Biomimetic Reduction of Nimesulide with $NaBH_4$ Catalyzed by Metalloporphyrins

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The biomimetic reduction of anti-inflammatory drug, nimesulide (1) with sodium borohydride catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides [TAPFe(III)Cl] has been studied in organic solvents under anaerobic and aerobic conditions.

Key words biomimetic reduction; nimesulide; metalloporhyrin; sodium borohydride; 4-aminonimesulide; 4′-hydroxynimesulide

Nimesulide (4-nitro-2-phenoxymethanesulfonanilide) (**1**) is a potent nonsteroidal anti-inflammatory, analgesic and anti-pyretic agent. It inhibits cyclooxygenase-2 selectively[1,2] and reduces prostaglandin proinflammatory activity without interfering with the production of cytoprotective prostaglandins of gastric mucous membrane.[3] 4-Aminonimesulide (**2**) (reductive metabolite) and 4′-hydroxynimesulide (**3**) (oxidative metabolite) have been reported as minor and major metabolites of **1**, respectively, in urine and feces[4—6] of man (Chart 1).

Further **1** is a protonophore and mitochondrial NAD(P)H oxidant agent whereas **2** has been reported as supressor of the above mitochondrial responses.[7] It has also been shown that the reduced metabolite (**2**) partly protects against accumulation of reactive oxygen species (ROS) derived from the organelle under conditions of oxidative stress.[7] The combination of sodium borohydride and metalloporphyrins have been shown to mimic the various redox transformations of organic substrates catalyzed by cytochrome P450 and NAD(P)H, in absence or presence of molecular oxygen.[8—14] Herein, we report the biomimetic reduction of **1** with sodium borohydride catalyzed by metalloporphyrins in organic solvents under anaerobic and aerobic conditions.

In a typical run sodium borohydride (1200 mmol) was added to a mixture of **1** (100 mmol) and 5,10,15,20-tetraphenylporphyrinatoiron(III) chloride (TPPFe(III)Cl, 1 mmol) in methanol : dichloromethane (9 : 1, v/v) under nitrogen atmosphere. The reaction was stirred for 1 h at room temperature. The progress of the reaction was monitored by TLC and HPLC. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give **2** in 89% yield (Chart 2, Table 1). The formation of **2** was confirmed by comparison of HPLC retention time as well as other spectroscopic data[15] with that of authentic sample.

The presence of molecular ion peak at 277 in electron impact (EI)-MS shows the complete reduction of **1** to **2**. Further, the presence of a peak at 199 shows the loss of $-SO_2CH_3$ group from the parent molecule. The appearance of broad singlet at 3.7 ppm in ^{1}H-NMR shows the presence of $-NH_2$ group in the compound. The upfield chemical shifts of aromatic protons show the complete reduction of nitro group to amino group. The presence of two peaks around 3394 and 3339 cm^{-1} in IR spectrum also confirms the formation of **2**. The reduction of nimesulide is directly proportional to the substrate, $NaBH_4$ and iron(III) porphyrin ratio under N_2 atmosphere. As the ratio of iron(III) porphyrin and $NaBH_4$ is increased to 1 : 1200 mmol the reduction of nimesulide has completed within 1 h, whereas the complete reduction has not taken place even after 24 h with lower ratios of iron(III) porphyrin and $NaBH_4$. The results are presented in the Table 1.

The change of central metal atom of porphyrin from Fe to Mn, Ni, Co showed lesser catalytic activities than the Fe. The catalytic ability of metalloporphyrins are found to be in the following order: TPPFe(III)Cl>TPPMn(III)Cl>TPPNi(II)> TPPCo(II). However, the reduction of **1** with $NaBH_4$ catalyzed by robust iron(III)porphyrins like Cl_8TPPFe(III)Cl and Cl_8Cl_8TPPFe(III)Cl gave **2** in 95% and 96% respectively as compared to 89% with TPPFe(III)Cl.

The TLC examination of reduction of **1** after 30 min shows the presence of two additional products along with **2** and they disappeared after 1 h. Further, the *Rf* values of these products are found to be similar to that of 4-nitrosonimesulide[16] (**4**) and 4-hydroxylaminonimesulide[17] (**5**) (*Rf* values **1**=0.71, **2**=0.43, **4**=0.63, **5**=0.28, silica gel, eluent 100% chloroform). This is further confirmed by HPLC [waters, C18 μ-bondapak, methanol : water (60 : 40 v/v)] analyses (retention times of **1** is 14.12, **2** is 9.04, **4** is 13.02 and **5** is 5.65). The reaction of **4** and **5** with $NaBH_4$ catalyzed by TPPFe(III)Cl gives **2** in 98% and 99% yield, respectively and complete conversion was observed within 30 min. Therefore, the reduction of **1** with $NaBH_4$/5,10,15,20-tetraarylporphyrinatoiron(III) chlorides (TAPFe(III)Cl) system is believed to proceed through **4** and **5** intermediates to form **2** either by

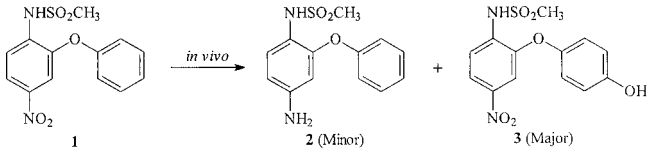

Chart 1

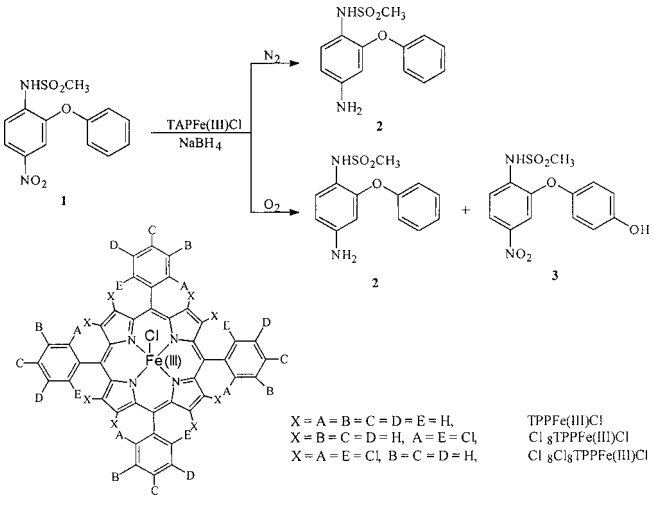

Chart 2

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Table 1. Reduction of Nimesulide and Related Compounds with $NaBH_4$ Catalyzed by TAPFe(III)Cl under N_2 Atmosphere

Run	System	$NaBH_4$ (mmol)	Time (h)	Conversion (%)[a]	Yield (%)[a]
1	**1**	200[b]	24	12	9
2	**1**/TPPFe(III)Cl	200	24	54	23
3	**1**/TPPFe(III)Cl	400	12	76	47
4	**1**/TPPFe(III)Cl	800	2	91	68
5	**1**/TPPFe(III)Cl	1200	1	100	89
6	**1**/Cl_8TPPFe(III)Cl	1000	0.5	100	95
7	**1**/Cl_8Cl_8TPPFe(III)Cl	1000	0.5	100	96
8	**4**/TPPFe(III)Cl	800	0.5	100	98
9	**5**/TPPFe(III)Cl	800	0.5	100	99

a) Based on the substrate, *b*) $NaBH_4$ alone.

Table 2. The Reduction of Nimesulide with $NaBH_4$ Catalyzed by TAPFe(III)Cl in Presence of Added Molecular Oxygen[a]

S. No.	Metalloporphyrin	% Yield[b]	
		2	**3**
1	TPPFe(III)Cl	20	Trace amounts
2	Cl_8TPPFe(III)Cl	11	4.5
3	Cl_8Cl_8TPPFe(III)Cl	10	4.8

a) 100 eq of molecular oxygen, Sub : cat : $NaBH_4$ = 100 : 1 : 400 mmol after 2 h at 25 °C, *b*) Based on the substrate and HPLC analyses, retention time of **2** is 9.04 and **3** is 11.86.

stepwise $1e^-$ or $2e^-$ processes.

The reaction of **1** with $NaBH_4$ catalyzed by TAPFe(III)Cl in presence of molecular oxygen gives **3** along with **2**. (Chart 2, Table 2) The structure of **3** was confirmed by the comparison of HPLC retention time with that of authentic sample as well as by other spectroscopic data.[18)]

The low catalytic activity of TPPFe(III)Cl with molecular oxygen in presence of reductant $NaBH_4$ is due to formation of μ-*oxo* dimer,[19)] whereas the high-valent iron-*oxo* intermediates formed from the halogenated and perhalogenated iron(III)porphyrin with molecular oxygen under reductive conditions are responsible for aromatic hydroxylation.[11,12,20,21)] The presence of molecular oxygen has remarkably effected the reduction of **1**. As the amount of oxygen bubbled into the reaction mixture is increased, the yield of **2** is further decreased even with 1200 mmol of $NaBH_4$. The detailed study on the oxidation of **1** with monooxygen donors catalyzed by metalloporphyrins will be published elsewhere.

In conclusion, the reduction of nimesulide **1** with cytochrome P450-NAD(P)H model system (TAPFe(III)Cl-$NaBH_4$) under anaerobic conditions gives exclusively reductive metabolite **2** whereas the oxidative metabolite **3** has also been formed along with **2** under aerobic conditions.

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References and Notes

1) Cullen L., Kelly L., Connor S. O., Fitzgerald D. J., *J. Pharmacol. Exp. Ther.*, **287**, 578—582 (1998).
2) Singh A. K., Chawla M., Singh A., *J. Pharm. Pharmacol.*, **52**, 467—486 (2000).
3) Shah A. A., Murray F. E., Fitzgerald D. J., *Rheumatology*, **38** (Suppl. 1), 19—23 (1999).
4) Carini M., Aldini G., Stefani R., Marinello C., Facino R. M., *J. Pharm. Biomed. Anal.*, **18**, 201—211 (1998).
5) Sarkar P., McIntosh J. M., Leavitt R., Gouthro H., *J. Anal. Toxico.*, **21**, 197—202 (1997).
6) Giachetti C., Tenconi A., *Biomed. Chromatogr.*, **12**, 50—56 (1998).
7) Mingatto F. E., Santos A. C. D., Rodrigues T., Pigoso A. A., Uyemura S. A., Curti C., *Br. J. Pharm.*, **131**, 1154—1160 (2000).
8) Sakai S., Kojima T., Arai T., *J. Chem. Soc. Dalton. Trans.*, **1994**, 7—11.
9) Sakaki S., Koga H., Tao K-I., Yamashita T., Iwashita T., Hamada T., *J. Chem. Soc. Dalton. Trans.*, **2000**, 1015—1017.
10) Sakaki S., Mitarai S., Ohkubo K., *Chem. Lett.*, **1991**, 195—198.
11) Okamoto T., Oka S., *J. Org. Chem.*, **49**, 1589—1594 (1984).
12) Kano K., Takagi H., Takeuchi M., Hashimoto S., *Chem. Lett.*, **1991**, 519—522.
13) Santa T., Mori T., Hirobe M., *Chem. Pharm. Bull.*, **33**, 2175—2178 (1985).
14) Mori T., Santa T., Higuchi T., Mashino T., Hirobe M., *Chem. Pharm. Bull.*, **41**, 292—295 (1993).
15) Data of 4-aminonimesulide (**2**): mp 169—171 °C; ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.90 (s, 3H, CH_3SO_2), 3.7 (br s, 2H, NH_2), 6.16 (s, 1H, NH), 6.35 (s, 1H, Ar-3H), 6.40 (d, 1H, J=8.45 Hz, Ar-5H), 6.99 (d, 2H, J=7.35 Hz, Ar′-2H, Ar′-6H), 7.16 (d, 1H, J=8.45 Hz, Ar-6H), 7.35 (m, 3H, Ar′-3H, Ar′-4H, Ar′-5H); IR (KBr, cm^{-1}): 3394, 3339, 3062, 2922, 2853, 1615, 1585, 1508, 1463, 1324, 1214, 1152, 969, 863, 797, 725, 688, 489; EI-MS (*m*/*z*): 277 (M^+), 206, 199, 171, 154, 99, 77, 43.
16) Data of 4-nitrosonimesulide (**4**): It is synthesized by potassium dichromate oxidation of **5** at 0 °C. mp 111—113 °C; ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.21 (s, 3H, CH_3SO_2), 6.79 (s, 1H, NH), 7.07 (d, 2H, J=7.2 Hz, Ar′-2H, Ar′-6H), 7.46 (m, 3H, Ar′-3H, Ar′-4H, Ar′-5H), 7.66 (s, 1H, Ar-3H), 7.78 (d, 1H, J=9.0 Hz, Ar-6H), 8.01 (d, 1H, J=9.0 Hz, Ar-5H); IR (KBr, cm^{-1}): 3369, 3015, 2958, 2862, 1627, 1566, 1518, 1493, 1404, 1289, 1145, 1020, 887, 786, 745, 645, 524; EI-MS (*m*/*z*): 292 (M^+), 262, 247, 187, 172, 154, 99, 77, 43.
17) Data of 4-hydroxylamine nimesulide (**5**): It is synthesized from **1** under mild and neutral conditions using Zn and NH_4Cl. mp 163—167 °C; ^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 2.86 (s, 3H, CH_3SO_2), 4.78 (s, 2H, $NHSO_2$ and OH), 6.14 (d, 1H, J=2.2 Hz, Ar-3H), 6.34 (dd, 1H, J=8.53 Hz, J=2.2 Hz, Ar-5H), 7.01 (d, 2H, J=7.83 Hz, Ar′-2H, Ar′-6H), 7.05 (d, 1H, J=8.53 Hz, Ar-6H), 7.11 (t, 1H, J=7.83 Hz, AAr′-4H), 7.35 (t, 2H, J=7.83 Hz, Ar′-3H, Ar′-5H), 8.47 (s, 1H, NHOH); IR (KBr, cm^{-1}): 3412, 3352, 3028, 2949, 1619, 1578, 1515, 1478, 1401, 1311, 1267, 1150, 1079, 971, 856, 802, 741, 680; EI-MS (*m*/*z*): 294 (M^+), 262, 247, 183, 168, 91, 77, 57, 41.
18) Data of 4′-hydroxynimesulide (**3**): mp 124—126 °C; ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.93 (s, 3H, CH_3SO_2), 6.7 (s, 1H, NH), 7.07 (d, 2H, J=7.47 Hz, Ar′-3H, Ar′-5H), 7.23 (d, 2H, J=7.47 Hz, Ar′-2H, Ar′-6H), 7.34 (d, 1H, J=8.5 Hz, Ar-6H), 7.46 (s, 1H, Ar-3H), 7.59 (d, 1H, J=8.5 Hz, Ar-5H); IR (KBr, cm^{-1}): 3482, 3286, 2924, 2854, 1591, 1519, 1342, 1215, 1153, 1078, 973, 908, 802, 469; EI-MS (*m*/*z*): 324 (M^+), 307, 275, 256, 223, 204, 154, 149, 123, 89, 71, 57, 41.
19) Ellis P. E., Jr., Lyons J. E., *Coord. Chem. Rev.*, **105**, 181—193 (1990).
20) Grinstaff M. W., Hill M. G., Birnbaum E. R., Schaefer W. P., Labinger J. A., Gray H. B., *Inorg. Chem.*, **34**, 4896—4902 (1995).
21) Dolphin D., Traylor T. G., Xie L. Y., *Acc. Chem. Res.*, **30**, 251—259 (1997).