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Autocatalytic Decomposition of *N*-Methylmorpholine *N*-Oxide Induced by Mannich Intermediates

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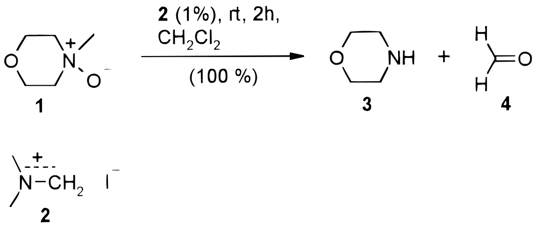
N-Methylmorpholine *N*-oxide (NMMO, **1**) is one of the most important amine oxides in organic synthesis.[1] It is frequently used in transition metal catalyzed oxidations of various organic structures.[2] Apart from these applications in the laboratory, it is employed on a large industrial scale as a solvent for cellulose in the textile industry.[3] During our investigations on oxidation reactions, we observed in several instances that NMMO as the oxidant was consumed far beyond the stoichiometric ratio, sometimes in fast exothermic processes. This excess consumption of **1** appeared to be rather random and did not obviously correspond to any changes in the reaction conditions. Furthermore, in these cases, the formation of large quantities of morpholine (**3**) was observed. This agrees with data on the formation of morpholine in randomly varying amounts during large-scale industrial applications of NMMO.[4]

Despite the differences in these processes, it seemed reasonable to assume common mechanisms that cause decomposition of NMMO under specific reaction conditions. Preliminary experiments showed that this breakdown was much faster than its reaction with a reductant. This could only mean that the decomposition of NMMO was caused by NMMO-derived byproducts present in the system, but not only by the reductant. Further investigations revealed that NMMO is completely inert toward its major degradation products *N*-methylmorpholine and morpholine and toward minor byproducts, such as formaldehyde (HCHO, **4**) or formic acid (HCOOH). However, a stoichiometric mixture of morpholine and HCHO degraded NMMO already when present in catalytic amounts (approximately 0.1% relative to **1**), a very surprising result. This decomposition proceeded independent of the solvent used as long as water was present in trace amounts.[5] In all cases, only **3** and **4** were formed as the reaction products.[6] Consequently, the same compounds that induce the decomposition of NMMO are in turn generated in the reaction.

Scheme 1



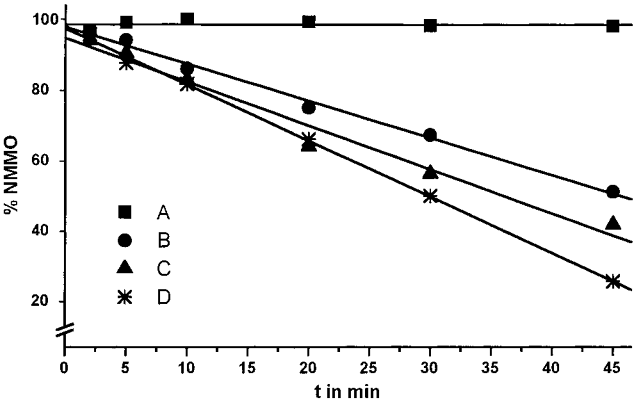


Figure 1. Degradation of NMMO into morpholine and HCHO by Eschenmoser's salt **(2)**. Decrease in NMMO concentration followed by capillary ion analysis: (A) NMMO, 1% **2**, addition of acid;[11] (B) NMMO·H_2O, 1% **2**, no additives; (C) NMMO, 1% **2**, no additives; (D) NMMO, 1% **2**, addition of base.[12]

To test whether carbenium−iminium ions, i.e., Mannich type intermediates that can be formed from **3** and **4** in neutral and acidic media,[7] are involved in the reaction as active species, we used dimethyl(methylene)iminium iodide (Eschenmoser's salt, **2**), a stable carbenium−iminium compound, instead of the morpholine/formaldehyde mixture. As shown in Scheme 1, *N*-methylmorpholine *N*-oxide (**1**) was completely degraded by only 1% of this compound (relative to **1**) into morpholine (**3**) and formaldehyde (**4**) within 70 min at room temperature, without formation of byproducts. In these reactions NMMO was either dissolved in chloroform or present as a solid. Evidently, catalytic amounts of Mannich intermediates are capable of decomposing NMMO in a "clean" process,[8] a novel reaction that has not been reported so far.

Investigations into the reaction kinetics[9] demonstrated that in the case of NMMO and NMMO monohydrate the rates of the degradation of **1** by 1% Eschenmoser's salt were fast and similar in magnitude (Figure 1, C and B). However, when NMMO·$2.5H_2O$, the second stable NMMO hydrate,[10]

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(1) Albini, A. *Synthesis* **1993**, 263.

(2) For illustrative examples, see: Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 4825. Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3287.

(3) Chanzy, H. *J. Polym. Sci. Polym. Phys. Ed.* **1980**, 1137.

(4) Buijtenhujs, F. A.; Abbas, M.; Witteveen, A. J. *Papier* **1986**, *40*, 615. Brandner, A.; Zengel, G. H. *Chem. Abstr.* **1982**, 977727d.

(5) No reaction was observed in carefully dried solvents if HCHO was supplied as a gas. The water provided by addition of HCHO as a 37% aqueous solution (formalin) was sufficient for the reaction to proceed. On the other hand, larger quantities of water stopped the reaction, e.g., addition of water in the double stoichiometric amount of NMMO.

(6) Both morpholine (**3**) and formaldehyde (**4**) were identified by comparison with authentic samples (NMR, MS). Before analysis, HCHO was characterized as 2,4-dinitrophenylhydrazone and dimedone adduct, respectively.

(7) Mannich reactions and intermediates have been extensively reviewed, see, for instance: Blicke, F. F. *Org. React.* **1942**, *1*, 303. Tramontini, M. *Synthesis* **1973**, 703.

(8) A typical experimental procedure is described in the following: To a 0.1 M solution of NMMO **(1)** in dry dichloromethane or dry chloroform were added 1% (relative to **1**) of **2** and after 5 min 1% (also relative to **1**) of water. The mixture was stirred at room temperature while flushing with nitrogen to remove the forming HCHO. In intervals of 10 min, a 0.5 mL aliquot was taken and analyzed by capillary ion analysis after extraction into 3 mL of ultrapure water (see ref 9). The reaction was finished when the electropherogram showed only morpholine **(3)**, but no remaining starting material. The 0.1 M solution of **1** in the above procedure can be replaced with pure NMMO. Here, the initial reaction temperature has to be set at approximately 100 °C to obtain a melt and then lowered gradually. Similarly, it is possible to substitute **2** and water for morpholine **(3)** (1% relative to **1)** and formaldehyde **(4)** (1% relative to **1**, as 37% aqueous solution).

(9) Kinetic measurements were carried out by quantifying NMMO and morpholine with capillary ion analysis. A Waters QE4000 instrument with the following general parameters was used: capillary column 60 cm × 75 μm; indirect UV detection at 214 nm (zinc lamp); hydrostatic sampling, sample time 10s, run voltage 20 kV. The electrolyte was prepared by adjusting a solution of 50 mM 4-methylbenzylamine, 50 mM 2-hydroxy-2-methylpropanoic acid (hydroxy-isobutyric acid), and 20 mM 18-crown-6 in ultrapure water to a pH of 3.3 ± 0.1 with additional hydroxy-isobutyric acid. Compounds **1** and **3** can be determined in the concentration range of 0.005 M to 2.5 and 0.001 M to 1.0 M, respectively. The identity of the product was confirmed by NMR.

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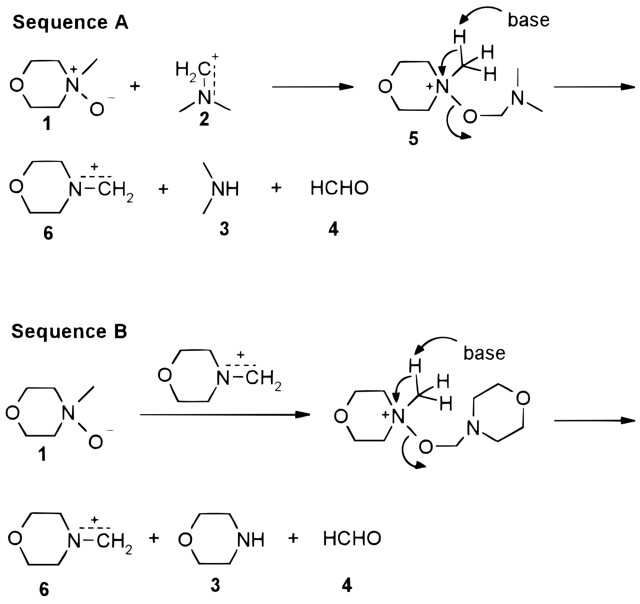
Scheme 2



was used as the starting material, no reaction occurred. Addition of small amounts of acid[11] inhibited the reaction (Figure 1, A). Only after extended reaction times did the catalytic degradation of NMMO commence again at a discernible rate. When larger amounts of acid—up to the same concentration as **2**—were used, the reaction did not proceed at all. In contrast, bases in comparatively small amounts[12] accelerated the decomposition of **1** (Figure 1, D), whereas addition of bases in larger amounts inhibited the reaction completely.

All of these observations lead to the reaction mechanism shown in Scheme 2. The initial step consists of an *O*-alkylation of NMMO **(1)** by a dialkyl(methylene)iminium ion (carbenium−iminium ion), the structure of which is obviously without influence on the further course of the reaction. Carbenium−iminium ions can be represented by different resonance structures; the one with the C-centered positive charge is required for the alkylation step. Alkylations as initial steps in the decomposition of amine oxide have not yet been reported in the literature, whereas reactions starting with either an acylation[13] of the oxygen in the N−O group or a complexation[14] at this site are well-established. The cation **5** resulting from the alkylation step is possibly cleaved in a concerted mechanism. In this process, the N−O bond is broken, and a "new" carbenium−iminium ion (*N*-methylenemorpholinium cation, **6**) is produced with concomitant removal of one proton from the *N*-methyl group. The leaving group formed from the initial catalyst subsequently forms secondary amine and formaldehyde, two compounds that can again generate carbenium−iminium ions (Scheme 1, sequence A). The *N*-methylenemorpholinium cation (**6**) starts a new catalytic cycle of the reaction by alkylating another molecule of **1** (Scheme 1, sequence B).

This mechanism can explain the observed effects of acids and bases on the reaction rate: small amounts of bases favor the abstraction of the proton from the *N*-methyl group but do not prevent the formation of carbenium−iminium ions. Addition of base in larger concentrations, however, counteracts the formation of carbenium−iminium ions and terminates the reaction. Acids positively affect the generation of carbenium−iminium ions but impede the deprotonation step, thus decelerating the reaction. Only after enough morpholine, as a base, has been produced to neutralize the acid, does the reaction rate increase. The presence of trace amounts of water is crucial for the protonation and deprotonation steps to proceed. The detrimental effects of larger amounts of water in the reaction mixture can be explained by its fast reaction with carbenium−iminium ions to the corresponding (hydroxymethyl)amines. Thus, water prevents the initial alkylation step by trapping the "alkylating agent".

To establish that a C-centered positive charge in a carbenium−iminium ion, and not a positive charge at a nitrogen as in an ammonium salt, is necessary to induce the decomposition of **1**, we replaced the catalyst **2** with tetramethylammonium iodide. However, no reaction was observed in this experiment.

Preliminary results indicate that the presented reaction can also be extended to other amine oxides. The degradation of trimethylamine oxide into dimethylamine and HCHO proceeded readily without formation of byproducts.

The carbenium−iminium ion can either be introduced into the reaction mixture as a stable reagent, as with compound **2**, or it can be formed as an intermediate in the course of the reaction. In the former case, the Mannich intermediates in sequences A and B of Scheme 2 are different. In the latter case, which represents the typical decomposition of NMMO by its degradation products, both sequences involve the same carbenium−iminium ion, the *N*-methylenemorpholinium cation (**6**). Morpholine (**3**) and formaldehyde (**4**) form *N*-hydroxymethylmorpholine, which produces the Mannich intermediate **6** after protonation and dehydration. This carbenium−iminium ion causes the degradation of NMMO into morpholine and HCHO regenerating **6**, according to the mechanism described above. Thus, the decomposition of **1** by the action of **6** is an autocatalytic process. The role of the carbenium−iminium ion is somewhat ambiguous here: it can be regarded *per definitionem* as an initiator, and as a catalyst as well. Through the autocatalytic nature of the reaction, only minute amounts of morpholine and HCHO are required to decompose large quantities of NMMO. This renders the prevention of the reaction seemingly very difficult if both compounds are present at the same time. However, the knowledge of the reaction mechanism allows us to suggest possible means to stabilize NMMO against the degradation by Mannich intermediates, which must be tested for each reaction system for practical feasibility. The removal of secondary amines from the mixture, e.g., by binding on acidic solids, is conceivable, as well as the depletion of HCHO by flushing with inert gases or by trapping reactions.

In summary, we have described a novel reaction, the autocatalytic degradation of *N*-methylmorpholine *N*-oxide by carbenium−iminium ions (Mannich intermediates) and investigated mechanism and kinetics of this process. The reaction can be seen as a likely cause for hitherto inexplicable "spontaneous" degradation reactions in reaction mixtures containing NMMO.

Acknowledgment. We would like to thank Doz. Dr. H. Sixta, Lenzing AG, Austria, for helpful advice.

Supporting Information Available: Experimental procedures, analytical data, and capillary ion analysis data of starting materials and reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) NMMO forms two stable hydrates, a monohydrate (NMMO·H_2O) and a disesquihydrate NMMO·2.5 H_2O: Berchiesi, G. *J. Mol. Liquids* **1982**, *38*, 213.

(11) Trifluoroacetic acid (0.1% relative to NMMO, 10% relative to the catalyst **2**) was used.

(12) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was employed (0.1% relative to NMMO, 10% relative to **2**).

(13) Polonowski, M.; Polonowski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190. Huisgen, R.; Bayerlein, F.; Heydkamp *Chem. Ber.* **1959**, *92*, 3223. See also ref 1.

(14) Griffith, W. P.; Ley, S. V.; Whitcombe, W. P.; White, A. D. *J. Chem, Soc., Chem. Commun.* **1987**, 1625. Ray, R.; Matteson, D. S. *J. Indian Chem. Soc.* **1982**, *59*, 119. Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1989**, *30*, 4857.