ChemComm

Amavadine as a catalyst for the peroxidative halogenation, hydroxylation and oxygenation of alkanes and benzene

Patrícia M. Reis, José Armando L. Silva, João J. R. Fraústo da Silva* and Armando J. L. Pombeiro*

Centro de Química Estrutural, Complexo I, Instituto Superior Técnico, Av. Rovisco Pais, 1049-001 Lisboa, Portugal. E-mail: pcd1950@popsrv.ist.utl.pt; pombeiro@popsrv.ist.utl.pt

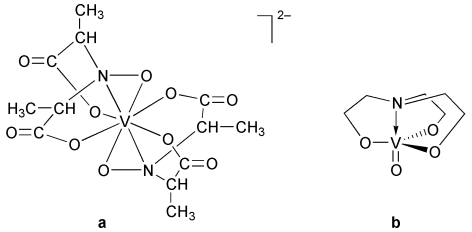
Received (in Cambridge, UK) 10th July 2000, Accepted 31st July 2000
First published as an Advance Article on the web 14th September 2000

Synthetic amavadine models, $[V(HIDPA)_2]^{2-}$ and $[V(HIDA)_2]^{2-}$ [where HIDPA and HIDA stand for the basic forms of 2,2′-(hydroxyimino)dipropionic and 2,2′-(hydroxyimino)diacetic acid, respectively], exhibit haloperoxidase- or peroxidase-type activities, and act as catalysts for the selective peroxidative monohalogenation, hydroxylation or oxo-functionalization of alkanes or aromatic compounds such as benzene and mesitylene at room temperature.

The roles of vanadium in biology have been the object of current and growing interest[1] from both biological and chemical perspectives. In particular, the biological role of amavadine, the natural bare octacoordinated vanadium(IV) complex $[V(HIDPA)_2]^{2-}$, [$HIDPA^{3-}$ = basic form of (*S*,*S*)-2,2′-(hydroxyimino)dipropionic acid][2] present in some *Amanita* fungi, is still an intriguing matter, although circumstantial evidence has started to emerge suggesting[3] that it can act either as a peroxidase which catalyses the oxidation of particular thiols to disulfide products, or as a catalase by promoting the decomposition of H_2O_2. Vanadium(V) haloperoxidases which have been found mainly in some brown and red marine algae have also raised much interest and their structures and functions have been investigated,[1] inorganic biomimetic reagents proposed and other vanadium complexes applied[4–6] to the peroxidative oxidation of alkenes and aromatic hydrocarbons. However, alkanes have been much less studied[6b,c,7] and only very rarely has a catalytic activity of vanadium been recognized for such reactions.

We now report that saturated (*e.g.* cyclohexane or cyclooctane) and aromatic (benzene or mesitylene) hydrocarbons can be oxidized catalytically, at room temperature, by a system composed of synthetic amavadine models and H_2O_2 in acidic medium, to give halo-, hydroxo- or oxo-functionalized compounds, thus suggesting a potential wider biological role for naturally occurring amavadine than that considered so far and demonstrating the capacity of a biogenic vanadium complex, much simpler than an enzyme, to catalyse, in mild conditions, the functionalization of alkanes, a challenging problem[8] in modern chemistry. Moreover, this complex constitutes, to our knowledge, the first reported vanadium catalyst for the peroxidative halogenation of alkanes.

In effect, we have observed that $Ca[V(HIDPA)_2]$ (the Ca^{2+} salt of synthetic amavadine) **a** or its model $Ca[V(HIDA)_2]$



a **b**

[HIDA = basic form of 2,2′-(hydroxyimino)diacetic acid], in a two-phase water–NCMe system also containing H_2O_2, KBr and HNO_3 (in high excess relative to the vanadium compound), catalyse at room temperature the peroxidative bromination of saturated and aromatic hydrocarbons, as shown in Tables 1 and 2 for typical experiments with cyclohexane and benzene to give bromocyclohexane and bromobenzene, respectively, according to the overall reaction (1). Catalytic chlorination (using KCl instead of KBr) also occurred for benzene and, in all the cases, only the mono-halogenated products were selectively obtained.

$$RH + Br^- + H_2O_2 + H^+ \xrightarrow{\text{Amavadine}} RBr + 2H_2O \quad (1)$$

The activity of the system increases with the amounts of H_2O_2 and of the acid, but beyond a limit (*e.g. ca.* 150 molar ratio for H_2O_2, relatively to vanadium, for the case of the bromination of cyclohexane) no further increase is observed and the activity can even decrease. Values of the turnover number (TON) are given in Tables 1 and 2 for typical essays (6 h reaction time) and indicate that both vanadium complexes have a comparable

Table 1 Amavadine catalysed peroxidative bromination,[a] hydroxylation[b] and oxygenation[b] of cyclohexane

			Turnover number (TON)[d]		
V complex	H_2O_2 : V[c]	HNO_3 : V[c]			
Bromination:					
$Ca[V(HIDPA)_2]$	175	3610	10	—	—
$Ca[V(HIDA)_2]$	175	50	0	—	—
	175	290	2	—	—
	175	580	5	—	—
	175	1155	6	—	—
	175	2890	17	—	—
	175	3610	15	—	—
$[VO\{N(CH_2CH_2O)_3\}]$	175	2890	9	—	—
Hydroxylation and oxygenation:					
$Ca[V(HIDPA)_2]$	220	72	—	18	4
	440	72	—	32	4
	880	72	—	32	—
	440	144	—	30	3
$Ca[V(HIDA)_2]$	110	72	—	11	4
	220	72	—	33	7
	440	72	—	33	4
	880	72	—	25	4
	220	36	—	25	6
	220	144	—	21	6
	440	0	—	3	0.7
	440	144	—	42	8
	440	290	—	37	10
	440	580	—	26	8
$[VO\{N(CH_2CH_2O)_3\}]$	440	72	—	46	7

[a] Two-phase liquid system: V complex (0.010 mmol), cyclohexane (5 mmol), KBr (2.5 mmol), H_2O (2.5 cm^3), NCMe (2.5 cm^3), H_2O_2 and HNO_3 (amounts given in the Table), 20 °C, 6 h. [b] V complex (0.010 mmol), cyclohexane (5 mmol), NCMe (2.5 cm^3), H_2O_2 and HNO_3 (amounts given in the Table). [c] Molar ratio relative to the V complex. [d] Moles of product per mole of V complex [corrected for blanks (for an high excess of acid in the absence of V complex, the halogenated product is detected in lower yield)], determined by GLC or GC-MS, using an internal standard, after separation from the vanadium and ionic species. The molar yields (%) relative to the substrate (*i.e.* moles of product per 100 moles of substrate) are given by 0.2 × TON.

DOI: 10.1039/b005513l

Table 2 Amavadine catalysed peroxidative bromination and hydroxylation of benzene[a]

V complex	H_2O_2:V	HNO_3:V	Turnover number (TON) BrC_6H_5	PhOH
Bromination:				
$Ca[V(HIDPA)_2]$	175	5050	9	—
$Ca[V(HIDA)_2]$	175	3610	10	—
	175	5050	11	—
$[VO\{N(CH_2CH_2O)_3\}]$	175	3610	9	—
Hydroxylation:				
$Ca[V(HIDPA)_2]$	440	72	—	6
$Ca[V(HIDA)_2]$	440	72	—	16
$[VO\{N(CH_2CH_2O)_3\}]$	440	72	—	8

[a] See footnotes to Table 1.

activity. Hence, *e.g.* TON *ca.* 10–15 for the molar ratios H_2O_2:V = 175 and HNO_3:V = 3610.

No activity was found for the free (hydroxyimino)dicarboxylic acids H_3·HIDPA or H_3·HIDA and the active species has the metal in the 5+ oxidation state (the starting blue V^{IV} complexes are oxidized by H_2O_2 to the corresponding red V^V forms, as observed by the immediate colour change of the reaction solution on addition of the peroxide). The presence of vanadium in the 5+ oxidation state has also been demonstrated in the vanadium-dependent bromoperoxidases and the formation of peroxo–vanadium complexes as active intermediate species has been proposed.[1a,b] In our system, the hydroxyimine(1−) groups, η^2-(O–N<), of the $HIDPA^{3-}$ or $HIDA^{3-}$ ligands that bind to the metal are isoelectronic with peroxide(2−) and therefore the oxidized complexes relate to bis(peroxo)-vanadium(V) species. Nevertheless, the presence of H_2O_2 is required for the detection of activity and the vanadium-promoted Br^- oxidation by H_2O_2 (to HOBr or a derivative thereof) occurs in the aqueous phase and the halogenation of the organic substrate in the organic phase (NCMe). The vanadium complexes are soluble in both solvents and the peroxidative halogenation occurs smoothly even without addition of a phase-transfer agent.

Apart from behaving as catalysts for the halo-functionalization of alkanes and aromatics, as shown above, synthetic amavadine and its model can also catalyse, at room temperature, the hydroxylation (reactions 2) and/or oxo-functionalization of these types of substrates. The reactions occur in homogeneous conditions (single-phase system), by treatment of an acetonitrile solution of the vanadium complex, in the presence of H_2O_2 and HNO_3, with the substrate (Tables 1 and 2).

$$RH + H_2O_2 \xrightarrow{\text{Amavadine}} ROH + H_2O \qquad (2)$$

The system does not require so high an acidic medium as for bromination, and the activity towards oxygenation of cyclohexane to cyclohexanol and cyclohexanone, which is already detected without added acid (overall TON = 4, 6 h reaction time), reaches a maximum (overall TON *ca.* 50 in the $[V(HIDA)_2]^{2-}$ system) for an acid:vanadium molar ratio of *ca.* 140 (for H_2O_2:V = 440). The alcohol is always the main product, but the ketone also forms. The selectivity is dependent on the experimental conditions, in particular the amounts of H_2O_2 and HNO_3, and *e.g.* for the above conditions, the obtained cyclohexanol/cyclohexanone molar ratio is 5.3, whereas a value of 9.2 is reached for HNO_3:V = 72 (also for H_2O_2:V = 440).

The selective oxidation to the alcohol, although less extensive, occurs for benzene (that forms exclusively phenol, TON = 16 or 6 for the corresponding $[V(HIDA)_2]^{2-}$ or $[V(HIDPA)_2]^{2-}$ systems), whereas mesitylene (1,3,5-trimethylbenzene) is oxidized to the aldehyde (3,5-dimethylbenzaldehyde) (TON = 13 or 7, respectively) rather than to the alcohol.

Attempts to characterize active intermediate vanadium species are under way, as well as the extension of the work to other substrates and to other amavadine models and related complexes. In particular, we have also observed catalytic activity towards the above reactions for various vanadium(V) complexes with other polydentate ligands with N,3O-donor atom sets such as triethanolaminate, *e.g.* $[VO\{N(CH_2CH_2O)_3\}]$ **b** (see Tables 1 and 2), aminocarboxylates, *etc.*

To the best of our knowledge, this study provides the first examples of vanadium catalysts for the peroxidative halogenation of alkanes, at room temperature. It might be expected that natural amavadine showed similar properties, *i.e.* the possibility to act as a haloperoxidase or a peroxidase, catalysing the peroxidative halogenation, hydroxylation and/or oxygenation of organic substrates, but we note that, since for the halogenation reactions the pH was very low, the results cannot be directly extrapolated to biological conditions. Curiously, the vanadium-dependent haloperoxidases, which probably developed later, since vanadium is in the oxidation state 5+, catalyse halogenation reactions at pH 5–6 to give products that appear to have defensive roles. On the basis of electrochemical studies[3] we have suggested that amavadine, which, as stated, is a simple complex, not an enzyme, may act as a kind of primitive peroxidase (towards thiols) or as a catalase (if substrates other than H_2O_2 are not present), behaving also as a protective agent against external microbial pathogens or host body damage. Halogenation of alkanes and aromatics which, as shown in this work, occur in the laboratory at room temperature but very low pH for the particular substrates studied, is unlikely to occur *in vivo* with the substrates studied but may eventually be viable in less extreme (even physiological) pH conditions for other more favourable substrates.

This work has been partially supported by the Fundação para a Ciência e a Tecnologia and the PRAXIS XXI programme, Portugal.

Notes and references

1 (*a*) *Vanadium Compounds*, ed. A. S. Tracey and D. C. Crans, ACS Symposium Series no. 711, ACS, Washington, 1998; (*b*) *Metal Ions in Biological Systems*, ed. H. Siegel and A. Siegel, Marcel Dekker Inc., New York, vol. 31, 1995; (*c*) *The Biological Chemistry of the Elements*, ed. J. J. R. Fraústo da Silva and R. J. P. Williams, Clarendon Press, Oxford, 1993.

2 (*a*) M. A. A. F. C. T. Carrondo, M. T. L. S. Duarte, J. C. Pessoa, J. A. L. Silva, J. J. R. Fraústo da Silva, M. C. T. A. Vaz and L. Vilas-Boas, *J. Chem. Soc., Chem. Commun.*, 1988, 1158; (*b*) R. E. Berry, E. M. Armstrong, R. L. Beddoes, D. Collison, S. N. Ertok, M. Helliwell and C. D. Garner, *Angew. Chem., Int. Ed.*, 1999, **38**, 795; (*c*) E. Bayer, E. Koch and G. Anderegg, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 545.

3 (*a*) C. M. M. Matoso, A. J. L. Pombeiro, J. J. R. Fraústo da Silva, M. F. C. Guedes da Silva, J. A. L. Silva,, J. L. Baptista-Ferreira and F. Pinho-Almeida, in ref. 1(*a*), ch. 18, pp. 241–247; (*b*) M. F. C. Guedes da Silva, J. A. L. Silva, J. J. R. Fraústo da Silva, A. J. L. Pombeiro, C. Amatore and J.-N. Verpeaux, *J. Am. Chem. Soc.*, 1996, **118**, 7568.

4 (*a*) A. Butler, M. J. Clague and G. E. Meister, *Chem. Rev.*, 1994, **94**, 625; (*b*) D. Rehder, *Coord. Chem. Rev.*, 1999, **182**, 297.

5 (*a*) B. Sels, D. De Vos, M. Buntinx, F. Pierard, A. Kirsch-De Mesmaeker and P. Jacobs, *Nature*, 1999, **400**, 855; (*b*) J. V. Walker, M. Morey, H. Carlsson, A. Davidson, G. D. Stucky and A. Butler, *J. Am. Chem. Soc.*, 1997, **119**, 6921; (*c*) B. J. Hamstra, G. J. Colpas and V. L. Pecoraro, *Inorg. Chem.*, 1998, **37**, 949; (*d*) C. V. Dinesh, R. Kumar, B. Pandey and P. Kumar, *J. Chem. Soc., Chem. Commun.*, 1995, 611.

6 (*a*) A. E. Gekhman, I. P. Stolarov, N. I. Moiseeva, V. L. Rubaijlo, M. N. Vargaftik and I. I. Moiseev, *Inorg. Chim. Acta*, 1998, **275–276**, 453; (*b*) G. B. Shul'pin, D. Attanasio and L. Suber, *J. Catal.*, 1993, **142**, 147; (*c*) H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer and R. Weiss, *J. Am. Chem. Soc.*, 1983, **105**, 3101.

7 (*a*) I. I. Moiseev, A. E. Gekhman and D. I. Shishkin, *New J. Chem.*, 1989, **13**, 683; (*b*) P. R. H. P. Rao, A. V. Ramaswany and P. Ratnasamy, *J. Catal.*, 1993, **141**, 604; (*c*) P. R. H. P. Rao and A. V. Ramaswany, *J. Chem. Soc., Chem. Commun.*, 1992, 1245.

8 (*a*) *Catalytic Activation and Functionalisation of Light Alkanes*, ed. E. G. Derouane, J. Haber, F. Lemos, F. Ramôa Ribeiro and M. Guinet, NATO ASI Series, vol. 44, Kluwer Academic Publ., Dordrecht, The Netherlands, 1998; (*b*) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879.