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Oxidation of adenine and adenosine derivatives by dimethyldioxirane (DMDO) using halogenated metalloporphyrins as catalysts

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Abstract

In an effort to evaluate the reactivity of nucleobases with halogenated metalloporphyrins, adenine and adenosine derivatives were oxidized by dimethyldioxirane (DMDO) as oxygen atom donor using Mn[(Cl_{16})TDMPP]Cl and Mn[(Cl_8)TDCPP]Cl porphyrins as catalysts. The role of hydrogen bonding interactions in the selectivity of the reaction was investigated through the oxidation of adenine and adenosine derivatives bearing hydrogen bond donors on the sugar moiety or on the N-9 side chain. This procedure is a useful synthetic tool for the selective C-8 versus N-1 oxidation of purine derivatives.
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1. Introduction

It is well established that the oxidation of purine DNA bases by oxygen free radicals, which result from the action of ionizing radiations, light and ultrasound, is one of the major forms of oxidative base damage [1–4]. These modifications have important biological implications including a number of lesions that do not block DNA replication, change the structural relationship between adjacent base pairs, and are implicated in mutagenicity and aging [5–7]. There are two major products that result from the oxidation of purine nucleobases, oxopurines and purine-*N*-oxides. Oxopurines were detected in neoplastic liver of fish, as well as in urine samples of humans [8]. Uric acid (8-oxoxanthine) and their derivatives are used in obesity-treating pharmaceuticals, cosmetics, and antidandruff preparations [9]. Purine *N*-oxides show anticoccidial [10], antitumor [11], oncogenic [12,13] and mutagenic [14] properties. Oxopurines and purine-*N*-oxides are mainly prepared by oxidation of the parent purines [15–20]. Metalloporphyrins are able to selectively oxidize purine nucleobases when embedded in DNA [21–25]. Nevertheless, with the exception of the oxidation of adenosine-5′-monophosphate (AMP) by [Mn(Mepy)$_4$P](OAc)$_5$/$KHSO_5$ [26], and the photosensitized oxidation of guanine by meso-tetrakis (1-pyrenyl)porphyrinato gold(III) acetate [27], few data are available about the selectivity of metalloporphyrins in the synthesis of oxopurines and purine-*N*-oxides. Metalloporphyrins containing halogenated substituents at the β-pyrrole positions of the macrocycle are of current interest since they show to be stable and efficient catalysts for the oxidation of organic substrates [28–30]. During our studies on the oxidation of uracil derivatives and pyrimidine nucleosides [31–33], we found that the hydroxyl groups of the sugar moiety on 2′-deoxyribonucleosides are suitable H-bonding donors for halogenated metalloporphyrins [34]. The selectivity observed in the epoxidation of thymidine derivatives was correlated to the presence of methoxy groups in the 2′,6′-position of the phenyl rings as H-bonding acceptors, and to the saddle-shaped conformation of the metalloporphyrin ring. Moreover, in a previous communication we briefly reported that adenine and adenosine derivatives were oxidized by dimethyldioxirane (DMDO) as oxygen atom donor using Mn[(Cl_{16})TDMPP]Cl and Mn[(Cl_8)TDCPP]Cl porphyrins as catalysts [35].

Herein, we describe extensively these data showing that the selectivity of the oxidation, that is C-8 versus N-1 purine ring oxidation, can be switched on the basis of the structure of the catalyst, and on the position and the

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presence of H-bonding donors on the adenine and adenosine derivatives. Examples of affinity of metalloporphirins toward purine nucleobases by non-covalent interactions are currently available [36–39], however they have not been related to the selectivity of purine ring oxidation.

2. Experimental

All commercial products were of the highest grade available and were used as such. Hydrogen peroxide was a 35% aqueous solution (Aldrich). NMR spectra were recorder on a Bruker (200 MHz). Gas chromatography and gas chromatography-mass spectroscopy (GC-MS) of the reaction products were performed after derivatization with bis-trimethylsilyl trifluoroacetamide (BSTFA) using a SPB column (25 m × 0.30 mm and 0.25 mm film thickness) and isothermal temperature profile of 80 °C for the first 2 min, followed by a 10 °C/min temperature gradient to 200 °C for 10 min. The injector temperature was 200 °C. Chromatography grade helium was used as the carrier gas. Elemental analyses were performed on a Carlo Erba microanalyzer. When necessary, chromatographic purification were performed on columns packed with silica gel, 230–400 mesh, for flash technique. Mass spectra were recorded with an electron beam of 70 eV.

2.1. Starting materials

Porphyrins **A** and **B** free bases and their metallo derivatives (vide infra) were synthesized according to literature procedures [40,41]. 9-(*n*-Hexan-1′-yl) adenine **1**, 9-[4′-(acetoxy)-*n*-butan-1′-yl] adenine **2**, 9-[4′-(hydroxy)-*n*-butan-1′-yl] adenine **3**, 9-[4′-(hydroxy)-*n*-butan-1′-yl]purine **4**, 9-[3′-(hydroxy)-*n*-propan-1′-yl] adenine **5**, and 9-[5′-(hydroxy)-pentan-1′-yl) adenine **6**, were prepared in accord to the procedure described by Holy and co-workers [42,43]. 2′,3′,5′-N^6-tetra-*O*-acetyl adenosine **15** and 2′,3′-di-*O*-isopropylidene adenosine **16** were prepared using the procedure described by Fox et al. [44].

2.1.1. 9-(n-Hexan-1′-yl) adenine 1

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.09$ (s, 1H, NCHN), 7.70 (s, 1H, NCHN), 4.06 (t, $J = 7.3$ Hz, 2H, NCH_2CH_2), 1.69 (m, 2H, $NCH_2CH_2CH_2CH_2CH_2$), 1.34 (m, 6H, $NCH_2CH_2CH_2CH_2CH_2CH_3$), 0.7 (t, $J = 6.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 155.4$ (C), 152.3 (NCHN), 149.3 (C), 140.3 (NCHN), 118.8 (C), 43.8 (NCH_2CH_2), 30.9 ($NCH_2CH_2CH_2CH_2$), 29.7 (NCH_2CH_2), 25.9 ($NCH_2CH_2CH_2$), 22.1 (CH_2CH_3), 13.5 (CH_3). MS (70 eV); *m/z* 219. $C_{11}H_{17}N_5$: calcd. C 60.25, H 7.81, N 31.94; found C 60.25, H 7.81, N 31.90.

2.1.2. 9-[4′-(Acetoxy)-n-butan-1′-yl] adenine 2

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.1$ (s, 1H, NCHN), 7.73 (s, 1H, NCHN), 4.08 (t, $J =$ 7.1 Hz, 2H, $NCH_2CH_2CH_2CH_2O$), 3.89 (t, $J = 6.3$ Hz, 2H, NCH_2CH_2), 1.9 (s, 3H, CH_2COOCH_3), 1.83 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.52 (m, 2H, $NCH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 169.1$ ($OCOCH_3$), 155.3 (C), 152.0 (NCHN), 149.1 (C), 144.1 (NCHN), 118.3 (C), 63.0 (CH_2OCOCH_3), 43.1 (NCH_2CH_2), 26.0 ($NCH_2CH_2CH_2$), 25.0 ($NCH_2CH_2CH_2$), 20.1 ($OCOCH_3$). MS (70 eV); *m/z* 249. $C_{11}H_{15}N_5O_2$: calcd. C 53.0, H 6.07, N 28.10, O 11.46; found C 53.0, H 6.07, N 28.09.

2.1.3. 9-[4′-(Hydroxy)-n-butan-1′-yl] adenine 3

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.04$ (s, 1H, NCHN), 7.77 (s, 1H, NCHN), 4.05 (t, $J = 7.3$ Hz, 2H,CH_2CH_2OH), 3.42 (t, $J = 6.22$ Hz, 2H, NCH_2CH_2), 1.77 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.38 (m, 2H, $NCH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 155.5$ (C), 152.5 (NCHN), 149.0 (NCHN), 149.3 (C), 140.4 (C), 61.2 (CH_2OH), 43.8 (NCH_2CH_2), 29.5 ($NCH_2CH_2CH_2$), 26.7 (NCH_2CH_2). MS (70 eV); *m/z* 207. $C_9H_{13}N_5O$: calcd. C 52.16, H 6.32, N 33.79; found C 52.16, H 6.31, N 33.76.

2.1.4. 9-[4′-(Hydroxy)-n-butan-1′-yl] purine 4

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.88$ (s, 1H, NCHN), 8.40 (s, 1H, NCHN), 7.84 (s, 1H, NCHN), 4.39 (m, 2H, NCH_2CH_2), 3.92 (br. s, OH), 3.38 (m, 2H, NCH_2CH_2OH), 1.68–1.75 (m, 4H, CH_2CH_2). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 152.5$ (CH), 149.45 (C) , 148.6 (CH), 142.7 (CH), 134.0 (C), 61.4 (CH_2OH), 42.5 (NCH_2CH_2), 29.2 ($NCH_2CH_2CH_2$), 23.8 (NCH_2CH_2). MS (70 eV); *m/z* 192. $C_9H_{12}N_2O$: calcd. C 56.24, H 6.29, N 29.15; found C 56.23, H 6.29, N 29.10.

2.1.5. 9-[3′-(Hydroxy)-propan-1′-yl] adenine 5

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.07$ (s, 1H, NCHN), 7.7 (s, 1H, NCHN), 4.11 (t, $J = 6.8$ Hz, 2H, CH_2CH_2OH), 3.9 (t, $J = 5.7$ Hz, 2H, NCH_2CH_2), 2.03 (m, $J = 6.8$, 5.7 Hz, 2H, $NCH_2CH_2CH_2$) ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 155.0$ (C), 152.1 (NCHN), 149.5 (C), 144.0 (NCHN), 120.0 (C), 57.3 ($NCH_2CH_2CH_2$), 40.1 (NCH_2CH_2), 31.5 (NCH_2CH_2). MS (70 eV); *m/z* 193. $C_8H_{11}N_5O$: calcd. C 49.73, H 5.74, N 36.25; found C 49.72, H 5.74, N 36.28.

2.1.6. 9-[5′-(Hydroxy)-n-pentan-1′-yl] adenine 6

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 7.88$ (s, 1H, NCHN), 7.74 (s, 1H, NCHN), 4.0 (t, $J = 7.3$ Hz, 2H,CH_2CH_2OH), 3.43 (t, $J = 6.22$ Hz, 2H, NCH_2CH_2), 1.71 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.42 (m, 2H, $NCH_2CH_2CH_2$), 1.40 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 155.5$ (NCHN), 152.9 (C), 149.4 (C), 144.1 (NCHN), 123.8 (C), 60.2 (CH_2CH_2OH), 43.2 (NCH_2CH_2), 32.6 (CH_2CH_2), 29.4 (CH_2CH_2), 21.2 (CH_2CH_2). MS (70 eV); *m/z* 222. $C_{10}H_{17}N_5O$: calcd. C 53.79, H 7.67, N 31.37; found C 53.79, H 7.68, N 31.38.

*2.1.7. 2′,3′,5′-N^6-tetra-O-acetyl adenosine **15***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.59$ (s, 1H, NCHN), 8.30 (s, 1H, NCHN), 6.14 (m, 1H, $H_{1'}$), 5.85 (m, 1H, $H_{2'}$), 5.55 (m, 1H, $H_{3'}$), 4.30–4.41 (m, 3H, $H_{5',5''}+H_{4'}$), 2.60 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.05 (s, 3H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 170.8$ (CO), 170.0 (CO), 169.3 (CO), 169.1 (CO), 152.2 (NCHN), 150.8 (C), 149.3 (C), 141.6 (NCHN), 121.9 (C), 86.0 (CH), 79.9 (CH), 76.3 (CH), 70.3 (CH), 62.7 (CH_2), 25.3 (CH_3), 20.4 (CH_3), 20.1 (CH_3), 20.0 (CH_3). MS (70 eV); *m/z* 435.

*2.1.8. 2′,3′-Di-O-isopropylidene adenosine **16***

Colourless crystals, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.37$ (s, 1H, NCHN), 8.24 (s, 1H, NCHN), 6.21 (m, 1H, CH), 5.32 (m, 1H, CH), 5.11 (m, 1H, CH), 4.89 (m, 1H, CH), 3.53 (m, 2H, CH_2), 1.31 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 153.6$ (NCHN), 150.8 (C), 148.3 (C), 140.7 (NCHN), 115.3 (C), 102.5 (C), 92.8 (CH), 88.1 (CH), 85.3 (CH), 82.9.4 (CH), 62.5 (CH_2OH), 27.5 (CH_3), 25.5 (CH_3). mp 221–222° [[44], mp 221–222]. MS (70 eV); *m/z* 307.

2.2. Oxidation reactions—general procedure

In a typical experiment, dimethyldioxirane (DMDO, 1.2 eq./mol, 0.09N acetone solution) [45] was added to a solution of the adenine or adenosine derivatives **1–8** (1.0 mmol) in CH_2Cl_2 or CH_2Cl_2/CH_3COCH_3 mixture (1:0.1 v/v) (5.0 ml) in the presence of the manganese porphyrin **A** or **B** (1.0×10^{-2} mmol) at 25 °C. The progress of the reaction was monitored by thin-layer chromatography (SiO_2; CH_2Cl_2/CH_3OH 95:5). The solvent was evaporated under reduced pressure, and the products were purified by flash chromatography on silica gel.

*2.2.1. 9-(n-Hexan-1′-yl) adenine-1-oxide **7***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.51$ (s, 1H, NCHN), 7.86 (s, 1H, NCHN), 4.12 (t, J=7.3 Hz, 2H, NCH_2CH_2), 1.80 (m, 2H, $NCH_2CH_2CH_2CH_2CH_2$), 1.23 (m, 6H, $NCH_2CH_2CH_2CH_2CH_2CH_3$), 0.79 (t, $J = 6.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 152.9$ (C), 148.7 (NCHN), 144.7 (NCHN), 121.5 (C), 114.7 (C), 43.3 (NCH_2CH_2), 32.2 ($NCH_2CH_2CH_2CH_2$), 28.6 (NCH_2CH_2), 27.6 ($NCH_2CH_2CH_2$), 23.0 (CH_2CH_3), 14.2 (CH_3). MS (70 eV); *m/z* 235. $C_{11}H_{17}N_5O$: calcd. C 56.15, H 7.28, N 29.77; found C 56.20, H 7.28, N 29.77.

*2.2.2. 9-[4′-(Acetoxy)-n-butan-1′-yl] adenine-1-oxide **8***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.7$ (s, 1H, NCHN), 8.1 (s, 1H, NCHN), 4.35 (t, $J =$ 7.1 Hz, 2H, $NCH_2CH_2CH_2CH_2O$), 4.11 (t, $J = 6.3$ Hz, 2H, NCH_2CH_2), 2.1 (s, 3H, CH_2COOCH_3), 1.95 (quint, $J =$ 4.9, 7.2 Hz, 2H, $NCH_2CH_2CH_2CH_2$), 1.65 (m, $J = 6.5$, 4.6 Hz, 2H, $NCH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 169.2$ ($OCOCH_3$), 155.0 (C), 152.1 (NCHN), 149.2 (C), 144.0 (NCHN), 118.0 (C), 63.2 (CH_2OCOCH_3), 43.0 (NCH_2CH_2), 26.0 ($NCH_2CH_2CH_2$), 25.0 ($NCH_2CH_2CH_2$), 20.1 ($OCOCH_3$). MS (70 eV); *m/z* 265. $C_{13}H_{21}N_5O_3$: calcd. C 48.91, H 5.70; found C 48.81, H 5.70.

*2.2.3. 7,8-Dihydro-8-oxo-9-[4′-(hydroxy)-n-butan-1′-yl]adenine **9***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.08$ (s, 1H, NCHN), 4.10 (t, $J = 7.3$ Hz, 2H,CH_2CH_2OH), 3.41 (t, $J = 6.22$ Hz, 2H, NCH_2CH_2), 1.77 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.40 (m, 2H, $NCH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 156.4$ (NCHN), 151.3 (C), 150.4 (C), 149.2 (C), 146.8 (C), 115.9 (C), 61.9 (CH_2OH), 41.3 (NCH_2), 30.8 (CH_2CH_2), 25.2 ($NCH_2CH_2CH_2$). MS (70 eV); *m/z* 223. $C_9H_{13}N_5O_2$: calcd. C 48.42, H 5.87, N 31.37; found C 48.38, H 5.87, N 31.35.

*2.2.4. 9-[4′-(Hydroxy)-n-butan-1′-yl] adenine-1-oxide **10***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.04$ (s, 1H, NCHN), 7.77 (s, 1H, NCHN), 4.05 (t, $J = 7.3$ Hz, 2H,CH_2CH_2OH), 3.42 (t, $J = 6.22$ Hz, 2H, NCH_2CH_2), 1.77 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.38 (m, 2H, $NCH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 152.8$ (C), 148.7 (NCHN), 144.7 (NCHN), 122.9 (C), 114.7 (C), 61.9 (CH_2OH), 42.9 (NCH_2CH_2), 32.3 ($NCH_2CH_2CH_2$), 25.1 (NCH_2CH_2). MS (70 eV); *m/z* 223. $C_9H_{13}N_5O_2$: calcd. C 48.42, H 5.87, N 31.37; found C 48.40, H 5.87, N 31.33.

*2.2.5. 9-[4′-(Hydroxy)-n-butan-1′-yl] purine-1-oxide **11***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 12.34$ (br. S, NH), 8.67 (s, 1H, NCHN), 8.28 (s, 1H, NCHN), 4.17 (m, 2H, NCH_2CH_2), 3.62 (br. s, OH), 3.41 (m, 2H, NCH_2CH_2OH), 1.57–1.66 (m, 4H, CH_2CH_2). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 157.0$ (C), 152.5 (CH) , 141.8 (C), 135.3 (CH), 121.1 (C), 61.0 (CH_2OH), 41.2 (NCH_2CH_2), 29.4 ($NCH_2CH_2CH_2$), 27.8 (NCH_2CH_2). MS (70 eV); *m/z* 208. $C_9H_{12}N_2O$: calcd. C 51.92, H 5.81, N 26.91; found C 51.93, H 5.81, N 26.90.

*2.2.6. 9-[3′-(Hydroxy)-propan-1′-yl] adenine-1-oxide **12***

Mp 263–265 °C ($CHCl_3$–MeOH), ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.35$ (s, 1H, NCHN), 7.63 (s, 1H, NCHN), 4.10 (t, $J = 6.8$ Hz, 2H, CH_2CH_2OH), 3.90 (t, $J =$ 5.7 Hz, 2H, NCH_2CH_2), 2.0 (m, 2H, $NCH_2CH_2CH_2$).). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 149.8$ (C), 148.0 (C), 149.0 (C), 144.7 (CH), 134.1 (CH), 116.9 (C), 62.4 (CH_2OH), 38.28 (NCH_2), 29.29 (CH_2CH_2). MS (70 eV); *m/z* 209. $C_8H_{11}N_5O_2$: calcd. C 45.93, H 5.30, N 33.48; found C 45.93, H 5.30, N 33.47.

*2.2.7. 9-[5′-(Hydroxy)-n-pentan-1′-yl] adenine-1-oxide **13***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.01$ (s, 1H, NCHN), 7.61 (s, 1H, NCHN), 4.08 (t, $J = 7.3$ Hz, 2H,CH_2CH_2OH), 3.40 (t, $J = 6.22$ Hz, 2H, NCH_2CH_2), 1.70 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.40 (m,

2H, $NCH_2CH_2CH_2$), 1.37 1.40 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 156.5$ (NCHN), 150.95 (C), 150.4 (C), 149.8 (C), 119.0 (C), 60.2 (CH_2CH_2OH), 41.9 (NCH_2CH_2), 32.7 (CH_2CH_2), 28.38 (CH_2CH_2), 22.2 (CH_2CH_2). MS (70 eV); *m/z* 238. $C_{10}H_{16}N_5O_2$: calcd. C 50.41, H 6.77, N 29.39; found C 50.41, H 6.77, N 29.38.

2.2.8. *7,8-Dihydro-8-oxo-9-[5′(hydroxy)-pentan-1′-yl]adenine* ***14***

Mp 268–270 °C ($CHCl_3$–MeOH), ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.01$ (s, 1H, NCHN), 4.08 (t, $J = 7.3$ Hz, 2H,CH_2CH_2OH), 3.40 (t, $J = 6.22$ Hz, 2H, NCH_2CH_2), 1.70 (m, 2H, $NCH_2CH_2CH_2CH_2$), 1.40 (m, 2H, $NCH_2CH_2CH_2$), 1.37 1.40 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 156.5$ (NCHN), 150.95 (C), 150.4 (C), 149.8 (C), 119.0 (C), 60.2 (CH_2CH_2OH), 41.9 (NCH_2CH_2), 32.7 (CH_2CH_2), 28.38 (CH_2CH_2), 22.2 (CH_2CH_2).). MS (70 eV); *m/z* 238. $C_{10}H_{16}N_5O_2$: calcd. C 50.41, H 6.77, N 29.39; found C 50.41, H 6.77, N 29.35.

2.2.9. *2′,3′,5′-N^6-tetra-O-acetyl adenosine-1-oxide* ***17***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.6$ (s, 1H, NCHN), 8.05 (s, 1H, NCHN), 6.1 (d, $J = 5.3$ Hz, 1H, CH), 5.83 (t, $J = 6.1$, 5.3 Hz, 1H, CH), 5.56 (t, $J = 5.2$, 4.9 Hz, 1H, CH), 4.39 (m, 3H, $CHCH_2OH$, CH_2OH), 2.1 (s, 12H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 172.0$ (C=O), 170.0 (C=O), 167.0 (C=O), 164.0 (C=O), 148.0 (NCHN), 144.0 (C), 142.0 (NCHN), 120.0 (C), 115.0 (C), 86.0 (CH), 80.0 (CH), 73.0 (CH), 70.0 (CH), 62.0 (CH_2OH), 20.5 (CH_3), 19.8 (CH_3), 19.3 (CH_3), 18.95 (CH_3). MS (70 eV); *m/z* 451. $C_{18}H_{21}N_5O_9$: calcd. C 47.90, H 4.69, N 15.52; found C 47.90, H 4.69, N 15.54.

2.2.10. *7,8-Dihydro-8-oxo-2′,3′-di-O-isopropylidene adenosine* ***18***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 7.9$ (s, 1H, NCHN), 5.9 (d, $J = 4.1$ Hz, 1H, CH), 5.05 (t, $J = 6.5$, 4.5 Hz, 1H, CH), 5.01 (t, $J = 1.5$, 6.8 Hz, 1H, CH), 4.45 (d, $J = 1.6$ Hz, 1H, $CHCH_2OH$), 3.84 (m, 1H, CH_2OH), 1.59 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 155.0$ (NCHN), 150.2 (C), 149.3 (C), 147.0 (C=O), 118.0 (C), 102.5 (C), 83.1 (CH), 79.2 (CH), 76.1 (CH), 69.0 (CH), 63.0 (CH_2OH), 25.0 (CH_3), 24.8 (CH_3). MS (70 eV); *m/z* 323. $C_{13}H_{17}N_5O_5$: calcd. C 48.29, H 5.30, N 21.66; found C 48.29, H 5.31, N 21.65.

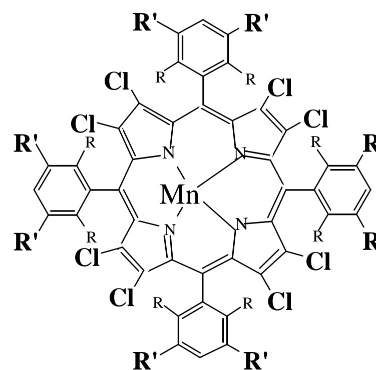
2.2.11. *2′, 3′-Di-O-isopropylidene adenosine-1-oxide* ***19***

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3 + CD_3OD$): $\delta = 8.36$ (s, 1H, NCHN), 8.25 (s, 1H, NCHN), 5.98 (d, $J = 4.1$ Hz, 1H, CH), 5.06 (t, $J = 6.5$, 4.5 Hz, 1H, CH), 4.81 (t, $J = 1.5$, 6.8 Hz, 1H, CH), 4.17 (d, $J = 1.6$ Hz, 1H, $CHCH_2OH$), 3.53 (m, 1H, CH_2OH), 1.39 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 153.0$ (C), 149.0 (NCHN), 146.0 (NCHN), 120.3 (C), 115.1 (C), 105.2 (C), 84.3 (CH), 84.1 (CH), 77.6 (CH), 73.4 (CH), 62.3 (CH_2OH), 25.0 (CH_3). MS (70 eV); *m/z* 323. $C_{13}H_{17}N_5O_5$: calcd. C 48.29, H 5.30, N 21.66; found C 48.29, H 5.30, N 21.65.

3. Results and discussion

The oxidation of 9-(*n*-hexan-1′-yl) adenine **1**, 9-[4′-(acetoxy)-*n*-butan-1′-yl] adenine **2**, 9-[4′-(hydroxy)-*n*-butan-1′-yl] adenine **3**, 9-[4′-(hydroxy)-*n*-butan-1′-yl]purine **4**, 9-[3′-(hydroxy)-*n*-propan-1′-yl] adenine **5** and 9-[5′-(hydroxy)-pentan-1′-yl) adenine **6** has been studied. The catalysts were Mn[(Cl_{16})TDMPP]Cl, (catalyst **A**), and Mn[(Cl_8)TDCPP]Cl (catalyst **B**) [40,41], where (Cl_{16})TDMPP is the dianion of 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetrakis-(3′,5′-dichloro-2′,6′-dimethoxyphenyl) porphyrin, and (Cl_8)TDCPP is the dianion of 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetrakis(2′,6′-dichlorophenyl) porphyrin. The structure of catalysts **A** and **B** are reported in Fig. 1.

The oxidations of title compounds were performed by adding dimethyldioxirane (DMDO, 1.2 eq./mol, 0.09N acetone solution) [45] to a solution of **1–6** (1.0 mmol) in CH_2Cl_2 or CH_2Cl_2/CH_3COCH_3 mixture (5.0 ml) in the presence of catalytic amounts of catalysts **A** and **B** (1.0×10^{-2} mmol) at 25 °C. The reaction of adenine derivatives with DMDO in the absence of metalloporphyrins was previously reported [16]. When manganese tetrakis-(2,6-dimethoxyphenyl) porphyryn chloride [Mn(TDMPP)Cl] was used as non-halogenated catalyst, a low conversion of **1** was observed, both due to catalyst low stability and activity. The corresponding purine N-1 oxide derivative, 9-(*n*-hexan-1′-yl) adenine-1-oxide **7**, was found in low amount (15%) as the only recovered product. The oxidation of **1** using either **A**/DMDO or **B**/DMDO catalytic systems gave **7** in high yield as the only recovered product (Table 1, entries 1–2, Scheme 1). In order to compare the efficiency of catalysts **A** and **B** their turnover numbers are reported in Table 1. The oxidation of **2** with catalysts **A** and **B** afforded 9-[4′-(acetoxy)-*n*-butan-1′-yl] adenine-1-oxide **8** in 91 and 93%



Mn[(Cl_{16})TDMPP]Cl(catalyst **A**): R=OCH_3,R '=Cl
Mn[(Cl_8)TDCPP]Cl (catalyst **B**): R=Cl,R '=H

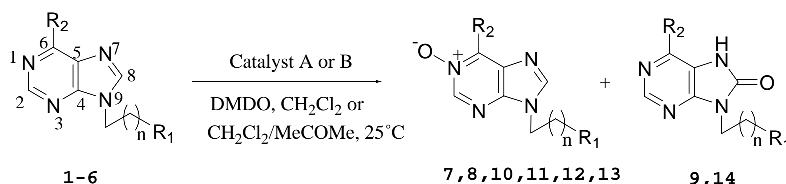
Fig. 1. Structure of catalysts **A** and **B**.

Table 1
Manganese tetraphenylporphyrin catalysed oxidations of adenosine and purine derivatives **1–8**[a]

Entry	Substrate	Catalyst[b]	Product(s)	Conversion (%)	Yield (%)[c]	Turnover number[d]
1	**1**	**A**	**7**	79	95	101000
2	**1**	**B**	**7**	81	97	94000
3	**2**	**A**	**8**	72	91	92000
4	**2**	**B**	**8**	75	93	87000
5	**3**	**A**	**9**	51	98	65000
6	**3**	**B**	**10**	65	93	76000
7	**4**	**A**	**11**	75	98	96000
8	**5**	**A**	**12**	77	92	98000
9	**5**	**B**	**12**	81	94	94000
10	**6**	**B**	**13**	87	95	101000
11	**6**	**A**	**14 (13)**	96	80 (15)	122000
12	**15**	**A**	**17**	83	93	106000
13	**15**	**B**	**17**	85	91	99000
14	**16**	**A**	**18 (19)**	73	70 (25)	93000
15	**16**	**A**[d]	**18**	76	91	97000
16	**16**	**B**	**19**	88	98	102000
17	**16**	**B**[d]	**19**	81	97	94000

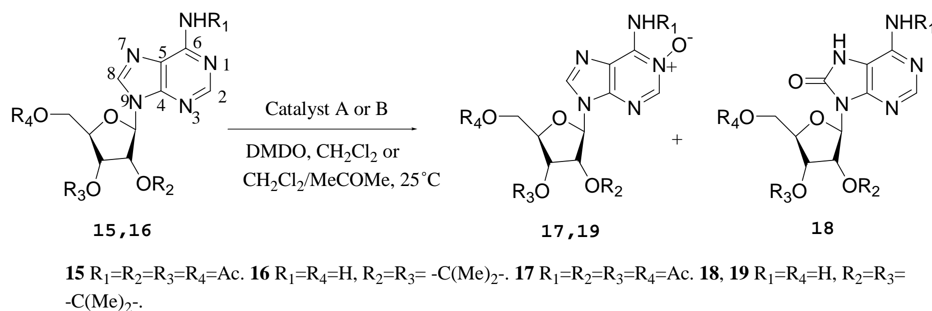
[a] Conditions: CH_2Cl_2/CH_3COCH_3 mixture, catalytic amount of catalysts **A** and **B** (1.0×10^{-2} mmol), 1.2 eq./mol of DMDO, 8.0 h at 25 °C.
[b] Catalyst **A**: Mn[(Cl_{16})TDMPP]Cl; catalyst **B**: Mn[(Cl_8)TDCPP]Cl.
[c] Here and elsewhere the yield was calculated considering the converted substrate. Only starting material was recovered as by-product in each case.
[d] Reaction performed in CH_2Cl_2. Turnover numbers were calculated as the moles of substrate converted per gram of catalyst.

yields, respectively (Table 1, entries 3–4, Scheme 1). These results are in contrast with the 8-oxo functionalization of adenine derivatives when treated with DMDO alone [16], showing a different reaction pathway in the presence of manganese porphyrins. The catalysts were recovered almost unchanged after the oxidations and bleaching experiments, performed with DMDO in the same solvent mixture, showed the high stability (90–95% of catalysts recovered) of halogenated manganese porphyrins. Noteworthy, the oxidation of **3** with catalyst **A** in CH_2Cl_2/CH_3COCH_3 mixture (5 ml, 1:0.1 v/v) afforded the corresponding 8-oxo derivative, 7,8-dihydro-8-oxo-9-[4′-(hydroxy)-*n*-butan-1′-yl]adenine **9**, in 98% yield, in addition to unreacted substrate (Table 1, entry 5, Scheme 1). Probably, the different chemo- and regioselectivity observed in the oxidation of **3** can be attributed to the presence of hydrogen bond interactions between the free OH group on the adenine N-9 side chain and polar substituents (as for example the methoxy moiety) on catalyst **A**. This hypothesis was first confirmed by the oxidation of **3** with catalyst **B** which does not carry acceptors of hydrogen bond. Under these experimental conditions 9-[4′-(hydroxy)-*n*-butan-1′-yl] adenine-1-oxide **10** was recovered in 93% yield (Table 1, entry 6, Scheme 1). With the aim to evaluate the generality of this transformation, we performed the oxidation of 9-[4′-(hydroxy)-*n*-butan-1′-yl]purine **4**. Since the OH hydrogen bond donor is on the purine N-9 side chain, compounds **3** and **4** are expected to react with catalyst **A** in a similar way. 7,8-Dihydro-8-oxo-9-[4′-(hydroxy)-*n*-butan-1′-yl]purine **11** was obtained in quantitative yield (Table 1, entry 7, Scheme 1). The presence of hydrogen bond between **3** and catalyst **A** was confirmed by ^{1}H NMR titration experiments, which showed a significant shift of the signal of OH protons in the presence of different amounts of porphyrin. As for example, a value of $\Delta\delta$ (ppm) = ca. 2.0 was observed for the OH proton under the conditions [**3**] = 1.0 mM and [Mn[(Cl_{16})TDMPP]Cl] = 1.1 mM. Moreover, in an attempt to determine whether the manganese porphyrins accept the adenines as apical ligands, titration experiments were performed with the full coordinated nickel derivative of catalyst **A**. Also in this latter case, a significant shift of the signal of OH protons was observed. A similar behaviour was not obtained with catalyst **B**. Even



1 n=4, R_1=Me, R_2=NH_2. **2** n=3, R_1=OAC, R_2=NH_2. **3** n=3, R_1=OH, R_2=NH_2. **4** n=3, R_1=OH, R_2=H.
5 n=2, R_1=OH, R_2=NH_2. **6** n=4, R_1=OH, R_2=NH_2. **7** n=4, R_1=Me, R_2=NH_2. **8** n=3, R_1=OAC, R_2=NH_2.
9, 10 n=3, R_1=OH, R_2=NH_2. **11** n=3, R_1=OH, R_2=H. **12** n=2, R_1=OH, R_2=NH_2. **13**, **14** n=4, R_1=OH, R_2=NH_2.

Scheme 1.



15 R_1=R_2=R_3=R_4=Ac. **16** R_1=R_4=H, R_2=R_3= -C(Me)$_2$-. **17** R_1=R_2=R_3=R_4=Ac. **18**, **19** R_1=R_4=H, R_2=R_3= -C(Me)$_2$-.

Scheme 2.

if we have not studied in detail the mechanism of the reaction, a "cytochrome P-450 like" route, which involves a high valent porphyrin manganese-oxo complex, might be proposed for the formation of 7,8-dihydro-8-oxo purine derivatives [46,47]. The length of the adenine N-9 side chain bearing free OH moiety was the most relevant variable for the selectivity of the oxidation. Thus, the oxidation of adenine derivative **5** with catalysts **A** and **B** gave 9-[3′-(hydroxy)-propan-1′-yl] adenine-1-oxide **12** in high yield (Table 1, entries 8–9, Scheme 1). On the other hand, 9-[5′-(hydroxy)-*n*-pentan-1′-yl] adenine-1-oxide **13** was obtained in the oxidation of **6** with catalyst **B**, while a mixture of **13** and 7,8-dihydro-8-oxo-9-[5′(hydroxy)-pentan-1′-yl]adenine **14** (molar ratio ca. 1:4) was recovered with catalyst **A** (Table 1, entries 10–11, Scheme 1). Thus, the N-9 acyclic side chain 4–5 carbon atoms in length and a free OH group are important structural features to obtain 7,8-dihydro-8-oxo derivatives.

Successively, 2′,3′,5′-N^6-tetra-*O*-acetyl adenosine **15**, and 2′,3′-di-*O*-isopropylidene adenosine **16**, were oxidized as selected models of purine nucleosides. Independently from the catalyst used, the oxidation of **15** in CH_2Cl_2/CH_3COCH_3 mixture (5.0 ml, 1:1 v/v) afforded the corresponding N-1 oxide derivative **17** in high yield (Table 1, entries 12–13, Scheme 2).

Adenosine N-1-oxide derivatives are usually prepared by oxidation with peracids under stoichiometric conditions. Monoperoxysulfate is also used for preparing them from adenosine-containing oligomers [48]. However, these methods are expensive and result in large amounts of acids and inorganic salts as waste. The oxidation of **16** with catalyst **A** in CH_2Cl_2/CH_3COCH_3 mixture (5 ml, 1:0.1 v/v), gave 7,8-dihydro-8-oxo-2′,3′-di-*O*-isopropylidene adenosine **18** in 70% yield, in addition to 2′,3′-di-*O*-isopropylidene adenosine-1-oxide 19 in 25% yield, and unreacted substrate (Table 1, entry 13, Scheme 2).

The polarity of the reaction medium was the most important factor for the selectivity of the oxidation, since the reaction performed in CH_2Cl_2 (5.0 ml) yielded **18** as the only recovered product (Table 1, entry 14, Scheme 2). Probably, the non polar environment provided by CH_2Cl_2 around the adenosine derivative makes the H-bond interaction (and other polar interactions) between the 5′-OH group on the ribose moiety and catalyst **A** more prominent. The same reaction performed with catalyst **B** using both CH_2Cl_2/CH_3COCH_3 mixture or CH_2Cl_2 gave the 2′,3′-di-*O*-isopropylidene adenosine-1-oxide **19** in high yield (Table 1, entries 15–16, Scheme 2).

4. Conclusion

Molecular recognition processes based on hydrogen bond interactions (or other polar interactions) are probably responsible for the selectivity of the oxidation of adenine and adenosine derivatives by DMDO using catalysts **A** and **B**. As shown in Table 1, the two catalysts showed comparable oxidation efficiencies. Independently on the experimental conditions, the oxidations performed with Mn[(Cl_8)TDCPP]Cl (catalyst **B**), lacking any acceptor of hydrogen bond, gave adenine-1-oxide derivatives in high yields as the only recovered products. A different selectivity was observed with Mn[(Cl_{16})TDMPP]Cl (catalyst **A**) bearing polar methoxy substituents on the porphyrin ring. In this latter case, biologically important 7,8-dihydro-8-oxo adenine and adenosine derivatives can be selectively synthesized. The role of the OH group on the purine N^9-side chain on the selectivity of the oxidation was elucidated by selectively blocking them. Noteworthy, an adenine N-9 side chain 4–5 carbon atoms in length and a free OH group were the most important variables to obtain 8-oxo derivatives. The present study is expected to offer novel applications both for metalloporphyrin/purine nucleosides recognition processes and for the selective oxidation of biologically active purine derivatives.

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