N-OXIDATION OF 2-SUBSTITUTED PYRIDINES AND QUINOLINES BY DIMETHYLDIOXIRANE: KINETICS AND STERIC EFFECTS

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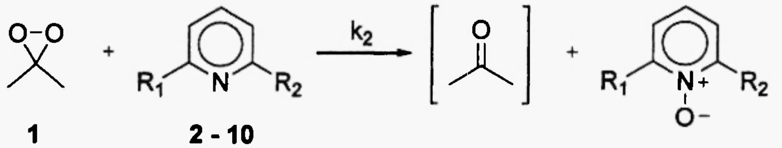
Abstract: The oxidation of 2-substituted pyridines and selected *N*-containing aromatic heterocycles by dimethyldioxirane (**1**) produced the corresponding *N*-oxides as the sole products, quantitatively in most cases. The second order rate constants for *N*-oxidation by **1** in dried acetone at 23 °C were determined for a series of 2-substituted pyridines **2-10**, quinolines **11-14** and isoquinolines **15,16**. An excellent correlation of log k_2 with Taft (σ^*) constants was obtained for 2-substituted pyridines (R = Me, Et, Pr^n, Pr^i, 3-pentyl) with the exception of the data for 2-*t*-butylpyridine. The results for the substituted quinolines and isoquinolines followed the same trends observed with the pyridines. Steric effects due to 2-substitution and peri-interactions can substantially reduce reactivity. The results provide insights into the geometrical requirements for *N*-oxidation by dimethyldioxirane.

Introduction

Dioxiranes are versatile electrophilic oxygen-atom transfer agents for the oxidation of a diverse range of functional groups on organic substrates.[1] Because of the ease and economy of preparation, dimethyldioxirane (**1**) has been extensively studied. Several methods have been developed for the us of **1** *in situ*[2] or isolated in solution.[3] The epoxidation of olefins by **1** has been extensively investigated,[1,3] has been shown to occur via an electrophilic spiro-transition state[4] and is quantitative in the majority of cases. However, the mechanism of *N*-oxidation by **1** has not been extensively studied. Most reports have focused on product studies, with those for aromatic heterocyclic *N*-oxidation by **1**[5] generally limited to substituted pyridines and quinolines. Recently, we have reported on a kinetic study of pyridine *N*-oxidation by **1** that showed[6] the process to be an electrophilic reaction with a highly polar transition state. While reactivity of **1** in epoxidation is sensitive to steric effects, essentially no data are available on the effect of structure on the reactivity of *N*-containing aromatic heterocyclics. We report here the first kinetic data for the oxidation of a series of 2-substituted pyridines and selective *N*-containing aromatic heterocycles by **1** in dried acetone.

Results and Discussion

The reaction of dimethyldioxirane (**1**) with a series of 2-substituted pyridines **2-10** in dried acetone produced the corresponding *N*-oxides as the sole observable products in all cases as expected (eq. 1).[2c,2e,3a]



(1)

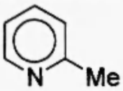
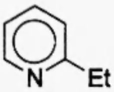
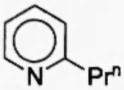
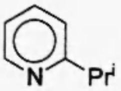
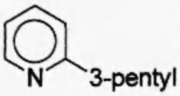
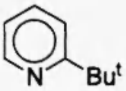
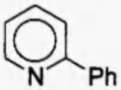
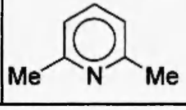
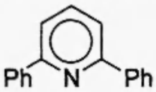
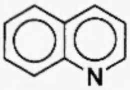
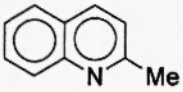
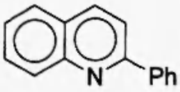
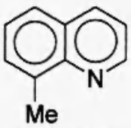
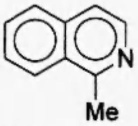
1 **2 - 10**

2 R_1 = H, R_2 = Me; **3** R_1 = H, R_2 = Et; **4** R_1 = H, R_2 = Pr^n; **5** R_1 = H, R_2 = Pr^i
6 R_1 = H, R_2 = 3-pentyl; **7** R_1 = H, R_2 = Bu^t; **8** R_1 = H, R_2 = Ph; **9** R_1 = R_2 = Me; **10** R_1 = R_2 = Ph

Similarly, the reaction of **1** with quinoline (**11**), 2-methylquinoline (**12**), 2-phenylquinoline (**13**), 8-methylquinoline (**14**), isoquinoline (**15**), and 1-methylisoquinoline (**16**) yielded the corresponding *N*-oxides as the sole products. A three-fold excess of **1** was employed for all product studies except for those with compounds **7** and **14** where a 10-fold excess of **1** was added. Isolated yields of the *N*-oxides were essentially quantitative (98%) for all the compounds except for the *N*-oxidation of **7** and **14** in which ~50% and only a trace of product were obtained, respectively. The *N*-oxides were proven by comparison of spectral and physical data to those of authentic samples.[7]

The kinetics for the *N*-oxidation of **2-16** by dimethyldioxirane was determined using UV techniques.[8] As expected, the *N*-oxidation was found to be of the first order with respect to each of the reagents and second order overall. The second order rate constants (k_2's), determined in dried acetone under pseudo-first order conditions, were within experimental error (±10%) regardless of which reagent was in excess. For convenience, the majority of the kinetic experiments were carried out with the *N*-containing aromatic heterocycle in excess. The k_2 values are summarized in Table-1. The reaction mixtures from the kinetic experiments were checked by GC-MS for product formation. In all cases with the exception of that for **14**, a signal for the appropriate amount of *N*-oxide was observed.

Table-1 : Second Order Rate Constants[a] for the *N*-Oxidation of 2-Substituted Pyridines **2-10**, Quinolines **11-14** and Isoquinolines **15**,**16** by **1** in Dried Acetone at 23 °C.

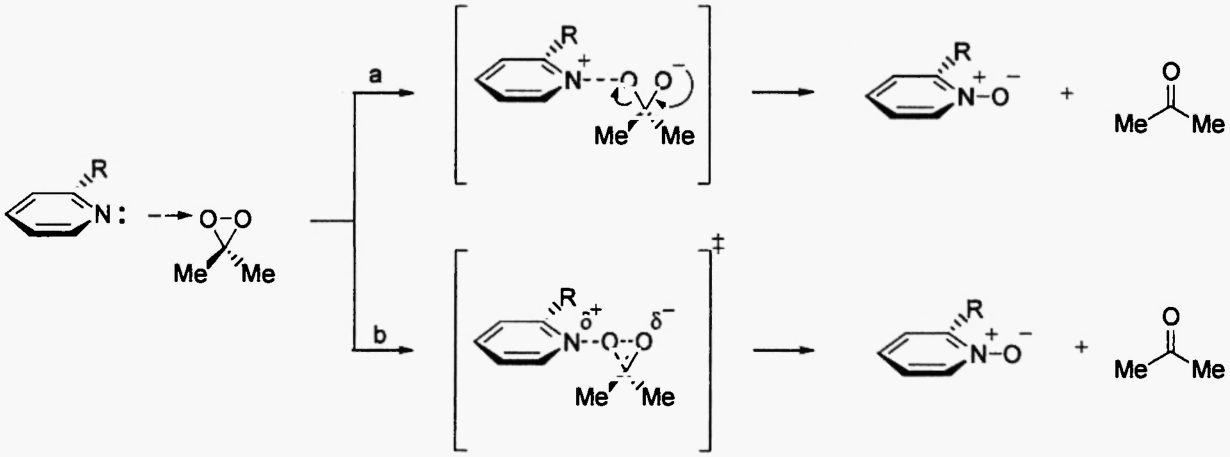
#	Structure	$k_2(M^{-1}s^{-1})^a$	k_{rel}
2		0.70 ± 0.02	0.48
3		0.39 ± 0.02	0.27
4		0.38 ± 0.01	0.26
5		0.16 ± 0.01	0.11
6		0.14 ± 0.01	0.10
7		~0.00001	~10^{-5}
8		0.33 ± 0.01	0.22
9		0.35 ± 0.02	0.24
10		0.22 ± 0.01	0.15
11		0.33 ± 0.02	0.22
12		0.15 ± 0.01	0.10
13		0.11 ± 0.01	0.23
14		NR[b]	--
15		1.47 ± 0.08	1.0
16		1.01 ± 0.05	0.69

[a] Average of at least 3 determinations

[b] No reaction observed under these conditions.

All of the k_2 values for the 2-substituted pyridines were lower than that for pyridine (k_2=0.78 $M^{-1}s^{-1}$) and substantially lower than that for 4-methylpyridine (k_2=2.35 $M^{-1}s^{-1}$).[5] Clearly 2-substitution decreases the reactivity toward *N*-oxidation by **1**. The k_2 value of *N*-oxidation of isoquinoline is greater than that for pyridine while that for quinoline is lower. The extremely low reactivity of 8-methylquinoline (**14**) clearly shows that peri-interactions are important. In general the effect of "ortho" substitution in both the quinoline and isoquinoline systems are in agreement with the trends observed (reduced reactivity) for the similarly substituted pyridines. Potential synthetic applications of dimethyldioxirane *N*-oxidation can be deduced from the k_{rel} values listed in Table 1. A plot of the log k_2 values for the *N*-oxidation of 2-alkylpyridines with Taft σ^* values (**2-7**) afforded an excellent correlation (slope = 3.25, r = 0.99) for **2-6** if the result for **7** is excluded. The log k_2 values for pyridine oxidation decrease linearly as the size of the 2-substituent increases to a certain size. This indicates that steric factors play a role in restricting the approach of **1** to the lone pair on nitrogen. The estimated k_2 value for compound **7**, however, deviates significantly (~ 4 orders of magnitude) from that predicted by the Taft σ^* values. This substantial deviation from linearity suggests that there is a limiting geometric requirement for approach of **1** to the oxidation site.

Mechanistically, *N*-oxidation can be viewed as either electrophilic attack by **1** or nucleophilic attack of the nitrogen lone pair on oxygen. Two mechanistic extremes can be postulated for the N-oxidation of aromatic heterocycles: (a) a two-step ionic and (b) a concerted process (see Scheme 1). For the two-step process (route a), one might expect an essentially linear attack of the lone pair toward the O-O bond. For the concerted route (b), expectations might be for a transition state that is tilted (similar to that proposed for epoxidation). Both of the two extreme processes would be expected to show similar mechanistic behavior since the rate determining step in route (a) would be expected to be the formation of the ionic intermediate. Thus, the transition state for (b) and that for the first step of (a) would be very similar in ionic character. Computer modeling of the two extremes will be necessary to differentiate between them.



Scheme-1: Two mechanistic extremes (a) two step and (b) concerted, for electrophilic oxidation of pyridines by dimethyldioxirane.

In conclusion, the rate of oxidation of *N*-containing aromatic heterocycles by dimethyldioxirane can be dramatically reduced by steric effects from peri-interactions and/or ortho substitution. The magnitude of the reduced reactivity is large enough to be of synthetic utility in certain cases.

Acknowledgments

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References and Notes

1. For selected reviews see: (a) R. Curci, in A. Baumstark (Ed.), *Advances in Oxygenated Processes* Vol. 2, JAI Press, Greenwich, CT, 1990; (b) W. Adam, L. Hadjiarapoglonu, R. Curci and R. Mello, in W. Adam (Ed.), *Organic Peroxides*, Chapt. 4, Wiley and Sons, Chichester, England 1992; (c) W. Adam and L. Hadjiarapoglonu, *Top. Curr. Chem.* **164**, 45 (1993); (d) R. Curci, A. Dinai and M. Rubino, *Pr. Appl. Chem.* **67**, 811 (1995); (e) R.W. Murray and M. Singh, in A.R. Katritzky, (Ed.) *Comprehensive Heterocyclic Chemistry II*, Vol. 1A, Chapt. 14, Elsevier Science Ltd., Tarrytown, NY, 1996; (f) W. Adam, C.R. Saha-Moeller and C.-G. Zhao, in L.E. Overman, (Ed.), *Organic Reactions*, Vol. 61, Chapt. 2, John Wiley & Sons, Inc., Hoboken, NJ, (2002).

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7. Authentic samples of the *N*-oxides were prepared by published methods. The *N*-oxides of **2**, **11** and **15** were commercially available. *N*-oxides of **3-5**, **7-9**: D. W. Boykin, P. Balakrishnan and A.L. Baumstark. *Mag. Res. Chem.*, **23**, 695 (1985), and all references therein; *N*-oxides of **12** and **14**: D. W. Boykin, P. Balakrishnan and A.L. Baumstark. *J. Heterocycl. Chem.*, **22**, 981 (1985), and all references therein; *N*-oxide of **10**: R. N. Carde, P. C. Hayes, G. Jones and C. J. Cliff. *J. Chem. Soc., Perk. Trans.* 1 (1981) 1132; *N*-oxide of **13**: . Ahmad, M. S. Habib, Ziauddin and B. Bakhtiari., *J. Org. Chem.* **31**, 2613 (1966); *N*-oxide of **16**: O. Buchardt, J. Becher and C. Lohse. *Acta. Chem. Scand.* **19**, 2807 (1965)

8. The loss of **1** was monitored at λ = 370 nm (ε = 5.1 $M^{-1}cm^{-1}$) rather than at 330 nm (normally employed for epoxidation kinetics) to avoid complications due to absorption by the product(s).

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