



Exploration of structural motifs influencing solid-state conformation and packing of unclosed cryptands sharing the same 19-membered macrocyclic core



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ABSTRACT

The crystal structures of a series of readily available, highly crystalline bisamide unclosed cryptands (UCs), sharing the same 19-membered macrocyclic core were thoroughly studied in order to rationalize their organization in the solid state. Despite structural variations introduced into intraannular substituents, mode of their attachment to the macrocyclic core, and relative acidity of exterior amide protons, UCs adopted only three well-defined geometries in all 10 analyzed crystals. This structural resemblance between conformations of UCs, however, is not translated into similarities in terms of intermolecular interactions and crystal packing. This contradicting *intra*- and *intermolecular* solid-state behavior is likely connected with an ability of these macrocyclic compounds to engage in numerous interactions of comparable energy within the crystal lattice.

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1. Introduction

Macrocyclic compounds are the core of the supramolecular chemistry from its very beginnings.¹ The underlying principle of embedding geometrical constraints produced by the cyclic scaffold that ensure high level of preorganization gave rise to a variety of more complex supramolecular architectures.² For example, macrocyclic compounds proved to be excellent hosts for cations,³ anions,⁴ and neutral⁵ guests. Recently, we developed and investigated new class of macrocyclic host molecules, named *unclosed cryptands* (UCs),⁶ having a suitably functionalized substituent (lariat arm) installed at the intraannular position of the macroring. The presence of a flexible lariat arm provides additional anchoring points for the selective guest binding, similarly as in the case of structurally related cryptands.⁷ Bis- and tetraamide UCs of medium size, i.e. between 19 and 26-membered macrorings, proved to efficiently complex various guests, in particular anions^{6d,6e} and neutral molecules,^{6b,c} using a dense network of hydrogen bonds,

both in solution and in the solid state. However, in contrast to cryptands, the synthesis of UCs is more convenient providing desired macrocyclic compounds in considerably higher yields, and thus paves the way for a scope of relatively easy structural modifications.^{6a,6d}

In this contribution we discuss solid state structures of several newly designed analogues of the parent UC **1a**, which was previously shown to form chiral crystals.⁸ To allow for direct comparisons among the compounds, we have decided to keep the 19-membered macrocycle core intact, and vary, one at a time, the lariat arm aryl ring substituents, the macrocycle – lariat arm linker, and the relative acidity of amide protons.

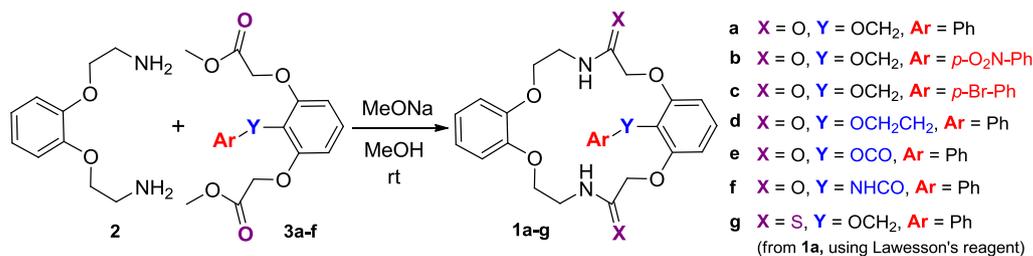
2. Results and discussion

The synthesis of proposed bisamides, presented in [Scheme 1](#), follows the well-established protocol with a key step being macrocyclisation reaction involving *bis*-amine **2** and *bis*-(methyl)esters **3a-f** in methanol, mediated by sodium methoxide. This methodology typically offers high yields of macrocyclic products and is tolerant toward variety of functional groups.^{6a,6d,6e,9} In addition, linear macrocycle precursors are easily synthetically accessible.

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Accordingly, we obtained two analogues of parent compound **1a**, that possess small substituents in *para* position of the lariat ring (**1b** and **1c**), and two analogues that differ in macrocycle-lariat arm linker (**1d** and **1e**). In addition, a set of four already published^{10,11} structures of different solvates of another relevant linker-analogue **1f** was included in this study. Also, to probe the influence of acidity of amide protons, we synthesized the thioamide **1g** by treating compound **1a** with Lawesson's reagent. X-Ray suitable crystals of new compounds were obtained from methanol.



Scheme 1. Sodium methoxide mediated macrocyclisation reaction leading to unclosed cryptands **1**. The synthesis of compounds **1a**, **1e**, and **1f** was already reported in refs 8, 10 and 11, respectively.

Compound **1a** crystallizes in the space group $P2_12_12_1$ (Fig. 1a). At the level of a single molecule, the symmetry is broken by the existence of an internal hydrogen bond between the oxygen atom in the lariat arm and one of the two amide protons, that corresponds to N–O_{Bn} distances of 3.06 Å (H-bonding) and 3.66 Å (non-bonding). For the purpose of uniform presentation of different conformations adopted by UCs in crystals, hence to facilitate their direct visual comparison, in all the figures, UCs are presented in the same way as for compound **1a**, that is: the resorcine ring is located to the left and viewed perpendicular to the plane of the picture. Further, to cross compare the geometry of molecules in crystals, we call the conformation of **1a** *T-shaped*.

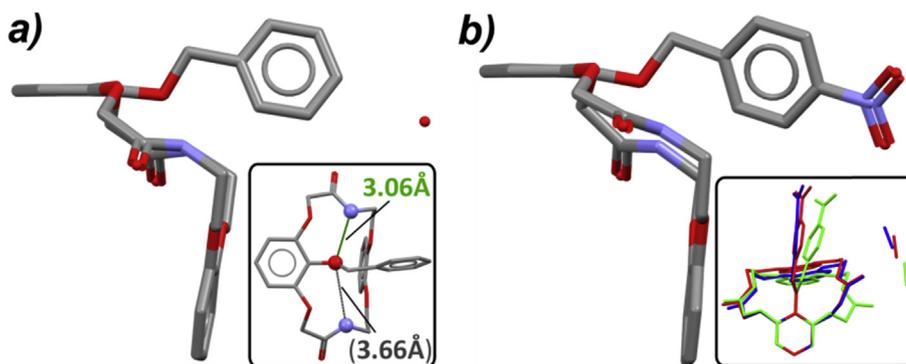


Fig. 1. X-Ray structures of: a) UC **1a**, insert: intramolecular hydrogen bond; b) UC **1b**, insert: superimposition of crystallographically independent molecules in the asymmetric unit (**1bA** - green, **1bB** - blue, **1bC** - red; macrocyclic heteroatoms were used for RMS overlay); hydrogen atoms and solvents omitted for clarity.

Compound **1a** crystallizes as monohydrate and the water molecule is localized outside the macrocyclic cavity, close to the *para* position of the lariat arm ring. We concluded, that introduction into the *para* position a small substituent, that could potentially occupy the position of water molecule in **1a**, might potentially not alter crystal the packing scheme. Thus, we obtained and crystallized *para* substituted nitro- and bromo-analogues **1b** and **1c**. In both of them water is not present in the lattice, as expected, although the crystallinity changed as well.

In the asymmetric unit of *p*-nitro analogue **1b** (Fig. 1b) there are

three independent molecules, each adopting a similar *T-shaped* conformation as in case of UC **1a**. The internal NH–O_{Bn} hydrogen bonds differentiate the “sides” of molecules although the lengths of these bonds varied significantly in each conformation, i.e. the corresponding N–O_{Bn} distances are 3.12 Å and 3.59 Å; 3.23 Å and 3.24 Å; 3.12 Å and 3.42 Å, for **1bA**, **1bB**, and **1bC**, respectively. Compound **1b** crystallizes in low symmetry space group *P*-1 as MeOH solvate, with one methanol molecule per macrocycle well localized external to the macrocyclic cavity. Strikingly, in the crys-

tals of UC **1a** we never found methanol despite being used for crystallization.

Contrary to the UCs **1a** and **1b**, the bromo-derivative **1c** adopts a *C-shaped* conformation in the crystal (Fig. 2a), in which the electron-rich catechol ring and electron-poor lariat aromatic ring π - π stack in a face-to-face mode. Again, there is an internal hydrogen bond differentiating the “sides” of a macrocycle, that involve one of the amide NHs and etheric O_{Bn} atoms. The corresponding N–O_{Bn} distances are 3.15 Å and 3.69 Å. Compound **1c** crystallizes in the space group $P2_1/n$. Similarly, as in the crystal structures of **1a** and **1b**, a molecule of methanol is not present within the crystal lattice.

The first of the linker-analogues, **1d**, structurally differ from **1a** by the presence of additional methylene group in the macrocycle–pendant arm linker. There are two crystallographically independent molecules of UC **1d** in the crystal (Fig. 2b), both asymmetric, that, in respect to the internal hydrogen bonds, corresponds to N–O_{Bn} distances of 3.00 Å and 3.79 Å in conformation **1dA** and 3.05 Å and 3.71 Å in disordered conformation **1dB**. In both conformations macrocycle **1d** adopts *C-shaped* geometry. The disorder in conformation **1dB** is limited to the pendant arm that occupies two different, although well-defined,

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