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Preliminary communication

ENOLATE-CATION ASSOCIATION AFFECTS REGIOSELECTIVITY OF NUCLEOPHILE REACTIONS WITH ORGANOIRON COMPLEXES

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Summary

It has been found that a considerable degree of regiochemical control may be achieved during addition of stable enolate nucleophiles to tricarbonyl(cyclohexadienyl)iron complexes of general structure I by changing the enolate countercation. The results indicate an interplay between steric, coulombic and frontier orbital controlling factors during the bond-forming reaction.

Tricarbonyl(cyclohexadienyl)iron complexes of general structure I in our hands are currently proving to show considerable promise as precursors for the synthesis of steroids [1], trichothecenes [2], aspidosperma alkaloids [3] and a range of spirocyclic compounds [4]. Since all of these synthetic endeavours are dependent upon the addition of nucleophiles at the substituted C(1) terminus of the dienyl ligand, to generate complexes of type II, which may be converted to useful 4,4-disubstituted cyclohexenones [5], it is essential that we begin to understand the factors which control the position of nucleophile attack, so that we can obtain the maximum yield of II with minimum formation of complexes of type III, resulting from nucleophile addition to the C(5) terminus. Whilst the dienyl complex Ia reacts regiospecifically in the desired mode with a wide range of stabilised enolate nucleophiles [6], we have found that mixtures of II and III are produced when the 1-substituent is larger than methyl [7]. Despite the availability of a considerable amount of kinetic information about reactions of simple tricarbonylcyclohexadienyliron complexes with nucleophiles [8], the factors controlling these reactions have not been delineated. Since both ^{13}C NMR data [9] and molecular orbital calculations [10] indicate that for the parent complex IV, C(2) and C(4) have a greater positive charge than C(1) and C(5), we might have expected that if nucleophile addition were under charge control, then reaction would occur at the former posi-

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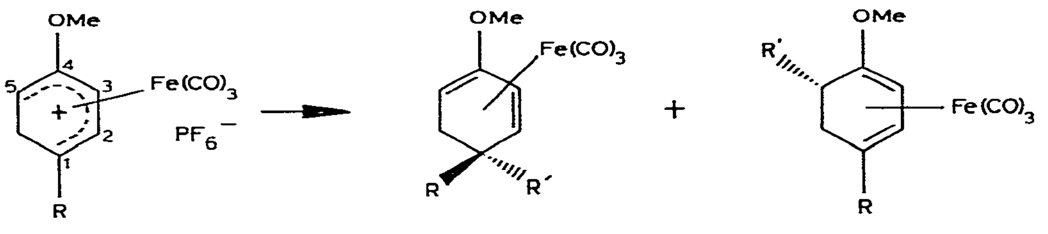
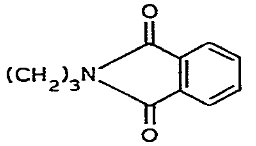


(II) (III)

(Ia, R = Me ;
Ib, R = Et ;
Ic, R = $(CH_2)_2CO_2Me$;
Id, R =



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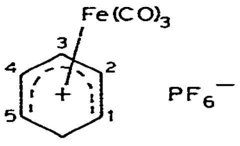
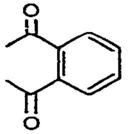


(IV)

(a, R = Me, R′ = Various ;
b, R = Et, R′ = $CH(CO_2Me)_2$;
c, R = Et, R′ = $CH(COMe)CO_2Me$;
d, R = Et, R′ = $CH(CN)_2$;
e, R = $(CH_2)_2CO_2Me$, R′ = $CH(CO_2Me)_2$;
f, R = $(CH_2)_2CO_2Me$, R′ = $CH(COMe)CO_2Me$;
g, R = $(CH_2)_2CO_2Me$, R′ = $CH(CN)_2$;
h, R = $(CH_2)_3NPhth$, R′ = $CH(CO_2Me)_2$;
i, R = $(CH_2)_3NPhth$, R′ = $CH(COMe)CO_2Me$
j, R = $(CH_2)_3NPhth$, R′ = $CH(CN)_2$;
Phth =



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tions. The fact that this particular complex reacts with nucleophiles entirely at the dienyl termini appears to indicate that the reaction is most likely predominantly under frontier orbital control. Unfortunately, the exact nature of the lowest unoccupied molecular orbital (LUMO) of the complex, probably the most important orbital of all, is unknown [11]. With unsymmetrical complexes of type I, we have felt for some time that the observed regioselectivity is the result of a charge controlling effect superimposed on the frontier orbital effect, which differentiates the two termini, and this is supported by ^{13}C NMR spectra [9].

We initially undertook the studies described in this paper in order to try and obtain improved regiocontrol in the reactions of complexes I. Whilst there are a number of conceivable ways to achieve this, we chose to investigate how enolate nucleophiles could be modified to alter regioselectivity in their reactions with complexes already at hand from previous synthetic studies [3,4]. Thus, complexes Ib, Ic and Id were treated with the lithium, sodium and potassium enolates of dimethylmalonate, methyl acetoacetate and malononitrile, under identical conditions. The ratios of the products II/III, readily obtained from the integrated ^1H NMR spectra of the mixtures, are summarised in Table 1. The results obtained are interesting and unexpected. It is immediately apparent that there is a gradual increase in this ratio on changing from lithium through sodium to potassium enolates of dimethyl malonate and methyl acetoacetate, whilst the countercation has a negligible effect with malononitrile enolates. It is well known [12] that the degree of association

TABLE 1

DEPENDENCE OF REGIOISOMER RATIOS ON NUCLEOPHILE AND COUNTERACTION[a]

Dienyl complex	Enolate nucleophile	Ratio[b] of II/III with cation indicated			Products
		Li^+	Na^+	K^+	
Ib	$\bar{C}H(CO_2Me)_2$	3.0	4.6	5.6	IIb + IIIb
Ic	$\bar{C}H(CO_2Me)_2$	2.1	3.8	5.7	IIe + IIIe
Ic	$\bar{C}H(CO_2Me)_2$-18-C-6	—	5.6	—	IIe + IIIe
Id	$\bar{C}H(CO_2Me)_2$	1.5	2.8	4.6	IIh + IIIh
Id	$\bar{C}H(CO_2Me)_2$-18-C-6	—	4.2	—	IIh + IIIh
Ic	$\bar{C}H(CN)_2$	4.3	5.1	4.8	IIg + IIIg
Id	$\bar{C}H(CN)_2$	3.3	3.3	3.3	IIj + IIIj
Ib	$\bar{C}H(COMe)CO_2Me$	—	1.2	2.0	IIc + IIIc
Id	$\bar{C}H(COMe)CO_2Me$	n.r.	0.5	1.2	IIi + IIIi

[a] Reactions carried out in THF at 0°C. [b] Determined by ^1H NMR spectra of product mixtures.

between metal cation and oxyanions follows the order $Li^+ > Na^+ > K^+$, so our results indicate that a "naked" enolate has a greater preference for attack at the dienyl terminus with higher positive charge than does the associated enolate. This is supported by the observation that dimethyl sodiomalonate in the presence of 18-crown-6 gives the same ratio of II/III as does dimethyl potassiomalonate. The negligible effect and better regioselectivity with malono nitrile derivatives is consistent with the inability of the linear nitrile groups to chelate the metal cation.

In the light of these results we propose that nucleophile addition to unsymmetrical dienyl complexes, whilst apparently under overall frontier orbital control, is subject to the following more subtle effects which influence the selectivity observed in the reaction: (a) steric demand of the substituents, (b) a charge, or coulombic effect and, less obviously (c) a "secondary" orbital controlling effect. The steric effect is self-explanatory, on comparing the reactivity of Ia, Ib etc., with the same nucleophile. It is evident (see above) that p—π conjugation of the methoxy substituent in complexes I, involving the bonding orbitals ψ_1 and ψ_2 (Fig. 1). leads to a build-up of electron density at C(5) compared to C(1). A nucleophile which is susceptible mainly to charge (coulombic) interaction would then prefer to attack at C(1), as observed for the non-associated enolates, which are expected to carry a full negative charge.

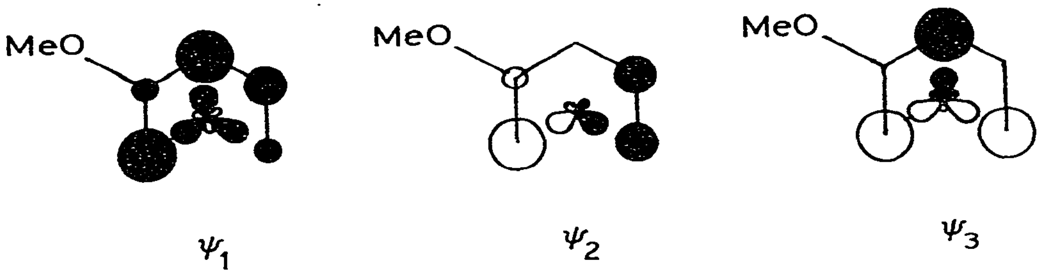

Fig. 1. Bonding MO's for tricarbonyl(2-methoxypentadienyl)iron complexes. (See ref. 5 for explanation of orbital diagrams.)

When the negative charge is reduced by coordination to a metal cation (Li^+) a more subtle effect comes into play. The most plausible explanation is that on coordination the nucleophile HOMO is lowered in energy [13], becoming closer to the dienyl-$Fe(CO)_3$ LUMO. Whilst the coulombic effect still dominates in most cases, the increased addition at C(5) probably reflects the importance of frontier orbital interaction [14]. In fact, the observed chemistry leads us to suspect that the LUMO is composed of the dienyl ϕ_2 in an antibonding combination with iron hybrid orbitals, shown in Fig. 2. This combination for the methoxy-substituted complexes would have a larger coefficient at C(5) than at C(1), resulting in an orbital interaction which would favour nucleophile addition at C(5). It will be necessary to await rigorous theoretical investigation to confirm these proposals, but we anticipate that the experimental facts will be of considerable aid for such studies.

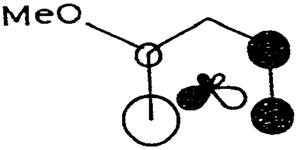

Fig. 2. Possible LUMO for tricarbonyl(2-methoxypentadienyl)iron complexes.

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