Enzymatic Resolution of a Chiral Organometallic Ester: Enantioselective Hydrolysis of 2-Ethoxycarbonylbuta-1,3-dienetricarbonyliron by Pig Liver Esterase

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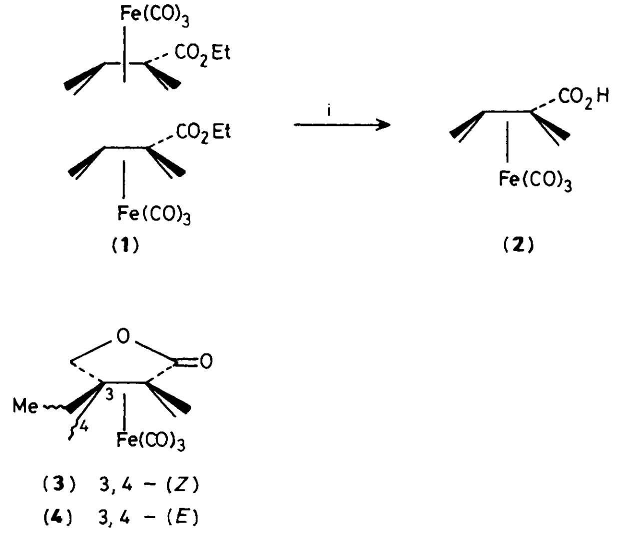
2-Ethoxycarbonylbuta-1,3-dienetricarbonyliron (1) was resolved by enantioselective hydrolysis, catalysed by pig liver esterase, to give the enantiomers of the corresponding acid in a state of high optical purity.

Although there is great interest in the preparation of enantiomerically pure organometallic compounds, relatively few chiral members of this class have been prepared in optically active form. A few 1,3-diene tricarbonyliron complexes have been resolved, almost all by classical means (formation of diastereoisomeric derivatives).[1—3] An attempt to prepare optically active complexes by transfer of the $Fe(CO)_3$ group from chiral enone complexes to prochiral dienes gave products with enantiomeric excesses (e.e.s) as high as 40%.[4]

As part of a programme of investigation into synthetically useful biotransformations we have studied the enzymatic hydrolysis of the ester (1).[5] The ability of hydrolytic enzymes to recognise chirality of the type exhibited by this complex so far has not been explored. However, we are able to report what to our knowledge is the first example of an enzymatic resolution of an organometallic complex. Thus the racemic ester (1) is hydrolysed enantioselectively to the corresponding crystalline acid (2) by pig liver esterase (PLE). Under the defined experimental conditions† the reaction reached completion after approximately 40 hours. When the reaction was stopped after 30 hours, the product carboxylic acid (2) was isolated in 40% yield.‡ When the hydrolysis was allowed to proceed for 50 hours the unhydrolysed ester was recovered and hydrolysed (LiOH) to give the acid (2) in 38% yield.‡ Chiral analysis of the product acids was effected by formation of the corresponding amides with (*S*)-(−)-2-phenylethylamine,§ in the 400 MHz n.m.r. spectra of which the signals attributable to the methyl groups of the 2-phenylethylamide components were fully resolved.



Scheme 1. *Reagents and conditions*; i, PLE/phosphate buffer pH 7.0.

Both the enzymatic hydrolysis product (acid A) and the acid obtained from the unhydrolysed ester (acid B) were found to be of 85% e.e. The optical purity of both acids was raised to >98% by one recrystallisation.¶

The circular dichroism (c.d.) spectrum of acid A (laevorotatory) is shown in Figure 1.

The c.d. spectra of only a few 1,3-diene tricarbonyliron complexes have been determined. However, it has been

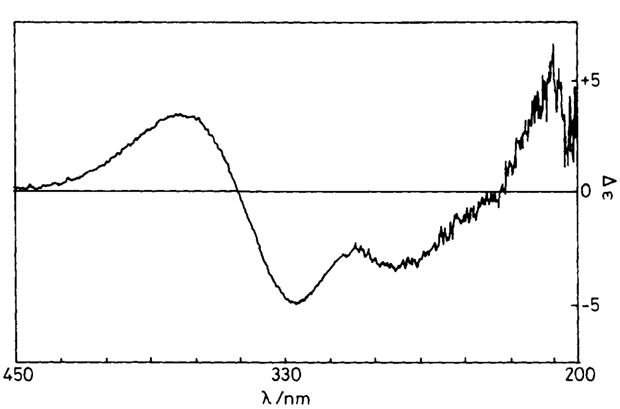


Figure 1. The circular dichroism spectrum in MeOH of the acid (2) derived from the ester (1) by PLE-catalysed hydrolysis.

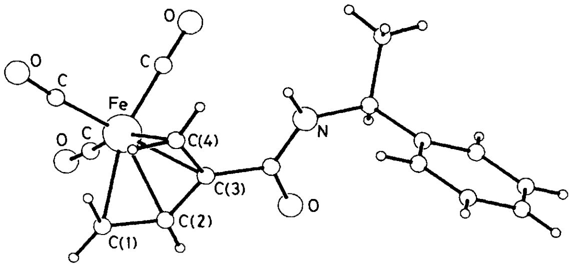


Figure 2. Molecular structure of the amide of (+)-2-carboxy-1,3-dienetricarbonyliron with (*S*)-(−)-α-methylbenzylamine.

Crystal data: monoclinic, space group $P2_1$, a = 11.479(4), b = 18.413(7), c = 16.645(4) Å, β = 106.18(2)°, U = 3379(2) Å, Z = 8 (four independent molecules in the asymmetric unit), R = 0.073 for 2606 unique observed $[I/\sigma(I) \geqslant 2.0]$ reflections.

Principal dimensions (averages): Fe–C(CO) 1.78(1), Fe–C(1), 2.13(1), Fe–C(2) 2.07(1), Fe–C(3) 2.05(1), Fe–C(4) 2.09(1), C(1)–C(2) 1.39(2), C(2)–C(3) 1.40(2), C(3)–C(4) 1.41(2), C(3)–C(5) 1.46(2) Å.

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† The ester (1) (50 mg, 1.88×10^{-4} mol) in methanol (4 ml) and phosphate buffer (0.2 M, pH 7.0, 16 ml) was stirred at room temperature with PLE (40 µl, 48 enzyme units).

‡ Based on total starting material.

§ The acids were converted into the imidazolide (1.05 equiv. of *N,N'*-carbonyldi-imidazole, $CDCl_3$, N_2, 1 h followed by (*S*)-(−)-2-phenylethylamine (1.05 mol. equiv.). Reaction overnight gave 100% conversion to the amide. The solution was filtered and its n.m.r. spectrum was recorded.

¶ Acid A: $[\alpha]_D^{20}$ −10.7° (*c* 0.5, $CHCl_3$), m.p. 129—130 °C; acid B: $[\alpha]_D^{20}$ + 11° (*c* 1, $CHCl_3$), m.p. 133—134 °C. Solvent for recrystallisation: diethyl ether–light petroleum, b.p. 40—60 °C.

suggested[2,6,7] that for a range of chiral transition metal complexes, the sign of the c.d. maximum attributable to d–d transitions should be related to absolute configuration. Such a correlation has been suggested to apply in the particular case of 1,3-diene tricarbonyliron complexes.[2] For such compounds, the sign of the lowest energy transition in the range 340—390 nm has been proposed as diagnostic of the absolute configuration. The c.d. curves of the complexes (**3**) and (**4**), which are structurally related to the acid (**2**), both exhibited strong positive maxima near 390 nm ($\Delta\varepsilon$ +5.05, +4.6, respectively).[7] Accordingly, the laevorotatory acid A ($\Delta\varepsilon$ +3.57, 376 nm) was tentatively assigned the absolute configuration indicated for (**2**). This assignment was confirmed by an *X*-ray crystal structure determination of the anide of the dextrorotatory acid with (*S*)-(−)-α-methylbenzylamine (Figure 2).

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