

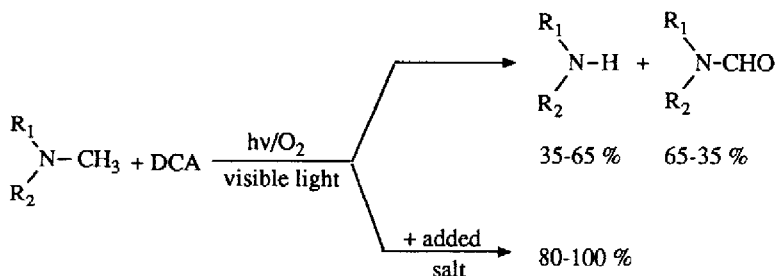
ELECTRON-TRANSFER ACTIVATION. SALT EFFECTS ON THE PHOTOOXIDATION  
OF TERTIARY AMINES : A USEFUL N-DEMETHYLATION METHOD

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**Abstract :** Photooxidation of tertiary methylamines sensitized by electron acceptors like 9,10-dicyanoanthracene is shown to proceed by two distinct ways depending on the presence of added salts. In the absence of added salt both nor and N-formyl compounds were obtained while with added salt the nor-derivative is obtained highly efficiently.

The growing interest in photoinduced electron transfer reactions has raised new efforts to control the outcome of these processes. One very interesting result is the recent discovery that added salts can greatly affect these reactions<sup>1</sup>. In one of the most striking examples of this phenomenon, Mizuno, Otsuji and coworkers<sup>2</sup> recently reported that the photooxidation of several biphenyl derivatives is enhanced by the addition of Mg(ClO<sub>4</sub>)<sub>2</sub>. We now report a novel photooxidation of tertiary methylated amines under mild conditions in the presence of added salts like LiClO<sub>4</sub> or Mg(ClO<sub>4</sub>)<sub>2</sub>.

Irradiation of an acetonitrile solution of the amine in the presence of a catalytic amount of 9,10-dicyanoanthracene (DCA), under oxygen bubbling, affords both nor and N-formyl compounds in variable yields. In the presence of an added salt, like LiClO<sub>4</sub> or Mg(ClO<sub>4</sub>)<sub>2</sub>, the nor-derivative is obtained highly efficiently. The reaction provides a new strategy for selective N-demethylation of tertiary methylamines.



In a typical case, a solution of tropinone **1a** (2 mmol) and DCA (0.02 mmol) in acetonitrile (50 ml) with variable amounts of LiClO<sub>4</sub> is irradiated under oxygen bubbling for 30-90 minutes with a 500 W high-pressure Hg lamp through a U.V. cut-off glass filter ( $\lambda \geq 420$  nm) at 20 °C. After reaction (followed by t.l.c.) the products are separated by flash chromatography on alumina.

Table 1 summarizes the representative results of the added salts effects on the DCA-sensitized photooxidation of **1a**. Examination of the Table reveals the salt concentration dependence of the nortropine **1b** formation and its dramatic increase for 0.25 to 0.30 equiv. salt concentration. A typical curve is shown in Figure 1.

Table 1. Dependence of the DCA-sensitized photooxidation of tropinone **1a** on the concentration of added  $\text{LiClO}_4$ <sup>a</sup>.

$\text{LiClO}_4$ (equiv.)	product ratio (%) <sup>b</sup>		Notes
	<b>1b</b>	<b>1c</b>	
-	35	65	<i>a. Similar results were obtained in using <math>\text{Mg}(\text{ClO}_4)_2</math>.</i> <i>b. Determined by <math>^1\text{H NMR}</math> data and h.p.l.c..</i>
0.1	70	30	
0.25	100	-	
0.30	90	10	
0.40	85	15	
0.50	80	20	
1	50	50	
5	43	57	

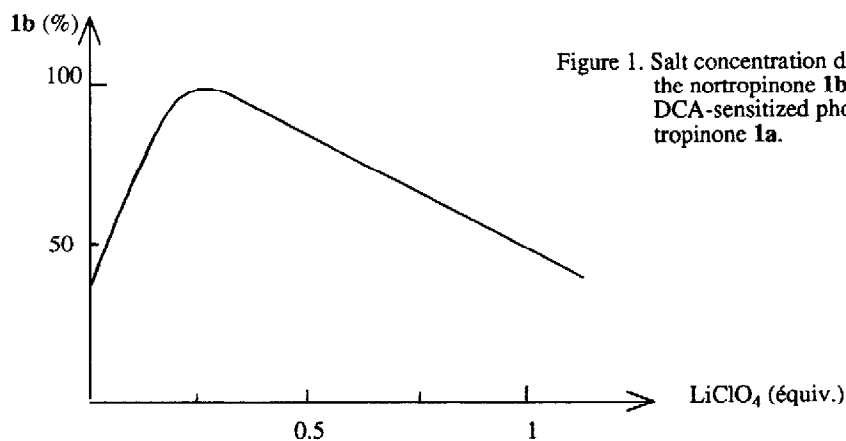
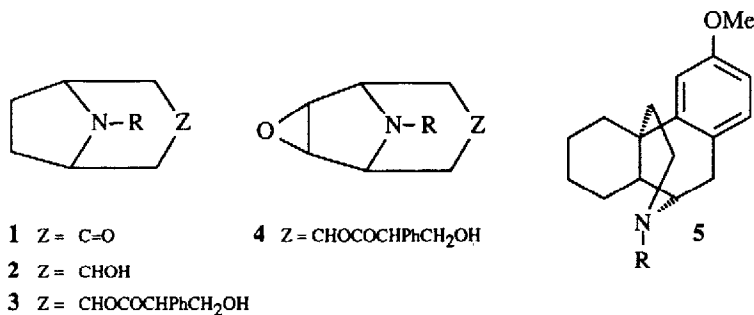


Figure 1. Salt concentration dependence of the nortropine **1b** formation from DCA-sensitized photooxidation of tropinone **1a**.



a, R = CH<sub>3</sub>; b, R = H; c, R = CHO

A similar effect of added salt, with an optimum of concentration, was observed for several other tertiary methylamines ; the corresponding data are summarized on Table 2.

Table 2. DCA-sensitized photooxidation of various tertiary amines in the absence and presence of added  $\text{LiClO}_4^a$ , at optimum concentration.

Amine		$\text{LiClO}_4$ (equiv.)	Products ratio (%) <sup>b</sup>	
			$\text{>NH}$	$\text{>NCHO}$
Tropinone	<b>1a</b>	-	<b>1b</b> 35	<b>1c</b> <sup>3</sup> 65
		0.25	100	-
Tropine	<b>2a</b>	-	<b>2b</b> 73	<b>2c</b> <sup>4</sup> 27
		0.25	85	15
Atropine	<b>3a</b>	-	<b>3b</b> 52	<b>3c</b> <sup>5</sup> 48
		0.5	100	-
Scopolamine	<b>4a</b>	-	<b>4b</b> 50	<b>4c</b> <sup>6</sup> 50
		0.5	82	18
Dextromethorphan	<b>5a</b>	-	<b>5b</b> 43	<b>5c</b> <sup>7</sup> 57
		0.5	83	10

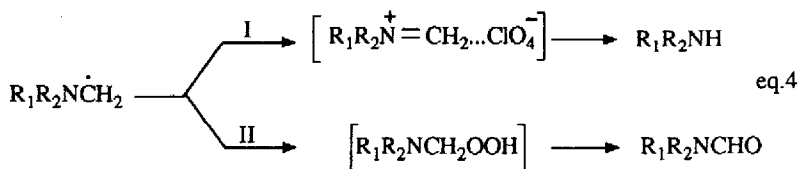
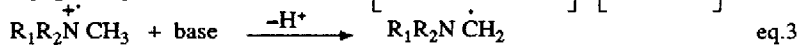
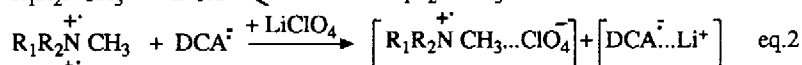
a. Similar results were obtained using  $\text{Mg}(\text{ClO}_4)_2$ .

b. All products were characterized by IR,  $^1\text{H}$  NMR and mass spectrometry.

These photo-oxidations are believed to proceed from an initial electron transfer along the following sequence (Scheme 1) giving rise to an  $\alpha$ -amino radical<sup>8</sup> which may react in two ways :

- either by electron loss giving an iminium ion, subsequently hydrolyzed into the secondary amine (eq. 4, step I).

- or, by recombination with an oxygen species ( $\text{O}_2$ ,  $\text{O}_2^{\cdot-}$  or  $\text{HO}_2^{\cdot}$ ) giving the N-formyl derivative, probably via an  $\alpha$ -hydroperoxy amine (step II).



Scheme 1

The effect of added salts is at the same time to increase the overall rate of photooxidation by a factor of 2 to 3 and to favor step I over step II.

Acceleration of the reaction appears to be in keeping with the results of preceding authors<sup>9</sup> who have shown that added salts increase both the proportion of a radical-ion pair dissociation, via pair exchange, (eq. 2), and the lifetime of radical-ions, slowing down the rate of back electron transfer.

The more unexpected orientation effect arises probably from the stabilisation of the iminium ion by an ionic association which favors its formation from the neutral radical though alternatively a trapping of  $O_2^-$  cannot be excluded.

As regards the occurrence of an optimum for the N-demethylation ratio in relation to the added salt concentration, several factors may come into play, such as the increasing viscosity of the medium which could favour a combination of the iminium ion with *in situ* generated  $O_2$ , leading finally to the N-formyl derivative ; further work would be required to rationalize this point.

## References and Notes

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5. 3c.  $M^+$  303 (11%,  $C_{17}H_{21}NO_4$ ), 273, 154, 110; IR ( $CHCl_3$ ,  $cm^{-1}$ ) 1660 (CHO), 1730 (ester);  $^1H$  NMR ( $CDCl_3$ ,  $\delta$ ) 3.85 (2H, d,  $CH_2OH$ ), 4.45 (1H, m,  $CHNCHO$ ), 5.15 (1H, t,  $CHCH_2OH$ ), 7.30 (5H, m, H aro.), 8.06 (1H, s, CHO).
6. 4c. m.p. 78°C;  $M^+$  317 (3%,  $C_{17}H_{19}NO_5$ ); IR (KBr,  $cm^{-1}$ ) 1670 (CHO), 1730 (ester);  $^1H$  NMR ( $CDCl_3$ ,  $\delta$ ) 3.68 (2H, d,  $CH_2OH$ ), 4.50 (2H, m,  $CHNCHO$ ), 5.10 (1H, t, -CHOCO-), 7.35 (5H, m, H aro.), 8.0 (1H, s, CHO).
7. 5c.  $M^+$  285 (22%,  $C_{18}H_{23}NO_2$ ), 213, 171;  $[\alpha]_D = +157^\circ$  (c = 1,  $CH_3OH$ ); IR ( $CHCl_3$ ,  $cm^{-1}$ ) 1670 (CHO);  $^1H$  NMR ( $CDCl_3$ ,  $\delta$ ) 3.80 (3H, s,  $OCH_3$ ), 6.86 (3H, m, H aro.), 7.98 and 8.15 (1H, 2s, two rotamers, CHO).
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