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Confirmation by trapping, synthesis, and reactivity of 2,3-dehydro-*N*-methylmorpholine (DNMM)

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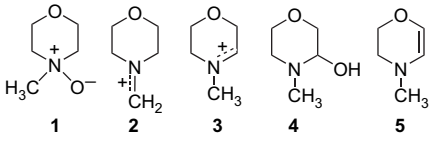
Abstract—The elusive 4-methyl-3,4-dihydro-2*H*-[1,4]oxazine (2,3-dehydro-*N*-methylmorpholine, DNMM, **5**) was confirmed to occur as degradation product of *N*-methylmorpholine-*N*-oxide (**1**) by trapping with the α-tocopherol-derived *ortho*-quinone methide in a hetero-Diels–Alder reaction with inverse electron demand. The regioselectivity of the addition was in good agreement with DFT computational data. An authentic sample of **5** was synthesized from formmorpholide (**16**) via 2-methoxy-formmorpholide in 38% overall yield.

1. Introduction

N-Methylmorpholine-*N*-oxide (NMMO, **1**) is used in bulk quantities as a cellulose solvent in the Lyocell process, which is a new and environmentally benign industrial approach to the production of man-made cellulosic fibers.[1] In addition, it is a frequently applied oxidant in organic synthesis,[2] mainly used in combination with catalytic amounts of transition metal catalysts.[3]

In previous studies, we have addressed the chemistry of NMMO in different reaction systems, especially under Lyocell process conditions,[4] and have shown that the NMMO-derived carbenium–iminium ions (**2**, **3**) play a key role in NMMO and Lyocell chemistry.[5] Later we reported on the first example of a carbenium–iminium ion interconversion, observed between these two *Mannich* intermediates.[20] The *ring*-centered **3** is rearranged into the *exo*-centered **2** via a highly organized transition state involving one molecule of water. As the reverse reaction is not observed, the latter intermediate usually predominates in NMMO chemistry. While intermediate **2** adds water to produce *N*-(hydroxymethyl)-morpholine, which subsequently degrades into morpholine and formaldehyde, species **3** would form 3-hydroxy-4-methylmorpholine (**4**), possibly giving rise to 2,3-dehydro-*N*-methylmorpholine (4-methyl-3,4-dihydro-2*H*-[1,4]oxazine, DMM, **5**) by elimination. Indeed, a compound having a molecular weight of 99—which would agree with compound **5**—was found as NMMO-derived byproduct in Lyocell dopes by gas chromatography/mass spectrometry, but so far this compound could neither be isolated nor unambiguously identified. Compound **5**, if indeed present, would be a highly reactive intermediate undergoing condensation and fragmentation reactions and thus contributing significantly to the undesired discoloration of NMMO-based cellulose solutions and the resulting Lyocell products. Thus, the confirmation of its absence or presence as byproduct in NMMO chemistry was a matter of high practical relevance, and so was the synthesis of an authentic sample: compound **5**—although seemingly having a rather simple structure—has not been reported so far.



2. Results and discussion

Unambiguous confirmation of the presence of **5** in a rather complex reaction mixture requires a selective reaction and a good separability of the formed trapping product. Especially the second demand is not trivial since reaction mixtures containing NMMO and its byproducts are highly polar, strongly oxidative multi-component mixtures. In the case of Lyocell dopes, working is additionally complicated by the high viscosity of the medium and process temperatures of about 100 °C. Considering these requirements we came back to our strategy of using α-tocopherol (vitamin E, **6**) or suitable derivatives (**7**) as trapping agents.[6] Due to their strongly lipophilic, isoprenoid side chain, these compounds and their trapping products are separable by

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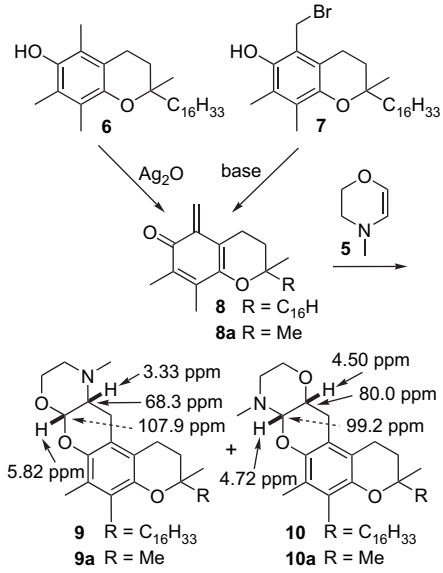
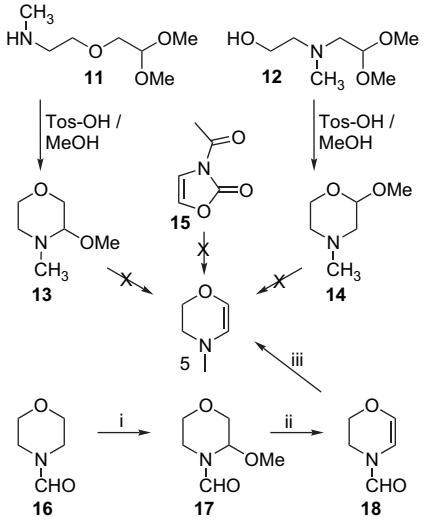
extraction with apolar solvents, such as *n*-hexane or petrol ether, even from very complex media, without the danger of co-extracting other byproducts. If a selective reaction can be found to trap one specific compound in a complex reaction mixture, this compound can be reliably separated and purified in the form of its tocopherol-derived trapping product.

As dehydro-NMM represents an electron-rich olefin, a hetero-Diels–Alder process with inverse electron demand would be a suitable trapping reaction. With the *ortho*-quinone methide **8** derived from α-tocopherol as the actual trapping agent, confirmation of the presence of DNMM in Lyocell dopes under conditions similar to processing succeeded (Scheme 1), and so did the trapping in organic extractives of Lyocell dopes containing the majority of NMMO-derived byproducts. The trapping agent was formed by oxidation of **6** with Ag_2O or alternatively, by thermal elimination of HBr from 5a-bromo-α-tocopherol (**7**).[7] Upon trapping, DNMM (**5**) was converted into tetracyclic compound **9** along with smaller amounts of its regioisomer **10** (Scheme 1), which were readily extracted into *n*-hexane. Only tocopherol-derived compounds were found in the extract. Referred to the starting amount of NMMO, between 0.08 and 0.11% of the amine *N*-oxide had been converted into DNMM and trapped. However, the total amount of DNMM actually formed can safely be assumed to be larger, as the trapping reaction was rather unlikely to proceed quantitatively. The NMR data of the two regioisomers are largely similar. Only the protons and the carbons at the two annulation sites showed significant differences by which the two compounds can be easily distinguished (see Scheme 1).



Scheme 1. Trapping of 2,3-dehydro-*N*-methylmorpholine (**5**) by the α-tocopherol-derived *ortho*-quinone methide (**8**) generated in situ; structure and characteristic NMR features of the two isomeric trapping products.

The synthesis of pure DNMM was surprisingly challenging. Exploring retrosynthetic alternatives we encountered the somewhat paradox fact that a wealth of methods for sophisticated structure was available, but the syntheses got more intricate and the variants more limited the simpler the target structure was. All attempts to achieve simultaneous ring closure and elimination starting from either [2-(2,2-dimethoxy-ethoxy)-ethyl]-methyl-amine (**11**) or 2-[(2,2-dimethoxy-ethyl)-methyl-amino]-ethanol (**12**) failed, and so did all trials to eliminate the methoxy group in a separate step, starting from the intermediately formed 3-methoxy-*N*-methyl-morpholine (**13**) or 2-methoxy-*N*-methyl-morpholine (**14**), respectively. Conversion of the methoxy substituents in **13** and **14** into tosyloxy groups succeeded in fair yields, but subsequent elimination failed at our hands. Deprotection/alkylation sequences on the commercially available 3-acetyl-3*H*-oxazol-2-one (**15**) were unsuccessful either. Evidently, the target compound was quite reactive, which made us come up with the concept to employ a moiety stabilizing the double bond to be introduced, and then to cleave off this auxiliary group after placement of the double bond. One obvious choice was an acyl substituent at the nitrogen, giving an amide, which by the partial double bond nature of its carbon–nitrogen bond would exert a stabilizing effect. Most conveniently, a formyl group should be chosen, which could be directly converted into the *N*-methyl motif by reduction. The synthetic sequence formmorpholide (**16**)→3-methoxy-4-formylmorpholine (**17**)→2,3-dehydro-formmorpholide (**18**)→2,3-dehydro-*N*-methylmorpholine (**5**) was eventually successful, providing the target compound as a clear, colorless liquid in 38% overall yield (Scheme 2). Dehydro-NMM proved to be highly unstable in acidic media, upon prolonged (>20 min) contact to air, and against water, especially at temperatures above 40 °C, giving rise to brown discoloration products, which quickly solidified into a polymeric, nearly black char. Also exposure to sunlight (in a glass vial) caused a visible brown discoloration, but without formation of viscous polymerization products. By contrast, DNMM was stable against non-aqueous bases, and could be stored over anhydrous K_2CO_3 under inert gas in the dark at rt for at least 4 months without changes.



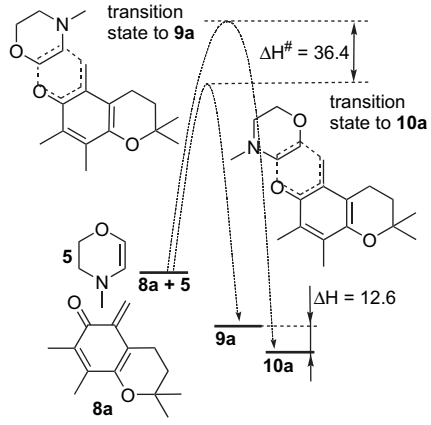
i = NBS (3 eq. over 5 h), MeOH / HCOOH (v/v = 19/1), 8h, reflux, 62%; **ii** = TfOH (0.03 eq.), $CHCl_3$, 30 min, -20 °C to reflux, 92%; **iii** = $LiAlH_4$, Et_2O, -30 °C, 4 h, 79%

Scheme 2. Synthesis of 2,3-dehydro-*N*-methylmorpholine (**5**) via 4-formyl derivatives **16** and **17**.

An alternative preparation of **17** by anodic oxidation in methanol has been described,[8] but no NMR data of the two atropisomers have been published so far. The elimination approach using catalytic amounts of TfOH at –20 to 80 °C was superior in yield (92%) and workup to a previously published procedure using solid ammonium bromide at 215 °C (73%).[9] Neat **5** was used for the preparation of authentic samples of the trapping products **9** and **10**.

It should be noted that the key intermediate 3-methoxy-4-formylmorpholine (**17**) as well as amide **18** each exist as a mixture of two atropisomers due to the restricted rotation around the amide bond.[10] Dynamic NMR—recording the temperature dependence of the chemical shift difference of the atropisomeric amide protons—allows determining the rotational barrier with regard to the rate constant for the rotation process k_r and the free activation enthalpy ΔG_r of the rotation,[11] which were found to be 122.8 s^{-1} and 72.4 kJ mol^{-1} for **17**, and 135.8 s^{-1} and 89.6 kJ mol^{-1} for **18**, respectively.[12] The higher value for the rotational barrier in **18** reflects the conjugational stabilization effect. The coalescence temperatures of **17** and **18**—the temperatures at which the corresponding resonances of the two atropisomers start to fall together—were 92 °C and 106 °C, respectively, as compared to 86 °C for *N*,*N*-dimethylacetamide.

The *ortho*-quinone methide **8** reacts as electron-deficient, heteroanalogous diene in Diels–Alder reactions. Its reaction with ethylvinyl ether, which has been frequently used in mechanistic studies,[13] proceeds regioselectively in a way that the α-carbon of the vinyl reacts with the quinone methide oxygen, and the vinylic β-carbon with the methylene carbon of the quinone methide. This regioselectivity can be readily explained by ionic resonance forms of the coreactants or alternatively by the frontier orbital theory. With DNMM as the coreactant, the situation was less unambiguous, as the compound is both a vinyl ether and an eneamine so that two directions of addition—leading to tetracycles **9** and **10**—become possible according to theory. Indeed, these two addition products were found by experiment (see Scheme 1). Computations on the DFT level, performed on the truncated model compounds **8a**, **9a**, and **10a** possessing a methyl group instead of the isoprenoid side chain, predicted **10a** to be 12.6 kJ mol^{-1} more stable than **9a** (see Scheme 3). Assuming the reaction to proceed under thermodynamic control, this would translate into product **10a** being formed slightly predominantly, contrary to experiment. However, the difference between the transition states leading to **9a** and **10a**, respectively, was calculated to be 36.4 kJ mol^{-1}, the lower activation energy leading to product **9a**, which evidently agreed better with the experiment. The dependence of the product distribution from the reaction temperature[14] allowed estimating the difference between the free activation energies for formation of **9** and **10**, which was 32.4 kJ mol^{-1}, meaning that the activation energy for the formation of **9** was by this value lower than for the formation of **10**.[15] This was in quite satisfying agreement with the calculated value of 36.4 kJ mol^{-1}.



Scheme 3. Schematic representation of the computed reaction energetics for the formation of the two regioisomers in the reaction of **5** and **8a** to **9a** and **10a**. Values are given in kJ mol^{-1}.

3. Conclusions

By trapping with a tocopherol-derived *ortho*-quinone methide reacting as an electron-deficient diene (**8**), the presence of 4-methyl-3,4-dihydro-2*H*-[1,4]oxazine (DNMM, **5**) was confirmed in reaction mixtures of NMMO (Lyocell dopes), which implies a significant contribution of this compound to the observed discoloration effect of both Lyocell dopes and the fibers resulting therefrom. The compound is also involved in nitrogen fixation to the Lyocell product, primarily by addition of cellulosic hydroxyls to the double bond in **5**. The amount of 3-(4-methylmorpholinyl) groups attached to cellulose was proportional to the amount of coreacting DNMM as seen by microanalysis.

The regioselectivity of the trapping reaction was correlated with computations on the DFT level. The experimentally observed ratio between the resulting regioisomeric Diels–Alder products (**9** and **10**) agreed well with the computed activation energy data for the transition states leading to those products.

The synthesis of DNMM was accomplished by introducing an *N*-formyl structure as an auxiliary group temporarily stabilizing the endocyclic double bond. The atropisomerism of unsaturated formamide **18** was more pronounced than that of formamide **17** demonstrating the stabilization effect by conjugation. The target compound **5** was obtained in about 35% yield, starting from formmorpholide (**16**).

4. Experimental

4.1. General

All chemicals were commercially available. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G60 (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded at 300.13 MHz, ^{13}C NMR spectra at 75.47 MHz in $CDCl_3$ as the solvent and TMS as the internal standard. Data are given in parts per million. ^{13}C peaks were assigned by means of APT, HMQC, and HMBC spectra; 'd.i.' denotes peaks with double intensity.

Computations, as implemented through Spartan Pro 02 by Wavefunction, Inc., Irvine, CA, USA, were carried out on geometries pre-optimized by the semi-empirical PM3 method. For full geometry optimization the widely employed B3LYP hybrid method, which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang, and Parr[16] parametrized by Becke,[17] was used, along with the double-zeta split valence basis sets 6-31+G*,[18] which includes diffuse functions. Transition states and minima were confirmed by analysis of the calculated vibrational spectrum. For all transition states the number of imaginary frequencies was 1, for all minimum geometries it was 0.

4.1.1. Formmorpholide, 16. A mixture of morpholine (17.4 g, 0.2 mol), ethyl formate (74 g, 1.0 mol), and toluenesulfonic acid (0.05 g) was refluxed (55 °C) for 4 h. Excess ester was distilled off and the residue was fractionated under reduced pressure to afford 4-formylmorpholine as viscous liquid (20.2 g, 88%, n_D^{20}=1.488, bp (5 Torr)=96–98 °C, bp=233–235 °C), which was directly used for further manipulation.

4.1.2. 3-Methoxy-4-formylmorpholine, 17. A solution of 4-formylmorpholine (3.45 g, 30 mmol) in methanol (190 mL) and formic acid (concn, 10 mL) was heated to reflux, and *N*-bromosuccinimide (16.0 g, 90 mmol) was added in portions over 5 h. Refluxing was continued for 3 h, the solution was cooled to rt. The solution was concentrated to a volume of about 50 mL, methylene chloride (100 mL) was added, and the mixture was extracted five times with 2 N NaOH (20 mL), washed with brine and dried over $MgSO_4$ overnight. Removal of the solvent provided a residue, which was distilled under reduced pressure to afford 3-methoxy-4-formylmorpholine as a colorless, viscous liquid (2.70 g, 62%, bp (1 Torr)=96–98 °C, n_D^{20}=1.339[19]). *trans*-Atropisomer (75%): ^{1}H NMR: δ 3.18 (dt, 1H, N–CH_A), 3.28 (s, 3H, O–CH_3), 3.45–3.63 (m, 2H, O–CH_2), 3.94–4.08 (m, 2H, O–CH_2), 4.07 (dd, 1H, N–CH_B), 4.46 (m, 1H, N–CH), 8.21 (s, 1H, CHO). ^{13}C NMR: δ 36.1 (5-C), 54.3 (O–CH_3), 65.9 (6-C), 69.7 (2-C), 83.1 (3-C), 160.9 (CHO). *cis*-Atropisomer (25%): ^{1}H NMR: δ 3.28 (dd, 1H, N–CH_A), 3.34 (s, 3H, O–CH_3), 3.45–3.63 (m, 2H, O–CH_2), 3.59–3.63 (dt, 1H, N–CH_B), 3.94–4.08 (m, 2H, O–CH_2), 5.33 (m, 1H, N–CH), 8.20 (s, 1H, CHO). ^{13}C NMR: δ 41.2 (5-C), 55.4 (O–CH_3), 66.6 (6-C), 69.1 (2-C), 77.0 (3-C), 162.0 (CHO).

4.1.3. 2,3-Dihydro-[1,4]oxazine-4-carbaldehyde (2,3-dehydro-formmorpholide, 18). To a solution of 3-methoxy-4-formylmorpholine (1.45 g, 10 mmol) in chloroform (60 mL) was added triflic acid (45 mg, 26 μL, 0.03 equiv) at −20 °C. The solution was heated to reflux for 30 min and subsequently cooled to rt. The solvent was removed and the residue chromatographed on silica gel to provide acylenamine **18** as colorless liquid (1.04 g, 92%, n_D^{20}=1.355[19]). ^{1}H NMR (2 atropisomers): δ 3.68–3.72 (m, 1H, N–CH_A), 3.98–4.05 (m, 2H, N–CH_B, O–CH_A), 4.45 (m, 1H, O–CH_B), 6.04 and 6.06 (2d, 2×1H, N–CH=), 6.41 and 6.46 (2d, 2×1H, O–CH=), 7.86 and 8.08 (2s, 2×1H, CH=O). ^{13}C NMR (2 atropisomers): δ 39.1, 42.4 (5-C), 66.6, 67.3 (6-C), 96.3, 101.2 (3-C), 122.3, 122.5 (2-C), 157.8, 160.3 (CHO). *M*=113.1. Anal. Calcd for $C_5H_7NO_2$: C 53.09, H 6.24, N 12.38. Found C 52.99, H 6.40, N 12.33.

4.1.4. 4-Methyl-3,4-dihydro-2*H*-[1,4]oxazine (DNMM, 2,3-dehydro-*N*-methylmorpholine, 5). To a solution of acylenamine **18** (0.8 g, 7.0 mmol) in diethyl ether (50 mL) was added $LiAlH_4$ (10.0 mmol) at −30 °C. The mixture was stirred at this temperature for 4 h, and warmed to 0 °C. Concentrated aqueous NH_4Cl solution was added and the organic phase separated. The aqueous layer was extracted three times with diethyl ether (20 mL), and the combined extracts were dried over $MgSO_4$. Removal of the solvent and microdistillation over $CaCO_3$ at ambient pressure provided DNMM (**5**) as colorless liquid (548 mg, 79%, n_D^{20}=1.362, bp=84–87 °C). For long-term storage, the substance should be kept at −20 °C in the dark over basic alumina to avoid discoloration and polymerization reactions. ^{1}H NMR: 2.44 (s, 3H, N–CH_3), 2.98 (dd, 1H, N–CH_A, *J*=11.9, 1.9 Hz), 3.08 (dt, 1H, N–CH_B, *J*=11.0, 2.8 Hz), 3.78 (dd, 1H, O–CH_A, *J*=11.9, 2.8 Hz), 4.13 (dt, 1H, O–CH_B, *J*=11.0, 1.9 Hz), 5.86 (d, 1H, *J*=17.4 Hz, N–CH=), 6.24 (d, 1H, *J*=17.4 Hz, O–CH=). ^{13}C NMR: δ 39.0 (N–CH_3), 58.3 (N–CH_2), 60.5 (O–CH_2), 112.1 (N–CH=), 122.9 (O–CH=). *M*=99.1. Anal. Calcd for C_5H_9NO: C 60.58, H 9.15, N 14.13. Found C 60.50, H 9.26, N 13.97.

4.2. Hetero-Diels–Alder reaction of DNMM with in situ-generated *ortho*-quinone methide (8)

α-Tocopherol (1.00 g, 2.32 mmol) and DNMM (**5**, 0.50 g, 5.0 mmol) was dissolved in 20 mL of dry *n*-hexane. Freshly prepared Ag_2O (0.65 g, 2.81 mmol) was added to the tocopherol solution in four equal charges at intervals of about 5 min. The reaction mixture was stirred for another 10 min and the solids were filtered off through a layer of Celite. The solvent was evaporated, and the oily residue was chromatographed on silica gel (*n*-hexane/toluene, v/v=9:1) to afford tetracycles **9** (683 mg, 55.7%) and **10** (242 mg, 19.8%) in a molar ratio of 2.8:1.

3,5,6,8-Tetramethyl-3-(4,8,12-trimethyltridecyl)-2,3,7a,-8,9,10,11a,12-octahydro-1*H*-4,7,11-trioxa-8-aza-benzo[*a*]anthracene, **9**. ^{1}H NMR: δ 0.70–1.89 (m, 38H, 3-CH_2, 2a-CH_3, and $C_{16}H_{33}$ chain), 2.11 (s, 3H, 7a-CH_3), 2.15 (s, 3H, 8b-CH_3), 2.31 (s, 3H, N–Me), 2.34 (m, 1H, N–CH_{2A}), 2.54–2.60 (m, 2H, 5a-CH_{2A}, N–CH_{2B}), 2.60 (t, 2H, 4-CH_2), 2.75 (s, 2H, 5a-CH_{2B}), 3.33 (m, 1H, N–CH), 3.60–3.68 (m, 2H, O–CH_2), 5.82 (d, 1H, ^3J=3.7 Hz, O–CH–O). ^{13}C NMR: δ 11.6 (8b-CH_3), 12.4 (7a-CH_3), 20.3 (4-CH_2), 20.8 (5a-CH_2), 23.5 (2a-CH_3), 32.4 (3-CH_2), 39.4 (N–CH_3), 54.2 (N–CH_2), 62.5 (O–CH_2), 68.3 (N–CH), 74.2 (2-C), 107.9 (O–CH–O), 115.0 (4a-C), 115.5 (5-C), 122.2 (7-C), 123.5 (8-C), 145.3 (6-C), 147.5 (6-C); isoprenoid side chain: 19.7 (C-4a′), 19.8 (C-8a′), 21.0 (C-2′), 22.67 (C-13′), 22.74 (C-12a′), 24.5 (C-6′), 24.7 (C-10′), 28.0 (C-12′), 32.6 (C-8′), 32.7 (C-4′), 37.3 (C-7′), 37.4 (C-9′), 37.5 (C-5′), 37.6 (C-3′), 39.3 (C-11′), 39.7 (C-1′). *M*=527.8. Anal. Calcd for $C_{34}H_{57}NO_3$: C 77.37, H 10.88, N 2.65. Found C 77.27, H 11.02, N 2.57.

3,5,6,11-Tetramethyl-3-(4,8,12-trimethyl-tridecyl)-1,2,3,9,-10,11,11a,12-octahydro-7a*H*-4,7,8-trioxa-11-aza-benzo[*a*]anthracene, **10**. ^{1}H NMR: δ 0.70–1.89 (m, 38H, 3-CH_2,

2a-CH_3, and $C_{16}H_{33}$ chain), 2.10 (s, 3H, 7a-CH_3), 2.15 (s, 3H, 8b-CH_3), 2.35 (s, 3H, N–Me), 2.34–2.40 (m, 2H, N–CH_{2A}, N–CH_{2B}), 2.62 (m, 3H, 4-CH_2, 5a-CH_{2A}), 2.79 (m, 1H, 5a-CH_{2B}), 3.58–3.68 (m, 2H, O–CH_2), 4.50 (m, 1H, O–CH), 4.72 (d, 1H, ^3J=3.6 Hz, O–CH–N). ^{13}C NMR: δ 11.6 (8b-CH_3), 12.4 (7a-CH_3), 20.0 (4-CH_2), 23.5 (2a-CH_3), 24.9 (5a-CH_2), 32.4 (3-CH_2), 36.1 (N–CH_3), 50.2 (N–CH_2), 68.6 (O–CH_2), 74.4 (2-C), 80.0 (O–CH), 99.2 (O–CH–N), 115.1 (4a-C), 115.6 (5-C), 122.5 (7-C), 123.1 (8-C), 145.8 (6-C), 147.3 (6-C); isoprenoid side chain: 19.7 (C-4a′), 19.8 (C-8a′), 21.0 (C-2′), 22.67 (C-13′), 22.74 (C-12a′), 24.5 (C-6′), 24.7 (C-10′), 28.0 (C-12′), 32.7 (C-8′, C-4′), 37.3 (C-7′), 37.4 (C-9′), 37.4 (C-5′), 37.6 (C-3′), 39.3 (C-11′), 39.6 (C-1′). M=527.8. Anal. Calcd for $C_{34}H_{57}NO_3$: C 77.37, H 10.88, N 2.65. Found C 77.36, H 11.08, N 2.33.

4.3. Trapping of DNMM in NMMO reaction mixtures (Lyocell dopes)

A 6.6 wt % solution of cellulose (0.2 g) in NMMO monohydrate (3.0 g) was prepared by melting a mixture of both components in a 50 ml flask in an inert atmosphere. After keeping for 2 h at 120 °C the mixture had turned dark brown. Into the hot mixture 5a-bromo-α-tocopherol (**6**, 510 mg, 1.0 mmol) dissolved in dioxane (5 mL) was added. Thermal degradation of **7** produces *ortho*-quinone methide **8** as the actual trapping agent in situ. After cooling to rt the solids were triturated with *n*-hexane (100 mL), and the solvent was removed. The oily residue was chromatographed on silica gel (*n*-hexane/toluene, v/v=3:1), and the fraction with a R_f=0.83 on TLC (*n*-hexane/toluene, v/v=3:1) was again chromatographed on silica gel using *n*-hexane/toluene, v/v=19:1. The trapping products **9** (1.8 mg) and **10** (1.5 mg) were obtained in pure form (sum 3.3 mg, 0.11% relative to NMMO) and were identical to authentic samples (see above).

Acknowledgements

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12. This is in good agreement with the previously determined values of *N*,*N*-dimethylacetamide (k_r=117.4 s^{-1}, ΔG_r=74.25 kJ mol^{-1}): see Ref. 6b.
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14. Estimated by the ^{1}H NMR integrals of the crude reaction mixture. The *ortho*-quinone methide **8** was produced in situ by adding 5a-bromo-α-tocopherol (**7**) into the DNMM solution and pulverized KOH, which caused immediate elimination of HBr with concomitant formation of **8**. Experimentally, the ratio between **9** and **10** was determined to be 98:2 at 0 °C, 96:4 at rt, 89:11 at 50 °C, 73:27 at 80 °C, and 58:42 at 100 °C. From these values follows a $\Delta E^{\#}$ of 32.4 kJ mol^{-1}.
15. With R being the ratio between **9** and **10** follows: R=exp $(-(\Delta E^{\#}_9-\Delta E^{\#}_{10})/RT)$, so that a plot 'ln R versus 1/T' gives the slope $-\Delta(\Delta E^{\#})/R$, and thus the difference of activation energies.
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