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CHEMICAL SOURCE OF SINGLET OXYGEN, OR ITS SYNTHETIC EQUIVALENT. GENERATION FROM RESIN-BOUND PEROXOMOLYBDATE

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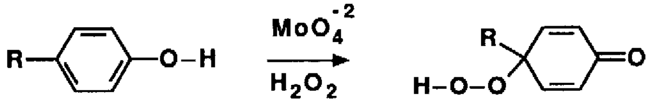
Abstract: Singlet oxygen, or its synthetic equivalent, is generated by the action of resin-bound molybdate on hydrogen peroxide. Resin-bound peroxomolybdate converts reactant olefins to their ene, [4+2] and [2+2] cycloaddition or secondary products.

Over the past several years singlet oxygen, $^1O_2$, has emerged as a powerful synthetic reagent for the introduction of the peroxide function or its supersedents with a remarkable degree of regioselectivity[1]. This reagent has evoked more recent interest because it can provide explicit routes to analogs of naturally occurring peroxides[2], many reported to possess potent biological[3] or pharmacologic properties[4]. The routine use of $^1O_2$ in synthesis has focused not on the initial peroxidic products, however, but their chemically altered functions to avoid problems of uncertain structural fragility. Although the most popular method for generating singlet oxygen for synthesis employs photooxygenation[5], chemical sources of singlet oxygen could provide convenient or even preferred alternatives for synthesis.

To circumvent the complications of mixed aqueous solvents and product isolation characteristic of the classical chemical methods, we chose to bind a metal-peroxo complex to a macroreticular resin. Diperoxomolybdate, MoO_6^{-2}, and the anionic exchange resin, Amberlyst A-26®, seemed to be excellent candidates for the initial study. The molybdate-peroxo complex, formed upon reaction of H_2O_2 on MoO_4^{-2} in neutral, aqueous alcohol solvents, appears to be the among the best methods for the oxidative dearomatization of *p*-alkylphenols to their dienenone hydroperoxides[6], equation 1. Molybdate and hydrogen peroxide are also reported to react with limonene, β-ionone, anthracene and hinokiol, to yield product mixtures identical to those obtained with singlet oxygen generated through photooxygenation[6].



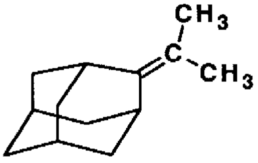
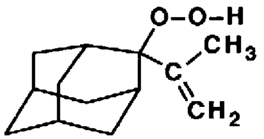
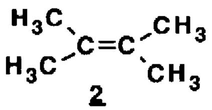
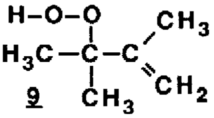
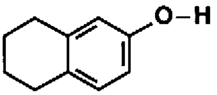
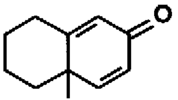
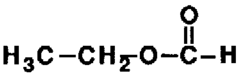
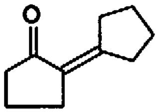
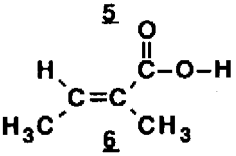
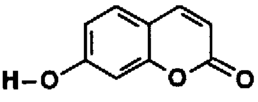
(eqn 1)

Molybdate bound Amberlyst A-26® was prepared by passing aqueous sodium molybdate through a column of the resin[7]. The complexed resin was dried *in vacuo* and found to contain 1.03 meq of molybdate per 1.00 g of resin complex. Because twice this amount of Cl^- was removed, the molybdate was attached to the resin as MoO_4^{-2} rather than $NaMoO_4^-$. Approximately 47% of the original Cl^- ions present on the resin remained unexchanged by molybdate. The peroxo complex was formed by passing a 9-fold molar excess of 30% H_2O_2[8] at 0° C through a short column filled with the molybdate bound Amberlyst A-26®. To remove water, the resin was flushed with methanol at 0° C and any dischargeable solvent then expelled under pressure. We were pleased to find that less than 0.6% of the original H_2O_2 can be eluted by repeated methanol washes. Only 22% of the original H_2O_2 is expected to react with molybdate to form the strong MoO_6^{-2} complex[9], equation 2. The remainder must H-bond to the complex, act as an HOO^- counterion to the resin alkyl ammonium ions, strongly solvate the resin, or be decomposed by or react with free amine groups in the resin.

$$MoO_4^{-2} + 2\,H_2O_2 \rightarrow MoO_6^{-2} + 2\,H_2O \qquad \text{(eqn 2)}$$

In a typical synthesis procedure[10], the organic reactant is added as a solution in methanol, methanol/*t*-butanol or dichloromethane at a concentration of 1.0 meq of reactant for each 2.2 meq of original molybdate ion. The reaction proceeds to completion overnight at 20-25° C, or until the color of the red-brown peroxomolybdate complex disappears, or until the reaction is complete as determined by TLC. The peroxide products are obtained by washing the resin with dichloromethane or methanol. Any unreacted hydrogen peroxide remains firmly bound to the resin.

Excellent yields of peroxidic products were obtained from alkenes expected to undergo the ene, and the [4+2] and [2+2] cycloaddition reactions with $^1O_2$, Table. Both isopropylideneadamantane, 1, and 2,3-dimethyl-2-butene, 2, uniquely formed the ene products, 8 and 9, predicted from $^1O_2$. The phenol, 5,6,7,8-tetrahydro-2-naphthol, 3, gave a

REACTANT	PRODUCT	CONDITIONS	% YIELD*,**
 1	 8	b	98.9 (d, e, f, g)
 2		c	86 (f, h)
 3	 10	b	65 (e, j, f, m)
$H_3C-CH_2-O-CH=CH_2$ 4	 $H_3C-CH_2-O-\overset{O}{\overset{\|}{C}}-H$ 11	a	16 (i)
 5	?	a	(j)
	?	a	(j)
 7	No Reaction	a	

* reaction solvent = a/ methanol, b/ methanol/ *t*-butanol, c/ dichloromethane. ** product structures were confirmed by comparing physical properties with those of authentic samples, prepared by literature procedures: d/ m.p., e/ IR, f/ ^1H NMR. Yield determined by g/ isolation of product, h/ NMR, i/ GLPC; j = 100% reaction as measured by TLC, structure of products undetermined.

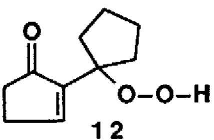
high yield of the hydroperoxydienone, **10**, which is also formed through photooxygenation via a mechanism thought to involve rearrangement of an embryonic endoperoxide from [4+2] cycloaddition with $^1O_2$[6] or by an electron transfer between the reactants[11]. Ethyl vinyl ether, **4**, gave a small amount of ethyl formate, **11**, the expected by-product from fission of a dioxetane from a [2+2] cycloaddition with $^1O_2$[12]. 2-Cyclopentylidenecyclopentanone, **5**, and tiglic acid, **6**, underwent complete reaction, but the organic products were too strongly bound to the molybdate-resin to allow for isolation. 7-Hydroxycoumarin, **7**, which resists photooxygenation[13], is also inert to reaction with resin-bound peroxomolybdate.

The intermediacy of singlet oxygen in these conversions remains unproven. Another molybdenum/ peroxide complex, molybdenum (IV) oxide pyridine diperoxide, (py)$MoO(O_2)_2$, produces low yields of the same [2+2] cycloaddition and secondary products from alkoxyadamantylidenes and 2,3-diphenyl-5,6-dihydro-1,4-dioxine as those derived from $^1O_2$[14]. Here, it is thought that a radical ion pair and subsequent single electron transfers convert a first formed oxacyclopropane into a dioxetane. Still, compelling evidence that singlet oxygen is the sole oxygen-containing product from the diperoxomolybdate anion, MoO_6^-, follows from a D_2O, solvent isotope effect of 13 for formation of rubene-2,3,8,9-tetracarboxylate endoperoxide in aqueous, basic medium and other quantitative evidence[8]. This value is in agreement with the 14 ± 1 times longer half-life of $^1O_2$ in D_2O than H_2O[15].

The involvement of cation radicals, arising from oxidation of an olefinic bond, doesn't seem likely. Even though cation radical catalyzed chain (CRCC) oxygenations[16] can give explicit singlet oxygen products with either triplet oxygen or superoxide, isopropylideneadamantane, **1**, does not yield any ene products (**8**) while 2,3-dimethyl-2-butene, **2**, gives acetone, pinacolone and 2,3-dimethyl-2-hydroperoxybutane as the principal products[17]. These findings are at odds with our results with the resin-bound diperoxomolybdate, Table. The lack of reactivity of 7-hydroxycoumarin, **7**, is probably due to its physical quenching of singlet oxygen[18], or to its redox potential preventing oxidation[19].

The addition of 1,4-diazabicyclo[2.2.2]octane, DABCO, a physical quencher[20] of $^1O_2$, at 25 mol % relative to the alkene[21], isopropylideneadamantane, **1**, revealed no kinetic inhibition of product formation. We do not take this evidence as definitively excluding the intermediacy of $^1O_2$, because the loss of DABCO's free electron pairs upon complexation with peroxomolybdate would also repress its ability to quench singlet oxygen.

This procedure is a high yield alternate to photooxygenation when the peroxidic products are relatively stable and monodentate. Excess hydrogen peroxide remains strongly bound to the resin and water can be largely excluded from the products formed. Highly functionalized peroxides complex too strongly with the molybdate ion for removal. The hydroperoxides, **12** and **13**, prepared by photooxygenation of 2-cyclopentylidenecyclopentanone, **5**[22], and tiglic acid, **6**[23], respectively, bind to molybdate so strongly that even citrate and tartrate can not free them. Peroxo-metal complexes carrying additional ligands might overcome this problem. Finally, there is the potential for unusual proximate effects if the organic reactant should be bound to the resin at a site close to where $^1O_2$ is generated. Closely related, the microheterogeneous effect[24], leading to a rate enhancement, is a well established phenomenon for photooxygenations with sensitizers covalently bound to ligands that also complex the acceptor.



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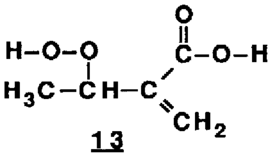

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[7] Amberlyst A-26® is dried by passing 2.5 volumes of methanol through a column of the resin followed by removal of residual solvent *in vacuo*. A solution of 50.17 g of $NaMoO_4 \cdot 2\ H_2O$ in 315 ml of water is slowly passed through a column of 87.8 g of dried resin and followed by three aqueous washes of 200 ml each. The resin is washed with acetone until the elutent is colorless and is dried *in vacuo*.

[8] **CAUTION:** Hydrogen peroxide is a strong oxidant and may undergo rapid, metal-ion catalyzed decompositions.

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[10] In a typical procedure, 6.17 g (equal to 6.36 mmol of MoO_4^{-2}) of dry molybdate-resin complex is placed into a 60 ml column and cooled. 5.68 ml (56.8 mmol) of cold 30% H_2O_2 is added followed by three portions of 0° C methanol, sufficient to cover the top of the resin. Each methanol wash is individually purged by applying pressure at the column top with a larger rubber bulb. A solution of 0.500 g (2.84 mmol) of compound 1 in 6.0 ml of 25/75 v/v *tert*-butanol/ methanol at r.t. is added, then sufficient methanol to cover the top of the resin. The total volume of solvent is approximately 8.0 ml. The contents of the column are briefly warmed in a 30° C water bath to bring precipitated substances into solution and the reaction mixture then kept at 25°. After 20 hrs, the resin is washed with 50 ml of methanol. Solvent removal *in vacuo* at 25° gives 0.585 g (2.81 mmol) (98.9%) of pure 8.

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[13] Sensitizers = methylene blue, Bengal rose B, and meso-tetraphenylphorphin, solvents = methanol and dichloromethane, light sources = 500 watt sodium lamp, 1000 watt tungsten/halogen lamp

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[21] Concentrations of reactants: 1 = 0.36 M, DABCO = 0.088 M, H_2O_2 = 7.10 M in CH_2Cl_2; 6.36 mmol of polymer-bound MoO_4^{-2} is present, wetted by 8.0 ml of solution.

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