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Ferrocene remains a prominently topical molecule serving the teaching of many different aspects of chemistry

70 Years Ferrocene!

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Abstract: Some of the most important features of ferrocene chemistry – structure, reactivity, redox properties, and applications – are presented. Their value in the context of conveying many fundamental aspects of molecular chemistry is considered.

Keywords: Ferrocene · Ferrocenium · Redox chemistry · Metallation · Organometallic chemistry

Happy Birthday Ferrocene! Despite its age and for many reasons, some of which will become apparent here, ferrocene remains eminently important when teaching not only organometallic chemistry. From the structural and stereochemical aspects of innumerable derivatives to redox properties, and disparate applications, ferrocene may be the starting point for the discussion of many fundamental concepts, as reflected at least by my own experience.

'As a possible route to fulvalene', Kealy and Pauson reported in 1951 their reaction of a cyclopentadienyl Grignard reagent with $FeCl_3$.[1] This led to an unexpected, new, orange, crystalline iron compound of elemental composition $FeC_{10}H_{10}$, they designated as 'di*cyclo*-pentadienyl iron'. Soon thereafter, Miller, Tebboth and Tremaine,[2] described the completely different reaction of cyclopentadiene with 'reduced iron' (as used as catalyst in ammonia synthesis) at elevated temperature, which gave the very same compound.[3] However, both research groups postulated the same wrong structure,[4] *i.e.* having only one carbon atom of each cyclopentadienyl ring interacting with the iron atom, thereby implying a polar C-Fe σ-bond. Soon to become eminent chemists – G. Wilkinson and R.B. Woodward[5] and, independently, E.O. Fischer[6] – swiftly took up the structural issue and recognized the correct 'sandwich'[7] structure, in which the two equivalent cyclopentadienyl rings (η^5-Cp) bind to iron using their aromatic 6e-π-system.[8] The fundamentally new compound class of the metallocenes[9] was born!

Besides its exceptional thermal stability, ferrocene displays an extremely rich derivative chemistry that has been often, though superficially, compared to that of benzene. Thus, for example, ferrocene can be acylated under Friedel-Crafts conditions, thereby showing its aptitude to undergo aromatic electrophilic substitutions. However, as compared to that of benzene, ferrocene's metallation chemistry is far more important. Alkyllithium reagents are very well-suited for the generation of ferrocenyllithium or, selectively, the 1,1'-dimetallated derivative [Fe(CpLi)$_2$]. Such organolithium compounds invariably display di- or polynuclear structures mostly stabilized by coordinating solvent molecules (Fig. 1).[10] Subsequent reactions with a wide variety of electrophiles lead to the corresponding substitution products. In the early days of ferrocene chemistry, the very prolific research group of Nesmeyanov[11] has shown that metallation, in terms of a C–H activation, is also possible with simple Hg(II) complexes. In this context, the very recently reported tenfold (!) mercuration of ferrocene can be viewed as the apotheosis of metallation reactivity[12] (Fig. 1).

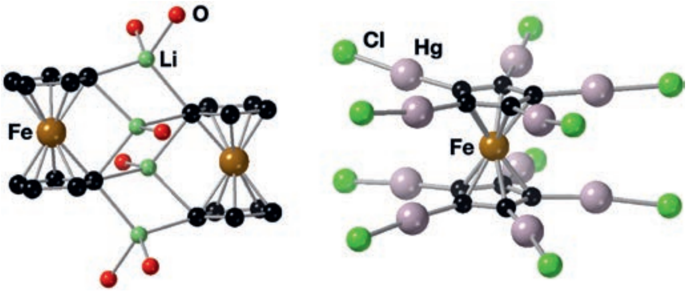
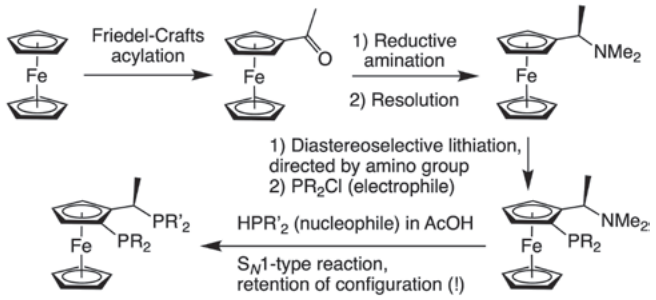


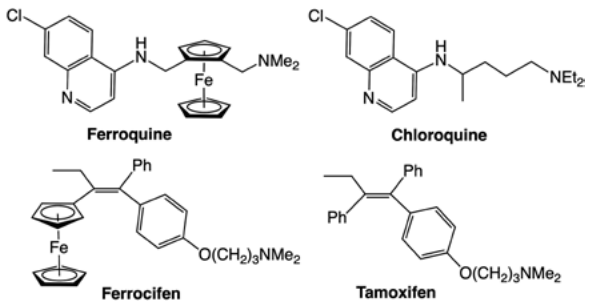
Fig. 1. Left, the structure of the dinuclear [Fe(CpLi)$_2$]$_2$ with the coordinated THF molecules indicated by their respective oxygen atom only (CCDC 296320). Right, the structure of [Fe(η^5-C$_5$(HgCl)$_5$)$_2$], coordinated DMSO molecules are omitted for clarity (CCDC 2047737).

Both electrophilic substitution and metallation are used in syntheses of 1,2-disubstituted ferrocenes by the consecutive introduction of two different groups, thus leading to chiral structures.[13] This has been used extensively, for example, for the preparation of enantiopure ferrocenyl ligands for asymmetric catalysis, *e.g.* of the *Josiphos*-type, which have found widespread applications both in academia and industry (Scheme 1).[14]



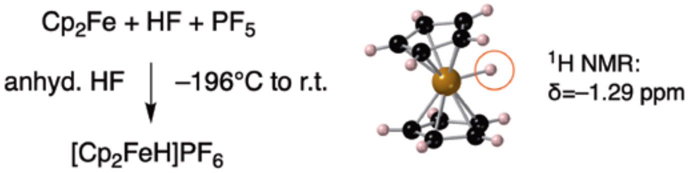
Scheme 1. A general approach to chiral ferrocenyl diphosphines.

Yet another 1,2-disubstituted derivative, Ferroquine, represents the first example of a ferrocene-containing molecule to have reached Phase II clinical trials as antimalarial drug. Recently, its antitumor activity has also been demonstrated.[15] Furthermore, a monosubstituted ferrocene, Ferrocifen, is a drug candidate for the treatment of breast cancer. Both compounds, which arguably represent a breakthrough for ferrocene in medicinal chemistry, are illustrated in Scheme 2, together with their 'all-organic' counterparts that inspired their development.



Scheme 2. The incorporation of a ferrocenyl fragment into the scaffold of known drugs may lead to improved drugs.

Turning to a more fundamental aspect of reactivity, the protonation of ferrocene has attracted the attention of experimentalists since the early days, due to its mechanistic relevance for electrophilic substitution. By virtue of NMR studies, it was concluded already in 1960 that protonation by the superacid $HAlCl_4$ occurs at the Fe atom.[16] However, a salt of $[Cp_2FeH]^+$ was not characterized by X-ray crystallography until 2017 (Scheme 3).[17]



Scheme 3. Synthesis and structure of $[Cp_2FeH]PF_6$, only the cation is shown (CCDC 1546862).

Structure and analytical data of protonated ferrocene confirm its identity as a hydrido complex of iron in its formal oxidation state +IV. Thus, the protonation of a metal center of an organometallic complex can be viewed, as in this prototypical case, as the simplest possible form of an oxidative addition.[18]

Last but not least, the electrochemical properties of ferrocene need to be mentioned. The corresponding one-electron oxidation is a reversible reaction, though the parent ferrocenium ion, $[FeCp_2]^+$, tends to slowly decompose in solution.[19] Nevertheless, the couple ferrocene/ferrocenium represents a standard electrode for the study of electrochemical processes in organic solvents. From an electrochemical perspective, one of the most important characteristics of ferrocene is that the redox potential can be finely tuned by the introduction of appropriate substituents.[20] In the $E_{1/2}$ range from +0.403 V vs. SCE in MeCN for $FeCp_2^+/FeCp_2$ to –0.096 V for the decamethylferrocene couple ($FeCp^*_2{}^+/FeCp^*_2$) one can roughly say that every methyl group is worth a contribution of *ca.* 50 mV to $E_{1/2}$. On the other hand, electron-withdrawing groups make the corresponding ferrocene less oxidizable than the parent compound and extend the $E_{1/2}$ range by another 0.5 V to more positive values, such as for example in the case of 1,1'-diacetylferrocene.[21]

Ferrocene and its derivatives remain both a playground for fundamental studies and for a variety of possible applications. To conclude this brief overview, one can simply say: Ferrocene is able to boast an extremely rich and disparate chemistry, most likely like no other known organometallic molecule, thereby being an enduring source of inspiration for both research and teaching.

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