Guest-Responsive Materials

DOI: 10.1002/ange.201302822

Actuated Conformational Switching in a Single Crystal of a Homodithiacalix[4]arene**

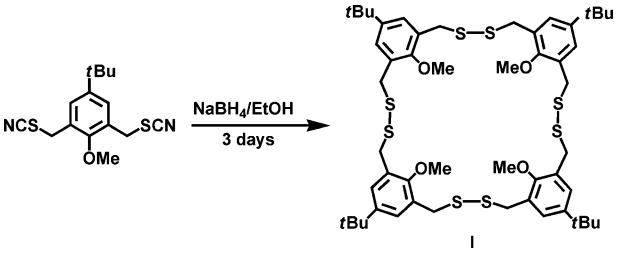
Joice Thomas, Gunter Reekmans, Peter Adriaensens, Luc Van Meervelt, Mario Smet, Wouter Maes, Wim Dehaen, and Liliana Dobrzańska**

There are many reports discussing the conformational flexibility of calix[4]arenes in solution.[1] On the other hand, similar studies concerning the solid state have received considerably less attention, even for the more extended and simultaneously more plastic calixarenes.[2] Furthermore, no studies have been performed on single crystals, most likely because they are generally still perceived as unalterable and rigid, despite an increasing number of reports proving that the opposite is true.[3]

We report herein a phenomenon taking place in a single crystal of homodithiacalix[4]arene, the first member of a novel family of "homodiheteracalix[4]arenes", with diatomic hetera bridges introduced in the macrocyclic ring, in this case disulfide. In contrast with the extensive literature on single-crystal-to-single-crystal transformations (SCSCT) taking place in metal–organic networks,[4] the number of reports regarding SCSCT for organic solids is very limited to date and only encompasses a couple of examples.[5] This is attributed to the fact that cooperative molecular motion is much more easily achieved for frameworks than in molecular crystals.

To the best of our knowledge, reversible, solvent-induced conformational switching in a single crystal of an organic solid has not been reported to date. Moreover, the process is correlated with the formation/disappearance of channels in the structure. Jones et al. observed a change in conformation of an organic cage induced by solvent; however the single crystal did not survive this transformation, and a detailed study was performed on powdered bulk material instead.[5g] Keeping in mind that the structural changes observed in our case do not lead to loss of the crystal integrity, the transformation seems to be quite remarkable.

The compound **I** (Scheme 1) was obtained by applying the concept of dynamic covalent chemistry (DCC), an attractive approach whereby a reversible reaction is performed under



Scheme 1. Synthetic path towards homodithiacalix[4]arene **I**.

equilibrium control, yielding the desired molecule in a selective way, in this case a macrocycle with covalent disulfide bonds (for details, see the Supporting Information).[6] It resembles a previously reported homothiacalix[4]arene.[7] This, combined with our interest in macrocycle synthesis,[8] spurred our interest in finding a procedure to introduce a second bridging S atom into the macrocyclic ring, aimed at increasing its size and flexibility.

Compound **I** was characterized by MS, ^{1}H, and ^{13}C NMR spectroscopy in solution (see the Supporting Information). Beside this characterization, crystals suitable for X-ray analyses were grown by slow evaporation in air from a THF solution (**1,3-a**; the naming refers to the conformation adopted by the macrocyclic ring; see below). The X-ray diffraction study (see the Supporting Information)[9] revealed that **1,3-a** crystallizes as a THF solvate in the $P4_2/n$ tetragonal space group with a quarter of the macrocycle and a disordered THF molecule with partial site occupancy factor in the asymmetric unit. The calixarene molecule adopts the 1,3-alternate conformation with all the methoxy groups pointing outside the folded macrocycle (Figure 1). The conformation is stabilized by several weak C–H···π, C–H···O, C–H···S intramolecular interactions, with the C–H···π interactions influencing the position of C1, which is oriented towards the ring, and the C–H···S, together with intermolecular weak hydrogen bonding C10–H10B···S1^{i}, affecting the orientation of the methoxy groups (for details and symmetry operations, see the Supporting Information, Table S1). The C–H···S intermolecular interactions (C10–H10B···S1^{i} and C8–H8B···S2^{ii}) hold the host molecules together, thereby forming a 3D supramolecular assembly.

The packing diagram (Figure 1) reveals an interesting feature, not so common among calixarenes (which are mostly

[*] Dr. J. Thomas, Prof. L. Van Meervelt, Prof. M. Smet, Prof. W. Maes, Prof. W. Dehaen, Dr. L. Dobrzańska
Department of Chemistry KU Leuven
Celestijnenlaan 200F, 3001 Leuven (Belgium)
E-mail: Wim.Dehaen@chem.kuleuven.be
lianger@chem.kuleuven.be
G. Reekmans, Prof. P. Adriaensens, Prof. W. Maes
Institute for Materials Research (IMO-IMOMEC)
Organic and (Bio)Polymer Chemistry, Hasselt University
Agoralaan 1—Building D, 3590 Diepenbeek (Belgium)

[**] We thank the Hercules Foundation for supporting the purchase of a diffractometer through project AKUL/09/0035, and BELSPO for providing the frame of the IAP 7/05 FS2 network. L.D. thanks Dr. J. Alen for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302822.

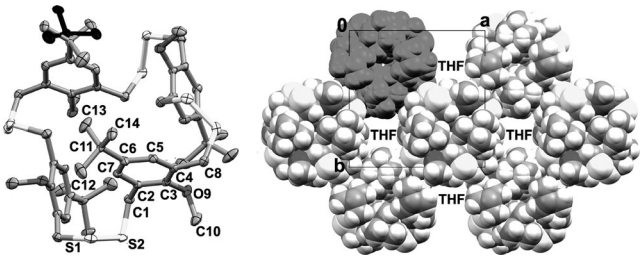


Figure 1. Left: **1**,**3-a** with the atom labeling of the asymmetric unit (ellipsoids set at 50% probability). H atoms and solvent molecules are omitted for clarity; minor disorder is only shown for one of the *tert*-butyl groups (in black). Right: packing diagram, space-filling representation.

known for the occurrence of isolated voids),[10] namely the presence of undulated continuous 1D channels expanding along the *c* axis, with internal van der Waals dimensions ranging from about 3.6 to 7.2 Å (Supporting Information, Figure S1).[11] The contractions in the channels are resulting from the presence of protruding methoxy and *tert*-butyl groups. The formation of apertures in the crystal lattice is enabled by the columnar packing of the macrocycles stacked above each other, whereby the packing efficiency of an assembly of four adjacent columns is less than optimal. The interstitial space thus formed is filled with disordered THF molecules that weakly interact with the host assembly by C–H···O interactions that involve the O atoms from the THF molecules as hydrogen bond acceptor and the methoxy and *tert*-butyl group of the host as donors. These interactions additionally stabilize the orientation of the methoxy groups, and presumably cause positional disorder of the *tert*-butyl groups over two sites, with occupancy factors 0.635(6) and 0.365(6), whereby the minor contributing part (Figure 1, black *tert*-butyl group) is pulled towards the channel.

As C–H···O interactions are considered to be weak, a thermogravimetric analysis was performed to assess whether the removal of the solvent molecules from the channels is possible (Supporting Information, Figure S2). This analysis revealed that the THF molecules can be completely removed at about 120 °C in one weight-loss step (the mass loss of ca. 7% corresponds well with the loss of one THF molecule for each calixarene molecule). The high temperature needed for guest removal, which is well above the boiling point of the solvent, confirms the presence of weak interactions between the guest and host. Furthermore, the thermogram reveals that the process does not trigger immediate decomposition of the host assembly which remains stable until about 220 °C. This encouraged us, based on previous experience,[12] to attempt the removal of the solvent molecules from the crystal lattice. For this purpose, crystals of **1,3-a** were heated at 130 °C for 4 min. As the visual appearance of the crystal did not change during the heating, a single-crystal X-ray analysis was performed again. To our surprise, the resulting structure was extremely different, even though the crystals did not show any sign of damage. The **1,2-a** phase (see the Supporting Information) obtained after heating belongs to the triclinic centrosymmetric space group $P\bar{1}$ and shows the presence of half of a calixarene molecule in the asymmetric unit (Figure 2).[9] As expected, the solvent molecules are no longer present, but their removal causes changes at both the molecular and supramolecular level. The most striking is the conformational alternation in the macrocycle, which switches

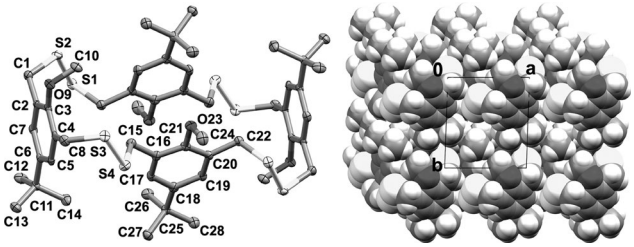


Figure 2. Left: **1**,**2-a** with the atom labeling of the asymmetric unit, (ellipsoids set at 50% probability). H atoms are omitted for clarity. Right: packing diagram, space-filling representation.

from 1,3-alternate to 1,2-alternate. The methoxy groups in this centrosymmetric molecule point alternately outside and towards the macrocyclic ring, being held in place by weak intramolecular C–H···S hydrogen bonds (Supporting Information, Table S1). The molecules pack quite efficiently in the crystal, and new intermolecular interactions are established involving the *tert*-butyl groups, namely C13–H13···Cg1^{i} (whereby Cg1 is the centroid of C2–C7 benzene ring; C13···Cg1 is 3.661(3) Å, C-H-Cg1 is 157°) and C27–H27A···S3^{ii} (C27···S3 is 3.827 Å, C-H-S is 159°), which were not present in **1,3-a**. As a reminder, in **1,3-a** the intermolecular interactions encompassed weak C–H···S hydrogen bonding involving the methylene bridges, methoxy groups, and both sulfur atoms.

The packing of **1,2-a** shows the presence of rows of molecules expanding along the *a* axis, held together by C8–H8A···S2^{iii} and C27–H27A···S3^{ii}, which are linked into 2D layers in the *ac* plane by means of C10–H10B···S2^{iv} hydrogen bonding. These layers are held together by the C–H···π contacts mentioned above.

The centroid to centroid distances between opposite phenyl rings in the macrocycle of **1,2-a** are 11.91 and 4.11 Å, whereas the corresponding distance in the higher symmetry structure **1,3-a** is 7.55 Å. This indicates that the solvent removal simultaneously causes elongation and shrinking of the macrocycle by more than 4 and 3 Å respectively, accompanied by rotation of the aryl rings and reorientation of the methoxy groups (Supporting Information, Figure S3). At the same time, the **1,2-a** supramolecular assembly was reorganized, as the macrocyclic rings do not only change in shape, but also relocate themselves in the crystal lattice, thereby filling the space that was occupied by the guest molecules beforehand.

To check whether or not the process is reversible, the **1,2-a** crystals were immersed for 3 min in a THF solution and monitored continuously under the microscope. Once again, the crystals remain visually intact, but a single-crystal X-ray study shows that the crystal structure has returned to the **1,3-a** phase (Figure 3). The guest molecules somehow managed to diffuse into the crystal lattice, causing structural rearrangements.

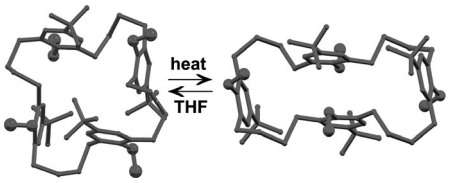


Figure 3. Plot presenting the conformational changes taking place in **I** during SCSCT: Left: **1,3-a** form; Right: **1,2-a** form; methoxy groups shown as balls.

It is worth highlighting that all changes take place in a very short timeframe of under 4 min. A few examples concerning SCSCT in organic solids might help to put this in perspective: It took about a month of soaking crystals of cholic acid in acetophenone,[5a] a time so long that without constant monitoring of the crystals it is hard to assess what really happened to the system; three days of exposure to solvent vapors for a tetrahedral organic cage,[5g] 24 h of exposure to MeOH vapor for a tetraphosphonate cavitand (the authors state that the process of molecular cooperativity needs time as in their case, trying to speed up the process by soaking the crystals in MeOH causes loss of crystallinity,[5h] and finally for *p-tert*-butylcalix[4]arene, 15 min of soaking in vinyl bromide.[5c]

The conformational interconversion was additionally monitored by ^{13}C solid-state NMR spectroscopy on bulk powdered material. The spectrum of **1,3-a** was recorded (Figure 4, top), and the sample was subsequently heated for

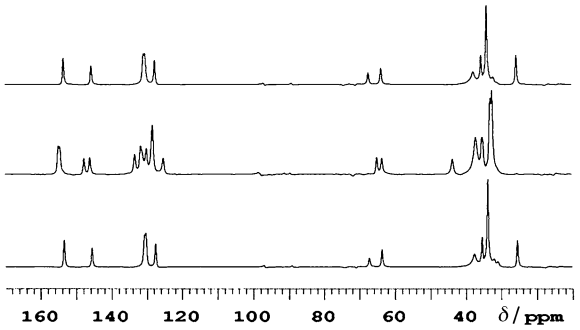


Figure 4. Monitoring of the conformational change by ^{13}C solid-state NMR spectroscopy (for the chemical shifts, see the Supporting Information, Figure S4).

4 min at 130 °C and another spectrum was taken (Figure 4, middle). It is clear from this spectrum that the THF molecules were removed, as the solvent peaks ($\delta = 25.6$ and 67.3 ppm) disappeared. Moreover, the spectrum clearly reflects the lower symmetry in the **1,2-a** form. Finally, the sample was left in THF vapor at 30 °C for 3 days, which confirmed the reversibility of the process (Figure 4, bottom).

Following this result, we attempted to grow crystals from other solvents. In the case of acetonitrile, only the guest-free **1,2-a** phase was obtained. To confirm this on the bulk material (Supporting Information, Figure S5), the **1,2-a** sample was left in acetonitrile vapor for four and half days and a ^{13}C solid-state NMR spectrum was collected. As expected, there were no changes in the spectrum. We performed the same study for ethyl acetate (four days exposure to vapor) and obtained the same result, namely the only form observed was **1,2-a**. Furthermore, **1,3-a** single crystals exposed to ethyl acetate vapor for three days transformed into **1,2-a**, whereas **1,3-a** crystals that were not exposed retained the same structure even after several months. An X-ray study was also performed for a single crystal grown from acetone, revealing once again formation of the dense empty phase. This indicates selectivity of the transformation that is only induced by a stimulant possessing a certain particular constitution.

The presented phenomenon points out that flexibility of the organic molecules also exists in the solid state and can occur under suitable conditions. The changes induced by external stimuli in a single crystal of an organic solid can affect to high extent its molecular structure. The present transformation can serve as a perfect example for the study of recognition processes, allowing us to follow in situ the formation/disappearance of weak interactions between host and guest, rearrangements that for long were hidden from us. The structural dynamics associated with the conformational changes are reminiscent of induced fit recognition between a protein and its substrate. The transformation described highlights once more the importance of the geometry and the composition of the guests/substrate in this course of action. The selectivity and reversibility of the process render it an attractive target for further studies, as this could ultimately lead to the discovery of new organic-based sensing devices or molecular traps.

There are, however, a couple of questions that still need to be addressed. How do the guest molecules push their way through the rather densely packed molecular assembly without disrupting the crystal integrity? A closer look at the packing of **1,2-a** indicates the presence of small openings between the supramolecular layers of macrocycles that could be mapped with a probe of radius < 0.79 Å. These apertures are enclosed by *tert*-butyl and methoxy groups (Supporting Information, Figure S6) and one might wonder if this is where the whole process starts (especially considering that the same groups interact with THF in the channel structure)? It could confirm the mechanism proposed earlier for a gas-induced solid-state transformation of nonporous *p-tert*-butylcalix[4]-arene, whereby the small interstitial lattice voids perceived between the layers of macrocycles were deemed to be a starting point for the diffusion of gas molecules, according to the authors.[13] Unfortunately the published study was to some extent performed on bulk material, as the crystal did not survive the transformation. In the current case, the crystal did survive the transformation (with the process even being reversible), showing that molecular cooperativity won over chaos that would result in conversion into the amorphic phase. Perhaps it will be established in the future which factors determine the softness of the crystal lattice and to which extent weak interactions contribute.

Further computational studies, which could shed some more light on the transformation, have been initiated. However, we can already conclude that the molecules, irrespective of their chemical composition, are not prisoners

of a crystal's (supposed) rigidity, as the right stimuli can uncover the freedom they really possess.

Received: April 5, 2013
Revised: June 5, 2013
Published online: July 19, 2013

Keywords: calixarenes · conformational switching · host–guest systems · molecular recognition · single-crystal-to-single-crystal transformations

[1] a) C. D. Gutsche, L. J. Bauer, *J. Am. Chem. Soc.* **1985**, *107*, 6052 – 6059; b) L. C. Groenen, J.-D. van Loon, W. Verboom, S. Harkema, A. Casnati, R. Ungaro, A. Pochini, F. Ugozzoli, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1991**, *113*, 2385 – 2392; c) S. Fischer, P. D. J. Grootenhuis, L. C. Groenen, W. P. van Hoorn, F. C. J. M. van Veggel, D. N. Reinhoudt, M. Karplus, *J. Am. Chem. Soc.* **1995**, *117*, 1611 – 1620; d) S. E. Biali, V. Bőhmer, J. Brenn, M. Frings, I. Thondorf, W. Vogt, J. Wőhnert, *J. Org. Chem.* **1997**, *62*, 8350 – 8360; e) C. Alemán, D. Zanuy, J. Casanovas, *J. Org. Chem.* **2006**, *71*, 6952 – 6957.

[2] For the first observation of the coexistence of two different conformations, namely cone and 1,2-alternate, in a calix[4]arene single crystal, which could be considered as a prelude to the phenomenon reported here, see: a) C. Fischer, T. Gruber, D. Eissmann, W. Seichter, E. Weber, *Cryst. Growth Des.* **2011**, *11*, 1989 – 1994; see also: b) S. Dey, K. Pal, S. Sarkar, *Tetrahedron Lett.* **2007**, *48*, 5481 – 5485.

[3] a) T. Endo, H. Murata, M. Imanari, N. Mizushima, H. Seki, S. Sen, K. Nishikawa, *J. Phys. Chem. B* **2013**, *117*, 326 – 332; b) D. Casarini, L. Lunazzi, A. Mazzanti, P. Mercandelli, A. Sironi, *J. Org. Chem.* **2004**, *69*, 3574 – 3577.

[4] a) M. Kawano, M. Fujita, *Coord. Chem. Rev.* **2007**, *251*, 2592 – 2605; b) M. K. Sharma, P. K. Bharadwaj, *Inorg. Chem.* **2011**, *50*, 1889 – 1897; c) Y.-C. Ou, W.-T. Liu, J.-Y. Li, G.-G. Zhang, J. Wang, M.-L. Tong, *Chem. Commun.* **2011**, *47*, 9384 – 9386; d) L. Wen, P. Cheng, W. Lin, *Chem. Commun.* **2012**, *48*, 2846 – 2848; e) J. Tian, L. V. Saraf, B. Schwenzer, S. M. Taylor, E. K. Brechin, J. Liu, S. J. Dalgarno, P. K. Thallapally, *J. Am. Chem. Soc.* **2012**, *134*, 9581 – 9584.

[5] a) M. Miyata, M. Shibakami, S. Chirachanchai, K. Takemoto, N. Kasai, K. Miki, *Nature* **1990**, *343*, 446 – 447; b) M. Kaftory, M. Botoshansky, M. Kapon, V. Shteiman, *Acta Crystallogr. Sect. B* **2001**, *57*, 791 – 799; c) J. Atwood, L. J. Barbour, A. Jerga, B. L. Schottel, *Science* **2002**, *298*, 1000 – 1002; d) D. Bardelang, K. A. Udachin, R. Anedda, I. Moudrakovski, D. M. Leek, J. A. Ripmeester, C. I. Ratcliffe, *Chem. Commun.* **2008**, 4927 – 4929; e) T. Tozawa, J. T. A. Jones, S. I. Swamy, S. Jiang, D. J. Adams, S. Shakespeare, R. Clowes, D. Bradshaw, T. Hasell, S. Y. Chong, C. Tang, S. Thompson, J. Parker, A. Trewin, J. Bacsa, A. M. Z. Slawin, A. Steiner, A. I. Cooper, *Nat. Mater.* **2009**, *8*, 973 – 978; f) D. Das, E. Engel, L. J. Barbour, *Chem. Commun.* **2010**, *46*, 1676 – 1678; g) J. T. A. Jones, D. Holden, T. Mitra, T. Hassel, D. J. Adams, K. E. Jelfs, A. Trevin, D. J. Willock, G. M. Day, J. Bacsa, A. Steiner, A. I. Cooper, *Angew. Chem.* **2011**, *123*, 775 – 779; *Angew. Chem. Int. Ed.* **2011**, *50*, 749 – 753; h) C. Massera, M. Melegari, E. Kalenius, F. Ugozzoli, E. Dalcanale, *Chem. Eur. J.* **2011**, *17*, 3064 – 3068; i) T. Hasell, M. Schmidtmann, C. A. Stone, M. W. Smith, A. I. Cooper, *Chem. Commun.* **2012**, *48*, 4689 – 4691.

[6] a) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 938 – 993; *Angew. Chem. Int. Ed.* **2002**, *41*, 898 – 952; b) P. T. Corbett, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652 – 3711; c) J.-M. Lehn, *Chem. Soc. Rev.* **2007**, *36*, 151 – 160; d) E. Moulin, G. Cormosw, N. Giuseppone, *Chem. Soc. Rev.* **2012**, *41*, 1031 – 1049.

[7] J. Thomas, K. van Hecke, K. Robeyns, W. van Rossom, M. P. Sonawane, L. van Meervelt, M. Smet, W. Maes, W. Dehaen, *Chem. Eur. J.* **2011**, *17*, 10339 – 10349.

[8] a) J. Thomas, W. Maes, K. Robeyns, M. Ovaere, L. Van Meervelt, M. Smet, W. Dehaen, *Org. Lett.* **2009**, *11*, 3040 – 3043; b) J. Thomas, L. Dobrzańska, K. Van Hecke, M. P. Sonawane, L. Van Meervelt, K. Woźniak, M. Smet, W. Maes, W. Dehaen, *Org. Biomol. Chem.* **2012**, *10*, 6526 – 6536; c) M. P. Sonawane, K. Van Hecke, J. Jacobs, J. Thomas, L. Van Meervelt, W. Dehaen, W. Van Rossom, *J. Org. Chem.* **2012**, *77*, 8444 – 8450; d) J. Thomas, W. Van Rossom, K. Van Hecke, L. Van Meervelt, M. Smet, W. Maes, W. Dehaen, *Chem. Commun.* **2012**, *48*, 43 – 45.

[9] CCDC 931552 (**1,2-a**) and 931553 (**1,3-a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] J. Tian, P. K. Thallapally, B. P. McGrail, *CrystEngComm* **2012**, *14*, 1909 – 1919, and references therein.

[11] After subtracting the THF molecules by applying the SQUEEZE instruction in Platon, the accessible space was estimated at about 20% of the total cell volume.

[12] a) L. Dobrzańska, G. O. Lloyd, H. G. Raubenheimer, L. J. Barbour, *J. Am. Chem. Soc.* **2005**, *127*, 13134 – 13135; b) L. Dobrzańska, G. O. Lloyd, H. G. Raubenheimer, L. J. Barbour, *J. Am. Chem. Soc.* **2006**, *128*, 698 – 699.

[13] P. K. Thallapally, B. P. McGrail, S. J. Dalgarno, H. T. Schaef, J. Tian, J. L. Atwood, *Nat. Mater.* **2008**, *7*, 146 – 150. For porosity of nonporous solids, see also: a) S. J. Dalgarno, P. K. Thallapally, L. J. Barbour, J. L. Atwood, *Chem. Soc. Rev.* **2007**, *36*, 236 – 245; b) D. H. Brouwer, I. L. Moudrakovski, K. A. Udachin, G. D. Enright, J. A. Ripmeester, *Cryst. Growth Des.* **2008**, *8*, 1878 – 1885; c) J. Tian, P. Thallapally, J. Liu, G. J. Exarhos, J. L. Atwood, *Chem. Commun.* **2011**, *47*, 701 – 703.

