Synthesis and Reactions of Pyridinium-Derived Aminals

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ABSTRACT

Synthesis and Reactions of Pyridinium-Derived Aminals

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This research focuses on the synthesis of a series of aminals which contain a pyridinium subunit : $\geqslant N^{+}\text{-}CH_2\text{-}O\text{-}$.

Theoretical calculations done on the (1-pyridinio)methoxide zwitterion propose that it is unlikely to form due to its instability.

We have evidence for the formation of this reactive intermediate through the trapping of it, in compounds such as: N-(hydroxymethyl) **75**, N-(acetoxymethyl) **76d-f** and N-(trimethylsiloxymethyl) **76b,c** pyridinium salts. In addition, we have discovered that the highly doubted pyridiniomethanol is stable enough to be isolated and undergo conversions to derivatives such as: N-(acetoxymethyl) **76d** and N-(chloromethyl) **72a** pyridinium chlorides and two N,N'-(methylene)bispyridinium salts **91a,b**.

Another aspect that was investigated in the process, concerned the nucleophilicity of the highly reactive species; formaldehyde and its ability to displace a moiety bound to the nitrogen on pyridine to create a $N\text{-}CH_2\text{-}O\text{-}[R]$ functionality.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

INDEX TO TABLES

CHAPTER I. INTRODUCTION

Pyridine is a nitrogen-containing heterocyclic compound that can also be referred to as a tertiary amine. The trivalent nitrogen possesses a lone pair of electrons that can be readily donated to a variety of electrophilic species to create pyridinium salts.

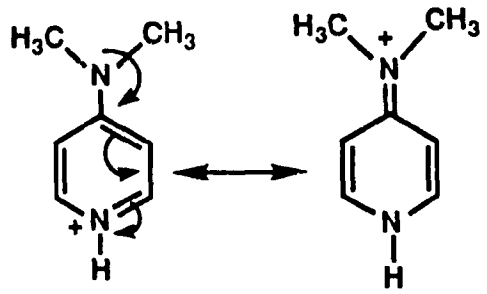
Pyridine can react with electrophiles such as protons, simple alkyl halides, acyl halides and even other pyridinium salts to yield both stable and unstable compounds. The latter sometimes react further with a second nucleophile until a more stable structure is produced. Therefore, pyridine can be considered to be both a base and a nucleophile and under appropriate conditions, this compound can also react at various positions on the ring.

1. PYRIDINIUM SALTS

1.1. Protonation of pyridine and its derivatives

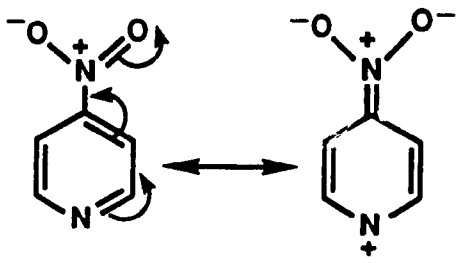
N-protonated pyridine has a $pK_a = 5.20$ and therefore is more acidic than N-protonated aliphatic amines ($pK_a \sim 10$). Pyridine can therefore be considered a weaker base than aliphatic amines. Nonetheless, pyridine and its derivatives are regularly used as bases in organic reactions. Substituents exert an influence on the relative acidity of the protonated pyridine nitrogen, either increasing it due to their electron-withdrawing nature or decreasing it via an electron-donating effect.

These substituents, it has been found in a well known study[1], affect basicity in very different ways. A strongly electron-withdrawing group raises the pK_a by both resonance and inductive means. Through resonance electron delocalisation, an electron donating dimethylamino substituent can strongly stabilise a protonated pyridine[2]. The position of the substituent can influence basicity as well. While a t-butyl group on the 4-position may increase basicity through inductive effects, if two t-butyl groups are present on both ortho carbons as in 2,6-di-t-butylpyridine, the steric effect outweighs the electronic ones. The pK_a in this case drops to 3.58. The smaller methyl groups on 2,6-lutidine provide much less steric hindrance to nucleophilic attack by the pyridine nitrogen, while they exert a strong electronic effect which greatly increases the basicity of the substituted pyridine ($pK_a = 6.69$).



In terms of electron-withdrawing substituents, a comprehensive study[1] has concluded that any resonance effects contributed to the pyridinium ion acidity (pyridine basicity) are small or negligible.

That is, resonance structures contribute minimally to the proton abstracting ability of pyridine.



Pyridinium ion acidity increases with the following substituents in the para positions; $CH_3C(O) \sim RC(O)O < CF_3 < CN < NO_2$; this order reflects that expected as a result of inductive effects.

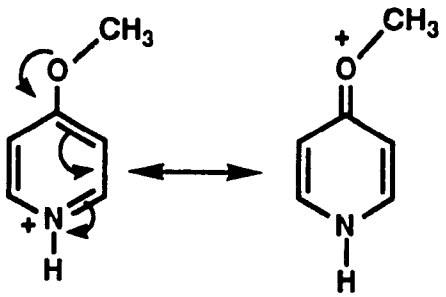
This can be contrasted to the effect that strong pi-donor substituents have on the acidity of the pyridinium cation. The resonance structures contributing to the stability of the protonated pyridinium cation have a much greater influence on decreasing its acidity. Pyridine basicity increases in the order;

$$m\text{-}OCH_3 < H < m\text{-}CH_3 < p\text{-}CH_3 < p\text{-}OCH_3 << p\text{-}NH_2 < p\text{-}NMe_2$$

$$pK_a = \quad 4.91 \qquad 5.2 \qquad 5.68 \qquad 6.02 \qquad 6.47 \qquad 9.25 \qquad 9.71$$

due to both inductive and resonance effects exerted by these electron-donating substituents[3].

The influence of resonance stabilization is especially evident when comparing the 3-methoxy-pyridinium ion, where the



electron-donation or attraction can only be inductive, to 4-methoxypyridinium ion where the stability of the ion is greatly enhanced by the resonance effect. Johnson et al[3] also concluded that all of the substituent effects observed with respect to nitrogen reactivity are intrinsic properties of the heterocycle itself and not a result of reaction type or solvent. This intrinsic nature of pyridine and its derivatives applies not only to protonation of the nitrogen but also to its reaction with other electrophiles, i.e. alkyl halides, etc.

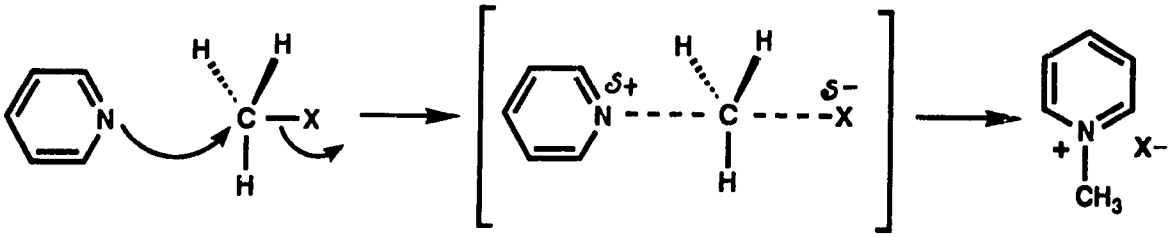
1.2. Alkylation/Arylation of pyridines

1.2.1. General principles (dependence on substituents and solvent).

Before discussing the effects of electron-withdrawing or releasing substituents on pyridine nitrogen reactivity, it is necessary to understand the mechanism of salt formation from pyridine and alkyl/aryl halides. The Menschutkin reaction, which is simply the N-alkylation of pyridine, has always been thought to occur through a classical S_N2 mechanism ie. a one-step displacement of a leaving group by a nucleophilic attack from the opposite side.

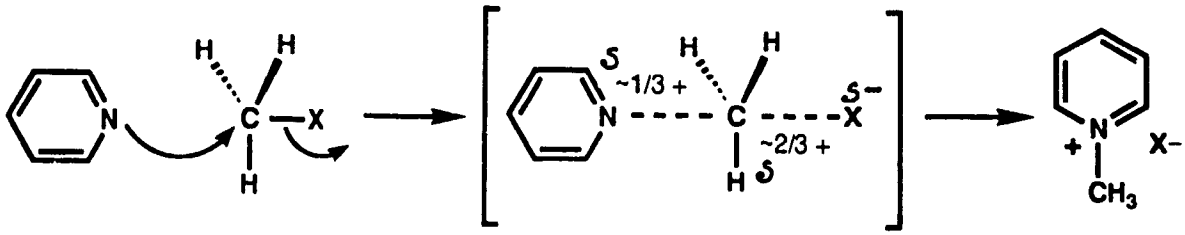
This school of thought has been challenged by Arnett and Reich[4], who state that the classical S_N2 transition state structure where the extent of bond-making and bond-breaking is about equal, is incorrect.

Scheme 1



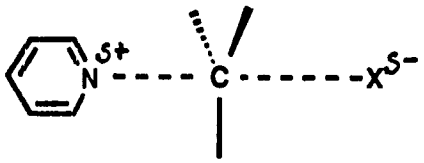
The transition state they propose involves less than 30% bond formation between the pyridine nitrogen and the alkyl α-carbon, while the αC-halide bond is highly polarized (largely ruptured).

Scheme 2



This of course involves quite extensive participation by an aprotic dipolar solvent to stabilize (solvate) the large positive charge developed about the carbocation as well as the negatively charged leaving group.

Kevill[5] refutes this novel proposal on the grounds that the transition state is of a higher energy than that formed through classical S_N2 route making for a rather unstable structure. He maintains that this transition state structure involves the build-up of almost 2/3 positive charge on the αC as well as a very large negative charge on the leaving anion. This would require an unrealistic amount of solvation to stabilize.



Kevill concludes that the classical S_N2 approach is more accurate, with approximately synchronous bond-making and bond-breaking so as to minimize the build-up of charge on the αC of the electrophile.

In terms of the effect that substituents have on pyridine nitrogen reactivity, this appears to be an intrinsic property of the heterocycle and influences N-alkylation similarly to the way it does protonation[3]. That is not to say that solvent type does not affect

reaction rates. It appears that the alkylation of various substituted pyridines with ethyl iodide occurs slightly faster in methylene chloride than in nitromethane while in a protic solvent, such as methanol, the reaction rate decreases by two orders of magnitude. Another difference between solvents like methylene chloride and methanol is how they affect alkylation rates of various substituted pyridines.

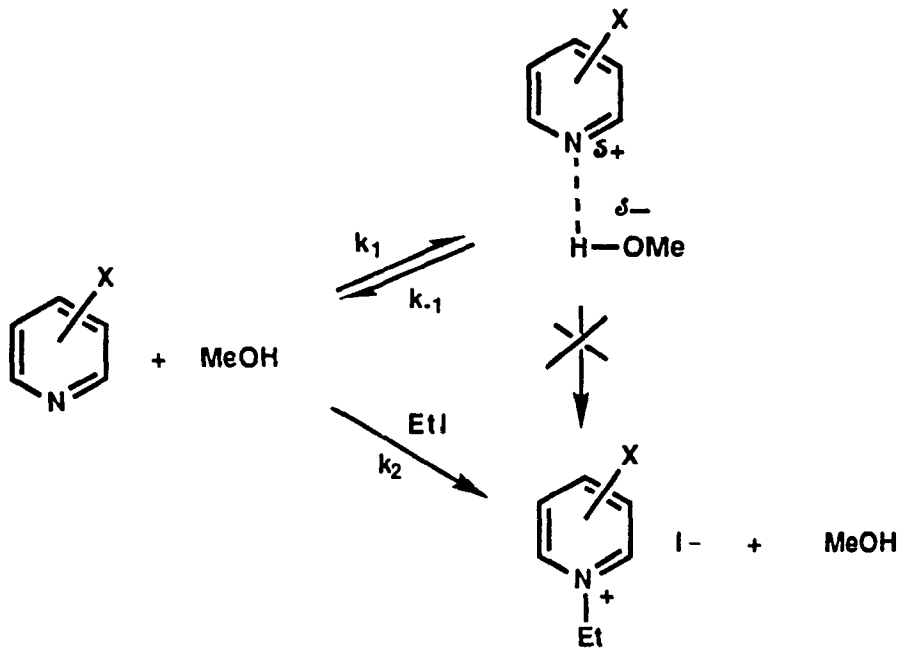
Table 1 Alkylation Rates of Substituted Pyridines in Methylene Chloride and Methar ol

SUBSTITUENT	Rate Coefficient X 10^6 (CH_2Cl_2*)	Rate Coefficient X 10^6 (MeOH)
4-NMe_2	787	1.47
4-OEt	117	1.15
4-Me	89.1	1.21
4-H	32.9	1.12
4-COMe	9.44	1.07
4-COEt	9.17	-
4-CN	2.36	-

* similar rate changes occur in solvents like CH_3NO_2 , $HCONMe_2$ and CH_3CN

Pyridine is much more sensitive to the electron-withdrawing or donating nature of its substituents in dipolar aprotic solvents than in methanol. An explanation for this could be provided by the fact that solvation of the pyridine nitrogen, by H-bonding with methanol, decreases its reactivity.

Scheme 3

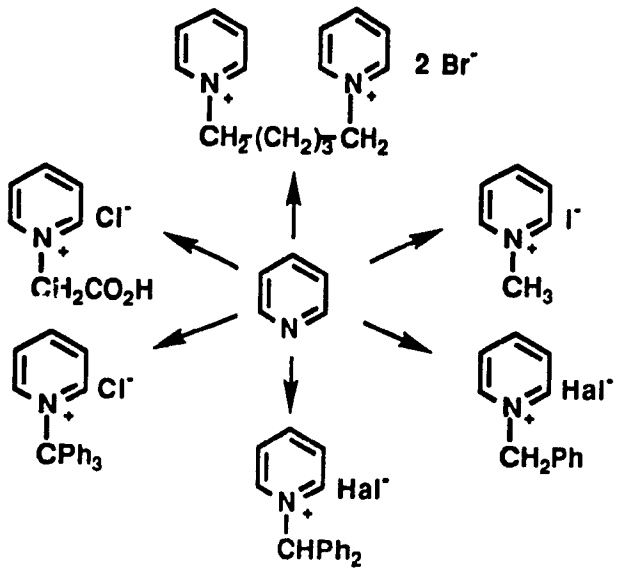


Free pyridine probably exists in equilibrium with the hydrogen bonded species and therefore, since reaction with ethyl iodide can only occur on the former, the rate drops considerably. From the kinetic experiments performed, it was concluded that the H-bonded form of pyridine greatly predominates over the free molecule. The rate of alkylation, then, becomes dependent on the equilibrium constant.

1.2.2. Some alkylations of pyridine and its derivatives

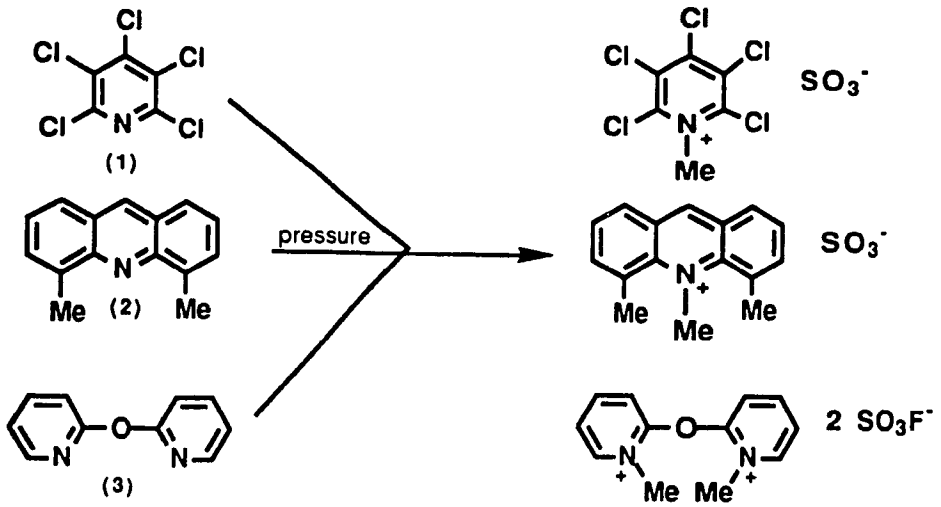
Pyridine undergoes a variety of alkylations based on the classical Menschutkin reaction[6].

Scheme 4



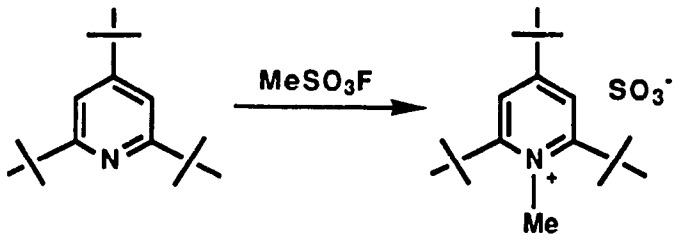
Most alkylations of pyridine and its derivatives can be achieved quite readily under mild conditions unless either the heterocycle or the alkylating agent is very sterically hindered. Methylation is usually a very straightforward reaction unless the compound to be methylated is, for example, pentachloropyridine **1**, acridine **2**, or di-2-pyridyl ether **3**. These have all been quaternized successfully with the "super-methylating" agent, methyl fluorosulfonate[6]

Scheme 5



2,6-Di-t-butylpyridine can be methylated with methyl iodide under pressure to yield only 20% of the desired product, yet 2,4,6-tri-t-butylpyridine reacts with methyl fluorosulfonate to produce, in 60% yield, the corresponding N-methylated pyridine.

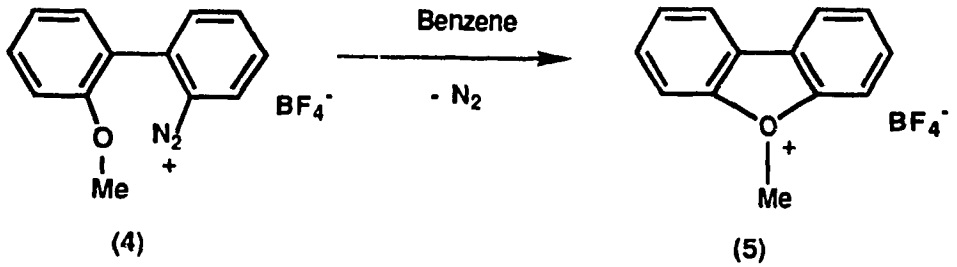
Scheme 6



This product is quite stable even at 250°C and one explanation may be that the 2 and 6 t-butyl groups behave like "claws" keeping the N-methyl groups in place[7].

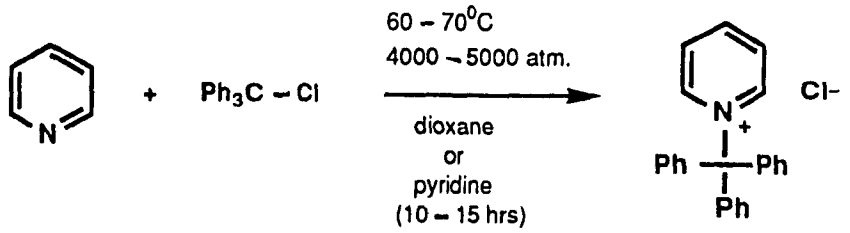
Pentachloropyridine has also been methylated in 32% yield using the Meerwin reagent[8] which is generated by heating **4** to yield O-methyldibenzofuranium fluoroborate **5**, the latter which functions as a very powerful methylating agent.

Scheme 7



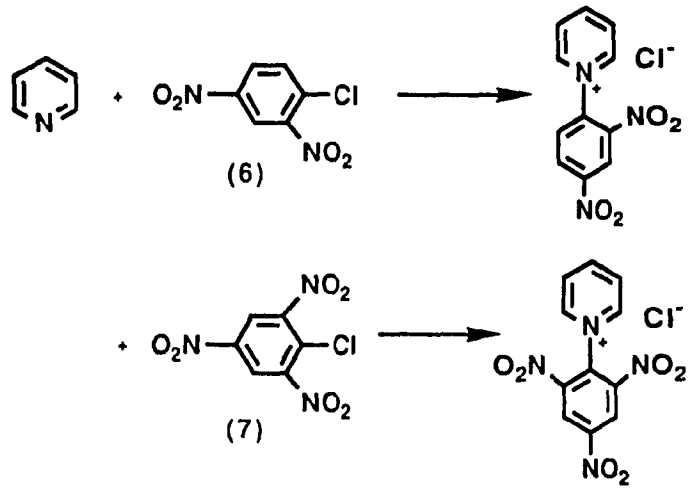
As mentioned, N-alkylations/arylations can also present a problem if the electrophilic species itself is very sterically hindered. A good example of this is the N-tritylation of pyridine which requires very high pressures and elevated temperatures[9].

Scheme 8



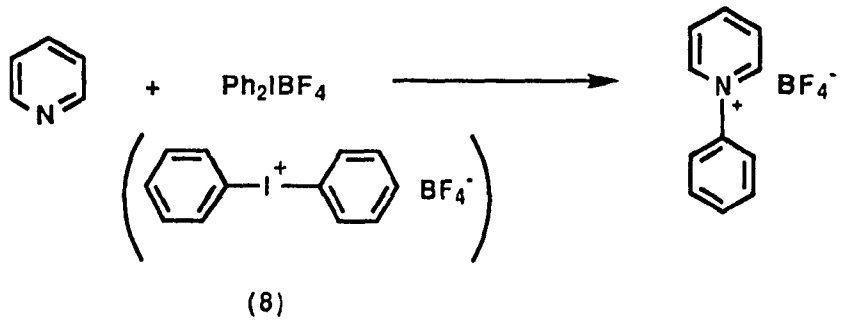
Another reaction, under both steric and electronic control, is the N-arylation of pyridine which only occurs with activated aryl halides i.e. 2,4-dinitrochlorobenzene **6** or picryl chloride **7**.

Scheme 9



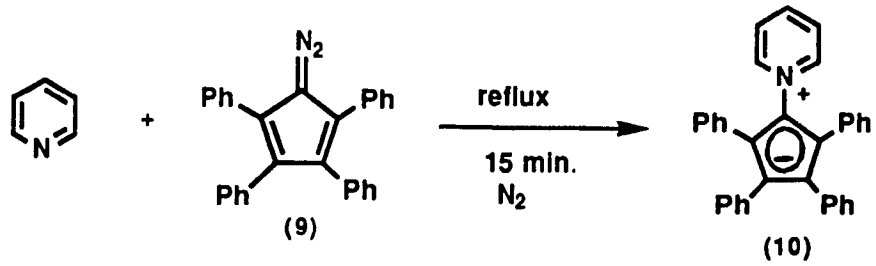
Pyridine can also be arylated with a simple phenyl ring using the reagent diphenyliodonium fluoroborate **8**[6].

Scheme 10



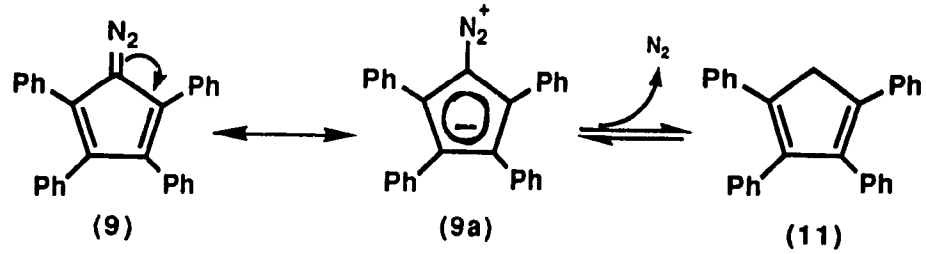
Lastly, a very interesting N-alkylation involves the displacement of N_2 to yield pyridinium tetraphenylcyclopentadiene **9**[10].

Scheme 11



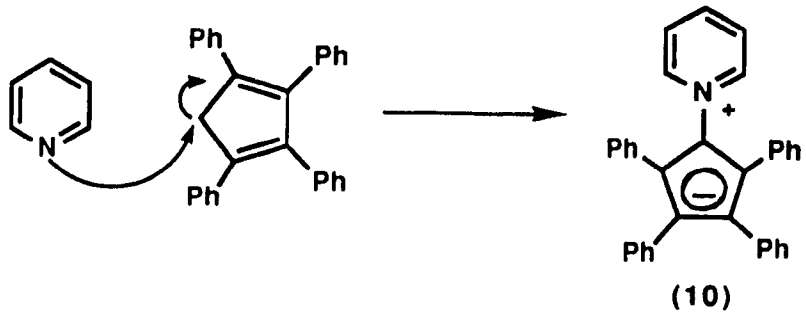
It is presumed that **9**, which also exists as the resonance form **9a**, undergoes thermolysis to yield the reactive carbene **11** in situ.

Scheme 12



It, in turn, reacts with pyridine to yield the desired product **10**. The mechanism may involve nucleophilic attack by the pyridine nitrogen on the carbene; the driving force perhaps being formation of aromaticity on the cyclopentane ring.

Scheme 13

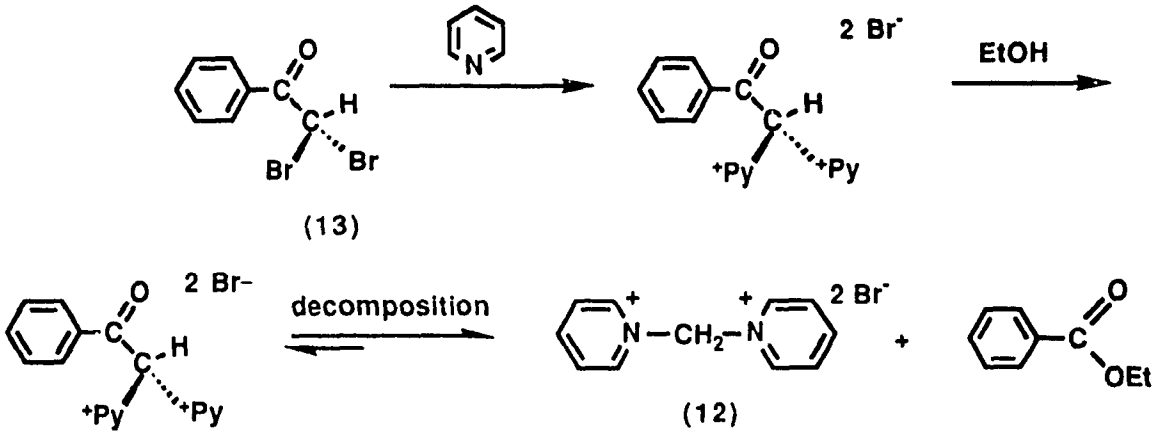


The final compound **10** is known to be a stable ylide, possibly because both ring systems are aromatic and the charges are well stabilized over many resonance forms.

1.2.3. Synthesis of 1,1'-(methylene)bispyridinium compounds

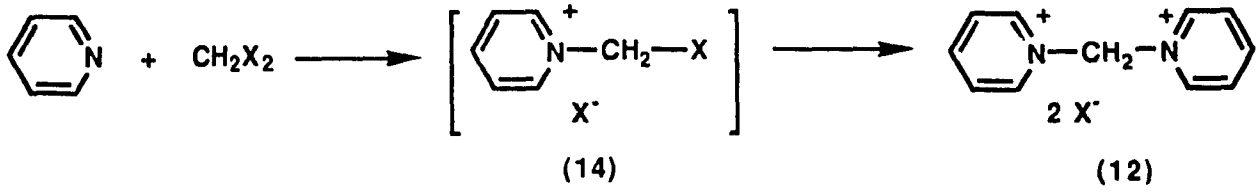
A number of 1,1'-(methylene)bispyridinium halides **12** have been synthesized by two main methods. The first to have developed a preparation for this compound was Krohnke[11] from ω,ω-dibromoacetophenone **13** and pyridine in ethanol. The mechanism involves successive attacks by two pyridine molecules[12];

Scheme 14



The salts **12** can also be formed via a reaction of pyridine with various dihalomethanes but their relative reactivities with pyridine varies[12].

Scheme 15



12 (X-)	Conditions
I-	50°C / 18 hrs / CH_2Cl_2
Br-	70°C / 72 hrs / CH_2Cl_2 / MeCN
Cl-	25°C / 10 kbar / 18 hrs / CH_2Cl_2

Dihalomethane activity follows the well established order; $CH_2Cl_2 < CH_2Br_2 < CH_2I_2$ with CH_2I_2 reacting the fastest, at the lowest temperature and CH_2Cl_2 the slowest, requiring additional pressure. It is interesting to note that the rate of formation of the mono(halomethyl)pyridinium salt is slower than that of the desired product **12**. The authors believe that the formation of salt **14** facilitates the displacement of the second halide (from **14**) by activating the α-methylene carbon towards nucleophilic attack by another pyridine molecule.

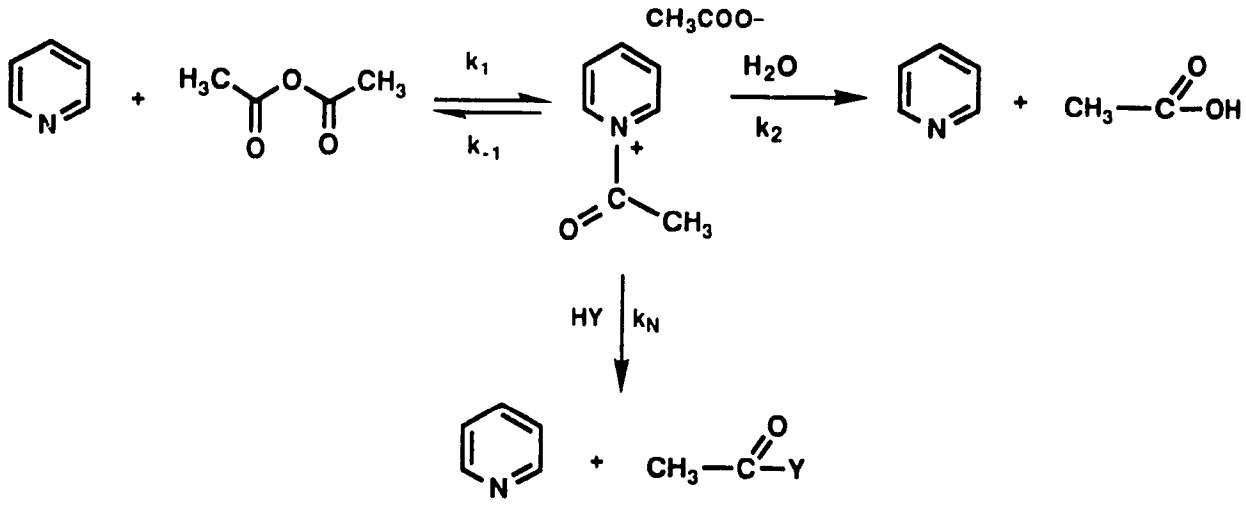
Similar syntheses were then attempted with some derivatives of pyridine. The same basic experimental technique was used, which consisted of refluxing equimolar amounts of the 4-substituted pyridines and dibromomethane in acetonitrile or ethanol. The time requirements tended to be less if the substituent was electron-donating. The reaction mixture with 4-(dimethylamino)pyridine was refluxed for only a few hours to yield the desired product. Surprisingly, the NMR of the methylene protons, although correct in splitting and integration, appeared at a chemical shift that was 1.2 ppm upfield from that of the unsubstituted compound **12**. Many of the other bispyridinium salts synthesized (4-CH_3, 4-CN, 4-$C(O)C_6H_5$, 4-CHO) did not display this extreme upfield shift in the methylene peak, but much more closely resembled the parent compound(+/- 0.3 ppm)[13].

1.3. Synthesis of acyl-pyridinium salts

1.3.1. Kinetics and pyridine as a nucleophilic catalyst

Pyridine can be N-acylated readily by acyl halides or acyl anhydrides but the resulting pyridinium compounds are not very stable; They are easily hydrolyzed by H_2O or nucleophiles HY (methanol and other protic solvents). Pyridine behaves as an excellent leaving group and can be displaced by even moderately strong nucleophiles[14].

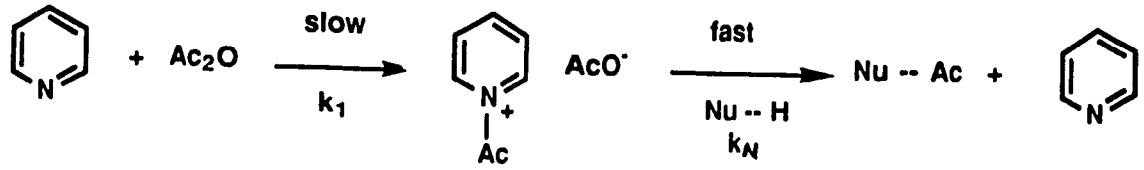
Scheme 16



For this reason, pyridine is referred to as a nucleophilic catalyst. The instability of an N-acylated pyridine, as opposed to N-acylated 1° or 2° aliphatic amines, is due to the fact that it cannot lose a proton in order to stabilize itself as a neutral amide. As for tertiary amines, they are probably too sterically hindered, relative to pyridine, to react.

In terms of the kinetics of the reaction, the formation of the N-acyl pyridinium salt is the rate determining step, while the subsequent nucleophilic attack and breakdown of the intermediate occurs at a much faster rate.

Scheme 17



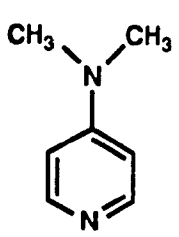
The transition state structure between the N-acylated reactant and the product will occur along the reaction coordinate depending on the strengths of the nucleophile and leaving group. If both are moderately good, the transition state closely resembles a tetrahedral intermediate with about equal bond-formation and bond-breaking. If both are very good, then the transition state will be earlier (with little bond-making and bond-breaking) and if they are poor, the transition state will occur late (with extensive bond-making and bond-breaking)[15].

Pyridine's leaving group ability is influenced by the nature of any substituents on the ring. An electron-donating 4-methoxy group can greatly stabilize the N-acylated pyridine, allowing it to form and react with a nucleophile.

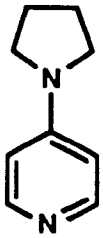
Therefore the catalytic ability of substituted pyridines follows the order; 3-NO_2 < 3-Cl < H < 3-CH_3 < 4-CH_3 < 4-NMe_2[16]

1.3.2. DMAP and other pyridine-derived acylating agents

Compared to pyridine, 4-dialkylaminopyridines are about 10^4 times more efficient as nucleophilic acylating catalysts[17]. Due to the resonance stabilisation of the N-acylpyridinium salts offered by the electron-donating dialkylamino group, these salts form in high concentrations and this accounts for their exceptional catalytic ability. Two examples of such compounds are 4-dimethylaminopyridine (DMAP) **15** and 4-pyrrolidinopyridine (PPY)**16**.



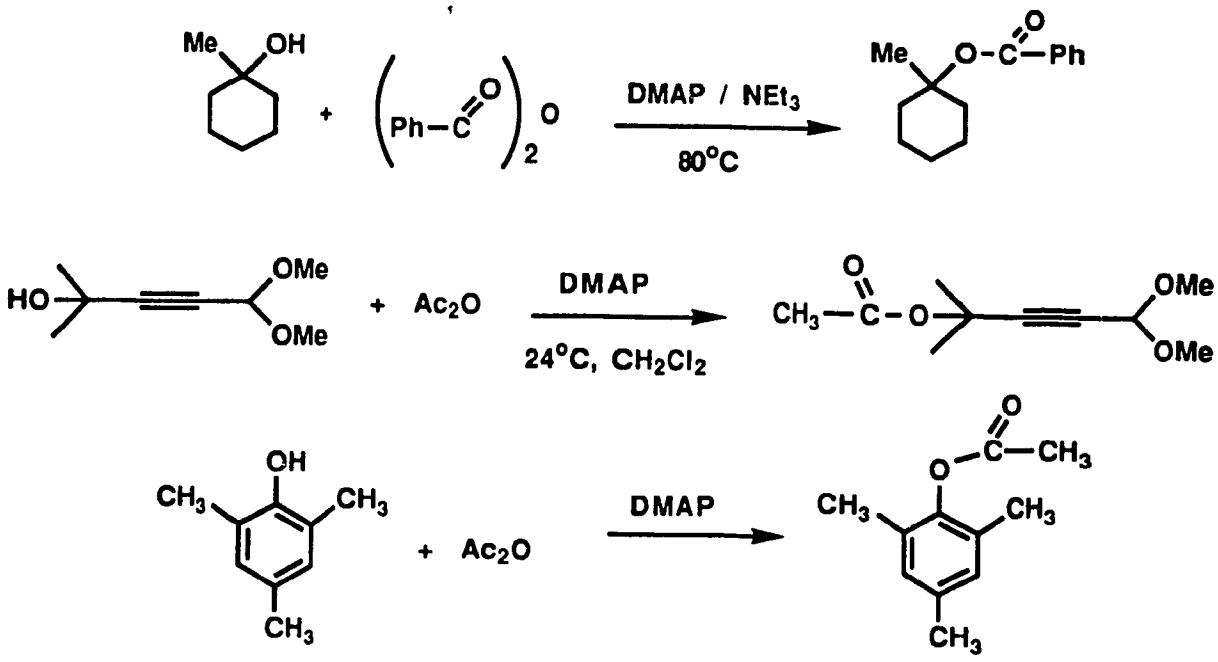
(15)



(16)

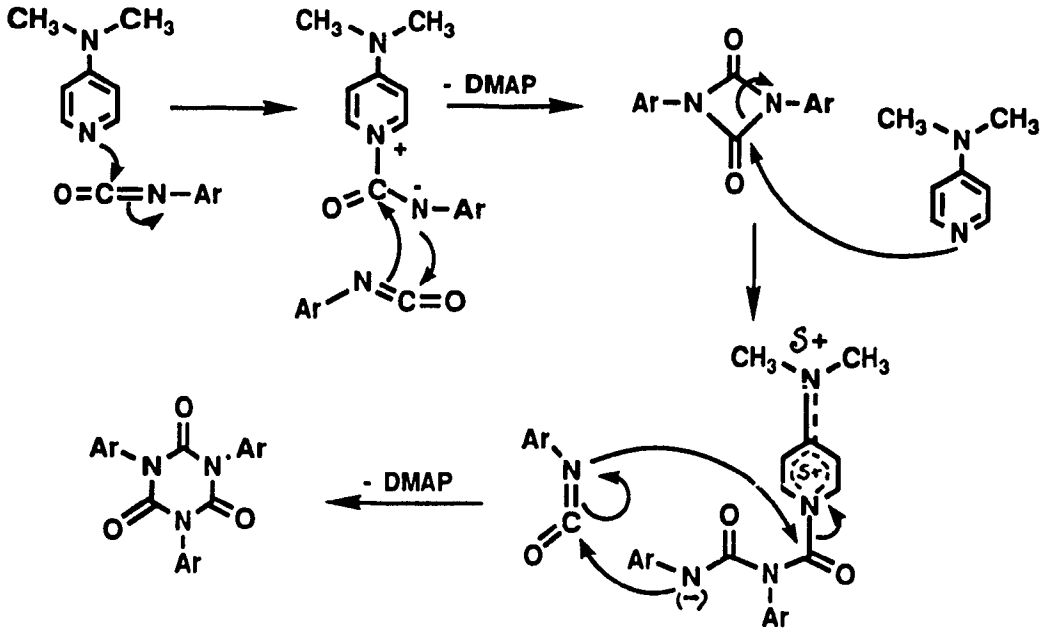
DMAP and PPY can commonly be used in the acylation of sterically hindered secondary and tertiary alcohols as well as phenols, whose acylation cannot be promoted by pyridine.

Scheme 18



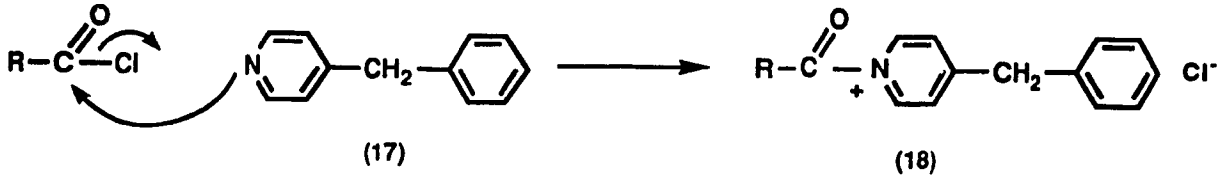
A very interesting oligomerization reaction which is catalyzed by DMAP is possible between arylisocyanate molecules; first the dimer forms and then the trimer.

Scheme 19



A very versatile acylating agent has been synthesized[18], from acyl chlorides and 4-benzylpyridine 17.

Scheme 20

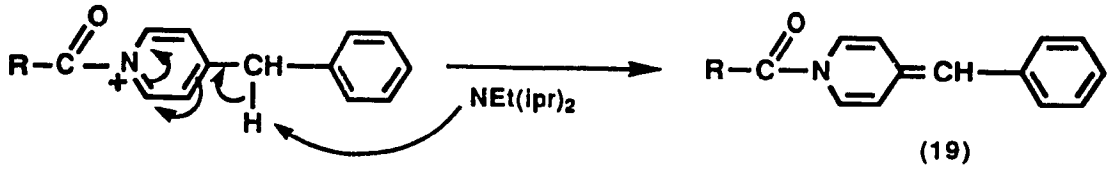


(17) (18)

Once the acylated structure **18** has been formed, a very acidic methylene proton is created.

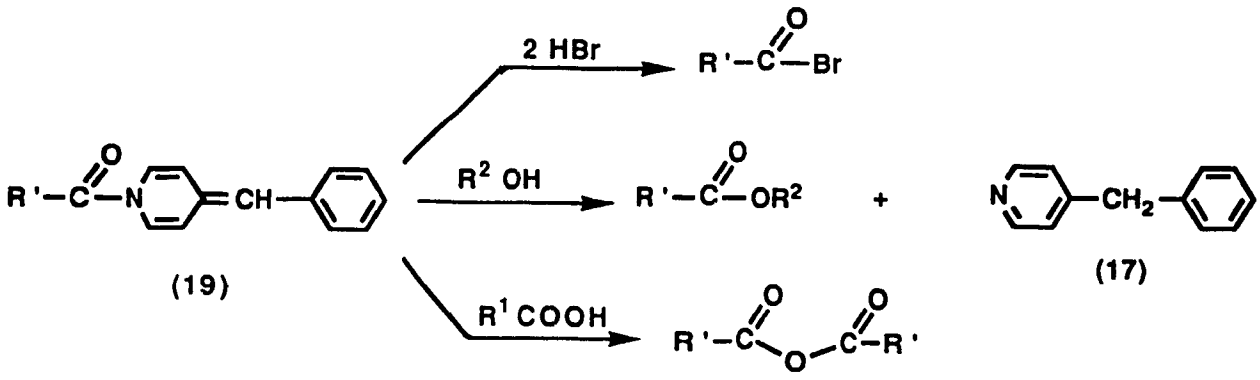
It is removed by the subsequent addition of base to create the ultimate acylating agent, 1-acyl-4-benzylidene-1,4-dihydropyridine **19**.

Scheme 21



Compound **19** can then catalyze the acylation of a bromide ion (in the form of HBr), alcohols, and carboxylic acids while regenerating **17**. This is useful for acylating nucleophiles possessing an acidic proton.

Scheme 22



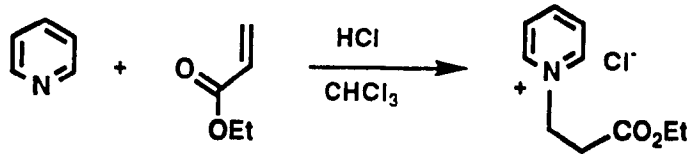
Therefore it serves as a unique route for the conversion of acyl chlorides to acyl bromides, esters, and anhydrides.

1.4. Displacement of a proton from protonated pyridinium salts by nucleophiles

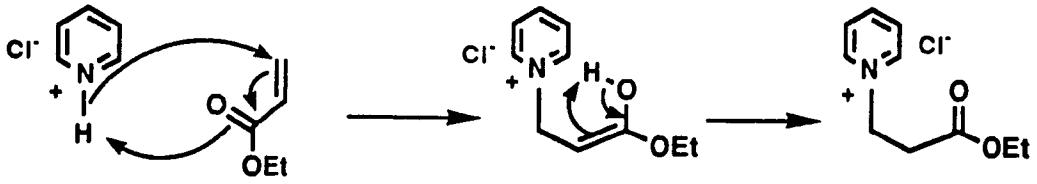
Pyridine must not necessarily be in its neutral form in order for the heteroatom to react with another compound. Reactions are possible between protonated pyridinium salts and reagents which behave as both nucleophiles and electrophiles. Examples of these are reactions between protonated pyridinium halides and alkenes or alkynes.

The following type of reaction[6] is said to work best using pyridinium hydrochloride.

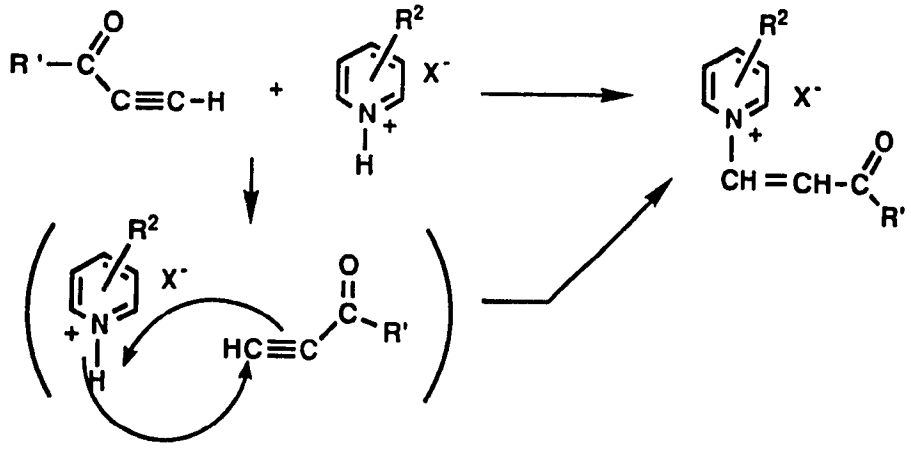
Scheme 23



It follows the proposed mechanism below;

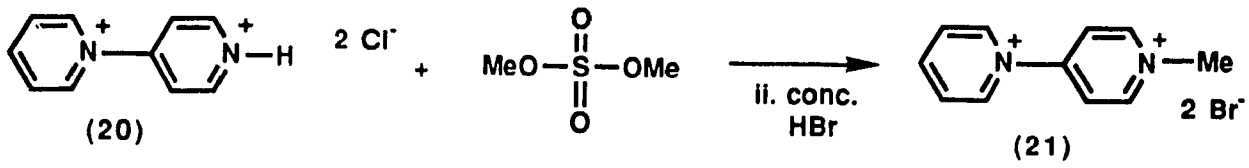


Similarly, alkynes may also be considered to be electron-donating and electron-accepting[19] ;



The compound 1-(4'-pyridyl)pyridinium chloride hydrochloride **20** can be converted to 1-(1'-methyl-4'-pyridyl)pyridinium dibromide **21** by the replacement of a proton with a methyl group[20].

Scheme 24

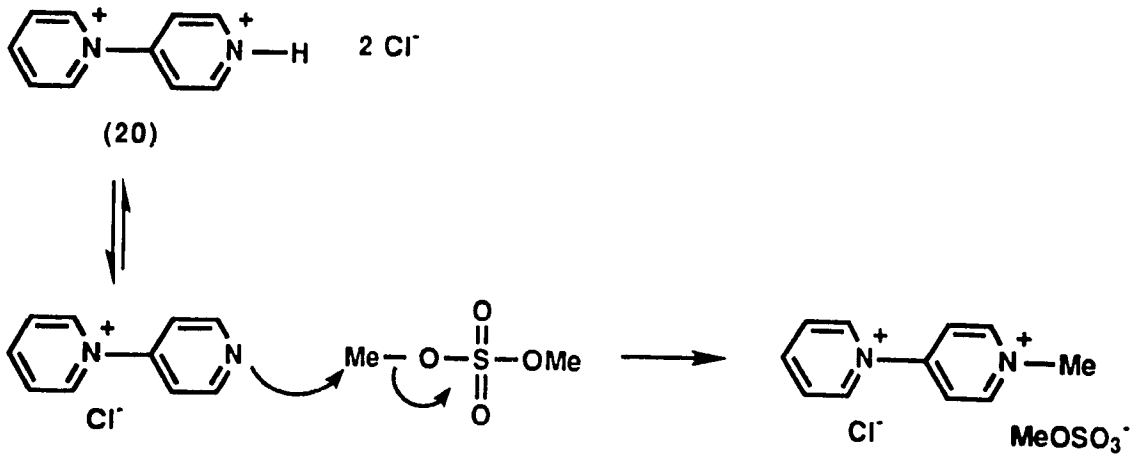


(20) (21)

Following methylation by dimethylsulphate, the methylosulphate and chloride counterions were replaced by bromide (from HBr). When the reaction was attempted with methyl iodide, the only result was the conversion of **20** to the corresponding diiodide.

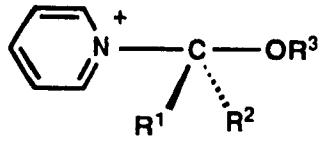
It is likely that some of **20** exists as the deprotonated form which reacts readily with dimethylsulphate but not with methyl iodide. This is probably because of the difference in alkylating ability between dimethylsulphate and methyl iodide.

Scheme 25

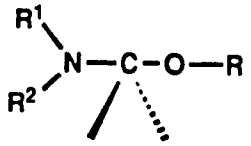


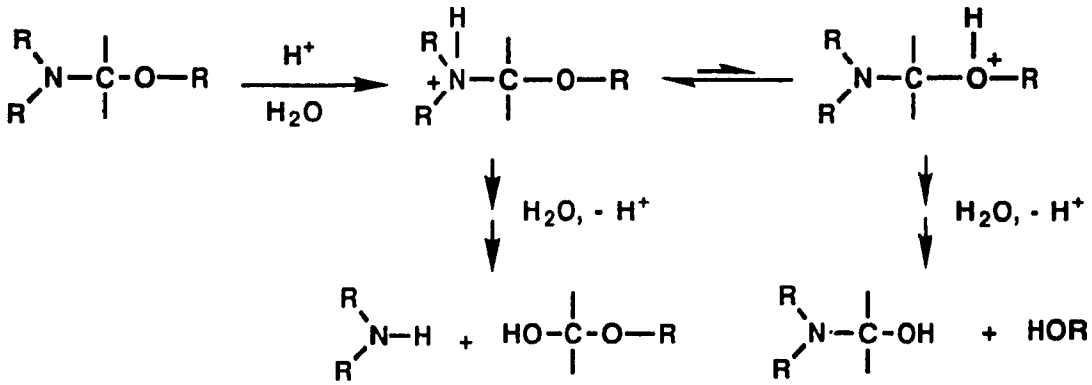
2. PYRIDINIUM - DERIVED AMINALS

Pyridinium-derived aminals, unlike neutral aminals, contain a tetravalent cationic sp^2-hybridized nitrogen.



Neutral aminals, are considerably less stable presumably since they can be easily protonated in an acidic medium which would result, most likely in the hydrolysis of the N - C bond.

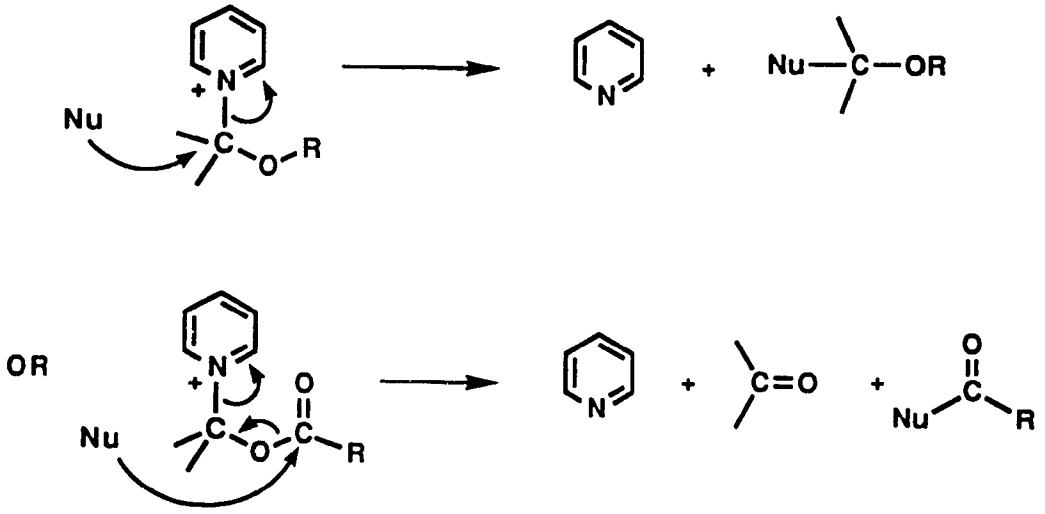




Pyridinium aminals are not susceptible to this acidic hydrolysis since the quaternary nitrogen cannot be protonated. Even if the oxygen atom were protonated (which would be energetically disfavoured since the molecule was already positively charged), there are no lone pair electrons on the nitrogen in order to stabilize it.

For this reason, some N-alkyl/acyloxymethylpyridinium salts are surprisingly stable in aqueous or alcoholic acidic media. Nonetheless, under basic conditions they can be decomposed by nucleophilic attack.

Scheme 26

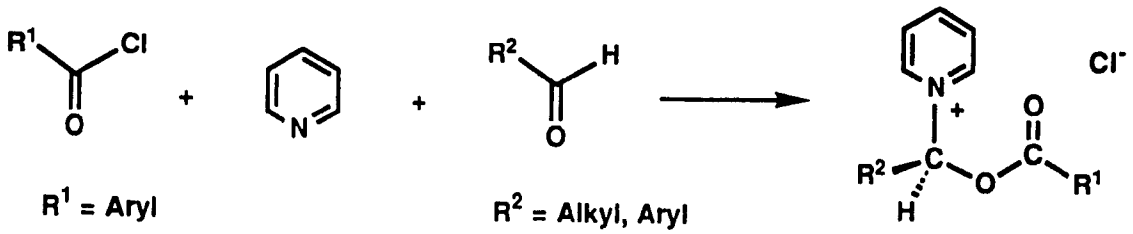


Therefore, like N-acylpyridinium salts, these compounds too can behave as intermediates in the acylation or alkylation of a second nucleophile.

2.1. Aminals derived from acylated pyridinium compounds

E. Anders[21] describes a synthetic scheme for making N-(arylcarbonyloxy) alkylpyridinium salts **22** from pyridine, arene carboxylic acid chlorides and various aryl aldehydes.

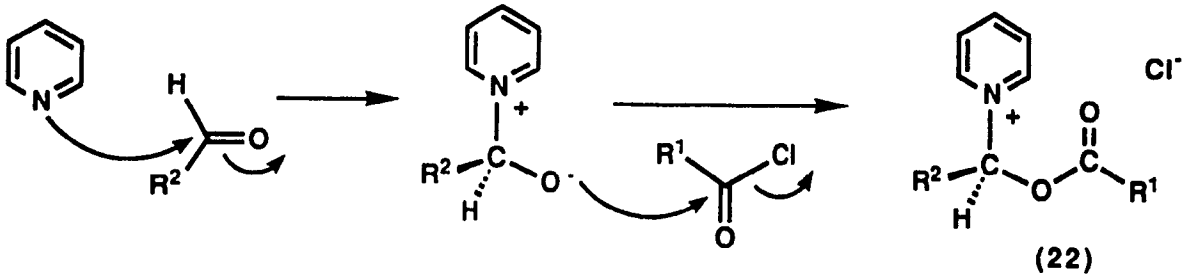
Scheme 27



(22)

Since salts **22** are very hygroscopic, usually crystallizing with one mole of H_2O, the chloride counterions were exchanged with BF_4^-, $SbCl_6^-$, or FSO_3^-. Salts containing these anions do not exhibit this characteristic. In terms of the order of addition, the aldehyde is added to a solution of pyridine followed by the aryl chloride. Therefore, the mechanism may follow the initial formation of a pyridinioalkoxide intermediate which subsequently reacts with the aryl chloride to yield the desired product[22].

Scheme 28

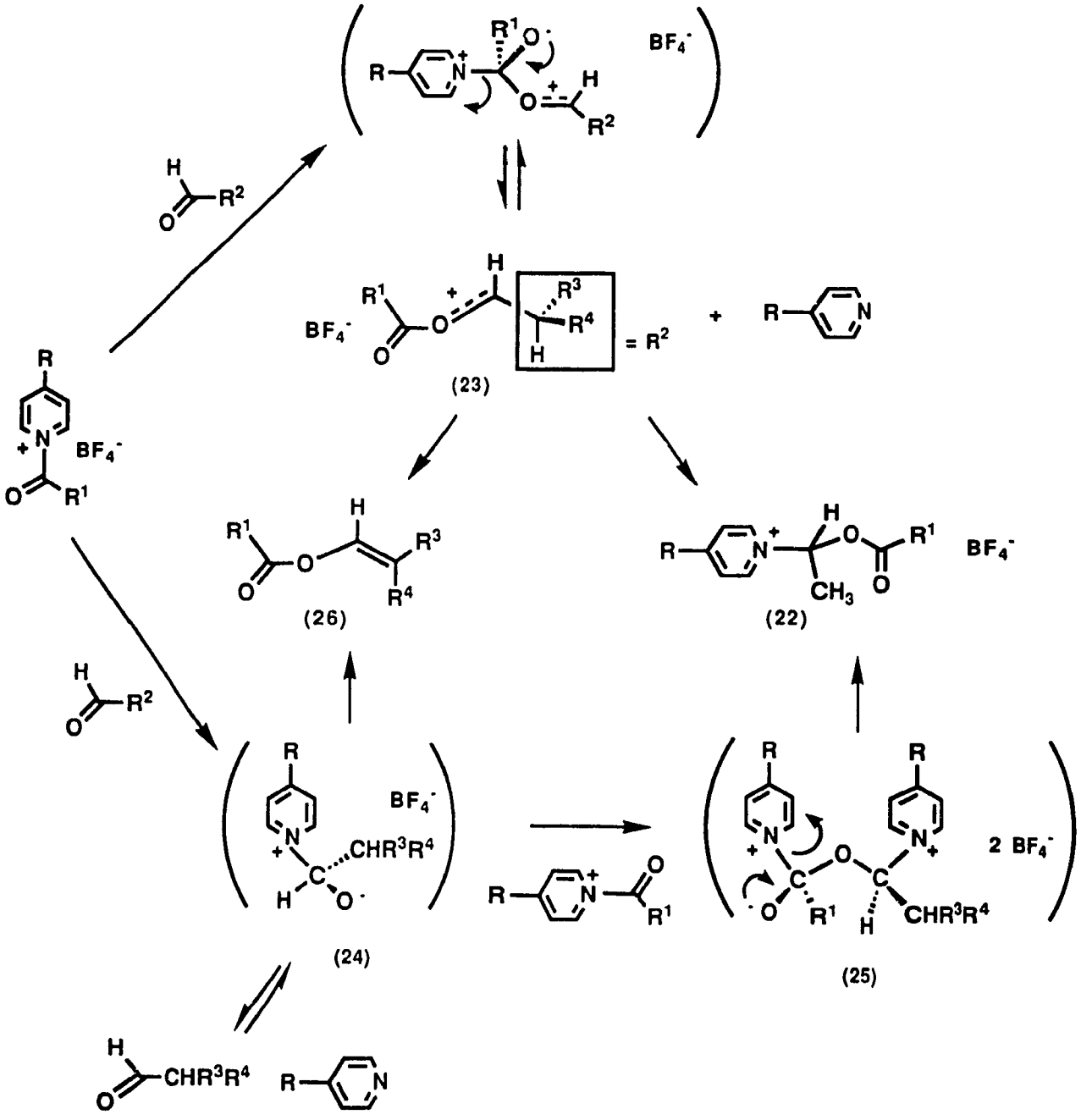


(22)

Alternatively the mechanism may be more complicated, including a number of molecular

rearrangements and intermediates during the course of the reaction. Aside from reacting with the aldehyde to form a zwitterion, pyridine can also be N-acylated by the aryl chloride and the reaction pathway can begin from there.

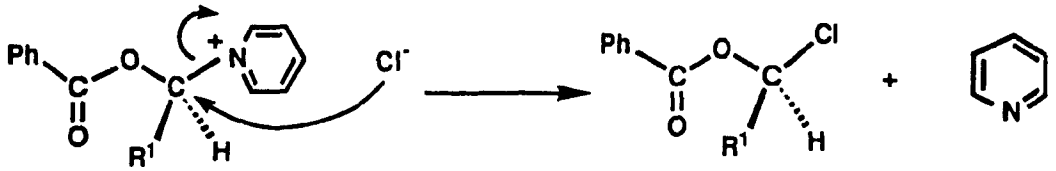
Scheme 29



The authors suggest that the synthesis of **22** could follow one or both of the initial reaction pathways, mainly determined by the formation of the carbenium ion **23** and the zwitterion **24**. It has also been determined that varying the reaction conditions can control whether **22** or **26** is formed. When the reaction is performed at room temperature and excess base (4-benzylpyridine) is present, the pyridinium salt **22** predominates while under reflux conditions (with no excess base), the product is **26**. It appears logical that under reflux conditions the more thermodynamically stable alkenic ester would be formed while at room temperature the less stable pyridinium salt is kinetically favoured.

Several publications discuss nucleophilic substitutions of **22** to synthesize either neutral compounds (regenerating pyridine) or new pyridinium salts. Heating N-(arylcarbonyloxy)alkylpyridinium to about 150°C results in the chloride counter ion nucleophilically displacing pyridine.

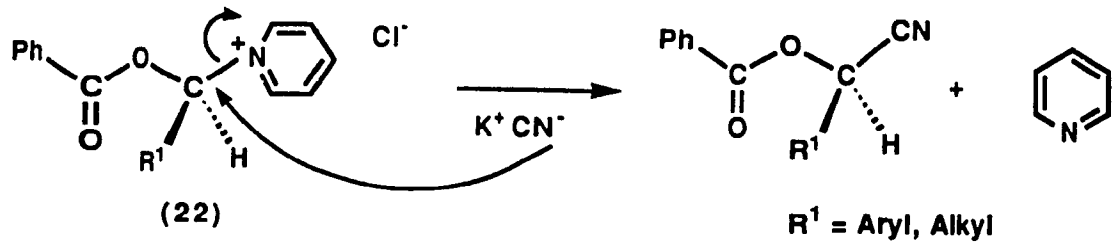
Scheme 30



(22) R^1 = Ph

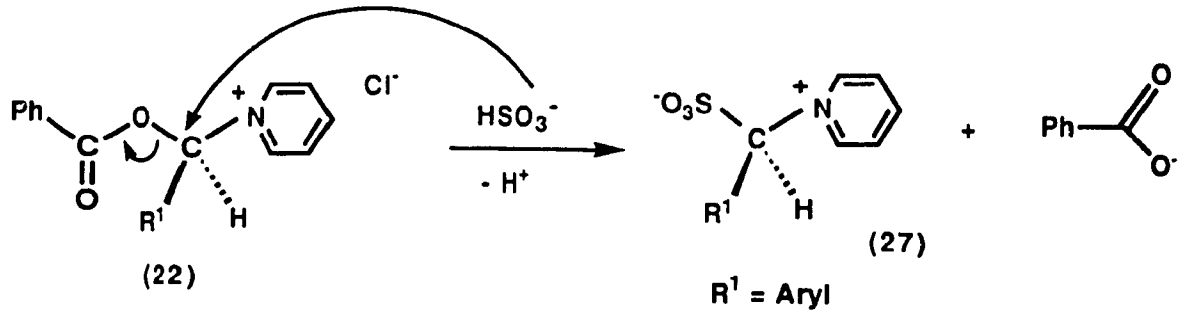
Reaction with aqueous KCN (under mild conditions, 25°C) also results in the displacement of pyridine by CN^-.

Scheme 31



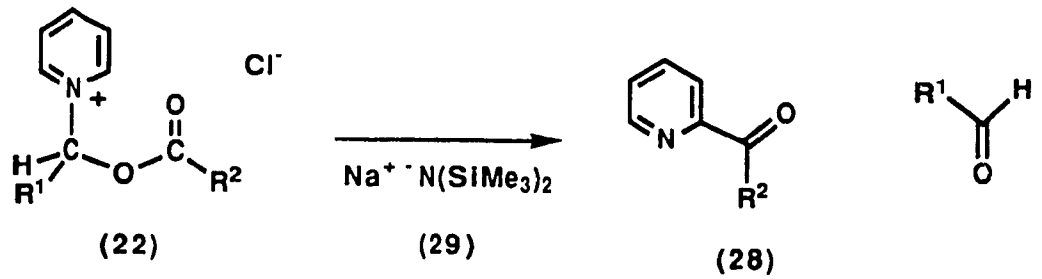
Interestingly though, pyridine is not always the leaving group upon attack by a nucleophile. When $KCN/NaHSO_3$ is reacted with **22**, the bisufite ion displaces a benzoate ion to yield the betaine **27**[21].

Scheme 32



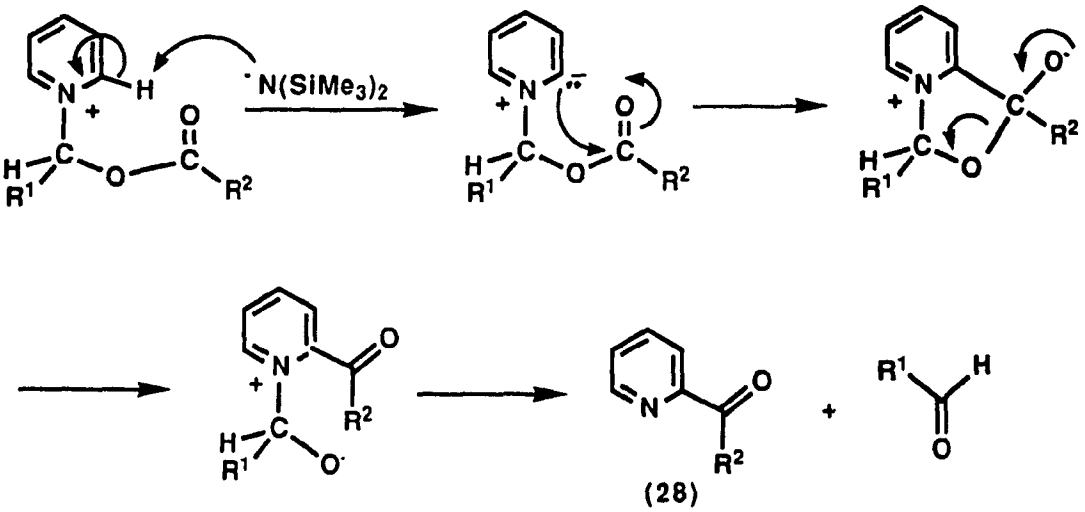
An intramolecular transformation has also been achieved in the conversion of **22** to 2-acylpyridine **28** using sodium bis(trimethylsilyl)amide **29**[23].

Scheme 33



Theoretical and experimental studies have shown that **22** is deprotonated by **29** at the ring C-2 (ortho position) and the resulting anionic centre attacks the γ-carbonyl carbon to yield an intermediate that is eventually converted to **28** and the original aldehyde.

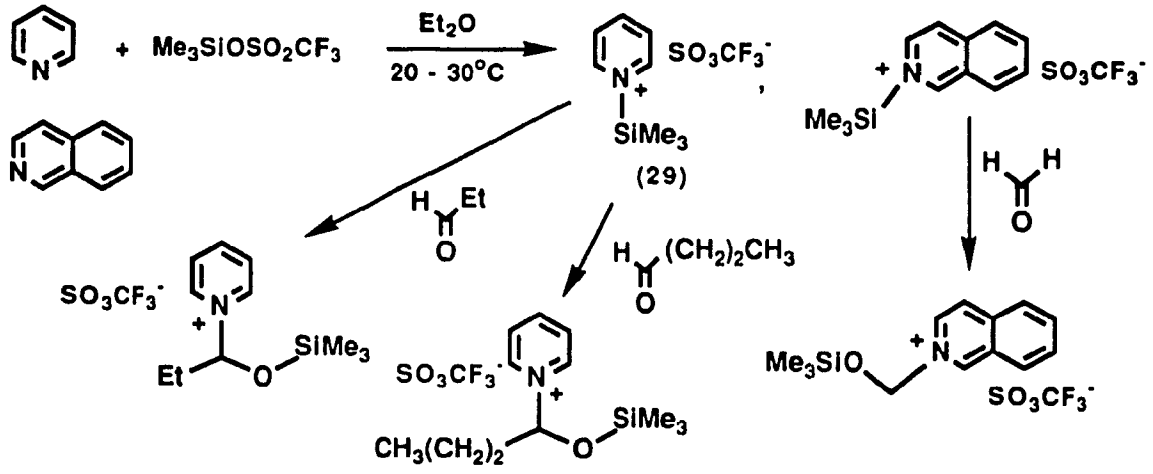
Scheme 34



2.2. Aminals derived from silylated pyridinium compounds

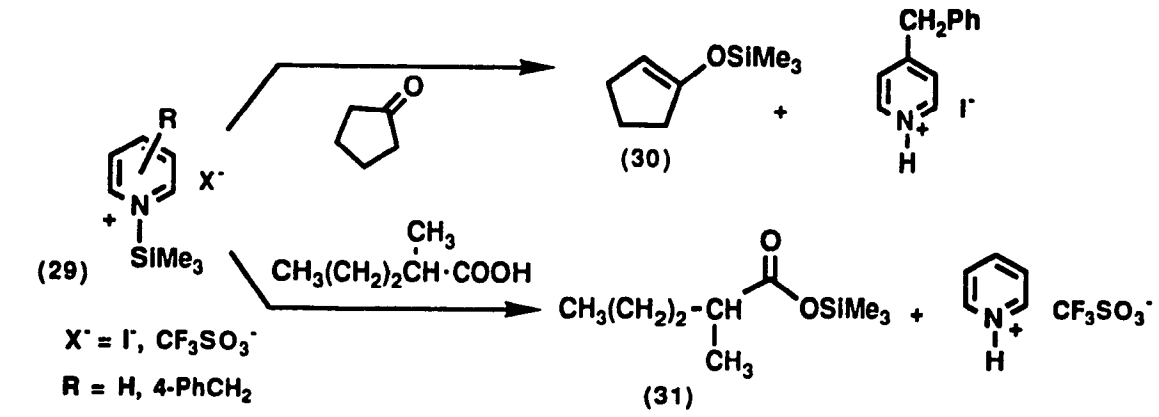
Just as pyridine can promote acylation, it can also catalyze silylation. Pyridine or isoquinoline can be silylated with trimethylsilyl iodide or triflate in ether to yield an N-trimethylsilylated compound **29** that can react further with other nucleophilic species[24]. One such reaction occurs with aldehydes to yield a variety of N-(trimethylsiloxyalkyl)pyridinium and isoquinolinium triflates.

Scheme 35



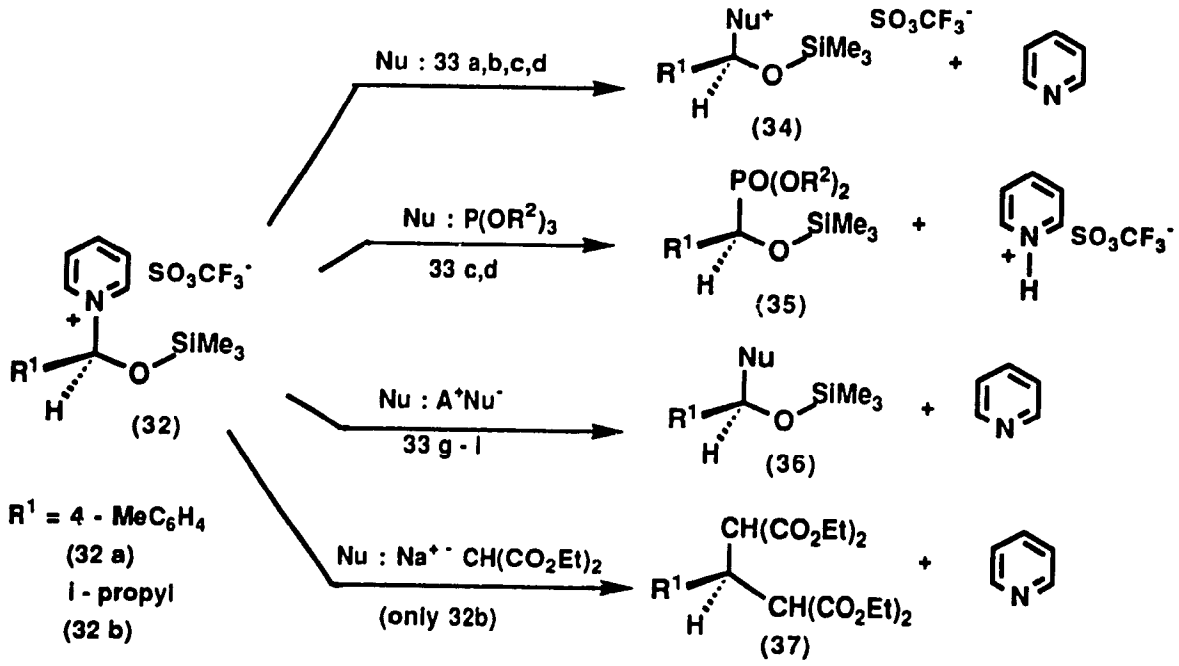
The aldehydes essentially insert themselves between the silicon atom and the quaternary nitrogen. The reactions occur quite readily over a 15 minute period at room temperature. Intermediate **29** can also react with ketones and carboxylic acids to yield trimethylsiloxy alkenes **30** and trimethylsilyl esters **31** respectively. These reactions have only been successful with pyridines.

Scheme 36



Of particular interest to Anders' group were the possible conversions of the N-[(trimethylsiloxy)alkyl]pyridinium salts **32** to other compounds via nucleophilic attack and displacement of pyridine. Both neutral and anionic nucleophiles are involved in the following reactions[25];

Scheme 37



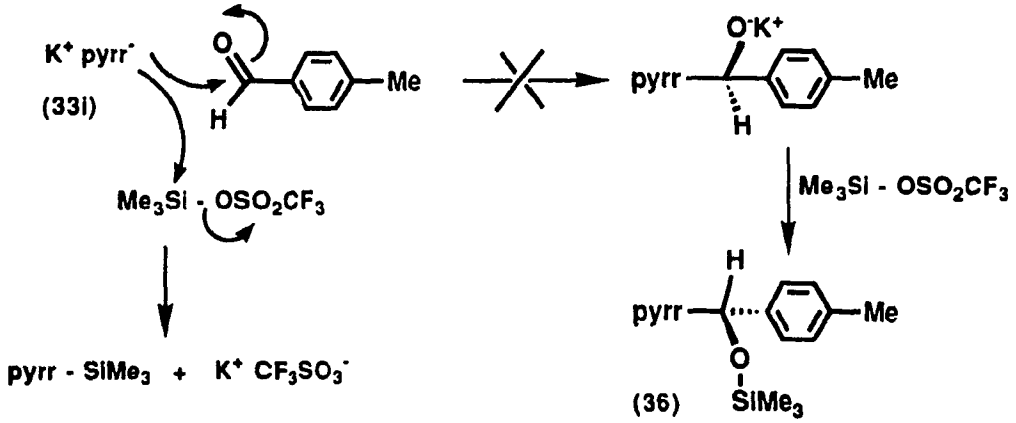
The syntheses with **32a** were the most successful, indicating the advantage of an electron-withdrawing phenyl ring towards nucleophilic substitution.

	Nu		
33a	PPh_3	g	Na^+PhS^+
b	PBu_3	h	$Et_4N^+CN^-$
c	$P(OMe)_3$	i	K^+Pyrr^-
d	$P(OEt)_3$	j	$Na^+CH(CO_2Et)^{2-}$
e	$4\text{-}PhCH_2Py$	k	MeMgI
f	1-MeIm	l	PhMgI

Unlike the first three classes of reactions, where only pyridine is displaced, the fourth reaction **j** involves the additional substitution of the trimethylsiloxy group by a second molecule of sodium diethylmalonate. Some of the compounds synthesized were new, while others were known, but the synthetic route to their formation was novel.

The reaction used to synthesize **36** was attempted as a one-pot synthesis from tolualdehyde, trimethylsilyltriflate and **33i** but the desired product, **36** was not obtained. This stresses the effectiveness of pyridine as a catalyst for nucleophilic substitution. It is possible that, without pyridine, **33i** reacts with trimethylsilyltriflate (TMS) instead of the desired reaction with tolualdehyde followed by reaction with TMS.

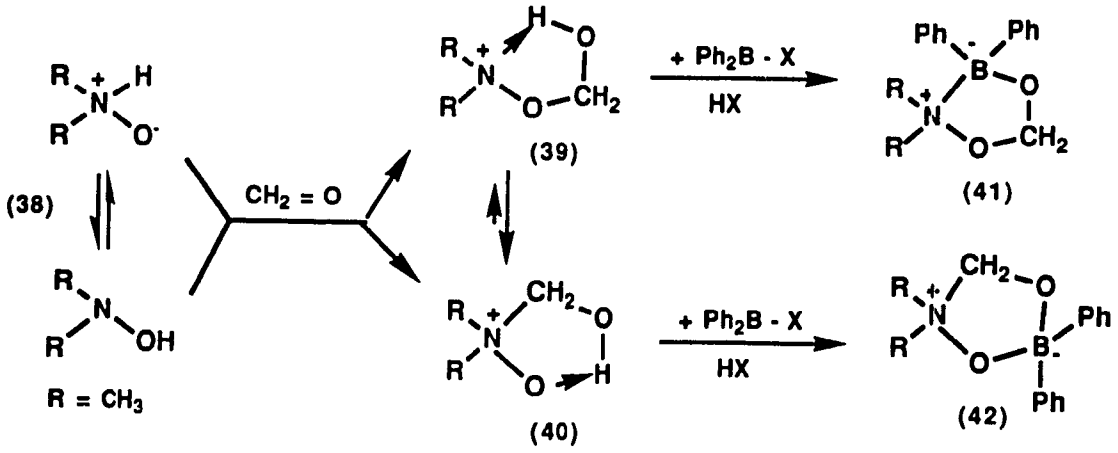
Scheme 38



2.3. Synthesis of N-hydroxymethyl(heterocyclic) compounds

Experiments with the model compound N-hydroxydialkylamine **38** and formaldehyde have been performed to determine which heteroatom, N or O, was the more nucleophilic. Initially it was thought[26] that formaldehyde addition was occurring at the oxygen yielding N-hydroxymethyloxydialkylamines **39**.

Scheme 39

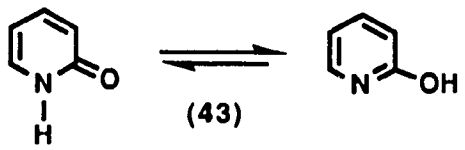


The product of formaldehyde addition was further reacted with diphenylboron compounds (Ph_2B-X) to yield what was believed to be **41**. Later, evidence surfaced in the form of chemical and physical data that indicated **40** to be a much more likely intermediate. More proof was provided by x-ray crystallographic studies which indicated that indeed **42** was the product of reaction with the diphenylboron compounds.

If **39** and **40** were present in unknown proportions, the reaction with an electrophilic agent such as Ph_2B-X would shift the equilibrium, if any, by removing the

more nucleophilic structure. The assumption was made that Ph_2B-X reacts equally well with a nitrogen or oxygen nucleophile. In this case it was concluded that nitrogen was the better electron donor to formaldehyde.

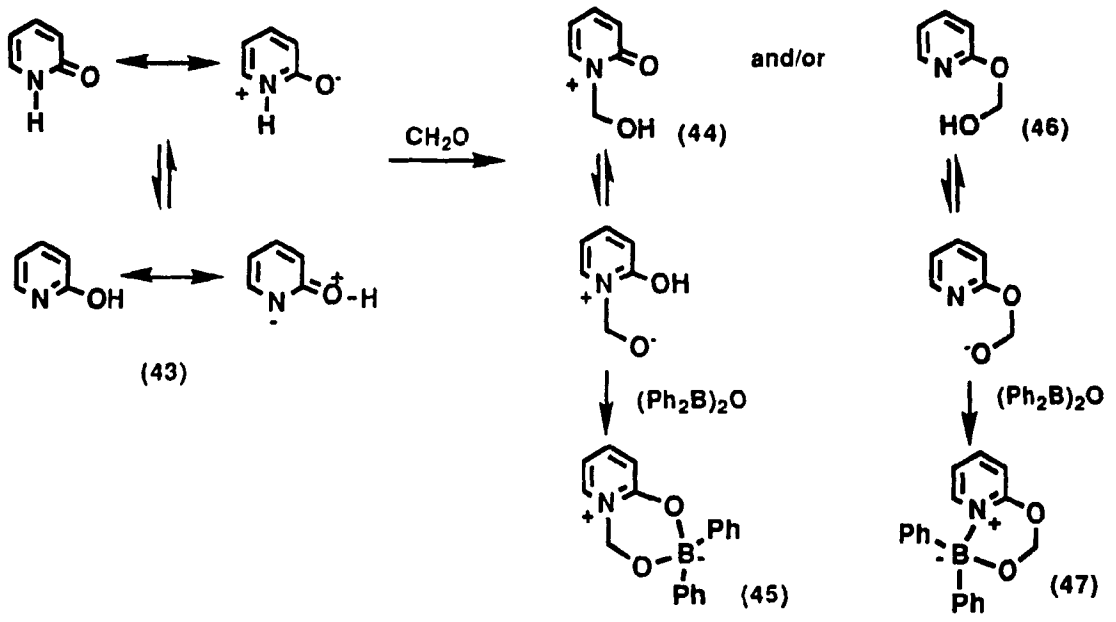
Like hydroxylamines, experiments were later concluded with an analogous compound, 2-pyridone **43**, in order to study its electron-donating qualities.



(43)

The 2(1H)-pyridone is a tautomeric heterocycle existing both as the lactam and as the 2-hydroxypyridine. Both the oxygen and the nitrogen can be alkylated depending on the alkylating agent and the reaction conditions, but in this case formaldehyde as an electrophile was explored. The N-hydroxymethyl-2-pyridone **44** has already been prepared[27]. Kleigel and Rettig[28] have synthesized **44** and reacted it with oxybis(diphenylborane) in order to characterize the resulting product and gain some insight into the nucleophilic character of 2-pyridone. X-ray crystallography confirmed that the reaction of a pyridone-formaldehyde adduct with oxybis(diphenylborane), does indeed result in structure **45**.

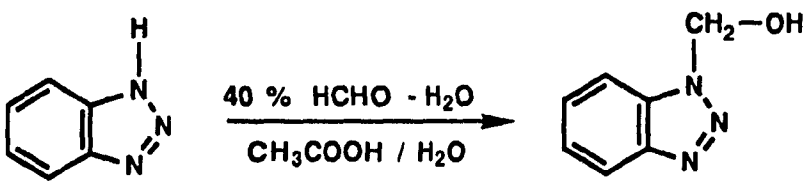
Scheme 40



One can conclude that the reaction with formaldehyde occurs at the nitrogen, not oxygen, to produce intermediates **44**. As in the case of N-hyroxydialkylamines, there are both steric and electronic reasons to explain the stability of **45** over **47**. The greater separation of charges between the positive nitrogen and the negative boron atom as well as the distance between the two phenyl groups and the pyridine ring might all be contributing factors.

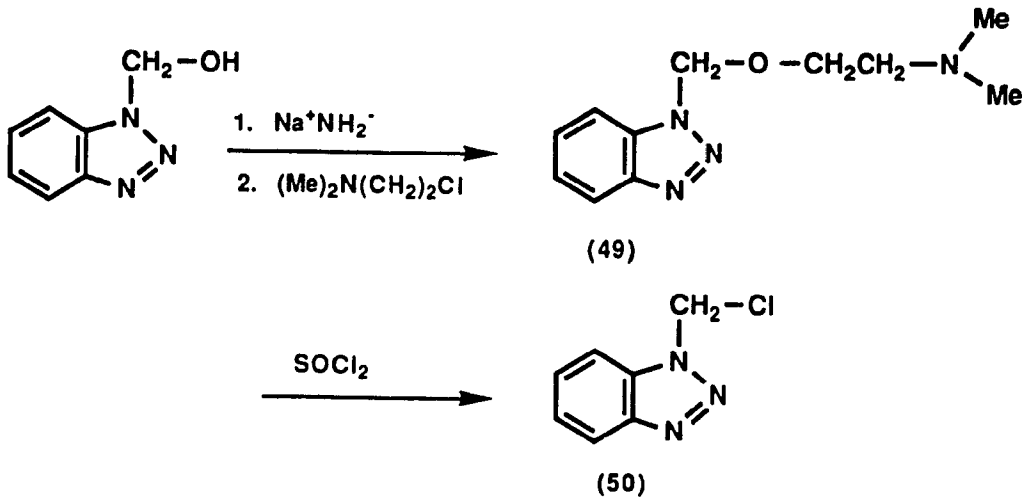
Lastly, N-hydroxymethylbenzotriazole **48** has been synthesized from benzotriazole and formalin[29] with glacial acetic acid as the solvent.

Scheme 41



In an initial attempt to synthesize N-(dimethylamino)-methylbenzotriazole by the above method, but with the addition of dimethylamine, the same compound **48** was produced. Several reactions were then possible with **48** including its conversion to the dimethylaminoethyl ether **49** as well as to N-chloromethylbenzotriazole **50** :

Scheme 42

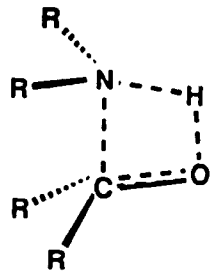


Compound **48** has also been synthesized using a basic medium which is a common method for making hydroxymethyl compounds i.e. from formalin, benzotriazole and sodium acetate.

Until now, N-(hydroxymethyl)pyridinium salts have not been synthesized although an extensive theoretical study has been conducted on its stability and its likelihood to form.

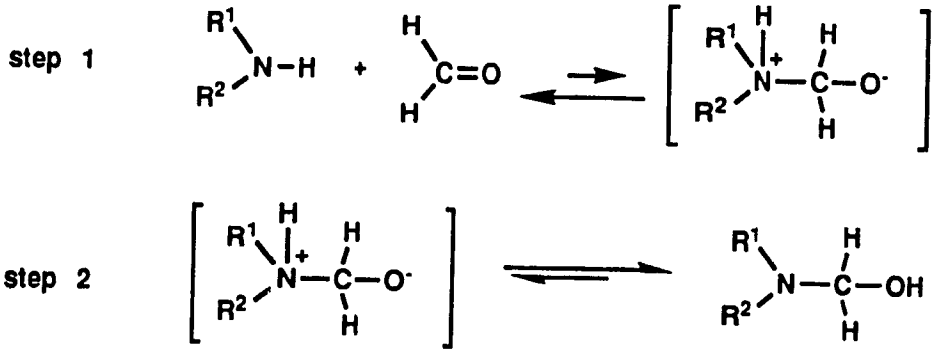
The reaction between various amines (NH_3, NH_2R, NHR_2) and simple carbonyl compounds (CH_2O, CH_3CHO, CF_2O) have been studied. Different conclusions have been reached by two groups of researchers who state that the reaction occurs in one or two steps.

Yamataka et al[30] believe, from their theoretical calculations, that the formation of aminals from amines and carbonyl compounds occurs in one step through a four centred transition state. This has been likened to the results obtained upon the addition of water to formaldehyde. Ab initio MO calculations were carried out for five different sets of reactions, using both the 3-21G and the larger 6-31G* basis sets to calculate the activation and reaction energies, as well as reactant, product and transition state structures. An attempt was made to understand the relation, if any, between transition state structures and reactivities. All of the four centred transition states had the following general structure, with the N-H undergoing bond-breaking, N-C and O-H, bond-making and C-O undergoing bond-elongating.



Shokhen et al[31] have proposed a very different reaction course which takes place in two steps. The first involves the formation of an energetically unfavourable zwitterion by the attack of an amine on formaldehyde, followed in the second step by an intramolecular proton transfer from nitrogen to oxygen.

Scheme 43



All of the amines (NH_3, $MeNH_2$, Me_2NH, NH_2NH_2, NH_2CHO) were studied with respect to their reactions with only one carbonyl compound, formaldehyde. The MINDO/3 semi-empirical MO method was used to estimate the pathways by which the amine molecules move toward the carbonyl group. Along the reaction coordinate, geometrical parameters such as bond lengths, valence and torsional angles were calculated in order to give an accurate representation of the geometrical changes that the reagents undergo throughout the course of the reaction.

These studies have shown that, as the amine approaches the formaldehyde molecule, the carbon changes gradually from its initial planar configuration to tetrahedral in the zwitterionic intermediate. It remains tetrahedral in the final carbinolamine. In terms of the charge distribution on the zwitterion, the authors have concluded that most of the positive charge is concentrated, not on the nitrogen, but on the carbon atom. Theoretically, the relative stability of this zwitterionic compound is largely dependent on the substituents on the nitrogen. In addition, the formation of the zwitterionic transition state can be considered the rate-determining step so that if it cannot form, the carbinolamine cannot be synthesized.

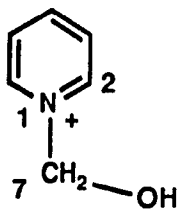
The next step to consider is the energy requirement for proton transfer from nitrogen to oxygen. This depends on both the strength of the N-H bond which is determined, in part, by the substituents on nitrogen as well as on the nucleophilicity of the anionic oxygen. While the first step is more energetically favoured for amines with NH_2 and OH substituents and less with CH_3, the second step is energetically favourable for all cases. One explanation for this is the fact that the energy required to break the N-H

bond is more than compensated for by the exothermic formation of the O-H bond. In all cases, the net energy expenditure is negative for the overall formation of products from reactants.

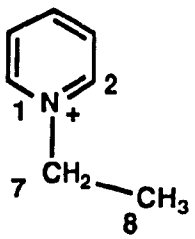
Most relevant to this research, though, was the understanding of the conformation of the N-hydroxymethylpyridinium cation **51g**. In an attempt to evaluate the conformational preferences of NAD^+ and NADH, **51g** and the N-ethylpyridinium cation **51c** were used as model compounds.

Wu and Houk[32] were interested in the relation of the nicotinamide ring to the glycosidic bond of the tetrahydrofuran ring and the energy barrier to rotation about the N-C bond. They wanted to test some of the chemical aspects of the NAD^+ molecule with theoretical calculations on model compounds. For example, there are two classes of alcohol dehydrogenase enzymes - A-specific and B-specific - which bind NAD^+ in its anti and syn-conformation respectively. There is also a question about which is a stronger reducing agent: anti or syn NADH.

These model compounds, **51g** and **51c** were optimized with respect to their geometries using the familiar 3-21G and 6-31G* basis sets. The two basis sets gave different calculations for optimum C_2-N_1-C_7-OH dihedral angles of **51g** but gave almost identical results for optimization of **51c**. For the pyridiniomethanol, 0° and 30° were determined to be the most favourable depending upon which MO calculation was used.



(51g)

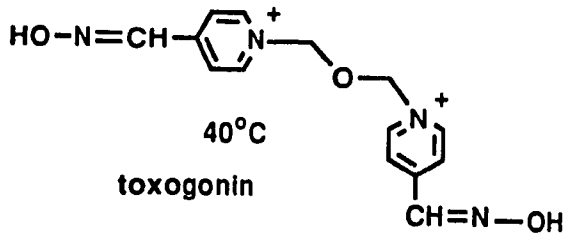


(51c)

Table 2 Relative Energies Calculated for **51g** and **51c** at Various Dihedral Angles

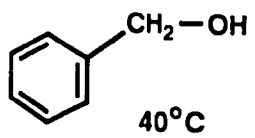
Dihedral angle	51g		51c	
C_2-N_1-C_7-X (^{0})	X=OH		X=CH_3	
	3-21G	6-31G*	3-21G	6-31G*
0	0.0	0.3	4.5	4.7
20	0.3	0.3	3.7	3.9
30	0.8	0.0		
40	1.2	0.2	1.8	1.9
60	2.7	0.1	0.4	0.5
80	4.0	0.3	0.1	0.1
90	4.2	0.2	0.0	0.0

It has been shown that the 3-21G basis set tends to exaggerate electronic interactions while 6-31G* gives more reliable estimations. When this 30° calculation is compared to similar dihedral angles of some known compounds such as toxogonin and benzyl alcohol, the numbers more closely resemble the angle calculated with the 6-31G* basis set.



40°C

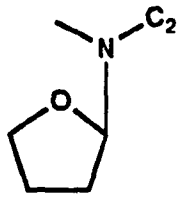
toxogonin



40°C

benzyl alcohol

Even the dihedral angle of the glycosidic bond of ribose with the plane of the bases in DNA and RNA is about 20°. Therefore it appears that the planes of these heteroaromatic rings



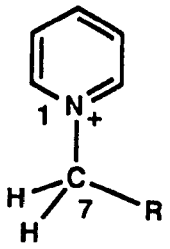
prefer to be near, but not exactly parallel to, the plane of the sugar ring. From this information, and the calculations done on the N-hydroxymethylpyridinium cation **51g**, it was determined that the NAD^+ glycosidic dihedral angle was 30° or 150° depending on the conformation.

In terms of the barrier to rotation about the N_1-C_7 bond, it was concluded that steric and electronic forces opposed each other and the calculated barriers were therefore small. The authors note the lack of a single model compound for experimental study.

A more comprehensive study of N_1-C_7 bond lengths and pyridinioalkoxide zwitterion stability has been carried out by semi-empirical MNDO calculations[33]. Several N-alkylpyridinium compounds **51** (including **51g**) were examined in terms of their bond lengths, heats of formation, and their net atomic charge on C_7.

Table 3 General Characteristics of Compound **51** Determined using Semi-Empirical MNDO Calculations

51	R	bond length (N_1-C_7)	net atomic charge on C_7	ΔH_f (kcal/mol)
a	Cl	1.494	+0.22	185.0
b	H	1.500	+0.17	188.0
c	CH_3	1.508	+0.13	181.9
d	NH_2	1.527	+0.26	188.8
e	F	1.527	+0.39	144.3
f	OC(O)H	1.524	+0.34	115.1
g	**OH**	**1.538**	**+0.32**	**140.2**
h	OCH_3	1.540	+0.35	146.8
i	$OSiMe_3$	1.563	+0.43	47.8

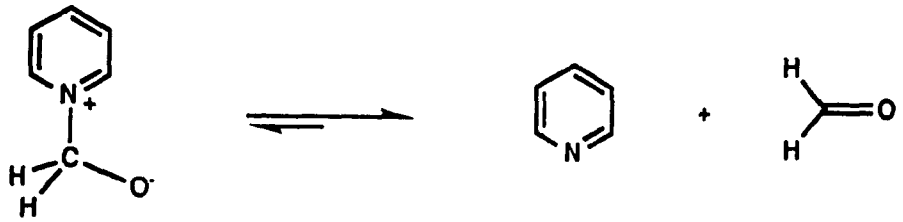


(51)

From these characteristics, certain general reactivity trends can be concluded including the susceptibility of the C_7 atom towards nucleophilic attack, which follow the order; R = OC(O)H < OH < OCH_3 < $OSiMe_3$

These oxygen residues (R), cause a stretching of the N_1-C_7 bond that is very destabilizing to structures **51** making nucleophilic attack on C_7 and the resultant displacement of the pyridine moiety increasingly easy. Now, in order to synthesize compounds f-i, one can envision all of them being derived from a common intermediate **52** which undergoes equilibrium shown in scheme 44.

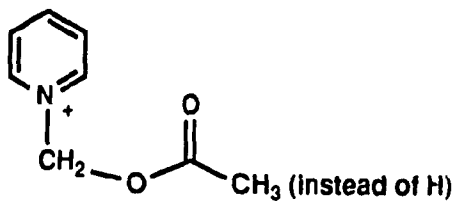
Scheme 44



(52)

Because of its presumed tendency to revert to pyridine and the aldehyde, intermediate **52** has not been detected by ^{1}H NMR spectroscopy. Even when the protons on C-α are replaced by various stabilizing groups, and the reaction is performed under very different conditions, it has never been possible to directly observe this intermediate. In addition, MNDO calculations are in accordance with experimental data. An attempt to theoretically describe the compounds **52**, even with electron-withdrawing groups such as F replacing one of the protons, resulted always in the prediction that the structure would split into pyridine and the corresponding aldehyde, based on thermodynamic considerations.

To our knowledge, none of the compounds **51f** through **51i** have been synthesized. The results section of this thesis will deal with our synthesis and isolation of the N-(hydroxymethyl)pyridinium and N-(trimethylsiloxymethyl)pyridinium salts. In addition, a compound **53** analogous to **51f** has been prepared from pyridine, formaldehyde and acetyl chloride.



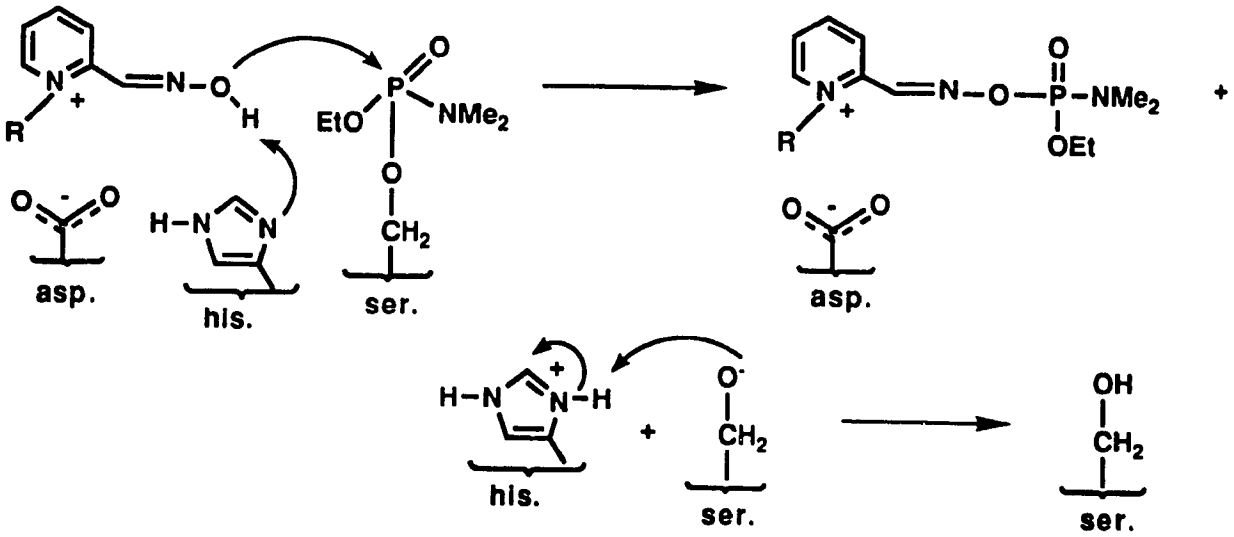
(53)

2.4. Acetylcholinesterase reactivating agents

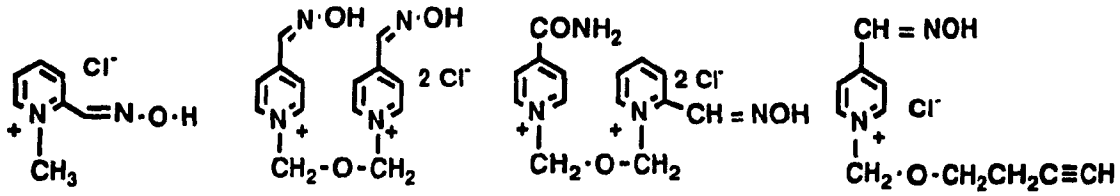
Some of the most useful pyridinium-derived aminals are a series of pyridinium salts which function as acetylcholinesterase (AchE) reactivators following enzyme inhibition by organophosphorus poisons. These organophosphonates are better known as nerve gas reagents, and they block the active site of the enzyme thus preventing it from catalyzing the hydrolysis of the neurotransmitter acetylcholine to choline and acetate ion. As acetyl choline builds up in the nerve synapses, nerve impulses continue. This essentially causes overstimulation that eventually leads to paralysis and death[34].

Organophosphorus esters inhibit the active site by phosphorylating the hydroxyl group of a catalytic serine residue in AchE irreversibly thus preventing it from interacting with the ester group of acetylcholine. AchE reactivators possess an oxime group on the 2 or 4 position of the pyridinium ring which behaves as a nucleophile to displace the phosphonate group.

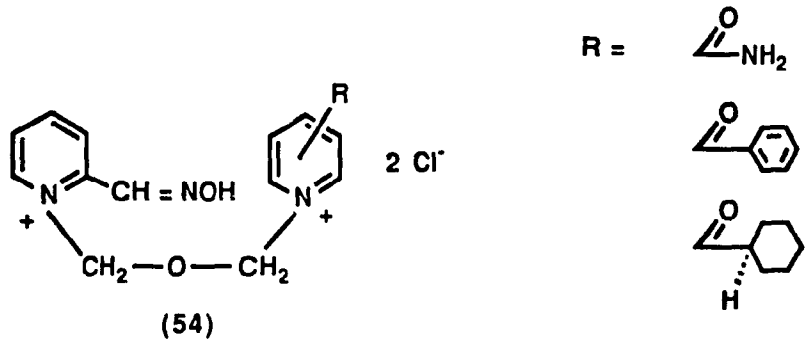
Scheme 45



Examples of such pyridinium aldoximes include;



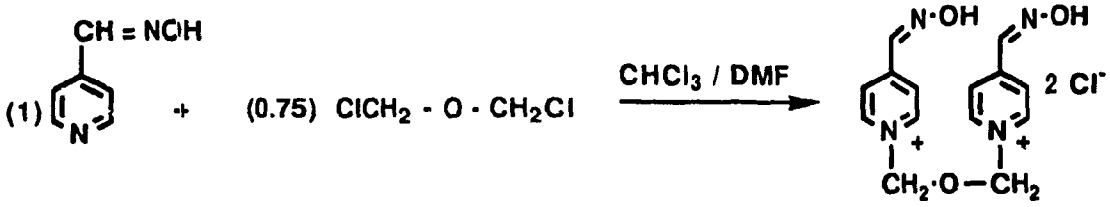
Compounds having the following general structure **54** are referred to as "Hagedorn Oximes", named after the researcher who contributed the greatest to the synthesis of bis(pyridiniomethyl)ether aldoximes.



(54)

One of the most potent bispyridinium salts synthesized by Hagedorn et al[35] is toxogonin (bis-[4-hydroxyiminomethylpyridiniomethyl] ether dichloride);

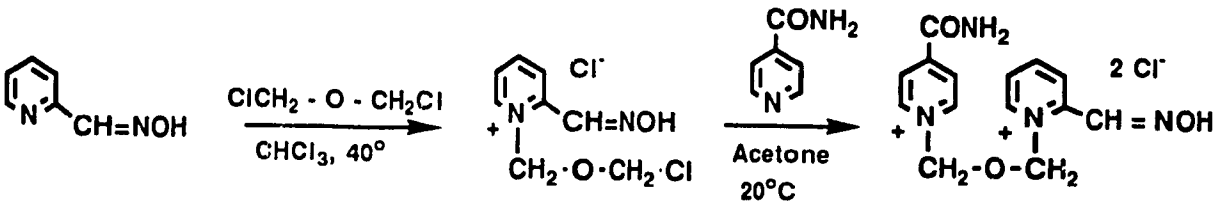
Scheme 46



While it has proven to be more effective than 2-PAM at reversing the effects of organophosphorus poisoning from compounds like EPMP (ethyl p-nitrophenylmethyl phosphonate), it is ineffective at treating intoxication by GD (3,3-dimethyl-2-butyl methylphosphonofluoridate).

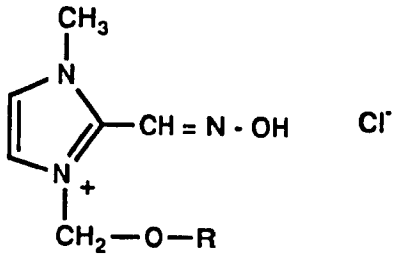
Several compounds reported by Olgies and Schoene, have been found to be effective therapy against GD poisoning and they all have the general structure **54**. The synthesis of HI-6, one of the most potent of these compounds is shown in scheme 47.

Scheme 47



Since the synthesis of the above compounds, other researchers[36] have attempted to achieve a similar AchE reactivating ability with other heteroaromatic aldoximes, some monoquaternary. In one case these compounds **55** were synthesized from 1-methylimidazole.

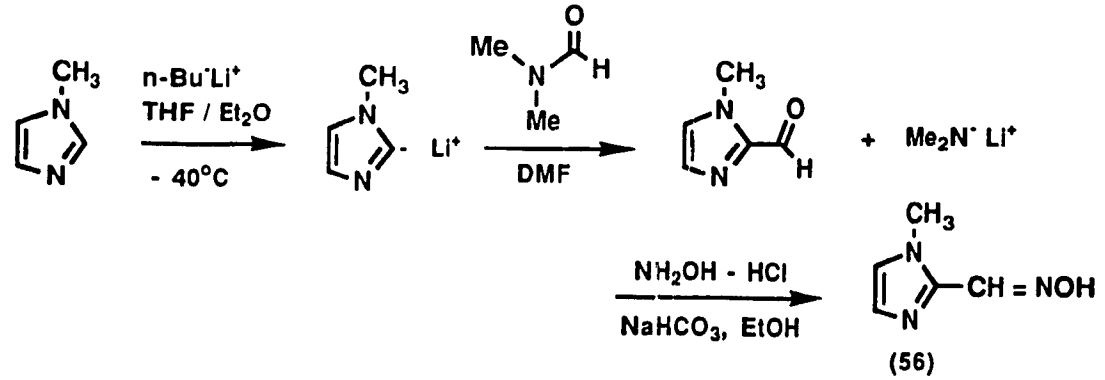
55	R
a	CH_3
b	$CHMe_2$
c	CH_2CMe_3
d	$CH(Me)CMe_3$
e	$(CH_2)_3Me$
f	$(CH_2)_7Me$
g	CH_2-C_6H_5
h	$(CH_2)_3$-C_6H_5
i	CH_2-$C_{10}H_7$



(55)

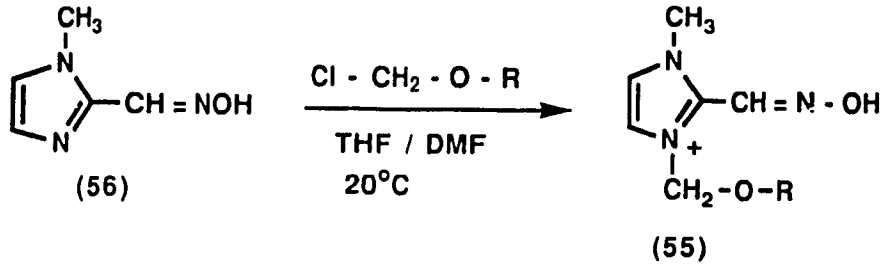
The conversion of 1-methylimidazole to 1-methylimidazole-2-aldoxime **56** occurs by the following reaction scheme:

Scheme 48



Quaternization of the second imidazole nitrogen to yield the desired compounds **55** simply involves a reaction with the appropriate chloromethyl ether.

Scheme 49

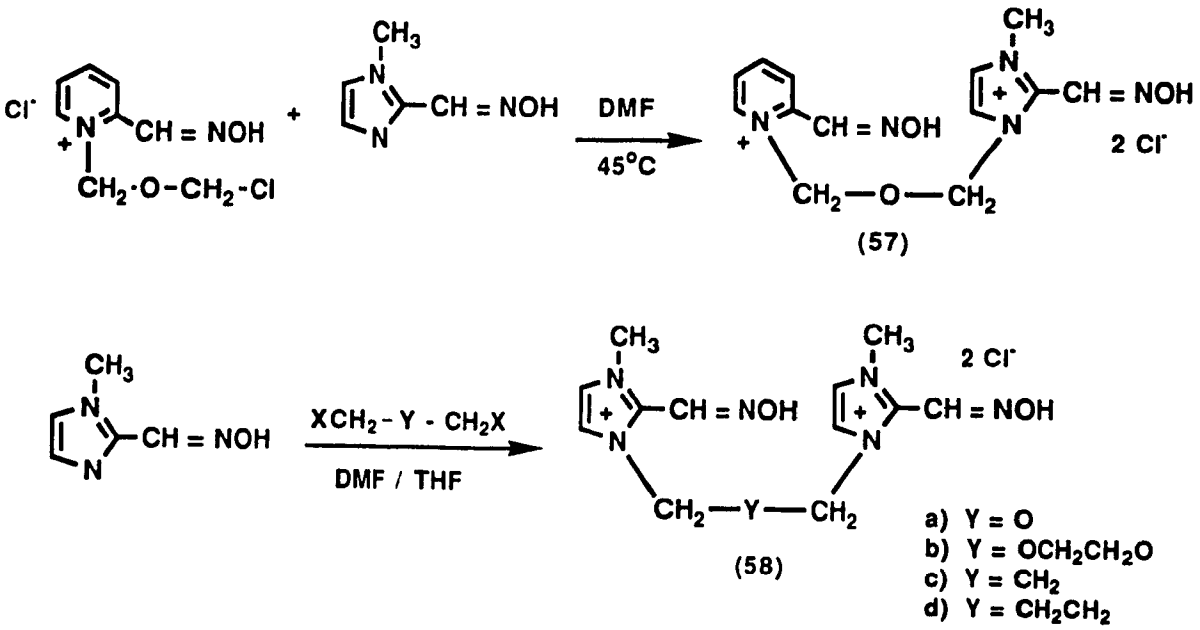


In terms of their reactivating abilities, some were compared to 2-PAM, while others were considerably less effective, but none exhibited the potency of HI-6 towards GD intoxication. Subsequently, twelve new 1-methyl-3-alkoxymethylimidazolium aldoximes **55** were synthesized[37] but their biological activity towards GD-inhibited eel was no better than the results obtained with the first nine. Depending on the 3-alkoxymethyl substituent,

some of these compounds can reactivate EPMP-phosphonylated human AchE as well or slightly better than 2-PAM.

Several bis(heteroaromatic) aldoximes have also been synthesized[37] either made up of two imidazolium rings or of one pyridinium and one imidazolium ring connected by a variety of ether or alkyl linkages.

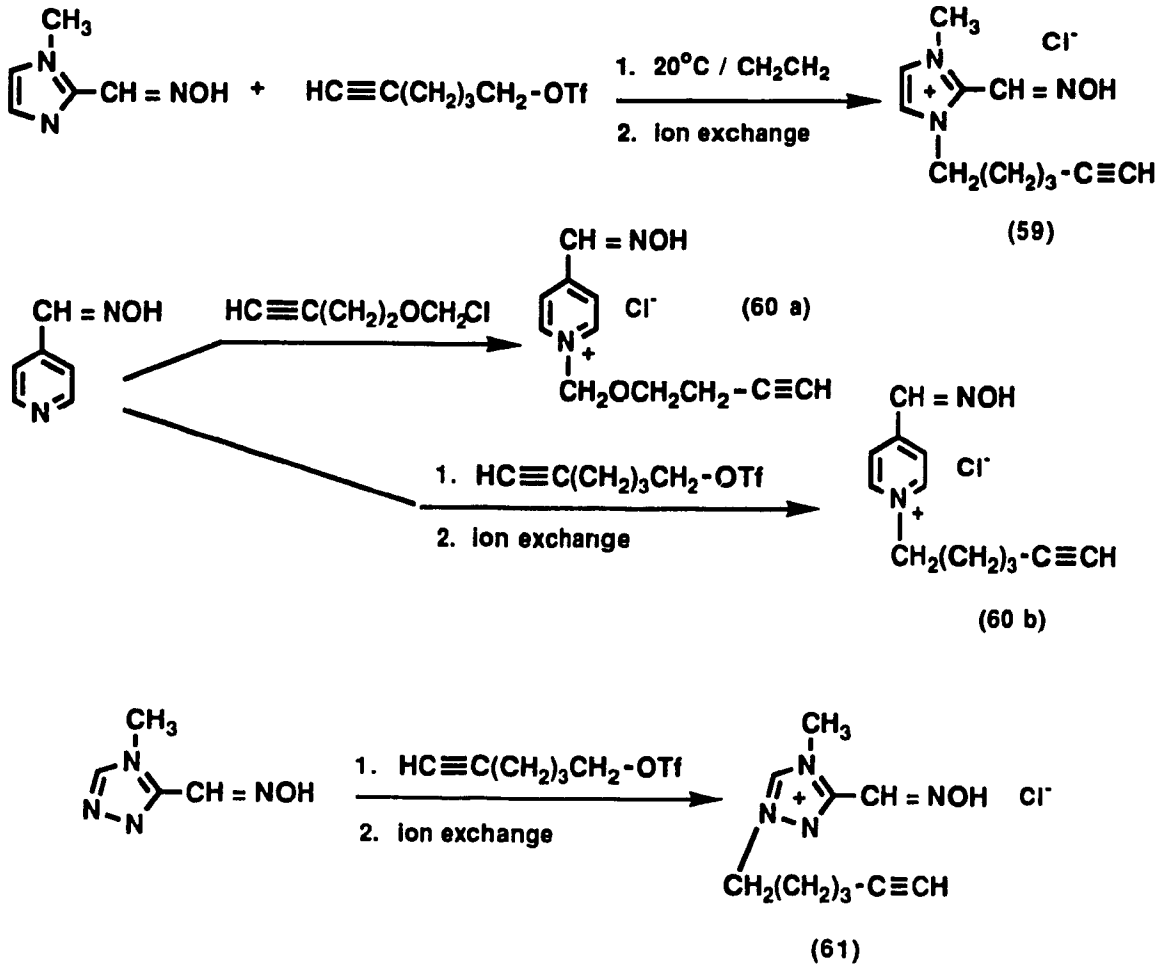
Scheme 50



Some of the salts **58** were synthesized using diiodomethyl compounds but the resulting products were passed through an ion exchange column to yield the dichlorides.

Compounds **57** and **58a,b** were found to be moderate to potent reactivators of GD- and EPMP-inhibited AchE. Lastly, a series of N-alkenyl and N-alkynyloxymethyl-imidazolium **59**, pyridinium **60**, and triazolium **61** chlorides were synthesized and their abilities to reactivate EPMP-inhibited human AchE has been examined[38].

Scheme 51



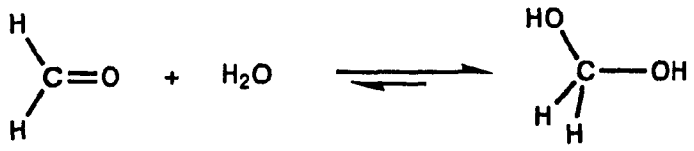
All, except **61** showed activity comparable to 2-PAM. Removal of the ether linkage showed a distinct increase in reactivation potency from **60a** to **b**, and results indicate that the pyridinium salts are still the most effective of the three heteroaromatic products.

3. FORMALDEHYDE AS A SYNTHETIC REAGENT

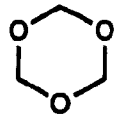
3.1. Harnessing anhydrous monomeric formaldehyde

Monomeric formaldehyde exists in its natural state as a gas and, if care is taken to prevent self-polymerization, it can also be cooled to a liquid at -19°C and to a solid at -118°C. Because it polymerizes so readily from gas or liquid, it is usually dealt with as a polymer, or in solution. Monomeric formaldehyde exists almost completely in aqueous solution, as the hydrated form.

Scheme 52



As a polymer,it may exist in three common forms; trioxane **62,** paraformaldehyde **63**, or α-polyoxymethylene **64**[39].



$(- CH_2O -)_3$

(62)

$H (CH_2O)_n OH$

$n = \sim (6 - 100)$

(63)

$H (CH_2O)_n OH$

$n = \sim (100 - 300)$

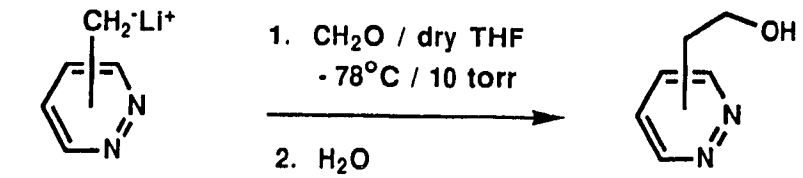
(64)

Both **63** and **64** can be depolymerized by heating (150°-180°C) to yield gaseous formaldehyde, but it will be contaminated with traces of water, formic acid, methanol, etc. If a reaction is to be performed with an aqueous solution of formaldehyde, it must be one that is not water sensitive. This factor limits its synthetic utility since the reactivity of

many compounds will be quenched with H_2O. Therefore it is necessary, for synthetic purposes, to be able to obtain formaldehyde in an anhydrous solution in its monomeric form for just enough time to allow it to react with another molecule instead of itself. To this end, a useful method involves the depolymerization of paraformaldehyde with heat to yield formaldehyde gas which can be bubbled into a suitable anhydrous solvent. Unlike water or alcohol which forms a hydrate or hemi-acetal respectively, with the formaldehyde, a suitable anhydrous organic solvent should be one that stabilizes the monomer without reacting with it. An example of such a solvent is diethyl ether, in which monomeric formaldehyde can be stored in solution at -78°C under argon for an extended period of time[40].

Recently though, a slight improvement has been made on this technique by the use of a more polar ether: tetrahydrofuran (THF). While formaldehyde gas is introduced into anhydrous THF at a solvent temperature of -78°C, solutions 0.3 to 3.3 M can be maintained intact for several days even at 0°C. Evidence for this is provided by ^{1}H-NMR spectra which indicates the presence of aldehyde protons of the pure monomeric form, at δ 9.54 ppm[41]. This solution has been used to hydroxymethylate 4- **(65)** and 3-pyrazinylmethyl lithium **(66)**;

Scheme 53

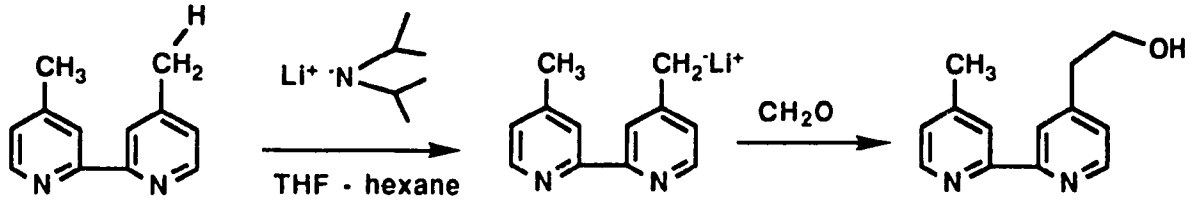


(65) or (66)

The reaction is quenched with water once the stirred mixture has reached room temperature after an hour.

A similar technique was used to hydroxymethylate 4,4'-dimethyl-2,2'-bipyridine **67** to yield 4'-(beta-hydroxyethyl)-4-methyl-2,2'-bipyridine **68**[42] using formaldehyde that was prepared by thermal decomposition of paraformaldehyde over a period of 2 hours.

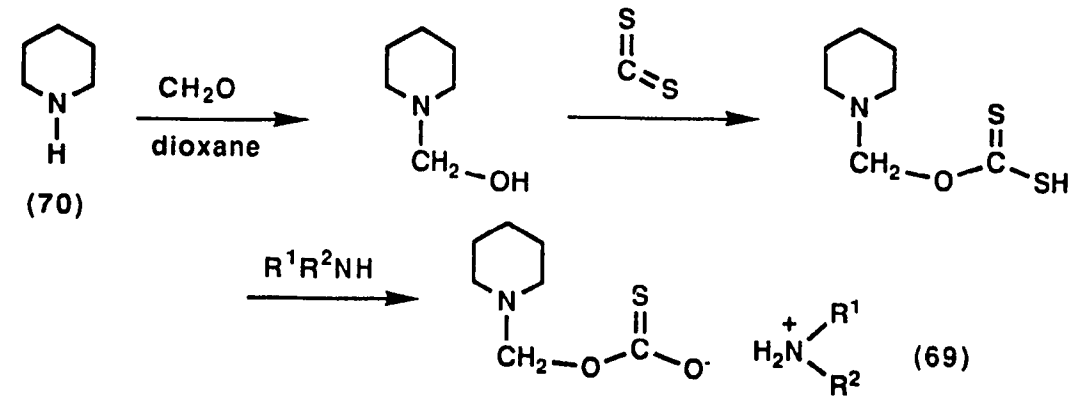
Scheme 54



(67) (68)

Dioxane may also be suitable to sustain formaldehyde in monomeric form since it serves as the solvent in the synthesis of salts **69** from formaldehyde, piperidine, carbon disulfide and a secondary amine[43]. Piperidine **70** is refluxed with formaldehyde in dioxane, followed by the addition of carbon disulfide and finally the appropriate 2° amine. One can envision the following reaction scheme.

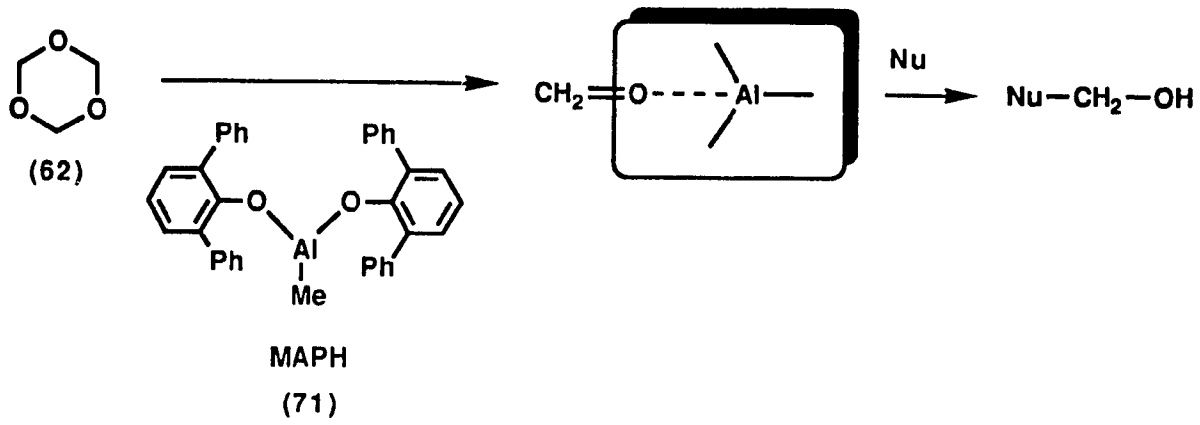
Scheme 55



(70) (69)

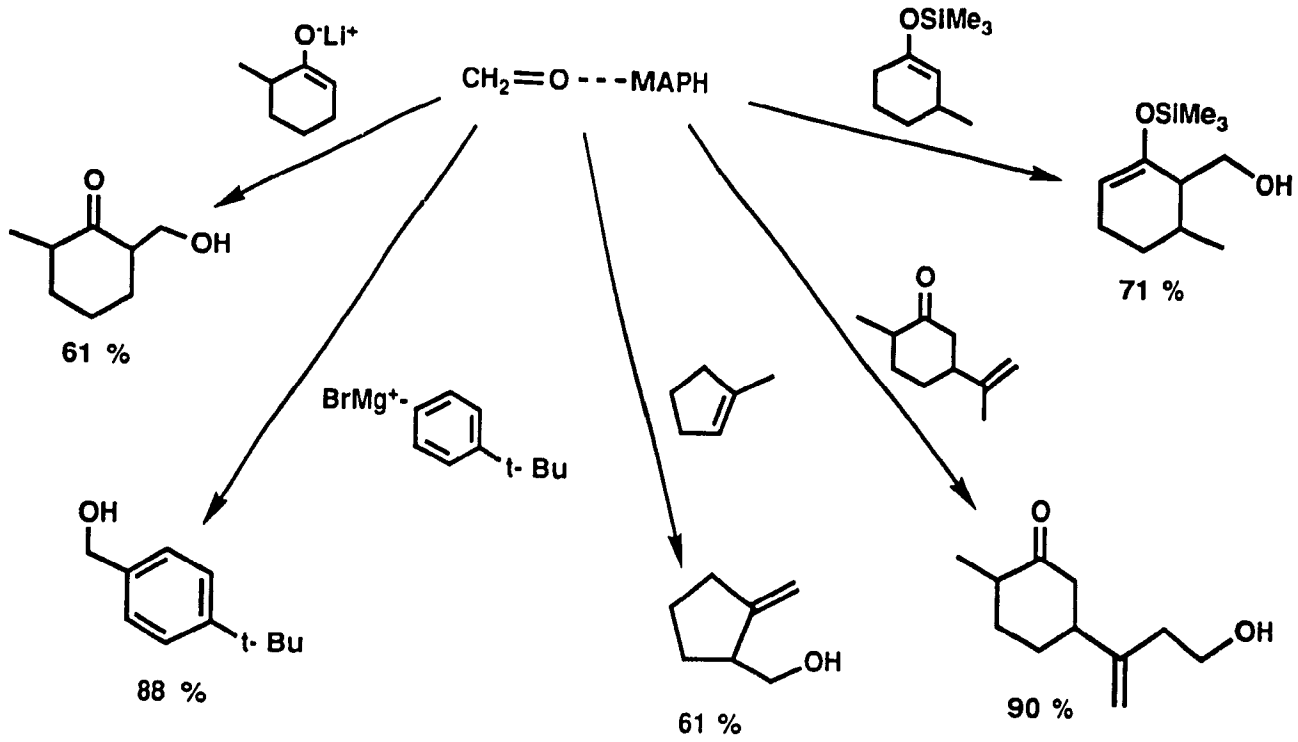
A different method of harnessing monomeric formaldehyde for use in synthesis has been developed by Yamamoto et al[44]. It involves trapping the monomer with a bulky aluminum ligand, MAPH (methylaluminum bis[2,6-diphenylphenoxide]) **71**, and thus preventing self-polymerization. Not only can MAPH trap formaldehyde, but it can do so from trioxane **62** as a source and at 0°C and in a relatively non-polar solvent such as methylene chloride.

Scheme 56



The CH_2=O MAPH complex is stable at 0°C for 5 hrs, and then gradually decomposes at room temperature. It can be used to hydroxymethylate various olefinic compounds, as well as carbanions.

Scheme 57



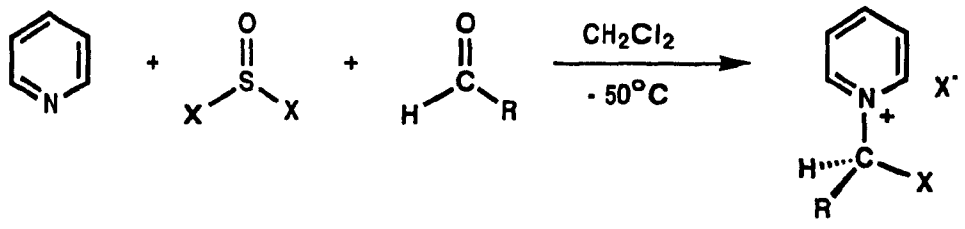
The great advantage to this technique is that it eliminates the need to generate formaldehyde by the sometimes messy task of thermal decomposition of paraformaldehyde.

3.2 Synthesis of N-(haloalkyl)pyridinium salts

(specifically chloromethylpyridinium chlorides)

A synthetic method has been developed for the preparation of N-(haloalkyl)pyridinium halides **72** from pyridine, thionyl chloride (or bromide) and an aldehyde[45].

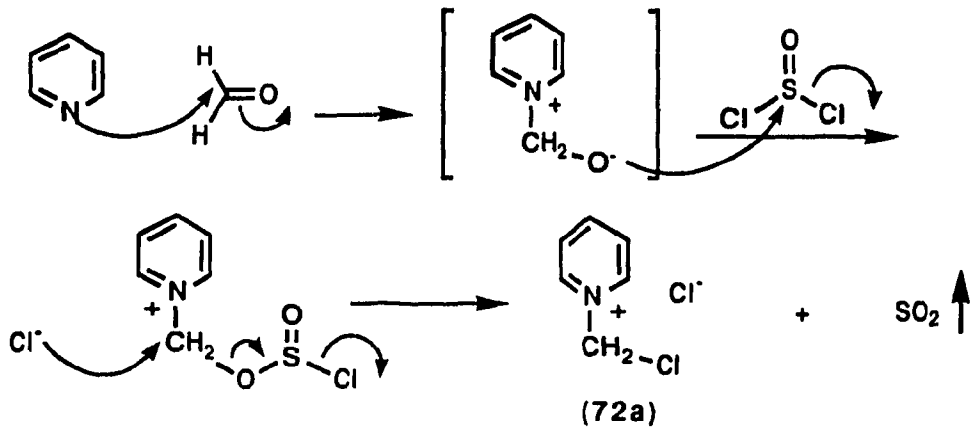
Scheme 58



R = 4-MePh, $CH(Ph)_2$, Et, n-propyl, Ph **(72)**

Recently this reaction has been attempted with formaldehyde, thionyl chloride, and pyridine[46]. The proposed mechanism is as follows.

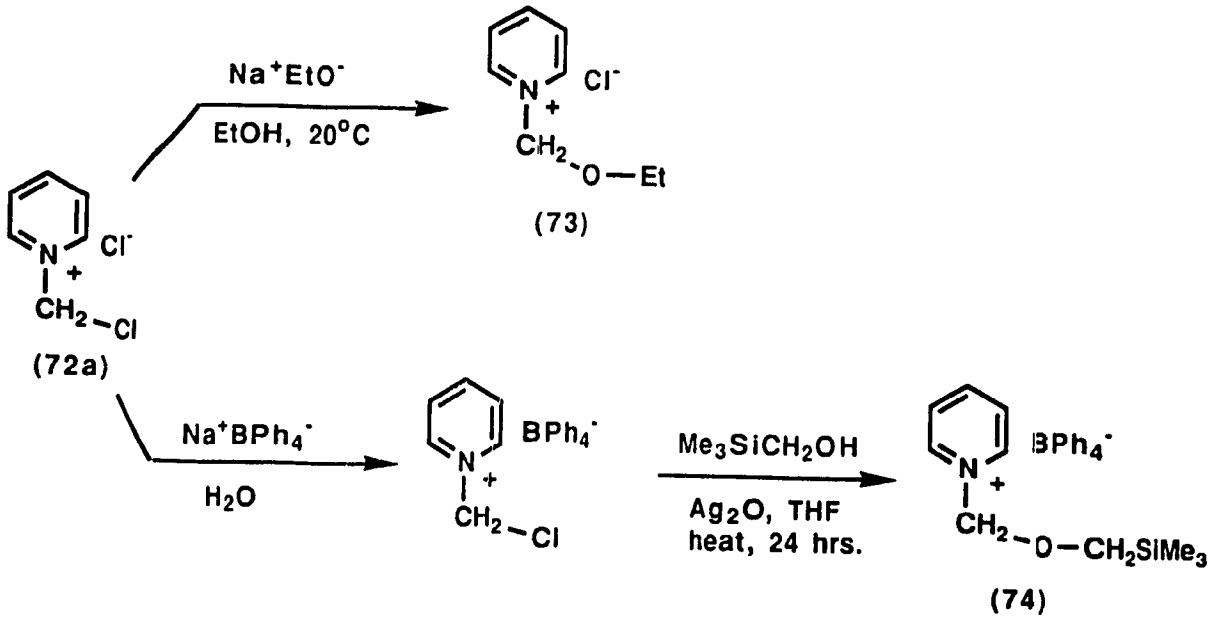
Scheme 59



(72a)

Thermal depolymerization of paraformaldehyde was used to obtain monomeric formaldehyde, but the solvent in this case was methylene chloride. Unlike diethylether or THF which can stabilize the aldehyde monomer at -78°C or 0°C respectively, for a period of time, there is no evidence that methylene chloride can do so. Therefore, it is suggested that formaldehyde reacts immediately with pyridine to form a pyridiniomethoxide species that is stable enough at -50°C to be trapped by thionyl chloride to yield N-chloromethylpyridinium chloride **72a**. These compounds are of interest in that they can undergo preferential displacement of the halide ion instead of pyridine by various nucleophiles. In the case of **72**, chloride, and especially bromide ion, can be displaced by F^-, SO_3^-, PPh_3, PhS^-, 1-methylimidazole and phthalimide. Compound **72a** has been reacted with oxygen nucleophiles, and can be converted to N-ethoxymethylpyridinium chloride **73** with ethoxide ion, or to the trimethylsilylmethyl ether **74** using trimethylsilylmethanol and silver oxide.

Scheme 60

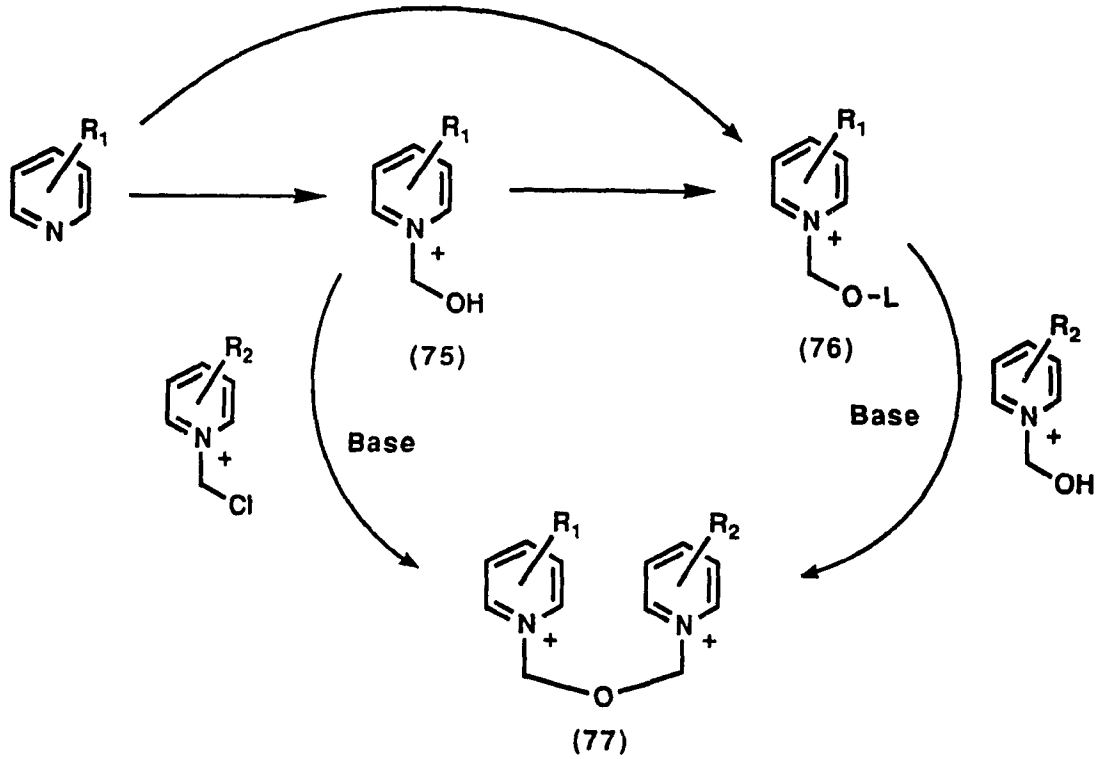


CHAPTER II. OBJECTIVES OF THIS STUDY

The objective of this work is to develop new synthetic methods for the synthesis of bispyridiniomethyl ethers **77** without the use of potentially carcinogenic bishalomethyl ethers: $(XCH_2)_2O$. In addition, we were interested in constructing the molecule from one pyridinium ring, through the dimethyl ether linkage, to the other so as to potentially replace the latter with some other heterocycle such as a sulfonium moiety.

Our research focused on the synthesis and substitution reactions of the N-(hydroxymethyl)pyridinium cation **75** whose formation alone is surprising. Its ability to form and be isolable was highly doubted according to theoretical calculations[33].

Scheme 61



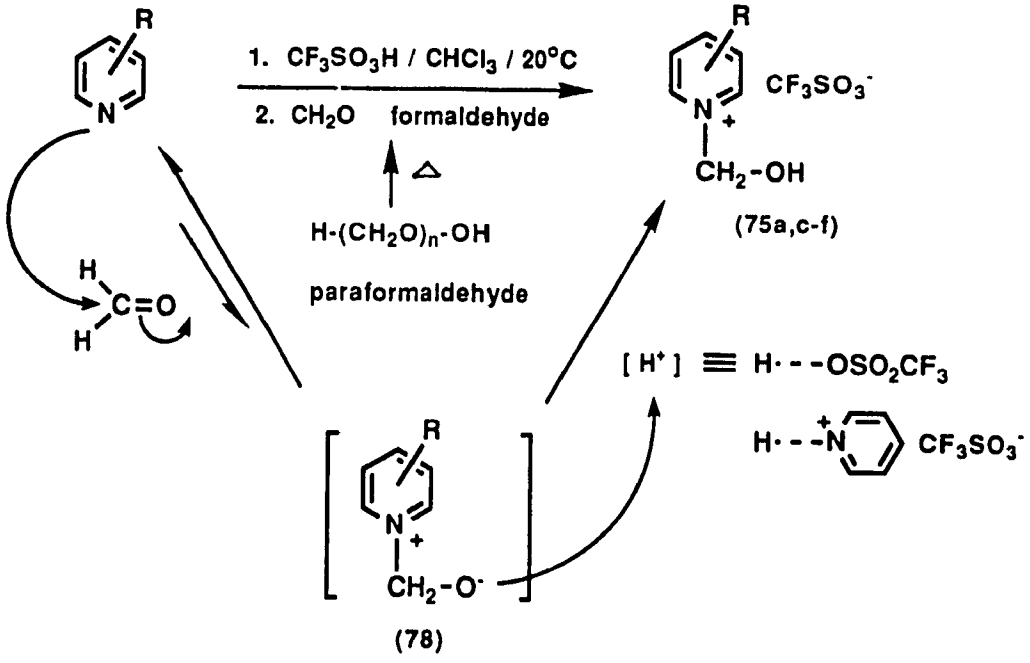
CHAPTER III. RESULTS AND DISCUSSION

1. SYNTHESIS OF N-(HYDROXYMETHYL)PYRIDINIUM SALTS

As mentioned in the introductory section, Anders did extensive study on the theoretical aspects of the N-(hydroxymethyl)pyridinium cation; i.e. heats of formation, bond lengths, and transition state structures. An experimental confirmation of their theoretical predictions, that the pyridiniomethanol cation would be unstable and prone to decomposition before isolation, had not been attempted.

In our research lab, this compound has been synthesized and the evidence we present for its formation comes in the form of ^{1}H and ^{13}C NMR, I.R., FAB mass spectra, and elemental analysis for **75a,b**. Four transformations of this molecule are also reported. The proposed mechanism for the synthesis of pyridiniomethanols **75** is as follows:

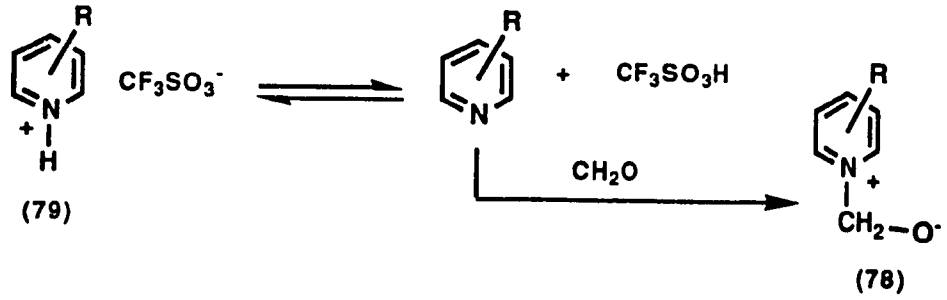
Scheme 62



1.1. N-(hydroxymethyl)pyridinium triflate and chloride.

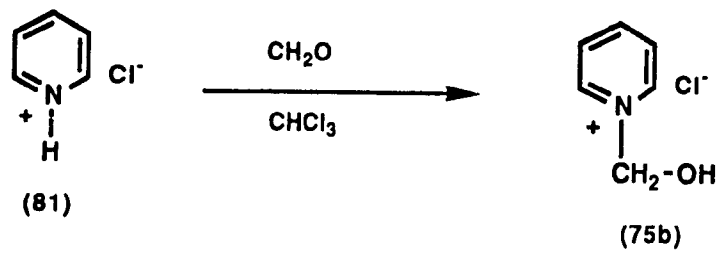
The parent (unsubstituted) pyridiniomethanols **75** have been synthesized as both the triflate **75a** and chloride **75b** salts. Regarding the former, the experimental method involves the initial addition of triflic acid to pyridine in chloroform to yield, protonated pyridinium triflate **79** which precipitates out of the chloroform solution as a white solid. Formaldehyde gas is then passed into the resulting mixture resulting in the desired product. The existence of **79** in equilibrium with free pyridine, which is soluble in chloroform, may explain why some pyridine is available to react with the incoming formaldehyde monomer to yield the pyridiniomethoxide zwitterion **78**.

Scheme 63



In an attempt to validate the synthesis of **75a**, the latter compound, N-(hydroxymethyl)pyridinium chloride **75b** has been synthesized using pyridinium hydrochloride and formaldehyde in chloroform at room temperature.

Scheme 64

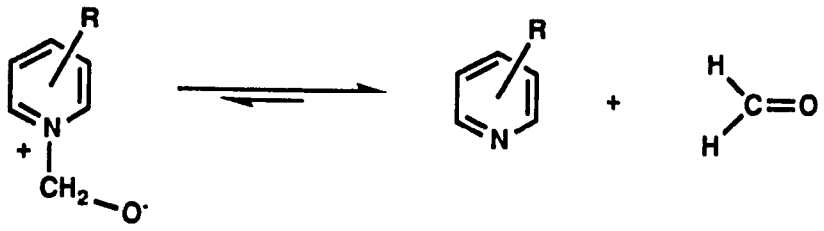


1.2. Pyridiniomethanols synthesized from substituted pyridines

While the synthesis of **75a** in chloroform is quite straightforward, the syntheses of 4-formylpyridiniomethanol **75c**, 4-oxime-pyridiniomethanol **75d**, 4-amido-pyridiniomethanol **75e**, and 3-amidopyridiniomethanol **75f** are not. In chloroform alone the products form in very low yield and contain substantial amounts of polymerized formaldehyde. Changing the solvent to a solution of 5-10% dimethylformamide (DMF) in chloroform or methylene chloride results in a major improvement in product purity. Compound **75c** can also be synthesized readily in acetonitrile; the polarity of this solvent probably provides a better stabilizing medium for the formation of this salt. For some reason, presently unclear, acetonitrile is unsuitable for the synthesis of salts **75d** and **75e** even though all the starting reagents, the substituted pyridine, triflic acid, and gaseous formaldehyde are completely dissolved.

Attempts to observe, if not isolate, structure **78** by ^{1}H NMR in deuterated tetrahydrofuran(THF) at low temperatures have proven fruitless. Our expectation was that if a polar aprotic anhydrous solvent can stabilize an extremely reactive molecule such as formaldehyde at low temperatures (so that it can be detected by NMR), the same could be done for the potentially unstable zwitterion. Unfortunately, this compound has proven to be far too short-lived to be observed directly. If an electrophilic species is not already present in solution to react with it, (e.g. H^+), it seems to decompose to starting materials.

Scheme 65

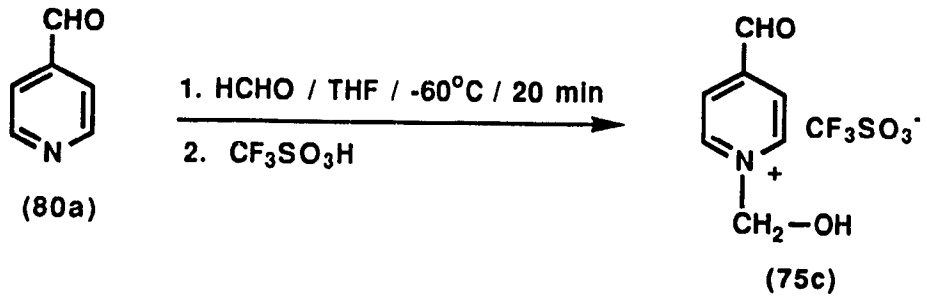


(78)

Consequently, we concluded that triflic acid had to be in solution before the addition of formaldehyde in order for the desired product to be formed.

Later though, it was discovered that pyridine-4-carboxaldehyde **80a** could be converted to the corresponding 4-formyl pyridiniomethanol **75c** at low temperatures even if the order of addition is reversed. That is, formaldehyde gas is bubbled into a solution of pyridine in THF at -50 to -70°C, and the resulting mixture can be stirred for up to 20 min. before the addition of triflic acid.

Scheme 66



(80a)

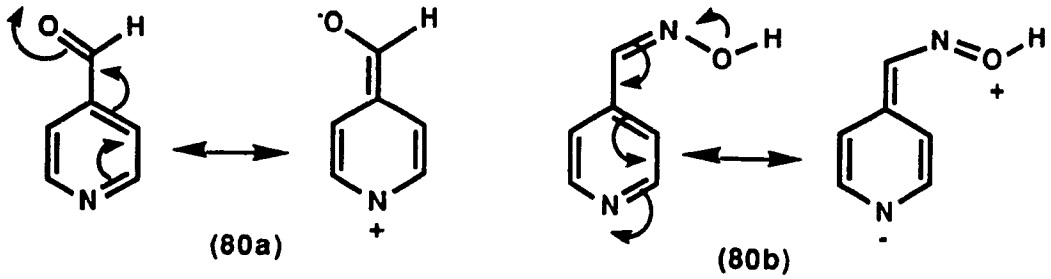
(75c)

While this may provide some indication of the formation of a zwitterionic species, there is no strong evidence that formaldehyde and **80a** form an adduct such as **78** in the cold THF solution.

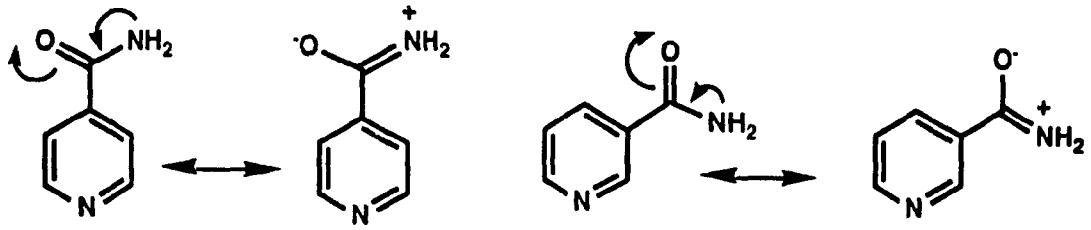
The yield of the desired product **75c**, synthesized by this method, was about equal to that obtained by the previous method. Due to solubility considerations, this technique was not attempted with the aldoxime or with the two amides, but surprisingly, when the reaction was tried with the most potent of the nucleophiles, pyridine, the desired compound **75a** was not produced. It is possible that pyridine, because it is a stronger base than **80a**, catalyzes the polymerization of formaldehyde[39 p 121].

Generally though, the reactions were performed at room temperature in less than 15 min. and the molar ratios of the nucleophile/triflic acid were usually ~1.15:1 since the yields seemed best when a slight excess of (substituted)pyridine was used.

Therefore, to conclude, in addition to the parent compound **75a** it is possible to synthesize and obtain evidence for several substituted pyridiniomethanols, derived from pyridine-4-aldoxime **80b**, pyridine-4-carboxaldehyde **80a**, isonicotinamide **80c**, and nicotinamide **80d**. All these compounds contain substituents that are inductively electron-withdrawing, thus decreasing the nucleophilicity of the nitrogen, although the oxime group on **80b** will also donate electron density through resonance delocalization.



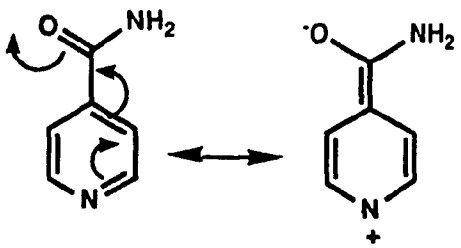
The amides **80c** and **80d** though, would be expected to display less of a decrease in nucleophilicity[47] due to the ability of the amide group to undergo resonance stabilization without strongly interacting with the pyridine ring.



(80c) (80d)

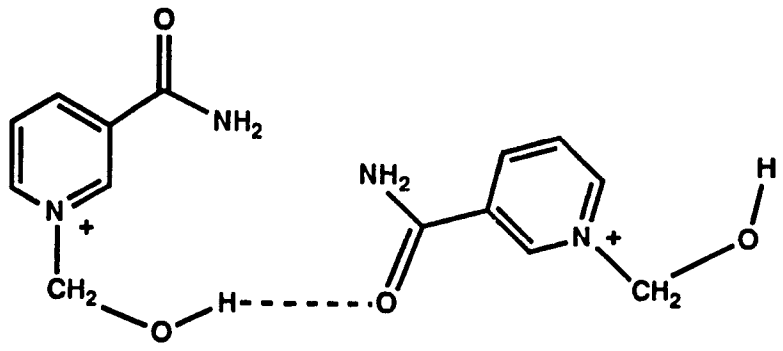
Of course, of the two compounds above, **80c** would still be expected to be less nucleophilic based on the fact that, unlike **80d**, it does exist as a resonance hybrid as do **80a** and **80b**.

Consequently, in terms of reactivity towards an electrophilic species, of the four compounds, one would expect **80d** to display the greatest nucleophilicity.



Experimentally though, the situation has proven to be quite the opposite, in that, **80d** seems to be the least reactive (by a small margin), and this is supported by a rough correlation of chemical reactivities to pK_a values (80d, 3.33; 80c, 3.61; 80b, 4.73; 80a, 4.74)[48]. In addition, once the final pyridiniomethanol has been formed, it decomposes much more readily than the salts derived from **80a,b** and **c**. Of the four substituted pyridines, **80c** gives the highest apparent yield, almost as high as pyridine itself, which is the most reactive and produces the most stable compound.

These results contradict theoretical predictions, which claim that the resonance hybrid structure of the N-substituted 4-amido pyridine (unlike the corresponding 3-amido compound) is more conducive to the breakdown of the salt.



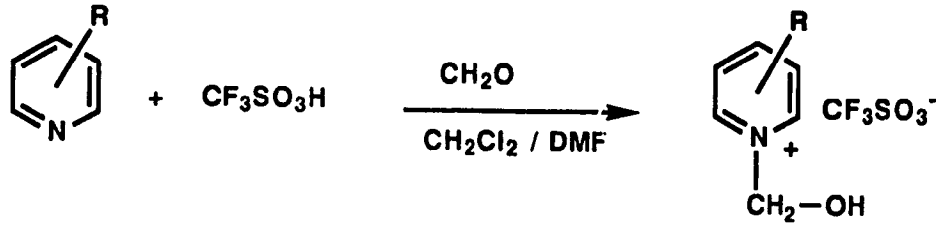
It is possible that the molecules orient themselves in such a way that the hydroxyl groups are more easily deprotonated.

Either way, ^{1}H NMR indicates clearly how, with time, the integration of the characteristic methylene singlet decreases, while the signals representing formaldehyde polymers simultaneously increase in size. This is a common phenomenon that occurs with time to all of the compounds **75** but the rate at which it occurs with the N-(hydroxymethyl)nicotinamidium triflate **75f** (from **80d**) greatly surpasses the others.

1.3. Relative yields and methods of purification

The basic reaction scheme for the synthesis of compounds **75** is as follows:

Scheme 67



(75a,c-f)

Table 4 Hydroxymethylation of Substituted and Unsubstituted Pyridines

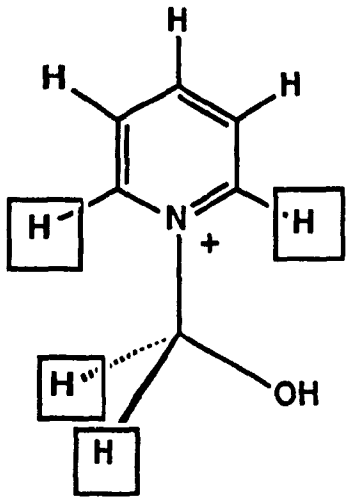
R	Product	Yield (%)
H	**75a**	85
H	**75b**	75 (based on crude product)
4-CHO	**75c**	74
4-CH=NOH	**75d**	53
4-$CONH_2$	**75e**	80-85
3-$CONH_2$	**75f**	decomposes
2-CHO		results ambiguous
2-CH=NOH		results ambiguous

*from NMR integration represents the (%) of CH_2 (methylene protons)/(2 pyridinium protons). This formula is defined in greater detail on page 66-7.

The above salts **75** were generally too sensitive to hydrolysis and/or protic solvents such as ethanol or methanol so as to be amenable to recrystallization by these solvents. Trituration with water or various alcohols would have proven very useful for removing the traces of polymerized formaldehyde that were usually observed by ^{1}H NMR in the final product. Unfortunately, as already mentioned, the desired products themselves were soluble and readily hydrolysed by the same solvents thus making separation of the impurities by this method, almost impossible. These compounds were all isolated as oils except **75b** which solidified upon drying. With the exception of **75b**, attempts to recrystallize **75a-f** from polar aprotic solvents such as THF and acetonitrile were unsuccessful. Subsequent crystallizations were tried from mixed solvent systems, i.e. dissolving the oil in THF or acetonitrile, followed by addition of chloroform or diethyl ether. Unfortunately, the products obtained by this method consisted of oils instead of crystals.

We were able to achieve the recrystallization of **75b** from acetonitrile and observe about a 10% increase in purity over the crude reaction product. Further recrystallizations did not result in substantial increases in purity. The final product displayed a purity of about 88%. Although it is more obvious from the NMR spectrum of **75b**, we believe that the major impurities in the crude pyridiniomethanol products are unreacted N-protonated pyridinium salts. In the case of **75b**, the unreacted pyridinium hydrochloride **81** can be successfully removed by recrystallization with acetonitrile since it is slightly more soluble in this solvent than the alcohol.

The problem with the triflate alcohols is the fact that they are more readily soluble than the N-protonated pyridinium triflates and therefore do not come out of solution.



(82)

We report the relative purities of the products based on their ^{1}H NMR data. Knowing that the peaks representing the pyridinium protons were indicative of both the desired pyridiniomethanol and the protonated pyridinium salt (which was the major impurity), the integration of two of these protons at δ ~8.5 ppm was used to represent the standard for two protons. The methylene peak at δ 5.9-6.3 ppm, depending on the alcohol, would only be present on the pyridiniomethanol and so an estimate of the amount present in the crude mixture i.e. the proportion of the crude mixture that is the actual desired compound (% COMPOUND) can be calculated.

$$\% \text{ COMPOUND} = \delta\ 5.9\text{-}6.3 \text{ ppm } (CH_2) / \delta \sim 8.5 \text{ ppm (2 py CH's)} \times 100$$

1.4. Characterization; ^{1}H and ^{13}C NMR, IR, and FAB mass spectra

Despite the lability of these compounds, during purification, considerable evidence exists for their formation (as it does for the parent compound **75a**) based on ^{1}H and ^{13}C NMR, I.R., and FAB mass spectra. In fact the mass spectral results provide some of the strongest evidence supporting the existence of these structures since in all cases, a prominent peak exists at the mass/charge (m/z) of the corresponding cations.

Table **5** FAB Mass Spectral Peaks of N-(Hydroxymethyl)Pyridinium Salts

	cationic formula weight, g/mol (based on most abundant isotope)	m/z peak (% of highest mass peak observed)	Base peak
75a	110	110.1 (100)	$75a^{+}$
75b	110	110.1 (100)	$75b^{+}$
75c	138	138.1 (27)	$(75c^{+}- CH_2O)$
75d	153	153.1 (31)	$(75d^{+}- CH_2O)$
75e	153	153.1 (38)	$(75e^{+}- CH_2O)$
75f	153	153.0 (11)	$(75f^{+}- CH_2O)$

In terms of the ^{1}H and ^{13}C NMR data, in general, there are several trends that indicate that these structures indeed have a common pyridiniomethanol ($\geq N^{+}-CH_2-O-H$) backbone, and therefore belong to a family of compounds.

Their methylene peaks all appear within δ 0.2 ppm of one another and the chemical shift is typical of protons sandwiched between an electronegative oxygen and a strongly electron-withdrawing quaternary nitrogen. The methylene protons of trioxane appear at δ 5.1 ppm while those of other aminals (>N-CH_2-O-R) appear anywhere from δ 6.35 ppm for thymidine, δ 6.6 ppm for compound A and as low as δ 5.5 ppm for salt B. All our compounds 75 fall in the expected chemical shift range. In contrast, neutral aromatic methanols exhibit methylene or methine peaks more upfield at δ 4.7 and 5.7 respectively for compounds C and D[49].

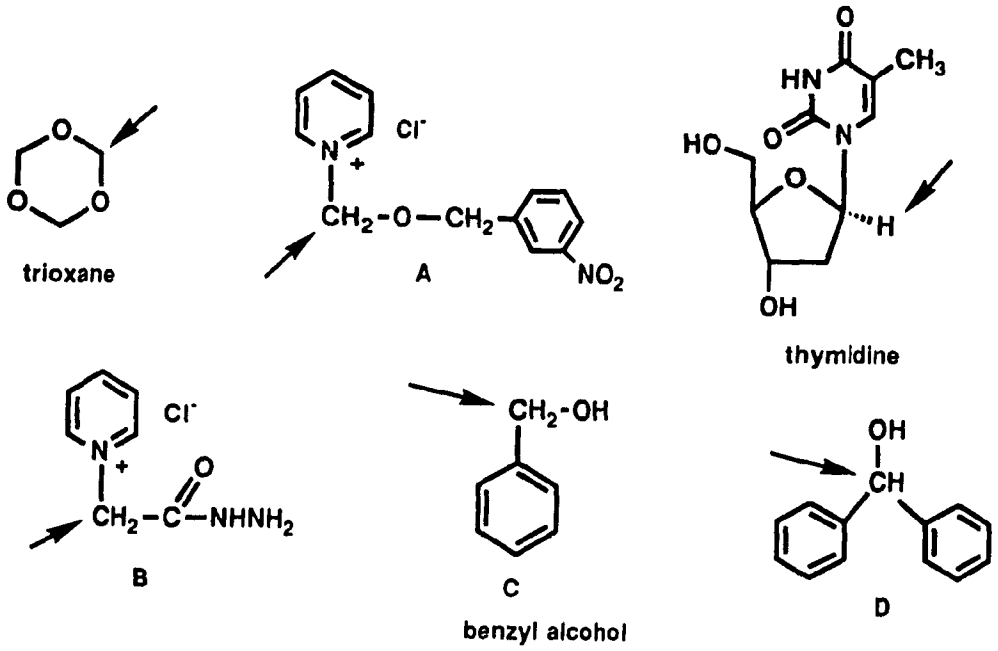
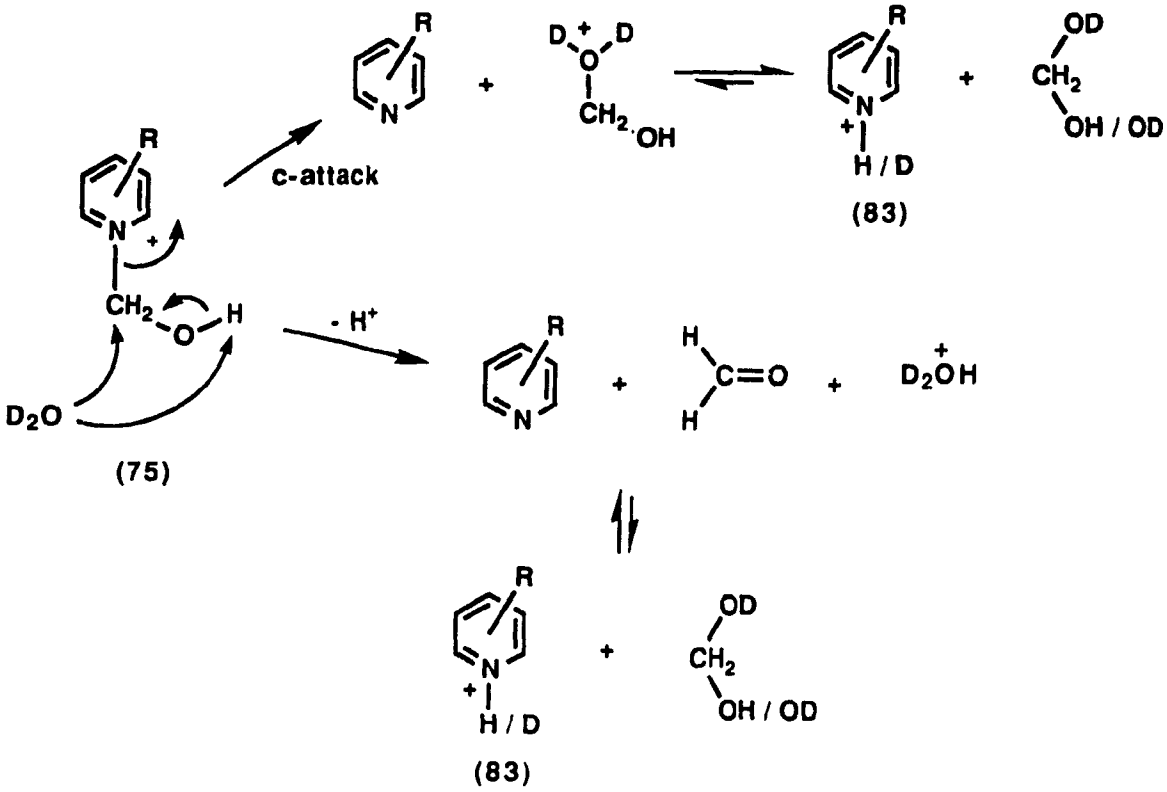


Table 6 Proton and Carbon-13 NMR Chemical Shifts of the Methylene Groups of Compounds 75

	methylene protons (CH_2)	
	δ ^{1}H NMR (ppm)	δ ^{13}C NMR (ppm)
75a	6.1	84
75b	5.9	83
75c	6.2	85
75d	6.1	84
75e	6.2	84
75f	6.2	84

The hydroxyl protons of the triflate salts generally appear as broad peaks between δ 7.3 and 8.0 ppm but for the chloride salt **75b,** they are buried under the pyridinium hydrogen peaks. The hydroxyl protons can be exchanged by the addition of D_2O. Since these compounds can be readily hydrolysed, this decomposition can be monitored by ^{1}H NMR as well. Several mechanisms may be proposed for this degradation since there are two different ways in which H_2O (or D_2O) can attack the molecule.

Scheme 68



Either mechanism is consistent with the disappearance of a hydroxyl peak and the appearance of two new peaks at $\delta \sim 4.1$ and ~ 4.8 ppm which can be accounted for by the methylene and hydroxyl groups of the formaldehyde hydrate that forms.

The salt is susceptible to S_N2 attack at the methylene carbon or can be deprotonated at the hydroxyl proton. This makes the molecule very unstable and an unlikely candidate for recrystallization or column chromatography. In fact, attempts to purify these compounds by reverse phase column chromatography or HPLC were unsuccessful even though anhydrous solvents were used. No separation was observed and the compounds showed signs of decomposition.

Infrared spectroscopy was also used to characterize the structures; confirmation was obtained for the presence of hydroxyl groups from absorption bands at 3300 cm^{-1}, and of C-O bonds by a stretch band at 1100 cm^{-1}. Although not by itself conclusive, the method does indicate the presence of distinct functional groups and in combination with the other methods of detection, helps put together a strong case for the existence of structures **75**.

2. DERIVATIVES OF PYRIDINIOMETHANOL

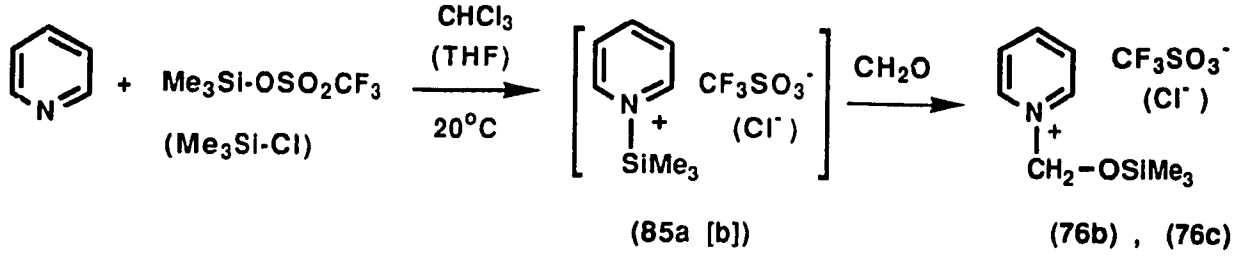
2.1. One-step syntheses from pyridine and its derivatives

In addition to the hydroxymethyl pyridinium salts, other N-substituted pyridines have been synthesized that contain the pyridiniomethoxy moiety. They were prepared by the same general method used to create compounds **75** which involves combining pyridine and an appropriate electrophile in a suitable solvent followed by the addition of gaseous formaldehyde.

2.1.1 N-(trimethylsiloxymethyl)pyridinium triflate and chloride

Two electrophilic species were used. trimethylsilyl triflate and trimethylsilyl chloride. The basic reaction for the syntheses of **76b** and **76c** is shown in scheme 69

Scheme 69



(85a [b]) **(76b) , (76c)**

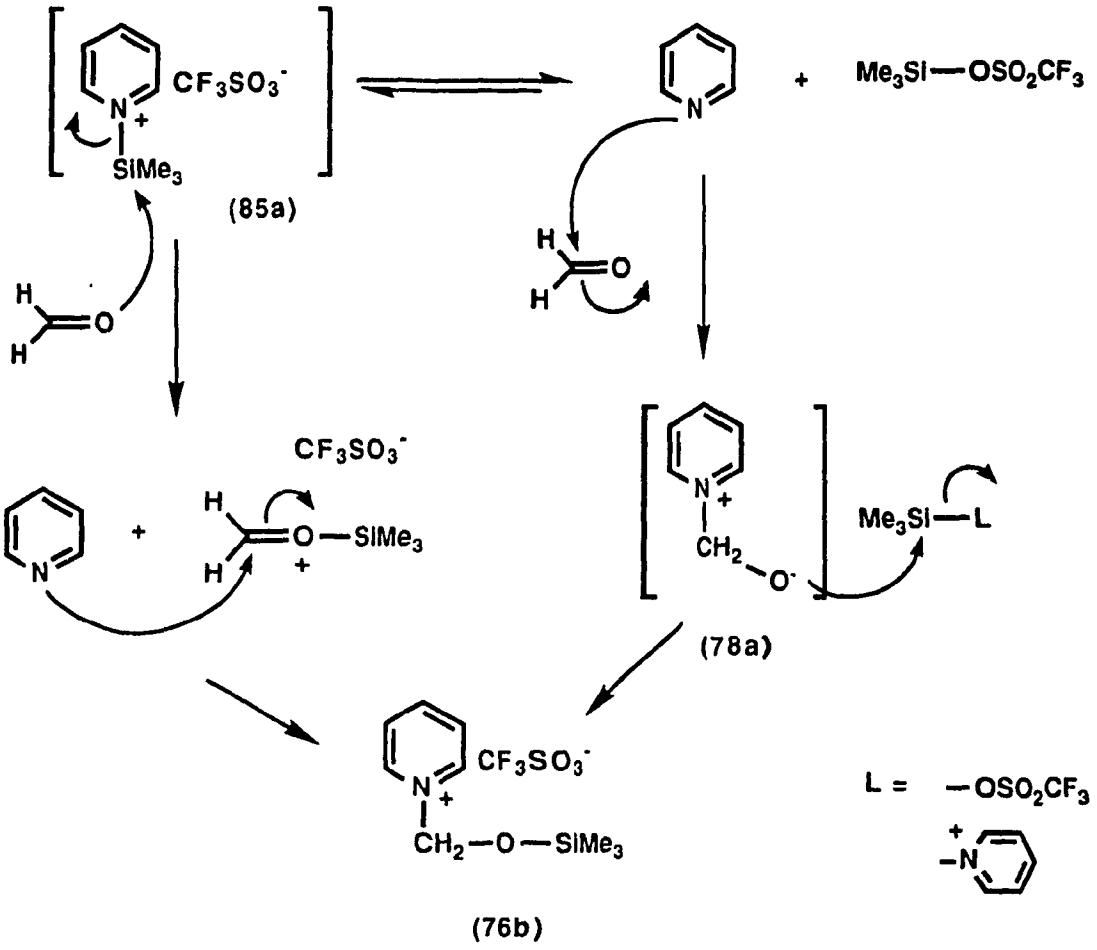
In N-methylpyridinium chloride, the $\overset{+}{N}$-C bond is quite strong and the methyl carbon, unlike one between an oxygen and a quaternary nitrogen, is not very susceptible to nucleophilic attack. For this reason w. chose to create the more labile $\overset{+}{N}$-Si bond[24] that could be more easily replaced with formaldehyde.

The reaction with trimethylsilyl triflate was performed in chloroform and resulted in a crude product of very high purity. In order to obtain good results with trimethylsilyl chloride, THF was used as solvent. This told us something about which solvents work best with compounds having different leaving groups. It seems that with a chloride ion, which is a relatively poor leaving group, it is necessary to use an aprotic solvent of relatively high polarity in order to stabilize not only the incoming formaldehyde monomer and/or the leaving chloride ion, but all the transient structures. With an exceptionally good leaving group such as the triflate ion, solvation is not as necessary and it is this property, not solvation, that probably brings the reaction to completion.

The same reaction that had been attempted with trimethylsilyl chloride in methylene chloride was not very successful, as proven by the ^1H NMR spectrum of the resulting compound. This spectrum displayed a methylene peak of insufficient integration at δ 6.0 ppm. The NMR of the product did, though, show considerable multiple signals at δ ~5 ppm probably representing polymerized formaldehyde. An improvement in the leaving group ability of the triflate resulted in a substantial improvement in yield. Not only were the integrations of the methylene and trimethylsilyl peaks (relative to the pyridinium peaks) indicative of a product that was of much greater purity but there was almost a complete disappearance of peaks resulting from impurities such as polymerized formaldehyde.

There are two different proposed pathways for the formation of **76b** stemming either from free pyridine or from the N-silylated compound **85a**.

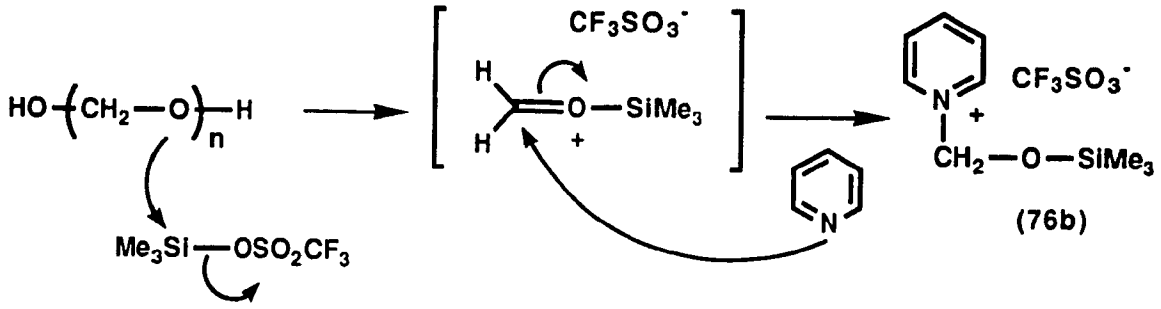
Scheme 70



Not only does trimethylsilyl triflate more readily silylate pyridine via the first reaction pathway, but it serves as an excellent silylating agent for the pyridiniomethoxide ion **78a** if the mechanism follows the second pathway.

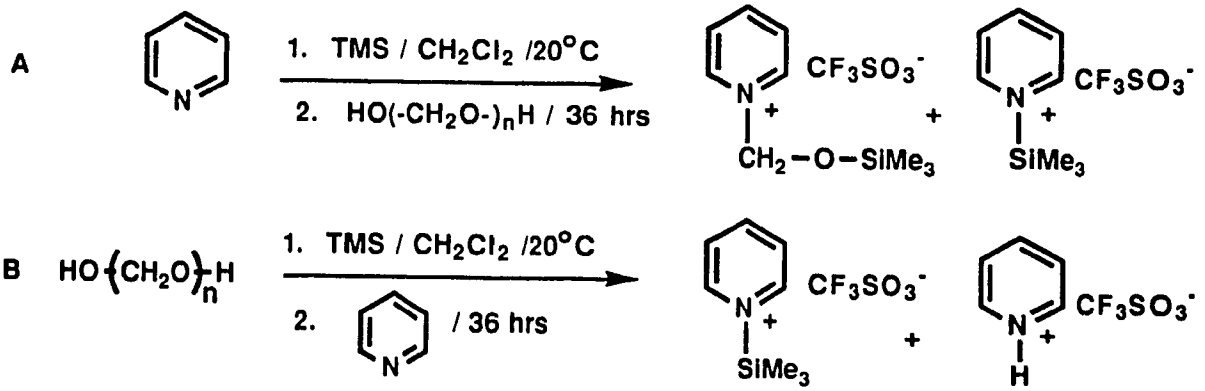
Because of the success of the above reaction, the same procedure was attempted with pyridine, trimethylsilyl triflate and solid paraformaldehyde. We were interested in finding out whether trimethylsilyl triflate could catalyze the depolymerization of the polymerized formaldehyde as well as silylate the oxygen atoms so as to render the carbonyl carbon susceptible to attack by pyridine.

Scheme 71



The reaction was performed two ways;

Scheme 72



By method A, some of the desired product seemed to have formed (~35% crude yield according to ^1H NMR integration) while method B yielded mostly what seemed to be a

combination of the silylated pyridine and protonated pyridinium triflate although the source of protons is unknown.

Regardless of the synthetic method, the final product (the chloride **76c** or the triflate **76b**) was no more amenable to purification than the corresponding pyridiniomethanols. If anything, these silyl compounds were even more sensitive to hydrolysis as proven by ^1H NMR: the addition of several drops of D_2O virtually decomposed the product completely. This was observed as a substantial reduction in integration of the methylene singlet at δ 6.3 ppm for the chloride and 6.0 ppm for the triflate salt.

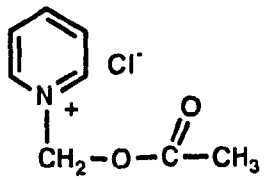
In contrast, the addition of D_2O to compounds **75** exchanges the hydroxyl proton and it also results in a decrease in the intensity of the methylene peak but not to quite the same extent (more so for the chloride salt).

In fact, even if the trimethylsiloxymethylpyridinium salts are placed under vacuum for an extended period, they begin to decompose. This has been observed especially for the chloride salt which, when placed under vacuum for 4-5 hours, is converted almost completely to the corresponding alcohol. Not only is there a shift in the methylene peak from δ 6.3 to 6.0 ppm but the doublet representing the ortho pyridinium protons shifts from δ 9.5 to 9.2 ppm which indicates a conversion of **76c** to **75b**.

As with **75b**, we attempted a recrystallization of **76c** from acetonitrile but it was much more soluble in this solvent than **75b**, presumably because of the trimethylsilyl group and consequently it did not crystallize out.

2.1.2. N-(acetoxymethyl)pyridinium salts synthesized from pyridine, nicotinamide, and isonicotinamide

One of the most stable compounds synthesized in this series was the pyridiniomethanol derivative, N-(acetoxymethyl)pyridinium chloride **76d.**



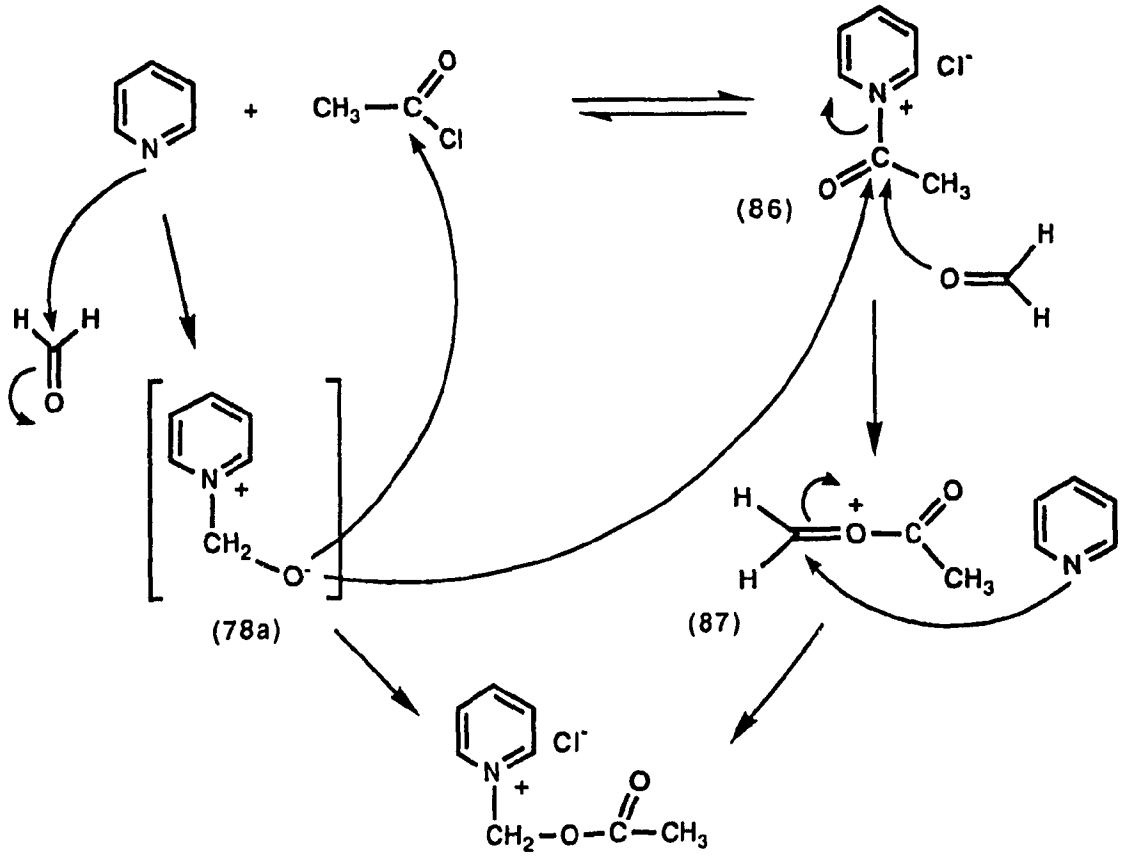
(76d)

The initial aim of this synthesis was to provide additional evidence for the existence of compounds **75a** and **75b**. We were interested in using the pyridiniomethanols as reactants to see if indeed, like other alcohols, they could be acetylated using an appropriate base.

Interestingly, compound **76d** can also be prepared in one-step from pyridine, formaldehyde and acetyl chloride by the same method used to make **76c**. Although this compound has less synthetic utility, it is produced in high yield and is stable to water. Because of its stability, it can be recrystallized from solvents such as ethanol under conditions which partially decompose other pyridiniomethanols. The combination of pyridine and acetyl chloride in THF or acetonitrile yields a compound that precipitates out of solution. The addition of gaseous formaldehyde under the surface of the liquid, results in the synthesis of a crude product that is almost 100% pure.

Therefore, a logical assumption in this case, as in the case with pyridine and triflic acid, is that a certain proportion of the intermediate **86** that forms is probably soluble in THF (or acetonitrile), or that it exists in equilibrium with pyridine and acetyl chloride, both of which are also soluble. This offers one explanation as to why it is possible to add a gaseous compound to a slurry mixture and obtain such a high yield of the desired compound. See scheme 73

Scheme 73

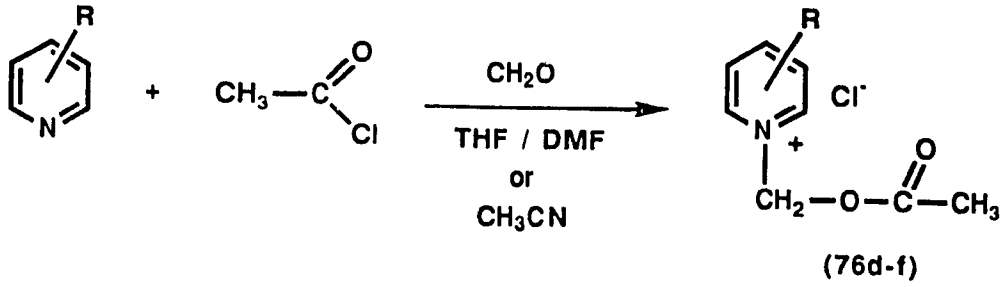


If the reaction stems from dissolved N-acetylpyridinium chloride **86**, then it may follow the mechanism of nucleophilic catalysis discussed in section 2.2 of chapter I. In this case formaldehyde would be the competing nucleophile, but the difference from the situation in section 2.2 is the fact that the product **87** that forms is likely to be too unstable to exist on its own. Therefore, any free pyridine reacts with it to yield the final stable structure **76d**.

If one takes solubility into consideration, it is more likely that the compound that precipitates out of the solvent is **86** while what remains soluble are the reactants. The reaction probably follows the route where free pyridine forms a zwitterion with formaldehyde which is subsequently acetylated via free acetyl chloride or **86**.

As with the syntheses of the pyridiniomethanols, these acetylations have also been attempted with various substituted pyridines, **80a-d**.

Scheme 74



(76d-f)

Table 7 Yields Obtained from the Syntheses of Compounds **76**

R	Product	Yield (%)
H	**76d**	62
3-$CONH_2$	**76f**	35
4-$CONH_2$	**76e**	26
4-CHO	reaction unsuccessful	
4-CH=NOH	reaction unsuccessful	

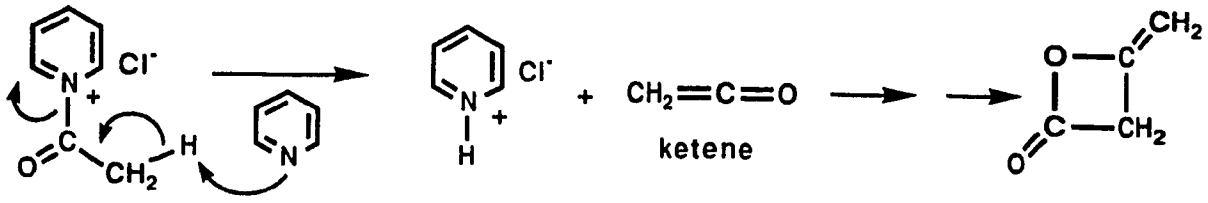
Although the yields of **76f** and **76e** are not as high as that of **76d**, these compounds are stable to hydrolysis and can be easily recrystallized from ethanol / methanol solvent mixtures. Two or three recrystallizations afford a compound which is almost 100% pure by ^{1}H NMR. Unfortunately, these purification procedures cause the loss of product and low net yields.

It is difficult to explain why the reactions with pyridine-4-carboxaldehyde **80a** and pyridine-4-aldoxime **80b** were unsuccessful since the ^{1}H NMR spectra of the crude products provide no clear evidence of what compounds are present. The ambiguity arises from the question as to whether the formyl and/or oximino groups react with acetyl chloride, formaldehyde or with both. In the cases of compounds **76d**, **76f** and **76e**, there were some distinct indications that the reactions had yielded compounds that had a similar $\rangle N^+$-CH_2-O-C(O)-CH_3 aminal subunit. Unlike the hydroxymethyl pyridinium salts, the

methylene protons appear on ^{1}H NMR at about δ 6.5-6.6 ppm, which is about 0.5 ppm downfield and this may be a result of the more deshielding effect that the ester moiety produces as compared to the hydroxyl group. In addition, as compared to the chemical shift of the methyl group of acetyl chloride which appears at δ ~2.8 ppm, the methoxy protons of **72a** occur farther upfield at δ 2.2 ppm. The integration of the two groups indicates a ratio of 2:3 confirming the fact that these are indeed methylene and methyl groups.

It was also necessary to ensure that there had not been any formation of another unstable carbonyl compound, a ketene, which could have conceivably formed through the deprotonation of the acetylated pyridine by a second pyridine molecule as shown in scheme 75.

Scheme 75



Lastly, very strong evidence was provided by FAB mass spectra where the peaks corresponding to the formula weights of the corresponding cations appeared either as the molecular ion or as one of the more prominent peaks;

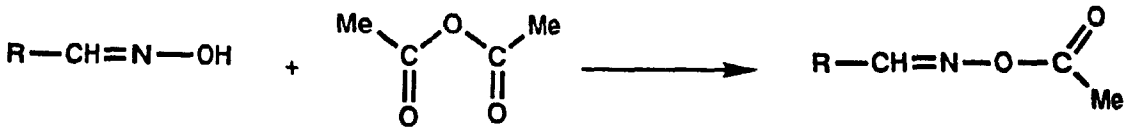
Table 8 FAB Mass Spectral Peaks of Compounds **76**

	molecular weight of cation, g/mol (based on most abundant isotope)	m/z peak (% of highest mass peak)	Base peak
76d	152	100	$76d^+$
76f	195	100	$76f^+$
76e	195	37	Cs^+

Therefore, returning to the substituted pyridines **80b** and **80a**, attempts to acetoxymethylate these compounds seemed, from ^1H NMR spectra, successful but with the simultaneous synthesis of numerous other products. Although the presence of a small peak or multiplet of peaks can be observed at the characteristic chemical shift of δ 6.5-6.6 ppm, there are extra peaks that cannot be explained. For example, a series of peaks were found (in the pyridinium proton region of δ 8.0 to 9.5 ppm) which indicated a mixture of unidentifiable products. As well, the integration ratio of 2:3 for methylene : methyl observed for **76d**, **76f** and **76e** was not observed.

In the case of the 4-aldoxime **80b**, it is known that an oxime hydroxyl group can be readily acetylated using acetic anhydride; therefore it is conceivable that acetyl chloride can function as an acylating agent as well.

Scheme 76



Therefore, **80b** was reacted with acetyl chloride, the product was well dried to remove all volatile compounds, and then a ^{1}H NMR spectrum was taken. It seemed to indicate a mixture of unreacted **80b** and some **80b** acetylated-oxime but there was no indication of quaternization of pyridine nitrogen. If this is the case, one can safely conclude that the oxime reacts, preferentially over the nitrogen, with acetyl chloride.

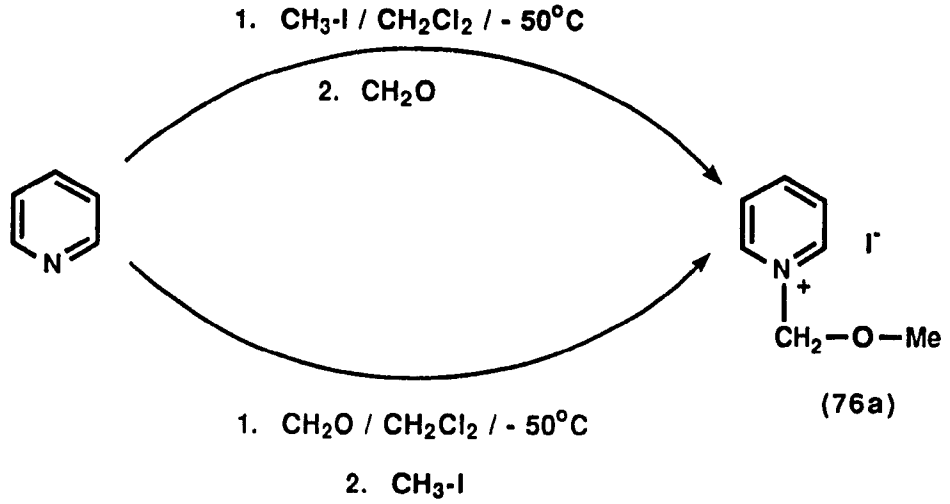
The same reaction, with the subsequent addition of formaldehyde, yielded a product(s) whose NMR consisted of a series of pyridinium proton peaks between δ 8.2 and 9.7 ppm that did not correspond to the expected product, two singlets at δ 6.7 and 6.0 ppm and an other series of singlets at δ 2.2 and 2.3 ppm.

Pyridine-4-carboxaldehyde **80a** was also reacted with acetyl chloride and formaldehyde in two different solvents; acetonitrile and THF/DMF, but both solvents yielded the same end result. The ^{1}H NMR of the crude product, in this case as in the reaction products above, was interpreted as evidence of the formation of a series of undesirable products.

2.1.3. Attempted synthesis of N-(methoxymethyl)pyridinium iodide

The synthesis of N-(methoxymethyl)pyridinium iodide **76a** was attempted from pyridine, formaldehyde, and methyl iodide as the electrophile. The reaction was performed under two different reaction conditions shown in scheme 77.

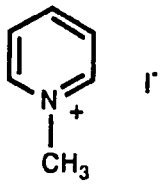
Scheme 77



The only difference in the reaction conditions was the order of addition of the reagents: methyl iodide and formaldehyde. The idea was the same in both cases; in the first case, low temperature was used in order to slow down or even prevent the reaction between pyridine and methyl iodide so that free pyridine would be available to react with formaldehyde. We anticipated that the resulting pyridiniomethoxide species **78a** would be much more nucleophilic, at -50°C, than pyridine and it would react with methyl iodide preferentially instead of pyridine.

In the second experiment, formaldehyde and pyridine were combined first with the aim of creating a zwitterion **78a** that could exist temporarily, in equilibrium with the starting reagents (as a result of the low temperatures). Addition of methyl iodide followed immediately so as to react with **78a** before it decomposed completely to pyridine and polymerized formaldehyde.

Unfortunately, the formation of an N-(methyl)pyridinium salt occurs much more quickly and the resulting product is probably not in equilibrium with the neutral reagents in order to allow for the insertion of a CH_2O moiety. In addition, methylene chloride may not be the most suitable solvent in which to attempt to stabilize a zwitterionic compound such as **78a**. The compound that formed in both cases was simply N-methylpyridinium iodide **84**.

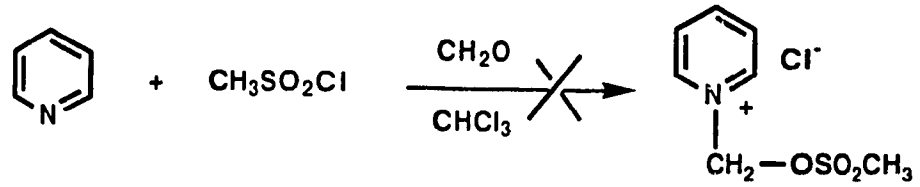


(84)

2.1.4. Miscellaneous reactions

Another product that has eluded us is the synthesis of N-(mesyloxymethyl)pyridinium chloride **88** from pyridine, mesyl chloride and formaldehyde.

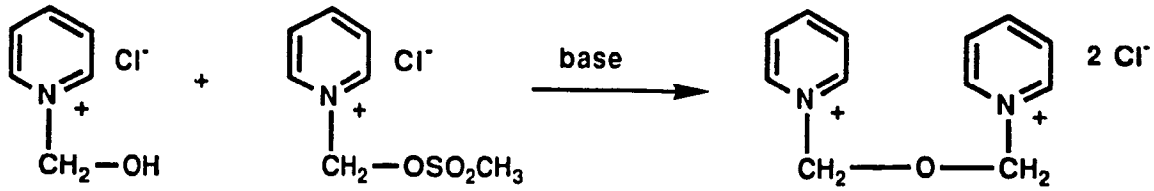
Scheme 78



(88)

The synthetic purpose of a compound such as **88** is to provide a good leaving group that can be displaced via attack, by the hydroxyl group of compound **75b**, on the methylene carbon of **88** to create an ether linkage.

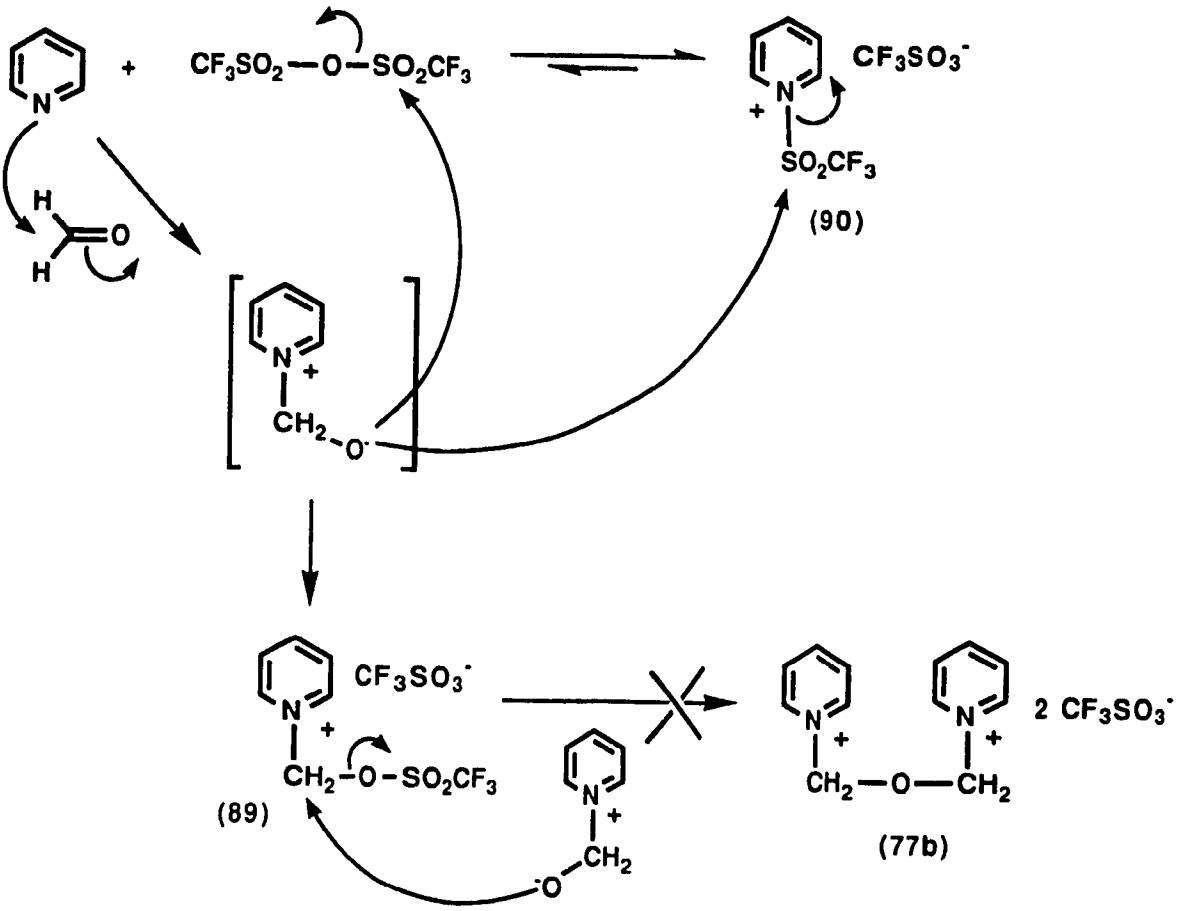
Scheme 79



(75b) **(88)** **(77a)**

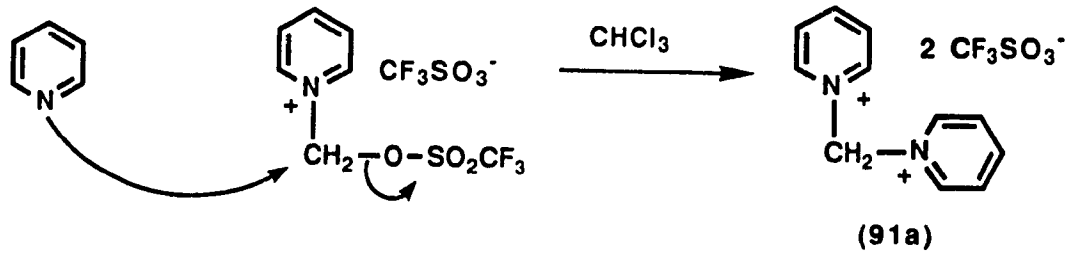
Since mesylation was not successful, triflic anhydride seemed to be an appropriate alternative as a means by which to synthesize a bis(pyridiniomethyl) ether **77a**. Not only can triflic anhydride behave as an excellent triflating agent, but the resulting compound **89** would then conceivably contain an excellent leaving group. The proposed mechanism would follow scheme 80

Scheme 80



Unfortunately, while the mechanism appears applicable up until the formation of the intermediate **89**, the second molecule to displace the triflate leaving group is not the pyridiniomethoxide. Instead, pyridine is probably the incoming nucleophile and the resulting molecule is a known compound, the 1,1'-(methylene)bispyridinium salt **91**[12,13] which has been synthesized with chloride, bromide, and iodide counterions but not, to our knowledge, with triflate **91a**. As mentioned in the introductory section, two different reaction schemes have been used to form the compound **91**, but the mechanism we propose provides an alternate route.

Scheme 81



(91a)

The product obtained (**91a**) conformed to the ^{1}H NMR data obtained for the previously synthesized salts i.e. a typical downfield shift of the singlet, representing the methylene protons, to δ ~7.6 ppm as well as the characteristic splitting and integration of peaks resulting from unsubstituted pyridinium rings. This dication, 1,1'-(methylene)bispyridinium has been synthesized with halide counterions and the chemical shift of the methylene protons in these compounds has been found to appear in the region of δ 7.5-7.6 ppm[12,13].

We found that the best results were obtained when 0.5 equivalents of triflic anhydride were used for every molar equivalent of pyridine and a slight excess of formaldehyde was bubbled into the reaction mixture (~1.2 equiv.). The crude product was of relatively high purity and it recrystallized readily from ethanol/methanol solvent mixtures. To further confirm our finding, a FAB mass spectrum was obtained and ideally we would have been interested in seeing a prominent peak at m/z = 86 (172/2 since the cation was doubly charged). Although this peak was virtually nonexistent, we observed numerous peaks representing cluster compounds which include one, two, or more

molecules of the counterion together with one or several molecules of the dication. In addition, a peak at 171 $(M-H)^+$ indicated the possible deprotonation of the dication which is consistant with fact that the methylene protons are quite acidic[13]. This information provides substantial evidence for the formation of the proposed structure.

Attempts were further made to try to synthesize and isolate the intermediate **89** in order to provide additional support for the mechanism that had been proposed to explain the formation of **91a**, but they were unsuccessful. Even when an excess of triflic anhydride was used, a lower yield of **91a** resulted but not **89**. Due to the very efficient nature of the leaving group, the intermediate **89** may be too unstable to be isolated, but logically, it would have to have been formed in order to explain the presence of a methylene moiety between two pyridinium rings.

Compounds **77b** and/or **89** were also synthetic targets which we attempted to form by reacting N-(hydroxymethyl)pyridinium triflate with triflic anhydride in the presence of various hindered bases. These will be discussed in the following chapter.

2.2 Derivatization of the N-(hydroxymethyl)pyridinium cation

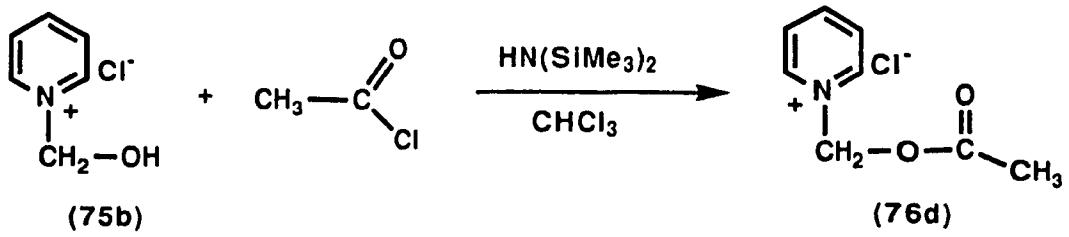
As mentioned in the previous section, one common method of confirming the structure of a new compound and its functional groups is to react it in a known way, i.e. by an established reaction, to see if it yields the expected product.

We therefore attempted several conversions of our pyridiniomethanol to the corresponding acetate ester, mesylate, triflate, and chloride. Although only the first and last reactions worked as intended, the others yielded interesting compounds that were stable, and unlike the starting material, could be purified by recrystallization.

2.2.1. Acetylation of pyridiniomethanol

Scheme 82 represents the reaction used to synthesize **76d**.

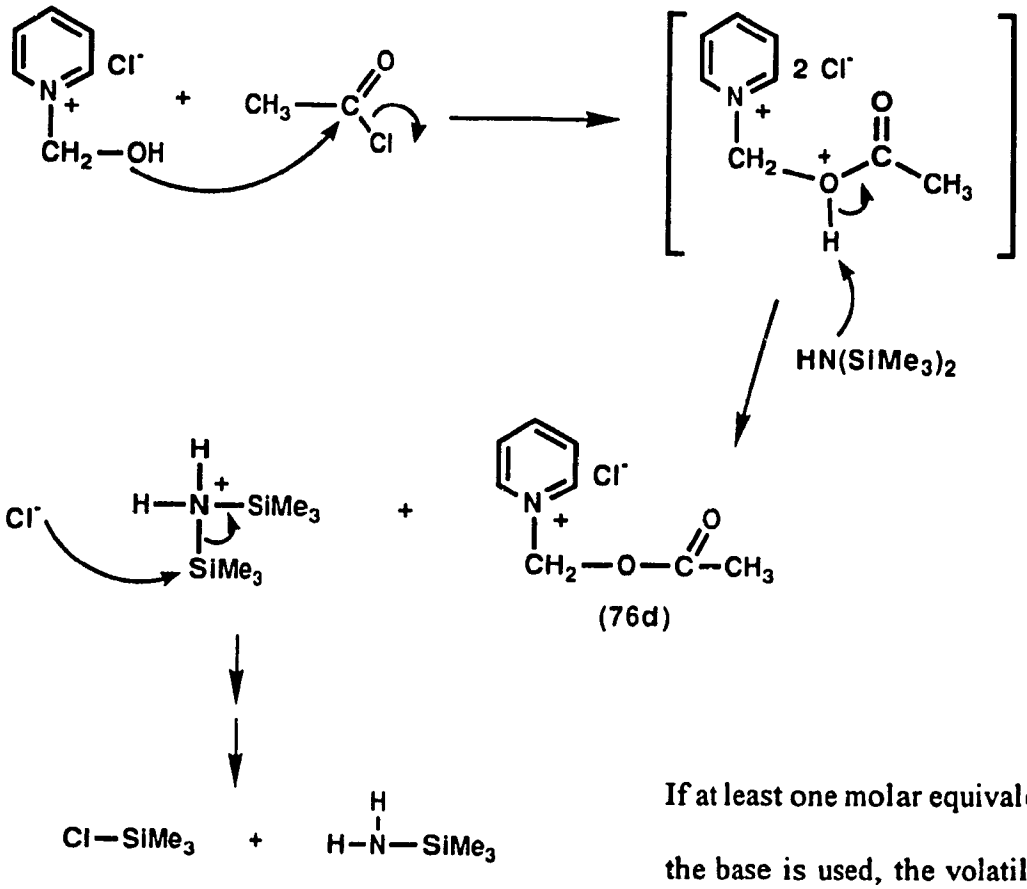
Scheme 82



When pyridine was used as the base (instead of hexamethyldisilazane), although the desired product seemed to have formed (according to NMR), it was very difficult to separate the products. Functioning as a base, pyridine deprotonates the pyridiniomethanol **75b** to yield pyridinium hydrochloride. The ^{1}H NMR spectrum indicated very clearly the presence of two compounds; **76d** and pyridinium hydrochloride in a ratio of 1:2 and although the latter is soluble in chloroform while the desired compound is not, both dissolved completely. Therefore chloroform could not be used as a trituration solvent and as later discovered, nor could methylene chloride, ether, or ethyl acetate. An attempt was then made to recrystallize the crude product directly from ethanol or propanol but unfortunately, after about one week, the only compound that finally crystallized was pyridinium hydrochloride. Because their solubilities in various solvents is so similar, this presents a problem much like the one encountered when we attempted to purify the substituted pyridiniomethanols where the desired alcohol was to be separated from the N-protonated pyridine.

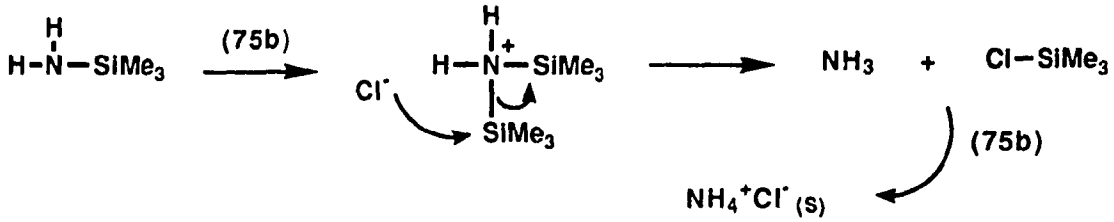
For this reason, we used hexamethyldisilazane since it was a sufficiently strong base (pK_a=7.55)[47] and once it was consumed, it left no residual compound behind in the crude reaction mixture. The mechanism would follow scheme 83.

Scheme 83



If at least one molar equivalent of the base is used, the volatile by-products of the reaction, trimethylsilyl chloride and trimethylsilylamine, can be removed by sufficient drying. The only problem arises if too little base is used, in which case the resulting trimethylsilylamine continues to function as a base and eventually produces ammonium chloride which may remain as a solid residue.

Scheme 84



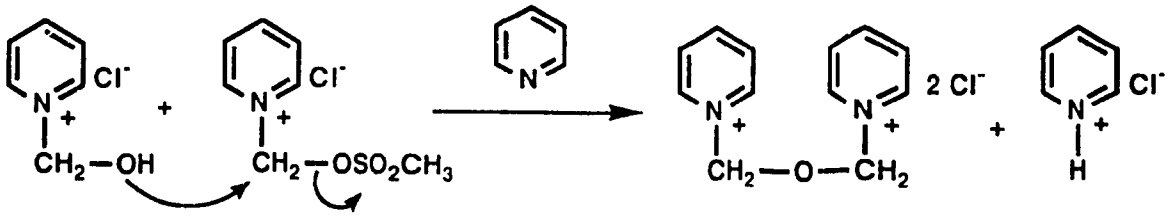
Indeed, the resulting crude product showed no indication, by NMR, of any peaks resulting from trimethylsilyl groups or of the presence of ammonium chloride therefore the desired reaction seemed to have gone to completion. NMR data also indicated a complete disappearance of any methylene peak at δ 6.0 ppm characteristic of the starting material, pyridiniomethanol, while a clear singlet at δ 6.5 ppm was present. This is consistent with the chemical shift of the methylene protons on the desired compound **76d** and provides strong evidence that a complete conversion from alcohol to ester had been achieved.

2.2.2. Attempted mesylation of pyridiniomethanol

Hexamethyldisilazane was also used in the attempted mesylation of pyridiniomethanol **75b** but unfortunately the ^{1}H NMR spectrum of the resulting product indicated that reaction had not succeeded. The same reaction was then performed using pyridine as a base and surprisingly, since the solvent used was chloroform, the pyridinium hydrochloride formed remained behind in solution while the product that was filtered and washed showed no indication of impurities. Proton NMR indicated the disappearance of the methylene singlet at δ 6.0 ppm and the appearance of one at δ 6.8 ppm; there was a slight downfield shift of protons on the pyridinium ring (especially ortho), but there was no peak present representing the methyl protons of the mesyl group.

At first it seemed that perhaps the ether linkage had been created which could be explained by a similar mechanism as the one proposed for the synthesis of the bispyridiniomethyl ether using triflic anhydride.

Scheme 85

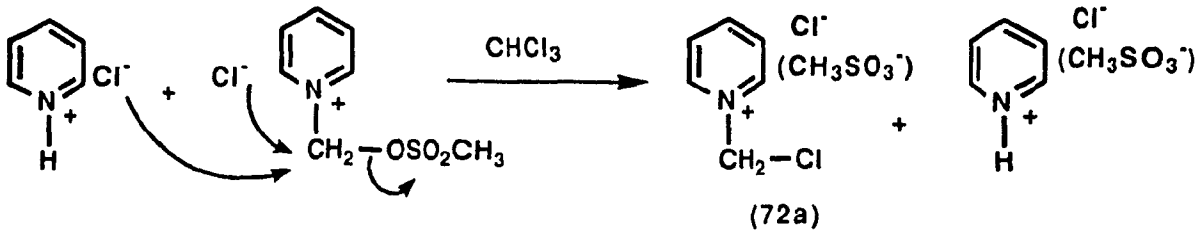


(88) (77a)

Later, with the aid of FAB mass spectra and NMR spectral comparisons, it was discovered that the compound formed was in fact N-(chloromethyl)pyridinium chloride.

Since like the triflate, the mesylate is a good leaving group, it is evident that it can be readily displaced if a sufficiently nucleophilic species is present in solution.

Scheme 86



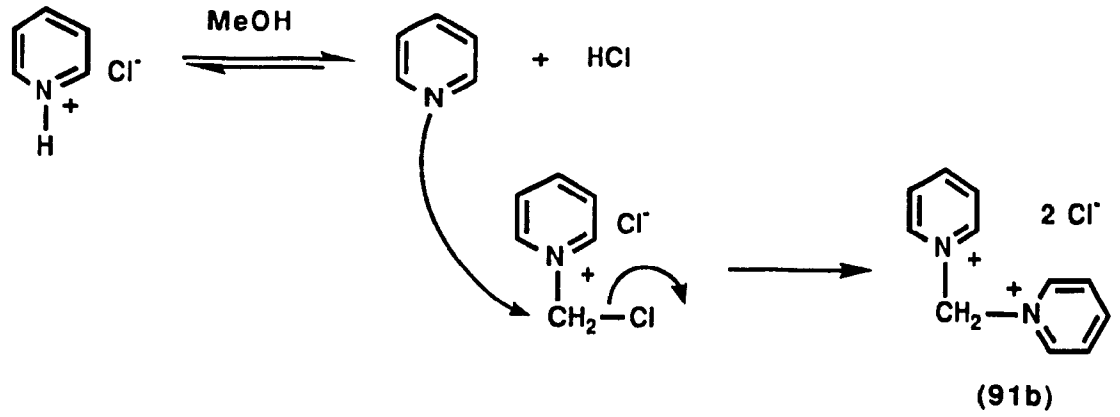
(72a)

In some initial attempts, the appearance of a methyl peak about 1 ppm upfield from its chemical shift in mesyl chloride led us to believe that the desired mesylate **88** had been formed. It is more probable that the upfield peak was due to the presence of a mesylate counterion either to the pyridinium or to the chloromethylpyridinium cation.

Compound **72a** has been synthesized previously from pyridine, thionyl chloride, and formaldehyde, but its formation through this route is new and although the intermediate **88** itself has not been isolated, evidence for its formation exists through the synthesis of **72a**. Attempts to purify this compound gave rather curious results. When the compound was recrystallized from methanol or methanol / ether, the NMR of the resulting crystals was quite different from that of the solvent-washed product. The characteristic methylene peak at δ 6.8 ppm disappeared and in its place a new singlet was present at δ 7.4 ppm and in addition, it integrated for only 1 proton. This result seemed very similar to that obtained in the NMR spectrum for 1,1'-(methylene)bispyridinium triflate **91a**, the methylene peak of which is also shifted downfield at 7.7 ppm.

Since the crude product obtained, after several washings with methylene chloride, seems to contain about a 2:1 mixture of **72a** : protonated pyridine **81**, the process of recrystallization which involves some heating may result in the phenomenon outlined in scheme 87.

Scheme 87

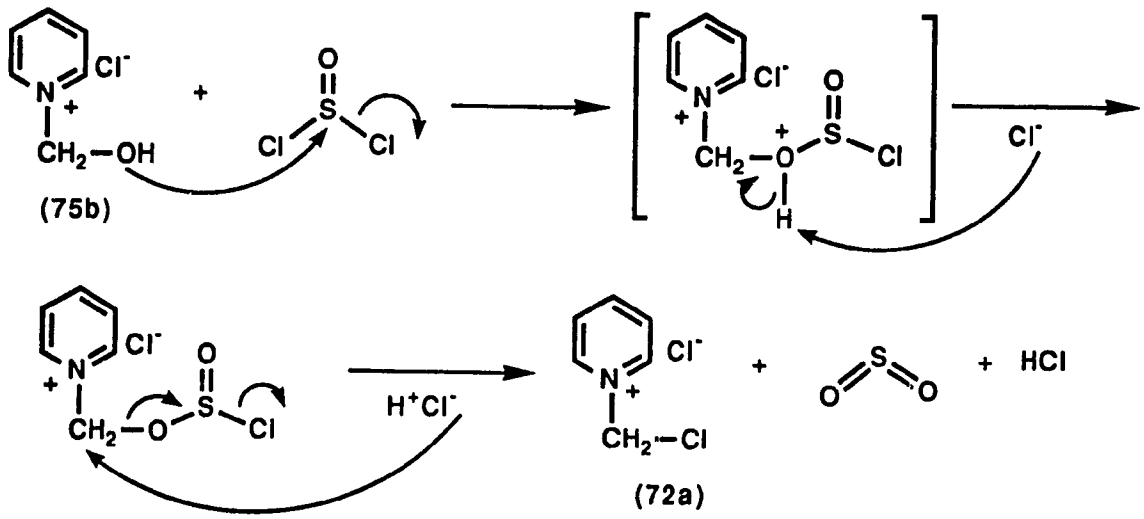


Evidence from the FAB mass spectrum taken, indicates that the chloride salt **91b** is the most likely product. The cluster compounds that appeared, together with a peak at $(M-H)^+$, presumably resulting from the deprotonation of the methylene group[13], indicate the existence of a dication.

2.2.3. Reaction of pyridiniomethanol with thionyl chloride

It is possible to synthesize **72a** directly by refluxing **75b** with thionyl chloride for approximately two hours. The proposed mechanism follows scheme 88:

Scheme 88



The excess thionyl chloride is removed under vacuum and the remaining traces were washed off with methylene chloride. The crude product left behind exhibits a virtually complete conversion from alcohol to alkyl halide and can be recrystallized from ethanol / ether. This conversion provides additional evidence for the existence of the pyridiniomethanol by showing that it does behave as an alcohol in the presence of thionyl chloride.

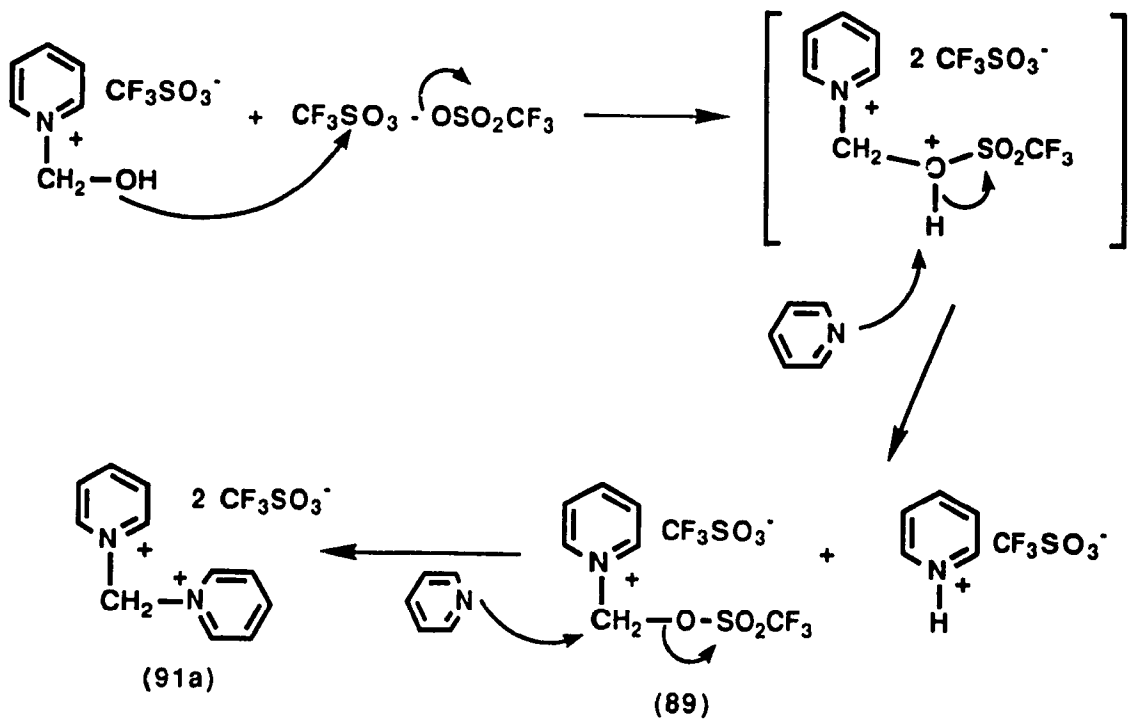
It should be noted that an improvement has been made upon the original synthesis of **72a** which consisted of delivering gaseous formaldehyde above the surface of a solution of pyridine and thionyl chloride in methylene chloride maintained at -50°C[46]. The reaction can readily be performed at room temperature in THF or chloroform if the formaldehyde is bubbled directly into the solution and unlike the previous method, the reaction need not be stirred for an additional two hours. A higher purity is obtained when using THF as a solvent.

2.2.4. Synthesis of 1,1'- (methylene)bispyridinium triflate and attempts to create a bispyridiniomethyl ether

Several attempts were made to synthesize either the intermediate **89** or the bispyridiniomethyl ether **77b** by reacting one equivalent of the hydroxymethyl pyridinium triflate **75a** with 1.0 or 0.5 equivalents of triflic anhydride and 1.0 equivalent of base. The quantity of triflic anhydride chosen depended on whether the aim was to synthesize **89** or **77b** respectively. Since pyridine was unsuitable as a base, yielding compound **91a**, we turned to several other hindered bases: 1,6-di-tert-butylpyridine, triethylamine, and hexamethyldisilazane but all attempts were fruitless.

Finally, compound **91a**, which can be formed from pyridine, triflic anhydride, and formaldehyde, can also be synthesized from the alcohol **75a**. The best results i.e. the purest product is obtained when two equivalents of pyridine are used for every equivalent of **75a** and triflic anhydride. A plausible explanation is simply that one equivalent of pyridine is needed to deprotonate the hydroxyl group of **75a** and the second is needed to act as a nucleophile on the intermediate **89**. The mechanism follows scheme 89:

Scheme 89

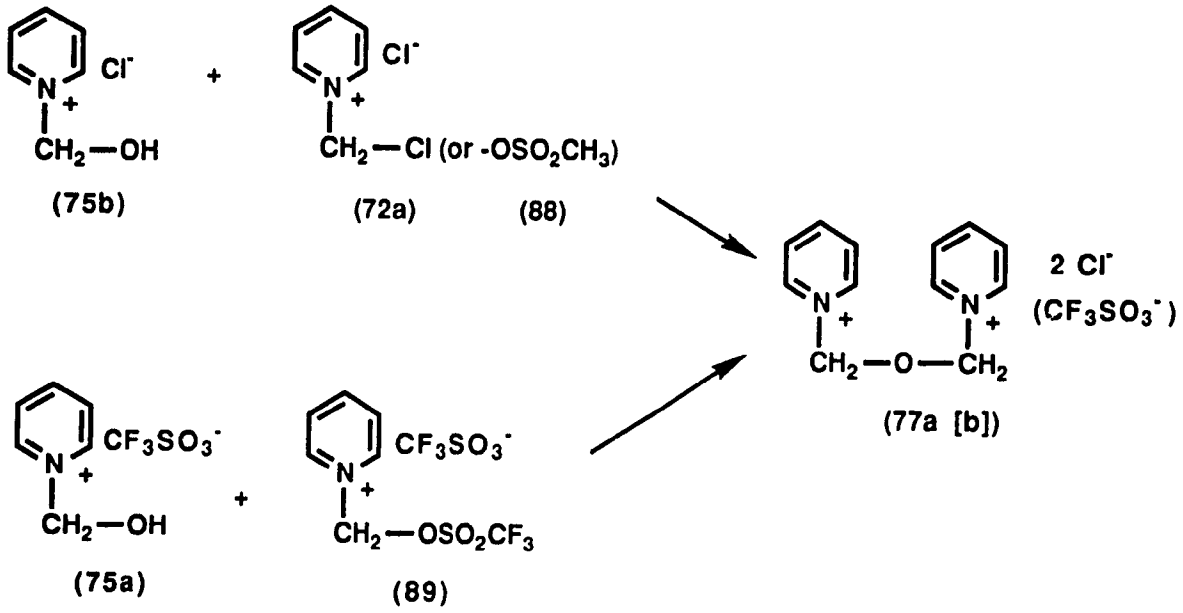


The reaction was also carried out in chloroform and the desired product **91a** precipitated from solution and could simply be filtered off. Surprisingly the ^{1}H NMR of the crude product indicated a sufficiently high degree of purity that in this case, as in the conversion of **75b** to **72a**, recrystallization was considered to be unnecessary.

CHAPTER IV. CONCLUSION

The aim of our project was to develop methods for the formation of a bis-pyridiniomethyl ether linkage using the pyridiniomethyl cation (**75a** or **75b**) and one of its derivatives (**72a**, **88**, or **89**) which contains a good leaving group.

Scheme 90



Although the complete synthesis of **77a/b** was not successful, compounds **75a,b** were synthesized and are of interest on their own and for the derivatives that can be formed from them. A great deal of insight was gained regarding the spectral characteristics and physical properties of these pyridinium salts as well as the reaction conditions necessary to achieve their synthesis.

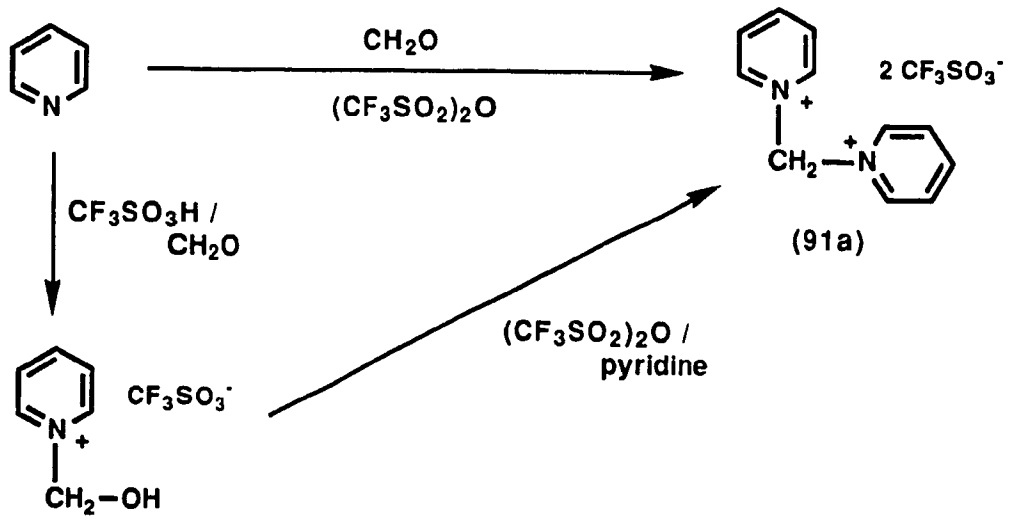
These salts can be divided into two general categories; those that are stable to hydrolysis and which can be recrystallized to purity and those that are quite unstable and,

with the exception of **75b**, are not amenable to purification by recrystallization or column chromatography. While stable salts can be synthesized quite readily without much dependence on solvent type, the reactions yielding unstable compounds are greatly influenced by the particular solvent used. For example, the success of the synthesis of compounds **75d** and **75e** was determined by whether acetonitrile or a methylene chloride / DMF mixture was used.

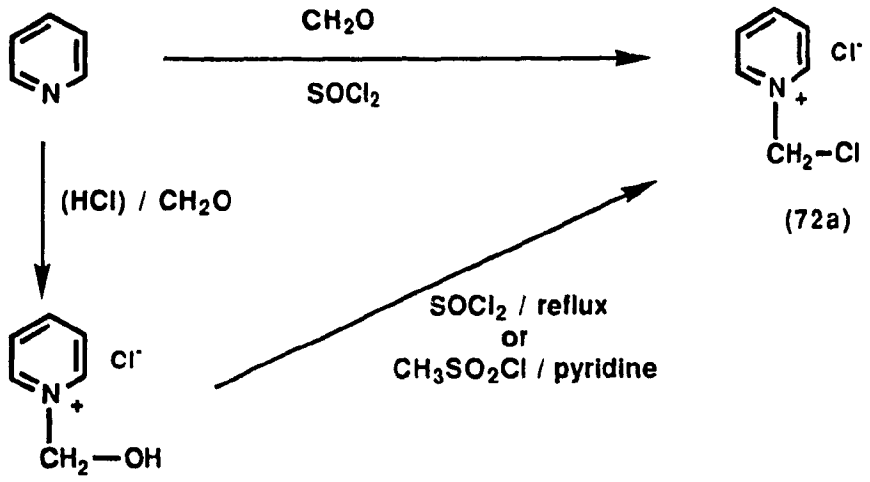
Another aspect of these reactions that should be noted is the challenge of harnessing depolymerized formaldehyde. Formaldehyde gas polymerizes readily and as a result, it has the tendency to solidify at the end of the glass tube that delivers it under the surface of the solution. Therefore, much trial and error was required in order to discover the often delicate balance of solvent, temperature, and reagent quantities that prevented this.

Lastly, three of the compounds synthesized can be formed via two or, in one case, even three routes;

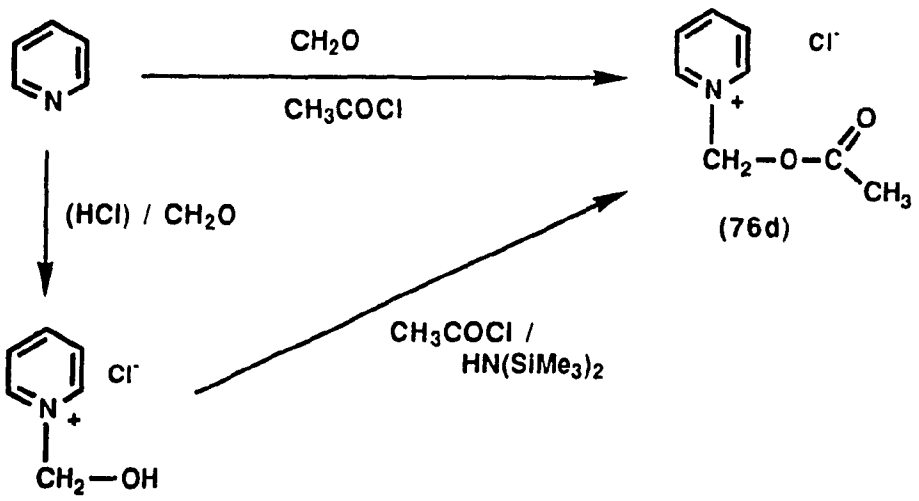
Scheme 91



Scheme 92



Scheme 93



Reaction schemes 91,92 and 93, besides adding credibility to the existence of the pyridiniomethanol compound, also provides a variety of methods by which to synthesize **91a**, **72a** and **76d**.

CHAPTER V. EXPERIMENTAL

Chemicals were purchased from the Aldrich Chemical Co. Solvents and liquid reagents were purified by distillation prior to use. Pyridine was refluxed and then distilled from potassium hydroxide in order to remove water. Pyridine-4-carboxaldehyde was distilled from magnesium sulphate under reduced pressure (~15 mm Hg). Dimethylformamide was dried with calcium oxide followed by distillation under reduced pressure (~15 mm Hg) from magnesium sulphate.

Solvents such as THF were rendered anhydrous by refluxing and distilling from 50% sodium dispersion in paraffin using benzophenone as an indicator. Chloroform and acetonitrile were both dried by distilling from phosphorus pentoxide.

All of the above reagents and solvents were then stored either under nitrogen or in a sealed flask over 4A molecular sieves. Solid reagents such as paraformaldehyde, nicotinamide, isonicotinamide, pyridine-4-aldoxime and pyridinium hydrochloride were dried under vacuum in the presence of desiccant and then stored in a desiccator or in a desiccant vacuum box. Pyridinium hydrochloride was dissolved in chloroform and then dried with sodium or magnesium sulphate.

All reactions were carried out under dried nitrogen and the reaction vessels as well as syringes were oven-dried before use.

Proton (^{1}H) and carbon-13 (^{13}C) magnetic resonance were recorded on an AMX-300 Bruker instrument.

Deuterated solvents used were deuterochloroform, dimethylsulphoxide-d_6, acetone-d_6 and deuterium oxide which was used to exchange acidic protons. All of these deuterated solvents (except D_2O) contained tetramethylsilane (TMS) as an internal standard.

Chemical shifts are expressed in parts per million (ppm) downfield from TMS and peak multiplicities are referred to as; singlet(s), doublet(d), triplet(t), quartet(q), doublet of doublets (dd) and multiplet(m). Coupling constants (J) are expressed in hertz (Hz).

Mass spectra were measured on a Kratos Concept 2H mass spectrometer and signals are reported as m/z.

Infrared spectra were recorded on a BOMEM Michelson 102 FT-IR spectrometer and samples were prepared using either sodium chloride disks or potassium bromide pellets. Band positions are reported in reciprocal centimetres (cm^{-1}).

Elemental analysis were performed by Oneida Research Services, inc., Whitesboro, New York

N-(trimethylsiloxymethyl)pyridinium triflate 76b

Trimethylsilyltriflate (2.0 ml, 10.4 mmol) was added to a solution of pyridine (1.0 ml, 12.7 mmol) in acetonitrile (12 ml) at 20°C, in a three-necked flask. Paraformaldehyde (0.45 g, 15 mmol) was heated to 180°-210°C in a separate two-necked flask and the resulting formaldehyde gas was carried by a stream of nitrogen into solution (under the surface of the liquid). After the gas was added, the solution was stirred for another 10 min. and then the solvent and excess reagents were removed by rotary evaporation followed by vacuum pumping overnight.

The product was a colourless oil (3.37 g, 92% purity). **IR** : 1160 (C-O stretch); 764, 859, 1269 ($SiMe_3$ stretches) cm^{-1}. **^{1}H NMR ($CDCl_3$)** δ: 0.2, s, 9H ($OSiMe_3$); 6.0, s, 2H (NCH_2O); 8.1, t (J=7.03), 2H (meta); 8.5, t (J=7.8), 1H (para); 8.97, d (J=6.2), 2H (ortho) ppm. **^{13}C NMR**: 0.2 ($OSiMe_3$); 83 (NCH_2O); 128 (ring $C_{3,5}$); 142 (ring $C_{2,4}$); 146 (ring C_4) ppm. **FAB MS m/z** : 182.1 (molecular ion).

N-(trimethylsiloxymethyl)pyridinium chloride 76c

Trimethylsilylchloride (1.9 ml, 15 mmol) was added to a solution of pyridine (1.2 ml, 15 mmol) in THF (10-12 ml) at 20°C, in a three-necked flask. Formaldehyde, obtained by thermal depolymerization of paraformaldehyde (0.68 g, 22.5 mmol), was added to the solution by the same procedure described for **89**. The work-up was also similar.

The product was a colourless solid (3.11 g, 85% purity). **IR** : 1102 (C-O stretch); 756, 845, 1255 ($SiMe_3$ stretches) cm^{-1}. **^{1}H NMR ($CDCl_3$)** δ: 0.15, s, 9H ($OSiMe_3$); 6.33, s, 2H (NCH_2O); 8.14, t (J=7.11), 2H (meta); 8.57, t (J=7.78), 1H (para); 9.5, d (J=6.23), 2H (ortho) ppm. **^{13}C NMR** : -0.4 ($OSiMe_3$); 82.4 (NCH_2O); 128 (ring $C_{3,5}$); 142.4 (ring $C_{2,6}$); 146.6 (ring C_4) ppm. **FAB MS m/z** : 182.0 (65% of highest mass peak observed), Base peak is Cs^+ at 132.8.

N-(hydroxymethyl)pyridinium triflate 75a

Gaseous formaldehyde, obtained from thermal depolymerization of paraformaldehyde (0.75 g, 25 mmol), was bubbled into a solution of pyridine (2.0 ml, 25 mmol) and triflic acid (1.76 ml, 20 mmol) in chloroform (20 ml) at 20°C. The resulting oil was washed twice with 5-10 ml of chloroform and then maintained under vacuum for 16 hrs. to remove traces of solvents and/or reagents.

The product was a colourless oil (5.06 g, 85% purity). **IR** : 3300 (O-H stretch); 1106 (C-O stretch) cm^{-1}. **^{1}H NMR (Acetone-d_6)** δ: 7.7, br.s, 1H (COH); 6.1, s, 2H (NCH_2O); 8.3, t, 2H (meta); 8.8, t (J=7.2), 1H (para); 9.2, d, 2H (ortho) ppm. **^{13}C NMR**: 84 (NCH_2O); 129 (ring $C_{3,5}$); 143 (ring $C_{2,6}$); 148 (C_4) ppm. **FAB MS m/z** : 110.1 (molecular ion).

Anal. Calcd. for $C_7H_8F_3NO_4S$: C, 32.44; H, 3.09; N, 5.40; S, 12.37

Found: C, 32.24; H, 3.35; N, 5.15; S, 11.85

N-(hydroxymethyl)pyridinium chloride 75b

Formaldehyde (1.51 g, 37.7 mmol) was bubbled into a solution of pyridinium hydrochloride (2.9 g, 25 mmol) in chloroform or acetonitrile (10 ml) at 20°C. The resulting oil was then washed several times with chloroform to remove excess pyridinium hydrochloride. The product was maintained under vacuum overnight and the compound solidified.

Recrystallization (acetonitrile) yielded colourless crystals (1.25 g, 40%) of 88% purity. **IR** : 3122 (broad O-H stretch); 1086 (C-O stretch) cm^{-1}. **^{1}H NMR (DMSO-d_6)** δ: 8.9, br.s, 1H (COH); 5.9, s, 2H (NCH_2O); 8.2, t (J=7.0), 2H (meta); 8.6, t (J=7.75), 1H (para); 9.2, d (J=5.7), 2H (ortho) ppm. **^{13}C NMR** : 82.5 (NCH_2O); 128 (ring $C_{3,5}$); 142.5 (ring $C_{2,6}$); 146.5 (ring C_4) ppm. **FAB MS m/z** : 110.1 (molecular ion).

Anal. Calcd. for C_6H_8NOCl (with 0.5 mols H_2O): C, 46.64; H, 5.82; N, 9.06; Cl, 22.94

Found: C, 47.02; H, 5.76; N, 9.03; Cl, 20.78

N-(hydroxymethyl)-4-formyl-pyridinium triflate 75c

Formaldehyde (0.22 g, 7.5 mmol) was bubbled into a solution of pyridine-4-carboxaldehyde (0.55 ml, 5.8 mmol) and triflic acid (0.44 ml, 5.0 mmol) in acetonitrile (12 ml). The excess solvent and reagents were removed under vacuum.

The product was a yellow oil (1.52 g, 74% purity). **IR** : 3312 (O-H stretch); 1717 (C=O stretch) cm^{-1}. **^{1}H NMR (Acetone-d_6)** δ: 9.0, br.s, 1H (C-OH); 6.2, s, 2H (NCH_2O); 10.37, s, 1H (CHO); 8.64, d (J=2.77), 2H (meta); 9.43, d (J=5.38), 2H (ortho) ppm. **^{13}C NMR** : 84.7 (NCH_2O); 190.4 (CHO); 127.4 (ring $C_{3,5}$); 145 (ring $C_{2,6}$); 149 (ring C_4) ppm. **FAB MS m/z** . 138.1 (27% of highest mass peak observed), Base peak is ($75c^+$-CH_2O) at 108.1.

N-(hydroxymethyl)-4-oxime-pyridinium triflate 75d

Pyridine-4-aldoxime (0.65 g, 5.5 mmol) and triflic acid (0.44 ml, 5.0 mmol) were added to a solvent mixture of methylene chloride / DMF (11 ml : 0.8 ml). Gaseous formaldehyde (0.25 g, 8.4 mmol) was added to this solution according to the same procedure as previously described. The reaction mixture was diluted with methylene chloride (50 - 75 ml) and the oily product was washed several times with methylene chloride (10 - 20 ml portions) in order to remove DMF. The product was maintained under vacuum overnight.

The product was a yellow oil (0.65 g, 53% purity). **IR** : 3344 (O-H stretch); 1012 or 1099 (C-O stretch); 1631 (oxime CH=N stretch); 3433 (oxime O-H stretch) cm^{-1}. **^{1}H NMR (Acetone-d_6)** δ: 8.3, br.s, 1H (COH); 6.06, s, 2H (NCH_2O); 8.5, s, 1H (CH=N); 8.4, d (J=7.08), 2H (meta); 9.1, d (J=6.87), 2H (ortho); 12.0, br.s, 1H (C=NOH) ppm. **^{13}C NMR** : 84 (NCH_2O); 94.1 (CH=N); 125 (ring $C_{3,5}$); 143.3 (ring $C_{2,6}$); 146.3 (ring C_4) ppm. **FAB MS m/z** : 153.1 (31% of highest mass peak observed), Base peak is ($75d^+$- CH_2O) at 123.1.

N-(hydroxymethyl)isonicotinamidium triflate 75e

The synthesis and work-up of this compound followed a similar procedure to that described for **83**. In this case isonicotinamide (0.65 g, 5.5 mmol), triflic acid (0.44 ml, 5.0 mmol) and formaldehyde (0.25 g, 8.4 mmol) in a solvent mixture of methylene chloride / DMF (20 ml : 1.7 ml) was used.

The product was a viscous colourless oil (0.81 g, 80-85% purity). **IR** : 3411 (O-H stretch); 1031 or 1169 (C-O stretch); 1671 (amide C=O stretch) cm^{-1}. **^{1}H NMR (Acetone-d_6)** δ: 7.6, br.s, 1H (C-OH); 8.3, br.s, 1H ($CONH_2$); 6.16, s, 2H (NCH_2O); 8.6, d (J=6.36), 2H (meta); 9.3, d (J=6.64), 2H (ortho) ppm. 13C NMR : 84.3 (NCH_2O); 165 ($CONH_2$); 127 (ring $C_{3,5}$); 144 (ring $C_{2,6}$); 150.6 (ring C_4) ppm. **FAB MS m/z** : 153.1 (38% of highest mass peak observed), Base peak is ($75e^+$- CH_2O) at 123.1..

N-(chloromethyl)pyridinium chloride 72a

Method 1. (from pyridine)

Formaldehyde (0.6 g, 20 mmol) is bubbled into a solution of pyridine (0.81 ml, 10 mmol) and thionyl chloride (0.73 ml, 10 mmol) in chloroform or THF (6 ml) at 20°C. The resulting solution was concentrated under vacuum to dryness and the remaining white solid was recrystallized from Ethanol/ether (1.1 g, 68%).

Method 2. (from 75b)

N-(hydroxymethyl)pyridinium chloride (0.3 g, 2.0 mmol) was refluxed in thionyl chloride (5-7 ml) for 1 hr. 45 min. The reaction mixture was concentrated under vacuum, followed by addition of methylene chloride (15 ml) to precipitate the desired product. The product was washed several times with methylene chloride to remove traces of thionyl chloride. The product was almost 100% pure according to ^{1}H NMR spectra.

The crude white solid (0.2 g, 61%) of ~100% purity could be recrystallized from Ethanol/ether solvent mixture.

Method 3. (from 75b)

Mesyl chloride (0.3 ml, 4.0 mmol) was added to an emulsion of N-(hydroxymethyl)pyridinium chloride (0.6 g, 4.0 mmol) in chloroform (3-4 ml) at 20°C to form a homogeneous solution. Pyridine (0.32 ml, 4.0 mmol) was added slowly, and the resulting solution was stirred for 1.5 to 2 hrs. The solution was concentrated under vacuum overnight to remove the volatile reagents, and was then washed 2-3 times with methylene chloride (10-15 ml). The crude solid indicated a 2 : 1 mixture of the desired compound **72a** / pyridinium hydrochloride **81**. Recrystallization produced what appeared to be 1,1'-(methylene)bispyridinium chloride **91b**.

Washing the crude product gave a light beige solid (0.56 g, 68% purity) that, when recrystallized from methanol resulted in darker crystals (0.08 g, 6%).

N-(chloromethyl)pyridinium chloride : **IR** : 726 (C-Cl stretch) cm^{-1}. **^{1}H NMR (DMSO-d_6)** δ: 6.82, s, 2H (NCH_2O); 8.3, dd (J=6.88), 2H (meta); 8.8, dd (J=6.65), 1H (para); 9.6, d (J=5.11), 2H (ortho) ppm. **^{13}C NMR** : 64 (NCH_2O); 129 (ring $C_{3,5}$); 146 (ring $C_{2,6}$); 148 (ring C_4) ppm. **FAB MS m/z** : 128.0 (molecular ion).

1,1'-(methylene)bispyridinium chloride **91b** : **^{1}H NMR (D_2O)** δ: 7.51, s, 2H (NCH_2N); 8.37, t (J=6.49), 4H (meta) ; 8.91, t (J=6.59), 2H (meta); 9.40, d (J=5.28), 4H (ortho) ppm. **^{13}C NMR** : 78.7 (NCH_2N); 130 (ring $C_{3,5}$); 146 (ring $C_{2,6}$); 150.6 (ring C_4) ppm. **FAB MS m/z** : Base peak: 171.1 (C^{2+}- H^+), 207 ($C^{2+}A^-$), 449.1, 451.1 ($C^{2+}{}_2A^-{}_3$), 693.2 ($C^{2+}{}_3A^-{}_5$)

N-(acetoxymethyl)pyridinium chloride 76d

Method 1. (from pyridine)

Formaldehyde (0.21 g, 7.0 mmol) was bubbled into a solution of pyridine (0.4 ml, 5.0 mmol) and acetyl chloride (0.36 ml, 5.0 mmol) in THF or acetonitrile (10-12 ml) at 20°C. The resulting solution was vacuum pumped to dryness and then washed with methylene chloride to remove traces of solvent. ^{1}H NMR shows the product to be virtually 100% pure.

Recrystallization from ethanol/ether or n-propanol yields white crystals (0.58 g, 62%).

Method 2. (from 75b)

Acetyl chloride (0.5 ml, 7.0 mmol) was added to an emulsion of N-(hydroxymethyl)pyridinium chloride (0.73 g, 5.0 mmol) in chloroform (3-4 ml) to create a homogeneous solution that was subsequently cooled to 0°C. Hexamethyldisilazane (2.08 ml, 10.0 mmol) was then added and the solution was stirred overnight. The supernatant liquid was decanted and residual base or decomposition products such as trimethylsilylchloride and trimethylsilylamine were removed under vacuum. The crude reaction mixture was then recrystallized, (with a substantial loss of desired product), using ethanol/ether or n-propanol to give colourless crystals (0.085 g, 9%).

N-(acetoxymethyl)pyridinium chloride: **IR** : 1188 (C-O stretch); 1699 (ester C=O stretch) cm^{-1}. **^{1}H NMR (DMSO-d_6)** δ: 2.14, s, 3H ($OCOCH_3$); 6.5, s, 2H (NCH_2O); 8.3, t (J=7.02), 2H (meta); 8.75, t (J=7.81), 1H (para), 9.3, d (J=5.57), 2H (ortho) ppm. **^{13}C NMR** : 20.6 (CH_3); 79 (NCH_2O); 180 (OCO); 128 (ring $C_{3,5}$); 145 (ring $C_{2,6}$); 148 (ring C_4) ppm. **FAB MS m/z** : 152.1 (molecular ion).

1,1'-(methylene)bispyridinium triflate 91a

Method 1. (from pyridine)

Formaldehyde (0.12 g, 4.0 mmol) was bubbled into a solution of pyridine (0.24 ml, 3.0 mmol) and triflic anhydride (0.25 ml, 1.5 mmol) in chloroform (5-10 ml) at 20°C. The solution was then pumped to dryness and the solid residue was recrystallized from ethanol to yield needle-like colourless crystals (0.57 g, 80%)

Method 2. (from 75a)

Triflic anhydride (0.25 ml, 1.5 mmol) was added to an emulsion of N-(hydroxymethyl)pyridinium triflate (0.55 g, 2.1 mmol) in chloroform (5 ml) followed by pyridine (0.24 ml, 3.0 mmol). The work-up was similar to that described in Method 1, with the exception that the crude reaction product was virtually 100% pure. Washing with methylene chloride yielded a white solid (0.74 g, ~100% purity). The product could be recrystallized from ethanol.

1,1'-(methylene)bispyridinium triflate : **^{1}H NMR (Acetone-d_6)** δ: 7.7, s, 2H (NCH_2N); 8.43, t (J=6.91), 4H (meta); 8.95, t (J=7.87), 2H (para); 9.73, d (J=5.6), 4H (ortho) ppm. **^{13}C NMR** : 79 (NCH_2N); 130 (ring $C_{3,5}$); 147 (ring $C_{2,6}$); 150 (ring C_4) ppm. **FAB MS m/z** : 171.1 (C^{2+}- H^+), 321.1 ($C^{2+}A^-$), 791.0 ($C_2^{2+}A_3^-$), 1261.6 ($C_3^{2+}A_5^-$), Base peak is $(gly)^+$.

N-(acetoxymethyl)nicotinamidium chloride 76f

Formaldehyde (0.22 g, 7.3 mmol) was bubbled into a solution of nicotinamide (0.61 g, 5.0 mmol) and acetyl chloride (0.36 ml, 5.0 mmol) in acetonitrile (12 ml) at 20°C. The resulting solution was evaporated to dryness and washed with methylene chloride to remove acetonitrile. The crude solid was recrystallized several times to remove all unreacted nicotinamide resulting in considerable loss of desired product.

Recrystallization from methanol or methanol/water yielded a white solid (0.41 g, 35%). **IR** : 1219 (C-O stretch); 1755 (ester C=O stretch); 1699 (amide C=O stretch) cm^{-1}. **^{1}H NMR (DMSO-d_6/D_2O)**; Deuterium oxide was added to exchange out the amide protons. δ: 2.1, s, 3H ($OCOCH_3$); 6.37, s, 2H (NCH_2O); 8.2, dd (J=6.27), 1H (meta); 8.97, d (J=8.11), 1H (para); 9.17, d (J=6.16), 1H (ortho); 9.44, s, 1H (ortho) ppm. **^{13}C NMR** : 20.3 (CH_3); 170.1 (OCO); 163.1 ($CONH_2$); 79.4 (NCH_2O); 128.1 (ring C_5); 133.6 (ring C_3); 144.7, 145.9, 146.5 (ring $C_{2,6,4}$) ppm. **FAB MS m/z** : 195.1 (molecular ion).

N-(acetoxymethyl)isonicotinamidium chloride 76e

The synthesis, reagent proportions and work-up procedures were the same as those for compound **76f**.

Recrystallization from methanol (twice) yielded colourless crystals (0.3 g, 26%). **IR** : 1220 (C-O stretch); 1760 (ester C=O stretch); 1652 (amide C=O stretch) cm^{-1}. **^{1}H NMR (DMSO-d_6/D_2O)**; Amide protons were exchanged out using deuterium oxide. δ: 2.1, s, 3H ($OCOCH_3$); 6.36, s, 2H (NCH_2O); 8.36, d (J=6.86), 2H (meta); 9.17, d (J=6.92), 2H (ortho) ppm. **^{13}C NMR** : 20.2 (CH_3); 164.2 ($CONH_2$); 170.2 (OCO); 79.1 (NCH_2O); 126 (ring $C_{3,5}$); 145.7 (ring $C_{2,6}$); 150.1 (ring C_4) ppm. **FAB MS m/z** : 195.1 (37% of highest mass peak observed), Base peak is Cs^+.

CHAPTER VI. REFERENCES

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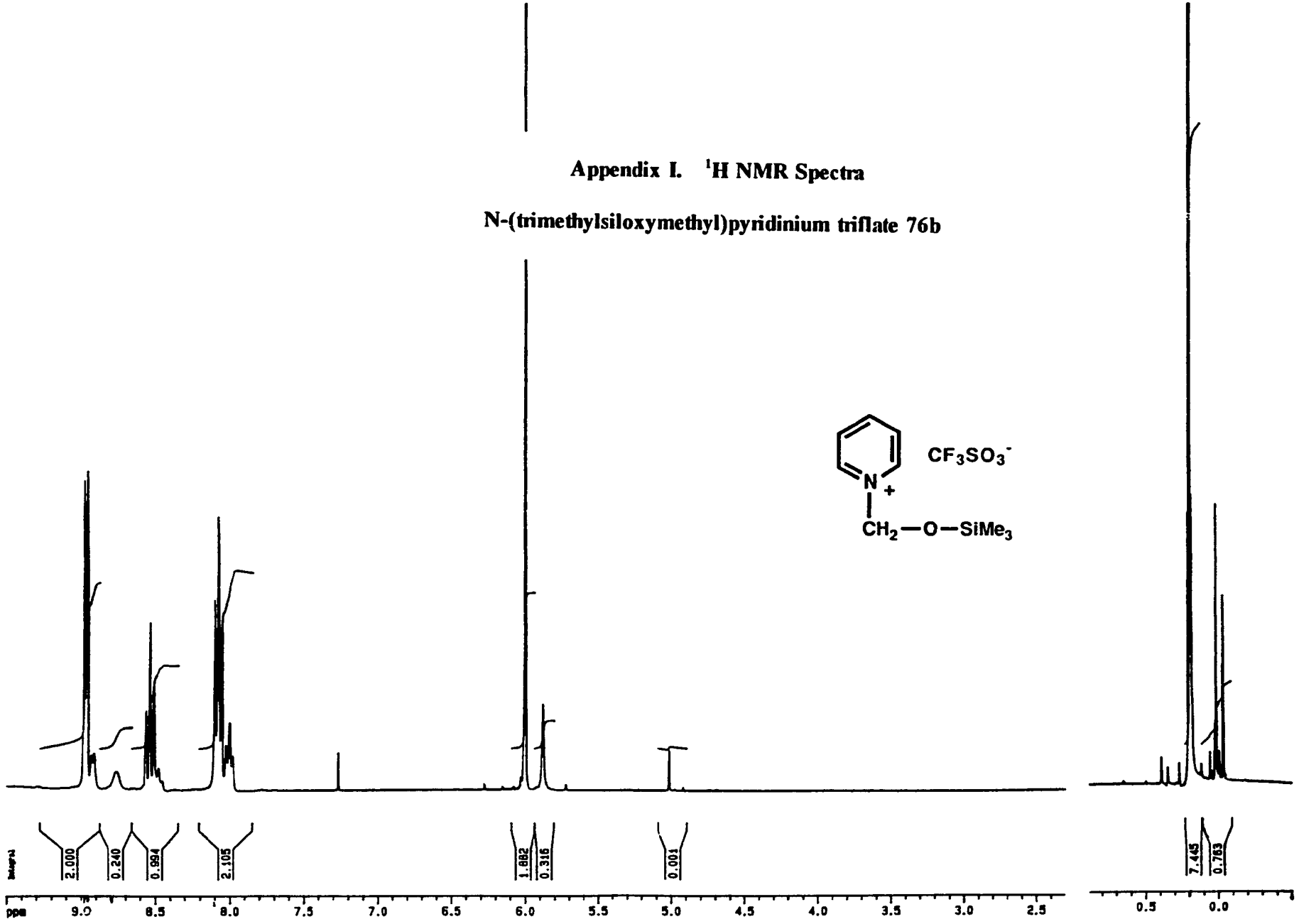
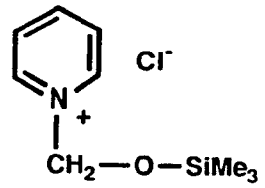
Appendix I. ^{1}H NMR Spectra

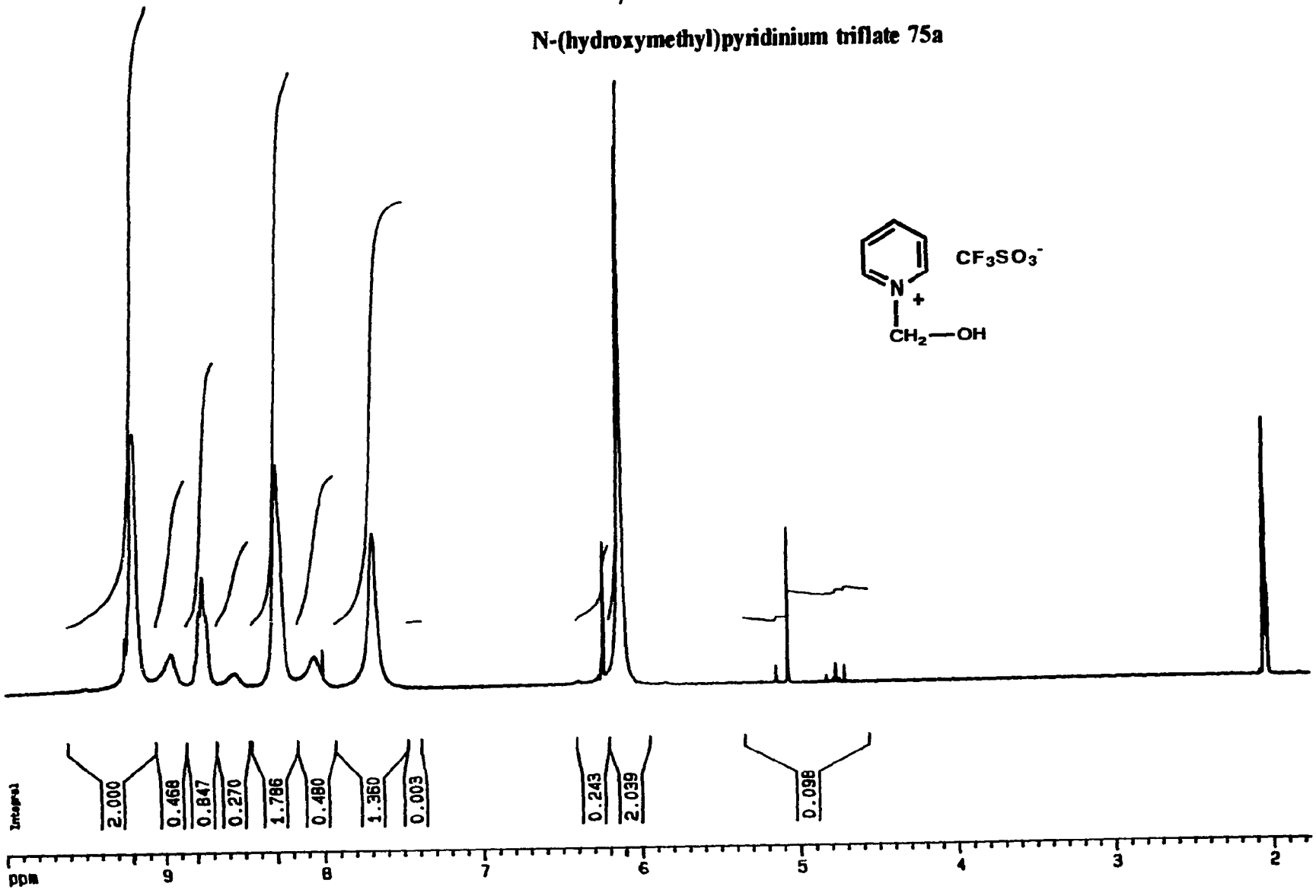
N-(trimethylsiloxymethyl)pyridinium triflate 76b



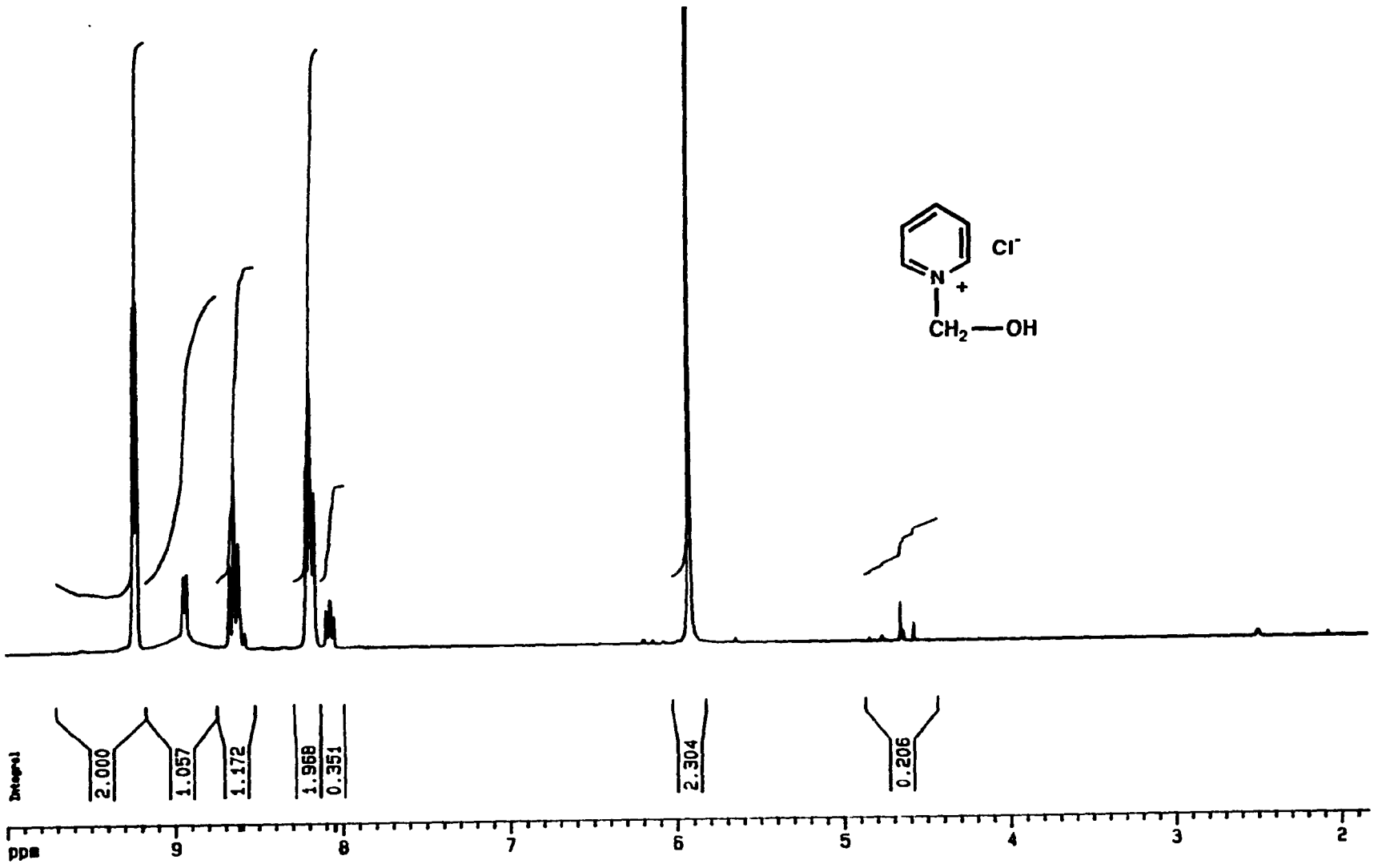
N-(trimethylsiloxymethyl)pyridinium chloride 76c



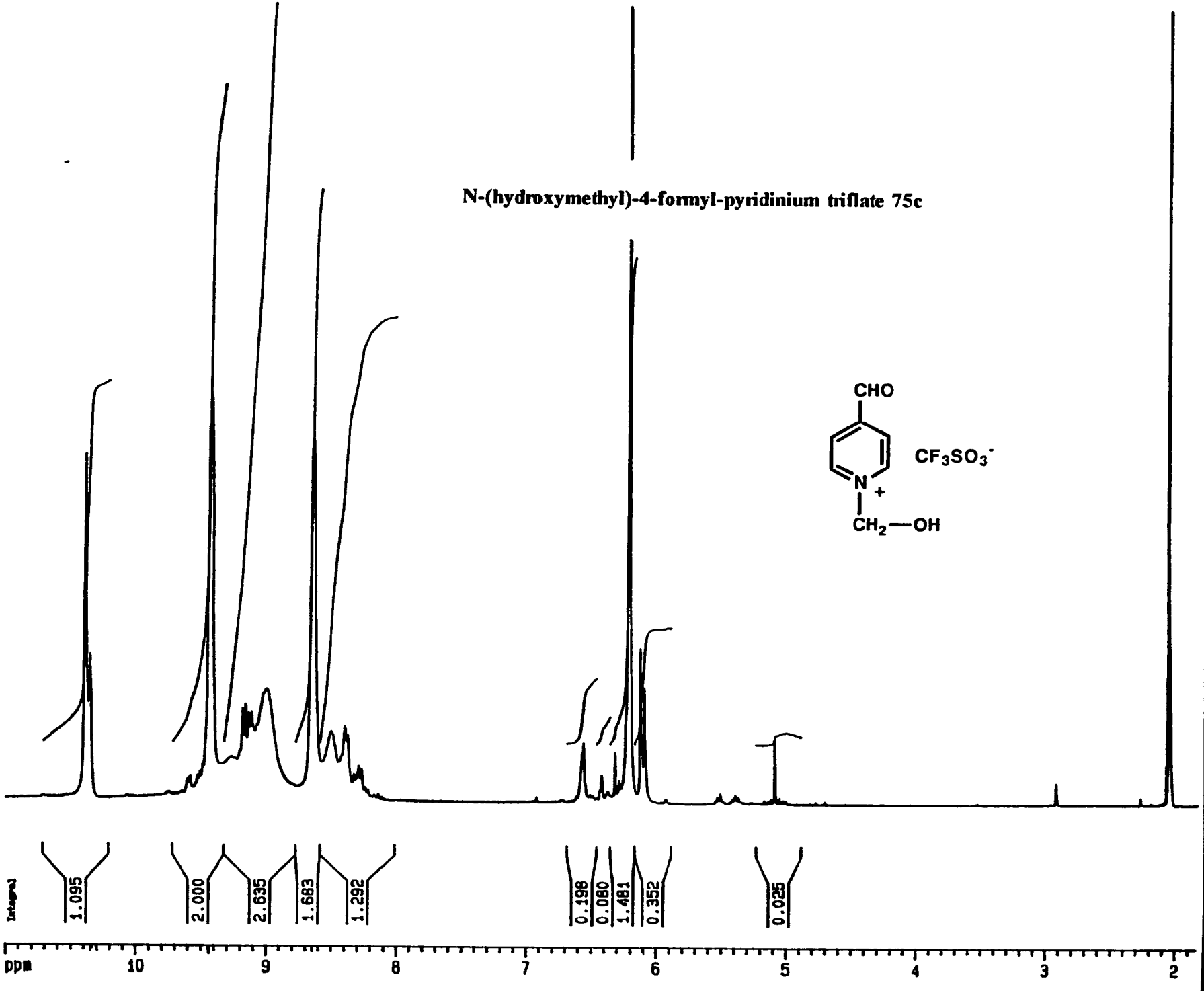
N-(hydroxymethyl)pyridinium triflate 75a



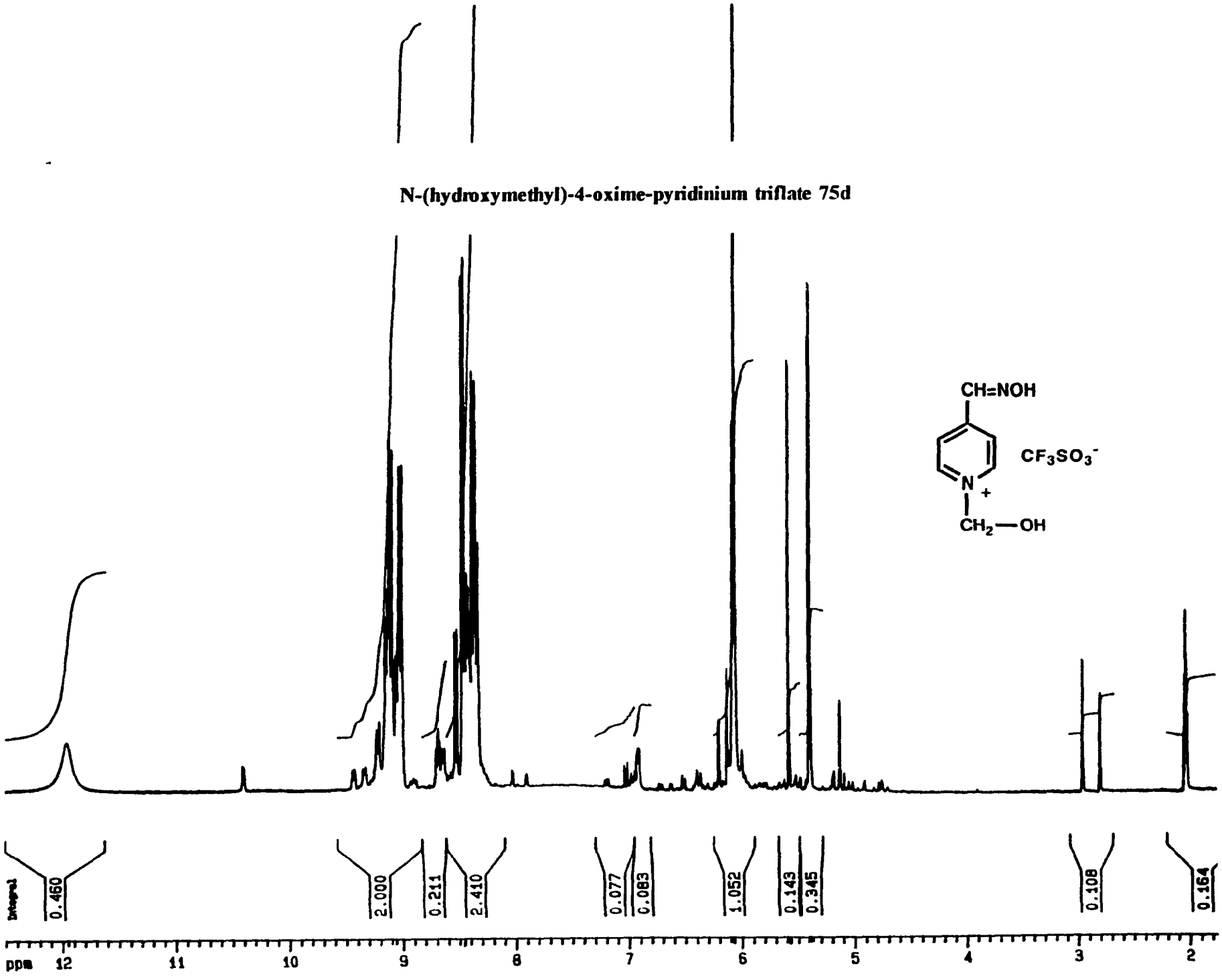
N-(hydroxymethyl)pyridinium chloride 75b



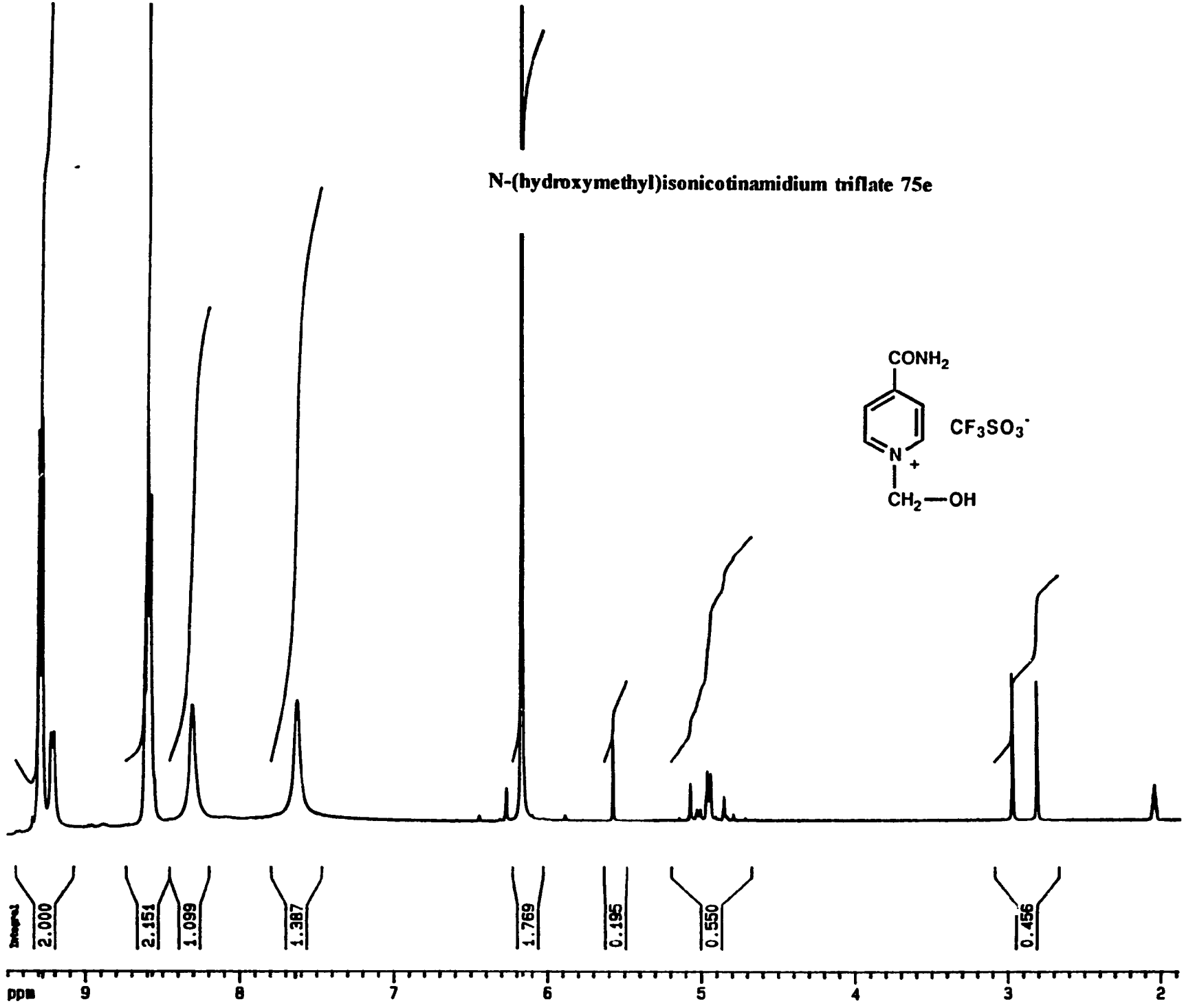
N-(hydroxymethyl)-4-formyl-pyridinium triflate 75c



N-(hydroxymethyl)-4-oxime-pyridinium triflate 75d



N-(hydroxymethyl)isonicotinamidium triflate 75e



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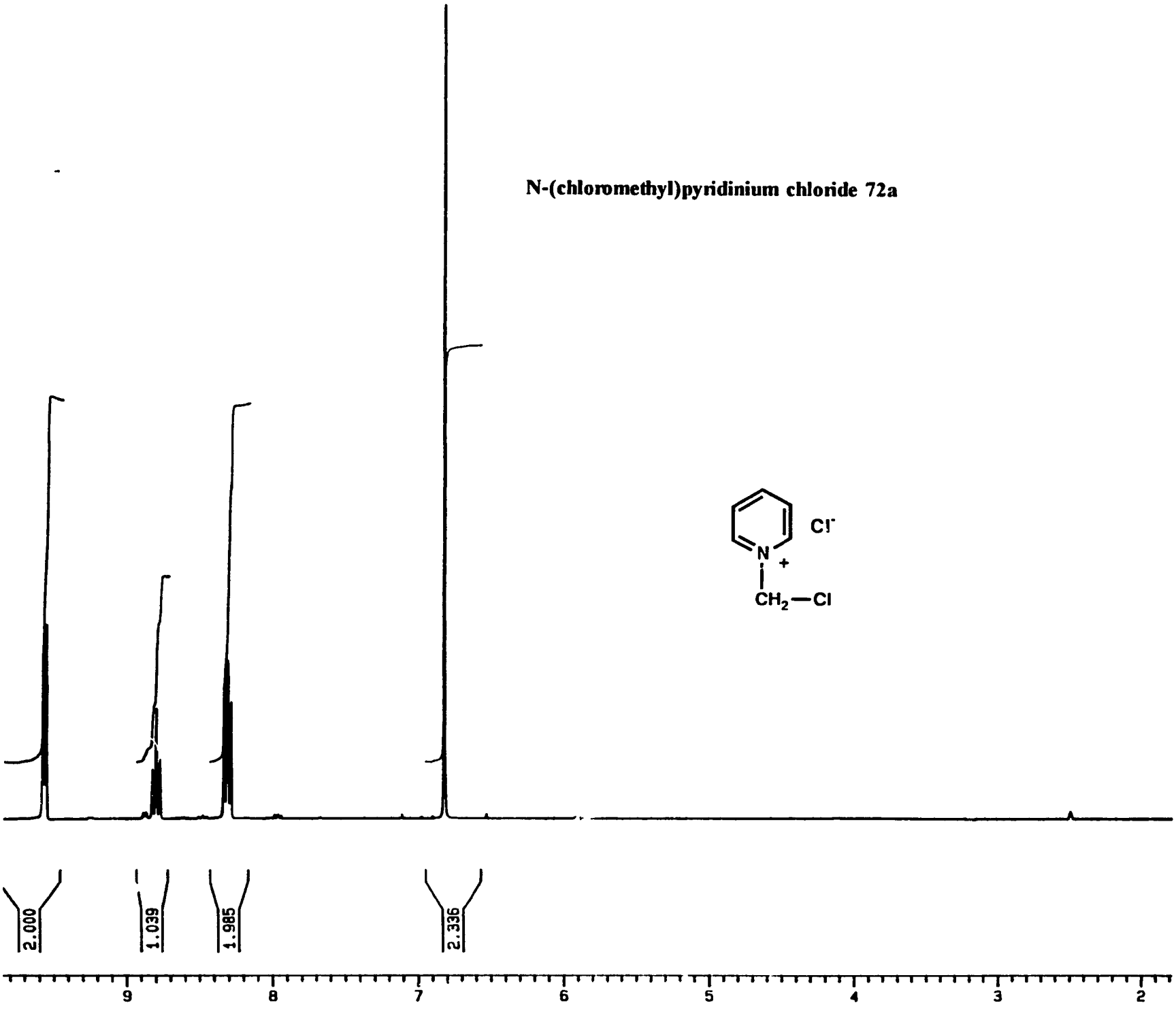
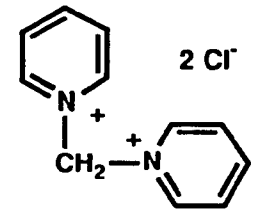
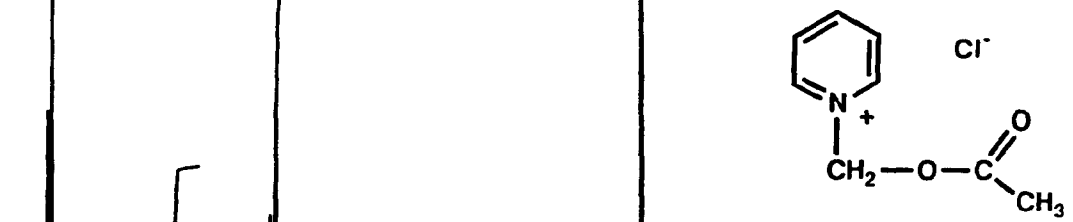


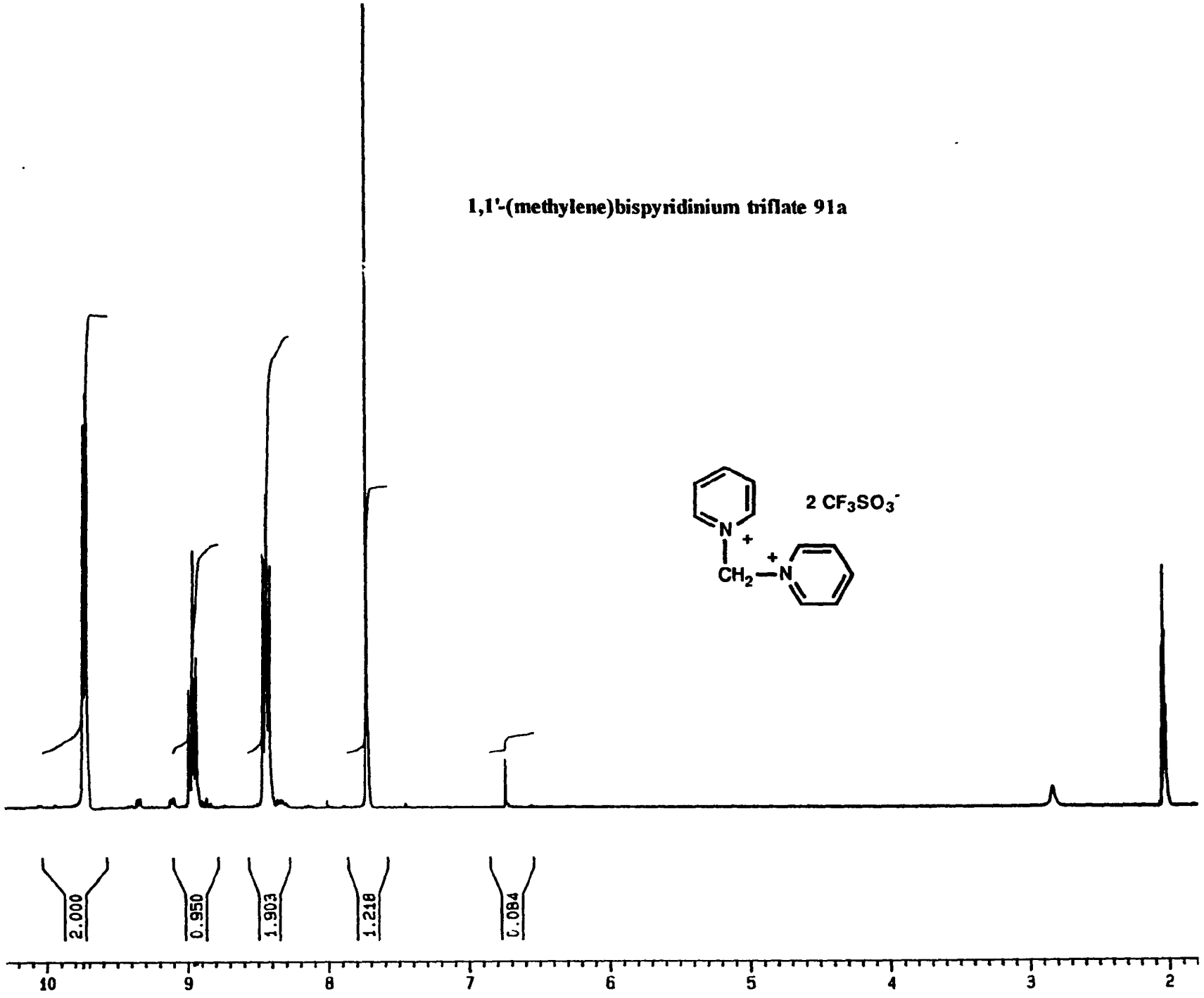
1,1'-(methylene)bispyridinium chloride 91b



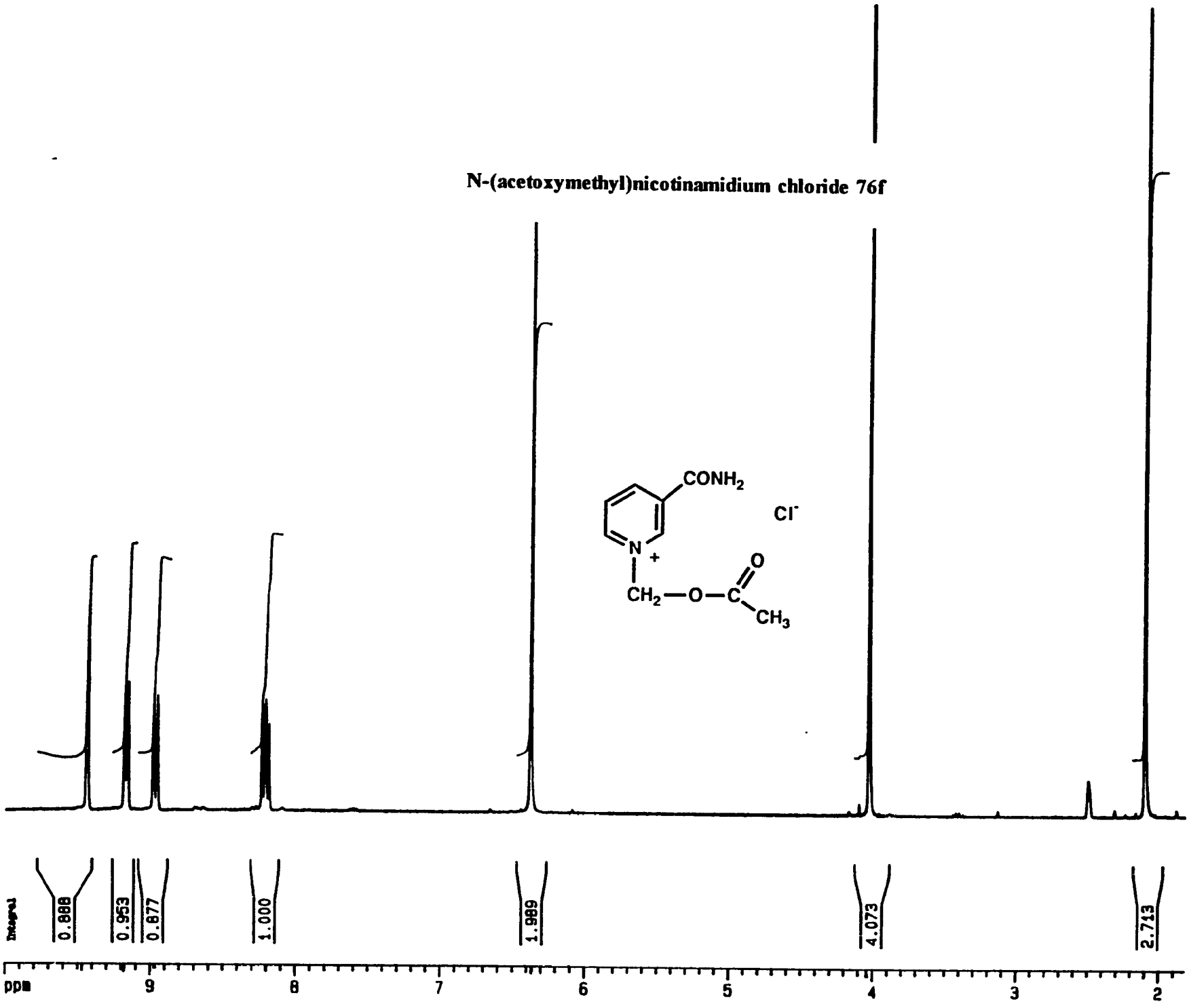
N-(acetoxymethyl)pyridinium chloride 76d



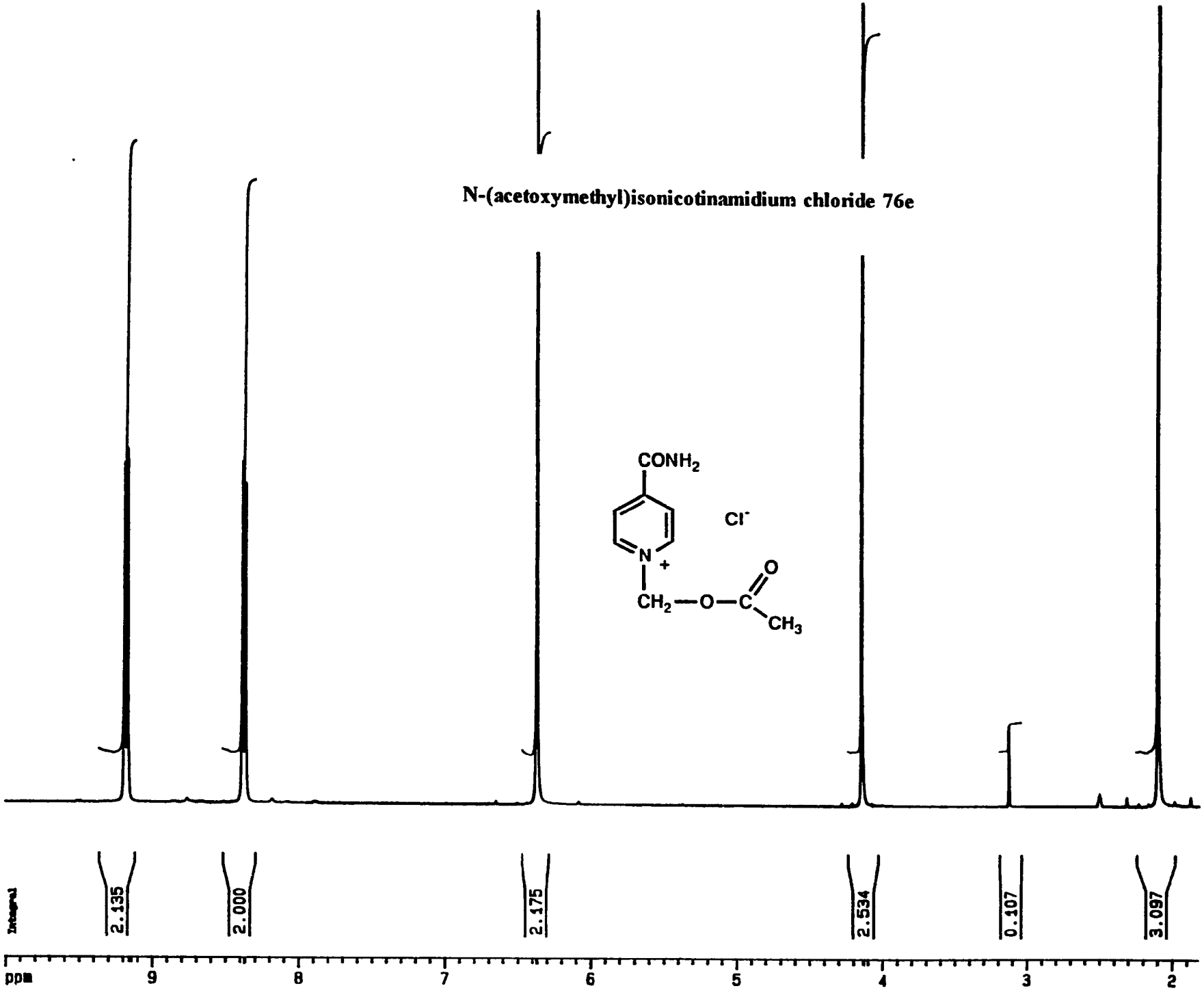
1,1'-(methylene)bispyridinium triflate 91a



N-(acetoxymethyl)nicotinamidium chloride 76f

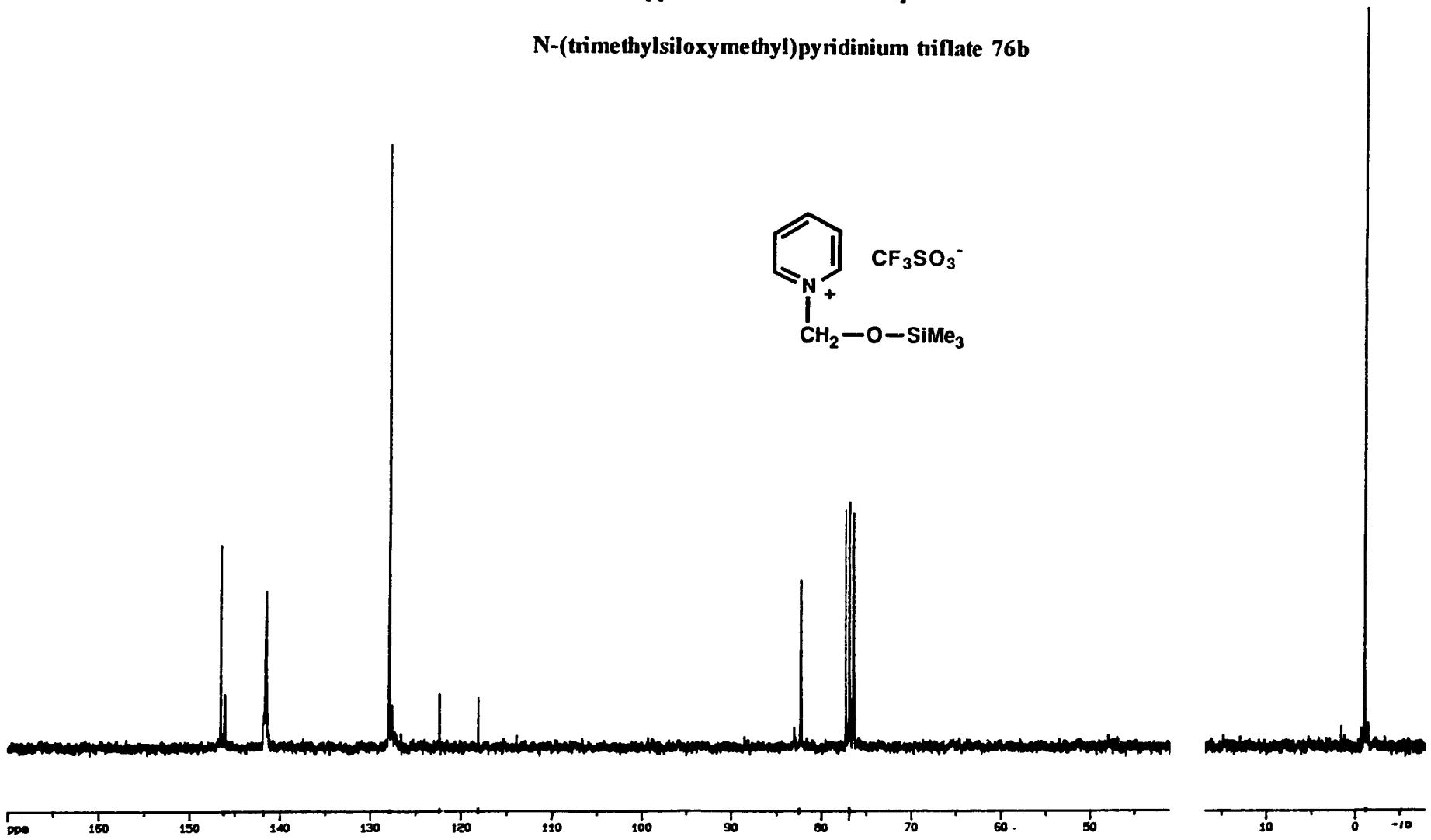


N-(acetoxymethyl)isonicotinamidium chloride 76e

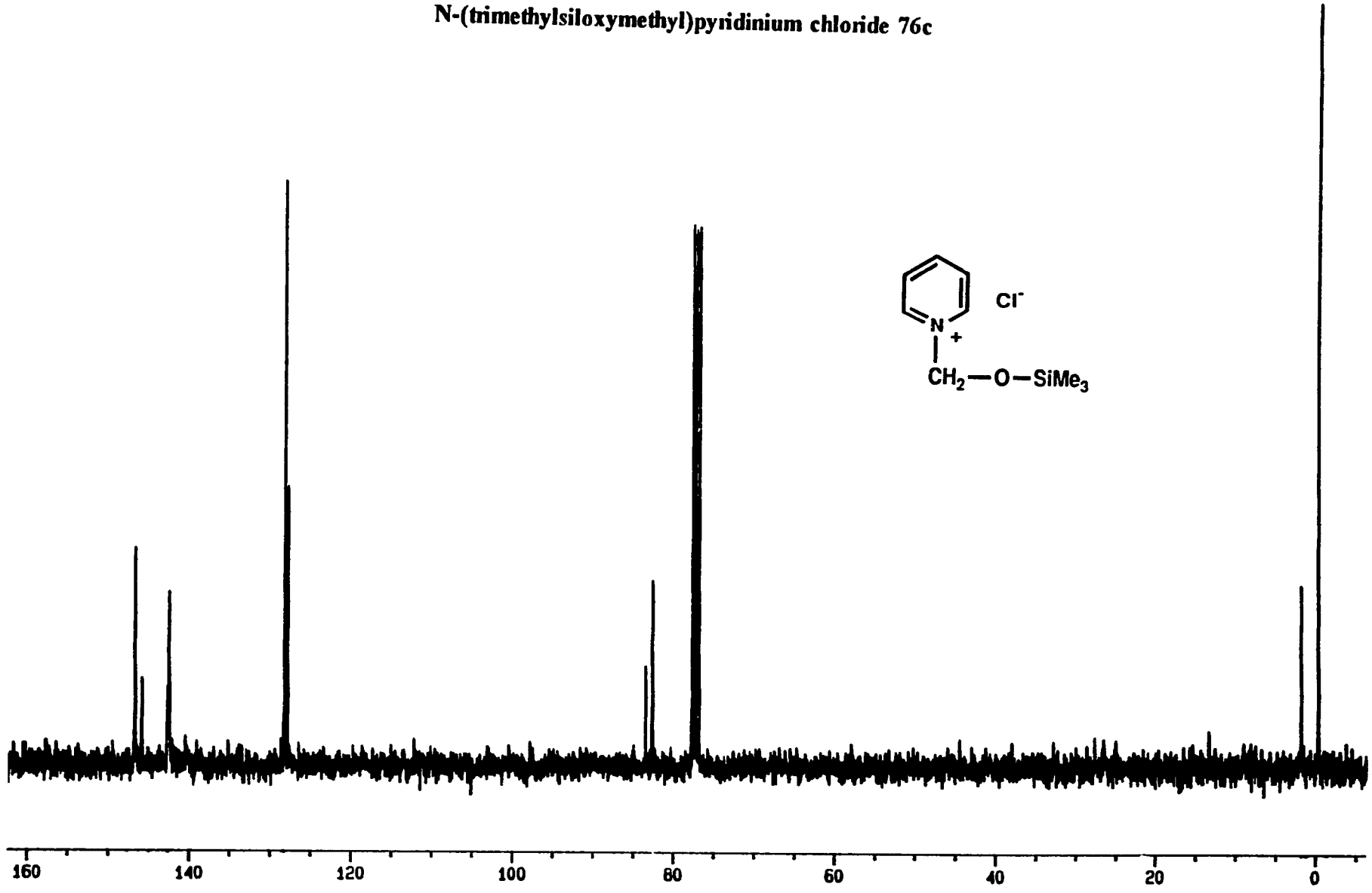


Appendix II. ^{13}C NMR Spectra

N-(trimethylsiloxymethyl)pyridinium triflate 76b

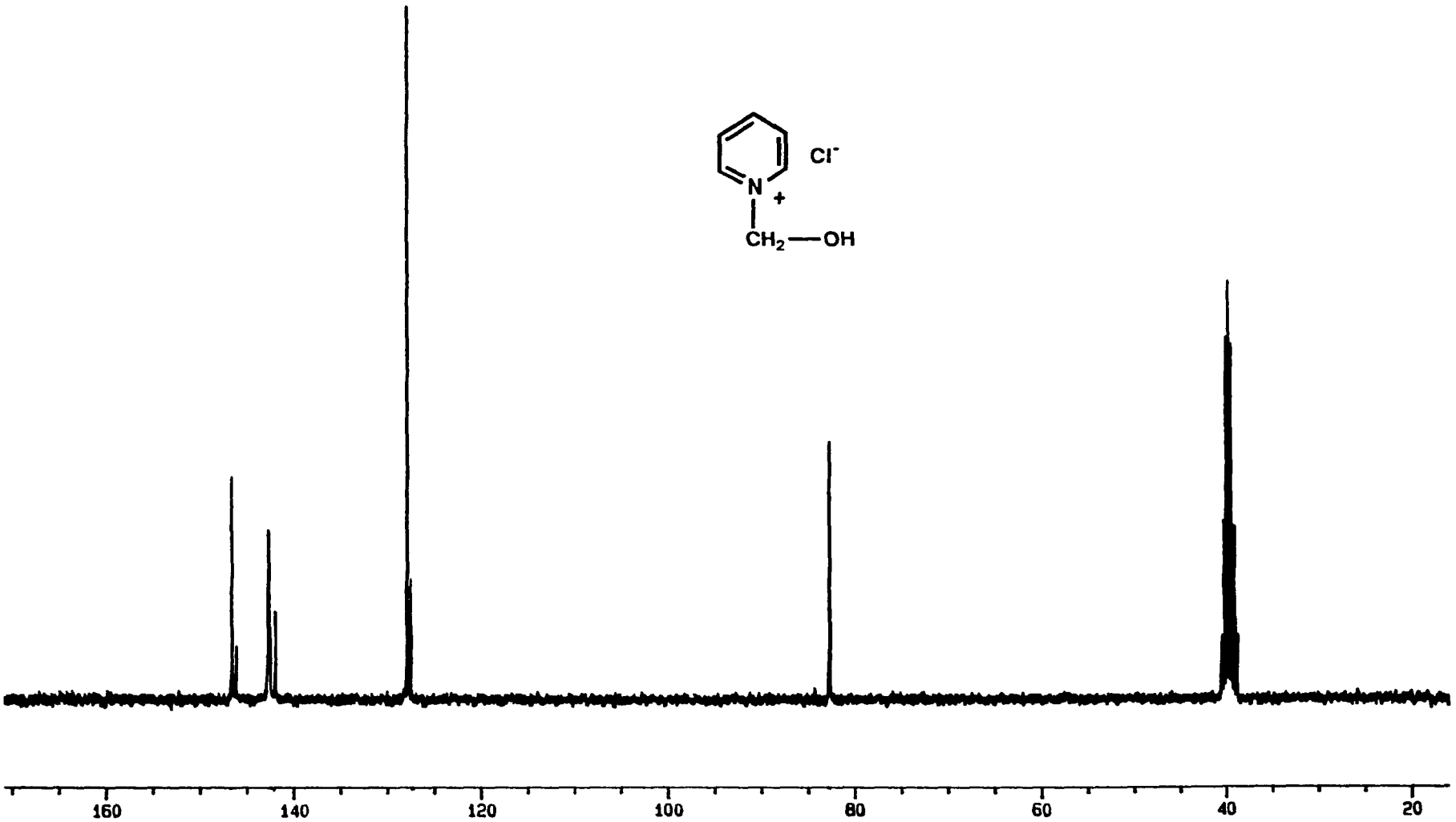


N-(trimethylsiloxymethyl)pyridinium chloride 76c

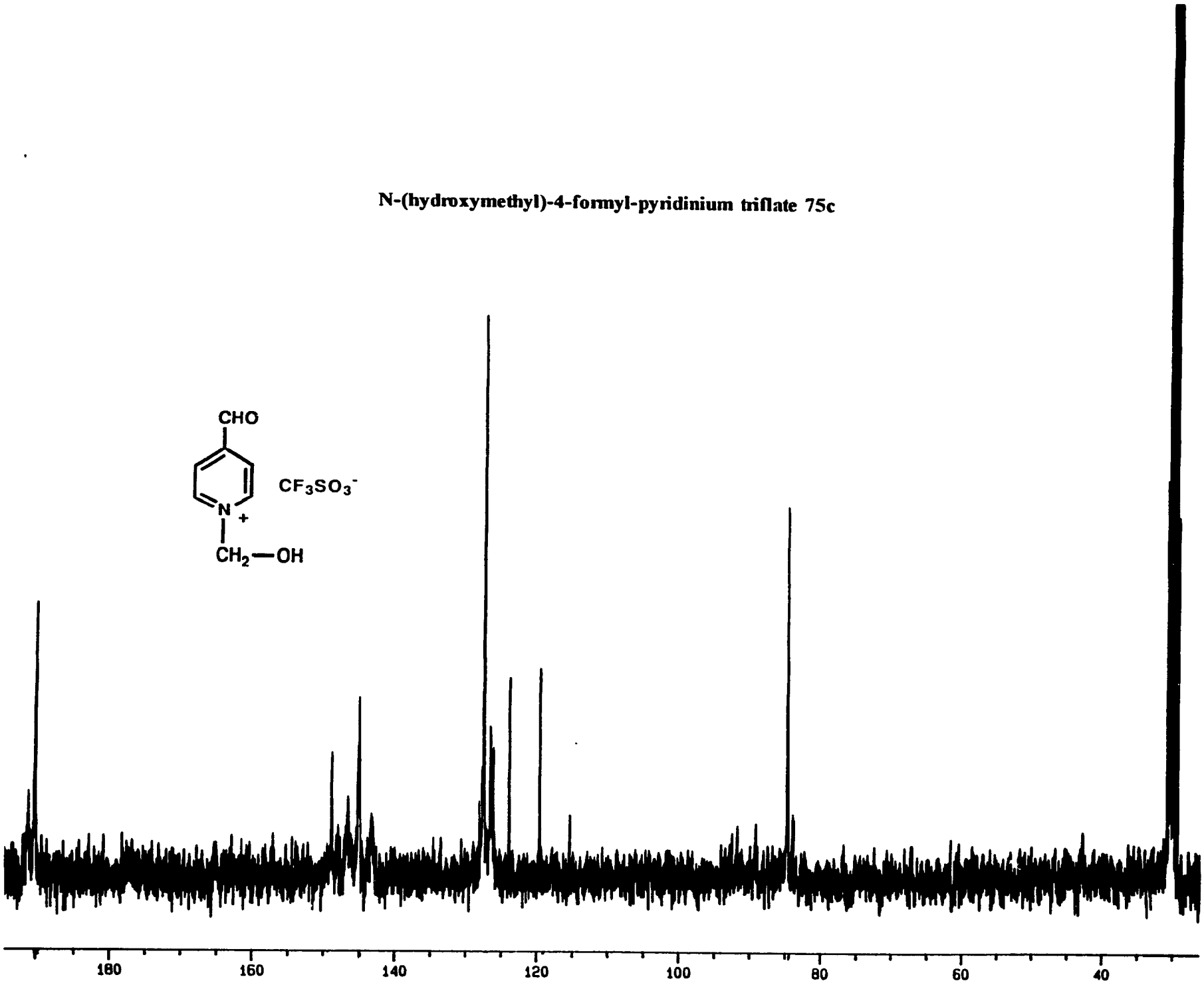


N-(hydroxymethyl)pyridinium triflate 75a

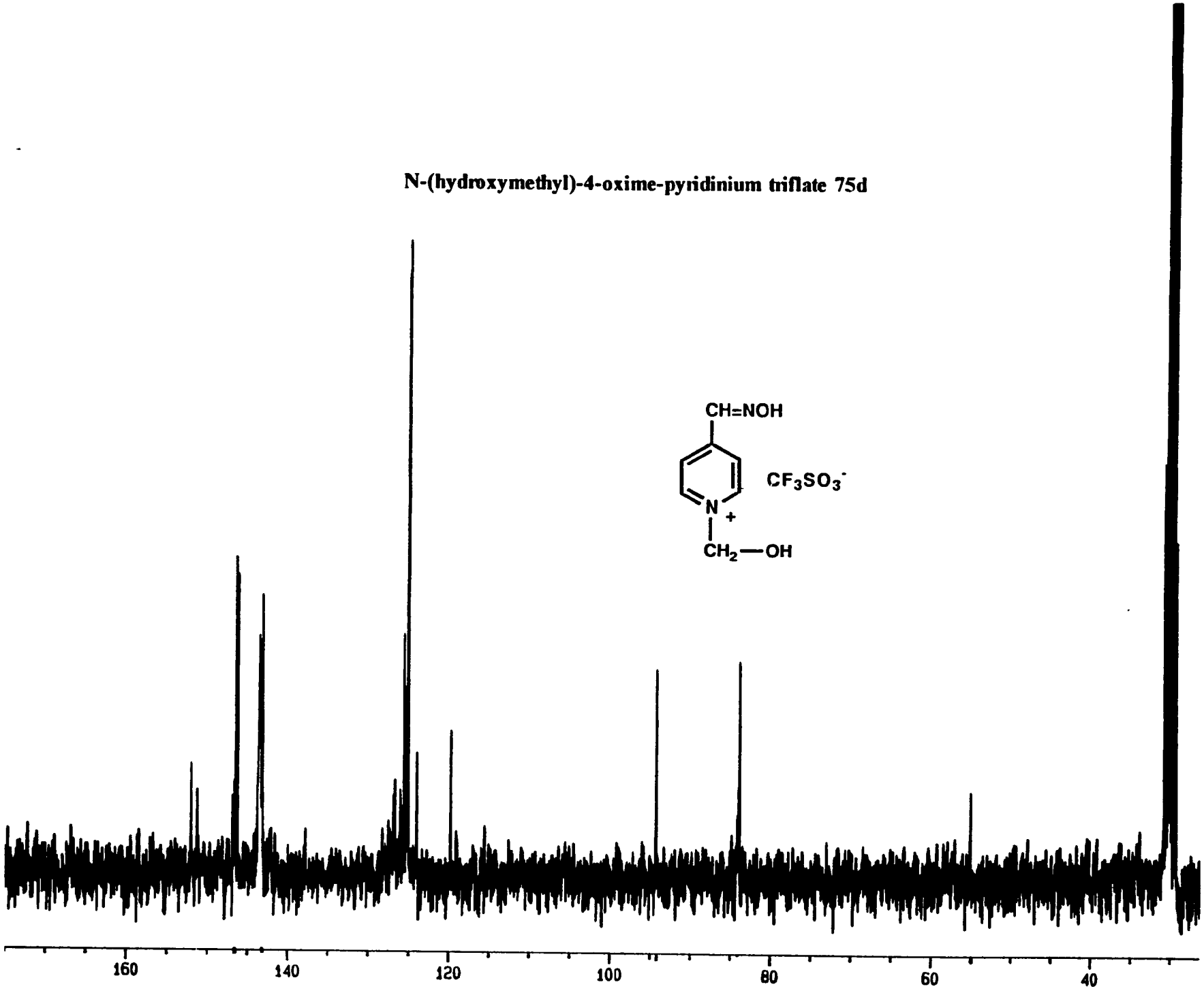
N-(hydroxymethyl)pyridinium chloride 75b



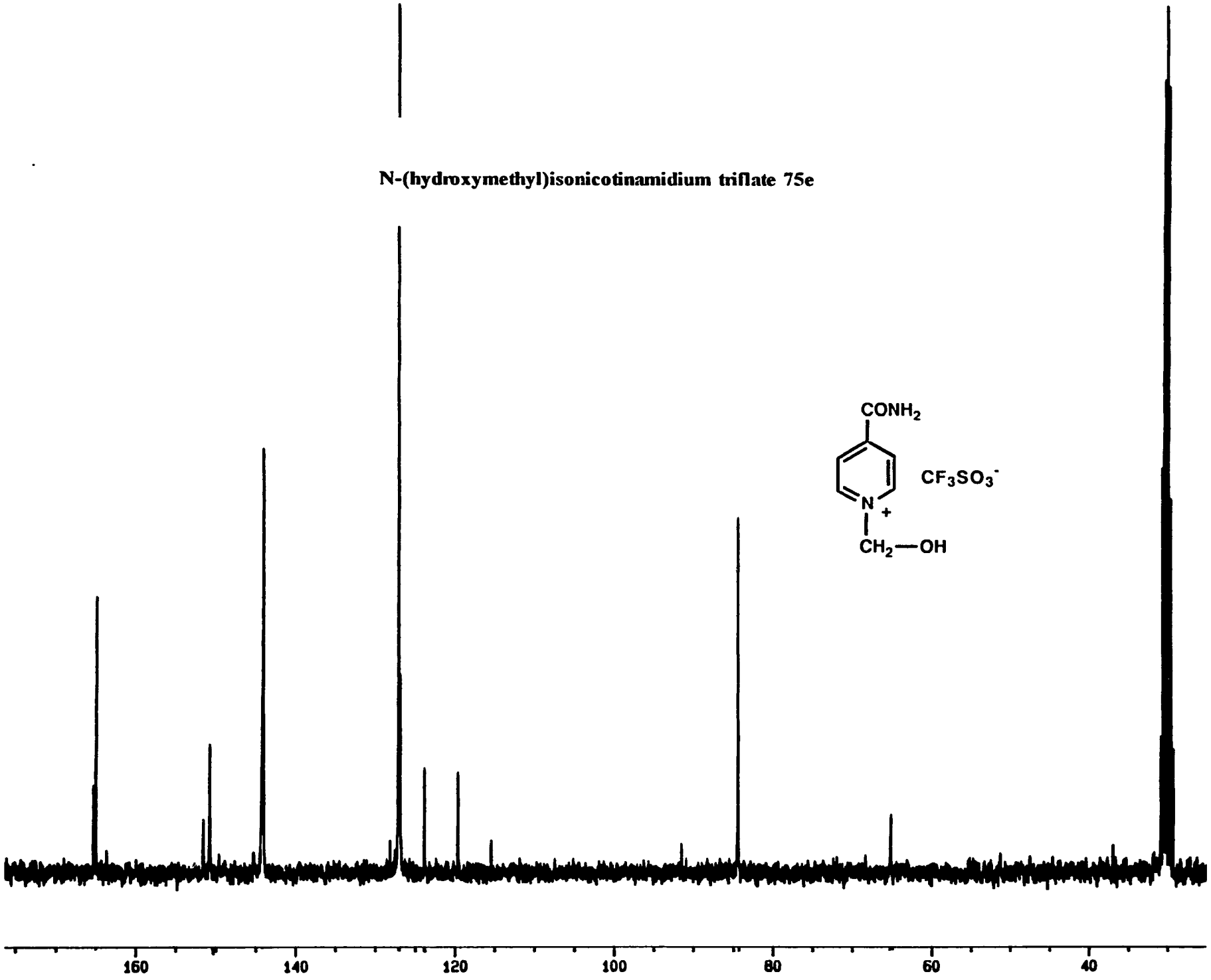
N-(hydroxymethyl)-4-formyl-pyridinium triflate 75c



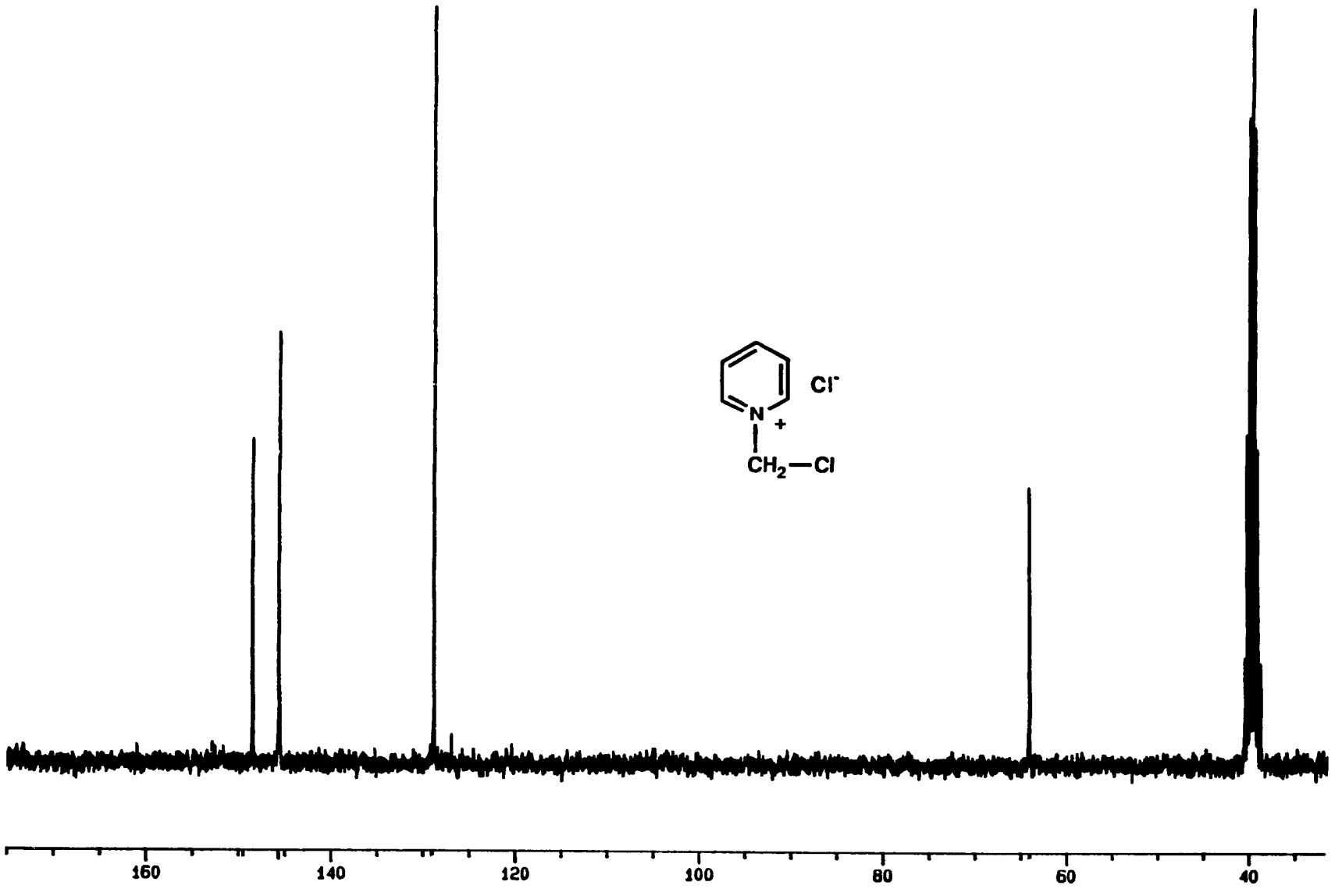
N-(hydroxymethyl)-4-oxime-pyridinium triflate 75d



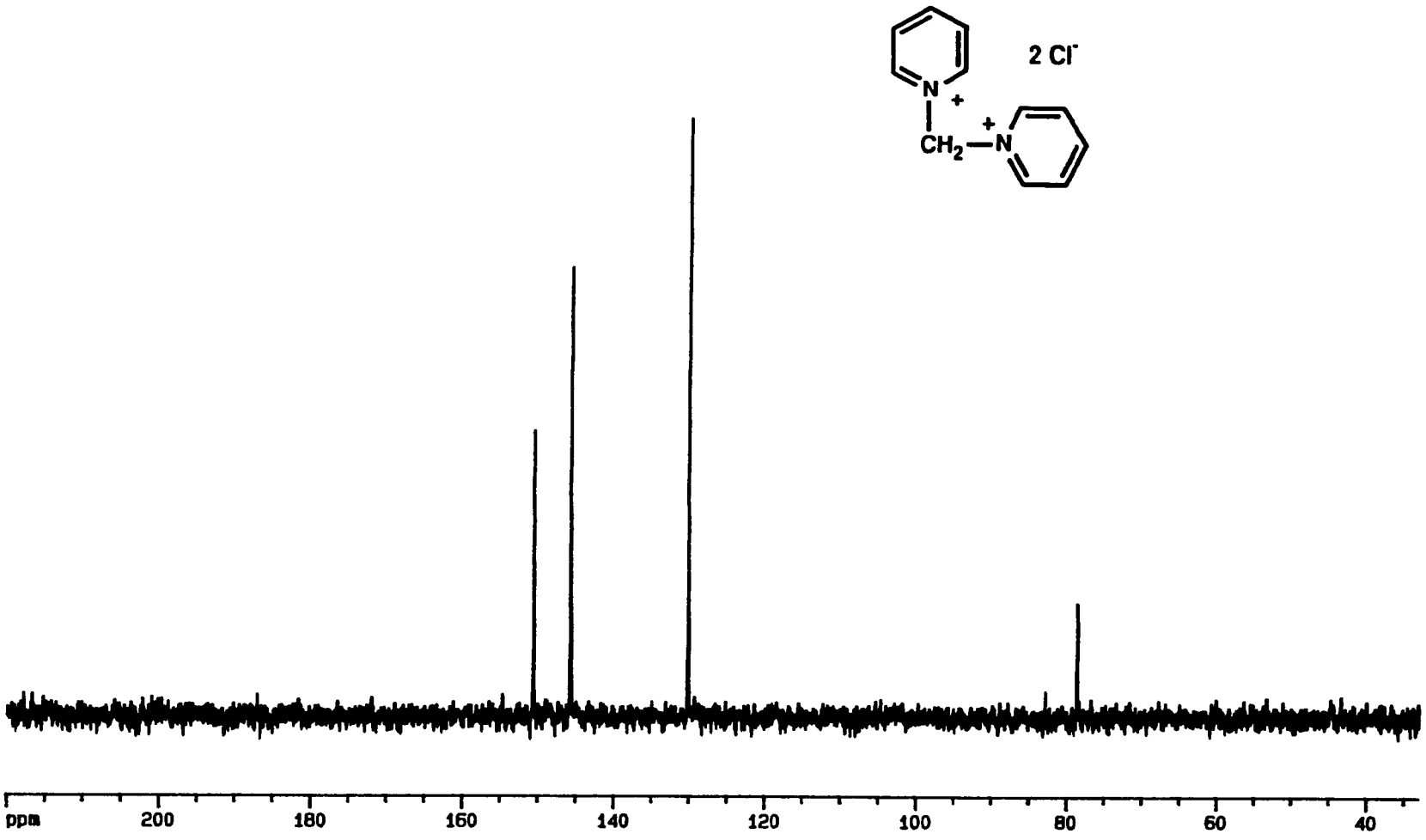
N-(hydroxymethyl)isonicotinamidium triflate 75e



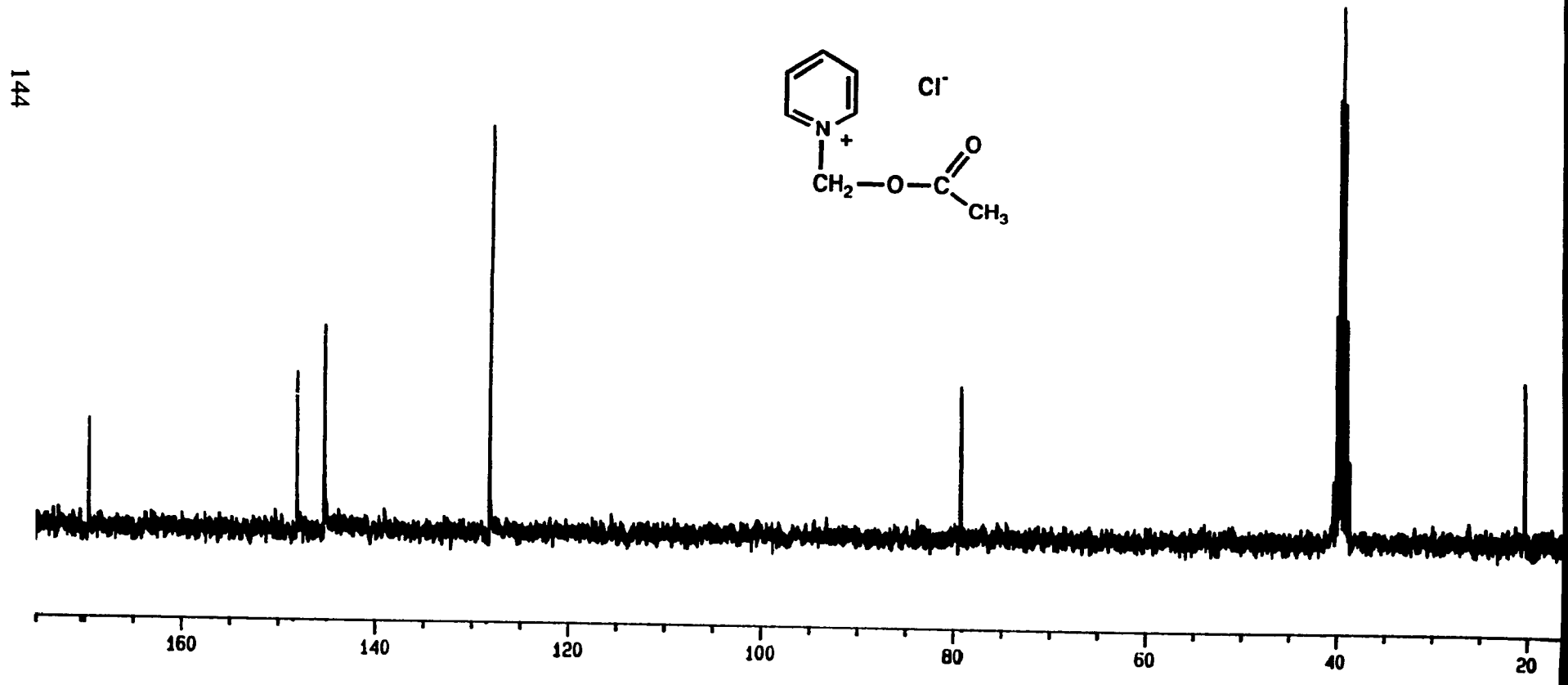
N-(chloromethyl)pyridinium chloride 72a



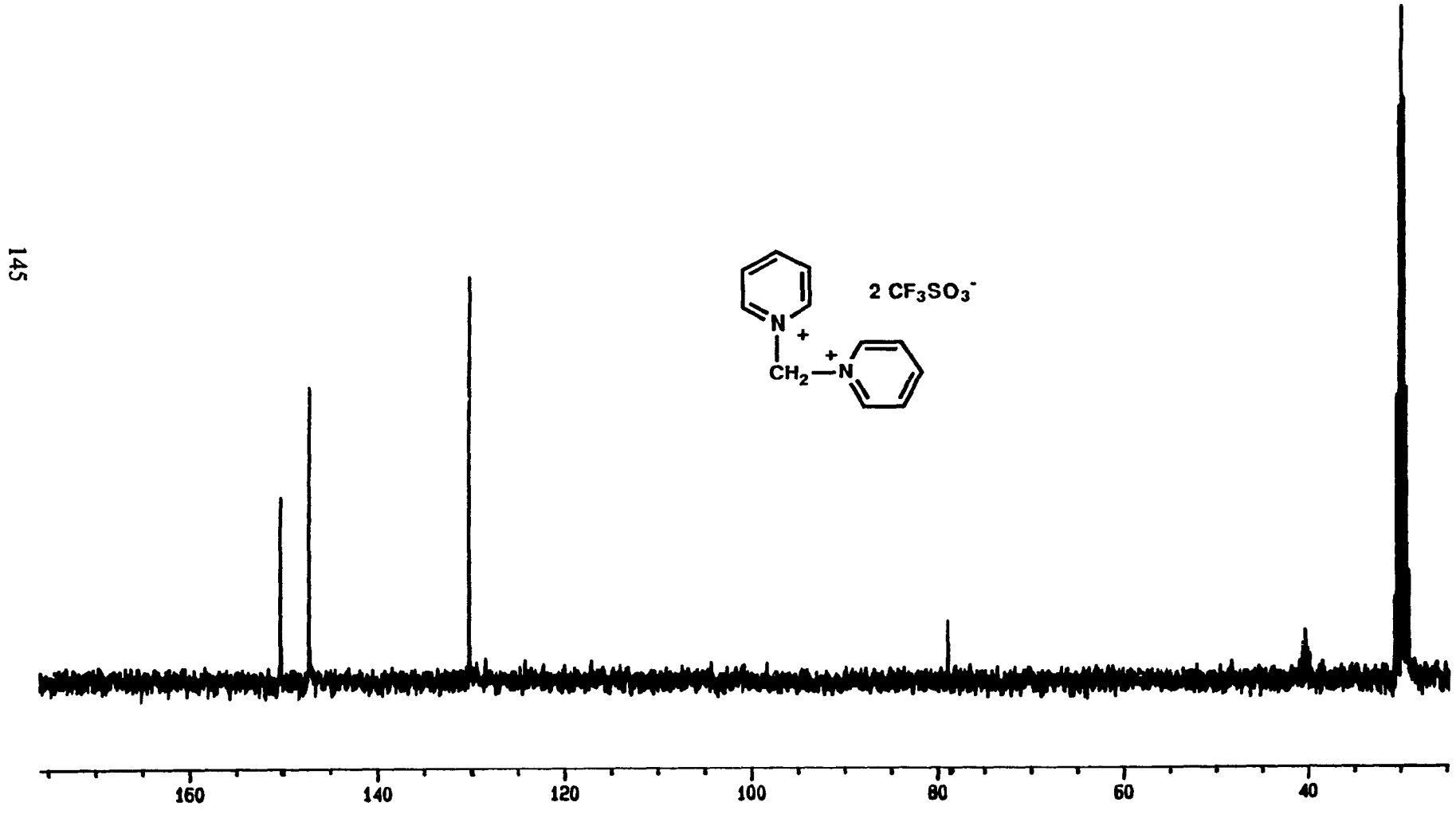
1,1'-(methylene)bispyridinium chloride 91b



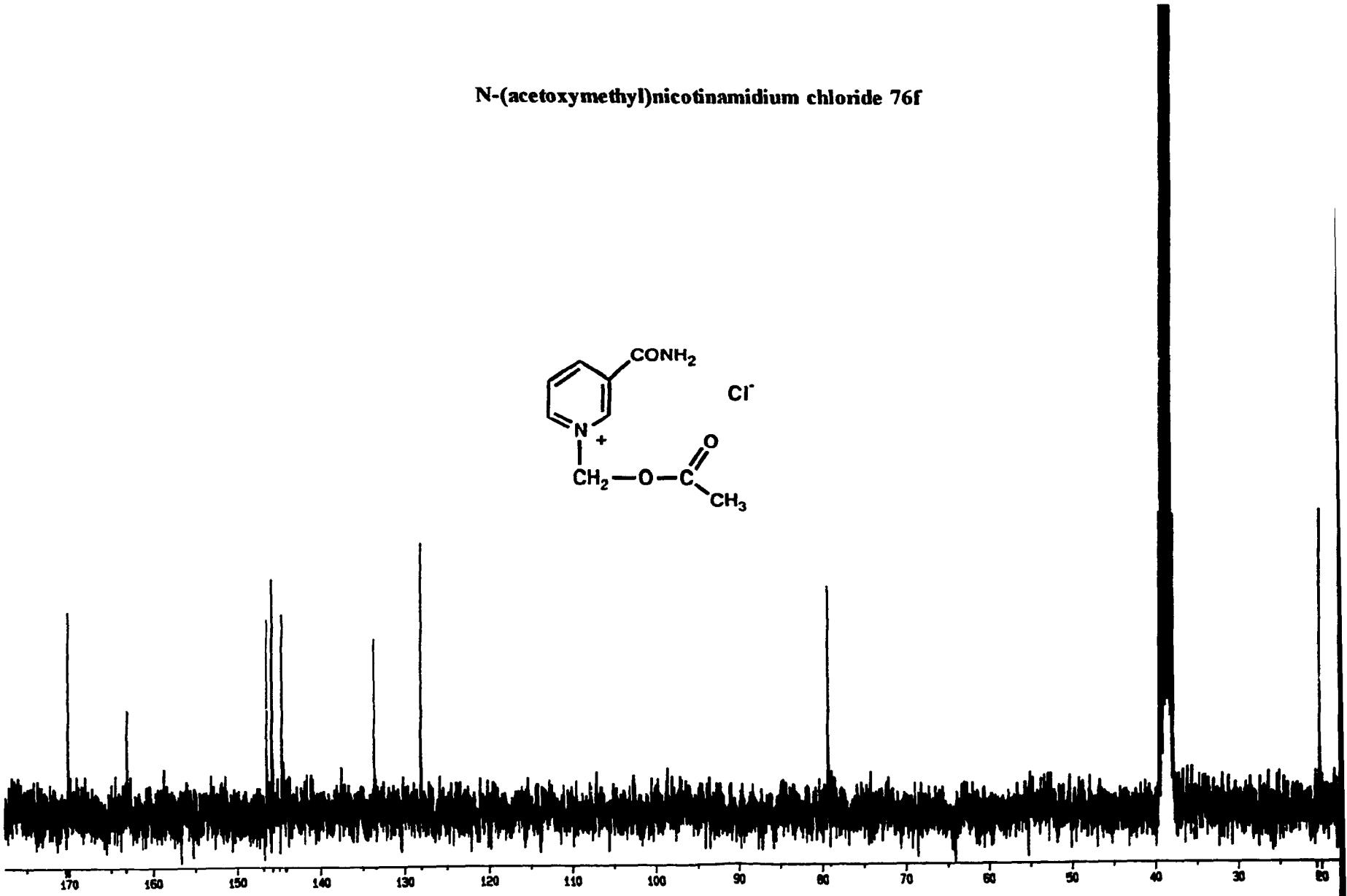
N-(acetoxymethyl)pyridinium chloride 76d



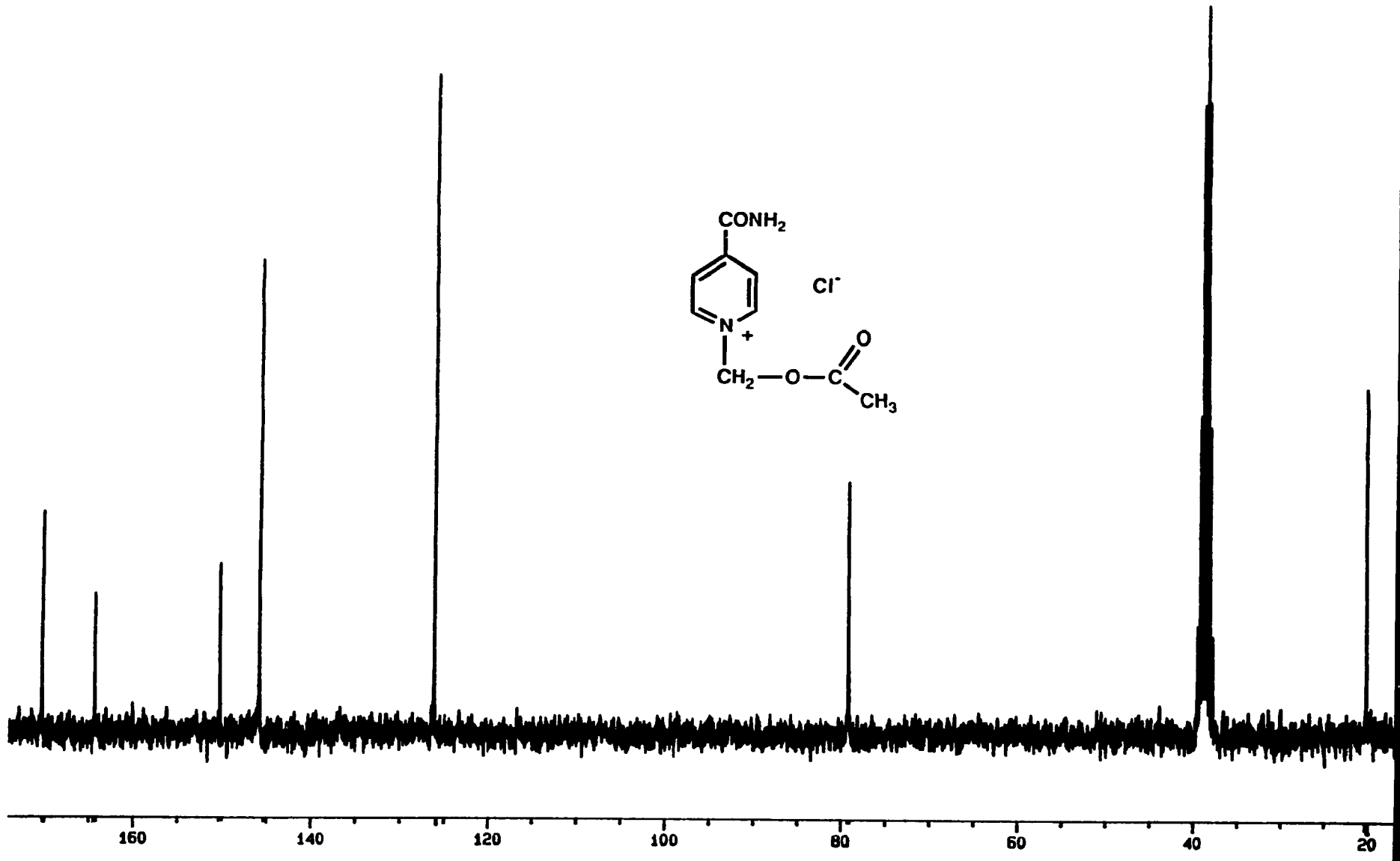
1,1'-(methylene)bispyridinium triflate 91a



N-(acetoxymethyl)nicotinamidium chloride 76f

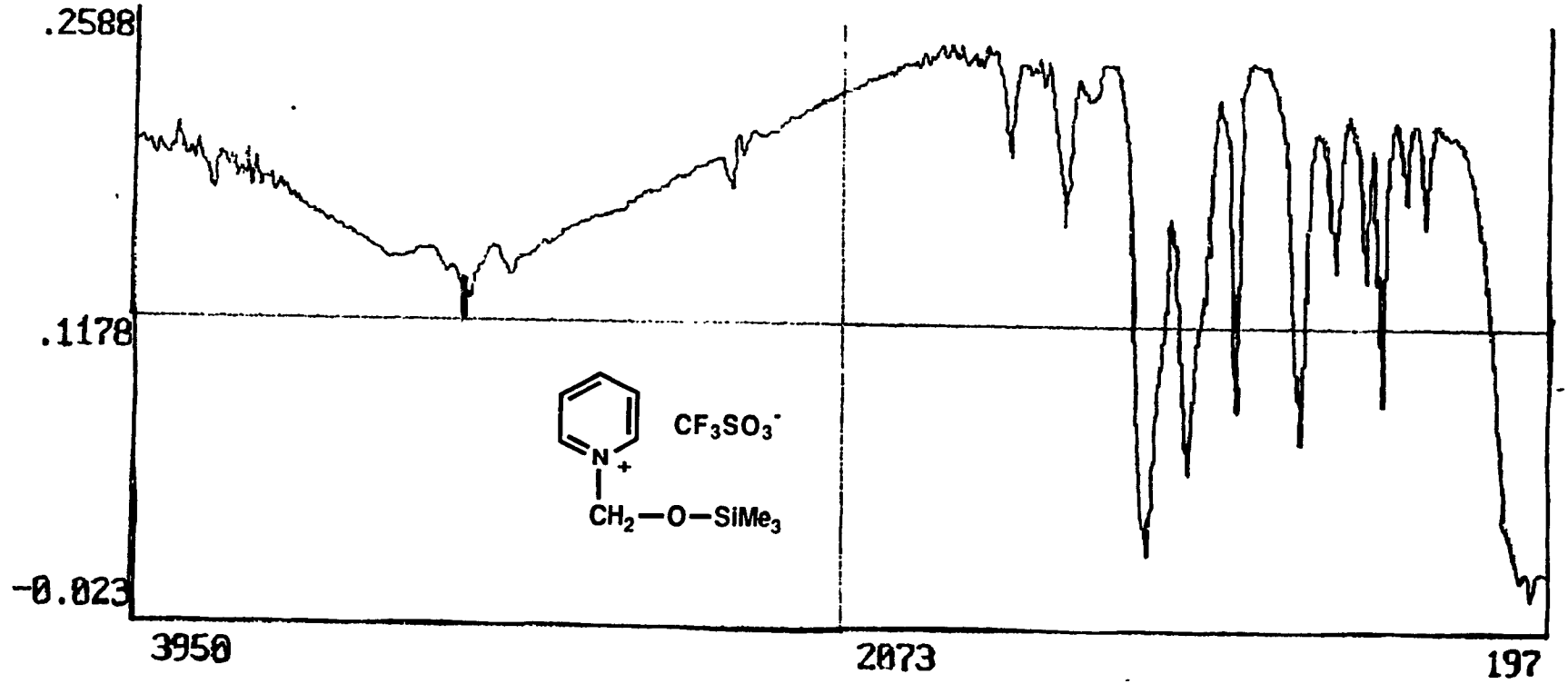


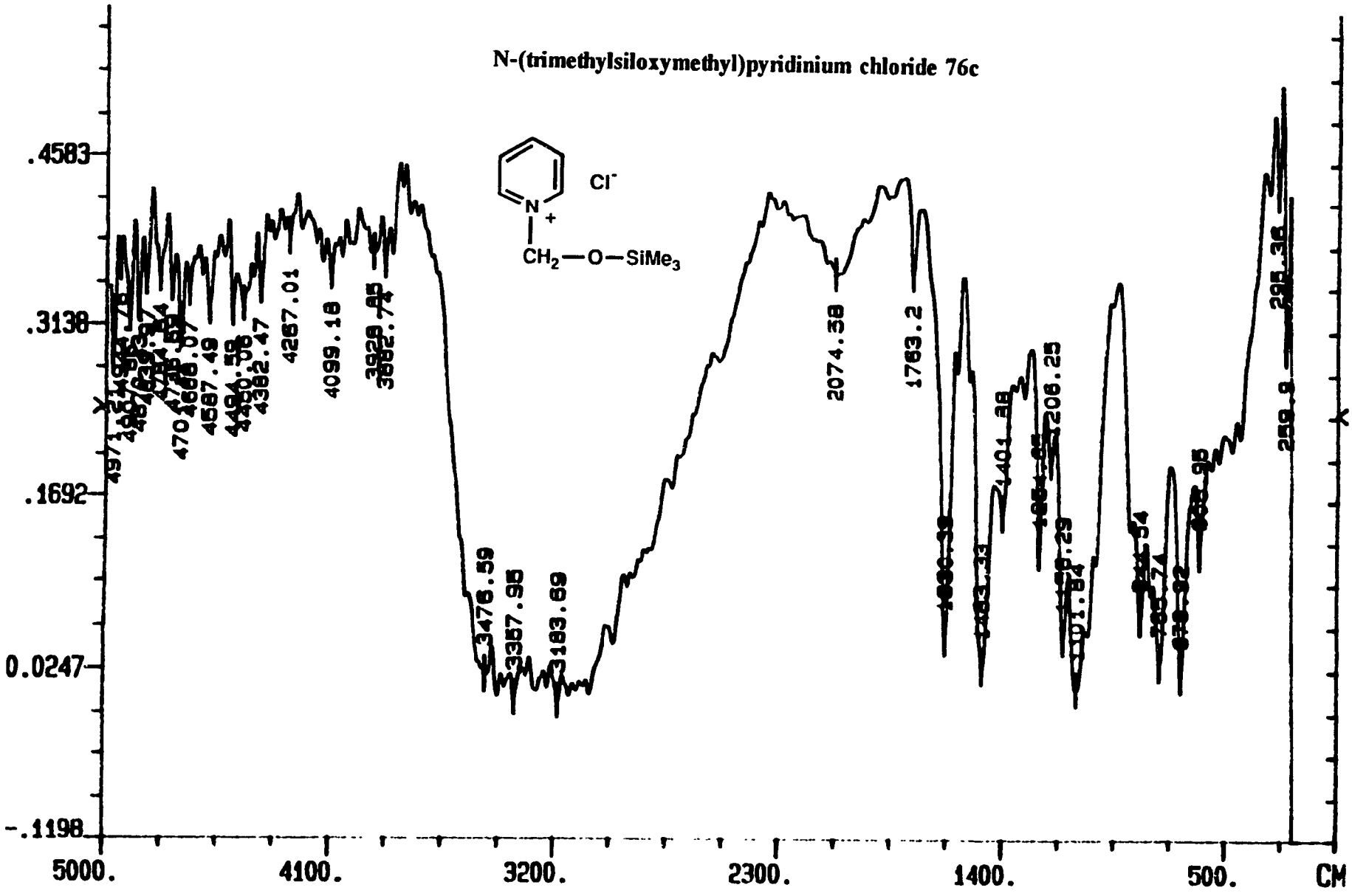
N-(acetoxymethyl)isonicotinamidium chloride 76e



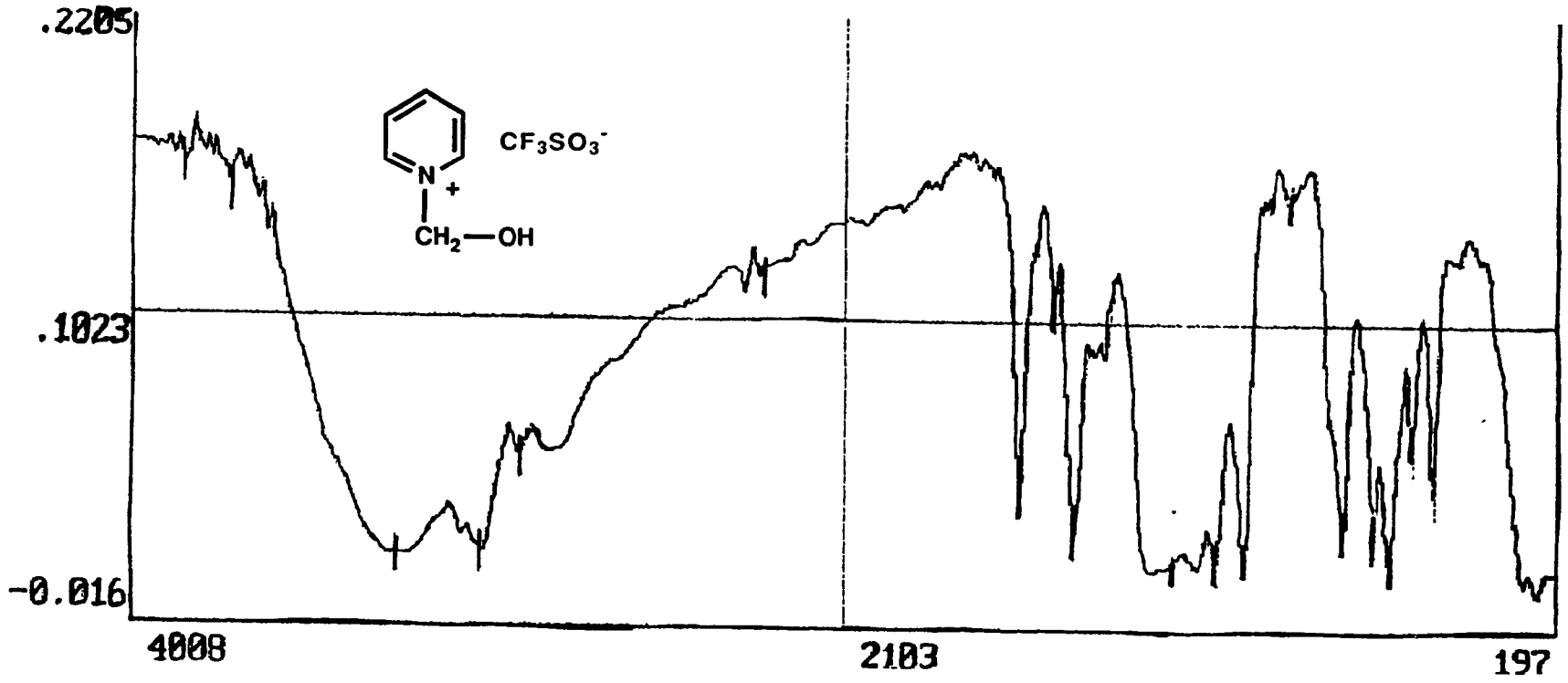
Appendix III. FT-IR Spectra

N-(trimethylsiloxymethyl)pyridinium triflate 76b

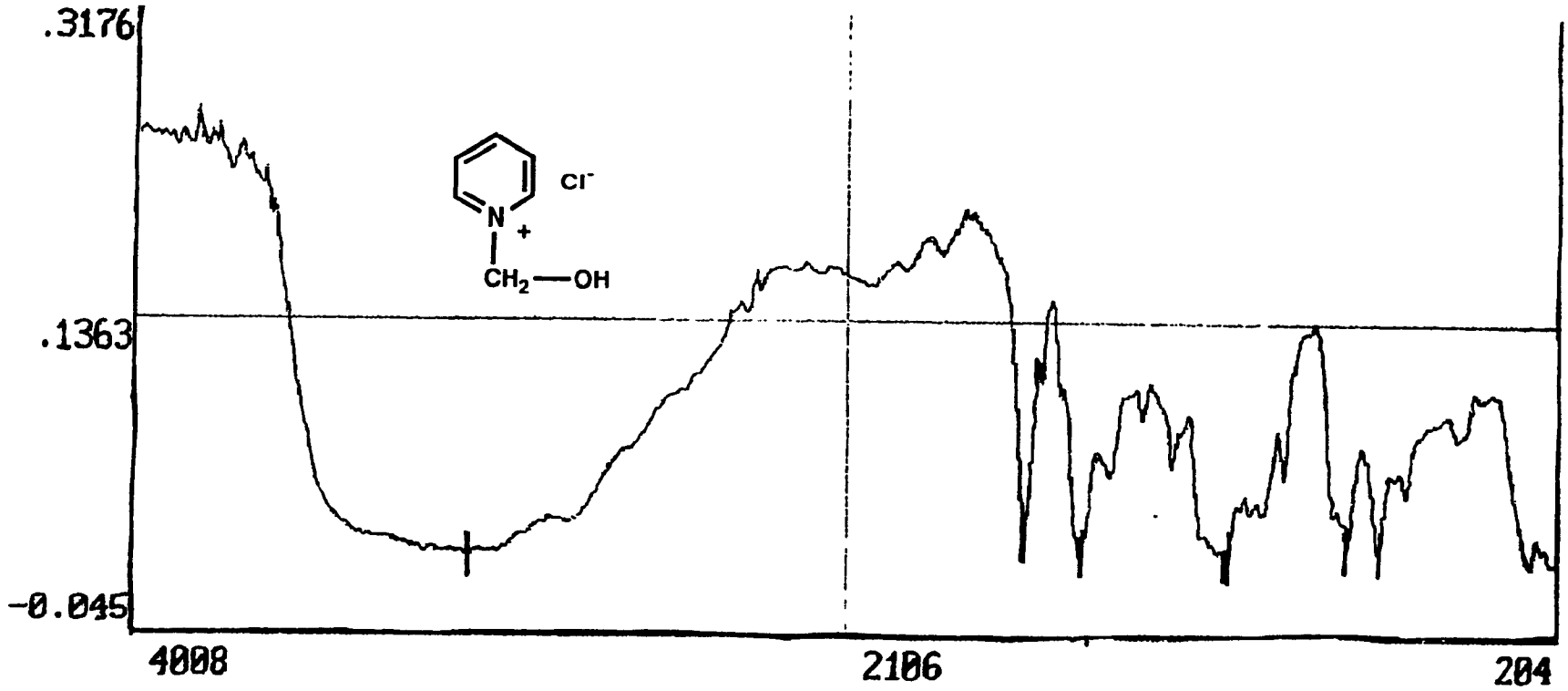



N-(trimethylsiloxymethyl)pyridinium chloride 76c
Cl⁻
N⁺
CH2—O—SiMe3
.4583
.3138
.1692
0.0247
-.1198
5000.
4100.
3200.
2300.
1400.
500.
CM
4287.01
4099.18
3882.74
3476.59
3357.95
3183.89
2074.38
1783.2
1401.38
1206.25
259.8
295.36

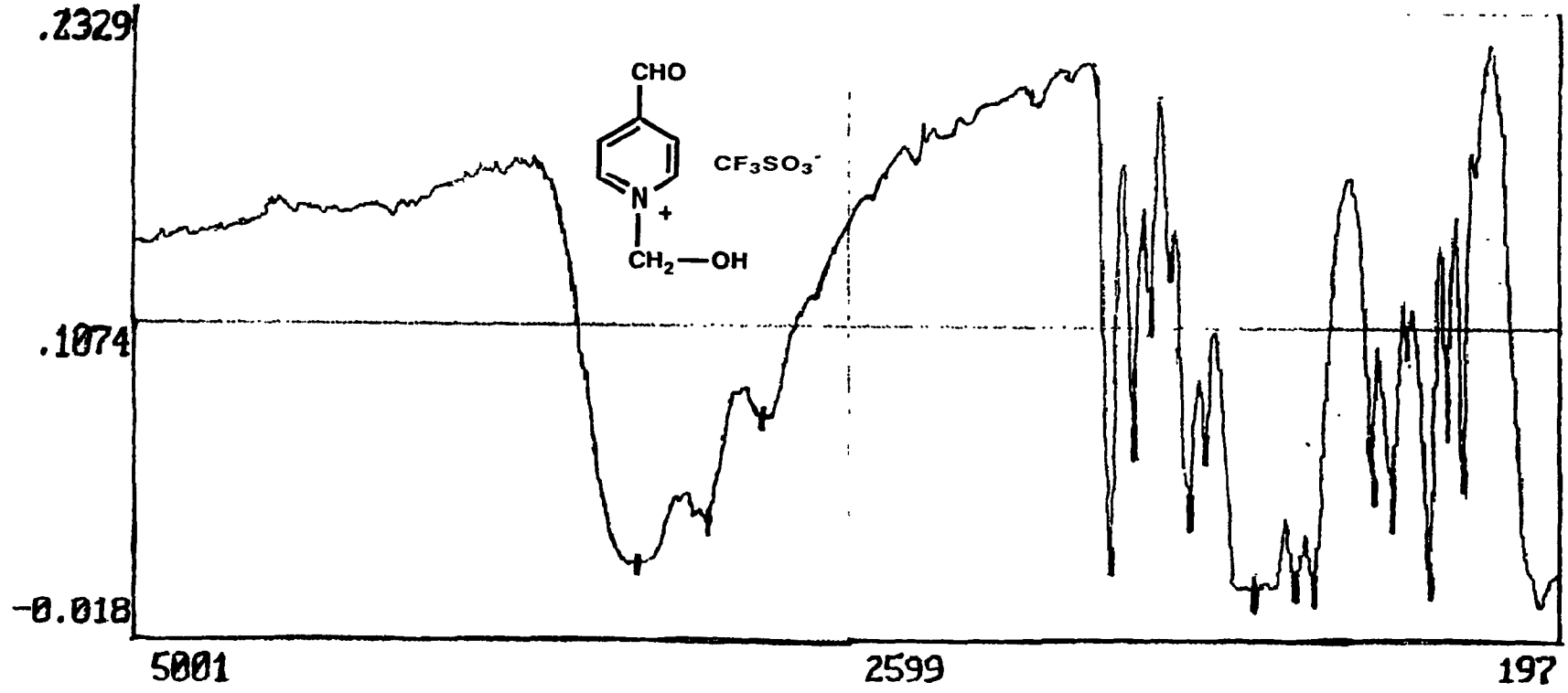
N-(hydroxymethyl)pyridinium triflate 75a

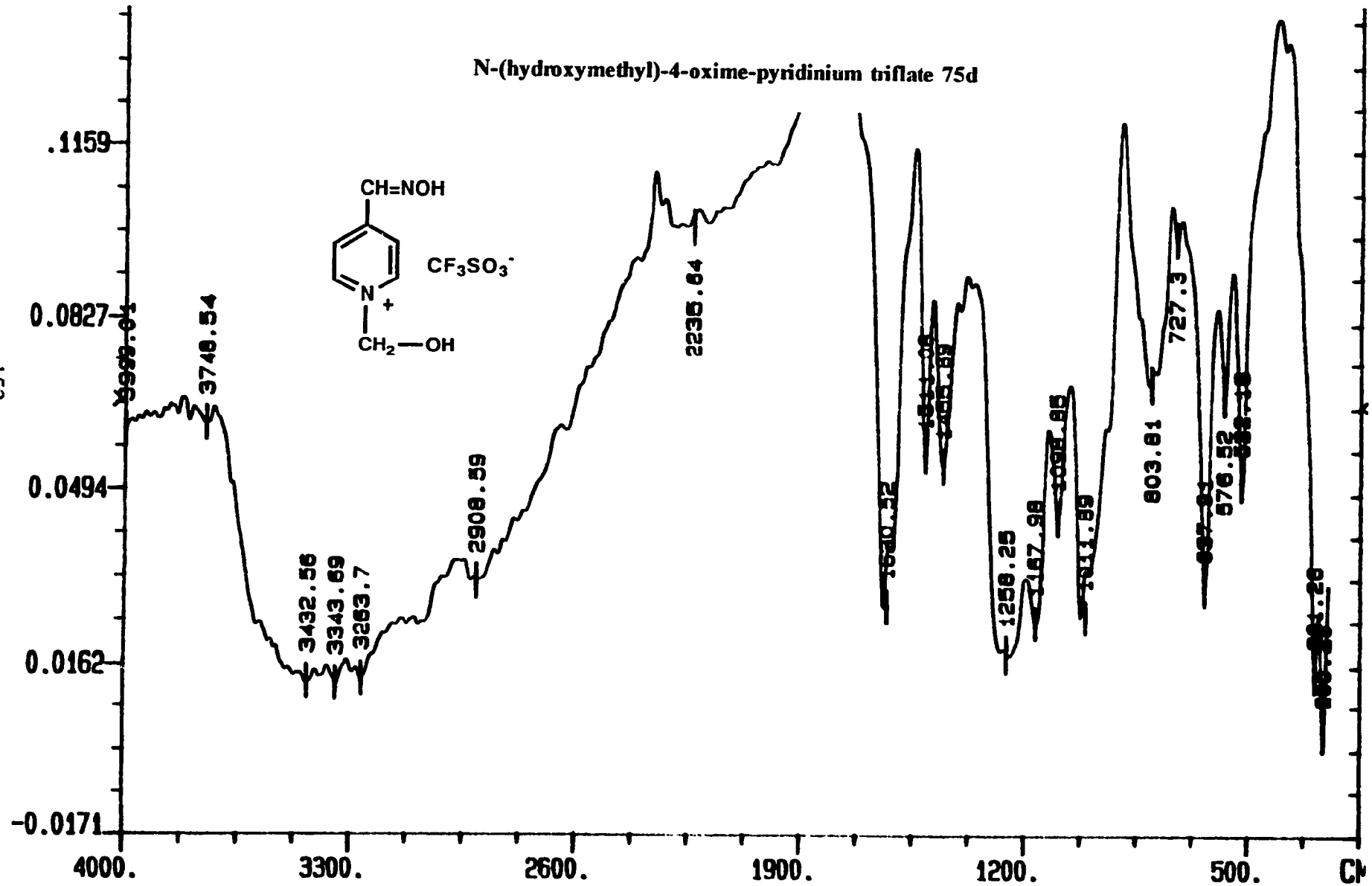


N-(hydroxymethyl)pyridinium chloride 75b

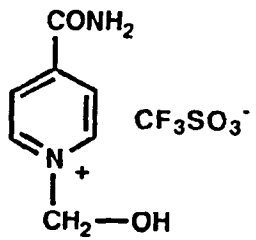


N-(hydroxymethyl)-4-formyl-pyridinium triflate 75c

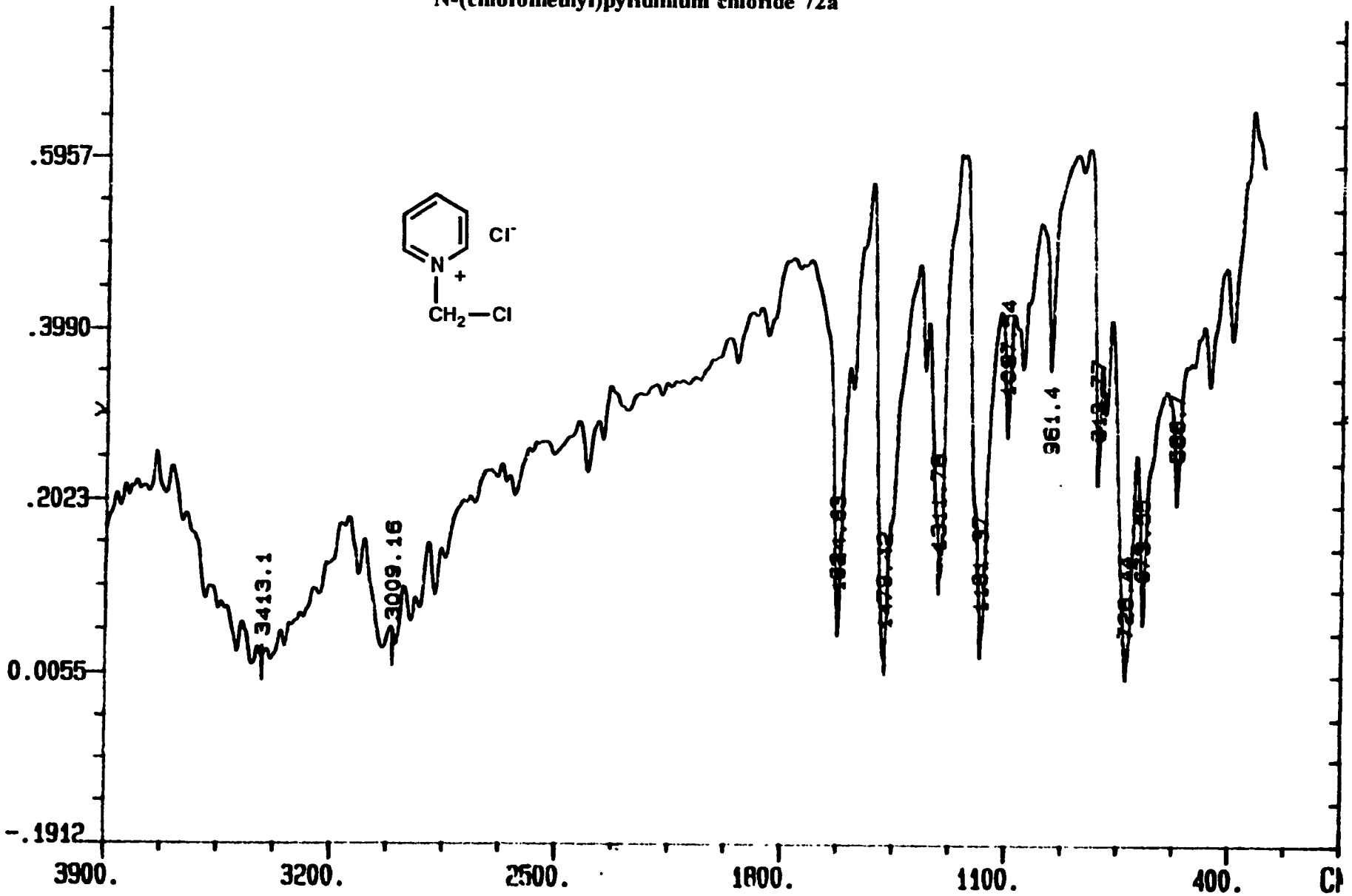


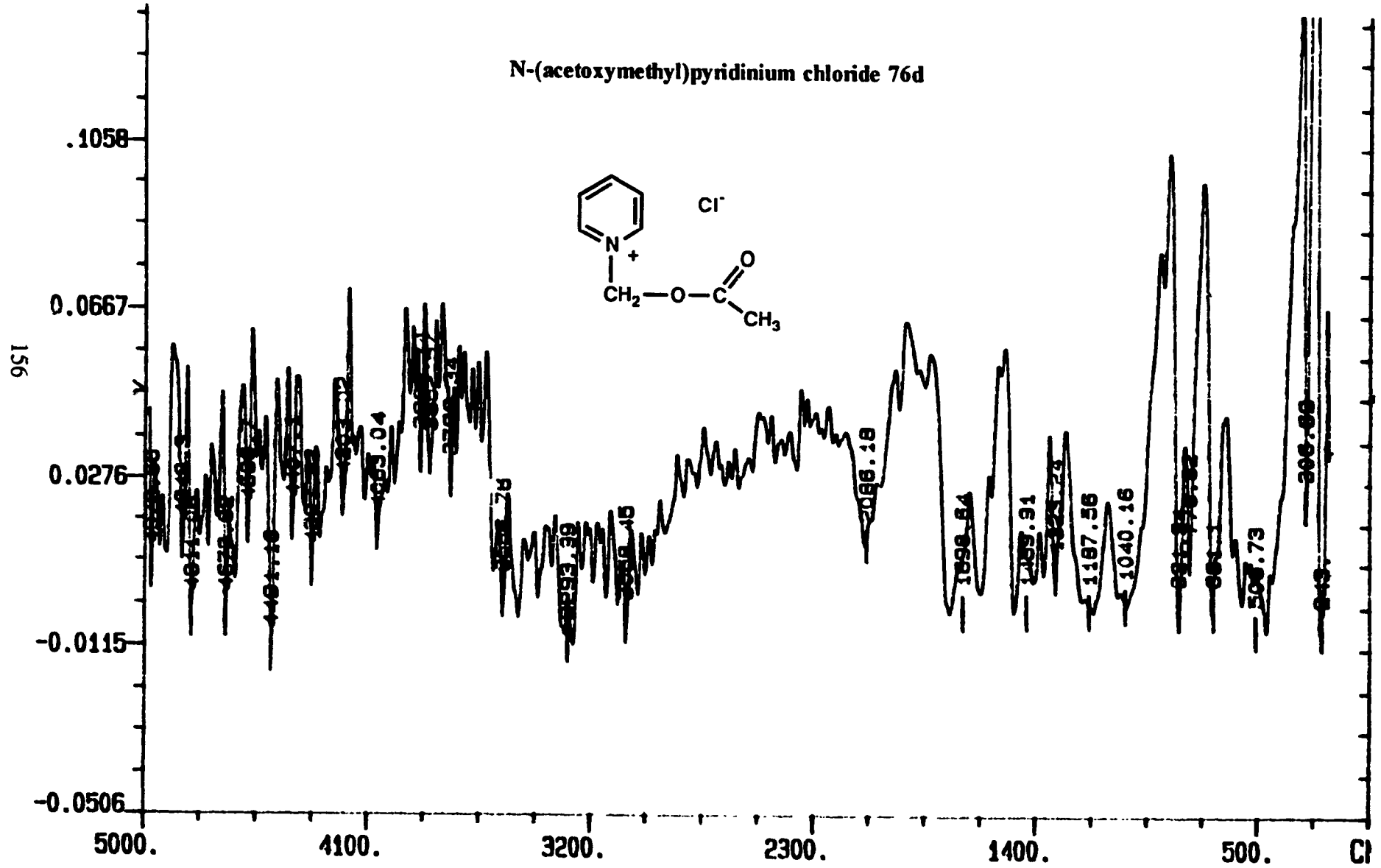

N-(hydroxymethyl)-4-oxime-pyridinium triflate 75d
CH=NOH
CF3SO3-
N+
CH2—OH
.1159
0.0827
0.0494
0.0162
-0.0171
3740.54
3432.56
3343.69
3283.7
2908.59
2235.84
1258.25
803.81
727.3
576.52
4000.
3300.
2600.
1900.
1200.
500.

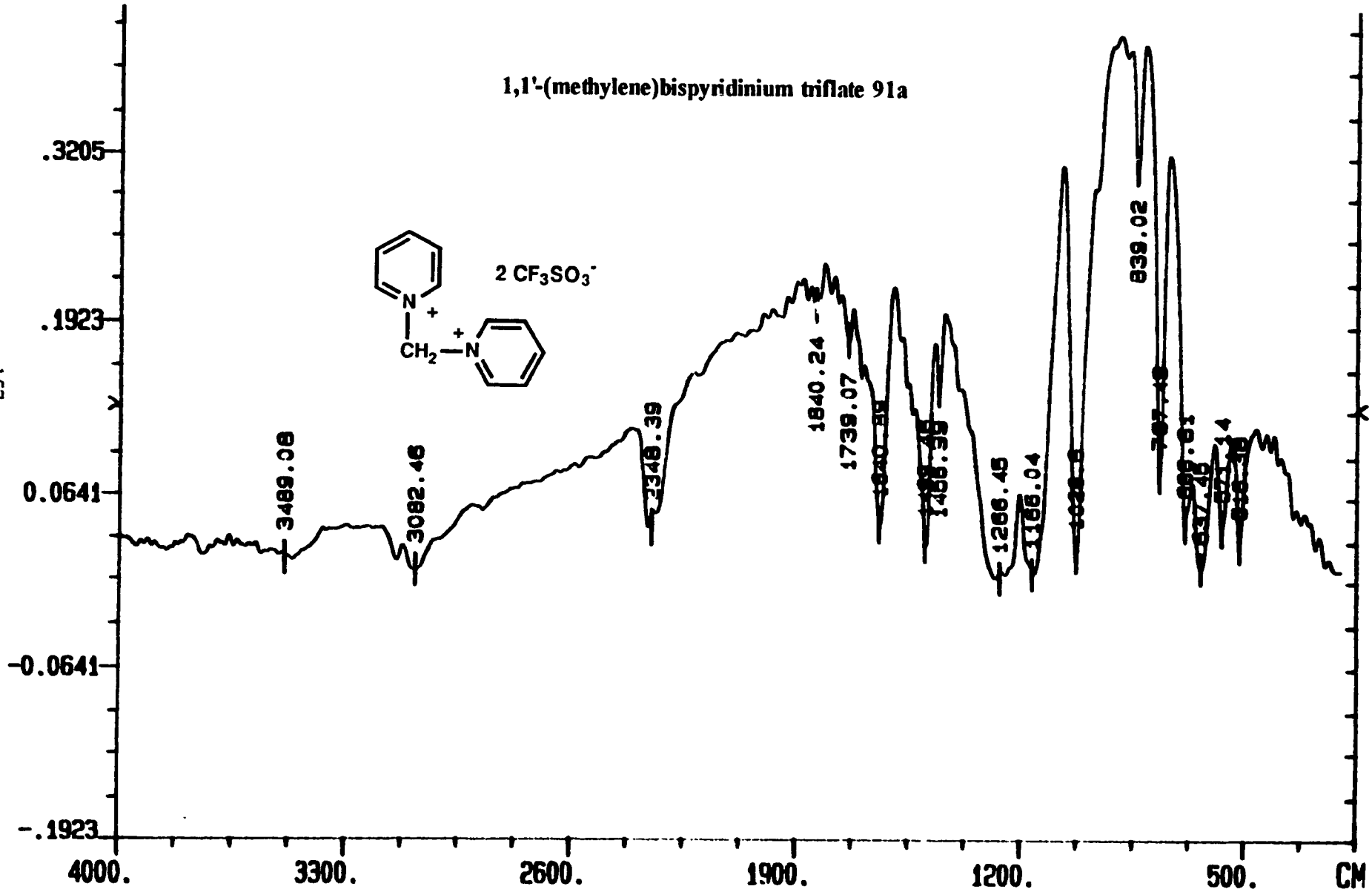
N-(hydroxymethyl)isonicotinamidium triflate 75e



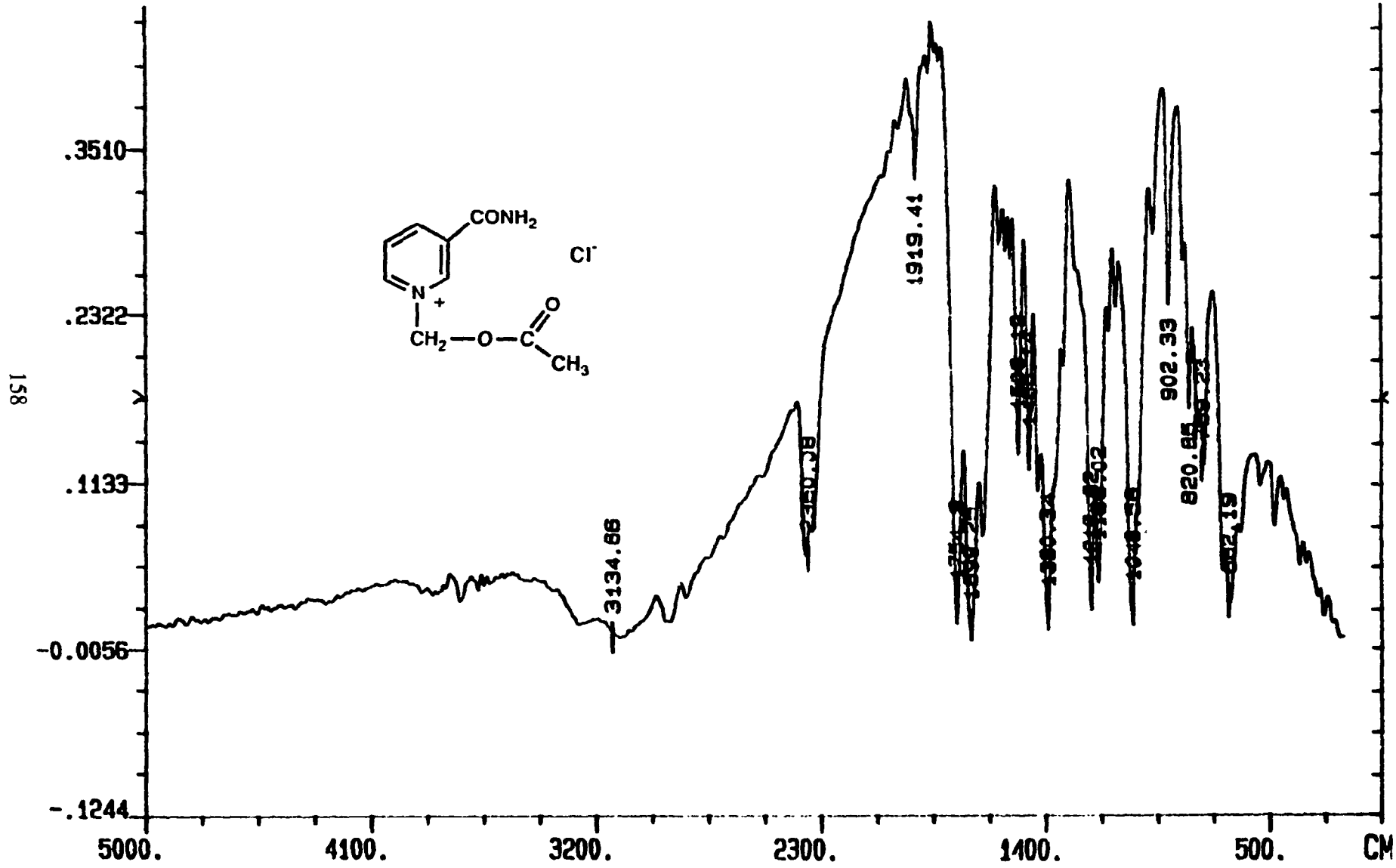
N-(chloromethyl)pyridinium chloride 72a

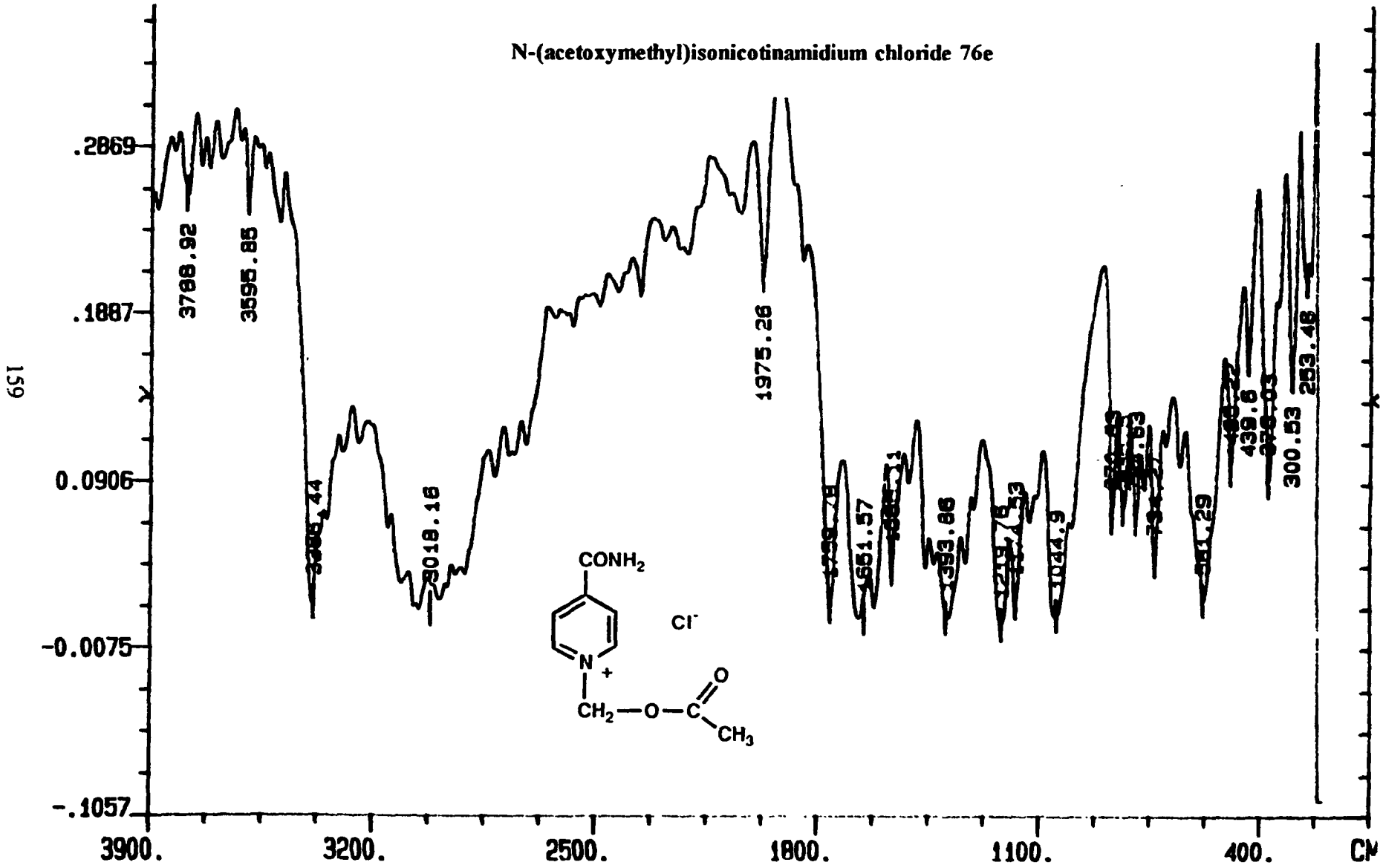



N-(acetoxymethyl)pyridinium chloride 76d
Cl⁻
N⁺
CH₂—O—C
O
CH₃
.1058
0.0667
0.0276
-0.0115
-0.0506
156
Y
5000.
4100.
3200.
2300.
1400.
500.
1187.36
1040.16


1,1'-(methylene)bispyridinium triflate 91a
2 $CF_3SO_3^-$
.3205
.1923
0.0641
-0.0641
-.1923
Y
3489.08
3082.46
2348.39
1840.24
1739.07
1488.36
1266.45
1188.04
839.02
4000.
3300.
2600.
1900.
1200.
500.
CM

N-(acetoxymethyl)nicotinamidium chloride 76f




N-(acetoxymethyl)isonicotinamidium chloride 76e
.2869
.1887
0.0906
-0.0075
-.1057
Y
3788.92
3595.85
3018.16
1975.26
1651.57
1044.9
439.8
300.53
253.48
CONH2
Cl-
N+
CH2—O—C
O
CH3
3900.
3200.
2500.
1800.
1100.
400.
CM