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Author's Review

Metallocenes, Strong Electron Donors. A Mechanistic Review

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The great stability of α-metallocenyl carbocations is well known. There is general agreement that the electrons from the region between the two cyclopentadienyl rings are most effective in accounting for this stability. Electron transport may involve conjugation with the π-system of the pentadienyl rings or direct participation of metal electrons. The study of the secondary α-deuterium kinetic isotope effect (α-D KIE) can help, under certain circumstances, in solving the problem.

We have recently determined the α-D KIEs in acetolysis and formolysis of dideuterioferrocenylmethyl benzoate and found that, in the presence of $LiClO_4$ (which prevents reversion from the solvent-separated to contact ion-pairs), the ratios k_H/k_D at 25 °C are 1.53 ± 0.02 (acetolysis) and 1.48 ± 0.03 (formolysis). The solvolyses exhibited a special salt effect, indicating the presence of solvent-separated ion-pairs and the return to contact ion-pairs. The high values of the KIE strongly suggest that both solvolyses are limiting dissociation processes with a carbenium ion-like transition state, which is stabilized mainly by conjugation with the π-system of the pentadienyl rings.

For both solvolyses, the ratios of Arrhenius pre-exponential factors A_H / A_D are significantly less than unity; whether tunnelling plays a role in causing this effect is discussed.

Consistent with a dissociative (S_N1) mechanism, in similar solvolyses a general tendency has been observed for faster reactions in solvents of higher ionizing power. However, we observed even a somewhat lower solvolysis rate in formic acid than in acetic acid, though the ionizing power of formic acid is much higher than that of acetic acid. This phenomenon is, at least partially, explained by the reaction being of the protonated ester, or protonated contact ion pair, so that the neutral leaving group becomes virtually insensitive to changes in solvent ionizing power. In addition, there is evidence that has been recently published, that the cationic charge of the ferrocenylmethylcarbenium ion is effectively spread through the ferrocenyl moiety.

Partial oxidation of iron(II) in certain solvents is also possible. The mentioned charge dispersion is in agreement with recent computations based on the density functional theory.

The antitumour activity of metallocenes is described. This activity is being seen as due to strong electron donation of these complexes. The ferrocenes activity as chiral nucleophile catalysts is described, which can mediate kinetic resolutions of chiral secondary alcohols, yielding large enantiomeric excess. This activity is also related to the ferrocene electron donation ability, enabling temporary binding of the chiral catalyst. A short survey of the use of ferrocenes for molecular recognition is given, as well as a short survey on metal-metal interactions in linked metallocenes. Activity of metallocene derivatives as catalysts for polymers is also briefly described.

INTRODUCTION

Metal π-Complexes

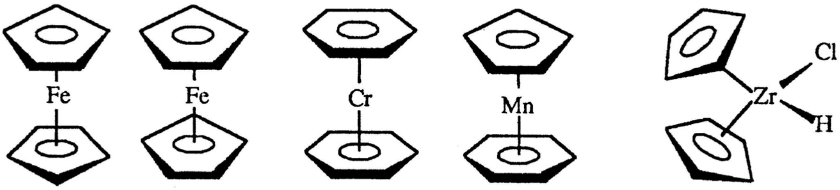
For many years it was puzzling that metal atoms, which were not considered good Lewis acids, could form adducts with CO, considered to be a poor donor toward most Lewis acids. An example is the chromiumhexacarbonyl, $Cr(CO)_6$. On the other hand it was stressed that chromium, having 24 electrons, by accepting 6 × 2 electrons from 6 CO molecules, will fill its orbitals to a total of 36 electrons, which is the electron configuration of krypton. The LCAO approximation method (linear combination of atomic orbitals) helped to explain the stability of these adducts as being due to a two-way acid base interaction between the metal and CO: the metal synergically interacts with CO, acting as an acid and a base, while CO simultaneously behaves as a donor and acceptor. In 1955 Ernst Otto Fisher, University of Munich, showed that an increase of the number of chromium electrons to 36 can be achieved by three π-electron pairs of benzene, like, *e.g.*, in benzene chromium tricarbonyl, $(C_6H_6)Cr(CO)_3$. Cyclopentadienyl, $C_5H_5^-$, has also been known to form compounds with metal atoms.

Ferrocene was discovered in 1951,[1] and an extensive exploration of metallocene chemistry followed.[2–4] X-ray studies, as well as a variety of other physical and chemical evidence, showed that ferrocene has a »sandwich« structure. For their pioneering work on the chemistry of metallocenes, Ernst Otto Fischer, Technische Universität München, and Geoffrey Wilkinson (Imperial College London) shared the Nobel Prize in 1973. Ferrocene was shown to be bis(pentahaptocyclopentadienyl) iron, $(\eta^5\text{-}C_5H_5)_2$ Fe. (Instead of η some authors use h, standing for hapto, from the Greek word haptein, meaning to fasten). Thus, the $C_5H_5^-$ ligand is said to be a pentahaptocyclopentadienyl group.

There are basically three types of complexes formed by $\eta^5\text{-}C_6H_5^-$, $\eta^6\text{-}C_6H_6$, and related molecules[5] (Figure 1):

(A) $(\pi\text{-R})_2M$ are symetrical »sandwich« type complexes represented by ferrocene (1a) and (1b) (staggered and eclipsed structures, respectively), dibenzenechromium (2), and $(\eta^5$-cyclopentadienyl)$(\eta^6$-benzene)manganese (3);

(B) $(\eta^5\text{-}C_6H_5)_2ML_x$ are bent metallocenes where L represents some other ligands such as H^-, R^-, halide, olefin, or NO. An example is (4).



(1a) (1b) 2 3 4

Figure 1.

The »sandwich« structure of ferrocene and its extraordinary thermal stability (up to 500 °C) contributed to the extensive and still lively research in the field.

As already mentioned, stable organometalic compounds of transition metals will have a total of 18 valence electrons around the metal, *i.e.* they will have the »effective atomic number« (EAN) of the next higher inert gas.[6] There are exceptions. Molecules having only 16 valence electrons can be just as stable as 18 electron molecules of the same metal.

BONDING IN $[\eta^5\text{-}(C_5H_5)_2Fe]$ COMPLEXES

Cyclopentadiene is a weak acid (p$K_a \approx 20$) and reacts with various bases giving salts. Because of the stability of the $C_5H_5^-$ anion, the cyclopentadienyl-metal compounds were treated as containing $C_5H_5^-$ anion and metal cation. Thus, ferrocene is commonly regarded as composed of Fe^{2+} cation and 2 $C_5H_5^-$ anions. The Fe^{2+} in ferrocene has 3 d electron pairs ($3d^6$ configuration), and pentadienyls have 3 π pairs per one (η^5-$C_5H_5^-$), which makes a total of (3 + 2 × 3) = 9 pairs, or 18 valence electrons. This is also the EAN of the next higher inert gas krypton and explains the extremely high stability of ferrocene (melting point 174 °C; boiling point 249 °C).

The nature of bonding between a transition metal and an unsaturated ring is well understood, but the picture can still be improved in quantitative sense.[7–9] It appears that bonding does not depend critically on whether the rotational orientation of the pentadienyl rings in $(\eta^5\text{-}C_2H_5)_2M$ is staggered (Figure 1, configuration 1a), or eclipsed (Figure 1, configuration 1b).[10] In any case, the barrier to rotation is low (about 8–20 kJ mol^{-1}); nevertheless, it appears that the eclipsed configuration is more stable.[11–13] In condensed phases, especially crystals, where there are intermolecular energies of the same or greater magnitude than the barrier, either configuration may be found.[10]

The overlap of the e_1-type d orbitals (d_{xz} and d_{yz}) of iron and the e_1-type ring π orbitals is excellent.[10]

STABILITY OF α-METALLOCENYL CARBOCATIONS

Metallocenes undergo most of the typical aromatic reactions, *e.g.* Friedel-Crafts acylation, sulfonation, *etc.* The Friedel-Crafts acylation occurs 3×10^6 times faster than with benzene.[14]

The great stability of α-metallocenyl carbocations is well known.[15–22] The best demonstration of the electron releasing effect of the ferrocenyl group is the isolation of its stable salts.[23] There is general agreement that electrons from the region between the two cyclopentadienyl rings are most effective in accounting for this stability. The observed rate enhancement due to the ferrocenyl group (Fc), as compared with that of the phenyl group,[24] and the stereospecifity of solvolysis, may be explained either by model A involving conjugation with the π-system[16] or by model B involving metal participation[25–29] (Figure 2). The study of the secondary α-deuterium kinetic isotope effect (α-D KIE) can, under certain circumstances, help in solving the problem.

SECONDARY α-DEUTERIUM KINETIC ISOTOPE EFFECT AND THE STRUCTURE OF FERROCENYLMETHYL CARBOCATION TYPE TRANSITION STATE

The secondary α-D KIE is a powerful tool in elucidation of the mechanism of nucleophilic substitutions. After the first observation of sizable α-D KIE in presumed carbocation processes reported independently by four different groups,[28–33] these effects were used to determine if a mechanism is a dissociative or a synchronous displacement (the $k_H / k_{\alpha\text{-}D}$ ratio in the latter case being arround 1.00).

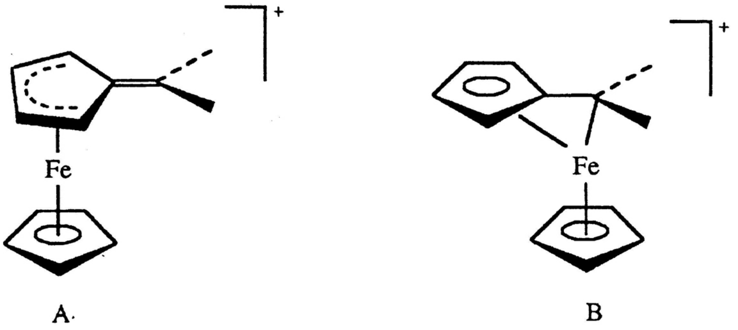


Figure 2. Possible structure of the ferrocenylmethylcarbocation involving conjugation with π-system (A), and involving Fe–C_{exo} bond formation (B). The formation of both structures exhibits very similar values of the entropy of activation (about 30 J mol^{-1} K^{-1}).

The α-D KIE effect on a limiting solvolysis is thought to be principally due to the lowering of the H–C–H out of plane bending force constant, which is expected to accompany the breaking of the –C–X bond. The smaller effect in nucleophilic reactions may arise from a partially compensating gain of a new bending force produced by partial covalent attachement of the nucleophile to carbon. Several review articles on that subject have been published.[34–36]

The S_N2 transition state model can be applied to the reactions involving neighbouring group participation. Participation which involves bridging may not occur simultaneously with the departure of the leaving group so that the transition state can still resemble the reactant. On the other hand, if bridging is pronounced in the transition state, a decrease in magnitude of the α-D KIE is to be expected.[35,37] It has been recently suggested that α-effects are reduced by σ- but not π-bonds.[38,39]

HIGH SECONDARY α-DEUTERIUM KINETIC ISOTOPE EFFECTS FOR THE PRIMARY CARBON-OXYGEN CLEAVAGE IN FORMOLYSIS AND ACETOLYSIS OF DIDEUTERIOFERROCENYLMETHYL BENZOATE

A few years ago we determined[40] the secondary α-deuterium kinetic isotope effect in acetolysis of ferrocenyl-1,1-dideuteriomethyl benzoate at 298 K as $k_H/k_D = 1.50$ (geometric mean = 22.5% per one D). This appears to be one of the largest α-D KIE observed for carbon-oxygen cleavage. The maximum α-D KIE for an oxygen leaving group was found by other investigators[41–44] to be about 22%.

Primary alkyl derivatives normally do not solvolyze by the limiting dissociative mechanism, hence the maximum α-D KIE for the primary derivatives is not known, but calculations[41,44] and experiments[45] suggest that the magnitude of this effect might be larger for the primary derivatives than for the secondary ones.[46] The kinetic and stereochemical evidence has led to the conclusion that the solvolyses of β-ferrocenylalkyl tosylates are dissociative in nature and very nearly »limiting«.[24,27]

As previously pointed out,[48] the rates of solvolyses in various media can be best summarized in terms of the ionizing power and nucleophilicity of the solvent, as suggested by Winstein *et al.*[49] In a limiting solvolysis, the rate depends on the ionizing power rather than on the nucleophilicity of the solvent. Thus, the rates of limiting solvolysis are about the same in solvents of comparable ionizing power but different nucleophilicity. On the other hand, the reactions which proceed by attack of the solvent on carbon with nearly synchronous displacement of a leaving group proceed faster in solvents of greater nucleophilicity. These criteria have led to the conclusion that acetolyses of β-ferrocenylalkyl tosylate are dissociative, nearly »limiting« processes.[24]

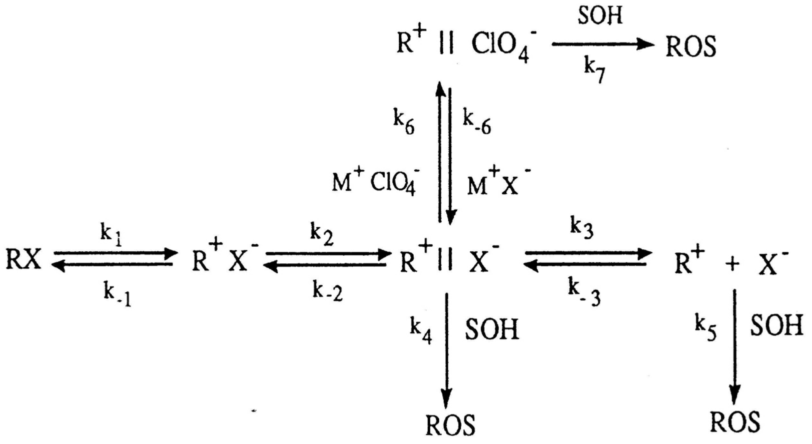
As already mentioned, we determined the secondary α-deuterium kinetic isotope effect in the acetolysis of dideuterioferrocenylmethyl benzoate and found it to be one of the largest observed for carbon-oxygen cleavage (geometric mean = 22.5% per D). The solvolysis exhibited a special salt effect, indicating the presence of solvent-separated ion-pairs and the return to contact ion-pairs. The high value of the α-D KIE strongly suggests that the acetolysis is a limiting dissociation process with a carbenium ion-like transition state stabilized mainly by conjugation with the π-system of the pentadienyl rings. This result was compared with a previously-determined α-D KIE of only 11.4% per D in ethanolysis of dideuterioferrocenylmethyl acetate and benzoate, respectively,[46] where the stabilization of the transition state probably involves some $Fe–C_{exo}$ bond formation. On the other hand, we determined previously[22] the α-D KIE in the solvolysis of ferrocenyl-1,1-dideuteriomethyltrimethylammonium iodide in aqueous solution as k_H/k_D = 1.06 ± 0.04 at 80 °C (about 3% per one D). The small isotope effect supports the transition state model involving participation of electrons localized on the iron atom. The calculated H/D fractionation factors, from valence force fields, are similar for carbon, fluorine and nitrogen leaving atoms.[51] It is therefore reasonable to assume that the limiting α-deuterium isotope effect for a nitrogen leaving group should be similar to that for oxygen, fluorine, or carbon, *i.e.* about 20% per deuterium atom, calculated for a temperature of 80 °C. It should be pointed out that 1,1-dideuterio-2-ferrocenylethyl tosylate solvolyses[24] in acetone-water, at 30 °C, with k_H/k_D = 1.27 (*i.e.* k_H/k_D, calculated per one deuterium atom = 1.14). This isotope effect is compatible with the presence of some neighbouring group participation, as evidenced by comparison with situations in which such participation is known to exist (formolysis of 1,1-dideuterio-2-anisylethyl tosylate[24] gives k_H/k_D of 1.11 per D at 30 °C). A larger iron participation and a smaller isotope effect should be expected for $FcCD_2N(CH_3)_3I$ (Fc = ferrocenyl) than for $Fc\text{-}CH_2CD_2OTs$, because it is known that the stabilizing effect of the ferrocenyl group is larger on α- than on β-carbon. Of course, one should have in mind that the reaction involving a relatively poor leaving group, such as $N(Me)_3$, might involve some nucleophilic attack by solvent molecules, with consequent lessening of the α-D KIE. But, if so, it would remain unclear why the rate of formation of the ferrocenylcarbinol, from 0.05 molar ferrocenylmethyltrimethyl ammonium salt, is practically independent of the hydroxide ion concentration,[52] the rate being the same in water and in 0.2 M aqueous sodium hydroxide.

POSSIBLE CONTRIBUTION OF TUNNELLING TO THE HIGH SECONDARY α-DEUTERIUM KINETIC ISOTOPE EFFECT

The high α-D KIE, both in acetolysis and formolysis, prompted a study of the temperature dependence of the solvolysis rates, and of the α-D KIE, in order to see if tunnelling might be operative.[50] That tunnelling can contribute to secondary isotope effects is supported by model calculations, which predict appreciable tunnel corrections when the bending motions of the non-transferred proton are coupled with the stretching motion of the tranferred proton.[53] Calculations also predict that tunnelling can lead to the same sort of abnormal temperature dependence as observed for primary isotope effects, the ratio of Arrhenius pre-exponential factors A_H/A_D (or A_H/A_T) being significantly less than unity. An experimental example of this behaviour is the reaction of $PhCHTCH_2N(Me)_3^+$ with EtO^-, which gives $A_H/A_T = 0.705 \pm 0.024$.[54] Tunnelling is expected to be diminished when an atom heavier than the proton is transferred, and $(k_H/k_T)_{sec}$ is in fact less when deuterium is transferred than when protium is transferred.[54] One might not expect tunnelling to be important in solvolyses of ferrocenylmethyl esters because oxygen (mass 16) is now the transferred atom. The system appeared ideal to provide a critical test because the isotope effect is large, and it is easier to measure the temperature dependence of a large isotope effect than of a small one.

As already pointed out, the acetolysis and formolysis of dideuterioferrocenylmethyl benzoate exhibit large secondary α-D KIEs, and an abnormal temperature dependence has been also observed.[50] In the presence of $LiClO_4$ (*ca.* 0.1 mol dm^{-3}), which prevents the reversion from solvent-separated to contact ion-pairs, k_H/k_D at 25 °C amounted to 1.53 ± 0.02 (acetolysis) and 1.48 ± 0.03 (formolysis).[50] In the presence of $LiClO_4$, the ratios of Arrhenius pre-exponential factors A_H/A_D are significantly less than unity and amount to 0.49 ± 0.01 (acetolysis) and 0.38 ± 0.04 (formolysis). It has been suggested[50] that these surprisingly low values result from a change in the rate-determining step over the temperature range of about 25° from formation of the solvent-separated ion-pair at low temperature to reaction of the dissociated carbocation with solvent at highest temperatures. Values of A_H / A_D for primary deuterium isotope effects that are considerably lower than unity have been known for some time, and have usually been explained as a consequence of tunnelling.[55] Values below unity have also been found for secondary deuterium isotope effects and have been given a similar explanation.[54]

The mechanism of solvolyses of ferrocenylmethyl benzoate can be best understood in terms of the Winstein mechanism for solvolysis (Scheme 1).[56] In the presence of lithium perchlorate, we can assume that the solvent-separated ion-pair reacts rapidly by the k_6 and k_7 route to give solvolysis products. This appears to be at least the major pathway. In this interpretation, the dissociation of the intimate ion-pair (the k_2 step) is mainly or entirely rate determining.



Scheme 1.

In the absence of lithium perchlorate, upon addition of sodium benzoate, a rate depression was observed (Figure 3) which had been previously explained[50] as being due to common ion rate depression. This explanation should be corrected. Taking into account that the ionization constants (K_i) of formic, benzoic and acetic acids are 1.8 ± 10^{-4}, 6.0 ± 10^{-5}, and 1.8 ± 10^{-5}, mol dm^{-3}, respectively, it should be concluded that sodium benzoate added to formic acid must be largely converted to benzoic acid and sodium formate. Even in glacial acetic acid (which is a somewhat weaker acid than benzoic acid), the large excess of acetic acid would probably convert the added ben-

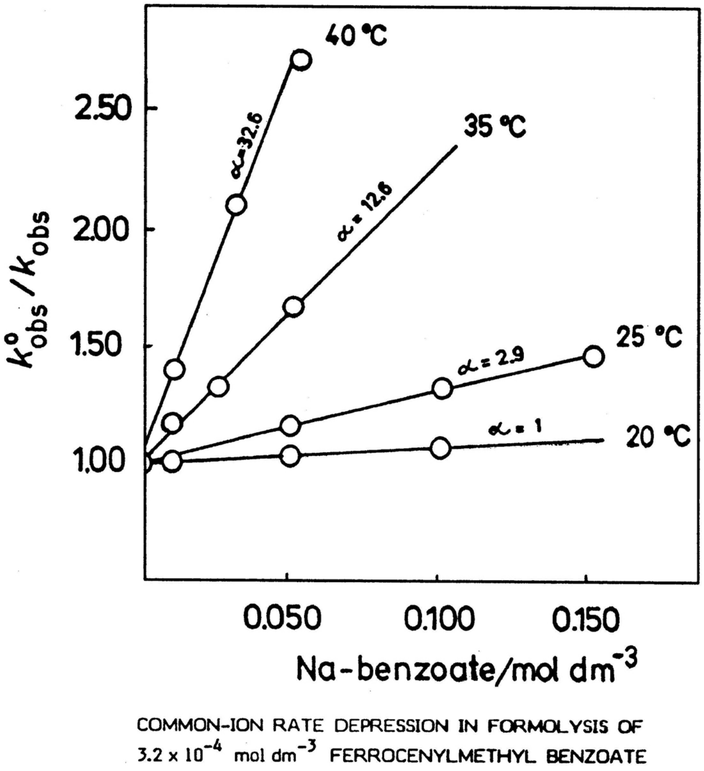


Figure 3. Rate depression of formolysis of 3.2×10^{-4} mol dm^{-3} ferrocenylmethyl benzoate upon addition of sodium benzoate (taken from Ref. 50).

zoate to benzoic acid and sodium acetate. The rate depression effect is, therefore, due to the formate ion in formic acid, and the acetate ion in acetic acid. If the formolysis and acetolysis are acid catalyzed, the buffering effect of formate (or acetate) ions would cause a rate depression. This explanation is in agreement with the observation that the acetolysis of trityl acetate is very strongly catalyzed by mineral acids (*vide infra*).

The rate decrease upon addition of sodium benzoate is strongly temperature dependent, the temperature range being only 20 °C (Figure 3). Over this temperature range, the main rate determining step changes from k_2 at the lowest to k_5 at the highest temperature. A maximal secondary isotope effect is expected for the k_2 step because there is no covalent bonding to R^+, while a smaller isotope effect is expected for the k_5 step bacause a new covalent bond has started to form between R^+ and SOH. For details, the original literature[50] should be consulted.

Finally, one might ask if it is reasonable to ascribe the abnormal temperature dependence in the presence of $LiClO_4$ to tunnelling. The postulated rate determining step in this case is the conversion of the contact ion pair to the solvent-separated ion-pair, so the answer depends on whether motion of the α-hydrogens contributes to the motion along the reaction coordinate.[54] If the α-carbon is already planar in the contact ion pair, it is difficult to see how such motion could contribute. If it is still non-planar in the contact ion-pair and becomes planar as the solvent separated ion-pairs forms, then motion of the α hydrogen will contribute to the motion along the reaction coordinate, and a contribution of tunnelling is a possibility. In any event, the low A_H / A_D values cannot be taken as a proof of tunnelling because of mechanistic complexity.

ABILITY OF FERROCENE TO STABILIZE A CARBENIUM ION

The ability of ferrocene to stabilize the positive charge has been recognized by several authors.[57–60] Ferrocenylmethylium ions have been isolated as stable salts, *e.g.* as tetrafluoroborates.[61] Several groups have studied the kinetics of their reactions with different nucleophiles.[57,61–65] Crystal structure and mechanistic investigations on these ions have been published.[25,66–68] X-ray analysis of ferrocenyldiphenylcarbenium tetrafluoroborate[69] enabled determination of the Fe–C_{exo} distance of 271.5 pm, and showed that C_{exo} is bent to iron, the angle being 20.7 °. It has been calculated that the direct interaction of iron electrons with the cationic C_{exo} stabilizes the ferrocenylmethylcarbenium ion. It was concluded that the cation can be described as η^6 iron-fulvene with a small charge on C_{exo}. ^{13}C-NMR chemical shifts of the *para*-carbons in phenyl-substituted carbenium ions have been used as a probe for determining the positive charge at the carbenium center.[70] Other authors[65] also came to the conclusion that the positive charge in ferrocenylmethyl carbenium ions is located only to a small extent on C_{exo}.

Computational study of the stabilization of 2-ferrocenylmethyl cation was recently performed[71] using the density functional theory (Becke3LYP). Within designated symmetry constraints, geometries were optimized with a quasi-relativistic effective core potential for iron and standard double zeta sets 6-31G(d.p) with a set of *d* polarization functions for carbon and *p* polarization functions for hydrogen atoms. The resulting structure was found to be a hybrid of the previously proposed structures where the α-carbon is bent out of the cyclopentadienyl plane towards the iron center with no ring slippage. The formation of the ferrocenyl *vs.* benzyl cation is favoured by over 100 kJ mol^{-1}. This stabilization is claimed to be due to the sharing of the positive charge by cyclopentadienyl rings, effectively spreading the charge throught the ferrocenyl moiety.[71]

SOLVENT VARIATIONS AND THE RATES OF SOLVOLYSES OF FERROCENYLMETHYL ESTERS

More than forty years ago it was shown that triphenylmethyl (trityl) acetate solvolyzes in either aqueous dioxane or methanol almost entirely by alkyl-oxygen bond fission.[72] In addition, a general tendency has been observed for faster solvolyses of this type in solvents of higher ionizing power, consistent with a dissociative (S_N1) mechanism, with a carboxylate leaving group.

Recently, the solvolysis of ferrocenylmethyl acetate has been studied in 2,2,2-trifluoroethanol (TFE)–ethanol mixtures and in aqueous ethanol, acetone, and TFE.[74] For 19 solvents, a fair correlation with Y_{OTs} values has been obtained. This correlation was much improved when Y_{OTs} values were replaced with the derived solvent ionizing power (Y_{OAc}) values. The latter correlation, with a slope close to unity, supported the S_N1 assignement for ferrocenylmethyl acetate solvolyses.[74] The same authors obtained an excellent correlation against their Y_{OAc} values for α-ferrocenylethyl acetate solvolysis, too. Since it has previously been shown[58] that the introduction of an α-methyl group into ferrocenylmethyl acetate leads to only a 10-fold increase in the rate of solvolysis (in 80% acetone), it has been concluded[74] that most of the dispersion of positive charge must be into the ferrocenyl system, and introduction of the α-methyl group provides only a minor route for further charge dispersion, which is in agreement with the already mentioned recent computations based on the density functional theory.[71]

RELATIVE RATES OF SOLVOLYSES OF FERROCENYLMETHYL BENZOATE IN FORMIC AND ACETIC ACIDS

A kinetic study of the acetolysis of trityl acetate was carried out earlier.[73] The measured specific rates were about 300 times higher than the predicted values.[74] A possible explanation, consistent with the powerful catalysis by mineral acids of solvolyses in aqueous-organic solvents,[72] is that the actual reactant in acetic acid is not the neutral acetate but an equilibrium concentration of the faster reacting protonated species,[74] a general idea suggested previously.[75]

As already pointed out, the stabilization of the ferrocenylmethyl carbenium ion can be explained either by involving conjugation with the π-system of pentadienyl rings (model A), or by involving metal participation (model B), Figure 2. The extremely high α-D KIEs for both formolysis and acetolysis of 21.7 and 23.8%, respectively, (geometric means calculated per one α-D, at 298.16 K) strongly suggest that both solvolyses are S_N1 processes and that the direct participation of iron electrons to α-carbon can be neglected.

However, the most unusual feature is the observation of lower solvolysis rates in formic acid than in acetic acid.[50] Table I contains Y (ionizing power) and N (nucleophylicity values) for formic acid, acetic acid, and 100 and 96% (v/v) ethanol. We can see that both acids are equally poorly nucleophilic, but the difference in their ionizing power is large.

TABLE I

Characterization of the solvents mentioned in terms of their ionization power Y, and nucleophylicity N

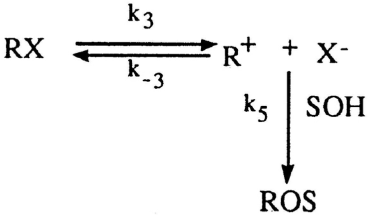
Solvent	*t*-Buthyl chloride scale[76]		2-Adamantanyl tosylate scale77	
	Y	N	Y	N
HCOOH	2.05	–2.05	3.04	–2.35
CH_3COOH	–1.64	–2.05	–0.61	–2.35
100% EtOH	–2.03	0.09	–1.75	0.00
96% EtOH	–1.40*	0.07**		

* Interpolated from the data: –2.03 (100%), –1.68 (98%), –1.29(95%), 0.00(80%), 0.60(70%), v/v EtOH (from Ref. 76).

** Because water and ethanol are of comparable nucleophylicity, its change in EtOH–H_2O mixtures is small (Ref. 78); interpolated from the data for 100, 90, and 80% v/v EtOH (from Ref. 76).

The mentioned results of Kevill *et al.*,[74] who found that the rates of solvolyses of ferrocenylmethyl acetate increase with increasing the solvent ionizing power, and our observation of close similarity in reaction rates of formolysis and acetolysis of ferrocenylmethyl benzoate, in spite of the large difference in ionization power of these two acids,[50] prompted the reinvestigation of our kinetic data. The new measurements[79] fully support our earlier results.

The close similarity in reaction rates of formolysis and acetolysis could be explained by the reaction involving the protonated ester, as discussed by Kevill *et al.*[74] They pointed out that the rates of S_N1 solvolyses with a neutral leaving group are virtually insensitive to changes in solvent ionizing power.[80] If so, the new problem has been discussed by the same authors,[74] namely why formolysis rates are actually lower than one would anticipate based on other available Y_x values for this solvent, and in addition why the protonated species would react in S_N1 reactions at a lower rate than the original substrate. A partial answer might be found in the supposition that the protonation takes place on the contact ion pair (Scheme 1), the rate-determining step being a combination of both, k_1 and k_2. On the other hand, the cationic charge is obviously effectively spread through the ferrocenyl moiety,[71] possibly involving a partial oxidation of iron(II) in certain solvents. That metallocenes represent a solvent-dependent electron transfer system has been pointed out recently.[81] Unfortunately, the question remains why the rates in formic acid are somewhat lower than in acetic acid. In the absence of $LiClO_4$, at lower temperature (293.16 K), k_{obs} for acetolysis and formolysis amount to $(3.42 \pm 0.03) \times 10^{-4}$ and $(2.45 \pm 0.15) \times 10^{-4}$, s^{-1}, respectively.[50] At that temperature, the rate depression effect upon addition of sodium benzoate is negligible, as seen from Figure 3. On the other hand, the rate depression is very large at 313.6 K, suggesting a change in the mechanism: at that temperature, the concentration of the contact ion-pair (Scheme 1) seems to be very much reduced and the formation of the final reaction product appears to take place over the free ion, R^+, the rate determining step being mainly the step k_5. This step should be partly dependant on the solvent bimolecular contribution. The bimolecular solvent contribution appears to be somewhat larger with acetic acid than with formic acid. If so, one should expect this contribution to increase at higher temperatures, when, in the absence of $LiClO_4$, the Scheme 1 is practically reduced to Scheme 2. Indeed, at 313.16 K, the ratio of k_{obs} for acetolysis and formolysis is 1.69, the rate constants being $(32.21 \pm 0.90) \times 10^{-4}$ and $(19.04 \pm 0.80) \times 10^{-4}$, s^{-1}, respectively, while at 293.16 K the same ratio is 1.40, the rate constants being $(3.42 \pm 0.03) \times 10^{-4}$ for acetolysis and $(2.45 \pm 0.15) \times 10^{-4}$, s^{-1}, for formolysis.[50] The α-D KIE is very much reduced with increased temperature, as it should be expected for reactions with increased bimolecular solvent contribution: at 293.16 K, KIE for α-D (geometric mean) for acetolysis and formolysis (in the absence of $LiClO_4$) amounted to $(23.3 \pm 0.1)\%$, and $(26.6 \pm 3.0)\%$, respectively, while at 313.16 K, KIE is reduced to $(9.1 \pm 1.9)\%$ (acetolysis) and $(10.1 \pm 2.8)\%$ (formolysis).[50] In the presence of $LiClO_4$, at lower temperatures (293.16 K), when the reaction product ROS is considered to be formed exclusively over routes k_1, k_2, k_6, and k_7, the acetolysis and formolysis specific rates amounted to $(49.44 \pm 0.49) \times 10^{-4}$ and $(11.66 \pm 0.31) \times 10^{-4}$, s^{-1}, respectively.[50] Under these conditions, the solvolyses clearly follow



Scheme 2.

the S_N1 mechanism, as manifested by very high α-D KIE of (25.0 ± 1.3)% (acetolysis), and (22.5 ± 1.6)% (formolysis). Since, under these conditions, the bimolecular interference of the solvents is excluded, the slower rates in formic acid are puzzling. As already mentioned, the ionization constants for formic, benzoic, and acetic acids are 1.8×10^{-4}, 6.0×10^{-5}, and 1.8×10^{-5}, respectively, and the corresponding pK_a values are 3.74, 4.19, and 4.76. If protonation of the contact ion pair (Scheme 1) does take place, one might argue that the protonation is better in the stronger formic acid than in acetic acid, though in both acids protons are extensively available.

Other physical properties of the two solvents might also play an important role, *e.g.* solvent friction. Recently, the solvent dependence of the electron transfer in metallocenes was analyzed in terms of the mentioned property.[81–84]

ANTITUMOUR ACTIVITY OF METALLOCENES

Transition metal compounds showing tumour inhibiting efficacy are mainly represented by metallocene complexes of the type shown in Figure 4A (M = Ti, V, Nb, Mo: *e.g.*, X = Cl).[85–89] These complexes have shown antiproliferative activity against various experimental tumours, *e.g.* Erlich ascites tumour, sarcoma 180, B16 melanoma, colon 38 carcinoma, Lewis lung carcinoma, as well as against xenografted human carcinoma.[90] Whereas the antitumour metallocene dihalides (Figure 4A) are neutral compounds, the metallocenium cations (M = Fe, Co; *e.g.*, X = $FeCl_4$ (Figure 4B) are cytostatically active. The antitumour activity of these compounds has been detected against Erlich ascites tumour.[90] An excellent review article on non-platinum group metal antitumour agents, including history, current status and perspectives appeared a few years ago.[91] The antitumour activity of metallocenes is expected to be due to their electron-donating ability.

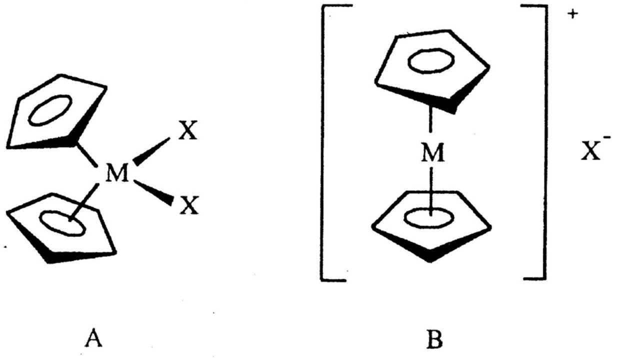


Figure 4.

FERROCENES AS NUCLEOPHILIC CATALYSTS CAN MEDIATE KINETIC RESOLUTIONS

Chiral π-complexes of heterocycles with transition metals can serve as effective catalysts for an array of useful organic reactions.[92,93] The most efficient nucleophilic catalysts previously used had planar structures[94] (*e.g.*, pyridine, 4-(dimethylamino)-pyridine, imidazole) thereby requiring the design of an asymmetric environment in the vicinity of an sp^2-hybridized nucleophilic atom.[95] In a recent paper,[96] as the authors called it, a second-generation system for kinetic resolution has been described that employs 2 mole per cent of an iron complex as the chiral catalyst, and acetic anhydride as the acylating agent (Figure 5). Since one enantiomer of the alcohol reacts faster than the other, the result is a kinetic resolution that leaves the unreacted alcohol in 95% enantiomeric excess at 62% conversion. As it has been pointed out,[97] the method could be applied to a number of interesting products including α-hydrogen acids, psychoactive arylethanolamines, pyrethrin insecticides, phenol-type antibiotics, *etc.* It is important to note that the stereoactivity displayed by the described catalysts is attributed largely to the η^5-C_5Ph_5 group.[96] Although the ferrocene framework is a common component of a chiral catalyst,[98,99] a significant improvement has been made by demonstrating that an increase in the steric bulk of a remote cyclopentadienyl ring can lead to a significant improvement in enantioselectivity.[96] Decreased enantioselectivity upon substitution of an η^5-C_5H_5 group with a more bulky η^5-C_5Me_5 group has been reported.[100] The use of »supracyclopentadienyl« ligands in organometallic chemistry has been previuosly discussed.[101]

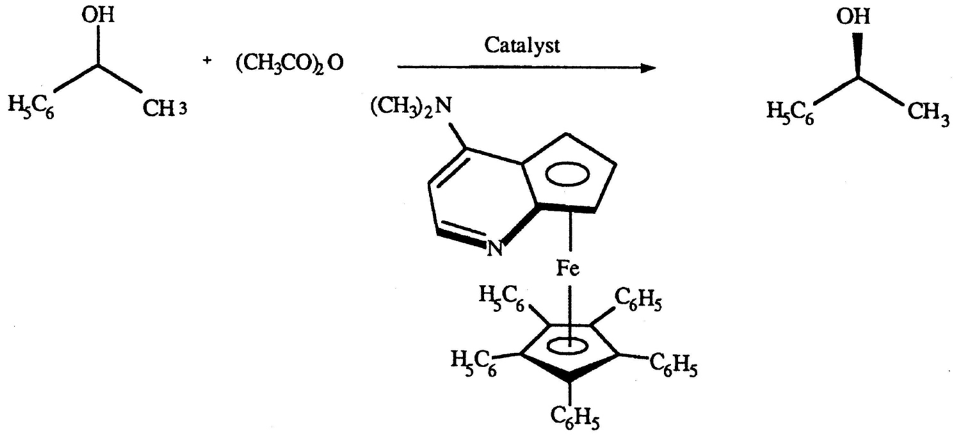


Figure 5. A nucleophilic ferrocene type catalyst enables kinetic resolution of chiral secondary alcohols with 95% enantiomeric excess at 62% conversion.

FERROCENES AND MOLECULAR RECOGNITION

Crown ethers afforded the opportunity to prepare a variety of synthetic cation transport agents. The anion recognition is a relatively recent topic although the first published anion receptor appeared in 1968, only one year after the discovery of crown ethers.[102] Recently, a great interest is being shown in the syntheses of redox-active mycrocyclic receptors that contain a redox centre in close proximity to a cation or anion binding site. Gokel *et al.*[103] first considered the consequences of oxidation of the iron(II) centre of ferrocene,[103] and in their following paper[104] they utilized the fact that the two coplanar cyclopentadienyl rings of ferrocene can rotate around the iron centre. Thus, in the case of functionalized ferrocenes, a wide range of relative orientations of the substituents on pentadienyl may be achieved. Since rotational barriers in substituted ferrocenes are low, as already mentioned in the Introduction, it is possible to design a system which has all the correct functionality for binding a particular molecule, but not yet the functionality in the correct spatial position.[105] Correct spatial arrangement is induced by the substrate, which organizes the functional groups of the receptor in an optimal manner by selective rotation of the cyclopentadienyl rings, as it has been recently pointed out.[105] These systems can be designed to recognize electrochemically the binding of a charged »guest« either through space interaction and /or through bond linkages between the receptor site or redox centre.[106] The ferrocene redox couple is such that neutral ferrocene can be converted easily into the ferrocenium cation. Ferrocenes d-electrons may or may not serve as donors for a bound cation, but when iron(II) is oxidized to iron(III), a repulsive positive charge is placed in proximity to the bound cation.[106] This change diminishes the cation binding capacity of the ligand. It is claimed that the complexation occurs within the cavity, rather than on the periphery.[106] Most of the reported redox-responsive ligand systems gave examples of »guest«-redox couple perturbations in organic solvents such as acetonitrile and dichloromethane. Using new water-soluble polyaza and polyammonium ferrocene macrocyclic ligands, the electrochemical recognition of a variety of transition metal cations (Ni^{2+}, Cu^{2+}, Zn^{2+}) and phosphate anions (HPO_4^{2-}, ATP) in the aqueous environment has been made possible.[107]

Anion recognition continues to attract considerable reseach interest.[108,109] This interest may be attributed to the biological role played by anions. For example, enzymatic binding and reactions with ATP are the basis of free energy in metabolism and the majority of enzymes act on anionic substrates.[108] Several classes of artificial anion receptors have been reported, which are capable not only of binding but also of electrochemically recognizing anions.[110] Such receptors have a potential application in the production of electochemical anion sensors.

METAL–METAL INTERACTIONS IN LINKED METALLOCENES

Studies of linked metallocenes enabled the construction of a range of molecules comprising more than one metallocene unit. In particular, the interactions between metal centres have been studied. Several potential applications of such metallocene systems can be envisaged. For example, metallocene polymers can lead to interesting low-dimensional conductors.[111] Distinct Fe^{II} and Fe^{III} sites in various monooxidized biferrocenes, between which electron transfer can take place, can lead to semiconductivity. Several studies have centered on the use of binuclear metallocenes for third-order nonlinear optical properties. An excellent paper by S. Barlow and D. O'Hare[111] reviews various classes of linked metallocenes, covering the literature up to early 1996.

METALLOCENE DERVATIVES, CATALYSTS FOR POLYMERS

Ziegler-Natta catalyses have long remained the only organometallic catalyses in macromolecular chemistry. The area was revolutionized by the discovery that zirconocene derivatives catalyze the polymerization of propene.[112] At the same time, strong industrial interest has prompted a worldwide development in the field. The first polymers based on metallocene-type catalysts have recently appeared on the market[113] under the names: Hostacen (Hoechst AG), Exact (Exxon), and Affinity (Dow). The metals zirconium and hafnium appear to be the most important metals in synthetic preparations.

The transition-metal-catalyzed ring-opening polymerization of silicon-bridged, strained, ring-tilted ferrocenophans, yields poly(ferrocenylsilane)s with intriguing properties.[114]

CONCLUDING REMARKS

The problems discussed in this review are primarily mechanistic and cover only partly the chemistry of ferrocene and related compounds. The remarkable structural and bonding forms displayed by these compounds provided the initial impetus for the immense and continuing research.

The most important chemical characteristic of ferrocene remains its ability to act as an electron releasing substituent, and the metallocenyl group is one of the strongest inductive electron releasing agents known. This electron donor ability is further exemplified by its great propensity to undergo electrophilic substitutions. The consequence is an actual and potential practical use of ferrocenes and related compounds in industry. The theoretical and practical aspects of ferrocene chemistry guarantee that this subject will remain for some time one of the most active areas of inorganic chemistry.

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SAŽETAK

Metaloceni, jaki elektron-donori. Mehanistički pregled

Smiljko Ašperger

Velika stabilnost α-metalocenilnih karbokationa dobro je poznata. Postoji opća suglasnost da su elektroni između dva ciklopentadienilna prstena odgovorni za tu stabilnost. Prijenos elektrona može, u načelu, uključiti konjugaciju s π-sustavom pentadienilnih prstena ili pak izravnu participaciju elektrona metala. Proučavanje sekundarnoga α-deuterijskog kinetičkog izotopnog efekta (α-D KIE) može, pod određenim okolnostima, omogućiti rješenje problema.

Nedavno smo odredili α-D KIE u acetolizi i formolizi dideuterioferocenilmetilbenzoata i našli da, u nazočnosti $LiClO_4$ koji sprečava povrat otapalom separiranoga ionskog para u kontaktni ionski par, k_H / k_D iznosi, na 25 °C, 1,53 ± 0,02 (acetoliza) odnosno 1,48 ± 0,03 (formoliza). Solvolize su pokazale da postoji specijalni solni efekt, što otkriva postojanje otapalom separiranoga ionskog para i povrat u kontaktni ionski par. Visoke vrijednosti α-D KIE pokazuju da su obje solvolize disocijacijski procesi koji uključuju prijelazno stanje karbenium-ionskog tipa, a ono je stabilizirano konjugacijom s π-sustavom pentadienilnih prstena.

Kod obje solvolize omjeri Arrheniusovih pred-eksponencijalnih faktora, A_H / A_D, znatno su manji od jedinice, što je dovelo do razmatranja da li tuneliranje uzrokuje taj efekt.

Sukladno disocijacijskom (S_N1) mehanizmu, u sličnim solvolizama općenito je nađeno da su solvolize brže u otapalima veće ionizacijske moći. Mi smo, međutim, našli čak nešto niže brzine u mravljoj od one u octenoj kiselini, iako je ionizacijska moć mravlje kiseline mnogo veća od one octene kiseline. Taj se fenomen može, barem djelomično, protumačiti pretpostavkom da je reakcijska vrsta protonirani ester, ili pak protonirani kontaktni ionski par, tako da je nenabijena odlazeća skupina stvarno neovisna o ionizacijskoj moći otapala. Tome govori u prilog nedavno objavljeno zapažanje da je kationski naboj ferocenilmetilkarbenijeva iona raspršen na čitavu ferocenilnu molekulu. Djelomična oksidacija željeza(II) u određenim otapalima također dolazi u obzir. Spomenuta disperzija naboja sukladna je s nedavnim računima koji se temelje na teoriji »funkcionalne gustoće«.

Opisana je i antitumorska aktivnost metalocena. Ona se povezuje s jakom elektron-donorskom sposobnosti tih kompleksa.

Također se opisuje aktivnost ferocena kao kiralnih nukleofilnih katalizatora, koji mogu posredovati u rezoluciji kiralnih sekundarnih alkohola i dovesti do velikoga enantiomernog suviška tvari. Taj je učinak povezan s elektrodonorskom sposobnošću ferocena, što omogućuje prolazno vezivanje kiralnog katalizatora.

Dan je i kratak prikaz primjene ferocena u »molekulskom prepoznavanju«, kao i kratak prikaz međudjelovanja u povezanim metalocenima. Napomenuto je također djelovanje metalocena kao katalizatora za stvaranje polimera.