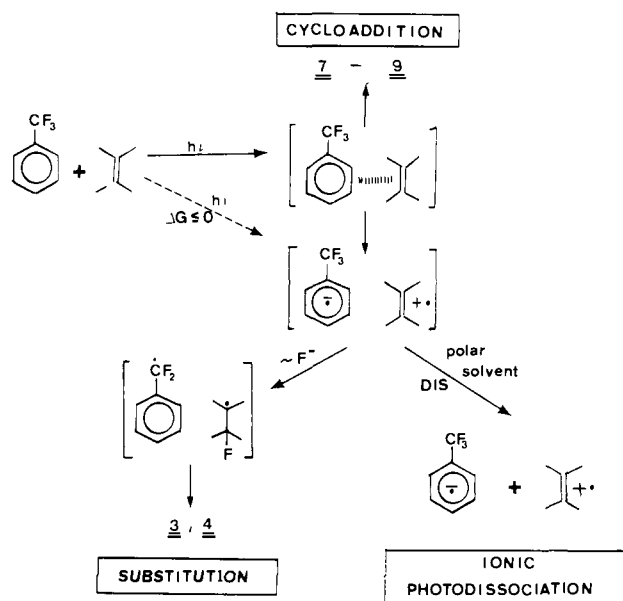


Scheme II. Proposed Mechanism of Photoreactions of  $\alpha,\alpha,\alpha$ -Trifluorotoluene (1) with Olefins



and the substitution takes place via an ion pair as the intermediate analogous to other systems, studied by McCullough,<sup>12</sup> Arnold,<sup>13</sup> and Lewis,<sup>14</sup> one should expect a dependence of the mode selectivity on the electron transfer enthalpies  $\Delta G$ . These  $\Delta G$  values can be easily calculated by means of the Rehm-Weller equation.<sup>15</sup> A simplified version of this equation for 1,4-dioxane (dielectric constant,  $\epsilon$  2.2) as solvent is given as follows:

$$\Delta G(\text{eV}) = E_{1/2}^{\text{ox}}(\text{D}) - E_{1/2}^{\text{red}}(\text{A}) - \Delta E_{\text{excit}} + 0.82$$

with  $E_{1/2}^{\text{ox}}(\text{D})$  = oxidation potential of the donor,  $E_{1/2}^{\text{red}}(\text{A})$  reduction potential of the acceptor, both in acetonitrile, and  $\Delta E_{\text{excit}}$  = excitation energy (here of 1). The results of such a calculation are shown in Table I and clearly demonstrate that substitution is preferred in systems of exothermic electron transfer. As a consequence these latter systems also exhibit a strong solvent effect; i.e., the quantum yields of product formation decrease by a factor up to 3.5 when changing the solvent polarity from  $\epsilon$  2.02 (cyclohexane) to  $\epsilon$  37.5 (acetonitrile). These effects may be best rationalized in assuming a competition between product formation and ionic photodissociation, which we have studied in more detail in ketone-olefin systems.<sup>1,16</sup>

We conclude from these results a mechanism of product formation as shown in Scheme II. The assumption of an exciplex intermediate seems reasonable, even in systems that exhibit exothermic electron transfer, since the rate constants of fluorescence quenching of 1 by olefins do not follow the theoretical curve of direct electron transfer reported by Rehm and Weller.<sup>17</sup>

In particular these rate constants are even higher in systems of endothermic electron transfer as shown in Figure 1. Again a more detailed discussion of this phenomenon concerning the luminescence quenching of 1,2-diketones and arenes has been presented elsewhere and will be published soon.<sup>16</sup>

Fluorinated ketones like  $\alpha,\alpha,\alpha$ -trifluoroacetophenones do show significant charge-transfer quenching as reported by Wagner.<sup>18</sup>

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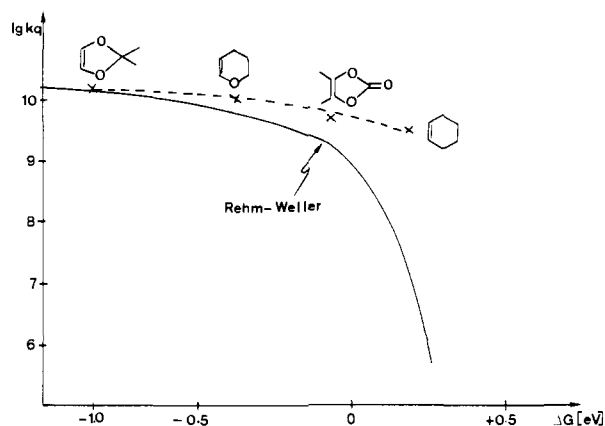


Figure 1. Correlation between measured rate constants of fluorescence quenching of 1 by various olefins (X) and the free enthalpy of radical ion pair formation  $\Delta G$  in acetonitrile (Rehm-Weller, theoretical curve for electron transfer as the primary step; see ref 17).

However, a similar C-F bond cleavage has not been observed in these systems since  $\Delta G$  of electron transfer is endothermic according to the Rehm-Weller equation.<sup>19</sup>

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(19) Even with the strongest acceptor *p*-(trifluoromethyl)- $\alpha,\alpha,\alpha$ -trifluoroacetophenone and toluene as donor ( $E_{1/2}^{\text{ox}} = 2.13$  V vs. SCE in  $\text{CH}_3\text{CN}$ )  $\Delta G$  is positive according to the Rehm-Weller equation.

## Evidences for an Efficient Demethylation of Methoxyellipticine Derivatives Catalyzed by a Peroxidase

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Demethylation of methoxylated aromatic compounds usually requires rather drastic reaction conditions in preparative organic chemistry: nitric acid,<sup>1</sup> argentic oxide,<sup>2</sup> or ceric ammonium nitrate.<sup>3</sup> A mild method of aromatic O-demethylation can be still considered as a useful goal for organic synthesis of multifunctional molecules. Whereas easy O- and N-demethylation can be performed by cytochrome P-450 enzymes,<sup>4-6</sup> peroxidases have been

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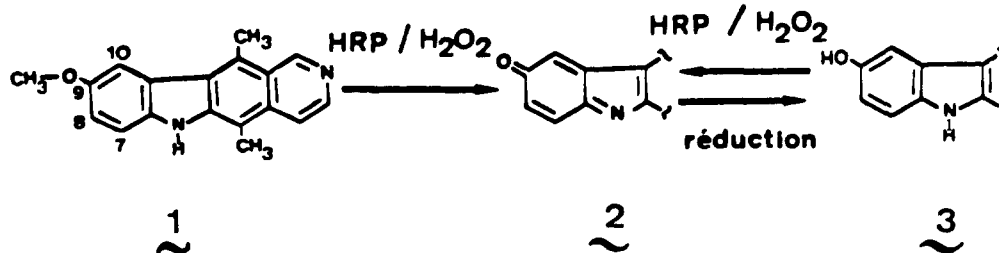
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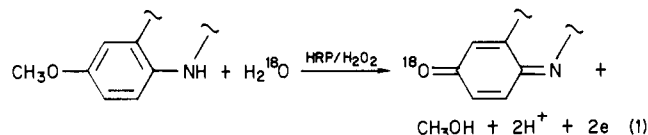
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Scheme I. Peroxidase-Catalyzed Demethylation of 9-Methoxyellipticine (1) in the Corresponding Quinone Imine Derivative 2



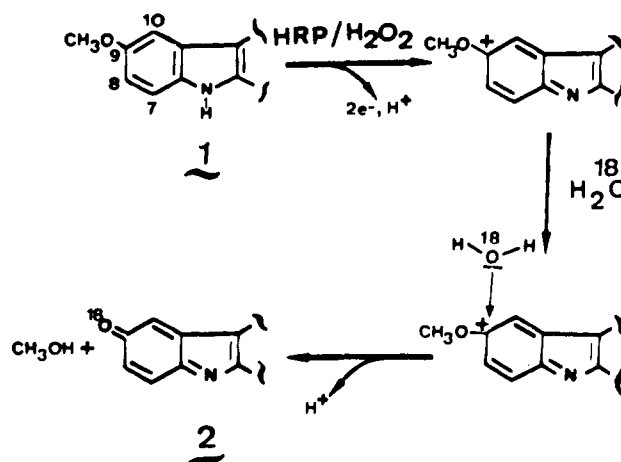
reported up to now as being only able to catalyze N-demethylation,<sup>5c,d</sup> as observed during the oxidative transformation of various xenobiotic molecules. However, despite well-documented N-dealkylation reactions by peroxidases,<sup>5b,c,d</sup> no reaction of O-demethylation seems to have been reported in the literature. Therefore, we wish to present our recent work on an apparent O-demethylation aromatic reaction catalyzed by a peroxidase (horseradish peroxidase or HRP) in the presence of hydrogen peroxide, obtained in the case of 9-methoxyellipticine 1, a cytotoxic agent.<sup>7</sup> Experiments with labeled water indicate that a key step of the reaction involved a demethoxylation via cleavage of an oxygen-aromatic carbon bond.

In a typical experiment, 9-methoxyellipticine (25 mg, 70 μmol) in 200 mL of phosphate buffer (pH 5.0) is transformed by HRP<sup>8</sup> (1 mg, 25 nmol) and H<sub>2</sub>O<sub>2</sub> (500 μmol) in 9-oxo-ellipticine 2 within 2 min at room temperature (see Scheme I). The isolated and purified quinone imine 2 (16 mg, yield 64 %) has been identified by <sup>1</sup>H NMR, UV-visible, and MS data and compared to an authentic sample obtained from the peroxidase oxidation of 9-hydroxyellipticine 3.<sup>9</sup> From HPLC data, the quinone imine derivative 2 represents at least 90% of the starting material. The remaining products are probably oligo- or polymers. Whereas formaldehyde is formed during the peroxidase-catalyzed N-demethylation,<sup>5c,d</sup> methanol is detected in the present case of O-demethylation. The quinone imine 2/methanol ratio is 1/1; the methanol was quantified by gas chromatography (Porapak QS 2-m column, ethanol as standard). One equivalent of hydrogen peroxide is consumed per molecule of 9-methoxyellipticine in agreement with the reaction stoichiometry indicated in eq 1. In



order to establish the origin of the oxygen atom in methanol, the peroxidase demethylation was performed in H<sub>2</sub><sup>18</sup>O (98% enriched, CEA, Saclay). No <sup>18</sup>O was incorporated in methanol (checked by GC-MS), whereas MS analysis of 2 revealed that <sup>18</sup>O was nearly quantitatively incorporated in the quinone imine compound (90 ± 8%). It should be noted that the peroxidase oxidation of 3 under the same conditions did not afford the labeled quinone imine 2, consequently indicating that the quinone imine 2 did not exchange its oxygen atom with H<sub>2</sub><sup>18</sup>O. These experimental data are in favor of a demethoxylation step as a key step for this peroxidase-catalyzed demethylation<sup>10</sup> (see Scheme II). The

Scheme II. Proposed Mechanism for the Peroxidase Demethylation of 2: Methanol Formation After a Demethoxylation Step



overall stoichiometry of this enzymatic demethylation corresponds to eq 1.

The same demethylation by HRP/H<sub>2</sub>O<sub>2</sub> is observed for N<sup>2</sup>-methyl-9-methoxyellipticinium, a quaternized form of 1. In that case the highly reactive corresponding quinone imine cannot be isolated,<sup>9</sup> but is evidenced by its adducts with various nucleophiles<sup>11</sup> (e.g., N-acetylcysteine).

This horseradish peroxidase demethylation is also observed with formation of methanol in the case of simple chemical models like *p*-anisidine and *N*-methyl-*p*-anisidine or quinacrine, an acridine derivative able to bind to nucleic acids after peroxidase activation.<sup>12</sup> Likewise, O-deethylation of phenetidine was observed with formation of ethanol. This drug is, with acetaminophen, one of the prior metabolites of phenacetin<sup>13</sup> for which was previously proposed a mechanism of deethylation catalyzed by cytochrome P-450 and occurring via an arene oxide.<sup>14</sup>

Furthermore other heme-containing or peroxidase enzymes are able to catalyze also these O-dealkylation reactions in the presence of hydrogen peroxide. As examples, chloroperoxidase, methemoglobin, myoglobin, microperoxidase, and cytochrome C catalyze this reaction by a factor of 40–100 lower than horseradish peroxidase itself.

We are currently working on further investigations of this peroxidase-catalyzed demethylation in relationship with our studies on molecular aspects of cytotoxic properties of 9-substituted ellipticine derivatives,<sup>15</sup> in particular on the possible role of elec-

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trophilic quinone imine generated from these antitumor agents by oxidative bioactivation.

**Acknowledgment.** We thank J. Chenu for a gift of 9-methoxy- and 9-hydroxyellipticine, B. Monsarrat for the mass spectra, and Professor C. Paoletti for his constant interest throughout this work. The Sanofi Co. is gratefully acknowledged for a financial support.

**Registry No. 1,** 10371-86-5; **2,** 76004-29-0; peroxidase, 9003-99-0.

### A Linear Chain with Alternating Ferromagnetic and Antiferromagnetic Exchange: $\text{Cu}(\text{hfac})_2\cdot\text{TEMPOL}$

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It was recently suggested that  $\text{Cu}(\text{hfac})_2\cdot\text{TEMPOL}$  could behave like an alternating linear magnetic chain.<sup>1</sup> We show here that the material indeed behaves in that fashion, and provides an example in which the sign of the exchange also alternates.

The compound bis[(hexafluoroacetyl)acetonato][(4-hydroxy-2,2,6,6-tetramethylpiperidiny)]-*N*-oxycopper(II), hereafter abbreviated as above, contains<sup>2</sup> polymeric chains of planar  $\text{Cu}(\text{hfac})_2$  units bridged by TEMPOL ligands. Each copper ion is hexacoordinated by four oxygen atoms of two hfac<sup>-</sup> ions, one O(H) and one N-O atom of two different TEMPOL ligands, as shown in Figure 1. At high temperatures,<sup>1</sup> the magnetic behavior is characteristic of a system comprised of two independent spin  $S = 1/2$  moieties. As the temperature of the sample is decreased, the spins interact ferromagnetically, leading to a spin-triplet ground state for the pair. The exchange constant, based on an analysis using the familiar Bleaney-Bowers expression, was found to be  $2J/k = 19$  K, with an estimated standard error of 7 K.<sup>1</sup> The average  $g$  value for the adduct was found to be 2.08. At temperatures of 4.2 K and below, one therefore expects the system to consist of spin  $S = 1$  units with  $\langle g \rangle = 2.08$ , and the question is is there a (weak) magnetic link between the pairs via the saturated ligand and the hydrogen bond?

The zero-field susceptibility of the compound is illustrated over the temperature interval 50 mK to 4.2 K in Figure 2, and the low-temperature data are shown at higher resolution in Figure 3; the experimental procedures have been described elsewhere.<sup>3</sup> The data above 2 K may be fit by the Curie-Weiss law with  $\langle g \rangle = 2.1$  and a  $\theta = 0.21$  K. At lower temperatures the data increase and go through a broad maximum at about 80 mK. This is behavior characteristic of an antiferromagnetic linear chain, which is suggested by the following data analysis.

The curve through the data in the figures is based on the familiar theoretical result for a spin-1 linear chain, the modified classical result of Fisher.<sup>4</sup> The susceptibility is calculated as

$$\chi = \chi_c \left( \frac{1 + \mu}{1 - \mu} \right)$$

where

$$\chi_c = N g^2 \mu_B^2 S(S+1) / 3kT \quad \mu = \coth K - 1/K$$

$$K = 2J'S(S+1) / kT$$

<sup>†</sup> Visiting Professor in Chicago, Summer, 1984.

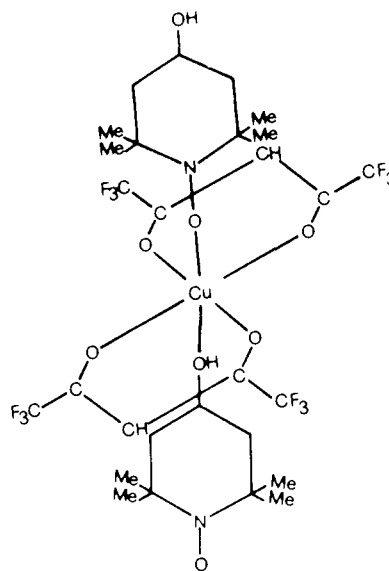
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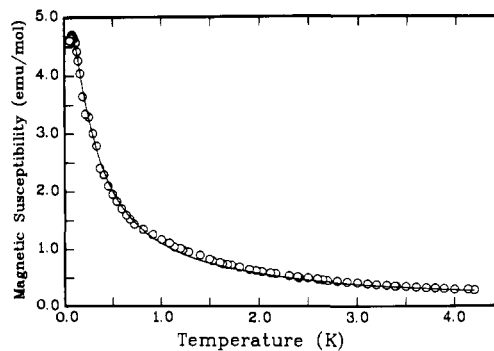
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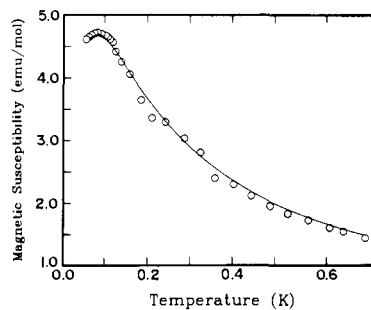
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**Figure 1.** Repeating structural unit (schematic) of the  $\text{Cu}(\text{hfac})_2\cdot\text{TEMPOL}$  chain.



**Figure 2.** Magnetic susceptibility of the compound, along with the fit described in the text.



**Figure 3.** Low-temperature data, along with the fit. Note that the origin is offset.

and the fit, for  $S = 1$ , yields  $\langle g \rangle = 2.2$  (1) and  $2J'/k = -78$  (2) mK. This is quite a weak exchange constant but is reasonable for the proposed rather lengthy superexchange path. An analysis similar to this one has been provided on high-field magnetization data on (4-benzylpiperidinium)- $\text{CuCl}_3$ .<sup>5</sup>

The ratio of the exchange constants is  $2J'/2J = -0.078/19 = -0.004$ , and this is the alternation parameter  $\alpha$  as written in the usual Hamiltonian,

$$H = -2J \sum_{i=1}^{N/2} (\vec{S}_{2i} \cdot \vec{S}_{2i-1} + \alpha \vec{S}_{2i} \cdot \vec{S}_{2i+1})$$

A number of chains with alternation parameter  $0 < \alpha < 1$  have been reported recently,<sup>6</sup> but this is one of the few examples in

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