CrystEngComm

COMMUNICATION

View Article Online

Published on 10 May 2013. Downloaded by Monash University on 07/06/2013 19:59:28.

H/F isosteric substitution to attest different equienergetic molecular conformations in crystals[†]‡

Cite this: DOI: 10.1039/c3ce40697k

Received 26th February 2013, Accepted 9th May 2013 Amol G. Dikundwar,^a Ch. Venkateswarlu,^b R. N. Chandrakala,^b Srinivasan Chandrasekaran^{*b} and Tayur N. Guru Row^{*a}

DOI: 10.1039/c3ce40697k

www.rsc.org/crystengcomm

The sequential replacement of aromatic H-atoms by F-atoms in 1,6-bis(phenylcarbonate) hexa-2,4-diyne allows access to its possible iso-energetic "syn", "gauche" and "anti" conformations.

The crystallization of organic molecules depends on several factors with the molecular conformation being the key component. With the X-ray crystallographic technique providing an unambiguous determination of 3D structure in the solid state, conformational analysis has become facile in molecular crystals. The specific conformation of a molecule in a crystal results from a delicate balance of intra and intermolecular forces such as dipole-dipole interactions, steric (van der Waals) interactions and hydrogen bonding.^{1,2} While the interactions within a molecule ensure conformational locking, the intermolecular interactions provide tools for crystal engineering, exploiting conformational flexibility in the molecule. In the literature, there are several examples where different molecular conformations of a compound have been obtained by allowing the molecules to assemble in a different crystallization milieu. Such an 'experimental conformational scan' has been conventionally achieved by conformational polymorphism³ and cocrystallization experiments.⁴ The variability in the conformation of a molecule may also be brought about by decorating the surface of a molecule with substituents providing both electronic and steric influences. In this article, we explore the utilization of the isosteric (equi-volume) properties of a hydrogen atom and a fluorine atom in constituting different equi-energetic molecular conformations of the conformationally flexible molecule, 1,6-bis(phenylcarbonate) hexa-2,4-diyne, 1 (Scheme 1).

The repertoire of a molecule in adopting a specific molecular conformation decides the efficiency of the intermolecular packing in the solid state.⁵ The basic rules governing molecular packing indicate that molecules with a centre of symmetry prefer to acquire an inversion centre in the crystal lattice leading to crystal structures with centrosymmetric space groups.⁶ In a centrosymmetric conformation with the molecular dipole moment being zero, the resulting crystal structure is nearly always centrosymmetric.⁷ However, Brock and Dunitz⁸ demonstrated that centrosymmetric molecules can even adopt noncentrosymmetric conformations and pack with a higher crystallographic symmetry at the expense of noncovalent intermolecular interactions.9 When present in a non-centric conformation, molecules can arrange so as to cancel the intermolecular dipoles resulting in a centrosymmetric organization or they can even afford a polar crystal packing.⁷ Interestingly, in the literature, there have been arguments that a particular conformation is inherent in a molecule, which is mainly determined by its covalent connectivity with the intermolecular interactions being just a consequence of the crystal packing.¹⁰ On the contrary, there are several reports explaining the stabilization of unusual molecular conformations through molecular aggregation in the solid, liquid and gas states.¹¹ This issue takes prime importance in cases where the molecular conformation observed in the crystal structure deviates significantly from the ideal conformation calculated for the gas phase or in solution.12

The non-availability of any strong H-bonding pairs makes **1** a suitable candidate to examine the effect of fluorination on the resulting molecular conformations in the solid state.¹³ In its



Scheme 1 Chemical structures of compounds 1–6 with a general scheme for their synthesis.

^aSolid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560012, Karnataka, India. E-mail: ssctng@sscu.iisc.ernet.in;

Fax: +91-080-23601310; Tel: +91-080-22932796

^bDepartment of Organic Chemistry, Indian Institute of Science, Bangalore 560012, Karnataka, India. E-mail: scn@orgchem.iisc.ernet.in; Fax: +91-80-23600529; Tel: +91-80-22932404

[†] In memory of Professor A. Srikrishna (1955-2013)

[‡] Electronic supplementary information (ESI) available: detailed synthetic procedures and characterization data for compounds **1–6**; CIFs, ORTEPs and packing diagrams of compounds **1–6** and CSD search details. CCDC numbers 759062 and 922272–922275. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ce40697k

crystalline form, **1** adopts an unusually folded molecular conformation with the two diacetylene spaced aryl carbonate groups oriented in a "*cisoid*" fashion with the torsion angle, ϕ being 8.4(1)° (Fig. 1). Molecules with this chiral dissymmetric conformation pack in the centrosymmetric space group *Pccn* with half a molecule in the asymmetric unit (Z = 4).¹⁴

Intrigued by the elusive conformation of 1, we carried out a Cambridge Structural Database (CSD)¹⁵ search to obtain an overall estimate of the different molecular conformations adopted by such symmetrically disubstituted diacetylenes. The search results (see ESI[†]) clearly indicated a preference towards the centrosymmetric molecular conformation with the torsion angle, $\phi = 180^{\circ}$ as depicted in Fig. 2. This prompted us to probe the gas phase molecular conformation of 1. Geometry optimization calculations (Table 1) suggested the most stable conformation to be the untwisted one with the torsion angle of 77.6°, whereas the generally preferred "anti" conformation ($\phi = 180^\circ$, indicated by CSD) lies just above this on the energy axis ($\Delta E_{SP} = 0.08$ kcal mol⁻¹, Table 1). Within computational uncertainties, these conformations can be called iso-energetic. More importantly, the energy gaps between the crystal conformation $(8.4(1)^{\circ})$ and the conformations mentioned above $(77.6^{\circ} \text{ and } 180^{\circ})$ are significantly small (Table 1) indicating the possibility of conformational flipping upon a slight manipulation at the molecular or supramolecular levels.

Taking into account the equi-volume (isosteric) nature of the Hand F-atoms and inspired by the peculiarly "inert" behavior of the "organic" fluorine in crystals,¹³ it was thought that the H/F isosteric interchange could be exploited to show the predicted conformations of **1** in crystals. Accordingly, compounds **2**, **3**, **4**, **5** and **6** were designed (Scheme 1); **2**, **3** and **4** are *ortho*, *meta* and *para* monofluorinated analogs of **1**, whereas **5** and **6**§ are 2,4,6trifluro and pentafluoro analogs, respectively. The crystal structures¹⁴ of compounds **2**, **3**, **4**, **5** and **6** indeed exhibited interesting trends in terms of their molecular conformations (Fig. 3) with the corresponding energy values (Table 1).

Although both **2** and **4** adopt a similar conformation to that of **1** ($\phi = 8.6(1)^{\circ}$ and $\phi = 4.1(1)^{\circ}$, respectively), compound **3**, which has its *meta* H-atom replaced by an F-atom, adopts an entirely different "*gauche*" conformation with $\phi = 85.7(1)^{\circ}$ which is closer to the gas phase optimized structure (77.6°) of **1**. Compounds **5** and **6**, on the other hand, adopt a well anticipated open "*transoid*" conformation with $\phi = 180^{\circ}$. Although both **5** and **6** adopt "*anti*"



Fig. 1 The crystal conformation of 1,6-bis(phenylcarbonate) hexa-2,4-diyne.



Fig. 2 A plot of number of hits *versus* the torsion angle (φ) for the symmetrically 1,6-disubstituted hexa-2,4-diyne structures with a diacetylene spacer; the substituent group R ranges from simple methyl groups to bulkier polysub-stituted groups (total no. of hits = 79).

conformations, they differ significantly with the former being completely open (extended) and the latter being partially open (unextended) (Fig. 3(d) and 3(e), respectively).

As the molecular conformations in crystals are primarily guided through noncovalent interactions,^{11,12} it is important to rationalize the genesis of a particular conformation based on the supramolecular packing features involved. A close inspection of the isostructural crystal packing of 1, 2 and 4 reveals that the molecules in the twisted conformation are held together mainly with (Ph)C_{meta}-H···O hydrogen bonds and C_{sp3}-H···π interactions as shown in Fig. 4. Interestingly, the C-H…O hydrogen bond formed through the involvement of the meta H-atom (H9) with the carbonyl oxygen (O2) seems to be an important prerequisite satisfying the geometry (spatial) requirements for the efficient packing of the molecules in the twisted conformation. The replacement of one of the meta H-atoms (participating in the (Ph)C_{meta}-H···O interaction) on the phenyl rings by an F-atom flips the molecular conformation from "cisoid" to "gauche" whereas, the further replacement of the 2,4,6 positioned H-atoms and all five ring H-atoms by F-atoms results in an ideal "anti" conformation of compounds 5 and 6 where the main intermolecular interactions are Csp3-H···O and Csp3/sp2-H···F hydrogen bonds (Fig. S1-S6, ESI[†]). It is important to note that the trifluoroand pentafluoro-substitution on the phenyl ring results in the

Table 1	Conformational energy	y differences in 1 , 2 , 3	3, 4, 5 and 6 ^a
-			

ΔE (kcal mol ⁻¹)	
$\Delta E_{\mathrm{Opt-SP}}$	
0.525	
0.560	
0.506	
0.208	
0.416	
1.340	

 a Opt: optimized geometry; SP: single point energies at the given $\phi.$ Calculations performed at the b3lyp/6-31++g(d,p) level using Gaussian 09. 16



Fig. 3 Molecular conformations of (a) 1,6-bis(2-fluorophenylcarbonate) hexa-2,4-diyne, 2; (b) 1,6-bis(3-fluorophenylcarbonate) hexa-2,4-diyne, 3; (c) 1,6-bis(4-fluorophenylcarbonate) hexa-2,4-diyne, 4; (d) 1,6-bis(2,4,6-trifluorophenylcarbonate) hexa-2,4-diyne, 5; (e) 1,6-bis(2,3,4,5,6-pentafluorophenylcarbonate) hexa-2,4-diyne, 6 in their respective crystal structures.



Fig. 4 The packing diagram of **1** showing the intermolecular C–H···O and C– H··· π interactions (these packing features are conserved in the isostructural crystals of **2** (o-fluoro analog) and **4** (p-fluoro analog)).

increased acidity of the protons and also in the reversal of the polarity of the ring (π to π_F).¹⁷ Along with the steric factors, these effects may also have leading contributions towards the genesis of the "*anti*" conformations of compounds **5** and **6**.

In conclusion, it is shown that the selective substitution of H-atoms by F-atoms can be exploited to explore the conformational landscape of a flexible molecule containing little energy difference among various conformations. Furthermore, the results clearly show the unequivocal dominance of the weak intermolecular interactions (herein a guiding C–H···O interaction supported by a surrogate C–H··· π interactions)¹⁸ in stabilizing unusual molecular conformations, as opposed to an ideal conformation, in crystals. A mutual compromise between the molecular symmetry, the crystallographic site symmetry and the intermolecular H-bonds (supramolecular synthons) can conceive, bear and nurture the so-called "unusual" molecular conformations in the solid state.

AGD thanks CSIR, New Delhi for SRF. CV thanks CSIR for the Shyama Prasad Mukherjee (SRF) Fellowship and TNGR thanks DST, India for the J. C. Bose Fellowship.

Notes and references

§ The crystal structure of compound **6** has already been reported by us (CCDC 784071; ref. 9) and has been used here for comparison with other related structures.

- 1 A. Gavezzotti, J. Am. Chem. Soc., 1985, 107, 962.
- 2 J. D. Dunitz and A. Gavezzotti, *Angew. Chem., Int. Ed.*, 2005, 44, 1766.

- 3 A. Nangia, Acc. Chem. Res., 2008, 41, 595 and references therein.
- 4 (a) A. Mukherjee, P. Grobelny, T. S. Thakur and G. R. Desiraju, *Cryst. Growth Des.*, 2011, 11, 2637; (b) S. Mahapatra, T. S. Thakur, S. Joseph, S. Varughese and G. R. Desiraju, *Cryst. Growth Des.*, 2010, 10, 3191.
- 5 (a) A. I. Kitaigorodskii, Organic Chemical Crystallography, Consultants Bureau, New York, 1961; (b) A. I. Kitaigorodskii, Molecular Crystals and Molecules, Academic Press, New York, 1973; (c) P. Dauber and A. T. Hagler, Acc. Chem. Res., 1980, 13, 105; (d) M. C. Etter, Acc. Chem. Res., 1990, 23, 120.
- 6 (a) J. W. Yao, J. C. Cole, E. Pidcock, F. H. Allen, J. A. K. Howard and W. D. S. Motherwell, Acta Crystallogr., Sect. B: Struct. Sci., 2002, 58, 640; (b) E. Pidcock and W. D. S. Motherwell, Acta Crystallogr., Sect. B: Struct. Sci., 2004, 60, 539.
- 7 (a) J. K. Whitesell, R. E. Davis, L. L. Saunders, R. J. Wilson and J. P. Feagins, *J. Am. Chem. Soc.*, 1991, 113, 3267; (b) A. Dey and G. R. Desiraju, *Chem. Commun.*, 2005, 2486.
- 8 C. P. Brock and J. D. Dunitz, Chem. Mater., 1994, 6, 1118.
- 9 A. G. Dikundwar, Ch. Venkateswarlu, R. O. Piltz, S. Chandrasekaran and T. N. Guru Row, *CrystEngComm*, 2011, 13, 1531.
- 10 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1993.
- 11 O. Takahashi, Y. Kohno and M. Nishio, *Chem. Rev.*, 2010, **110**, 6049 and references therein.
- 12 (a) C. R. Jones, P. K. Baruah, A. L. Thompson, S. Scheiner and M. D. Smith, *J. Am. Chem. Soc.*, 2012, **134**, 12064; (b) A. Sharma, I. Reva, R. Fausto, S. Hesse, Z. Xue, M. A. Suhm, S. K. Nayak, R. Sathishkumar, R. Pal and T. N. Guru Row, *J. Am. Chem. Soc.*, 2011, **133**, 20194; (c) D. Chopra, T. N. Guru Row, E. Arunan and R. A. Klein, *J. Mol. Struct.*, 2010, **964**, 126.
- 13 (a) L. Shimoni and J. P. Glusker, *Struct. Chem.*, 1994, 5, 383; (b)
 J. A. K. Howard, V. J. Hoy, D. O'Hagan and G. T. Smith, *Tetrahedron*, 1996, 52, 12613; (c)
 J. D. Dunitz and R. Taylor, *Chem.-Eur. J.*, 1997, 3, 89; (d) J. D. Dunitz, *ChemBioChem*, 2004, 5, 614; (e) K. Reichenbacher, H. I. Suss and J. Hulliger, *Chem. Soc. Rev.*, 2005, 34, 22; (f) D. Chopra and T. N. Guru Row, *CrystEngComm*, 2008, 10, 54; (g) D. Chopra and T. N. Guru Row, *CrystEngComm*, 2011, 13, 2175; (h) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, 40, 3496.
- 14 Crystal data: **1**, CCDC 759062, MF: $C_{20}H_{14}O_6$; orthorhombic; a = 9.5387(15) Å; b = 23.2080(36) Å; c = 7.4056(12) Å; V = 1639.41(4) Å³; T = 150 K; space group, *Pccn*, Z = 4; $R_{obs} = 0.030$; $wR_{2obs} = 0.077$; $\Delta\rho_{min,max} = -0.18$, 0.18 e Å⁻³; gof = 1.04; **2**, CCDC

922274, MF: $C_{20}H_{12}F_2O_6$; orthorhombic; a = 9.9560(50) Å; b =22.6650(50) Å; c = 7.4420(50) Å; V = 1679.31(15) Å³; T = 150 K; space group, *Pccn*, Z = 4; $R_{obs} = 0.037$; w $R_{2obs} = 0.092$; $\Delta \rho_{min,max}$ = -0.19, 0.19 e Å⁻³; gof = 1.06; **3**, CCDC 922273, MF: $C_{20}H_{12}F_2O_6$; monoclinic; a = 20.8305(12) Å; b = 3.9051(3) Å; c =22.4954(12) Å; $\beta = 110.433(7)^{\circ}$; V = 1714.78(44) Å³; T = 150 K; space group, $P2_1/n$, Z = 4; $R_{obs} = 0.036$; w $R_{2obs} = 0.097$; $\Delta \rho_{min,max}$ = -0.22, 0.16 e Å⁻³; gof = 1.05; 4, CCDC 922275, MF: $C_{20}H_{12}F_2O_6$; orthorhombic; a = 9.6359(9) Å; b = 23.7478(21) Å; c= 7.2680(6) Å; V = 1663.15(3) Å³; T = 150 K; space group, *Pccn*, Z = 4; R_{obs} = 0.037; w R_{2obs} = 0.101; $\Delta \rho_{\text{min,max}}$ = -0.21, 0.23 e Å⁻³; gof = 1.04; 5, CCDC 922272, MF: C₂₀H₈F₆O₆; triclinic; a = 5.2422(3) Å; b = 7.1560(4) Å; c = 13.2155(7) Å; $\alpha = 93.426(4)^{\circ}$; $\beta =$ 98.645(4)°; $\gamma = 109.868(5)°$; $V = 457.66(10) \text{ Å}^3$; T = 150 K; space group, $P\bar{1}$, Z = 1; $R_{obs} = 0.029$; $wR_{2obs} = 0.073$; $\Delta \rho_{min,max} = -0.20$, 0.19 e Å⁻³; gof = 1.02; **6**, CCDC 784071; MF: C₂₀H₄F₁₀O₆; monoclinic; a = 5.8951(9) Å; b = 10.1943(16) Å; c = 17.245(2) Å; β = 108.115(5)°; $V = 985.0(2) \text{ Å}^3$; T = 150 K; space group, $P2_1/n$, Z =2; $R_{\text{obs}} = 0.050$; $wR_{2\text{obs}} = 0.114$; $\Delta \rho_{\min,\max} = -0.18$, 0.26 e Å⁻³; gof = 1.15.

- 15 F. R. Allen, Acta Crystallogr., Sect. B: Struct. Sci., 2002, 58, 380. [ConQuest 1.15; Feb 2013 update].
- 16 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian 09 Revision A.1, Gaussian Inc., Wallingford, CT, 2009.
- (a) M. R. Battaglia, A. D. Buckingham and J. H. Williams, *Chem. Phys. Lett.*, 1981, 78, 421; (b) H. Adams, J.-L. J. Blanco, G. Chessari, C. A. Hunter, C. M. R. Low, J. M. Sanderson and J. G. Vinter, *Chem.–Eur. J.*, 2001, 7, 3494.
- 18 M. Nishio, Phys. Chem. Chem. Phys., 2011, 13, 13873.