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Mimicking the Vanadium Bromoperoxidases Reactions: Mild and Selective Bromination of Arenes and Alkenes in a Two-Phase System.

Valeria Conte, Fulvio Di Furia* and Stefano Moro

Università di Padova, Dipartimento di Chimica Organica, Centro Studi Meccanismi Reazioni Organiche del CNR,
via Marzolo 1, 35131 Padova, Italy

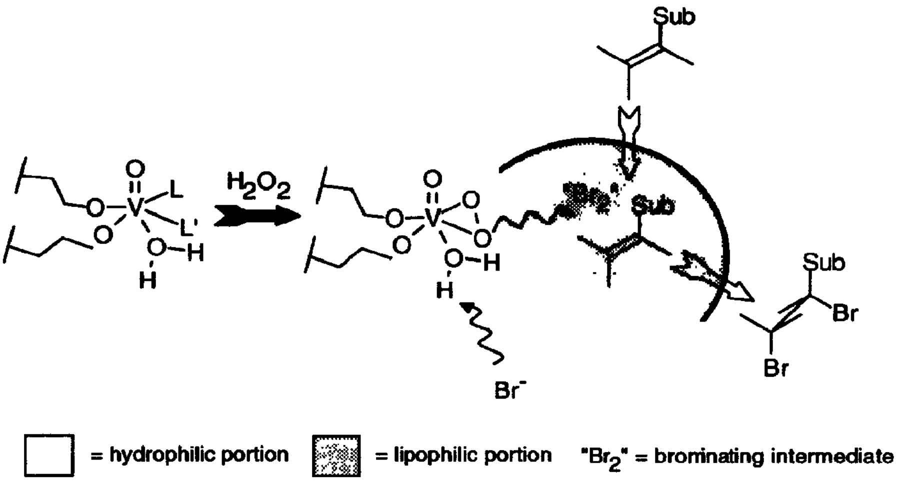
Abstract: Vanadium bromoperoxidases catalyze the oxidation of bromide ion by hydrogen peroxide to a bromine-equivalent intermediate. This, in turn, brominates organic molecules. The hypothesis is made that the former reaction takes place in the hydrophilic portion of the enzyme whereas the latter proceeds in a hydrophobic one in which the brominating intermediate is rapidly transferred. We have reproduced such situation by employing a two-phase ($H_2O/CHCl_3$) system. In the aqueous acid phase H_2O_2 and catalytic amounts of NH_4VO_3 are present, together with KBr. The substrates, i.e. aromatic hydrocarbons and alkenes are dissolved in $CHCl_3$. The bromination proceeds smoothly with stirring, at 25°C, providing high yields of the corresponding brominated products.

Bromoperoxidases (V-BrPO) are vanadium containing enzymes, isolated from marine algae, which play a major role in the biosynthesis of brominated compounds.[1-3] Their commonly accepted mode of action involves the catalysis of the oxidation of bromide ion by hydrogen peroxide to form a bromine-equivalent intermediate whose nature is still obscure.[4-6] Such an intermediate may then either brominate organic substrates or react with another molecule of H_2O_2 forming singlet oxygen.[7,8] It may be conceived that the former reaction is favored over the latter due to the possibility of the intermediate to migrating from the hydrophilic portion of the enzyme, in which the bromide oxidation takes place, to the hydrophobic one in which bromination may occur. As far as the mechanism of bromide ion oxidation is concerned, it is proposed that V-BrPO exerts its catalytic effect by forming, with H_2O_2, a peroxovanadium complex which is a much more effective oxidant than H_2O_2.[9] The situation described above is depicted in a rather simplified way in the Figure.

Based on this hypothesis we developed a synthetic procedure for the bromination of organic substrates involving a two-phase ($H_2O/CHCl_3$) system. In the acid (pH=0.90, $HClO_4$) aqueous phase (20 ml) KBr (1 mmole), H_2O_2 (0.4 mmoles) and NH_4VO_3 (0.2 mmoles) are dissolved. Under these conditions, all vanadium is present as the oxo-monoperoxo aquo complex

$[VO(O_2)(H_2O)_n]^+$, as revealed by ^{51}V-NMR.[10-13] The Table lists the results of the bromination of a series of aromatic compounds and olefins carried out at 25°C with stirring (500 r.p.m.). It has been confirmed by direct experiments that in absence of vanadium only traces of brominated products are obtained. In fact, the uncatalyzed oxidation of Br^- by H_2O_2 under our experimental conditions in inconveniently slow.

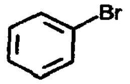
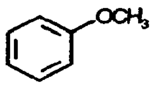
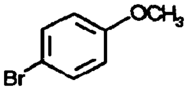
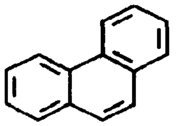
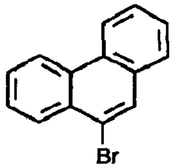
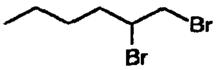
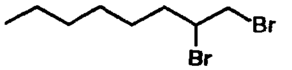
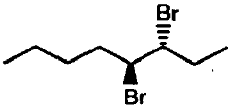
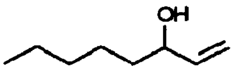
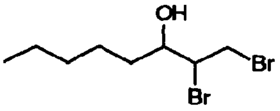
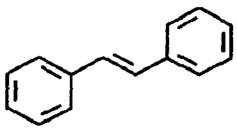
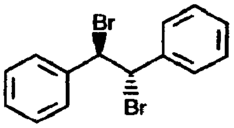
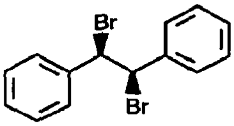
Figure



In all cases, with the exception of the scarcely reactive benzene and phenanthrene, entries 1 and 3, the yields of brominated compounds, determined by GS-MS analysis at complete disappearance of the substrate ca 6 hours, are almost quantitative. This indicates that the competitive decomposition of H_2O_2 which is only in two-fold excess over the substrate is minimized, at least for sufficiently reactive substrates. Also, a rational is offered for the beneficial effect exerted by the two-phase system since it may be envisaged that the easy transfer of the bromine-equivalent in $CHCl_3$, where bromine is liberated, avoids further reaction with H_2O_2 or with the peroxo vanadium species in water.[14,15] In fact, when the oxo monoperoxo vanadium aquo complex (0.1 mmoles), formed in situ from H_2O_2 and NH_4VO_3, is reacted with KBr (1 mmole) in a aqueous solution (pH = 0.9 $HClO_4$) the yield of bromine produced is rather low, not exceeding the 20% of the initial amount of hydrogen peroxide. Such a low yield is attributed to the subsequent reaction of the bromine formed with the peroxides.[16,17]

The oxidation procedure reported presents synthetic advantages. These are related to the use of simple and relatively inexpensive reagents and also to the ease of isolation of the products which are obtained almost pure simply by separating the two phases and by evaporating the organic one, dried over $MgSO_4$. It has also been directly proved that, upon addition of more H_2O_2 and substrate, the system keeps operating until complete disappearance of KBr.

Table: Bromination of arenes and alkenes with H_2O_2 and KBr, catalyzed by NH_4VO_3 in a two phase system 20 ml H_2O/20 ml $CHCL_3$, at 25°C[a]

Entry	Substrate	Products	Yield(s)[b]
1			40^c
2			>98
3			50^c
4			>98
5			95
6			>98
7			>98
8		 (1)  (2)	95^d
9	*cis*-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	$CH_3(CH_2)_7CHBrCHBr(CH_2)_7COOH$	>98

a.water: KBr (1 mmole), H_2O_2 (0.4 mmoles), NH_4VO_3 (0.2 mmoles) and $HClO_4$ (pH=0.9); $CHCl_3$: Substrate (0.2 mmoles).

b.Yields calculated by GS-MS after complete disappearance of the substrate. The identity of the products has been confirmed by comparison of their MS and ^1H-NMR spectra with authentic samples.

c.Conversion of the substrate after complete disappearance of H_2O_2. No other products are detected.

d.**1**:**2** = 85:15

A comparison with more traditional brominating systems confirms the synthetic significance of the proposed procedure which provides similar results. Thus, we have repeated the reaction of entry 6 by using Br_2 (0.4 mmoles) in 20 ml $CHCl_3$ or KBr-$KBrO_3$ in the two phase,$H_2O/CHCL_3$, system under conditions identical to those reported in the Table. In both cases the complete conversion of the substrate was obtained in ca 4 hours with a 98% yield.

The efficiency of our procedure is also fairly strong, though indirect, evidence that we are mimicking the action of V-BrPO. Thus, the system is suitable for mechanistic studies of the chemistry of such enzymes.

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