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UNUSUAL MECHANISM OF THE METHANOLYSIS OF 1-CYANOFORMAMIDINES

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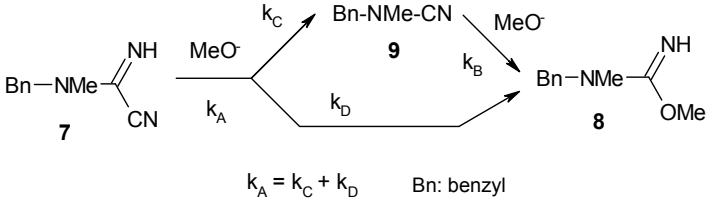
Base-catalyzed methanolysis of *N*-benzyl-*N*-methyl-1-cyanoformamidine (**7**) gives methyl *N*-benzyl-*N*-methylcarbamimidate (**8**) as final reaction product. Transient formation of *N*-benzyl-*N*-methylcyanamide (**9**) was observed also. Kinetic data showed two competitive routes in action: (i) **7** → **9** → **8** and (ii) directly **7** → **8**. The proposed reaction mechanism is based on the dual behaviour of **7**: (i) as an acid and (ii) as an electrophile.



INTRODUCTION

Amidines (**1**, Scheme 1) and especially formamidines (**1**, R=H) have been used extensively as pharmacological agents,[1a] pesticides,[1b] electrophiles,[1c] in asymmetric preparations,[1d] as well as protective groups for primary amino function, for example in nucleosides.[1e] In this last case, the deprotection is achieved usually by hydrolysis and this might explain why chemists have been so attracted by this reaction,[1e, 2-4] including theoretically.[5a-d]

Generally, the hydrolysis studies agree with the mechanism presented in Scheme 1. The transient tetrahedral intermediate, the hemiorthoamide **2**, can be cleaved in two different ways, depending on the single bond which is broken: $N^{(1)}$-C or C-$N^{(2)}$ (path *a* or *b*, respectively). Different amide+amine mixtures result through these pathways, but the prevailing route is that giving the more basic amine.[1e, 4d] Hydrolysis rate is subjected to general acid-base catalysis.[4b] Usually, the base-catalyzed reactions are more rapid than those in acid media.[4b, 5a]

It is known that the C=N group in amidines is hydrolyzed under milder conditions than the C≡N in nitriles or the C=O group in amides or esters.[6a] However, when additional organic functions like C=O or C≡N are present in **1**, close to the amidine moiety, the expected trend in reactivity is no more followed. Two examples of alcoholysis of carbonyl-containing formamidines are offered in Scheme 2: the carbonylic carbon atom and not the amidine central carbon is attacked in **3** (preferentially)[6b] and **4** (solely).[6c]

Another example is the hydrolysis of 1-cyanoformamidine **5** (Scheme 3).[7a-b] The carbamylformamidine **6** was the first reaction intermediate formed, regardless of the acidic (i) or basic (ii) reaction medium. This experimental reactivity order (C≡N > C=N) in **5** was just the opposite of that expected.

During our studies on the RuO_4-mediated oxidation of secondary aliphatic amines[8] we found various reaction products, but in particular conditions 1-cyanoformamidines prevailed. For instance, the oxidation of benzylmethylamine in the presence of NaCN gave *N*-benzyl-*N*-methyl-1-cyanoformamidine (**7**) as main compound, accompanied by some hydrolysis products. Preliminary experiments[8] on the hydrolysis of **7** seemed to indicate the implication of both C≡N and C=N groups, similarly to Schemes 1 and 3.

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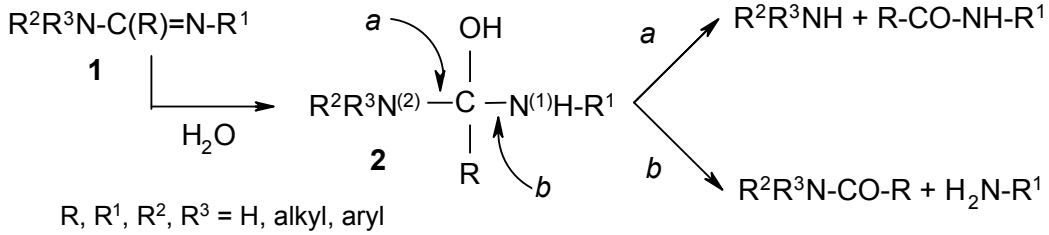
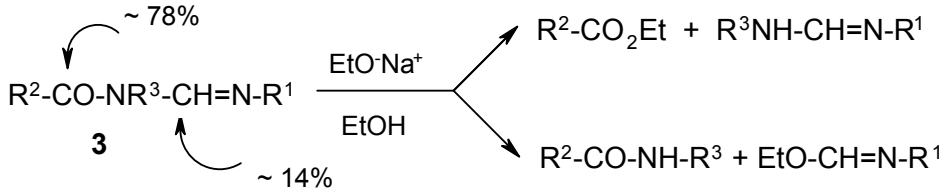
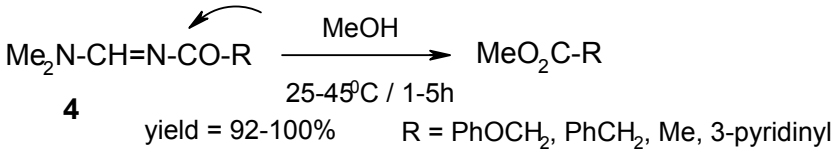
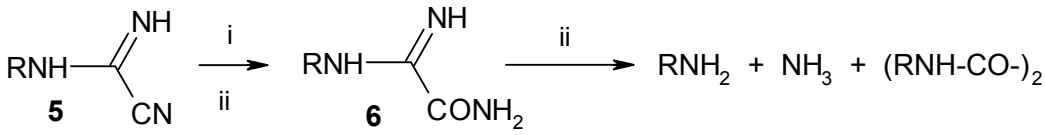


Scheme 1





Scheme 2



Scheme 3

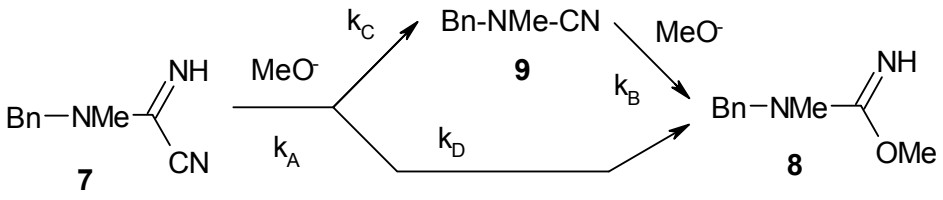
Contrarily to hydrolysis, the information about the amidine alcoholysis is very poor. Some examples with carbonyl-containing formamidines were already shown in Scheme 2, but analogous reactions with 1-cyanoformamidines are lacking. We present in this paper the unexpected results obtained for the methanolysis of **7**.

RESULTS

The final methanolysis product of **7** was methyl carbamimidate **8**, but small amounts of cyanamide **9** were observed transiently during the reaction (Scheme 4). At any time, the mass law of equation 1 was followed. Throughout this paper, the concentration of a particular compound (*e.g.* **7**) is indicated by its number or formula in right brackets (*i.e.*, [**7**]), eventually with a zero subscript if the initial concentration is intended.

$$[\mathbf{7}]_0 = [\mathbf{7}] + [\mathbf{8}] + [\mathbf{9}] \qquad \text{(eq. 1)}$$

A typical course of reaction is shown in Figure 1, where the variation of concentration of a particular compound (relative to $[\mathbf{7}]_0$) was depicted against time. Compound **9** is a true intermediate since it appears at the beginning and is transformed entirely in **8** towards the end of the reaction. In analogous reaction conditions, cyanamide **9** behaved as an ordinary nitrile[9] by giving the same **8**. As presented below, the rates are first order in MeONa and first order in the starting material (**7** or **9**). However, by choosing $[MeO^-]_0 >> [\mathbf{7}]_0$ (as in Fig. 1), all methanolyses can be treated as *pseudo*-first order reactions, because $[MeO^-] \approx [MeO^-]_0$ during the reaction. The second order rate constants were determined by varying the ratio $[MeO^-]_0$ / $[\mathbf{7}]_0$, within the *pseudo*-first order approximation.



$k_A = k_C + k_D$ Bn: benzyl

Scheme 4

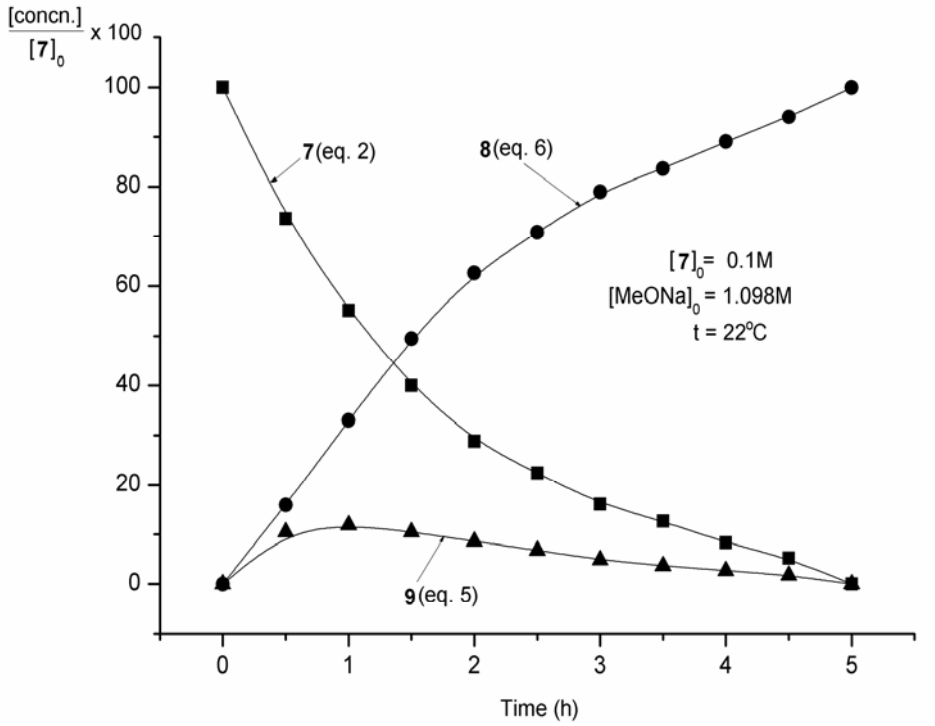


Fig. 1 – Methanolysis of formamidine **7**.

Variation of [**7**] with time is described by equation 2, where the rate constant k_A is explicitated below.

From separate experiments, we obtained the equation 3 for the transformation of **9** to **8**. The corresponding rate constant k_B is about 2.8 times greater than k_A.

Maintaining the *pseudo*-first order conditions for the consecutive "unimolecular" reactions **7** → **9** → **8** and knowing k_A and k_B, the variation of [**9**] with time should agree to equation 4.[10]

However, to our surprise, the calculated values of [**9**] were constantly greater than the experimental ones. In other words, it seemed that only some part of **7** followed the sequence **7** → **9** → **8**. The remaining part of **7** was transformed into **8** by another route, without passing through **9**. This is depicted in Scheme 4, where k_A in equation 2 is now the sum of two new rate constants k_C and k_D.

In this case, the equation 4 is replaced by equation 5, where k_C is unknown.

$$[\mathbf{7}] / [\mathbf{7}]_0 = \exp(-k_A t), \text{ where } k_A\ (22^oC) = 1.57 \times 10^{-4} \times [MeO^-]_0 \quad (s^{-1}) \qquad \text{(eq. 2)}$$

$$[\mathbf{9}] / [\mathbf{9}]_0 = \exp(-k_B t), \text{ where } k_B\ (22^oC) = 4.46 \times 10^{-4} \times [MeO^-]_0 \quad (s^{-1}) \qquad \text{(eq. 3)}$$

$$[\mathbf{9}] / [\mathbf{7}]_0 = \frac{k_A}{k_B - k_A} \times \{\exp(-k_A t) - \exp(-k_B t)\} \qquad \text{(eq. 4)}$$

$$[\mathbf{9}] / [\mathbf{7}]_0 = \frac{k_C}{k_B - k_A} \times \{\exp(-k_A t) - \exp(-k_B t)\}, \quad \text{(eq. 5)}$$

where $k_A = k_C + k_D$

k_C (22°C) = 0.61 k_A = 0.96 x 10^{-4} x $[MeO^-]_0$ (s^{-1})

k_D (22°C) = 0.39 k_A = 0.61 x 10^{-4} x $[MeO^-]_0$ (s^{-1})

A convenient value for k_C was found by employing in equation 5 values $k_C < k_A$ and comparing the calculated [**9**] with the experimental values. The best fit was obtained with $k_C = 0.61\ k_A$, as indicated above. It results that amidine **7** reacts with methoxide anion by two concurrent ways: (i) through the intermediacy of cyanamide **9** and (ii) directly to the final product **8**. The first route occurs about $k_C / k_D \approx 1.6$ times faster than the second.

The curve describing the variation of [**9**] with time (Fig. 1) has a maximum. It occurs when d[**9**]/dt = 0, which means at $t_{max} = (1/(k_B - k_A)) \times \ln(k_B/k_A) = 55$ min. The variation of [**8**] with time in Figure 1 was calculated with the equation 6 (derived from eq. 1), where $[\mathbf{7}]/[\mathbf{7}]_0$ and $[\mathbf{9}]/[\mathbf{7}]_0$ come from equations 2 and 5, respectively.

$$[\mathbf{8}] / [\mathbf{7}]_0 = 1 - [\mathbf{7}] / [\mathbf{7}]_0 - [\mathbf{9}] / [\mathbf{7}]_0 \quad \text{(eq. 6)}$$

Same kinetic results were obtained working in CD_3ONa/CD_3OD medium. The final product was now Bn-NMe-C(=ND)-OCD_3 (**8a**), whatever the starting material (**7** or **9**). When the genuine final reaction mixture was diluted with water in order to isolate **8a** (see Experimental), the obtained product was instead Bn-NMe-C(=NH)-OCD_3 (**8b**). This means that the hydrogen atom of the N-H group in **7** and **8** is interchangeable with deuterium in basic media.

DISCUSSION

Considering all aforementioned experimental information, we imagined a mechanism, shown in Scheme 5, aiming to explain the two routes. The steps 1-4 describe the first route (**7** → **9** → **8**) and the last two steps (5 and 6) are connected to the second route (**7** → **8**). Three new structures (**10-12**) are introduced in Scheme 5. They can be considered either as intermediates or as transition states, but the following kinetic treatment is the same.

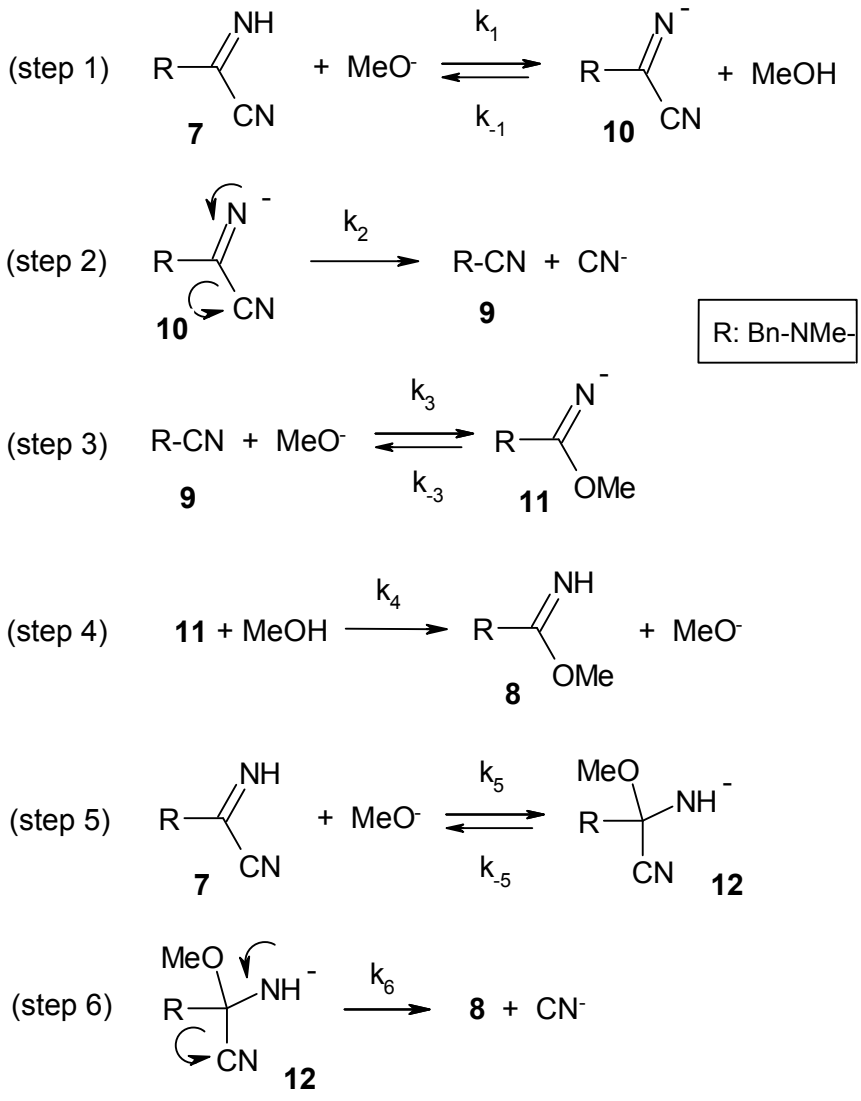
Structure **10**, generated in step 1, is the source of cyanamide **9** (step 2) through a convenient expulsion of cyanide anion, a good leaving group. The subsequent transformations **9** → (**11**) → **8** (steps 3 and 4) describe the generally accepted mechanism for the base-catalyzed alcoholysis of a nitrile.[9] Species like **10** or **11** are involved in the deuterium/hydrogen exchange reaction proved for **8a** → **8b**, as mentioned before.

The direct transformation of **7** into **8** (steps 5 and 6) implies the transient formation of **12**. Similarly to step 2, the driving force for the generation of **8** from **12** (step 6) is the electronically assisted elimination of CN^-. Steps 5 and 6 are similar to those of Scheme 1, but with one notable difference. Contrarily to **2**, the C-CN bond instead of $C\text{-}N^{(1)}/C\text{-}N^{(2)}$ is broken now in the tetrahedral intermediate **10**. Clearly, the cyanide anion is a better leaving group than an aminic moiety.

According to steps 1-6 of Scheme 5, the variation of [**7**] with time is described by the differential equation 7. Concentrations of the two intermediates **10** and **12**, present in equation 7, can be found by assuming the steady state approximation: their concentrations are small and d[**10**]/dt (eq. 8) and d[**12**]/dt (eq. 9) can be safely considered zero. In this case, [**10**] and [**12**] are given by the corresponding equations 10 and 11, respectively. With these values, the equation 7 becomes the equation 12, for which the analytical solution is identical to the experimental equation 2, if $k_1 = k_C$, $k_5 = k_D$, $k_A = k_C + k_D$, and $[MeO^-] = [MeO^-]_0$.

Scheme 5 suggests the differential equation 13 for the variation of [**9**] with time. Considering d[**11**]/dt = 0 (eq. 14), the resulted value of [**11**] (eq. 15) can be introduced into equation 13, together with the known value of [**10**] (eq. 10). The newly resulted differential equation 16 can be solved by the well known integrating factor method.[10, 11] Its integrated solution is identical to the experimental equation 5 if $k_1 = k_C$, $k_3 = k_B$, and $[MeO^-] = [MeO^-]_0$.

It results that the mechanism proposed in Scheme 5 leads to kinetic expressions for [**7**], [**8**], and [**9**] in accord with the experimentally observed equations. We must remember that all equations 2-5 are valid only in *pseudo*-first order conditions.



Scheme 5

$$d[\mathbf{7}]/dt = -k_1\,[MeO^-]\,[\mathbf{7}] + k_{-1}\,[MeOH]\,[\mathbf{10}] - k_5\,[MeO^-]\,[\mathbf{7}] + k_{-5}\,[\mathbf{12}] \quad \text{(eq. 7)}$$

$$d[\mathbf{10}]/dt = k_1\,[MeO^-]\,[\mathbf{7}] - k_{-1}\,[MeOH]\,[\mathbf{10}] - k_2\,[\mathbf{10}] = 0 \quad \text{(eq. 8)}$$

$$d[\mathbf{12}]/dt = k_5\,[MeO^-]\,[\mathbf{7}] - k_{-5}\,[\mathbf{12}] - k_6\,[\mathbf{12}] = 0 \quad \text{(eq. 9)}$$

$$[\mathbf{10}] = k_1\,[MeO^-]\,[\mathbf{7}] / (k_{-1}\,[MeOH] + k_2) \quad \text{(eq. 10)}$$

$$[\mathbf{12}] = k_5\,[MeO^-]\,[\mathbf{7}] / (k_{-5} + k_6) \quad \text{(eq. 11)}$$

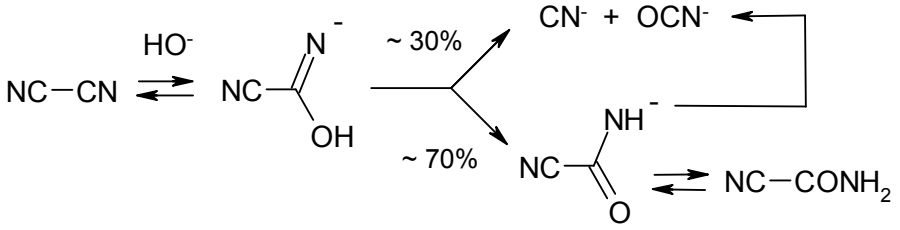
$$d[\mathbf{7}]/dt = -(k_1\,[MeO^-] + k_5\,[MeO^-])\,[\mathbf{7}], \quad \text{if } k_2 >> k_{-1}\,[MeOH] \text{ and } k_6 >> k_{-5} \quad \text{(eq. 12)}$$

$$d[\mathbf{9}]/dt = k_2\,[\mathbf{10}] - k_3\,[MeO^-]\,[\mathbf{9}] + k_{-3}\,[\mathbf{11}] \quad \text{(eq. 13)}$$

$$d[\mathbf{11}]/dt = k_3\,[MeO^-]\,[\mathbf{9}] - k_{-3}\,[\mathbf{11}] - k_4\,[MeOH]\,[\mathbf{11}] = 0 \quad \text{(eq. 14)}$$

$$[\mathbf{11}] = k_3\,[MeO^-]\,[\mathbf{9}] / (k_4\,[MeOH] + k_{-3}) \quad \text{(eq. 15)}$$

$$d[\mathbf{9}]/dt = k_1\,[MeO^-]\,[\mathbf{7}] - k_3\,[MeO^-]\,[\mathbf{9}], \quad \text{if } k_4\,[MeOH] >> k_{-3} \quad \text{(eq. 16)}$$



Scheme 6

The dual mechanism of Scheme 5 resembles in some way to the one proposed for the hydrolysis of cyanogen (Scheme 6).[12] However, in this last case, the two routes start from the same intermediate, the cyanogen having no N-H bond as in **7**.

The mechanism depicted in Scheme 5 is different from those anticipated in Schemes 1-3. In our opinion, the unexpected behaviour of 1-cyano-formamidine **7** towards the methoxide anion is due mainly to the presence of the cyano substituent, a good leaving group in basic conditions. At the same time, it is interesting to see **7** acting with MeO^-/MeOH either as an acid (step 1) or as an electrophile (step 5).

EXPERIMENTAL

General

Elemental analyses were performed with EAS32 Station Costech 2002. NMR spectra were acquired on a Varian ICON 300 apparatus, operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). The corresponding chemical shifts (δ scale) were referenced to internal TMS (δ_H = 0 ppm) or $CDCl_3$ (δ_C = 77.16 ppm). Interproton coupling constants *J* were given in Hz. Mass spectra were obtained with a GC 6890 Agilent Technologies gas chromatograph coupled with a MS 5975B mass spectrometer, using 70 eV as ionization energy. Preparation and characterization of **7** and **9** were reported by us previously.[8]

Methyl *N*-benzyl-*N*-methylcarbamimidate (**8**)

To a methanolic solution of sodium methoxide [prepared from metallic Na (83 mg, 3.6 at-mg) in anhydrous methanol (2.5 mL)] is added **9** (110 mg, 0.74 mmol) dissolved in methanol (1 mL) and the clear solution is magnetically stirred at room temperature for 6 hours. The solution is diluted with water (10 mL) and extracted with chloroform (3 × 5 mL). The combined organic extracts are dried on anhydrous Na_2SO_4 and the solvent is removed to leave **8** as a colorless oil (120 mg; yield 91%). Elemental analysis. Theoretical (%) for $C_{10}H_{14}N_2O$: C (67.39), H (7.92), N (15.72); found (%):C (67.71), H (8.20), N (15.58). Further purification by column chromatography or distillation failed.

^{1}H-NMR spectrum ($CDCl_3$, δ, ppm): 2.83 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 4.43 (s, 2H, Ph-CH_2), 7.19 (dd, *J* = 7.2 and 1.4, 2H, H_o), 7.25 (tt, *J* = 7.3 and 1.4, 1H, H_p), 7.33 (tt, *J* = 7.1 and 1.4, 2H, H_m).

^{13}C-NMR spectrum ($CDCl_3$, δ, ppm): 35.3 (NCH_3), 53.0 (Ph-CH_2), 53.7 (OCH_3), 127.0 (C_o), 127.1 (C_p), 128.5 (C_m), 138.1 (C_i), 161.45 (C=N).

MS spectrum (m/z, %): 178 (M^+, 46), 177 (25), 163 (57), 121 (11), 120 (100), 106 (25), 91 (53).

Trideuteromethyl *N*-benzyl-*N*-methylcarbamimidate (**8b**)

It was obtained from **7** or **9** during the kinetic experiments in CD_3ONa/CD_3OD, followed by dilution with water (see below). Its NMR features are identical to those of **8**, except the lack of OCD_3 signal.

MS spectrum (m/z, %): 181 (M^+, 39), 180 (20), 166 (17), 164 (10), 163 (25), 121 (14), 120 (100), 106 (25), 91 (58), 77 (10), 65 (19), 61 (13), 44 (15), 42 (23).

Kinetic measurements

Method A (Fig. 1). A methanolic solution of MeONa [obtained from metallic sodium (631.4 mg; 27.45 at-mg) and anhydrous methanol (15 mL)] was diluted with a solution of formamidine **7** (purity 99%; 437 mg, 2.5 mmol) and *p*-dimethoxybenzene (pDMB; 60 mg, 0.435 mmol; internal standard) in anhydrous methanol (about 5 mL). The whole mixture was diluted to a volume of 25 mL and then transferred into the reaction vessel immersed in a constant-temperature bath at 22°C. The initial concentrations were $[\mathbf{7}]_0$ = 0.1 M, $[MeO^-]_0$ = 1.098 M and [pDMB] = 0.0174 M. Aliquots of 1.5 mL were withdrawn with a syringe, poured into cold water (10 mL), and extracted with dichlorometane (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was dissolved in $CDCl_3$ and analyzed by NMR and GC-MS. The NMR integrals were measured against those of pDMB occuring at 6.81 ppm (4H) and 3.75 ppm (6H). Second-order rate constants were obtained by varying the ratio $[\mathbf{7}]_0$ / $[MeO^-]_0$.

Method B. Alternatively, the reaction was monitored in CD_3ONa/CD_3OD directly in the NMR tube, using correspondingly reduced masses and volumes. The new kinetic results were identical to those previously obtained. This means that cyanamide **9** was not an artefact of sample manipulation.

Analogous kinetic experiments were performed with cyanamide **9** and either CH_3ONa/CH_3OH (*A*) or CD_3ONa/CD_3OD system (*B*). In the last case, the final reaction product present in the NMR tube was Bn-NMe-C(=ND)-OCD_3 (**8a**). When treated as in method *A* (with water and CH_2Cl_2), the isolated compound corresponded to Bn-NMe-C(=NH)-OCD_3 (**8b**) (see above).

CONCLUSIONS

1-Cyanoformamidine **7** undergoes basic methanolysis to carbamimidate **8** by two routes: (i) through the intermediacy of cyanamide **9** and (ii) directly. All reactions show second order kinetics,

first order in both MeONa and starting material (**7** or **9**). The respective rate constants (at 22°C) are quite similar: 0.96 x 10^{-4} $M^{-1}s^{-1}$ (**7** → **9**), 0.61 x 10^{-4} $M^{-1}s^{-1}$ (**7** → **8**), 4.46 x 10^{-4} $M^{-1}s^{-1}$ (**9** → **8**). A reaction mechanism is proposed and discussed.

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