Published in final edited form as:

Cryst Growth Des. 2009 April 1; 9(5): 2191–2197. doi:10.1021/cg800902u.

Molecular Solids from Symmetrical Bis(piperazine-2,5-diones) with Open and Closed Monomer Conformations

Nathan W. Polaske, Gary S. Nichol, Lajos Z. Szabó, and Bogdan Olenyuk*

Department of Chemistry, The University of Arizona, Tucson, AZ 85721

Abstract

The design, synthesis and solid state structures of a new class of xylylene-linked bis(1,4-piperazine-2,5-diones) are reported in an effort to extend the molecular framework of piperazine-2,5-diones. These compounds were derived from piperazine-2,5-dione as the core structure, synthesized via a new efficient route, and their crystal structures were determined. We examined the effects of side chain substitution on conformations of the linked bis-DKPs. Crystallization of 3,3'-[1,4-phenylenebis(methylene)]-bis[6-(hydroxymethyl)-1,4-dimethylpiperazine-2,5-dione] yielded molecular solids with an unusual network of “C”-shaped monomers held together by four intermolecular hydrogen bonds per asymmetric unit. Similarly, intermolecular interactions between the iodomethyl groups in 3,3'-[1,4-phenylenebis(methylene)]-bis[6-(iodomethyl)-1,4-dimethylpiperazine-2,5-dione] result in the monomers adopting a “C”-shape in the solid state. Assembly of the monomers with side chains converted to methyl groups or tert-butyldimethylsilyl ethers, thereby lacking these stabilizing intermolecular interactions, results in an infinite array of “S”-shaped conformations. These results suggest that the interplay between the attractive intermolecular interactions and repulsive steric interactions of the substituents at the C6 and C6' positions of the diketopiperazine rings is important in determining the solid-state conformations of xylylene-linked bis(piperazine-2,5-diones).

Introduction

Synthetic molecules that adopt predictable conformations in the solid state and interact via weak intermolecular associative forces have applications in crystal engineering,¹ supramolecular chemistry,² catalysis,³ and in development of new technologies for information storage.⁴ Diketopiperazines (DKPs, 1,4-piperazine-2,5-diones) have attracted considerable attention because of their ability to form well-positioned noncovalent interactions,⁵ primarily by reciprocal amide-to-amide hydrogen bonding and by π -stacking.⁶ The presence of these predictable interactions,⁷ either weakly dipolar⁸ or strongly dipolar,⁹ and the ability to maintain long range order in solution has resulted in an increased number of applications of DKPs in crystal engineering.¹⁰ In addition, the reversible aggregation in solution arising from the dynamic nature of the noncovalent interactions between the individual piperazine-2,5-dione rings¹¹ opens an intriguing possibility for their applications as environmentally-responsive polymers¹² or as designed switchable surfaces.¹³

olenyuk@email.arizona.edu.

Supporting Information Available. Detailed synthetic procedures and spectroscopic data for all compounds, X-ray crystallographic data for bis-DKPs **7-10**. This material is available free of charge via the Internet at <http://pubs.acs.org>. Crystallographic data for **7-10** have been deposited with the Cambridge Crystallographic Data Centre (959710, 959711, 682580 and 682581 respectively) and can be obtained from www.ccdc.cam.ac.uk.

Bis(1,4-piperazine-2,5-diones) contain two DKP rings connected either directly or via a central linker. A *p*-xylylene linker was chosen because of its rigidity and well-defined conformational space of the methylene groups. Early conformational studies of cyclic dipeptides also indicated preferred stacking of the phenyl rings of benzylic side chains and the DKP rings due to favorable dipole-dipole interactions.¹⁴ Examination of molecular models of the xylylene-linked bis-DKPs revealed two main low-energy conformations: closed, “C”-shaped or open, “S”-shaped (Chart 1). Control of these conformations and the ability of fine tuning of the properties of bis-DKPs, for example via an accurate placement of the donor or acceptor functional groups, could provide rapid access to networks with predictable interaction patterns and supramolecular polymers with well-defined long-range order in the solid state. However, structures of this class of linked bis(1,4-piperazine-2,5-diones) have not been explored - to our knowledge, the mono-*N*-alkylated bis-DKPs reported by Ishida *et al.*, are the only examples known to date.¹⁵

Experimental Section

X-Ray Crystallographic Experimental Details

Single crystals of compounds **7-9** were obtained by slow crystallization of their ethanol solutions. Data were collected using graphite-monochromated MoK α radiation. In all cases the crystal temperature was maintained at 120 K using an Oxford Cryosystems Cryostream. The diffractometer control program SMART¹⁶ was used for data collection, SAINT¹⁷ was used for data integration and reduction. A wavelength of 0.7749 Å was used and data were measured using a Bruker APEXII CCD detector, controlled with the APEXII¹⁸ software suite. Data for **10** were collected at the Small Molecule Crystallography Beamline 11.3.1 through the Service Crystallography at Advanced Light Source (SCrALS) program at the Lawrence Berkeley National Laboratory.

Face-indexed absorption corrections were applied using SADABS 2007/4.¹⁹ The structures were solved by direct methods and refined using SHELXTL.²⁰ Molecular diagrams were produced using ORTEP 3²¹ for Windows and Mercury 1.5.²² Hydrogen atoms were either freely refined (**7**) or refined using a riding model (**8**) with $U_{\text{iso}}\text{H} = 1.5U_{\text{eq}}(\text{C})$ for methyl hydrogen atoms and $U_{\text{iso}}\text{H} = 1.2U_{\text{eq}}(\text{C})$ for all others.

Results and Discussion

In order to expand the framework of linked piperazine-2,5-diones for crystal engineering, we investigated the chemical synthesis and the structural aspects of this class of self-assembling monomers. The detailed examination of their solid-state structure first necessitated development of an efficient synthetic access. Herein we report a convergent synthesis of xylylene-linked bis-DKPs and the investigation of their solid state structure.

Preparation of Bis(piperazine-2,5-diones)

Many previously reported syntheses of the substituted piperazine-2,5-diones relied on the cyclization of the chosen amino acids in the formation of the DKP core.^{15, 23} We found these strategies difficult for the preparation of the xylylene-linked bis-DKPs because of the multiple protection and deprotection steps needed in the synthesis of these compounds. In addition, preparation of the *N*-alkylated bis-DKPs posed additional synthetic challenges in using the *N*-alkylated amino acids for coupling. Therefore, we opted for the direct modification of the *N*-alkylated diketopiperazine core via carbanion chemistry.

Synthesis of the linked bis-DKPs started from the inexpensive, commercially available piperazine-2,5-dione (**1**). The 1,4-dimethyl-2,5-piperazinedione (**2**) was prepared by *N*-

methylation of **1** with sodium hydride and dimethyl sulfate in DMF as outlined in Scheme 1. While only a moderate yield (65%) of **2** was obtained, this procedure was found to give **2** of superior purity as compared to other literature methods.²⁴ The synthesis of β -amido ester **3** was accomplished in 78% yield by first treating **2** with potassium *tert*-butoxide in THF at -78 °C, then by the adding dimethyl carbonate. Reduction of **3** was at first problematic, as the substrate was either unreactive under typical reducing conditions or it decomposed under strenuous conditions. However, we found that Ca(BH₄)₂, or an equimolar mixture of NaBH₄ and CaCl₂, were effective reducing agents for this class of β -amido esters,²⁵ furnishing an alcohol *via* a selective reduction of the ester group in high yield. Therefore, we employed this reactant for reduction of the methyl ester **3** to alcohol **4**. The *tert*-butyldimethylsilyl ether **5**²⁶ was synthesized in a one-pot procedure from **3** with an overall yield of 74%.

In order to install the xylylene linker, α,α' -dibromo-*p*-xylene **6** was reacted with **5** in the presence of LHMDs. This reaction was completed in 2 h at -78 °C, providing the 1,4-xylylene-linked piperazine-2,5-dione **7** in 77% yield. The compound **7** was formed as a racemic mixture with the *trans* relative stereochemistry of the piperazinedione side chains. A 2.5:1 ratio of **5** to **6** was found to give optimal yield of **7**. Finally, deprotection of the TBS groups was achieved with a 2% solution of HCl in EtOH at 40 °C for 24 h under ultrasonic irradiation. Thus, the final compound **8** was synthesized as a 1:1 mixture of 2 C₂-symmetrical isomers in 21% overall yield from **1**.

Structures of Linked Bis(piperazine-2,5-diones)

A crystal structure of **8** was obtained, showing that this linked bis-DKP crystallizes in a closed, “C”-shaped conformation in the *P*2₁/*c* space group (Figure 1). This is unexpected, as the few previously reported bis-DKPs regardless of stereochemistry favored an “S”-shaped structure in the solid state,¹⁵ most likely due to a steric clash between the bis-DKP side chains at the C6 and C6' positions. The calculated powder diffraction pattern from this structure (Figure S1, Supporting Information) agrees well with that obtained experimentally at room temperature (Figure S2), showing that the crystalline form of this compound was homogeneous and that the crystal selected for analysis was representative of the bulk sample.

Crystal growth and the molecular conformations in the solid state are affected by numerous factors. Formation of hydrogen bonds adds significant stability to the structure. The sterically disfavored “C”-shaped structure could be a result of strong intermolecular hydrogen bonds originating from the sidechain hydroxyl groups (2.07 Å and 1.91 Å) and from additional stabilization by the two weaker intramolecular C-H...O interactions of C(2)-H(2)...O(4) and C(18)-H(18)...O(2) (2.31 Å and 2.55 Å, respectively). A possible explanation for the formation of the “C”-shaped structure is that stabilization of the crystal lattice resulting from the favorably placed intermolecular hydrogen bonds could outweigh possible energetic penalty created by steric interactions of the bis-DKP side chains, resulting in the formation of a solid with closed, “C”-shaped monomers.

To test this hypothesis, we obtained a crystal structure of bis-DKP **7** with the hydroxyl groups converted to bulky silyl ethers, which disrupted the side chain hydrogen bonding (Figure 2). Compound **7** crystallized in an enantiopure form with monomers adopting an “S”-shaped conformation.

Another interesting observation was that the crystal structure of **7** shows “S”-shaped conformation, similar to the previously reported mono-*N*-alkylated bis-DKPs.⁶ In the case of compound **7**, weak hydrogen bonds are found between the α -protons and the amide carbonyls. In contrast to the previously reported piperazine-2,5-diones,¹⁵ both compounds, crystallized from ethanol, show an absence of solvent of crystallization, thus simplifying characterization of their ordered solid-state assemblies. In addition, the substitution of both nitrogens of the

DKP rings allows one to solve the typical solubility problems associated with the use of diketopiperazines, making their synthesis and crystallization more operationally straightforward.

To further explore the series, two additional bridged piperazine-2,5-diones were designed: bis (iodomethyl) substituted DKP **9** and dimethyl substituted DKP **10**. The iodomethyl groups have additional steric bulk, but they are still capable of site-to-site interactions. Compound **10**, with its side chain methyl groups, should be lacking additional stabilizing interactions.

Compound **9** was synthesized in one step from **8** by converting hydroxyl groups into iodides under modified Garegg's conditions²⁷ with triphenylphosphine and 2.5 equiv. of iodine (Scheme 1). Conversion of **9** into **10** was carried out by catalytic hydrogenation over Pd/C. The solid state structures of **9** and **10** were studied by X-ray crystallography. To exclude the possibility of concomitant polymorphism, powder diffraction patterns were calculated from these single-crystal structures. Comparison of experimentally obtained powder diffraction data revealed a good agreement between the calculated and experimentally derived data for both compounds (see Supporting Information).

Compound **9** crystallized in the monoclinic space group $P2_1/n$ with two crystallographically unique molecules (**9a** and **9b**) in the asymmetric unit. The molecular structure of **9a** is depicted in Figure 3a, overlay of **9a** and **9b** - in Figure 3b. Despite the presence of bulky iodomethyl groups, the compound has adopted a “C”-shaped conformation. Both piperazine-2,5-dione rings are essentially planar with mean planes fitted through each ring with both independent molecules having similar conformations.

The “C” shape allows for the maximization of relatively weak iodine-iodine interactions. Attractive iodine-iodine contacts have been reported and the Cambridge Structural Database (January 2008 update) contains 26 examples of compounds featuring $RH_2C...I-CH_2R$ interactions, with a mean I...I distance of 3.832 Å.²⁸ Molecule **9a** contains two refined I...I distances of 3.8526(6) Å and 3.8249(4) Å, similar to the distances found in 1,2-diiodoethane (3.8816(4) Å).²⁹ As with 1,2-diiodoethane, inter-halogen interactions,^{30,31} can be assumed as a main stabilizing force.

Halogen-halogen interactions are of two main types. In type I geometry the approach is characterized by similar angles θ_1 and θ_2 and in type II the angles are very different: $\theta_1 \cong 180^\circ$ and $\theta_2 \cong 90^\circ$ (Scheme 2).³⁰ In both types of interactions, the iodine atoms are able to participate in I---I contacts shorter than Σ_{vdw} (=3.96 Å) in relation to their atomic radii.³² These heavy atoms are polarized positively in the polar region (along the C-I vector) and negatively in the equatorial region (perpendicular to the C-I vector) and hence, favor type II geometry a result of stabilization from the dual polarization in the $C-I^{(d+)}...I^{(d-)}-C$ direction. The I---I interactions in both structures **9a** and **9b** show type II geometry, where the polar δ^+ region of one elliptical iodine atom points toward the equatorial δ^- region of an adjacent iodine. These interactions, along with the C-H...O hydrogen bonded $R_2^2(8)$ zigzag motif (Figure 3c), allow the molecule to pack as chains. The packing of molecule **9b** is different - there is only one I...I interaction (3.8249(4) Å) with no readily defined C-H...O interactions, although the molecules still pack as chains (Figure 3d). The relative orientations of the two independent chains can be seen from the *b*-axis packing diagram in Figure 4.

The structure of **10** is shown in Figure 5a. The compound has adopted an “S” shaped conformation despite the fact that the methyl groups are the least sterically bulky substituents within the series. This is because the methyl groups C7 and C22 do not provide any intermolecular interactions which could potentially stabilize an alternative “C” shape observed

in bis-DKPs **8-9**. The solid state packing shows no significant intermolecular contacts between side chains other than some weak hydrogen bonding (Figure 5b).

Overall, our structural investigation of compounds **7-10** suggest that solid state conformations of the studied bis(1,4-piperazine-2,5-diones) depend upon the choice of functional groups at the periphery of the DKP rings. The presence of the hydrogen bond donating functionalities, such as hydroxyl groups, or the iodomethyl groups with relatively weak site-to-site interactions favor closed, “C”-shaped conformations.

Conclusions

A new class of symmetrical, xylene-linked *N*-alkylated bis(1,4-piperazine-2,5-diones) has been designed and synthesized and their solid-state structures have been examined. Although the detailed analysis of the interactions resulting in open and closed conformations within the series of linked bis(piperazine-2,5-diones) awaits further studies, our data suggest that both the intermolecular interactions between the side chains at the 6,6' positions of the DKP rings and the steric bulk of the side chains play an essential role in determining their solid state conformations. Even the relatively weak side chain-to-side chain interactions, such as inter-halogen interactions or hydrogen bonds between the hydroxyl groups and amide carbonyls, result in the molecules adopting a “C”-shaped conformation. In the absence of such stabilizing interactions, the open “S”-shape is adopted. The closed, “C”-shaped conformation can gain in better overall close packing because of the folded, spheroid-like shape of the molecules. The bis-DKPs in the open, “S”-shaped conformation are generally able to make stronger intermolecular interactions. The interplay between the forces of close packing and the intermolecular contacts could be the driving force for the observed solid state conformations.

All reported molecular solids are thermally stable, with melting points above 200 °C. The high thermal stability opens an opportunity for the future design of high-temperature conformational polymorphs, capable of reversible and concerted reorganizations in the solid state upon heating and cooling.³³ Such polymorphs could expand our understanding of how organic molecular solids can support the development of crystalline molecular machines and devices that can undergo collective, correlated movements. The reported structures, with additional modifications to the linkers or the DKP rings, could also serve as building blocks for metallo-supramolecular assemblies, metal-organic polygons, polyhedra and other designed metal-organic materials. The efficient synthesis of the reported bis(1,4-piperazine-2,5-diones) provides rapid access to these compounds for future applications in crystal engineering. Further synthetic and structural studies of this class of bis-DKPs and the resulting molecular solids are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support by the University of Arizona Office of the Vice President for Research is gratefully acknowledged. We also thank the National Science Foundation (CHE-0748838) and National Institutes of Health (R21 CA 129388) for funding. Single crystal and powder X-ray diffractometers were purchased with support of the National Science Foundation grants CHE-9610374 and CHE-9974726. We thank Dr. Brendan Twamley, University of Idaho, for data collection of **9** and Dr. Jeanette A. Krause and Dr. Allen G. Oliver for data collection of **10** as part of the Service Crystallography at the Advanced Light Source (SCrALS) program. SCrALS is supported by the U.S. Department of Energy, Office of Energy Sciences Materials Sciences Division, under contract DE-AC02-05CH11231.

References

- (1). (a) Kitaigorodsky, AI. *Molecular Crystals and Molecules*. Academic Press; New York: 1973. (b) Desiraju, GR. *Crystal Design: Structure and Function*. Vol. Vol. 7. Wiley; Chichester: 2003. (c) Desiraju, GR. *The Crystal as a Supramolecular Entity*. Vol. Vol. 2. Wiley; Chichester: 1996. (d) Desiraju, GR.; Parshall, GW. *Crystal Engineering: The Design of Organic Solids*. Vol. Vol. 54. Elsevier; Amsterdam: 1989. (e) Seddon, KR.; Zaworotko, M. *Crystal Engineering: The Design and Application of Functional Solids*. Vol. Vol. 539. Kluwer Academic; Dordrecht: 1999. (f) Wright, JD. *Molecular Crystals*. Cambridge University Press; Cambridge: 1987. (g) Moulton B, Zaworotko MJ. *Chem. Rev* 2001;101:1629–1658. [PubMed: 11709994]
- (2). (a) Lehn, J-M. *Supramolecular Chemistry: Concepts and Perspectives*. Wiley-VCH; Weinheim: 1995. (b) Lyssenko KA, Lenev DA, Kostyanovsky RG. *Tetrahedron* 2002;58:8525–8537. (c) Whitesell, JK. *Organized Molecular Assemblies in the Solid State*. Wiley; Chichester: 1999. (d) Steed, JW.; Atwood, JL. *Supramolecular Chemistry*. Wiley; Chichester: 2000. (e) Brienne MJ, Gabard J, Leclercq M, Lehn JM, Cesario M, Pascard C, Cheve M, Dutrucrosset G. *Tetrahedron Lett* 1994;35:8157–8160.
- (3). (a) Yamada YMA. *Chem. Pharm. Bull* 2005;53:723–739. [PubMed: 15997125] (b) Yoon JH, Park YJ, Lee JH, Yoo J, Jun CH. *Org. Lett* 2005;7:2889–2892. [PubMed: 15987162] (c) Yang J, Ding SJ, Radosz M, Shen YQ. *Macromolecules* 2004;37:1728–1734. (d) Ding SJ, Yang J, Radosz M, Shen YQ. *J. Polym. Sci. Pol. Chem* 2004;42:22–30.
- (4). (a) Feng M, Gao L, Du SX, Deng ZT, Cheng ZH, Ji W, Zhang DQ, Guo XF, Lin X, Chi LF, Zhu DB, Fuchs H, Gao HJ. *Adv. Funct. Mater* 2007;17:770–776. (b) Kroutvar M, Ducommun Y, Heiss D, Bichler M, Schuh D, Abstreiter G, Finley JJ. *Nature* 2004;432:81–84. [PubMed: 15525984] Diederich F. *Pure Appl. Chem* 2005;77:1851–1863.
- (5). (a) Martins MB, Carvalho I. *Tetrahedron* 2007;63:9923–9932. (b) Palacin S, Chin DN, Simanek EE, MacDonald JC, Whitesides GM, McBride MT, Palmore GTR. *J. Am. Chem. Soc* 1997;119:11807–11816.
- (6). MacDonald JC, Whitesides GM. *Chem. Rev* 1994;94:2383–2420.
- (7). Chin DN, Palmore GTR, Whitesides GM. *J. Am. Chem. Soc* 1999;121:2115–2122.
- (8). (a) Williams LJ, Jagadish B, Lyon SR, Kloster RA, Carducci MD, Mash EA. *Tetrahedron* 1999;55:14281–14300. (b) Williams LJ, Jagadish B, Lansdown MG, Carducci MD, Mash EA. *Tetrahedron* 1999;55:14301–14322.
- (9). Jagadish B, Williams LJ, Carducci MD, Bosshard C, Mash EA. *Tetrahedron Lett* 2000;41:9483–9487.
- (10). (a) Weatherhead-Kloster RA, Selby HD, Miller WB, Mash EA. *J. Org. Chem* 2005;70:8693–8702. [PubMed: 16238297] (b) Kloster RA, Carducci MD, Mash EA. *Org. Lett* 2003;5:3683–3686. [PubMed: 14507204] (c) Jagadish B, Carducci MD, Bosshard C, Gunter P, Margolis JI, Williams LJ, Mash EA. *Cryst. Growth Des* 2003;3:811–821. (d) Palmore GTR, Luo TJM, McBride-Wieser MT, Picciotto EA, Reynoso-Paz CM. *Chem. Mat* 1999;11:3315–3328. (e) Palmore GTR, McBride MT. *Chem. Commun* 1998:145–146. (f) Kostyanovsky RG, El'natanov YI, Krutius ON, Lyssenko KA, Chervin, Lenev DA. *Mendeleev Commun* 1999:109–111. (g) Kostyanovsky RG, Lyssenko KA, Lenev DA. *Mendeleev Commun* 1999:154–156. (h) Lenev DA, Lyssenko KA, Kostyanovsky RG. *Mendeleev Commun* 2004:312–314.
- (11). Ridvan L, Budesinsky M, Tichy M, Malon P, Zavada J, Podlaha J, Cisarova I. *Tetrahedron* 1999;55:12331–12348.
- (12). Brunsveld L, Folmer BJB, Meijer EW, Sijbesma RP. *Chem. Rev* 2001;101:4071–4097. [PubMed: 11740927]
- (13). Liu Y, Mu L, Liu BH, Kong JL. *Chem.-Eur. J* 2005;11:2622–2631.
- (14). Kopple KD, Ohnishi M. *J. Am. Chem. Soc* 1969;91:962–970. [PubMed: 5778278]
- (15). Ishida Y, Aida T. *J. Am. Chem. Soc* 2002;124:14017–14019. [PubMed: 12440899]
- (16). SMART. Bruker AXS, Inc.; Madison, WI, USA: 2007.
- (17). SAINT. Bruker AXS, Inc.; Madison, WI, USA: 2007.
- (18). APEX II. Bruker AXS Inc.; Madison, WI, USA: 2008.

- (19). Sheldrick, GM. SADABS: Program for Empirical Absorption Correction of Area Detector Data. University of Göttingen; Germany: 1996.
- (20). Sheldrick GM. Acta Crystallogr. Sect. A 2008;64:112–122. [PubMed: 18156677]
- (21). Farrugia LS. J. Appl. Cryst 1997;30:565.
- (22). Macrae CF, Edgington PR, McCabe P, Pidcock E, Shields GP, Taylor R, Towler M, van De Streek J. J. Appl. Crystallogr 2006;39:453–457.
- (23). Movassaghi M, Schimidt MA, Ashenhurst J. 2008;47:1485–1487.
- (24). Karrer P, Granacher C, Schlosser A. Helv. Chim. Acta 19225:139–141.
- (25). Klutchnko S, Hoefle ML, Smith RD, Essenburg AD, Parker RB, Nemeth VL, Ryan M, Dugan DH, Kaplan HR. J. Med. Chem 1981;24:104–109. [PubMed: 6259352]
- (26). Chai CLL, Elix JA, Huleatt PB. Tetrahedron 2005;61:8722–8739.
- (27). Garegg PJ, Samuelsson B. J. Chem. Soc.-Perkin Trans. 1 1980:2866–2869.
- (28). Nangia A. CrystEngComm 2002;1–9.
- (29). Akkerman F, Buschmann J, Lentz D, Luger P, Rodel E. J. Chem. Crystallogr 2003;33:969–975.
- (30). (a) Nath NK, Saha BK, Nangia A. New J. Chem 2008;32:1693–1701. (b) Saha BK, Nangia A, Nicoud JF. Cryst. Growth Des 2006;6:1278–1281. (c) Saha BK, Jeti RKR, Reddy LS, Aitipamula S, Nangia A. Cryst. Growth Des 2005;5:887–899.
- (31). (a) Aakeroy CB, Fasulo M, Schultheiss N, Desper J, Moore C. J. Am. Chem. Soc 2007;129:13772–&. [PubMed: 17956090] (b) Chopra D, Thiruvenkatam V, Manjunath SG, Row TNG. Cryst. Growth Des 2007;7:868–874. (c) Gonnade RG, Bhadbhade MM, Shashidhar MS, Sanki AK. Chem. Commun 2005:5870–5872. (d) Zordan F, Brammer L, Sherwood P. J. Am. Chem. Soc 2005;127:5979–5989. [PubMed: 15839698] (e) Paulini R, Muller K, Diederich F. Angew. Chem.-Int. Edit 2005;44:1788–1805. (f) Moorthy JN, Venkatakrishnan P, Mal P, Dixit S, Venugopalan P. Cryst. Growth Des 2003;3:581–585. (g) Bosch E, Barnes CL. Cryst. Growth Des 2002;2:299–302. (h) Pedireddi VR, Reddy DS, Goud BS, Craig DC, Rae AD, Desiraju GR. J. Chem. Soc.-Perkin Trans. 2 1994:2353–2360.
- (32). (a) Logothetis TA, Meyer F, Metrangolo P, Pilati T, Resnati G. New J. Chem 2004;28:760–763. (b) Brammer L, Espallargas GM, Adams H. CrystEngComm 2003;5:343–345.
- (33). Sokolov AN, Swenson DC, MacGillivray LR. Proc. Natl. Acad. Sci. U. S. A 2008;105:1794–1797. [PubMed: 18245387]

Figure 1.

(a) ORTEP diagram of **8** with anisotropic displacement ellipsoids at the 50% probability level and (b) packing of **8** in the solid state, illustrating two distinct O-H...O hydrogen bond patterns, one an $R_2^2(14)$ motif with the molecules related by crystallographic inversion and the second a $C(7)$ motif linking molecules related by screw axis symmetry.

Figure 2.

(a) ORTEP diagram of **7** with anisotropic displacement ellipsoids at the 50% probability level and (b) its crystal packing, illustrating the C-H...O hydrogen bonding pattern.

Figure 3.

(a) ORTEP diagram of a crystallographically unique *R,S,S,R* isomer **9a** with anisotropic displacement ellipsoids at the 50% probability level, (b) an overlay of **9a** (blue) and **9b** (orange) formed by fitting together the two central aryl rings, with an rms deviation of 0.0174. (c) Packing of the symmetry equivalents of **9a**, illustrating the favorable I...I and C-H...O interactions with $R_2^2(8)$ motif highlighted in red; (d) I...I interactions between **9b** and symmetry equivalents.

Figure 4.

(a) Packing diagrams of **9**, viewed along the *b*-axis and (b) along the plane parallel to the diketopiperazine rings in the crystallographically unique molecule **9a**. Molecule **9a** is shown in blue, **9b** in orange. Pink dashed lines denote C-H...O and light blue dashed lines indicate I...I interactions.

Figure 5.

(a) ORTEP diagram of an *R,S,S,R* isomer of **10** with anisotropic displacement ellipsoids at the 50% probability level and (b) its packing in the solid state, viewed along the *c* axis.

Scheme 1.
Synthesis of xylylene-linked bis(1,4-piperazine-2,5-diones).

Scheme 2.
Type I and type II halogen---halogen interactions.

Chart 1.
Schematic representation of two conformational isomers of xylylene-linked bis (piperazine-2,5-diones): closed, (A) “C”-shaped and open, (B) “S”-shaped.

Table 1Crystallographic Data and Structure Refinement for **7-10**.

	7	8	9	10
formula	C ₃₄ H ₅₈ N ₄ O ₆ Si ₂	C ₂₂ H ₃₀ N ₄ O ₆	C ₂₂ H ₂₈ I ₂ N ₄ O ₄	C ₂₂ H ₃₀ N ₄ O ₄
form weight (g·mol ⁻¹)	675.02	446.50	666.28	414.50
temp (K)	120(2)	120(2)	90(2)	120(2)
radiation	MoK α	MoK α	MoK α	synchrotron
cryst syst	triclinic	monoclinic	monoclinic	orthorhombic
space group	$\overline{P}1$	$P2_1/c$	$P2_1/n$	$P2_12_12_1$
<i>a</i> (Å)	6.4182(19)	18.859(7)	19.4966(12)	6.4714(3)
<i>b</i> (Å)	14.220(4)	9.300(3)	10.7894(7)	11.9785(16)
<i>c</i> (Å)	20.976(6)	12.455(5)	22.9663(14)	26.743(4)
α (deg)	101.343(4)	90	90	90
β (deg)	93.648(4)	97.290(5)	91.2210(10)	90
γ (deg)	93.178(4)	90	90	90
<i>V</i> (Å ³)	1868.8(9)	2166.8(14)	4830.0(5)	2073.1(17)
<i>Z</i>	2	4	8	4
<i>Z'</i>	1	1	2	1
μ (mm ⁻¹)	0.141	0.101	2.640	0.093
no reflns	11477	14124	64971	23270
unique reflns	6023	4175	11983	2465
final <i>R</i> indices	$R_1 = 0.0441$	$R_1 = 0.0432$	$R_1 = 0.0392$	$R_1 = 0.0354$
(<i>I</i> > 2 σ (<i>I</i>))	$wR_2 = 0.1013$	$wR_2 = 0.1064$	$wR_2 = 0.0857$	$wR_2 = 0.0794$
<i>R</i> indices	$R_1 = 0.0793$	$R_1 = 0.0822$	$R_1 = 0.0574$	$R_1 = 0.0579$
(all data)	$wR_2 = 0.1256$	$wR_2 = 0.1389$	$wR_2 = 0.0941$	$wR_2 = 0.0903$
GOF	1.039	1.027	1.048	1.038

X-ray powder diffraction data for **7-10** were collected on a Philips X'Pert MPD Pro powder diffractometer using Cu K α radiation and a rotating flat sample stage. Scans were performed in the 2θ range 5 - 90 degrees with a step size of 0.008 and a time of 20 seconds per step. Philips Data Collector and X'Pert Plus software were used for diffractometer control and data analysis. Summary of crystal data and structure refinements are given in Table 1. Additional crystallographic details are reported in the Supporting Information.