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Synthesis of *N*-methylmorpholine *N*-(^{17}O-oxide) and *N*-methylmorpholine ^{15}*N*-(^{17}O-oxide)

Martina Opietnik,[a] Antje Potthast,[a] Takuya Kitaoka,[b] and Thomas Rosenau[a]*

***N*-Methylmorpholine *N*-(^{17}O-oxide) and *N*-methylmorpholine ^{15}*N*-(^{17}O-oxide) were prepared from *N*-methylmorpholine and ^{15}*N*-methylmorpholine by oxidation with $H_2{}^{17}O_2$. The facile one-pot procedure provided yields of 82 and 76%, respectively. The labeled hydrogen peroxide was obtained by electrolysis of $H_2{}^{17}O$ followed by autoxidation of 2-ethylanthraquinol with the molecular oxygen $^{17}O_2$ generated. The compounds serve for mechanistic studies into gold nanoparticle generation in NMMO solution.**

Keywords: *N*-methylmorpholine *N*-oxide; NMMO; gold nanoparticles; ^{17}O-labeling; amine *N*-oxide

Introduction

Tertiary amine *N*-oxides are not only rewarding synthetic targets[1] but also multi-faceted compounds with numerous applications in synthetic organic chemistry, e.g. as intermediates in multi-step syntheses,[2] as *N*-protected forms of tertiary and aromatic amines,[3] as oxidants[4] and as non-ionic surfactants.[5] In particular *N*-methylmorpholine-*N*-oxide (NMMO) is one of the most important and most frequently used amine *N*-oxides. It is applied as a cellulose solvent in large-scale industrial fiber making (Lyocell process).[6,7] Recently, NMMO has been described as a medium to prepare carbohydrate-conjugated gold nanoparticles.[8] The mechanism of this reaction is a complex redox process, with both NMMO and tetrachloroaurate being reduced (to *N*-methylmorpholine and elemental Au, respectively), and chloride being oxidized to chlorate, in turn. For studies of the complex intermediates of this reaction, NMMO and ^{15}N-NMMO, both ^{17}O-labeled at the *N*-oxide oxygen, were required at a 100 mg-scale, the preparation of the labeled compounds being described in the following. All reaction steps were comprehensively optimized with oxygen reagents of natural isotopic abundance before entering the runs with the rare and expensive ^{17}O-enriched material.

Results and discussion

N-Methylmorpholine (NMM) is quite readily oxidized into NMMO by hydrogen peroxide, which is usually applied as excess 30% aqueous solution.[9] Direct preparation of ^{17}O-labeled hydrogen peroxide from $H_2{}^{17}O$(**1**) was not practicable when working with small amounts of less than 1 ml, and usage of excess oxidant was ruled out in addition by the prohibitively high costs of the ^{17}O-reagents. An alternative approach was the generation of hydrogen peroxide from $^{17}O_2$ (**2**),[10] which was obtained quantitatively in a standard electrolysis cell. The principle of the industrial H_2O_2 production process, autoxidation of 2-alkylanthraquinol (**3**) with molecular oxygen,[11] proved to be well applicable also on a small lab scale, working with 80 cm^3 of $^{17}O_2$ gas. To consume the valuable $^{17}O_2$ (**2**) completely, the anthraquinol was applied in 5-fold molar excess in a toluene/1-octanol solvent mixture. However, contrary to the bulk process, the $H_2^{17}O_2$(**4**) was not separated from the mixture by liquid–liquid extraction into water, but was immediately consumed in the oxidation of *N*-methylmorpholine (**5**), which was directly added to the reaction mixture. Thus, H_2O_2 generation and NMM oxidation were carried out as one-pot procedure, which was possible since the generated NMMO (**6**) did not interfere with excess anthraquinol. With a 5-fold molar excess of tertiary amine relative to the generated hydrogen peroxide, the latter was consumed quantitatively after 4 h. Separation of the NMMO (**6**) was readily possible by aqueous extraction. To obtain the anhydrous material and not one of the NMMO hydrates,[7] it is imperative to remove any water by azeotropic distillation with toluene. This was followed by recrystallization and sublimation as the final purification steps. The synthesis approach starting from $H_2^{17}O$(**1**) is shown in Figure 1.

In the case of ^{15}*N*-methylmorpholine, which was available from previous work,[12] application of a large excess was not realistic. When NMM and generated hydrogen peroxide were

[a]*Department of Chemistry, University of Natural Resources and Applied Life Sciences (BOKU Vienna), Muthgasse 18, A-1190 Vienna, Austria*

[b]*Department of Forest and Forest Products Sciences, Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan*

**Correspondence to: Thomas Rosenau, Department of Chemistry, University of Natural Resources and Applied Life Sciences (BOKU Vienna), Muthgasse 18, A-1190 Vienna, Austria.*
E-mail: thomas.rosenau@boku.ac.at

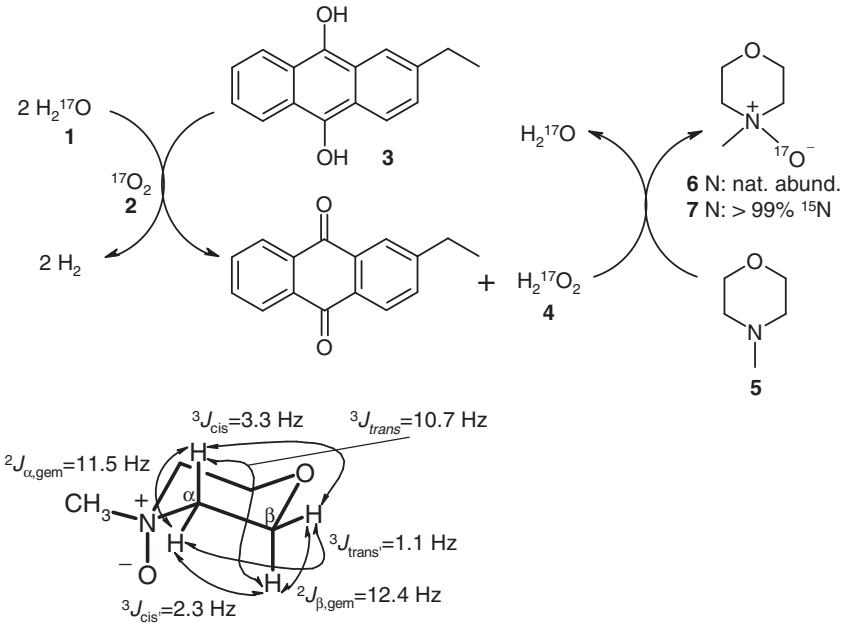

Figure 1. Synthesis of *N*-methylmorpholine *N*-(^{17}O-oxide) (**6**) and *N*-methylmorpholine ^{15}*N*-(^{17}O-oxide) (**7**) from $H_2^{17}O$, and homonuclear $^nJ_{H,H}$ coupling constants (0.1 M in $CDCl_3$).

used in a roughly equimolar ratio, the oxidation stagnated after about 40% conversion, and it was also not possible to drive the reaction to completion by higher reaction temperatures. This problem was overcome by adding a small amount of water ($H_2^{17}O$ to avoid isotopic scrambling). The water generated from H_2O_2 in the oxidation process itself was evidently not sufficient, as it is likely bound to NMMO by strong hydrogen bonds and not freely available. The highly concentrated *aqueous* hydrogen peroxide, resulting after water addition, was now able to oxidize NMM, which was completely consumed within 2 h. The valuable ^{17}O-labeled water was again recovered by distillation with toluene as the azeotropic carrier. Separation and purification of the ^{15}N-product was carried out as in the case of the non-^{15}N material.

Conclusion

Introduction of ^{17}O in the *N*-oxide moiety of *N*-methylmorpholine-*N*-oxide succeeded via oxidation of NMM (**5**) with $H_2^{17}O_2$(**4**). The labeled hydrogen peroxide was not commercially available – it was prepared from $H_2^{17}O$ by electrolysis and reduction of the evolved $^{17}O_2$ with 2-ethylanthraquinol. The yields relative to the used ^{17}O-water were approx. 80%. The major part (70–75%) of $H_2^{17}O$, both produced from $H_2^{17}O_2$ and added to expedite the NMM oxidation, can be recovered by water collection with toluene, which is advantageously used also as component of the solvent mixture. The preparation method is quite robust, and was able to provide the ^{17}O-labeled amine *N*-oxides **6** and **7** in multi-100 mg amounts, sufficient for comprehensive kinetic and NMR studies.

Experimental

General

Commercial chemicals were of the highest grade available and were used without further purification. Reagent-grade solvents were used for all extractions and workup procedures. Distilled water was used for all aqueous extractions and for all aqueous solutions. The organic solvents used were distilled before use. TLC was performed using Merck silica gel 60 F_{254} pre-coated plates. All given yields refer to isolated, pure products. Melting points, determined on a Kofler-type micro hot stage with Reichert–Biovar microscope, are uncorrected. Elemental analyses were performed at the Microanalytical Laboratory of the Institute of Physical Chemistry at the University of Vienna.

^{1}H NMR spectra were recorded at 400.13 MHz for ^{1}H, 100.41 MHz for ^{13}C NMR and 54.22 MHz for ^{17}O with $CDCl_3$ as the solvent if not otherwise stated. Chemical shifts, relative to TMS (^{1}H: 0.0 ppm, ^{13}C: 0.0 ppm) and acetone (^{17}O: 571.0 ppm), are given in δ values, coupling constants in Hertz.

Preparation of ^{17}O-labeled NMMO

In a 250 ml-flask, a solution of 2-ethylanthraquinol (2-ethylanthracene-9,10-diol, 5.000 g, 21 mmol) in toluene (50 ml) and 1-octanol (50 ml) was purged with argon gas for 10 min at r.t. (20°C). The vessel was closed with a gas-tight septum and $^{17}O_2$ (80 cm^3, 3.57 mmol) was added through a gas syringe, and the mixture was stirred vigorously for 4 h at 40°C in a way that the gas phase and the liquid phase were intimately mixed. Care has to be taken that no mixing with atmospheric oxygen can occur; other precautions, such as against over-pressure, are not necessary. The mixture was cooled to −5°C (ice bath), and freshly distilled *N*-methylmorpholine (101.15, 2.025 g, 20 mmol) was added. The mixture was stirred for 2 h at −5°C, heated to 60°C over 15 min and stirred for additional 2 h. By applying reduced pressure (50 mbar at 60°C), the $H_2^{17}O$ formed as byproduct water was recovered by co-evaporation with toluene (azeotropic distillation). After cooling to r.t., the mixture was extracted five times by water (20 mL each). The combined aqueous extracts were extracted with dichloromethane (three times 10 mL) and evaporated to a volume of about 2 mL. The viscose remainder was co-evaporated three times with toluene (50 mL each) to give a waxy solid that was recrystallized from

acetone. Final purification was done by Kugelrohr sublimation (0.05 mbar), providing pure *N*-methylmorpholine-*N*-^{17}O-oxide (344 mg, 2.93 mmol, 82.5% rel. to O_2). Care should be taken that the temperature does not exceed 130°C due to possible instabilities of the amine *N*-oxide. The ^{1}H and ^{13}C NMR data were consistent with our previous detailed analysis.[13] ^{1}H NMR ($CDCl_3$, 0.1 M): δ 3.11 (dd, 2H, N-CH_{eq}), 3.26 (s, 3H, N-CH_3), 3.38 (dt, 2H, N-CH_{ax}), 3.78 (dd, 2H, O-CH_{eq}), 4.44 (dt, 2H, O-CH_{ax}). For $J_{H,H}$ coupling constants see Figure 1. ^{13}C NMR ($CDCl_3$, 0.1 M): δ 60.86 (N-CH_3), 61.52 (N-CH_2), 65.72 (O-CH_2). ^{17}O NMR ($CDCl_3$ 0.1 M, 1% acetone-^{17}O): δ 255 (N-O). Microanalysis: calcd. for $C_5H_{11}N^{16}O^{17}O$ (118.15): C: 50.86, H: 9.38, N: 11.86; found: C: 51.04, H: 9.42, N: 11.80. Comparison to non-labeled material: microanalysis: calcd. for $C_5H_{11}NO_2$ (117.15): C: 51.26, H: 9.46, N: 11.96; found: C: 51.31, H: 9.56, N: 11.88.

Preparation of ^{17}O-labeled ^{15}N-NMMO

In a 250 ml-flask, a solution of 2-ethylanthraquinol (2-ethylanthracene-9,10-diol, 5.000 g, 21 mmol) in toluene (50 ml) and 1-octanol (50 ml) was purged with argon gas for 10 min at r.t. (20°C). The vessel was closed with a gas-tight septum and $^{17}O_2$ (80 cm^3, 3.57 mmol) was added through a gas syringe, and the mixture was stirred vigorously for 4 h at 40°C in a way that the gas phase and the liquid phase were intimately mixed. The mixture was cooled to −5°C (ice bath), and freshly distilled *^{15}N*-methylmorpholine (102.15, 0.350 g, 3.43 mmol) was added. The mixture was stirred for 2 h at −5°C and $H_2^{17}O$ (0.1 mL, 5.26 mmol) was added, and the stirring was continued for 1 h. The mixture was heated to 60°C and stirring was continued for additional 1 h. By applying reduced pressure (50 mbar at 60°C), the $H_2^{17}O$ (both the fraction generated as byproduct and the fraction added) was recovered by co-evaporation with toluene (azeotropic distillation). After cooling to r.t., the mixture was extracted five times by water (20 mL each). The combined aqueous extracts were extracted with dichloromethane (three times 10 mL) and evaporated to a volume of about 2 mL. The waxy remainder was co-evaporated three times with toluene (50 mL each) and the resulting solid recrystallized from acetone. Final purification was done by Kugelrohr sublimation (0.05 mbar), providing pure *N*-methylmorpholine-*^{15}N*-^{17}O-oxide (323 mg, 2.71 mmol, 76% rel. to O_2). Care should be taken that the temperature does not exceed 130°C due to possible instabilities of the amine *N*-oxide. ^{1}H NMR ($CDCl_3$, 0.1 M): δ 3.11 (dd, 2H, N-CH_{eq}), 3.26 (s, 3H, N-CH_3), 3.38 (dt, 2H, N-CH_{ax}), 3.78 (dd, 2H, O-CH_{eq}), 4.44 (dt, 2H, O-CH_{ax}). ^{13}C NMR ($CDCl_3$, 0.1 M): δ 60.86 (N-CH_3, d, $^{1}J_{C,N} = 11.4$ Hz), 61.52 (N-CH_2, d, $^{1}J_{C,N} = 5.5$ Hz), 65.72 (O-CH_2, d, $^{2}J_{C,N} = 0.6$ Hz). ^{15}N NMR ($CDCl_3$, 0.1 M): δ 101.2 (N-O, m, br). ^{17}O NMR ($CDCl_3$ 0.1 M, 1% acetone-^{17}O): δ 256 (N-O, d, $^{1}J_{N,O} = 24$ Hz). Microanalysis: calcd. for $C_5H_{11}^{15}N^{16}O^{17}O$ (119.14): C: 50.40, H: 9.31, N: 11.76; found: C: 50.48, H: 9.38, N: 11.64.

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