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Direct high-performance liquid chromatographic resolution of planar chiral tricarbonyl (η^6-arene)–chromium(0) complexes

Claudio Villani[1], William H. Pirkle*

School of Chemical Sciences, University of Illinois, Urbana, IL 61801, USA

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Abstract

Thirty-four disubstituted tricarbonyl (η^6-arene)–chromium complexes having planar chirality were examined by HPLC on a recently developed chiral stationary phase (CSP). This CSP contains "active sites" comprised of clefts formed by the perpendicular disposition of π-acidic 3,5-dinitrobenzamide groups relative to π-basic naphthyl groups. Thirty of the thirty-four show different retention factors for their enantiomers. A mechanistic hypothesis which accounts for the enantiodiscrimination is presented. The arene, using the face *anti* to the tricarbonylchromium, enters the cleft and undergoes simultaneous face-to-face and face-to-edge π–π interactions with the aromatic "walls" of the cleft. Hydrogen bond formation provides a third attractive interaction, facilitating enantiodiscrimination.

1. Introduction

Disubstituted tricarbonyl (η^6-arene)–chromium complexes are chiral when the substituents are different and either *ortho* or *meta* to each other. Owing to the altered reactivity of the arenes in these chromium complexes, the steric shielding exerted by the bulky metal fragment, and the ease of removal of the chromium moiety, there has been a rapid increase in the use of planar chiral (arene) tricarbonyl–chromium complexes in asymmetric synthesis [1–3]. Although a number of synthetic applications of enantiomerically pure complexes have been described, there are relatively few examples of the chromatographic separation of the enantiomers of these complexes on chiral stationary phases (CSPs). For these few examples, analytical-scale separations have been conducted on stationary phases in which carbohydrate derivatives have been coated on silica [4–6] whereas microcrystalline triacetylcellulose has been used for preparative-scale separations [7–9].

In the present paper, we describe the chromatographic behavior of thirty-four chiral chromium–tricarbonylarene complexes on CSP 1, a new brush-type CSP [10,11]. In 30 of the 34

* Corresponding author.

[1] Present address: Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Universitá "La Sapienza", P.le A. Moro 5, 00185 Rome, Italy.

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cases, complete or extensive separation of the enantiomers was noted. A recognition model which accounts for the enantioselectivity observed for this class of analytes is presented.

2. Experimental

2.1. Chiral stationary phase

A commercial (*S*,*S*)-Whelk-O 1 (250 × 4.6 mm; Regis Technologies, Morton Grove, IL, USA) was used for this work.

2.2. Analytes

The racemic chromium complexes were obtained using the standard procedure of thermolysis of $Cr(CO)_6$ in the presence 1–2 mmol of the disubstituted arene in refluxing di-*n*-butyl ether–tetrahydrofuran [12]. As an example, the preparation of (η^6-N-pivaloyl-*o*-toluidine)Cr$(CO)_3$ (**6e**) is described in detail. A mixture of N-pivaloyl-*o*-toluidine (500 mg, 1.72 mmol) and $Cr(CO)_6$ (400 mg, 1.82 mmol) in degassed dibutyl ether (30 ml) and tetrahydrofuran (THF; 3 ml) was heated to reflux for 15 h, cooled, and filtered through a short pad of neutral alumina to remove unreacted $Cr(CO)_6$. Removal of the solvent in vacuo, followed by column chromatography (silica gel, CH_2Cl_2), yielded **6e** (450 mg, 1.37 mmol) as yellow crystals: ^{1}H NMR (C^2HCl_3) δ 1.31 (9 H, s), 2.17 (3 H, s), 5.10–5.20 (1 H, m), 5.35–5.45 (2 H, m), 6.13 (1 H, d, J = 9.0 Hz), 6.88 (1 H, bs); IR (KBr) 3320, 1959, 1888, 1654, 1522 cm^{-1}. Analysis, calculated for $C_{15}H_{17}NO_4Cr$: C, 55.05; H, 5.20; N, 4.28; Cr, 15.90; found: C, 55.35; H, 5.30; N, 4.32; Cr, 15.62. 2-*exo*-Alkylated-1-tetralone complexes [13] (**4d–h**) and N-acylated indole complexes [14] (**5b–f**) were obtained as described in the literature. The chromium complexes were identified by the typical upfield shifts of the aromatic protons of the complexed ring found in the ^{1}H NMR spectra (1–2 ppm relative to the free aromatic ligand) and by the strong CO stretching bands (1990–1880 cm^{-1}) of the $Cr(CO)_3$ group in the Fourier transform (FT) IR spectra.

2.3. Instrumentation

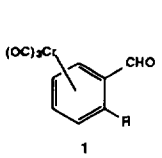
Chromatography was performed using an Anspec-Bischoff Model 2200 isocratic HPLC pump, a Rheodyne 7125 injector with 20-μl sample loop and a Milton Roy LDC UV Monitor D fixed-wavelength detector operating at 254 nm. A Rudolph Autopol III with a 20-cm flow cell was used to monitor the sign of $[\alpha]_D$. A Jasco 500 A spectropolarimeter equipped with a flow cell was used for the on-line recording of circular dichroism (CD) spectra. ^{1}H NMR spectra were obtained using a Varian-XL (200 MHz) spectrometer using tetramethylsilane (δ 0.00 ppm) as an internal reference. FT-IR spectra were obtained (KBr pellets) on a IBM IR-32 spectrometer. Elemental analyses were provided by the University of Illinois microanalytical laboratory.

3. Results and discussion

The data obtained in the resolutions of the racemic $Cr(CO)_3$ complexes on the (*S*,*S*)-Whelk-O 1 stationary phase are summarized in Table 1. Most of the compounds examined can be baseline-resolved on the (*S*,*S*)-Whelk-O 1 using 20% 2-propanol in hexane as a mobile phase. These "standard conditions" are used for comparative purposes and are not necessarily optimal for a given analyte. In instances where these conditions afford separation factors of less than 1.1, reduced concentrations of 2-propanol and/or lower temperatures will afford greater resolution values. The use of methylene chloride as a polar modifier gives further improvement in resolutions of the chromium complexes of *ortho*-substituted benzaldehydes **1a** and **b** and acetophenones **2a** and **b**.

Common to the successfully resolved analytes is the presence of an oxygen atom in the arene framework to act as a hydrogen bond acceptor. Non-acylated *ortho*-toluidine or 1,2,3,4-tetrahydroquinoline complexes are not resolved and only marginal separation (observable by polarimetric detection) is obtained for the indole complex, **5a**. In the series of α-tetralone complexes, **4**, enantioselectivity increases with the

Table 1
Chromatographic data for the resolution of tricarbonyl (η^6-arene)–chromium complexes **1–8** on the (*S,S*)-Whelk-O 1



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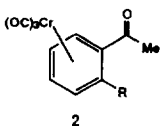

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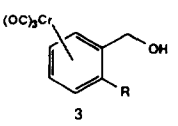

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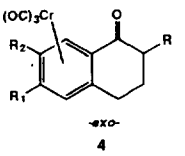

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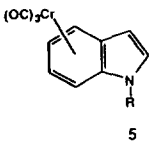

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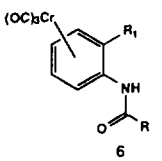

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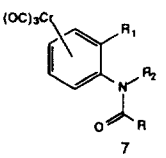

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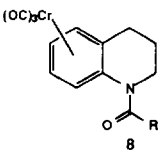

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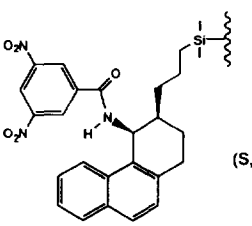


(S,S) Whelk-O 1 CSP

Compound	R	R_1	R_2	k'_1	α	$[\alpha]_D$
1a	CH_3			4.28*	1.07*	+
1b	OCH_3			7.57*	1.09*	+
2a	CH_3			3.57*	1.06*	+
2b	OCH_3			8.00*	1.00*	+
3a	CH_3			1.77	1.11	+
3b	OCH_3			3.22	1.15	+
4a	H	H	H	4.48	1.08	+
4b	H	H	OCH_3	3.82	1.07	+
4c	H	OCH_3	H	5.93	1.18	+
4d	CH_3	H	H	2.25	1.19	+
4e	n-C_3H_7	H	H	1.48	1.23	+
4f	Allyl	H	H	1.63	1.21	+
4g	CH_3	OCH_3	H	2.91	1.29	+
4h	Allyl	OCH_3	H	2.07	1.37	+
5a	H			1.57	1.00	+
5b	CO–CH_3			6.79	1.04	+
5c	CO–n-C_3H_7			3.36	1.00	−
5d	CO–n-C_5H_{11}			2.36	1.09	−
5e	CO–n-C_9H_{19}			1.34	1.13	−
5f	CO–*tert.*-C_4H_9			2.28	1.00	−
6a	CH_3	CH_3		4.93	1.62	−
6b	n-C_3H_7	CH_3		3.14	1.86	−
6c	n-C_5H_{11}	CH_3		2.43	1.88	−
6d	n-C_9H_{19}	CH_3		1.79	1.99	−
6e	*tert.*-C_4H_9	CH_3		2.44	1.75	−
6f	*tert.*-C_4H_9	C_2H_5		1.71	1.75	−
6g	*tert.*-C_4H_9	iso-C_3H_7		1.14	1.75	−
6h	*tert.*-C_4H_9	*tert.*-C_4H_9		0.78	1.65	−
6i	*tert.*-C_4H_9	OC_2H_5		1.86	1.69	−
7	*tert.*-C_4H_9	CH_3	CH_3	2.10	1.00	/

(Continued on p. 66)

Table 1 (*continued*).

Compound	R	R_1	R_2	k'_1	α	$[\alpha]_D$
8a	CH_3			11.86	2.08	–
8b	n-C_3H_7			3.71	2.50	–
8c	n-C_5H_{11}			3.14	2.73	–
8d	n-C_9H_{19}			2.30	2.74	–
8e	*tert.*-C_4H_9			2.29	2.46	–

α = Chromatographic separation factor; k'_1 = retention factor of the first-eluted enantiomer using 20% (v/v) 2-propanol in hexane as the mobile phase (asterisk: 30% CH_2Cl_2), flow-rate 2.0 ml/min, temperature 20°C. The $[\alpha]_D$ column gives the sign of $[\alpha]_D$ of the first-eluted enantiomer.

introduction of a *para*-methoxy group and/or an *exo*-alkyl substituent. Elution order, based on polarimetric detection and comparison with literature data [1], is uniform throughout the series, the (1*R*)-enantiomers being more retained on the (*S*,*S*)-CSP. N-Acylindole complexes show reduced enantioselectivity and a change in the sign of rotation of the less retained enantiomer as one passes from **5b** to **5c–f**. The signs of $[a]_D$ have not been related to the absolute configurations of these compounds and while we suspect that there has been an inversion in the order of elution, a change in the sign of rotation cannot be excluded. A change in the order of elution might occur if there is a change in the analyte's conformational preferences (i.e., *E*/*Z* isomerism around the N–CO bond) with an increase in the size of the acyl substituent. Greater enantioselectivities are obtained for the chromium complexes of N-acylated *ortho*-substituted anilines **6a–i** and N-acylated 1,2,3,4-tetrahydroquinolines **8a–e** (Fig. 1).

The elution order for the type **6** and type **8** amide complexes can be established, since (+)-**6a** is known to have the (1*S*)-configuration [15,16]. The on-line recorded CD spectra of the more retained enantiomers of **6a**, **6e** and **8e** are very similar, each having a positive Cotton effect around 320 nm. Since the sign of $[\alpha]_D$ of the least retained enantiomer is always negative, it is believed that each of the more retained enantiomers of the type 6 and type 8 amide complexes listed has the (1*S*)-configuration. Inspection of the data in Table 1 shows that enantioselectivity increases as the steric bulk of the acyl substituent increases. However, the size of the *ortho*-alkyl substituent has little effect on enantioselectivity. On the other hand, no chiral recognition is observed for the corresponding N-methyl derivative, **7**. This can be rationalized by the chiral recognition model depicted in Fig. 2. Here, the chiral selector and each of the analyte enantiomers are shown in stable, highly populated (in solution) conformations. The amide complexes have the carboxamide carbonyl oxygen close to the *ortho*-aromatic hydrogen and the smaller amide hydrogen close to the *ortho* substituent. The aromatic ring is essentially coplanar with the

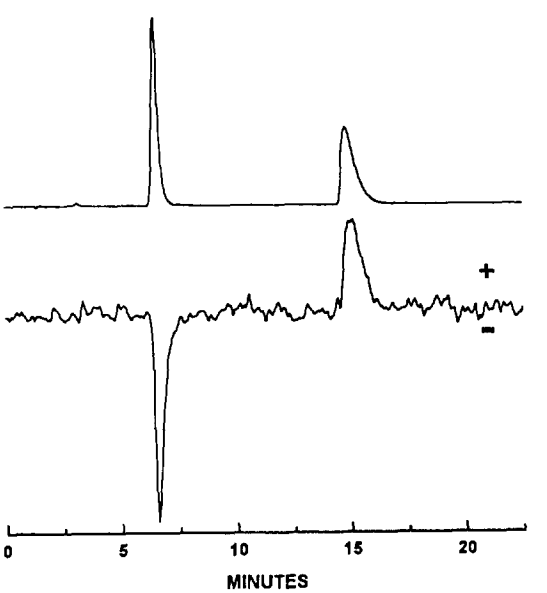


Fig. 1. Resolution of the enantiomers of **8e** on CSP 1, with simultaneous UV (top) and CD (bottom) detection at 320 nm.

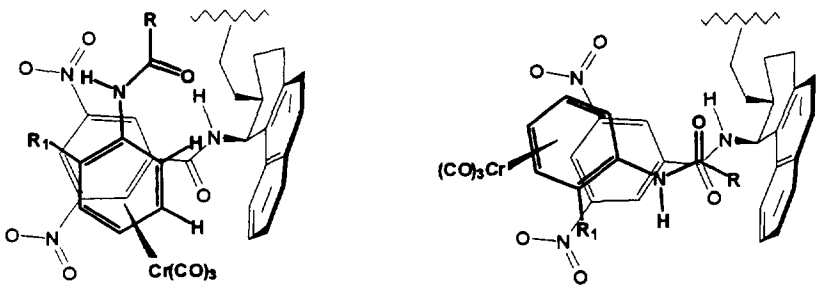
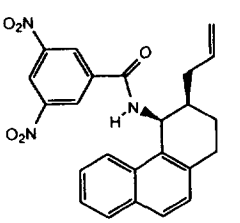


Fig. 2. Proposed recognition model between CSP 1 and the least (left) and most (right) retained enantiomers of amide-type tricarbonyl–chromium complexes.

plane of the carboxamide group. Chemical shifts of the aromatic *ortho*-hydrogens are diagnostic of conformational preferences. In **6a–e** and **8a–e**, they are strongly deshielded (0.6–0.8 ppm) with respect to the remaining aromatic hydrogens. The selector is depicted in the conformation found in the solid state by X-ray diffraction analysis [17].

There are numerous examples of molecular complexes between arenetricarbonyl–chromium compounds and aromatic electron acceptors [18–21]. The principal attractive interactions invoked in the formation of the most stable diastereomeric adsorbate (Fig. 2, left) are a hydrogen bond between the amide N–H of the CSP and the carbonyl oxygen of the analyte and simultaneous face-to-face and face-to-edge $\pi-\pi$ interactions [22] between the aromatic portion of the analyte as it occupies the cleft formed by the 3,5-dinitrobenzamide and the naphthyl group. Even should the less strongly complexed enantiomer enter a cleft, it could not enjoy these three attractive interactions simultaneously. In endeavoring to undergo the hydrogen bonding and face-to-face $\pi-\pi$ interactions, the less strongly complexed enantiomer would, as depicted on the right in Fig. 2, instead of an attractive face-to-edge interaction, encounter a repulsive steric interaction between the alkyl substituent, R, of the analyte and the naphthyl ring of the CSP. The extent of "destabilization" afforded by this interaction would be expected to be related to the effective size of R. In the case of the tertiary amide derivative, **7**, the plane of the carboxamide group is perpendicular to that of the aromatic ring, for all the aromatic hydrogens give a single ^{1}H NMR signal, indicating that they are remote from the carbonyl oxygen. This places the carboxamide oxygen, an essential interaction site, in a different spatial relationship with respect to the other binding sites. This is presumably responsible for the inability of CSP 1 to differentiate between the enantiomers of **7**. Should the carboxamide oxygen be *endo* to the tricarbonyl–chromium portion of the complex, it is evident that neither enantiomer of **7** could utilize this oxygen as a hydrogen bond donor while undergoing a face-to-face $\pi-\pi$ interaction.

The proposed mode of association is consistent with ^{1}H NMR data obtained from mixtures of (*S,S*)-**9**, a soluble analogue, of the selector used in CSP 1, and each of the enantiomers of **8e**. For example, the resonance of the NH hydrogen of (*S,S*)-**9** (0.047 *M* in $C^2H_2Cl_2$, $\delta = 6.65$ ppm) is shifted downfield by 0.20 and 0.10 ppm, respectively, in the presence of equimolar amounts of (1*S*)-**8e** or (1*R*)-**8e**. This indicates more extensive hydrogen bond formation in the former mixture, a mixture containing the enantiomer more strongly retained by CSP 1.



(S,S)-9

Upfield shifts of 0.17 and 0.02 ppm are also observed for the *ortho*-hydrogens of (1*S*)-**8e** and (1*R*)-**8e**, respectively (0.047 *M* in $C^2H_2Cl_2$, $\delta =$

6.32 ppm) in the presence of equimolar amounts of (*S*,*S*)-**9**. This is consistent with more extensive face-to-face $\pi-\pi$ interaction in the former mixture which contains the enantiomer more strongly retained by CSP 1. Alternatively, these shifts could conceivably arise from small but unequal changes in the dihedral angles of the planes of the carboxamide and arene groups on complexation.

Acknowledgements

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References

[1] A. Solladié-Cavallo, in L. Liebeskind (Editor), *Advances in Metal-Organic Chemistry*, Vol. 1, JAI Press, Greenwich, 1989, pp. 99–133.
[2] S.G. Davies, J.J. Donohoe and J.M.J. William, *Pure Appl. Chem.*, 64 (1992) 379–386.
[3] M. Uemura, T. Minami, M. Shiro and Y. Hayashi, *J. Org. Chem.*, 57 (1992) 5590–5596.
[4] T.E. Bitterwolf, T.L. Hubler and R. Todine, *J. Macromol. Sci., Chem.*, A27 (1990) 1437–1446.
[5] Y. Yamazaki, M. Morohashi and K. Hosono, *J. Chromatogr.*, 542 (1991) 129–136.
[6] G. Carrea, P. Pasta, S. Colonna and N. Gaggero, *J. Chromatogr.*, 600 (1992) 320–322.
[7] K. Schlögl, *J. Organomet. Chem.*, 300 (1986) 219–248.
[8] V. Gajda, S. Toma and M. Widhalm, *Monatsh. Chem.*, 120 (1989) 147–156.
[9] E. Francotte, *J. Chromatogr. A*, 666 (1994) 565–601.
[10] W.H. Pirkle, C.J. Welch and B. Lamm, *J. Org. Chem.*, 57 (1992) 3854–3860.
[11] W.H. Pirkle and C.J. Welch, *J. Liq. Chromatogr.*, 15 (1992) 1947–1955.
[12] C.A.L. Mahaffy and P.L. Pauson, *Inorg. Synth.*, 28 (1990) 136–140.
[13] G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, 97 (1975) 4667–4672.
[14] C.W. Holzapfel and F.W.H. Kruger, *Aust. J. Chem.*, 45 (1992) 99–107.
[15] S. Rosca and C.D. Nenitzescu, *Rev. Roumaine Chim.*, 15 (1970) 259–263.
[16] J. Paul and K. Schlögl, *Monatsh. Chem.*, 102 (1971) 788–797.
[17] W.H. Pirkle, C.J. Welch and S. Wilson, *Chirality*, in press.
[18] O.L. Carter, A.T. McPhail and G.A. Sim, *J. Chem. Soc. (A)*, (1966) 822–838.
[19] H. Kobayashi, M. Kobayashi and Y. Kaizu, *Bull. Chem. Soc. Jpn.*, 46 (1973) 3109–3116.
[20] R. Lal De, J. Von Seyerl, L. Zsolnai and G. Huttner, *J. Organomet. Chem.*, 175 (1979) 185–191.
[21] P.G. Sennikov, V.A. Kuznetsov, A.M. Egorochkin, N.I. Sirotkin, R.G. Nazarova and G.A. Razuvaev, *J. Organomet. Chem.*, 190 (1980) 167–176.
[22] W.H. Pirkle and C.J. Welch, *Tetrahedron Asymmetry*, 5 (1994) 777–780.