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# Complex Formation between Co(Salophen) and *N*-Methylmorpholine *N*-Oxide (NMO)

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**Dedicated to Professor Göran Bergson on the occasion of his 65th birthday**

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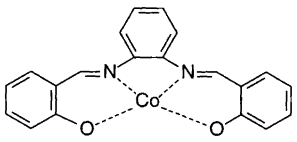
In connection with a project on the *in situ* generation of amine *N*-oxides as oxidants in transition-metal-catalyzed reactions, we were interested in mild oxidations of tertiary amines to *N*-oxides by hydrogen peroxide and molecular oxygen [eqn. (1)].[1] The aliphatic tertiary amine *N*-methylmorpholine (NMM) would be an interesting substrate to oxidize since its corresponding *N*-oxide (NMO) is a commonly employed oxidant in reactions involving transition metal catalysis.[2,3]

$$\text{amine} \xrightarrow[H_2O_2 \text{ or } O_2]{\text{catalyst}} \text{amine } N\text{-oxide} \qquad (1)$$

Oxidation reactions with molecular oxygen and hydrogen peroxide have been widely studied in recent years.[4,5] These oxidants are environmentally friendly, and also have a high degree of available oxygen compared with many other commonly employed oxidizing agents. Although they have a high oxidation potential with respect to the formation of water, the activation barrier is relatively high and often the presence of a catalyst is necessary for mild oxidations to occur.[4,6] Biomimetic compounds such as metal macrocycles[7–13] and flavin analogues[1,14–16] are some examples of catalysts which have been employed in order to overcome this energy barrier.

We considered Co(salophen) (**1**), a metal-containing compound that has been successfully applied in aerobic electron transfer reactions,[7,17,18] as a possible catalyst for mild amine oxidations [eqn. (1)]. A related metal macrocycle, a manganese porphyrin, was recently described by Mansuy *et al.* to catalyze $H_2O_2$ oxidation of aromatic *N*-heterocycles to *N*-oxides.[12,19] A possible problem in these types of oxidations is that the amine *N*-oxide can coordinate to the metal, resulting in inhibition of the reaction. In fact, a few examples of complex formation between *N*-oxides and metal macrocycles have been reported.[20,21] There is also a recent report describing an isolated complex involving intramolecular coordination between a pyridine *N*-oxide and a chiral Mn(salen).[20b] We therefore decided to study the possible complex formation between **1** and *N*-oxides. We report here on the observations of such a complex between Co(salophen) (**1**) and *N*-methylmorpholine *N*-oxide (NMO).




**1**

## Results and discussion

Complex formation between **1** and NMO was monitored by $^1$H NMR spectroscopy. It was found that the chemical shift values for some of the protons in NMO were strongly affected by the presence of the paramagnetic cobalt compound **1** (Fig. 1). The protons most strongly influenced were those in close proximity to the *N*-oxide in the molecule ($H^a$, $H^b$ and the methyl protons), suggesting complex formation between the N–O part of NMO and cobalt in **1**. For example, the signal from proton $H^a$ was shifted from 2.8 ppm in a cobalt-free solution to 0.2 ppm in the presence of 25 mol% of **1**. An even larger upfield movement was observed for the

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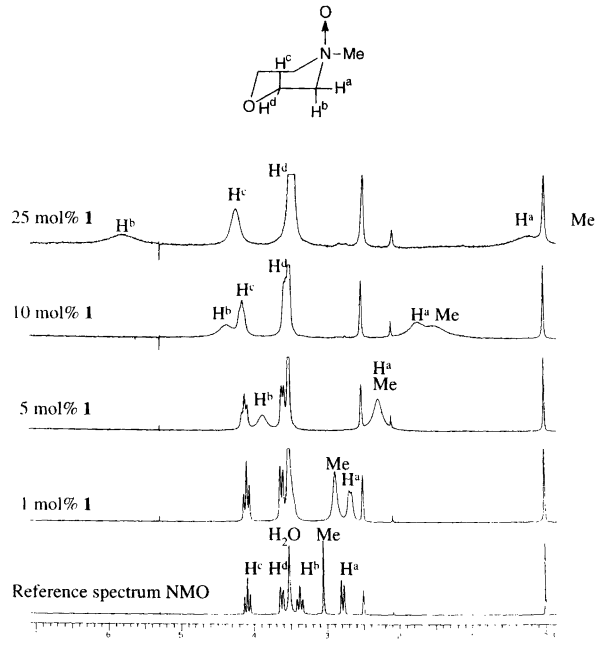


*Fig. 1.* $^1H$ NMR study of complex formation between Co(salophen) (**1**) and NMO in ($^2H_6$)DMSO.[22]

*N*-methyl group at 3.05 ppm, which was moved to a negative shift value (−0.75 ppm, not shown in Fig. 1). Proton $H^b$, which is geminal to $H^a$, was instead shifted considerably downfield (about 2.3 ppm). Protons further away from the *N*-oxide functional group were only weakly affected ($H^c$ and $H^d$).

In a separate study, NMO was added in portions to a solution of the cobalt complex **1** in ($^2H_6$)DMSO and the protons in **1** were observed. In this case very large changes in shift values were recorded, with some protons in **1** showing shift differences of almost 15 ppm on addition of the *N*-oxide. The most extensive shift differences were observed during addition of the first two equivalents of the *N*-oxide. We interpret these results as the formation of a 2:1 complex between NMO and Co(salophen) (Fig. 2). This would be in accordance with the known behavior of some metalloporphyrins in the presence of amine *N*-oxides (*vide supra*).[21]

Interestingly, in a similarly performed NMR study there was no indication of complex formation between the amine NMM and cobalt compound **1**. This supports our interpretation that complexation between NMO and Co(salophen) (**1**) is possible via coordination of the axial oxygen atom in the *N*-oxide to the cobalt atom.

In conclusion, the amine *N*-oxide NMO forms a 2:1 complex with Co(salophen) (**1**), whereas there is no similar interaction between the amine NMM and **1**. Owing to this complex formation cobalt compound **1** may not be an ideal catalyst to employ in oxidations of tertiary amines to *N*-oxides.[23]

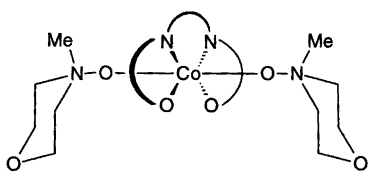


*Fig. 2.* A 2:1 complex between NMO and Co(salophen) (**1**).

## Experimental

The $^1H$ NMR spectra were recorded at 300 MHz. ($^2H_6$)DMSO was used both as solvent and internal standard. *N*-Methylmorpholine *N*-oxide (NMO) and *N*-methylmorpholine (NMM) were purchased from Aldrich and Fluka, respectively. All commercial chemicals were used as received without further purification. Co(salophen) **1** was prepared according to a literature procedure.[7]

A. *Addition of Co(salophen)* (**1**) *to NMO (reported in Fig. 1).* A solution of **1** in ($^2H_6$)DMSO (0.17 M) was added in portions (5–25 µl at a time) to a solution of NMO (11 mg, 0.096 mmol) in ($^2H_6$)DMSO (1.0 ml). After each addition a $^1H$ NMR spectrum was recorded. Because of the paramagnetic properties of **1** the resolution of the spectra decreased, but it was still high enough for determination of the differences in chemical shift values. The total addition volume was 125 µl, which corresponds to 0.25 equivalents of **1** to NMO.

B. *Addition of NMO to Co(salophen)* (**1**). A solution of NMO in ($^2H_6$)DMSO (1.12 M) was added portionwise (5–25 µl at a time) to a solution of **1** (18 mg, 0.048 mmol) in ($^2H_6$)DMSO (0.7 ml). After each addition a $^1H$ NMR spectrum was recorded. The total addition volume was 200 µl, which corresponds to 4.0 equivalents of NMO to **1**.

C. *Addition of Co(salophen)* (**1**) *to NMM.* The $^1H$ NMR study was performed in accordance with procedure A except for the replacement of NMO by NMM (0.096 mmol). The total addition volume was 100 µl, which corresponds to 0.20 equivalents of **1** to NMM.

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18. For aerobic oxygen transfer reactions with metal macrocycles as catalysts, most likely the presence of an extra reducing agent is necessary for activation of molecular oxygen, see Ref. 10.
19. There are also examples of the reverse reaction, i.e. the use of amine *N*-oxides as oxygen donors in combination with metal macrocycles [see for example Ref. 10; Shannon, P. and Bruice, T. C. *J. Am. Chem. Soc. 103* (1981) 4580; Ostovič, D., Knobler, C. B. and Bruice, T. C. *J. Am. Chem. Soc. 109* (1987) 3444; Ohtake, H., Higuchi, T. and Hirobe, M. *Heterocycles 40* (1995) 867]. However, the reaction is described to be reversible and thus oxidation of amines should also be possible, which has been nicely demonstrated by Mansuy *et al.* (see Ref. 12).
20. (a) Formation of a stable complex between a manganese porphyrin and an aromatic *N*-oxide, $[Mn^{III}TPP(2,6\text{-lutidine } N\text{-oxide})_2]^+ClO_4^-$ has been reported. See Hill, C. L. and Williamson, M. M. *Inorg. Chem. 24* (1985) 3024; (b) for an intramolecular coordination of a pyridine *N*-oxide to a Mn(salen) complex, see Finney, N. S., Pospisil, P. J., Chang, S., Palucki, M., Konsler, R. G., Hansen, K. B. and Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl. 36* (1997) 1720.
21. NMO and $MnTPPClO_4$ form a 2:1 complex, which have been isolated. In the complex the *N*-oxide oxygen atoms act as axial ligands to the metal in the macrocycle. However, this complex is rather reactive in alkane hydroxylations, i.e. the *N*-oxide transfers its oxygen atom to the manganese porphyrin in the presence of a suitable substrate. See Brown, R. B. J., Williamson, M. M. and Hill, C. L. *Inorg. Chem. 26* (1987) 1602.
22. The reference spectrum of NMO shows a compound in the chair conformation with $H^e$ and $H^b$ in axial positions and the methyl group as an equatorial substituent. The preference for this conformation is described in the literature [Cook, M. J., Katritzky, A. R. and Mañas, M. M. *J. Chem. Soc. B* (1971) 1330]. The assignment of the proton signals was further confirmed by $^1H$ homodecoupling and NOE experiments.
23. Preliminary experiments support this conclusion. Thus, the attempted Co(salophen)-catalyzed oxidation of NMM to NMO employing $H_2O_2$ or $O_2$ as the terminal oxidant failed.

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