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1-Methylisocytosine as a ligand for (dien)M^{II} (M = Pt, Pd) and Pt-promoted deamination to 1-methyluracil

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Abstract

1-Methylisocytosine (1-MeIC) can be protonated at the endocyclic N(3) position (pK_a of 1-MeICH^+, 4.02 ± 0.04) or complexed at this position with (dien)M^{II} (M = Pt, Pd). X-ray crystal structures of the protonated species **1** as well as the Pd (**2**) and Pt (**3**) complexes are reported, and gas phase structures of the cation **2** and **3** have been calculated by *ab initio* methods. These results are compared with results from X-ray crystallography. At high pH, the Pt complex **3** undergoes deamination of the exocyclic N(2)H_2 group to the 1-methyluracilate complex. As compared to the situation with 1-methylcytosine (1-MeC), the accelerating effect of (dien)Pt^{II} is much less pronounced, however.

Keywords: Isocytosine; (dien)M^{II} complexes; X-ray crystallography; Deamination

1. Introduction

Isocytosine (2-aminopyrimidine-4-(3*H*)-one) (ICH) is structurally related to the canonical bases cytosine and guanine (Chart 1). Even though ICH is not involved directly as a carrier of the genetic code, it is biologically relevant and it has numerous medical applications [1]. Various 2-aminopyrimidine-4-ones have anticancer, antiviral or antibacterial properties [1b–f] or are valuable agrochemicals [1g].

Platinum complexes of isocytosine and its derivatives have attracted considerable attention because of their antitumor activity [2]. A few examples of spectroscopically [3] or crystallographically characterized metal complexes of isocytosine derivatives [3c–f] are known from literature. In the course of our studies on isocytosine [3e,3f], we have also synthesized the 1-methyl derivative of isocytosine, 1-MeIC. In the present work, we report the preparation and structural characterization of Pt(II) and Pd(II) complexes of 1-MeIC. We were also interested in finding out whether these cationic complexes undergo deamination to the corresponding complexes of 1-methyluracilate (1-MeU) under alkaline conditions or not. As has been previously reported by us [4], facile deamination of cytosine takes place in cationic Pt(II) complexes of 1-methylcytosine and 1,5-dimethylcytosine (1,5-DiMeC).

2. Experimental

2.1. Starting materials

[PtI(dien)]I [5], [PdBr(dien)]Br [6], and 1-methylcytosine (1-MeC) [7] were prepared according to the methods given in the literature. Isocytosine (ICH) was purchased from Sigma and D_2O was obtained from Deutero GmbH, Kastellaun (Germany).

2.2. Synthesis of 1-MeIC

The methylation of ICH was carried out in an analogous manner as 1-MeC [7]. Isocytosine (4.0 g, 0.04 mol), 70.0 ml of hexamethyldisilazane (HMDS) and 5.8 ml of

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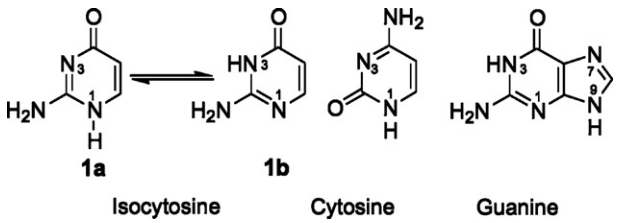

Chart 1. Structural relationship between isocytosine, cytosine and guanine.

trimethylchlorosilane (TMCS) were added to a 250 ml round-bottom flask. The mixture was stirred and refluxed at 140 °C until the solution became clear. The reaction mixture was cooled to 40 °C and 28 ml of methyliodide (CH_3I) was slowly added to the flask. The solution was again heated to reflux at 80 °C, with stirring, overnight. The reaction mixture was treated then with 230 ml of 6 N acetic acid at room temperature to hydrolyze the trimethylsilyl protecting group. The solution was evaporated to dryness under reduced pressure to yield a slightly yellow product. The crude product, a mixture of 1-MeIC and 3-MeIC, was washed with a large amount of water and redissolved in minimum amount of ethanol, and subsequently kept at 4 °C for a day. White crystalline product precipitated out of the solution which was purified by gel filtration over the sephadex G25 column. Yield 60%. The product (1-MeIC) was identified by elemental analysis and single-crystal X-ray diffraction analysis of fully protonated 1-MeIC. *Anal.* Calc. for $C_5H_7N_3$: C, 48.0; H, 5.6; N, 33.6. Found: C, 47.5; H, 5.7; N, 33.6%. ^{1}H NMR (200 MHz, δ ppm, D_2O, pD 4.0): 7.56 (d; $^3J = 7.6$ Hz; H6), 5.98 (d; H5), 3.53 (s; CH_3). Raman (solid state, $\tilde{\nu}$ cm^{-1}): 1451(1), 1408(1), 1289(8), 982(1), 972(1), 796(10), 615(2), 552(1).

2.3. Syntheses of the complexes

[1-MeICH]$_4$(NO_3)$_3$(ClO_4) (**1**) was obtained as follows: 20.2 mg (0.16 mmol) of 1-methylisocytosine was dissolved in 2 ml of H_2O and pH of the solution was adjusted to 4.5 (pK_a value of 1-methylisocytosine) with HNO_3, $HClO_4$ and NaOH. Colorless crystals appeared after a few days which were characterized by X-ray crystallography. *Anal.* Calc. for $C_{20}H_{32}N_{15}O_{17}Cl$: C, 30.4; H, 4.1; N, 26.6. Found: C, 30.0; H, 4.0; N, 27.0%. Raman (solid state, $\tilde{\nu}$ cm^{-1}): 1508(9), 1473(1), 1290(1), 1272(6), 1249(6), 1207(1), 1047(10), 798(5), 790(8), 772(7), 719(1), 623(1), 607(3), 555(3), 547(4).

[Pd(1-MeIC-*N*3)(dien)](ClO_4)$_2$ (**2**): To a suspension of [PdBr(dien)]Br (25.0 mg, 0.07 mol) in 1 ml of water, $AgClO_4$ (27.8 mg, 0.14 mol) was added. The reaction mixture was stirred at 40 °C in dark for 4 h and AgBr was filtered off. To the clear solution, 1-methylisocytosine (4.2 mg, 0.03 mmol) was added and the reaction mixture was stirred at 40 °C for 4 h. The solution was then rotary-evaporated to near dryness. The residue was redissolved in a minimum quantity of water. Pale yellow crystals appeared at 4 °C after one day which were removed from solution and later dried under vacuum. Yield 75%. A single-crystal was picked and characterized by X-ray crystallography. *Anal.* Calc. for $C_9H_{20}N_6O_9PdCl_2$: C, 20.3; H, 3.8; N, 15.7. Found: C, 20.0; H, 3.5; N, 15.5%. ^{1}H NMR (200 MHz, δ ppm, D_2O, pD 2.0): 7.49 (d; $^3J = 7.6$ Hz; H6), 5.90 (d; $^3J = 7.6$ Hz; H5), 3.52 (s, CH_3), 3.35 – 2.90 (m; dien). Raman (solid state, $\tilde{\nu}$ cm^{-1}): 1464(1), 1273(1), 935(10), 840(1), 791(3), 633(2), 576(4).

[Pt(1-MeIC-*N*3)(dien)](ClO_4)$_2$ (**3**): Addition of $AgClO_4$ (71.6 mg, 0.36 mmol) to a suspension of [PtI(dien)]I (100.4 mg, 0.180 mmol) in 5 ml of water resulted in the immediate precipitation of AgI. The mixture was stirred at 40 °C in dark for 4 h and AgI was filtered off. To the clear solution, 1-methylisocytosine (22.0 mg, 0.18 mmol) was added and the reaction mixture was stirred at 40 °C for two days. The solution was evaporated at room temperature to a volume of 2.0 ml. Colorless crystals suitable for X-ray crystallography were isolated in 65% yield at 4 °C after a few days. *Anal.* Calc. for $C_9H_{20}N_6O_9PtCl_2$: C, 17.4; H, 3.2; N, 13.5. Found: C, 17.0; H, 3.2; N, 13.1%. ^{1}H NMR (200 MHz, δ ppm, D_2O, pD 6.2): 7.73 (d; $^3J = 7.6$ Hz; H6), 5.77 (d; $^3J = 7.6$ Hz; H5), 3.59 (s, CH_3), 3.35 – 2.90 (m; dien). Raman (solid state, $\tilde{\nu}$ cm^{-1}): 1464(1), 1408(1), 1264(8), 933(10), 811(2), 790(3), 634(2), 546(4).

2.4. Instrumentation

^{1}H NMR Spectra were recorded on Varian FT NMR Mercury 200 (200.13 MHz), instrument at 23 °C. The spectra were measured with presaturation of the water resonance using sodium-3-(trimethylsilyl)propanesulfonate (TSP, $\delta = 0$ ppm) as internal reference. Acidity constants were determined using pD dependent ^{1}H NMR spectroscopic measurements in D_2O. The uncorrected pH* values were measured with a pH meter (Metrohm 6321; combination glass electrode) in D_2O solutions. pH* values were adjusted by addition of DNO_3 or NaOD solutions. pD values were obtained by adding 0.4 to the uncorrected pH meter reading. pK_a values were evaluated with a Levenberg–Marquardt nonlinear least-squares fit method [8]. The obtained acidity constants were then transformed to the values valid for H_2O according to the literature [9]. The deamination products of 1-MeIC and [Pt(1-MeIC-*N*3)(dien)](ClO_4)$_2$ (**3**) were identified by means of ^{1}H NMR spectroscopy by adding 1-methyluracil (1-MeUH) to the alkaline, aged solution of 1-MeIC (clean superposition of resonances of added nucleobase with resonances due to the deaminated product) and by comparison with the spectrum of [Pt(1-MeU-*N*3)(dien)]$^+$ (identical chemical shifts), respectively.

Raman spectra were recorded on a Coderg T800 with argon (514.5 nm) or krypton laser (647.1 nm) excitation.