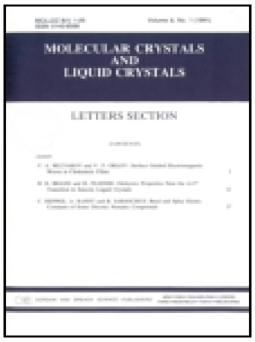

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Crystal structures of D-*N*-(2-adamantyl)phenylglycinol and L-*N*-(2-adamantyl)diphenylphenylalinol: Chiral amino alcohols utilized as ligands for catalytic asymmetric hydroamination

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ABSTRACT
Amino alcohols are important ligands for the asymmetric catalytic hydroamination of aminoallenes to form chiral pyrrolidines. Herein, we report the crystal structures of two chiral amino alcohols, D-N-(2-Adamantyl)phenylglycinol and L-N-(2-Adamantyl) diphenylphenylalinol, that function as ligands within transition metal complexes that catalyze the hydroamination of aminoallenes. Both molecules crystallize in the noncentrosymmetric orthorhombic space group $P2_12_12_1$. Inter- and intramolecular hydrogen bonding plays an important role in stabilizing each alcohol in the solid state in the absence of a transition metal. The presence of these hydrogen bonds has been verified by single crystal X-ray diffraction and their overall strength determined by computational methods.

KEYWORDS
Supramolecular chemistry; chiral amino alcohol; hydrogen bonding

Introduction

The process of adding an N-H bond across an unsaturated carbon-carbon bond, also known as the hydroamination reaction, has seen greater attention in recent years, because it represents an economical pathway to synthesize nitrogen-containing compounds that have industrial and pharmaceutical applications [1–3]. An example of this chemistry is the synthesis of chiral pyrrolidone heterocycles via metal-catalyzed hydroamination of aminoallenes. Even though this type of reaction is favored thermodynamically, the use of a catalyst is essential to overcome the electronic repulsion between the nitrogen and the unsaturated carbons [4]. When this reaction was first studied approximately 30 years ago, the initial catalysts employed were based upon late transition metals such as silver, mercury, and palladium [5–7]. In recent years, however, research groups have studied the use of titanium and tantalum-based catalysts to achieve higher yields at lower cost for this asymmetric reaction [8–14].

For the latter class of catalysts, the synthesis of separate monomeric tantalum alkoxide complexes utilizing both the L- and D-isomers of *N*-(cyclohexyl)diphenylvalinol as chelating ligands has been reported [14]. Within that same manuscript, the crystal structure for only the monomeric tantalum catalyst incorporating L-*N*-(cyclohexyl)diphenylvalinol as a ligand was

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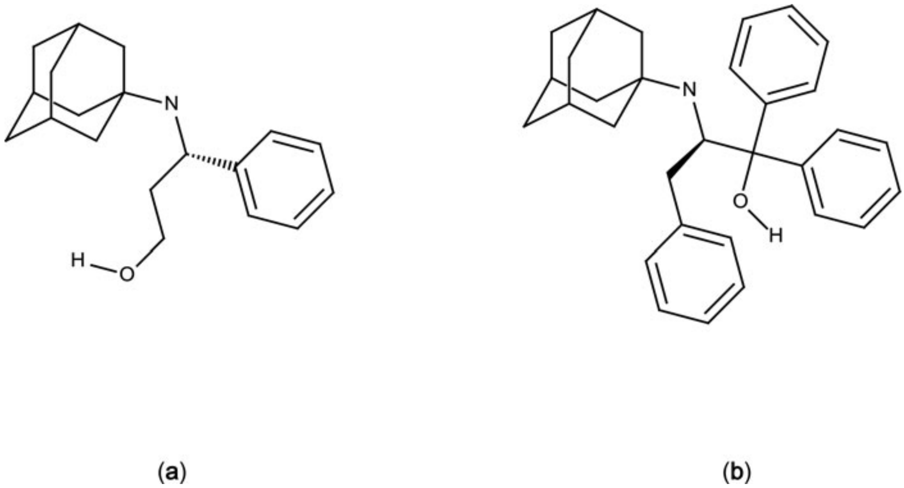

Figure 1. Renderings of D-*N*-(2-Adamantyl)phenylglycinol **1** and L-*N*-(2-Adamantyl)diphenylphenylalinol **2**.

also communicated. Ultimately, the tantalum catalysts using these two chiral amino alcohols as ligands promoted the successful catalytic cyclization of aminoallene to a chiral pyrrolidine with a 74% and 79% enantiomeric excess for the former and the latter alcohols, respectively. Later as interest in the catalytic complexes propagated, attempts to crystallize the alcohol ligands were conducted in order to characterize their solid state structures. Ultimately, such attempts were successful given the structural report of D-*N*-(cyclohexyl)diphenylvalinol, the first amino alcohol structure of this type to be determined [15].

In this manuscript, we report the solid state structure of two additional chiral amino alcohols, D-*N*-(2-Adamantyl)phenylglycinol **1** and L-*N*-(2-Adamantyl)diphenylphenylalinol **2** (Fig. 1). To date, both have been utilized as ligands for transition metal complexes capable of catalyzing asymmetric hydroamination reactions [13,14]. The former alcohol was employed as a ligand on both dimeric titanium and monomeric tantalum catalysts to yield hydroamination products having enantiomeric excesses of 8% and 5%, respectively [16]. The latter, similar to L- and D-*N*-(cyclohexyl)diphenylvalinol, was used as a ligand on a monomeric tantalum catalyst that produced a product mixture having an enantiomeric excess of 25%. Similar to our previously reported structure of D-*N*-(cyclohexyl)diphenylvalinol, both **1** and **2** display evidence of O-H•••N hydrogen bonding which is critical to stabilizing their respective structures in the absence of coordination to transition metal centers. In addition, the overall strength of these hydrogen bonds was determined by means of computational chemistry at various levels of theory.

Experimental

Crystal growth procedure

All reagents were purchased from commercial suppliers and used without further purification. The syntheses of both **1** and **2** have been published previously [13,14]. Diffraction quality crystals for both samples were grown by slow evaporation from a flame-sealed glass pipette containing ~25 mg of each alcohol dissolved in a 7:1 diethyl ether: ethanol solution with a total volume of 1.5 mL.

Single-crystal x-ray crystallography

A pale yellow block-like crystal of **1** with dimensions 0.54 0.45 0.40 mm^3 was secured to a glass fiber using Dow Corning grease and placed into the cold gaseous nitrogen stream of a Bruker APEXII diffractometer. A hemisphere of data was collected in multirun mode with ω as the rotation axis using Mo-K$_{\alpha 1}$ radiation (λ 0.71073 Å) at 100 K. Data collection and initial indexing were handled using SMART [17]. Frame integration, Lorentz-polarization corrections, and final cell parameter calculations were carried out using SAINT [18]. Multiscan absorption corrections were performed using SADABS [19].

For **2**, a pale-yellow block-like crystal with dimensions 0.55 0.45 0.26 mm^3 was secured to a cryoloop using Dow Corning grease and single crystal X-ray diffraction data was collected using a Rigaku SCXMini X-ray diffractometer equipped with a Rigaku Mercury 70 CCD camera. Data was collected at 170 K using graphite-monochromated Mo-K$_{\alpha 1}$ radiation (λ 0.71073 Å). Data collection, initial indexing, frame integration, Lorentz-polarization corrections, and final cell parameter calculations were carried out using CrystalClear [20]. Multiscan absorption corrections were performed using REQAB [21].

For both structures, the space group $P2_12_12_1$ was unambiguously assigned by analysis of the symmetry and systematic absences by utilizing PLATON [22]. The structures were solved using direct methods and difference Fourier techniques. The stereochemical orientations of both **1** and **2** were confirmed upon closer analysis of their respective Flack parameters. All hydrogen atoms were attached via the riding model at calculated positions. The final structural refinement includes anisotropic temperature factors on all non-hydrogen atoms. Structure solution and refinement of all crystallographic data was performed using SHELXS and SHELXL [23]. Crystallographic data of the structural analyses for both **1** and **2** are listed in Table 1. CCDC files 1041708 and 1041709 contain the

Table 1. X-ray crystallographic and refinement data for **1** and **2**.

Compound	1	2
CCDC code	1041708	1041709
Formula	$C_{18}H_{25}N_{12}O_1$	$C_{31}H_{35}N_1O_1$
Formula weight	271.4	437.62
Temp.	100(2)	170(2)
Space group	$P2_12_12_1$	$P2_12_12_1$
a, SÅ	6.7051(3)	6.422(8)
b, SÅ	10.6858(4)	18.693(2)
c, SÅ	21.1723(8)	20.620(3)
α, deg	90	90
β, deg	90	90
γ, deg	90	90
volume, SÅ^3	1512.86(11)	2475.5(5)
Z	4	4
Density (calculated), mg m^3	1.192	1.174
μ, mm^1	0.073	0.07
Scan	ω scan	ω scan
θ range for data collection, deg	1.92–28.87	3.16–27.47
Reflections measured	18169	20464
Independent observed reflns.	3748	5607
Independent reflns. [*I*2σ]	3677	4732
Data restraints parameters	3746 0 265	5607 30 378
R_{int}	0.0148	0.02929
Final *R* Indices [*I*2σ]	*R*1 0.0307, *wR*2 0.0843	*R*1 0.0421, *wR* 2 0.0917
R Indices (all data)	*R*1 0.0312 *wR*2 0.0849	*R*1 0.0523 *wR* 2 0.0970
Goodness-of-fit on F^2	1.041	1.06

supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.ukdata_requestcif.

Theoretical calculations

Interaction energies were computed for each alcohol by performing electronic structure calculations using the program GAMESS [24]. For **1** the computations were performed on a pair of adjacent molecules, while for **2** only a single molecule was used. The atomic coordinates incorporated into the calculations were derived from crystallographic data. The crystallographic position of the hydrogen atoms are not routinely located by difference map, so the hydrogen coordinates were determined from a molecular mechanics optimization performed with all non-hydrogen atoms frozen at their determined locations. This calculation was performed by using an MMFF94 force field with the program Avogadro [25].

Once the atomic coordinates had been determined, the interaction energies were computed at both the DFT and MP2 levels using a 6–311++G(d,p) basis set. For **1**, this was accomplished by comparing the computed energy of the molecular pair to that of the two separated molecules. The counterpoise method of Boys and Bernardi was used to correct for basis set superposition error (BSSE) [26]. In the case of **2**, the hydrogen-bonding interaction was computed by comparing the energy of the crystallographic determined geometry to that of a structure in which the hydroxyl hydrogen was rotated away from the nitrogen lone pair, effectively breaking the hydrogen bond.

Results and discussion

Both chiral alcohols, D-*N*-(2-Adamantyl)phenylglycinol **1** (Fig. 2) and L-*N*-(2-Adamantyl) diphenylphenylalinol **2** (Fig. 3), crystallize in the noncentrosymmetric orthorhombic space group $P2_12_12_1$. The asymmetric unit for both crystals contains a single molecule of each alcohol demonstrating C_1 point symmetry around the chiral carbon. Confirmation of each molecule's stereochemistry was achieved by analysis of each molecule's Flack parameter, which approached zero through successive rounds of crystallographic structure refinement.

In the case of the solid state structure of D-*N*-(cyclohexyl)diphenylvalinol, inspection of the O-C-C-N torsion angles between its free alcohol and ligated amido alkoxide forms provided useful information to assess the overall stereochemical orientation [15]. Regarding the pair of alcohols discussed in this communication, a correlation between torsion angle and stereochemical orientation was more difficult to determine. For example, despite having opposite stereochemical orientations, the O-C-C-N torsion angles for **1** and **2** were measured at similar values of −55.593(2)° and −57.368(5)°, respectively.

Inspection of both structures offered evidence indicative of O-H•••N hydrogen bonding. Within **1**, an intermolecular hydrogen bond between the hydroxyl group and amine nitrogen on a neighboring molecule generates a one-dimensional polymeric chain that runs parallel to the crystallographic *a*-axis (Fig. 2b). As a consequence of this noncovalent interaction, an interatomic distance between the oxygen and nitrogen atoms of 2.768(2) Å was observed. Due to the 2_1 screw symmetry operation, a second molecule of **1** is positioned in such a way that it is related to the first by a 180° rotation and subsequent translation of one half the length of the unit cell. Within **2**, an intramolecular O-H•••N hydrogen bond was observed at an interatomic distance of 2.794(2) Å between the hydroxyl group and the amine nitrogen (Fig. 3).

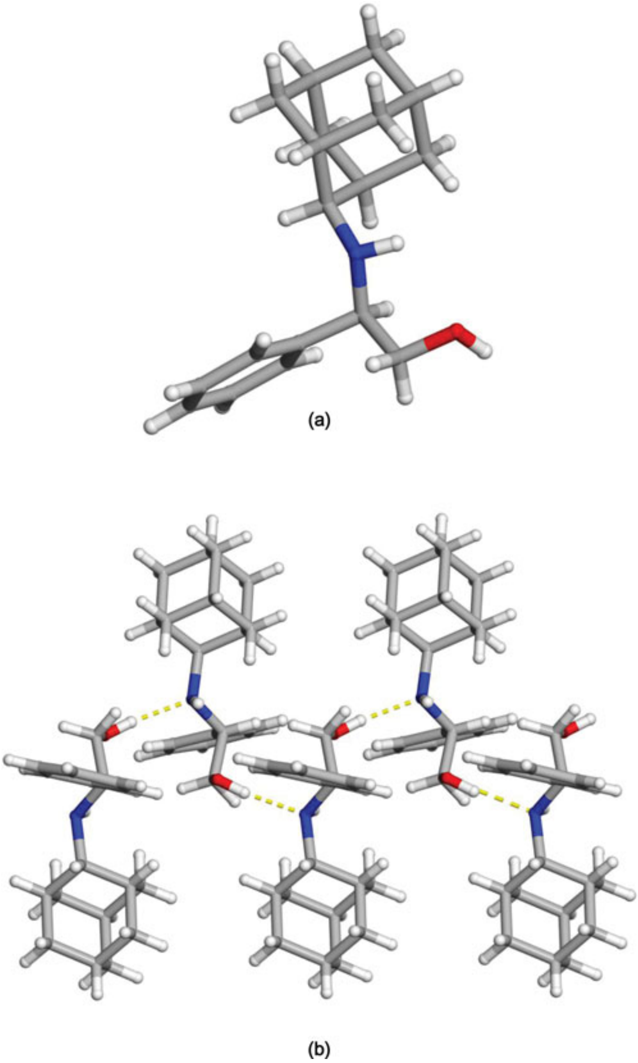

Figure 2. **(a)** X-ray crystal structure of D-*N*-(2-Adamantyl)phenylglycinol **1**. **(b)** View of the intermolecular O-H•••N hydrogen bond that produces the one-dimensional chain running along the crystallographic *a*-axis.

In spite of utilizing the same atoms in their respective O-H•••N hydrogen-bonding patterns, the intermolecular versus intramolecular arrangement of that bonding authors dramatic differences in each structure's C-C-O-H torsion angle which was observed to be 39.39(16)° for **1** versus −103.002(2)° for **2**. This torsion angle disparity between the structures notwithstanding, their O-H•••N hydrogen bonds not only encompass the environment where each might ligate to a transition metal center, but also stabilize their respective conformations in the solid state.

The strength of this hydrogen-bonding interaction within each crystal was estimated by means of electronic structure calculations performed both at the Density Functional level using the M06–2X density functional and via second order perturbation theory (MP2 calculations). To calculate the interaction energy in **1,** the difference between the energy of the molecular pair and that of the separate molecules was determined. To correct for BSSE, the full set of orbitals used for the molecular pair was also used to compute the energy of the

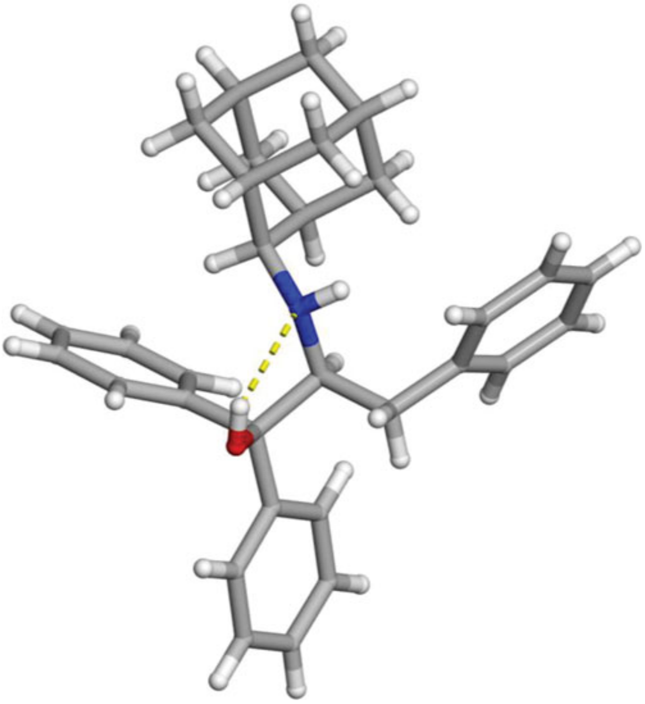

Figure 3. X-ray crystal structure of L-*N*-(2-Adamantyl)diphenylphenylalinol **2** illustrating the intramolecular O-H•••N hydrogen bond.

separate molecular fragments. Fragment relaxation was not incorporated into the correction. The interaction energy computed in this manner is sometimes expressed as 'E_{el} + BSSE' and is analogous to D_e for a diatomic molecule.

For **1**, interaction energy of −12.7 kcalmol was obtained using the M06–2X density functional while MP2 computations yielded a value of −11.5 kcal mol where a negative value implies an attractive interaction. One would anticipate that an O-H•••N hydrogen bond would be the primary contributor to this interaction energy, although not all of the energy is necessarily due to hydrogen bonding. With this in mind, it is instructive to compare the computed interaction energy to previously reported hydrogen bond energies. The energies obtained from the present computations fall into the range of what is commonly termed "moderate" hydrogen bonding. Previous computations of the binding energy between methanol and various small amines yielded values for E_{el} + BSSE in the range of 31–34 kJmol (−7.4 to −8.1 kcalmol) [27]. The higher value found within **1** may involve a stronger hydrogen bond, or the difference may be due to contributions from other intermolecular interactions.

The strength of the intramolecular O-H•••N hydrogen bond in **2** was estimated by taking the difference between the energy of the crystallographic determined geometry and the energy of a structure with the hydroxyl hydrogen rotated away from the nitrogen lone pair. The hydrogen bond was disrupted by varying the C-C-O-H torsion angle within the molecule. All other bond lengths and angles were maintained at their original values. A change in the torsion angle will alter the interactions between the hydroxyl hydrogen and other atoms in the molecule. Thus the energy difference between the two configurations will represent the O-H•••N hydrogen bond energy plus the change upon rotation of other intramolecular interactions.

Table 2. Energy changes (kcal mol) within **2** for the intramolecular hydrogen bond upon rotation of the C-C-O-H torsion angle by the specified values.

Theory	θ 120°	θ 180°	θ 240°
DET (MO6–2X)	11.4	12.1	8.3
MP2	11.4	11.6	8.5

To determine the effect of the angle of rotation on the computed interaction energy, the C-C-O-H torsion angle was changed by 120°, 180°, and 240° in a counterclockwise direction as viewed looking down the O-C bond. The interaction energies obtained using both density functional and MP2 theories are shown in Table 2. The variation of the energy value with respect to the torsion angle suggests that, in addition to breaking the hydrogen bond, changes in the torsion angle also affect the interaction of the hydroxyl hydrogen atom with other fragments of the molecule. Nevertheless, the range of energy obtained was between −8 and −12 kcalmol which is consistent with other values previously obtained for O-H•••N hydrogen bonds [27].

Further discussion regarding the structural properties of the alcohols is required based upon the inspection of the O-C-C and C-C-N bond angles within the O-C-C-N bridge. The observed bond angles in **1** were measured to be 111.873(2)° and 106.6780(19)° and for **2** were 107.27(15)° and 108.19(16)°. To assess the level of distortion from each angle's expected 109.5° value, it was essential to compare them to analogous molecules serving as ligands within reported dimeric titanium and monomeric tantalum catalysts [13,14]. Within the dimeric titanium catalyst, containing a ligand similar to **1**, the angular values were determined to be 104.9(5)° and 106.3(4)°, respectively. Meanwhile, for the monomeric catalytic complex containing an analogue of **2**, those angles were measured at a value of 103.5(2)° and 104.4(2)°, respectively. Assuming **1** and **2** would bind in a manner similar to those ligands found within the coordination environments of the catalysts, it would appear that the chelation of the alcohols as amidoalkoxide ligands to the transition metal imposes larger distortions for the carbon bond angles from their expected 109.5° angular value than those generated by the hydrogen-bonding environment in the free alcohol.

Conclusion

Herein, the structures of two chiral amino alcohols D-*N*-(2-Adamantyl)phenylglycinol **1** and L-*N*-(2-Adamantyl)diphenylphenylalinol **2** characterized by X-ray diffraction methods are presented. Within **1**, an intermolecular O-H•••N hydrogen bond exists between neighboring molecules yielding a one-dimensional polymeric chain. For **2**, an intramolecular O-H•••N hydrogen bond was observed within the solid state structure. The presence of these hydrogen bonds and their strength were verified and determined through computational methods. Efforts persist to crystallize and determine structures of other amino alcohols, as well as the catalytic complexes to which they may be bound to further appreciate the effect metal chelation and or hydrogen bonding has on molecular structure distortions in the solid state.

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