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Dimethyldioxirane-Mn(Cl16)TDMPPCl Porphyrin as Efficient and Chemoselective Epoxidizing Reagent of Uracil Derivatives.

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Abstract: Dimethyldioxirane (DMDO) was employed as oxygen donor in metalloporphyrins catalyzed selective epoxidation of uracil derivatives.

Uracil epoxides are important intermediates in DNA oxidative transformations because they are formed as initial photooxidation products[1] and they may be responsible for the formation of protein-nucleic acid cross-linkings.[2] Recently, we have described[3] the first known synthesis of uracil epoxides using dimethyldioxirane (DMDO)[4] as epoxidizing agent, and we have also shown that these epoxides may be useful synthetic intermediates for the preparation of selective inhibitors of the *Sendai* virus.[5] Unfortunately, the low yields, and the formation of appreciable amounts of diols as by-products, lowered the synthetic advantage of DMDO.

In order to found new and selective method for the epoxidation of uracils, our attention was next turned to the use of metalloporphyrins as catalysts. Porphyrin metal complexes have been shown to be powerful and selective epoxidizing agents in the presence of iodosylbenzene (PhIO),[6] sodium hypochloride (NaOCl),[7] molecular oxygen,[8] potassium monopersulfate ($KHSO_5$),[9] alkyl hydroperoxides,[10] and hydrogen peroxide.[11] Moreover, activated porphyrins have been shown to cause DNA strand scission.[12] Different pathways involving C-H hydroxylation of the sugar moiety have been proposed to play an important role in this oxidative DNA trasformation,[13] but only little attention was focused on the porphyrins catalyzed oxidation of the nucleic acid bases, with exception of a report on the oxidation of adenosine 5'-monophosphate with $KHSO_5$ and a water-soluble manganese porphyrin.[14] To the best of our knowledge, there are no reports dealing with oxidations of uracil derivatives by reactive oxometal porphyrins. Here we describe new and efficient routes for the selective epoxidation of uracil derivatives by activated porphyrin catalysts.

FeTDMPPCl, MnTDMPPCl [where TDMPP is the dianion of 5,10,15,20-tetra(2,6-dimethoxy)phenylporphyrin], and Mn(Cl16)TDMPPCl [where (Cl16)TDMPP is the dianion of 2,3,7,8,12,13,17,18-octachloro-5,10,15,20-tetra(2,6-dimethoxy, 3,5-dichloro)phenylporphyrin] were used as

catalysts.[15] All catalysts were found to be unable to catalyze the epoxidation of 1,3-dimethyluracil **1**, 1,3,5-trimethyluracil (1,3-dimethylthymine) **2**, and 1,3,6-trimethyluracil **3**,[16] by PhIO or NaClO as the oxygen-atom donors, also in the presence of imidazole as cocatalyst.[17] In the absence of a metalloporphyrin, compounds **1**, **2**, and **3** remained almost unchanged after 24h when exposed to H_2O_2 in a 1:1 CH_2Cl_2/CH_3CN mixture at 20°C. Instead, the selective epoxidation of the uracil ring by H_2O_2 was obtained in the presence of metalloporphyrins and imidazole. 1,3-Dimethyl-5,6-dihydro-5,6-oxiranyl derivatives **4**, **5**, and **6** were obtained as only recovered products in variable yields depending on the catalyst used; Mn(Cl16)TDMPPCl being the most active catalyst (Scheme, Table, Entries 1-3, 4-5 and 6-7).[18]

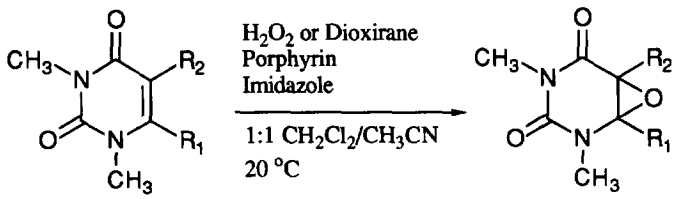
Entry	Substrate	Oxidant	Catalyst	Product	R_1	R_2	Yield(%)
1	1	H_2O_2	FeTDMPPCl	4	H	H	5
2	1	H_2O_2	MnTDMPPCl	4	H	H	15
3	1	H_2O_2	Mn(Cl16)TDMPPCl	4	H	H	30
4	2	H_2O_2	MnTDMPPCl	5	H	CH_3	5
5	2	H_2O_2	Mn(Cl16)TDMPPCl	5	H	CH_3	10
6	3	H_2O_2	MnTDMPPCl	6	CH_3	H	7
7	3	H_2O_2	Mn(Cl16)TDMPPCl	6	CH_3	H	45
8	1	DMDO	FeTDMPPCl	4	H	H	20
9	1	DMDO	MnTDMPPCl	4	H	H	40
10	1	DMDO	Mn(Cl16)TDMPPCl	4	H	H	68
11	2	DMDO	MnTDMPPCl	5	H	CH_3	21
12	2	DMDO	Mn(Cl16)TDMPPCl	5	H	CH_3	49
13	3	DMDO	MnTDMPPCl	6	CH_3	H	52
14	3	DMDO	Mn(Cl16)TDMPPCl	6	CH_3	H	70

Table: Oxidations of 1,3-dimethyluracil derivatives **1**, **2**, and **3** with H_2O_2 and DMDO in the presence of catalytic amount of metalloporphyrin and imidazole. DMDO oxidations were carried out using the oxidant in isolated form (0.08N acetone solution).

When DMDO was used as oxygen atom donor,[19] a high chemoselectivity was obtained in the oxidation of compounds **1**, **2**, and **3** in the presence of Mn(Cl16)TDMPPCl and imidazole, to give the corresponding epoxides as only recovered products in good yields. Upon slow addition of DMDO (as ca. 0.08 N acetone solution)[20] to a solution of **1** (100 mg, 0.7 mmol) and imidazole (6 mg, 0.08 mmol) in a 1:1 CH_2Cl_2/CH_3CN mixture containing FeTDMPPCl (0.07 mmol), the epoxidation of the C-5,6 double bond takes place with selective formation of the epoxide **4** within less than 24h at 20°C (Scheme, Table, Entry 8). Under identical conditions, but with MnTDMPPCl and Mn(Cl16)TDMPPCl as catalysts, the yield of the epoxide **4** increased and was found 40% and 68%, respectively (Table, Entries 9 and 10). Similar results were obtained in the

oxidation of the C-5,6-substituted uracils **2** and **3**. The epoxides **5** and **6** were isolated as main products in good yields (Table, Entries 11-12, and 13-14); while only traces of the corresponding diols were found in the reaction mixture.

Scheme



1, 2, 3 **4, 5, 6**

1, 4: $R_1=R_2=H$
2, 5: $R_1=H$, $R_2= CH_3$
3, 6: $R_1=CH_3$, $R_2= H$

The absence of diols as undesired by-products and the high yields obtained for the epoxides in the oxidation of uracil derivatives with DMDO and porphyrins, with respect to the same reactions carried out in the absence of catalyst, suggests a different reaction pathway. Probably, the formation rate of a high-valent porphyrin intermediate (e.g. Mn^{IV}) is higher than the direct oxygen-atom transfer from DMDO to the C-5,6 double bond, without any other possible partecipation to processes of oxiranyl-ring opening. Moreover, the high chemoselectivity showed in this transformation suggests its application in the epoxidation of pyrimidine nucleosides.

Further studies about the formation and the possible role of these epoxides in the cleavage mechanism of DNA with reactive oxometal porphyrins, by oxygen atom transfer from H_2O_2 and DMDO, are in course in our laboratories.

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18. Selected data for 1,3-dimethyl-5,6-dihydro-5,6-oxiranyluracil **4**: ^{1}H-NMR ($CDCl_3$) δ 4.99 (1H, d, J= 3.0 Hz, H-6), 4.30 (1H, d, J= 3.0 Hz, H-5), 3.16 (3H, s, N-CH_3), 3.12 (3H, s, N-CH_3).^{13}C-NMR ($CDCl_3$) δ 171.1 (C), 153.2 (C), 80.02 (CH), 68.7 (C), 34.7 (CH_3), 27.5 (CH_3). Mass Spectrum m/e= 156 (M^+, 87%).
Selected data for 1,3,5-trimethyl-5,6-dihydro-5,6-oxiranyluracil **5**: ^{1}H-NMR ($CDCl_3$) δ 4.44 (1H, s, H-6), 3.08 (3H, s, N-CH_3), 3.0 (3H, s, N-CH_3), 1.37 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$) δ 173.92 (C), 152.34 (C), 84.92 (CH), 71.84 (C), 35.33 (CH_3), 28.07 (CH_3), 23.22 (CH_3). Mass Spectrum m/e= 170 (M^+, 65%).
Selected data for 1,3,6-trimethyl-5,6-dihydro-5,6-oxiranyluracil **6**: ^{1}H-NMR ($CDCl_3$) δ 5.60 (1H, s, H-5), 3.38 (3H, s, N-CH_3), 3.30 (3H, s, N-CH_3), 2.21 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$) δ 152.62 (C), 151.41 (C), 101.22 (CH), 84.04 (C), 32.02 (CH_3), 28.43 (CH_3), 17.59 (CH_3). Mass Spectrum m/e= 170 (M^+, 73%).
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