Computational study of the chromatographic enantioseparation of tris(acetylacetonato)cobalt(III) complexes on an arginine complex of cobalt(III) acting as a chiral selector

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Abstract: A computational procedure for the modelling of chromatographic separation of neutral tris(acetylacetonato)cobalt(III) into enantiomers on a dinitrobis(arginine)cobalt(III) complex as a chiral selector is described. Predicted elution order calculated from the differences in total energy of interaction for Λ and Δ selectands is in agreement with the experimental results. Predictive power of the method and its possible practical applications in designing efficient chiral stationary phases is demonstrated.

Keywords: Co(III) complexes, chromatographic enantioseparation, molecular mechanics, computational modelling, chirality.

INTRODUCTION

The importance of the production of optically active compounds in such diverse fields as, *e.g.*, pharmaceutics, natural products chemistry, or agrochemistry, coupled with the key theoretical significance of chiral molecules for understanding of basic chemical phenomena, is generating a vigorous continued interest in this topic.[1]

The need for a better understanding of chiral phenomena at the molecular level has made the computational modelling of chromatographic enantioseparations[2] an area of considerable recent interest, as evidenced by the numerous articles in several specialized journals (including *Tetrahedron: Asymmetry, Enantiomer, Chirality*, and *Molecular Asymmetry*) dedicated to this topic.

Most of the computational studies reported so far were concerned with the enantioseparation on natural macromolecules (polypeptides,[3] polysaccharides,[4] and their deriva-

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tives) or synthetic chiral macromolecules[5] acting as chiral selectors (also known as chiral stationary phases) in high-performance liquid or gas chromatography. Depending upon the nature of the chosen chiral selector either the short-range dispersion forces or the long-range electrostatic forces were identified[2] as most responsible for enantioselectivity. The overall shape of the chiral selector was found to be determinate for the efficiency of the enantioseparation. In this respect selectors are generally classified as open (*e.g.,* flat surfaces), half-open (*e.g.,* with hemispheric cavities), and closed (*e.g.,* cylindrical)[6] with their binding efficiencies increasing roughly in that order.

The present work originated from the earlier study[7] by one of us, which showed that neutral tris(acetylacetonato) complexes of trivalent transition metals could be efficiently resolved into enantiomers on a $[Co(S–Arg)_2(L)_2]^+$ complex (with L = NO_2^- or Cl^- ligands) acting as a chiral stationary phase (CSP). That report represented the first, and to our knowledge still the unique, published result describing a chromatographic enantioseparation on a chiral selector consisting of a transition metal complex, that surpassed in efficiency most of the other known enantioseparation methods.[8]

To gain further insight into the mechanism of enantiodiscriminating interactions responsible for the resolution, we have carried out a computational modelling of the interactions between Λ and Δ $[Co(acac)_3]$ and the CSP. We have followed a molecular mechanics approach using the computational methods and parameters taken over from our previous conformational studies on coordination compounds, with a number of modifications described below.

COMPUTATIONAL DETAILS

Initial coordinates of $[Co(acac)_3]$ were constructed by imposing exact $\mathcal{D}_3$ symmetry to the structure obtained from the published single-crystal X-ray diffraction study by Kruger and Reynhardt.[9] Both enantiomers were constructed from the same atomic coordinates. In the present molecular mechanics simulations the selectand was treated as a rigid structure.

Initial structure of $[Co(S–Arg)_2(NO_2)_2]^+$ corresponded to that found in the single-crystal X-ray diffraction study of the nitrate dihydrate $\Lambda(+)_{589}$ diastereoisomer by Watson, Kamberi and Ćelap.[10] The compound was actually used as the chiral selector in our chromatographic separations.

Point charges of $[Co(acac)_3]$ were computed by semi-empirical MO calculations using either the ZINDO/1[11] program or the extended Hückel program of Hoffmann.[12]

Point charges on $[Co(s–Arg)_2(NO_2)_2]^+$ were compiled using the selected values from the published *ab initio* calculations[13–15] for the Arg sidechain. Missing values were estimated by performing extended Hückel calculations[12] on the relevant fragments of cobalt(III) complexes containing coordinated Arg and nitro groups, and by adjusting the obtained values with respect to the published ones to ensure the correct sum and the chemically reasonable charge distribution.

Point charges on NO_3^- and lattice water were computed using the MICROMOL *ab initio* program of Colwell *et al.*[16]

Molecular mechanics calculations were performed with a substantially modified version of the CFF program package.[17] Since both the selectand and the CSP were treated as rigid structures, only the intermolecular van der Waals, electrostatic, and hydrogen bonding interactions were considered. Consequently, only the Lennard-Jones "6–12" type functions for all required atom pair types were used. The functions were supplemented with simple Coulomb terms with distance-dependent dielectric constant:

$$E_{\text{NB-pairs}} = \sum_{i \neq j} \left[\in_{ij} \left(\frac{r_{ij}{}^*}{r_{ij}} \right)^{12} - 2 \in_{ij} \left(\frac{r_{ij}^*}{r_{ij}} \right)^{6} + \frac{e_i \cdot e_j}{D(r) \cdot r_{ij}} \right]$$

where r^*_{ij} and $\in_{ij}$ represent equilibrium distance and energy, respectively, e_i and e_j are point charges on atoms i and j, and $D(r)$ is a variable dielectric constant.

Parameters for the Lennard-Jones "6–12" functions were derived by a least–squares fit to the "exp-6" functions[17] with the parameters used extensively in our previous molecular mechanics calculations on coordination compounds.[18] Missing values (*e.g.,* for Arg sidechain atoms) were extrapolated from the AMBER99 force field for proteins[19] taking care that the internal consistency of the entire parameters set is preserved.

Definition of a CSP surface and the periodic boundary conditions are described in the Results section below.

For energy minimization, a grid-search technique followed by the conjugate-gradient method of Powell[20] was used. In the latter algorithm a choice between the Fletcher-Reeves[21] and the Polack-Ribiere[22] scheme for updating the conjugate gradient direction is offered.

RESULTS

Rigidity of the selectand in the present treatment is justified by the fact that acac rings in a tris(bidentate) structure are indeed essentially planar in all known structures.The only possible internal degree of freedom is the trigonal twist[23] as a function of the radius of the central metal atom. However, a change of the trigonal twist angle, in the range that includes all reported values for different transition metal ions, did not influence the results of the present calculations to any appreciable degree, so the twist angle was fixed at the averaged crystallographic value of 68º for the cobalt(III) structure.

The active surface of the CSP was defined on the atomic level by the method of inspection. Various cross-sections were examined starting from the planes parallel to those with the smallest values for Miller indices. Planes that intersect covalent bonds were discarded, and those that do not (or almost do not intersect the bonds) were considered. In this way we selected planes (2 2 0) and (0 0 1). By inspection of the three-dimensional lattice of $[Co(S–Arg)_2(NO_2)_2]NO_3 \cdot 2H_2O$ it is clearly seen (Fig. 1) that the former plane does not intersect any of the covalent bonds, so it is reasonable to suppose that the crystal should preferentially cleave along that plane. The plane (0 0 1) has similar properties (see Fig. 2).
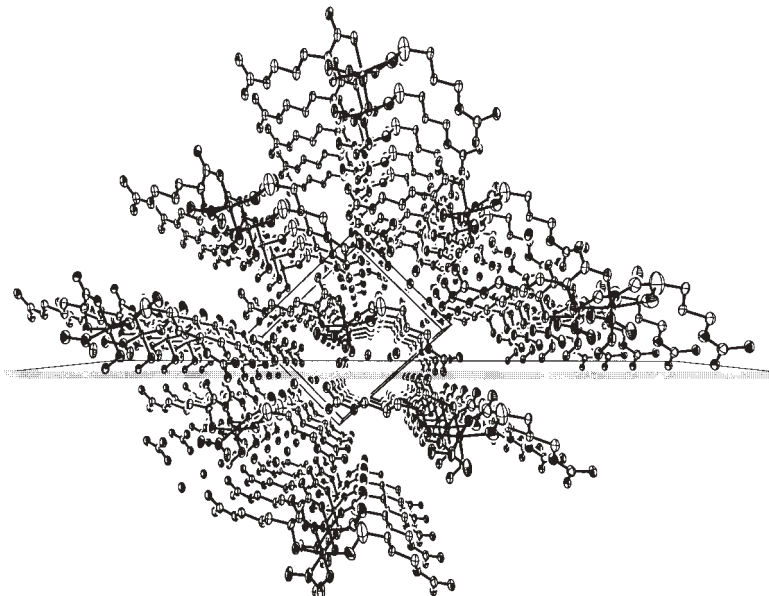
Fig. 1. Plane (2 2 0) forming a cross-section of the crystal lattice of $[Co(S–Arg)_2(NO_2)_2]NO_3 \cdot 2H_2O$.
Approximate projection along the crystallographic c axis is shown. One unit cell is indicated by solid
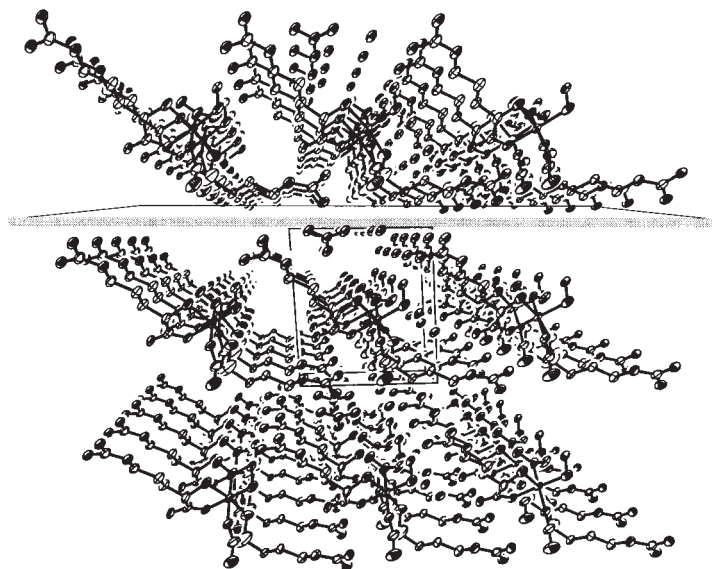black lines.

Fig. 2. Cross-section of the crystal lattice of $[Co(S–Arg)_2(NO_2)_2]NO_3 \cdot 2H_2O$ by the (0 0 1) plane.
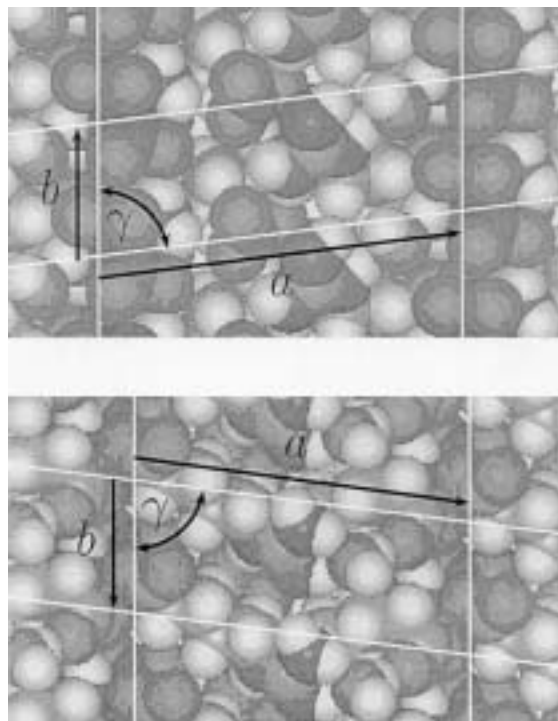See caption to Fig. 1. for further details.

Fig. 3. Two complementary surfaces (in CPK display style) produced by bisecting the crystal lattice of [Co(S–Arg)$_2$(NO$_2$)$_2$]NO$_3$·2H$_2$O along the (2 2 0) plane. The repeating motive of the surface is defined by the vectors a and b and the angle γ (a = 15.375Å, b = 5.701Å and γ = 82.78º).

Our task here is exactly opposite to that of defining the planes in crystal growth simulation, because the CSP is experimentally prepared by grinding the crystalline substance. To our knowledge this simple protocol has not been previously described in this context. Both cross-sections, (2 2 0) and (0 1 0), give forth to the two complementary surface definitions each (for example, Fig. 3), which are easily assembled from the crystallographic atomic coordinates. Owing to the translational symmetry of the surfaces, it was possible to apply periodic boundary conditions in the calculation of nonbonded distances, viz.:

$$r_{ij} = \{(\Delta x_{ij} + \kappa_a + \lambda b \cos \gamma)^2 + (\Delta y_{ij} + \lambda b \sin \gamma)^2 + (\Delta z_{ij})^2\}^{1/2}$$

where Δx_{ij}, Δy_{ij} and Δz_{ij} represent differences in x, y and z coordinates of the atoms i and j; a, b and γ are unit cell parameters relevant to the chosen plane; κ and λ are integers (0, ± 1, ± 2, …) that define the extent of unit translations along in-plane a and b axes (Fig. 3). The cut-off distance for nonbonded interactions was implicitly defined in this work by imposing a limit to the number of translations along a and b, ($a > b$), as: $-1 < k < 1$; $-2 < \lambda < 2$ for the (2 2 0) plane, and $-2 < k < 2$; $-2 < \lambda < 2$ for the (0 0 1) plane. Due to the lack of any experimental evidence that would indicate the contrary, CSP was also treated as a rigid structure in the present modelling of enantioseparation.
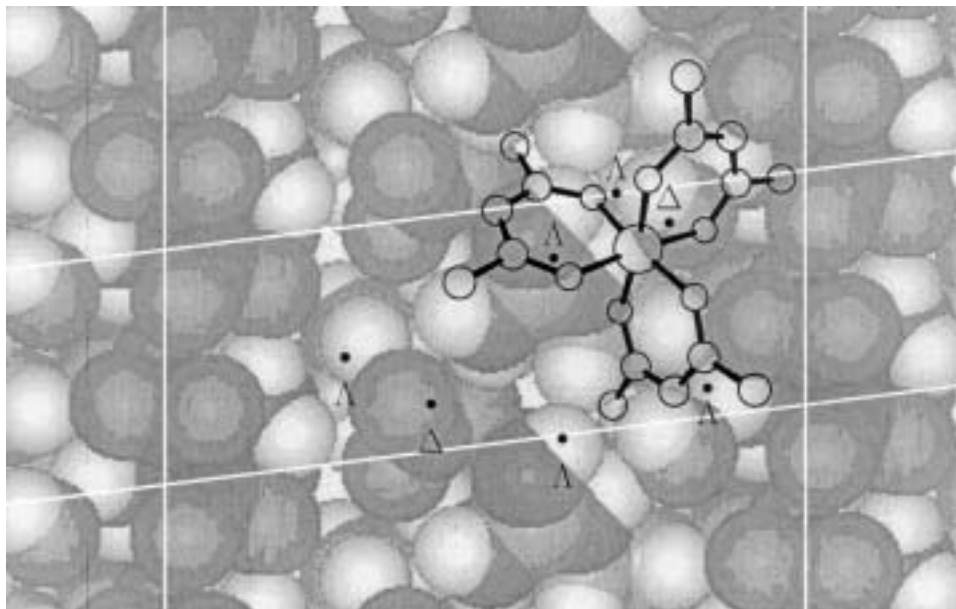
Fig. 4. Positions of Δ and Λ selectand molecules, with respect to the unit cell motive on one of the (2 2 0) CSP planes, which are identified as the low energy local minima. Only one of the two complementary (2 2 0) surfaces is shown to illustrate the modelling results of this work. One Δ selectand which forms the most stable transient complex with CSP is represented in full ball-and-stick display style, with hydrogens removed for clarity, the other selectand positions being represented by their centers of mass only. The CSP surface is represented in CPK display style. For other details of the CSP surface see caption to Fig. 3.

Lennard-Jones function were chosen both for the van der Waals and for hydrogen-bond interactions. In the latter case the angular dependence, in the form suggested by Vedani,[24] was applied:

$$E_{\text{H-bond}} = (A_{\text{DA}}/r^i - C_{\text{DA}}/r^j) \cos^m(\theta_{\text{DHA}}) \cos^n(\chi_{\text{HAA'A''}})$$

where exponents i and j have the standard values for the "6–12" function; exponents m (= 0,2,4) and n (=0,2) depend on the donor atom (D); and angles θ and χ define the bond angles on H and on the acceptor atom (A), respectively. However, the results appeared not to be sensitive with respect to such function refinement.

Minimization procedure was guided by the fact that the CSP surface (in any of the examined cases) did not contain characteristic binding sites. Therefore, the initial screening of the surface was performed by calculating the energy of the CSP–selectand interaction on a series of grid points covering the entire surface of the unit cell motive (such as, for example, the one shown in Fig. 3) at various distances from the mean CSP plane. In this way the most favorable distance of the selectand from the CSP was determined for each projected point. Then a "full" minimization was performed starting from each of such positions, allowing all three translations and three Eulerian rotations of the selectand with respect to the CSP to vary.

Results for the two complementary CSP planes corresponding to the (2 2 0) cross-section are presented in Tables I and II. Corresponding positions of the selectand with respect to the unit cell motive on the CSP plane, which are identified as local minima, are indicated in Fig. 4. The results for the (0 0 1) cross-section (not shown) are qualitatively similar to those presented, so that the following discussion and conclusions apply equally to both pairs of complementary CSP surfaces treated in this work.

TABLE I. Modelling results for the interaction of the Δ, Λ -selectand with the (2 2 0) surface of the CSP.

Selectand coordinates[a]			E(Total) (kJ/mol)	P (%)	$\overline{H}^0$(kJ/mol)	$\overline{G}^0$ (kJ/mol)
x/a	y/b	z[b]				
Λ-[Co(acac)$_3$]						
0.689	0.988	8.404	−128.0	0.1344		
0.281	0.403	7.945	−118.6	0.0030		
0.623	0.007	8.900	−112.2	0.0002		
0.600	0.758	7.714	−144.2	94.1550		
0.597	0.742	7.768	−137.3	5.7074		
0.796	0.161	8.411	−104.0	<0.0001		
					−143.80	−144.37
Δ-[Co(acac)$_3$]					,	
0.401	0.177	8.337	−142.7	0.5122		
0.407	0.194	8.323	−143.9	0.8358		
0.769	0.758	8.198	−127.6	0.0012		
0.403	0.185	8.428	−148.8	6.1301		
0.411	0.198	8.388	−150.9	14.0223		
0.743	0.710	8.218	−155.1	78.4986		
					−154.00	−155.74

[a]Coordinates of the selectand center of mass x and y are expressed as fractional coordinates w.r.t. a and b. [b]Coordinate z is the distance from the plane of the CSP metal atoms.

TABLE II. Modelling results for the interaction of the Δ, Λ-selectand with the (2 2 0) surface complementary to that presented in Table I.

Selectand coordinates[a]			E(Total) (kJ/mol)	P (%)	$\overline{H}^0$(kJ/mol)	$\overline{G}^0$ (kJ/mol)
x/a	$1 - y/b$	z				
Λ-[Co(acac)$_3$]						
0.048	0.645	5.930	−195.6	0.0009		
0.119	0.774	5.628	−224.3	99.7782		
0.101	0.790	5.774	−209.2	0.2209		
0.077	0.702	6.060	−159.5	<0.0001		
0.506	0.355	7.194	−144.8	<0.0001		
0.054	0.726	5.938	−165.1	<0.0001		
					−224.27	−224.31
Δ-[Co(acac)$_3$]					,	
0.295	0.403	6.176	−213.1	<0.0001		

TABLE II. Continued

Selectand coordinates[a]			E(Total) (kJ/mol)	P (%)	$\overline{H}^0$(kJ/mol)	$\overline{G}^0$ (kJ/mol)
x/a	$1-y/b$	z				
0.319	0.355	6.406	–278.0	99.9588		
0.286	0.387	6.012	–225.9	<0.0001		
0.336	0.382	6.316	–252.7	0.0037		
0.337	0.376	6.296	–258.2	0.0340		
0.562	0.356	6.316	–252.6	0.0035		
					–277.98	–277.99

[a]See footnotes to Table I.

DISCUSSION AND CONCLUSION

The elution order can be determined from the computed energies of interaction between the selectand and the CSP surface. In cases with multiple local minima (such as those shown in Tables I and II) the binding energy was obtained by summing over all individual interaction energies and averaging them according to Boltzmann statistics:

$$\overline{E} = \sum_{i=1}^{l} E_i^{\text{calc}} P_i$$

where $\overline{E}$ is the mean enthalpy of interaction; E_i^{calc} is the (calculated) individual energy for the i-th configuration; P_i is the fraction of the Boltzmann population for the i-th configuration; and l is the number of configurations (local minima). $\overline{E}$ was converted into mean Gibbs free energy of interaction, $\Delta\overline{G}$, by correcting for the entropy in the usual way, and eventually related to the enantiomeric separation factor, α, through $\Delta(\Delta\overline{G}) = -RT \ln \alpha$, where $\Delta(\Delta\overline{G}) = \Delta\overline{G}_\Delta - \Delta\overline{G}_\Lambda$. The latter relation is valid since chromatographic retention processes are well described by equilibrium thermodynamics.[25] Our results for both of the (2 2 0) cross-section surfaces (Tables I and II) as well as for the (0 0 1) surfaces (not shown) indicate that the Λ enantiomer of the selectand forms a less stable transient complex with the CSP and is therefore eluted first. This is in agreement with the elution order found experimentally.[8,26]

Furthermore, the close inspection of the equilibrium configurations of the selectand–CSP transient complexes shows that the selectand tends to adopt a preferable orientation with respect to CSP with its trigonal axis perpendicular to the CSP surface in all cases. This is consistent with the fact that for a highly symmetrical molecule, such as [Co(acac)$_3$], the only enantiodiscriminating contact with a chiral surface could be achieved along the direction of its C_3 axis. This validates the "three-contact-point" model for enantiodiscrimination of Pirkle[27,28] (taking also into consideration its generalization by Topiol[29,30]). What distinguishes this system from all the other examples described in the literature is that in our case the three contact points are indeed *equivalent* (related through a cyclic permutation by the C_3 symmetry operation) and that enantiodiscrimination arises only from the

propeller form of the selectand as a source of its chirality. Therefore, the classical "three-contact-point" model in our case may only be regarded as a gross simplification. A more accurate explanation for enantiodiscrimination would require a model comprising a larger number of contact points. This is corroborated by the fact that typically about 15–20 pairwise atom-atom interactions (less than 4Å) between the selectand and the CSP, which contribute to the demarcation between Δ and Λ absolute configurations of the former species, have been discerned in all local equilibrium configurations of the transient selectand – CSP complexes.

The predictive power of the modelling presented in this work remains useful both for the determination of absolute configurations of resolved selectands, as well as in a design of chiral selectors with improved enantioselectivity.

ИЗВОД

ПРОУЧАВАЊЕ ХРОМАТОГРАФСКОГ РАЗЛАГАЊА НА ЕНАНТИОМЕРЕ ТРИС(АЦЕТИЛАЦЕТОНАТО)КОБАЛТ(III) КОМПЛЕКСА НА АРГИНИНСКОМ КОМПЛЕКСУ КОБАЛТА(III) КАО ХИРАЛНОМ НОСАЧУ УЗ ПОМОЋ РАЧУНАРА

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Описан је нов рачунарски поступак за моделирање хроматографског разлагања неутралног трис(ацетилацетонато)кобалт(III) комплекса на енантиомере на хиралном носачу од динитро-бис(аргинин)кобалт(III) комплекса. Редослед елуирања који је предсказан на основу прорачуна разлике у укупној енергији интеракција за Λ и Δ селектанте је у потпуној сагласности са експерименталним резултатима. Тиме је показана могућност предвиђања коју има ова метода, као и њена примена у дизајнирању ефикасних хиралних стационарних фаза.

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