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Thomas E. Bitter Wolf[a]; T. L. Hubler[a]; R. Todime[a]
[a] Department of Chemistry, University of Idaho, Moscow, Idaho

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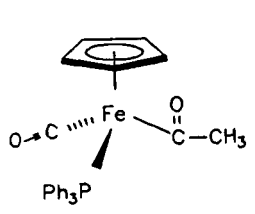
SEPARATION OF RACEMIC MIXTURES OF ORGANOMETALLIC COMPLEXES BY USING CHIRAL SOLID SUPPORTS

THOMAS E. BITTERWOLF,* T. L. HUBLER, and R. TODIME

Department of Chemistry
University of Idaho
Moscow, Idaho 83843

INTRODUCTION

Chiral organometallic compounds are becoming increasingly important for the elucidation of reaction mechanisms and as reagents for the synthesis of chiral organic compounds with high stereoselectivity. Several reviews describing these compounds and their applications to organic chemistry have appeared [1]. Chirality can arise in these materials through several mechanisms illustrated by Compounds **I–IV**. Compound **I** is chiral by virtue of the presence of four different ligands in a pseudotetrahedral geometry about the iron atom. In this regard, **I** is analogous to a classical chiral carbon compound. Compounds **II** and **III** contain a chiral group either on the metal or on the ring, respectively.



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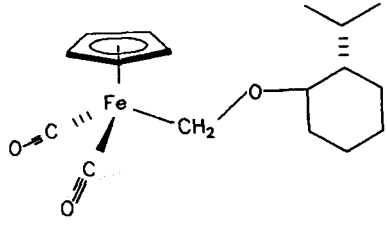

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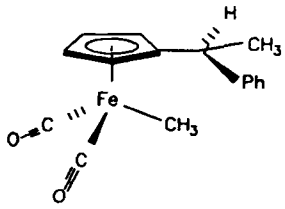

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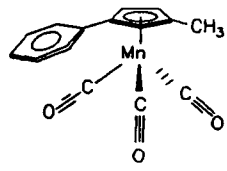
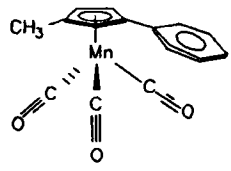
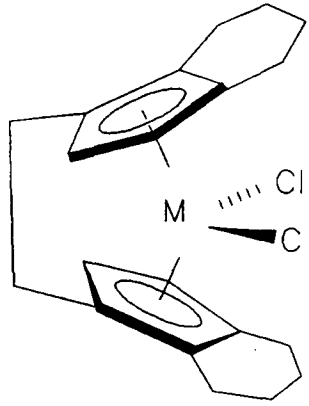




IV

Compounds such as **IV**, for which two racemates are illustrated, are unique and are chiral by virtue of metal complexation to the prochiral faces of a 1,2,- or 1,3-asymmetrically disubstituted arene or cyclopentadienyl ring. 1,2-Disubstituted ferrocene, cymantrene, and arene-chromiumtricarbonyl compounds of this type have been known for many years. Recently, several ferrocenyl phosphine complexes of this class have become important as chiral ligands in active catalytic metal complexes [2].

Interest in this laboratory has been directed toward the synthesis of chiral arene and cyclopentadienyl metal complexes in the hope that the steric environment produced by the ring substituents might influence the stereochemistry of reactions occurring at the metal. Recent reports by Brintzinger and coworkers, and others, describing the remarkable ster-



V

eocontrol of polymerization by 1,2-bis(tetrahydroindenyl)ethane metal dihalides, **V**, of the Group IV elements illustrate this concept [3]. We anticipate that in addition to catalytic applications, these materials will have a role in biomedical applications as either pharmaceutical agents themselves or as bioassay markers on enzymes or antibodies, as polymer-bound chiral catalysts, or as second-order harmonic materials.

In considering the expansion of this field into a large number of chiral organometallic compounds, it became necessary to identify methods for resolving racemic mixtures which would be applicable to entire classes of compounds. Traditional methods of enantiomeric separation and purification have depended upon the use of a homochiral resolving agent to form diastereomers, followed by the separation of the diastereomers by using some physical method such as chromatography or fractional crystallization. This is an intensely time-consuming methodology which presumes the presence of reactive functional groups on the chiral molecule and on the successful identification of a resolving agent which gives separable diastereomers.

Recent advances in the preparation of chiral solid supports in high pressure liquid chromatography (HPLC) have made it possible to resolve racemic mixtures of numerous classes of organic compounds at the analytical and preparative scale. Several reviews of this field have appeared [4]. Schlögl and coworkers utilized triacetylcellulose as a solid support for the resolution of tricarbonylchromium-complexed *o,o'*-bridged biphenyls and other compounds [5]. Armstrong et al. resolved metallocene enantiomers of Type **II** by using columns containing β-cyclodextrin bound to silica gel [6]. Similarly, Kawajiri and Motohashi demonstrated that ferrocenyl ketones form inclusion complexes with β-cyclodextrin and that reduction of the ketones with $NaBH_4$ yields optically active alcohols of Type **III** [7]. The optical yields of these alcohols were then determined by separation of the enantiomers on a Chiralpac OP column in which a functionalized polymethacrylate bound to silica gel serves as the solid support. Gladysz and coworkers achieved the separation of several chiral cyclopentadienyl rhenium complexes of Type **I** by using a Chiralcel OD column in which functionalized cellulose carbamate on silica gel serves as the solid support [8].

With the exception of the elegant contributions of Schlögl and coworkers, no other investigations of compounds of Type **IV** have been carried out. This communication will present preliminary results of our surprisingly successful investigation of the application of Chiralcel OD columns to the separation of enantiomers of Type **IV**.

RESULTS AND DISCUSSION

Columns Employed

Derivatized cellulose carbamate solid supports were developed by Okamoto's group and are now available from Daicel under the trade name Chiralcel [9]. The Chiralcel series of HPLC columns consists of arene-functionalized cellulose carbamate adsorbed on macroporous silica. Four columns are now available in this series, and they differ in the substituents on the phenyl ring of the carbamate. The solid supports vary according to the nature of the functional groups on the arene ring. For example, the arene ring in the OD columns is 3,5-dimethyl substituted, Fig. 1. The high cost of these columns has precluded our carrying out a complete survey of separations on each column of this series, but a selected set of compounds has been screened on all of the columns of this series. It was found that optimal separation was observed on the Chiralcel OD column; thus, all work was carried out on this type of column.

Synthesis of Materials

Tricarbonyl chromium arene compounds of Type **IV** (Table 1) are readily prepared by reaction of an appropriate arene with chromium hexacarbonyl in butyl ether : THF (10 : 1) mixtures as described by several workers [10]. Alternately, tris(acetonitrile)chromium tri-carbonyl may be used as a metallating agent with a concurrent reduction in reaction time from about 3 days to 1 day. Unprotected acetyl- or formyl-substituted arenes have been found to undergo considerable decomposition, and thus these compounds are converted to their dioxolane derivatives prior to metallation. The protecting group can be easily removed in acetone with a catalytic amount of *p*-toluenesulfonic acid [11]. All compounds were recrystallized and their purity was confirmed by using conventional HPLC on a

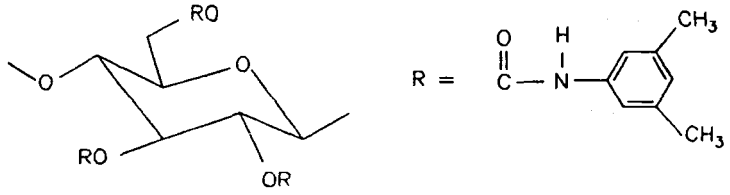


FIG. 1.

TABLE 1. Retention Times (min) and Selectivity Factors (α) for Arene Chromium Tricarbonyl Complexes on Chiralcel OD

Compound	$t_{R'1}$	$t_{R'2}$	α
η^6-Fluorene $Cr(CO)_3$	75.7	77.5	1.02[a]
η^6-9,10-Dihydrophenanthrene $Cr(CO)_3$	63.7	80.8	1.27
η^6-10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene $Cr(CO)_3$	83.2	96.1	1.16
η^6-*endo*-Tetrahydroindeno[1,2-*a*]indene $Cr(CO)_3$	51.7	95.8	1.85
η^6-*endo*-9-Methoxyfluorene $Cr(CO)_3$	83.2	103.6	1.24
η^6-2-Acetyl toluene $Cr(CO)_3$	66.8	69.7	1.04[a]
η^6-1-Indanone $Cr(CO)_3$	229.8	240.6	1.05[a]
η^6-1-Tetralone $Cr(CO)_3$	98.6	107.4	1.09
η^6-2-Acetyl toluene ethylene ketal $Cr(CO)_3$	31.8	38.5	1.21
η^6-3-Acetyl toluene ethylene ketal $Cr(CO)_3$	64.7	67.8	1.05[a,b]
η^6-Ethyl-*o*-toluate $Cr(CO)_3$	$t_{R'}$ = 20.7	(FR: 0.30 mL/min)	~1.00[a,c]
η^6-Ethyl-*m* toluate $Cr(CO)_3$	16.1	19.2	1.19[d]
η^6-2-Acetyl anisole ethylene ketal $Cr(CO)_3$	258.7	460.9	1.78[b]
η^6-Dihydrocoumarin $Cr(CO)_3$	38.3	41.6	1.09
η^6-*o*-Toluidine $Cr(CO)_3$	114.0	128.0	1.12[e]
η^6-*m*-Toluidine $Cr(CO)_3$	45.1	64.7	1.43[f]
η^6-*m*-Methyl anisole $Cr(CO)_3$	49.6	73.6	1.48

[a]Not baseline resolved.
[b]Flow rate 0.1 mL/min.
[c]Flow rate 0.3 mL/min.
[d]Flow rate 0.4 mL/min.
[e]Flow rate 0.5 mL/min.
[f]Flow rate 1.0 mL/min.

silica gel column. The detailed synthesis and spectral characterization of all new compounds will be reported elsewhere.

Chiral cyclopentadienyl compounds of Type **IV** are well known for the ferrocene series and for cymantrene where they can be prepared by conventional organic synthetic routes. The expanding interest in chiral Group **IV** metallocene dichlorides as polymerization catalysts has prompted several groups, including our own, to examine routes to ring-substituted cyclopentadienyl synthons which can be used in the synthesis of broad families of chiral cyclopentadienyl compounds. Compounds which we have examined are listed in Table 2. The 1-phenyl-2-methyl and 1-phenyl-3-methyl cyclopentadienyl manganese tricarbonyl and rhodium dicarbonyl complexes described here were prepared by reaction of the respective disubstituted cyclopentadienyl thallium reagent with either $BrMn(CO)_5$ or $[ClRh(CO)_2]_2$ by using procedures analogous to those which we have employed previously [12]. The methyl,phenyl cyclopenta-

TABLE 2. Retention Times (min) and Selectivity Factors (α) for Cyclopentadienyl Manganese and Rhodium Complexes on Chiralcel OD

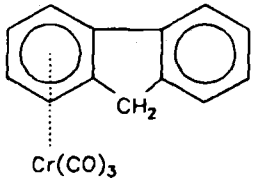
Compound	$t_{R'1}$	$t_{R'2}$	α
η^5-2-Phenyl methyl cyclopentadienyl $Mn(CO)_3$	11.4	14.3	1.25[c]
η^5-3-Phenyl methyl cyclopentadienyl $Mn(CO)_3$	8.0	9.2	1.15[c]
η^5-2-Phenyl methyl cyclopentadienyl $Rh(CO)_2$	$t_{R'}$ = 19.1 min		1.00[a,d]
η^5-3-Phenyl methyl cyclopentadienyl $Rh(CO)_2$	29.3	35.6	1.22[b]
η^5-2-Phenyl methyl cyclopentadienyl $Rh(CO)\ PPh_3$	$t_{R'}$ = 7.1 min		1.00[a,c]
η^5-3-Phenyl methyl cyclopentadienyl $Rh(CO)\ PPh_3$	16.6	21.4	1.29
η^5-2-Acetyl methyl cyclopentadienyl $Rh(CO)\ PPh_3$	19.8	43.2	2.18

[a]Not baseline resolved
[b]Flow rate 0.1 mL/min.
[c]Flow rate 0.4 mL/min

dienyl rhodium(carbonyl)triphenylphosphine complexes were prepared from the dicarbonyl derivatives by ligand exchange in refluxing benzene [13]. 1-Acetyl-2-methylcyclopentadienyl rhodium(carbonyl) triphenylphosphine was similarly prepared from a mixture of 1-acetyl-2-methyl- and 1-acetyl-3-methyl-cyclopentadienyl thallium and $[ClRH(CO)_2]_2$. In this case it was not possible to separate the substitutional isomers of cyclopentadienyl rhodium dicarbonyl, and even separation of the triphenylphosphine derivatives was tedious. Again, detailed spectral, crystallographic, and synthetic details will be presented elsewhere.

Separation of Chiral Mixtures

Chromatographic separation of the enantiomers of Type **IV** organometallic compounds was carried out using a Daicel Chiralcel OD analytical column with 10% isopropanol in heptane as an eluant. The retention times and resolution efficiencies (α) are presented in Tables 1 and 2. Flow rates varied from 0.5 mL/min to 0.05 mL/min to optimize the separation efficiency. Unless otherwise noted in the tables, compounds were separated to base line resolution.



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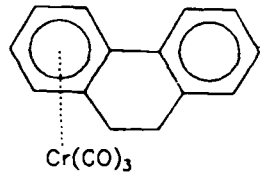

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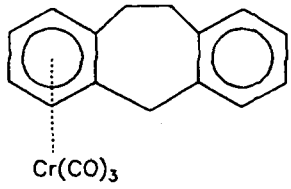

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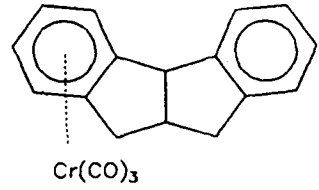
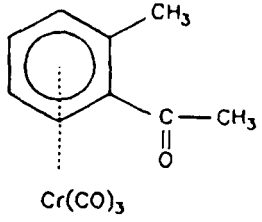


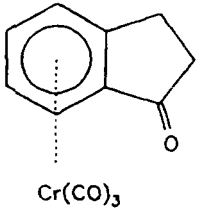
IX

Several simple diarene compounds containing a single tricarbonyl chromium moiety were chromatographed. Fluorene chromium tricarbonyl, **VI**, was not well resolved by this technique, but the tricarbonyl chromium derivatives of 9,10-dihydrophenanthrene, **VII**, dibenzocycloheptane, **VIII**, and diindane, **IX**, were well resolved with the latter having an extraordinary separation. This last compound exists in *endo* and *exo* forms, Fig. 2, and the sample chromatographed was shown previously to be pure *endo*. The isomers of *endo*-9-methoxyfluorene chromium tricarbonyl are well separated in contrast to the poor separation of the parent fluorene. Schlögl reported an α value of 1.07 for the separation of the isomers of the fluorene compound on triacetylcellulose [5b] which is slightly higher than the 1.02 value observed in this work.

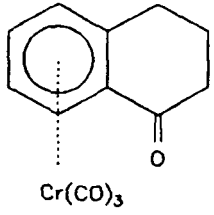
1,2-Disubstituted arene tricarbonyl chromium complexes such as the closely related series 1-methyl-2-acetylbenzene, **X**, indanone, **XI**, and tetralone, **XII**, were found to have very small values of α. Only a few 1,2- and 1,3-pairs of compounds have been examined thus far, and there does not appear to be a clear pattern of α value relative to ring substitution.



X



XI



XII

Several compounds have been examined in which the arene ring has a methyl group *meta* to a second substituent. In these cases it appears that higher α values are found for electron-donating groups than for electron-withdrawing groups. We anticipate that pending work on a greatly expanded set of complexes will help to clarify these observations.

Several disubstituted cyclopentadienyl metal complexes have been examined. 1-Phenyl-2-methyl- and 1-phenyl-3-methylcyclopentadienyl derivatives of tricarbonyl manganese and dicarbonyl rhodium have been examined. For the manganese series the 1,2-disubstituted compound is better separated than the 1,3-, while for the rhodium compounds the 1,2-derivative is unresolved even at 0.05 mL/min and the 1,3-derivative gives excellent separation. Substitution of a triphenylphosphine for a carbonyl

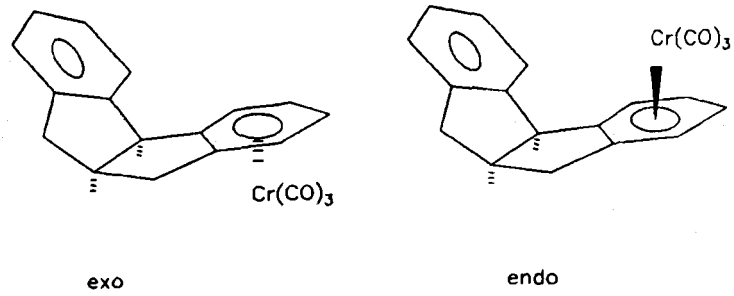


FIG. 2.

on the rhodium compounds does not seem to have a significant effect on the separation.

Given the small number of compounds in the current collection, there does not appear to be any clear pattern emerging to make it possible to predict *a priori* which racemic mixtures will separate cleanly and which will not. Despite this limitation, the application of chiral solid supports to the separation of racemic mixtures of arene and cyclopentadienyl metal complexes has been effectively demonstrated. We anticipate that this technique will be applicable to the analysis of reactions in which stereoselective reagents such as enzymes or chiral stoichiometric reactants are used in reactions with racemic mixtures of organometallic complexes. Of equal importance, many materials have been found to possess α values which are sufficiently large ($\alpha > 1.2$) to suggest that preparative scale separations are feasible. This technique offers an attractive alternative to classical resolution techniques for the enantiomeric purification of organometallic compounds which have potential catalytic or biomedical applications.

ACKNOWLEDGMENTS

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