Journal of Molecular Structure 1154 (2018) 373–381

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Anagostic interactions in chiral separation. Polymorphism in a [Co(II)(L)] complex: Crystallographic and theoretical studies

Firas F. Awwadi*, Hamdallah A. Hodali

Department of Chemistry, The University of Jordan, Amman 11942, Jordan

A R T I C L E I N F O

Article history:
Received 21 June 2017
Received in revised form
19 October 2017
Accepted 19 October 2017
Available online 20 October 2017

Keywords:
Chiral separation
Polymorphism
cis-1,2-Disubstituted cyclohexane conformers
Anagostic interactions
Conformation analysis
DFT calculations

A B S T R A C T

Syntheses and crystal structures of two polymorphs of the complex [Co(II)(L)], where H_2L = 2,2'-[*cis*-1,2-diaminocyclohexanediylbis (nitrilo-methylidyne)]bis (5-dimethyl-amino]phenol, have been studied. The two polymorphs concomitantly crystallized by vapour diffusion of solvent. The first polymorph (I) crystallized as a racemate in the centrosymmetric tetragonal $I4_1/a$ space group. The second polymorph (II) crystallized in the chiral orthorhombic space group $P2_12_12_1$. The chiral conformers of symmetrical *cis*-1,2-disubstituted cyclohexane molecules cannot be resolved in the liquid or gas phases, due to the rapid ring inversion. In the present study, the two chiral conformers are present in crystals of polymorph I, whereas, only one chiral conformer is present in crystals of polymorph II. Crystal structure analysis indicated that the formation of two different polymorphs of [Co(II)(L)] complex can be rationalized based on C—H⋯Co anagostic interactions. Density Functional Theory (DFT) calculations indicated that C—H⋯Co interactions are due to HOMO-LUMO interactions.

1. Introduction

Solid state polymorphism refers to different arrangements of crystalline species inside crystalline lattices. Different polymorphs, especially conformational polymorphs, are expected to have different physical properties [1–3] including solubility, density, optical, magnetic … etc. Variation in solubility caused by different polymorphs is important in pharmacology as it leads to different pharmacokinetics. A well-known example of the effect of polymorphism on solubility is the drug Ritonavir which is used to treat Acquired Immunodeficiency Syndrome (AIDS). The formation of a new stable conformational polymorph of Ritonavir with reduced solubility leads to reduced bioavailability, which required reformulation of the drug [2].

The polymorphism phenomenon is not very well understood yet. The general methodology of studying polymorphism is either by preparing different polymorphs serendipitously or intentionally and then rationalizing the supramolecular structure of the different polymorphs using the weak noncovalent interactions connecting the crystalline units or conformational differences [4]. So far, there is no guaranteed method to obtain different polymorphs [3,5]. However, there is significant progress in the area of crystal structure prediction [6]. Different crystallization conditions may results in the formation of different polymorphs including solvent of crystallization [7–9], temperature [10,11], pH [12], pressure [13,14] and the use of auxiliary molecules [7].

The arrangement of different conformers leads to the formation of conformational polymorphs [1], whereas different arrangements of a conformer result in the formation of packing polymorphs. Thirty-six percent of the reported polymorphs in the Cambridge Structural Database is conformational polymorphs [1]. Symmetrical *cis*-1,2-disubstituted cyclohexane molecules exist as two equivalent non-separable conformers in the liquid and gas phases due to the rapid inversion of the cyclohexane ring. As shown in Fig. 1, A and B′ are identical enantiomers and so are B and A'.

Crystallization of symmetrical *cis*-1,2-disubstituted cyclohexane as pure enantiomer is rare, only nine organic and one organometallic examples are known [15–23]. None of these ten examples crystallizes as different polymorphs. In this paper, we report the synthesis and crystal structure of two polymorphs of [Co(II)(L)] where H_2L = 2,2'-[*cis*-1,2-diamino-cyclohexanediylbis (nitrilo-methylidyne)]bis (5-dimethyl-amino]phenol (Fig. 2). Polymorph (I) crystallizes as a racemate in the centrosymmetric space group $I4_1/a$ space group, while polymorph (II) crystalizes as pure enantiomers in the chiral space group $P2_12_12_1$. The two polymorphs crystallize concomitantly from the same solution with approximately 1:1 ratio

---

* Corresponding author.
E-mail address: fawwadi@yahoo.com (F.F. Awwadi).

https://doi.org/10.1016/j.molstruc.2017.10.073

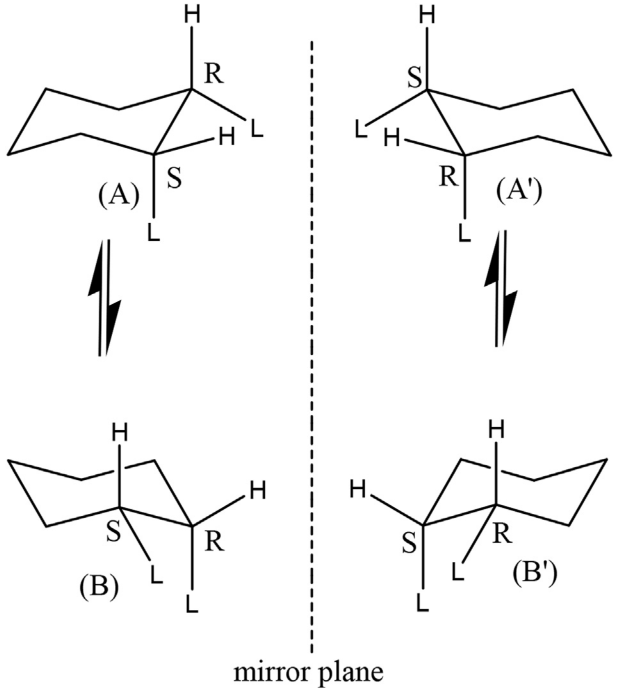

Fig. 1. The enantiomeric conformers of symmetrical *cis*-1,2- disubstituted cyclohexane molecules. The assignment of R and S configuration for the two chiral centers in (A) is arbitrary.

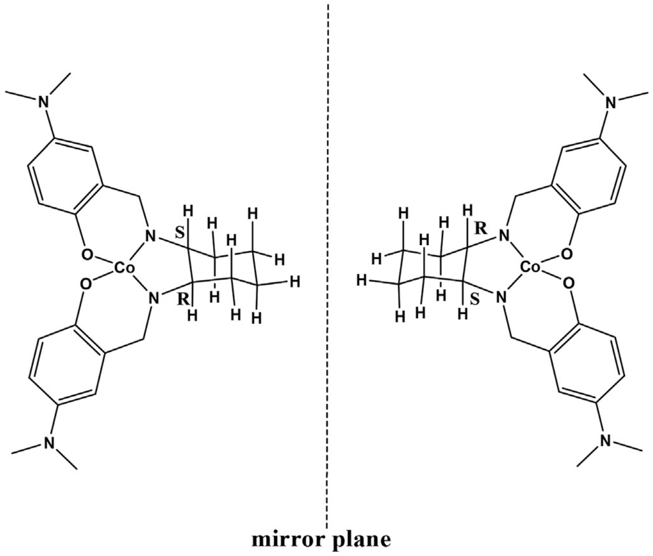

Fig. 2. The two chiral conformers of [Co(II)(L)]. The assignment of R and S configuration for the two chiral centers in the left image is arbitrary.

as inspected under microscopy. To our knowledge, these two polymorphs are the first examples in the literature in which symmetrical *cis*-1,2-disubstituted cyclohexane complexes crystallizes as a racemate (Polymorph I) and pure enantiomer (Polymorph II).

2. Experimental

2.1. Preparation of 4-N,N-dimethylamino-2-hydroxybenzaldehyde

The compound was prepared following the literature procedure with some modifications [24]. The Vilsmeier Haack adduct was prepared by addition of $POCl_3$ (15.0 mL, 0.16 mol) dropwise to dry DMF (30 mL) at 0 °C, and the mixture was then stirred for 30 min at the same temperature. To the adduct, a solution of 3-(*N*,*N*-dimethylamino)phenol (11.0 g, 80.3 mmol) in dry DMF (23 mL) was added dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature, stirred for 4 h, and then heated at 85–90 °C for 30 min. The reaction mixture was allowed to cool to room temperature and kept at that temperature with stirring overnight. It was then poured into crushed ice and neutralized with saturated aqueous solution of Na_2CO_3 (120 mL). The precipitate was filtered off, washed with water and dried in a vacuum oven at 25 °C for 4 h. Yield: 9.00 g (68%), m.p. 78–79 °C (lit. 80.5–81 °C). The compound was used without further purification. ^1H NMR (500 MHz, $CDCl_3$) (Fig. S1-S3): δ = 11.56 (1H, s, OH), 9.47 (1H, s, CHO), 7.24 (1H, d, *J* = 9 Hz, H-6), 6.24 (1H, dd, *J* = 9, 2.1 Hz, H-5), 6.03 (1H, d, *J* = 2.1 Hz, H-3), 3.02 (6H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (Fig. S4): δ = 192.4, 164.1, 156.2, 135.2, 111.7, 104.6, 97.2, 40.1. FT-IR: νCO = 1628 cm^{-1}.

2.2. Preparation of 2,2'-[cis-1,2-diaminocyclohexanediylbis(nitrilo-methylidyne)]-bis(5-dimethyl-amino]phenol, (H_2L)

A solution of 4-(*N*,*N*-dimethylamino)-2-benzaldehyde (1.00 g, 6.05 mmol) in dry ethanol (25 mL) was introduced into a 150-mL two-necked round bottomed flask equipped with a dropping funnel, a condenser, a nitrogen inlet and connected to a bubbler. *cis*-1,2-Diaminocyclohexane (0.346 g, 3.03 mmol) in dry ethanol (20 mL) was added dropwise. After the addition was complete, the reaction mixture was refluxed for 2 h. The reaction mixture was allowed to cool to room temperature and the solid was filtered off and washed with ethanol (2 × 10 mL). The yellow product was dried in a vacuum oven at 50 °C for 4 h. Yield: 1.16 g (94%), m.p. 190–192 °C. 1H NMR (500 MHz, $CDCl_3$) (Fig. S5-S7).: δ = 13.93 (2H, s, OH), 8.07 (2H, s, CHO), 7.03 (2H, d, *J* = 8.2 Hz, H-6, H-6′), 6.18 (2H, dd, 8.2, 2.0 Hz, H-7,H-7′), 6.13 (s, 2H, H9,H9′), 3.55 (2H, m, H-1,H-1′), 3.00 (12H, s, CH_3), 1.56–1.97 (8H, m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$) (Fig. S8): δ = 166.0, 162.4, 153.9, 132.7, 109.0, 103.4, 99.1, 67.4, 40.1, 30.4, 22.6. FT-IR: νC = N = 1614 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_4O_2$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.17; H, 8.36; N, 13.75. HRMS ((+)-ESI): *m*/*z* = 409.25980 (calcd. 408.54 for $C_{24}H_{33}N_4O_2$, $[M + H]^+$).

2.3. Preparation of the cobalt complex, [Co(II)(L)]

A solution of the Schiff base H_2L (0.500 g, 1.22 mmol) in dry methanol (25 mL) was introduced into a 150-mL two-necked round bottomed flask equipped with a dropping funnel, a condenser and a nitrogen inlet and connected to a bubbler. Cobalt acetate tetrahydrate (0.304 g, 1.22 mmol) in dry methanol (20 mL) was added dropwise. After the addition was completed, the dark-brown reaction mixture was refluxed for 4 h. It was then cooled to room temperature and the solid precipitate was collected and washed with small amount of methanol. The orange-red product was dried in a vacuum oven at 50 °C for 4 h. Yield: 88%, m.p. 275–280 °C (dec.). . FT-IR: νC = N = 1575 cm^{-1}. Suitable crystals for single x-ray analysis were obtained by a vapour diffusion method, using the combination CH_2Cl_2/diethyl ether with diffusion of diethyl ether vapour into dichloromethane solution.

2.4. Crystal structure determinations

The crystal structures of cobalt polymorphs (I) and (II) were determined at room temperature using 'Xcalibur, Eos'