An NMR and Raman Study of Trifluoroacetic Anhydride in Pyridine

Uffe Anthoni, Daniel Christensen, Carsten Christophersen[†] and Per Halfdan Nielsen

Chemical Institute, The H. C. Ørsted Institute University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

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Equimolar amounts of pyridine and trifluoroacetic acid anhydride (TFAA) form an equilibrium mixture containing similar amounts of TFAA, pyridine, and a 1:1 adduct. The formation of solid N-trifluoroacetylpyridinium trifluoroacetate on cooling to $-78\,^{\circ}C$ has been claimed previously. This product is now shown to be pyridinium trifluoroacetate formed by partial hydrolysis. The 1:1 TFAA–pyridine mixture is characterized by ^1H, ^{13}C, ^{19}F, and ^{14}N NMR spectroscopy and by Raman spectroscopy. The latter definitely excludes the N-trifluoroacetylpyridinium trifluoroacetate structure for the 1:1 complex. Instead, this is a σ-complex with a partial dipolar structure arising from attack of the pyridine nitrogen on the C = O group in TFAA. The enhanced reactivity of TFAA in pyridine is attributed to the presence of this complex. Furthermore, strong π–π interactions are present between TFAA and free pyridine.

Pyridine (1) is an efficient catalyst for acetylations with acetic acid anhydride (AAA), forming small amounts of the very reactive acetylpyridinium ion (3a) via the dipolar, tetrahedral intermediate (2a) (Fig. 1).[1–3] Other N-nucleophiles react in the same way with AAA with a change in the rate-determining step from breakdown to formation of the (more-or-less dipolar) intermediate as the nucleophile increases its basicity.[3] On cooling, acetylpyridinium ions are stabilized and, e.g., 80% is found at $-100\,^{\circ}C$ by NMR spectroscopy in mixtures of the strong base 4-dimethylaminopyridine with AAA.[4]

observation is in accordance with results showing[6] that introduction of the electronegative fluorine destabilizes acetylium ions. However, Moore and Goldstein[7] reported the preparation of 3b as a rather unstable white, very hygroscopic salt from TFAA and pyridine in anhydrous Et_2O at $-78\,^{\circ}$. Neither elemental analysis nor m.p. was reported and 3b was characterized only by showing ^1H NMR spectral data similar to those of pyridinium salts. In an attempt to stabilize 3b, stoichiometric amounts of pyridine and TFAA in CD_2Cl_2 were cooled to $-90\,^{\circ}C$.[8] However, ^1H and ^{13}C NMR spectra unam-
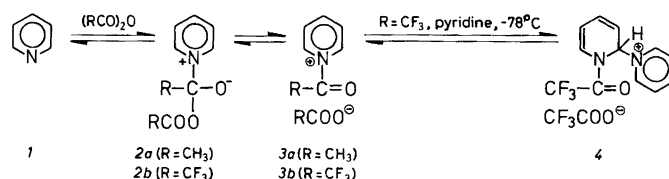

Fig. 1. Equilibria in mixtures of pyridine and acid anhydrides.

Although it is well known that trifluoroacetylation with trifluoroacetic acid anhydride (TFAA) is strongly catalyzed by pyridine, the nature of the reactive species is unknown. Forbus et al.[5] prepared trifluoroacetylpyridinium triflate in good yield, but were unable to observe any comparable formation of trifluoroacetylpyridinium trifluoroacetate (3b) at room temperature in $CDCl_3$ as determined by ^1H and ^{19}F NMR spectroscopy. This

biguously showed that 1,2-dihydropyridine 4 was formed. The generation of this type of salt was attributed to the large charge–dipole destabilization effect introduced upon formation of the pyridinium salt 3b. At present, therefore, considerable confusion exists as to whether 3b exists at room temperature, although the available evidence suggests that it may be formed transiently in the cold and decompose depending on the temperature and solvents.[9] Reaction sequences are still explained[10] by proposing that 'pyridine accentuates the electrophilicity of

[†] To whom correspondence should be addressed.

the anhydride through formation of *N*-trifluoroacetyl-pyridinium trifluoroacetate'. The present investigation was undertaken in order to establish firm experimental evidence for evaluating this statement.

On attempted preparation of the solid 1:1 pyridine–TFAA complex of Moore and Goldstein[7] using scrupulously dried reagents, no precipitate was formed in ether at −78°C. However, even minor amounts of moisture immediately gave rise to formation of pyridinium trifluoroacetate with properties resembling those reported by Moore and Goldstein for **3b**. We conclude that the alleged formation of **3b** under these conditions is, in fact, due to hydrolysis of the reaction mixture.

Table 1 summarizes the NMR results of a 1:1 pyridine–TFAA mixture and relevant reference compounds. The changes induced in the ^{19}F and ^{13}C chemical shifts of the TFAA moiety on being mixed with equimolar amounts of pyridine are too small and concentration-dependent to allow any deductions to be made. However, the corresponding changes in ^{1}H, ^{13}C, and ^{14}N chemical shifts of the pyridine ring are useful. The ^{1}H NMR signals are very broad and their position strongly dependent on dilution with $CDCl_3$ both for pyridine and the 1:1 pyridine–TFAA mixture, i.e., the changes in the spectra reflect, to a large extent, solvation shifts. The only results relevant for discussing complex formation between TFAA and pyridine are thus the ^{13}C and ^{14}N signals originating from the pyridine ring. Although not wholly consistent, the changes in chemical shifts observed in the sequence pyridine, pyridine–TFAA, pyridinium trifluoroacetate indicate that complex formation takes place in a 1:1 pyridine–TFAA mixture. The complex formation persists, albeit with diminished concentration, on dilution with $CDCl_3$ (molar proportion pyridine:TFAA:$CDCl_3$ equal to 1:1:3). However, owing to fast exchange, these results do not enable us to distinguish between formation of moderate amounts of **2b** or **3b** in the equilibrium.

A comparison of the Raman spectrum of the 1:1 pyridine–TFAA mixture with those of pure pyridine and TFAA was much more informative (Table 2). Heating the mixture from ca. −10°C to +35°C served to distinguish between perturbed bands due to unchanged pyridine or TFAA (increased intensity) and new bands originating

from the product (decreasing intensity). In the temperature interval investigated band positions were unchanged. The spectra of the corresponding 1:1 pyridine-d_5–TFAA mixture allowed a definitive assignment of all new bands by noting whether they were unchanged (TFAA) or displaced (pyridine) on deuteriation.

The results listed in Table 2 demonstrate that (i) all bands due to TFAA and pyridine are displaced somewhat in the mixture and (ii) the changes in the C=O stretching frequencies of TFAA are not identical in pyridine-d_0 and pyridine-d_5. This strongly indicates the presence of perturbed TFAA and pyridine molecules due to formation of weak π–π (and/or dipole–dipole) complexes. The mixture displays one further set of signals with strong frequency shifts (usually 30–50 cm^{-1}) compared with those of the components due to (1:1) σ-complex formation. The relative intensities of corresponding bands from perturbed pyridine (π) and pyridine–TFAA (σ) in the mixture (Table 2) may be used as a rough measure of the amounts present since the intensity of these bands is probably not strongly changed on complex formation. It may thus be estimated that ca. one half of the components are converted into the 1:1 compound in the mixture. Qualitatively the changes in band position were in accordance with expectations, e.g., the shifts of the CO stretching frequencies at 1877 and 1810 cm^{-1} to 1734 and 1694 cm^{-1} reflect the diminished double bond character in **2b**. However, comparison with other Raman data definitively rules out the occurrence of the salt **3b**.

The argument is the following. If *N*-trifluoroacetyl-pyridinium and trifluoroacetate ions are present (as in **3b**) the spectrum should reflect the presence of solvated ions, tight ion-pairs, or both. Since only one new band arises for each parent band, the latter possibility can be ruled out. The Raman characteristics for pyridine and pyridinium do not differ strongly, but TFAA and trifluoroacetates display a conspicuous difference in the CO stretching region which can be used diagnostically. In TFAA two bands are observed due to the symmetric and antisymmetric CO–O–CO stretching modes.[11] The former is strong and appears at highest frequency (1877 cm^{-1}) while the latter is weaker and situated at frequencies lower by ca. 70 cm^{-1}. In trifluoroacetates, the

Table 1. NMR spectra of a 1:1 pyridine–TFAA mixture and reference compounds.

		TFAA			Pyridine						
	Solvent	CF_3	CF_3	CO	2-H	3-H	4-H	2-C	3-C	4-C	14-N
TFAA	Benzene	113.5		149.6							
	$CDCl_3$	113.5	94.5	149.8							
Pyridine	None				8.03	6.52	6.89	150.0	123.8	135.8	0
	$CDCl_3$				8.62	7.29	7.69	149.8	123.6	135.8	−3.1
TFAA–pyridine	None	114.7		150.0	8.0br	7.2br	7.2br	143br	125br	143br	−9.0
	$CDCl_3$	113.3	94.6	148.6	8.23	6.93	7.34	147.9	123.2	135.9	−9.2
Pyridinium TFA	$CDCl_3$	116.3	96.1	161.9	8.90	7.90	8.36	142.5	126.4	143.8	−84

Table 2. Key bands in the Raman spectra of a 1:1 pyridine–TFAA mixture[a] at room temperature compared with pure pyridine and TFAA.

Assignment	Pyridine d_0	Pyridine d_5	TFAA	Pyridine–TFAA (1:1) d_0 π	Pyridine–TFAA (1:1) d_0 σ	Pyridine–TFAA (1:1) d_5 π	Pyridine–TFAA (1:1) d_5 σ
Pyr v_{CH}	3057(89)	2295(57)		3066(49)	3095(47)	2302(72)	2323(56)
TFAA $v_{C=O}$			1877(66)	1874(10)	1734(57)	1875(18)	1733(65)
TFAA $v_{C=O}$			1810(22)	1801(4)	1694(34)	1808(4)	1655(70)
Pyr v_{ring}	1580(11)	1537(6)		1584(13)	1630(13)	1544(13)	1582(18)
Pyr v_{ring}	1028(76)	1002(11)		1024(100)	1032(92)	1002sh	1014(32)
Pyr v_{ring}	988(100)	964(100)		993(57)	1024(100)	865(80)	982(100)
TFAA $v_{C=C}$			871(56)	872(13)	844(17)	877(44)	845(22)

[a] The frequencies arise from π- and σ-complex formation between pyridine and TFAA (see the text). The intensities are given in parentheses relative to the strongest band (100).

strong symmetric COO stretching mode is (allowing for solvation and covalent character) found[15–17] in the range 1350–1450 cm^{-1} while the much weaker antisymmetric mode occurs at 1680–1750 cm^{-1}. The similar shifts and intensities of the CO bands appearing on mixing pyridine and TFAA (1734 cm^{-1} and 1694 cm^{-1}) correspond closely to those expected for **2b**, i.e., coordinated TFAA with reduced C = O double-bond character. This reflects the inductive effect of fluorine diminishing the polarity of the coordinating C = O groups in TFAA. The structure **3b** can be excluded since no new strong band is observed in the region 1100–1600 cm^{-1} from trifluoroacetate.

In conclusion, therefore, we assign the structure **2b** to the complex formed on mixing pyridine and TFAA at room temperature. This structure is in accordance with the solubility in Et$_2$O even at − 78°C. Furthermore, in trifluoroacetylations involving TFAA with pyridine as solvent we propose **2b** to be the reactive intermediate. Unusual products arise in the reaction between TFAA and tryptophan derivatives in pyridine[18] which may be attributed to the presence of the tightly attached trifluoroacetate leaving group.

Experimental

General. The NMR spectra were recorded at ambient temperature on a Bruker AM 250 or UNITY 400 NMR spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained with SiMe$_4$ as the reference. Measurements of the ^{19}F resonances were made at 376.29 MHz with trifluoroacetic acid as the reference. The ^{14}N chemical shifts were determined at 18.08 MHz with pyridine as the reference. Commercial TFAA was purified by slow distillation from phosphorus pentaoxide and the fraction boiling sharply at 39.5°C was collected and stored under nitrogen. Commercial pyridine (pyridine-d_5) was dried over solid KOH pellets for one week, distilled, and the fraction boiling between 115 and 116°C was collected and stored under nitrogen. The 1:1 pyridine–TFAA mixtures were prepared by mixing equimolar amounts with strict exclusion

of humidity directly in the quartz tubes used for recording the Raman spectra.

Raman spectra. All NIR-FT Raman spectra were obtained on a Bruker IFS 66 FT spectrometer equipped with an FRA 106 Raman module applying NIR laser excitation (Nd/YAG, 1064 nm) and a Ge detector cooled with liquid nitrogen. The samples were kept in high quality quartz tubes using 180° scattering configuration. All samples were examined with a laser power of 300 mW and a spectral resolution of 4–6 cm^{-1}. For the spectra obtained at room temperature 200–500 scans (6–15 min) were recorded. Since a thermostat was not available, only 150 scans were used for the cooled samples in order to minimize errors due to changes in temperature. The spectra were recorded immediately after cooling, but, strictly speaking, these spectra are rather mean values of the interval from − 5°C to − 15°C. A similar reservation applies to the spectra of the heated samples, considered to be means of the interval + 40°C to + 30°C.

Attempted preparation of **3b**. Following the directions given by Moore and Goldstein[7] equimolar amounts of dry pyridine and TFAA were mixed in dry ether to give an almost clear solution. On cooling to − 78°C, a colourless precipitate was formed which was filtered off and dried. The yield was much less (< 10%) than that stated by Moore and Goldstein (49%), but had the same offensive properties (strong smell of pyridine and giving off acidic vapours). It melted sharply at 80–81°C, solidified on cooling, and melted again at 79–80°C, i.e., it was not unstable as previously claimed. The CHN analysis corresponded to pyridinium trifluoroacetate, and the infrared spectrum was identical with a commercial specimen of this salt (m.p. 83–86°C). By mixing pyridine and TFAA carefully dried as described above no precipitate occurred on cooling to − 78°C. We conclude that the eventual formation of this salt is due to small amounts of moisture in the components and that a solid 1:1 pyridine–TFAA complex cannot be prepared by this method.

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