Mechanism of the dimethyldioxirane oxidation of *N*,*N*-dimethylanilines

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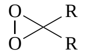
Relative rates of dimethyldioxirane oxidation of a number of *para*-substituted *N*,*N*-dimethylanilines in acetone at 5 °C are compared with those of reactions with methyl iodide and other oxidants. The reactions with dimethyldioxirane followed the Hammett relationship with a ρ value of -1.0. Measurement of the second order rate constants for the dimethyldioxirane reactions in aqueous acetonitrile containing potassium nitrate at 21 °C, showed better correlation with the Hammett relationship ($\rho = 0.89$) than with the Okamoto–Brown model ($\rho^+ = 0.56$). The reaction rates are accelerated greatly in the presence of water such that the respective pseudo first order rate constants for the oxidation of *N*,*N*-dimethyl-4-nitroaniline in acetone and water are 6.3×10^{-3} and $5.86\ \mathrm{s}^{-1}$, respectively. All of the data are consistent with a concerted electrophilic mechanism and there is no evidence of free radical or electron transfer reactions.

Introduction

In recent years, dioxiranes **1** have been used to carry out a wide variety of synthetically useful transformations.[1] However, some mechanistic details remain unclear and evidence has been presented suggesting that some dioxirane reactions may occur *via* bis(oxyl) diradicals **2**.



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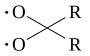

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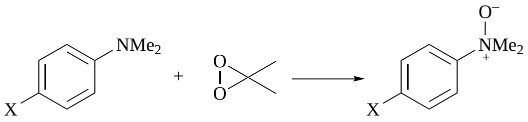
Epoxidation,[2] sulfur oxidation[3] and C–H insertion[4] reactions of dimethyldioxirane have been shown to be electrophilic by means of linear free energy relationship (LFER) correlations and a mechanistic study by Adam and Golsch[5] concluded that the dimethyldioxirane oxidation of nitrogen heteroarenes follows an S_N2 mechanism. Other studies, however, on the oxidation of *para*-substituted benzaldehydes to the corresponding acids and an LFER study on the oxidation of some α-methylbenzyl alcohols by Baumstark and co-workers[6,7] have shown evidence of radical character, as has recent work on alkene epoxidation[8] and alkane oxidation[9] by Minisci and co-workers. Also, studies by Crandell[10] and Curci[11] and their co-workers on the dimethyldioxirane oxidation of phenols and by Adam and Schonberger[12] on the oxidation of hydroquinones propose electron transfer processes.

We report an investigation into the nature of the dimethyldioxirane oxidation of a series of *para*-substituted *N*,*N*-dimethylanilines in an attempt to further probe the mechanism of amine oxidations and explore the possibility of substituent-induced changes of mechanism. The relative rates of oxygen transfer by dimethyldioxirane to the nitrogen of several *N*,*N*-dimethylanilines are described and compared to the relative rates obtained for methyl iodide methylation, benzoyl peroxide oxidation and *tert*-butyl hydroperoxide oxidation. The substrates are sterically identical around the nitrogen so the only factor affecting the rate of reaction is the electron demand of the *para*-substituent. Methyl iodide was used because, as in Adam's study,[5] it is reported to react with tertiary amines *via* a well established S_N2 mechanism. Benzoyl peroxide and *tert*-butyl hydroperoxide, like dimethyldioxirane, are both neutral peroxides. Benzoyl peroxide dealkylates tertiary amines and its rate determining step is thought to be electrophilic.[13] *tert*-Butyl hydroperoxide, also, dealkylates tertiary amines but is thought to react *via* a homolytic process involving *tert*-butoxyl radicals.[14] *tert*-Butyl hydroperoxide in the presence of a vanadium catalyst, which is reported[15] to lead to *N*-oxidation rather than dealkylation, was also used.

Results and discussion

The competition reactions were carried out by mixing one equivalent of the *para*-substituted *N*,*N*-dimethylaniline with one equivalent of the unsubstituted *N*,*N*-dimethylaniline in an acetone solution and adding one equivalent of dimethyldioxirane–acetone solution. The reactions were carried out at 0–5 °C and continued overnight to ensure total consumption of the dimethyldioxirane, enabling 50% conversion to be assumed. Relative reaction rates were determined by monitoring the consumption of starting material by HPLC. In each case, the *N*-oxide was the major product and no evidence was found for dealkylation [reaction (1)]. The reactions of dimethyldioxirane with each *N*,*N*-dimethylaniline were carried out to confirm this and the products obtained were compared with *N*-oxides prepared using performic acid.[16]



(1)

The competition reactions were repeated, replacing the dimethyldioxirane with (*i*) methyl iodide, (*ii*) benzoyl peroxide, (*iii*) *tert*-butyl hydroperoxide and (*iv*) *tert*-butyl hydroperoxide and vanadyl acetylacetonate. As with dimethyldioxirane, these reactions were run at 0–5 °C and continued to completion. The *tert*-butyl hydroperoxide reaction was also carried out at 70 °C as this is the more usual temperature at which to carry out dealkylations of tertiary amines with this reagent.[14]

The results of the competition reactions are shown in Table 1 and were calculated by determining the ratio of the reactants remaining at the end of the reaction. Here the unsubstituted

Table 1 Summary of the relative data for the reaction of *para*-substituted *N*,*N*-dimethylanilines in acetone with the reagents shown

	k_{rel}					
X	Dimethyldioxirane 0–5 °C	Methyl iodide 0–5 °C	Benzoyl peroxide 0–5 °C	*tert*-Butyl hydroperoxide 0–5 °C	*tert*-Butyl hydroperoxide 70 °C	*tert*-Butyl hydroperoxide + catalyst
MeO	2.13 ± 0.19	3.65 ± 1.14	27.6 ± 12.9	1.19 ± 0.08	0.89 ± 0.01	1.03 ± 0.10
H	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Cl	0.87 ± 0.01	0.70 ± 0.02	0.06 ± 0.02	0.86 ± 0.01	0.52 ± 0.12	1.13 ± 0.03
NO_2	0.18 ± 0.04	0.65 ± 0.10	0.03 ± 0.02	0.91 ± 0.08	0.52 ± 0.10	0.43 ± 0.06

Table 2 Summary of the relative rate data and substituent constants used in the LFER plot for the reaction of dimethyldioxirane with *para*-substituted *N*,*N*-dimethylanilines in acetone at 0–5 °C

			Run 1		Run 2	
X	σ^a	σ^{+b}	k_{rel}	log k_{rel}	k_{rel}	log k_{rel}
MeO	−0.27	−0.78	2.13	0.33	2.91	0.46
H	0.00	0.00	1.00	0.00	1.00	0.00
Cl	0.23	0.11	0.87	−0.06	0.49	−0.31
NO_2	0.78	0.79	0.18	−0.74	0.23	−0.64
$R_H{}^c$				0.987		0.964
ρ^d				−0.99		−1.01
$R_{OB}{}^e$				0.963		0.979
ρ^{+f}				−0.67		−0.71

[a] Taken from ref. 18. [b] Taken from ref. 19. [c] R_H, Correlation coefficient for Hammett plot. [d] R_{OB}, Correlation coefficient for Okamoto–Brown plot. [e] ρ, Hammett constant. [f] ρ^+, Okamoto–Brown constant.

Table 3 Run 3: absolute second order rate constants for the reactions of dimethyldioxirane with *para*-substituted *N*,*N*-dimethylanilines in 50 : 50 acetonitrile–0.1 M KNO_3 solution

X	k_x/dm^3 mol^{-1} s^{-1}	k_{rel}	log k_{rel}
MeO	1777	1.60	0.20
H	1109	1.00	0.00
Cl	611	0.55	−0.26
NO_2	213	0.19	−0.72
R_H			0.998
ρ			−0.89
R_{OB}			0.952
ρ^+			−0.58

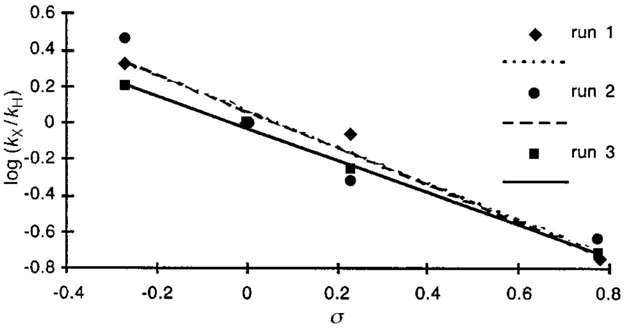


Fig. 1 LFER plots of log (k_X/k_H) *versus* σ for the reaction of dimethyldioxirane with *N*,*N*-dimethylanilines

amine in each series has been given an arbitrary value of 1 and the other rates in the series were calculated relative to this.

The results obtained indicate a similar qualitative trend for dimethyldioxirane oxidation as for the electrophilic methyl iodide and benzoyl peroxide reactions. The reactivity decreased in the order MeO > H > Cl ⩾ NO_2.[17] The *tert*-butyl hydroperoxide reactions are less susceptible to changes in substituent, the difference in rates being less marked, as would be expected for a non-electrophilic reaction. These trends suggest that the dimethyldioxirane oxidation of *N*,*N*-dimethylanilines is electrophilic. All the reactions were run to completion, therefore, the relative rates obtained reflect a minimum difference in reactivity.

The Hammett[18] relationship was applied to the dimethyldioxirane results giving an approximate ρ value of −0.99 (run 1, Table 2). Similar treatment of the data with the Okamoto–Brown[19] relationship gave $\rho^+ = -0.67$. The highest negative ρ value reported for a dimethyldioxirane reaction is −2.76 by Murray and Gu[4] for the C–H insertion reaction into *para*-substituted cumenes. Lower values (−0.77 and −0.76) have been reported by Murray *et al.*[3] for the electrophilic dimethyldioxirane oxidation of *para*-substituted aryl methyl sulfides and sulfoxides, respectively.

The dimethyldioxirane competition reactions were repeated in a second run (Table 2) using a slightly different approach. In this case the relative rates were calculated by comparing the initial concentrations of anilines with the final concentrations making no assumptions about the percentage conversion. The Hammett[18] relationship was applied to data from both runs (Table 2) yielding a mean ρ value of −1.00 which suggests that the conclusions drawn by Murray on the electrophilic nature of the cumene and sulfide oxidations can be equally applied to the dimethylaniline oxidations.

Although the relative rate measurements enable a competitive assessment to be made between substrates they provide no direct measure of the rate of reaction itself. In a third approach, therefore, absolute second order rate constants for reactions of dimethyldioxirane each with a known excess of the dimethylaniline were determined by controlled potential amperometry on the polarographic reduction wave of dimethyldioxirane. This avoids the large background interferences inherent with spectroscopic methods for the detection of dimethyldioxirane. The data obtained are summarised in Table 3.

The reactions of dimethyldioxirane and *para*-substituted *N*,*N*-dimethylanilines follow the Hammett relationship with a ρ value of −0.89 which is similar to that obtained from the relative rate data (Fig. 1). The agreement is good considering that the two experimental approaches were conducted at different temperatures and in different solvents. The electrochemical measurements were carried out in aqueous acetonitrile at 21 °C whereas the relative rate data were generated in acetone at 0–5 °C. The excellent correlation observed with the Hammett plot of the absolute rate data suggests that this relationship is more appropriate than that from the Okamoto–Brown[20] plot and lends further support to the hypothesis that the dimethyldioxirane oxidation of substituted dimethylanilines is a concerted electrophilic process.

The dimethyldioxirane oxidations show obvious similarities to reactions of dimethylanilines with methyl iodide (Menschutkin reaction) which has a reported[21] ρ value of −3.30 at 35 °C in 90% aqueous acetone. Whereas, in the latter reactions the transition state is thought to have developed almost a full positive charge, the reactions with dimethyldioxirane clearly have much less charge development (Fig. 2) and may be a result, in

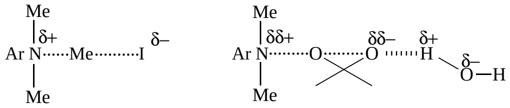


Fig. 2 Transition states for the reactions of dimethylanilines with MeI and dimethyldioxirane

Table 4 Pseudo first order rate constants for the reaction between dimethyldioxirane and *N*,*N*-dimethyl-4-nitroaniline in various solvents at 25 °C

Solvent	k/s^{-1}	ε
Water	5.86	78.5
Water–acetone	1.55×10^{-1}	—
Acetone	6.30×10^{-3}	20.7
Dichloroethane	4.10×10^{-4}	10.4
Acetonitrile	4.50×10^{-4}	37.5
Acetonitrile[a]	6.88	37.5
Ethyl acetate	8.00×10^{-5}	6.02
pH 1, 0.1 M Buffer soln	5.05	—
pH 10, 0.1 M Buffer soln	6.52	—
pH 5, 0.1 M Buffer soln	5.19	—
pH 5, 0.01 M Buffer soln	6.34	—

[a] (Trifluoromethyl)methyldioxirane.

part, of steric crowding in the transition state. Hydrogen bonding is also thought to be important (see below).

The rapidity of the reactions in aqueous acetonitrile is surprising in view of our earlier observation that *N*,*N*-dimethyl-4-nitroaniline was effectively unchanged after many hours of reaction with dimethyldioxirane in acetone. Interestingly oxidation of *N*,*N*-dimethyl-4-nitroaniline at 0 °C with dimethyldioxirane (10 equiv.) in 50% aqueous acetone on a preparative scale showed significant conversion to the *N*-oxide after only one hour. The ^{1}H NMR spectrum of the *N*-oxide in the reaction mixture showed the expected peaks at δ 8.37 (2H^3, d, *J* 9), 8.21 (2H^2, d, *J* 9) and 3.7 (NMe$_2$, s). The reaction mixture also contained some starting material and a minor impurity that we were unable to isolate.

The possibility of a strong solvent effect, as has been observed[22–24] in other dioxirane oxidations, was investigated kinetically by monitoring the loss of the UV absorbance of *N*,*N*-dimethyl-4-nitroaniline when reacted with an excess of dimethyldioxirane. The pseudo first order rate constants were calculated in a number of solvents and the results are summarised in Table 4.

With the exception of acetonitrile the pseudo first order rate constant decreases with the relative permittivity of the medium. This is a similar trend to that observed in the Menschutkin reaction in which, as here, factors other than relative permittivity are involved.[21] Significantly there is a large increase in the reaction rate in water and the increased reaction rate remains relatively constant irrespective of the pH or ionic strength. The magnitude of the rate increase in water is almost certainly not due to the effects of relative permittivity alone and probably arises from the strong hydrogen bonding nature of the solvent. Such solvents would be expected to stabilise both the transition state (Fig. 2) and the *N*-oxide reaction products which readily form stable hydrates.[25] Direct evidence of the latter was observed particularly in the ^{1}H NMR spectrum of *N*,*N*-dimethyl-4-nitroaniline *N*-oxide. D$_2$O solutions of the *N*-oxide showed resonances at δ 8.19 (2H^3, d, *J* 9), 7.89 (2H^2, d, *J* 9) and 3.5 (NMe$_2$, s). Evaporation of the D$_2$O and suspension of the hydrated residue in CDCl$_3$ containing sieves afforded a ^{1}H NMR spectrum identical to that of the *N*-oxide originally isolated (see earlier). The role of hydrogen bonded solvents in accelerating oxidation rates has previously been recognised by Murray and Gu in studies of the dimethyldioxirane epoxidation of ethyl (*E*)-cinnamate[23] and oxidation of C–H bonds.[24] We and others have suggested intramolecular hydrogen bonding could be important in some dimethyldioxirane oxidations[26,27] and very recently *ab initio* model studies on primary amine oxidations with dimethyldioxirane has confirmed the importance of solvent and hydrogen bonding effects.[28]

The rate constants observed in water are comparable to those obtained for the oxidation of *N*,*N*-dimethyl-4-nitroaniline using (trifluoromethyl)methyldioxirane in a relatively unreactive solvent such as acetonitrile. It is speculated that the presence of water promotes faster reaction times and yields without recourse to the use of fluorinated dioxiranes which are experimentally more difficult to handle.

All the data obtained are consistent with conclusions that the dimethyldioxirane oxidation of dimethylanilines is electrophilic in nature and does not involve the bis(oxyl) diradical **2** or electron transfer. In this respect the mechanism agrees with the conclusions drawn by Curci and co-workers for the epoxidation and oxygen insertion into alkane C–H bonds.[29]

Experimental

Materials

Acetone was distilled from potassium permanganate prior to use. Oxone ($2\mathrm{KHSO_5 \cdot KHSO_4 \cdot K_2SO_4}$) was supplied by Aldrich and used without further treatment. *N*,*N*-Dimethylaniline and *N*,*N*-dimethyl-4-nitroaniline were supplied by Lancaster and used as received. Dimethyldioxirane–acetone solutions were synthesised according to literature procedure.[30] Methyl iodide, benzoyl peroxide, *tert*-butyl hydroperoxide and vanadyl acetylacetonate were supplied by Lancaster and used as received.

N,*N*-Dimethyl-4-methoxyaniline and *N*,*N*-dimethyl-4-chloroaniline were prepared according to literature procedures using sodium cyanoborohydride and *para*-formaldehyde in glacial acetic acid.[31] The purity was checked using ^{1}H NMR spectroscopy and melting point data.[32] The *N*-oxides of the *N*,*N*-dimethylanilines were prepared using performic acid also according to literature procedures.[16]

Instrumentation

NMR spectra were recorded using a Bruker AC 250 spectrometer. Amperometric measurements were recorded using a BAS CV50W voltametric analyser with a hanging mercury drop electrode and using the timebase mode for the kinetic measurements. Spectrophotometric measurements were recorded on a Beckmann 640i spectrophotometer using the kinetics accessory. HPLC was performed using: Perkin-Elmer series 3 pump, Perkin-Elmer LC55B spectrophotometric detector and Spectraphysics integrator. A Hewlett Packard 1090 diode array detector was also used. The chromatographic conditions used for the first run were as follows: column, µBondapak C18 10 µm 3.9 × 300 mm; eluent, 6 : 4 methanol–water (NO$_2$ and Cl), 1 : 1 methanol–water (MeO); flow rate, 1 ml min^{-1}; detection, UV@240 nm; injection volume, 20 µl.

The second set of results were obtained using the HPLC method given below: column, Spherisorb S5 C1 15 cm × 4.6 mm; eluent, 0.05 M phosphate buffer, 0.1% triethylamine pH 3.5 (NO$_2$ and Cl), pH 4.0 (MeO); flow rate, 1 ml min^{-1}; detection, UV@210 nm; injection volume, 20 µl.

Relative rate studies of *N*,*N*-dimethylanilines

An equimolar stock solution of *N*,*N*-dimethylaniline and *para*-substituted *N*,*N*-dimethylaniline in acetone was prepared. An aliquot of this solution was removed, placed in a flask covered with aluminium foil to protect it from light, and cooled to 0–5 °C in an ice bath. One equivalent of dimethyldioxirane solution was then added to the flask and the reaction stirred magnetically overnight. Starch–iodide paper showed no remaining oxidant. A 50 µl sample was removed and analysed by HPLC. Two determinations were made for each reaction and each reaction was carried out in duplicate.

The above procedure was repeated using aliquots of the same stock solution and the following reagents: methyl iodide, benzoyl peroxide and *tert*-butyl hydroperoxide. The *tert*-butyl hydroperoxide reactions were also carried out at 70 °C and in the presence of vanadyl acetylacetonate (0.025 equiv.). All the reactions were run to completion. The relative rates were calculated by determining the ratio of reactants remaining at the end of the reaction. This was achieved by first constructing a calibration graph of actual ratio of unsubstituted aniline to substituted aniline *versus* observed peak area ratio for a series of standard solutions containing varying known ratios of aniline to substituted aniline. Using this graph, observed peak area ratios of aniline to substituted aniline obtained from the chromatogram were converted to actual ratios. The reactions were run to completion, consuming all the dioxirane, therefore, 50% conversion could be assumed and the relative rates calculated by taking the reciprocal of the ratio of aniline to substituted aniline remaining at the end of the reaction. A summary of the relative rate data obtained is given in Table 1.

The dimethyldioxirane competition reactions were repeated and analysed using quantitative HPLC. Again two determinations were made for each reaction and each reaction was done in duplicate. Standards of each *N*,*N*-dimethylaniline were prepared and used to quantify the amounts of each present at the end of the reaction. The relative rates were calculated using eqn. (2),[4] where ΔC = change in concentration of reactants.

$$k_{\mathrm{rel}} = \frac{k_{\text{p-substituted aniline}}}{k_{\text{aniline}}} = \frac{\Delta C_{p\text{-substituted aniline}}}{\Delta C_{\text{aniline}}} \qquad (2)$$

Oxidation of the *N*,*N*-dimethylanilines with dimethyldioxirane

Solutions of each of the *N*,*N*-dimethylanilines in acetone were oxidised using 2 equiv. of dimethyldioxirane–acetone solution. Concentration of the product solution *in vacuo* gave the *N*-oxides as the only products by ^{1}H NMR and HPLC.

Constant potential amperometric rate studies

The absolute rates of reaction were determined by monitoring the loss of current due to the polarographic reduction of dimethyldioxirane on addition of a solution of the anilines. A solution of dimethyldioxirane (0.13 mM, 10 ml) prepared by adding an appropriate volume of dimethyldioxirane in acetone to a mixture of potassium nitrate solution (0.1 M) and acetonitrile (50% v/v), was placed in the electrochemical cell. The solution was stirred at 600 rpm while the test aniline solution (50–250 µl, 0.06 M in acetonitrile) was added to the cell. The loss in current was monitored with time under the following instrumental settings: potential = +80 mV, sampling time = 100 s, interval time = 50 ms, sensitivity = 1 µA, reference electrode Ag^+/Ag, temperature 21 °C. The pseudo first order rate constants were determined by plotting the ln *I* *versus* time (final current = zero). Second order rate constants were determined by plotting the pseudo first order rate constants *versus* molar concentration of aniline. Standard linear regression statistics were used to calculate the slope of these lines.

Spectrophotometric rate studies

The spectophotometric rates were determined by monitoring the loss of UV absorbance of *N*,*N*-dimethyl-4-nitroaniline on addition of dimethyldioxirane. A solution of *N*,*N*-dimethyl-4-nitroaniline (0.03 mM, 2.5 ml) in the appropriate solvent was placed in a 1 cm cuvette and the solution stirred magnetically. Dimethyldioxirane solution in acetone (0.07 M, 60 µl) was aspirated into the cell and the loss of absorbance as a function of time was recorded with the following instrumental settings: λ = 400–425 nm depending on $\lambda_{\max}$ in each solvent, interval time = 0.1 s, read average time = 0.05 s, run time = 30–3000 s, temperature thermostatted at 25 °C. The pseudo first order rate constants were determined by plotting ln absorbance *versus* time (the absorbances of the *N*-oxides at these wavelengths were negligible) using standard linear regression statistics to calculate the slopes and hence rate constants.

Note added in proof. Dimethyldioxirane oxidation of *N*,*N*-dimethylaniline to the *N*-oxide has very recently been reported.[33]

Acknowledgements

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