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Studies into reactions of *N*-methylmorpholine-*N*-oxide (NMMO) and its hydrates with cyanuric chloride

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Abstract—The course of the reaction between *N*-methylmorpholine-*N*-oxide (NMMO, **1a**) and cyanuric chloride (**2**) is strictly dependent on the hydrate water content of the amine oxide. In solid phase, both substances undergo an explosion-like, extremely exothermic reaction. In solution, this process becomes controllable and leads to a quantitative degradation of NMMO into morpholine and formaldehyde, with **2** only acting as an inducing agent. The reaction can be conducted in a way that a clean deoxygenative demethylation is achieved. The monohydrate of NMMO (**1b**) is quantitatively converted into *N*-methylmorpholine and hypochlorous acid by the action of **2**. This conversion can be used in synthesis either to deoxygenate tertiary amine *N*-oxide monohydrates, or to produce chlorohydrins in non-aqueous, organic media in superior yields. The semisesquihydrate of NMMO (**1c**) reacts with **2** under consumption of water until non-hydrated NMMO is present, which is then further converted into morpholine and HCHO, as in the case of **1a** being directly employed as the starting material.

1. Introduction

N-Methylmorpholine-*N*-oxide (NMMO, **1a**) is used in transition metal-catalyzed oxidations of various organic structures[1] and can possibly be regarded as the most important amine *N*-oxide in organic synthesis.[2] Apart from such laboratory-scale applications, it is employed also as a bulk chemical in the textile industry to dissolve cellulose in derivatization-free fiber-making processes.[3] During our studies on the deoxygenation of amine oxides[4] and investigations into the chemistry of NMMO-derived byproducts and decomposition reactions of NMMO[5–7] we observed an 'incompatibility' between NMMO and substituted chlorotriazines or cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, **2**), the latter being very common anchor groups in textiles dyeing and finishing, which prompted us to study the mechanisms of chemical interaction in the system NMMO/cyanuric chloride in more detail.

When dry, pulverized cyanuric chloride was added onto pure non-hydrated NMMO (**1a**)[8] without mixing, the two white solids discolored within seconds to a dark-brown semisolid, and then decomposed into a black remainder under evolution of gases and extreme release of heat. When the two solids were not layered, but quickly mixed, the reaction became so violent and exothermic that jets of flames resulted. The same effect was observed if the monohydrate of NMMO (**1b**) was used, even without mixing. In the case of a dry atmosphere, the reaction was noticeably decelerated: the mixture became at least stable for about 1 min. The catalytic effect of traces of water on the rate of the decomposition could be vividly demonstrated by adding a small drop of water to the solids, or by letting water vapor diffuse into the reaction vessel. Deep temperatures also prolonged the induction period before the reactions became uncontrollable. However, a stabilization of the mixture for longer than approx. 3–4 min could not be achieved. In any case, the highly exothermic degradation process caused a complete decomposition of the reactants to charred products.

Considering that both NMMO and cyanuric chloride are rather 'conventional' bulk chemicals with a supposedly straightened-out chemistry, the observation of thermal runaway reactions was quite startling, especially for a solid-phase reaction that by all means was expected to proceed quite moderately. It was furthermore of interest whether the reaction could be directed toward a less ambiguous course under different, milder reaction conditions, or whether it could even be utilized in synthesis.

2. Results and discussion

2.1. The reaction between non-hydrated NMMO and cyanuric chloride

In organic solution, the reaction between NMMO (**1a**) and cyanuric chloride (**2**) could be controlled much better than

Keywords: tertiary amine *N*-oxides; NMMO; cyanuric chloride; reaction mechanism; isotopic labeling; trapping reactions.

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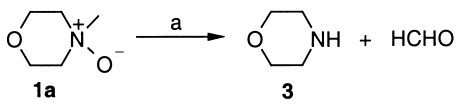
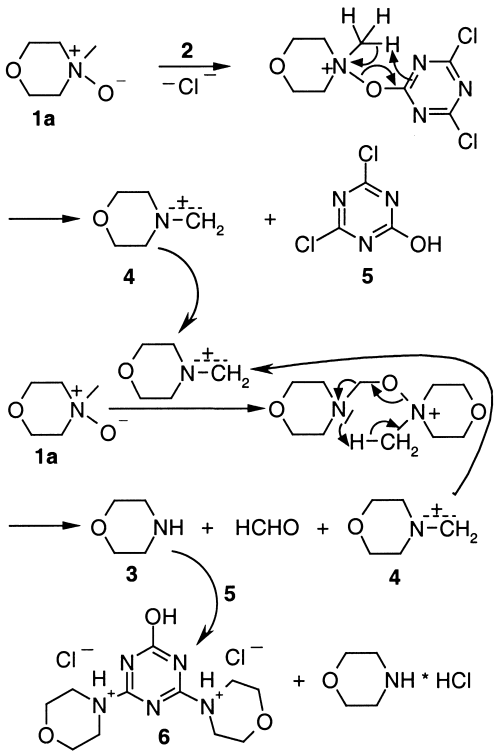


Scheme 1. Deoxygenative demethylation of anhydrous NMMO. (a) Cyanuric chloride (**2**) (0.01 equiv.), K_2CO_3 (0.1 equiv.), $CHCl_3$, 0°C to rt, 15 min, yield >98%.

in solid phase. Only effective cooling to 0°C and slow addition of dissolved **2** into the solution of **1a** was required. Under those mild reaction conditions a selective reaction proceeded that caused quantitative decomposition of NMMO into morpholine (**3**) and formaldehyde (Scheme 1). Catalytic amounts of **2** proved to be sufficient to completely degrade NMMO into morpholine and formaldehyde.

The mechanism of this reaction consists of an initiation step involving **2** and a catalytic cycle without further participation of cyanuric chloride (Scheme 2). The initial step is the nucleophilic attack of NMMO at the positively charged carbon of cyanuric chloride, with chloride being the leaving group. The *O*-acylated intermediate is then fragmented under cleavage of the N–O bond and production of a carbonium–iminium ion, *N*-(methylene)morpholinium (**4**) with concomitant release of a proton from the *N*-methyl group. The overall process in this initial step is an intramolecular redox reaction of NMMO, with the *N*-methyl group being oxidized to an *N*-hydroxymethyl group and the amine *N*-oxide being reduced to the amine (Scheme 2). The conversion can thus be considered as a Polonowski type reaction.[9] The cyanuric chloride used as inducer is converted into 4,6-dichloro-2-hydroxy-1,3,5-triazine (**5**) in this process, which reacts finally with the morpholine generated to the bis(hydrochloride) of 4,6-bis(morpholin-4-yl)-2-hydroxy-1,3,5-triazine (**6**).[10]



Scheme 2. Mechanism of the deoxygenative demethylation reaction.

The subsequent second reaction step, which effects the quantitative conversion of **1a** into morpholine and formaldehyde, is an autocatalytic process. An *N*-(methylene)morpholinium cation (**4**) initiates the reaction by alkylating another molecule of **1a**. The resulting intermediate fragments into **3** and HCHO, regenerating the carbonium–iminium ion **4** in turn. Thus, NMMO is decomposed without further participation of **2** in this catalytic cycle (Scheme 2). The mechanism of the reaction, which is similar to the recently reported autocatalytic decomposition of NMMO by Mannich intermediates,[6] was additionally supported by trapping the intermediate **4** in a Mannich type reaction with 2-acetonaphthone.[11]

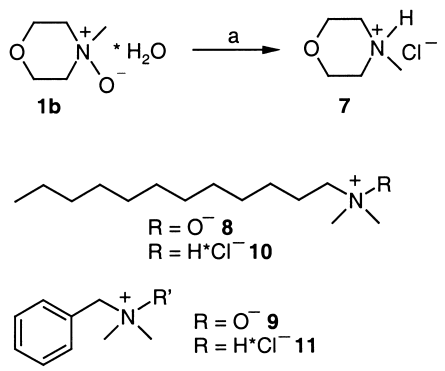
The use of catalytic amounts (1%) of **2** in combination with finely powdered, anhydrous potassium carbonate (stoichiometric ratio 1:10) allowed a neat deoxygenative demethylation of NMMO (**1a**) without formation of NMMO-derived byproducts. The potassium carbonate binds the evolving HCl, thus avoiding the formation of morpholinium chloride, but does not react with **2** or interfere with its catalytic action. With this variant of the procedure, morpholine was obtained in quantitative yield from NMMO. Quantification of the released formaldehyde was attempted by trapping with dimedone,[12] and afforded the corresponding dimedone adduct in a 92.5% yield.

2.2. The reaction between NMMO monohydrate and cyanuric chloride

To our surprise, replacing NMMO (**1a**) for its monohydrate **1b** changed the course of the reaction completely. Instead of morpholine, the hydrochloride of *N*-methylmorpholine (**7**·HCl) became the only NMMO-derived product. Apart from this, cyanuric chloride was required in stoichiometric amounts to achieve complete conversion of **1b**. A slow release of a gas was observed during the reaction, which was identified as oxygen containing some hydrogen chloride. When cyanuric chloride was applied together with excess anhydrous potassium carbonate, the evolved gas consisted of neat oxygen without admixed HCl.

At first, no plausible mechanism for a direct generation of molecular oxygen from **1b** and **2** could be rationalized. Then the observation of a typical stinging odor upon an attempted aqueous work-up pointed to formation of hypochlorous acid (HOCl), which subsequently decomposed into oxygen and hydrogen chloride. This decomposition, $2HOCl \rightarrow 2HCl + O_2 + 92.5\ kJ\ mol^{-1}$, is a most characteristic reaction of HOCl. It proceeds immediately for HOCl generated in situ in non-aqueous media, but is much slower in aqueous solutions.[13]

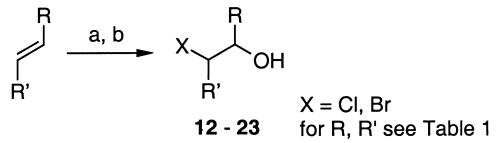
To demonstrate the in situ formation of HOCl in the system NMMO monohydrate/cyanuric chloride and to quantify the amount produced, we used the high affinity of HOCl towards sulfite which is neatly oxidized to sulfate, almost independently of the reaction medium. The addition of a mixture of sodium sulfite and cyanuric chloride (**2**) completely suppressed the evolution of gases (both HCl and O_2), and gave pure **7**·HCl in a quantitative yield: evidently, HOCl was trapped immediately upon its generation so that any side reactions of HOCl could be



Scheme 3. Deoxygenation of tertiary amine *N*-oxide monohydrates. (a) Cyanuric chloride/Na_2SO_3 (1.5 equiv.), $CHCl_3$, −5°C, 10 min, 93–96%.

prevented from the beginning. As sulfite is inert towards NMMO and molecular oxygen, the formation of sulfate can only be caused by HOCl as the oxidant. Determination of the sulfate formed[14] showed a nearly quantitative formation (92–94%) of HOCl from **1b**.

As indicated, two reagents were required to achieve a quantitative conversion of **1b** into **7**: cyanuric chloride to effect the N–O bond activation and cleavage, and sodium sulfite to reduce the intermediate HOCl to HCl. The HCl converts the produced *N*-methylmorpholine (**7**) into its insoluble hydrochloride, thus preventing a further reaction of **7** as the nucleophile with **2** or **5** to (*N*-methylmorpholin-4-yl)triazinium chlorides.[15] By means of this reagent mixture, tertiary amine *N*-oxide monohydrates can neatly be



Scheme 4. Synthesis of halohydrins from olefins with the system NMMO monohydrate/2,4,6-trihalo-1,3,5-triazine. (a) **1b** (1.1 equiv.), **2** (1.1 equiv.), $CHCl_3$, 10 min at −10°C, −10°C to rt, (b) Na_2SO_3, 15 min, rt, 46–94%.

deoxygenated (Scheme 3), as also shown for two other examples, dodecyl-*N*,*N*-dimethylamine-*N*-oxide·H_2O (**8**) and benzyl-*N*,*N*-dimethylamine-*N*-oxide·H_2O (**9**), which gave the corresponding tertiary amines dodecyl-*N*,*N*-dimethylamine (**10**) and benzyl-*N*,*N*-dimethylamine (**11**) in excellent yields (93 and 95%, respectively).

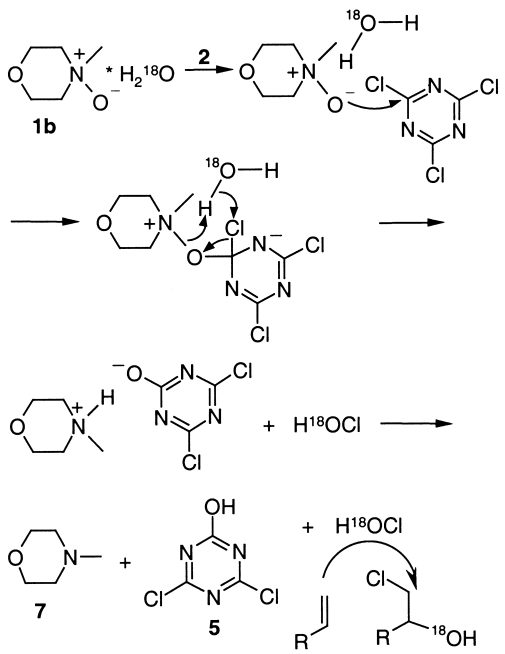
In the above-described procedure, the HOCl generated was immediately destroyed and not further utilized for chemical transformations. However, the reaction between **1b** and **2** offers some advantageous aspects for the generation of HOCl, which conventional systems are lacking. In preliminary experiments to demonstrate the potential of this method for synthesis, the system of **1b** and **2** was used as a source of HOCl to be added to double bonds to produce chlorohydrins (Scheme 4). Allyl alcohol and allyl chloride were chosen as simple model coreactants to explore the potential of the system and to optimize the reaction conditions. Due to the fact that in the case of **1b** and **2** as the HOCl source the reaction did not have to be stopped prior to a complete conversion of the allyl compound, also the overall yields were satisfactory: 65% for allyl alcohol and 77% for allyl chloride. These results could be optimized to 77 and 84%, respectively, e.g. by employing **2** and **1b** in a 1.1-fold excess relative to the olefin. Also other example olefins were converted into the corresponding chlorohydrins **12**–**23** (cf. Table 1) according to the optimized procedure. For bromohydrin formation, cyanuric chloride (**2**) was simply replaced by cyanuric bromide (**2a**) without yield penalty.

The initial step in the reaction mechanism of the HOCl generation is the nucleophilic attack of the *N*-oxide oxygen of NMMO monohydrate at a carbon in **2**, analogous to the reaction of non-hydrated NMMO. If attack of the hydrate water, producing HCl and 4,6-dichloro-2-hydroxy-1,3,5-triazine (**5**), would be the initial step, then **5** should react with **1a** or **1b** to the observed products, which is not the case. Thus, reaction of the hydrate water with **2** as initial step can be ruled out. The subsequent fragmentation must proceed in a way that the N–O bond is broken and a chlorine cation is released which is accepted by the hydrate water to form HOCl. Although the first reaction step, the

Table 1. Synthesis of halohydrins from olefins with the system NMMO monohydrate (**1b**)/2,4,6-trihalo-1,3,5-triazine (**2** or **2a**)

Starting olefin/cyanuric halide[a]	Product halohydrin	Yield[b]
Allyl alcohol/**2**	3-Chloro-propan-1,2-diol (**12**)	77
Allyl alcohol/**2a**	3-Bromo-propan-1,2-diol (**13**)	85
Allyl chloride/**2**	1,3-Dichloro-propan-2-ol (**14**)	84
Allyl bromide/**2**	1-Bromo-3-chloro-propan-2-ol (**15**)	82
Allyl chloride/**2a**	1-Bromo-3-chloro-propan-2-ol (**15**)	85
Allyl bromide/**2a**	1,3-Dibromo-propan-2-ol (**16**)	78
4-Penten-1-ol/**2**	5-Chloro-pentan-1,4-diol (**17**)	46
4-Penten-1-ol/**2a**	5-Bromo-pentan-1,4-diol (**18**)	51
1-Decene/**2**	1-Chloro-decan-2-ol (**19**)	94
1-Decene/**2a**	1-Bromo-decan-2-ol (**20**)	88
Phytol[c]/**2**	2-Chloro-3,7,11,15-tetramethyl-hexadecan-1,3-diol (**21**)	83
3,4-Dehydro-α-tocopheryl acetate[d]/**2**	3-Chloro-4-hydroxy-α-tocopheryl acetate[e] (**22**)	88
3,4-Dehydro-α-tocopheryl acetate[d]/**2a**	3-Bromo-4-hydroxy-α-tocopheryl acetate[f] (**23**)	85

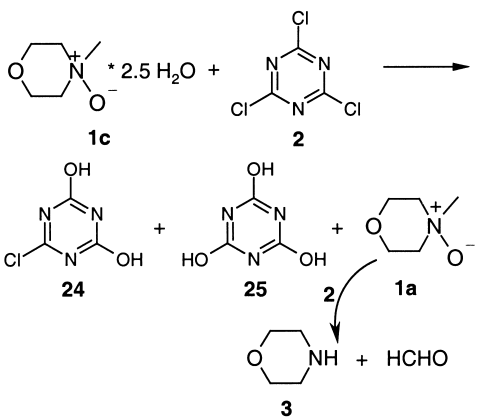
[a] 2,4,6-Trichloro-1,3,5-triazine (**2**) was used for synthesis of chlorohydrins; 2,4,6-tribromo-1,3,5-triazine (**2a**) for bromohydrins.
[b] Isolated yields in % after purification.
[c] IUPAC name: 3,7,11,15-tetramethyl-2-hexadecen-1-ol.
[d] IUPAC name: acetic acid 2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-tridecyl)-2*H*-chromen-6-yl ester.
[e] IUPAC name: acetic acid 3-chloro-4-hydroxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-tridecyl)-chroman-6-yl ester.
[f] IUPAC name: acetic acid 3-bromo-4-hydroxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-tridecyl)-chroman-6-yl ester.



Scheme 5. Mechanism of chlorohydrin formation by addition of HOCl, generated from NMMO monohydrate/cyanuric chloride, to olefins.

nucleophilic attack of the oxygen of the N–O bond at **2**, is the same for both NMMO (**1a**) and NMMO monohydrate (**1b**), the further course of the reaction is different, which can only be caused by the water bound in hydrated form. In organic solvents, the hydrate water of **1b** is generally not 'free', but remains linked to the highly polar N–O structure by strong hydrogen bonds.[16] This close proximity and strong bonding of the hydrate water to the N–O structure probably favors a concerted reaction mechanism as shown in Scheme 5.

While a direct confirmation of this mechanism appeared unfeasible, using isotopically labeled starting material could provide at least an indirect proof. For this purpose, NMMO monohydrate containing ^{18}O in the hydrate water moiety was prepared. With this material, the reaction of ^{18}O-labeled **1b** should provide isotopically pure **5** containing only ^{16}O and isotopically pure chlorohydrin containing only ^{18}O, provided that the mechanistic proposal in Scheme 5 is correct, whereas isotopic scrambling in the products should occur for mixed or more complex mechanisms. Employing 1-decene and allyl bromide as olefins, it was demonstrated by GC–MS that the produced chlorohydrins contained only ^{18}O, but no ^{16}O. This result confirmed that the oxygen in the generated HOCl originated exclusively from the hydrate water in **1b**, but not from the N–O oxygen, which pleads in favor of a mechanism involving a chlorine(+1) intermediate that is taken up by water to form HOCl as shown in Scheme 5.



Scheme 6. Reaction of NMMO semisesquihydrate (**1c**) with **2**.

2.3. The reaction between NMMO semisesquihydrate and cyanuric chloride

The reaction of NMMO semisesquihydrate (**1c**) and cyanuric chloride (**2**) proceeded again in a different way. Here, the hydrate water was consumed by a simple hydrolytic reaction with **2** to give 6-chloro-2,4-dihydroxy-1,3,5-triazine (**24**) and cyanuric acid (**25**). Up to a reaction time of about 30 min, no NMMO was consumed while water and cyanuric chloride reacted steadily (Scheme 6).

The reaction stopped if no excess cyanuric chloride was present. Otherwise, the decomposition of NMMO into morpholine and formaldehyde, as described in Schemes 1 and 2, was initiated. Interestingly, the 'drying effect' of the cyanuric chloride did not stop at the relatively stable stage of the monohydrate, but proceeded further. As the degradation of NMMO into morpholine and HCHO (see Schemes 1 and 2) is very fast and catalyzed already by minute amounts of **2**, it was not possible to determine whether the degradation of NMMO commences only after all hydrate water was completely consumed or whether it starts already when the net content of water in the system falls below the monohydrate level. This observation stands in contrast to non-chemical dehydration of the 2.5 hydrate, e.g. by azeotropic distillation, which can be stopped at the monohydrate stage.

The same behavior as for **1c** is true for NMMO with a higher water content, i.e. concentrated aqueous solutions of NMMO. An excess of **2** consumes all the water present until **1a** remains, and concomitantly initiates the decomposition of **1a** into morpholine and HCHO.[17]

3. Conclusion

From the preliminary results obtained with NMMO, the deoxygenative demethylation of tertiary *N*-methyl-*N*-oxides with a mixture of catalytic cyanuric chloride and anhydrous potassium carbonate appears to have a good potential to become a general approach for demethylating tertiary amines via the corresponding amine *N*-oxides,[18] which is of special interest in alkaloid chemistry. Compared to existing procedures to effect the same transformation, the procedure would offer the advantages of using readily available reactants and having a strikingly simple work-up.

The same applies for the deoxygenation of tertiary amine *N*-oxide monohydrates: the use of the two readily available solid chemicals as deoxygenating agent, cyanuric chloride

and sodium sulfite, is a clear benefit of the method as no special reagent preparation is required. The same deoxygenation reaction, carried out in the absence of sulfite, gives rise to HOCl formation, which can be used in syntheses of chlorohydrins. Also here, some positive aspects can be noted: first, HOCl is generated in a non-aqueous medium. Halogens, which are always present in aqueous solutions of hypochlorite according to chemical equilibria in the system, are absent, and also side reactions that occur when *N*-chloroamines are used as the source of HOCl are avoided. This obsoletes the interruption of the chlorohydrin formation at lower degrees of conversion,[19] which is commonly done to avoid extensive byproduct formation, however, at the expense of yield.[20] Second, the total amount of HOCl to be released can be precisely determined by the amount of **1b** and **2** employed, due to the unambiguous course of the generation reaction. The exact dosage thus possible cannot be achieved with aqueous hypochlorite, and is at least difficult with *N*-chloroamines. Third, the system is non-basic and non-alkaline which would allow conversions also of unstable, base-sensitive compounds.

In summary, the reactions between cyanuric chloride and NMMO in its different hydration stages revealed some new facets of an interesting chemistry. The clarification of the underlying reaction mechanisms was the prerequisite to advancing these reactions into more general synthetic procedures in the future.

4. Experimental

4.1. General remarks

^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75.47 MHz with $CDCl_3$ as the solvent and TMS as the internal standard—if not stated otherwise. Chemical shifts are given in ppm throughout. ^{13}C peaks were assigned by means of HMQC and HMBC spectra. GC–MS was done on a Thermo instrument with ion trap detector (EI, 70 eV, positive ion mode), and on a HP device with quadrupole detection (EI, 70 eV). Elemental analyses were performed at the microanalytical laboratory of the Institute of Physical Chemistry at the University of Vienna, and were within acceptable limits for all new compounds (±0.25%). All chemicals used were of reagent grade; the solvents were dried prior to usage according to standard procedures.

For the ^{13}C NMR measurements of cyanuric acid derivatives in D_2O, the pH value has to be carefully adjusted as the shifts are strongly pH-dependent. In the present study, spectra were recorded at a pD of 8.0, adjusted with NaOD in D_2O, producing the following ^{13}C NMR data: 4,6-dichloro-2-hydroxy-1,3,5-triazine (**5**): δ 168.2, 169.6; 4,6-dimorpholino-2-hydroxy-1,3,5-triazine (**6**): δ 52.6, 66.8, 166.4, 169.9; 6-chloro-2,4-dihydroxy-1,3,5-triazine (**24**): δ 161.2, 172.1; cyanuric acid (**25**): δ 159.5.

4.2. Reaction of hydrate-free NMMO with cyanuric chloride, general procedure

To a solution of NMMO (**1a**, 10 mmol) in 50 ml of dry chloroform was added cyanuric chloride **2** (0.1 mmol) dissolved in 2 ml of dry chloroform and pulverized, anhydrous K_2CO_3 (1 mmol). The mixture was stirred at 0°C (ice bath) while flushing with nitrogen to remove the forming HCHO. After 15 min the mixture was warmed to rt, the solids were removed by filtration through a layer of basic alumina. After removal of the solvent in vacuo pure morpholine (92%) was obtained. ^{1}H NMR: δ 1.71 (s, 1H, N*H*), 2.87 (t (m), 4H, N–CH_2), 3.67 (t (m), 4H, O–CH_2).

4.3. Reaction of NMMO monohydrate with cyanuric chloride: deoxygenation, general procedure

Na_2SO_3 (15 mmol) was added to a solution of NMMO monohydrate (**1b**, 10 mmol) in 50 ml of dry chloroform. A solution of **2** (10 mmol) in 20 ml of chloroform was added dropwise under stirring during 5 min, maintaining an efficient cooling to −5°C (ice/NaCl mixture). After 10 min the mixture was allowed to reach rt. The solids were separated by filtration, washed with 5 ml of diethyl ether, and the combined filtrate was discarded. Release of the free base from the solid remainder by dissolution in aqueous sodium carbonate, followed by extraction with diethyl ether, washing and drying of the organic phase according to standard techniques afforded pure *N*-methylmorpholine (96%). ^{1}H NMR: δ 2.16 (s, 3H, N–CH_3), 2.28 (t, 4H, N–CH_2), 3.59 (t, 4H, O–CH_2).

The same procedure was applied to deoxygenate tertiary amine *N*-oxides, employing dodecyl-*N*,*N*-dimethylamine-*N*-oxide monohydrate (**8**) and benzyl-*N*,*N*-dimethylamine-*N*-oxide monohydrate (**9**) instead of **1b**. The monohydrates were generated in situ by addition of 1 equiv. of water to the solution of the amine *N*-oxide. *N*,*N*-Dimethyl-dodecylamine (**10**), colorless, viscous liquid, (93%). ^{1}H NMR: δ 0.90 (t, 3H, CH_2–CH_3), 1.32 (m, 18H, CH_2), 1.90 (m, 2H, N–CH_2–CH_2), 3.20 (s, 6H, N–CH_3), 3.26 (m, 2H, N–CH_2). Benzyl-*N*,*N*-dimethylamine (**11**), colorless, viscous liquid (95%). ^{1}H NMR: δ 2.27 (s, 6H, N–CH_3), 3.45 (s, 2H, N–CH_2), 7.30 (m, 5H, ^{Ar}C*H*).

4.4. Reaction of NMMO monohydrate with cyanuric chloride: chlorohydrin formation, general procedure

To a solution of olefin (10 mmol) and NMMO monohydrate (**1b**, 11 mmol) in 50 ml of dry chloroform was added cyanuric halide (**2** or **2a**) (22 mmol) dissolved in 30 ml of chloroform under stirring at −10°C (ice/NaCl bath). The mixture was stirred for additional 10 min and warmed to rt. Dry sodium sulfite (10 mmol) was added, and the mixture was stirred for additional 15 min. After removal of the solids by filtration, the organic phase was washed twice with aqueous 2 M HCl, twice with 2 M NaOH, then with water and was dried over Na_2SO_4. Evaporation of the solvents in vacuo afforded the crude chlorohydrins in yields between 72 and 94%, see Table 1 for compounds and analytical data. For bromohydrin formation, the same procedure was used, simply replacing cyanuric chloride for cyanuric bromide. For starting materials, nomenclature and yields, see Table 1.

4.4.1. 3-Chloro-propan-1,2-diol (12). ^{1}H NMR: δ 3.62 (dd, 1H, CH_2Cl), 3.64 (m, 1H, CH_2Cl), 3.66 (dd, 1H, CH_2OH), 3.75 (dd, 1H, CH_2OH), 3.86 (s, 2H, OH), 3.93 (m, 1H, CH). ^{13}C NMR: δ 45.8 (CH_2Cl), 63.8 (CH_2OH), 71.9 (CH).

4.4.2. 3-Bromo-propan-1,2-diol (13). ^{1}H NMR: δ 3.47 (m, 3H, CH_2Br, CH_2OH), 3.69 (m, 1H, CH_2OH), 3.76 (CH), 4.07 (s, 2H, OH). ^{13}C NMR: δ 34.5 (CH_2Br), 64.4 (CH_2OH), 71.3 (CH).

4.4.3. 1,3-Dichloro-propan-2-ol (14). ^{1}H NMR: δ 2.53 (s, b, 1H, OH), 3.69 (d, 4H, CH_2), 4.07 (quint., 1H, CH). ^{13}C NMR: δ 45.9 (CH_2Cl), 71.0 (CH).

4.4.4. 1-Bromo-3-chloro-propan-2-ol (15). ^{1}H NMR: δ 2.23 (s, 1H, OH), 3.45 (dq, 2H, CH_2Br), 3.60 (m, 2H, CH_2OH), 4.10 (m, 1H, CH). ^{13}C NMR: δ 35.1 (CH_2Br), 47.1 (CH_2Cl), 70.7 (CH).

4.4.5. 1,3-Dibromo-propan-2-ol (16). ^{1}H NMR: δ 3.14 (s, 1H, OH), 3.56 (d, 4H, CH_2), 4.03 (m, 1H, CH). ^{13}C NMR: δ 35.4 (CH_2Br), 69.9 (CH).

4.4.6. 5-Chloro-pentan-1,4-diol (17). ^{1}H NMR: δ 1.50 (m, 3H, $^{3}CH_2$ (1H), $^{2}CH_2$), 1.69 (m, 1H, $^{3}CH_2$), 3.41 (m, 1H, $^{5}CH_2Cl$), 3.55 (m, 1H, $^{5}CH_2Cl$), 3.59 (t, 1H, $^{1}CH_2OH$), 4.11 (m, 1H, ^{4}CHOH), 4.50 (s, b, 2H, OH). ^{13}C NMR: δ 29.4 ($^{3}CH_2$), 30.0 ($^{2}CH_2$), 47.9 ($^{5}CH_2Cl$), 60.9 ($^{1}CH_2OH$), 70.7 (^{4}CHOH).

4.4.7. 5-Bromo-pentan-1,4-diol (18). ^{1}H NMR: δ 1.35 (m, 1H, $^{3}CH_2$ (1H), 1.55 (m, 3H, $^{3}CH_2$ (1H), $^{2}CH_2$), 2.98 (m, 1H, $^{5}CH_2Br$), 3.15 (m, 1H, $^{5}CH_2Br$), 3.62 (t, 1H, $^{1}CH_2OH$), 3.72 (s, 2H, OH), 4.15 (m, 1H, ^{4}CHOH). ^{13}C NMR: δ 30.1 ($^{2}CH_2$), 31.4 ($^{3}CH_2$), 38.4 ($^{5}CH_2Br$), 61.5 ($^{1}CH_2OH$), 69.9 (^{4}CHOH).

4.4.8. 1-Chloro-decan-2-ol (19). ^{1}H NMR: δ 0.85 (t, 3H, $^{10}CH_3$), 1.25 (m, 10H, 5×CH_2), 1.50 (m, 3H, $^{3}CH_2$ (1H)), $^{4}CH_2$), 1.62 (m, 1H, $^{3}CH_2$ (1H)), 3.38 (dd, 1H, $^{1}CH_2Cl$), 3.56 (dd, 1H, $^{1}CH_2Cl$), 4.04 (m, 1H, ^{2}CHOH), 4.82 (s, 1H, OH). ^{13}C NMR: δ 14.2, 22.2, 25.0, 29.4, 29.5, 29.7, 31.5 ($^{3}CH_2$), 32.0, 47.9 ($^{1}CH_2Cl$), 72.0 (^{2}CHOH). Anal. calcd for $C_{10}H_{21}OCl$ (192.73): C, 62.32; H, 10.98; Cl, 18.40. Found: C, 62.45; H, 11.09.

4.4.9. 1-Bromo-decan-2-ol (20). ^{1}H NMR: δ 0.87 (t, 3H, $^{10}CH_3$), 1.26 (m, 13H, 6×CH_2, $^{3}CH_2$ (1H)), 1.52 (m, 1H, $^{3}CH_2$ (1H)), 2.97 (dd, 1H, $^{1}CH_2Cl$), 3.21 (dd, 1H, $^{1}CH_2Cl$), 3.80 (s, 1H, OH), 4.18 (m, 1H, ^{2}CHOH). ^{13}C NMR: δ 14.1, 22.2, 25.6, 29.1, 29.4, 29.7, 32.0, 33.1 ($^{3}CH_2$), 38.9 ($^{1}CH_2Br$), 70.2 (^{2}CHOH). Anal. calcd for $C_{10}H_{21}OBr$ (237.18): C, 50.64; H, 8.92; Br, 33.69. Found: C, 50.78; H, 8.88.

4.4.10. 2-Chloro-3,7,11,15-tetramethyl-hexadecan-1,3-diol (21). ^{1}H NMR: δ 0.85 (m, 12H, 4×CH_3), 1.04–1.62 (m, 21H, 9×CH_2, 3×CH), 1.12 (s, 3H, $^{3}C-CH_3$), 3.20 (s, 1H, OH), 3.62 (t, 1H, ^{2}CHCl), 3.67 (m, 1H, $^{1}CH_2OH$), 3.87 (m, 1H, $^{1}CH_2OH$). ^{13}C NMR: δ 19.8, 19.9, 21.1, 22.6 (d.i.), 24.4, 24.5, 28.3, 31.0, 33.0, 36.7, 37.6, 37.7, 37.8, 39.2, 39.4, 60.7 ($^{1}CH_2OH$), 66.9 (^{2}CHCl), 74.2 ($^{3}C-OH$). Anal. calcd for $C_{20}H_{41}O_2Cl$ (349.00): C, 68.83; H, 11.84; Cl, 10.16. Found: C, 68.59; H, 12.02.

4.4.11. 3-Chloro-4-hydroxy-α-tocopheryl acetate (22). ^{1}H NMR: δ 2.08 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3CO), 4.48 (d, 1H, ^{3}CH, ^{3}J=6.3 Hz), 5.05 (t, 1H, ^{4}CH, ^{3}J=6.3 Hz). ^{13}C NMR: δ 12.0; 13.3; 13.7 (^{5a}C, ^{7a}C, ^{8b}C), 20.3 (OAc), 60.3 (^{3}C), 70.5 (^{4}C), 77.1 (^{2}C), 119.3 (^{4a}C), 123.0 (^{5}C), 126.1 (^{7}C), 129.8 (^{8}C), 147.5 (^{8a}C), 148.2 (^{6}C), 169.2 (CO). Resonances of the isoprenoid side chain are not given. Anal. calcd for $C_{31}H_{51}O_4Cl$ (523.20): C, 71.17; H, 9.83; Cl, 6.78. Found: C, 71.08; H, 10.02.

4.4.12. 3-Bromo-4-hydroxy-α-tocopheryl acetate (23). ^{1}H NMR: δ 2.09 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.31 (s, 3H, CH_3CO), 4.32 (d, 1H, ^{3}CH, ^{3}J=6.1 Hz), 5.03 (t, 1H, ^{4}CH, ^{3}J=6.1 Hz). ^{13}C NMR: δ 11.9; 13.3; 13.4 (^{5a}C, ^{7a}C, ^{8b}C), 20.5 (OAc), 58.4 (^{3}C), 71.2 (^{4}C), 77.0 (^{2}C), 119.5 (^{4a}C), 123.6 (^{5}C), 125.6 (^{7}C), 130.2 (^{8}C), 147.7 (^{8a}C), 148.2 (^{6}C), 169.4 (CO). Resonances of the isoprenoid side chain are not given. Anal. calcd for $C_{31}H_{51}O_4Br$ (567.64): C, 65.59; H, 9.06; Br, 14.08. Found: C, 65.45; H, 8.92.

4.5. Synthesis of NMMO·$^{18}OH_2$

Anhydrous NMMO was twice recrystallized from acetone (HPLC quality), followed by recrystallization from dry chloroform and drying in vacuo. The NMMO (52 mmol, 6.10 g) was dissolved in dry chloroform (50 ml) at rt, and ^{18}O-labeled water (40 mmol, 0.99 g, d=1.110 g cm^{-3}) was added. The solution was concentrated to a volume of about 25 ml at a bath temperature of 40°C, and cooled to rt. Dry diethyl ether (20 ml) was added, upon which the monohydrate crystallized. The mixture was kept at −20°C overnight, the solids were collected by filtration and dried in vacuo to give NMMO·$^{18}OH_2$ (92%) in long, colorless needles, mp 78°C. ^{1}H NMR (300 MHz, $CDCl_3$, 5 mg ml^{-1}) 2.70 (s, 2H, H_2O), 3.14 (dd, 2H, N–CH_2), 3.26 (s, 3H, N–CH_3), 3.38 (dt, 2H, N–CH_2), 3.78 (dd, 2H, O–CH_2), 4.43 (dt, 2H, O–CH_2,). ^{13}C NMR: δ 60.86 (N–CH_3), 61.52 (N–CH_2), 65.72 (O–CH_2).

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11. Briefly, the trapping reagent 2-acetonaphthone (5% rel. to **1a**) was added under stirring 1 min after addition of **2**, and was converted into the trapping product, *Mannich* base β-(4-morpholino)-propionaphthone (82%). For experimental details see: Potthast, A.; Rosenau, T.; Kosma, P.; Chen, C. L.; Gratzl, J. S. *Holzforschung* **2000**, *54*, 101.
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15. Addition of excess K_2CO_3 to the reaction mixture prevents the formation of **7**·HCl. In this case, a mixture of 6-(*N*-methylmorpholin-4-yl)-2,4-dichloro-1,3,5-triazinium chloride (main product) and 6-(*N*-methylmorpholin-4-yl)-2-hydroxy-4-chloro-1,3,5-triazinium chloride was produced by reaction of free **7** with **2** and **5**, respectively. The completely dechlorinated triazines, i.e. 2,4,6-tris(*N*-methylmorpholin-4-yl)-1,3,5-triazinium trichloride from **2** and 4,6-bis(*N*-methylmorpholin-4-yl)-2-hydroxy-1,3,5-triazinium dichloride from **5**, were not found. The nucleophilic substitution of the third Cl at the triazine ring was evidently too slow under the prevailing conditions.
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