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Oxidation of substituted pyridines by dimethyldioxirane: kinetics and solvent effects

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Abstract—The oxidation of a series of substituted pyridines by dimethyldioxirane (**1**) produced the expected *N*-oxides in quantitative yields. The second order rate constants (k_2) for the oxidation of a series of substituted pyridines (**2a**–**g**) by dimethyldioxirane were determined in dried acetone at 23 °C. An excellent correlation with Hammett sigma values was found ($\rho = -2.91$, $r = 0.995$). Kinetic studies for the oxidation of 4-trifluoromethylpyridine by **1** were carried out in the following dried solvent systems: acetone ($k_2 = 0.017\,M^{-1}\,s^{-1}$), carbon tetrachloride/acetone (7:3; $k_2 = 0.014\,M^{-1}\,s^{-1}$), acetonitrile/acetone (7:3; $k_2 = 0.047\,M^{-1}\,s^{-1}$), and methanol/acetone (7:3; $k_2 = 0.68\,M^{-1}\,s^{-1}$). Kinetic studies of the oxidation of pyridine by **1** versus mole fraction of water in acetone [$k_2 = 0.78\,M^{-1}\,s^{-1}$ ($\chi = 0$) to $k_2 = 11.1\,M^{-1}\,s^{-1}$ ($\chi = 0.52$)] were carried out. The results showed the reaction to be very sensitive to protic, polar solvents.

1. Introduction

Dioxiranes are versatile oxidizing agents that efficiently transfer an oxygen atom to a variety of different substrates.[1] Dimethyldioxirane (**1**) has been extensively studied, and several methods developed for the formulation of **1** either in situ[2] or isolated in solution.[3] Oxidation by **1** has been shown to be electrophilic in nature[4] as well as quantitative in the majority of cases. The mechanism of olefin epoxidation by **1** has been extensively investigated.[1,3] An area of expanding interest is the oxidation of heteroatoms by **1**, especially nitrogen-containing substrates. In the presence of excess dimethyldioxirane **1**, primary amines can be successively oxidized to the nitro compounds.[5a,b,c] Secondary amines have been shown to be oxidized to the hydroxylamines, but undergo an additional oxidation to the nitroxide.[5d–g] Tertiary amines are oxidized cleanly to the corresponding *N*-oxides.[6a] Aromatic azines such as pyridines and quinolines have been reported to quantitatively yield the corresponding *N*-oxides upon reaction with dioxiranes.[6b] When given the presence of other oxidizable functional groups, such as aldehydic or olefinic substituents, preferential *N*-oxidation by **1** has been observed.[6a–d] Furthermore, the oxidation of aromatic diazines such as pyrazines by **1** has been shown to afford the mono- and in selected cases the di-*N*-oxides depending on reaction conditions.[6e] While relative reactivities for oxidation of selective substituted pyridines by dimethyldioxirane have been determined by product studies,[6d] no rate constants for *N*-oxidation by **1** have been reported. Furthermore, no solvent effects on *N*-oxidation by dioxiranes have been reported. We report here the first kinetic data for the oxidation of a series of substituted pyridines by **1** in acetone and in mixed solvent systems.

2. Results and discussion

The reaction of dimethyldioxirane (**1**) with a series of substituted pyridines (**2a**–**g**)[7] produced the corresponding *N*-oxides (**3a**–**g**) as the sole observable products in all cases as expected (rxn. 1).[2c,e,3a] A 3-fold excess of dioxirane was employed for product studies on the less reactive pyridines, whereas only 1.1 equiv of **1** were necessary for the more reactive substrates. Isolated yields were essentially quantitative (98%). *N*-Oxides were proven by comparison of spectral and physical data to those of authentic samples. The product studies were in

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Keywords: Kinetics; *N*-Oxidation; Solvent effects; Dimethyldioxirane; Pyridines.

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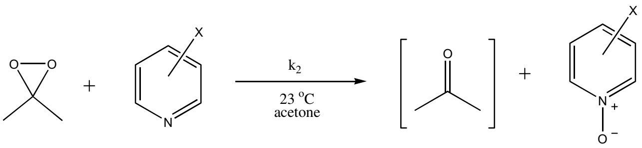
excellent agreement with those reported for several of the pyridines.[6b]



1

2 [a X = 4-CN; b X = 4-CF$_3$; c X = 3-Br; d X = H; e X = 4-Ph f X = 4-Me; g X = 4-OMe]

3a-g

(1)

The kinetics for rxn. 1 was determined using UV techniques.[8] As expected the reaction was found to be of the first order with respect to each of the reagents; second order overall. The second order rate constants (k_2's) determined in dried acetone under equimolar or pseudo first order conditions were within experimental error (±15%). All k_2 values are the average of at least three determinations. The k_2 values ($M^{-1}s^{-1}$) in dried acetone at 23 ± 0.3 °C were determined for the reaction of **1** with: 4-cyanopyridine (**2a**, $k_2 = 0.014 \pm 0.001$), 4-trifluoromethylpyridine (**2b**, $k_2 = 0.017 \pm 0.002$), 3-bromopyridine (**2c**, $k_2 = 0.041 \pm 0.006$), pyridine (**2d**, $k_2 = 0.78 \pm 0.02$), 4-phenylpyridine (**2e**, $k_2 = 1.01 \pm 0.06$), 4-methylpyridine (**2f**, $k_2 = 2.36 \pm 0.26$), and 4-methoxypyridine (**2g**, $k_2 = 5.36 \pm 0.27$). The reaction mixtures from the kinetics experiments were checked by GC/MS for product formation. In all cases, a signal for the appropriate amount of the corresponding pyridine *N*-oxide was observed.

The Hammett plot of the substituted pyridines yielded an excellent fit with sigma values (Fig. 1) with a rho of −2.91 ± 0.13 ($r = 0.995$). The rho value is in agreement with that previously reported in the Hammett study of substituted pyridine *N*-oxidation by peroxybenzoic acid ($\rho = -2.35$, 25 °C) in 50:50 dioxane/water.[9] The rho value for the oxidation of pyridine by **1** is consistent with an electrophilic mechanism, and also shows that oxidation is very sensitive to substituent effects. In contrast, the analogous studies for the epoxidation of olefinic compounds by **1** have been shown to correlate with sigma plus values to give rho plus values of −0.90 for 4-substituted styrenes,[3b] −1.53 for substituted ethyl cinnamates,[10a] and −1.03 for 4-substituted chalcones.[10b]

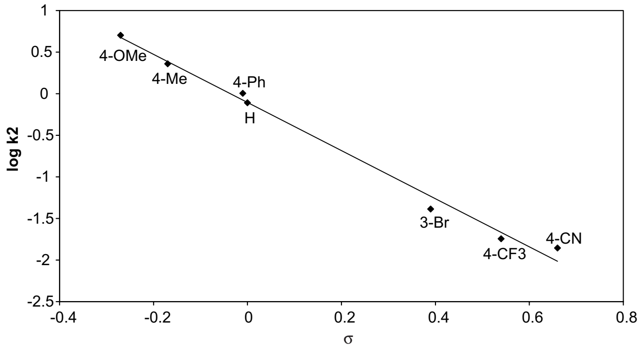


Figure 1. Hammett plot of log k_2 for the oxidation of pyridines **2a**–**g** by dimethyldioxirane (**1**) at 23 °C in acetone.

Despite the difference in type of correlation, the results are mechanistically consistent due to a lack of direct conjugation of the nitrogen lone pair in the aromatic azines. A study by Adam and Golsch[6d] looked at competitive *N*-oxidation of substituted pyridines by **1** in comparison to *N*-methylation. Their data of relative reactivity ratios showed that the oxidation of substituted pyridines occur via an S_N2 mechanism rather than an electron transfer mechanism. Comparison of ratios of appropriate k_2's for *N*-oxidation of selected pyridines in the current study are in good agreement with the ratios of relative reactivities reported by Adam and Golsch.[6d]

The effect of solvent polarity on the oxidation of **2b** by **1** was studied under pseudo first order conditions at 23 °C. The kinetic experiments were conducted in acetone with 70% (v/v) of either carbon tetrachloride, acetonitrile or methanol (Table 1). The second order rate constant obtained in 70% carbon tetrachloride was found to be $0.014 \pm 0.002\,M^{-1}s^{-1}$, slightly slower than that of the more polar solvent, acetone ($0.017 \pm 0.002\,M^{-1}s^{-1}$), while addition of 70% of the more polar solvent, acetonitrile ($0.048 \pm 0.017\,M^{-1}s^{-1}$), resulted in a 2.8-fold increase in the second order rate constant over that of acetone. In contrast, addition of 70% methanol resulted in a rate constant of $0.68 \pm 0.07\,M^{-1}s^{-1}$, a 40-fold increase over that in acetone.[11] A study by Gilbert et al. reported a 3.3-fold decrease in the magnitude of the rate constant for epoxidation of *cis*-stilbene by dimethyldioxirane **1** in 100% carbon tetrachloride compared to that of acetone.[12a] Previous work in this lab has shown that oxidation of 2-methyl-2-pentene has a similar rate constant in 90% dried carbon tetrachloride/acetone to that of dried acetone.[12b] In addition, it was shown that the epoxidation of 2-methyl-2-pentene by **1** in a 90% methanol/acetone solution had a 27-fold increase in the magnitude of the rate constant from that of acetone. Subsequently, the effect of added water on the oxidation of **2d** by **1** was examined. The second order rate constants were determined at 23 °C in acetone versus mole fraction of water. Kinetic runs were carried out under equimolar conditions, with $\chi_{H_2O} \leqslant 0.5$ to avoid solubility problems. The value of the rate constant was found to increase significantly as the mole fraction of water (χ_{H_2O}) increased (Fig. 2).

Interestingly, the magnitude on the effect of pyridine oxidation is found to be substantially greater than that seen for the epoxidation of 4-methoxystyrene.[3b] Substitution of deuterium oxide for water in a 0.30 mole fraction experiment yielded a k_2 value of $5.42 \pm 0.32\,M^{-1}s^{-1}$, similar to that obtained for water ($5.90 \pm 0.15\,M^{-1}s^{-1}$). Within experimental error, the k_{H_2O}/k_{D_2O} ratio is close to unity, indicating that proton

Table 1. Second order rate constants for the oxidation of **2b** by **1** in various solvents at 23 °C

Solvent (v/v)	k_2 ($M^{-1}s^{-1}$)	k_{rel}
Dried acetone (100%)	0.017 ± 0.002	≡1
Acetone/CCl$_4$ (30:70)	0.014 ± 0.002	0.8
Acetone/acetonitrile (30:70)	0.048 ± 0.017	2.8
Acetone/methanol (30:70)	0.68 ± 0.07	40

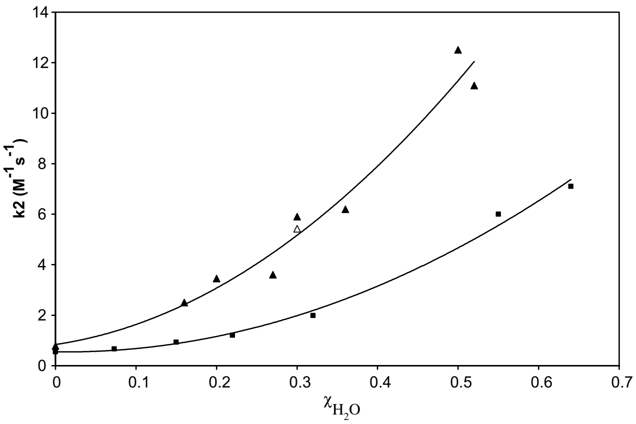


Figure 2. Plot of the oxidation of pyridine by dimethyldioxirane (**1**) versus mole fraction of H_2O (▲) or 0.3 mole fraction of D_2O (△). Plot of k_2 versus mole fraction of water for 4-methoxystyrene (■) adapted from Ref. 3b. The lines shown represent polynomial regression fits ($r = 0.983$ for pyridine, $r = 0.995$ for *p*-methoxystyrene).

catalysis is not a primary factor in the enhancement of pyridine oxidation.

3. Conclusions

The first kinetic data for *N*-oxidation by dimethyldioxirane (**1**) have been determined. The kinetic data show that, in general, pyridine *N*-oxidation by **1** is faster than most epoxidations by **1**, with notable exceptions of certain tetrasubstituted alkenes. In addition, *N*-oxidation of substituted pyridines has been shown to be very sensitive to substituent effects. The study is the first to show that *N*-oxidation by **1** is significantly enhanced by protic, polar solvents.

Acknowledgements

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