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Transition Metal-Diene Complexes in Organic Synthesis - 29.[1]

Separation of Planar Chiral Tricarbonyliron-Diene Complexes at Cyclodextrin Bonded Chiral Stationary Phases by HPLC

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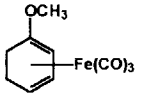
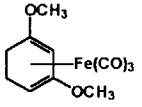
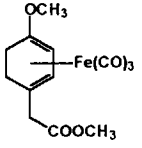
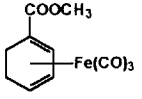
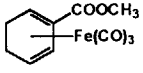
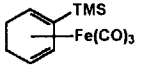
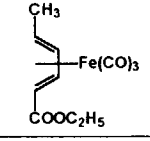
Abstract: A broad range of racemic planar chiral tricarbonyl(η^4-diene)iron complexes was separated into their enantiomers by chiral HPLC on commercial β-cyclodextrin columns.

Tricarbonyl(η^4-1,3-diene)iron complexes are useful transition metal π-complexes for organic synthesis.[2] Moreover, it has been shown that planar chiral tricarbonyl(η^4-1,3-diene)iron complexes are excellent starting materials for enantioselective synthesis.[3] Among the methods for the preparation of the enantiopure complexes are the separation of racemic complexes *via* diastereoisomers,[4] the diastereoselective complexation of enantiopure diene ligands,[5] the separation of planar chiral complexes by enzymatic reactions,[6] and the enantioselective complexation of prochiral 1,3-dienes by chiral tricarbonyliron transfer reagents.[7] However, most of these methods are very limited and turned out to be successfully applicable only to a few examples. A convenient and high yield synthesis of tricarbonyl(η^4-1,3-diene)iron complexes was achieved by 1-aza-1,3-diene catalyzed complexation of 1,3-dienes with pentacarbonyliron.[8] We are currently seeking for a general and convenient access to planar chiral tricarbonyliron complexes. With this objective, we recently developed an enantioselectively catalyzed complexation of prochiral dienes by using chiral 1-aza-1,3-diene catalysts.[1,9] A problem was, that the analytical methods for determining the enantiomeric excess were restricted to the transformation into diastereoisomers and/or the measurement of the optical rotation value. We now describe a simple method for the separation of the enantiomers of planar chiral tricarbonyl(η^4-1,3-diene)iron complexes by high performance liquid chromatography (HPLC) on inexpensive commercial β-cyclodextrin columns.[10]

A complete baseline separation of the racemic planar chiral tricarbonyl(η^4-1,3-diene)iron complexes **1-7** by chiral HPLC[11] was achieved by optimization of the different parameters: type and dimension of the columns, flow rate, column temperature, eluent (Table 1, Figures 1 and 2).

A few observations we made during our study can be generalized. Commercial β-cyclodextrin columns[12] are suitable for the separation of racemic mixtures of planar chiral tricarbonyliron-diene complexes.[13] The racemic cyclohexadiene complexes **1-4** and the butadiene complex **7** were easily resolved at a permethylated β-cyclodextrin, while the enantiomers of the cyclohexadiene complexes **5** and **6** were separated at a non-methylated β-cyclodextrin. Much better resolutions of the enantiomers were obtained by cooling the column to 0°C[14] and using an acetonitrile/water mixture as the eluent. The separation factor α is a measure for the quality of the separation with respect to the peak maxima. The value R_S is a measure for the resolution of the two peaks based on the widths at half height of the gaussian peak.[15] Both values given in Table 1 indicate the high degree of enantiomer separation which was achieved in each case by the present technique.

Table 1. Separation of tricarbonyliron-diene complexes by high performance liquid chromatography on β-cyclodextrin columns [a]

	Complex	Column [b]	T	Eluent	p [c]	c [d]	k'(i) [e]	k'(j) [e]	α [f]	R_S [g]	t_{exp} [h]
1		β-PM	0°C	MeCN/H_2O = 40 : 60	14.3	1	8.52	10.23	1.20	1.80	50
2		β-PM	0°C	MeCN/H_2O = 35 : 65	15.4	2	9.09	11.04	1.21	1.77	55
3		β-PM	20°C	MeOH/H_2O = 50 : 50	22.7	5	13.81	15.06	1.09	0.75	80
		β-PM	0°C	MeCN/H_2O = 26 : 74	17.1	5	27.69	31.28	1.13	1.39	140
4		β-PM	0°C	MeCN/H_2O = 25 : 75	16.7	2	24.48	28.49	1.16	1.31	135
5		β-OH	20°C	MeOH/H_2O = 50 : 50	20.0	4	13.96	14.81	1.06	0.82	80
		β-OH	0°C	MeCN/H_2O = 35 : 65	15.3	5	12.72	14.65	1.15	1.68	70
6		β-OH	20°C	MeOH/H_2O = 75 : 25	15.4	2	3.18	3.99	1.25	1.81	25
		β-OH	0°C	MeCN/H_2O = 80 : 20	8.7	2	1.76	2.87	1.63	1.91	20
7		β-PM	20°C	MeOH/H_2O = 50 : 50	18.0	1	9.46	10.16	1.07	0.94	55
		β-PM	0°C	MeCN/H_2O = 25 : 75	16.7	1	21.98	24.91	1.13	1.15	120

a) Knauer HPLC system; flow: 0.5 ml/min; sample volume: 5 µl (solution of complex in MeCN or MeOH); peak detection using a UV/VIS detector at λ = 254 nm.

b) β-PM: HPLC-column of permethylated β-cyclodextrin from Macherey-Nagel (Nucleodex β-PM; particle size: 5 mm; column dimensions, length: 200 mm, Ø: 4 mm); β-OH: HPLC-column of non-methylated β-cyclodextrin from Macherey-Nagel (Nucleodex β-OH; particle size: 5 mm; column dimensions, length: 200 mm, Ø: 4 mm).

c) Pressure in MPa. d) Concentration in mg/ml. e) Retention factor of the first eluted enantiomer i: $k'(i) = (t_{R,i} - t_0) / t_0$; $t_{R,i}$: total retention time of enantiomer i; t_0: hold-up time; retention factor of the second eluted enantiomer j: $k'(j) = (t_{R,j} - t_0) / t_0$; $t_{R,j}$: total retention time of enantiomer j. f) Separation factor $\alpha = k'(j) / k'(i)$.

g) Peak resolution: $R_S = 1.18 (t_{R,j} - t_{R,i}) / (w_{h,i} + w_{h,j})$; $w_{h,i}$,$w_{h,j}$: widths at half height of the Gaussian peaks for i and j. h) Experimental-time in minutes.

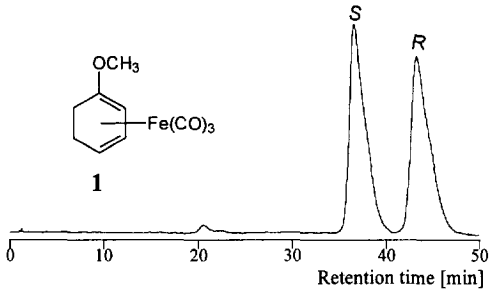


Figure 1. Separation of **1** by HPLC at a permethylated β-cyclodextrin.

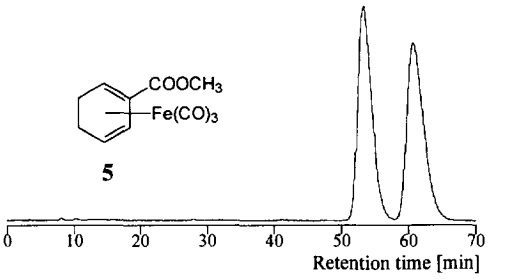


Figure 2. Separation of **5** by HPLC at a non-methylated β-cyclodextrin.

An enantioenriched sample of complex **1**, prepared by asymmetric catalysis of the complexation of the corresponding diene, was used for the assignment of the absolute configuration of the two enantiomers of **1**.[1]

Planar chiral tricarbonyl(η^4-1,3-diene)iron complexes have been applied to synthetic organic chemistry. For example, complex **3** is a building block for the diastereoselective synthesis of iron-complexed spiroquinoline ring systems[16] and complex **4** served as a precursor for an enantioselective total synthesis of shikimic acid.[17]

In conclusion, we found a direct method for the separation of planar chiral tricarbonyl(η^4-1,3-diene)iron complexes at commercial β-cyclodextrin columns. The method described above offers not only an analytical probe for the fast and accurate determination of the enantiomeric excess of optically active planar chiral tricarbonyl(η^4-1,3-diene)iron complexes, but also could be used to resolve racemic complexes of this type on a preparative scale.

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