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The regiochemistry of reduction of mono-ethyl fumarate and maleate using a ruthenium BINAP catalyst

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Abstract

The regiochemistry of the reduction of mono-ethyl fumarate using *bis*(carboxylato){2,2′-*bis*(diphenylphosphino)-[R]-1,1-binapthyl}-ruthenium(II) (Ru[BINAP]) in H_2/CH_3OD is reported and occurs opposite to the regiochemistry observed in the reduction of tiglic acid. Reduction of mono-ethyl maleate with D_2/CH_3OD is very sluggish but produces *meso*-dideuteriosuccinic acid with high stereoselectivity. Reduction of mono-ethyl maleate with Ru[BINAP]$(O_2CR)_2$ and H_2/CH_3OD results in mono-ethyl succinate-d_1 with nearly complete loss of regiochemistry.

The mechanism of reduction of α,β-unsaturated carboxylic acids by *bis*(carboxylato){2,2′-*bis*(diphenylphosphino)-[R]-1,1-binaphthyl}ruthenium(II) (Ru[BINAP]) has recently been studied by Ashby and Halpern.[1] The mechanistic scheme suggested by the results of this and other work[2] is briefly summarized in Fig. 1 for the reduction of tiglic acid. Reduction was observed to be both regio- and stereoselective. The proposed mechanism, which is based on kinetic, stereochemical and isotopic substitution studies, suggests that the reduction proceeds through an initial carboxylate complex that collapses to an intermediate ruthenium bound lactone. Hydrogen from two sources is utilized. The hydrogen transferred during formation of the five membered ring lactone originates from dihydrogen while a proton from the solvent is incorporated during protonation of the carbon–ruthenium bond.

Recently, we have reported the reduction of the half ethyl ester of fumaric acid with D_2/CH_3OD using both R- and S-Ru[BINAP] to synthesize chiral succinic acid-d_2.[3] We would like to report the regiochemistry of this reduction on the half ethyl esters of fumaric and maleic acids.

Reductions of mono-ethyl fumarate half ester with R-Ru[BINAP] and isolation of the corresponding succinate using D_2 and CH_3OD, H_2 and CH_3OD and D_2 and CH_3OH (4 atm., 85 hrs., 25°C) were performed as previously reported.[3,4] When the NMR spectra were run in DMSO-d_6/D_2O and Na_2CO_3 was added to the solution, some of the ^1H and ^{13}C resonances shifted allowing for analysis and

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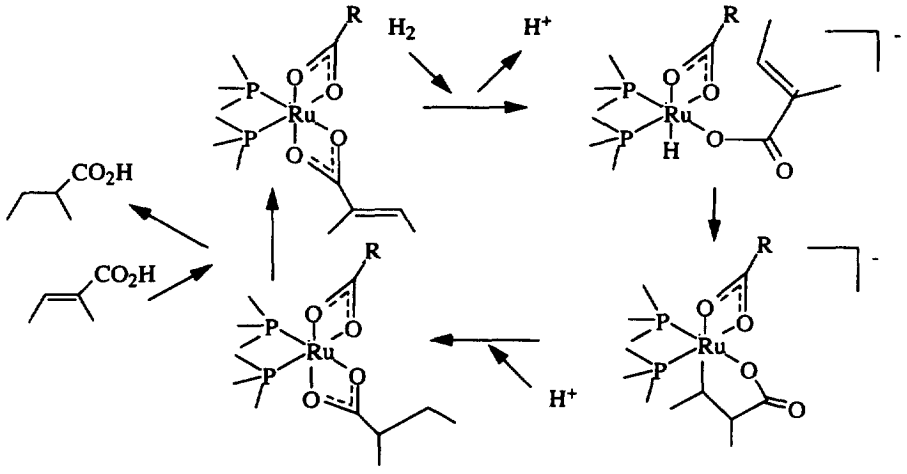
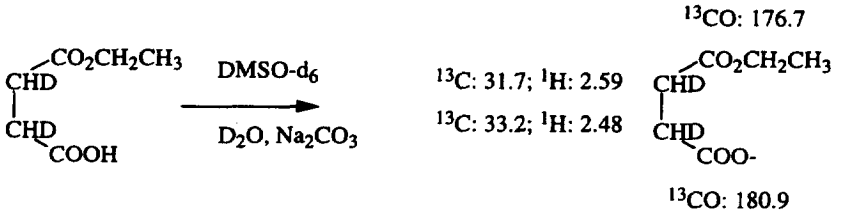


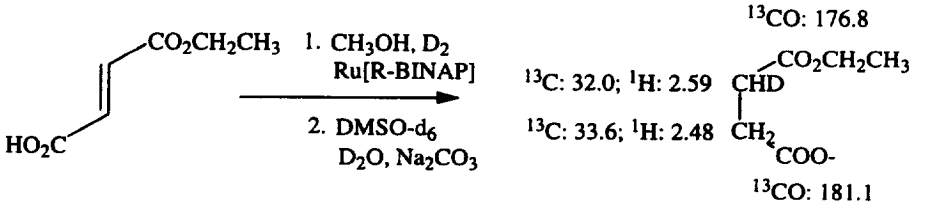
Fig. 1. Mechanistic scheme for the Ru[BINAP] catalyzed hydrogenation of tiglic acid[1]

assignment of the chemical shifts. The chemical shift assignments are based on the results of 2D-NMR experiments conducted on the half ethyl esters of 2,3-dideuterio- and deuteriosuccinic acids and on the observed behavior of the ^{13}C and ^{1}H resonances of some reference compounds run under similar conditions.[5]



^{1}H–^{13}C HMBC and HMQC experiments obtained on a Bruker ARX-500 spectrometer using a 5 mm inverse detection broad band probe on mono-ethyl succinate-d_2 in DMSO-d_6/D_2O/Na_2CO_3 confirmed that the upfield methylene hydrogen (*ca.* δ 2.48) was α to the carboxylate group (*ca.* δ 180.9).[5] Some correlation was observed between the hydrogens of both methylene groups and the two carbonyls but the most intense signal was observed between the low field carbonyl carbon at δ 180.9 and the higher field methylene hydrogen at δ 2.48. It was also possible to confirm that the upfield methylene proton (δ 2.48) was attached to the downfield ^{13}C methylene resonance (*ca.* δ 33.2) on the basis of the multiplicity observed from coupling to deuterium in both the ^{13}C and ^{1}H NMR spectra of the CHD group in mono-ethyl succinate-d_1.

Reduction of mono-ethyl fumarate using CH_3OH and D_2 using the conditions given above resulted in the isolation of mono-ethyl succinate-d_1 in 80% yield. The carbon and proton chemical shifts are given below. Examination of the spectra clearly identified the location of the majority of the isotopic label. The ^{1}H NMR spectrum of the mono-ethyl succinate-d_1 isolated exhibited a multiplet at *ca.* 2.59 and a doublet at *ca.* δ 2.48. Proton integration of the four peaks resulted in a ratio of 3.0 ($\mathbf{CH_3}$), 2.0 ($CH_3\mathbf{CH_2}$), 1.36 (**CHD**), and 1.94 ($\mathbf{CH_2}$). The 6% deuterium at δ 2.48 corrected for an isotopic abundance of approximately 70% results in an estimate of the regioselectivity of 90±15%. A singlet was the predominate peak observed for the proton decoupled ^{13}C of the methylene carbon at *ca.* δ 33.6 and a 1:1:1 triplet was observed for the methylene carbon at *ca.* δ 32.0.



Reversing the source of the deuterium by using H_2 and CH_3OD in the reduction resulted in a reversal of the multiplicities observed in the ^{13}C and ^1H spectra of the methylene positions. Hydrolysis of the half ester of ethyl succinate-d_1 afforded [2R]-succinic-d_1 acid. This sample had an apparent molar ellipticity of less than half (~35%) of that expected for an enantiomerically pure sample of succinic-d_2 acid.[3] The relatively low level of incorporation of deuterium (*ca.* 70%) limits the synthetic usefulness of this reaction.

On the basis of the results just described, we conclude that H or D from the solvent ends up attached to the carbon α to the carboxylic acid. The spectra are consistent with the presence of a small amount of isotopic label at the other methylene group in both reductions. While this may result from the lack of regiospecificity, it may also be caused by other processes known to scramble the label between the reducing agent and the solvent.[1]

A comparison of the regiochemical results of these experiments to those observed for tiglic acid in Fig. 1 appear contrary to expectations. Reduction according to this figure should result in the H or D from the solvent locating β to the carboxylic acid group. Interpretation of the regiochemical results observed for mono ethyl fumarate in terms of the general mechanism scheme outlined in Fig. 1 suggests that formation of a four membered ring lactone competes favorably in this case. Obviously, other explanations are also possible.

The unexpected regiochemical results observed in the reduction of the fumarate system, prompted us to examine the reduction of mono-ethyl maleate (prepared by controlled hydrolysis of diethyl maleate) with both D_2/CH_3OD and H_2/CH_3OD. Reduction in this case was considerably slower (4 atm., 170 hrs., 25°C) and raised the possibility that reduction was preceded by geometric isomerization. The 2,3-dideuteriosuccinic acid isolated following hydrolysis was examined both by CD and IR. A baseline CD spectrum was obtained; the IR spectrum was identical to the spectrum of the *meso*-succinic-d_2 acid obtained from an independent source and different from the spectra of the chiral and *dl* acids.[6] Reduction of mono-ethyl maleate in H_2/CH_3OD afforded the corresponding succinate-d_1. In the ^1H NMR spectrum of the internal methylene groups, both appeared as triplets integrating nearly 1/1 (δ 2.48/2.59: 0.53/0.58), suggesting that scrambling of the label between the solvent and dihydrogen competes favorably with the rate of reduction. The ^1H area ratio, implies that slightly more deuterium is located α to the carboxylate group and this is consistent with the results observed with the fumarate esters. Reduction of mono-ethyl maleate is stereoselective and may occur with the same regiochemistry as reduction of the fumarate half ester.

In conclusion, we find that the regiochemistry of the reduction of mono-ethyl fumarate and maleate differs from that observed for tiglic acid. Preferential reduction of the *re–re* face of the fumarate[3] with the R-[BINAP]Ru complex is contrary to the observed stereochemistry in the reduction of many other α,β-unsaturated carboxylic acids. Any relationship between the regiochemistry observed and the stereochemistry of reduction remains to be determined.

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