

# Observations on the transition-metal catalysed oxidation of alkanes in trifluoroacetic acid: urea–hydrogen peroxide/TFA as a convenient method for the oxidation of unactivated C–H bonds

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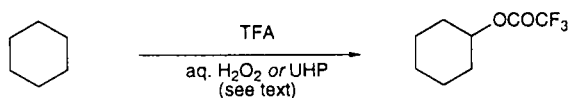
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Oxidation of cyclohexane in TFA using 30% aqueous H<sub>2</sub>O<sub>2</sub> or urea–H<sub>2</sub>O<sub>2</sub> (UHP) gives cyclohexyl trifluoroacetate in good yield, although the reaction is not accelerated by rhodium or ruthenium catalysts casting doubt on earlier claims on the role of transition-metals in oxidations in TFA.

The oxidation of unactivated C–H bonds in alkanes is often regarded as one of the Holy Grails of organic chemistry.<sup>1</sup> Whereas in Nature such oxidations are efficiently carried out by enzymes, there exists no single general laboratory or industrial method, despite the undoubted commercial importance of such a process. Nevertheless a number of methods have been developed which do effect the oxidation of unactivated C–H bonds: these include oxidations in superacid media,<sup>2</sup> using peroxide type reagents (including peracids, dioxiranes and oxaziridines),<sup>3</sup> ozone,<sup>4</sup> various cytochrome P450 models,<sup>5</sup> and a range of metal mediated oxidations,<sup>6</sup> including Gif chemistry.<sup>7</sup> Much of the current work in this area focuses on the use of transition-metal catalysed processes, and in view of our own interest in reactions catalysed by dirhodium(II) carboxylates,<sup>8</sup> we were intrigued to see a *Chemical Communication* in which dirhodium tetraacetate was reported to catalyse the oxidation of cyclohexane by hydrogen peroxide in TFA.<sup>9</sup> As a prelude to investigating the role of dirhodium(II) catalysts in other oxidation reactions, we have reinvestigated this original work, and report our results herein.

In their communication, Nomura and Uemura reported that a variety of rhodium salts (0.1–0.3 mol%) catalysed the oxidation of cyclohexane by 30% aqueous hydrogen peroxide in TFA. The yields of cyclohexyl trifluoroacetate were consistently 62–65% irrespective of the rhodium salt used, and the authors suggested a mechanism involving a highly reactive oxorhodium species.<sup>9</sup> The use of strongly acidic media is quite common in metal catalysed oxidations of hydrocarbons since (a) the conjugate base of a strong acid is a poor  $\sigma$ -donor and therefore enhances the electrophilicity of the metal ion, and (b) the esterification of the alcohol, the primary product of alkane oxidation, protects it from further oxidation.<sup>10</sup> However, it appears that the authors did not carry out a blank reaction in TFA in the absence of the rhodium salt.<sup>9</sup> This is somewhat surprising since many years earlier Deno and Messer also reported the oxidation of cyclohexane to cyclohexyl trifluoroacetate (73% yield) under more or less identical conditions (30% aqueous H<sub>2</sub>O<sub>2</sub> in TFA) but in the absence of any metal salt.<sup>11</sup> Therefore our initial experiments were designed to investigate this apparent anomaly (Scheme 1). When cyclohexane (5 mmol) was treated with 30% aqueous H<sub>2</sub>O<sub>2</sub> (15 mmol) in TFA (12 ml) in the presence of dirhodium tetraacetate (1 mol%) at room temperature, oxidation to cyclohexyl trifluoroacetate



Scheme 1

did indeed occur as evidenced by gas chromatographic analysis which clearly showed disappearance of the hydrocarbon and formation of the ester over 12 h (Fig. 1). When the blank experiment was run under identical conditions but in the absence of the rhodium complex a very similar plot was obtained (Fig. 1). The results show that this particular oxidation of cyclohexane clearly proceeds in the absence of the metal complex, and furthermore dirhodium tetraacetate does not catalyse the reaction.

In order to obtain rate constants for the oxidation of cyclohexane in TFA, aqueous H<sub>2</sub>O<sub>2</sub> was replaced by the urea hydrogen peroxide complex (UHP), a convenient solid source of anhydrous H<sub>2</sub>O<sub>2</sub>. This enabled the use of a large excess of peroxide to create pseudo-first order reaction conditions. Under these conditions (2.5 mmol cyclohexane in 2 ml CH<sub>2</sub>Cl<sub>2</sub>, 22 mmol UHP, 10 ml TFA), rates for the oxidation of cyclohexane in the presence ( $k = 2.9 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ) and absence ( $k = 3.3 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ) of dirhodium tetraacetate were readily obtained (Fig. 2). Given the error in the determination of rate constants (estimated as  $\pm 10\%$ ), the rates of these two reactions are clearly similar. In both the 30% aqueous H<sub>2</sub>O<sub>2</sub>–TFA and UHP–TFA oxidations, trace amounts of cyclohexanol were also observed. In a separate blank experiment it was shown that cyclohexanol is readily esterified in TFA, and therefore the alcohol is presumably the initial product of oxidation.

We also investigated the use of ruthenium catalysts based on the RuCl<sub>3</sub>–TFA system reported by Murahashi *et al.*,<sup>12</sup> which was also thought to involve a metal oxo complex as the oxidant. Again it was evident that RuCl<sub>3</sub> also had no effect on the rate of cyclohexane oxidation in TFA ( $k = 3.1 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ). Therefore, we conclude that claims of transition-metal catalysed oxidations of hydrocarbons in peroxide–TFA systems should be viewed with caution in cases where the appropriate blank experiments have not been carried out. This view concurs with that of Hogan and Sen who have independently concluded that the role of the metal in C–H oxidation reactions carried out in TFA needs to be reassessed.<sup>10,13</sup>

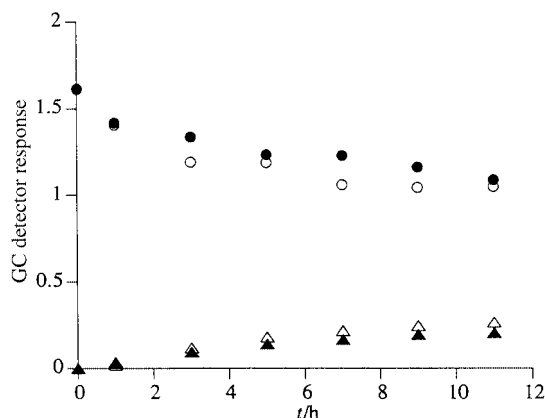
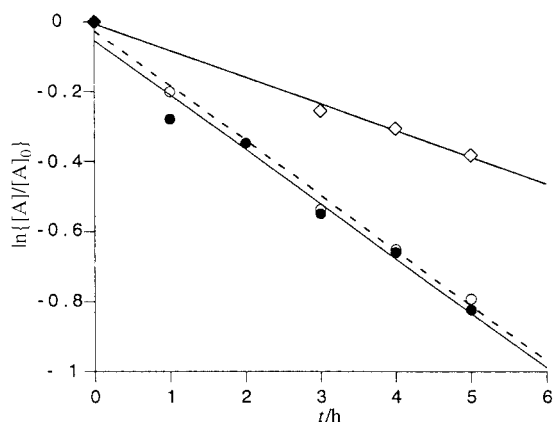


Fig. 1 Cyclohexane consumption and cyclohexyl trifluoroacetate formation vs. time in 30% aqueous hydrogen peroxide–TFA in the absence (○/Δ) or presence (●/▲) of dirhodium tetraacetate.

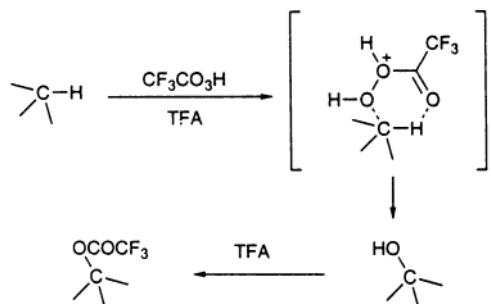


**Fig. 2** Oxidation of cyclohexane by UHP-TFA in absence (○) or presence (●) (1 mol%) of dirhodium tetraacetate, and oxidation of cyclohexane- $d_{12}$  (◇), where  $[A]_0$  is the initial concentration of cyclohexane.

In the work of Deno *et al.* using 30% aqueous  $H_2O_2$  in TFA,<sup>11,14</sup> it was assumed that the active oxidant was peroxytrifluoroacetic acid which participated in a concerted oxidation mechanism *via* a cyclic transition state, the electrophilic nature of the oxidant being further enhanced by protonation (Scheme 2). To shed further light on the mechanism of the UHP-TFA oxidation, we compared the rate of oxidation of cyclohexane with its perdeuterated analogue ( $k = 1.4 \times 10^{-5} M^{-1} s^{-1}$ ) (Fig. 2). The observed kinetic isotope effect of  $2.3 \pm 0.2$  is in accord with previous studies using peracids as oxidants, and is possibly indicative of a concerted (*cf.* Scheme 2) or oxenoid type mechanism.<sup>3a</sup> Unfortunately alternative mechanisms involving radical hydrogen abstractions cannot be completely ruled out, since although such reactions usually exhibit a significantly larger deuterium isotope effect ( $k_H/k_D \approx 4-8$ ),<sup>15</sup> the isotope effect can be as low as 1.<sup>16</sup>

The preparative oxidation of hydrocarbons was briefly investigated, and some illustrative examples are shown in Table 1. Cyclohexane, cycloheptane ( $k = 6.4 \times 10^{-5} M^{-1} s^{-1}$ ) and cyclooctane were all oxidized to the corresponding esters; norbornane gave the ester of *exo*-norborneol as the major product, and although adamantane was rapidly oxidized to the tertiary ester, with no sign of the secondary ester by GC, the product was unstable under the reaction conditions. *n*-Hexane gave a mixture of 2- and 3-hexyl trifluoroacetates (ratio = 47:53) with no evidence for oxidation at the terminal methyl group. Compounds containing aromatic rings (*n*-propylbenzene, cumene, tetralin) were completely decomposed in either 30% aqueous  $H_2O_2$ -TFA or in UHP-TFA.<sup>17</sup>

In summary, we have shown that UHP-TFA is a simple system for the oxidation of unactivated C-H bonds in alkanes; such reactions are not accelerated by rhodium or ruthenium



**Scheme 2**

**Table 1** Preparative scale hydrocarbon oxidation using UHP-TFA

Alkane	Product	Yield (%)
		80
		78
		45 <sup>a</sup>
		67 <sup>a,b</sup>
		<sup>c</sup>

<sup>a</sup> GC yield; the reaction mixture is more complex. <sup>b</sup> Only the *exo*-product was observed. <sup>c</sup> Product not stable under reaction conditions; identified by GC by comparison with an authentic sample; 2-adamantyl trifluoroacetate was not present (GC).

catalysts, and therefore claims of metal catalysis of related reactions in TFA should be viewed with caution.

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