Polyhedron 67 (2014) 191–198

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Structural studies of diaminocyclohexane-containing aza-crown ether macrocycles and their Zn(II) complexes

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ARTICLE INFO

Article history:
Received 30 July 2013
Accepted 28 August 2013
Available online 4 September 2013

Keywords:
Macrocycles
Zn(II) complexes
Conformational analysis
NMR spectroscopy
X-ray crystallography
Diaminocyclohexane

ABSTRACT

A series of C_2-symmetrical, diaminocyclohexane-containing macrocycles has been shown to form Zn(II) complexes of 1:1 stoichiometry in methanol. The larger, more flexible members of the series (*R*)-**2** and (*R*)-**3** demonstrate similar behavior in that they undergo metal ion exchange slowly on the NMR timescale and exhibit spectra reflective of C_2-symmetry at all temperatures studied. NMR, X-ray crystallographic, and molecular modeling studies suggest that Zn(II) coordination significantly enhances the conformational rigidity of (*R*)-**2** and (*R*)-**3** by enforcing *anti* conformations about both *N*-benzyl bonds. In contrast, the Zn(II) complex of the smallest, most rigid member of the series (*R*)-**1** shows significant exchange broadening by ^{1}H NMR at room temperature. Variable temperature NMR studies of this complex reveal asymmetry at low temperatures (−80 °C) and C_2-symmetry at elevated temperatures (60 °C), indicating that the complex assumes a relatively long-lived asymmetrical conformation. Additionally, the *ortho*-linked naphthyl-containing macrocycle (*R*)-**4** is shown by X-ray crystallography to possess a diaxial conformation in the solid state, which is thought to be stabilized by crystal packing forces.

1. Introduction

The supramolecular chemistry of both naturally occurring and synthetic macrocycles has attracted considerable attention over the past several decades [1–4]. Conformational restrictions inherent to molecules of cyclic topology may constrain the spatial arrangements of multiple chemical groups within the ring, enabling selective multi-point binding of guest molecules of complementary structure, and ultimately the emergence of higher function at the molecular level (e.g., molecular recognition, transport, catalysis). Rings of sufficient size may envelop guests within their internal cavities, and thereby enhance interaction selectivity. This strategy is exemplified by some of the simplest biomolecules showing the capacity for molecular recognition [5,6]; and its application towards the development of synthetic receptors represents a rich field of research [7–10].

The successful creation of macrocyclic receptors requires both conformational analysis of the system under study and assessment of the binding interactions involved. While an impressive variety of functional compounds has been adapted from well-established macrocyclic scaffolds including cyclodextrins [11], calixarenes [12], porphyrins [13], macrocyclic peptides [14], and curcubiturils [15]; there is also considerable interest in the *de novo* design of novel macrocyclic systems [16–21], which affords the opportunity to tailor stereochemistry, conformational behavior and functional group composition. Previously, we synthesized a series of chiral, C_2-symmetrical aza-crown ether macrocycles, including those shown in Fig. 1, and found their abilities to differentially bind enantiomers of mandelic acid (MA) derivatives to be markedly affected by ring size and linkage geometry [22]. Each macrocycle contains the *trans*-1,2-diaminocyclohexane (DACH) subunit, which serves as a source of both chirality and chemical reactivity. The vicinal amino groups are appended through *N*-benzylic linkages to rigid arene spacers, which are in turn connected through flexible oligoethylene glycol chains. A combination of X-ray crystallographic, nuclear magnetic resonance (NMR) and molecular mechanics studies revealed significant variations in conformational flexibility about the *N*-benzyl bonds among the *meta*-linked macrocycles (*R*)-**1**, (*R*)-**2**, (*R*)-**3**, which parallels their abilities to differentiate MA enantiomers by NMR [22].

The utility of metal coordination as an associative interaction in molecular recognition processes [23], and the ability of the DACH subunit to chelate labile metal ions [24], led us to examine Zn(II) complexation by the macrocycles shown in Fig. 1. The Zn(II) ion was chosen because it is kinetically labile, oxidatively stable, has a high affinity for amine ligands, and is amenable to study by NMR. While metal complexes of non-macrocyclic *N*-benzylated DACH ligands have been widely employed in enantioselective catalysis [25–27] and elsewhere [28–30], and numerous polynuclear

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0277-5387/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.poly.2013.08.062

DACH-derived macrocyclic metal complexes are known [3,31–33]; mononuclear macrocyclic metal complexes which may be capable of coordinating guest molecules within their interior cavities are potentially very attractive as supramolecular receptors and have been less well studied [34].

Herein, we present structural studies indicating that the *meta*-linked macrocycles (*R*)-**1**, (*R*)-**2**, and (*R*)-**3** form Zn(II) complexes in methanol of 1:1 stoichiometry through chelation by their DACH subunits. Additionally, we report the X-ray crystal structure of the *ortho*-linked naphthalene-containing macrocycle (*R*)-**4**, which possesses an unusual diaxial conformation in the solid state.

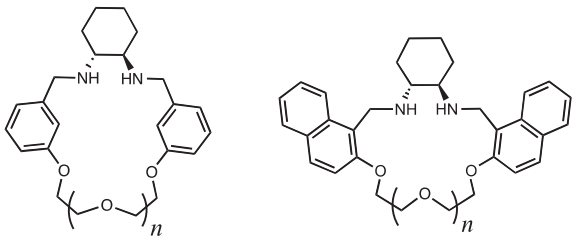
2. Experimental

2.1. General

The compounds shown in Fig. 1 were prepared as previously reported [22]. NMR spectra were recorded on a JEOL Eclipse Plus 300 spectrometer equipped with a Eurotherm temperature controller and are referenced to the solvent. The reported temperatures were calibrated against a methanol standard and are thought to be accurate to 0.3° [35]. Conformational searches were performed using the MMFF force field with Spartan 04 for Macintosh v1.0.3 (Wavefunction, Inc. Irvine, CA, USA) running on a PowerMac G5 (OS 10.5.2).

2.2. Crystallographic data collection and refinement

Crystals of (*R*)-**2:ZnCl$_2$** were grown by evaporation from a methanol-d_4 solution, whereas crystals of (*R*)-**4** were grown from hot DMSO. X-ray diffraction data were collected on a Bruker APEX 2 CCD platform diffractometer (Mo Kα (λ = 0.71073 Å) for (*R*)-**2:ZnCl$_2$**); Cu Kα (λ = 1.54178 Å) for (*R*)-**4**) at 125 K. Crystals were mounted in a nylon loop with Paratone-N cryoprotectant oil. The structures were solved using direct methods and standard difference map techniques, and were refined by full-matrix least-squares procedures on F^2 with SHELXTL (Version 6.14) [36]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on carbon were included in calculated positions and were refined using a riding model. Hydrogen atoms on nitrogen were located in the difference map and refined semi-freely with the help of a distance restraint. PLATON [37] was used to verify all stereochemical configuration designations. ORTEP-3 [38] was used to generate Figs. 4 and 9A. Additional crystallographic data and refinement information are given in Table 1.



n = 1, (*R*)-**1**
n = 2, (*R*)-**2**
n = 3, (*R*)-**3**

n = 1, (*R*)-**4**
n = 2, (*R*)-**5**

Fig. 1. Structures of the macrocycles examined in this study.

3. Results and discussion

3.1. Structural studies of (*R*)-*2:Zn(II)*

In order to investigate the binding of Zn(II) by the macrocycles from Fig. 1 ^{1}H NMR titrations were performed in methanol-d_4. Fig. 2 shows that the introduction of $ZnCl_2$ to a solution of (*R*)-**2** causes most of the ^{1}H NMR signals of the free ligand to diminish in intensity while a series of downfield-shifted resonances assignable to a Zn(II) complex of C_2 symmetry emerge. These spectral changes continue with increasing [$ZnCl_2$] until a full molar equivalent has been added, at which point the original signals for (*R*)-**2** are no longer detectable and no further changes are observed with additional $ZnCl_2$. The spectra were invariant with time after the addition of each aliquot, indicating that the equilibrium for Zn(II) binding is established rapidly, although the superposition of two sets of signals in most cases when $0 < [Zn(II)]_0/[(R)\text{-}\mathbf{2}]_0 < 1$ shows that metal ion exchange is slow on the NMR timescale. Specifically, the observation of slow exchange for the transition $H_k \rightarrow H_{k'}$ (Δ = ca. 228 Hz) establishes that the rate of Zn(II) ion exchange (k_{ex}) is less than 506 s^{-1} [39]. Integration of the signals for (*R*)-**2** and the complex (*R*)-**2:Zn(II)** yielded the binding isotherm shown in Fig. 3, which displays a linear increase in [(*R*)-**2:Zn(II)**] with added $ZnCl_2$ up to a molar ratio of unity, thus confirming that the complex is of 1:1 stoichiometry and that virtually no unbound $ZnCl_2$ exists in the presence free (*R*)-**2**.

The spectral changes depicted in Fig. 2 are consistent with chelation of the Zn(II) ion by the DACH subunit. The large complexation induced chemical shift for the proton residing *ortho* to both arene substituents (H_k from Fig. 2) is likely a consequence of its orientation toward the macrocyclic interior and proximity to the neighboring amine group. The resonances for the *H*–C–N atoms (H_e, H_f, and H_g) and the phenoxy-bound methylene H atoms (H_l and H_m) are also markedly downfield shifted upon Zn(II) complexation; with the latter pair becoming significantly differentiated, which suggests that coordination restricts conformational motion about the aryl ether bonds. The overall correspondence of signals between the spectra of the free ligand and complex in the slow exchange regime indicates that the C_2 symmetry of the system is preserved upon metal binding (i.e., both stereogenic *N* atoms adopt the same configuration in the complex), which is commonly observed in the complexes of DACH derivatives with tetrahedral metal ions [40–43].

Crystals of the complex (*R*)-**2:ZnCl$_2$** were obtained by slow evaporation from d_4-methanol and characterized by X-ray crystallography. The asymmetric unit contains two crystallographically independent molecules of (*R*)-**2:ZnCl$_2$** that pack into the crystal through off-set intermolecular face-to-face -stacking between phenylene rings [44] (plane-to-plane angles 8.03(9)° and 10.0(1)°; centroid-to-centroid distances 3.756(2) and 3.885(2) Å, see Supplementary data) to form 1-dimensional chains. The geometries of the two complexes are so similar that only one is presented in Fig. 4 and discussed. The complex displays a distorted tetrahedral geometry about the metal center with chelation by the DACH subunit and coordination of two chloride ions. The bond angles (N21–Zn2–N22 = 86.53(8)°; Cl23–Zn2–Cl24 = 116.51(3)°), and N–Zn bond lengths (N21–Zn2 = 2.084(2) Å; N22–Zn2 = 2.081(2) Å) are typical for DACH-$ZnCl_2$ complexes [40–43]. Both of the stereogenic *N* atoms assume (*S*) configurations, which orients the *N*-benzylic bonds approximately parallel to the nearest equatorial H atoms of the cyclohexane chair, and contributes to the approximate planarity of the structure. The two phenylene groups are nearly parallel (5.46(9)° angle), and each is rotated slightly outward from *anti* relationships with their respective adjoining cyclohexyl methine C atoms (dihedral angles: C21–N21–C226–C224 = 154.7(2)°;