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SOME METALATION AND METHOXYMERCURATION REACTIONS IN FERROCENE SERIES

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Since ferrocene is quite vulnerable to oxidation yielding the ferricenium ion, its reactivity towards electrophilic reagents can only be tested by reliable kinetic studies for a relatively limited number of reactions. For example, halogenation by the familiar electrophilic reagents cannot be directly effected [1]. Likewise, the acid-catalyzed nature [2] of such an oxidation prevents the study of other reactions requiring even moderately strong acidic media, unless the reaction with the electrophilic reagent is sufficiently rapid. In the present report we wish to consider two types of reactions with electrophiles: ring substitution and addition to a vinylic side-chain.

RING SUBSTITUTION

In recent years a few electrophilic ring substitutions have received some attention in kinetic studies. They include hydrogen isotope exchange [3], protodesilylation [4, 5], protodeboronation [4], and mercuration [6].

Due to the peculiar aromatic-like structure [1] of ferrocenes, their reactivity in these reactions appears to be very high. Comparison with the related benzenoid compounds by the closest available parent compounds displays rate factors of 5 to 9 orders of magnitude, as shown in Table 1. Such data can be taken to reflect the highly π-electron excessive character of the Cp rings. It has also been suggested that the metal atom may have a role in determining the high reactivity of the system by preliminary metal—electrophile interaction [10]. This is one of the aspects of the reaction mechanism for which more physical organic work is required.

We wish to report on some recent results obtained by mercuration with mercuric acetate and thalliation with thallium(III) acetate.

Mercuration and thalliation of ferrocene compounds

Experimental methods

The mercuration kinetics were carried out under pseudo-first order conditions, by using a large excess of the ferrocene compound, i.e., 3×10^{-3}—

TABLE 1

Reactivity of the ferrocene system (Fc) relative to the benzene system (Bz)

Reaction	Substrate used for comparison	k_{Fc}/k_{Bz}
H/D exchange [a]	Ferrocene vs. toluene (H_0, −1.38)	10^6
Protodesilylation [b]	R—SiMe3, ferrocene vs. benzene derv.	1.7×10^5
Protodeboronation [c]	R—B(OH)$_2$, ferrocene vs. benzene derv.	7×10^6
Mercuration [d]	Ferrocene vs. benzene	10^9

[a] Data from ref. 3.

[b] In 0.12 M HCl (1:4 v/v) H_2O—MeOH mixture [4]; in 0.126 M HCl (2:5 v/v) H_2O—MeOH mixture [7].

[c] In 20% H_2SO_4 (1:2 v/v) H_2O—EtOH mixture [4]; data extrapolated at 20.1% H_2SO_4 from ref. 8.

[d] With $Hg(OAc)_2$ in AcOH [6, 9].

1×10^{-2} M, with respect to mercuric acetate (~ 2×10^{-4} M). The reaction rate was measured spectrophotometrically with a Beckman DB-GT self-recording spectrophotometer, equipped with a thermostatic bath. The observed increase in absorbance was recorded at wavelengths chosen in such a way as to correspond to the minimum absorption of the starting substrate, i.e., 302, 308, and 312 nm for ferrocene, ethylferrocene, and 1,1′-diethylferrocene, respectively.

The thalliation of ferrocene was effected by the dropwise addition of a solution of thallium(III) acetate (0.9 g, 0.0024 mole) in anhydrous methanol (80 ml) to a stirred solution of the substrate (9.3 g, 0.050 mole) in 120 ml of dry benzene, over a ½ h period. After additional 2 h stirring, the solvent was extracted from the resulting brown solid residue with petroleum ether (b.p. 40—70°C) and, finally, the crude product was recrystallized from a dichloromethane—petroleum ether mixture. The NMR spectrum of the product shows signals in the region typical of a monosubstituted ferrocene (~45).

Unlike mercuration, thalliation of ferrocene is not practicable in acetic acid because the substrate is oxidized to the ferricenium ion quite rapidly. In methanol solution both product analysis (NMR, see above) and the rate study could be effected. The electronic spectrum was recorded in the range 270—670 nm and showed no band for the oxidized form in the 620 nm region. The introduction of the $Tl(OAc)_2$ group is accompanied by an absorbance increase in the 295—350 nm region.

The rates of thalliation of the ferrocene compounds were measured by the same method as that of mercuration and at the same wavelengths. Typical kinetic data are reported in Table 2.

Influence of the metalating agent

Second-order rate coefficients (Table 3) were calculated from the observed first-order rate coefficients and were found to be satisfactorily constant over a

TABLE 2

Typical kinetic data for the thalliation of ferrocene at 25.3°C ($k_2 = (4.2 \pm 0.5) \times 10^{-2} M^{-1} s^{-1}$)

Ferrocene $M \times 10^3$	$Tl(OAc)_3$ $M \times 10^4$	$10^4 \times k_{obs}$ (s^{-1})	$10^2 \times k_2$ ($M^{-1} s^{-1}$)
15.30	1.52	6.15	4.0
11.90	1.52	3.80	3.2
9.65	1.52	3.54	3.7
8.40	1.52	3.65	4.4
8.32	1.52	3.89	4.7
7.88	1.52	3.46	4.4
4.82	1.52	2.62	5.4

three-fold variation in the concentration of ferrocene for both reactions (Table 2). The mercurating agent, $Hg(OAc)_2$, in methanol solution was found to be 6.2 times as reactive as the thalliating agent, $Tl(OAc)_3$, at 25.3°C.

Solvent and structure effects

Preliminary rate measurements [6] for the mercuration of ferrocene in acetic acid solution have now been refined and duplicated to yield more accurate values. A mean value of $7.2 \pm 0.3\ M^{-1}\ s^{-1}$ was obtained for the second-order rate constant at 25.3°C. The extension of this work to the reaction in methanol solution, which was required for a comparison with the thalliation reaction (see above), revealed an appreciable solvent effect. The reaction in

TABLE 3

Second-order rate coefficients for the thalliation and mercuration of some ferrocene derivatives, at 25.3°C

Substrate	Reagent	Solvent	k_2 ($M^{-1} s^{-1}$)
Ferrocene	$Hg(OAc)_2$	AcOH	7.2
Ethylferrocene	$Hg(OAc)_2$	AcOH	16.3
1,1′-Diethylferrocene	$Hg(OAc)_2$	AcOH	20.2
Ferrocene	$Hg(OAc)_2$	MeOH	0.25
Ethylferrocene	$Hg(OAc)_2$	MeOH	1.06
1,1′-Diethylferrocene	$Hg(OAc)_2$	MeOH	1.4
Ferrocene	$Tl(OAc)_3$	MeOH	0.04
Ethylferrocene	$Tl(OAc)_3$	MeOH	0.13
1,1′-Diethylferrocene	$Tl(OAc)_3$	MeOH	0.27

acetic acid was found to be 29.8 times as fast as that in methanol. We believe that this effect reflects a difference in the solvating ability of the two solvents toward the mercuric cation (or a polarized precursor), acetic acid being less nucleophilic than methanol and a poorer solvating medium. Solvent effects in these reactions are being given further attention in our Laboratory.

Ethyl substitution gives rise to a relatively small rate increase. 1,1-Diethyl substitution does not appear to be additive in both solvents. For example, in methanol solution while the $k_{\mathrm{Et}}/k_{\mathrm{H}}$ ratio is 4.2, the $k_{1,1\text{-diEt}}/k_{\mathrm{H}}$ ratio is only 5.6. This lack of additivity has already been noted in other cases [11(a)] and may be taken as an indication that a rate-determining iron—electrophile bond formation is not involved in the reaction. In agreement with this view, in the oxidation reaction which implies metal involvement, additivity is indeed observed [11].

It is interesting to note that on going from methanol to acetic acid the reaction selectivity decreases somewhat, the $k_{\mathrm{Et}}/k_{\mathrm{H}}$ ratio dropping from 4.2 to 2.3. This selectivity order is consistent with a less solvated, more reactive mercuric cationic species in the acetic acid solvent.

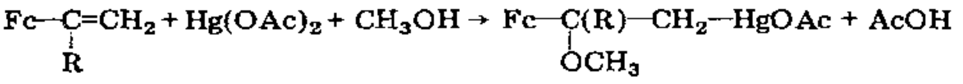
ADDITION TO A VINYLIC SIDE-CHAIN

We have undertaken a study of the electrophilic addition to vinylferrocenes in order to compare benzenoid and metallocene reactivity and obtain information on whether the reaction mechanisms are essentially of the same type or not. In particular, we are currently interested in obtaining information on the following points: (i) influence of the ferrocenyl group on the rate of electrophilic addition; (ii) reaction selectivity with regard to competing ring substitution and (iii) nature of the carbocationic intermediate, especially in connection with the hypothesis that the iron lone pair may stabilize a supposedly "open" carbocation.

We present some results on the methoxymercuration by mercuric acetate in methanol solution. This and related reactions have received attention in recent years in the general field of olefines [12—15] from the mechanistic point of view. The reaction has a wide scope in syntheses.

Experimental methods

In order to prepare the addition product (eqn. 1) mercuric acetate (0.6 g, 0.0038 mole) was slowly mixed with the vinylferrocene (0.8 g, 0.0038 mole



$$\mathrm{Fc{-}\underset{R}{C}{=}CH_2 + Hg(OAc)_2 + CH_3OH \rightarrow Fc{-}\underset{OCH_3}{C}(R){-}CH_2{-}HgOAc + AcOH} \tag{1}$$

$\mathrm{R = H, CH_3}$

for R = H) in anhydrous methanol solution under a nitrogen atmosphere and the resulting solution was stirred for 10 min. The reaction mixture was treated with water and the organomercurial was extracted with dichloromethane. After removal of the unreacted starting material, the solid product showed no vinyl proton signals in the region 4.9—5.2 δ while a complex signal in the region 2 δ appeared (—$HgOCOCH_3$ protons). The structure of the product was proved by reduction with sodium borohydride (0.38 g, 0.010 mole) in 2.5 *M* sodium hydroxide (20 ml). The reaction is expected to yield α-methoxyethylferrocene (MEFc) as a consequence of a reductive cleavage of the C—Hg bond. The product of reduction was recovered by extraction of the reaction solution with CCl_4 and obtained by standard procedures as an oil, which was purified by column chromatography (alumina) on elution with petroleum ether, b.p. 40—70°C. The IR and NMR of the appropriate fraction were found to be identical to those of an authentic sample of α-methoxyethylferrocene.

Equation (1) was verified for R=H and CH_3. The reaction kinetics were performed by following the decrease with time in absorbance of the band at 276 nm, which is attributed to the double bond. The apparatus was the same as that used for the ring metalation reactions (see above). Strictly second-order kinetics were observed.

Addition reactivity

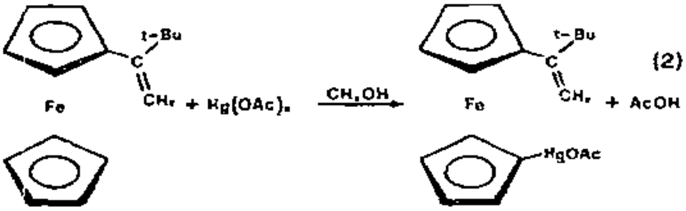
The second-order rate constants for R=H and CH_3 (see eqn. 1) were found to be $(2.30 \pm 0.35) \times 10^2$ and $(9.3 \pm 1.2) \times 10^2 M^{-1} s^{-1}$, respectively at 25.3°C. Although these values reflect the very high reactivity of the double bond toward the electrophilic mercurating agent, it seems unlikely that the electron-releasing effect of the ferrocenyl group is a major factor. A very high reactivity is also observed, under admittedly not strictly comparable conditions, in the hydroxymercuration of olefines by mercuric perchlorate in aqueous solution [12] and by mercuric acetate in aqueous THF [15]. For example, in the former, cyclohexene exhibited a rate constant equal to $(5 \pm 1) \times 10^3 M^{-1}s^{-1}$ and in the latter, styrene proved to be less reactive than cyclohexene by a factor of 0.28. Thus, a phenyl group appeared to be deactivating although an unequivocal interpretation has not been provided [15]. Furthermore, these reactions appeared to be only moderately selective [13] since a *p*-methoxy group in the styrene series showed a rate increase by only a factor of 10.

As to the influence of the CH_3 group (R = CH_3 in eqn. 1; $k_{CH_3}/k_H = 4$), it appears to be in the same order as that found for the hydroxymercuration of alkenes [15] and consequently, to have similar implications on the distribution of the positive charge in the reaction intermediate [12—15].

While a more accurate assessment of the above structural effects requires further quantitative work, no exceptional rate-enhancing factor due to the structure of the ferrocenyl group would seem to emerge from the present data.

The competing ring substitution

In agreement with the high relative rate of side-chain addition (k_2, 2.3×10^2 M^{-1} s^{-1} for vinyl ferrocene, R = H) as compared with ring mercuration (k_2, 0.25 M^{-1} s^{-1} for ferrocene), no evidence was found for ring mercuration with R = H and CH_3 (eqn. 1). In contrast, with R = *t*-Bu, the reaction was diverted essentially to ring substitution (eqn. 2).



In this case, the NMR spectrum still exhibits the expected signals for the vinyl group protons as obtained with α-*t*-butylvinylferrocene (5.0 δ region) and, moreover, has the characteristic features of a 1,1′-disubstituted ferrocene (absence of the singlet expected for a non-substituted Cp ring) and of an acetoxymercury group (broad signals in the 1.0 δ region). Furthermore, on treating α-*t*-butylvinylferrocene with $Hg(OAc)_2$ in methanol solution, the band attributed to the double bond (λ_{max}, 276 nm) was found to remain unchanged over a sufficiently long period of time.

The above phenomenon can essentially be envisaged as the result of a steric effect [15]. However, establishing the mechanism of this phenomenon by which such an effect operates requires further study.

CONCLUDING REMARKS

In the ring substitution of ferrocene lack of additivity of the effects of the 1,1′-diethyl groups would discourage the hypothesis [10] of a primary interaction of the electron-donating iron with the electrophilic mercury. Although further evidence is needed for the ring mercuration reaction, it is worth noting that definite evidence in contrast with such a hypothesis was found for ring substitutions involving proton as the electrophilic reagent [4].

The available results show that the reactivity of electrophilic addition to the unsaturated side-chain of vinylferrocene does not seem to benefit from a particularly strong rate-enhancing influence due to the special structure of the adjacent ferrocenyl group. This may imply that the addition mechanism involves an intermediate with a considerable mercurinium ion character. Evidence for the tendency to form an intermediate of this kind is supported by recent observations [15]. Although special rate-enhancing effects of the ferrocenyl group other than π—π conjugation of the Cp ring with the adjacent "open" carbonium ion could be envisaged as due to an interaction between the electron-donating iron and the electron-deficient α-carbon [16], delocalization of the positive charge from the latter carbon in mercurinium ion formation would effectively reduce the importance of both π—π conjugation and iron—carbonium ion interaction.

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