Role of the Nature of the Metal Centre in the Catalysed Addition of β-Dicarbonyls to Electrophilically Activated Nitriles

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The reaction of methyl acetoacetate with trichloroacetonitrile to give 2-amino-1,1,1-trichloro-3-methoxycarbonyl-4-oxo-2-pentene is catalysed, at room temperature, by acetylacetonate complexes [M(acac)$_n$] (n = 2 or 3). The catalytic efficiency of the metal centres follows the order $\mathrm{Zn^{II} \simeq Co^{II} > Mn^{II} > Mn^{III} > Ni^{II} > Cu^{II} > Fe^{II} \simeq Fe^{III}}$, which can be related (with the exception of $\mathrm{Fe^{II}}$) to the degree of ionic character of the M–O bond, in the metallo-organic ring. The metals $\mathrm{Al^{III}}$, $\mathrm{Cr^{III}}$, and $\mathrm{Pd^{II}}$ are catalytically inactive because of their inertia towards ligand exchange.

Metal β-carbonylenolate complexes, *e.g.* [M(acac)$_n$] (acac = acetylacetonate), have been shown to be very efficient catalysts in the addition reaction of C–H acidic β-dicarbonyls (HL) to various electrophiles (E),[1–3] equation (1), and synthetic applications of this finding have been developed in this and other laboratories.[4–9] In fact, this metal-based catalytic approach turned out to be not only far more convenient in terms of chemioselectivity than the conventional one[10] based on basic catalysts, but also suitable for enantioselective syntheses[6] and, more generally, for new synthetic routes.[11,12]

$$\mathrm{HL + E \xrightarrow{[M(acac)_n]} L{-}E{-}H} \qquad (1)$$

The mechanisms proposed for this important C–C bond-forming reaction always imply activation of the nucleophile *via* co-ordination to the metal, but they differ in the occurrence of an activating effect also on the electrophile. In all cases, an important role of the nature of the metal centre on the overall catalytic activity was observed, on a qualitative basis.[4,5]

We report here the first quantitative estimation of the catalytic efficiency of a series of bis- and tris-acetylacetonate complexes [M(acac)$_n$] (n = 2 or 3; M = $\mathrm{Mn^{II}}$, $\mathrm{Fe^{II}}$, $\mathrm{Co^{II}}$, $\mathrm{Ni^{II}}$, $\mathrm{Cu^{II}}$, $\mathrm{Zn^{II}}$, $\mathrm{Pd^{II}}$, $\mathrm{Cr^{III}}$, $\mathrm{Mn^{III}}$, $\mathrm{Fe^{III}}$, or $\mathrm{Al^{III}}$) in the reaction of methyl acetoacetate with trichloroacetonitrile at 20 °C in $\mathrm{CDCl_3}$.[4]

Experimental

All catalysts employed were used as received from Schuchardt or Baker ($\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$). Methyl acetoacetate (Fluka) and trichloroacetonitrile (Janssen) were high-purity products. The addition product, 2-amino-1,1,1-trichloro-3-methoxycarbonyl-4-oxo-2-pentene was characterised as already reported.[4]

Test reactions were performed in $\mathrm{CDCl_3}$ directly inside the n.m.r. tube, and concentration profiles determined by monitoring, at suitables times, the ^{1}H spectra of the reagents (peaks at δ 3.48 and 3.70, $\mathrm{CH_2}$ and $\mathrm{OCH_3}$) and of the product (peaks at δ 3.78 and 9.00, $\mathrm{OCH_3}$ and $\mathrm{NH_2}$). A Perkin-Elmer R32 instrument (90 MHz) was used and the sensitivity of this procedure was estimated to give reliable information up to (at least) 98% conversion. The initial concentrations of methyl acetoacetate and trichloroacetonitrile were 3.0 and 3.6 mol dm^{-3}, respectively, corresponding to a molar ratio of the reagents of 1:1.2. The catalyst concentration ranged from 1.0 to 0.1 mol% with respect to that of methyl acetoacetate.

Results and Discussion

The reaction is, with all investigated catalysts, selective towards the formation of 2-amino-1,1,1-trichloro-3-methoxycarbonyl-4-oxo-2-pentene. The yields at various reactions times and in the presence of the different catalysts employed are collected in the Table. It is seen that the catalytic efficiency is dependent on the nature of the metal centre, following the order $\mathrm{Zn^{II} \simeq Co^{II} > Mn^{II} > Mn^{III} > Ni^{II} > Cu^{II} > Fe^{II} \simeq Fe^{III}}$.

These results, coupled with those available on the general addition reaction of β-dicarbonyls to electrophiles catalysed by metal complexes,[4,5,13] suggest that the stoicheiometric mechanism can be depicted as in Scheme 1.

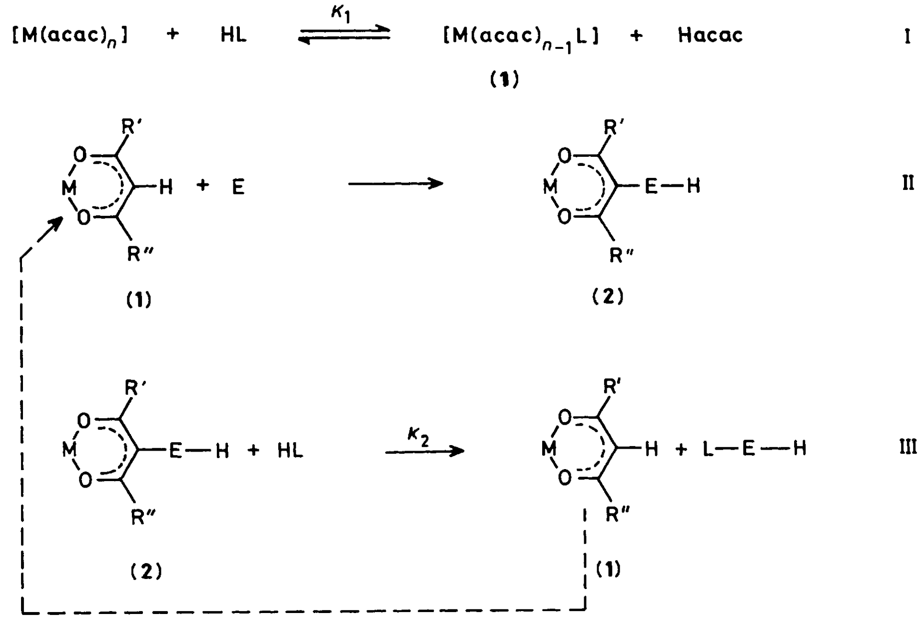
Step I is an equilibration reaction which generates *in situ* the actual catalyst. Step II represents the activation stage in which a new carbon–carbon bond is formed, and step III is a ligand-substitution reaction which regenerates the catalyst and liberates the organic adduct. The results reported herein can be discussed in the light of these individual steps of the proposed mechanism.

Step I: *Ligand Exchange.*—Ligand exchange reactions in metal acetylacetonate complexes are known to proceed through successive stages which involve mixed complexes of the type [M(acac)$_{n-m}$L$_m$] (L = β-carbonylenolate), whose relative concentrations at equilibrium are a function of the particular system considered.[14]

The indicated occurrence of only one ligand exchange (Scheme 1) does not exclude that more substituted species may also be involved, but it simply points out that *one* substitution step is sufficient to generate the metal catalyst.

In spite of the rather scattered thermodynamic and kinetic parameters available in the literature (in particular, no K_1 values in $\mathrm{CDCl_3}$ are available) some insight into the factors affecting the position of equilibrium I can be gained from the following observations.

For the copper(II) complexes, the co-ordinating affinity of the β-dicarbonyls in benzene decreases in the order dibenzoylmethane > acetylacetone > benzoylacetone ≫ ethyl acetoacetate > methyl acetoacetate, with a K_1 value of 7.8×10^{-3} for the benzoylacetone–ethyl acetoacetate exchange.[15] Moreover, it can be easily shown that the K_1 values are related to the stability of the complexes and to the acidity of the β-dicarbonyls, by the relation $K_1 = K_{\mathrm{ML}}K_{\mathrm{HL}}/K_{\mathrm{M(acac)}}K_{\mathrm{Hacac}}$, where K_{ML} and $K_{\mathrm{M(acac)}}$ are the stability constants of complexes (**1**) and [M(acac)$_n$] for the first ligand dissociation, and K_{HL} and K_{Hacac} are the acid constants of the corresponding β-dicarbonyls.



Scheme 1. Stoicheiometric mechanism for the metal-catalysed addition reaction of β-dicarbonyls to electrophiles

Comparison of the available data for the stability constants of acetylacetonate and ethyl acetoacetate complexes indicates that the values of the stability constants of Ni^{II} and Zn^{II} complexes maintain the same order of magnitude on passing from β-diketonate to β-ketoesterate ligands.[16–18] In the light of the Irving-Williams series,[19] this observed substantial invariancy should hold for all M^{II} metals of the first row and to a first approximation for all considered metals.

One important conclusion is that the K_1 values should mainly depend on the acidity of HL divided by that of Hacac, this ratio being 10^{-1} for the couple methyl acetoacetate/acetylacetone in water.[20] As a consequence, in the experimental conditions employed $\{[HL]_0/[M(acac)_n] \geqslant 100\}$ substantial amounts of catalyst (**1**) are expected to be formed *in situ* with all investigated complexes. Therefore, the great difference in the catalytic activity of the various metal centres has to be due to the kinetics of step I and/or to features of steps II and III.

It is convenient to point out, at this stage of the discussion, that acetylacetonate complexes of Pd^{II},[21] Cr^{III},[22] and Al^{III} [23] are very inert towards ligand exchange, so that, at 20 °C, equilibrium I cannot be established and the real catalyst cannot be produced. Their complete inactivity as catalysts is therefore attributable, at least, to the non-occurrence of step I and, as a consequence, these complexes will not be discussed further.

Step II: *Carbon–Carbon Bond Formation.*—This represents the crucial catalytic step in which a new carbon–carbon bond is formed. No evidence of the reverse reaction has ever been observed, thus indicating that step II is thermodynamically very favoured. An important consequence of this observed irreversibility is that, independently of the K_1 and K_2 values, the conversion to the L–E–H product has to be complete.

The rate of step II was specifically studied in the reaction of $[Cu(acac)_2]$ with C_2N_2, in CH_2Cl_2.[24] The addition–insertion reaction of cyanogen to the intercarbonylic methine group was found to be much slower than ligand exchange reactions in $[Cu(acac)_2]$, so that it was established as the rate-determining step in the addition of acetylacetone to cyanogen catalysed by $[Cu(acac)_2]$.[25]

In addition to these important kinetic findings, only scattered 'preparative' information is available on the rate of the attack of the metallo-organic nucleophile to the electrophiles investigated so far. Thus benzoyl cyanide[11,26] requires more severe conditions than cyanogen,[27] and particularly severe when Michael electrophiles are employed.[3]

Two intimate mechanisms are envisaged for step II (Scheme 2).* When Michael (or Michael-like) acceptors are involved, the direct attack of the methine carbon atom on the relevant electrophilic site is expected to be kinetically determined.[5,13] No ring opening appears to be needed for the activation of the electrophile [mechanism (i)]. On the contrary, when 'basic' electrophiles such as nitriles are involved, the availability of a free co-ordination site at the metal centre has to play an important role in enhancing the electrophilic character of the $-C{\equiv}N$ carbon atom [mechanism (ii)].[28] This proposed co-ordination is consistent, for example, with the following observations: (*i*) the reactivity order of nucleophilic attack to the CO and CN groups of benzoyl cyanide is reversed in the presence of $[Ni(acac)_2]$ catalyst;[11] (*ii*) metal catalysis causes $CH_2(CN)_2$ to behave as an electrophile *via* the CN carbon atom rather than as a nucleophile *via* the methylene group.[12] Moreover, nucleophilic attack of thallium(I) acetylacetonate on the co-ordinated benzonitrile of *trans*-bis(benzonitrile)dichloroplatinum(II) has been reported.[29]

However, owing to the expected low basicity of the *sp* lone pair of $CCl_3C{\equiv}N$, we feel that the interaction of the nitrile with the various metal centres here discussed may not be effective *in discriminating* the rates of step II as far as the specific electrophilic activation of the CN group is concerned. If this is true, the crux of the problem (*i.e.* discriminating ability) lies in the different electronic densities which are accumulated at the methine carbon atom, as the direct consequence of the degree of ionic character of the metal–enolate bonds. Thus, the higher is the charge transfer from the *anionic* ligand to the metal ion, the lower is the electron density at the nucleophilic site.

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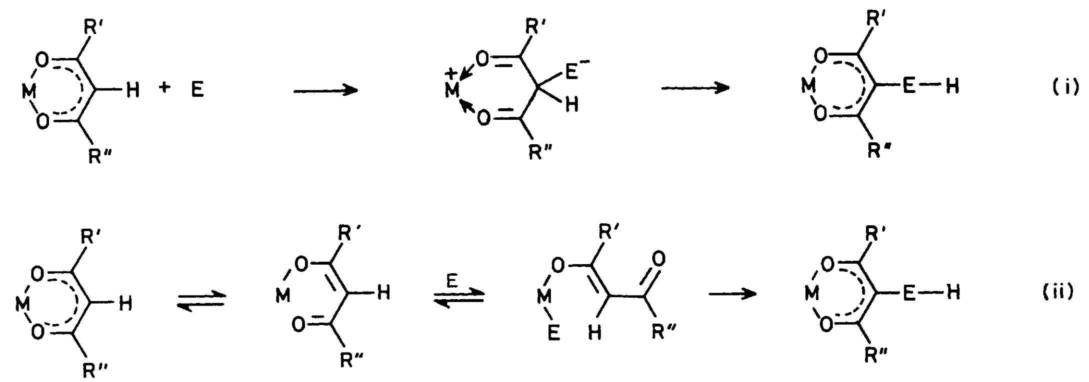
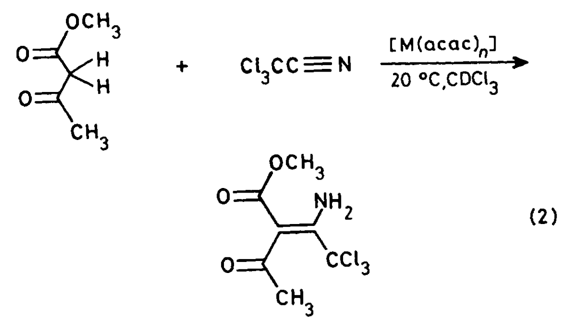
* An alternative mechanism involving metal–carbon bonded intermediates seems less likely owing to the very low tendency of these metal centres to exhibit such a bonding mode (S. Kawaguchi, *Coord. Chem. Rev.*, 1986, **70**, 51).



Scheme 2. Intimate alternative mechanisms for step II

Table. Catalytic efficiency of metal acetylacetonate complexes in reaction (2)[a]



(2)

Time (h)	24	6	1	1	1		
[Catalyst]	1	1	1	0.5	0.1	T.n.[b]	$\nu(C\cdots O)$[c]
[Zn(acac)$_2$]	98	98	98	98	95	950	1 592[d]
[Co(acac)$_2$]	98	98	98	98	95	950	1 588
[Mn(acac)$_2$]	98	98	98	98	55	550	1 605
[Mn(acac)$_3$]	98	98	60			60	1 588
[Ni(acac)$_2$]	93	82				14	1 590
[Cu(acac)$_2$]	75					3	1 580
[Fe(acac)$_2$]	25					1	1 580
[Fe(acac)$_3$]	25					1	1 565
[Al(acac)$_3$]	0					0	*e*
[Cr(acac)$_3$]	0					0	*e*
[Pd(acac)$_2$]	0					0	*e*
No catalyst	0					0	

[a] [Methyl acetoacetate] = 3.0 mol dm^{-3}, [$Cl_3CC\equiv N$] = 3.6 mol dm^{-3}; catalyst concentrations and yields (±2%) are mol% with respect to methyl acetoacetate. [b] Approximate turnover number (mol/mol) after 1 h. [c] Na(acac): $\nu(C\cdots O)$ = 1 620 cm^{-1} (J. P. Dismukes, L. H. Jones, and J. C. Bailar, jun., *J. Phys. Chem.*, 1961, **65**, 792). [d] From K. Nakamoto, P. J. McCarthy, A. Ruby, and A. E. Martell, *J. Am. Chem. Soc.*, 1961, **83**, 1272. [e] The $\nu(C\cdots O)$ values for [Al(acac)$_3$] (1 585 cm^{-1}), [Cr(acac)$_3$] (1 570 cm^{-1}), and [Pd(acac)$_2$] (1 570 cm^{-1}; see footnote *d*) are not quoted with the others because these complexes are inert towards ligand exchange (see text).

A way of testing this mechanistic conclusion would be a quantitative correlation of the observed catalytic activity with a measure of the ionic character of the metal–enolate bonds. If it is accepted that the equilibrium constant relevant to the first acac$^-$ dissociation from [M(acac)$_n$] complexes[16] is a reasonable probe of the metal–ligand bond character, a good correlation can be obtained, as shown in the Figure.

It is seen that, with the exception of Fe^{II}, the logarithm of the turnover number increases with log K_d, *i.e.* with the thermodynamic tendency of the metal centre to release the acetylacetonate ligand. On the other hand, the catalytic activity appears to be roughly related to C$\cdots$O stretching frequencies of the various catalysts (Table), and this is not surprising in view of the proposed correlation between such a spectroscopic parameter and the ionic character of the relevant metal–oxygen bonds.[30]

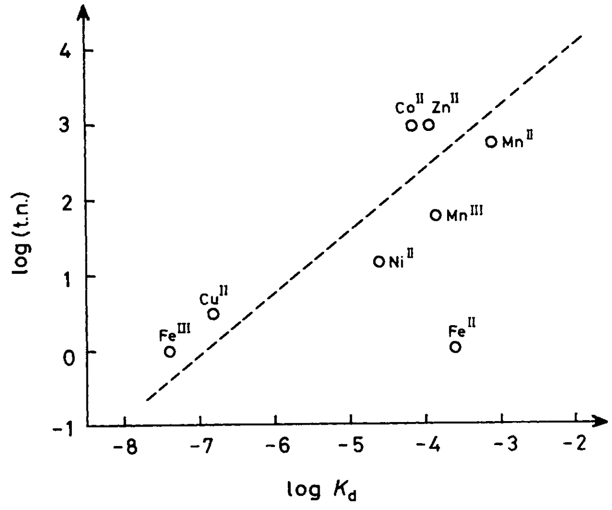


Figure. Plot of catalytic activity (log of turnover number) *versus* dissociation constants (log K_d) of the various metal acetylacetonate complexes for the reaction $[M(acac)_n] \rightleftharpoons [M(acac)_{n-1}]^+ + acac^-$. I = 0 mol dm^{-3}, 25 °C: Zn^{II}, −3.94; Co^{II}, −4.14; Mn^{II}, −3.09; Mn^{III}, −3.86 (I = 0.2 mol dm^{-3}); Ni^{II}, −4.60; Cu^{II}, −6.80; Fe^{II}, −3.60 (30 °C); Fe^{III}, −7.40 (30 °C)

Finally, it should be pointed out that the observed relationship between the rate of the overall catalytic process and a particular thermodynamic property expected to affect only the C–C bond-forming step suggests that the ligand exchange steps should be relatively fast.

Step III: *Ligand Exchange.*—In this ligand exchange step the organic adduct is displaced (with protonation) from the metal centre by the reacting β-dicarbonyl and the catalyst is renewed.

This exchange has been studied, at room temperature, for M = Cu, HL = acetylacetone, and L–E–H = 3-acetyl-2-amino-4-oxo-2-pentenenitrile (*i.e.* its adduct with C_2N_2) in CH_2Cl_2.[24] The reaction is fast (half-life *ca.* 5 min) and the value of the equilibrium constant K_2 is 1.2.

This last result would suggest that the functionalised L–E–H ligand has co-ordinating affinity similar to that of the parent β-dicarbonyl. Indirect support for this stems from the observation that hydrogen substitution by phenyl at the central carbon of acetylacetone affects the values of the formation constants of bivalent Co, Ni, Cu, and Zn complexes very little.[31]

As to the kinetics of steps I and III, the mechanism of ligand exchange reactions in metal β-carbonylenolate complexes generally implies preliminary ring opening followed by (*i*) co-ordination to the metal of external β-dicarbonyl in its enol form, (*ii*) proton transfer to the leaving ligand, and (*iii*) metal–ring closure. According to this and to our proposal for the intimate mechanism of step II, both the ligand exchange steps and the C–C bond-forming step should involve similar preliminary ring-opening processes.

The rate of this process has only been determined, to our knowledge, for [Fe(acac)$_3$];[32] however, some insight into the low limiting rate of the ligand exchange steps can be gained from mechanistic or catalytic studies (Cu^{II}, Zn^{II}),[24,35] and from extensive electrochemical investigations (Fe^{II}, Ni^{II}, Mn^{III}, Co^{II}).[34–36] These last, in particular, display a high ligand lability in solution to give very reactive co-ordinatively unsaturated metal complexes. The whole of this information clearly confirms that the metal catalysts considered here undergo relatively fast ligand exchange reaction (*i.e.* fast ring opening) at room temperature.

Conclusions

The source of the discriminating ability of the various metal centres lies in the 'microstep' in which the co-ordinated nitrile interacts with the methine group of the β-carbonylenolate moiety to give the new C–C bond. As a consequence of this, the overall reactivity of the system strongly depends, as already found, on the particular couple β-dicarbonyl/nitrile,[4,11,12] and, as shown here, on the nature of the metal catalyst.

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