METHAMPHETAMINE SYNTHESIS INHIBITION: DISSOLVING METAL REDUCTIONS

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1 Abstract

In this paper, we report the status of our investigation into the feasibility of introducing a chemical agent into agricultural grade anhydrous ammonia that will render the ammonia useless for methamphetamine synthesis. Our goal is to provide a means to reduce the number, ease, and stealth that clandestine methamphetamine laboratories using the dissolving metal, or Nazi, synthetic method currently enjoy.

We have conducted investigations of additives that span the broad classes of organic, inorganic, and organometallic reagents. We have identified numerous compounds and classes of compounds that effectively inhibit methamphetamine synthesis. Feasibility evaluations of these compounds are ongoing. However, we have identified two candidate reagents that possess properties useful for consideration as additives for anhydrous ammonia: ferrocene and 1,1,1,2-tetrafluoroethane. Details of the reactivity of these compounds and issues relating to their application for the inhibition of methamphetamine synthesis will be presented.

2 Introduction

2.1 Background

Of all the drugs of abuse, methamphetamine is the only one so simple to prepare that the individual user can make it independently [1]. It is estimated that 99 % of the clandestine laboratories in this country are involved in the illicit manufacture of methamphetamine. An increasing number of the clandestine methamphetamine laboratories (currently estimated at 20 % [2]) use a procedure known as a dissolving metal reduction [3], often referred to as the "Nazi" method, of over-the-counter cold medications ephedrine or pseudoephedrine [2]. The details for the synthesis are readily available from the literature [5] and the Internet. Unlike other synthetic drugs, less than 10 % of those arrested for the illicit synthesis of methamphetamine are trained chemists [1].

The relative ease with which methamphetamine is manufactured has led to a proliferation of small-scale "mom and pop" operations. The small-scale labs produce only a small amount of the methamphetamine available in this country [4]. However, clandestine laboratories, often operated by criminally minded individuals untrained in the handling of dangerous chemicals, pose threats of fire, explosion, poison gas, booby traps, and the illegal dumping of hazardous waste [4]. The solvent of choice used for

the Nazi synthesis is anhydrous ammonia, often obtained by theft from farmers' fields. The thieves normally pilfer only a few gallons of anhydrous ammonia but too often are the cause of major ammonia spills. Such spills not only result in the loss of thousands of gallons of ammonia for the farmer, but have resulted in the evacuations of entire towns due to the toxic cloud of ammonia produced [6].

The handling of anhydrous ammonia is an extraordinarily dangerous activity. The liquid is extremely cold (-28 ^{o}F) and the vapor is highly volatile. Contact of the liquid with skin or mucus membranes causes a combination of frostbite, direct ammonolysis of the skin by ammonia, and saponification of the epidermal fats by ammonium hydroxide formed by the reaction of ammonia and water [7]. A very real concern is severe injury to children who obtain the methamphetamine synthesis from the Internet without knowledge of the risks associated with the handling of anhydrous ammonia.

The small-scale clandestine laboratories are often considered to be more dangerous than the larger scale labs [4]. Smaller scale laboratories suffer from amateur chemists inexperienced in the handling of hazardous chemicals and the consequences of potential accidents. This point is evident from the large number of children present at clandestine laboratories [4]. Of the reported 7,200 clandestine laboratories seized in 1999, nearly 870 children were reported to be at the sites with 180 exposed to toxic chemicals and 12 found injured by the chemicals [8].

The small size of the clandestine methamphetamine labs and the brief time required for the methamphetamine synthesis provide stealth for the laboratories [9]. The required equipment will easily fit into the trunk of a car. The methamphetamine synthesis can be carried out in a hotel room or on the side of the road before disposing of the waste and concealing the laboratory equipment. The Nazi method enjoys the advantage of producing relatively little odor compared with other synthetic methods, greatly minimizing the risk of detection.

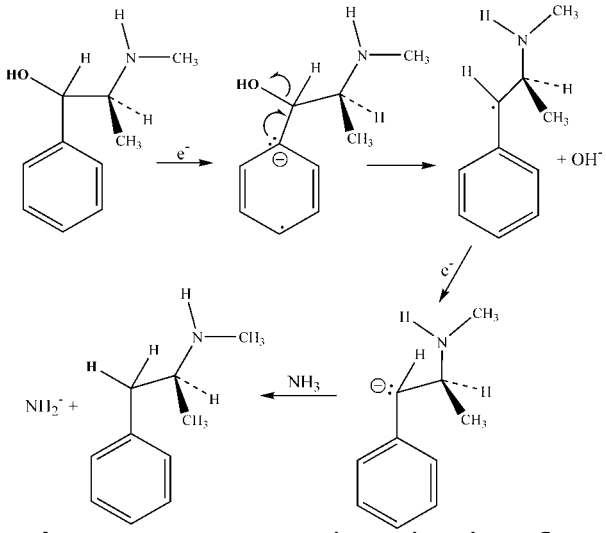
With these points in mind, the objective of our work is to increase the level of difficulty, time, equipment, and supplies necessary to synthesize methamphetamine by the Nazi method. Because the average methamphetamine producer has relatively low chemistry skills, increasing the level of difficulty is expected to significantly decrease the number of individuals capable of conducting the procedure. Additionally, by increasing the time, equipment, and supplies required for the synthesis, the risk of detection of the clandestine laboratory will increase as well.

2.2 The Nazi Synthetic Method

The key reagent in the Nazi methamphetamine synthesis is the solvated electron. The solvated electron is a potent reducing agent [10] and is sufficiently long-lived in liquid ammonia that it is useful for synthetic purposes [11]. Dissolving lithium (or sodium) metal in anhydrous ammonia generates the solvated electron, Scheme 1. The proposed mechanism of the Nazi reaction involves the two-electron reduction of ephedrine or pseudoephedrine to give the

$$\mathrm{Li(s)} \xrightarrow{\mathrm{NH_3}} \mathrm{Li(NH_3)}_n^{+} + \mathrm{e^-(NH_3)}_m$$

Scheme 1. Dissolution of lithium metal in anhydrous ammonia results in the formation of solvated lithium ions and electrons. The electron is the key reagent



Scheme 2. Proposed mechanism for the two electron, two-proton reduction of ephedrine or pseudoephedrine to methamphetamine

methamphetamine product, Scheme 2. *The synthesis of methamphetamine can be prevented if a reagent already present in the anhydrous ammonia scavenges the electron.*

2.3 Chemical Approaches to Electron Scavenging

The principle strategy in this study is to scavenge solvated electrons. In the absence of a suitable reducing agent, the reduction of ephedrine/pseudoephedrine can not take place, Scheme 2. This strategy can be further broken down into two distinct categories. The first is a stoichiometric approach that uses a compound capable of undergoing a finite number of one-electron reduction processes. Compounds that exhibit reactivity of this type will be referred to as stoichiometric compounds. Organic chemical compounds typically fall under this category. The disadvantage of this approach is that, in principle, the inhibitor can be overcome by the addition of excess lithium metal. Another approach is the use of a compound that is capable of catalyzing the conversion of the solvated electrons into an unreactive form. Compounds of this class will be referred to as catalytic compounds. The distinct advantage of catalytic compounds is that it is not feasible to overcome the catalyst by the addition of excess lithium. The catalyst will simply regenerate itself and consume the excess electrons. Metal compounds typically fall under this category.

2.4 Program Goals

In this paper we will provide an overview of our investigations to date. There are four important goals that we are interested in addressing. The first is to maximize the ability of the additive to prevent the illicit manufacture of methamphetamine, i.e., counter-production. The second is to minimize the ease with which the additive is defeated, i.e., counter-action. The third is to minimize or make transparent the impact of the additive on the legitimate use of anhydrous ammonia by the farmer. Lastly, we desire to limit the impact of the additive on the environment. In this paper we will focus on the first two goals, counter-production and counter-action. The other two goals will be reported on separately.

Table 1. Summary of Inhibition Results

Additive	Methamphetamine Yield [a]	Amount of Additive [b]
No additive [c]	89 ± 9 %	0.0 %
Water	86 %	0.6 %
Urea	37 %	23 %
Ammonium carbonate [d]	54 %	246 %
Boron trifluoride etherate	95 %	1 %
Citric acid	99 %	14 %
Ascorbic acid [e]	99 %	14 %
α-Tocopherol [f]	1 %	14 %
Butylated hydroxytoluene [g]	99 %	14 %
Trolox [h]	99 %	14 %
Pentamethylchromanol [i]	50 %	14 %
1-Chloromethyl naphthalene	1 %	14 %
Trichloroethylene	1 %	14 %
2-Chloro-6-(tri-chloromethyl)-pyridine [j]	31 %	10 %
1,1-Difluoroethane [k]	100 %	322 %
1,1,1,2-Tetrafluoroethane [l]	5 %	10 %
$FeCl_3$	19 %	1.0 %
$FeCl_3 + H_2O$ [m]	3 %	1.0 %
$FeCl_2$	0 %	1.0 %
$FeCl_2 + H_2O$ [m]	87 %	1.0 %
$FeSO_4$	94 %	1.0 %
$FeSO_4 + H_2O$ [n]	95 %	1.0 %
Fe(III) Citrate [o]	0 %	1.2 %
$Fe(acac)_3$ [p]	0 %	0.1 %
$Fe(F_3\text{-}acac)_3$ [p]	0 %	0.1 %
$Fe(F_6\text{-}acac)_3$ [p]	31 %	0.1 %
$Fe(CO)_5$	76 %	1.0 %
$Fe(CHD)(CO)_3$ [p]	100 %	0.1 %
Ferrocene	0 %	0.1 %
$MoOCl_4$	99 %	0.5 %
$MoOCl_4 + H_2O$ [m]	55 %	10 %
WF_6	92 %	273 %

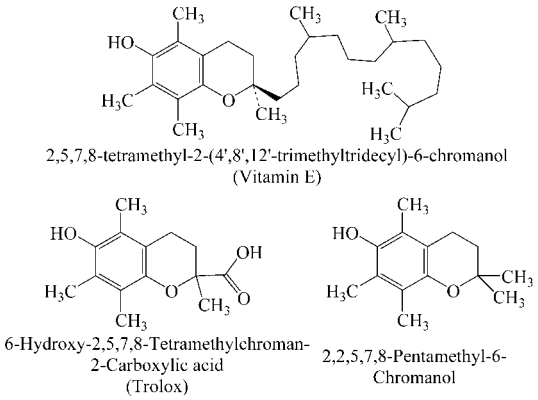


Figure 1. Structures of Vitamin E and derivatives.

[a] Methamphetamine synthetic yield as a percentage of the methamphetamine/ephedrine ratio. Unless otherwise indicated, the estimated error is ± 10 %. [b] As a mol % relative to the amount of lithium, i.e., amount of solvated electrons, used. [c] Average of ten observations. [d] A variable mixture of ammonium bicarbonate and ammonium carbamate. [e] Vitamin C. [f] Vitamin E. [g] BHT. [h] 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, a water soluble vitamin E derivative. [i] A vitamin E derivative. [j] The active ingredient in the anhydrous ammonia additive N-Serve. [k] HFC-152a. [l] HFC-134a. [m] 0.6 mol % water relative to lithium. [n] As the heptahydrate. [o] As the dihydrate. [p] Abbreviations: acac = acetylacetonate, F_3-acac = 1,1,1-trifluoroacetylacetonate, F_6-acac = 1,1,1,5,5,5-hexafluoroacetonate, CHD = cyclohexadiene.

3 Results and Discussion

Our investigations have been carried out predominantly by evaluating the yield of methamphetamine produced as a function of the nature of the additive. The results from these studies are summarized in Table 1.

3.1 Water

Water quenches the solvated electron by the reduction of ammonium,

$$H_2O + NH_3 \rightarrow OH^- + NH_4^+$$
$$NH_4^+ + e^- \rightarrow \tfrac{1}{2} H_2 + NH_3$$

to yield hydrogen gas and hydroxide. We investigated the addition of 4.2 mmol lithium and 0.61 mmol ephedrine to a 10 mL solution of liquid anhydrous ammonia containing 0.025 mmol of water. Under these conditions, the synthesis of methamphetamine was not inhibited within our margin of error. Only low concentrations of water were investigated in order to assess the contribution of waters of hydration and atmospheric contamination. The lack of significant methamphetamine synthesis inhibition at these concentrations is due to the use of excess lithium.

3.2 Organic Compounds

Of the non-metallic, non-halogenated compounds studied, α-tocopherol (Vitamin E, see Figure 1 for structure), was by far the

most active inhibitor that we have identified. The reaction was carried out using 0.61 mmol of Vitamin E in 10 mL anhydrous ammonia to which 4.2 mmol lithium and 0.61 mmol ephedrine was added. These results indicate that each Vitamin E molecule is capable of scavenging greater than 6.9 electrons. The limit of reactivity of this compound has not yet been evaluated.

Substitution of the long hydrocarbon chain of Vitamin E with a carboxyl group, i.e., Trolox, resulted in a complete loss of quenching efficiency. We have found that introduction of compounds containing carboxylic acids, i.e., citric acid, ascorbic acid, and Trolox, did not result in the inhibition of methamphetamine synthesis. The origin of this observation is unclear but it is likely that these acids are fully deprotonated in the basic ammonia solutions to give the conjugate base and the ammonium cation. The anionic nature of the conjugate base will likely result in a more negative reduction potential for the compound, reducing or eliminating the thermodynamic driving force for electron scavenging. We speculate that low concentrations of ammonium cations promote methamphetamine synthesis by assisting in the protonation of the methamphetamine precursor, Figure 2.

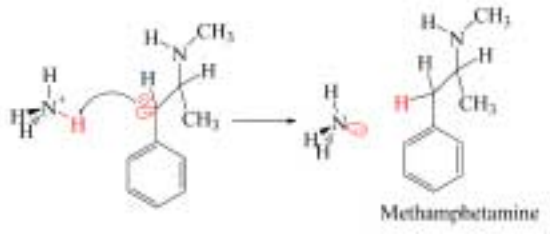


Figure 2. Proposed mechanism for the promotion of methamphetamine synthesis by low concentrations of the ammonium cation.

Replacement of the carboxylic acid group on Trolox with a methyl group, i.e., pentamethylchromanol, restored some of the inhibition activity observed with Vitamin E, but not all. At concentrations equivalent to those used in the Vitamin E investigation, the methamphetamine yield was reduced to 50 %. Remarkably, when the concentration of the pentamethylchromanol was reduced to 0.059 mmol, the methamphetamine yield remained at 50 %. The reason for this apparent independence of methamphetamine yield on the concentration of the pentamethylchromanol additive remains unclear.

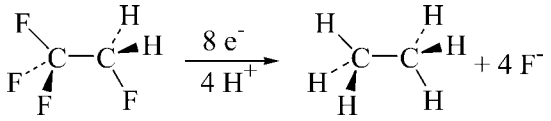
3.3 Halogenated Organic Compounds

The reduction of halogenated hydrocarbons using dissolving metal reductions is well established [12]. Taking advantage of this known reactivity, we have found many halogenated organic compounds to be very efficient methamphetamine synthesis inhibitors. A notable exception to this is a lack of reactivity observed for the compound 1,1-difluoroethane. Halogens serve as good leaving groups upon reduction. The reaction is probably driven partly by the solvation of the halide product in the polar ammonia solvent.

The hydrofluorocarbons (HFC's) 1,1-difluoroethane (HFC-152a) and 1,1,1,2-tetrafluoroethane (HFC-134a) are halogenated organic compounds that possess boiling points of –25 and –26 ^{o}C, respectively. Importantly, these boiling points are very close to that of ammonia, –33 ^{o}C. The close boiling points increase the likelihood that the halogenated organic compound will be carried over during a distillation of the ammonia [13], making it very difficult to remove the additive. Additionally, the halogenated compounds will remain below their boiling points in liquid ammonia, minimizing evaporative loss of the additive during storage. These two compounds, which pos-

sess ozone depletion potentials of zero, are being used as replacements for ozone depleting CFC-12 in refrigeration, aerosol and open-cell foam blowing applications.

Our reactivity studies indicated that HFC-134a is a remarkably efficient scavenger of solvated electrons in liquid ammonia. The capacity of a halocarbon is expected to be two electrons consumed for every halogen atom. HFC-134a possesses four fluorine atoms suggesting that it is capable of scavenging eight electrons to produce four fluorides and ethane, Scheme 4.



Scheme 4. Eight-electron reduction of 1,1,1,2-tetrafluoroethane (HFC-134a) to ethane.

Consistent with an eight-electron reduction, we have observed near zero methamphetamine yields, within our experimental error, at HFC-134a concentrations of 10 mol % relative to lithium, Figure 3.

Importantly, we have found that distillation of a mixture of HFC-134a in ammonia results in a distillate that effectively quenches the synthesis of methamphetamine. HFC-134a therefore effectively quenches the methamphetamine synthesis reaction and is difficult to remove from the ammonia.

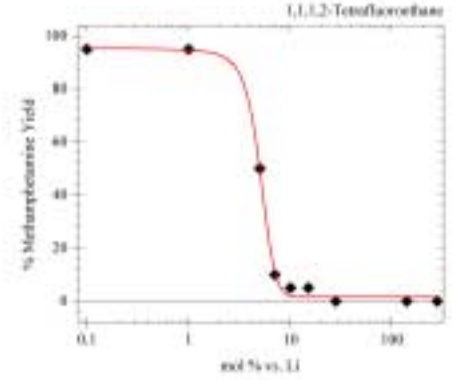


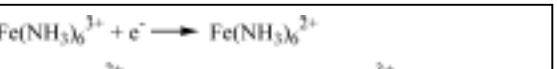
Figure 3. Methamphetamine yield dependence on the amount of 1,1,1,2-tetrafluoroethane dissolved in anhydrous ammonia.

Further investigations involving this compound are ongoing to better characterize this system.

In contrast to the HFC-134a system, HFC-152a was found to not be effective at inhibiting the methamphetamine synthesis, even at relatively high concentrations. While there are fewer fluorine atoms on HFC-152a, therefore reducing its capacity to scavenge solvated electrons, the apparent complete lack of reactivity was surprising. The lack of 1,1-difluorethane reactivity is currently under investigation in our laboratory.

3.4 Coordination Compounds

We have found Fe(III), as $FeCl_3$, to be a potent methamphetamine synthesis inhibitor. In a strongly coordinating solvent like ammonia, weakly coordinating ligands, like chloride, are expected to be displaced by ammonia to give the hexaamine complex, $Fe(NH_3)_6^{3+}$. The role of trace water is uncertain but its presence results in a significant increase in inhibition activity. Presumably, the presence of the water is resulting in a mixed ligand complex of the type $Fe(NH_3)_n(OH_2)_m$, where n is 4 or 5 and m is 1 or 2. The resulting mixed ligand complex appears to be more a efficient catalyst than the hexaamine.



Scheme 3. Presumed mechanism for the Fe(III) catalyzed conversion of solvated

In the presence of the solvated electron, the Fe(III) complex is expected to be reduced to Fe(II). Conceptually, two Fe(II) are capable of promoting the two electron reduction of the proton to give hydrogen gas, Scheme 3.

In reality, the mechanism is likely to be significantly more complex, involving stabilization of the intermediate oxidation and protonation states of the proton during reduction by direct coordination to the iron center [14]. Furthermore, it is not clear if only the Fe(III) and Fe(II) oxidation states are involved. The solvated electron is a strong reducing agent and Fe(I) is known to exist in aqueous solution [15]. Therefore, upon successful demonstration of the reactivity of Fe(III), we evaluated the reactivity of Fe(II). This compound was found to be an efficient inhibitor of methamphetamine synthesis. However, the reactivity trend in the presence of trace water was opposite that observed for Fe(III). The Fe(II) salt was significantly more efficient in the absence of water. Further investigation is required in order to sort out the details of the chemistry occurring with these compounds.

One of the principle problems encountered with the Fe(II) and Fe(III) coordination compounds we have studied has been their insolubility in anhydrous ammonia. Compounds that are insoluble in anhydrous ammonia are expected to be incompatible with the ammonia distribution infrastructure.

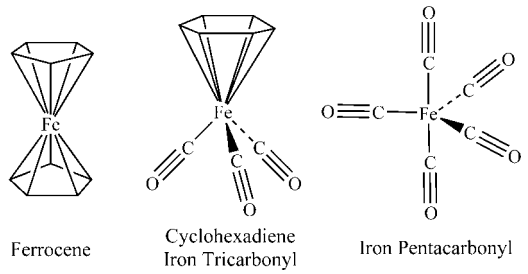


Figure 4. Structures of the organometallic compounds discussed in the text.

3.5 Organometallic Compounds

The organometallic compounds $Fe(CO)_5$ and $Fe(CHD)(CO)_3$ were found to be ineffective inhibitors at concentrations of 1.0 mol % and 0.1 mol % relative to lithium, respectively. However, ferrocene has proven to be a potent inhibitor, reducing the methamphetamine yield to near zero at concentrations as low as 0.1 mol % relative to lithium, Figure 5. This implies that each ferrocene molecule is scavenging 1,000 electrons. Ferrocene was found to be soluble in ammonia at the concentration needed for activity, i.e., 4×10^{-4} M. Solubility is important to minimize impact on the ammonia distribution infrastructure.

The efficiency of ferrocene as a catalyst for the inhibition of methamphetamine synthesis is remarkable. Ferrocene is in the lowest common oxidation state of this compound. Oxidation to the ferrocenium ion occurs at mild potentials, but this process is not likely to play a role in a reducing environment. To the best of our knowledge, reduction of ferrocene has not been reported in the literature.

Reduction of ferrocene probably results in a large structural reorganization, for example, partial or complete cyclopentadienyl dissociation. Such a process is likely to be critical to the catalytic function of the compound by opening up accessible coordination sites necessary for the stabilization of intermediates in the proton reduction mechanism.

4 Conclusions

At the present extent of our investigation, we have identified two potentially viable additives for anhydrous ammonia, each capable of inhibiting methamphetamine synthesis. The first, 1,1,1,2-tetrafluoroethane, cannot be removed by the simple distillation of the ammonia. Furthermore,

we have estimated and experimentally verified that each molecule of this compound is capable of scavenging ca. eight electrons. A high electron scavenging capacity is necessary to minimize the amount of additive necessary to inhibit the reduction reaction.

Ferrocene is another additive that is potentially useful as a methamphetamine synthesis inhibiting ammonia. This compound appears to be highly efficient at catalytically scavenging solvated electrons. It does not appear that the additive can be defeated by the addition of excess lithium metal. In order to defeat the catalyst, a cryogenic distillation is required. A cryogenic distillation of ammonia is difficult, dangerous, and requires additional equipment and supplies. The increased level of difficulty is expected to reduce the number of untrained chemists, i.e., the majority of the clandestine chemists, capable of carrying out the synthesis. The additional step will require additional time to carry out the synthesis. The additional equipment necessary to conduct the distillation will decrease the portability and the ease of concealment of the clandestine laboratory. Finally, the acquisition of the cryogenic supplies necessary to perform the distillation will increase the exposure of the clandestine chemist to surveillance.

In summary, the addition of either inhibitor is expected to both decrease the number of clandestine laboratories due to the increased level of difficulty and increase the probability of detection of the laboratory operation.

6 Acknowledgments

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