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Aerobic Oxidations of Unsaturated Substrates under Mukaiyama's Conditions: the Role of the Metal and of the Sacrificial Aldehyde

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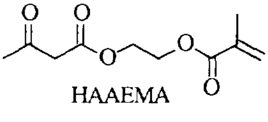
Abstract: Aerobic epoxidation of unsaturated substrates has been achieved under Mukaiyama's conditions (atmospheric pressure of dioxygen, in the presence of an excess of sacrificial aldehyde) with or without metal catalyst. The influence of light in non-catalysed reactions and the possible role of the aldehyde and of the metal complex in catalysed reactions are discussed. Two mechanistic pathways are proposed for Co(II) and Fe(III) [Ni(II)] catalytic centres.

Much attention has been recently focused on the aerobic oxidation of a great variety of organic substrates (alkenes, aldehydes, silyl enol ethers, silyl ketene acetals, ketones, lactams and alkanes) in the presence of aldehydes or acetals, with various transition-metal complexes as catalytic systems[1] (Mukaiyama's conditions).

In this context we have already explored the catalytic activity of polymerizable β-ketoesterate complexes such as Fe(AAEMA)$_3$, Ni(AAEMA)$_2$ and Co(AAEMA)$_2$ as catalytic centres (AAEMA$^-$ = deprotonated form of 2-(acetoacetoxy)ethyl methacrylate) towards the oxidation of organic substrates[2], with a view to laying the foundations for effecting the reactions under heterogeneous conditions.



HAAEMA

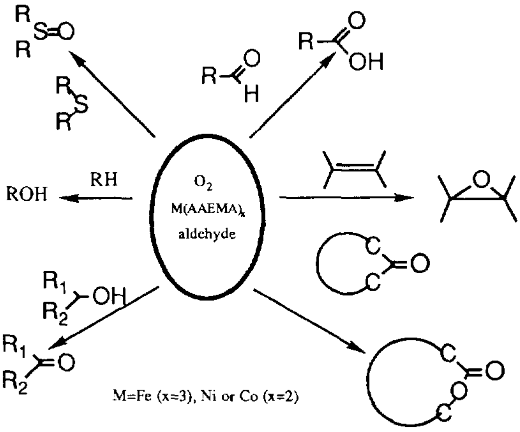
In spite of the great number of papers dealing with new applications of Mukaiyama's oxidation reaction, only a few reports have been devoted to elucidate the process of oxygen activation, and the subsequent mechanism of oxygen incorporation into organic molecules.

The first attempt to shed light on these aspects was made by Mukaiyama himself. He excluded the intermediacy of a free peroxyacid species[1c], on the basis of the enhanced β-diasterofacial selectivity in the metal catalysed epoxidation of cholesteryl benzoate, with respect to the *m*-chloroperbenzoic acid (*m*-CPBA) procedure. On the other hand, Nishida *et al.*, in some recent reports suggested that the reaction mixture of Ni(II) or Co (II) β-diketonate complexes and aldehyde or alcohols might induce the activation of molecular oxygen with formation of singlet oxygen-like active species[3]. On the same topic Laszlo suggested that the attachment of both dioxygen and aldehydic auxiliary to the metal centre would result in the *in situ* production of hydrogen peroxide and of the ketene corresponding to the employed aldehyde. The former would then participate in the olefin epoxidation, while the latter would be unstable and be converted into the carboxylic acid[4].

In addition to that, Kaneda showed that the presence of a metal complex is not strictly required for an efficient epoxidation of several unsaturated substrates[5], owing to the facile autooxidation of the reducing agent (α-branched aldehyde) into peroxyacid or peroxyacyl radical species.

Results and discussion

One of the most attractive feature of Mukaiyama's oxidation reaction, as outlined above, is its wide applicability to different classes of organic substrates. We have shown, in particular, that AAEMA$^-$ complexes of Fe(III), Ni(II) and Co(II) are active in the oxidation of alkenes, aldehydes, cyclic ketones, sulfides, alkanes and alcohols[2] (scheme 1).



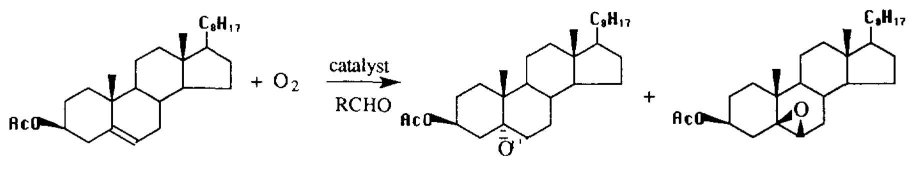
Scheme 1: catalytic activity of AAEMA$^-$ complexes in oxidation reactions

The conversion of cyclic ketones into the corresponding lactones proceeds with high efficiency in the presence of nickel(II) and iron(III) catalytic centres, whereas negligible conversion has been obtained by using the cobalt(II) complex. On the contrary, the oxidation of sulfides to sulfoxides or sulfones occurs smoothly with $Co(AAEMA)_2$ and sluggishly with Fe(III) or Ni(II) catalytic centres.

These findings may be indicative of the following working hypotheses: (a) different oxygen activation mechanisms may operate with different metals; (b) different oxygen transfer species may be involved in Fe(III) and Ni(II) or in Co(II) catalyzed oxidation reactions.

The first step towards the clarification of the mechanism under study was to take into account the possible involvement of oxidative agents formed by interaction of the sacrificial aldehyde and dioxygen. In this regard, the simplest ones to be thought are free peroxyacid, dioxirane and carbonyl oxide.

We have verified the discharge of free peroxyacid, as active species, in catalytic oxidation reactions (already suggested by Mukaiyama[1c]) by carrying out some experiments on the epoxidation of cholesteryl acetate **1** in the presence of 3-chlorobenzaldehyde as sacrificial reducing agent (scheme 2).



1 α β

R= *iso*-propyl or 3-chlorophenyl

Scheme 2: Epoxidation of cholesteryl acetate under Mukaiyama's conditions with *i*-butyraldehyde or 3-chlorobenzaldehyde

Table 1: Epoxidation of cholesteryl acetate **1** under Mukaiyama's conditions: 2.5 mmoles of **1**, 7.5 mmoles of sacrificial aldehyde, 10 ml of 1,2-dichloroethane (DCE) at room temperature and atmospheric pressure of O_2.

Entry	Catalyst	Reaction Time (h)	% Conv.	% Stereoisomer α	% Stereoisomer β
1^a	*m*-CPBA	24	100	79	21
2^b	$Fe(AAEMA)_3$	70	22	40	60
3^b	$Ni(AAEMA)_2$	70	19	37	63
4^b	$Co(AAEMA)_2$	70	25	35	65
5^c	$Fe(AAEMA)_3$	20	97	46	54
6^c	$Ni(AAEMA)_2$	20	98	48	52
7^c	$Co(AAEMA)_2$	20	87	32	68
8^d	none	100	80	79	21
9^e	none	60	5		
10^f	none	24	100	38	62
11^g	CoSANP	20	89	75	25

[a]: in dichloromethane ; [b]: in the presence of 3-chlorobenzaldehyde (3 equivalents) as sacrificial aldehyde; [c]: in the presence of 3 equivalents iso-butyraldehyde, from ref. 2b; [d]: carried out by us in the day light; [e]: carried out by us in the dark. [f]: conditions identical to those of entry 9, from ref.7; [g]: in acetonitrile, from ref. 6; CoSANP= [bis(salicylidene-N-phenethyl)]cobalt(II);

If free peroxyacid deriving from autoxidation of the aldehyde were the effective oxidizing agent, then the stereoselectivity observed in these experiments would have been, not only independent of the metal centre employed (which would have only an effect on the efficiency of the system), but equal to that observed in *m*-CPBA procedure (entry 1 of Table 1)[7]. Instead, the results collected in entries 2-4 of Table 1 show that the aromatic aldehyde reduced the efficiency of the reactions and, at the same time, induced a reversed stereoselectivity. On the contrary, the efficiency of the epoxidation reactions of **1**, carried out with *i*-butyraldehyde (entries 5-7) depends on the metal used, cobalt(II) being a little less efficient than nickel(II) or iron(III)[2b]. Our findings confirm Kaneda's observation, that the oxidation process is triggered also in the absence of Ni(II), Fe(III) or Co(II) centres. The results reported in entries 8 and 9 point out that this process is slower than the metal catalysed one and, noteworthy, almost totally inhibited when carried out in the absence of a light source. It is also apparent that, notwithstanding the similar reaction conditions, the results reported by us and Ramasseul[8] (entries 9 and 10 respectively) are totally in contrast.

The hypothesis that a dioxirane and/or a carbonyl oxide could be the active oxygen transfer species can be discarded on the basis of the following experimental observations: (a) contrary to what happens with dioxiranes,[9] neither amines nor polycondensed benzenes can be oxidized under Mukaiyama's conditions; (b) Mukaiyama's system gives the Baeyer-Villiger reaction (at least with nickel(II) and iron(III) catalytic centres) while dioxiranes do not; (c) no addition product of the possible carbonyl oxide to the sacrificial aldehyde has ever been observed in Mukaiyama's oxidation reactions.

In order to shed more light on the combined effect of the light and of the metal on the oxidation reaction, we have carried out several experiments with unsaturated substrates, such as norbornene 2, cyclohexene 3, benzydrylidenadamantane 4, *iso*-propylydenadamantane 5, citronellal 6, 1-octene 7 and 1-dodecene 8, that show peculiar reactivity towards different oxygen transfer species.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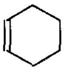
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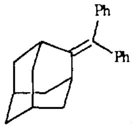

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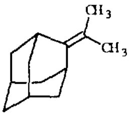

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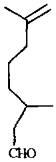

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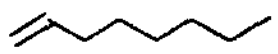
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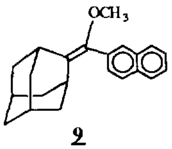

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The most representative results, summarized in tables 1 and 2, show that cyclic olefins such as 1, 2 and 3 were smoothly epoxidized in the absence of any metal complex only if the reaction was carried out in daylight (entries 8-9, tab.1; entries 1, 2, 4, 5, table 2). When the reaction was carried out in the dark, not only the substrate remained undisturbed (table 2), but also the sacrificial aldehyde was not converted into the corresponding carboxylic acid.

Table 2: Epoxidation of olefins (2.5 mmoles) by dioxygen (p atm) and *i*-butyraldehyde in DCE (10 ml) at room temperature: effect of the light.

Entry	Substrate	Catalyst	Reaction Time (h)	Cond.	Conversion in epoxide (%)
1	2	none	20	light	80
2	"	"	40	dark	0
3	"	Fe(AAEMA)$_3$	10	light or dark	93^a
4	3	none	20	light	80
5	"	"	40	dark	0
6	"	Fe(AAEMA)$_3$	10	light or dark	85^a
7	4	none	14	light	90
8	"	"	19	dark	44
9	5	"	14	light	35
10	"	"	14	dark	23
11	6	"	20	light	57
12	"	"	22	dark	49
13	"	Fe(AAEMA)$_3$	20	light or dark	90

^{a}: from ref. 2b.

Internal and hindered olefins such as **4**, **5**, and **6** are epoxidized both in the light and in the dark also in the absence of metal catalyst (entries 7-12 of Table 2), but in the latter case the reactions carried out in the dark are slightly slower than those carried out in the light. Moreover, metal catalysed reactions are always faster than non metal catalysed ones. For all the substrates **1**-**6** the corresponding epoxidations carried out under metal catalysis were not affected by the light parameter thus indicating that different pathways should be followed in the two procedures (i.e. with or without metal catalyst).

Terminal olefins such as **7** and **8** were not epoxidized without metal catalysis after 20 hour reactions. The epoxidation of **6** did not occur in the absence of sacrificial aldehyde (i.e. *i*-butyraldehyde), showing that the possible activation of the aldehyde function present in the substrate and its subsequent intramolecular oxidation is not operative.

In order to test Nishida's hypothesis[3] on the possible involvement of $^1O_2$ as reactive intermediate, we used catalytic results obtained with substrates **4**, **5** and methoxy(2-naphthyl)-methylideneadamantane **9**, whose reactivity towards singlet oxygen has been well ascertained[10] (see our previous communication).[11] The chosen probe molecules were easily converted, under our catalytic conditions, into the corresponding epoxides, instead of the expected 1,2-dioxetanes formed by singlet oxygen oxidation. This can be taken as a clue for the non involvement of $^1O_2$ in these metal catalysed reactions.

In order to gain information on the possible involvement of radical species in metal catalysed oxidations, often suggested in the literature, we have carried out the epoxidation reaction using Fe(AAEMA)$_3$ with cis- and trans-2-octenes **10a**-**b**. The results collected in table 3 show that, especially in the case of **10a**, metal catalysed reactions proceeded with a degree of isomerization at the double bond which strongly supports a radical pathway. To confirm this hypothesis we have carried out three reactions of norbornene under Mukaiyama's conditions with Fe(AAEMA)$_3$, Ni(AAEMA)$_2$ and Co(AAEMA)$_2$ in the dark and in the presence of catalytic amounts of *p*-hydroquinone, a well known radical scavenger. In all three cases no reaction took place, thus confirming the implication of a radical pathway for Fe(AAEMA)$_3$, Ni(AAEMA)$_2$ and Co(AAEMA)$_2$ catalysed reactions.

Table 3: Epoxidation of cis- and trans-2-octene (2.5 mmoles) by dioxygen (p atm) and *i*-butyraldehyde (7.5 mmoles) in DCE (10 ml) in the dark; reaction time =20 hours.

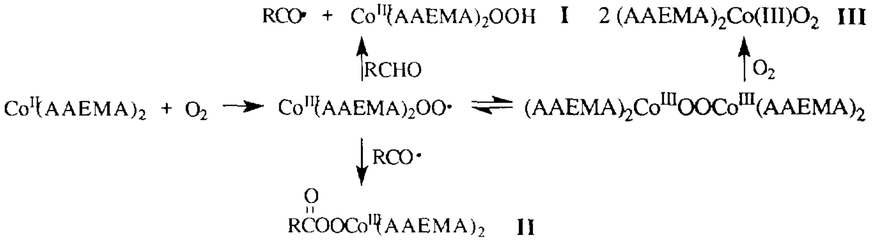
Entry	Substrate	Catalyst	Conv.%	cis/trans 2-epoxyoctane ratio
1	**10a**	Fe(AAEMA)$_3$	78	44/56
2	"	Ni(AAEMA)$_2$	80	50/50
3	"	Co(AAEMA)$_2$	87	33/67
4	**10b**	Fe(AAEMA)$_3$	69	12/88
5	"	Ni(AAEMA)$_2$	76	15/85
6	"	Co(AAEMA)$_2$	50	17/83

Although it is difficult to draw decisive conclusion on the mechanism of the reaction, some suggestions can be put forward. First of all, the observation that Co(AAEMA)$_2$ solutions are unstable in the air whereas Fe(AAEMA)$_3$ and Ni(AAEMA)$_2$ are not affected by molecular dioxygen suggests that the first step in cobalt catalysis could be the reaction with O_2 whereas the first step in iron(III) catalysis should be the reaction with the aldehyde.

In the following discussion we will restrict our comments to Co(II) and Fe(III), assuming that the reactivity of $Ni(AAEMA)_2$ resembles that of $Fe(AAEMA)_3$. This is supported by the similarity in reactivity exhybited by Ni(II) and Fe(III) based catalytic systems with respect to that exhibited by the Co(II). In this context it has been ascertained that the oxidation of cyclic ketones to the corresponding lactones proceeds with high efficiency in the presence of nickel(II) and iron(III) catalytic centres, whereas negligible conversion was obtained by using the cobalt(II) complex. On the contrary, the oxidation of sulfides to sulfoxides or sulfones occurs smoothly with $Co(AAEMA)_2$ and sluggishly with Fe(III) or Ni(II) catalytic centres[2b-c].

Co(II) chelates are known to form superoxo and/or μ-peroxo complexes by reaction with dioxygen[12]. In the initiation step, it is possible that $Co(AAEMA)_2$ binds dioxygen with formation of a superoxo complex, which may be in equilibrium with the more stable peroxo species.

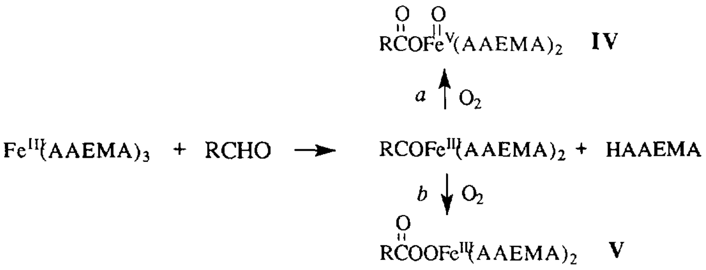
Since the basicity and radical character of molecular oxygen increase upon coordination to Co(II) complex, the superoxo complex, by reaction with the sacrificial aldehyde, may lead to the formation of the hydroperoxyl-Co(III) complex **I** and the acyl radical, which in turn may react with the superoxo complex to afford the acylperoxo Co(III) complex **II** (scheme 3). A similar pathway has been proposed by Iqbal for CoSANP catalysed oxidations[13]. The dimeric peroxo species might further on react with dioxygen affording the monomeric peroxo-species **III** as suggested by Busetto in the case of Co(salen) complexes[14].



Scheme 3: Possible oxygen activation in cobalt(II) catalysis

The oxidizing species in cobalt catalysis might therefore be the hydroperoxyl complex **I**, the coordinated peracyl radical **II**, or the peroxo-species **III**. It cannot be excluded that more then one of the aforementioned intermediates **I-III** be involved in the oxygen transfer process. The difference in stereoselectivity observed in the epoxidation of cholesteryl acetate carried out by CoSANP (entry 11 of table 1) and by $Co(AAEMA)_2$ with the same sacrificial aldehyde (*i*-butyraldehyde) at the same temperature (entry 7 of table 1) confirms that the oxidizing species is a metal complex whose reactivity depends also on the other ligands around the metal.

In the case of $Fe(AAEMA)_3$ catalysis we postulate first an interaction with the aldehyde with loss of a molecule of HAAEMA and formation of the acylradical Fe(III) species. A similar reaction has been proposed, for example, as the first step in iron(III) porphyrins catalysed epoxidation of propylene in the presence of propionaldehyde[15]. The acylradical Fe(III) species might react with dioxygen affording either an oxo iron(V) species **IV** or a peroxyacyl complex **V** similar to **II** (scheme 4).



Scheme 4: Possible oxygen activation in iron(III) or nickel(II) catalyses

Also in this case it is possible that both the intermediates **IV** and **V** play a role in the oxidation reactions.

The findings presented up to here point out that the reactions carried out in the presence or in the absence of metal catalyst are likely to proceed via different pathways. In particular, non metal catalysed reactions seem to occur via peroxyacid intermediates and, at least for the cyclic substrates considered, to be influenced by the light parameter. On the contrary metal catalysed reactions are dependent on both the sacrificial aldehyde and the metal centre used. Moreover a radical pathway seems to occur in all the catalytic reactions supporting the possible involvement of the intermediates **I-V** of schemes 3 and 4.

Experimental

The AAEMA$^-$ complexes were prepared by adding to an ethanol solution of the relevant metal nitrate, the solution obtained by dissolving in ethanol HAAEMA and a base such as KOH or triethylamine (metal: HAAEMA: base = 1: 1: 1)[16]. Gas chromatographic analyses were carried out on a Varian Vista 6000 instrument by using a capillary 30 m Carbowax 20M column or on a Hewlett Packard chromatograph using a 25 m SPB-1 capillary column. The aldehydes and the liquid olefins were distilled prior to use; cholesteryl acetate, norbornene and 1,2-dichloroethane were used as received. Substrates 4 and 5 were prepared according to McMurry's procedure[17] and the spectroscopic features of the corresponding epoxides were reported in ref. 11.

All reactions were carried out in Schlenk tubes. A solution containing a mixture of the catalyst (0.020 mmoles, when present), the olefin (2.5 mmol) and the aldehyde (7.5 mmol *iso*-butyraldehyde or 3-chlorobenzaldehyde) in 1,2-dichloroethane (10 ml) was stirred continuously under an atmosphere of oxygen or air at room temperature. The reactions in the dark were carried out by wrapping an aluminium foil all around the Schlenk.

The epoxides were purified by column chromatography and were identified by comparison of their MS spectra, IR and NMR spectra and retention times in GLC analysis with those of authentic samples.

Conversions and yields were calculated by GLC analyses by using the internal standard method.

The diastereomer α/β ratio in 5,6-epoxycolesteryl acetate was determined by ^{1}H NMR[18].

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