass spectrometry (HRMS) was performed on a Waters Q-TOF Premier Tandem mass spectrometer. Syntheses attempted are presented for their target compound. Assignment of any byproducts produced are listed separately. Compounds are named and numbered according to IUPAC guidelines.[79]

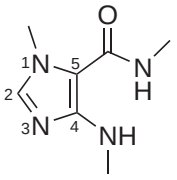
6.1.1 Imidazole-based models

_N_,1-dimethyl-4-(methylamino)-1_H_-imidazole-5-carboxamide (27)

A. Caffeine (200 mg, 1.03 mmol) was suspended in EtOH (1.6 mL), a solution of

NaOH (0.37 g, 9.27 mmol) in water (3.4 mL) was added and the reaction was refluxed for three hours. The reaction was allowed to cool, neutralised with dilute HCl and H_2O (10 mL) was added. HP-20 reverse-phase chromatographic beads (6 mL) were added and the suspension was stirred for two hours. The suspension was then loaded on an HP-20 reverse-phase chromatographic column (30 mL) equilibrated with water, the column was washed with water (100 mL) and eluted with CH_3OH (100 mL). The organic eluent was concentrated under reduced pressure to yield **27** (68.9 mg, 56%) as a pale yellow crystal. Recrystalisation from ethyl acetate was unsuccessful.

B. Caffeine (10.0 g, 51.5 mmol) was added to a solution of NaOH (2.40 g, 60 mmol) in H_2O (30 mL) and refluxed for two hours. The reaction was cooled with ice, HNO_3 (6.25 mL, 105 mmol) was added dropwise and the resulting white solid was filtered and washed with water. The precipitate was dissolved in a solution of K_2CO_3 (6.00 g, 43.4 mmol) in H_2O (20 mL), the resulting oil was extracted with $CHCl_3$ (3 x 20 mL) and the organic phase concentrated under reduced pressure to afford a white solid. Recrystalisation from ethyl acetate yielded **27** (3.22 g, 37%) as a white crystal.

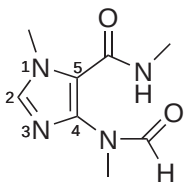


^{1}H-NMR ($CDCl_3$): δ_H 7.21 (s, 1H, C(2)*H*), 6.98 (br s, 1H, N(*N*)-*H*), 3.87 (s, 3H, N(1)*Me*), 3.68 (br s, 1H, N(4)*H*), 2.94 (d, J = 4.8 Hz, 3H, N(*N*)*H*), 2.89 (s, 3H, N(4)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 162.3 (*C*=O), 151.9 (*C*(4)), 137.3 (*C*(2)), 110.9 (*C*(5)), 34.9 (N(1)*Me*), 32.8 (N(4)*Me*), 25.7 (N(*N*)*Me*); HR-ESI-MS: $C_7H_{13}N_4O$ $[M+H]^+$ *m/z* found 169.1086, calcd 169.1089, Δ = -1.8 ppm.

4-[formyl(methyl)amino]-*N*,1-dimethyl-1*H*-imidazole-5-carboxamide (23)

27 (145 mg, 0.86 mmol) was suspended in formic acid (7 mL) and refluxed for 30 minutes. The reaction was concentrated under reduced pressure, H_2O (5 mL) was added and the resultant suspension filtered. The filtrate was concentrated under reduced pressure to yield a pale tan solid. Recrystallisation from ethyl acetate yielded **23** (10.6 mg, 6%) as a tan crystal.

B. Formic acid (2.21 mL, 58.6 mmol) and acetic anhydride (5.00 mL, 53.0 mmol) were heated together at 55 °C for two hours. The reaction was cooled, **27** (3.22 g, 19.1 mmol) was added and the reaction was stirred at room temperature for 12 hours. The reaction was concentrated under reduced pressure and the resulting pale yellow oil was crystallised from ethyl acetate to yield **23** (1.93 g, 51%) as a tan crystal.



Rotamer A: ^{1}H-NMR ($CDCl_3$): δ_H 8.26 (s, 1H,N4C=O*H*), 7.57 (br s, 1H, N(*N*)*H*), 7.39 (s, 1H, C(2)*H*), 3.82 (s, 3H, N(1)*Me*), 3.36 (s, 3H, N(4)*Me*), 2.84 (d, J = 5.4 Hz, 3H, N(*N*)*Me*); ^{1}H-NMR (CD_3OD): δ_H 8.28 (s, 1H,N4C=O*H*), 7.70 (s, 1H, C(2)*H*), 3.83 (s, 3H, N(1)*Me*), 3.37 (s, 3H, N(4)*Me*), 2.84 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (DMSO−d_6): δ_H 8.20 (s,

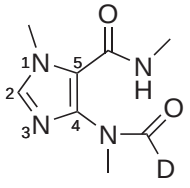
1H,N4C=O*H*), 7.69 (s, 1H, C(2)*H*), 7.46 (br s, 1H, N(*N*)*H*), 3.72 (s, 3H, N(1)*Me*), 3.26 (s, 3H, N(4)*Me*), 2.68 (d, J = 4.8 Hz, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 8.24 (s, 1H, N4C=O*H*), 7.67 (s, 1H, C(2)*H*), 3.76 (s, 3H, N(1)*Me*), 3.35 (s, 3H, N(4)*Me*), 2.83 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 164.3 (N(4)*C*=O), 160.5 (C(5)*C*=O), 138.2 (*C*(2)), 136.5 (*C*(4)), 121.7 (*C*(5)), 37.4 (N(4)*Me*), 34.4 (N(1)*Me*), 26.4 (N(*N*)*Me*); ^{13}C-NMR (DMSO−d_6): δ_C 163.2 (N(4)*C*=O), 159.8 (C(5)*C*=O), 137.7 (*C*(2)), 136.9 (*C*(4)), 119.6 (*C*(5)), 35.9 (N(4)*Me*), 33.5 (N(1)*Me*), 25.8 (N(*N*)*Me*); ^{15}N-NMR ($CDCl_3$): δ_N -129 (*N*(3)), -217 (*N*(1)), -258 (*N*(4)), -273 (*N*(*N*)).

Rotamer B: ^{1}H-NMR ($CDCl_3$): δ_H 8.29 (s, 1H,N4C=O*H*), 7.38 (s, 1H, C(2)*H*), 6.02 (br s, 1H, N(*N*)*H*), 3.91 (s, 3H, N(1)*Me*), 3.25 (s, 3H, N(4)*Me*), 2.93 (d, J = 5.4 Hz, 3H, N(*N*)*Me*); ^{1}H-NMR (CD_3OD): δ_H 8.25 (s, 1H,N4C=O*H*), 7.67 (s, 1H, C(2)*H*), 3.82 (s, 3H, N(1)*Me*), 3.21 (s, 3H, N(4)*Me*), 2.86 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (DMSO−d_6): δ_H 8.18 (s, 1H, N4C=O*H*), 7.96 (br s, 1H, N(*N*)*H*), 7.68 (s, 1H, C(2)*H*), 3.70 (s, 3H, N(1)*Me*), 3.07 (s, 3H, N(4)*Me*), 2.72 (d, J = 4.5 Hz, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 8.22 (s, 1H, N4C=O*H*), 7.64 (s, 1H, C(2)*H*), 3.75 (s, 3H, N(1)*Me*), 3.18 (s, 3H, N(4)*Me*), 2.86 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 163.8 (N(4)*C*=O), 159.9 (C(5)*C*=O), 141.3 (*C*(4)), 138.4 (*C*(2)), 118.4 (*C*(5)), 35.3 (N(1)*Me*), 32.6 (N(4)*Me*), 26.3 (N(*N*)*Me*); ^{13}C-NMR (DMSO−d_6): δ_C 162.5 (N(4)*C*=O), 159.8 (C(5)*C*=O), 140.4 (*C*(4)), 138.0 (*C*(2)), 117.7 (*C*(5)), 33.8 (N(1)*Me*), 31.5 (N(4)*Me*), 25.8 (N(*N*)*Me*); ^{15}N-NMR ($CDCl_3$): δ_N -127 (*N*(3)), -215 (*N*(1)), -262 (*N*(4)), -281 (*N*(*N*)).

HR-ESI-MS: $C_8H_{13}N_4O_2^+$ $[M+H]^+$ *m/z* found 197.1033, calcd 197.1039, Δ = 3.0 ppm; HR-ESI-MS: $C_8H_{12}N_4O_2Na^+$ $[M+Na]^+$ *m/z* found 219.0856, calcd 219.0858, Δ = -0.9 ppm.

4-[(^{2}H)formyl(methyl)amino]-*N*,1-dimethyl-1*H*-imidazole-5-carboxamide (103)

23 (6.0 mg, 0.0306 mmol) was dissolved in CD_3OD (0.55 mL) in an NMR tube and left to equilibrate for 5 days. The reaction was concentrated under reduced pressure to yield **103** as a white solid in quantitative yield.



Rotamer A: ^{1}H-NMR ($CDCl_3$): δ_H 7.57 (br s, 1H, N(*N*)*H*), 7.38 (s, 1H, C(2)*H*), 3.81 (s, 3H, N(1)*Me*), 3.39 (s, 3H, N(4)*Me*), 2.81 (d, J = 5.5 Hz, 3H, N(*N*)*Me*); ^{1}H-NMR (CD_3OD): δ_H 7.71 (s, 1H, C(2)*H*), 3.83 (s, 3H, N(1)*Me*), 3.34 (s, 3H, N(4)*Me*), 2.85 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 7.66 (s, 1H, C(2)*H*), 3.74 (s, 3H, N(1)*Me*), 3.38 (s, 3H, N(4)*Me*), 2.83 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 164.1 (N(4)*C*=O), 160.4 (C(5)*C*=O), 138.2 (*C*(2)), 136.7 (*C*(4)), 121.6 (*C*(5)), 37.3 (N(4)*Me*), 34.4 (N(1)*Me*), 26.2 (N(*N*)*Me*).

Rotamer B: ^{1}H-NMR ($CDCl_3$): δ_H 7.37 (s, 1H, C(2)*H*), 6.01 (br s, 1H, N(*N*)*H*), 3.90 (s, 3H, N(1)*Me*), 3.27 (s, 3H, N(4)*Me*), 2.94 (d, J = 5.5 Hz, 3H, N(*N*)*Me*);

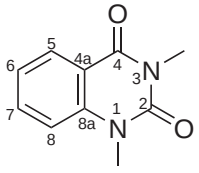
^{1}H-NMR (CD_3OD): δ_H 7.68 (s, 1H, C(2)*H*), 3.79 (s, 3H, N(1)*Me*), 3.22 (s, 3H, N(4)*Me*), 2.88 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 7.63 (s, 1H, C(2)*H*), 3.76 (s, 3H, N(1)*Me*), 3.21 (s, 3H, N(4)*Me*), 2.86 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 163.9 (N(4)*C*=O), 160.0 (C(5)*C*=O), 141.3 (*C*(4)), 138.4 (*C*(2)), 118.5 (*C*(5)), 35.2 (N(1)*Me*), 32.9 (N(4)*Me*), 26.1 (N(*N*)*Me*). HR-ESI-MS: C8H11DN4O2Na $[M+Na]^+$ *m/z* found 220.0919, calcd 220.0921, Δ = -0.9 ppm.

6.1.2 Benzene-based models

1,3-dimethyl-1,2,3,4-tetrahydroquinazoline-2,4-dione (32)

A. Under inert conditions benzoylene urea (0.83 g, 5.1 mmol) was dissolved in DMF (100 mL), K_2CO_3 (2.89 g, 20.91 mmol) and MeI (1.27 mL, 20.41 mmol) were added and the reaction stirred at room temperature for 36 hours. The reaction was filtered, HP20 beads (10 mL) were added and the suspension slowly diluted with H_2O until the concentration was approximately 5% DMF *v/v*. The suspension was then loaded onto a column of HP20 beads (60 mL) equilibrated with water. The column was washed with H_2O (300 mL), eluted with acetone (300 mL) and the eluent was concentrated under reduced pressure. Tituration from ethyl acetate with petroleum ether yielded **32** as a white powder (613 mg, 63%).

B. Under inert conditions **41** (110 mg, 0.52 mmol) was dissolved in THF (2 mL), NaH (25 mg, 1.04 mmol) was added and the reaction was stirred for 4 hours at 50 °C. The reaction was concentrated under reduced pressure, the residue was extracted with hot toluene and the organic phase was concentrated under reduced pressure to give a white solid. Purification by flash chromatography yielded **32** (54.4 mg, 55%) as a white solid.



^{1}H-NMR ($CDCl_3$): δ_H 8.22 (dd, J = 7.8, 1.7 Hz, 1H, C(5)*H*), 7.67 (ddd, J = 8.5, 7.3, 1.7 Hz, 1H, C(7)*H*), 7.26 (ddd, J = 8.0, 7.2, 1 Hz, 1H, C(6)*H*), 7.20 (d, J = 8.3 Hz, 1H, C(8)*H*), 3.61 (s, 3H, N(1)*Me*), 3.49 (s, 3H, N(3)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 161.9 (*C*(4)), 151.2 (*C*(2)), 140.4 (*C*(8a)), 135.0 (*C*(7)), 128.9 (*C*(5)), 122.9 (*C*(6)), 115.4 (*C*(4a)), 113.5 (*C*(8)), 30.8 (N(1)*Me*), 28.5 (N(3)*Me*); HR-ESI-MS: $C_{10}H_{10}N_2O_2Na^+$ $[M+Na]^+$ *m/z* found 213.0645, calcd 213.0640, Δ = 2.3 ppm.

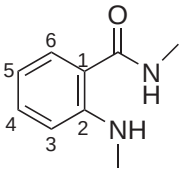
***N*-methyl-2-(methylamino)benzamide (30)**

A. *N*-methylanthranilic acid (30 mg, 0.2 mmol) was dissolved in $SOCl_2$ (5 mL) and refluxed for 3 hours. The reaction was concentrated under reduced pressure, THF (6 mL) was added and the solution was cooled. *Aq.* CH_3NH_2 (3.5 mL, 40% v/v, 41 mmol) was added dropwise and the reaction was stirred at room temperature for 12 hours. Extractions with $CHCl_3$ and ethyl acetate yielded no product.

B. **32** (100 mg, 0.53 mmol) was dissolved in *aq.* NaOH (0.655 mL, 2M, 1.31 mmol)

and refluxed for 36 hours. The reaction was cooled and saturated NH_4Cl (5 mL) was added. The solution was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were concentrated under reduced pressure to yield **30** as a white crystal (79 mg, 92%).

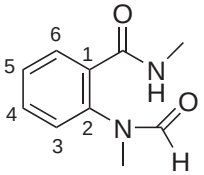
C. *N*-methylisatoic anhydride (9 g, 50.8 mmol) was dissolved in H_2O (26.6 mL), *aq.* CH_3NH_2 (9.62 mL, 40% w/w., 124 mmol) was added and the reaction was stirred at 50 °C for 1 hour. The reaction was cooled, diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with sat. *aq.* NH_4Cl (50 mL x 2), H_2O (50 mL x 2), brine (50 mL x 2), dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to yield **30** as a white powder (8.17 g, 98%).



^{1}H-NMR ($CDCl_3$): δ_H 7.42 (br s, 1H, N(2)*H*), 7.31 (t, J = 8.0 Hz, 1H, C(4)*H*, 7.30 (d, 7.6 Hz, 1H, C(6)*H*), 6.66 (d, J = 8.3 Hz, 1H, C(3)*H*), 6.56 (t, J = 7.3 Hz, 1H, C(5)*H*), 6.12 (br s, 1H, N(*N*)*H*), 2.94 (d, J = 4.9 Hz, 3H, N(*N*)*Me*), 2.85 (br s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 170.7 (*C*=O), 150.5 (*C*(2)), 132.8 (*C*(4)), 127.2 (*C*(6)), 115.4 (*C*(1)), 114.6 (*C*(5)), 111.2 (*C*(3)), 29.8 (N(2)*Me*), 26.6 (N)(*N*)*Me*); HR-ESI-MS: $C_9H_{12}N_2ONa$ $[M+Na]^+$ *m/z* found 187.0850, calcd 187.0847, Δ = 1.6 ppm; HR-ESI-MS: $C_9H_{13}N_2O$ $[M+H]^+$ *m/z* found 165.1031, calcd 165.1028, Δ = 1.8 ppm.

N-methyl-2-(*N*-methylformamido)benzamide(28)

Formic acid (1.15 mL, 30.42 mmol) and acetic anhydride (2.61 mL, 27.65 mmol) were heated together for 2 hours at 55 °C. The reaction was cooled, **30** was added and the reaction stirred at room temperature for 12 hours. The reaction was concentrated under reduced pressure and purified by flash chromatography to yield **28** as a white crystal (2.42 g, 86.2%).



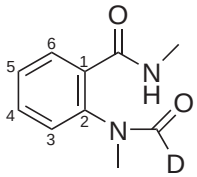
Rotamer A: ^{1}H-NMR ($CDCl_3$): δ_H 8.27 (s, 1H, N(2)C(O)*H*), 7.64 (dd,J = 7.5, 1.7 Hz, 1H, C(6)*H*), 7.51 (dt, J = 7.8, 1.7 Hz, 1H, C(4)*H*), 7.41 (dt, J = 7.5, 1.2 Hz, 1H, C(5)*H*), 7.20 (dd, J = 7.8, 1.0 Hz, 1H, C(3)*H*), 5.85 (br s, 1H, N(*N*)*H*), 3.26 (s, 3H, N(2)*Me*), 2.99 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (CD_3OD): δ_H 8.15 (s, 1H, N2C(O)*H*), 7.59–7.51 (m, 2H, C(4)*H*, C(6)*H*), 7.45 (dt, J = 7.3, 1.2 Hz, 1H, C(5)*H*), 7.37 (dd, J = 7.9, 0.9 Hz, 1H, C(3)*H*), 3.20 (s, 3H, N(2)*Me*), 2.87 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 7.98 (s, 1H, N2C(O)*H*), 7.50–7.45 (m, 1H, C(6)*H*, C(4)*H* or C(5)*H*), 7.42–7.34 (m, 2H, C(6)*H*, C(4)*H* or C(5)*H*), 7.25 (dd, J = 8.0, 0.7 Hz, 1H, C(3)*H*), 3.03 (s, 3H, N(2)*Me*), 2.73 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 167.6 (C(1)*C*=O), 162.6 (N(2)*C*=O), 139.4 (*C*(2)), 133.7 (*C*(1)), 131.5 (*C*(4)), 129.3 (*C*(6)), 128.1 (*C*(5)), 127.6 (*C*(3)), 33.8 (N(2)*Me*), 27.0 (N(*N*)*Me*).

Rotamer B: ^{1}H-NMR ($CDCl_3$): δ_H 8.25 (s, 1H, N(2)C(O)*H*), 7.55 (dd,J = 7.6, 1.2

Hz, 1H, C(6)*H*), 7.51 (dt, $J = 7.8$, 1.4 Hz, 1H, C(4)*H*), 7.41 (dt, $J = 7.5$, 1.2 Hz, 1H, C(5)*H*), 7.18 (dd, $J = 8.0$, 1.2 Hz, 1H, C(3)*H*), 6.30 (br s, 1H, N(*N*)*H*), 3.33 (s, 3H, N(2)*Me*), 2.93 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (CD_3OD): δ_H 8.19 (s, 1H, N(2)C(O)*H*), 7.59–7.51 (m, 2H, C(4)*H*, C(6)*H*), 7.45 (dt, $J = 7.3$, 1.2 Hz, 1H, C(5)*H*), 7.32 (d, $J = 8.2$ Hz, 1H, C(3)*H*), 3.37 (s, 3H, N(2)*Me*), 2.84 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 8.04 (s, 1H, N(2)C(O)*H*), 7.50–7.45 (m, 1H, C(6)*H*, C(4)*H* or C(5)*H*), 7.42–7.34 (m, 2H, C(6)*H*, C(4)*H* or C(5)*H*), 7.22 (d, $J = 8.1$ Hz, 1H, C(3)*H*), 3.21 (s, 3H, N(2)*Me*), 2.71 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 168.5 (C(1)*C*=O), 163.3 (N(2)*C*=O), 137.0 (*C*(2)), 136.2 (*C*(1)), 131.3 (*C*(4)), 128.7 (*C*(6)), 128.7 (*C*(5)), 127.8 (*C*(3)), 38.5 (N(2)*Me*), 26.7 (N(*N*)*Me*).
HR-ESI-MS: $C_{12}H_{13}N_2O_2$ $[M+H]^+$ *m/z* found 193.0983, calcd 193.0977, $\Delta = 3.1$ ppm; HR-ESI-MS: $C_{12}H_{12}N_2O_2Na$ $[M+Na]^+$ *m/z* found 215.0798, calcd 215.0796, $\Delta = 0.9$ ppm

N-methyl-2-(*N*-methyl(^{2}H)formamido)benzamide (49)

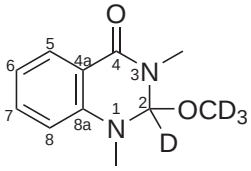
28 (6 mg, 0.031 mmol) was dissolved in D_2O (0.55 mL) and allowed to equilibrate for 22 hours. The reaction was concentrated under reduced pressure to yield **49** as a white crystal in quantitative yield.



Rotamer A: ^{1}H-NMR ($CDCl_3$): δ_H 7.64 (dd,$J = 7.5$, 1.7 Hz, 1H, C(6)*H*), 7.51 (dt, $J = 7.8$, 1.7 Hz, 1H, C(4)*H*), 7.41 (dt, $J = 7.5$, 1.2 Hz, 1H, C(5)*H*), 7.20 (dd, $J = 7.8$, 1.0 Hz, 1H, C(3)*H*), 5.85 (br s, 1H, N(*N*)*H*), 3.26 (s, 3H, N(2)*Me*), 2.99 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 7.46 (dt, $J = 7.8$, 1.9 Hz, 1H, C(5)*H*), 7.42–7.33 (m, 2H, C(4)*H*, C(6)*H*), 7.25 (dd, $J = 7.9$, 0.7 Hz, 1H, C(3)*H*), 3.21 (s, 3H, N(2)*Me*), 2.73 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 167.6 (C(1)*C*=O), 162.8 (N(2)*C*=O), 139.4 (*C*(2)), 133.7 (*C*(1)), 131.5 (*C*(4)), 129.3 (*C*(6)), 128.1 (*C*(5)), 127.6 (*C*(3)), 33.8 (N(2)*Me*), 27.0 (N(*N*)*Me*); ^{13}C-NMR (D_2O): δ_C 170.7 (C(1)*C*=O), 165.2 (N(2)*C*=O), 138.4 (*C*(2)), 132.6 (*C*(1)), 131.8 (*C*(4)), 128.6 (*C*(6)), 128.3 (*C*(5)), 127.3 (*C*(3)), 33.5 (N(2)*Me*), 26.2 (N(*N*)*Me*).
Rotamer B: ^{1}H-NMR ($CDCl_3$): δ_H 7.55 (dd,$J = 7.6$, 1.2 Hz, 1H, C(6)*H*), 7.51 (dt, $J = 7.8$, 1.4 Hz, 1H, C(4)*H*), 7.41 (dt, $J = 7.5$, 1.2 Hz, 1H, C(5)*H*), 7.18 (dd, $J = 8.0$, 1.2 Hz, 1H, C(3)*H*), 6.30 (br s, 1H, N(*N*)*H*), 3.33 (s, 3H, N(2)*Me*), 2.93 (s, 3H, N(*N*)*Me*); ^{1}H-NMR (D_2O): δ_H 7.48 (dt, $J = 7.5$, 1.7 Hz, 1H, C(5)*H*), 7.42–7.33 (m, 2H, C(4)*H*, C(6)*H*), 7.22 (dd, $J = 7.8$, 0.7 Hz, 1H, C(3)*H*), 3.19 (s, 3H, N(2)*Me*), 2.71 (s, 3H, N(*N*)*Me*); ^{13}C-NMR ($CDCl_3$): δ_C 168.5 (C(1)*C*=O), 163.4 (N(2)*C*=O), 137.0 (*C*(2)), 136.2 (*C*(1)), 131.3 (*C*(4)), 128.7 (*C*(6)), 128.7 (*C*(5)), 127.8 (*C*(3)), 38.5 (N(2)*Me*), 26.7 (N(*N*)*Me*); ^{13}C-NMR (D_2O): δ_C 170.6 (C(1)*C*=O), 164.8 (N(2)*C*=O), 136.5 (*C*(2)), 133.3 (*C*(1)), 132.0 (*C*(4)), 128.8 (*C*(6)), 128.2 (*C*(5)), 127.5 (*C*(3)), 38.0 (N(2)*Me*), 26.1 (N(*N*)*Me*).
HR-ESI-MS: $C_{10}H_{12}DN_2O_2$ $[M+H]^+$ *m/z* found 194.1042, calcd 194.1040, $\Delta = 1.0$

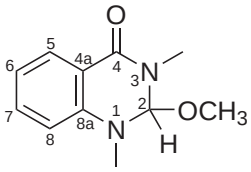
ppm.

2-($^2H_3$)methoxy-1,3-dimethyl-2-^{2}H-1,3,4-trihydroquinazolin-4-one (34)
28 (6 mg, 0.031 mmol) was dissolved in CD_3OD (0.55 mL) and left to equilibrate for 20 hours. Removal of the solvent under reduced pressure yielded **34** as a white solid in quantitative yield.



^{1}H-NMR ($CDCl_3$): δ_H 8.01 (d, J = 7.8 Hz, 1H, C(5)H), 7.42 (t, J = 7.1 Hz, 1H, C(7)H), 6.87 (t, J = 7.6 Hz, 1H, C(6)H), 6.68 (d, J = 8.3 Hz, 1H, C(8)H), 3.15 (s, 3H, N(1)Me), 3.04 (s, 3H, N(3)Me); ^{1}H-NMR (CD_3OD): δ_H 7.87 (d, J = 7.8 Hz, 1H, C(5)H), 7.48 (t, J = 7.4 Hz, 1H, C(7)H), 6.88 (t, J =7.8 Hz, 1H, C(6)H), 6.85 (d, J = 8.0 Hz, 1H, C(8)H), 3.15 (s, 3H, N(1)Me), 3.10 (s, 3H, N(3)Me); ^{13}C-NMR ($CDCl_3$): δ_C 162.5 (C(4)), 145.3 (C(8a)), 134.2 (C(7)), 128.5 (C(5)), 118.3 (C(6)), 113.8 (C(4a)), 110.2 (C(8)), 96.9 (C(2)), 49.3 (OMe), 34.7 (N(3)Me), 32.3 (N(1)Me); ^{13}C-NMR (CD_3OD): δ_C 164.7 (C(4)), 146.9 (C(8a)), 135.6 (C(7)), 128.7 (C(5)), 119.1 (C(6)), 114.8 (C(4a)), 112.2 (C(8)), 98.4 (C(2)), 35.3 (OMe), 35.3 (N(3)Me), 32.8 (N(1)Me).

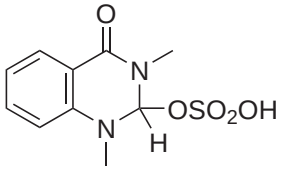
2-methoxy-1,3-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one (35)
Under inert conditions and with 3 Åmolecular sieves, **28** (135 mg, 0.70 mmol) was dissolved in CH_3OH (25 mL) and the reaction stirred at room temperature for 12 hours. The reaction was filtered and the filtrate concentrated under reduced pressure to yield a colourless oil that was a mixture of **35** and **28** (1:1.35 ratio).



^{1}H-NMR ($CDCl_3$): δ_H 7.96 (d, J = 7.8 Hz, 1H, C(5)H), 7.41 (t, J = 8.3 Hz, 1H, C(7)H), 6.85 (t, J = 7.5 Hz, 1H, C(6)H), 6.67 (d, J = 8.3 Hz, 1H, C(8)H), 5.77 (s, 1H, C(2)H), 3.13 (s, 3H, N(3)Me), 3.03 (s, 3H, N(1)Me), 2.93 (S, 3H, OMe); ^{13}C-NMR ($CDCl_3$): δ_C 163.0 (C(4)), 145.2 (C(8a)), 134.2 (C(7)), 128.3 (C(5)), 118.2 (C(6)), 113.5 (C(4a)), 110.2 (C(8)), 96.8 (C(2)), 49.3 (OMe), 34.6 (N(1)Me), 32.2 (N(3)Me).

6.1.3 Quinazolinium-based models

Attempted synthesis of (1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)oxidanesulfonic acid (42)



Under inert conditions, **28** (30 mg, 0.156 mmol) was dissolved in DMF (2 mL), $SO_3 \cdot$pyridine complex (99 mg, 0.624 mmol) was added and the reaction was stirred at rt for 4 days. The reaction was concentrated under reduced pressure to yield

starting material.

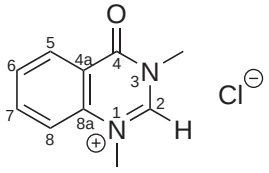
1,3-dimethyl-4-oxo-3,4-dihydroquinazolin-1-ium chloride (41)

A. **28** (30 mg, 0.156 mmol) was suspended in ethylchloroformate (0.3 mL, 3.12 mmol), pyridine (15 μL, 0.187 mmol) was added and the reaction refluxed for 4 days. H_2O (2 mL) was added and the reaction mixture was concentrated under reduced pressure to yield an oil which proved to be a mixture of **41** and pyridine (1:2.4, 57 mg, 98%).

B. Under inert conditions, **28** (400 mg, 2.08 mmol) was suspended in ethylchloroformate (8 mL, 84 mmol) and stirred overnight at 50 °C. The reaction was concentrated under reduced pressure and the resulting solid was rinsed with ethyl acetate (5 mL x 2). The liquid phase was decanted off to yield **41** as a white solid (379 mg, 86 %).

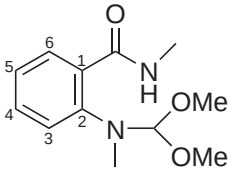
C. Under inert conditions 4-hydroxyquinazoline (500 mg, 3.42 mmol), $NaHCO_3$ (570 mg, 6.84 mmol) and MeI (10 mL, 160 mmol) were combined in a pressure tube. The tube was sealed and heated with stirring at 55 °C for 4 days. The reaction was partitioned (30 mL each) with diethyl ether, ethyl acetate, CH_3OH then H_2O, in that order. The insoluble purple precipitate resulting from the addition of H_2O was filtered and showed the presence of **41**, as the iodide salt, and **28**. Further purification was unsuccessful.

D. Under inert conditions **30** (24 mg, 0.132 mmol) was dissolved in CH_3OH (0.75 mL), **15** (52 μL, 0.39 mmol) and formic acid (17 μL, 0.43 mmol) were added and the reaction stirred at room temperature for 2 days. The reaction was concentrated under reduced pressure to yield **46** in quantitative yield. NEt_3 (50 μL) was added to attempt to complete the synthesis, however the sample quickly degraded back to **30**.



^{1}H-NMR ($CDCl_3$): δ_H 12.3 (s, 1H, C(2)*H*), 8.45 (d, J = 8.6 Hz, 1H, C(8)*H*), 8.03 (t, J = 7.3 Hz, 1H, C(6)*H*), 7.80 (t, J = 7.5 Hz, 1H, C(7)*H*), 7.74 (d, J = 8.1 Hz, 1H, C(5)*H*), 4.41 (s, 3H, N(3)*Me*), 3.98 (s, 3H, N(1)*Me*); ^{13}C-NMR ($CHCl_3$): δ_C 157.8 (*C*(8a)), 155.2 (*C*(2)), 138.2 (*C*(4)), 137.0 (*C*(5)), 130.1 (*C*(6)), 129.2 (*C*(8)), 119.7 (*C*(4a)), 117.3 (*C*(7)), 40.4 (N(3)*Me*), 36.3 (N(1)*Me*); HR-ESI-MS: $C_{10}H_{11}N_2O^+$ $[M]^+$ m/z found 175.0874, calcd 175.0871, Δ = 1.7 ppm.

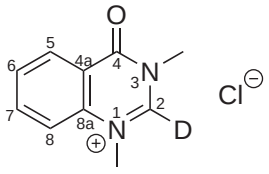
2-[(dimethoxymethyl)(methyl)amino]-*N*-methylbenzamide (46)



^{1}H-NMR ($CDCl_3$): δ_H 8.44 (s, 1H, N(2)C*H*), 7.32–7.30 (m, 2H, C(4)*H*, C(6)*H*), 6.66 (d, J = 8.6 Hz, 1H, C(3)*H*), 6.57 (t, J = 7.6 Hz, 1H, C(5)*H*), 2.95 (d, J = 4.6 Hz, 3H, N(*N*)*Me*), 2.85 (s, 3H, N(2)*Me*), 2.64 (s, 6H, N(2)C(O*Me*)$_2$).

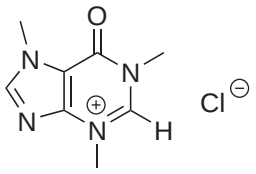
2-^{2}H-1,3-dimethyl-4-oxo-3,4-dihydroquinazolin-1-ium chloride (50)

41 (6 mg, 0.0286 mmol) was dissolved in D_2O (0.55 mL) and allowed to equilibrate for 4 hours. The reaction was concentrated under reduced pressure to yield **50** as a white crystal in quantitative yield.



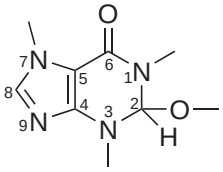
^{1}H-NMR ($CDCl_3$): δ_H 8.45 (d, J = 8.6 Hz, 1H, C(8)H), 8.03 (t, J = 7.3 Hz, 1H, C(6)H), 7.80 (t, J = 7.5 Hz, 1H, C(7)H), 7.74 (d, J = 8.1 Hz, 1H, C(5)H), 4.41 (s, 3H, N(3)Me), 3.98 (s, 3H, N(1)Me); ^{13}C-NMR ($CHCl_3$): δ_C 157.8 (C(8a)), 155.3 (C(2)), 138.2 (C(4)), 137.0 (C(5)), 130.1 (C(6)), 129.2 (C(8)), 119.7 (C(4a)), 117.3 (C(7)), 40.4 (N(3)Me), 36.3 (N(1)Me).

Attempted synthesis of 1,3,7-trimethyl-6-oxo-6,7-dihydro-1*H*-purin-3- ium chloride (47)



A. Under inert conditions in a distillation apparatus, **27** (394 mg, 2.34 mmol) was dissolved in CH_3OH (1 mL), DMFDMA (0.318 μL, 2.38 mmol) was added and the reaction was heated at 75 °C for 6 hours. The reaction was distilled to yield a golden oil residue composed of **48** and **23**. Addition of formic acid (0.25 mL) and CH_3OH (1 mL) led to the formation of **47**, however this quickly degraded.

2-methoxy-1,3,7-trimethyl-1,2,3,6-tetrahydro-1*H*-purin-6-one (48)

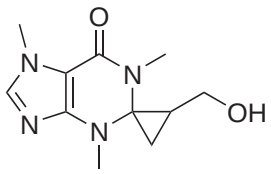


^{1}H-NMR ($CDCl_3$): δ_H 7.18 (s, 1H, C(8)H), 5.77 (s, 1H, C(2)H), 3.86 (s, 3H, N(7)Me), 3.14 (s, 3H, N(3)Me), 3.08 (s, 3H, OMe), 3.07 (s, 3H, N(1)Me); ^{13}C-NMR ($CDCl_3$): δ_C 157.9 (C(6)), 152.9 (C(4)), 139.2 (C(8)), 137.4 (C(5)), 99.0 (C(2)), 50.0 (OMe), 34.8 (N(7)Me), 32.4 (N(3)Me), 31.1 (N(1)Me).

6.1.4 Trapping a carbene

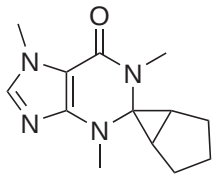
As a cyclopropane

Attempted synthesis of 2-(hydroxymethyl)-1',3',7'-trimethyl-3',7'-dihydrospiro[cyclopropane-1,2'-purin]-6'(1'H)-one (57)



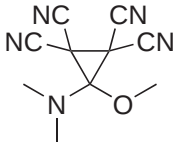
In an NMR tube **23** (6.4 mg, 0.032 mmol) was dissolved in CD_3OD (0.55 mL), allyl alcohol (22.7 μL, 0.33 mmol) was added and the reaction was followed by NMR spectroscopy for 5 days. Decrease of the formyl resonance was the only observable change.

Attempted synthesis of 1',3',7'-trimethyl-1',3',4',5',6',7'-hexahydrospiro [bicyclo[3.1.0]hexane-6,2'-purine]-6'-one (58)



In an NMR tube **23** (6.4 mg, 0.032 mmol) was dissolved in CD_3OD (0.55 mL), cyclopentene (32.0 μL, 0.35 mmol) was added and the reaction was followed by NMR spectroscopy for 7 days. Decrease of the formyl resonance was the only observable change.

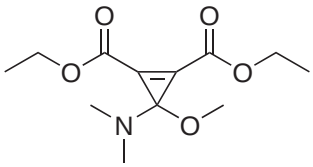
Attempted synthesis of 3-(dimethylamino)-3-methoxycyclopropane-1,1,2,2-tetracarbonitrile (62)



A. **15** (22.5 μL, 0.168 mmol) was dissolved in CH_2Cl_2 (2 mL) with tetracyanoethylene (65 mg, 0.507 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

B. **15** (22.5 μL, 0.168 mmol) was dissolved in THF (2 mL) with tetracyanoethylene (65 mg, 0.507 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

Attempted synthesis of ethyl 3-(dimethylamino)-3-methoxy-2-(propanoyl oxy)cycloprop-1-ene-1-carboxylate (61)

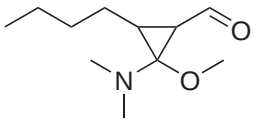


A. **15** (22.5 μL, 0.168 mmol) was dissolved in CH_2Cl_2 (2 mL) with diethylacetylene dicarbonate (81 μL, 0.506 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

B. **15** (22.5 μL, 0.168 mmol) was dissolved in THF (2 mL) with diethylacetylene dicarbonate (81 μL, 0.506 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

C. **15** (22.5 μL, 0.168 mmol) was dissolved in diethylacetylene dicarbonate (200 μL, 1.25 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

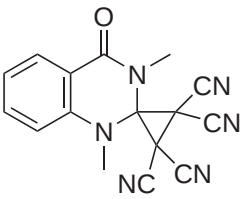
Attempted synthesis of diethyl 3-butyl-2-(dimethylamino)-2-methoxy cyclopropane-1-carbaldehyde (63)



A. **15** (22.5 μL, 0.168 mmol) was dissolved in CH_2Cl_2 (2 mL) with hept-2-en-1-al (66 μL, 0.504 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

B. **15** (22.5 μL, 0.168 mmol) was dissolved in THF (2 mL) with hept-2-en-1-al (66 μL, 0.504 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

Attempted synthesis of 1',3'-dimethyl-4'-oxo-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinazoline]-2,2,3,3-tetracarbonitrile (65)



A. **28** (20 mg, 0.104 mmol) was dissolved in CH_2Cl_2 (2 mL) with tetracyanoethylene (40 mg, 0.312 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

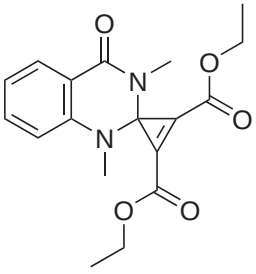
B. **28** (20 mg, 0.104 mmol) was dissolved in THF (2 mL) with tetracyanoethylene (40 mg, 0.312 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

C. Under inert conditions, **28** (40 mg, 0.208 mmol) was suspended in ethylchloroformate (1.9 mL) and stirred at 50 °C for 12 hours. The reaction was concentrated under reduced pressure to yield **41**. This was dissolved in THF (2 mL), tetracyanoethylene (133 mg, 1.04 mmol) and NaH (10 mg, 0.416 mmol) were added and the reaction stirred at room temperature overnight. The reaction was filtered and the precipitate washed with acetonitrile. The combined filtrate was concentrated under reduced pressure to yield a brown solid that was predominantly **41**.

(D). Under inert conditions **41** (37.2 mg, 0.177 mmol) was dissolved in degassed THF (24 mL) and tetracyanoethylene (23 mg, 0.177 mmol) was added. NaH (13.2 mg, 0.531 mmol) suspended in degassed THF (6 mL) was added and the reaction was stirred at room temperature for 8 days. The reaction was quenched with H_2O (10 mL), concentrated under reduced pressure and extracted into ethyl acetate (20 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to yield an oil that was largely composed of **30**.

(E). Under inert conditions **41** (240 mg, 1.14 mmol) was dissolved in degassed THF (24 mL), tetracyanoethylene (146 mg, 1.14 mmol) and NEt_3 (320 μL, 2.28 mmol) were added and the resulting crimson solution was stirred at room temperature for 9 days. The reaction was quenched with H_2O (10 mL), concentrated under reduced pressure and extracted into ethyl acetate (20 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to give an oil that was largely composed of **28**.

Attempted synthesis of 2,3-diethyl-1',3'-dimethyl-4'-oxo-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinazolin]-2-ene-2,3-dicarboxylate (64)



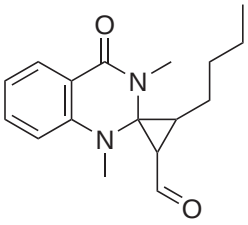
A. **28** (20 mg, 0.104 mmol) was dissolved in CH_2Cl_2 (2 mL) with diethylacetylene dicarbonate (50 μL, 0.312 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

B. **28** (20 mg, 0.104 mmol) was dissolved in THF (2 mL) with diethylacetylene dicarbonate (50 μL, 0.312 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

C. **28** (20 mg, 0.104 mmol) was dissolved in diethylacetylene dicarbonate (100 μL, 0.625 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

D. Under inert conditions **28** (40 mg, 0.208 mmol) was suspended in ethylchloroformate (1.9 mL) and stirred at 50 °C for 12 hours. The reaction was concentrated under reduced pressure to yield **41**. This was dissolved in THF (2 mL), tetracyanoethylene (133 mg, 1.04 mmol) and NaH (10 mg, 0.416 mmol) were added and the reaction stirred at room temperature overnight. The reaction was filtered and the precipitate was washed with acetonitrile. The combined filtrate was concentrated under reduced pressure to yield a brown solid that was an indistinquishable mess.

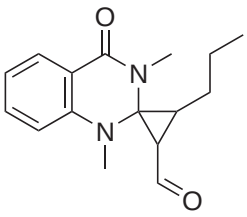
Attempted synthesis of 2-butyl-1',3'-dimethyl-4'-oxo-3',4'-dihydro- 1'*H*-spiro[cyclopropane-1,2'-quinazoline]-3-carbaldehyde (66)



A. **28** (20 mg, 0.104 mmol) was dissolved in CH_2Cl_2 (2 mL) with hept-2-en-1-al (41 μL, 0.313 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

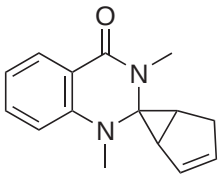
B. **28** (20 mg, 0.104 mmol) was dissolved in THF (2 mL) with hept-2-en-1-al (41 μL, 0.313 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

Attempted synthesis of 1',3'-dimethyl-4'-oxo-2-propyl-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinazoline]-3-carbaldehyde (67)



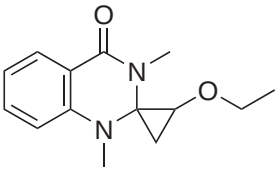
28 (20 mg, 0.104 mmol) was dissolved in THF (2 mL) with 2-hexenal (36 μL, 0.310 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

Attempted synthesis of 1',3'-dimethyl-3',4'-dihydro-1'*H*-spiro[bicyclo [3.1.0]hexane-6,2'-quinazolin]-2-en-4'-one (68)



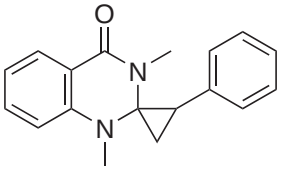
Formic acid (0.133 mL, 3.54 mmol) and acetic anhydride (0.3 mL, 3.21 mmol) were stirred together at 55 °C for 2 hours. The reaction was cooled to room temperature, **30** (79 mg, 0.487 mmol) was added and the reaction stirred at 25 °C for 12 hours. The reaction was concentrated under reduced pressure, 43 mg of the resultant **28** product was dissolved in CH_3OH (1.3 mL), cyclopentadiene (1 mL, 11.89 mmol) was added and the reaction was stirred at room temperature for 5 days. No change was observed by TLC and NMR spectroscopic analysis.

Attempted synthesis of 2-ethoxy-1',3'-dimethyl-3',4'-dihydro-1'*H*-spiro-cyclopropane-1,2'-quinazoline
-4'-one (71)



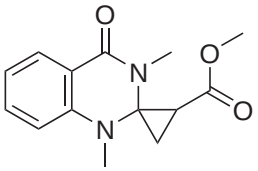
Under inert conditions **41** (20 mg, 0.094 mmol) was dissolved in degassed THF (5 mL), ethyl vinyl ether (20 μL, 0.209 mmol) and NaH (5 mg, 0.113 mmol) were added and the reaction was stirred at room temperature for 2 days. The reaction was concentrated under reduced pressure, toluene (5 mL) was added and the resulting precipitate filtered off. The filtrate was concentrated under reduced pressure and purified by flash chromatography to yield **30** (10 mg, 42%).

Attempted synthesis of 1',3'-dimethyl-2-phenyl-3',4'-dihydro-1'*H*-spiro-[cyclopropane-1,2'-quinazoline]-4'-one (69)



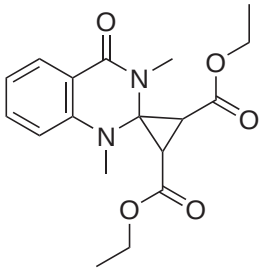
Under inert conditions **41** (20 mg, 0.094 mmol) was dissolved in degassed THF (5 mL), styrene (23 μL, 0.200 mmol) and NaH (5 mg, 0.113 mmol) were added and the reaction stirred at room temperature for 2 days. The reaction was concentrated under reduced pressure, toluene (5 mL) was added and the resulting precipitate filtered off. The filtrate was concentrated under reduced pressure to yield an impure oil that was a mixture of **28** and **32**.

Attempted synthesis of methyl 1',3'-dimethyl-4'-oxo-3',4'-dihydro-1'H-spiro[cyclopropane-1,2'-quinazoline]-2-carboxylate (70)



Under inert conditions **41** (20 mg, 0.094 mmol) was dissolved in degassed THF (5 mL), methyl acrylate (18 μL, 0.200 mmol) and NaH (5 mg, 0.113 mmol) were added and the reaction was stirred at room temperature for 2 days. The reaction was concentrated under reduced pressure, toluene (5 mL) was added and the resulting precipitate filtered off. The filtrate was concentrated under reduced pressure to yield an impure oil that was a mixture of **28** and **32**.

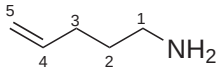
Attempted synthesis of 2,3-diethyl 1',3'-dimethyl-4'-oxo-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinazoline]-2,3-dicarboxylate (72)



Under inert conditions **41** (20 mg, 0.094 mmol) was dissolved in degassed THF (5 mL), diethyl maleate (32 μL, 0.200 mmol) and NaH (5 mg, 0.113 mmol) were added and the reaction was stirred at room temperature for 2 days. The reaction was concentrated under reduced pressure, toluene (5 mL) was added and the resulting precipitate filtered off. The filtrate was concentrated under reduced pressure to yield an impure oil that was a mixture of **28** and **32**.

pent-4-en-1-amine (77)

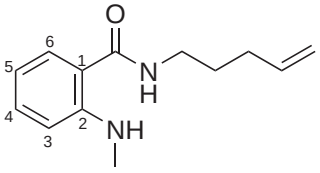
In a pressure tube 5-bromo-1-pentene (1 g, 6.71 mmol) was dissolved in sat. methanolic NH_3 (10 mL). The tube was sealed and heated to 90 °C for 24 hours. The reaction was allowed to cool and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (10 mL) and washed with sat. $NaHCO_3$ solution (2 x 10 mL) to generate the free amine. The organic phase was washed with H_2O, brine, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to yield **77** as a colourless oil (157 mg, 27.5%).



^{1}H-NMR ($CDCl_3$): δ_H 5.82 (ddt, J = 17.1, 10.0, 6.6 Hz, 1H, C(4)H), 5.02 (dd, J = 17.1, 1.7 Hz, 1H, C(5)Ha), 4.95 (dd, J = 10.0, 1.7 Hz, 1H, C(5)Hb), 2.61 (t, J = 7.4 Hz, 2H, C(1)H_2), 2.09 (dt, J = 7.2, 6.6 Hz, 2H, C(3)H_2), 1.59 (tt, J = 7.4, 7.4 Hz, 2H, C(2)H_2).

2-(methylamino)-*N*-(pent-4-en-1-yl)benzamide (78)

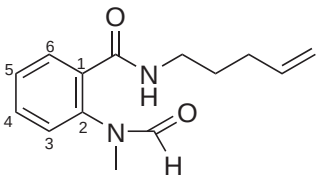
N-methylisatoic anhydride (200 mg, 1.15 mmol) was dissolved in H_2O (5 mL), pent-4-en-1-amine (200 mg, 2.3 mmol) was added and the reaction was stirred at 50 °C for 24 hours. The reaction was allowed to cool, diluted with H_2O (10 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with H_2O (20 mL x 2), brine (20 mL x 2), dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to yield a colourless oil. Purification by flash chromatography yielded **78** as a colourless oil (7.1 mg, 2.8%).



^{1}H-NMR ($CDCl_3$): δ_H 7.98 (dd, J = 8.1, 1.7 Hz, 1H, C(6)H), 7.38 (ddt, J = 8.5, 7.0, 1.5 Hz, 1H, C(4)H), 6.66 (d, J = 8.3 Hz. 1H, C(3)H), 6.61 (t, J = 7.3 Hz, 1H, C(5)H), 5.78 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H, N(N)C(4)H), 5.06 (dd, J = 17.7, 1.7 Hz, 1H, N(N)C(5)Ha), 5.01 (dd, J = 10.3, 1.3 Hz, 1H, N(N)C(5)Hb), 2.92 (s, 3H, N(2)Me), 2.87 (t, J = 8.3 Hz, 2H, N(N)C(1)H_2), 2.11 (dt, J = 7.3, 7.1 Hz, 2H, N(N)C(3)H_2), 1.75 (tt, J = 8.2, 7.3 Hz, 2H, N(N)C(2)H_2); ^{13}C-NMR ($CDCl_3$): δ_C 173.6 (C=O), 152.0 (C(2)), 137.1 (N(N)C(4)), 134.5 (C(4)), 132.4 (C(6)), 115.7 (N(N)C(5)), 114.0 (C(5)), 111.3 (C(1)), 110.6 (C(3)), 51.1 (N(N)C(1)), 32.4 (N(N)C(3)), 29.9 (N(2)Me), 23.1 (N(N)C(2)).

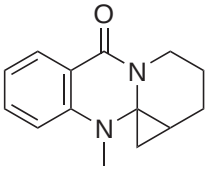
2-(*N*-methylformamido)-*N*-(pent-4-en-1-yl)benzamide (73)

Formic acid (1.15 mL, 30.42 mmol) and acetic anhydride (2.61 mL, 27.65 mmol) were heated together for 2 hours at 55 °C. The reaction was allowed to cool, **78** (7.1 mg, 0.03 mmol) was added and the reaction was stirred at room temperature for 12 hours. The reaction was concentrated under reduced pressure, azeotroped with toluene and the crude material purified by flash chromatography to yield **73** as a clear oil (5.2 mg, 70%).



^{1}H-NMR ($CDCl_3$): δ_H 8.16 (s, 1H, N(2)C(O)H), 7.96 (d, J = 7.0 Hz, 1H, C(6)H), 7.52 (t, J = 7.8 Hz, 1H, C(4)H), 7.40 (t, J =7.5 Hz, 1H, C(5)H), 7.22 (d, J = 7.8 Hz, 1H, C(3)H), 5.77 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H, N(N)C(4)H), 5.07 (dd, J = 17.6, 1.7 Hz, 1H, N(N)C(5)Ha), 5.02 (dd, J = 10.2, 1.7 Hz, 1H, N(N)C(5)Hb), 3.25 (s, 3H, H–14), 3.01 (t, J = 8.6 Hz, 2H, N(N)C(1)H_2), 2.14 (dt, J = 13.9, 7.3 Hz, 2H, N(N)C(3)H_2), 1.81 (tt, J = 7.3, 7.3 Hz, 2H, N(N)C(2)H_2); ^{1}H-NMR (DMSO−d_6): δ_H 8.03 (s, 1H, N(2)C(O)H), 7.82 (d, J = 7.6 Hz, 1H, C(6)H), 7.59 (t, J = 7.8 Hz, 1H, C(4)H), 7.43 (t, J = 7.6 Hz, 1H, C(5)H), 7.38 (d, J = 7.8 Hz, 1H, C(3)H), 5.80 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H, N(N)C(4)H), 5.02 (dd, J = 17.0, 1.7 Hz, 1H, N(N)C(5)Ha), 4.96 (dd, J = 10.2, 0.7 Hz, 1H, N(N)C(5)Hb), 3.10 (s, 3H, H–14), 2.64 (br s, 2H, N(N)C(1)H_2), 2.03 (dt, J = 12.7, 5.7 Hz, 2H, N(N)C(3)H_2), 1.55 (tt, J = 5.3, 5.3 Hz, 2H, N(N)C(2)H_2).

Attempted synthesis of 2-methyl-2,10-diazatetracyclo[8.5.0.0^{1,14}.0^{3,8}] pentadeca-3(8),4,6-trien-9-one (75)

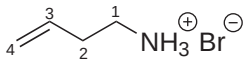


A. **73** (5.2 mg, 0.021 mmol) was dissolved in DMSO−d_6 (0.55 mL) and allowed to react at room temperature for 7 days. No change was observed by NMR spectroscopy.

B. **73** (5.2 mg, 0.021 mmol) was dissolved in CD_3OD (0.55 mL) and allowed to react at room temperature for 7 days. Solvolysis of the alkenyl amide was observed by NMR spectrometry.

but-3-en-1-ammonium bromide (81)

In a pressure tube 4-bromobut-1-ene (0.6 g, 3.7 mmol) was dissolved in sat. methanolic NH_3 (10 mL). The tube was sealed and heated to 90 °C for 24 hours. The reaction was allowed to cool and concentrated under reduced pressure to yield a white solid that was a mixture of but-3-en-1-ammoniumbromide and 4-bromobut-1-ene (1.5:1, 0.403 g, 59.7%).

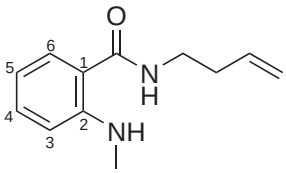


^{1}H-NMR (D_2O): δ_H 5.66 (ddt, J = 17.3, 11.5, 6.9 Hz, 1H, C(3)H), 5.08 (dd, J = 17.3, 1.5 Hz, 1H, C(4)Ha), 5.05 (dd, J = 11.4, 1.5 Hz, 1H, C(4)Hb), 2.93 (t, J = 6.8 Hz, 2H, C(1)H_2), 2.28 (dt, J = 15.9, 7.1 Hz, 2H, C(2)H_2).

***N*-(but-3-enyl)-2-(methylamino)benzamide (82)**

N-methylisatoic anhydride (0.66 g, 3.7 mmol) was dissolved in H_2O (15 mL), but-3-en-1-ammoniumbromide (0.403 mg, 2.65 mmol) was added and the reaction was stirred at 50 °C for 24 hours. The reaction was allowed to cool, diluted with H_2O (40 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with H_2O, brine, dried over $MgSO_4$, filtered and the filtrate

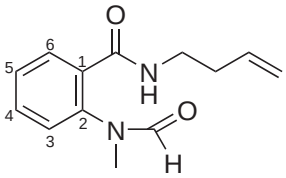
was concentrated under reduced pressure to give an impure brown solid. This was dissolved in H_2O (40 mL) and NaOH (0.45 g) was added to hydrolyse any remaining *N*-methylisatoic anhydride. The reaction was extracted with ethyl acetate and the organic phase was concentrated under reduced pressure to yield **82** as a brown solid (40 mg, 7.4%).



^{1}H-NMR ($CDCl_3$): δ_H 7.23 (t, J = 7.1 Hz, 1H, C(4)*H*), 7.20 (d, J = 7.8 Hz, 1H, C(6)*H*), 6.58 (d, J = 8.3 Hz. 1H, C(3)*H*), 6.49 (t, J = 7.8 Hz, 1H, C(5)*H*), 5.07 (dd, J = 17.1, 1.7 Hz, 1H, N(*N*)C(4)*Ha*), 5.05 (dd, J = 10.0, 1.6 Hz, 1H, N(*N*)C(4)*Hb*), 3.39 (dt, J = 6.6, 6.6 Hz, 2H, N(*N*)C(1)H_2), 2.77 (s, 3H, N(2)*Me*), 2.28 (dt, J = 6.8, 6.8 Hz, 2H, N(*N*)C(2)H_2).

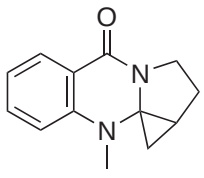
***N*-(but-3-enyl)-2-(*N*-methylformamido)benzamide (74)**

Formic acid (1.3 mL, 34.4 mmol) and acetic anhydride (2.6 mL, 27.54 mmol) were heated together for 1 hour at 100 °C. The reaction was cooled, **82** (40.6 mg, 0.199 mmol) was added and the reaction mixture was stirred at room temperature for 12 hours. The reaction was concentrated under reduced pressure, azeotroped with toluene and the crude material purified by flash chromatography to yield **74** as a clear oil (12.9 mg, 31%).



^{1}H-NMR ($CDCl_3$): δ_H 8.22 (s, 1H, N(2)C(O)*H*), 7.60 (dd, J = 7.8, 1.8 Hz, 1H, C(6)*H*), 7.49 (dt, J = 7.7, 1.4 Hz, 1H, C(4)*H*), 7.39 (dt, J = 7.7, 0.9 Hz, 1H, C(5)*H*), 7.18 (dd, J = 7.9, 1.1 Hz, 1H, C(3)*H*), 5.77 (ddt, J = 17.0, 10.2, 6.9 Hz, 1H, N(*N*)C(3)*H*), 5.13 (dd, J = 17.2, 1.3 Hz, 1H, N(*N*)C(4)*Ha*), 5.10 (dd, J = 10.3, 1.3 Hz, 1H, N(*N*)C(4)*Hb*), 3.49 (dt, J = 6.6, 6.6 Hz, 2H, N(*N*)C(1)H_2), 3.24 (s, 3H, H–13), 2.34 (dt, J =6.8, 6.8 Hz, 2H, N(*N*)C(2)H_2); ^{13}C-NMR ($CDCl_3$): δ_C 167.0 (C(1)*C*=O), 162.7 (N(2)*C*=O), 139.5 (*C*(2)), 135.1 (N(*N*)*C*(3)), 134.0 (*C*(1)), 131.6 (*C*(4)), 129.4 (*C*(6)), 128.2 (*C*(5)), 127.7 (*C*(3)), 117.9 (N(*N*)*C*(4)), 38.9 (N(*N*)*C*(1)), 33.9 (N(2)*Me*), 33.7 (N(*N*)*C*(2)).

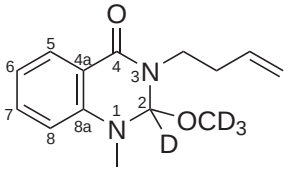
Attempted synthesis of 2-methyl-2,10-diazatetracyclo[8.4.0.0^{1,13}.0^{3,8}] tetradeca-3(8),4,6-trien-9-one (76)



A. In an NMR tube **74** (12.9 mg, 0.055 mmol) was dissolved in CD_3OD (0.55 mL) and allowed to react at room temperature for 7 days. **79** was observed forming by NMR spectroscopy.

B. In an NMR tube under inert conditions, **80** (20 mg, 0.09 mmol) was dissolved in degassed $CDCl_3$ (0.6 mL), NEt_3 (5 μL, 0.036 mmol) was added and the reaction was allowed to react at room temperature for 2 hours. Hydrolysis to **74** was observed by NMR spectroscopy.

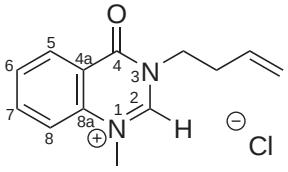
3-(but-3-en-1-yl)-2-($^2H_3$)methoxy-1-methyl-2-^{2}H-1,3,4-trihydro quinazolin-4-one (79)



^{1}H-NMR (CD_3OD): δ_H 7.87 (dd, J = 7.8, 1.7 Hz, 1H, C(5)H), 7.51 (dt, J = 7.6, 1.4 Hz, 1H, C(7)H), 6.89 (t, J = 7.6 Hz, 1H, C(6)H), 6.86 (d, J = 8.3 Hz, 1H, C(8)H), 5.87 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H, N(3)C(3)H), 5.11 (dd, J = 17.1, 1.5 Hz, 1H, N(3)C(4)Ha), 5.06 (dd, J = 10.4, 1.2 Hz, 1H, N(3)C(4)Hb), 3.86 (ddd, J = 14.4, 8.8, 6.1 Hz, 1H, N(3)C(1)Ha), 3.45 (ddd, J = 15.1, 8.8, 6.6 Hz, 1H, N(3)C(1)Hb), 2.54-2.39 (m, 2H, N(3)C(2)H_2).

3-(but-3-en-1-yl)-1-methyl-4-oxo-3,4-dihydroquinazolin-1-ium chloride (80)

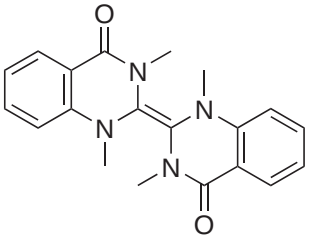
Under inert conditions **74** (12 mg, 0.052 mmol) was dissolved in ethylchloroformate (2 mL) and stirred at 50 °C for 12 hours. The reaction was concentrated under reduced pressure to give **80** as a white solid in quantitative yield.



^{1}H-NMR (DMSO−d_6): δ_H 10.24 (s, 1H, C(2)H), 8.35 (d, J = 7.6 Hz, 1H, C(8)H), 8.17 (t, J = 7.3 Hz, 1H, C(6)H), 8.03 (d, J = 8.1 Hz, 1H, C(5)H), 7.88 (t, J = 7.0 Hz, 1H, C(7)H), 5.90-5.82 (m, 1H, N(2)C(3)H), 5.14 (d, J = 7.0 Hz, 1H, N(2)C(4)Ha), 5.09 (d, J = 10.1 Hz, 1H, N(2)C(4)Hb), 4.17 (t, J = 6.8 Hz, 2H, N(2)C(1)H_2), 4.08 (s, 3H, N(1)Me), 2.52 (dd, J = 6.8, 6.4 Hz, 2H, N(2)C(2)H_2); ^{13}C-NMR (DMSO−d_6): δ_C 158.2 (C(8a)), 154.5 (C(2)), 138.5 (C(4)), 137.3 (C(5)), 134.3 (N(3)C(3)), 130.5 (C(6)), 128.4 (C(8)), 120.1 (C(4a)), 119.1 (N(3)C(4)), 118.7 (C(7)), 48.1 (N(3)C(1)), 39.7 (N(1)Me), 32.6 (N(3)C(2)); HR-ESI-MS: $C_{13}H_{15}N_2O$ $[M]^+$ m/z found 215.1182, calcd 215.1184, Δ = -0.9 ppm.

As a dimer

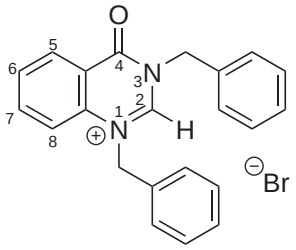
Attempted synthesis of 2-(1,3-dimethyl-4-oxo-1,2,3,4-tetrahydro quinazolin-2-ylidene)-1,3-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one (84)



Under inert conditions **41** (110 mg, 0.52 mmol) was dissolved in THF (2 mL), NaH (25 mg, 1.04 mmol) was added and the reaction was stirred for 4 hours at 50 °C. The reaction was concentrated under reduced pressure, the residue was extracted with hot toluene and the organic phase was concentrated under reduced pressure to give a white solid. Purification by flash chromatography yielded **32**.

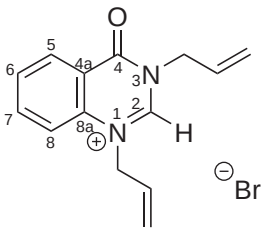
1,3-dibenzyl-4-oxo-3,4-dihydroquinazolin-1-ium bromide (91)

4-hydroxyquinazoline (1 g, 6.84 mmol) was suspended in EtOH (40 mL), $NaHCO_3$ (0.57 g, 6.84 mmol) and benzyl bromide (16.3 mL, 136.8 mmol) were added and the reaction was refluxed for 2 days. The reaction was allowed to cool and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (2 x 20 mL) and the organic phase was discarded. The remaining white solid was twice recrystalised from EtOH and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography to give a white powder that was composed of the desired product and silica. The solid was sonicated with ethyl acetate, filtered and the filtrate concentrated under reduced pressure to give a mixed oil/precipate residue. This was sonicated with $CHCl_3$ (3 x 20 mL), filtered through celite and the filtrate was concentrated under reduced pressure to give a white powder. This was purified by flash chromatography to yield a white solid that was a mixture of **91** and **104** (1:3).



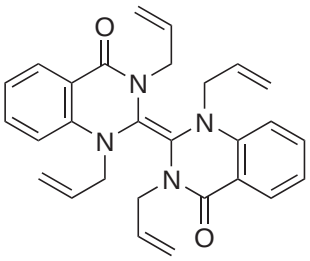
^{1}H-NMR ($CDCl_3$): δ_H 11.88 (s, 1H, C(2)*H*), 8.42 (d, J = 8.2 Hz, 1H, C(8)*H*), 8.39-8.24 (m, 2H, *Bn*), 7.90-7.64 (m, 5H, C(6)*H* & *Bn*), 7.53 (t, 1H, C(7)*H*), 7.40-7.28 (m, 5H, C(5)*H* & *Bn*), 6.08 (s, 2H, N(3)CH_2, 5.67 (s, 2H, N(1)CH_2; HR-ESI-MS: $C_{22}H_{19}N_2O$ $[M+]^+$ m/z found 327.1498, calcd 327.1497, Δ = 0.3 ppm.

4-oxo-1,3-bis(prop-2-en-1-yl)-3,4-dihydroquinazolin-1-ium bromide (105)
A. 4-hydroxyquinazoline (1 g, 6.84 mmol) was suspended in EtOH (40 mL), $NaHCO_3$ (0.57 g, 6.84 mmol) and allyl bromide (11.8 mL, 136.8 mmol) were added and the reaction was refluxed for 2 days. The reaction was filtered hot, the filtrate was concentrated under reduced pressure and the residue was washed with ethyl acetate (3 x 20 mL). The solid was recrystalised from CH_2Cl_2, the precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (2 x 10 mL) and the organic phase was concentrated under reduced pressure to yield a white powder that was a mixture of **94** and **106** (4:1, 15.8 mg, 0.7%).
B. 4-hydroxyquinazoline (1 g, 6.84 mmol) was suspended in EtOH (40 mL), $NaHCO_3$ (0.57 g, 6.84 mmol) and allyl bromide (10 mL, 115.9 mmol) were added and the reaction was refluxed for 2 days. The reaction was cooled and left to crsytallise in a fridge for 12 hours. The precipitate was filtered, washed with petroleum ether (3 x 40 mL) and then hot EtOH (3 x 40 mL). The latter filtrate was concentrated under reduced pressure, extracted with CH_2Cl_2 (2 x 20 mL) and concentrated under reduced pressure. The residue was recrystallised from acetone, the precipitate was filtered and the filtrate concentrated under reduced pressure to yield an orange oil that was a mixture of **105** and **106** (3:1, 98.6 mg, 4.9%).



^{1}H-NMR ($CDCl_3$): δ_H 11.43 (s, 1H, C(2)*H*), 8.44 (d, J = 8.0 Hz, 1H, C(8)*H*), 8.00 (t, J = 7.3 Hz, 1H, C(6)*H*), 7.79 (d, J = 9 Hz, 1H, C(5)*H*), 7.77 (t, J = 7.6 Hz, 1H, C(7)*H*), 6.31-6.14 (m, 2H, N(3)C(2)*H* & N(1)C(2)*H*), 5.68 (d, J = 18.1 Hz, 1H, N(3)C(3)*Ha*), 5.59 (d, J = 18.1 Hz, 1H, N(1)C(3)*Ha*), 5.57 (d, J = 5.1 Hz, 2H, N(3)C(1)H_2), 5.50 (d, J = 10.2 Hz, 1H, N(3)C(3)*Hb*), 5.43 (d, J = 10.0 Hz, 1H, N(1)C(3)*Hb*), 5.09 (d, J = 6.2 Hz, 2H, N(1)C(1)H_2); ^{13}C-NMR ($CDCl_3$): δ_C 157.1 (*C*(8a)), 153.7 (*C*(2)), 137.4 (*C*(4)), 136.8 (*C*(6)), 130.1 (*C*(7)), 129.5 (N(3)*C*(2)), 129.5 (N(1)*C*(2)), 129.5 (C–3), 123.0 (N(3)*C*(3)), 122.2 (N(1)*C*(3)), 120.3 (*C*(4a)), 118.2 (*C*(5)), 55.8 (N(3)*C*(1)), 51.4 (N(1)*C*(1)); HR-ESI-MS: $C_{14}H_{15}N_2O$ [M+]$^+$ m/z found 227.1181, calcd 227.1184, Δ = -1.3 ppm.

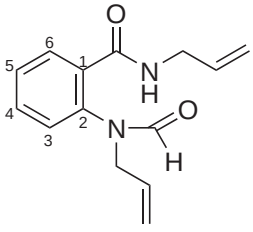
Attempted synthesis of 2-[1-ethenyl-4-oxo-3-(prop-2-en-1-yl)-1,2,3,4-tetrahydroquinazolin-2-ylidene]-1,3-bis(prop-2-en-1-yl)-1,2,3,4-tetrahydroquinazolin-4-one (86)



A. Under inert conditions **94** (34 mg, 0.110 mmol) was dissolved in degassed THF (10 mL), NaH (5.3 mg, 0.133 mmol) was added and the reaction was stirred for 12 hours at room temperature. The reaction was concentrated under reduced pressure and purified by flash chromatography to yield only the hydrolysis product of the starting material, **95**.

B. Under inert conditions in an NMR tube, **94** (19 mg, 0.084 mmol) was dissolved in degassed $CDCl_3$ (0.6 mL), NEt_3 (13 μL, 0.093 mmol) was added and the reaction was allowed to proceed for 6 days at room temperature. The reaction was concentrated under reduced pressure and purified by flash chromatography to yield only the hydrolysis product of the starting material, **95**.

N,*N*-bis(prop-2-en-1-yl)-2-(*N*-formamido)benzamide (95)



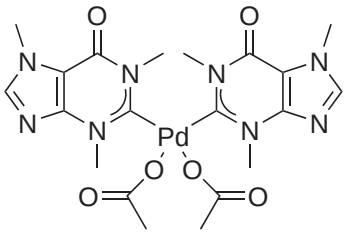
Rotamer A: ^{1}H-NMR ($CDCl_3$): δ_H 8.30 (s, 1H, N(2)C(O)*H*), 7.64 (dd, J = 8.1, 1.7 Hz, 1H, C(6)*H*), 7.48 (dt, J = 8.1, 1.7 Hz, 1H, C(5)*H*), 7.41 (dt, J = 7.6, 0.7 Hz, 1H, C(4)*H*), 7.22 (dd, J = 7.8, 1.2 Hz, 1H, C(3)*H*), 5.9-5.8 (m, 2H, N(*N*)C(2)*H* & N(2)C(2)*H*), 5.28-5.13(m, 4H, N(*N*)C(3)H_2 & N(2)C(3)H_2), 4.28 (d, J = 6.6 Hz, 2H, N(2)C(1)H_2), 3.96 (tt, J = 5.9, 1.5 Hz, 2H, N(*N*)C(1)H_2); ^{13}C-NMR ($CDCl_3$): δ_C 166.9 (C(1)*C*=O), 162.5 (N(2)*C*=O), 137.9 (*C*(2)), 134.5 (*C*(1)), 133.6 (N(*N*)*C*(2)), 132.3 (N(2)*C*(2)), 131.5 (*C*(5)), 129.4 (*C*(6)), 128.9 (*C*(3)), 128.4 (*C*(4)), 119.5 (N(2)*C*(3)), 117.6 (N(*N*)*C*(3)), 49.3 (N(2)*C*(1)), 42.6 (N(*N*)*C*(1));

Rotamer B: ^{1}H-NMR ($CDCl_3$): δ_H 8.25 (s, 1H, N(2)C(O)*H*), 7.58 (dd, J = 7.6, 1.7

Hz, 1H, C(6)H), 7.49 (dt, J = 7.5, 1.5 Hz, 1H, C(5)H), 7.41 (dt, J = 7.6, 0.7 Hz, 1H, C(4)H), 7.15 (dd, J = 7.8, 1.0 Hz, 1H, C(3)H), 5.9-5.8 (m, 2H, N(N)C(2)H & N(2)C(2)H), 5.28-5.13 (m, 2H, N(N)C(3)H_2 & N(2)C(3)H_2), 4.15 (d, J = 6.3 Hz, 2H, N(2)C(1)H_2), 3.92 (tt, J = 5.8, 1.5 Hz, 2H, N(N)C(1)H_2); ^{13}C-NMR ($CDCl_3$): δ_C 167.8 (C(1)C=O), 163.8 (N(2)C=O), 136.5 (C(2)), 135.8 (C(1)), 133.7 (N(N)C(2)), 132.8 (N(2)C(2)), 131.2 (C(5)), 129.0 (C(6)), 129.0 (C(3)), 128.4 (C(4)), 120.0 (N(2)C(3)), 117.1 (N(N)C(3)), 54.3 (N(2)C(1)), 42.5 (N(N)C(1)); HR-ESI-MS: $C_{14}H_{16}N_2O_2Na$ $[M+Na]^+$ m/z found 267.1108, calcd 267.1109, Δ = -0.4 ppm.

With organometallic compounds

Attempted synthesis of diacetoxybis(1,3,7-trimethyl-2,3,6,7-tetrahydro-1H-purin-6-on-2-ylidene) palladium(II) (97)



In an NMR tube **23** (6 mg, 0.031 mmol) was dissolved in CD_3OD (0.55 mL), $Pd(OAc)_2$ (7 mg, 0.031 mmol) was added and the reaction was allowed to react for 7 days. No change was observed by NMR spectroscopy.

diacetoxybis(1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylidene) palladium(II) (98)

A. **28** (20 mg, 0.104 mmol) was dissolved in CH_2Cl_2 (2 mL), $Pd(OAc)_2$ (40 mg, 0.178 mmol) was added and the reaction was stirred at room temperature under argon for three months. No change was observed by TLC analysis.

B. **28** (20 mg, 0.104 mmol) was dissolved in THF (2 mL), $Pd(OAc)_2$ (40 mg, 0.178 mmol) was added and the reaction was stirred at room temperature under argon for three months. No change was observed by TLC analysis.

C. **28** (40 mg, 0.208 mmol) was suspended in ethylchloroformate (1.9 mL) and the reaction was stirred and heated at 50 °C for 3 hours. The reaction was concentrated under reduced pressure, THF (2 mL), $Pd(OAc)_2$ (93.4 mg, 0.416 mmol) and NaH (10 mg, 0.416 mmol) were added and the reaction was stirred at room temperature for 3 hours. The reaction was filtered, the precipitate was washed with acetonitrile and the combined organic phases were concentrated under reduced pressure to yield an orange solid that was predominantly composed of **32**.

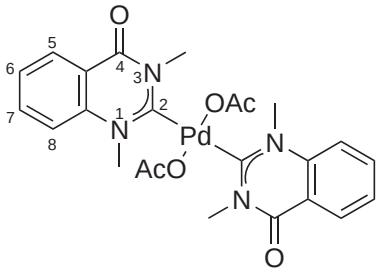
D. **41** (30 mg, 0.122 mmol) was dissolved in 'wet' DMSO (5 mL), $Pd(OAc)_2$ (13 mg, 0.058 mmol) was added and the reaction was stirred at room temperature for 12 hours. The reaction was filtered and the filtrate was concentrated under reduced pressure to yield a white solid that was predominantly unreacted starting material.

E. Under inert conditions **41** (30 mg, 0.122 mmol) was dissolved in THF (10 mL), NaOAc (10 mg, 0.116 mmol) and $Pd(OAc)_2$ (13 mg, 0.058 mmol) were added and the reaction was stirred for 12 hours at room temperature. The reaction was concentrated under reduced pressure, the residue was extracted with CH_2Cl_2 (2 x 10 mL) and the organic phase was concentrated under reduced pressure to give a golden oil that was composed of starting material and **32**.

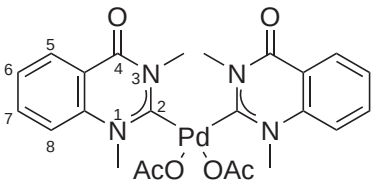
F. Under inert conditions in an NMR tube, **41** (12.1 mg, 0.057 mmol) was dissolved in degassed $CDCl_3$ (0.6 mL), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol) was added and the reaction was allowed to react at room temperature for 4 days. No change was observed by NMR spectroscopy.

G. Under inert conditions **41** (50 mg, 0.204 mmol) was dissolved in $Pd(OAc)_2$ (5 mL), Ag_2O (92 mg, 0.395 mmol) and $Pd(OAc)_2$ (46 mg, 0.204 mmol) were added and the reaction was stirred at room temperature for 4 hours. The reaction was filtered through celite and the filtrate was concentrated under reduced pressure to give a white solid that was composed of **28** and **32**.

H. Under inert conditions in an NMR tube, **41** (7 mg, 0.033 mmol) was dissolved in degassed $CDCl_3$ (0.55 mL), Ag_2O (15.3 mg, 0.066 mmol) and $Pd(OAc)_2$ (7.5 mg, 0.033 mmol) were added and the reaction was allowed to proceed at room temperature for 24 hours. **98** was observed by NMR spectroscopy.



trans



cis

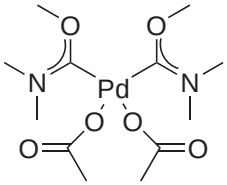
Isomer A: ^{1}H-NMR ($CDCl_3$): δ_H 8.33 (dd, J = 7.9, 1.5 Hz, 2H, C(5)H), 7.84 (ddt, J = 7.1, 2.5, 1.7 Hz, 2H, C(7)H), 7.57 (dd, J = 7.8, 2.5 Hz, 2H, C(8)H), 7.55 (t, J = 7.6 Hz, 2H, C(6)H), 4.69 (s, 6H, N(3)Me), 5.00 (s, 6H, N(1)Me), 1.95 (s, 3H, AcMe), 1.81 (s, 3H, AcMe); ^{13}C-NMR ($CDCl_3$): δ_C 199.1 (C(2)), 188.8 (AcC=O), 188.4 (AcC=O), 157.5 (C(4)), 138.8 (C(8a)), 134.1 (C(7)), 127.9 (C(5)), 126.5 (C(6)), 117.7 (C(4a)), 114.8 (C(8)), 43.5 (N(1)Me), 38.7 (N(3)Me), 22.2 (AcMe), 21.7 (AcMe).

Isomer B: ^{1}H-NMR (solvent): δ_H 8.23 (dd, J =8.6, 1.5 Hz, 2H, C(5)H), 7.68 (ddd, J = 9.0, 7.3, 1.7 Hz, 2H, C(7)H), 7.34 (dt, J = 7.6, 1.4 Hz, 2H, C(6)H), 7.28 (dd, J = 7.3, 0.9 Hz, 2H, C(8)H), 4.68 (s, 6H, N(3)Me), 4.99 (s, 6H, N(1)Me), 1.89 (s, 3H, AcMe), 1.70 (s, 3H, AcMe); ^{13}C-NMR (solvent): δ_C 199.2 (C(2)), 183.5 (AcC=O), 176.4 (AcC=O), 157.4 (C(4)), 138.3 (C(8a)), 134.2 (C(7)), 128.3 (C(5)), 126.1 (C(6)), 117.8 (C(4a)), 114.8 (C(8)), 43.8 (N(1)Me), 38.9 (N(3)Me), 21.5 (AcMe), 21.1 (AcMe).

HR-ESI-MS: $C_{20}H_{19}N_4O_2Pd$ [M-CH_3COOH-CH_3COO]$^+$ m/z found 451.0552, calcd 451.0548, Δ = 0.9 ppm; $C_{21}H_{21}N_4O_4Pd$ [M-CH_3COOH-CH_3COO+HCOOH]$^+$ m/z

found 497.0606, calcd 497.0603, Δ = 0.6 ppm; $C_{24}H_{27}N_4O_6Pd$ $[M+H]^+$ *m/z* found 571.0959, calcd 571.0971, Δ = 2.1 ppm.

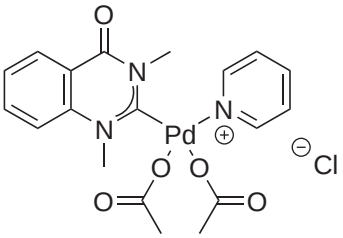
Attempted synthesis of diacetoxybis((dimethylamino)(methoxy) methylidene) palladium(II) (96)



A. **15** (22.5 μL, 0.168 mmol) was dissolved in CH_2Cl_2 (2 mL) with $Pd(OAc)_2$ (40 mg, 0.178 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

B. **15** (22.5 μL, 0.168 mmol) was dissolved in THF (2 mL) with $Pd(OAc)_2$ (40 mg, 0.178 mmol) and stirred at room temperature under argon for three months. No change was observed by TLC analysis.

Attempted synthesis of diacetoxy(1,3-dimethyl-4-oxo-1,2,3,4-tetrahydro quinazolin-2-ylidene)(pyridinium-1-yl)palladium(II) chloride (107)



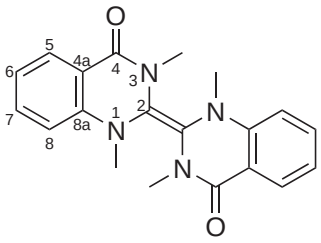
41 (30 mg, 0.122 mmol) was dissolved in pyridine (3 mL), K_2CO_3 (128 mg, 0.927 mmol) and $Pd(OAc)_2$ (55 mg, 0.245 mmol) were added and the reaction was refluxed for 3 hours. The reaction was filtered through celite and the filtrate was concentrated under reduced pressure to yield a yellow solid that was composed of **28** and **32**.

2-(1,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylidene)-1,3-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one (84)

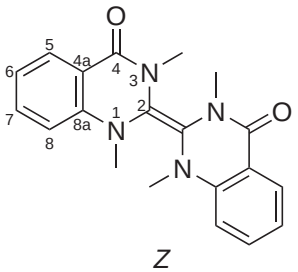
A. Under inert conditions **41** (50 mg, 0.204 mmol) was dissolved in CH_2Cl_2 (5 mL), Ag_2O (23 mg, 0.102 mmol) was added and the reaction was stirred at room temperature for 20 minutes. The reaction was centrifuged and the supernatant was removed and concentrated under reduced pressure to yield a white solid that was composed of **28** and **32**.

B. Under inert conditions **41** (50 mg, 0.204 mmol) was dissolved in CH_2Cl_2 (5 mL), Ag_2O (138 mg, 0.612 mmol) was added and the reaction was stirred at room temperature for 10 hours. The reaction mixture was filtered through celite, washed with ethyl acetate and the combined organic phases were concentrated under reduced pressure to yield a white solid that was composed of **28** and **32**.

C. Under inert conditions in an NMR tube, **41** (7.1 mg, 0.034 mmol) was dissolved in degassed $CDCl_3$ (0.55 mL), Ag_2O (15.6 mg, 0.067 mmol) was added and the reaction was allowed to proceed at room temperature for 2 hours. **84** was observed by NMR spectroscopy.



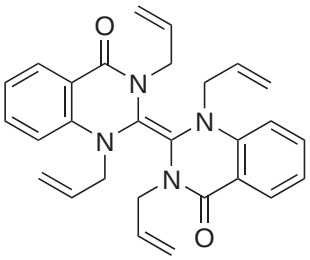
E



Z

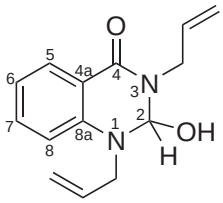
^{1}H-NMR ($CDCl_3$): δ_H 7.87 (d, J = 7.9 Hz, 2H , C(5)H), 7.38 (t, J = 7.8 Hz, 2H, C(7)H), 6.81 (t, J = 7.7 Hz, 2H, C(6)H), 6.65 (d, J = 8.3 Hz, 2H, C(8)H), 3.13 (s, 6H, N(3)Me), 3.00 (s, 6H, N(1)Me); ^{13}C-NMR ($CDCl_3$): δ_C 161.8 (C(4)), 142.0 (C(8a)), 133.9 (C(7)), 128.3 (C(5)), 118.7 (C(6)), 112.2 (C(8)), 111.7 (C(4a)), 106.8 (C(2)), 32.3 (N(3)Me), 34.9 (N(1)Me); HR-ESI-MS: $C_{21}H_{24}N_4O_3K$ $[M+MeOH+K]^+$ m/z found 419.1497, calcd 419.1485, Δ = -2.6 ppm; $C_{21}H_{24}N_4O_3Na$ $[M+MeOH+Na]^+$ m/z found 403.1755, calcd 403.1746, Δ = 2.2 ppm; $C_{21}H_{23}N_4O_3$ $[M+MeO]^-$ m/z found 379.1768, calcd 379.1770, Δ = -0.5 ppm.

Attempted synthesis of 2-[4-oxo-1,3-bis(prop-2-en-1-yl)-1,2,3,4-tetra hydroquinazolin-2-ylidene]-1,3-bis(prop-2-en-1-yl)-1,2,3,4-tetrahydro quinazolin-4-one (86)



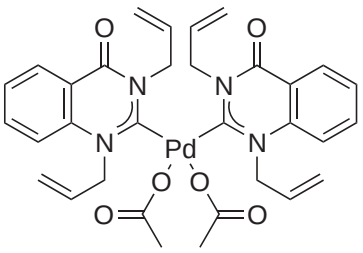
Under inert conditions in an NMR tube, **94** (20 mg, 0.065 mmol) was dissolved in degassed $CDCl_3$ (0.6 mL), Ag_2O (30.1 mg, 0.130 mmol) was added and the reaction was allowed to proceed at room temperature for 48 hours. **101** was observed by NMR spectroscopy.

2-hydroxy-1,3-bis(prop-2-en-1-yl)-1,2,3,4-tetrahydroquinazolin-4-one (101)



^{1}H-NMR ($CDCl_3$): δ_H 7.92 (dd, J = 7.8, 1.4 Hz, 1H, C(5)H), 7.36 (dt, J = 8.7, 1.5 Hz, 1H, C(7)H), 6.84 (t, J = 7.5 Hz, 1H, C(6)H), 6.73 (d, J = 8.4 Hz, 1H, C(8)H), 6.02-5.83 (m, 2H, N(3)C(2)H & N(1)C(2)H), 5.77 (s, 1H, C(2)H), 5.40-5.16 (m, 4H, N(3)C(3)H_2 & N(1)C(3)H_2), 4.72-4.67 (m, 1H, N(3)C(1)Ha), 4.09 (dd, J = 8.7, 5.0 Hz, 2H, N(1)C(1)H_2), 3.86 (dd, J = 15.9, 7.1 Hz, 1H, N(3)C(1)Hb); ^{13}C-NMR ($CDCl_3$): δ_C 161.4 (C(4)), 143.4 (C(8a)), 133.9 (C(7)), 133.1 (N(1)C(2)), 133.0 (N(3)C(2)), 128.8 (C(5)), 118.8 (C(6)), 118.0 (N(3)C(3)), 117.9 (N(1)C(3)), 114.8 (C(4a)), 112.7 (C(8)), 89.8 (C(2)), 50.5 (N(1)C(1)), 46.4 (N(3)C(1)); HR-ESI-MS: $C_{14}H_{17}N_2O_2$ $[M+H]^+$ m/z found 245.1294, calcd 245.1289, Δ = 2.1 ppm.

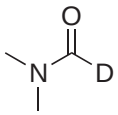
Attempted synthesis of diacetoxybis(4-oxo-1,3-bis(prop-2-en-1-yl)-1,2,3,4-tetrahydroquinazolin-2-ylidene)palladium(II) (108)



Under inert conditions in an NMR tube, **94** (20 mg, 0.065 mmol) was dissolved in degassed $CDCl_3$ (0.6 mL), aG_2o (30.1 mg, 0.130 mmol) and $Pd(OAc)_2$ (14.6 mg, 0.065 mmol) were added and the reaction was allowed to proceed at room temperature for 24 hours. No change was observed by NMR spectroscopy.

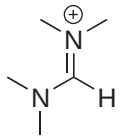
Species observed by mass spectrometry from DMFDMA kinetic studies

***N*,*N*-dimethyl(^{2}H)formamide (53)**



HR-ESI-MS: C_3H_6DNONa $[M+Na]^+$ *m/z* found 97.0491, calcd 97.0488, Δ = 3.1 ppm

[(dimethylamino)(^{2}H)methylidene]dimethylazanium (55)



HR-ESI-MS: $C_5H_{13}N_2$ $[M]^+$ *m/z* found 101.1082, calcd 101.1079, Δ = 3.0 ppm

6.2 Kinetic studies

Kinetic studies were recorded on a Varian DirectDrive 600 (600 MHz for ^{1}H) equipped with a Varian inverse-detected triple-resonance HCN cold probe operating at 25K. Variable temperature studies were performed on a Varian Unity Inova 300 (300 Mhz for ^{1}H). T_1 analyses of **23**, **28** and **41** were completed to ensure the pulse delay used in the kinetic studies was of a sufficient length to allow complete relaxation between pulses. pw90 calibrations were performed for all kinetic experiments involving **23**, but not for other analytes due to their faster half-life. 0.55 mL of deuterated solvent was used in each experiment. The experiment timing began upon first contact between the analyte and the solvent. The time for each data point represents the midpoint of acquisition of each FID. The integrals for all carbon-bound proton resonances of the analyte were defined and the sum of these normalised to a value of 100. In the case of the kinetic studies of **15**, only the amide acetal and dimethylamine resonances were integrated. The value reported is the integral of the formyl, amidine or amide acetal resonance, depending on analyte, and represents the contribution of this resonance to the total integral of 100. Data was analysed and models were fitted using OriginPro 8 (OriginLab Corp.) software, version 8.0724.

6.2.1 Imidazole-based models

Setup

Table 6.1 Composition of **23** kinetic experiments

Experiment	Solvent	Source of **23**	m (mg)	n[a] (mmol)	[**23**][b] (mmol/L)
PGKC4-4J	CD_3OD	PGKC4-4I	6.0	0.0306	55.60
PGKC4K-I	CD_3OD	PGKC4-4I	5.4	0.0275	50.04
PGKC4K-3	CD_3OD	PGKC4-4I	7.6	0.0387	70.43
PGKC4K-5	CD_3OD	PGKC5-3C/PGKC5-3F	1.1	0.0056	10.19
PGKC4K-6	CD_3OD	PGKC5-3C/PGKC5-3F	3.2	0.0163	29.65
PGKC4K-7	CD_3OD	PGKC5-3C/PGKC5-3F	9.7	0.0494	89.89
PGKC4K-11	CD_3OD	PGKC5-3C/PGKC5-3F	8.2	0.0418	75.99
PGKC5-3I	CD_3OD	PGKC5-3I	6.0	0.0306	55.60
PGKC5K-1	CD_3OD	PGKC5-3I	2.3	0.0117	21.31
PGKC5K-2	CD_3OD	PGKC5-3I	4.3	0.0219	39.85
PGKC5K-3	CD_3OD	PGKC5-3I	6.4	0.0326	59.31
PGKC5K-5	CD_3OD	PGKC5-3I	9.0	0.0459	83.40
PGKC5K-6	CD_3OD	PGKC5-3I	11.6	0.0591	107.5
PGKC5K-7[c]	CD_3OD	PGKC5-3I	6.4	0.0326	59.31
PGKC5K-8	CD_3OD	PGKC5-3I	13.8	0.0703	127.9
PGKC5K-14	D_2O	PGKC5-3I	6.0	0.0306	55.60
PGKC5K-17	D_2O	PGKC5-3I	6.0	0.0306	55.60

[a]Molar mass of **23** = 196.2 g/mol
[b]Total volume of solvent = 0.55 mL
[c]Triethylamine (9.7 μL, 0.0695 mmol) also added

Kinetic studies analysed by Initial-Rate method

Experiment parameters:

- acqusition time (at) = 10 seconds
- delay d1 (d1) = 60 seconds
- pulse width (pw) = pw90
- number of transients (nt) = 4
- pre-acquisition delay (pad) = 1520.5 seconds between acquisitions
- 13 acquisitions obtained

Analysis:

- integral of formyl proton resonance plotted against time
- linear model applied (as visualised on the graph and summarised in subsequent table)

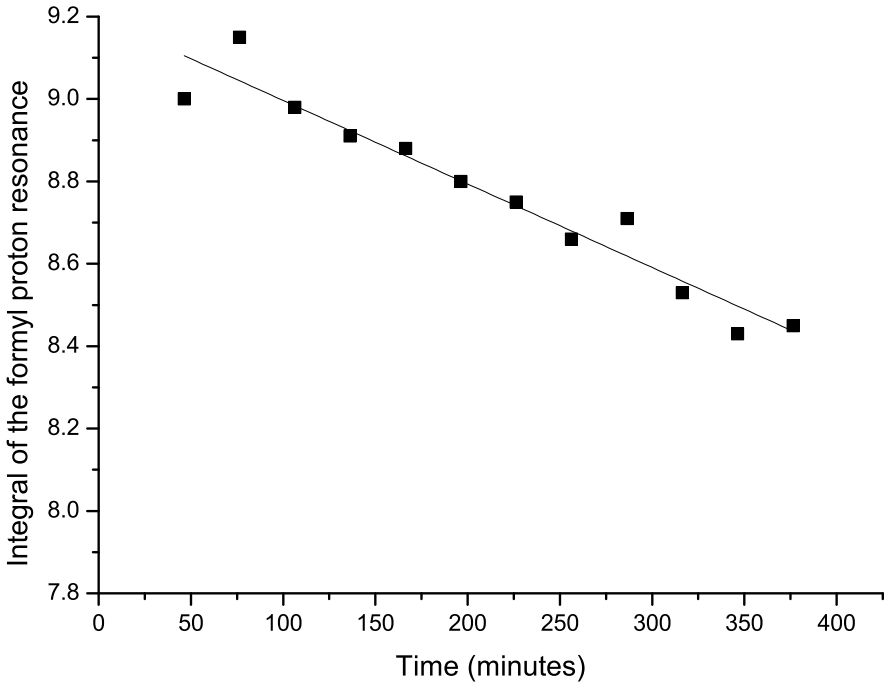


Figure 6.1 Formyl proton resonance with time in experiment PGKC4K-1

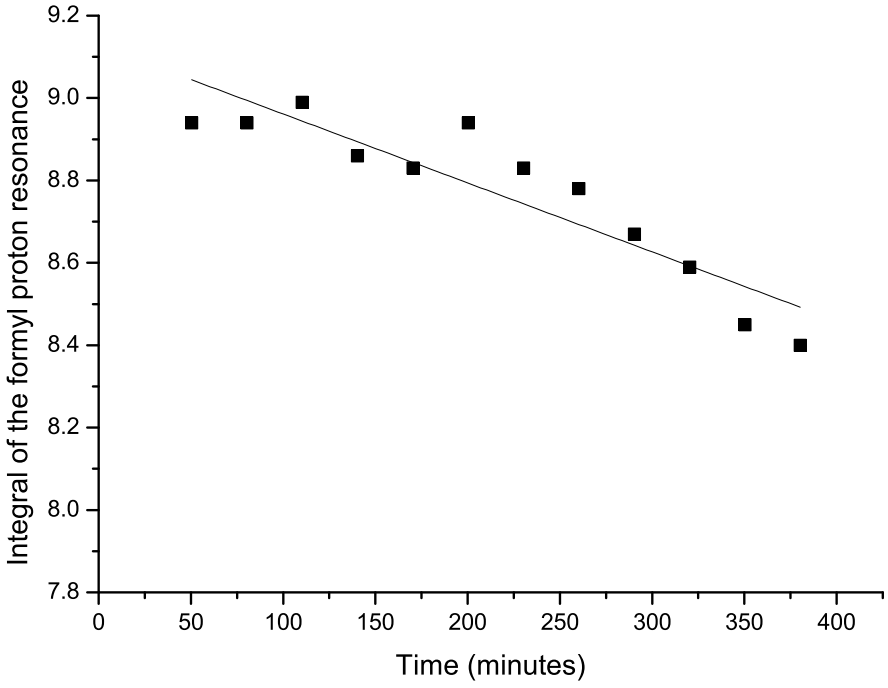


Figure 6.2 Formyl proton resonance with time in experiment PGKC4K-3

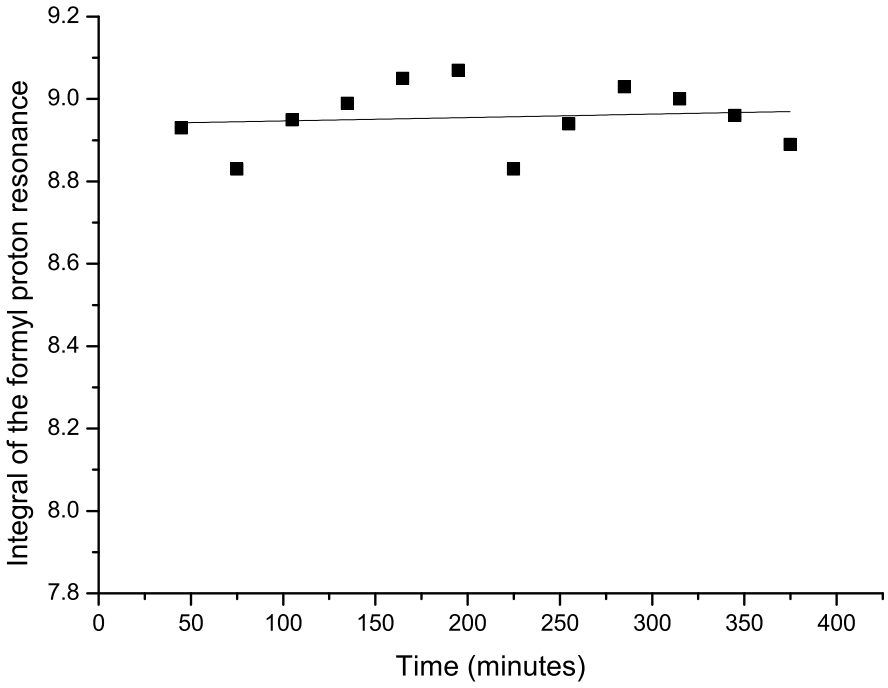


Figure 6.3 Formyl proton resonance with time in experiment PGKC4K-5

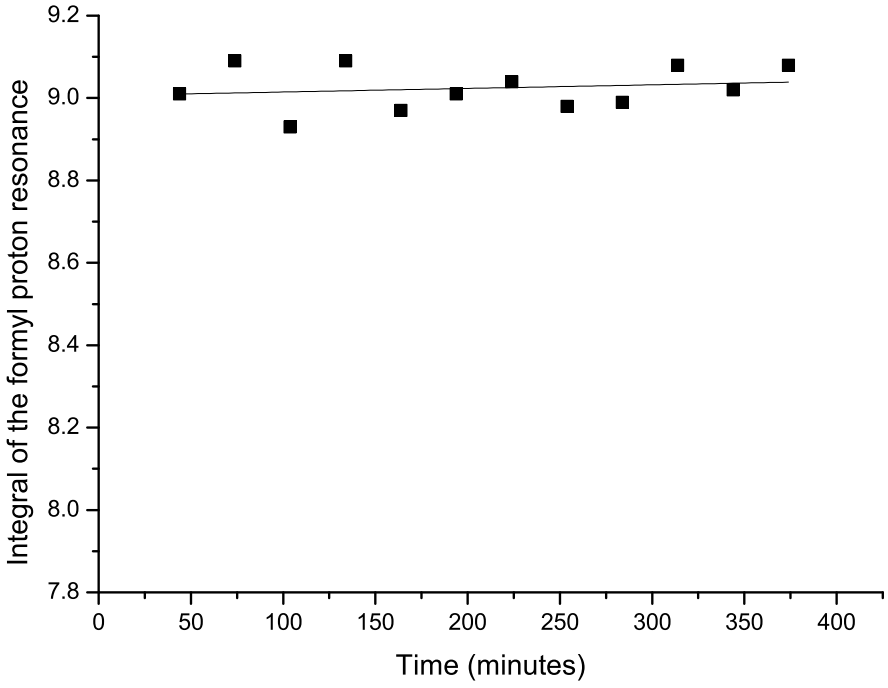


Figure 6.4 Formyl proton resonance with time in experiment PGKC4K-6

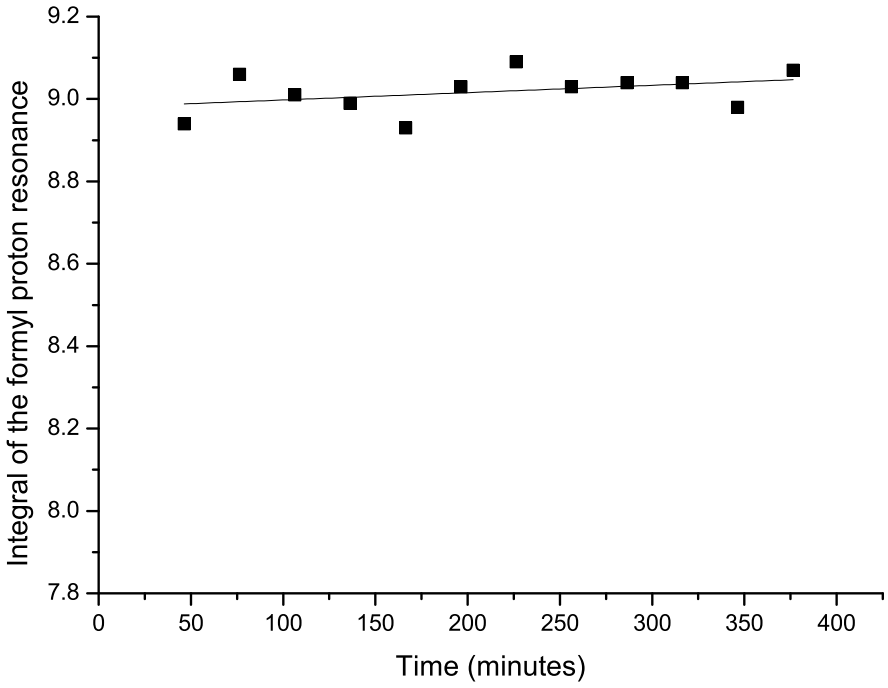


Figure 6.5 Formyl proton resonance with time in experiment PGKC4K-7

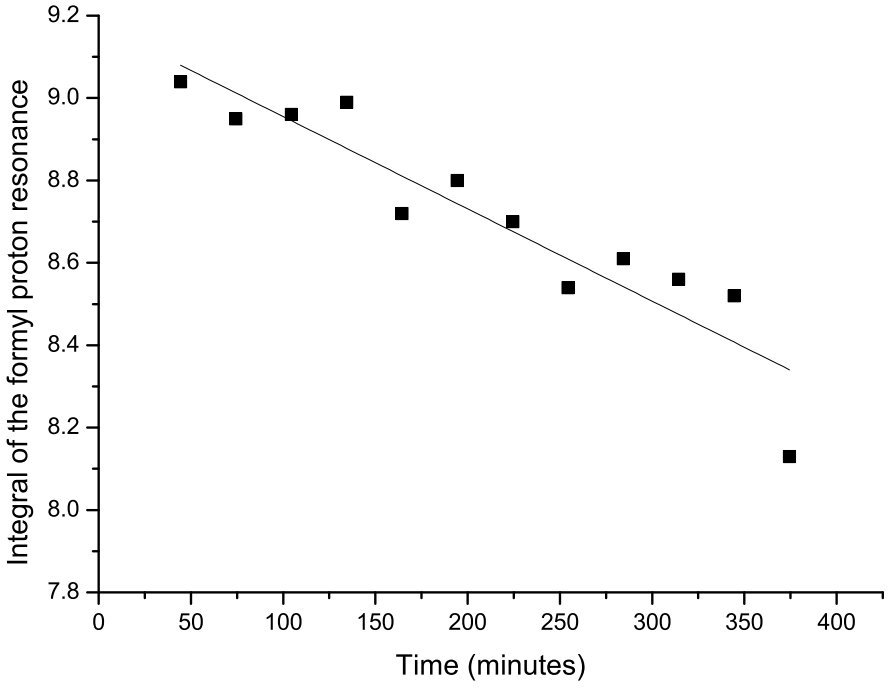


Figure 6.6 Formyl proton resonance with time in experiment PGKC5K-1

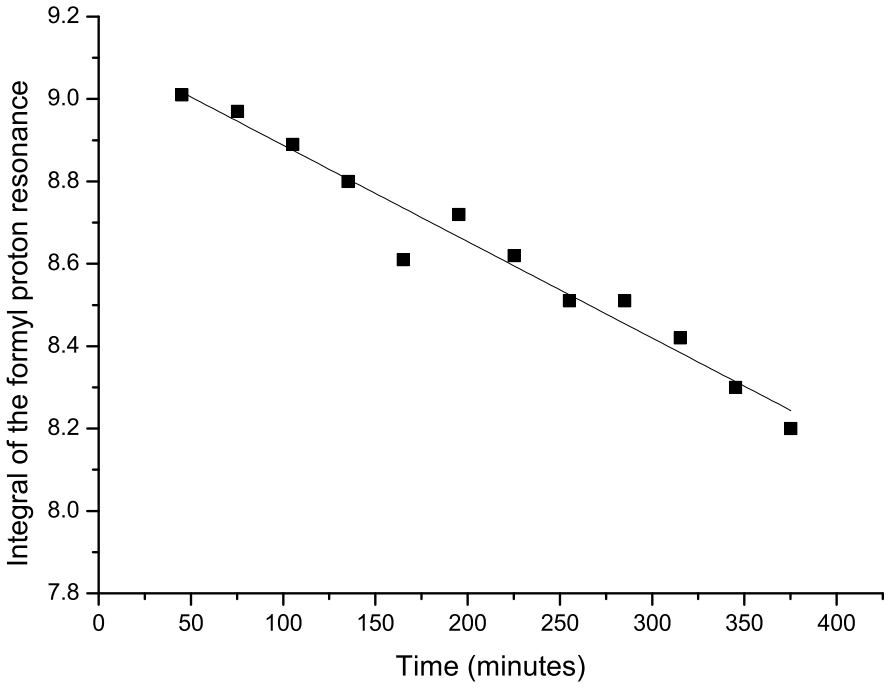


Figure 6.7 Formyl proton resonance with time in experiment PGKC5K-2

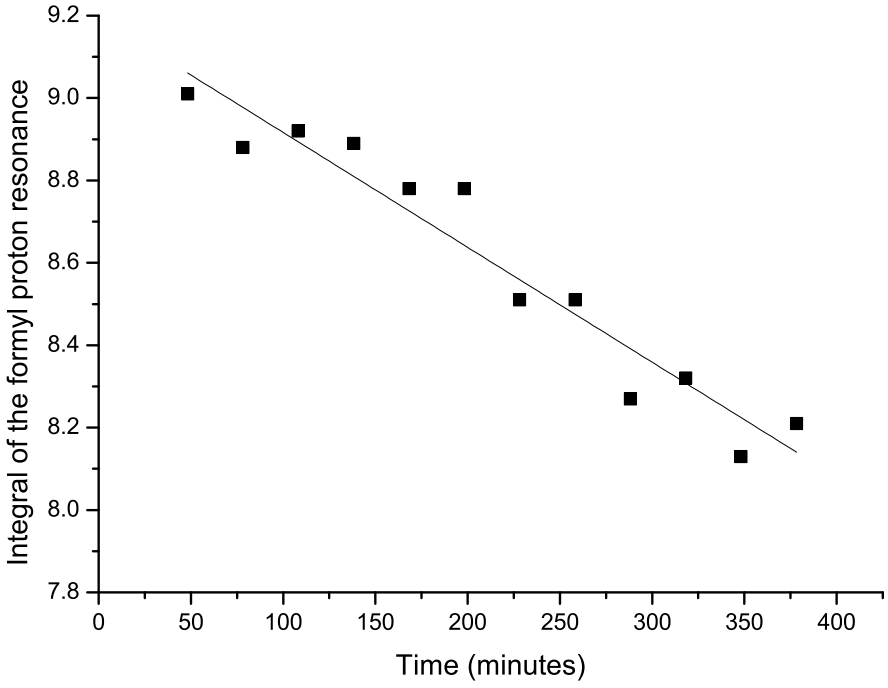


Figure 6.8 Formyl proton resonance with time in experiment PGKC5K-3

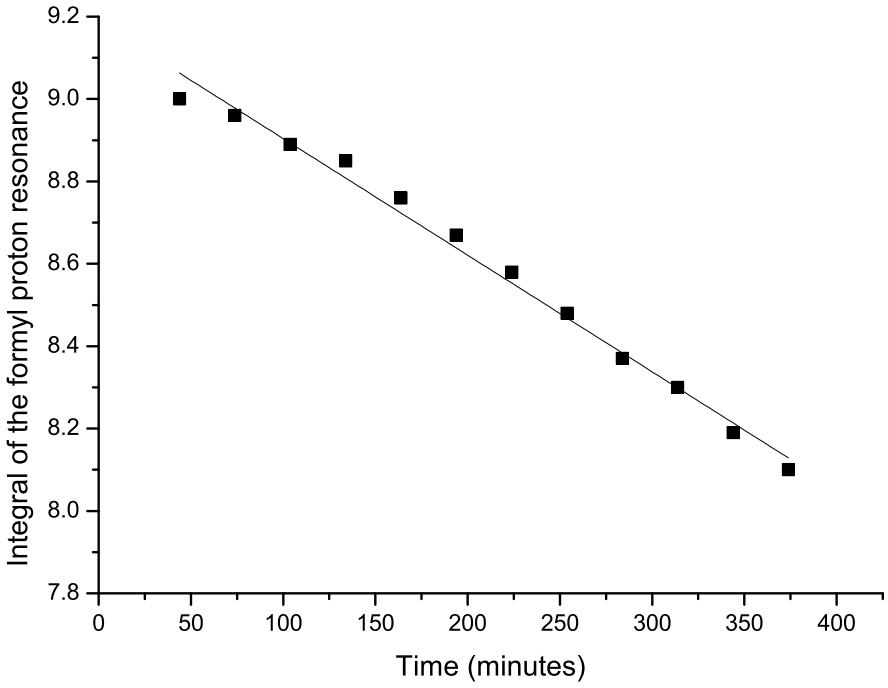


Figure 6.9 Formyl proton resonance with time in experiment PGKC5K-5

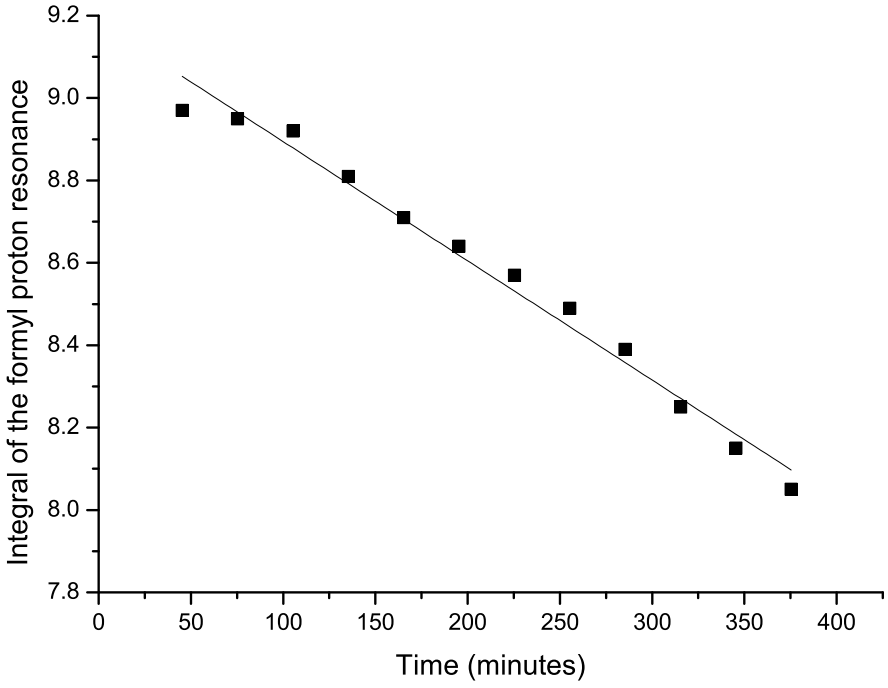


Figure 6.10 Formyl proton resonance with time in experiment PGKC5K-6

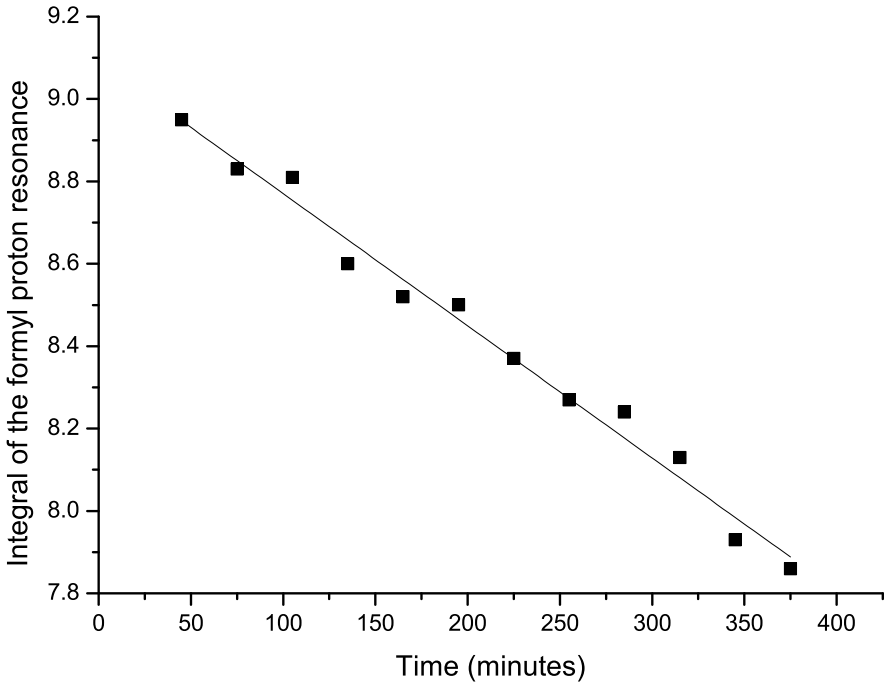


Figure 6.11 Formyl proton resonance with time in experiment PGKC5K-7

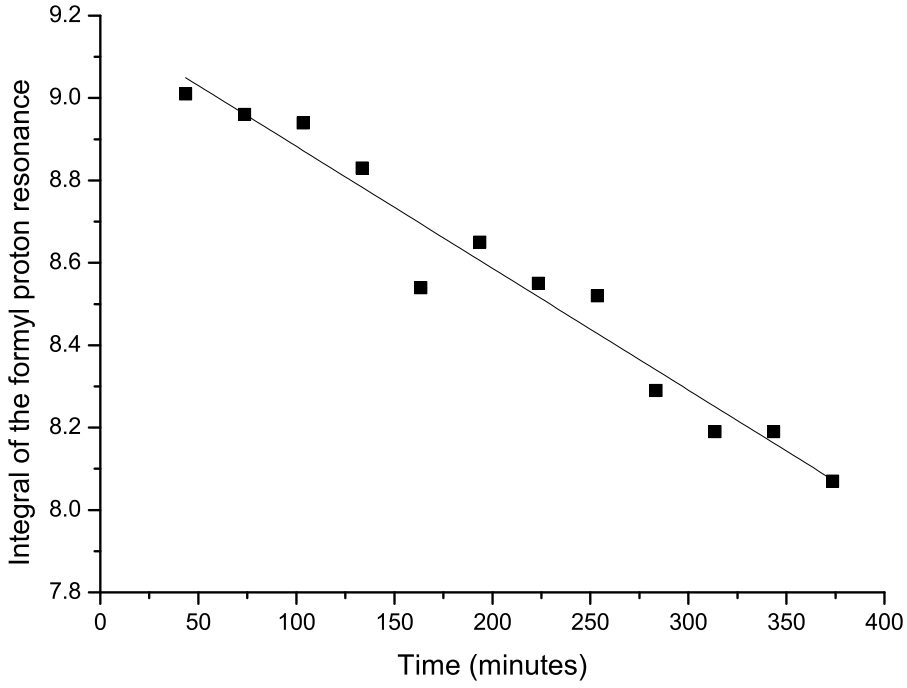


Figure 6.12 Formyl proton resonance with time in experiment PGKC5K-8

Table 6.2 Analysis of **23** kinetic experiments by Initial-Rate method

Experiment	[**23**] (mmol/L)	Initial rate (/min)	r^2
PGKC4K-1	50.04	-0.00203	0.928
PGKC4K-3	70.43	-0.00167	0.818
PGKC4K-5	10.19	-[a]	-
PGKC4K-6	29.65	-	-
PGKC4K-7	89.89	-	-
PGKC5K-1	21.31	-0.00224	0.848
PGKC5K-2	39.85	-0.00234	0.960
PGKC5K-3	59.31	-0.00279	0.925
PGKC5K-5	83.40	-0.00283	0.989
PGKC5K-6	107.5	-0.00290	0.982
PGKC5K-7	59.31[b]	-0.00321	0.984
PGKC5K-8	127.9	-0.00296	0.953

[a] An exponential decay curve could not be fitted to this data
[b] [Triethylamine] = 126.4 mmol/L

Kinetic studies analysed by Half-Life method

Experiment parameters:

- at = 4.1 seconds
- d1 = 0 seconds
- pw = pw60
- nt = 64
- acquisitions acquired at irregular intervals over a period of days
- continued until complete absence of formyl proton resonance observed

Analysis:

- integral of formyl proton resonance plotted against time
- exponential model applied (as visualised on the graph and summarised in subsequent table)

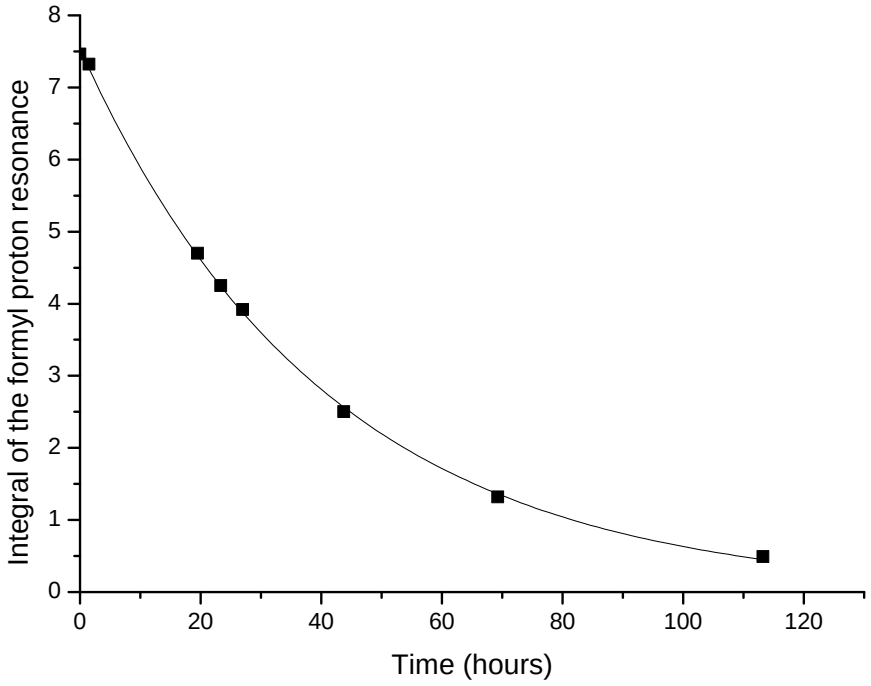


Figure 6.13 Formyl proton resonance with time in experiment PGKC4-4J

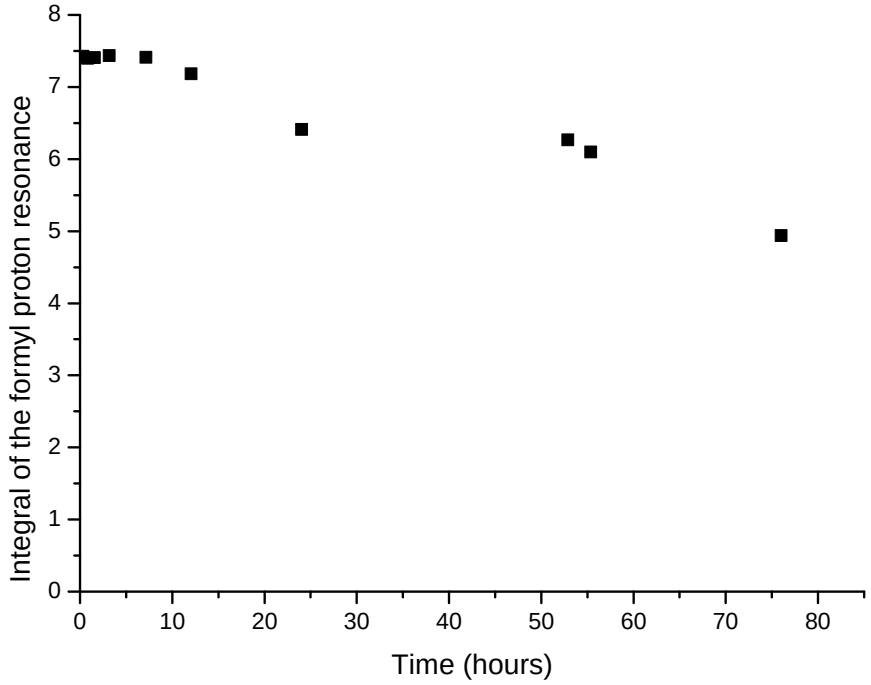


Figure 6.14 Formyl proton resonance with time in experiment PGKC4K-11

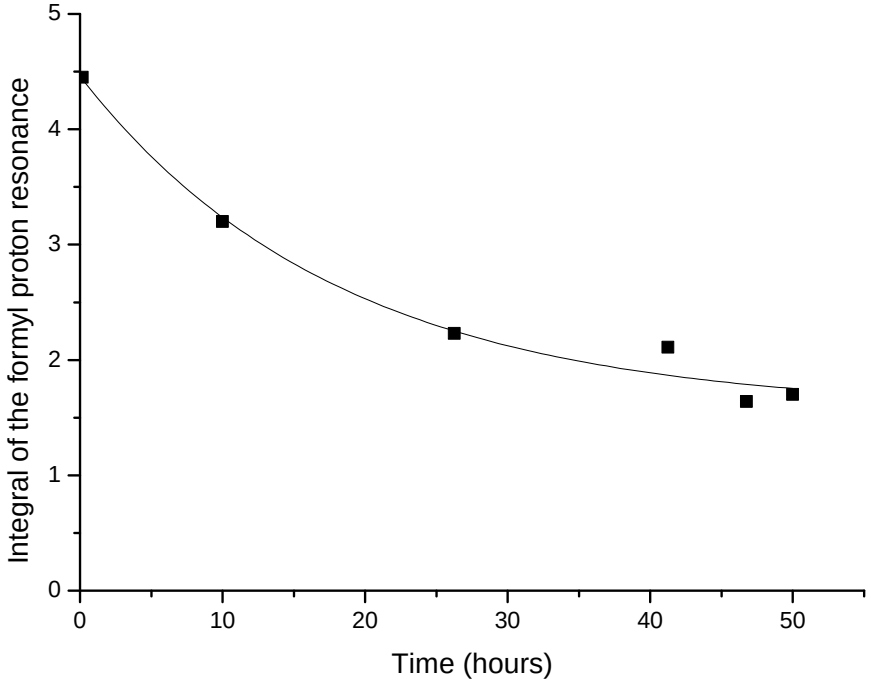


Figure 6.15 Formyl proton resonance with time in experiment PGKC5-3I

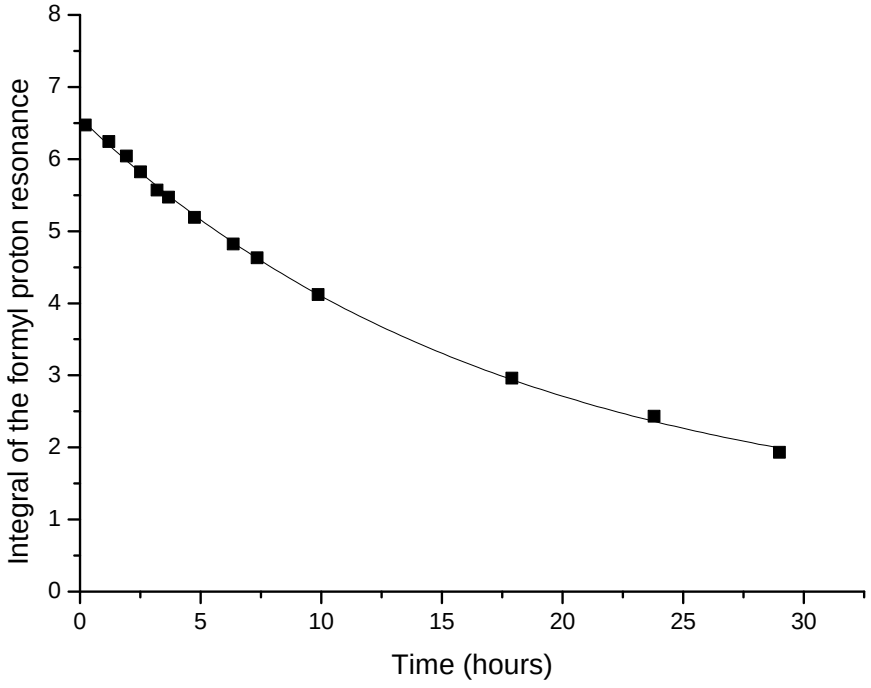


Figure 6.16 Formyl proton resonance with time in experiment PGKC5K-14

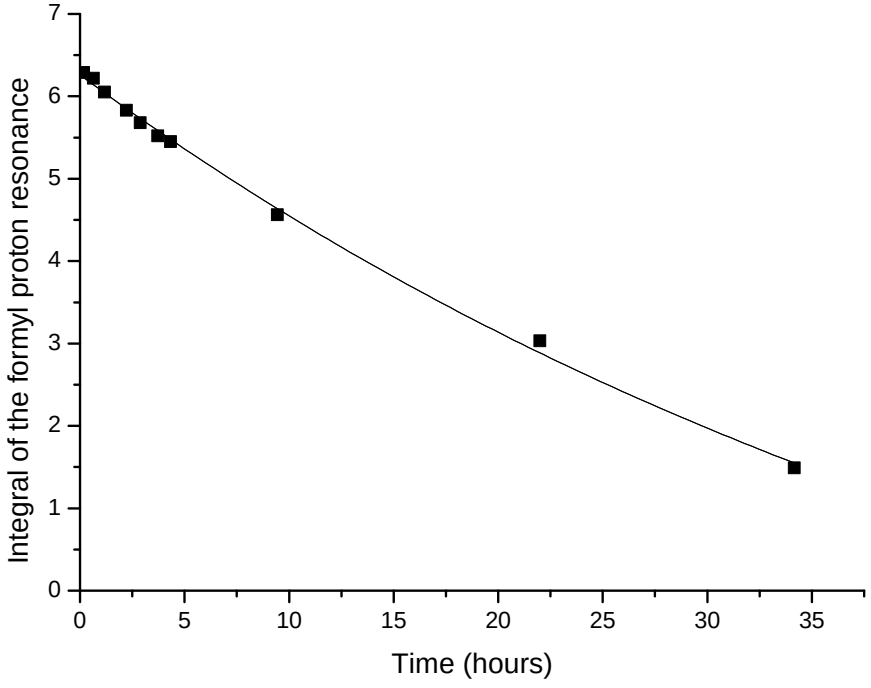


Figure 6.17 Formyl proton resonance with time in experiment PGKC5K-17

Table 6.3 Analysis of **23** kinetic experiments by Half-Life method

Experiment	[**23**] (mmol/L)	Exponential rate	r^2	Half-life (h)
PGKC4-4J	55.60	-0.0245	0.999	28.2
PGKC4K-11	75.99	-[a]	-	-
PGKC5-3I	55.60	-0.0550	0.976	12.6
PGKC5K-14	55.60	-0.0577	0.999	12.0
PGKC5K-17	55.60	-0.0193	0.997	36.0

[a]An exponential decay curve could not be fitted to this data

Variable-temperature studies

Setup:

- **23** (5.5 mg, 0.028 mmol) was dissolved in the nominated NMR solvent (0.55 mL)
- allowed to exchange for 5 hours prior to acquisitions

Experiment parameters:

- at = 3.4 seconds
- d1 = 0 seconds
- pw = pw60
- nt = 64
- acquisitions obtained at room temperature and -50 °C

Results:

- $CDCl_3$- no difference in spectra acquired at the different temperatures
- CD_3OD- no difference in spectra acquired at the different temperatures

6.2.2 Benzene-based models

Setup

Table 6.4 Composition of **28** kinetic experiments

Experiment	Solvent	**28**				Additive				
		Source	m (mg)	n (mmol)	[**28**][a] (mmol/L)	Identity	Volume (μL)	m (mg)	n[bc] (mmol)	[Additive][a] (mmol/L)
PGKC5K-11	CD_3OD	PGKC5-14H	6.0	0.0312	56.76					
PGKC5K-15	D_2O	PGKC5-17F	6.0	0.0312	56.76					
PGKC5K-16	D_2O	PGKC5-17E	6.0	0.0312	56.76					
PGKC5K-18	D_2O	PGKC5-17F	6.0	0.0312	56.76					
PGKC5K-19	D_2O	PGKC5-17F	6.0	0.0312	56.76	NEt_3	12.4		0.0889	161.6
PGKC5K-20	D_2O	PGKC5-17F	6.0	0.0312	56.76	CD_3COOD	5.4		0.0884	160.7
PGKC5K-21	D_2O	PGKC5-17F	12.0	0.0624	113.5					
PGKC5K-22	D_2O	PGKC5-17F	18.0	0.0937	170.3					
PGKC5K-23	D_2O	PGKC5-17F	6.0	0.0312	56.76	NEt_3	16.5		0.1183	215.1
PGKC5K-24	D_2O	PGKC5-17F	6.0	0.0312	56.76	NEt_3	8.3		0.0595	108.2
PGKC5K-25	D_2O	PGKC5-17F	10.0	0.0520	94.59					
PGKC5K-26	D_2O	PGKC5-17F	8.0	0.0416	75.67					
PGKC5K-27	D_2O	PGKC5-17F	4.0	0.0208	37.84					
PGKC5K-28	D_2O	PGKC5-17F	6.0	0.0312	56.76	NEt_3	220[d]		0.0312	56.64
PGKC5K-33	D_2O	PGKC5-17F	6.0	0.0312	56.76	KOH		6.6	0.1176	213.9
PGKC5K-34	D_2O	PGKC5-17F	6.0	0.0312	56.76	DMAP		7.2	0.589	107.2

[a]Total volume of solvent = 0.55 mL
[b]Density: triethylamine = 0.7255 g/mL; CD_3COOD = 1.049 g/mL
[c]Mr: triethylamine = 101.2 g/mol; CD_3COOD = 64.08 g/mol; KOH = 56.11 g/mol; DMAP = 122.17 g/mol
[d][Standard solution] = 141.6 mmol/L

Kinetic studies analysed by Initial-Rate method

Experiment parameters:

- at = 10 seconds
- d1 = 10 seconds
- pw = pw90
- nt = 12
- pad = 1560 seconds between acquisitions
- 13 acquisitions obtained

Analysis:

- integral of formyl proton resonance plotted against time
- linear model applied (as visualised on the graph and summarised in subsequent table)

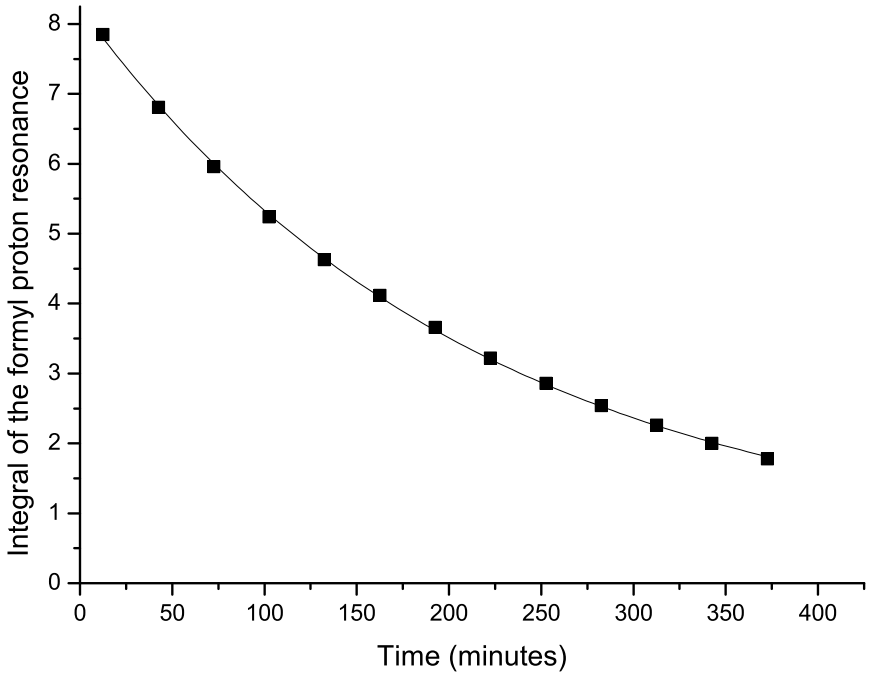


Figure 6.18 Formyl proton resonance with time in experiment PGKC5K-18

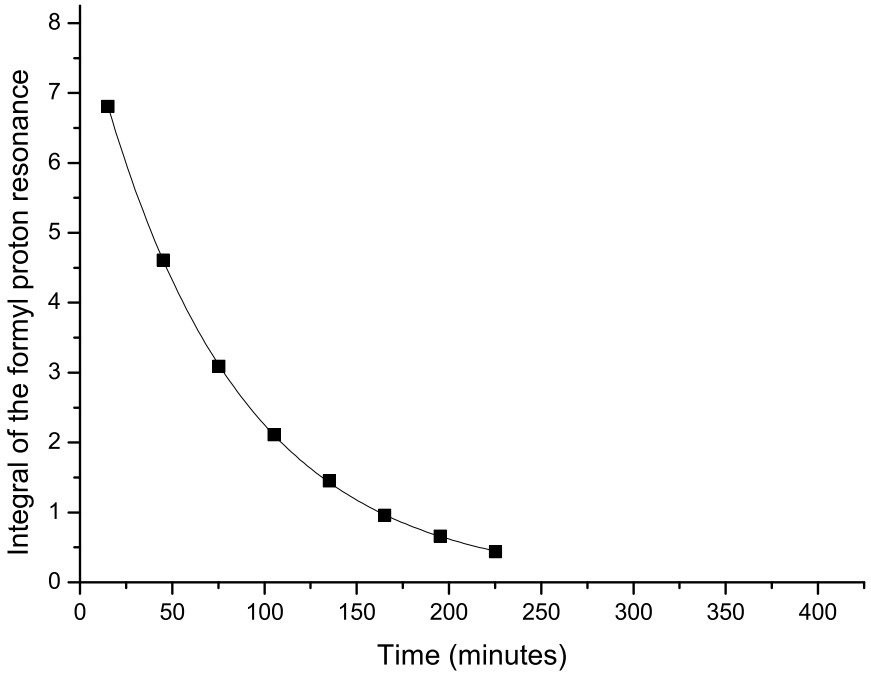


Figure 6.19 Formyl proton resonance with time in experiment PGKC5K-19

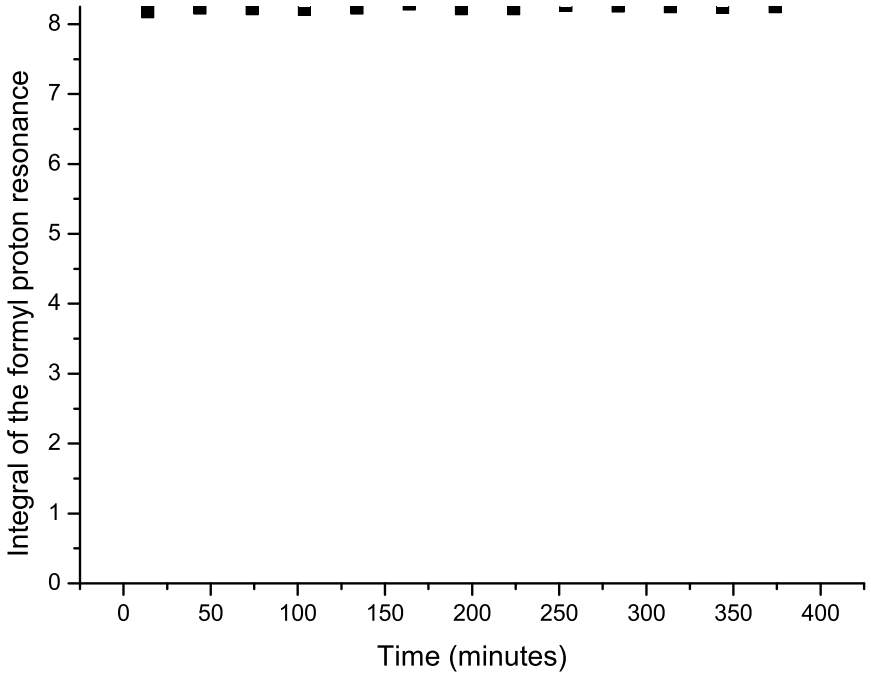


Figure 6.20 Formyl proton resonance with time in experiment PGKC5K-20

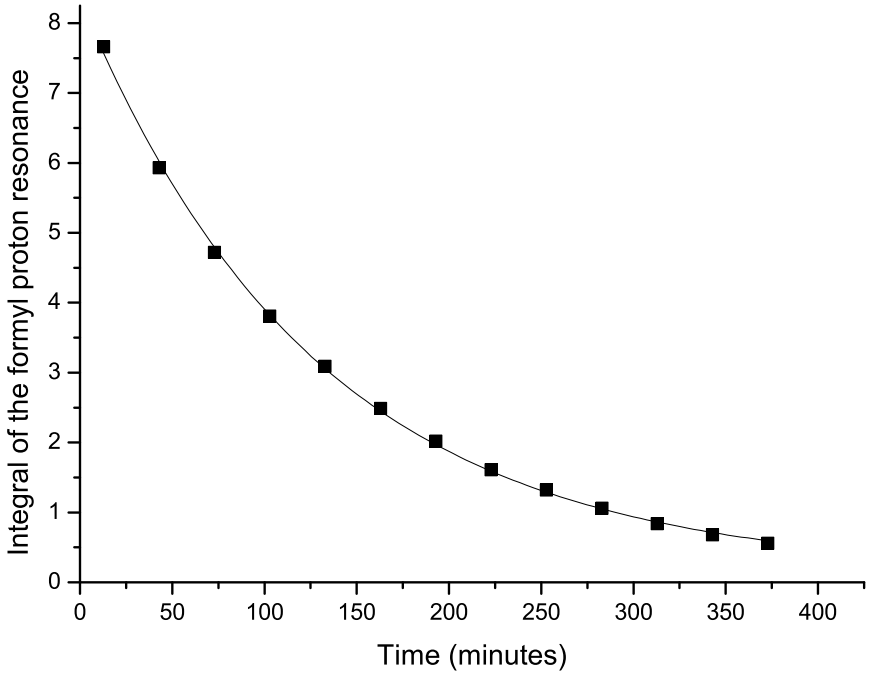


Figure 6.21 Formyl proton resonance with time in experiment PGKC5K-21

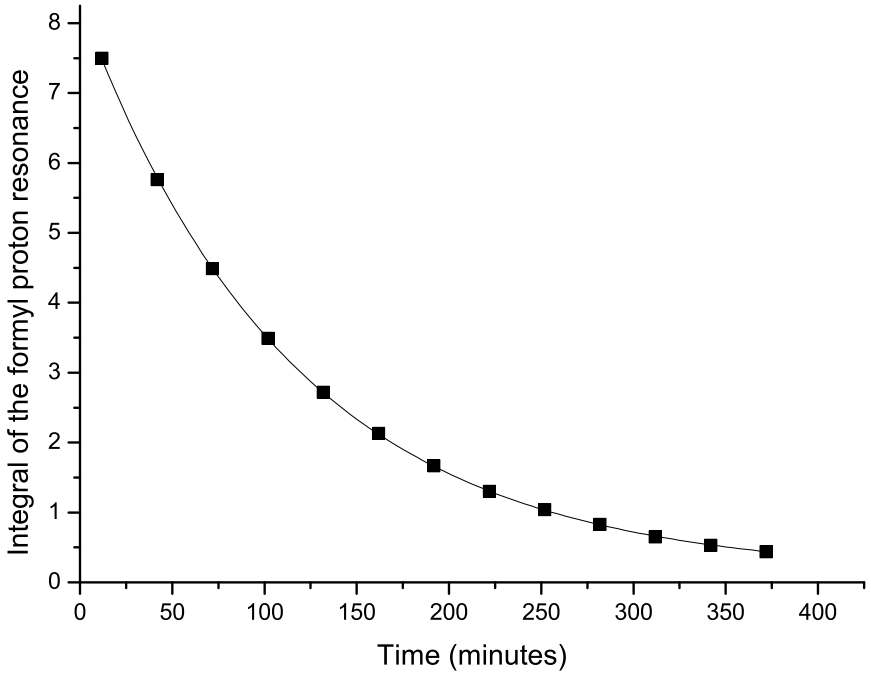


Figure 6.22 Formyl proton resonance with time in experiment PGKC5K-22

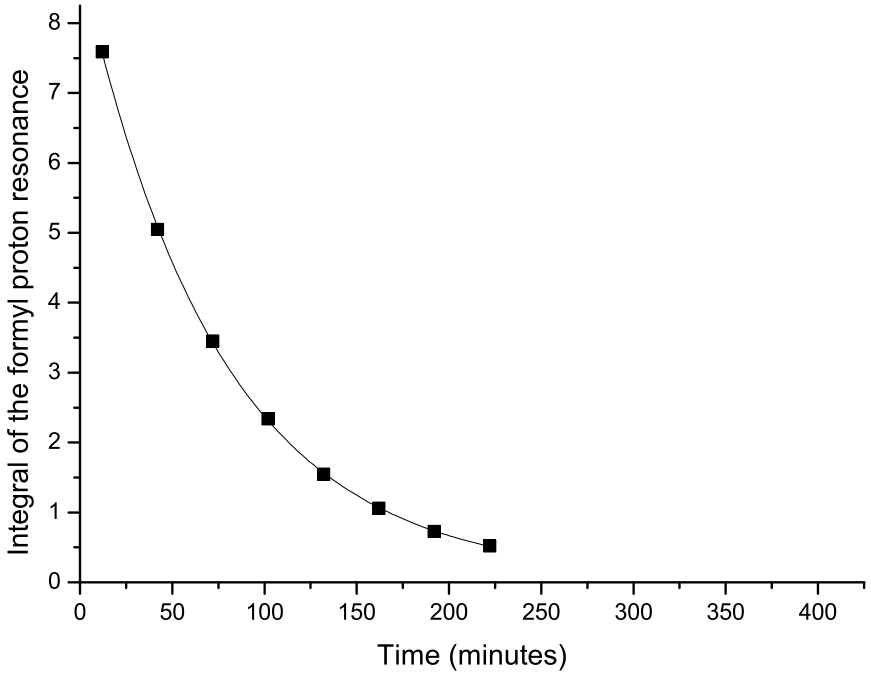


Figure 6.23 Formyl proton resonance with time in experiment PGKC5K-23

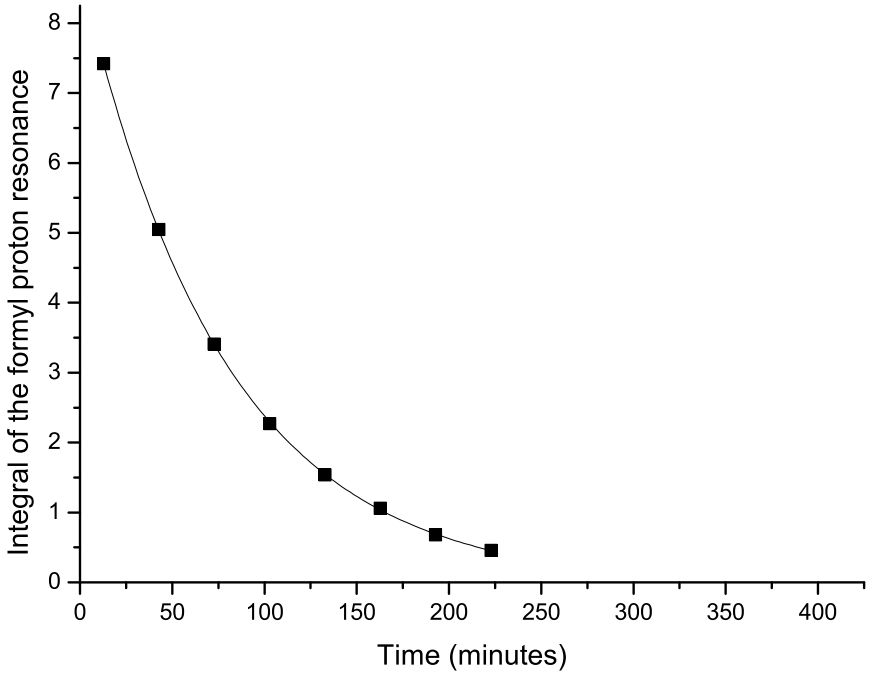


Figure 6.24 Formyl proton resonance with time in experiment PGKC5K-24

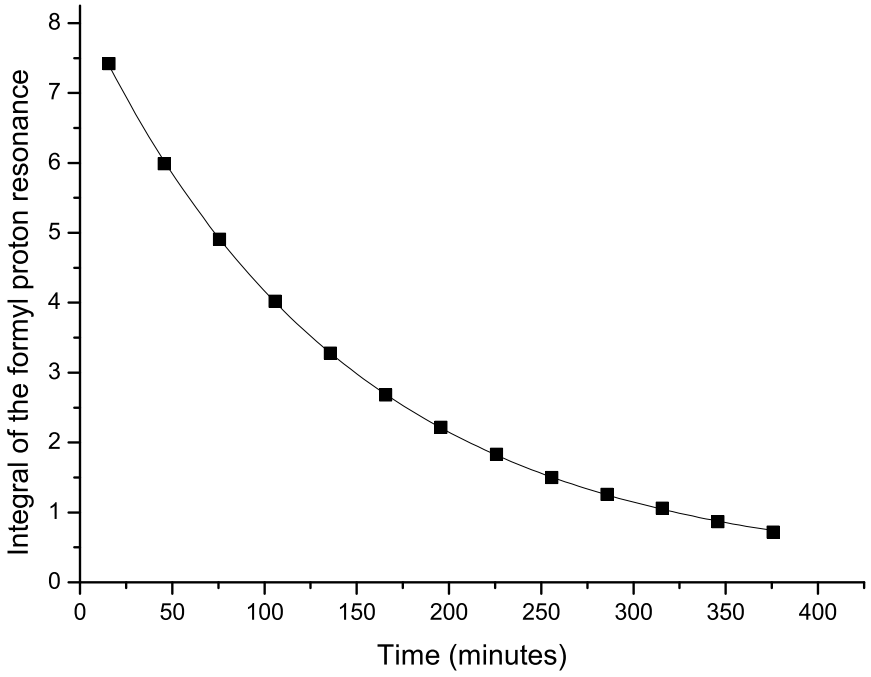


Figure 6.25 Formyl proton resonance with time in experiment PGKC5K-25

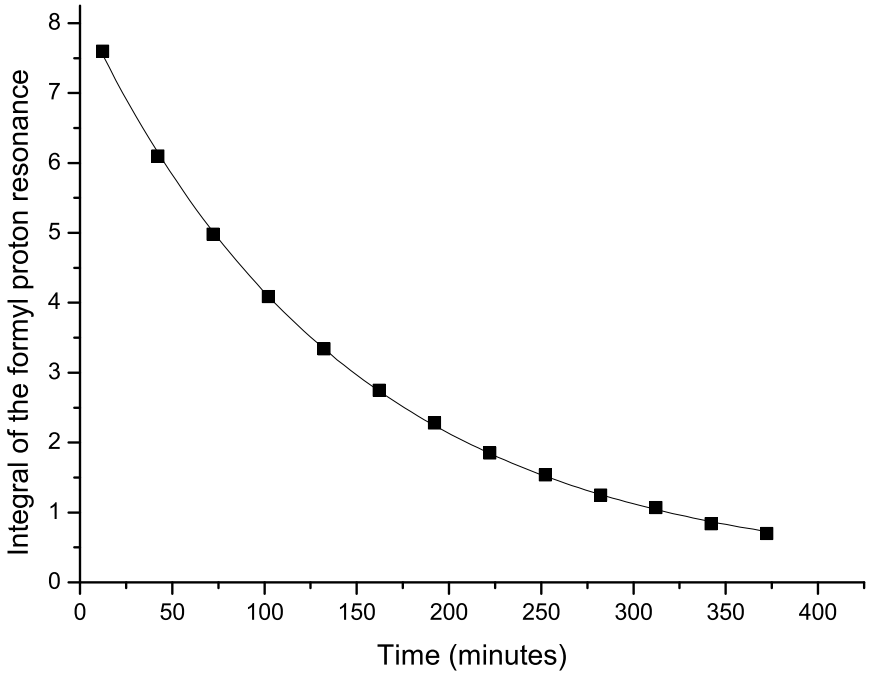


Figure 6.26 Formyl proton resonance with time in experiment PGKC5K-26

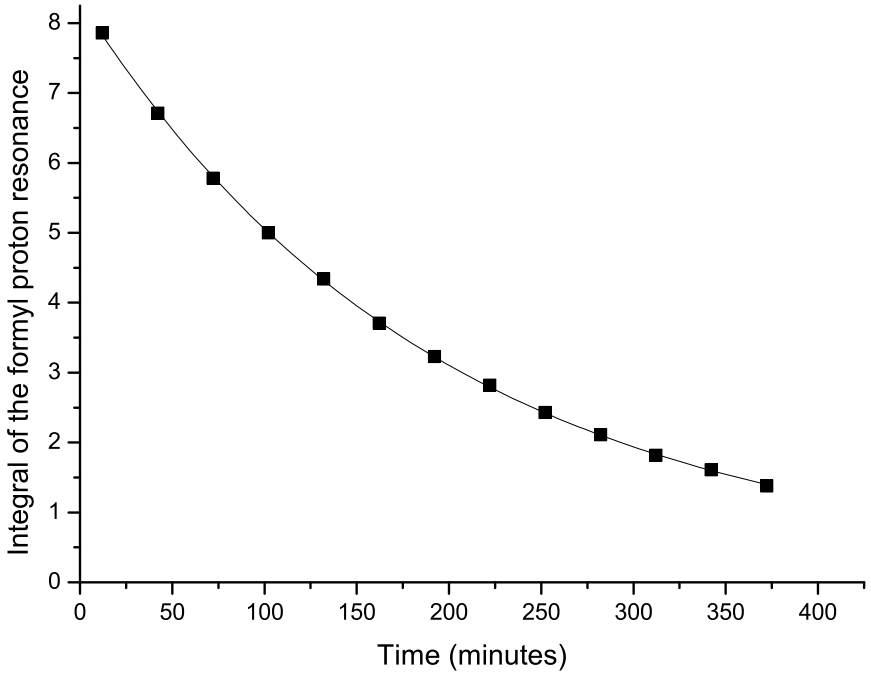


Figure 6.27 Formyl proton resonance with time in experiment PGKC5K-27

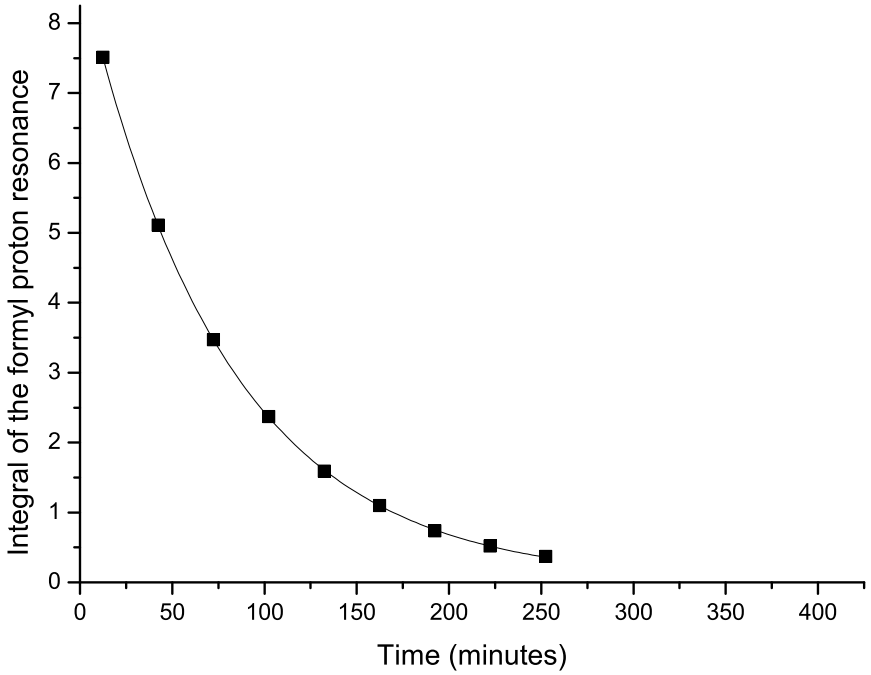


Figure 6.28 Formyl proton resonance with time in experiment PGKC5K-28

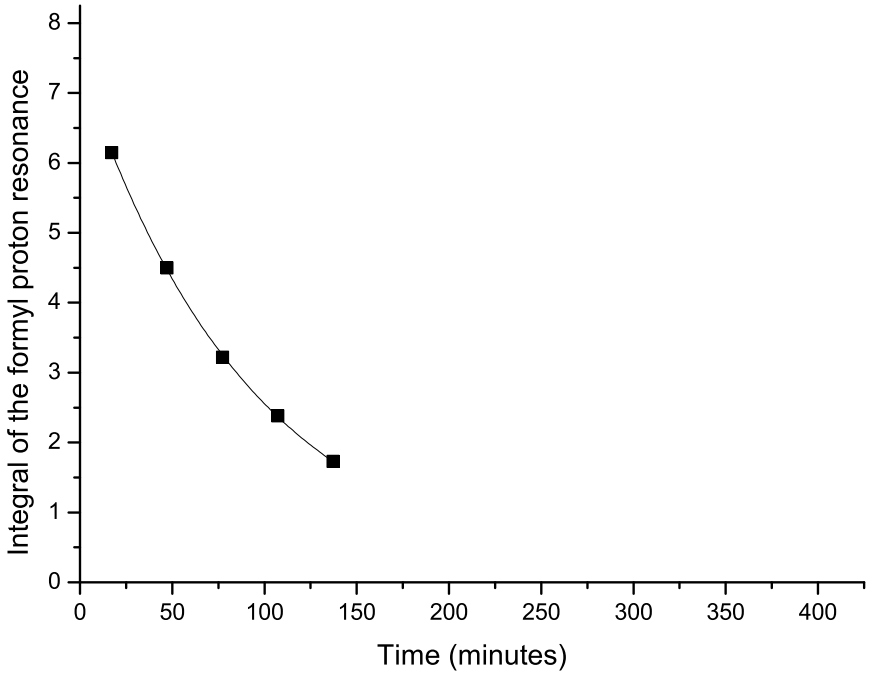


Figure 6.29 Formyl proton resonance with time in experiment PGKC5K-33

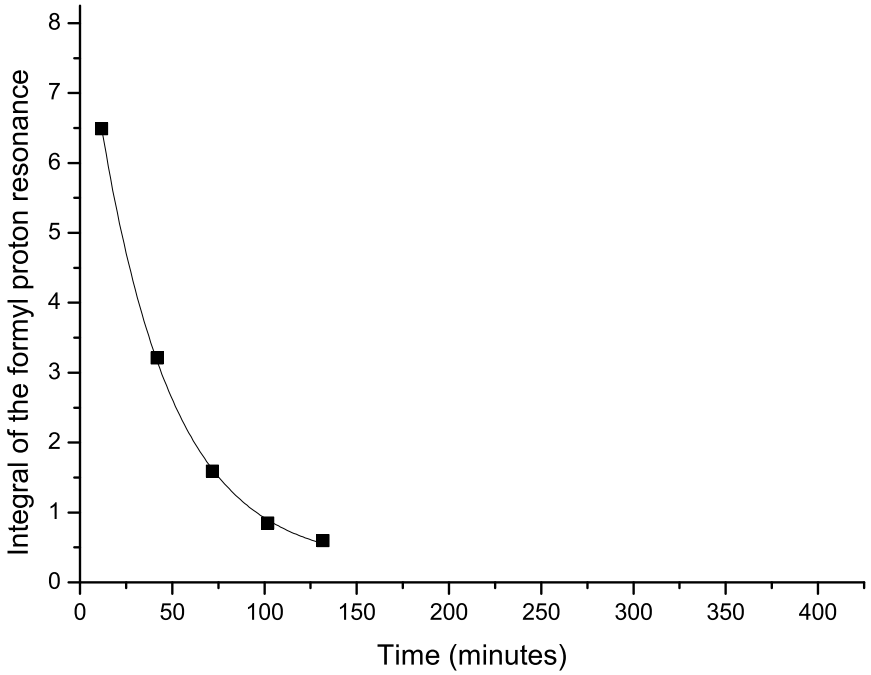


Figure 6.30 Formyl proton resonance with time in experiment PGKC5K-34

Table 6.5 Analysis of **28** kinetic experiments by Initial-Rate method

Experiment	[**23**] (mmol/L)	Additive	[Additive] (mmol/L)	Initial rate (/min)	r^2
PGKC5K-18	56.76			-0.0047	0.999
PGKC5K-19	56.76	NEt_3	161.6	-0.0131	0.999
PGKC5K-20	56.76	CD_3COOD	160.7	-[a]	-
PGKC5K-21	113.5			-0.0078	0.999
PGKC5K-22	170.3			-0.0087	0.999
PGKC5K-23	56.76	NEt_3	215.1	-0.0134	0.999
PGKC5K-24	56.76	NEt_3	108.2	-0.0129	0.999
PGKC5K-25	94.59			-0.0070	0.999
PGKC5K-26	75.67			-0.0070	0.999
PGKC5K-27	37.84			-0.0051	0.999
PGKC5K-28	56.76	NEt_3	56.64	-0.0130	0.999
PGKC5K-33	56.76	KOH	213.9	-0.0108	0.999
PGKC5K-34	56.76	DMAP	107.2	-0.0254	0.999

[a] An exponential decay curve could not be fitted to this data

Kinetic studies analysed by Half-Life method

Experiment parameters:

- at = 4.1 seconds
- d1 = 0 seconds
- pw = pw60
- nt = 64
- acquisitions acquired at irregular intervals over a period of days
- continued until complete absence of formyl proton resonance observed

Analysis:

- integral of formyl proton resonance plotted against time
- exponential model applied (as visualised on the graph and summarised in subsequent table)

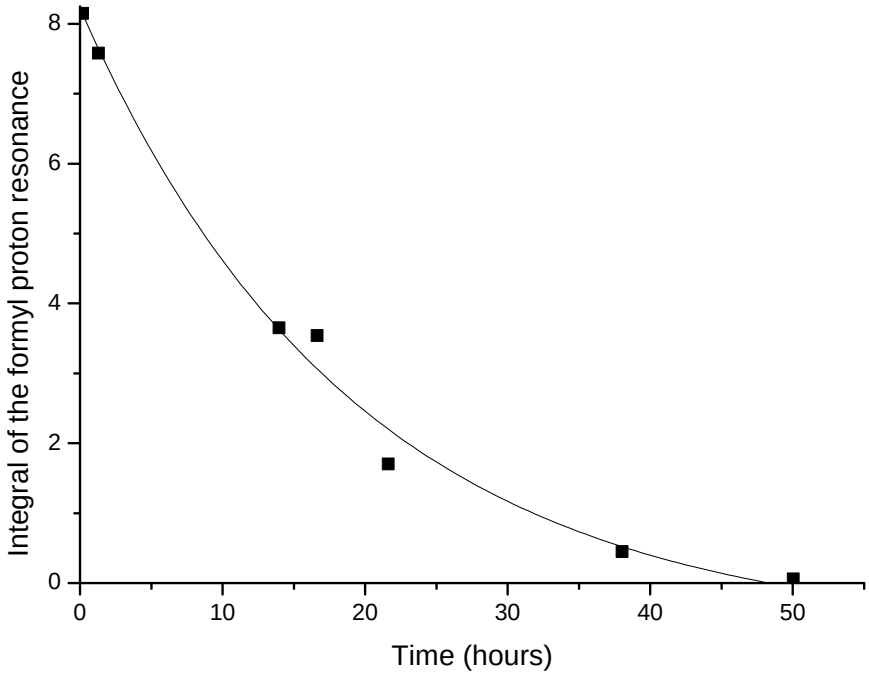


Figure 6.31 Formyl proton resonance with time in experiment PGKC5K-11

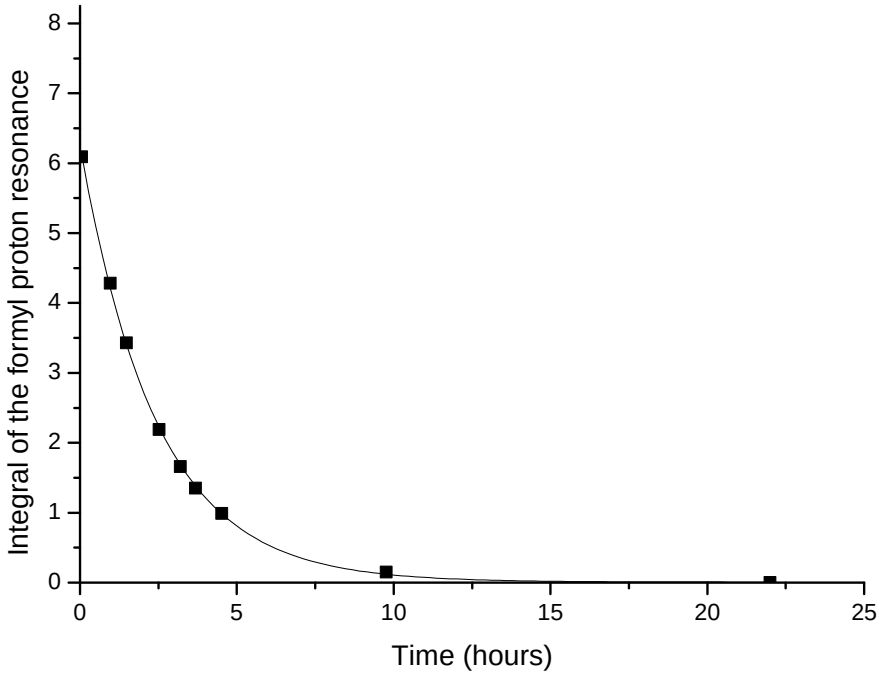


Figure 6.32 Formyl proton resonance with time in experiment PGKC5K-15

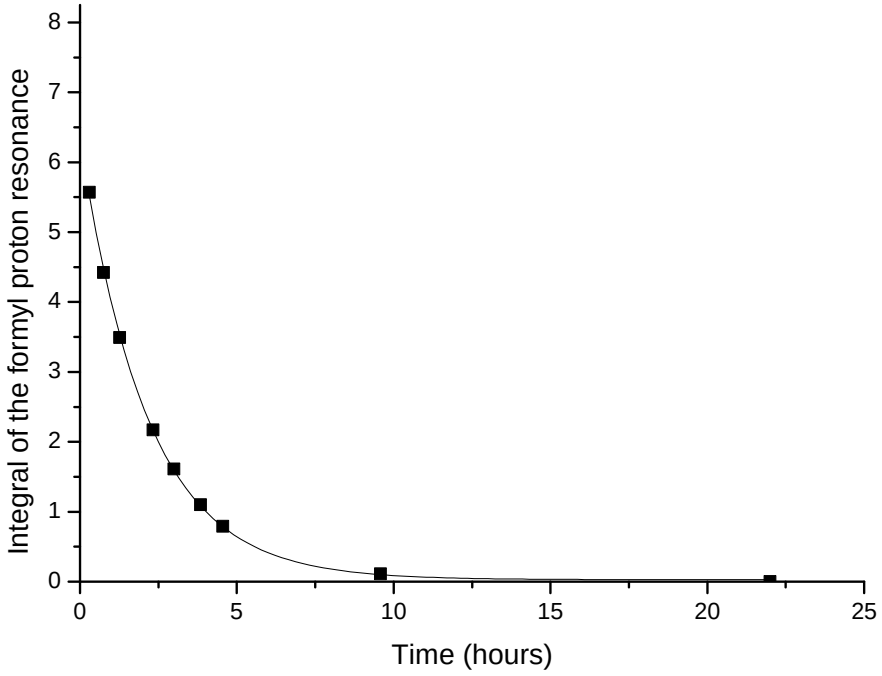


Figure 6.33 Formyl proton resonance with time in experiment PGKC5K-16

Table 6.6 Analysis of **28** kinetic experiments by Half-Life method

Experiment	[**28**] (mmol/L)	Exponential rate	r^2	Half-life (h)
PGKC5K-11	56.76	-0.0515	0.988	13.5
PGKC5K-15	56.76	-0.4107	0.999	1.7
PGKC5K-16	56.76	-0.0550	0.999	1.5

6.2.3 Quinazolinium-based models

Setup

Table 6.7 Composition of **41** kinetic experiments

Experiment	Solvent	**41**				Additive				
		Source	m (mg)	n (mmol)	[**41**][a] (mmol/L)	Identity	Volume (μL)	[Standard solution] (mmol/L)	n[b] (μmol)	[Additive][a] (mmol/L)
PGKC5K-36	D_2O	PGKC6-19A	6.3	0.0300	54.53					
PGKC5K-38	D_2O	PGKC6-28B	6.0	0.0286	51.93					
PGKC5K-49	D_2O	PGKC6-19A	1.0	0.0048	8.66					
PGKC5K-50	D_2O	PGKC6-19A	2.1	0.0100	18.18					
PGKC5K-51	D_2O	PGKC6-19A	3.0	0.0143	25.97					
PGKC5K-52	D_2O	PGKC6-19A	4.0	0.0190	34.62					
PGKC5K-54	D_2O	PGKC6-19A	2.0	0.0095	17.31	NEt_3	80.0	neat	573.5	1043
PGKC5K-59	D_2O	PGKC6-19A	2.0	0.0095	17.31	CD_3COOD	0.9	neat	14.73	26.79
PGKC5K-61	D_2O	PGKC6-19A	5.1	0.0243	44.14					
PGKC5K-62	D_2O	PGKC6-19A	2.0	0.0095	17.31	NEt_3	4.0	58.03	0.2321	0.4220
PGKC5K-63	D_2O	PGKC6-19A	2.0	0.0095	17.31	NEt_3	2.0	58.03	0.1161	0.2110
PGKC5K-64	D_2O	PGKC6-19A	2.0	0.0095	17.31	NEt_3	6.0	58.03	0.3482	0.6331
PGKC5K-65	D_2O	PGKC6-19A	2.0	0.0095	17.31	NEt_3	8.0	58.03	0.4642	0.8441
PGKC5K-66	D_2O	PGKC6-19A	2.0	0.0095	17.31	NEt_3	10.0	58.03	0.5803	1.0551
PGKC7-K-1	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	9.0	6.06	0.0545	0.0992
PGKC7-K-5	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	45.0	6.06	0.2727	0.4958
PGKC7-K-10	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	91.0	6.06	0.5515	1.0027
PGKC7-K-11	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	23.0	6.06	0.1394	0.2534
PGKC7-K-12	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	5.0	6.06	0.0303	0.0551
PGKC7-K-13	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	0.9	6.06	0.0055	0.0100
PGKC7-K-14	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	2.3	6.06	0.0138	0.0250
PGKC7-K-15	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	6.8	6.06	0.0413	0.0751
PGKC7-K-16	D_2O	PGKC6-37A	2.0	0.0095	17.31	NEt_3	68.2	6.06	0.4133	0.7514

[a]Total volume of solvent = 0.55 mL

[b]Density: triethylamine = 0.7255 g/mL, CD_3COOD = 1.049 g/mL; Mr: triethylamine = 101.2 g/mol, CD_3COOD = 64.08 g/mol

Kinetic studies analysed by Half-Life method

Experiment parameters:

- at = 10 seconds
- d1 = 10 seconds
- pw = pw90
- nt = 12
- pad = 0 seconds between acquisitions
- 13 acquisitions obtained

Analysis:

- integral of amidine proton resonance plotted against time
- exponential model applied (as visualised on the graph and summarised in subsequent table)

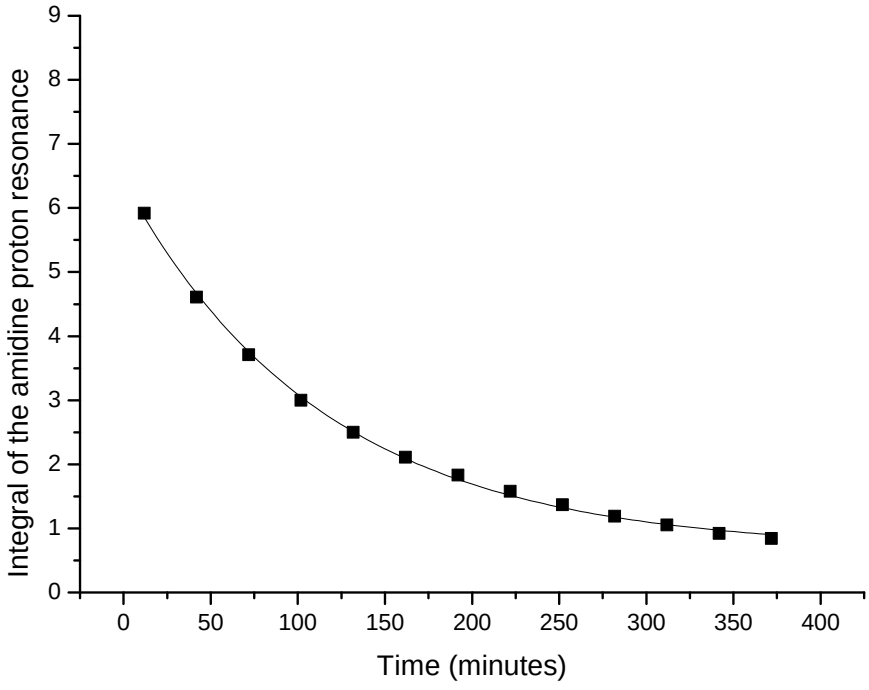


Figure 6.34 Amidine proton resonance with time in experiment PGKC5K-36

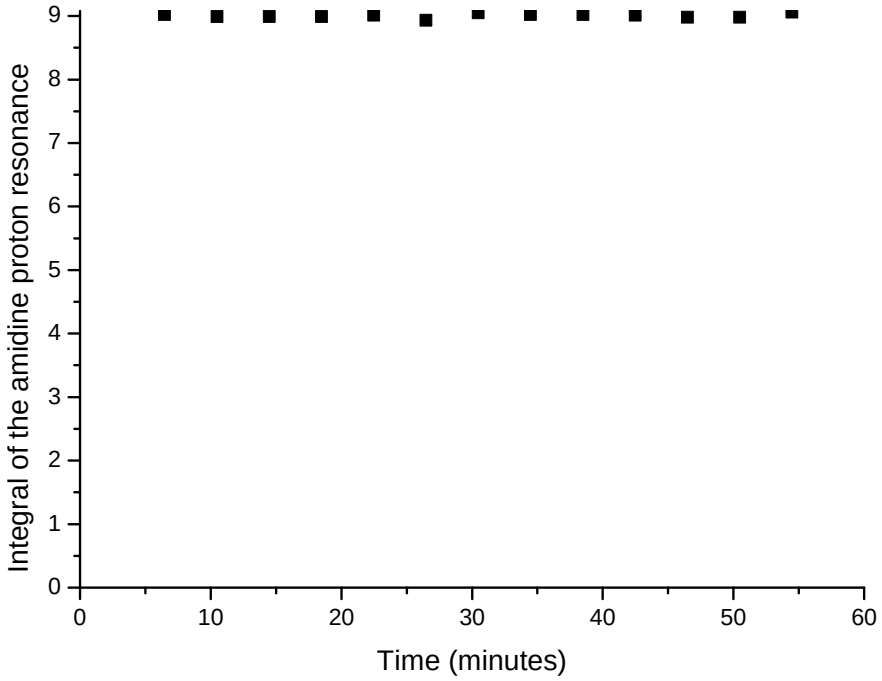


Figure 6.35 Amidine proton resonance with time in experiment PGKC5K-38

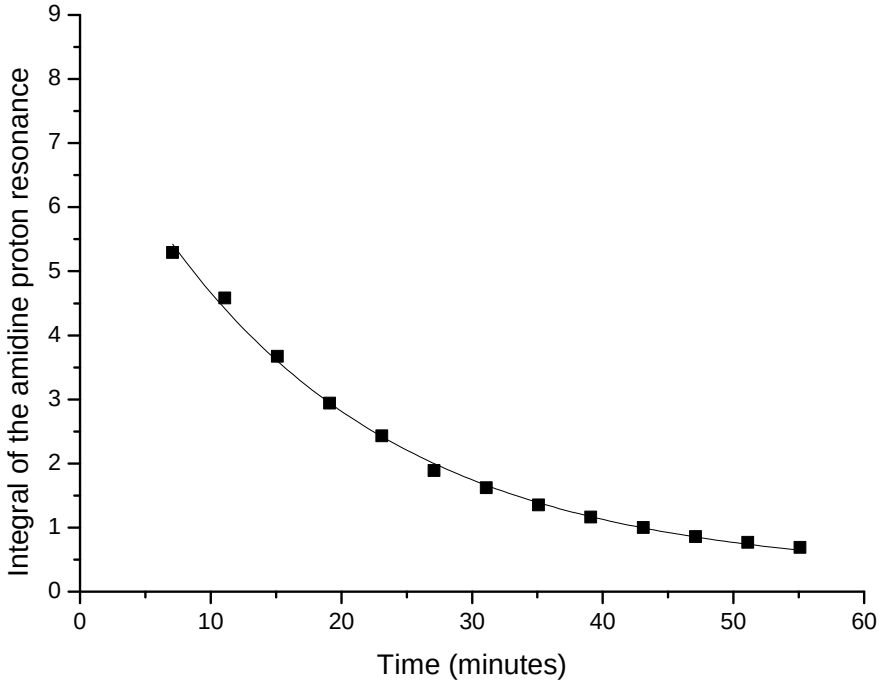


Figure 6.36 Amidine proton resonance with time in experiment PGKC5K-49

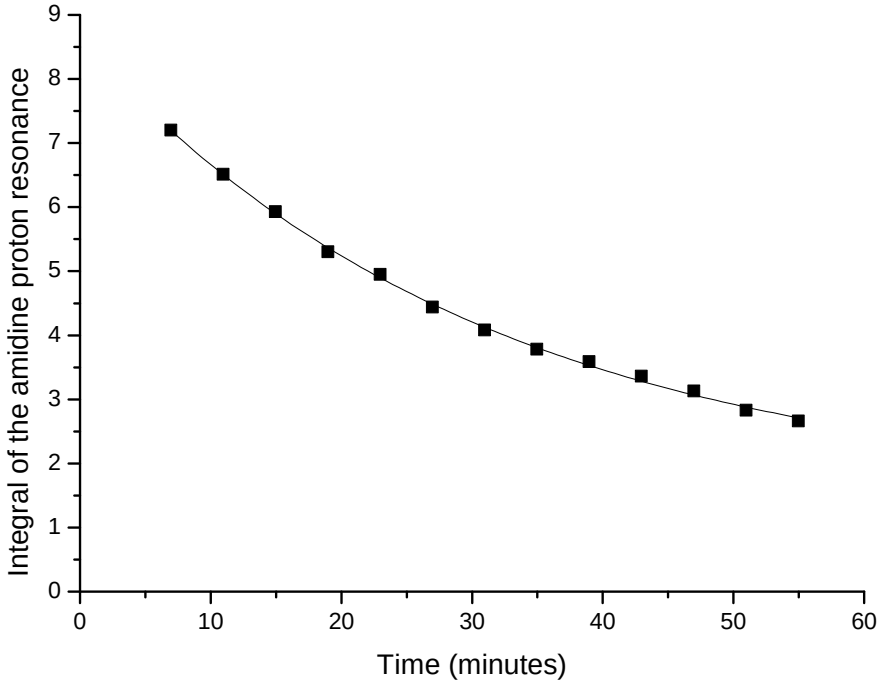


Figure 6.37 Amidine proton resonance with time in experiment PGKC5K-50

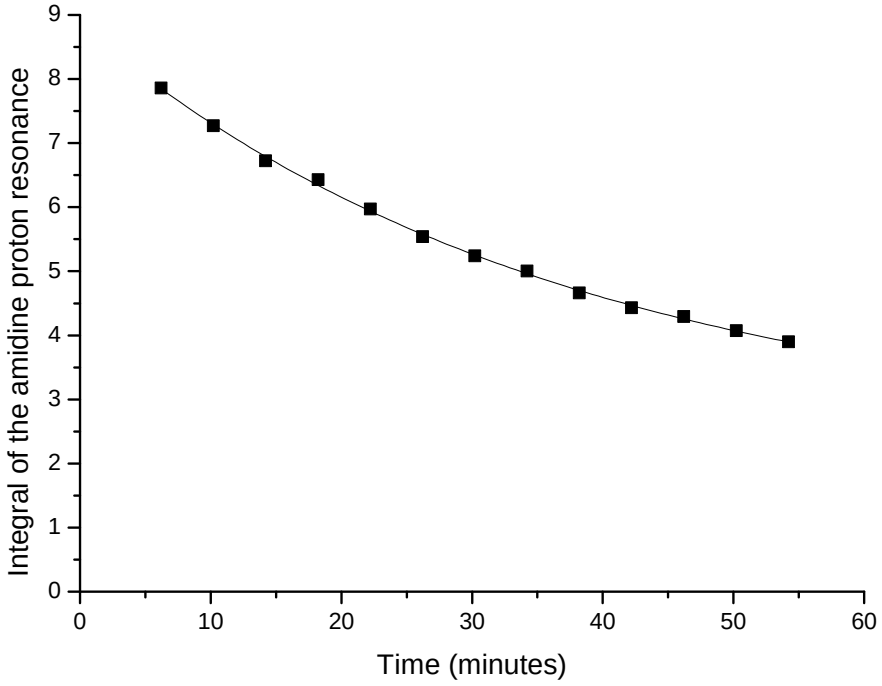


Figure 6.38 Amidine proton resonance with time in experiment PGKC5K-51

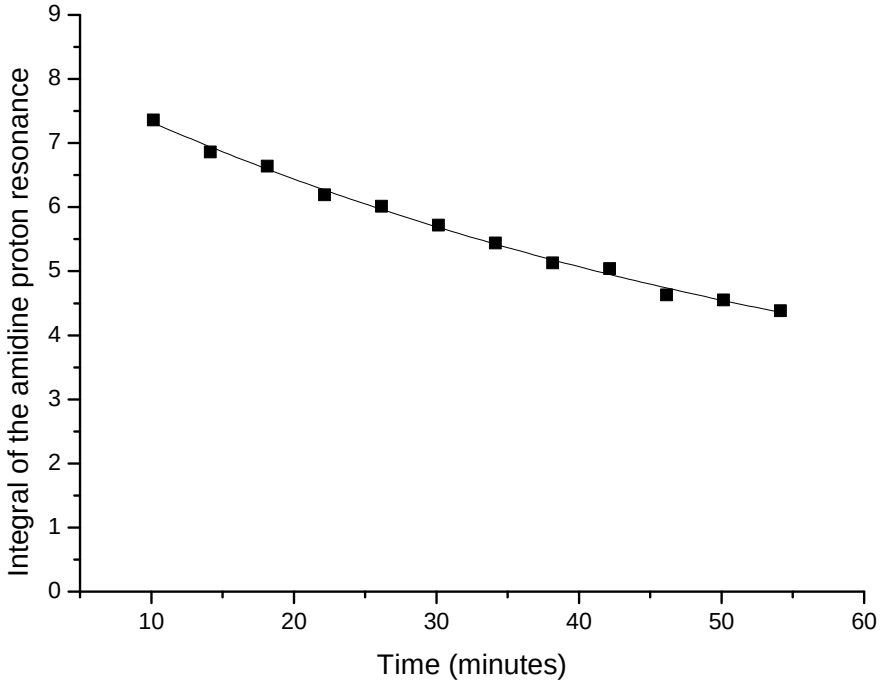


Figure 6.39 Amidine proton resonance with time in experiment PGKC5K-52

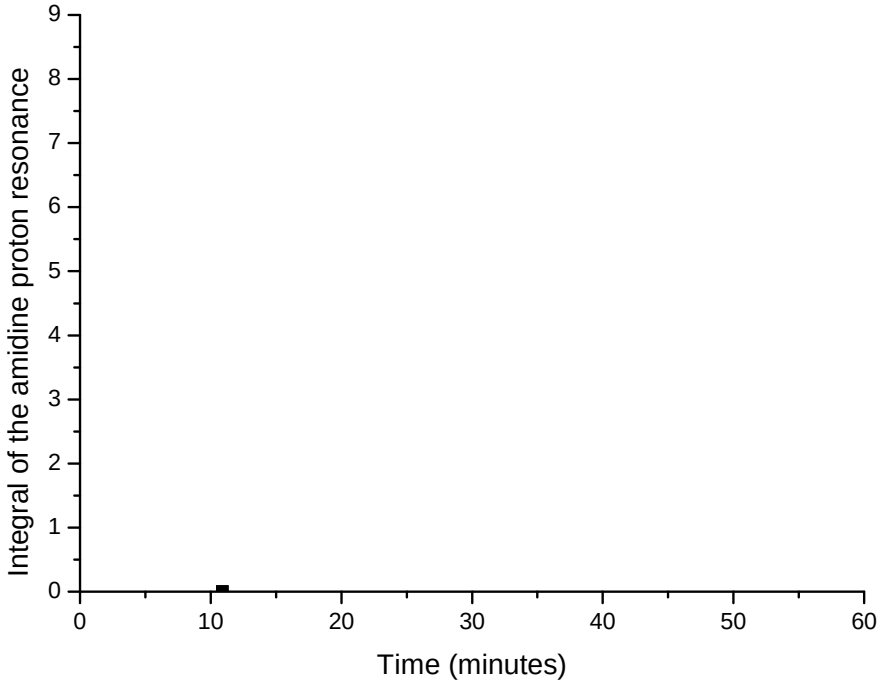


Figure 6.40 Amidine proton resonance with time in experiment PGKC5K-54

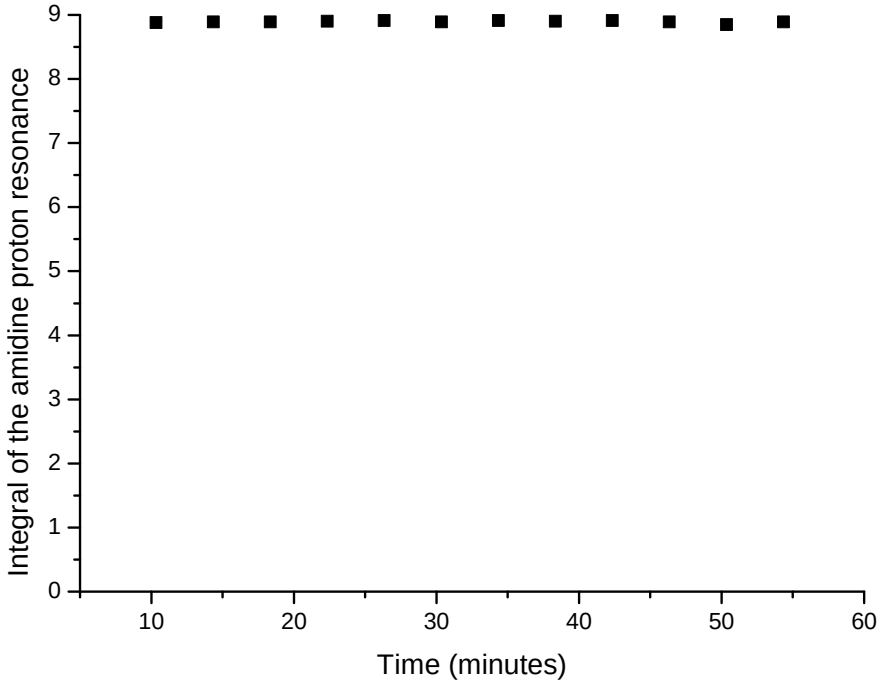


Figure 6.41 Amidine proton resonance with time in experiment PGKC5K-59

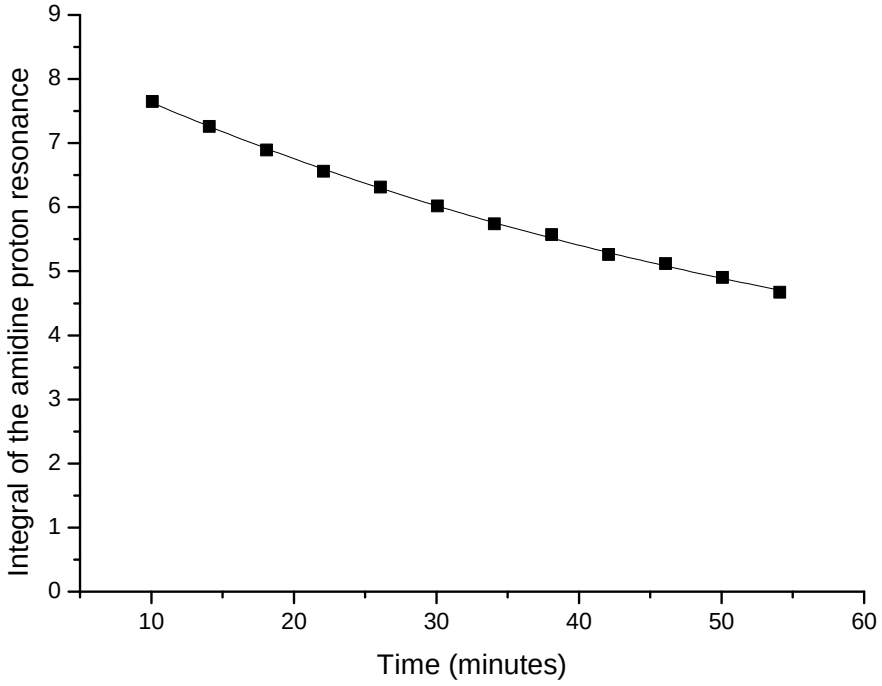


Figure 6.42 Amidine proton resonance with time in experiment PGKC5K-61

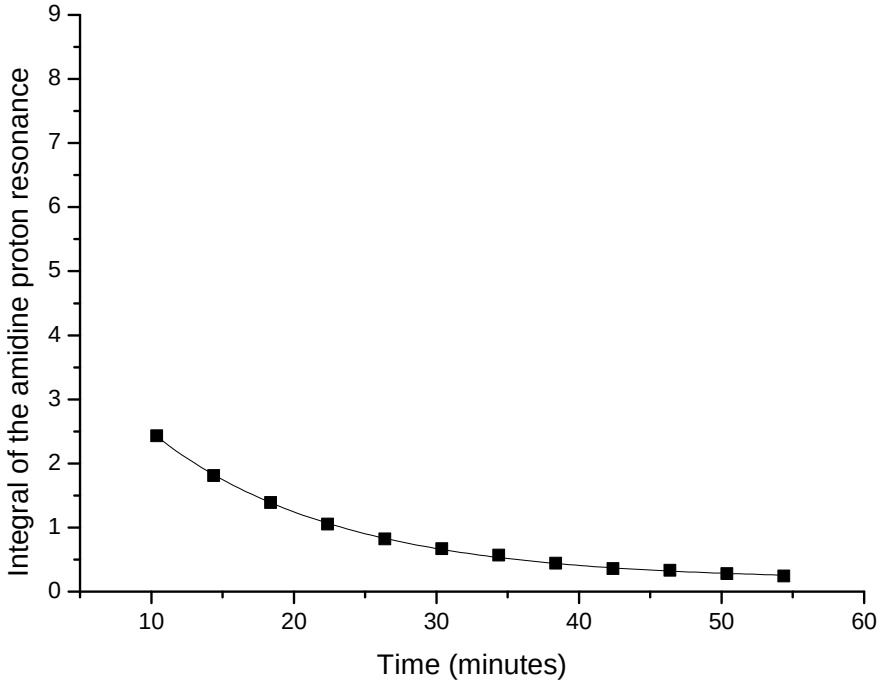


Figure 6.43 Amidine proton resonance with time in experiment PGKC5K-62

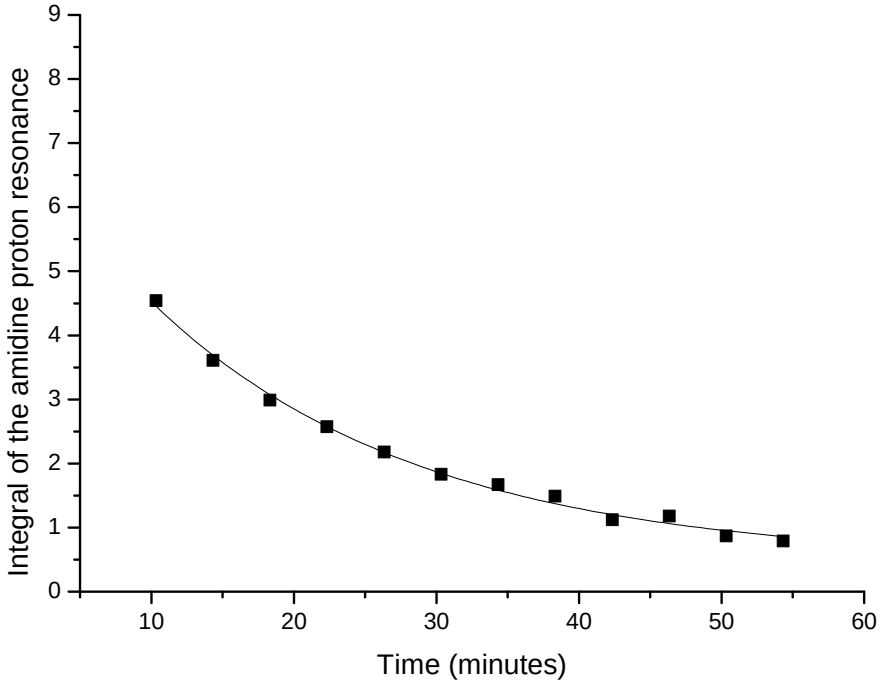


Figure 6.44 Amidine proton resonance with time in experiment PGKC5K-63

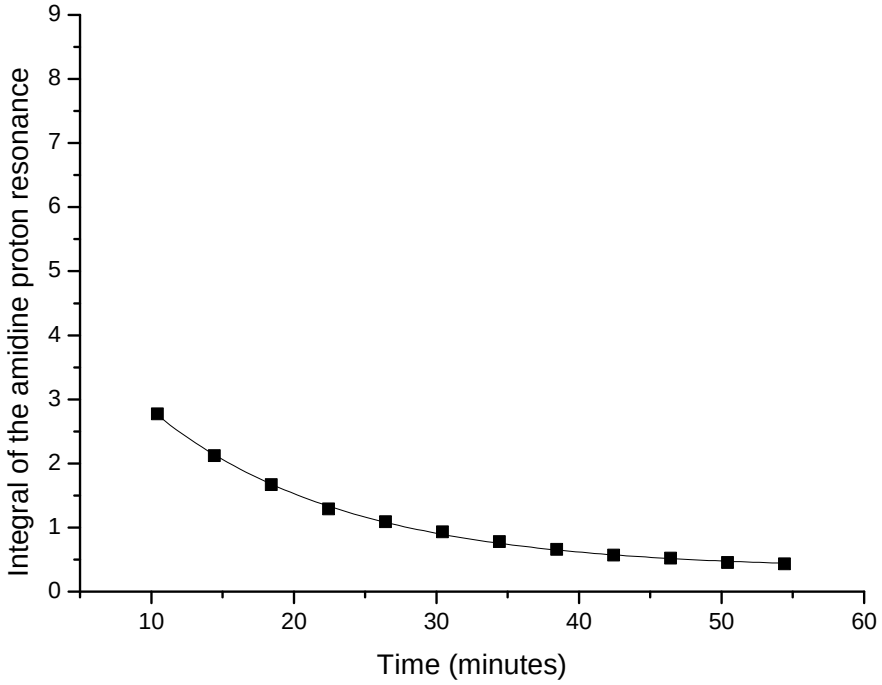


Figure 6.45 Amidine proton resonance with time in experiment PGKC5K-64

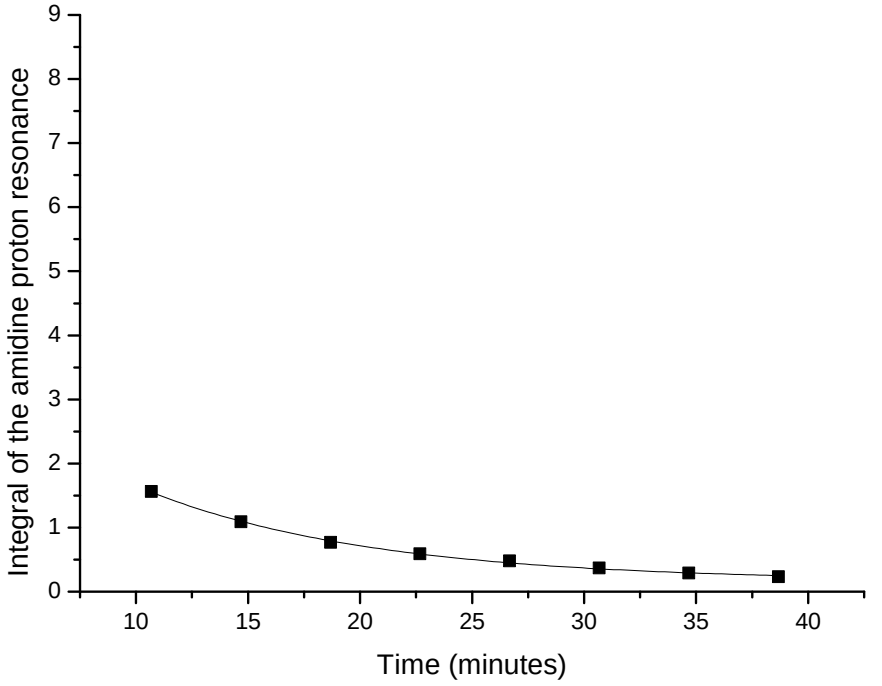


Figure 6.46 Amidine proton resonance with time in experiment PGKC5K-65

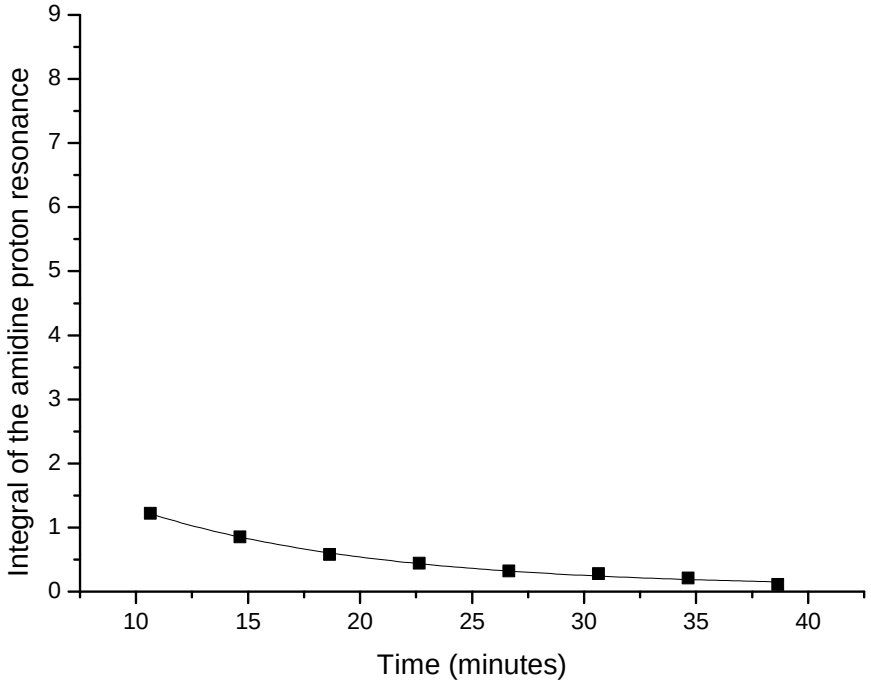


Figure 6.47 Amidine proton resonance with time in experiment PGKC5K-66

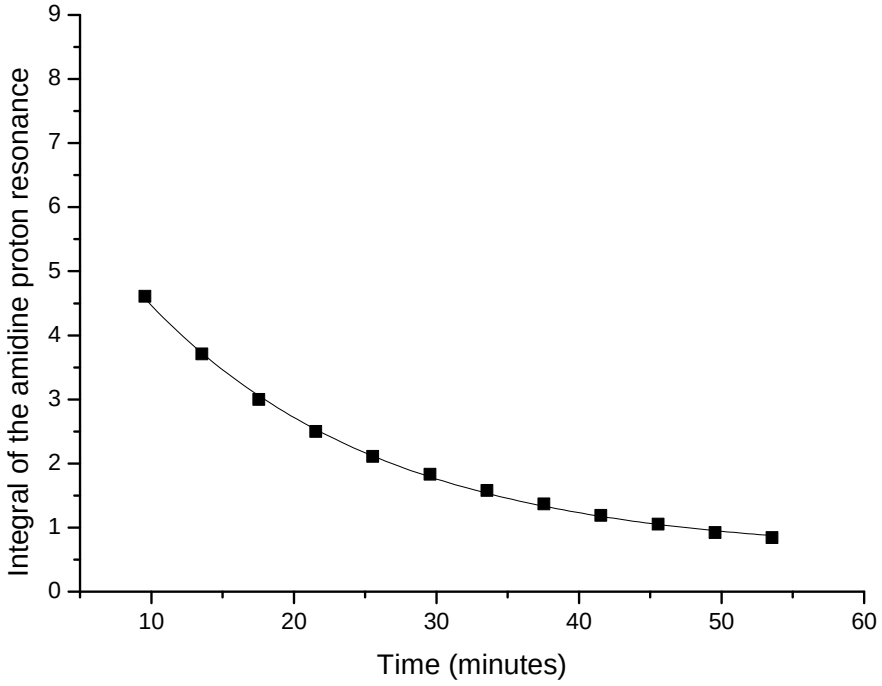


Figure 6.48 Amidine proton resonance with time in experiment PGKC7-K-1

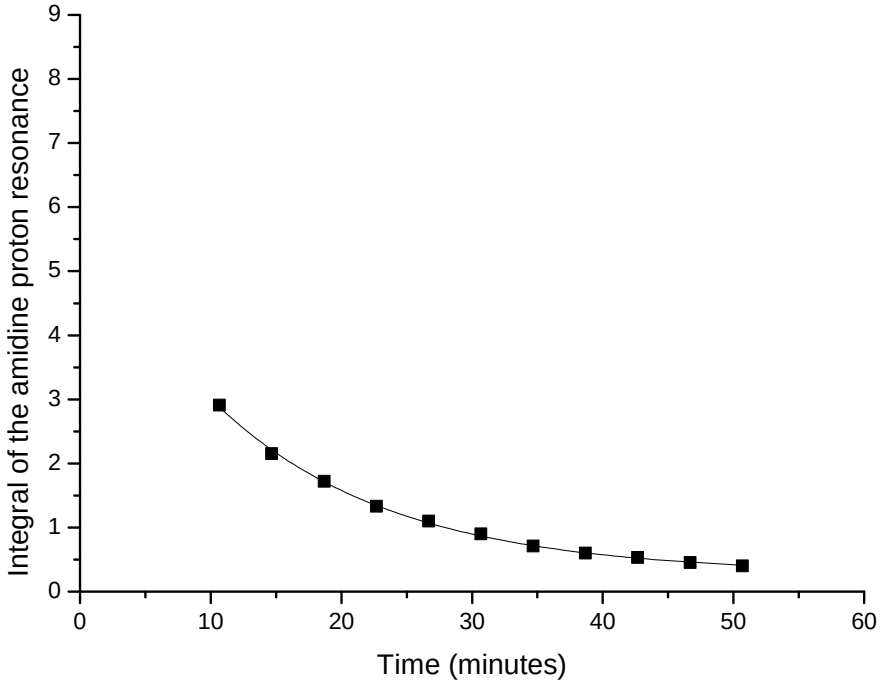


Figure 6.49 Amidine proton resonance with time in experiment PGKC7-K-5

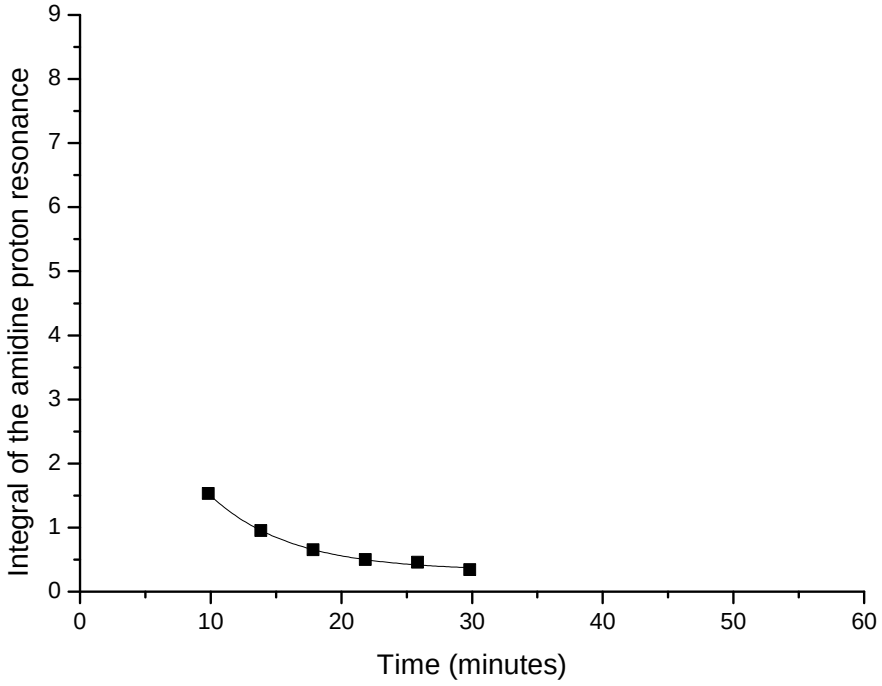


Figure 6.50 Amidine proton resonance with time in experiment PGKC7-K-10

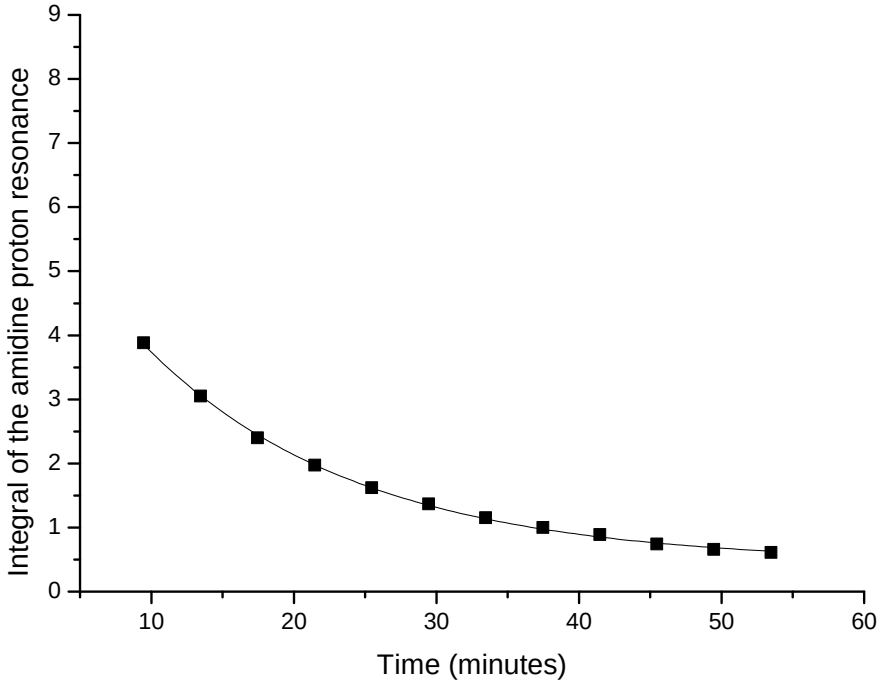


Figure 6.51 Amidine proton resonance with time in experiment PGKC7-K-11

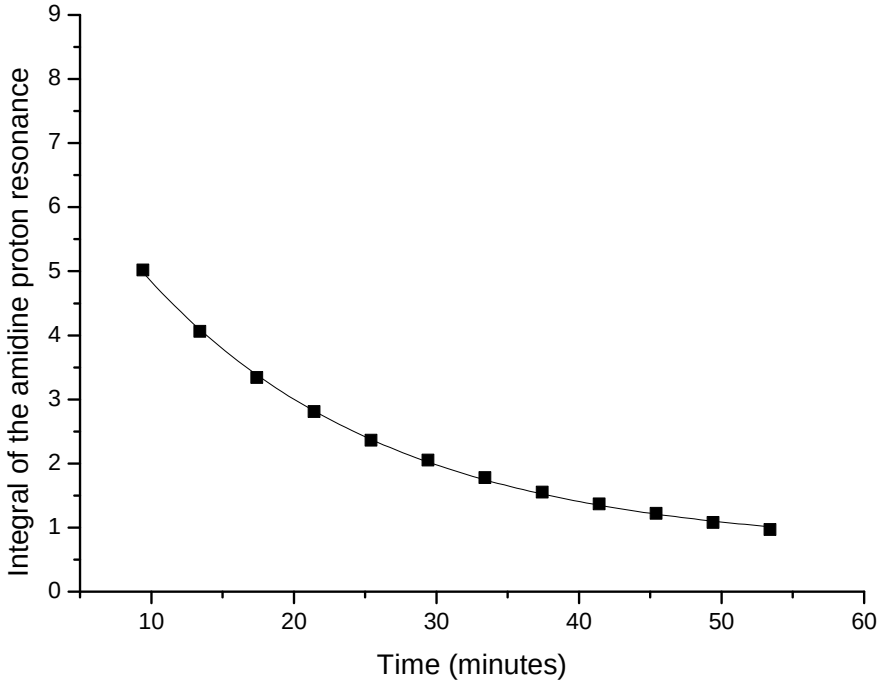


Figure 6.52 Amidine proton resonance with time in experiment PGKC7-K-12

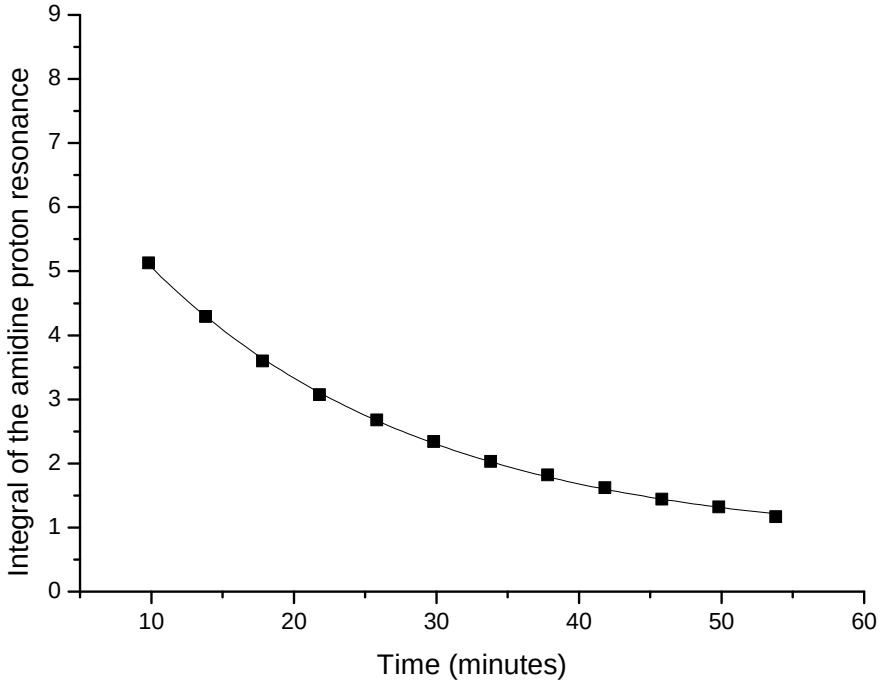


Figure 6.53 Amidine proton resonance with time in experiment PGKC7-K-13

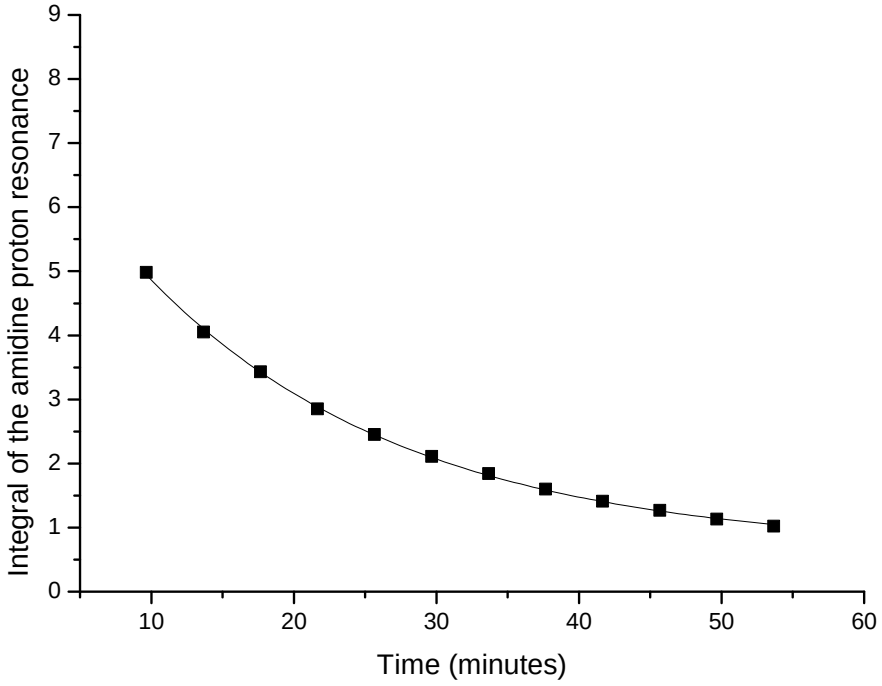


Figure 6.54 Amidine proton resonance with time in experiment PGKC7-K-14

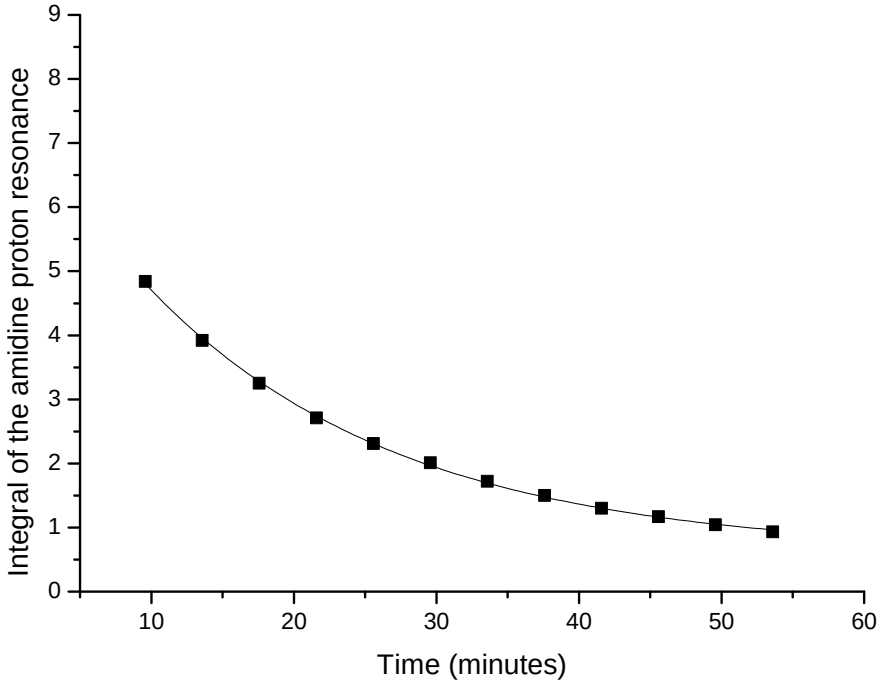


Figure 6.55 Amidine proton resonance with time in experiment PGKC7-K-15

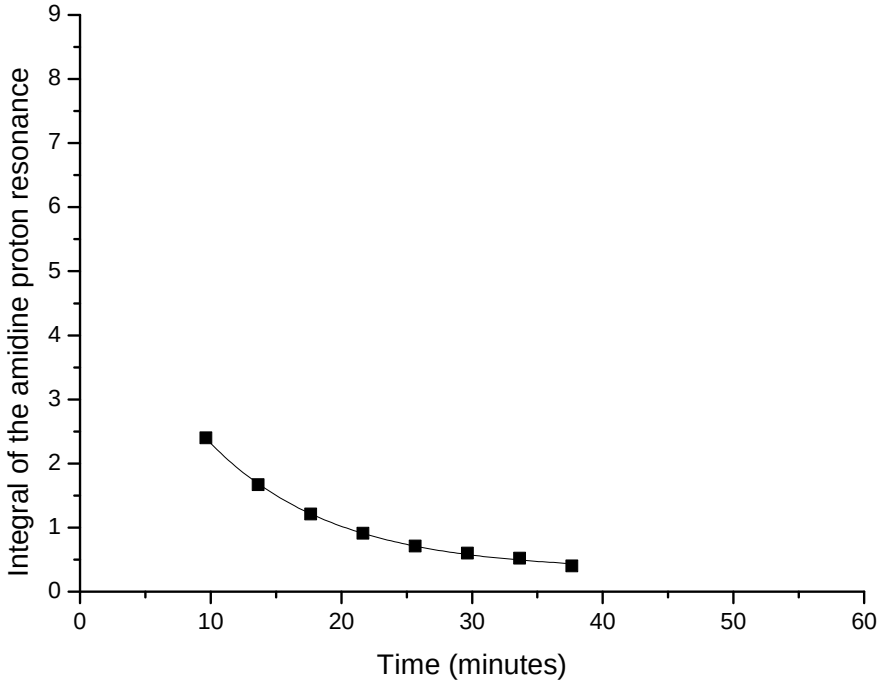


Figure 6.56 Amidine proton resonance with time in experiment PGKC7-K-16

Table 6.8 Analysis of **41** kinetic experiments by Half-Life method

Experiment	[**41**] (mmol/L)	Additive	[Additive] (mmol/L)	Exponential rate	r^2	Half-life (min)
PGKC5K-36	54.53			-0.0087	0.999	80.0
PGKC5K-38	51.93			-[a]	-	-
PGKC5K-49	8.66			-0.0547	0.997	12.7
PGKC5K-50	18.18			-0.0324	0.998	21.4
PGKC5K-51	25.97			-0.0270	0.999	25.7
PGKC5K-52	34.62			-0.0231	0.995	30.0
PGKC5K-54	17.31	NEt_3	1043	-[b]	-	-
PGKC5K-59	17.31	CD_3COOD	26.79	-[a]	-	-
PGKC5K-61	44.14			-0.0202	0.999	34.2
PGKC5K-62	17.31	NEt_3	0.4220	-0.0837	0.999	8.3
PGKC5K-63	17.31	NEt_3	0.2110	-0.0553	0.996	12.5
PGKC5K-64	17.31	NEt_3	0.6331	-0.0770	0.999	9.0
PGKC5K-65	17.31	NEt_3	0.8441	-0.1214	0.997	5.7
PGKC5K-66	17.31	NEt_3	1.0551	-0.1102	0.997	6.3
PGKC7-K-1	17.31	NEt_3	0.0992	-0.0649	0.999	10.7
PGKC7-K-5	17.31	NEt_3	0.4958	-0.0873	0.997	7.9
PGKC7-K-10	17.31	NEt_3	1.0027	-0.1518	0.999	4.6
PGKC7-K-11	17.31	NEt_3	0.2534	-0.0760	0.998	9.1
PGKC7-K-12	17.31	NEt_3	0.0551	-0.0622	0.999	11.1
PGKC7-K-13	17.31	NEt_3	0.0100	-0.0553	0.999	12.5
PGKC7-K-14	17.31	NEt_3	0.0250	-0.0586	0.999	11.8
PGKC7-K-15	17.31	NEt_3	0.0751	-0.0602	0.999	11.5
PGKC7-K-16	17.31	NEt_3	0.7514	-0.1163	0.999	6.0

[a] An exponential decay curve could be fitted to this data
[b] An exponential decay curve could not be accurately fitted to this data

6.2.4 DMFDMA

Setup

Table 6.9 Composition of **15** kinetic experiments

Experiment	Solvent	[**15**] (mmol/L)	Additive				
			Identity	Volume (μL)	[Standard solution] (mmol/L)	n[a] (μmol)	[Additive][b] (mmol/L)
PGKC7-K-DMFDMA-5	$CDCl_3$	59.75					
PGKC7-K-DMFDMA-6	CD_3OD	59.75					
PGKC7-K-DMFDMA-8	10% CD_3OD/$CDCl_3$	59.75					
PGKC7-K-DMFDMA-9	10% CD_3OD/$CDCl_3$[c]	59.75					
PGKC7-K-DMFDMA-10	10% CD_3OD/$CDCl_3$	59.75	CD_3COOD	2.02	neat	0.0331	60.12
PGKC7-K-DMFDMA-11	10% CD_3OD/$CDCl_3$	59.75	NEt_3	4.6	neat	0.0330	59.96
PGKC7-K-DMFDMA-12	10% CD_3OD/$CDCl_3$	59.75	CD_3COOD	10	60	0.0006	1.091
PGKC7-K-DMFDMA-13	10% CD_3OD/$CDCl_3$	59.75	CD_3COOD	20	60	0.0012	2.181
PGKC7-K-DMFDMA-14	10% CD_3OD/$CDCl_3$	59.75	NEt_3	2.3	neat	0.0165	29.98

[a]Density: triethylamine = 0.7255 g/mL, CD_3COOD = 1.049 g/mL; Mr: triethylamine = 101.2 g/mol, CD_3COOD = 64.08 g/mol
[b]Total volume of solvent = 0.55 mL
[c]neutralised with potassium carbonate

DMFDMA kinetic studies

Experiment parameters:

- at = 10 seconds
- d1 = 10 seconds
- pw = pw90
- nt = 12
- pad = 0 seconds between acquisitions
- 13 acquisitions obtained

Analysis:

- integral of amide-acetal proton resonance plotted against time
- exponential model applied (as visualised on the graph and summarised in subsequent table)

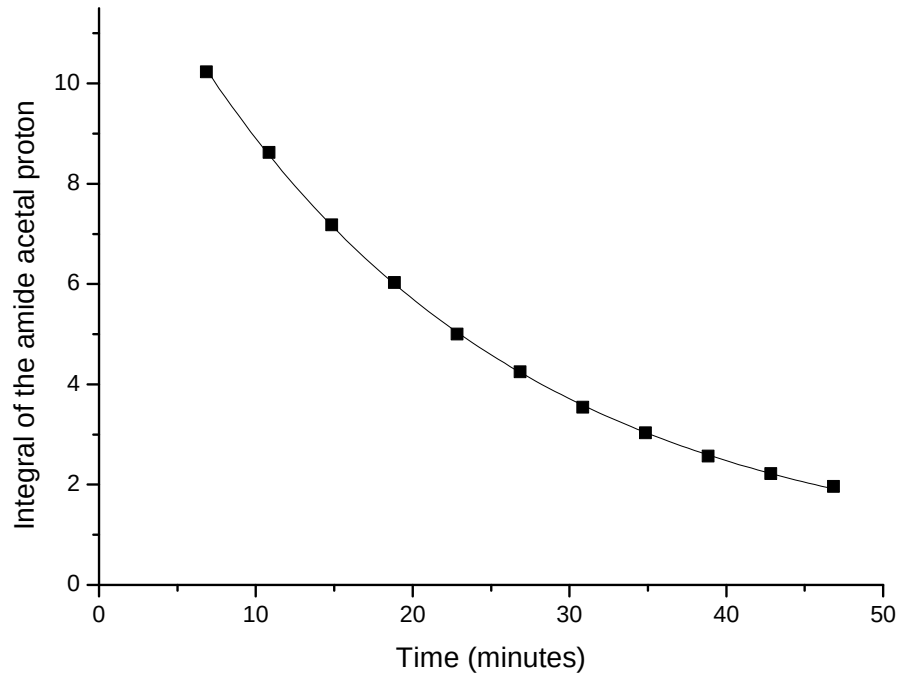


Figure 6.57 Amide-acetal proton resonance with time in experiment PGKC7-DMFDMA-8

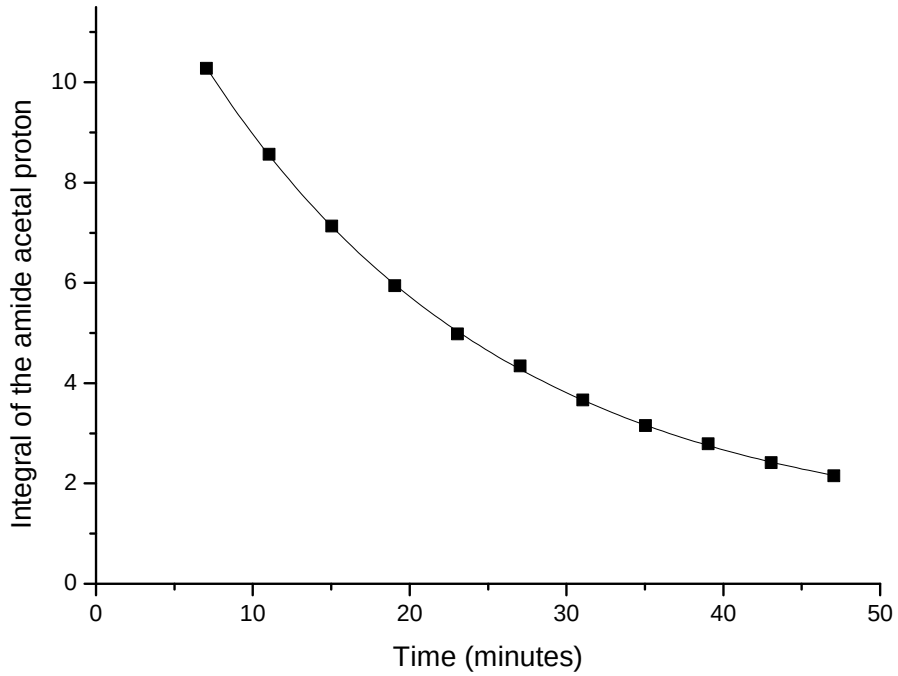


Figure 6.58 Amide-acetal proton resonance with time in experiment PGKC7-DMFDMA-9

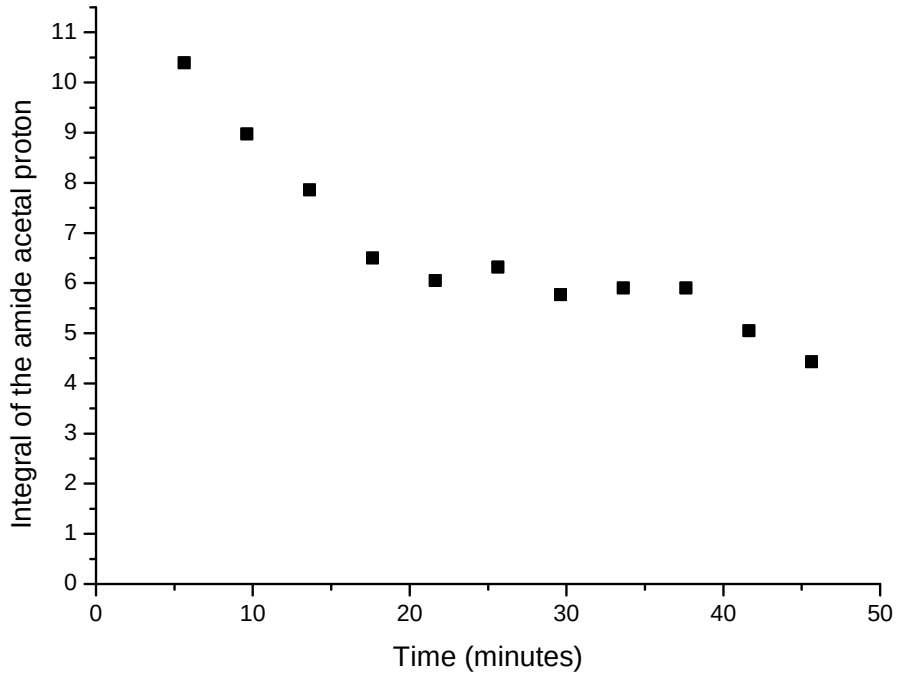


Figure 6.59 Amide-acetal proton resonance with time in experiment PGKC7-DMFDMA-10

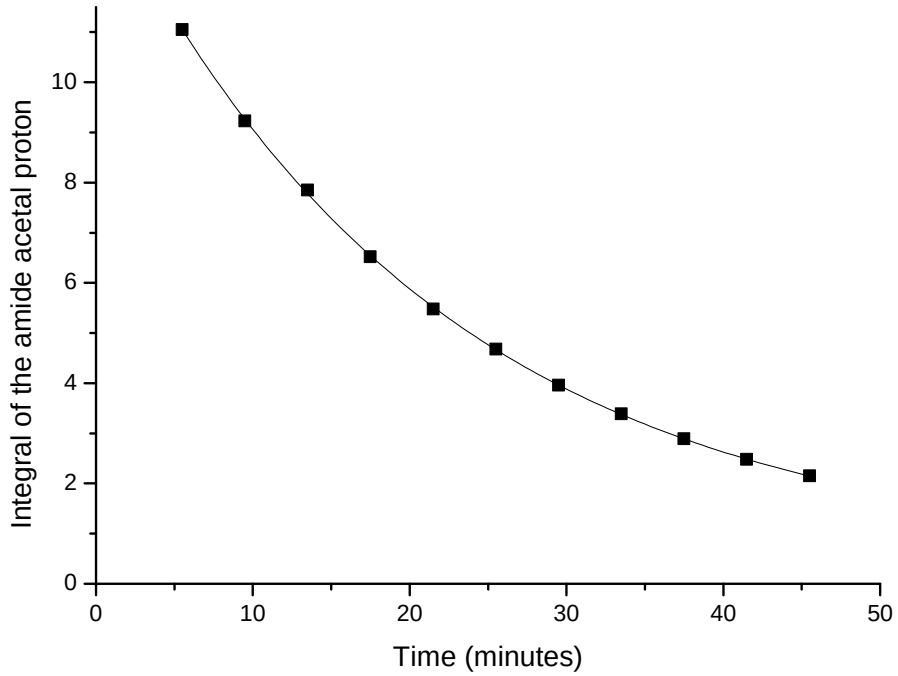


Figure 6.60 Amide-acetal proton resonance with time in experiment PGKC7-DMFDMA-11

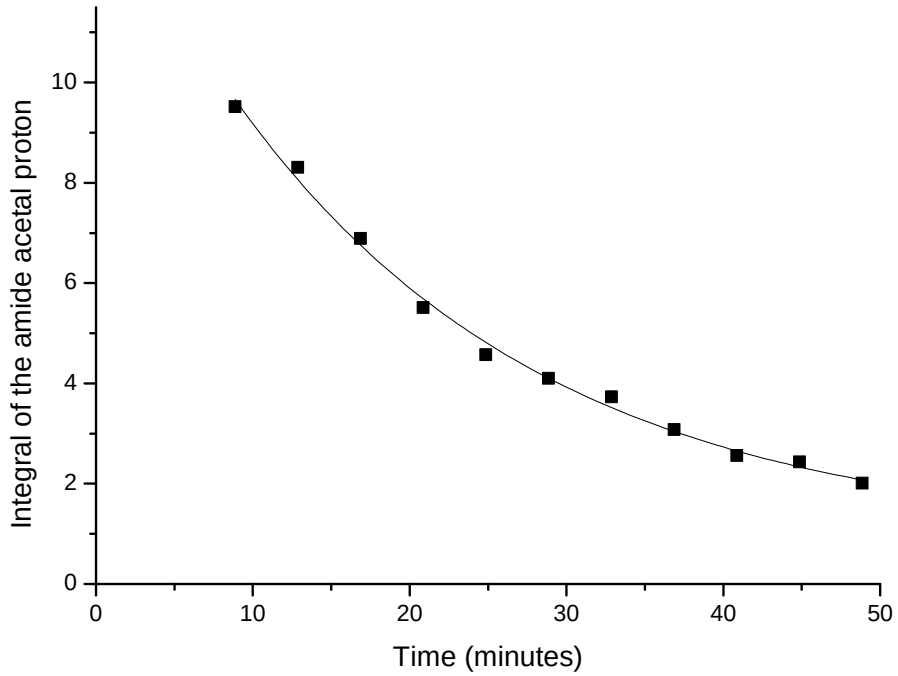


Figure 6.61 Amide-acetal proton resonance with time in experiment PGKC7-DMFDMA-12

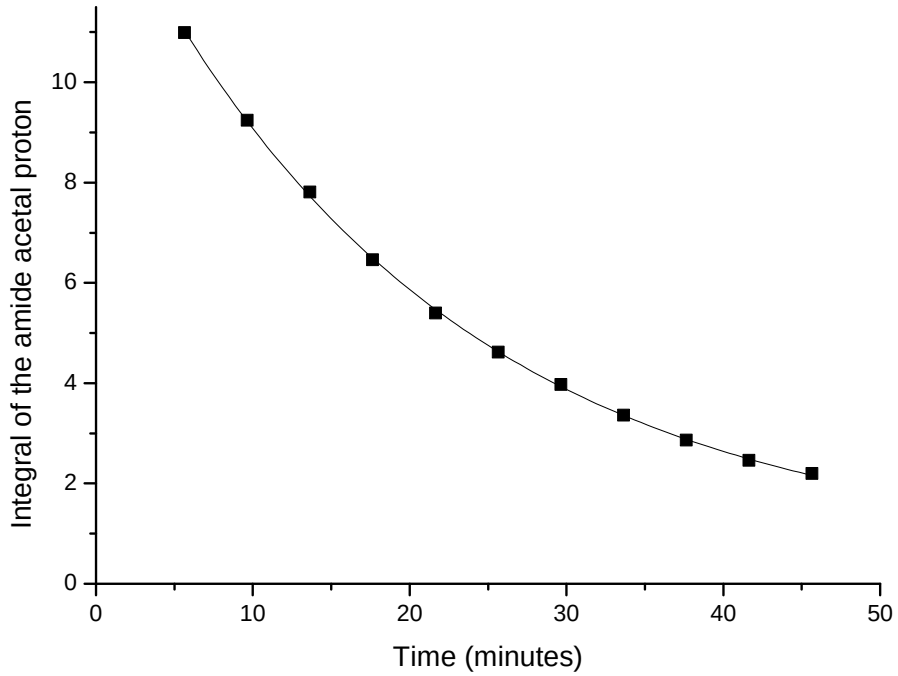


Figure 6.62 Amide-acetal proton resonance with time in experiment PGKC7-DMFDMA-13

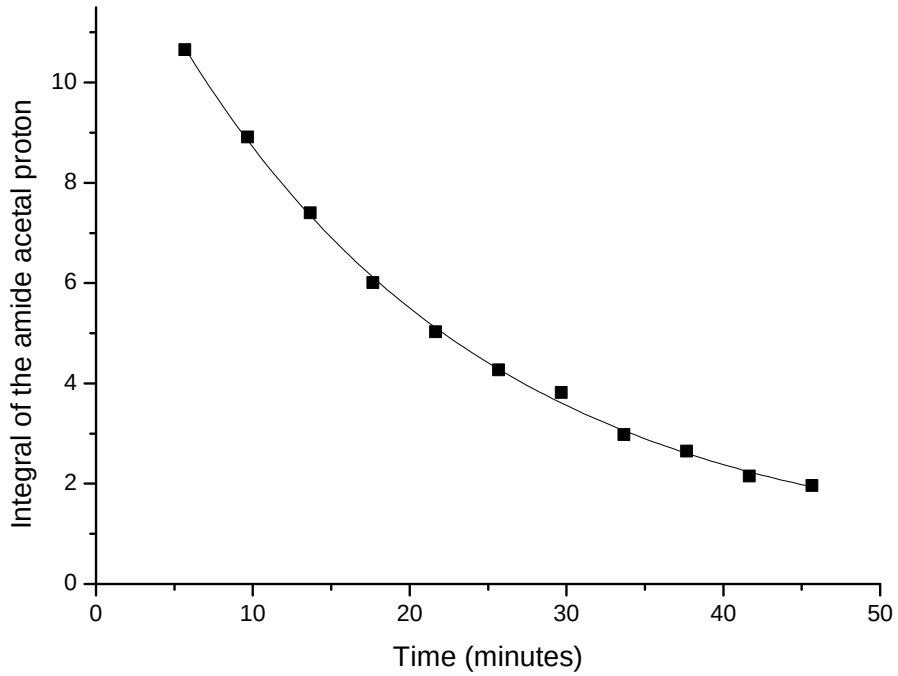


Figure 6.63 Amide-acetal proton resonance with time in experiment PGKC7-DMFDMA-14

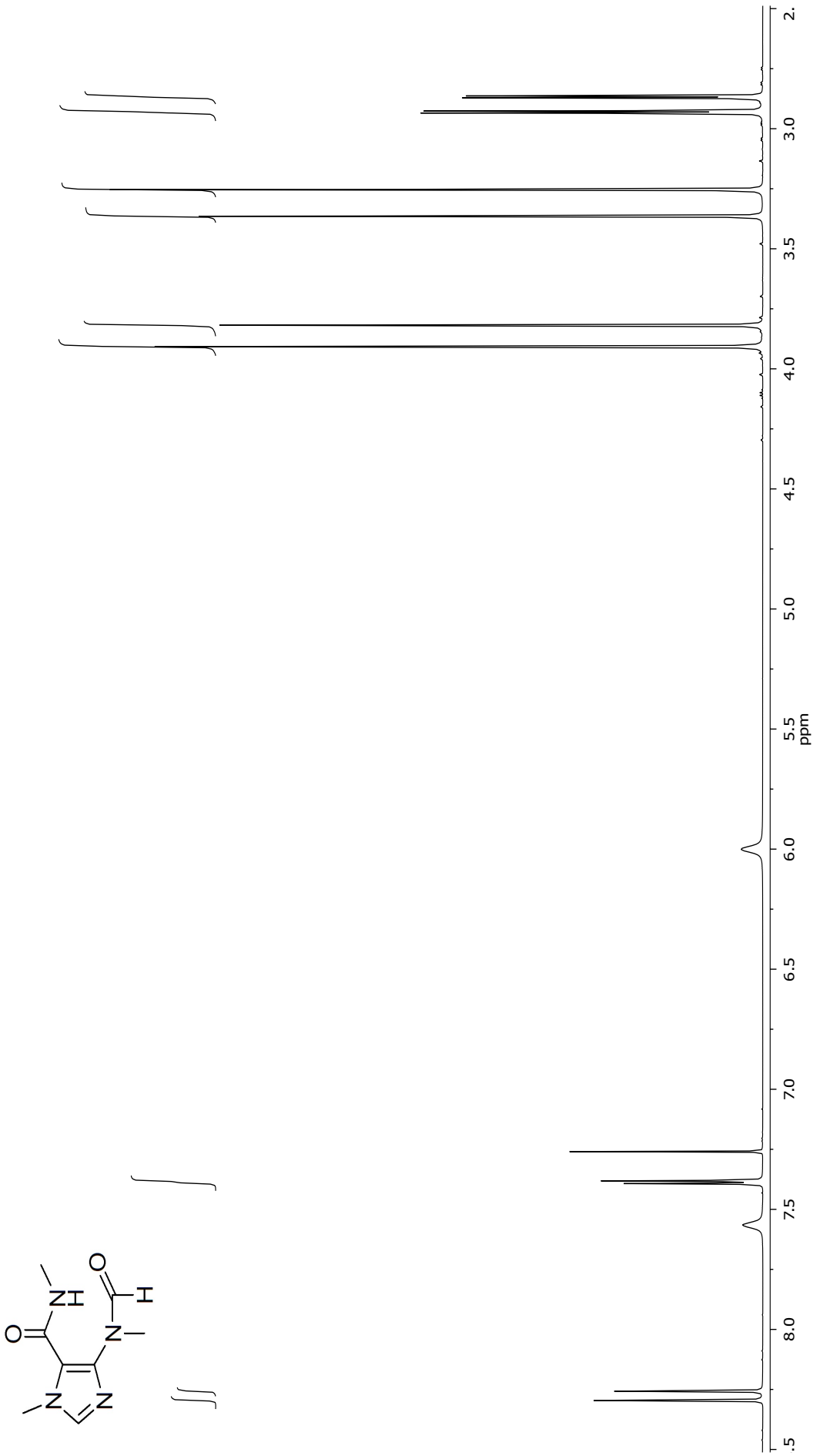
Table 6.10 Analysis of DMFDMA kinetic experiments by Half-Life method

Experiment	[DMFDMA] (mmol/L)	Additive	[Additive] (mmol/L)	Exponential rate	r^2	Half-life (min)
PGKC7-K-DMFDMA-8	59.75			-0.04764	0.999	14.5
PGKC7-K-DMFDMA-9	59.75			-0.05224	0.999	13.3
PGKC7-K-DMFDMA-10	59.75	CD_3COOD	60.12	-[a]	-	-
PGKC7-K-DMFDMA-11	59.75	NEt_3	59.96	-0.04646	0.999	14.9
PGKC7-K-DMFDMA-12	59.75	CD_3COOD	1.091	-0.05048	0.995	13.7
PGKC7-K-DMFDMA-13	59.75	CD_3COOD	2.182	-0.04769	0.999	14.5
PGKC7-K-DMFDMA-14	59.75	NEt_3	29.98	-0.05005	0.999	13.8

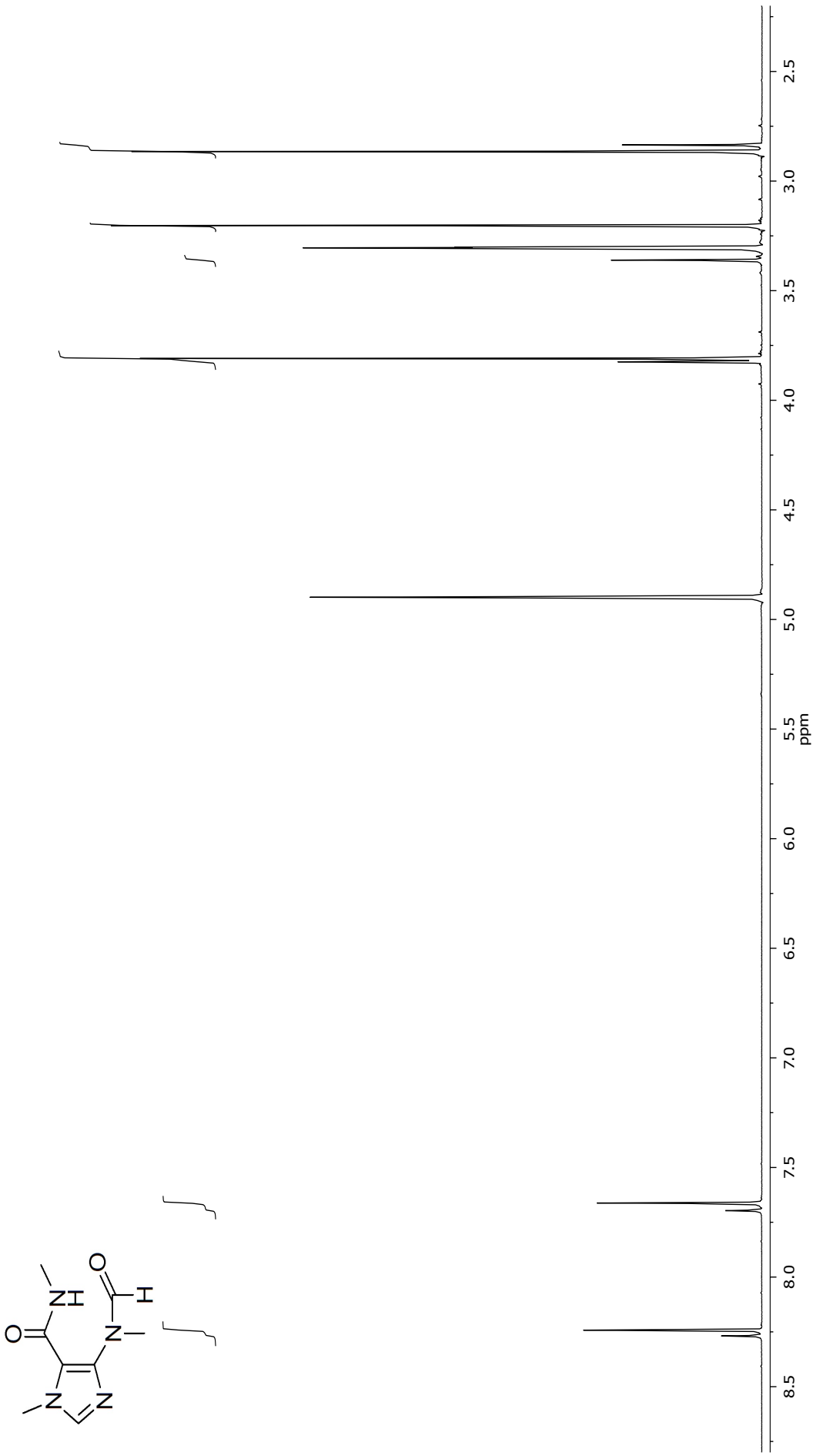
[a]An exponential decay curve could not be accurately fitted to this data

Spectra

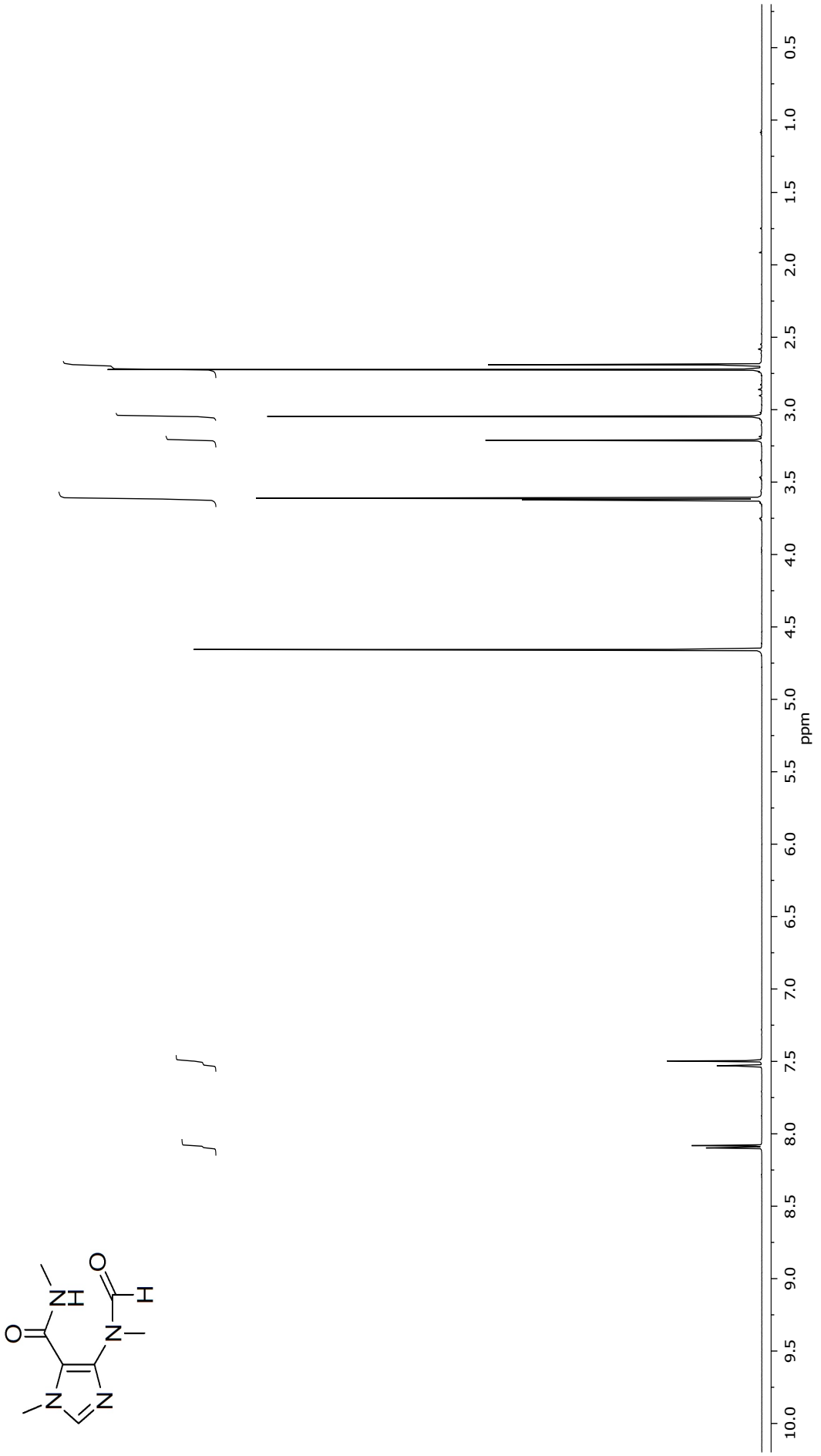
Selected spectra of key compounds



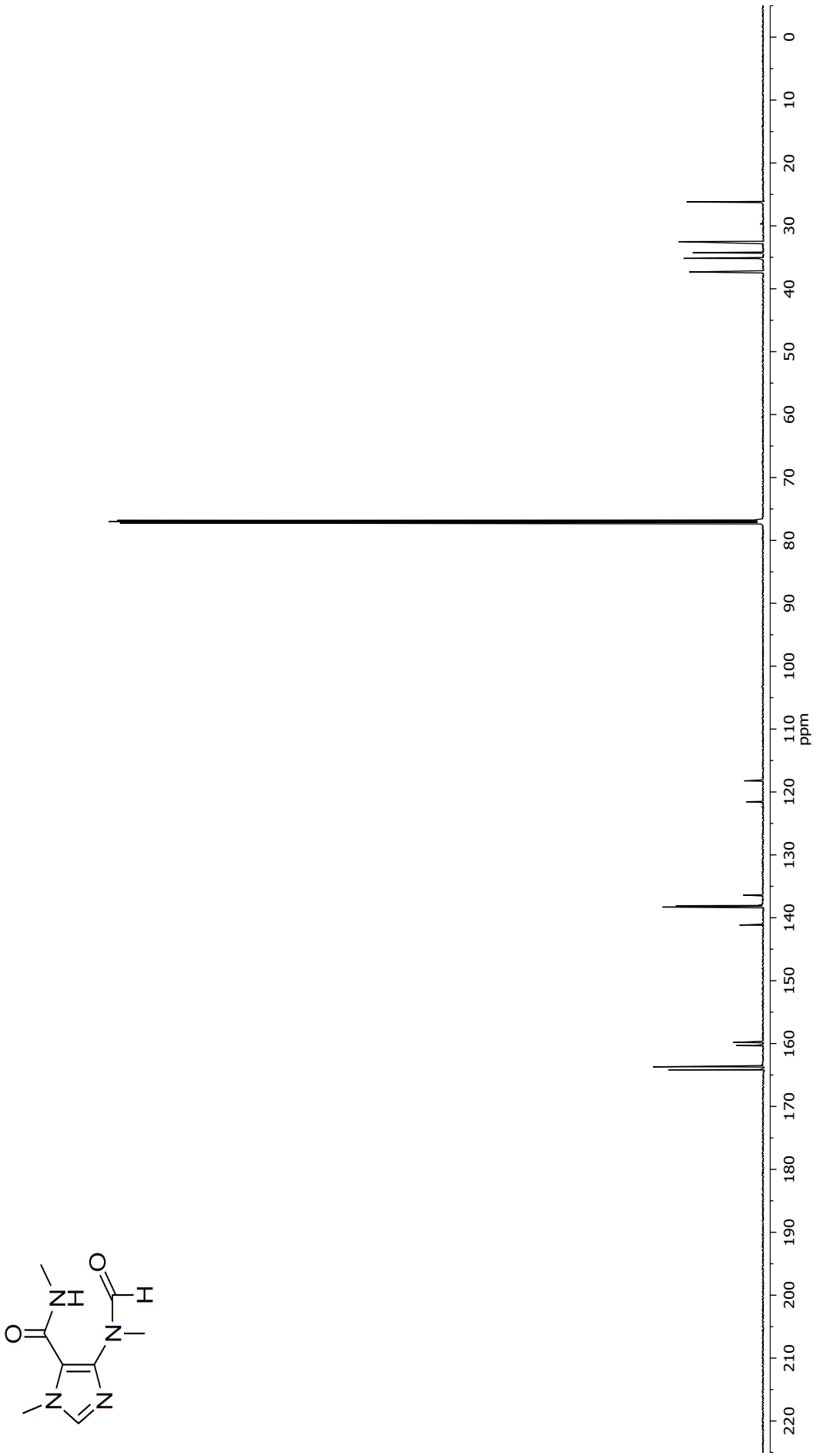
^{1}H-NMR spectrum of **23** (600 MHz, $CDCl_3$)



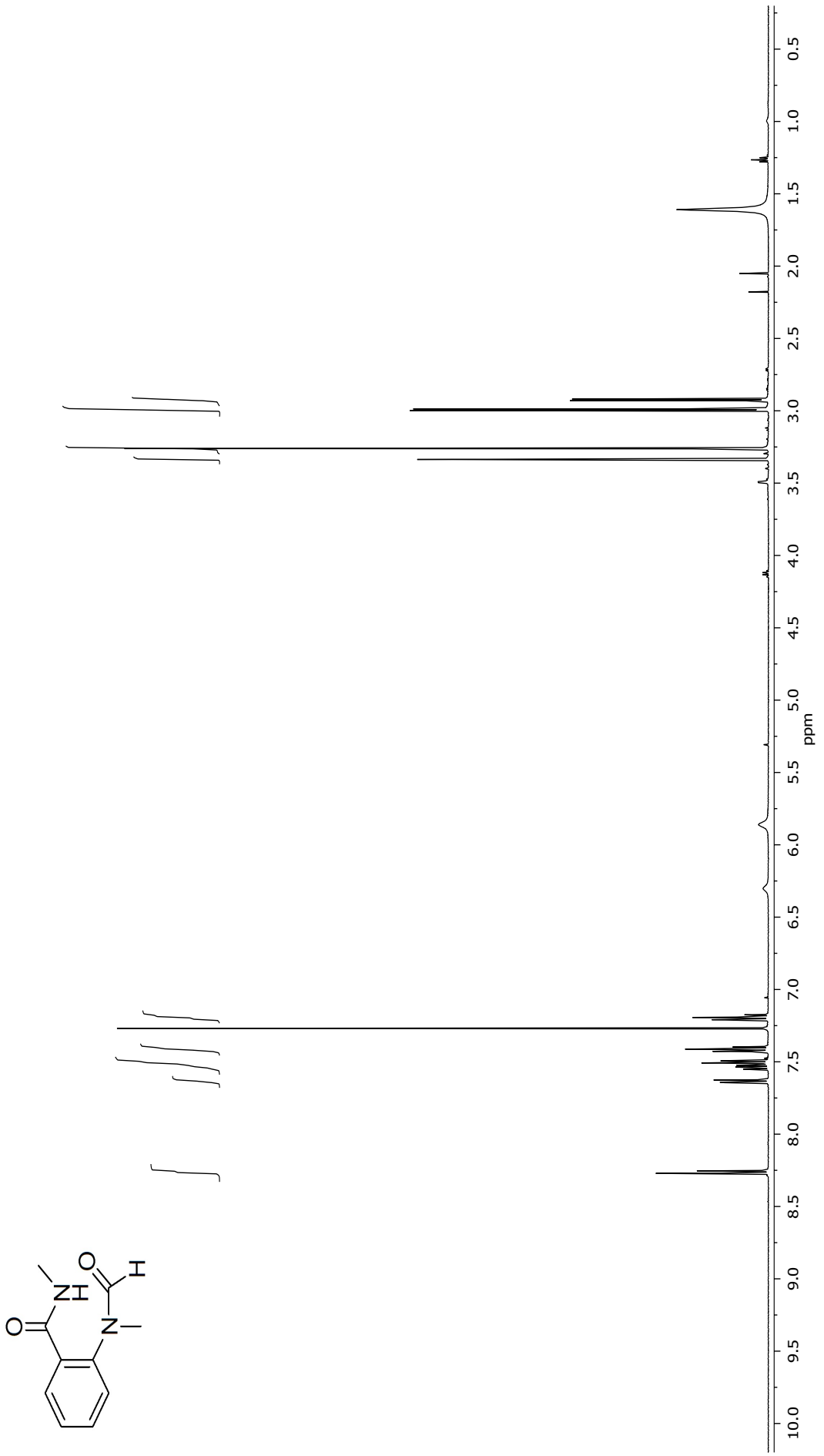
^{1}H-NMR spectrum of **23** (600 MHz, CD_3OD)



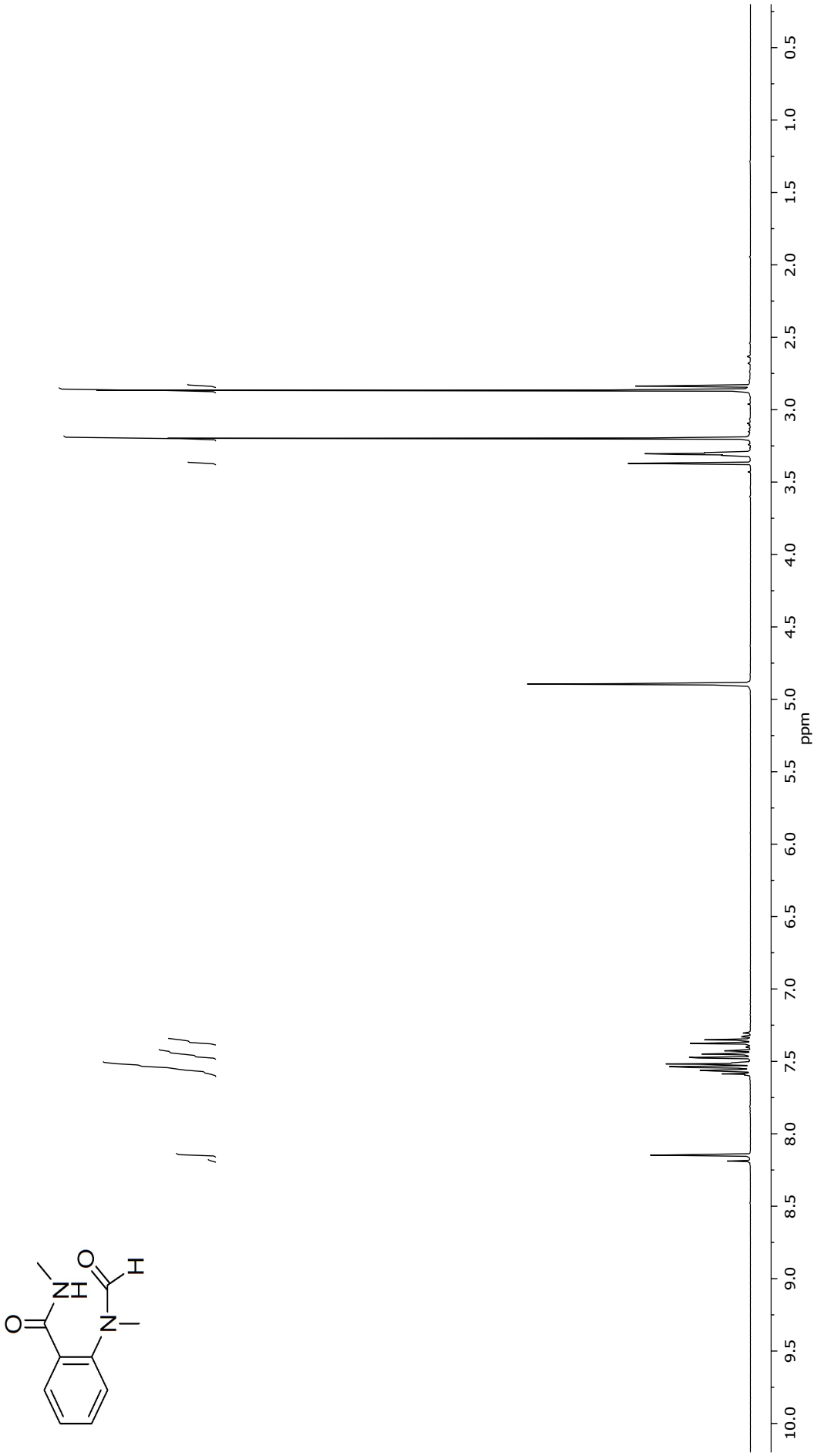
^{1}H-NMR spectrum of **23** (500 MHz, D_2O)



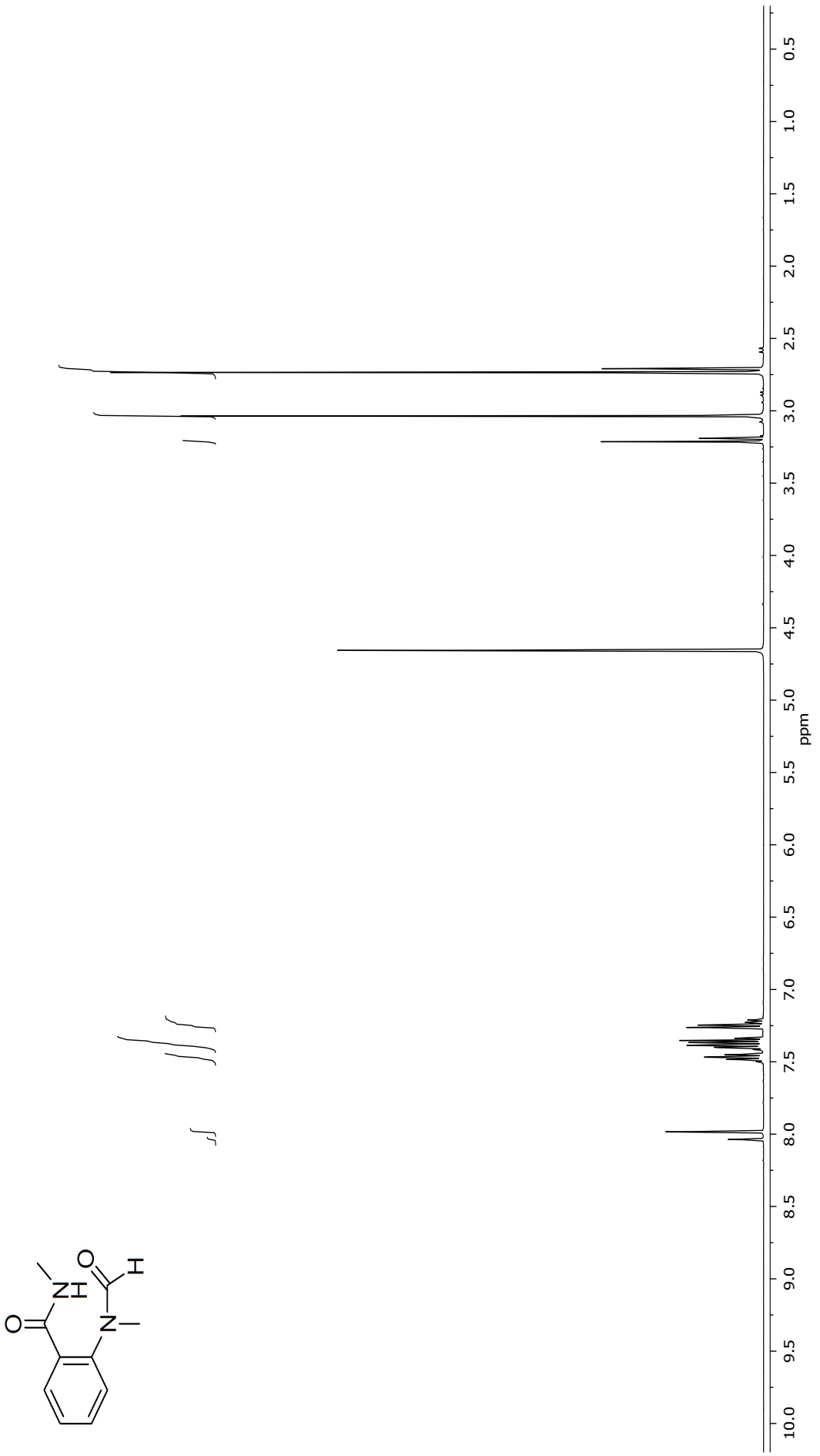
^{13}C-NMR spectrum of **23** (150 MHz, $CDCl_3$)



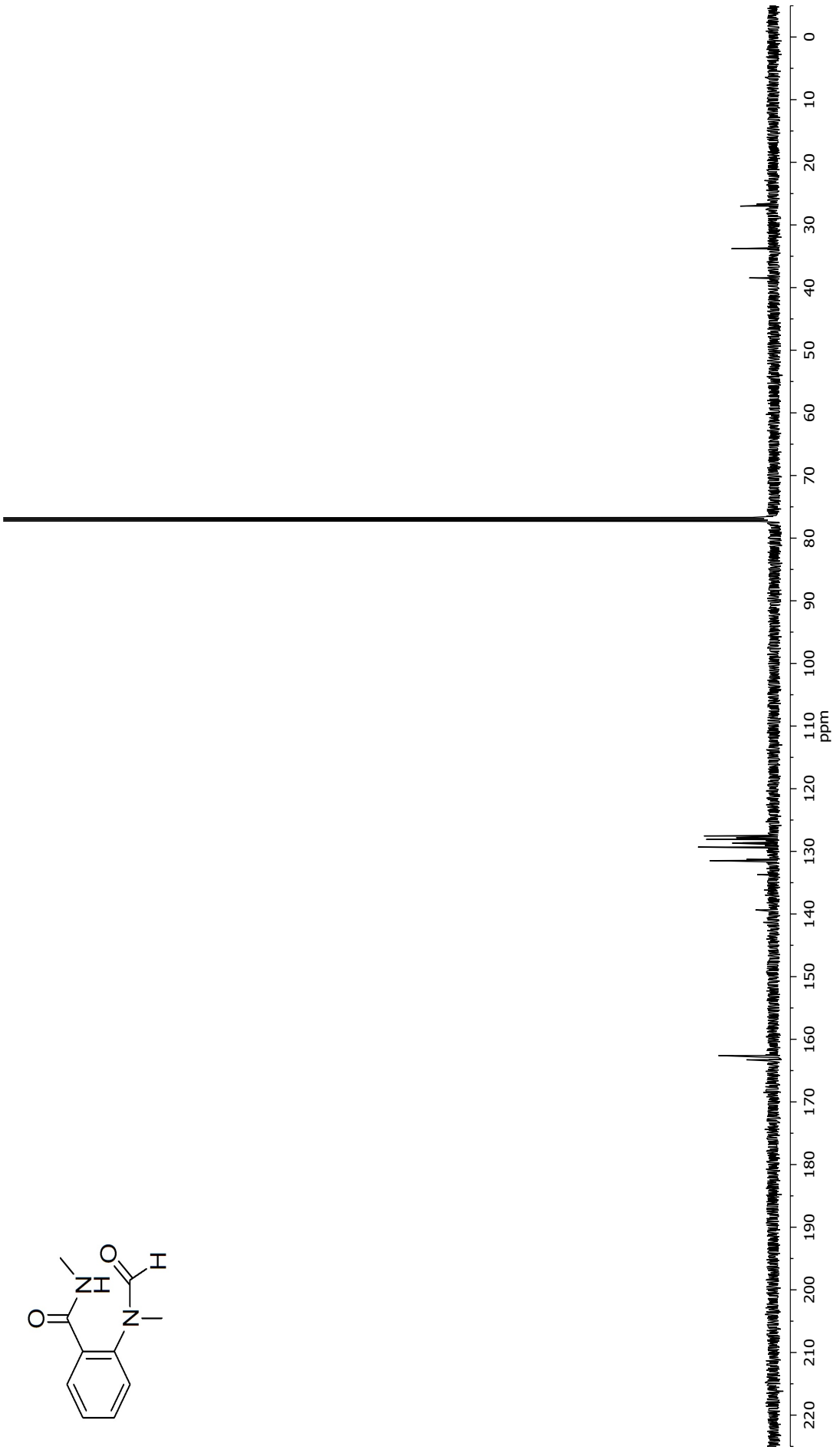
^{1}H-NMR spectrum of **28** (500 MHz, $CDCl_3$)



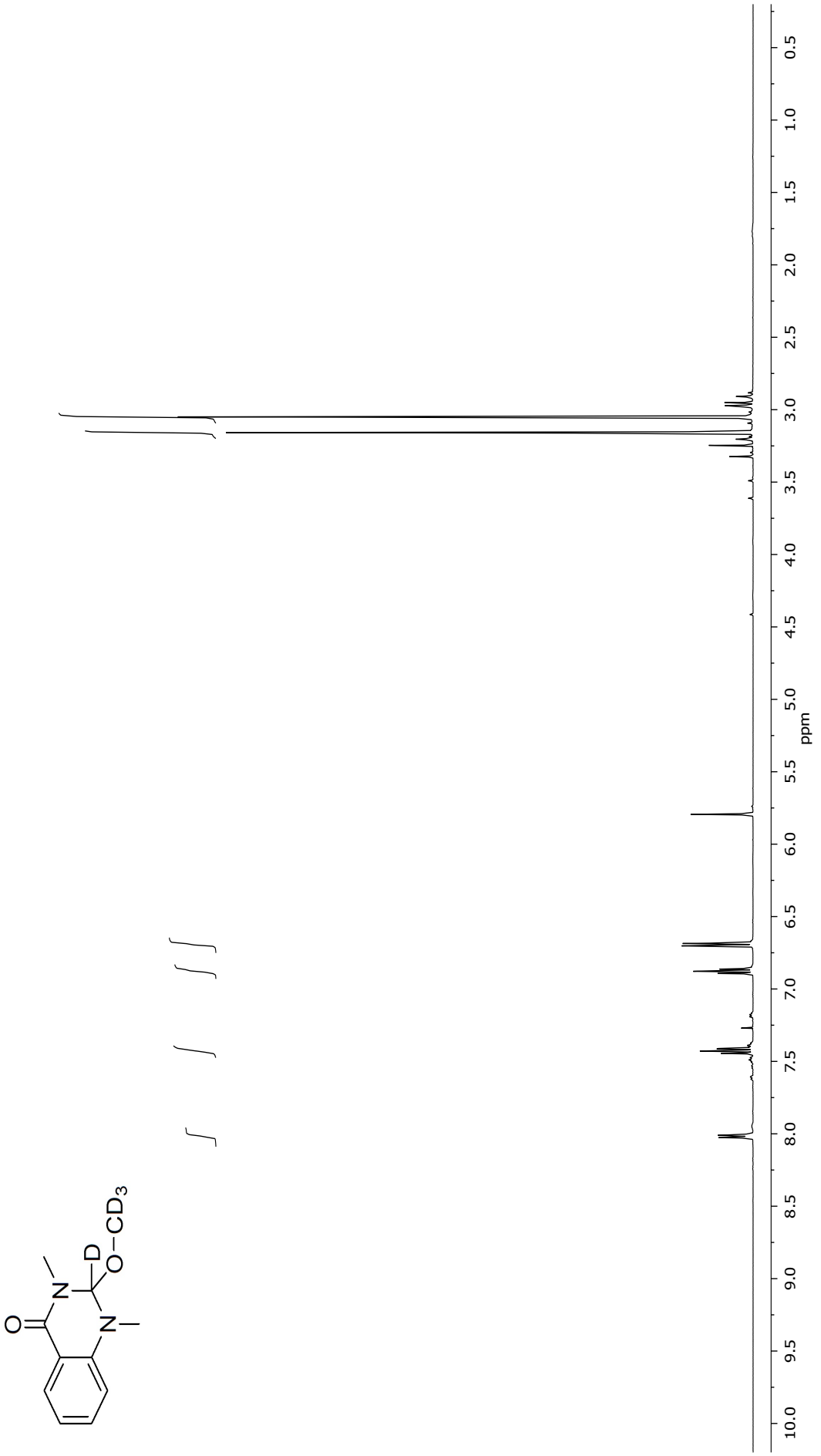
^{1}H-NMR spectrum of **28** (300 MHz, CD_3OD)



^{1}H-NMR spectrum of **28** (500 MHz, D_2O)

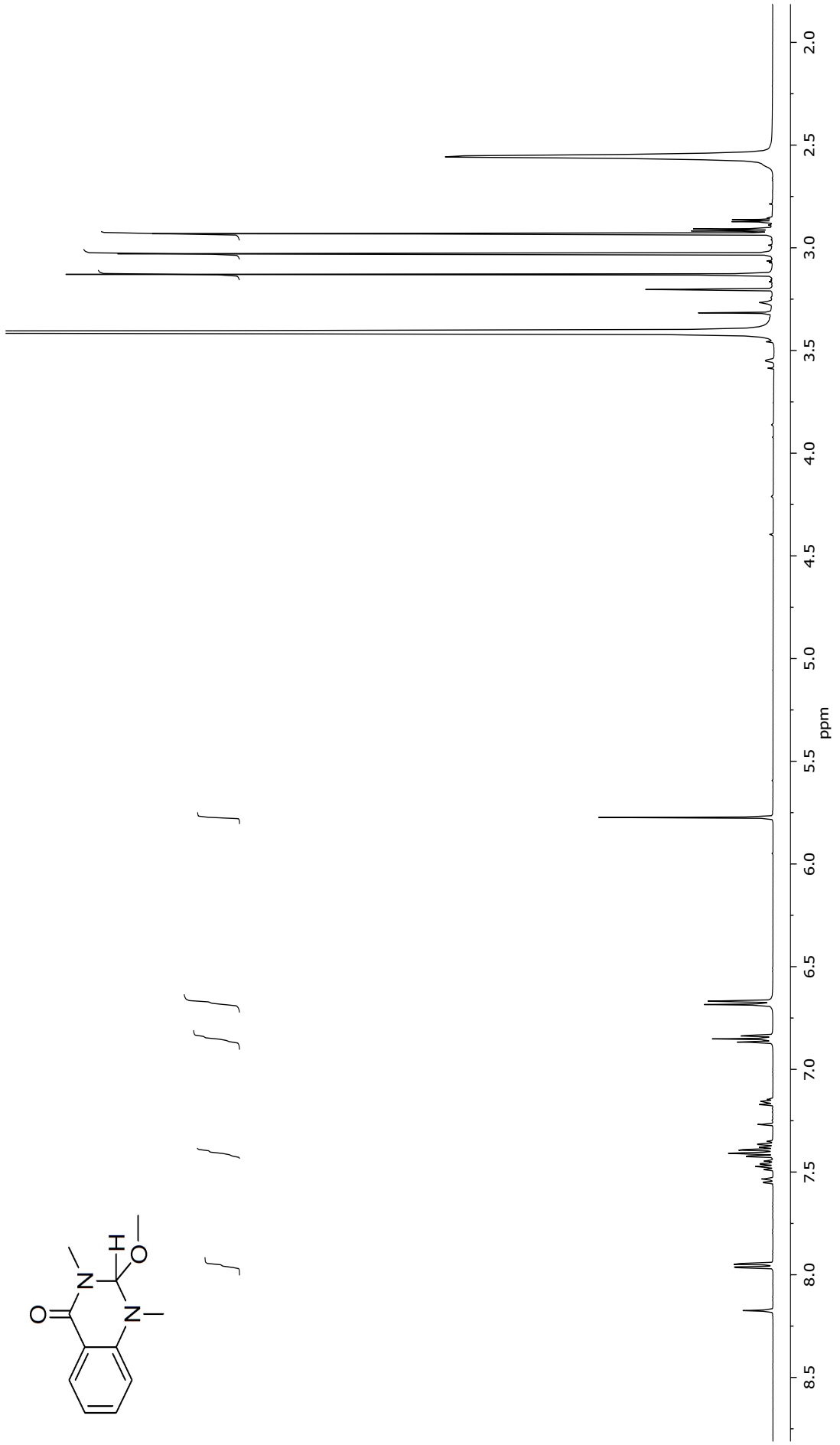


^{13}C-NMR spectrum of **28** (125 MHz, $CDCl_3$)

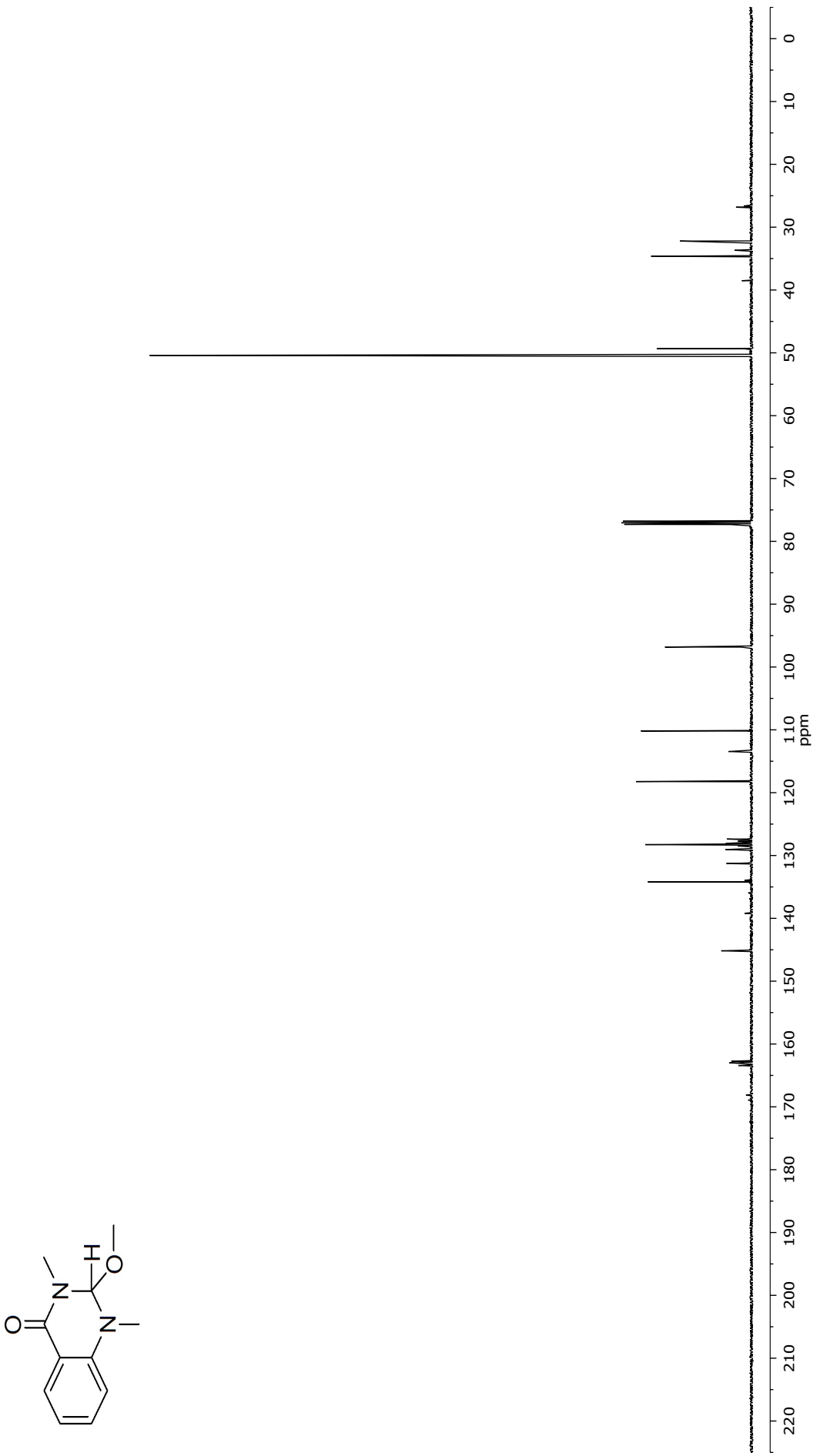


^{1}H-NMR spectrum of **34** (500 MHz, $CDCl_3$)

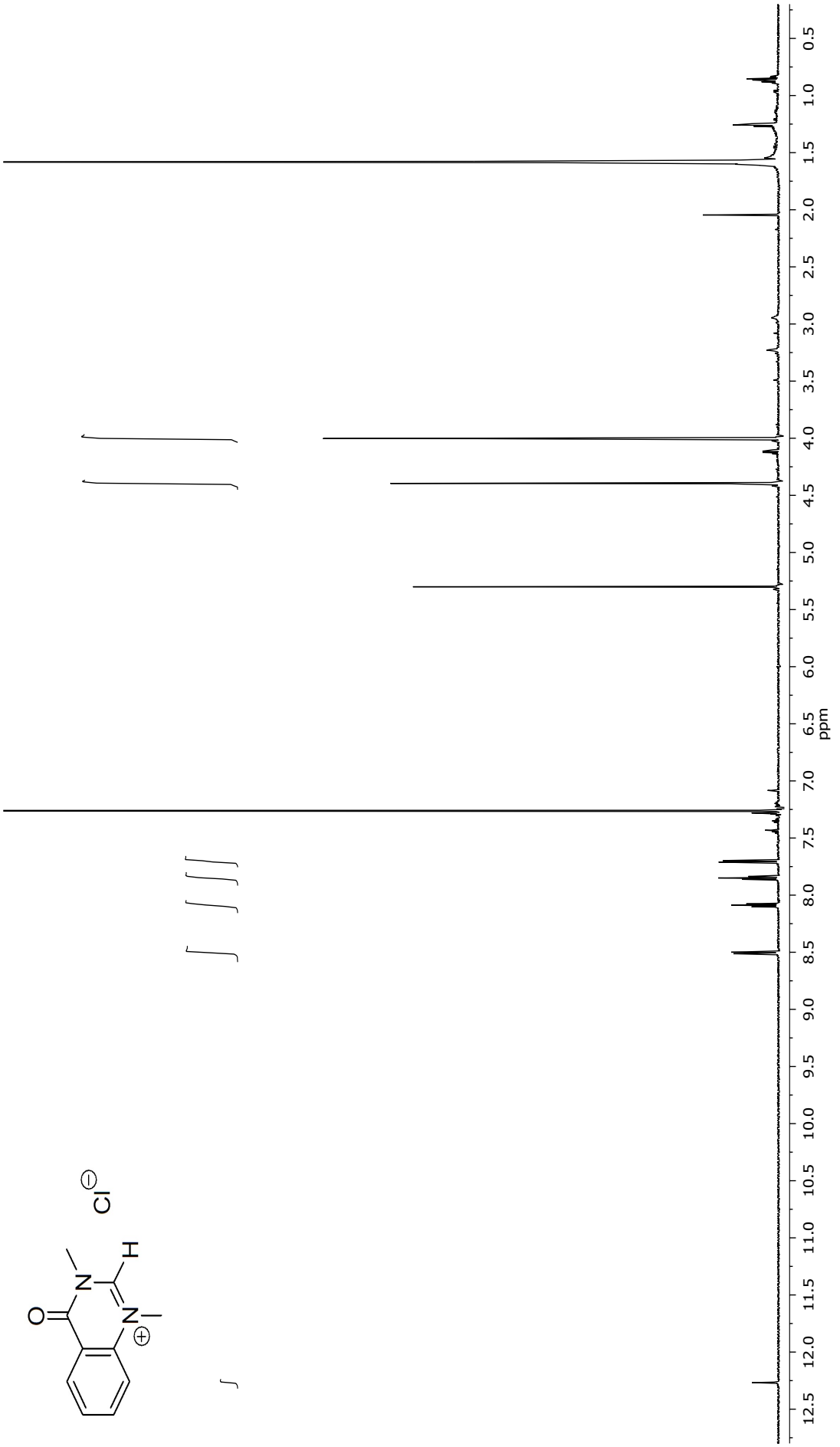
^{13}C-NMR spectrum of **34** (125 MHz, $CDCl_3$)



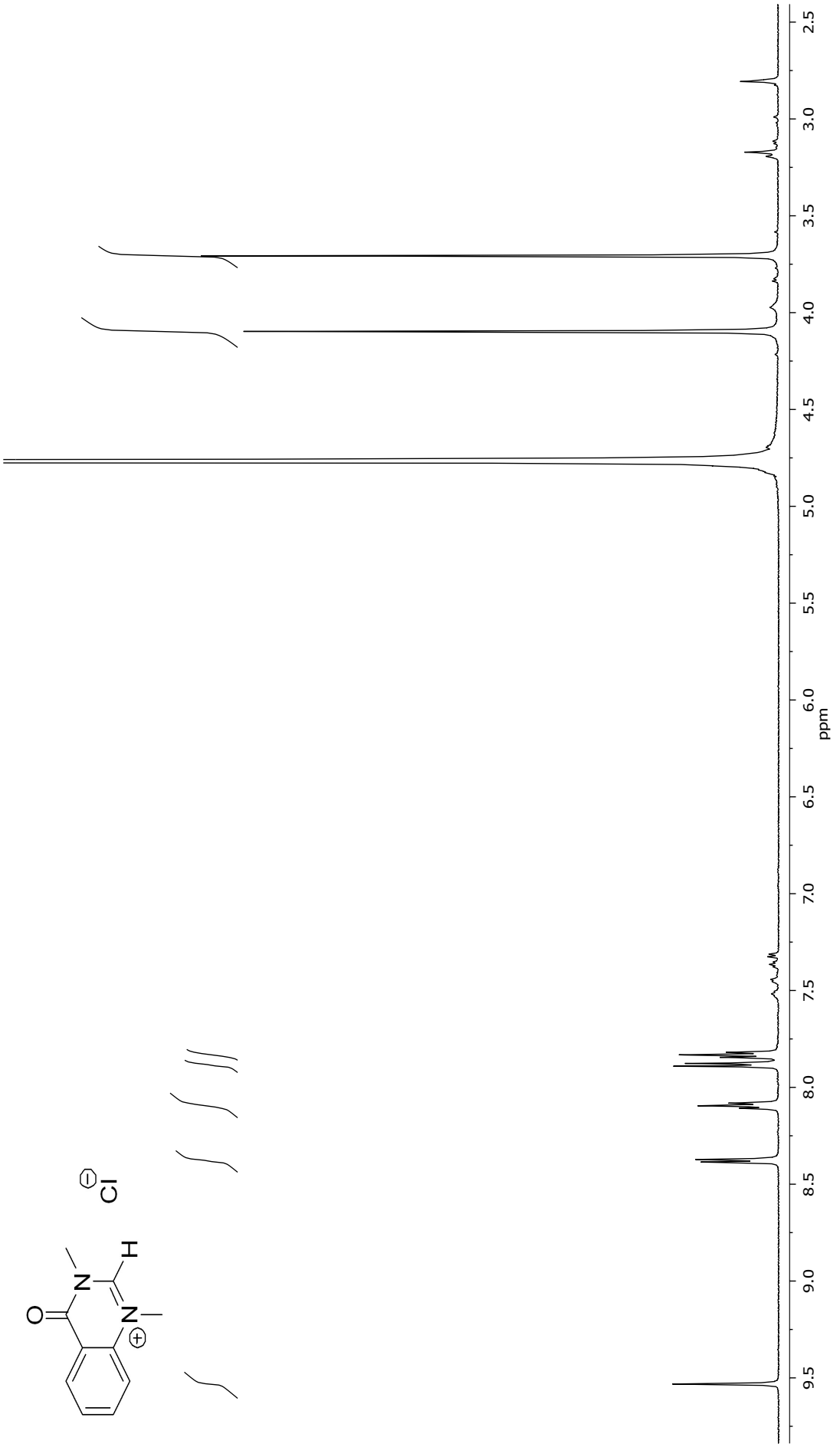
^{1}H-NMR spectrum of **35** (500 MHz, $CDCl_3$)



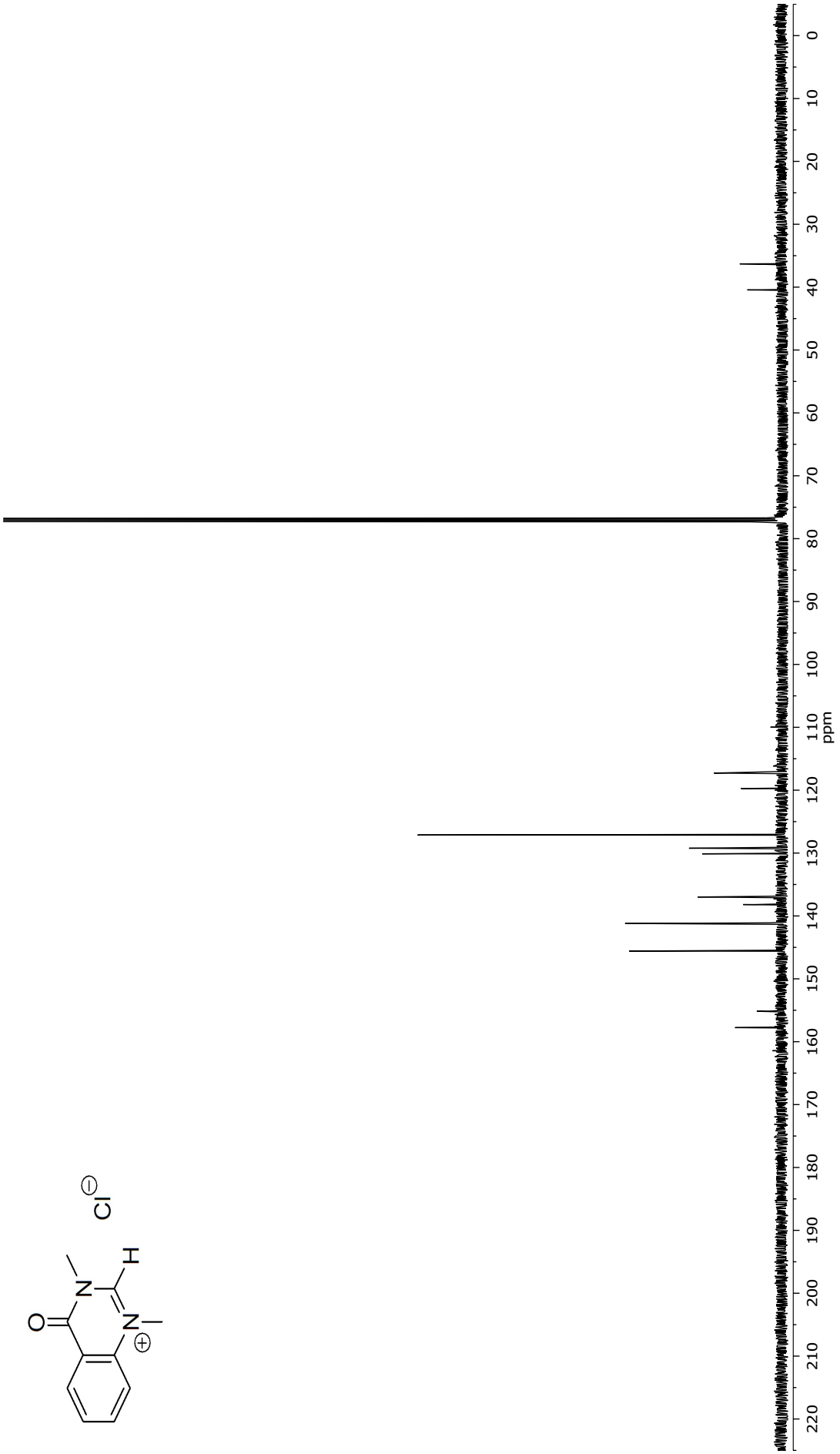
^{13}C-NMR spectrum of **35** (125 MHz, $CDCl_3$)



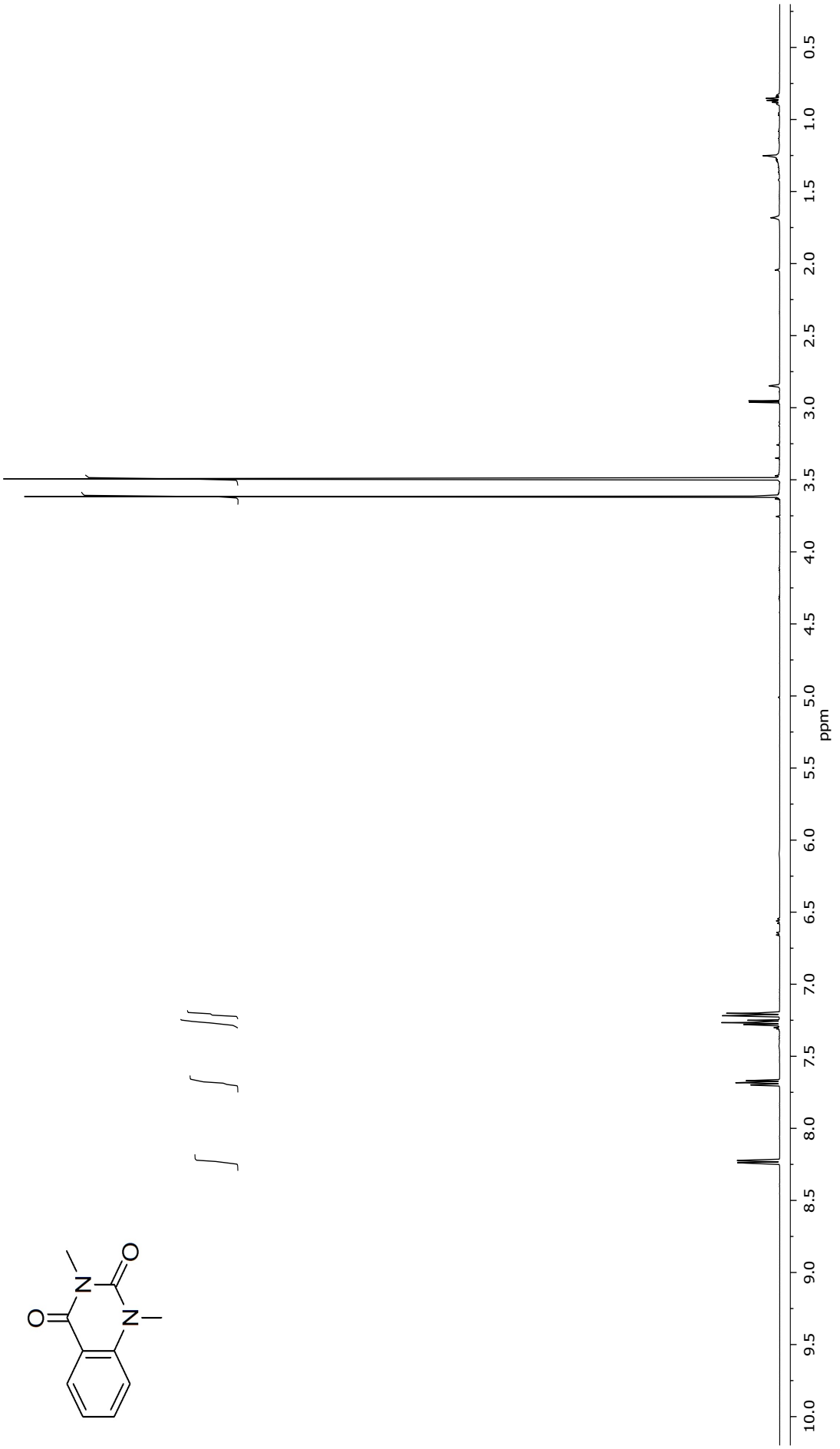
^{1}H-NMR spectrum of **41** (600 MHz, $CDCl_3$)



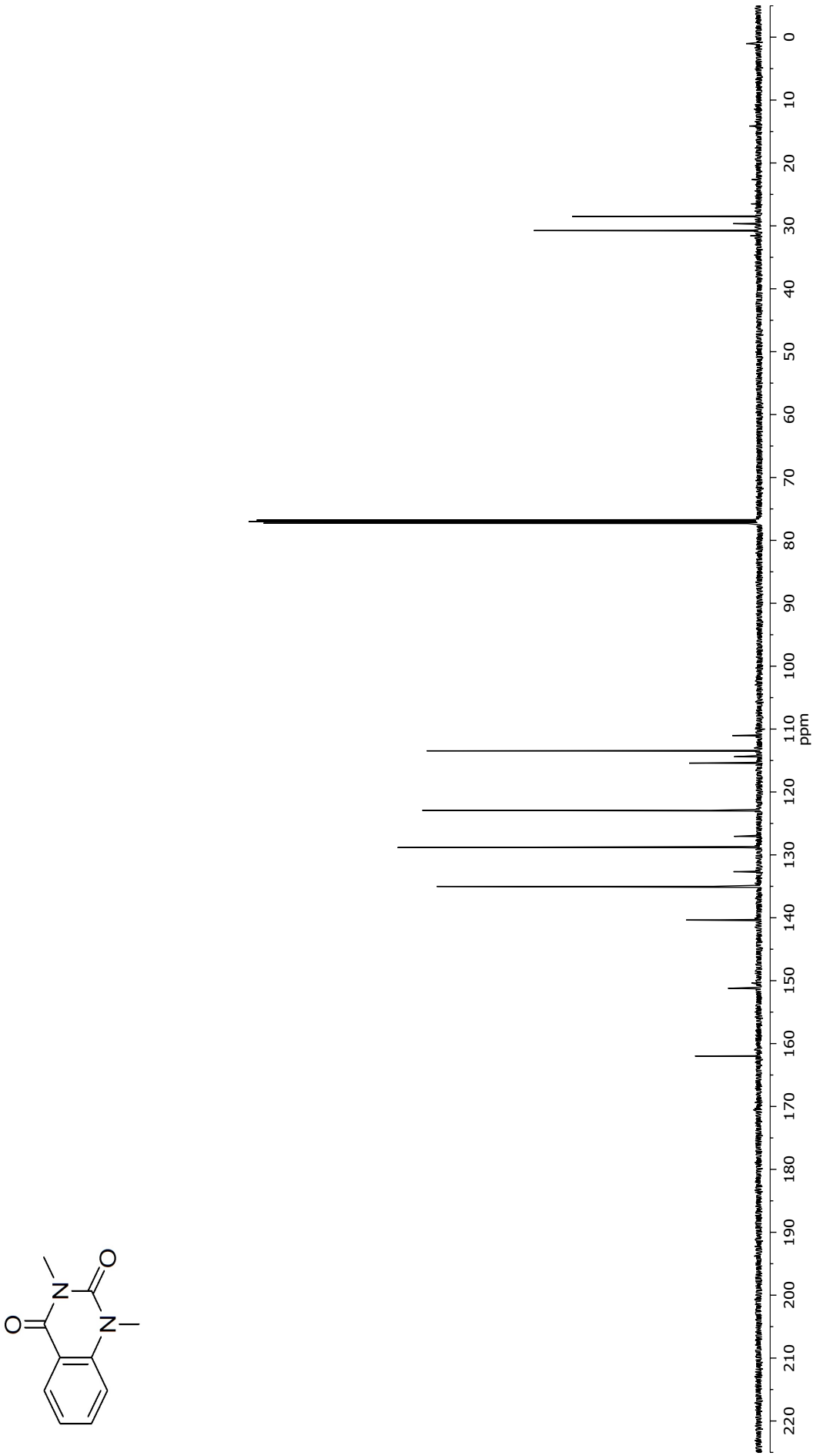
^{1}H-NMR spectrum of **41** (600 MHz, D_2O)



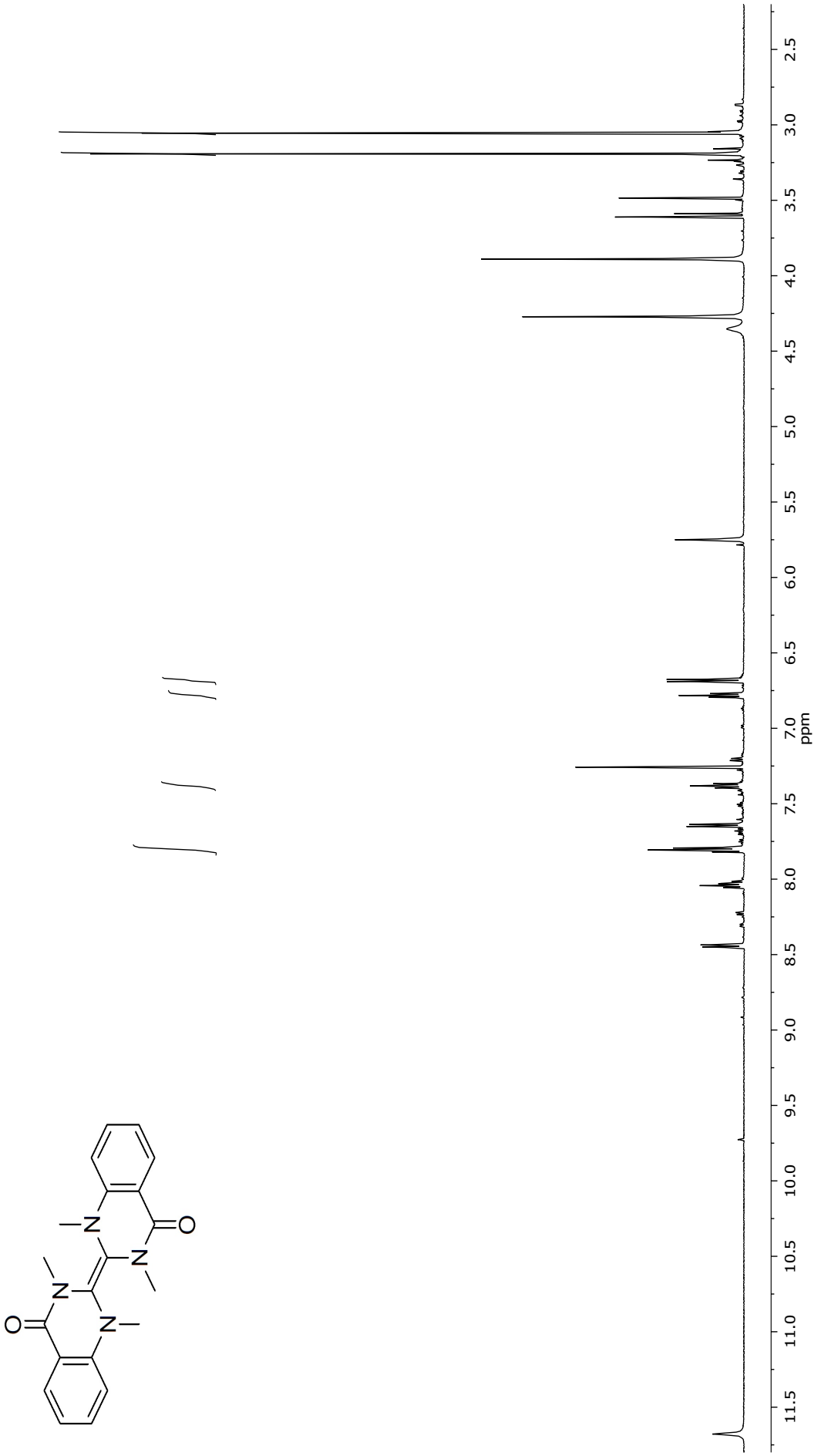
^{13}C-NMR spectrum of **41** with pyridine (125 MHz, $CDCl_3$)



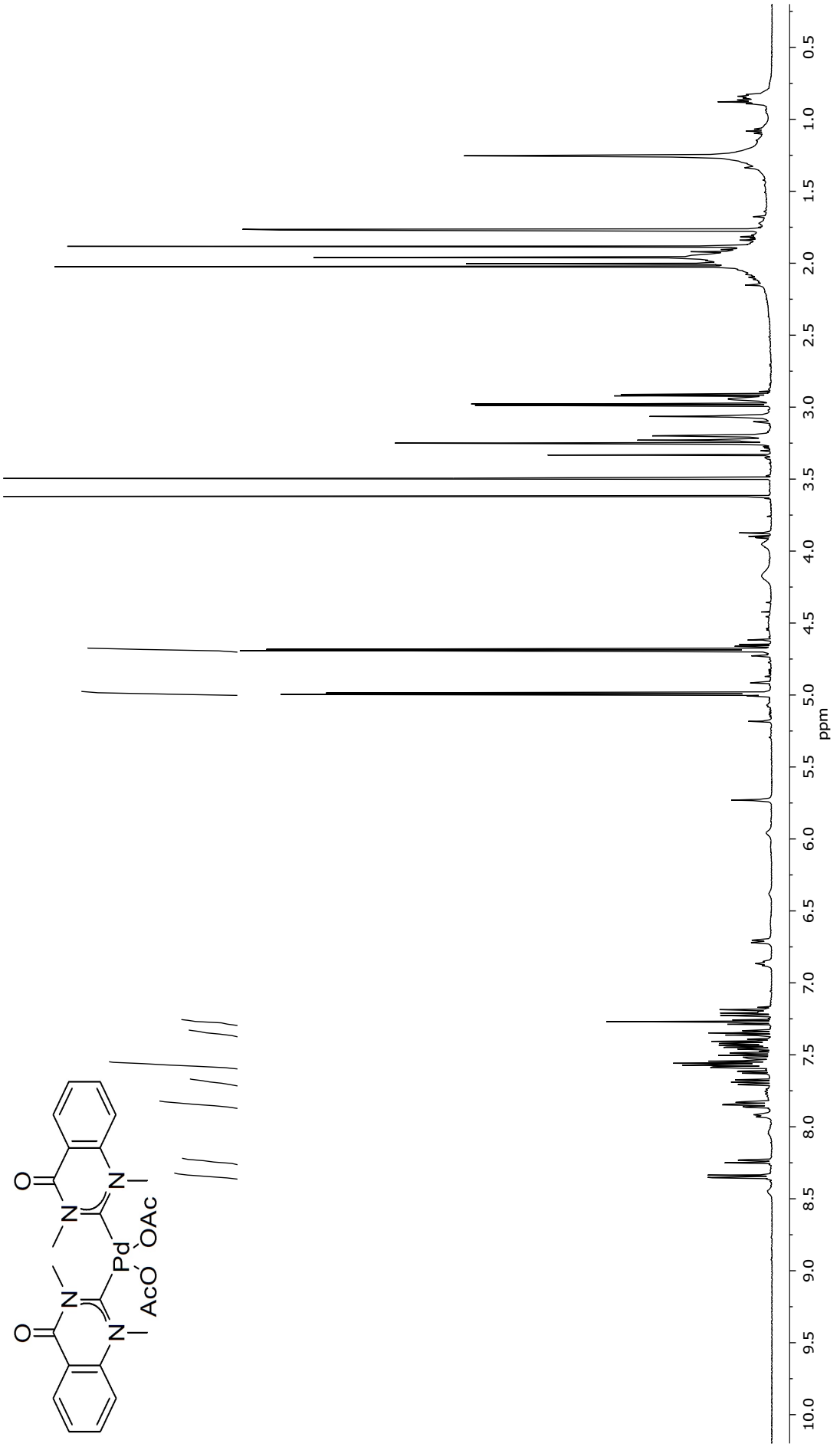
^{1}H-NMR spectrum of **32** (500 MHz, $CDCl_3$)



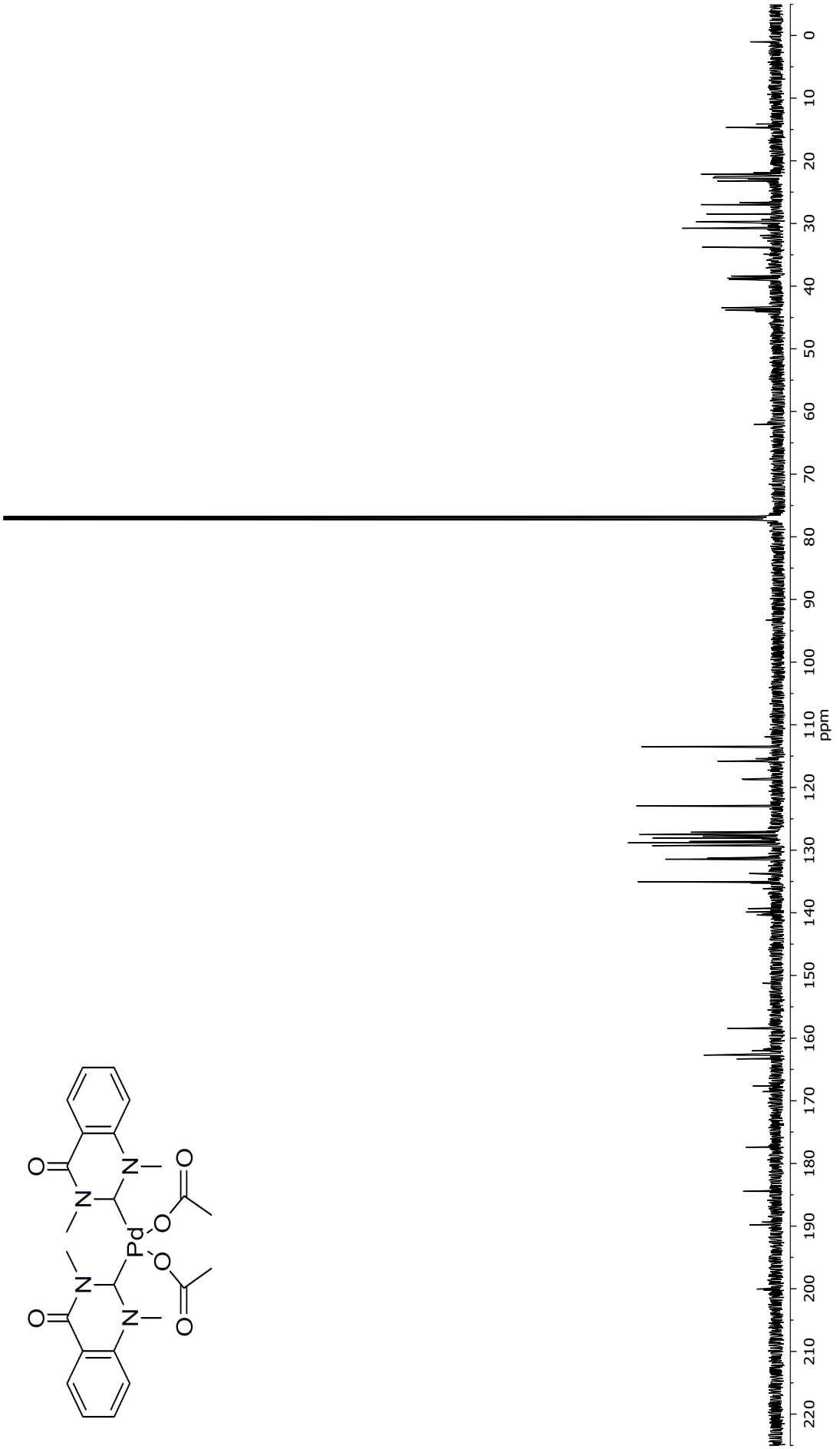
^{13}C-NMR spectrum of **32** (125 MHz, $CDCl_3$)



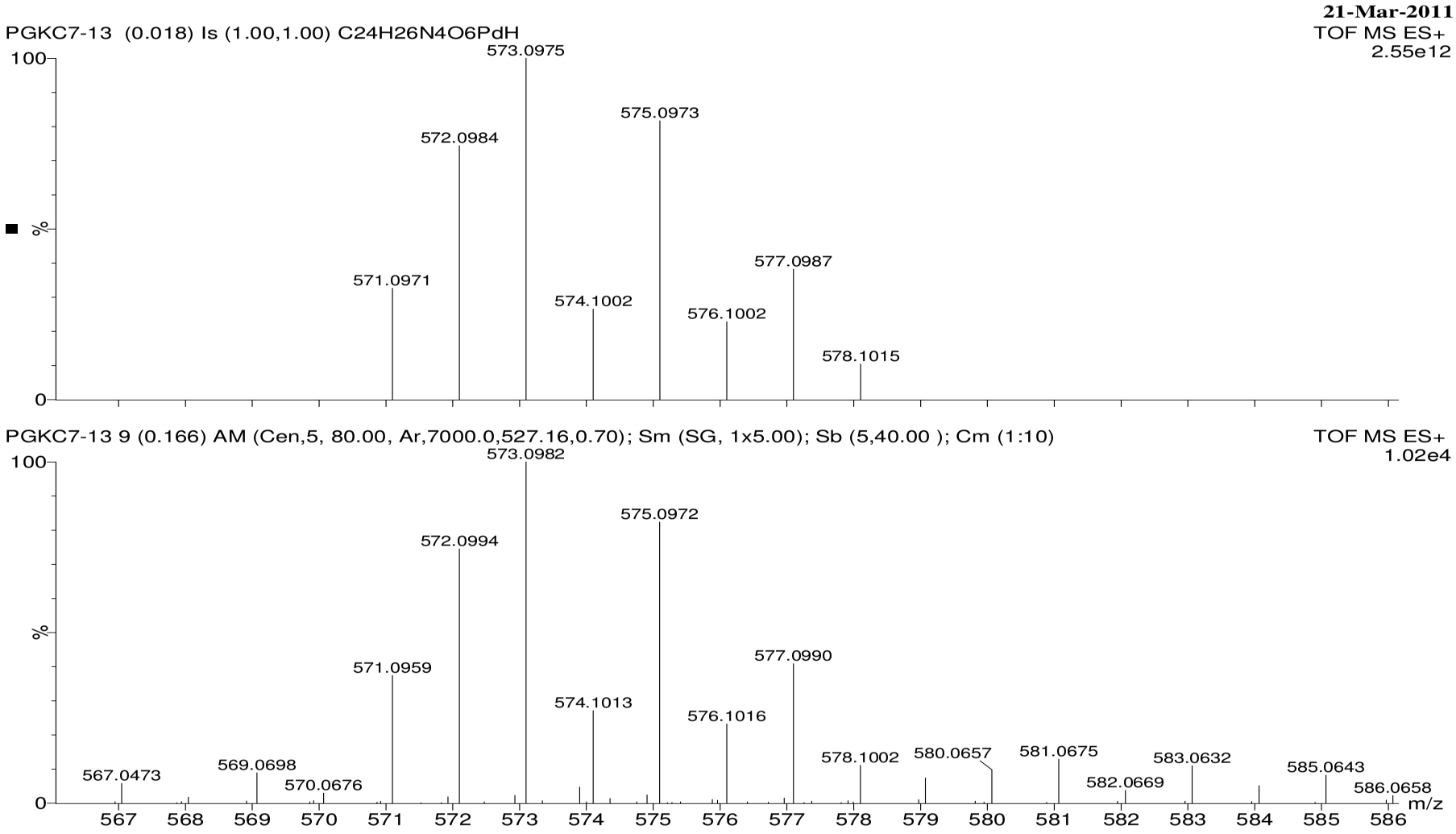
^{1}H-NMR spectrum of **84** (600 MHz, $CDCl_3$)



^{1}H-NMR spectrum of **98** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **98** (125 MHz, $CDCl_3$)



MS spectrum of **98** with predicted $[M+H]+$ for this species (HR-ESI-MS)

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