# Duality of the Permanganate Ion in the Oxidation of Imines. Oxidation of Imines to Amides

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The oxidation of imines with potassium permanganate in acetonitrile-water has been studied. The reaction gives the corresponding amide as the major product, in contrast to the oxidation of imines with potassium permanganate in methylene dichloride-water under phase-transfer conditions. A series of imines has been oxidized to the corresponding amides in reasonable yields. Several investigations have been performed in an attempt to obtain insight into the mechanism for the imine to amide oxidation. Electron spin resonance studies indicate that radicals are formed in the reaction mixture. PhCH=NBu<sup>t</sup> shows a first-order deuterium effect relative to PhCD=NBu<sup>t</sup> in the reaction with potassium permanganate. The use of [<sup>18</sup>O]water leads to an incorporation of the labelled oxygen in the amide. The mechanism for the permanganate oxidation of imines to amides is discussed; two reaction paths are considered, one in which water adds to the imine followed by an oxidation of the amino alcohol to the amide by the permanganate ion, while the other—a minor reaction path under the present reaction conditions—is an oxidation of the imine to the nitrone.

Although the permanganate ion,  $MnO_4^-$ , is a classic oxidation reagent in organic chemistry<sup>1</sup> it is still attractive and considered as 'a novel oxidant in organic chemistry.'<sup>2</sup> Many new properties of the permanganate ion oxidation, and mechanistic aspects of the oxygen transfer from the permanganate ion to substrates, have been presented during the last decade.<sup>1-3</sup>

It has been recently shown that imines 1 can be oxidized to nitrones 2 by use of potassium permanganate under phase-transfer conditions (PTC) in a methylene dichloride-water mixture [reaction (1)].<sup>4</sup>



The mechanism for the transfer of the oxygen atom from the permanganate ion to the imine was, based on the frontier orbital approach, described as an addition of the oxo-ligands in the permanganate ion to the imine, leading to cyclic intermediate 3, followed by cleavage [reaction (2)].<sup>4</sup> The reaction mechanism shown in reaction (2) is comparable to the addition of permanganate ion and osmium tetraoxide to alkenes.<sup>2,5,6</sup>



In the present work we shall show that, by a change of solvent and exclusion of the phase-transfer catalyst, another oxidation reaction takes place when imines are treated with potassium permanganate. The imines 1 are, by reaction with potassium permanganate in an acetonitrile-water solution, oxidized to the corresponding amides 4 [reaction (3)].† The permanganate ion probably acts in a different way in this solvent composition compared with the reaction in methylene dichloride-water under PTC. Different synthetic and mechanistic aspects of the oxidation of imines 1 to amides 4 by the permanganate ion will now be presented.

| Table   | 1   | Oxidation     | of    | imines    | 1    | to    | amides   | 4    | with    | pota   | ssium |
|---------|-----|---------------|-------|-----------|------|-------|----------|------|---------|--------|-------|
| perman  | nga | nate in aceto | oniti | rile-wate | er ( | see l | Experime | ntal | section | on for | more  |
| details | )   |               |       |           |      |       |          |      |         |        |       |

| Imi | ine 1   | Yield (%) of corresponding amide 4 |  |  |  |  |  |
|-----|---|------------------------------------|--|--|--|--|--|
| 1a  | PhCH=NBu <sup>1</sup>   | 73                                 |  |  |  |  |  |
| 1b  | p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH=NBu <sup>1</sup> | 50                                 |  |  |  |  |  |
| 1c  | p-ClC,H,CH=NBu  | 62                                 |  |  |  |  |  |
| 1d  | p-MeOC <sub>6</sub> H <sub>4</sub> CH=NBu <sup>1</sup>              | 77                                 |  |  |  |  |  |
| 1e  | PhCH=NPh  | <5                                 |  |  |  |  |  |
| 1f  | PhC(Et)=NPh   | _                                  |  |  |  |  |  |
| 1g  | Quinoline   | _                                  |  |  |  |  |  |
| 1ň  | PhCH=N[CH,],Me  | 57                                 |  |  |  |  |  |



#### Results

1. Oxidation of Different Imines.—Reaction of different imines, 1a-h, with potassium permanganate in acetonitrile-water leads to the formation of amides for the imines having a hydrogen bound to the carbon in the imine functionality. The reaction conditions are as follows: imine 1 (2.5 mmol) and KMnO<sub>4</sub> (5.0 mmol) are mixed in a mixture of MeCN (4 cm<sup>3</sup>) and water (2 cm<sup>3</sup>) and the whole was stirred at 50 °C for 0.5 h. Results are given in Table 1 (for more experimental details see the Experimental section).

It appears from Table 1 that reasonable yields of the amide are formed after 0.5 h, except for imine 1e where several cleavage products are observed. The ketimine 1f and quinoline 1g are inert to oxidation under the reaction conditions, even after prolonged reaction times (we shall return to the inertness of compound 1f later). The work-up procedure is important in determining the reaction yield; the results presented in Table 1 were obtained by addition of methylene dichloride (150 cm<sup>3</sup>) to the reaction mixture after the reaction had finished, followed by

<sup>+</sup> It should be noted that the oxidation of 2-bromophenanthridine by potassium permanganate in sulphuric acid has been found to give 2-bromophenanthridone and phenananthridone (ref. 7).



Fig. 1 ESR spectrum of the reaction imine 1a with potassium permanganate



Fig. 2 The increase in radical concentration as a function of time in the reaction of imine 1b with potassium permanganate

the addition of sodium sulphate to remove the water, excess of potassium permanganate and reduced permanganate species.

A change of the solvent composition to methylene dichloridewater in the case of imines 1a, 1b and 1d only gave small amounts (<3%) of the amide among other oxidized products (also in low yield) by reaction with potassium permanganate, even after 24 h reaction time.

Exclusion of water from the reaction mixture led, in the case of imine 1b as substrate, to regeneration of the starting imine in >96% yield and <2% yield of the amide 4b after 0.5 h reaction time.

In order to obtain information regarding the mechanism of the oxidation of imines to amides by potassium permanganate, we have studied the disappearance of substrates **1a–d** (NMR spectroscopy) as a function of time under second-order conditions. The change in reaction rate for imines **1a–d** was found to correlate with the Hammett  $\sigma$ -parameters with a  $\rho$ -value of -0.7. The rate constants for compounds **1a–d** were found to be  $3.8 \times 10^{-3} \text{ mol}^{-1} \text{ s}^{-1}$ ,  $1.0 \times 10^{-3} \text{ mol}^{-1} \text{ s}^{-1}$ ,  $2.5 \times 10^{-3} \text{ mol}^{-1} \text{ s}^{-1}$  and  $4.8 \times 10^{-3} \text{ mol}^{-1} \text{ s}^{-1}$ , respectively.

The reaction of compound 1a with potassium permanganate has also been studied in the presence of propylamine in the ratio 1a: propylamine 1:3. The following products were identified after 0.5 h reaction time [reaction (4)]:

PhCH=NBu<sup>t</sup>+C<sub>3</sub>H<sub>7</sub>NH<sub>2</sub>
$$\frac{KMnO_4}{MeCN-water}$$
 1a + 1h + 4a + 4h (4)  
1a

The product distribution in reaction (4) was: 1a, 4%; 1h, 93%; 4a, traces; 4h, 2-3%. The amide 4a can also be formed in < 5%yield, by reaction of benzaldehyde and 1,1-dimethylethylamine with potassium permanganate in acetonitrile-water [reaction (5)]. The major products in reaction (5) are benzoic acid and 2-methyl-2-nitropropane, which points to an oxidation of the substrates.

$$PhCHO + H_2NBu^{t} \frac{KMnO_4}{MeCN-water} PhCONHBu^{t}$$
(5)  
4a

2. ESR Studies.—A series of ESR experiments was performed in an attempt to obtain further insight into the mechanism of permanganate ion oxidation of imines to amides. The ESR spectrum of the reaction of imine **1a** with potassium permanganate in acetonitrile-water at room temperature is shown in Fig. 1. The radical formed is stable for > 15 min.

The g-value for the radical shown in Fig. 1 was calculated to be 2.0108 and the hyperfine splitting,  $a_N$ , was 8.1 G. The reaction of PhCD=NBu' with potassium permanganate under similar reaction conditions gave the same ESR spectrum as that shown in Fig. 1. The reaction of imines 1b and 1d with potassium permanganate also gives rise to ESR signals of the same type as above, but with changed hyperfine splittings and g-values. For imine 1b as the substrate,  $a_N = 7.7$  G and g = 2.0114, and with imine 1d as the substrate,  $a_N = 8.6$  G and g = 2.0111. Hence it appears that an electron-withdrawing group attached to the phenyl ring decreases the hyperfine splitting, while an electrondonating group increases the hyperfine splitting. Similar trends have also been observed in other radical systems.<sup>8</sup> A change of substrate to the ketimine 1f afforded no ESR signal, indicating that the CH-function is of importance for the formation of the radical.

The formation of the radicals for substrates 1a, 1b and 1d has been studied as a function of time by measurement of the increase in the ESR signal at the respective g-value. The radicals are formed by a second-order reaction; first order in the substrate and first order in potassium permanganate. The formation of the radical in the reaction of imine 1b with potassium permanganate, shown as the increase in ESR intensity, is depicted in Fig. 2 together with the theoretical fitted curve for the second-order reaction. Fig. 2 shows a good agreement between the experimental results and the theoretical curve. The reaction-rate constant for the formation of the radical shown in Fig. 2 has been calculated to be  $2.5 \times 10^{-6}$  $mol^{-1} s^{-1}$ . The reaction-rate constant for the formation of the radicals in the reaction of imines 1a and 1d with potassium permanganate has been calculated to be  $2.5 \times 10^{-6} \text{ mol}^{-1} \text{ s}^{-1}$ and  $2.1 \times 10^{-6} \text{ mol}^{-1} \text{ s}^{-1}$ , respectively. Please note that a direct comparison of the reaction-rate constants for the formation of the radicals and those found for the disappearance of 1a, b, d are not feasible as no direct comparison between the ESR intensity and 'yield' is available. It appears thus that the formation of the radicals from 1a and 1b is slightly faster than the radical formed from 1d, although the difference in reaction rate is not very significant. However, the concentration of the radicals formed are different; the radical formed from 1b are formed in a higher concentration (nearly twice as much) than the radicals formed from 1a and 1d.

We have found that the radical depicted in Fig. 1 can also be formed in the reaction of the nitrone  $PhCH=N^+(O^-)Bu^t$  with potassium permanganate in acetonitrile.

3. Isotopic Labelling Studies.—The isotope effect on the reaction rate has also been studied. The reaction rate for the formation of the radical (measured as the increase of ESR intensity at g = 2.0108) formed in the reaction of PhCH=NBu<sup>t</sup> and PhCD=NBu<sup>t</sup> with potassium permanganate in acetonitrile-

water gives  $k_{\rm H}/k_{\rm D}$  as *ca.* 8, a typical value for a primary-order isotope effect.<sup>9</sup> It should be mentioned here that the isotope effect for the reaction of benzaldehyde and [<sup>2</sup>H]benzaldehyde with potassium permanganate at a pH below 9.4 shows a nearly similar result.<sup>10</sup>

The reaction of PhCH=NBu<sup>t</sup> and PhCD=NBu<sup>t</sup> with potassium permanganate in acetonitrile-water has also been studied in terms of the yield of the amide, **4a**. The yield of **4a** is only a few percent lower when the deuterium labelled substrate is used compared with PhCH=NBu<sup>t</sup>. The yield of **4a** is thus not affected very much by the presence of deuterium in the substrate.

The reaction of **1b** with potassium permanganate in acetonitrile–<sup>18</sup>O-labelled water leads to an incorporation of <sup>18</sup>O into the amide, **4b**, in about 90% relative to the water employed [reaction (6)]. The aqueous phase in reaction (6) was neutral as the permanganate ion exchanges its oxygen slowly under these conditions.<sup>11</sup>



# Discussion

The permanganate ion is able to oxidize various substrates containing the imine function, -CH=N-, to the corresponding amide in acetonitrile-water as the solvent. It appears from the results in Table 1 that the ketimine 1f and quinoline 1g are not oxidized even after prolonged reaction times. However, it should be noted that 2-bromophenanthridine, by reaction with potassium permanganate in sulphuric acid, has been found to give 2-bromophenanthridone and phenanthridone.<sup>7</sup> We were not able to oxidize similar substrates to amides under our reaction conditions. Furthermore the ESR experiments and isotopic labelling studies showed that the CH-function in the substrate plays a crucial role in the formation of radicals by reaction with potassium permanganate. These results could indicate that the hydrogen in the CH-part of the imine is of importance for the formation of the amide and the radical observed in these reactions. The [18O]water labelling experiment, and the reaction where water is excluded from the solvent, indicate that the oxygen found in the amide originates from water.

The present results do not point to a 'simple mechanistic' interpretation; Scheme 1 shows a tentative mechanism.

Reaction path a in Scheme 1 is, first, a reversible addition of



Scheme 1 Reagents: i, water; ii, MnO<sub>4</sub><sup>-</sup>

water to the imine leading to the amino alcohol 5, followed by oxidation to give the amide 4. The first step in reaction path b is oxidation of the imine by the permanganate ion to the corresponding nitrone 2, which is then oxidized further to the nitroxide radical 6, or another type of nitroxide radical, which under the present conditions seems to be rather stable.<sup>12</sup>

We shall now discuss our results in relation to the mechanisms proposed in Scheme 1. The mechanism for the formation of amides is in agreement with the results obtained where water is excluded from the solvent and the  $[^{18}O]$  water

labelling experiment [reaction (6)]. <sup>1</sup>H NMR investigations of imine 1a in  $CD_3CN-D_2O$  showed no indication of the amino alcohol intermediate 5. This observation does not exclude the existence of intermediates 5, since amino alcohols are very difficult to observe spectrochemically.<sup>13</sup> As the pH of the water added in the present reactions is lower than 7 the equilibrium constant for the first step in reaction path in Scheme 1 should be expected to be higher for imine 1a than for imine 1d.<sup>14</sup> If the reactions presented here proceed *via* reaction path a the ratedetermining step should be the oxidation 5-4. The observed reactivity of the imines with potassium permanganate is parallel to that found for the potassium permanganate oxidation of substituted benzaldehydes<sup>10</sup> and substituted benzylamines.<sup>15</sup>

The ESR studies indicate that nitrones are probably also formed in the reaction of imines with potassium permanganate in acetonitrile-water, since the ESR spectrum of the reaction of imine **1a** with potassium permanganate is similar to that obtained in the reaction of PhCH=N<sup>+</sup>(O<sup>-</sup>)Bu<sup>t</sup> with potassium permanganate. However, the yield of the nitrones is very low compared with the yield of the amides, as the nitrones are not detected by <sup>1</sup>H NMR spectroscopy. The radicals are formed at slightly different rates, the radicals from imines **1b** and **1a** being formed faster than the radical formed from imine **1d**, whereas the concentration of the radical formed from imine **1b** is about twice that of the radicals formed from imines **1a** and **1d**.

Another mechanism could also be envisaged for the formation of amides from imines: the imines is first hydrolysed to an aldehyde and an amine; the aldehyde is then oxidized to a manganese ester<sup>10</sup> which, by reaction with the amine, could produce the amide. However, our results for the oxidation of imine **1a** in the presence of propylamine [reaction (4)] and the reaction of benzaldehyde, 1,1-dimethylethylamine and potassium permanganate [reaction (5)] do not support such a reaction path.

The present results point to a dual pathway for the reaction of imines with potassium permanganate; these two pathways could be paths a and b in Scheme 1: path a produces the amide, while reaction path b, leading to the nitrone followed by radical formation, could be a 'dead end.' This duality of the permanganate ion selectively to oxidize imines to different products in different solvent compositions might be a useful reaction in imine chemistry.

#### Experimental

<sup>1</sup>H NMR spectra were recorded in  $CDCl_3$  on a Varian Gemini 200 spectrometer. SiMe<sub>4</sub> was used as internal standard. Mass spectra were recorded on a MicroMass 7070F or Trio-2 spectrometer operating at 70 eV with a direct inlet. The ESR spectra were recorded at X-band at room temperature on a Bruker ER 200 spectrometer with a modulation frequency of 25 kHz and an amplitude of ~ 100 mG. The spectra were stored as 4 k discrete points.

*Materials.*—All the imines were synthesized according to the literature;<sup>14,16</sup> in the case of PhCD=NBu<sup>t</sup>, PhCDO was used instead of PhCHO. The potassium permanganate was used as received from the company and acetonitrile was refluxed over potassium permanganate–potassium carbonate for 24 h and then distilled before use. Water was distilled three times before use. <sup>18</sup>O-Labelled water of 75% isotopic purity was obtained from ICS Stable Isotopes.

General Procedure for the Potassium Permanganate Oxidation of Imines to Amides.—The imine (2.5 mmol) was dissolved in a mixture of MeCN (4 cm<sup>3</sup>) and water (2 cm<sup>3</sup>) (pH 4.1), then KMnO<sub>4</sub> (5 mmol) was added and the reaction mixture was stirred for 0.5 h (or the reaction time required for the different studies) at 50 °C. After completion of the reaction,  $CH_2Cl_2$  (150 cm<sup>3</sup>) was added followed by  $Na_2SO_4$ . The methylene dichloride phase was filtered through Hyflo and evaporated to give the products. The products can then be separated by column chromatography or preparative TLC, or directly analysed by spectroscopy. The products were identified by <sup>1</sup>H NMR and MS techniques. The <sup>1</sup>H NMR data were as follows: **4a**:  $\delta$  1.48 (9 H, s, Bu<sup>1</sup>), 5.95 (1 H, br s, NH), 7.41–7.48, 7.70–7.75 (5 H, m, Ph); **4b**:  $\delta$  1.48 (9 H, s, Bu<sup>1</sup>), 5.93 (1 H, br s, NH), 7.89 (2 H, d, Ph), 8.26 (2 H, d, Ph); **4c**:  $\delta$  1.47 (9 H, s, Bu<sup>1</sup>), 5.93 (1 H, br s, NH), 7.38 (2 H, d, Ph), 7.66 (2 H, d, Ph); **4d**:  $\delta$  1.46 (9 H, s, Bu<sup>1</sup>), 3.84 (3 H, s, OMe), 5.91 (1 H, br s, NH), 6.90 (2 H, d, Ph), 7.69 (2 H, d, Ph); **4h**:  $\delta$  0.99 (3 H, t, Me), 1.64 (2 H, sextet, CH<sub>2</sub>), 3.42 (2 H, q, CH<sub>2</sub>), 6.25 (1 H, br s, NH), 7.38–7.54, 7.75–7.80 (5 H, m, Ph).

The mass spectra for the amides all show  $M^+$  for the molecular ion, followed by further decomposition peaks.

General Procedure for the ESR Studies.—An aliquot (50 mm<sup>3</sup>) of the imine and an aliquot (50 mm<sup>3</sup>) of KMnO<sub>4</sub> (both substrates at the same concentration as for the synthetic reactions and in the same solvent composition) were mixed in an ESR glass tube and monitored in the ESR spectrometer and the spectra were recorded at room temperature.

Oxidation of Imine **1b** to Amide **4b** by Potassium Permanganate in the Presence of  $[^{18}O]$ Water.—Imine **1b** (0.12 mmol) was dissolved in a mixture of MeCN (0.3 cm<sup>3</sup>) and  $[^{18}O]$ water (0.15 cm<sup>3</sup>), then KMnO<sub>4</sub> (0.25 mmol) was added and the reaction mixture was stirred for 0.5 h. After completion of the reaction CH<sub>2</sub>Cl<sub>2</sub> (2 cm<sup>3</sup>) was added, followed by the addition of Na<sub>2</sub>SO<sub>4</sub>. The methylene dichloride phase was filtered and evaporated to give the products, which were analysed by GC-MS. The amide showed about 90% incorporation of <sup>18</sup>O-labelled oxygen relative to the water employed.

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## References

- 1 See, e.g., R. A. Sheldon and J. K. Kochi, Metal-Catalyzed Oxidations of Organic Compounds, Academic, New York, 1981; D. Arndt, Manganese Compounds as Oxidizing Agents in Organic Chemistry, Open Court, La Salle, IL, 1981; D. G. Lee, The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium, Open Court, La Salle IL, 1980; R. L. Augustine, Oxidation, Marcel Dekker, New York, 1969; R. Steward, in Oxidation in Organic Chemistry, ed. K. B. Wiberg, Academic; New York, 1965; Part A, p. 2.
- 2 For some recent reviews see, e.g., A. F. Fatiadi, Synthesis, 1987, 85; J. H. Boyer, Chem. Rev., 1980, 80, 495.
- 3 See, e.g., D. G. Lee, E. J. Lee and W. D. Chandler, J. Org. Chem., 1985, 50, 4306; F. Freeman and J. C. Kappos, J. Am. Chem. Soc., 1985, 107, 6628; H. Firoūzabadi, A. R. Sardarian, M. Naderi and B. Vessal, Tetrahedron, 1984, 40, 5001; N. A. Noureldin and D. G. Lee, J. Org. Chem., 1982, 47, 2790; S. L. Regen, S. Quici and S. J. Liaw, J. Org. Chem., 1979, 44, 2029.
- 4 D. Christensen and K. A. Jørgensen, J. Org. Chem., 1989, 54, 126.
- 5 See, e.g., M. Schröder, Chem. Rev., 1980, 80, 187.
- 6 K. A. Jørgensen and R. Hoffmann, J. Am. Chem. Soc., 1986, 108, 1867; see also W. Nugent and J. M. Mayer, Metal-Ligand Multiple Bonds, Wiley, New York, 1988.
- 7. H. Gilman and J. Eisch, J. Am. Chem. Soc., 1955, 77, 6379.
- 8 E. G. Janzen, Acc. Chem. Res., 1969, 2, 279.
- 9 T. H. Lowry and K. S. Richardson, Mechanism and Theory in Organic Chemistry, Harper and Row, 3rd ed., 1987, p. 232.
- 10 K. B. Wiberg and R. Steward, J. Am. Chem. Soc., 1955, 77, 1786.
- 11 G. A. Milles, J. Am. Chem. Soc., 1940, 62, 2833; N. F. Hall and O. R. Alexander J. Am. Chem. Soc., 1940, 62, 3455.
- 12 A. L. Bluhm and J. Weinstein, J. Am. Chem. Soc., 1970, 92, 1445.
- 13 A. Bruylants and E. Feytmants-De Medicis, in *The Chemistry of the Carbon-Nitrogen Bond*, ed. S. Patai, Interscience, New York, 1970, p. 469.
- E. H. Cordes and W. P. Jencks, J. Am. Chem. Soc., 1963, 85, 2844;
  J. B. Culbertson, J. Am. Chem. Soc., 1951, 73, 4818.
- 15 M.-M. Wei and R. Steward, J. Am. Chem. Soc., 1966, 88, 1974; H. Schechter, S. S. Rawalay and M. Tubis, J. Am. Chem. Soc., 1964, 86, 1701; H. Schechter and S. S. Rawalay, J. Am. Chem. Soc., 1964, 86, 1706.
- 16 K. N. Campbell, A. H. Sommers and B. K. Campbell, J. Am. Chem. Soc., 1944, 66, 82; W. P. Emmons, J. Am. Chem. Soc., 1957, 79, 5739; R. G. Pews, J. Org. Chem., 1967, 32, 1628.

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