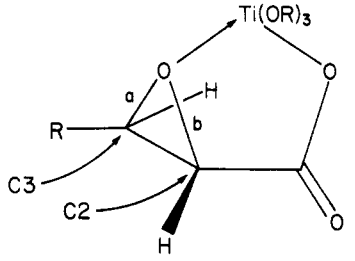
While it is unclear exactly why the presence of Ti(O-*i*-Pr)$_4$ provides such a strong tendency for 2,3-epoxy acids and secondary amides to be opened by nucleophiles at C-3, the observed regioselectivities may be rationalized by proposing the formation of an intermediate titanium complex such as **18**. Opening at C-3 occurs preferentially



18

for the reasons postulated in the previous communication. Furthermore, the π orbitals of the carbonyl group and bond b are essentially orthogonal, and thus acyl activation for substitution at C-2 is not possible.[11]

It is obvious that the use of Ti(O-*i*-Pr)$_4$ to direct the attack of nucleophiles to C-3 of 2,3-epoxy acids and amides holds considerable promise for the preparation of compounds of general structure **17**. Coupled with asymmetric epoxidation and the facile oxidation of epoxy alcohols to glycidic acids by the catalytic RuO_4/H_5IO_6 system,[4] this approach should provide ready access to these compounds in high enantiomeric purity.

Acknowledgment. We thank the National Science Foundation (CHE-8308355) and Merck and Company for generous support of this research. We are also grateful to the Izaak Walton Killam Memorial Foundation and the Natural Science and Engineering Research Council of Canada (NSERC) for postdoctoral fellowships to J.M.C.

Supplementary Material Available: Procedures for the preparation of epoxy acids **1** and **7–10**; general procedures for the Ti(O-*i*-Pr)$_4$-mediated reaction of epoxy acids with dialkylamines and thiophenol, azide, and cyanide; ^{1}H NMR data for the (a) methyl ester acetates of compounds **5**, **6**, **11**, **12**, and **17** (Nu = N_3 and CN) and (b) acetates of compounds **14** and **15** (15 pages). Ordering information is given on any current masthead page.

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An Unprecedented Selective Autoxidation of Tertiary Amines to Amine Oxides

Summary: Tertiary amines have been found to react directly with molecular oxygen under high O_2 pressures to give in an unexpected result the corresponding *N*-oxide in high yields.

Sir: During our studies of the oxygen oxidation of tertiary amines,[2] we have discovered a pathway in which the conversion to *N*-oxide is effected directly and selectively with no catalyst. This transformation proceeds, although slowly, in polar solvent media, under high oxygen pressures (~50 bar), and at elevated temperatures (90–130 °C), to afford in some instances >95% yield of the *N*-oxide (Table I). This result is in marked contrast to the previously reported autoxidations of tertiary amines where dealkylation is the predominant pathway. Amine oxides have previously only been observed as minor byproducts arising from the reaction of tertiary amine with an intermediate α-hydroperoxide.[3-5] Further, none of the known amine autoxidation pathways would predict amine oxide yields of >50%.

In a typical procedure a trimethylamine solution in water (2.4 M) was shaken under 71 bar air at 100 °C for 64 h. After this period, >95% conversion to the *N*-oxide resulted as monitored by HPLC and confirmed by isolation of the crystalline $Me_3NO{\cdot}2H_2O$. Non-water-soluble tertiary amines can be similarly oxidized in high yields, but homogeneous aqueous alcohol solutions must be used or a nonselective autoxidation occurs. In the alcohol cosolvent systems only low levels of alcohol oxidation products were observed, indicating that peracids derived from alcohol are not the *N*-oxide-producing oxidants in such systems.[6]

Kinetic data were obtained in aqueous systems to avoid problems with potential solvent oxidation. This necessitated the use of water soluble amines with relatively low volatility. For this reason the oxygen concentration (pressure) dependence was studied in H_2O at 125 °C for the oxidation of *N*-methylmorpholine (0.2 M) over the range of 40–100 bar O_2. At constant oxygen pressure the amine reacts in a pseudo-first-order manner. The rate of conversion to the *N*-oxide was found to be first-order in oxygen during the monitored period (~24 h). Amine oxide yields were >85% of converted amine during this period in all cases.

The structure of the tertiary amine plays a significant role in determining both the reaction rate and types of products obtained in these high-pressure autoxidations. The most selective conversion to *N*-oxides occur with aliphatic amines (Table I, entries 1–4). Phenyl-substituted tertiary amines, such as *N*,*N*-dimethylaniline, react at faster rates than aliphatic amines but afford complex mixtures of products with dealkylations predominating at low conversion. Aromatic amines such as pyridine are unreactive. When the α-carbon is activated, as in *N*,*N*-dimethylbenzylamine, a competitive cleavage of the carbon–hydrogen bond is observed, yielding benzaldehyde, but the pathway yielding *N*-oxide still predominates.

A rational mechanism for this oxidation can be suggested by our data. In the low-pressure oxidation of tertiary amines reported by Beckwich, the yield of amine oxide is limited to 50% by the fact that H_2O_2 or a hydroperoxide, derived from α-oxidation, is required for formation of amine oxide.[3] Our yields in excess of 50% indicate that the mechanism of oxidation changes significantly at the increased temperatures and pressures we employ. We believe that this reaction involves an initial electron

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0022-3263/85/1950-1563$01.50/0

Table I. Oxidation of Amines with Molecular Oxygen[13]

amine (concn, M)	solvent	P_{O_2}, bar	temp, °C	time, h	products, % yield (% NR_3 convn)
NMe_3 (0.5)	H_2O	14[a]	100	14	31.5% Me_3NO (32%)
NMe_3 (2.4)	H_2O	14	100	64	>95% Me_3NO (100%)
H^+NMe_3 (1.0)[b]	H_2O	86	100	64	0.4% Me_3NO
N,N-dimethyldodecylamine (0.22)	4:1 MeOH/H_2O	14	100	64	>95% *N,N*-dimethyldodecylamine oxide (100%)
N-methylmorpholine (0.20)	H_2O	71	115	72	62% *N*-methylmorpholine oxide (88%)
N,N-dimethylaniline (0.17)	4:1 MeOH/H_2O	71	104	23	<16% *N,N*-dimethylaniline oxide[c] (>90%)
pyridine	H_2O	71	100	16	0% *N*-oxide (0%)
N,N-dimethylbenzylamine (0.15)	2:1 MeOH/H_2O	71	116	7	56% *N,N*-dimethylbenzylamine oxide, 15% benzaldehyde (84%)

[a] 0.011 M O_2 in water.[12] [b] pH 2.2. [c] At low conversion (<20%) *N*-methylaniline is ~70% of converted amine.

transfer to yield an amine radical cation and superoxide (eq 1).[3] This accounts for the observed first-order de-

$$\underset{}{NR_3} + O_2 \rightleftarrows \underset{\mathbf{1}}{R_3N^{+}\cdot} + O_2^{-}\cdot \qquad (1)$$

pendence in NR_3 and O_2, as well as the slow reaction rates since this electron transfer is endothermic.[7] Such a rate-determining step is in accord with the studies of Beckwith et al. for low-pressure autoxidations in water.[3] The reactivity of amines in electron-transfer reactions has been well established by Smith[8] and Rosenblatt.[9]

The necessary divergence of mechanism must occur at the next step. Beckwith et al.[3] postulate α-deprotonation of the radical cation which is inconsistent with our results. In our case we believe the high oxygen concentration permits effective $^3O_2$ interception of the solvent-stabilized amine radical cation **1** before it can be deprotonated at the α-CH (eq 2). The alternative of a combination of **1** and

$$\underset{\mathbf{1}}{R_3N^{+}\cdot} + {}^3O_2 \rightleftarrows \underset{\mathbf{2}}{R_3N^{+}OO\cdot} \qquad (2)$$

superoxide to yield **3** is not supported by Beckwith et al.[3] and would be even more unlikely under the more strenuous conditions we employ. The hydroperoxy radical cation can be reduced either by a second tertiary amine moiety initiating a *chain reaction* or it might be reduced by superoxide directly. At this point our data do not allow us to distinguish between these possibilities. The net consequence of either of these steps is production of a zwitterionic species **3** analogous to that formed in the photooxidation of thioethers.[10] The zwitterion **3** would react with a second tertiary amine (in analogy to the thioether case[10]) to generate the *N*-oxide product (eq 3). The initial

$$\underset{\mathbf{3}}{R_3N^{+}OO^{-}} + NR_3 \rightarrow 2R_3NO \qquad (3)$$

electron transfer is the rate-limiting step in this mechanistic sequence. Our studies of the temperature dependence of the reaction for dimethyldodecylamine in 4:1 methanol/H_2O at 65 bar O_2 pressure yield an E_a = 19.1 kcal/mol and a $\Delta S^{\ddagger}$ -26.1 eu. These parameters are consistent with a bimolecular rate-determining step involving developing charge separation.[11]

In conclusion, we have shown that tertiary amines can be directly oxidized with molecular oxygen to give high yields of *N*-oxides. The mechanism appears to involve initial electron-transfer followed by oxygenation of the radical cation. Further mechanistic studies of this surprising reaction are in progress.

Registry No. NMe_3, 75-50-3; HN^+Me_3, 16962-53-1; Me_3NO, 1184-78-7; *N,N*-dimethyldodecylamine, 112-18-5; *N*-methylmorpholine, 109-02-4; *N,N*-dimethylaniline, 121-69-7; pyridine, 110-86-1; *N,N*-dimethylbenzylamine, 103-83-3; *N,N*-dimethyldodecylamine oxide, 1643-20-5; *N*-methylmorpholine oxide, 7529-22-8; *N,N*-dimethylaniline oxide, 874-52-2; *N,N*-dimethylbenzylamine oxide, 5400-82-8.

(7) We have measured the irreversible oxidation potential of *N,N*-dimethyldodecylamine in 4:1 MeOH/H_2O (0.1 M TBATFB) by cyclic voltammetry to be $E_p \sim 0.87$ V. The reduction potential for oxygen under similar conditions is $E_{1/2} \sim -0.25$ V. This corresponds to an energy gap of ~1.12 V (26 kcal/mol). Since these are irreversible oxidations, the actual energy difference will be less than the measured potential differences.

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(13) In a typical procedure, a homogeneous solution containing the tertiary amine in a glass line is placed in a high-pressure rocking autoclave fitted with sampling controls (all wetted parts see only glass or Teflon). The reaction samples are analyzed by reverse-phase HPLC techniques (0.02 N NH_4OAc + 0.02 N NH_4NO_3 in methanol/water) and analytical GC using fused silica capillary columns with FID.

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The Oxahydrindene Component of the Avermectins[1]

Summary: An intramolecular nitrile oxide cycloaddition involving a vinyl group at C3 and a nitrile oxide at C6 of a derivative of diacetone glucose provides a route to the oxahydrindene **2** stereochemically pure and appropriately functionalized for further elaboration.

Sir: The milbemycins[2] and avermectins[3] are relatively new families of broad spectrum, antihelminthic, antiparasitic agents, which are currently the foci of considerable biological and chemical interest. The avermectins, reported by Merck, Sharp and Dohme in 1979,[3a] are the more potent, and a patent medicine, Ivermectin, has recently been released for use in veterinary medicine.[4] The complex

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