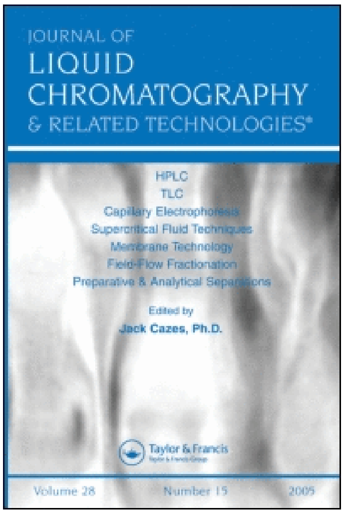

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OUTER-SPHERE LIGAND EXCHANGE CHROMATOGRAPHY ON BONDED CHIRAL SILICA GEL

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ABSTRACT

A bonded chiral phase for HPLC, obtained by reaction between a porous silica gel modified with N(aminoethylamino)propyl groups, and $\Lambda(+)[Co(en)_2(NO_2)_2]$ Br, was prepared in order to separate optical isomers by a outer-sphere complex mechanism. The extent of the stereoselectivity of this support was tested by sampling racemates of organics acids and of tris-oxalate complexes of cobalt(III) and chromium(III). Good resolution was achieved when strong interactions of the solute (tri-oxalates complexes) with the support were involved.

INTRODUCTION

It has long been known that optically active metal complexes may enantioselectively coordinate asymetric compounds in their second sphere (1-3). As may be expected from the outer-sphere complexation mechanism applied to liquid chromatography, the resolution of racemic mixtures on chiral supports has so far not been extended. For example the separation of the optical isomers of organic acids can be achieved on a cation-exchange resin column loaded with the Λ (+) form of optically active $[Co(en)_3]^{3+}$(4). However strong metal-solute interaction may give rise to a gradual leaching of the complex from the column(5).

Recently Chow and Grushka (6) prepared a siliceous bonded phase containing a $[Co(en)_3]^{3+}$moiety and used it for the separation by HPLC of mononucleotides. Such chemically bonded support should result promising, in a modern liquid chromatographic system, for the achievement of high efficiency and selectivity. In fact outer-sphere complex formation and dissociation are fast processes (7), and favor the rate of mass transfer. Further, depending on the nature of the ligand coordinated to the metal and that of the species to be separated, several interactions may take place (8,9). The above considerations led us to prepare a bonded chiral support containing Λ (+)tris-ethylenediaminecobalt(III) groups. In this paper the resolutions of some racemic mixtures are reported.

EXPERIMENTAL

Instrumentation

The HPLC instrumentation was constituted by a Perkin-Elmer liquid chromatographer Series 2 equipped with a Rheodyne 7105 injector valve, and a Perkin-Elmer LC 55 UV-VIS detector. Reflectance spectra were obtained using a Beckman DB-GT Spectrophotometer. For optical rotation measurements a Perkin-Elmer Model 141 polarimeter was used.

Preparation of the chiral phase

Silica gel modified in diamine form was prepared from LiChrosorb Si 60 (particle size 10 µm) (Merck) and 3-(2-aminoethyl amino)propyltrimetoxysilane (Serva) according to the method described by Engelhardt et al.(10). The C,H,N, analysis indicated a diamine group surface coverage corresponding to $2.5 \mu m/m^2$.

Cis-dinitro-bis(ethylenediamine)cobalt(III) bromide was prepared from *trans*-dichloro-bis(ethylenediamine)cobalt(III) chloride (11) following the method given by Worrell (12). It resolved in its levo and dextro forms as described by Dwyer and Garvan (13).

To a suspent ion of silica diamine (3,6 g) in 150 ml of water previosly adjusted to $p_H = 7.0$, 4.0 g of Λ(+)-*cis*-dinitro-bis-(ethylenediamine)cobalt(III) bromide were added, and the mixture stirred overnight at 55°C. The optical rotation of the aqueous solution containing dissolved Λ (+)-*cis*-dinitroamine complex was measured during the substitution reaction. No racemization occurred. The modified silica gel was filtered in a sintered glass funnel and washed with distilled water,methanol and acetone, and then vacuum dried for six hours at 60°C.

The C,H,N and Co anlysis revealed about $1.4 \mu m/m^2$ of cobalt(III) complex bonded on the support.

Column and samples

The column (250 x 4.0 mm I.D.,stainless steel) was packed by conventional slurry method (suspent ion in $MeOH\text{-}H_2O = 1:1$) using a Haskel pump Model DSTV-122 at 9000 p.s.i.

D (+)- and ℓ (-)-malic acid and d (-)- and ℓ (+)-tartaric acid and their racemic forms were supplied by Carlo Erba. Sodium cobalt(III) oxalate and sodium chromium(III) oxalate were prepared as described in the literature (14). Sodium cobalt(III) oxalate was resolved into its optical isomers (15).

Each sample, dissolved in the eluent,was injected in the column as freshly prepared solution.

RESULTS AND DISCUSSION

In the figure 1-4 the elution curves of some optically active compounds on the chiral modified silica gel are reported. In all experiences, with the exception of $\left[Cr(ox)_3\right]^{3-}$ available only as racemate, isomers and their racemic mixtures were sampled. However, owing to the eventual presence in the sample solutes of some impurity or decomposition species formed during the run, the resolved fraction were collected and their optical rotation measured. As shown in the figure 1 no separation between *d*(+)- and *ℓ*(-)-malic acid was obtained; however the isomers eluted individually shown a slight retention difference. When geometric specifities and increased electrostatic interactions are involved, stronger outer-sphere complexation takes place (9) and resolution is achieved (fig. 2,3 and 4). In table 1 the chromatographic data for the three pairs of isomers resolved are presented.

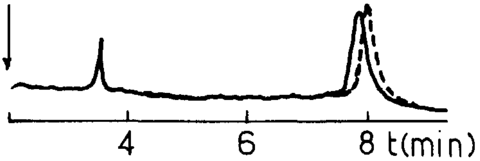

FIGURE 1. Elution of l(-)malic (——) and d(+)malic (---) acids eluted separately. Conditions: Eluent, 0.01M phosphate buffer to p_H=6.2; flow-rate, 1.0 ml/min; detector, UV 220 nm; attenuation, 0.05 AUFS.

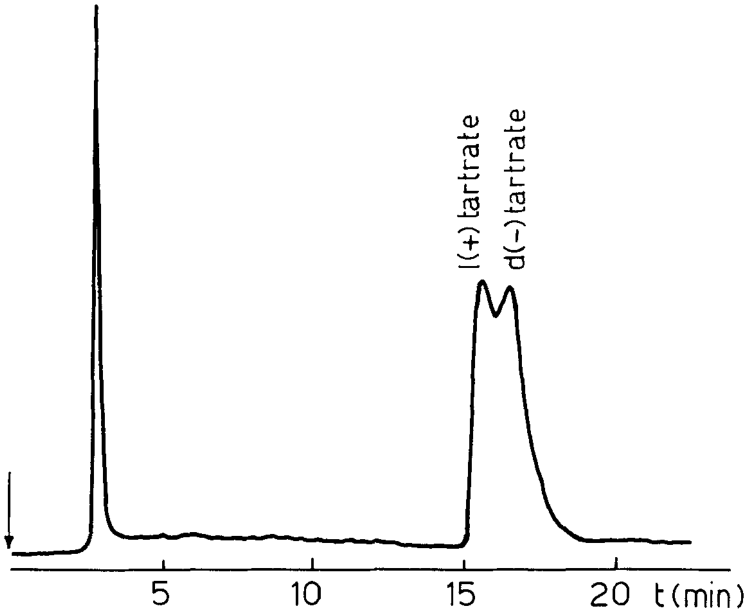

FIGURE 2. Elution curves of racemic tartaric acid. Conditions: Eluent,0.02M phosphate buffer to p_H=6.2; flow-rate,1.2 ml/min; detector,UV 220 nm;attenuation, 0.05 AUFS.

TABLE 1

k' values ,selectivity factor (k'_2/k'_1) and resolution R_s ($t_2-t_1/b_{(2)}+b_{(1)}$) of the three racemic mixtures

	k'	α	R_s
1) l(+) tartaric acid	4.57	1.08	0.45
2) d(-) tartaric acid	4.93		
1) Δ (-) $Cr(ox)_3^{3-}$	2.27	1.15	0.72
2) Λ (+) $Cr(ox)_3^{3-}$	2.60		
1) Δ (-) $Co(ox)_3^{3-}$	2.33	1.16	0.77
2) Λ (+) $Co(ox)_3^{3-}$	2.70		

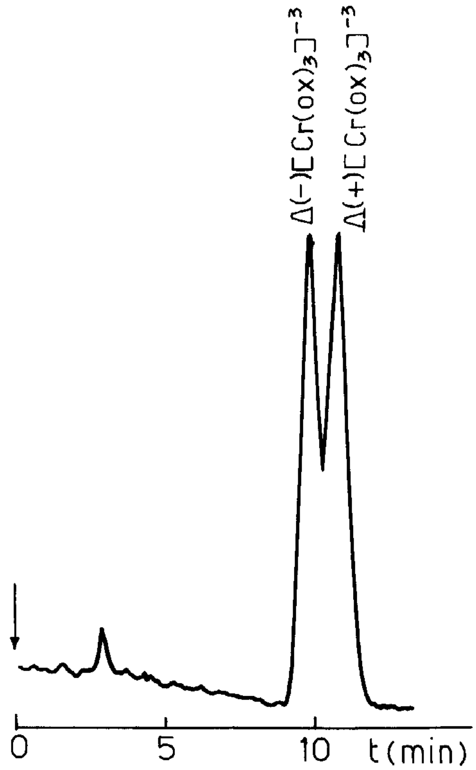

FIGURE 3. Elution curves of racemic $[Cr(ox)_3]^{3-}$ complex. Conditions: Eluent, 0.1M phosphate buffer to p_H=6.15; flow-rate, 1.0 ml/min; detector, VIS 425 nm; attenuation,0.02 AUFS.

Ga'al et al. (4) loaded a cation-exchange column with Λ-$[Co(en)_3]^{3+}$cation complex and completly resolved the isomers of the aspartic and mandelic acids. Our chromatographic system does not show a similar stereoselectivity, and this lower performance could be attributed to two different reasons. Elemental analysis of the modified support indicated that only a fraction of diamine groups (about 55%) reacted with Λ-cis-$[Co(en)_2(NO_2)_2]^{+}$ determining a poor optically active environment. In addition, pro-

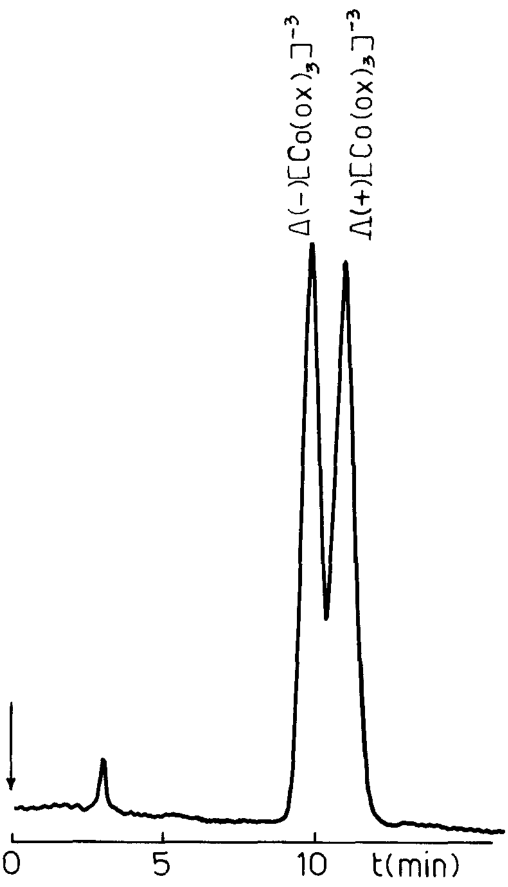

FIGURE 4. Elution curves of racemic $[Co(ox)_3]^{3-}$ complex. Condition: Eluent, 0.1M phosphate buffer to $p_H = 6.15$; flow-rate, 1.0 ml/min; detector, VIS 425 nm; attenuation, 0.02 AUFS.

bably only one of the amino group of the silica diamine substituted a $-NO_2$ group in the inner sphere of the cobalt(III) complex. This hypothesis is suggested by the reflectance spectra analysis of modified silica gel. In fact the shift to higher wavelengths of λ_{max} and λ_{min} (fig.5) indicates that the first of the two $-NO_2$ groups

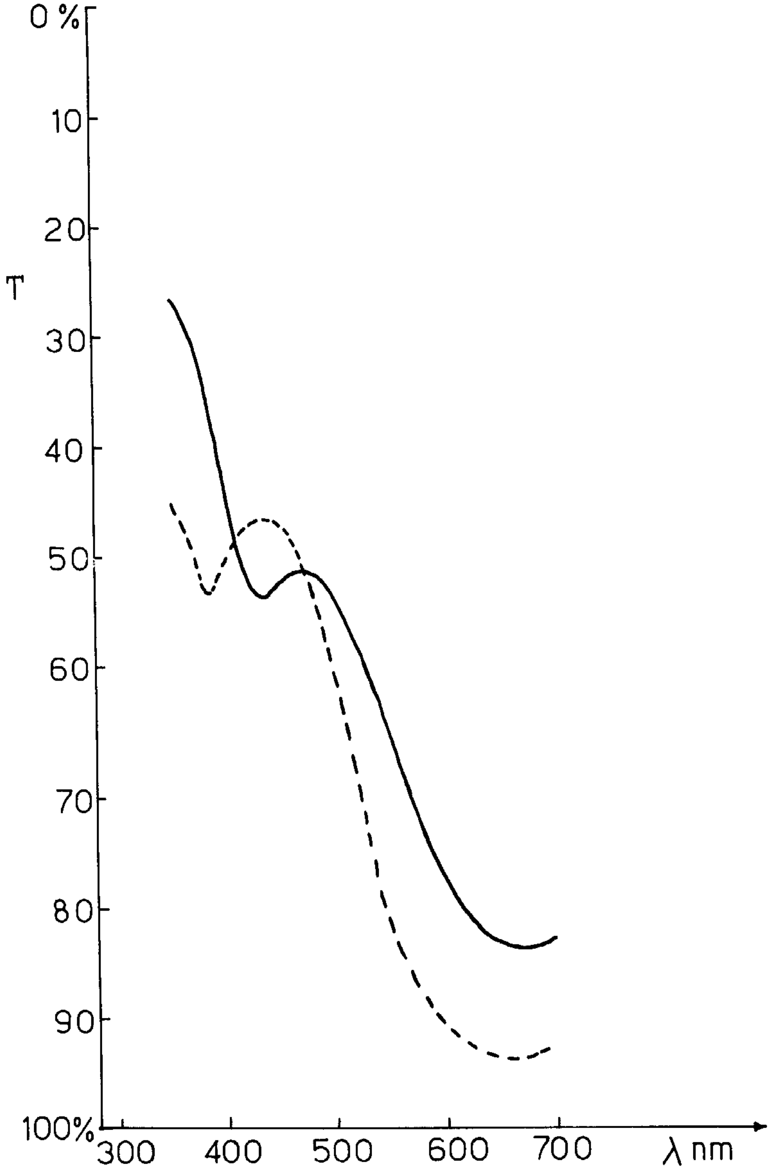

FIGURE 5. Visible Reflectance spectra of (+)-cis$\left[Co(en)_2(NO_2)_2\right]$Br (-----) and chiral modified silica gel (——).

is substituted by a -NH_2 group and the other by water or OH^- group (16,17).

The low reactivity of the diamine silica gel could be attributed to a hindering action of the medium water molecules,forming bridges between the free silanols and the amino functionalities bonded to the siliceous support.This hypothesis is supported by data to be reported in detail elsewhere (18),which have shown a much more superficial concentration of functional groups when the reaction between a lyposoluble aminocomplex of cobalt(III) and the diamine silica gel is carried out in an an anhydrous solvent, e.g. N-N'-dimethylformamide.

Furter work in order to improuve the preparation conditions of support containing either optically active or racemic forms of inert metal complexes is in progress. In addition the practical application of such supports to the separation of complex mixtures is under investigation.

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