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# Oxidation of *N*-Methyl-9-*t*-butylacridane by Iodosylbenzene Catalyzed by Tetrakis(pentafluorophenyl) Porphyrin Iron(III). A Tool to Investigate the Mechanism of the Oxidative *N*-Demethylation of Aromatic Tertiary Amines.

Enrico Baciocchi* and Andrea Lapi.

Dipartimento di Chimica and Centro CNR di Studio sui Meccanismi di Reazione, Università"La Sapienza", Piazzale A. Moro 5, 00185 Roma, Italy.

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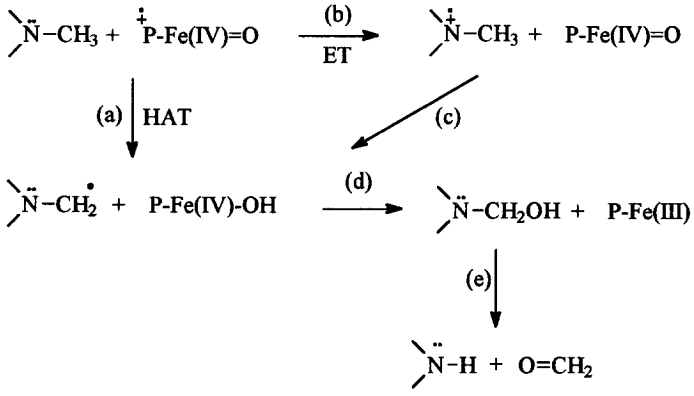
**Abstract:** The PhIO promoted oxidation of *N*-methyl-9-*t*-butylacridane (1) catalyzed by tetrakis(pentafluorophenyl) porphyrin iron(III) leads first to 9-*t*-butylacridane and then to acridine. It is suggested that 1 can represent a reliable machanistic probe to detect the intervention of radical cations in the oxidation of aromatic amines.



The mechanism of the enzymatic[1] and biomimetic[2] oxidative *N*-dealkylation of tertiary amines is still a subject of current and lively debate which particularly concerns the distinction between the hydrogen atom transfer (HAT) and the electron transfer (ET) mechanisms described in Scheme 1 (paths a,d and b,c,d, respectively) where $P^{\cdot+}Fe(IV)=O$ is the porphyrin iron-oxo complex radical cation suggested to be the active oxidant in both the enzymatic (P = protoporphyrin IX) and biomimetic (P = synthetic porphyrin) oxidations.[2,3] An intriguing situation is related to the recent suggestion that the oxidation of *N,N*-dimethylanilines catalyzed by cytochrome P450 occurs by a HAT mechanism[1d] whereas the biomimetic oxidation of the same substrates promoted by iron porphyrins appears to occur by an ET mechanism.[2c,4] There is therefore continuous interest for the development and application of new mechanistic probes which may provide additional information in this respect.




**Scheme 1**

We wish now to show that *N*-methyl-9-*t*-butylacridane (**1**) can represent a new and very reliable mechanistic probe to detect ET steps in the oxidation of tertiary aromatic amines. Accordingly, it has recently been reported that $\mathbf{1}^{\cdot+}$, electrochemically generated from **1**, undergoes either a very fast C-C bond cleavage to form a *t*-butyl radical and the *N*-methylacridinium cation or, in the presence of a pyridine base with a pKa ≥ 15.6 (in MeCN), is deprotonated at the *N*-methyl group eventually leading to acridine (**2**).[5] In this note we report on the study of the oxidation of **1** catalyzed by tetrakis (pentafluorophenyl)porphyrin iron(III) chloride (FeTPFPPCl).[6]

The reaction of **1** with iodosylbenzene in the presence of FeTPFPP was carried out in $CH_2Cl_2$, at room temperature using a substrate/oxidant/catalyst ratio of 50:10:1 Under these conditions, after 10 min, the reaction

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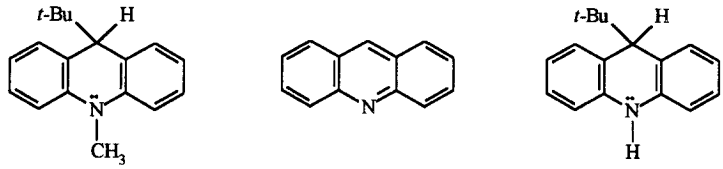
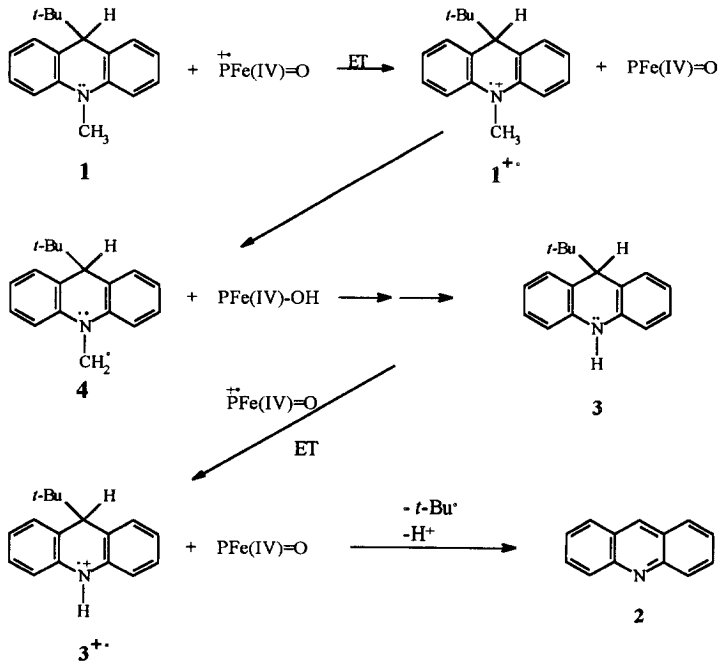
led to 9-*t*-butylacridane (**3**), as the exclusive reaction product. The yield was 13 %, with an excellent (97 %) mass balance. Formation of substantial amounts of formaldehyde was also observed. By decreasing the substrate/oxidant ratio, however, the formation of another product, acridine (**2**), was noted.[7] The **3/2** ratio was 4:1, when the substrate/oxidant ratio was 50:16 and **2** becomes the major reaction product when the substrate/oxidant ratio was 1:3. This clearly indicates that **2** derives from oxidation of **3**. Accordingly, it was established, in a separate experiment, that the oxidation of **3** under the reaction conditions leads to **2** as the exclusive product.



**1** **2** **3**

Thus, **1** reacts with $P^{\cdot+}Fe(IV)=O$ to form first the *N*-demethylated product **3**. This reaction might occur by a HAT mechanism (Scheme 1, paths a, d, e), but this possibility was immediately excluded by carrying out competitive oxidation of **1** with *N*-trideuteromethyl-9-*t*-butylacridane (**1-CD$_3$**). An intermolecular deuterium kinetic isotope effect as low as 1.24 ± 0.03) was determined, which is not consistent with a HAT mechanism.[8] Thus, the most reasonable interpretation of our results is that $\mathbf{1}^{\cdot+}$ is actually formed in the slow step of the reaction, but it undergoes deprotonation at the *N*-methyl group rather than de-*t*-butylation (Scheme 2).




**Scheme 2**

This suggestion is fully consistent with the observed $k_H/k_D$ value, which is that expected for a secondary deuterium kinetic isotope effect resulting from the different effect of $CH_3$ and $CD_3$ on the rate of formation of the aminium radical cation.[2b,2c] The deprotonation of $\mathbf{1}^{\bullet+}$, promoted very likely by PFe(IV)=O, gives the carbon radical **4**, which forms **3** *via* an intermediate carbinolamine (see paths d and e in Scheme 1). Once formed, **3** can react with $P^{\bullet+}$Fe(IV)=O by an ET mechanism leading to $\mathbf{3}^{\bullet+}$ which now gives **2** by the loss of the *t*-butyl group (Scheme 2).[9]

The observation that only *N*-methyl deprotonation of $\mathbf{1}^{\bullet+}$ occurs in the biomimetic reaction is of great interest as it would indicate that P-Fe(IV)=O is a relatively strong base with a $pK_a$ value which can be estimated to be $\geq$ *ca* 16 (*i.e.* $\geq$ $pK_a$ of 2,4,6-trimethylpyridine in MeCN), on the basis of Savéant's results mentioned above.[5] This is an important piece of information since a significant basicity of P-Fe(IV)=O has been called into play (without any proof, however) to rationalize the observation that the chloroperoxidase catalyzed *N*-demethylation of *N,N*-dimethylaniline exhibits a kinetic deuterium isotope effects much smaller than that of the corresponding reaction catalyzed by horseradish peroxidase.[10] It was suggested that in both cases a radical cation is formed, but that in the former reaction the proton abstracting base (P-Fe(IV)=O) is a much stronger base than the one ($H_2O$) supposed to operate in the second reaction This suggestion is consistent with our estimated lower limit for the $pK_a$ value of P-Fe(IV)=O.

In conclusion, our results, while confirming, by a different approach, that the biomimetic oxidative N-demethylation of tertiary aromatic amines takes place by an ET mechanism,[11] clearly show that **1** is a very reliable mechanistic probe to detect the intervention of radical cations in the oxidation of aromatic amines, which can also provide information, as in the present case, about the strength of the base operating under the reaction conditions. In view of the large number of important processes involving the oxidation of aromatic amines,[1] an increasing use of this simple probe can reasonably be predicted.

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5. (a) Anne, A.; Fraoua, S.; Moiroux, J.; Savéant, J. M. *J.Phys. Org. Chem.* **1998**, 11, 774-780. (b) Anne, A.; Fraoua, S.; Moiroux, J.; Savéant, J. M. *J. Am. Chem. Soc.* **1996**, 118, 3938-3945.
6. (a) It should be mentioned that a structurally similar molecule (*i.e.* 1-benzyl-4-*t*-butyl-1,4-dihydronicotinamide) has already been used as a probe to distinguish between an ET and a hydride transfer mechanism in the reaction of NADH bases with *p*-chloranil.[6b] (b) Anne, A.; Moiroux, J.; Savéant, J. M. *J. Am. Chem. Soc.* **1993**, 115, 10224-10230.

7. Product yields were determined by HPLC and GC-MS analysis. The reaction products were characterized by comparison with authentic specimens.
8. This value, determined by GC-MS analysis of the formaldehyde-dimedone adduct, is an average of three independent determinations.
9. However, other pathways appear possible under different reaction conditions. Thus Savéant and his associates in their electrochemical study found that **1** is converted to acridine by a two-electrons oxidation, without forming **3** as intermediate.[5a] They suggested that, once formed the carbinolamine *via* an oxidative route, a base promoted reaction takes place leading to acridine, $CH_2O$ and *t*-butyl carbanion. The reasons why the carbinolamine is not *N*-demethylated to produce **3**, under the Savéant's conditions, are presently not clear and further study appears necessary.
10. Okazaki, O.; Guengerich, F. P. *J. Biol. Chem.* **1993**, 268, 1546-1552.
11. Obviously, it would be of great interest the use of this probe in the oxidation promoted by cytochrome P450. We carried out some attempts in this respect, but so far without success. The substrate showed practically no reactivity with the enzyme, probably because of its extremely low solubility in the reaction medium.