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Radicals derived from *N*-methylmorpholine-*N*-oxide (NMMO): structure, trapping and recombination reactions

T. Rosenau,[a] A. Potthast,[a] H. Sixta[b] and P. Kosma[a,*]

[a]*University of Agricultural Sciences, Christian-Doppler-Laboratory, Institute of Chemistry, Muthgasse 18, A-1190 Vienna, Austria*
[b]*Lenzing AG, R&D Department, A-4860 Lenzing, Austria*

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Abstract—The two carbon-centered radicals 4-morpholinomethyl (**4**) and 4-methylmorpholin-3-yl (**5**), generated from the primary cation radical intermediate **3** by β-deprotonation, are the major radical species in reaction mixtures of *N*-methylmorpholine-*N*-oxide (**1**) as demonstrated by trapping reactions with γ-tocopherol. Carbon–carbon coupling products originating from the recombination of **4** and the reaction between **4** and **5** have been identified. Recombination of **4** with the primary cation radical **3** was shown to be the key step in the 'disproportionation' of **3** into *N*-methylmorpholine, morpholine and formaldehyde.

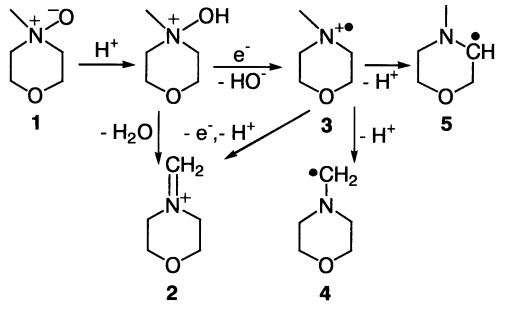
1. Introduction

N-Methyl-morpholine-*N*-oxide (NMMO, **1**) is one of the chemicals which are utilized not only in smaller quantities in research labs, but also as bulk chemicals on a large, industrial scale. NMMO is widely employed in organic synthesis for direct or transition metal-catalyzed oxidation of organic compounds,[1] especially for stereospecific *syn*-additions.[2] It is also used as a bulk solvent for cellulose in industrial fiber-making (Lyocell process).[3,4] Caution must be exercised in all processes involving NMMO as it is a relatively strong oxidant and tends toward uncontrollable decomposition reactions. There have been accounts of irregularities in the course of reactions with NMMO as the oxidant in organic synthesis,[5,6] as well as reports on the instability of NMMO solutions and the occurrence of unpredictable thermal runaway reactions upon industrial utilization of NMMO as cellulose solvent.[7,8]

The autocatalytic decomposition of NMMO into morpholine and formaldehyde catalyzed by a degradation product of NMMO, namely *N*-(methylene)morpholinium (**2**), has been demonstrated to be the major heterolytic pathway for the spontaneous degradation of NMMO.[9] Furthermore, it has been shown by the use of molecular probes[10] that side reactions of NMMO involve both heterolytic and homolytic pathways, and that those processes are closely interrelated by the ability of the radical species to form secondary products, such as **2**, which in turn decompose NMMO heterolytically.[11] NMMO-derived radicals are thus one major cause of irregularities in processes involving the amine oxide. However, none of these radical intermediates has been unambiguously identified or characterized so far, which gave impetus to the present study.

2. Results and discussion

Analogous to other tertiary amine oxides,[12,13] the primary radical species derived from NMMO was assumed to be the *N*-centered cation radical **3**, which is generated by cleavage of the N–O bond. For this breakage to occur, activation of the *exo*-oxygen by protonation and concomitant one-electron reduction is required, finally producing **3** and a hydroxyl ion.[14] Amine cation radicals are generally very labile and have a pronounced tendency towards mesolytic cleavage[15] of the C_α–H_β bond, which occurs in an extremely fast process resulting in uncharged *C*-centered α-amino radicals.[16] Hence, also the primary cation radical **3** must be expected to produce immediately the two neutral carbon-centered radicals **4** and **5** by release of a β-proton. We consequently hypothesized that the cation radical **3**, the *exo*-centered radical **4** and the ring-centered radical **5** were



Scheme 1. Primary radical species derived from NMMO.

Keywords: *N*-methylmorpholine-*N*-oxide; NMMO aminyl radicals; radical trapping; radical recombination; tocopherol.

* Corresponding author. Tel.: +43-1-36006-6055; fax: +43-1-36006-6059; e-mail: pkosma@edv2.boku.ac.at.

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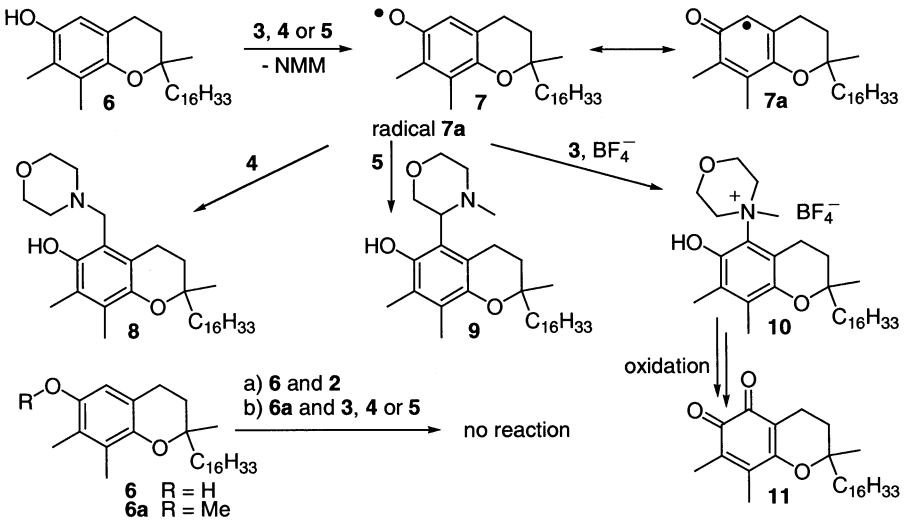


Scheme 2. Trapping of radicals **3**–**5** by γ-tocopherol.

the three main initial intermediates in homolytic reactions of NMMO (Scheme 1).

Cation radicals of tertiary amines without steric hindrance around the nitrogen, such as **3**, are rather intricate to investigate by EPR spectroscopy—detection mostly requires γ-irradiation in freon matrices at 77 K and provides only badly resolved spectra.[17,18] EPR was therefore considered inappropriate for the identification of radicals present in NMMO reaction mixtures. Unfortunately, also the application of conventional spin traps, such as substituted pyrroline-*N*-oxides, nitrones, or sterically hindered phenols, has been reported to fail in the presence of large amounts of tertiary amine oxides,[12,13] and has been unsuccessful also in our hands. However, a definite proof of the occurrence of radicals in reactions with the oxidant NMMO, i.e. reductions of the amine oxide, was provided by the use of γ-tocopherol (**6**), a component of natural vitamin E, as specific trapping agent. Along with its trapping products, **6** offers the advantage of supreme extractability into *n*-hexane or other apolar solvents due to the strongly lipophilic isoprenoid side chain, and can thus be readily separated even from very complex mixtures. An additional advantage is the almost complete absence of self-coupling reactions in contrast to other phenolic spin traps.

The reduction of NMMO to the corresponding radicals, which then couple with the trapping agent, was carried out with Fe(II) at four different temperatures. Other reductants, such as Mn(II) or Co(II), gave nearly identical results. Interaction of γ-tocopherol (**6**) with radicals generates a relatively stable γ-tocopheroxyl radical (**7**). While the *O*-centered form of the γ-tocopheroxyl radical has low affinity towards other radicals, its resonance structure **7a**, with the radical being centered at C-5, readily recombines with other radicals present in the mixture. Indeed, trapping products of all three radicals **3**–**5** have been isolated (Scheme 2).

The products **8** and **9** could in theory also have formed by electrophilic aromatic substitution (aminomethylation) involving *Mannich* intermediates, such as *N*-(methylene)-morpholinium ion **2**. However, as a prerequisite to the trapping experiments, it had been demonstrated beforehand that the reaction between the trapping reagent **6** and an excess of *Mannich* intermediate *N*-(methylene)-morpholinium chloride does not proceed under the typical trapping conditions at −78°C and 0°C, and is very slow at 20°C. In addition, 2-acetonaphthone, which had already been employed as a favorable means to detect **2** in NMMO mixtures,[19] gave no *Mannich* product under the original trapping conditions, but was readily converted into the corresponding *Mannich* base β-(morpholino)propionaphthone, if *N*-(methylene)morpholinium chloride was added to the reaction mixture. A further proof that the trapping products were formed homolytically, but not heterolytically by electrophilic aromatic substitution, was provided by the use of γ-tocopherol methyl ether (**6a**), which would exclusively react by electrophilic substitution—but not homolytically—due to the blocked phenolic

Table 1. Ratios of radicals **3**–**5** at different temperatures: calculated values and experimental data determined by trapping

T (°C)	Theoretical ratio **4/5** (%)[a]	Experimental ratio **4/5** (%)[b]	Yield of **8** and **9** (%)[c]	Recovery of **6** (%)
−78	99.47/0.53	100/0	46	41
0	98.69/1.31	100/0	47	34
20	97.03/2.97	98/2	32	32
50	95.95/4.05	96/4	28	35

[a] With the calculated activation energy difference $\Delta(\Delta E^{\#})$, the equilibrium ratios of **4** and **5** are given by $N_5/N_4=\exp(-\Delta(\Delta E^{\#})/RT)$, assuming an irreversible formation reaction for **4** and **5**.
[b] Isolated yields of coupling products **8** and **9**, error for **4** approx. ±3%.
[c] Sum of the yields of **8** and **9**, relative to trapping agent **6**.

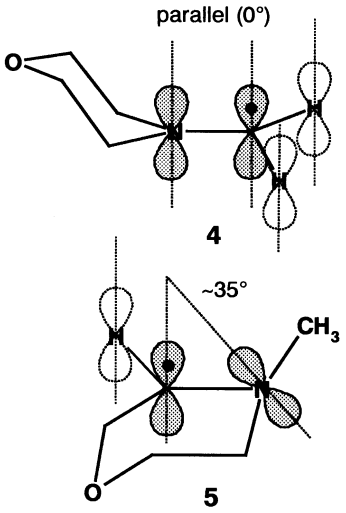
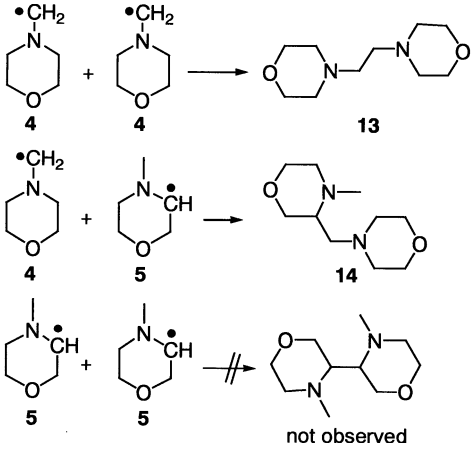


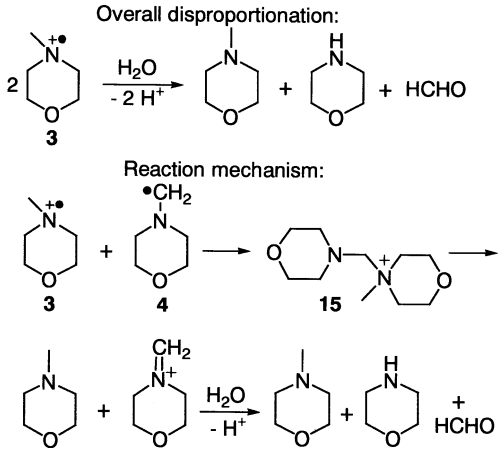
Figure 1. Illustration of hyperconjugative stabilization and approximate geometries, leading to higher stability of **4** as compared to **5**.

OH group. The fact that no trapping products were found in this case demonstrated unambiguously that the formation of **8** and **9** is indeed caused by homolytic reactions, but not by competitive heterolytic processes (Scheme 2).

Compound **8**, the major trapping product, originates from coupling of radical **4** with **7a**. Trapped **5** was also observed, however in significantly smaller amounts and only at higher reaction temperatures (2% vs. 98% of trapped **4** at 20°C and 4% vs. 96% of trapped **4** at 50°C), see Table 1. This agrees very well with theoretical considerations based on computations on the ab initio level. Also the trapping product of the primary cation radical **3**, ammonium cation **10**, was isolated by precipitation as the corresponding tetrafluoroborate in very small amounts. The extremely low yield of **10** appears plausible for three reasons: first, the stability of **3**, and thus its equilibrium concentration, is very low as it readily loses a β-proton to give the more stable **4** or **5**. Second, tertiary amine cation radicals recombine rather slowly with γ-tocopheroxyl radicals: while the recombination of γ-tocopheroxyl radicals with carbon-centered radicals is a diffusion-limited process with the rate being largely independent of the nature of the radical, the rate



Scheme 3. Radical recombinations with C–C bond formation, involving the carbon-centered radicals **4** and **5**.



Scheme 4. Disproportionation reactions involving radicals **3** and **4**.

constant for the recombination with amine cation radicals is about three orders of magnitude smaller.[20,21] Third, the trapping product is extremely thermolabile and sensitive towards oxidation. Even short exposure to air causes complete oxidative conversion into α-tocored **11**.[22]

Due to the differently fast recombination reactions, it is not justified to deduce the equilibrium ratio between **3** and **4** (or **3** and **5**) from the ratio of trapping products obtained, whereas the ratio between **4** and **5** in the NMMO reaction mixture can well be concluded from the amount of trapping products **8** and **9**, as done in Table 1.

Ab initio computations predicted the activation energy for the formation of **5** from **3** to be 8.5 kJ/mol more positive than that for the formation of **4** from **3**, which agreed very well with the experimental data from trapping (Table 1). In addition, the *exo*-centered radical **4** was calculated to be more stable by 2.3 kJ/mol (energy of formation) than the ring-centered radical **5**, which was unexpected at a first glance. However, optimum hyperconjugative stabilization in **4** and the lack of steric strain account for the higher stability of **4**: first, aminyl radicals generally experience strong hyperconjugative stabilization of the SOMO by neighboring orbitals. This applies also to the p-SOMO in **4** which can fully overlap with two pseudo-p-orbitals of the remaining two methylene protons and with the nitrogen n-p-orbital (0 or 180°), so that the hyperconjugative stabilization reaches its optimum. In contrast, in **5** there is only one pseudo-p-orbital at the ring proton, and the nitrogen n-p-orbital overlaps less effectively (34.6°) with the SOMO, so that the stabilization effect is much smaller. Second, the spin-bearing carbon, which is a sp^2 hybrid with a singly occupied p-orbital, has nearly planar geometry. This means no steric strain at the *exo*-carbon of **4**, but severe twisting of the chair conformation for the ring-centered radical **5**, rendering the latter energetically unfavorable (Fig. 1).

Upon reduction of NMMO by Fe(II) at −78°C in the absence of trapping reagents, two stable recombination products with newly formed carbon–carbon bonds were separated and identified: 1,2-bis(4-morpholino)ethane (**13**, 0.7% rel. to NMMO) and 3-(4′-morpholinomethyl)-4-methylmorpholine (**14**, 0.035% rel. to NMMO), see

Scheme 3. Although the absolute yields relative to NMMO were very low, the ratio of the products again reflected the theoretical results. The amount of **13**, which was generated from two molecules of **4**, was significantly larger than that of **14**, which was formed by recombination of **4** with **5**. The self-coupling product of **5** was not observed, evidently due to the very low concentration of **5** in the mixture and due to the sterically more demanding recombination.

The same major by-products, namely *N*-methylmorpholine, morpholine and formaldehyde, are found in all kinds of reactions involving NMMO, no matter if it is used as the oxidant in synthesis or if it is employed in an industrial process as cellulose solvent. The underlying reaction can be rationalized as disproportionation of the primary radical intermediate **3**. For the first time, it was experimentally demonstrated that this disproportionation occurs through radical coupling of **3** and **4**, giving the ammonium aminal intermediate **15**, which was isolated from the reaction mixture and characterized. Compound **15** is thermally very labile and, when dissolved in aqueous media, immediately decomposes in quantitative yields into *N*-methylmorpholine, morpholine and formaldehyde (Scheme 4). The corresponding recombination product of **3** and **5** has not been found. The ratio between the reaction rates of disproportionation, self-coupling of **4**, and coupling of **4** with **5** can be roughly approximated by the ratio *N*-methylmorpholine:**13**:**14**, which was determined to be 300:20:1.

A final proof of the nature of radical species **3**–**5** is provided by the fact that employing *N*-methylmorpholine together with an one-electron *oxidant* provides product mixtures nearly identical to the above-discussed reactions of NMMO with an one-electron *reductant*. This appears logical since both reactions generate the same initial intermediate, radical cation **3**.

3. Conclusions

In summary, trapping methodology unambiguously confirmed the presence of the nitrogen-centered radical cation **3** and the carbon-centered radicals **4** and **5**, with the latter two species being generated from **3** by C_α–H_β cleavage. Formation of **5** is kinetically and thermodynamically disfavored over formation of **4**, in agreement with computational results. The presence of the two *C*-centered radicals was additionally proven by isolation of the self-coupling product of **4**, and the recombination product of **4** and **5**. Disproportionation of the primary radical **3** proceeds by recombination of **3** with **4**, via an intermediate ammonium aminal (**15**), which readily fragments into *N*-methylmorpholine, morpholine and HCHO in aqueous media.

4. Experimental

4.1. General remarks

^{1}H NMR spectra were recorded at 300.13 MHz, ^{13}C NMR spectra at 75.47 MHz. $CDCl_3$ was used as the solvent with TMS as the internal standard—if not stated otherwise. Data are given in ppm units. ^{13}C resonances were assigned by means of HMQC and HMBC spectra. Nomenclature and numbering of the carbon atoms in chromans and tocopherols as proposed by the IUPAC[23,24] have been used throughout. The δ-values of the atoms of the isoprenoid side chain (C-1′ to C-13′) are well established and will not be listed in the following, since they are only very slightly affected by modifications of the chroman structure and are insignificant in terms of identification of the molecule concerned.[25,26] The abbreviation 'd.i.' denotes peaks from 2 equiv. carbons. Elemental analyses were performed at the microanalytical laboratory of the Institute of Physical Chemistry at the University of Vienna. All chemicals used were of reagent grade, all solvents were of HPLC grade. γ-Tocopherol was prepared from the cheaper and readily available α-tocopherol.[27] Computations reported throughout this paper used Hartree–Fock methods (6-311G**) with full geometry optimization of each structure, starting from pre-optimized geometries (PM3).

4.2. Isolation of trapping products 8 and 9

A solution of NMMO (**1**, 10 mmol, 1.19 g) and γ-tocopherol (**6**, 2 mmol, 0.833 g) in chloroform (100 mL) was cooled to −78°C under inert atmosphere. Finely powdered ferrous chloride (10 mmol, 1.27 g) was added at once, and the mixture was stirred for 5 h. Solids were removed by filtration and washed with 20 mL of chloroform. The combined filtrates were warmed to room temperature, concentrated to a volume of about 20 mL, and thoroughly extracted with water (five times 50 mL), HCl (0.1 M, three times 50 mL) and again water (50 mL), and dried over Na_2SO_4. The aqueous extracts were discarded. The organic phase was concentrated in vacuo, and the oily remainder was chromatographed on acidic aluminium oxide (Brockmann grade I). Elution with *n*-hexane (Caution! The substance is known to have neurotoxic effects!) gave unchanged γ-tocopherol (**6**, 41%, 0.34 g), α-tocored (**11**, 0.052 g, 6%) and some unidentified by-products (7%). Elution with *n*-hexane/$CHCl_3$ (v/v= 1:0⟶1:5) provided trapping product **8** as colorless oil (0.47 g, 46% rel. to **6**, 9.2% rel. to **1**).

The same procedure was used with different reductants and at different reaction temperatures and times: 0°C and 1 h; 20°C and 45 min, 50°C and 30 min. Upon reaction at 50°C, chromatographic separation of the product mixture with *n*-hexane/chloroform provided trapping product **9** (0.012 g, 1.1% rel. to **6**, 0.22% rel. to **1**) apart from **8** (0.277 g, 26.9% rel. to **6**, 5.4% rel. to **1**).

4.2.1. 2,7,8-Trimethyl-5-(morpholinomethyl)-2-(4,8,12-trimethyltridecyl)-6-chromanol, 8. ^{1}H NMR: δ 2.10 (s, 3H, $^{7a}CH_3$), 2.15 (s, 3H, $^{8b}CH_3$), 2.49 (m, 4H, N–CH_2), 2.59 (t, 2H, $^4CH_2$), 2.90 (s, 2H, $^{5a}CH_2$), 3.69 (m, 4H, N–CH_2–CH_2–O), 4.30 (s, b, 1H, OH); ^{13}C NMR: δ 12.5 (^{7a}C), 12.8 (^{8b}C), 19.4 (^{4}C), 31.1 (^{3}C), 52.4 (N–CH_2, d.i.), 54.2 (^{5a}C), 64.9 (CH_2–O, d.i.), 74.5 (^{2}C), 114.7 (^{4a}C), 116.4 (^{7}C), 124.0 (^{8}C), 125.6 (^{5}C), 145.1 (^{6}C), 146.6 (^{8a}C). Anal. calcd. for $C_{33}H_{57}NO_3$ (515.8): C, 76.84; H, 11.14; N, 2.72; found: C, 77.01; H, 11.32; N, 2.52.

4.2.2. 2,7,8-Trimethyl-5-(4-methyl-morpholin-3-yl)-2-(4,8,12-trimethyltridecyl)-6-chromanol, 9. ^{1}H NMR: δ

2.08 (s, 3H, $^{7a}CH_3$), 2.17 (s, 3H, $^{8b}CH_3$), 2.41 (s, 3H, N–CH_3), 2.43 (m, 2H, N–CH_2), 2.62 (t, 2H, $^{4}CH_2$), 3.55 (m, 2H, N–CH_2–CH_2–O), 3.61 (dd, 1H, N–CH–CH_2–O), 3.67 (dd, 1H, N–CH–CH_2–O), 4.03 (dd, 1H, N–CH), 4.85 (s, b, 1H, OH); ^{13}C NMR: δ 12.5 (^{7a}C), 12.7 (^{8b}C), 20.1 (^{4}C), 31.5 (^{3}C), 43.1 (N–CH_3), 53.9 (N–CH_2), 56.4 (N–CH), 64.4 (CH_2–O), 72.9 (CH–CH_2–O), 74.5 (^{2}C), 115.3 (^{4a}C); 116.6 (^{7}C), 123.8 (^{8}C), 125.6 (^{5}C), 144.8 (^{6}C), 146.3 (^{8a}C). Anal. calcd. for $C_{33}H_{57}NO_3$ (515.8): C, 76.84; H, 11.14; N, 2.72; found: C, 76.62; H, 11.40; N, 2.54.

4.3. Isolation of trapping product 10

A solution of NMMO (**1**, 100 mmol, 11.9 g) and γ-tocopherol (**6**, 20 mmol, 8.33 g) in chloroform (500 mL) was cooled to −78°C under inert atmosphere. Finely powdered ferrous chloride (100 mmol, 12.70 g) and tetrabutylammonium tetrafluoroborate (20 mmol, 6.60 g) were added at once, and the mixture was stirred for 2 h. *n*-Hexane (200 mL) was added, and the mixture was stirred for an additional hour. The mixture was warmed to room temperature, concentrated to a volume of about 200 mL at a temperature below 20°C, and again cooled to 0°C. Solids were removed by filtration, the filtrate was discarded. The residue was triturated with 50 mL of chloroform, then *n*-hexane was added (100 mL) and the mixture was left standing for 12 h at 0°C. The resulting precipitate was removed by filtration, washed with 10 mL of cold *n*-hexane, dried under reduced pressure and suspended in aqueous ethanol (v/v=1:1). The undissolved residue was removed by filtration and dried under reduced pressure, providing **10** as a white, waxy solid (0.012 g, 0.11% rel. to **6**, 0.02% rel. to **1**), mp 53–57°C.

4.3.1. 4-[6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-5-yl]-4-methyl-morpholinium tetrafluoroborate, 10. ^{1}H NMR: δ 1.99 (s, 3H, $^{7a}CH_3$), 2.11 (s, 3H, $^{8b}CH_3$), 2.93 (t, 2H, $^{4}CH_2$), 3.55 (s, 3H, N–CH_3), 3.58 (m, 4H, N–CH_2–CH_2–O), 4.14 (m, 2H, N–CH_2), 4.23 (dt, 2H, N–CH_2), 5.9 (s, b, 1H, OH); ^{13}C NMR: δ 12.2 (^{7a}C), 12.5 (^{8b}C), 20.1 (^{4}C), 30.3 (^{3}C), 54.9 (N–CH_3), 55.6 (N–CH_2, d.i.), 67.4 (O–CH_2, d.i.), 74.5 (^{2}C), 115.6 (^{4}C), 120.1 (^{7}C), 124.1 (^{8}C), 127.9 (^{5}C), 142.5 (^{6}C), 147.4 (^{8a}C). Anal. calcd. for the hydrogensulfate salt $C_{33}H_{59}NO_7S$ (613.90): C 64.57, H 9.69, N 2.28; found: C 64.42, H 9.90, N 2.14.

4.4. Isolation of coupling products 13 and 14

A solution of NMMO (**1**, 100 mmol, 11.9 g) in chloroform (500 mL) was cooled to −78°C under inert atmosphere. Finely powdered ferrous chloride (100 mmol, 12.70 g) was added at once, and the mixture was stirred for 5 h. Solids were removed by filtration and washed with 50 mL of chloroform. The combined filtrates were warmed to room temperature, concentrated to a volume of about 200 mL, and thoroughly extracted with saturated $NaHCO_3$ (five times 100 mL, not less!) and brine (50 mL), and dried over Na_2SO_4. The aqueous extracts were discarded. The organic phase was concentrated to a volume of about 10 mL and was chromatographed on acidic aluminium oxide (Brockmann grade I). Elution with methylene chloride/absolute ethanol (v/v=4:1) afforded the product amines in the order *N*-methylmorpholine, **13**, **14**, and morpholine (0.96 g, 11% rel. to NMMO), residual NMMO is retained on the column. While the secondary amine morpholine was cleanly separated, separation of **13** and **14** from the excess *N*-methylmorpholine was incomplete, so that the fractions containing the coupling products with *N*-methylmorpholine impurities were again chromatographed under identical conditions, giving the products *N*-methylmorpholine (1.07 g, approx. 11% rel. to NMMO), **13** (0.141 g, 0.7% rel. to NMMO), **14** (0.071 g, 0.035% rel. to NMMO).

4.4.1. 4-(2-Morpholinoethyl)morpholine, 13. ^{1}H NMR: δ 2.42 (m, 8H, N–CH_2–CH_2–O), 2.44 (s, 4H, N–CH_2–CH_2–N), 3.64 (m, 8H, N–CH_2–CH_2–O); ^{13}C NMR: δ 50.9 (N–CH_2–CH_2–N), 53.5 (N–CH_2–CH_2–O), 64.7 (N–CH_2–CH_2–O). Anal. calcd. for $C_{10}H_{20}N_2O_2$ (200.28): C, 59.97; H, 10.06; N, 13.99; found: C, 60.05; H, 10.12; N, 13.72.

4.4.2. 4-Methyl-3-(morpholinomethyl)morpholine, 14. ^{1}H NMR: δ 2.22 (m, 1H, N–CH_2–CH), 2.31 (N–CH_3), 2.32 (m, 4H, CH_2–N–CH_2–CH_2–O), 2.38 (m, 1H, CH–N–CH_2), 2.46 (m, 3H, CH–N–CH_2, N–CH, N–CH_2–CH), 3.38 (m, 1H, CH_3–N–CH_2–CH_2–O), 3.45 (m, 1H, CH_3–N–CH_2–CH_2–O), 3.53 (m, 2H, CH_2–N–CH_2–CH_2–O), 3.62 (m, 2H, CH_2–N–CH_2–CH_2–O), 3.71 (m, 1H, CH_3–N–CH–CH_2–O), 3.82 (m, 1H, CH_3–N–CH–CH_2–O); ^{13}C NMR: δ 47.2 (N–CH_3), 52.9 (–N–CH_2–CH), 53.9 (N–CH), 53.5 (CH_3–N–CH_2), 54.3 (CH–CH_2–N–CH_2, d.i.), 65.4 (CH_3–N–CH_2–CH_2–O), 68.2 (CH_2–N–CH_2–CH_2–O, d.i.), 70.1 (N–CH–CH_2–O). Anal. calcd. for $C_{10}H_{20}N_2O_2$ (200.28): C, 59.97; H, 10.06; N, 13.99; found: C, 60.11; H, 9.89; N, 13.76.

4.5. Isolation of intermediate 15

All preparation steps were carried out quickly under a flow of N_2 to minimize contact with air moisture. A solution of NMMO (**1**, 10 mmol, 1.19 g) in chloroform (100 mL) was cooled to −78°C under inert atmosphere. Finely powdered ferrous chloride (10 mmol, 1.27 g) was added at once, and the mixture was stirred for 30 min. After warming to room temperature, solids were removed by filtration and washed with 10 mL of chloroform. The combined filtrates were again cooled to −78°C, and 20 mL of chloroform containing one drop of concentrated sulfuric acid were added. The mixture became immediately cloudy. After stirring for 2 h, the precipitate was removed, washed with dry Et_2O (10 mL) and dried in vacuo to provide **15** as sulfate salt containing minor amounts (<2%) of **13**, **14**, *N*-methylmorpholine and morpholine as the respective sulfates.

4.5.1. 4-Methyl-4-(morpholinomethyl)morpholinium sulfate, 15. ^{1}H NMR: δ 2.84 (m, 2H, N–CH_2–CH_2–O), 2.92 (m, 2H, N–CH_2–CH_2–O), 3.21 (m, 2H, N^+–CH_2–CH_2–O), 3.24 (s, 3H, N^+–CH_3), 3.28 (m, 6H, N^+–CH_2–CH_2–O, N–CH_2–CH_2–O), 3.77 (m, 4H, N^+–CH_2–CH_2–O), 4.12 (dd, 2H, N_+–CH_2–N); ^{13}C NMR: δ 56.5 (N–CH_3), 62.4 (CH_2–N–CH_2–CH_2–O, d.i.), 64.0 (CH_3–N–CH_2–CH_2–O, d.i.), 66.5 (CH_2–N–CH_2–CH_2–O, d.i.), 69.1 (CH_3–N–CH_2–CH_2–O, d.i.), 79.3 (N–CH_2–N).

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