3-Pyridinecarboxaldehyde: A Model System for Superelectrophilic Activation and the Observation of a Diprotonated Electrophile

Douglas A. Klumpp* and Siufu Lau

Department of Chemistry, California State Polytechnic University, 3801 West Temple Avenue, Pomona, California 91768

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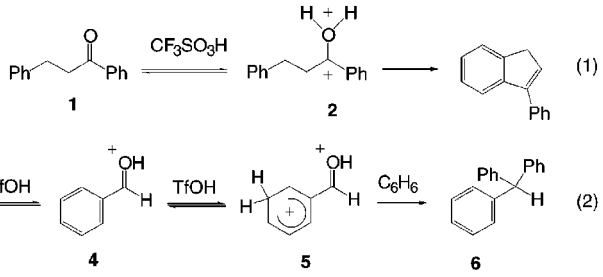
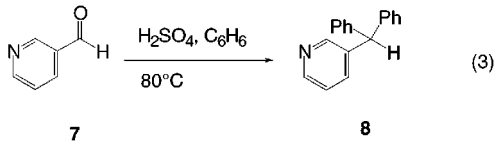
3-Pyridinecarboxaldehyde (**7**) has been studied as a model system for superelectrophilic activation. When compound **7** is compared with benzaldehyde (**3**) in acid-catalyzed condensation reactions with arenes, **7** is more reactive than **3**. Compound **7** reacts with chlorobenzene, *o*-dichlorobenzene, or nitrobenzene in CF_3SO_3H (triflic acid, TfOH) to give diaryl-3-pyridylmethanes, while **3** does not react with these deactivated arenes in TfOH. Moreover, **7** reacts with benzene in solutions as weakly acidic as $H_o = -9$, while **3** requires acidity in the range of $H_o = -11.5$ to -14 to reach a comparable level of electrophilic reactivity. Compound **7** was studied in acidic solution by ^{13}C NMR, and the diprotonated, dicationic species was observed at −60 °C in a solution of FSO_3H-SbF_5.

Introduction

The concept of superelectrophilic activation was first proposed by Olah, and since then, the study of superelectrophilic intermediates has been a very active area of research.[1] Superelectrophilic intermediates are typically generated when a cationic electrophile is protonated or coordinated by a Lewis acid to produce a dicationic species. For example, Shudo and Ohwada recently studied the cyclization of **1** in superacidic triflic acid (CF_3SO_3H, TfOH) and proposed the formation of superelectrophile **2**, which leads to the condensation product (eq 1).[2] In other recent studies, it was reported that benzaldehyde condenses with C_6H_6 in TfOH (eq 2).[3] This hydroxyalkylation reaction[4] was proposed to occur through diprotonated benzaldehyde, and theoretical analysis suggests that the second protonation occurs on the phenyl ring (**5**).[3a] Thus, the carboxonium ion (**4**) is protonated and the superelectrophilic intermediate (**5**) is sufficiently electrophilic to react with C_6H_6.



It was reported some time ago that 3-pyridinecarboxaldehyde (**7**) condenses with C_6H_6 in H_2SO_4 to give **8** (eq 3).[5] In contrast, benzaldehyde does not react with C_6H_6 in H_2SO_4 even though the carbonyl group is extensively protonated.[6] These results suggest that carboxonium ions can show enhanced electrophilic activity if an adjacent base-site is available for protonation. If compounds such as **7** can form dicationic electrophiles in strongly acidic media, then they may be suitable models for superelectrophilic intermediates. We have studied the electrophilic activation of **7**, and we report a comparison of **7** with benzaldehyde in hydroxyalkylation reactions, the direct observation of a dicationic species by low-temperature NMR, and the condensations of **7** with deactivated arenes in TfOH.



Results and Discussion

To compare the electrophilic reactivities of the two aldehydes, benzaldehyde (**3**) and **7** were reacted with C_6H_6 in solutions of TfOH and CF_3CO_2H (TFA) in ratios having varying acidity (Table 1).[1g,7] Aldehyde **3** is found to condense slowly with C_6H_6 in 100% TfOH ($H_o = -14$) and even more slowly in solutions of $H_o = -12.5$ and -11.5, whereas **7** condenses with C_6H_6 in solutions as weakly acidic as $H_o = -9$. These results are consistent with the formation of diprotonated intermediates preceding the electrophilic attack on C_6H_6. Benzaldehyde requires the more highly acidic media because the second

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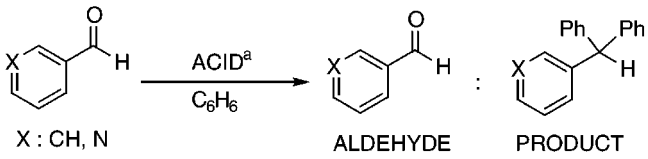
Table 1. Results from the Condensation Reaction of Benzene with Aldehydes in Solutions of Varying Acidity



aldehyde	acid, w/w TfOH/TFA	ratio[b] aldehyde/product
3, X:CH	100% TfOH ($H_o = -14.1$)	29:71
	78% ($H_o = -12.5$)	83:17
	43.5% ($H_o = -11.5$)	87:13
	22.1% ($H_o = -10.5$)	100:0
	5% ($H_o = -9$)	100:0
	100% TFA ($H_o = -2.7$)	100:0
7, X:N	100% TfOH ($H_o = -14.1$)	0:100
	78% ($H_o = -12.5$)	0:100
	43.5% ($H_o = -11.5$)	0:100
	22.1% ($H_o = -10.5$)	0:100
	5% ($H_o = -9$)	3:97
	100% TFA ($H_o = -2.7$)	100:0

[a] TfOH, CF_3SO_3H; TFA, CF_3CO_2H. [b] Product ratio determined by ^1H NMR integration.

Scheme 1

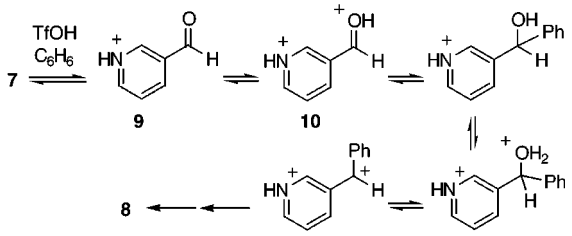


Table 2. ^{13}C NMR Data from 3-Pyridinecarboxaldehyde (7) in Acidic Solution

acid system (H_o)	^{13}C NMR data,[a] δ (ppm)
CF_3CO_2H (−2.7)	184.0 (c), 142.0, 140.2, 138.1, 129.2, 123.4
CF_3SO_3H (−14.1)	193.3 (c), 147.1, 144.9, 142.3, 131.3, 127.5
FSO_3H (−15.1)	201.0 (c), 149.7, 148.5, 146.1, 130.5, 129.5
SbF_5-FSO_3H (<−18)	208.6 (c), 155.8, 149.8, 144.6, 129.0, 125.2
	207.1 (c), 151.4, 150.5, 148.6, 129.0, 125.2

[a] Experiments with CF_3CO_2H or CF_3SO_3H were done at 25 °C; experiments with FSO_3H or SbF_5-FSO_3H were done at −70 °C with SO_2ClF diluent. (c) Indicates carbonyl signal.

protonation occurs at a weak base site, while **7** requires less acidic media because the ring nitrogen is first protonated (**9**) and then protonation of the carbonyl oxygen gives the reactive dication **10** (Scheme 1).

Compound **7** was also studied in acidic solutions by ^{13}C NMR spectroscopy (Table 2). With increasingly acidic media, the carbonyl resonance shifts progressively to an apparent maximum value in SbF_5-FSO_3H. These results indicate a growing positive charge on the carbonyl group as the acidity of the medium increases.[8] The ^{13}C NMR in SbF_5-FSO_3H shows peaks from two structures (Figure 1). On the basis of previous studies of the protonation of aldehydes,[3a,9] the ^{13}C NMR data suggest the formation of the isomeric dications **10a** and **10b**. The ^{13}C NMR spectrum shows three groups of peaks: carboxonium

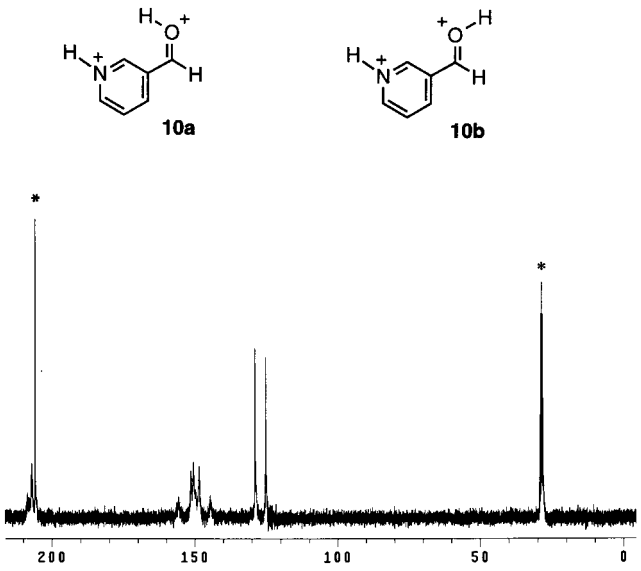
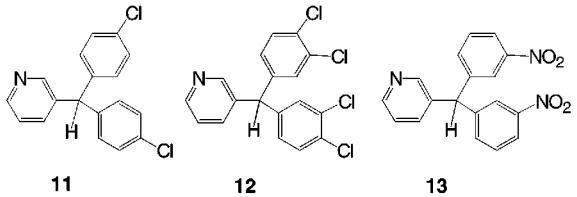


Figure 1. ^{13}C NMR spectrum of **10a**,**b** in $FSO_3H-SbF_5-SO_2ClF$ at −60 °C (asterisk denotes acetone-d_6 peaks).

carbons at 207 and 208 ppm; ring carbons C-2, C-4, and C-6 at 144 to 155 ppm; and ring carbons C-3 and C-5 at 125 and 129 ppm.[10] Ring carbons C-2, C-4, and C-6 show distinct absorptions for the isomeric structures **10a** and **10b**, whereas carbons C-3 and C-5 are magnetically equivalent for **10a** and **10b**. Benzaldehyde was studied under similar conditions, and the isomeric ions (**4**) were observed with carboxonium resonances appearing at 203 and 205 ppm.[3a] However, the diprotonated ion(s) from benzaldehyde could not be observed by NMR. Superelectrophilic dications (such as **5**) are difficult to observe directly because they are typically formed in very low concentrations.

To evaluate its reactivity as an electrophile, compound **7** was reacted with a series of deactivated aromatic compounds in TfOH.[11] Compound **7** reacts with chlorobenzene in TfOH to give product **11** in 62% isolated yield (along with other regioisomers), while under the same reaction conditions benzaldehyde does not react at all. Reaction of **7** and *o*-dichlorobenzene in TfOH gives **12** in 87% yield. Despite a significant deactivation of nitrobenzene toward Friedel−Crafts-type reactions, **7** reacts with nitrobenzene in TfOH to give a 10% yield of **13**. The remaining product balance is unreacted starting material. These data indicate that **7** generates very strong electrophilic intermediates in superacidic solution and that **7** is far more reactive than benzaldehyde as a protolytically generated electrophile.



We propose that **7** is more reactive than benzaldehyde because **7** more readily forms the dicationic intermediates. The dicationic intermediates are necessary for the electrophilic reactions with the deactivated arenes, particularly nitrobenzene. Dications **10a**,**b** are formed by protonation of a relatively strong base-site (the pyridyl

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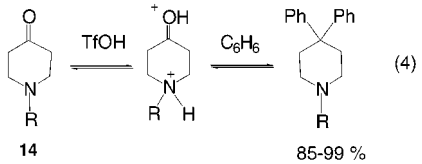
ring) and a weak base-site (the carbonyl). However, to form a dication from benzaldehyde, protonation must occur at the weakly basic carbonyl group and then subsequently at an even weaker base-site (either the phenyl ring or at the carboxonium ion). It suggests that adjacent base-sites may have an important influence on the reactivity of the carbonyl group.[12] This effect was shown recently in the superacid-induced condensations of piperidones (**14**) and arenes.[13] Piperidones condense with arenes in TfOH (eq 4), while under similar conditions, cyclohexanone does not react with benzene. Pro-



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tonation of a base-site adjacent to a carbonyl group may cause electrostatic and/or inductive effects,[14] and upon protonation of the carbonyl group, highly electrophilic intermediates are formed. In accord with Olah's concept of superelectrophilic activation, the chemistry of 3-pyridinecarboxaldehyde (**7**) further demonstrates the reactivities of dicationic electrophiles.[15]

Experimental Section

General Methods. 3-Pyridinecarboxaldehyde was purchased from Aldrich and used as received. Triflic acid was purchased from 3M Co., and trifluoroacetic acid was purchased from Aldrich; both acids were distilled under a dry, inert atmosphere prior to their use. Benzene, chlorobenzene, *o*-dichlorobenzene, and nitrobenzene were reagent-grade chemicals that were dried prior to their use. Column chromatography was done according to standard methods using Merck 5840-grade silica gel and reagent-grade solvents. Low-temperature NMR experiments were done according to published procedures.[16] Triple-distilled FSO_3H was used as received (Aldrich); SbF_5 was distilled prior to use. NMR experiments were done on a Varian 300 MHz instrument; HETCOR experiments were done on a Bruker 500 MHz instrument. High-resolution mass spectrum analyses were done by the Southern California Mass Spectrometry Laboratory, University of California, Riverside.

Procedure for Variable Acidity Reactions. Under an atmosphere of N_2, 0.050 mL of the aldehyde was combined with 1 mL of C_6H_6, and 4 mL (ca. 100 equiv) of the premixed acid solution was then added. The mixture was stirred for 20 h and then poured over ice. For benzaldehyde, the solution was extracted twice with 25 mL of $CHCl_3$; for **7**, the solution was first neutralized with NaOH, and then the solution was extracted with $CHCl_3$. The organic extracts were then washed with H_2O and brine and dried with $MgSO_4$. $CHCl_3$ was then removed by distillation, and the product(s) were analyzed by NMR.

Procedures for the Preparation Diaryl-3-pyridylmethanes. Method A. A 0.2 mL portion of 3-pyridinecarboxaldehyde (**7**) was dissolved in 1.0 mL of an aromatic compound (C_6H_6, C_6H_5Cl, or $C_6H_4Cl_2$), and 2 mL of TfOH was added. The reaction progress may be monitored by TLC (4:1 hexanes/ether). After 12 h, the mixture was poured over ice, the solution was neutralized with NaOH, and the products were extracted into $CHCl_3$. The organic extracts were then washed with H_2O and brine and dried with $MgSO_4$. Concentration in vacuo provided the crude products, which were then purified by recrystallization or column chromatography. **Method B.** For reaction with $C_6H_5NO_2$, method A was modified as follows: 0.2 mL of **7** was dissolved in 1.0 mL of $C_6H_5NO_2$, and 4 mL of TfOH was added. The solution was stirred at 130 °C for 48 h. The reaction was worked up as above, and the products were purified by column chromatography.

Bis(4-chlorophenyl)-3-pyridylmethane (11): ^{1}H NMR ($CDCl_3$) δ 5.52 (s, 1H), 7.03 (d, J = 8.4 Hz, 4H), 7.25−7.40 (m, 6H), 8.43 (s, 1H), 8.54 (d, J = 2.4 Hz, 1H), 8.51 (d, J = 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.0, 123.4, 128.8, 130.4, 132.9, 136.6, 140.6, 148.1, 150.5; HRMS $C_{18}H_{13}Cl_2N$ calcd 313.0425, found 313.0413.

Bis(3,4-dichlorophenyl)-3-pyridylmethane (12): ^{1}H NMR ($CDCl_3$) δ 5.42 (s, 1H), 6.87 (dd, J = 9.0, 2.1 Hz, 2H), 7.12 (d, J = 2.1 Hz, 2H), 7.22−7.34 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H), 8.36 (d, J = 2.4 Hz, 1H), 8.51 (dd, J = 4.8 Hz, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.6, 123.6, 128.4, 130.7, 130.9, 131.5, 133.0, 136.4, 137.0, 141.7, 148.6, 150.3; HRMS $C_{18}H_{11}Cl_4N$ calcd 380.9646, found 380.9632.

Bis(3-nitrophenyl)-3-pyridylmethane (13): ^{1}H NMR ($CDCl_3$) δ 5.74 (s, 1H), 7.22−7.28 (m, 4H), 7.35−7.53 (m, 3H), 7.92 (s, 2H), 8.10 (d, J = 8.1 Hz, 1H), 8.38 (s, 1H), 8.50 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.4, 122.5, 123.7, 123.8, 124.1, 130.0, 135.0, 136.4, 143.3, 148.6, 148.9, 150.3; HRMS $C_{18}H_{13}N_3O_4$ calcd 335.0906, found 335.0909.

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Supporting Information Available: ^{13}C, ^{1}H, and HETCOR NMR spectra of **7** in acidic solutions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Peak assignments were assigned based on the HETCOR NMR spectrum of **7** in TfOD and TfOH (see the Supporting Information).

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