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ARTICLE

Conformational switch in the crystal states of a calix[4]arene

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We report the discovery of a novel metastable polymorph of a propyloxy substituted calix[4]arene molecule which undergo two distinct transformations to form different conformers and packing arrangements. The first transition was found as a reversible thermal-induced rotation (180°) in two propyloxy moieties of the Closed-I form upon cooling (from 298 K to 100 K) which results in a new polymorph (Closed-II) and is an example of single-crystal-to-single-crystal transformation (SCSC). The second transition is an irreversible and remarkable change in packing and conformation (from close to open) at room temperature which was observed after keeping the mother crystals for few days in the liquor that results in Open conformer; this transformation is following the Ostwald's rule of stages and is the outcome of dissolvation/recrystallization of the metastable conformer (Closed-I).

Polymorphism occurs when a compound crystallizes with different internal structures which are closely related to its physical and chemical properties.[1-4] Given the fundamental impact of polymorphism on the physical/chemical properties (e.g. melting point, density, solubility and color) and utmost importance in the food and pharmaceutical industries, the field has witnessed a remarkable progress over past few decades.[5-9] Two proposed mechanisms for polymorphic transitions are reconstruction (i.e. major structural alteration including bond formation and cleavage) and topotactic or single-crystal-to-single-crystal (SCSC) transformation (i.e. the initial and final morphs are structurally close).[10] The majority of polymorphic transitions happen through topotactic mechanism where there is large structural (packing and conformational) similarities presented between mother and daughter crystals. Albeit only few examples of such transitions with considerable structural differences are reported in the literature.[11-14]

Moreover, Ostwald stated a phenomenon that “the solid first formed on crystallization of a solution or a melt is the least stable polymorph”.[15] This can be explained on the basis of irreversible thermodynamics, structural relationships, or a combined consideration of statistical thermodynamics and structural variation with temperature.[16-19] Therefore, the identification of the intermediate state will provide new insights into the transition kinetics in the crystallization process and reveals the principle of overall crystallization behavior. The intermediate state could also be a potential candidate as solid actuator with the external stimuli such as light, heat, pressure, etc.; despite its highly limited mobility in the solid state.[20-22] However, spontaneous transformation under mild condition with dramatic conformational/packing changes is a rare phenomenon.[23] Because nucleation step in the crystallization is kinetically controlled, the initial metastable form of crystals is favored over thermodynamically form.[24] Nevertheless, one of the most difficult tasks to date, is the discovery and synthesis of new metastable polymorphs with high reproducibility and stability from solution.[25]

Calix[4]arenes have been subjected of myriad investigations due to simple and straightforward synthesis/purification, modification and thier vast applications in different fields of (bio)chemistry.[26-28] Calix[4]arens can adopt different conformers (e.g. closed/boat and open/chair, see **Scheme 1**) which depends on several different factors. Therefore, many groups have investigated the conformational distribution of different calix[4]arenes in the solution using experimental and computational methods.[29-33] However, the development of calix[4]arene as polymorphism is limited, despite the report of a single-crystal-to-single-crystal (SCSC) transformation of a calix[4]arene based metal-organic framework system.[34] To the best of our knowledge, there is no report on the polymorphic transformation of calix[n]arenes family as pure organic molecule. In this study, we described two distinct conformational switch in a novel substituted calix[4]arenes (**Scheme 1**). This molecule showed great flexibility to undergo significant thermal-induced and spontaneous conformational switch that result in formation of different polymorphs. Herein, we characterized and analyzed the results with the aid of single crystal X-ray diffraction and powder XRD (PXRD) methods; moreover, the DFT analysis is provided in the supporting information.

In continuation of the discovery and synthesizing novel stimuli-responsive molecular switches in our group,[35-37] we considered calix[4]arenes as a potential candidate due to its great conformational flexibility.[26] To follow this goal, we employed Lewis acid, $BF_3 \cdot Et_2O$, as the catalyst for the

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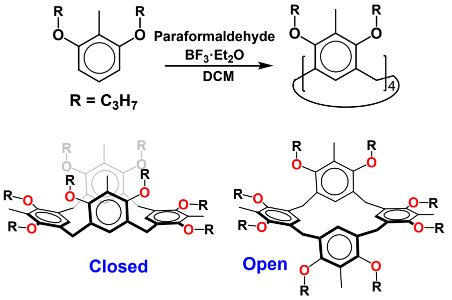

Scheme 1. The synthesis of OPr substituted calix[4]arene and its two distinct (Open and Closed) conformers.

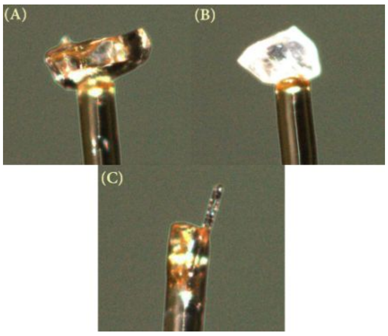

Fig. 1 Photograph of A (Closed-I, room temperature), B (Closed-II, crystals of A cooling to 100 K) and C (Open, room temperature after keeping A in the mother liquor for 5 days) modifications.

condensation reaction of 2,6-dipropoxytoluene with paraformaldehyde (**Scheme 1**) and obtained the desired calix[4]arene with high efficiency (see the ESI for experimental details). The X-ray quality crystals were grown from the slow evaporation of mix-solvent of chloroform/acetonitrile (1:1). Interestingly, we observed that the shape of the formed crystals changed after leaving them in the crystallization liquor at room temperature for a few days. The initial crystals presented a colorless prismatic morphology (A in **Figure 1**), whereas the crystals obtained after a couple of days demonstrated needle-shape structure (C in **Fig. 1**). However, the initially formed crystals (A) are stable at room temperature in dry form or under pure immersion oil on microscope slide for several weeks.

To gain better insight of the structure and conformational information, the single crystal X-ray diffraction experiments were performed. Surprisingly, we observed that the fresh crystals of A-modification do not survive sharp cooling from room temperature to 100 K and undergo cracking and breaking down mechanically. However, cooling the sample slowly (~2 deg/min) provide enough time for a transition into the B-modification at ~240 K. The partially disordered B-form undergoes complete ordering into B-modification (B in **Fig. 1**) at continuous cooling down to 100 K.

The crystal data were collected before and after thermal-induced transformation and provided conclusive information about the molecular structures at different temperature. Both A and B modifications are in Closed conformer, so in the rest of this context we refer them as Closed-I and Closed-II, respectively (**Fig. 2**). The Closed-I conformer (mother crystal) shows conformational change upon cooling; the new crystal structure at temperatures below 240 K is characterized with 180° rotation of two OPr groups from exo to endo orientation (Closed-II conformer, **Fig. 2**). The propyl moiety of the OPr groups located at two co-facial benzene rings and near to the rotated OPr groups have to move away slightly due to the hindrance caused in endo orientation. Due to the same reason, the corresponding benzene twist down by ~20° to provide more space for the endo shape (**Fig. S5** and **S6**, ESI).

In the crystal of Closed-I conformer, the co-facial benzene rings are almost parallel to each other with dihedral angle about 4.3° (and 8.6° in Closed-II) and plane-centroid distances about 4.9 Å (and 4.8 Å in Closed-II). Interestingly, we have been able to get the single X-ray crystal structure of intermediate state at 210 K (named as B_A modification). Comparatively, this modification has an approximate unit cell dimensions as B-form but keeps a

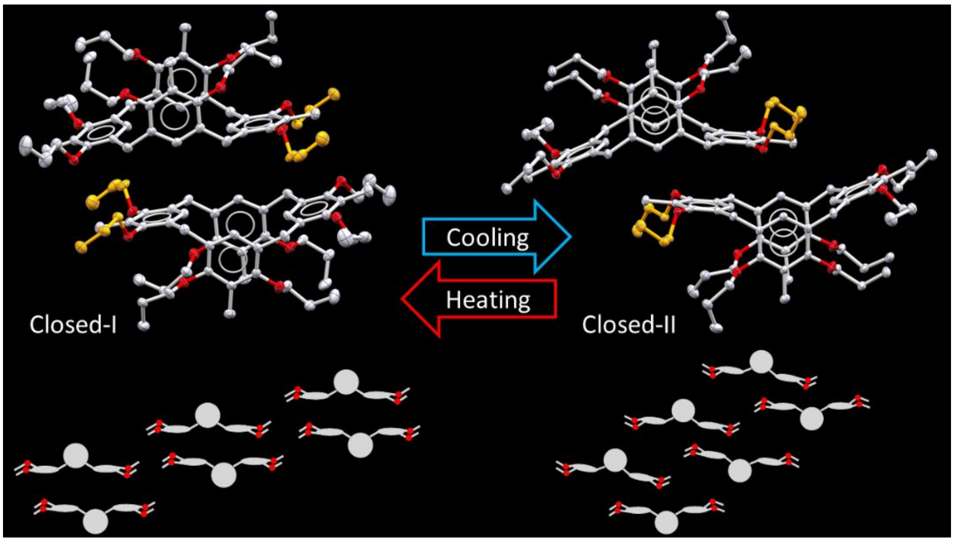

Fig. 2 The crystal structures of Closed-I (left, at 250 K) and Closed-II (right, at 100 K) conformers; hydrogen atoms are omitted for clarity and OPr groups which undergo thermal-induced conformational change are shown in orange (top). Schematic packing arrangement of Closed-I and –II modification (bottom).

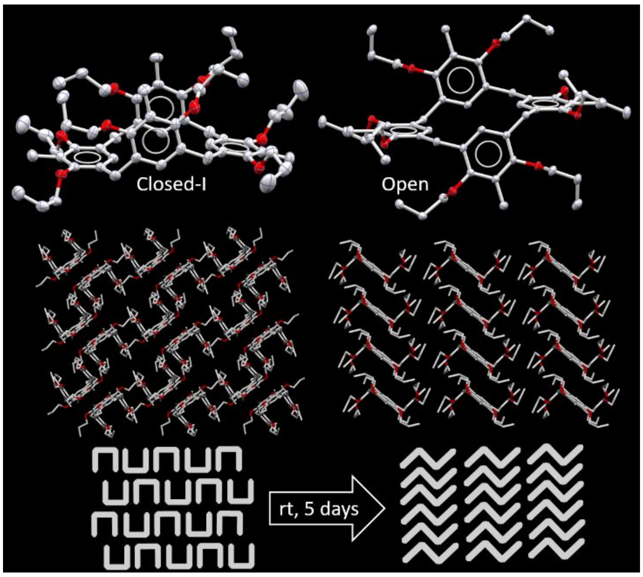

Fig. 3 The single crystal structures (top), molecular packing arrangements (middle) and schematic (bottom) representations of Closed-I (left, at 250 K) and Open (right, at 100 K) conformers; hydrogen atoms are omitted for the clarity.

small percentage of A-structure. At this temperature, the disordered structures of both polymorphs coexist in the ~80% (B) to ~20% (A) proportion.

Analyzing the packing patterns of the two "Closed" crystals showed that the molecules are associated pairwise with their flat planes and formed the outlying centrosymmetrically overlapping structure. However, this overlap is markedly different in Closed-I and Closed-II. At low temperatures, a homo couple between one benzene ring overlap with its inversion analog was observed (**Fig. 2**). However, at the higher temperatures, we found that the second molecule was slid along the flat plane significantly and formed two hetero couples between the benzene rings. In both cases, only weak stacking interaction were observed, with the closest center-to-center aromatic distance around 5.2 Å and 3.8 Å for Closed-I and Closed-II, respectively. Additionally, multiple weak C-H…π contacts were found in both structures. We speculated both interactions contributed the driving force account to this transformation.

As mentioned previously, the primary Closed-I crystals, left in mother liquor, recrystallizes to give bunches of transparent needle-like crystals of C modification (**Fig. 1**). The same transformation takes place under layer of immersion oil on microscope slide, if the oil was contaminated with the mother liquor (i.e. contained some chloroform). To the contrary of Closed conformers, the C-modification indicated completely different structure with Open conformer (**Scheme 1**) which are stable upon cooling to 100K and does not undergo thermal-induced phase transitions (**Fig. 3, Fig S11**). This Open conformation wa characterized with two aromatic rings lying in a plane and the two other benzene rings pointing to opposite direction which is similar to the reported conformer of unsubstituted calixarene.[38]

The Open conformer belongs to triclinic crystal system and has a crystallographically centrosymmetric chair conformation. The symmetry equivalents of flat benzene rings are approximately co-planar whereas the anti-parallel flipped rings are positioned perpendicular to this flat plane (dihedral angle 81.5°). The OPr groups are positioned in trans-fashion perpendicular to the adjacent benzene rings (**Fig. 3**).

Crystal data and refinement detail are summarized in **Table 1**. While crystal system and space groups are similar in four different morphs (triclinic, P$\bar{1}$), they differ significantly in cell dimensions and other structural parameters. The rotation on OPr group (from Closed-I to Closed-II) lead to the decrease in cell volume from 2649.12 Å^3 to 2509.49 Å^3 and give a more compact packing (**Fig. 2**). This compact packing is further

Table 1. Crystal data and refinement details of different modifications.

Compound	A (Closed-I)	B$_A$ (Intermediate)	B (Closed-II)	C (Open)
formula	$C_{56}H_{80}O_8$	$C_{56}H_{80}O_8$	$C_{56}H_{80}O_8$	$C_{56}H_{80}O_8$
crystal system, space group	Triclinic, P$\bar{1}$	Triclinic, P$\bar{1}$	Triclinic, P$\bar{1}$	Triclinic, P$\bar{1}$
a (Å)	12.6612	13.0566	12.9716	6.8417
b (Å)	14.1198	13.1211	13.0379	12.7268
c (Å)	15.7544	15.1852	14.9706	15.2879
α (°)	104.714	92.7541	95.6026	104.555
β (°)	96.728	96.9186	92.8626	99.233
ϒ (°)	99.499	94.0236	94.0129	98.058
V (Å^3)	2649.12	2571.97	2509.49	1248.84
Z	2	2	2	1
T (K)	250.0	210.1	99.8	100.1
ρ_{calc} (g/cm^3)	1.105	1.138	1.166	1.172
R$_1$,	0.0844,	0.0666,	0.0411,	0.0463,

wR$_2$	0.2636	0.1837	0.0981	0.0973

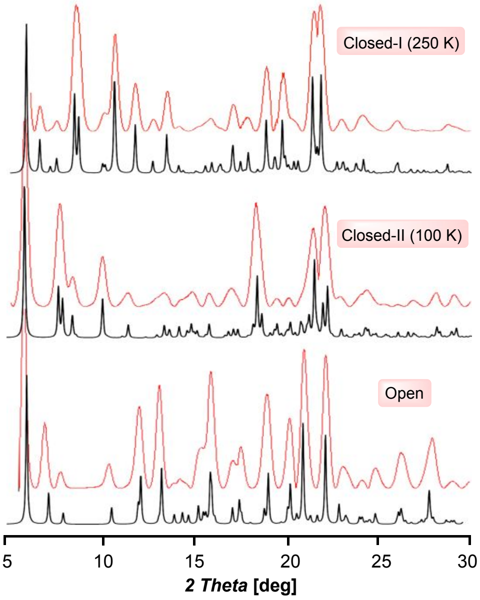

Fig. 4 Experimental (red) and simulated (black) PXRD patterns of Closed-I (250 K), Closed-II (100 K) and Open (100 K) polymorphs.

represented with the higher density value, 1.105 g/cm^3 and 1.166 g/cm^3 for Closed-I and Closed-II, respectively. As indicated in **Table 1**, the intermediate modification (B$_A$) parameters such as density and cell volume are between the two "Closed" forms exhibiting the transition process from Closed-I to Closed-II. Moreover, the crystal packing of Open form is tighter than Closed forms and bring about the physical property change, such as, the density of the crystal increases significantly from 1.105 g/cm^3 (Closed-I) to 1.172 g/cm^3 (Open).

In order to gain more information from bulk sample, we carried out powder-XRD experiments for Closed-I, Closed-II and Open morphs; experimental and simulated powder-XRD patterns are summarized in **Fig. 4**. Furthermore, for the purpose of confirming the transition and the reversibility of thermal-induced transition, the PXRD were collected from 270 K to 100 K and vice versa (**Fig. S10**, ESI). These data revealed a gradual change in the patterns which verify the transition from Closed-I to Closed-II. In addition, in a reverse process, the Closed-II crystals were heated to room temperature (**Fig. S9,** ESI) and reproduced the initial pattern for Closed-I, indicating that this is a thermal reversible transformation between two interchangeable crystals and follows the thermodynamically enantioitropic systems (**Fig. S8,** ESI).

Conclusions

In summary, we have successfully synthesized and isolated new metastable polymorph and report two distinct polymorphic transition in a novel calix[4]arene molecule. The first identified transition was found by cooling the Closed-I crystal to 240 K (or lower) and characterized as a Closed-II polymorph with 180° inversion in two of OPr groups and provided a more compact crystal packing. It is noteworthy to mention that this reversible transformation happened through single-crystal-to-single-crystal (SCSC) pathway in the organic calix[4]arene molecule. Second transition followed the "Ostwald stage rule" [35-37]. We discovered a remarkable and spontaneous change in molecule conformation as well as in crystalline packing pattern after keeping the mother crystals (Close-I) in the liquor for few days at room temperature to produce Open conformation crystals. The single crystal and powder X-ray diffraction investigation confirmed both transitions and suggested that calix[4]arene molecule initially crystalizes in a metastable form (Closed-I) and has great flexibility in its solid state to adopt the more stable crystal shape by either gradually transforming to Open conformation or to Close-II polymorph by thermal-induced.

Conflicts of interest

There are no conflicts to declare.

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