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COVALENT AMINATION OF 1-ALKYL- AND 1-ARYL-3-CARBAMOYLPYRIDINIUM CHLORIDES AS "MODEL" FOR ENZYMIC ACTIVITY OF RABBIT LIVER ALDEHYDE OXIDASE[1]

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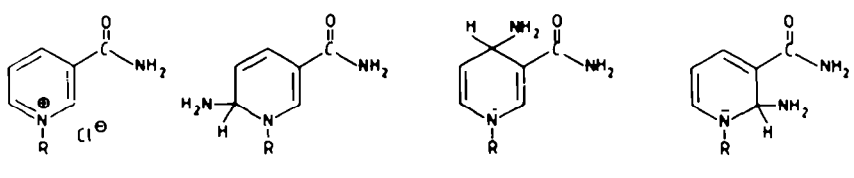
Abstract -The site of amination for 1-alkyl-3-carbamoylpyridinium chlorides in liquid ammonia is dependent on the identity of the 1-alkyl substituent. For the methyl, ethyl and n-propyl derivatives exclusively 6-adducts are found. Adduct formation takes place at C-6 and C-4, when the 1-substituent is an i-propyl or t-butyl group. The adduct ratio for the latter compounds is determined by the size of the substituent. 1-Aryl derivatives exhibit amination at C-2 and C-6 and the adduct ratios are dependent on the temperature. When the aryl substituent is a 2,4,6-trimethylphenyl group the 4-adduct is detected as well. A comparison is made between the sites of oxidation of these compounds by rabbit liver aldehyde oxidase and the covalent amination pattern in liquid ammonia. It is shown that covalent amination as a 'model" for the enzymic activity of aldehyde oxidase is particularly valuable in cases where the enzyme reaction is controlled by steric factors.

In previous papers the oxidation of 1-alkyl-(**1a–e**) and 1-aryl-3-carbamoyl-pyridinium chlorides (**1f–h**) by rabbit liver aldehyde oxidase into 1-alkyl(aryl)-dihydro-oxo-3-pyridinecarboxamides has been described.[2,3] It was found that the nature of the substituent on the ring nitrogen (N-1) has a significant influence on the site of oxidation by the enzyme. In cases where the substituent at position 1 is a methyl-, ethyl- or n-propyl group the site of oxidation is exclusively position 6. If the N-1 substituent is t-butyl, only position 4 is oxidized.[2] This result indicates that the site of oxidation shifts from position 6 to position 4 with increasing size of the alkyl substituent. The aryl compounds show a somewhat different behaviour. They are oxidized predominantly at position 6, however some oxidation occurred at position 4, especially in 3-carbamoyl-1-(p-methoxyphenyl) pyridinium chloride (**1g**). Exclusive oxidation at position 4 was found with 3-carbamoyl-1-(2,4,6-trimethylphenyl) pyridinium chloride (**1h**).

The mechanism for the oxidation by aldehyde oxidase[1] is assumed to involve an initial nucleophilic attack by a persulfide group[4] or another nucleophilic species[5] at the catalytic site of the enzyme, leading to an intermediary covalent σ-adduct. The position at which this adduct is formed determines the site where the oxo group is introduced in the substrate.

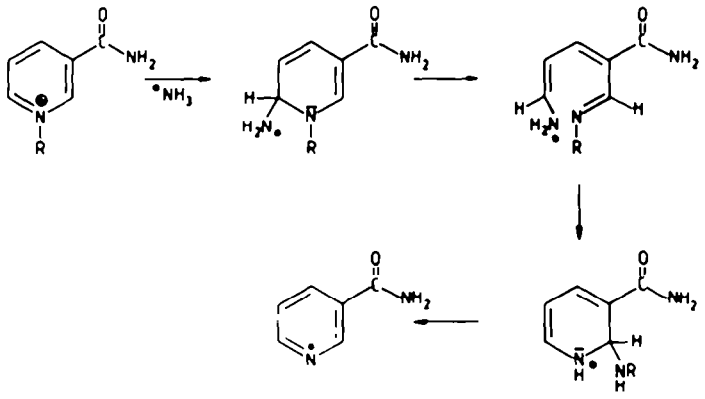
As a possible in-vitro model for covalent σ-adducts formed between compounds **1** and aldehyde oxidase, we considered the aminodihydro-3-pyridinecarboxamides, formed by reaction of **1** with liquid ammonia. In principle three σ-adducts i.e. the 6-amino-1,6-dihydro-(**2**), the 4-amino-1,4-dihydro (**3**) and the 2-amino-1,2-dihydro-3-pyridinecarboxamides (**4**) can be obtained. It has already been reported[6a,b] that 3-carbamoyl-1-methylpyridinium chloride (**1a**) gives exclusively **2a** in the temperature range -40 to $0°$. Replacement of the methyl substituent by a benzyl- or p-nitrobenzyl group does not change the addition pattern;[6b] with aliphatic amines exclusive addition at C-6 has also been observed for these compounds.[7,8] Addition of nucleophiles such as nitromethane,[9] nitromethide ion[10], sulfite,[9,11] methanethiolate,[12] ethanethiolate,[10], ethoxide,[13] cyanide[9,13–15] or hydroxide ions[9,12,13,16] to **1** usually takes a somewhat different course, resulting in the formation of σ-adducts in which the nucleophile is attached to C-4 and/or to C-2 and C-6. The striking similarity between the site



1 **2** **3** **4**

R = a CH_3, b C_2H_5, c n-C_3H_7, d i-C_3H_7, e t-C_4H_9

f C_6D_5, g 4-OCH_3-C_6H_4, h 2,4,6-triCH_3-C_6H_2



of nucleophilic addition in **1a** with liquid ammonia and amines and the position of oxidation of **1a** by aldehyde oxidase induced us to study the covalent amination of the pyridinium salts **1a–h** in liquid ammonia in more detail.

RESULTS AND DISCUSSION

Covalent amination of 1-*alkyl*-3-*carbamoylpyridinium chlorides* **1a–e**

The reaction of compounds **1a–c** with liquid ammonia gives rise to exclusive formation of the 6-amino-1,6-dihydro compounds **2a–c**, as evidenced by ^{1}H NMR spectroscopy (Table 1). All proton signals are shifted upfield compared to the corresponding signals of **1a–c** in D_2O. The shifts are most pronounced for the hydrogens attached to C-6 ($\Delta\delta$ 4.32–4.51 ppm), due to the newly formed tetrahedral centre at C 6. The correct signal assignment is based on the chemical shift values and the coupling patterns and confirmed by the data, obtained by measurement of the ^{1}H NMR spectrum of 3-carbamoyl-4-*deuterio*-1-ethylpyridinium chloride in liquid ammonia. These data are in agreement with values published.[6b] Variation over a wide temperature range (−70 to 0°) does not change the addition pattern. Prolonged exposure of for instance **1b** to liquid ammonia at room temperature leads to dealkylation, yielding 3-pyridinecarboxamide.[6a,b] It can be excluded that the dealkylation takes place by a nucleophilic attack of ammonia on the N-ethyl group: reaction of **1b** with ^{15}N-labelled ammonia (8.1% ^{15}N) resulted in a ^{15}N-excess in the 3-pyridinecarboxamide (about 8%). This proves that during the dealkylation a degenerate ring transformation has taken place which involves addition of the nucleophile as first step, followed by ring opening and closure (ANRORC-mechanism).[17]

The ^{1}H NMR spectra of compounds **1d, e** in liquid ammonia are rather complex (Figure 1). It is concluded that *two* aminodihydro compounds are obtained from **1d, e**, viz. the C-6 adducts **2d, e** and in addition the C-4 adducts **3d, e** (Table 1).

This is based on the chemical shifts of the C-6 adducts **2a–c**, the upfield shift values ($\Delta\delta$), the coupling constants and especially comparison with a more simple spectrum obtained from the reaction of 1-t-butyl-3-carbamoyl-4-deuteriopyridinium salt with liquid ammonia. The ratio of **2d/3d** is 9:1, the ratio of **2e/3e** 6:4. These ratios are independent of the temperature in the range from −70 to 0°. It is obvious from these results that the position of nucleophilic addition is not only dependent on the substitu-

Table 1. ^{1}H NMR data of the ring protons for 1-alkyl-6-amino-1,6-dihydro-3-pyridinecarboxamides **2** and 1-alkyl-4-amino-1,4-dihydro-3-pyridinecarboxamides **3** in liquid ammonia at −45°[a]

compound	H-2	Δδ[b]	H-4	Δδ[b]	H-5	Δδ[b]	H-6	Δδ[b]
2a	7.29	1.97	6.55	2.35	5.06	3.14	4.66	4.32
2b	7.33	2.05	6.49	2.44	5.04	3.22	4.72	4.39
2c	7.32	2.15	6.54	2.51	5.07	3.31	4.71	4.51
2d	7.40	1.99	6.49	2.44	5.02	3.24	4.73	4.45
3d	7.16	2.23	4.15	4.78	c	-	6.20	2.98
2e	7.64	1.82	6.66	2.29	5.26	3.07	5.01	4.35
3e	7.47	1.99	4.26	4.69	c	-	6.52	2.84

[a] Adduct **2**: $J_{2,4}$ = 1.5–1.8 Hz; $J_{2,6}$ = 1.1 Hz; $J_{4,5}$ = 9.1–9.8 Hz; $J_{5,6}$ = 4.8–5.4 Hz
adduct **3**: $J_{2,6}$ = 2.0 Hz; $J_{4,5}$ = 4.2 Hz; $J_{5,6}$ could not be determined due to overlap of signa

[b] Upfield shifts relative to the corresponding compounds **1** in D_2O

[c] Difficult to interpret due to overlap by the H-6 signal of the corresponding 6-adduct and to the low intensity for compound **3d**

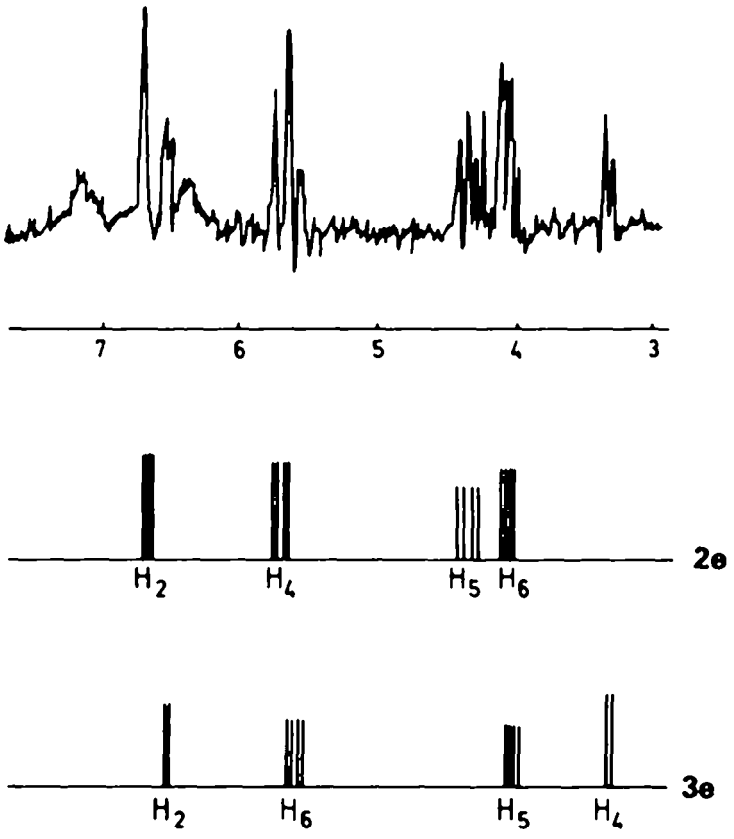


Fig. 1. ^{1}H NMR spectrum of 3-carbamoyl-1-t-butylpyridinium chloride **1e** in liquid ammonia showing the signals and their assignments due to 6-adduct **2e** and 4-adduct **3e**.

ent at position 3, as was stated before,[6a,b] but certainly on the nature of the substituent at position 1 as well. Moreover, it is evident that with an increasing size of the alkyl group at position 1, the addition at C-4 is promoted at the cost of addition at the adjacent C-6 position. Covalent amination in liquid ammonia is apparently rather susceptible to steric effects. This behaviour is also demonstrated by the addition pattern observed in the reaction of 3,5-dicarbethoxy-1-ethylpyridinium iodide (**5**) and its macrocyclic analogue **8** with liquid ammonia. In compound **8** position 4 is less accessible for addition of nucleophiles because of steric interference. The ^{1}H NMR spectrum of **5** in liquid ammonia at $-45°$ shows the presence of two σ adducts, viz. the C-6 (or C-2) adduct **6** and the C-4 adduct **7** (ratio 3:1). Adduct **6** is easily recognized by the appearance of three signals in the ratio 1:1:1, and adduct **7** by the presence of two signals with ratio 2:1 (Table 2). At temperatures lower than $-45°$, both adducts **6** and **7** are still present, but no accurate determination of the adduct ratio is possible due to limited solubility. At temperatures above $-45°$ the ^{1}H NMR spectrum changes: the signals attributed to **7** disappear, and

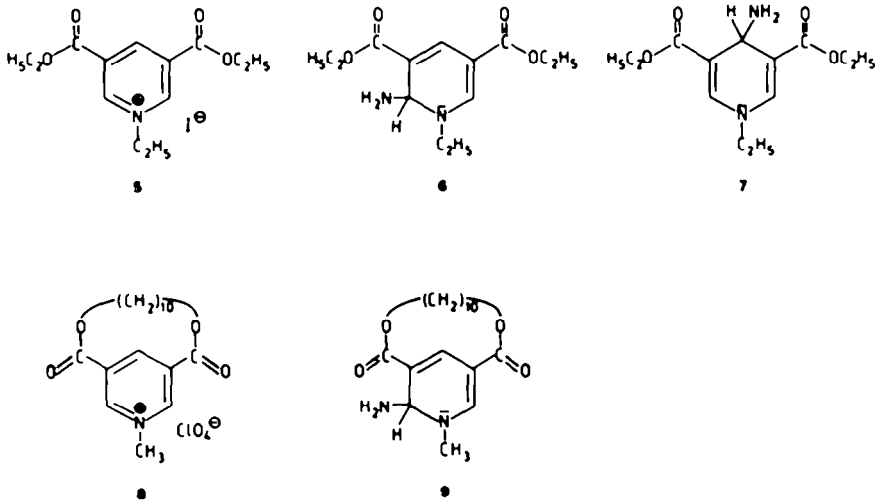


Table 2. Chemical shifts of the ring protons for compounds **5** and **8** and their σ-adducts in liquid ammonia at $-45°$[a]

compound	solvent	H-2	H-4	H-6
5	D_2O	9.73	9.47	9.73
6	NH_3	7.90	7.58	5.25
		1.83	1.89	4.48
7	NH_3	7.49	4.55	7.49
		2.24	4.92	2.24
8	DMSO-d_6	9.74	9.02	9.74
9	NH_3	7.81	7.60	5.14
		1.93	1.42	4.60

[a] Adducts 6 and 9: $J_{2,4}$ = 1.5 Hz; adduct 7: $J_{2,6}$ could not be determined

Table 3. Comparison between the site of amination with liquid ammonia at $-45°$ and the site of oxidation by aldehyde oxidase of compounds **1a–h**

compound	oxidation	amination
1a	C-6	C-6
1b	C-6	C-6
1c	C-6	C-6
1d	C-6/C-4	C-6, C-4
1e	C-4	C-6/C-4
1f	C-6/C-4	C-6/C-2
1g	C-6/C-4	C-6/C-2
1h	C-4	C-6/C-2/C-4

only the signals of adduct **6** remain. Apparently at low temperature a kinetically favoured process leading to **7** takes place; at higher temperature only the thermodynamically more stable adduct **6** is formed. Crown ester **8** in which position 4 is sterically hindered for nucleophilic addition gives exclusively the C-6 adduct in liquid ammonia at $-45°$ (Table 2). This result shows that position 4 in **8** is less accessible and that addition at C-6 is the most favoured process when no steric influence of the N-1 substituent is operative.

In Table 3 the qualitative data of the covalent amination patterns with **1a–e** are compared with the oxidation patterns found for these compounds in

Table 4. ^{1}H NMR data of the ring protons for 6-amino-1-aryl-1,6-dihydro-3-pyridinecarboxamides **2** and 2-amino-1-aryl-1,2-dihydro-3-pyridinecarboxamides **4** in liquid ammonia at $-45°$[a]

compound	H-2		H-4		H-5		H-6	
2f	7.65	1.94	6.71	2.48	5.52	3.00	5.19	4.19
4f	5.73	3.86	7.05	2.14	c		6.93	2.45
2g	7.55	1.97	6.70	2.46	5.45	3.03	5.14	4.19
4g	5.65	3.87	d		c		d	

[a] Adduct 2: $J_{2,4}$ = 1.5 Hz; $J_{4,5}$ = 9.0 Hz; $J_{5,6}$ = 5.5 Hz; $J_{4,6}$ = 1.8 Hz; $J_{2,6}$ ≤ 1.0 Hz
adduct 4: $J_{2,6}$ = 1.8 Hz; $J_{4,5}$ = 6.0 Hz; $J_{5,6}$ = 7.4 Hz; $J_{2,4}$ ≤ 1.0 Hz; $J_{4,6}$ ≤ 1.0 Hz

[b] Upfield shifts relative to the corresponding compounds 1 in D_2O

[c] Difficult to interpret due to overlap by the H-5 signal of the corresponding 6-adduct

[d] These signals lie under the phenyl multiplet

Table 5. ^{13}C NMR data of the ring carbons for compounds **1e–h** and their σ-adducts in liquid ammonia at $-55°$

compound	solvent	C-2	C-3	C-4	C-5	C-6
1e	D_2O	142.1	134.4	144.2	128.9	144.7
2e	NH_3	135.9	99.8	119.1	110.3	57.8
	"	6.2	34.6	25.1	18.6	86.9
3e	NH_3	131.3	103.4	40.9	106.4	122.5
	"	10.8	31.0	103.3	22.5	22.2
1f	D_2O	145.1	134.7	145.6	129.1	147.3
2f	NH_3	132.4	105.1	118.1	113.8	64.9
	"	12.7	29.6	27.5	15.3	82.4
4f	NH_3	60.5	118.3	123.7	97.7	129.8
	"	84.6	16.4	21.9	31.4	13.5
1g	D_2O	144.6	134.5	145.0	129.3	147.0
2g	NH_3	133.7	103.6	118.3	112.8	62.7
	"	10.9	30.9	26.7	16.5	84.3
4g	NH_3	60.9	116.2	123.9	96.3	130.2
	"	83.7	18.3	21.1	33.0	16.8
1h	D_2O	146.3	135.5	146.2	130.2	148.8
2h	NH_3	138.8	99.0	119.7	111.8	64.7
	"	7.5	36.5	26.5	18.4	84.1
3h	NH_3	135.7	105.0	40.4	105.9	125.8
	"	10.6	30.5	105.8	24.3	23.0
4h	NH_3	63.5	114.9	125.9	91.6	134.0
	"	82.8	20.6	20.3	38.6	14.8

reaction with aldehyde oxidase[2]. Evidently a good agreement exists between the position of addition by liquid ammonia and the nucleophilic species active in the aldehyde oxydase mediated reaction. Both reactions are susceptible to steric interference of the substituent at position 1, the enzymic oxidation to a greater extent than the amination reaction. This is understandable because the nucleophilic species in the enzymic reaction is fixed in the catalytic site of the enzyme molecule and therefore has a greater steric interaction with the N-1 substituent. In addition, the orientation of the substrate in the active site is of course sterically governed, leading to exclusive oxidation into a 4-oxo product in the case of the 1-t-butyl derivative **1e**.

Covalent amination of 1-aryl-3-carbamoylpyridinium chlorides (**1f–h**)

The chemical shifts and coupling constants derived from the ^1H NMR spectra of 1-aryl compounds **1f** and **1g** in liquid ammonia (Table 4) show that two σ adducts are obtained from both compounds, viz. the C-6 adducts **2f, g** and the C-2 adducts **4f, g**.

The adduct structures have been assigned based on our knowledge of the ^1H NMR data of C-6 adducts (**2a–e**), the upfield shifts, the magnitude of the coupling constants and especially the ^1H NMR spectra of the 4-deuterio derivatives of **1f** and **1g** in liquid ammonia. The main difference between the covalent amino adducts obtained from the 1-alkyl- and 1-aryl compounds is that the upfield shift values ($\Delta\delta$) of the hydrogens attached to the tetrahedral centres in the adducts are significantly smaller for the 1-aryl compounds.

Compound **1h** yields a more complicated ^1H NMR spectrum which arises from the presence of three σ-adducts; the C-6 adduct is formed in excess. Complete assignment of signals could not be made because of the complexity of the spectrum. Additional proof for the formation of the C-6, C-4 and C-2 adducts has been obtained from ^{13}C NMR spectroscopy (Table 5). Their chemical shifts are assigned by comparison with those of the 1-t-butyl derivative and by using the chemical shifts of related 1,4-dihydro compounds.[12]

Variation of the temperature from -70 to $-20°$ shows that the ratios C-2 adduct/C-6 adduct obtained from compounds **1f** and **1g** alter. In Table 6 this is illustrated for the σ-adducts obtained from **1f**. The amount of C-2 adduct decreases in favour of the C-6 adduct at higher temperature. It is interesting to note that the ratio of the three σ-adducts obtained from

Table 6. Isomer distribution of σ-adducts from 1-(pentadeuteriophenyl)-3-carbamoylpyridinium chloride **1f** at various temperatures

T (°C)	C-6 adduct 2f (%)	C-4 adduct 4f (%)
−70	60	40
−45	65	35
−20	80	20

1h remains unaffected by temperature variation over this range. At a temperature above 0° a fast reaction to 3-pyridinecarboxamide occurs with all three aryl compounds.

Comparing these results of covalent amination of **1f-h** with those obtained for oxidation by aldehyde oxidase,[3] it is evident that the similarity between these two reactions is very small (Table 3) and certainly less convincing as an "*in vitro*-model" than the corresponding reactions of the 1-alkyl derivatives (**1a–e**). This leads to the conclusion that in the 1-aryl compounds besides the steric influence of the aryl group, an electronic effect is operative which strongly influences the side of amination. The combined effect of steric and electronic effects makes comparison between σ-adduct formation and oxidation of limited value, since they probably operate in a different manner in both reactions.

EXPERIMENTAL

M.ps are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer equipped with a Varian EM-3940 variable temperature controller using DSS as an internal standard (δ = 0 ppm). Spectra in liquid ammonia were measured in sealed thickwalled NMR tubes. The proton chemical shifts in liquid ammonia were measured against the solvent signal (δ = 0.95 ppm). Isomer ratios were determined by integration of appropriate signals. ^{13}C NMR spectra were recorded on a Bruker CXP 300 spectrometer with acetone-d_6 (δ = 29.8 ppm) in liquid ammonia and dioxane (δ = 67.3 ppm) in D_2O as internal standards. Typical spectral parameters were: spectral width 15.000 Hz (1.85 Hz/point), acquisition time 0.27 s, pulse delay 1 s (C–H decoupled spectra) or 2s (C H coupled spectra) and pulse width 12 or 18 μs, respectively. Selective decoupling with **1e** and **1g** was carried out to check ^{13}C signal assignments. All NMR data were converted to the DSS scale by addition of the indicated values. The excess of ^{15}N in the compound investigated, was calculated from the (M + 1)/M ratio, as determined on an AEI MS-902 spectrometer equipped with a VG ZAB console. Column chromatography was carried out over Merck silica gel 60 (70–230 mesh ASTM).

Preparation of starting materials

1-Alkyl-3-carbamoylpyridinium chlorides (**1a–e**),[2] 3-carbamoyl-1-(p-methoxyphenyl) pyridinium chloride (**1g**)[3] and 3-carbamoyl-1-(2,4,6-trimethylphenyl) pyridinium chloride (**1h**)[3] were synthesized as described before. 4-Deuterated compounds of **1a**, **1b**, **1e** and **1g** were prepared according to the procedure of Caughey and Schellenberg.[18] NMR analysis indicated 85% deuteration of compound **1a**, 58% of compound **1g** (both after one oxidation-reduction cycle) and >95% of compounds **1b** and **1e** (three successive oxidation-reduction cycles). 3,14-Dioxa-18-methyl-18-azonia-bicyclo [14.3.1] eicosa-1(20),16,18-triene-2,15-dione perchlorate (**8**) was a gift from Prof. Dr. R. M. Kellogg. ^{15}N-labelled ammonia was prepared by reacting ^{15}N-labelled ammonium nitrate (from VEB Berlin-Chemie) with potassium hydroxide.

3-Carbamoyl-1-(pentadeuteriophenyl)pyridinium chloride (**1f**)

This compound was obtained from the reaction of 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride[19] with aniline-d_5 (>99% deuteration; from Merck), according to the method described before.[3] Yield 81% m.p. 253–254°. $C_{12}H_6D_5ClN_2O$: Calc C, 60.12; H(+D), 6.72; found C, 59.89; H (+D), 6.67.

3-Carbamoyl-4-deuterio-1-(pentadeuteriophenyl)pyridinium chloride

Two methods have been employed to prepare this compound:

(i) Direct introduction of deuterium in **1f**,[18] which gave a yield after one oxidation reduction cycle of 1%. ^{1}H NMR spectroscopy showed 70% deuteration.

(ii) An alternative procedure which involved first the introduction of deuterium[19] and secondly the introduction of the correct substituent on the ring nitrogen, using the ANRORC-mechanism.[17]

3-Carbamoyl-4-deuterio-1-methylpyridinium chloride (4.4 g, 25 mmol) was dissolved in 50 ml of liquid ammonia and reacted in sealed Carius tubes at room temperature. After 4 days the tubes were opened, the ammonia evaporated and the residue dissolved in absolute ethanol. This mixture was refluxed for 15 min and subsequently the solvent was distilled off. The residue was purified by column chromatography, eluting with ethyl acetate–methanol (9:1). The yield of demethylated product,[6a,b] 4-deuterio-3-pyridinecarboxamide (structure confirmed by ^{1}H NMR spectroscopy) was 58%. Reaction of this product to the desired compound was performed analogously to known synthetic procedures.[3,19] Starting with undeuterated **1a**, the overall yield of the complete method was 26%. The 4-deuterium content of the end-product was 73%, as established by ^{1}H NMR analysis.

3,5-Dicarbethoxy-1-ethylpyridinium iodide (**5**)

Diethyl-3,5-pyridinedicarboxylate[20] (0.5 g, 2.2 mmol) was refluxed for 12 h with an excess of ethyl iodide in 10 ml of acetophenone. After evaporation of the solvent and recrystallization of the residue from acetone–ether 0.76 g of **5** was obtained (yield 90%), m.p. 167–168°. $C_{13}H_{18}INO_4$: Calc C, 41.17; H, 4.78; found C, 41.22; H, 5.10.

^{15}N-labelling of 3-pyridinecarboxamide

3-Carbamoyl-1-ethylpyridinium chloride (43 mg, 0.23 mmol) was reacted with 3 ml of liquid ammonia (8.1% ^{15}N) according to the procedure described above. Yield 93%. The ^{15}N content of isolated 3-pyridinecarboxamide at N-1 was 8.0%.

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