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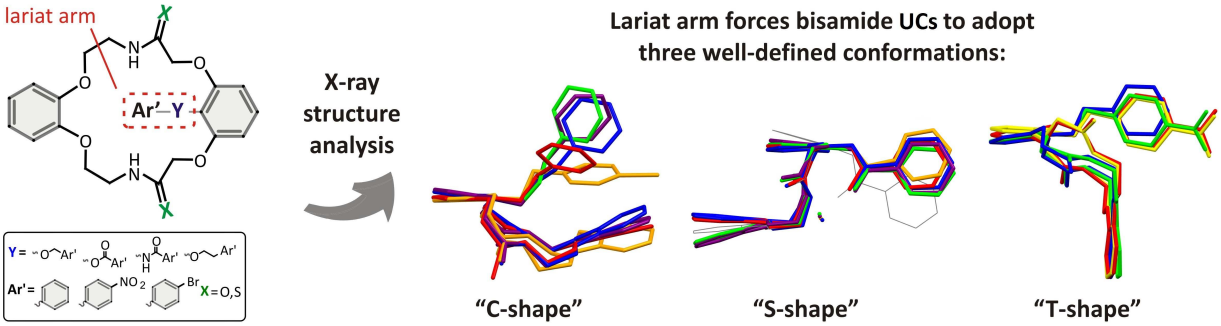

Exploration of structural motifs influencing solid-state conformation and packing of unclosed cryptands sharing the same 19-membered macrocyclic core

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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 *inter*molecular 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.

Keywords

Unclosed Cryptands; Macrocyclisation; Macrocycle; Azamacrocycle; Hydrogen Bond; Solid-state Chirality; Crystal Packing

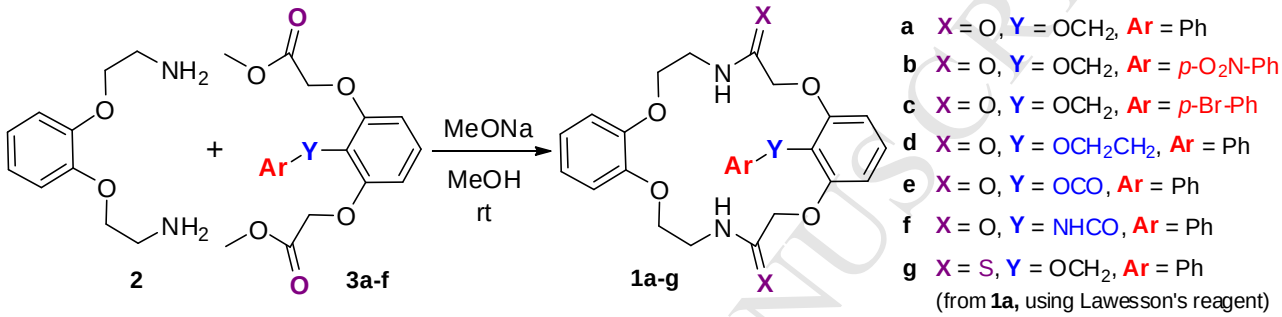
1. Introduction

Macrocyclic compounds are the core of the supramolecular chemistry from its very beginnings.[1] The underlying principle of embedding geometrical constrains 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 neutral[5] 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,e] 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,d]

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,d,e,9] In addition, linear macrocycle precursors are easily synthetically accessible. 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*.

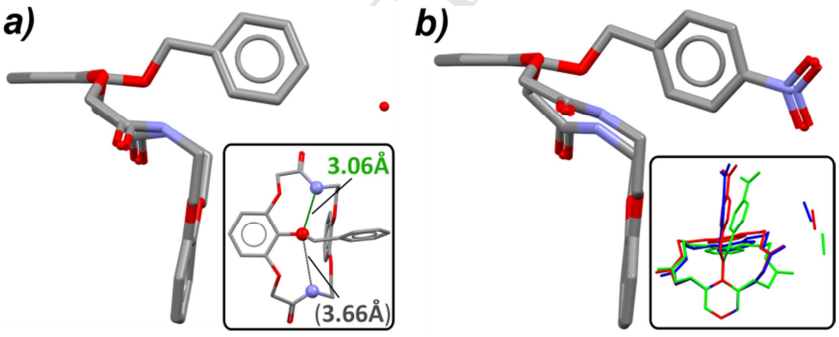


Figure 1. X-Ray structures of: *a)* UC **1a**, insert: intramolecular hydrogen bond; *b)* UC **1b**, insert: superimposition of crystallographically independent molecules in the asymmetric unit (**1bA** - green, **1bB** - blue, **1bC** – red; macroring heteroatoms were used for RMS overlay); hydrogen 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 crystals 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, positions in the lattice with equal probability (50:50 occupancy ratio). UC **1d** crystallizes in the space group $P2_1/n$ as solvate with disordered methanol and water, both localized externally to the macrocycles.

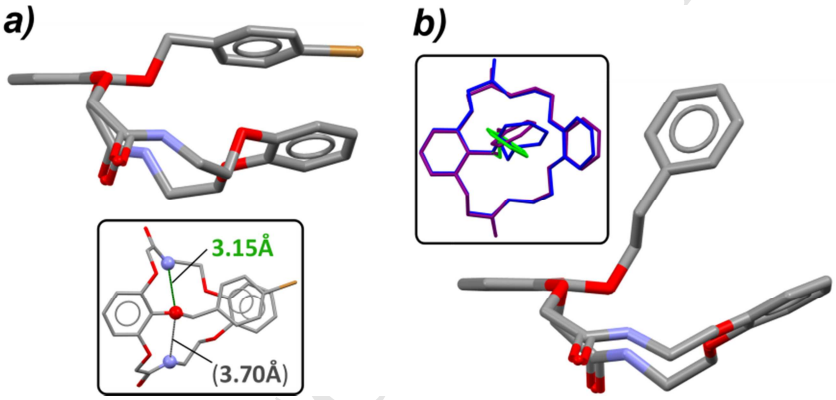


Figure 2. X-Ray structures of UCs: *a)* **1c**, insert: intermolecular hydrogen bond; *b)* **1d**, insert: superimposition of crystallographically independent molecules in the asymmetric unit (**1dA** - violet, **1dB** – blue and green; macroring heteroatoms were used for RMS overlay); hydrogen atoms and solvent molecules omitted for clarity.

The next linker analogue investigated was an ester **1e.** In the crystal, the pendant arm part of the structure is disordered, that is associated with the existence of the two forms of **1e**: a free ligand - **1eA** (**Fig. 3a**) and an intra-cavity complex with water- **1eB** (**Fig. 3b**), that differ by the distance of the lariat arm from the macrocyclic core. The refined occupancy ratio of the disordered moieties is equal to 0.64:0.36. A formal exchange of benzylic methylene (as in **1a**) into a carbonyl group brings an important change to electronic and geometry of the pendant arm, and hence can alter the conformation as well as H-bonding ability of the whole molecule. Indeed, UC **1e** adopts a different - *S-shaped* conformation (**Fig. 3c**) in both forms of a free ligand **1eA** and its water complex **1eB**. The internal H-bonds engage the carbonyl oxygen atom rather than the oxygen linking the arm to a resorcine ring (as in all described above structures lacking the carbonyl

group in the linker). In both forms, **1eA** and **1eB**, the intramolecular hydrogen bonds strongly differentiate "right" and "left" side of molecules. Interestingly, ester **1e** crystallizes forming chiral crystals, in the space group $P2_12_12_1$, the same as UC **1a**, although the packing scheme is different (see ESI). In the crystal lattice, the characteristic interaction motif is a π-π stacking between catechol and resorcine rings of neighboring molecules in a parallel displaced mode.

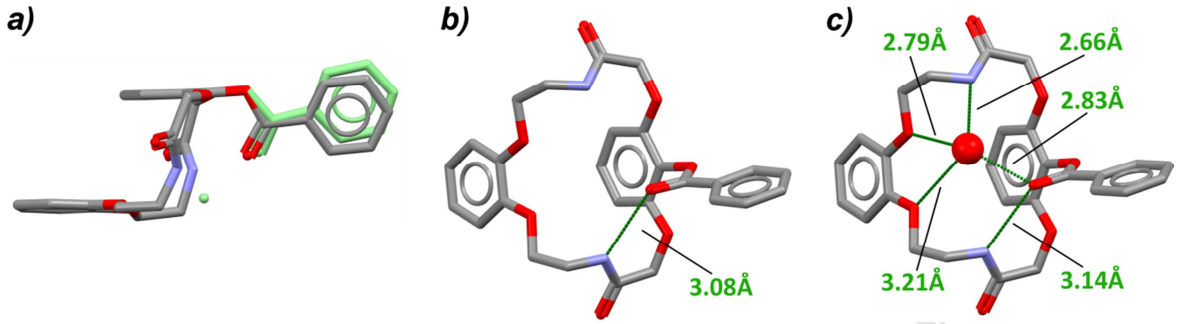


Figure 3. X-Ray structure of ester **1e**:*a)* higher occupancy free ligand form **1eA**, *b)* lower occupancy water complex form **1eB**, c) *S-shaped* geometry of **1e** (**1eA** in a common colors, **1eB** in green color); hydrogen atoms omitted for clarity.

Hence, we invoked another analogue of UCs **1a** and **1e**, amide **1f** (**Fig. 4**), of which crystals of four different solvates have already been published (CCDC refcodes: IDADAT, IPUPUF, IPUQAM, IPUQEQ).[10,11] Strikingly, in of all four different solvates, two of which (IPUPUF, IPUQAM) contain more than one conformer in the asymmetric unit, the geometry of amide UCs **1f** highly resembles the *S-shaped* geometry of ester **1e**. Namely, the carbonyl oxygen is H-bonded to one of the amide NHs. Moreover, in three solvates of **1f** (IPUPUF, IPUQAM, IPUQEQ) a water molecule is bonded in a macrocycle cavity and engaged in H-bonding in the same way as in case of ester **1e**.

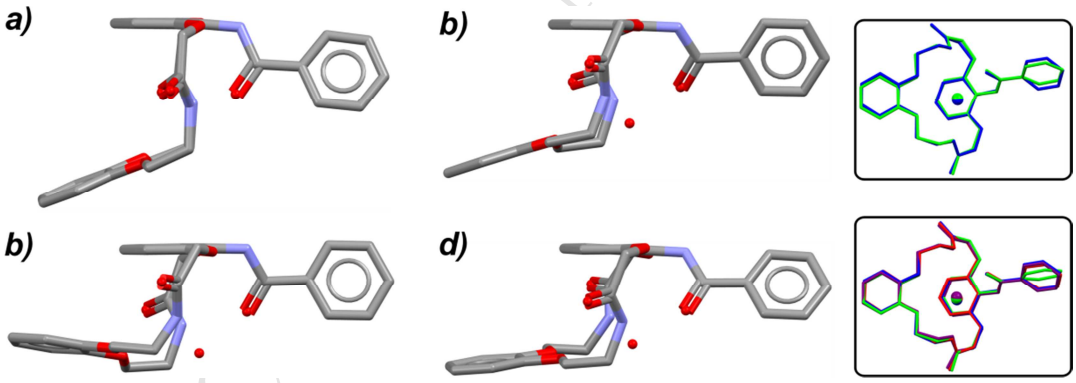


Figure 4. X-Ray structures of amides **1f**: *a)* IDADAT;[10] *b)* IPUPUF,[11] insert: superimposition of two crystalographically independent molecules in the asymmetric unit; *c)* IPUQEQ;[11] *d)* IPUQAM,[11] insert: superimposition of four crystalographically independent molecules in the asymmetric unit; hydrogen atoms and solvent molecules, except for intracavity water, omitted for clarity.

The last tested modification involved conversion of parent amide **1a** into a corresponding thioamide **1g**, by reacting compound **1a** with Lawesson's reagent. In principle, this should lead to only minor alteration of geometry and electronics of the molecule and hence the range intra- and inter-molecular interactions, however the solid state structure of UC **1g** differs significantly from amide **1a**. The thioamide **1g** adopts a *C-shaped* conformation. The internal NH-O_{Bn} hydrogen bond discriminates the "sides" of the molecule even more strongly than in the previous structures as the difference in the corresponding N-O_{Bn} distances reached 1 Å (3.02 Å for the H-bonded and 4.01 Å for non-bonded).

All of the presented UCs differ from the reference **1a** by only one structural aspect: insertion of additional group in a lariat ring (**1b** and **1c**) in a *para* position, that was otherwise occupied by water molecule in a

crystal of **1a**; extension of a linker by one methylene group (**1d**); replacement of a linker O-CH_2 with either O-CO (**1e**) or NH-CO (**1f**); and exchange of amide into thioamide groups (**1g**). However, when the conformations adopted by USs in all the crystals are considered (including multiple crystallographically independent molecules in crystals of **1b**, **1d**, **1f** IPUPUF, and **1f** IPUQAM, that accounts for 16 unique geometries), they fall into three categories, arbitrarily called *T-shaped*, *C-shaped* and *S-shaped*. The latter is exclusively chosen by all UCs containing carbonyl group in the linker - ester **1e** and amides **1f**. **Figure 6** presents superimposition of *S-shaped* UCs **1e** and **1f**. All compounds exhibit remarkable similarity in terms of conformation, with a slight exception of amide **1f** IDADAT. Also for all geometries, the H-bond network matches perfectly, including the internally bonded water molecule (except for **1f** IDADAT that do not bind water). Precisely, the variation of water position, among the structures presented in **Figure 6**, is lower than 0.34 Å (i.e the distance between two least matching water oxygen atoms). The remarkable stability of the *S-shaped* conformation for the carbonyl-linker UCs provides indirect proof of the important role of water in stabilizing the particular conformation,[6c] as water molecules occupy very well-defined positions in the cavity, reproducible among the different crystals, despite some functional difference (ester *vs* amide) and the very different way the compounds are packed in the lattice. Solvents molecules, present in different solvates of **1f** (acetone in **1f** IPUPUF, toluene in **1f** IPUQEQ, additional water in **1f** IPUQAM), were unable to alter the conformations either.

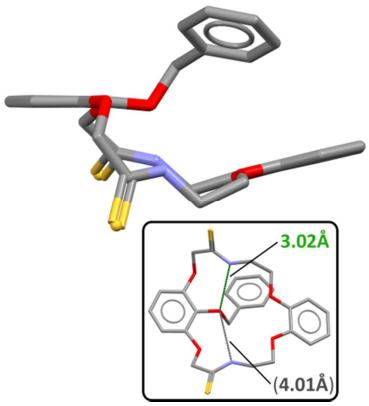


Figure 5. X-Ray structure of UC **1g**, insert: intermolecular hydrogen bond; hydrogen atoms omitted for clarity.

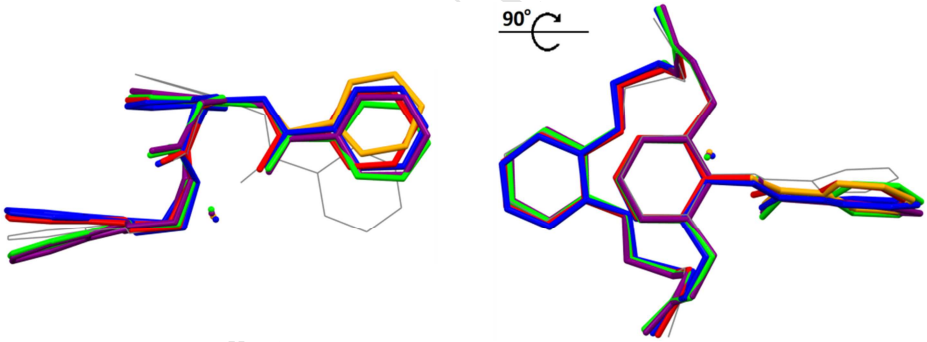


Figure 6. Superimposition[12] of *S-shaped* structures **1eA** (red), **1eB** (orange) and four solvates of **1f** (IDADAT- grey, IPUPUF - green, IPUQAM - violet, IPUQEQ - blue).

The same analysis was performed for *T-shaped* UCs **1a** and **1b**, for the latter, including its three solid state conformers (**Fig. 7**). In this case as well, there is a very good match among all four geometries. Strikingly, one of the conformers of **1b** resembles **1a** more than the other two of its own. The second geometry, adopted by UCs that did not contain a carbonyl group in the linker, we called *C-shaped*. **Figure 8** present the superimposition of all the *C-shaped* molecules of **1c**, **1d** (including its three conformers) and **1g**. In these UCs the macrocyclic part overlap very well, the differences in geometries are observed only within the flexible pendant arm.

At this point, it is worth adding that the same conformational behavior we found even among other less related to **1a** analogues that were prepared for different projects and are not recalled here in detail.[10,13] Namely, all UCs containing a carbonyl moiety in the linker (CCDC refcodes: QEKMID, QEKMOJ, IDACUM) uniquely adopted similar to described here, *S-shaped* conformations, whereas O-benzyl analogues (CCDC refocdes: QEKMUP, QEKNAW, QEKMEZ) exclusively adopted either *T-* or *C-shaped* conformation.

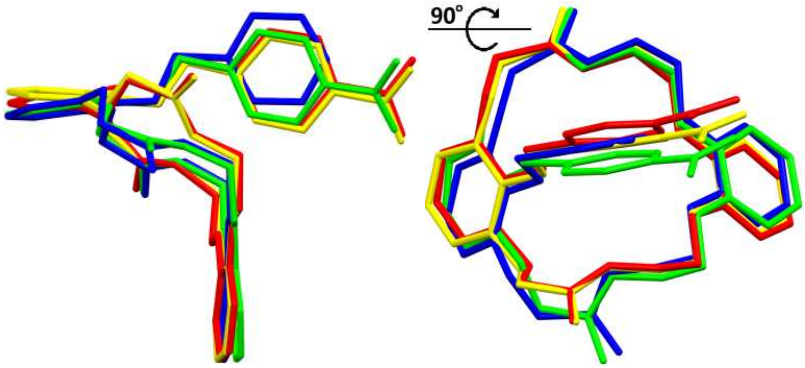


Figure 7. Superimposition[12] of *T-shaped* structures of macrocycles **1a** (blue) and **1b** (**1bA** – green, **1bB** - red, **1bC** - **yellow**).

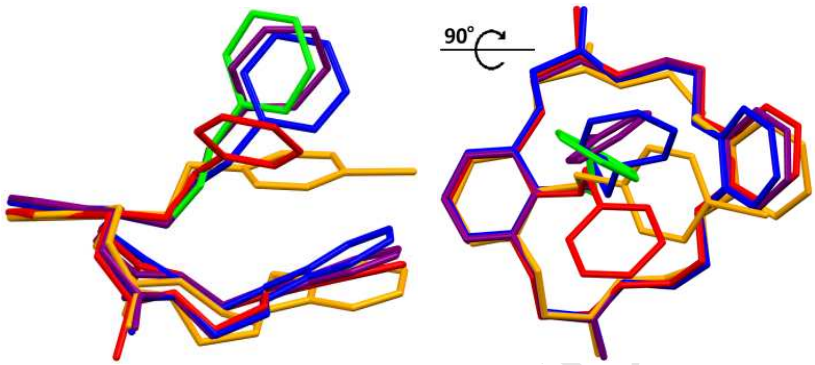
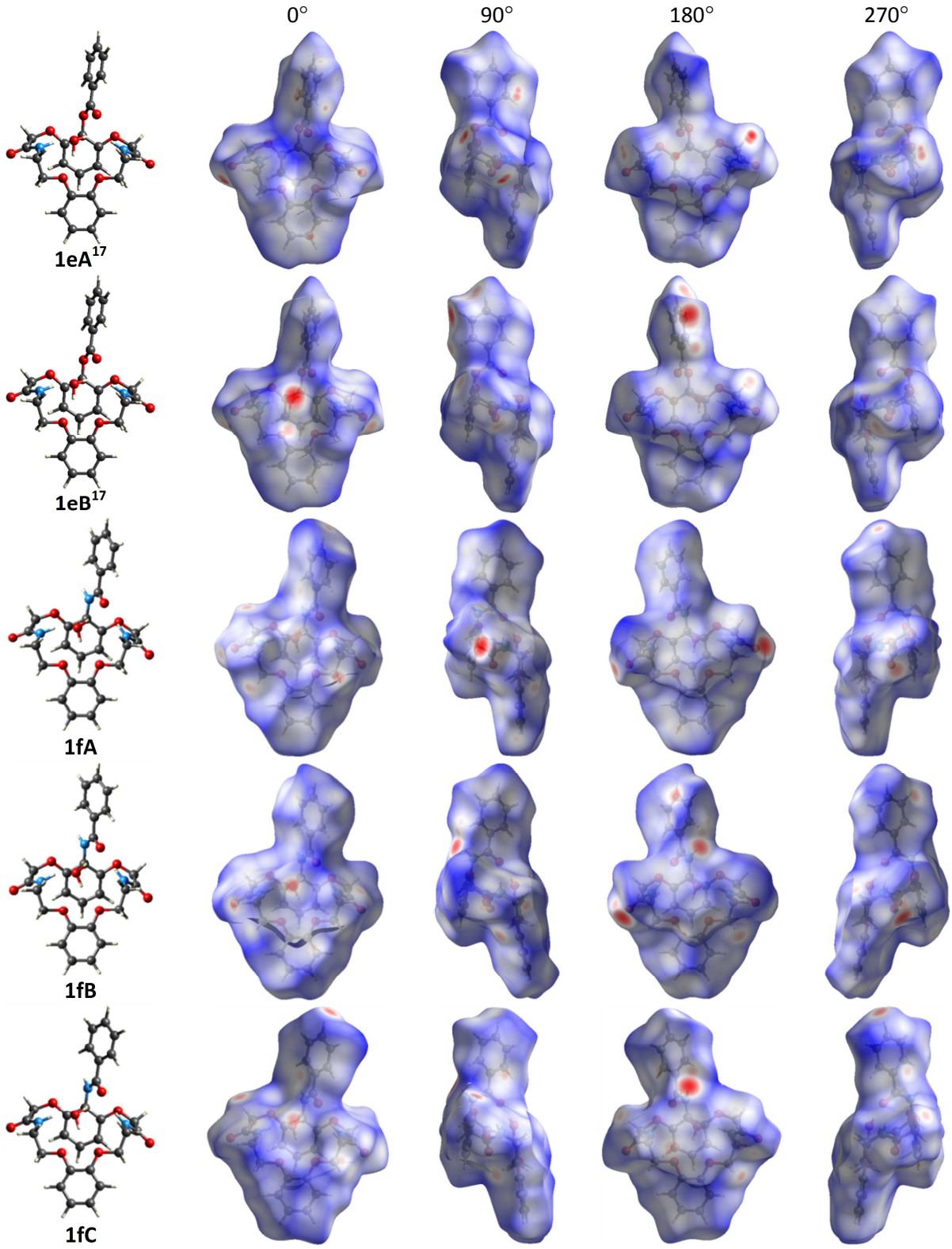


Figure 8. Superimposition[12] of *C-shaped* structures **1c** (orange), **1d** (**1dA** – violet, **1dB** – blue and green) and **1g** (red).

The similarities in the solid-state conformation of macrocycles and existence of similar intramolecular H-bonds within macrocyclic core, does not, however, correspond to virtually any similarities in crystal packing and intermolecular interactions within in the lattice. This solid state similarity/dissimilarity puzzle can be conveniently analyzed by the aid of Hirshfeld surfaces (HS) that, in a visual manner, show global intramolecular interactions in the crystals.[14] For that, we use the d_{norm} property mapped on the Hirshfeld surface.[15] D_{norm} is a van der Waals radii (vdW) normalized contact distance between the two nearest atoms belonging to two adjacent molecules in the crystal. While presented using the common red-white-blue coloring scheme, it especially highlights the strong contacts (the interatomic distance lower than the sum of vdW radii of the corresponding atoms) as red spots on the HS, to be distinguished from weak contacts that are colored blue (distances longer than vdW radii) and white (distance equal to the sum of vdW radii). As an example we have chosen the chiral ester **1e** and amide **1f** IPUQAM as a reference. Crystal of **1f** IPUQAM is most closely related to **1e** in terms of the structure and intra-cavity complexation of water.[16] A comparison of Hirshfeld surfaces with the d_{norm} property mapped for ester **1e** (complex with water **1eB** and a free ligand **1eA**)[17] and four conformers of amide **1f** IPUQUAM is shown in **Figure 9**. One can see that the geometries and, hence, the spatial arrangements of functional groups in all conformers are virtually the same and, so is the *potential* ability for intermolecular interactions. While, *in fact*, as clearly represented by red spots on the HS, the molecules are engaged in very different intramolecular interactions. Strikingly, these differences are visible not only for **1e** vs **1f** IPUQAM, but also among four conformers of the latter. We find it justified to assume that distinct maps of intermolecular contacts observed for analyzed UCs are a

consequence of the presence of numerous H-bond acceptors and donors, as well as local interactions between three electronically different aromatic rings (electron-rich catechol and resorcine rings in the macrocycle and electron-rich benzyl or electron-poor benzoyl rings in the lariat arm).[18] We assume that these structural features enable multiple, energetically similar interactions among the UCs, and with the variety of solvents, that, as a consequence, results in a differences in packing.



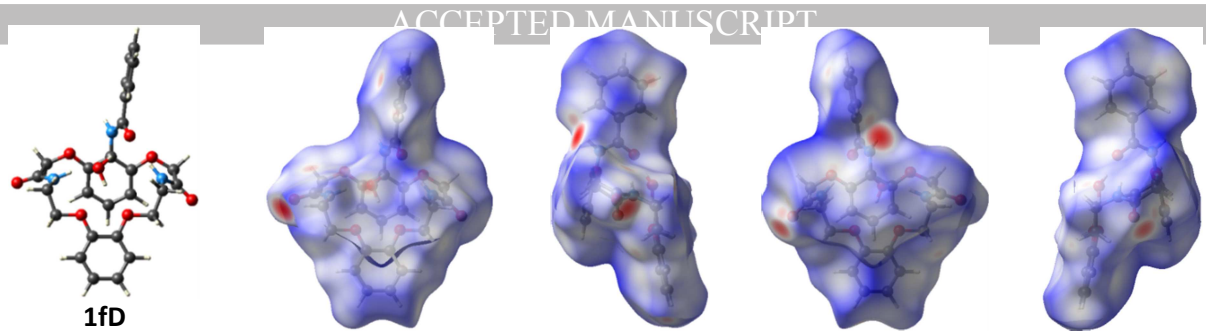


Figure 9. Ball and sticks representation and Hirshfeld surfaces mapped with d_{norm} property generated for the two forms of **1e** (**A**, **B**) and four conformers of **1f** IPUQAM (**A**-**D**).

An interesting observation came from the comparison of HS for **1a** and its thioamide analog **1g**. Despite large differences in conformations of macrocycles (i.e. *T*- and *C-shaped* for **1a** and **1g**, respectively), contribution of S···H interactions (18%) to the HS seems to compensate a small share of O···H interactions (7%) to such an extent that overall contribution of these interactions is comparable to that for "pure" O···H interactions (25%) in diamide **1a** (**Fig. S14** and **S15**). In addition, slightly larger contribution of the H···H interactions to the HS in **1g** (51%) than in **1a** (46%) is likely a result of the very short contacts between protons of the ethylene linkers in the former case which is exemplified by the sharp spike for the values of d_i and d_e close to 1.1-1.2 Å (**Fig. S14**).

3. Conclusions

A set of new unclosed cryptands, sharing the same 19-membered macrocyclic core, were obtained using a convenient synthetic methodology and were analyzed in respect to their solid state conformations and packing. Despite structural variations introduced into lariat arm substituents, in the macrocycle-arm linker as well as upon the change in the acidity of amide NHs, in 10 analyzed crystals, which accounts for 16 crystallographically independent molecules, UCs adopt only three well-defined conformations at the molecular level. The so-called *S-shaped* is uniquely adopted by UCs bearing a carbonyl group in the linker, whereas all "non-carbonyl" compounds prefer either *T-shaped* or *C-shaped* forms. Interestingly, in none of the solid-state conformations are the UC molecules symmetric. In the case of one compound a chiral crystal was obtained. Despite the high predictability of their conformations and *intra*molecular interactions, all UCs behave very differently in terms of *inter*molecular interactions and crystal packing. This contradicting *intra*- and *inter*molecular behavior is likely connected with an ability of these macrocyclic compounds to engage in numerous interactions of comparable energy within the crystal lattice.

4. Experimental Section

4.1. Synthesis. General Remarks

All solvents were of reagent grade quality. All reagents were purchased from Sigma-Aldrich and TCI Chemicals and used without further purification. Column chromatography was carried out using Merck Kieselgel 60 (63–100 µm mesh size), TLC was carried out on Merck Kieselgel F254 plates. The NMR spectra were recorded on a Bruker Mercury 400 instrument. Chemical shifts are reported in ppm and are set to solvent residue peak. The splitting pattern of multiplets is described by abbreviations (s – singlet, d – doublet, t – triplet, q ¬– quartet, dd – doublet of doublets, m – multiplet, c – covered signal, b – broad peak). *J* coupling constants values are reported in Hz. Mass spectral analyses were performed with the ESI-TOF technique on a Mariner mass spectrometer from PerSeptive Biosystem.

4.2. Synthesis. General procedure for macrocyclization of UCs

Sodium methoxide (5.0 mmol) in anhydrous methanol (20 mL) was added to a solution of 2,2'-[1,2-phenylenebis(oxy)]diethanamine **2** (1.0 mmol) and corresponding α,ω-diester **3b-d** (1.0 mmol) in methanol (180 mL). When both substrates were consumed (~ 7 days), the solvent was evaporated off and the residue was purified, employing column chromatography (DCM:methanol, 95:5, v/v) to obtain pure macrocycles. The synthesis of compounds **1a**, **1e** and **1f** was described in refs 8, 10 and 11, respectively.

UC 1b. Following General Procedure and using diester **3b** (400 mg, 1.0 mmol), macrocycle **1b** (220 mg, 44 %) was obtained. **^{1}H NMR** (400 MHz, DMSO) δ 7.93 (*d*, *J* = 8.7 Hz, 2H), 7.70 – 7.66 (*m*, 2H), 7.64 (*d*, *J* = 8.7 Hz, 2H), 7.15 – 7.07 (*m*, 1H), 6.94 (d, J = 8.4 Hz, 2H), 6.90 – 6.77 (*m*, 4H), 5.11 (*s*, 2H), 4.78 – 4.64 (*m*, 4H), 3.97 (*t*, *J* = 4.5 Hz, 4H), 3.60 – 3.39 (*m*, 4H). **^{13}C NMR** (101 MHz, DMSO) δ 168.44, 152.63, 147.97, 147.34, 144.56, 138.87, 128.86, 125.91, 123.73, 121.25, 113.04, 111.29, 74.95, 70.46, 67.62, 38.67. **ESI-MS:** 560.16 $[M+Na]^+$. **HRMS (ESI):** calc 560.1645 for $C_{27}H_{27}N_3O_9Na$, obtained 560.1647. **Elemental analysis:** calc C 59.05%, H 5.49%, N 7.38% for $C_{27}H_{27}N_3O_9$+CH_3OH, obtained C 59.35%, H 5.13%, N 7.54%.

UC 1c. Following General Procedure and using diester **3c** (440 mg, 1.0 mmol), macrocycle **1c** (178 mg, 31 %) was obtained. **UC 1c. ^{1}H NMR** (400 MHz, DMSO) δ 7.73 (*t*, *J* = 5.5 Hz, 2H), 7.33 (*s*, 4H), 7.09 (*t*, *J* = 8.4 Hz, 1H), 6.96 – 6.85 (*m*, 6H), 4.98 (*s*, 2H), 4.66 (*dd*, *J* = 34.5, 15.8 Hz, 4H), 3.98 (*t*, *J* = 4.6 Hz, 4H), 3.59 – 3.36 (*m*, 4H). **^{13}C NMR** (101 MHz, DMSO) δ 168.51, 152.79, 148.12, 138.91, 136.44, 131.59, 130.26, 125.77, 121.69, 121.39, 113.14, 111.53, 75.29, 70.69, 67.61, 38.70. **ESI-MS:** 595.09 $[M+Na]^+$. **HRMS (ESI):** calc 593.0899 for $C_{27}H_{27}BrN_2O_7Na$, obtained 593.0891. **Elemental analysis:** calc C 55.02%, H 4.96%, N 4.75%, Br 13.56% for $C_{27}H_{27}BrN_2O_7$+H_2O, obtained C 55.02%, H 5.02%, N 4.74%, Br 13.50%.

UC 1d. Following General Procedure and using diester **3d** (370 mg, 1.0 mmol), macrocycle **1d** (146 mg, 29 %) was obtained. **^{1}H NMR** (400 MHz, DMSO) *δ* 7.77 (*dd*, *J* = 6.4, 4.2 Hz, 2H), 7.19 – 7.12 (*m*, 3H), 7.09 – 7.04 (*m*, 1H), 7.02 – 6.98 (*m*, 2H), 6.95 – 6.87 (*m*, 6H), 4.68 (*dAB*, *J* = 15.8 Hz, 2H), 4.58 (*dAB*, *J* = 15.8 Hz, 2H), 4.13 (*t*, *J* = 7.5 Hz, 2H), 4.03 (*t*, *J* = 4.7 Hz, 4H), 3.67 – 3.58 (*m*, 2H), 3.51 – 3.41 (*m*, 2H), 2.88 (*t*, *J* = 7.5 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO) *δ* 167.93, 152.29, 147.80, 138.90, 137.25, 128.46, 128.15, 126.10, 125.00, 121.10, 113.07, 111.31, 74.77, 70.34, 67.32, 38.16, 35.61. **ESI-MS:** 529.19 $[M+Na]^+$. **HRMS (ESI):** calc 529.1951 for $C_{28}H_{30}N_2O_7Na$, obtained 529.1948. **Elemental analysis:** calc C 64.67%, H 6.36%, N 5.20% for $C_{28}H_{30}N_2O_7$+CH_3OH, obtained C 64.40%, H 6.11%, N 5.24%.

UC 1g. The macrocycle **1a** (250 mg, 0.50 mmol) and Lawesson reagent (650 mg, 1.5 mmol) was refluxed in toluene (30 mL) for 24 hours. Solvent was evaporated off under reduced pressure, and thus obtained yellow residue was purified employing column chromatography (DCM:methanol, 98:2→95:5, v/v) as the eluent, yielding macrocycle **1g** (0.2 g, 76%) as yellow solid. **^{1}H NMR** (400 MHz, DMSO) δ 9.59 (*t*, *J* = 5.0 Hz, 2H), 7.41 – 7.34 (*m*, 2H), 7.30 – 7.22 (*m*, 3H), 7.07 (*t*, *J* = 8.3 Hz, 1H), 7.00 – 6.86 (*m*, 6H), 5.09 (*dAB*, *J* = 16.6 Hz, 2H), 5.04 (*s*, 2H), 4.92 (*dAB*, *J* = 16.6 Hz, 2H), 4.23 – 4.06 (*m*, 4H), 4.06 – 3.73 (*m*, 4H). **^{13}C NMR** (101 MHz, DMSO) δ 197.20, 152.30, 148.09, 138.84, 136.84, 128.80, 128.74, 128.72, 125.70, 121.69, 113.77, 112.05, 77.06, 76.55, 66.21, 44.72. **ESI-MS:** 547.13 $[M+Na]^+$. **HRMS (ESI):** calc 547.1337 for $C_{27}H_{28}N_2O_5NaS_2$, obtained 547.1339. **Elemental analysis:** calc C 61.81%, H 5.38%, N 5.34%, S 12.22% for $C_{27}H_{28}N_2O_5S_2$, obtained C 61.55%, H 5.34%, N 5.21%, S 12.29%.

4.3. X-Ray Crystallography

The measurements of **1b**, **1d** and **1e** crystals were performed on a KM4CCD κ-axis diffractometer with graphite-monochromated MoK_α radiation. The data were corrected for Lorentz and polarization effects. Data collection, reduction and analysis were carried out with the Oxford Diffraction programs.[19] Particular absorption correction method that was applied is mention in the 'Crystal data and structure refinement

details' section in ESI. The structures were solved by direct methods[20] and refined using SHELXL.[21] Scattering factors were taken from International Tables.[22]

The measurements of **1c** and **1d** crystals were performed at on a Bruker D8 Venture Photon100 diffractometer equipped with a TRIUMPH monochromator and a MoKα fine focus sealed tube. Data collection, reduction and analysis were carried out with Bruker programs.[23a,b] Data were corrected for absorption effects using the multi-scan method (SADABS).[23c] The structures were solved and refined using SHELXTL Software Package.[20,21] Unless states otherwise (see: ESI), the non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated positions and refined within the riding model. The temperature factors of these hydrogen atoms were not refined and were set to be equal to either 1.2 or 1.5 times larger than U_{eq} of the corresponding heavy atom. The atomic scattering factors were taken from the International Tables.[22]

Selected crystal data and structure refinement parameters for UCSs **1b**-**1e** and **1g** are summarized in **Table 1**. More details regarding the above can be found in ESI. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

Table 1. Selected crystal data and structure refinement parameters for UCs **1b**-**1e** and **1g**.

	1b	**1c**	**1d**	**1e**	**1g**
CCDC no.	1472817	1472818	1472819	247076	1472816
Empirical formula	$C_{28}H_{31}N_3O_{10}$	$C_{27}H_{27}BrN_2O_7$	$C_{225}H_{249}N_{16}O_{63}$	$C_{27}H_{26.73}N_2O_{8.36}$	$C_{27}H_{28}N_2O_5S_2$
Formula weight [g/mol]	569.56	571.41	4185.39	513.03	524.63
Temperature [K]	100(2)	100(2)	100(2)	150(2)	293(2)
Wavelength [Å]	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Triclinic	Monoclinic	Monoclinic	Orthorombic	Monoclinic
Space group	*P*-1	$P2_1/n$	$P2_1/n$	$P2_12_12_1$	$P2_1/n$
Unit cell params:					
a [Å]	16.2762(15)	8.5223(10)	14.5271(13)	7.9512(16)	10.4421(11)
b [Å]	17.7332(15)	19.562(2)	15.4368(13)	8.7607(18)	15.4416(14)
c [Å]	17.951(3)	15.4538(19)	23.233(2)	35.018(7)	15.7716(16)
α [°]	16.366(11)	90	90	90	90
β [°]	96.698(12)	103.827(3)	91.970(2)	90	98.940(9)
γ [°]	112.632(8)	90	90	90	90
Volume [$Å^3$]	4017.4(8)	2501.7(5)	5207.0(8)	2439.3(9)	2512.2(4)
Z	6	4	1	4	4
Calc. density [g/cm^3]	1.413	1.517	1.335	1.397	1.387
Absorption coefficient [mm^{-1}]	0.108	1.694	0.098	0.105	0.254
F(000)	1800	1176	2215	1079	1104
Theta range for data collection [°]	2.58 to 25.00	2.49 to 25.05	2.94 to 25.05	3.91 to 25.05	2.93 to 28.81
Limiting indices	-19<=h<=19, -21<=k<=21, -21<=l<=21	-10<=h<=10, -23<=k<=23, -18<=l<=18	-17<=h<=17, -18<=k<=18, -27<=l<=27	-9<=h<=9, -10<=k<=8, -41<=l<=41	-14<=h<=14, -20<=k<=20, -21<=l<=21
Reflections collected/unique	59775 / 14124 [R(int) = 0.0877]	42658 / 4429 [R(int) = 0.0611]	85764 / 9212 [R(int) = 0.0306]	18570 / 4317 [R(int) = 0.0462]	46179 / 6264 [R(int) = 0.0305]
Data / restraints / parameters	14124 / 0 / 1481	4429 / 0 / 342	9212 / 2 / 793	4317 / 25 / 451	6264 / 0 / 437

Goodness-of-fit on F^2	0.880	1.078	1.040	1.091	1.115
Final R indices [I>2sigma(I)]	R1 = 0.0481, wR2 = 0.0881	R1 = 0.0232, wR2 = 0.0608	R1 = 0.0334, wR2 = 0.0782	R1 = 0.0345, wR2= 0.0842	R1 = 0.0378, wR2 = 0.1010
R indices (all data)	R1 = 0.1173, wR2 = 0.1104	R1 = 0.0255, wR2 = 0.0620	R1 = 0.0414, wR2 = 0.0840	R1 = 0.0400, wR2= 0.0885	R1 = 0.0518, wR2 = 0.1079
Largest diff. peak and hole [e $Å^{-3}$]	0.259 and -0.309	0.325 and -0.336	0.271 and -0.214	0.183 and -0.190	0.365 and -0.439
Flack parameter	-	-	-	-0.4(4)	-

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/xxxxxxxxxxxx

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