Synthesis and Structure of Novel Double Flexible Spacer Bridged Biscalix[4]arenes

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25,25',27,27'-Bis(1,3-dioxypropane)-bis(5,11,17,23-tetra-*tert*-butylcalix[4]arene-26,28-diol) (4) and 25,25',27,27'-bis(1,4-dioxybutane)-bis(5,11,17,23-tetra-*tert*-butylcalix[4]arene-26,28-diol) (5) were synthesized by the reaction of *p*-*tert*-butylcalix[4]arene (1) with preorganized 25,27-bis(3-bromoproxyl)calix[4]arene-26,27-diol (2) and 25,27-bis(3-bromobutoxyl)calix[4]arene-26,27-diol (3) in the presence of K_2CO_3 and KI. Compounds 4 and 5 were characterized with X-ray analysis and the selectivity of 4 and 5 toward K^+ over other alkali metal ions, alkaline metal ions as well as NH_4^+ were investigated with an ion-selective electrode.

Keywords Biscalix[4]arene, synthesis, X-ray structure, potassium selectivity, ion-selective electrode

Introduction

Recently, the design of receptor molecules with enforced cavities such as cavitand, hemicarceplex, reversible molecular capsule and cryptand have attracted a wide attention in the field of supramolecular chemistry.[1] The design of double calixarenes as such enforced cavities coupled in "head-to-head" fashion have been reported by Arduini, Böhmer, Shinkai and Vögtle *et al*.[2-6] Most of the double calix[4]arenes with enforced cavities lack the ability to acommdate potential guest molecules due to the absence of suitable binding sites. Meanwhile double calix[4]arenes coupled in "tail-to-tail" fashion have also been documented by Chen, Shinkai, Böhmer and Beer *et al*.[7-10] The respective synthetic yields are usually low for the inherent conformational flexibility in the parent calix[4]arene skeleton except in the cases reported by Chen and Beer. Some of these calix[4]arenes exhibit a sodium selectivity in the evaluation experiment.

As to the latter type of biscalix[4]arenes, the spacers which link the two calix[4]arene moieties are usually rigid, which strongly restricted their ion-selectivity in evaluation except Shinkai's ions oscillate receptors.[9] Because the linking spacers are too long to bind the guest ions relatively stable for Shinkai's oscillate receptors, it is still interesting to construct new biscalix[4]arenes connected in short spacers but flexible to bind ions selectively and investigate their structures. With this opinion in mind, we report the syntheses, X-ray structures and preliminary ionophoric properties of a new type of double flexible bridged biscalix[4]arenes **4** and **5**.

Results and discussion

Syntheses

A mixture of *p*-*tert*-butylcalix[4]arene (**1**) and 25,27-bis(bromoalkoxyl)-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene (**2**) or (**3**) (5 mmol) was refluxed for 15 days under nitrogen in THF in the presence of K_2CO_3 (10 mmol) and KI (1 mmol) (Scheme 1). After puri-

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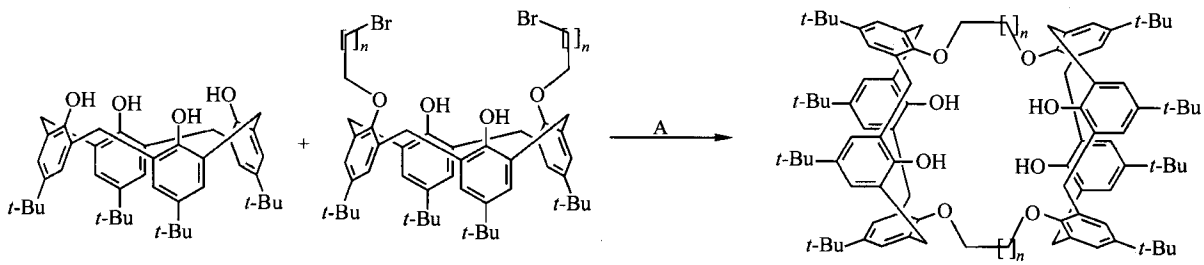
fied by column chromatography (petroleum ether: CH_2Cl_2 = 1:1), the pure products of 25,25′,27,27′-bis(1,3-dioxypropane)-bis(5,11,17,23-tetra-*tert*-butylcalix[4]-arene-26,28-diol) (**4**) and 25,25′,27,27′-bis(1,4-dioxybutane)-bis(5,11,17,23-tetra-*tert*-butylcalix[4]-arene-26,28-diol) (**5**) were obtained in 35% and 32% yields, respectively. However, while treatment of **1** with 25, 27-bis (2-bromoethoxyl)-26, 28-dihydroxy-*p*-*tert*-butylcalix[4]arene (**9**) or calix[4]arene (**6**) with 25, 27-bis(2-bromoethoxyl)-26, 28-dihydroxybutylcalix[4]-arene (**10**) (Chart 1) under the same condition, no biscalix[4]arenes were obtained. Surprisingly, the reaction of **6** (1 mmol) with 25,27-bis(2-bromoproxyl)-26,28-dihydroxycalix[4]arene (**7**) (1 mmol) in DMF under nitrogen atmosphere in the presence of K_2CO_3 and KI gave the product of 25-(3-hydroxylproxyl)calix[4]arene-26,27,28-triol (**8**) in 15% yield (Scheme 2). The mechanism for this reaction is still unclear. The conformation of all new compounds in solution was easily assigned on the basis of characteristic ^{1}H NMR patterns of the bridging methylene groups.[7]

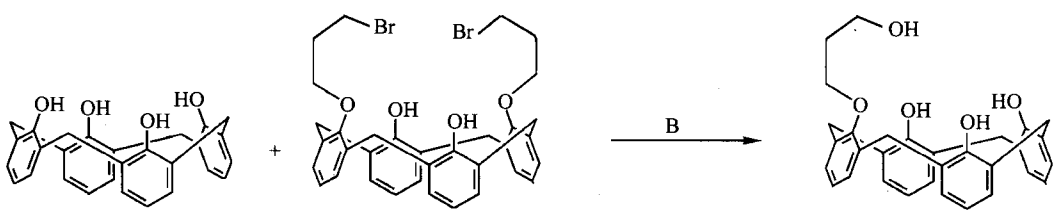
Scheme 1 A: K_2CO_3/THF/refluxed 15 days



1 **2, 3** **4, 5**

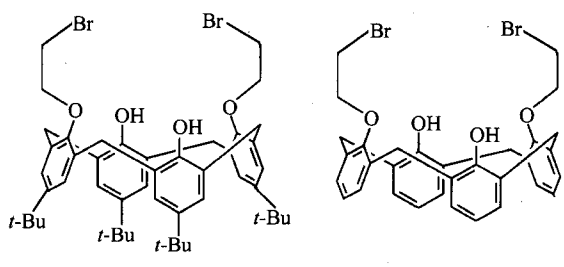
2, 4: n=2; **3, 5**: n=3

Scheme 2 B: K_2CO_3/DMF/100℃ for a week



6 **7** **8**

Chart 1



9 **10**

X-*ray crystal structures of* **4**, **5** and **8**

The structures of double flexible spacers bridged biscalix[4]arenes **4** and **5** were further proven by X-ray analysis as shown in Figs. 1 and 2. The two moieties of calix[4]arenyl unites of **4** and **5** all adopt cone conformation stabilized by intramolecular hydrogen bonds of the free hydroxyl groups. The two compounds include some aromatic solvents in their two hydrophobic cavities. Two 1,4-dimethylbenzene molecules were included in the two opposite cavities of **4** (not shown in Fig. 1). The distances between the methyl carbon of the guest in the cavity and the centroids of the four aromatic rings are 0.3540, 0.3551, 0.3820 and 0.3940 nm, respectively. The related distances of the methyl carbon of toluene molecules that are encompassed in the hydrophobic

cativies of **5** (not shown in Fig. 2) are 0.3565, 0.3605, 0.3771 and 0.3942 nm, respectively. The oxygen atoms between O(1) to O(4) and O(1A) to O(4A) of **4** and **5** form an ion-selective cavity. The cavity of **5** is relatively flexible comparing to that of **4** with the increase of carbon atoms as can be seen from Figs. 1 and 2. The O···O distances between adjacent phenolic oxygen atoms of **4** are between 0.2659 nm and 0.3002 nm. The distances between of O(1) and O(3), O(2) and O(4), and O(1) and O(3A) are 0.4485, 0.3496 and 0.4140 nm, respectively. The O···O distances between adjacent phenolic oxygen atoms of **5** are between 0.2741 nm and 0.2895 nm. The distances between of O(1) and O(2), O(3) and O(4), and O(1) and O(2A) are 0.4411, 0.3499 and 0.4714 nm, respectively.

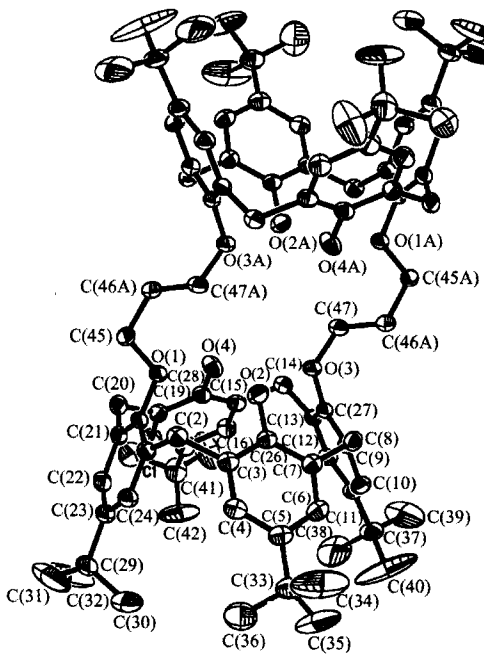


Fig. 1 Structure of **4**. The torsion angles of C(25)-O(1)-C(45)-C(46), O(1)-C(45)-C(46)-C(47A), C(45)-C(46)-C(47A)-O(3A), and C(27A)-O(3A)-C(47A)-C(46) are -171.8, -63.5, 174.0, and 80.8°, respectively.

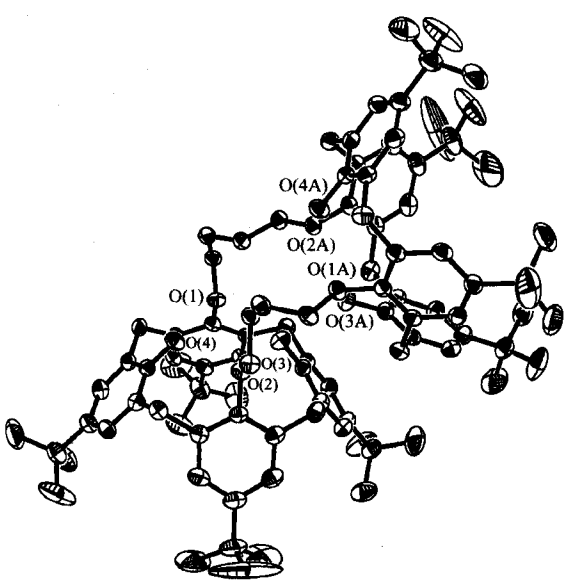


Fig. 2 Structure of **5**. The torsion angles of O(1)-C(47)-C(48)-C(46A), C(47)-C(48)-C(46A)-C(45A), C(48)-C(46A)-C(45A)-O(2A) are 59.7, 69.6 and -179.0°, respectively.

The structure of **8** was also characterized by X-ray analysis as illustrated in Fig. 3. Compound **8** has a strong binding tendency to DMF. Although compound **8** was purified by column chromatography, DMF can not be removed from the host. There are three binding sites of **8** with DMF *via* O—H···O_{DMF} hydrogen bond and C_{DMF}—H···O interactions in the solid state. The distance of O(5)···O(6) is 0.2535 nm. As documented,[11] the C—H···O interactions are usually weak. The

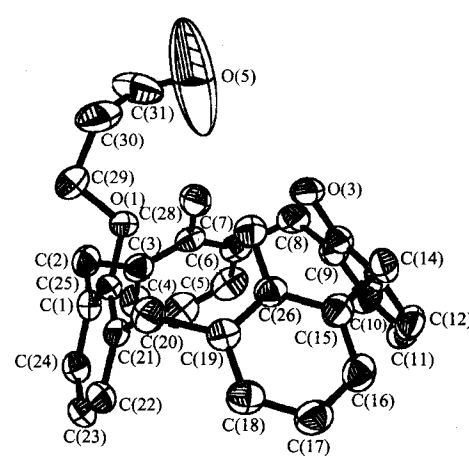


Fig. 3 Structure of **8**. The torsion angles of C(25)-O(1)-C(29)-C(30), O(1)-C(29)-C(30)-C(31), and C(29)-C(30)-C(31)-O(5) are 170.4, 52.6, and -117.1°, respectively.

distances of C(33)···O(5) and C(33)···O(4) are 0.3389 and 0.3318 nm, respectively. The aggregate system of **8**·**DMF** was further assembled *via* the hydrophobic cavity encasing the methyl carbon (C(32)) of DMF of the next unite. The distances of C(32) to the centroids of the four aromatic rings are 0.3565,

0.3642, 0.3957 and 0.4169 nm, respectively. Fig. 4 shows the infinite linear aggregate of **8**·**DMF**.

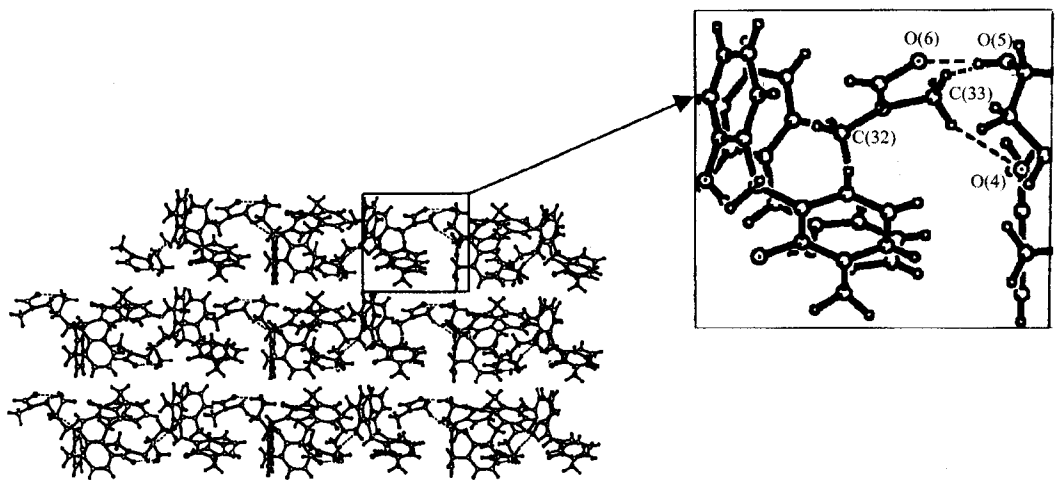


Fig. 4 Infinite linear molecular architectures of **8** formed through hydrogen bonding with DMF and self-inclusion.

K^+ *selectivity*

The selectivities of **4** and **5** toward K^+ over other interfering cations were investigated with an ion-selective electrode.[12,13] The selectivity coefficients ($K^{pot}_{K,M}$) for the electrodes consisting of **4**, and **5** were determined by matched potential method (Table 1). As shown in Table 1, polymer membranes containing **4** and **5** gave good $\log K^{pot}_{K,M}$ values ($\leqslant -3.0$) against alkaline metal cations Ca^{2+} and Mg^{2+}, but alkali metal cations Li^+, Na^+ as well as NH_4^+ gave some weak interference. It is interesting to note that, the selectivity of biscalix[4]-arenes **5** toward K^+ over alkali metal ions and ammonium is better than that of **4**, which indicated that the cavity of **5** is better matched with K^+ than that of **4**.

Table 1 Selectivity coefficients of K^+-ISEs based on ionophore **4** and **5**

Electrode No.	K^+	Na^+	NH_4^+	Li^+	Ca^{2+}	Mg^{2+}
1	0	-1.8	-0.8	-2.0	-3.0	-3.0
2	0	-1.3	-0.7	-1.7	-3.0	-3.0

Experimental

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker 200 MHz AC-P200 spectrometer in $CDCl_3$ solution. Tetramethylsilane was used as an internal standard. Elemental analyses were performed by a Perkin-Elmer 2400C analyzer. All solvents were purified by standard procedures. Compounds **1**, **2**, **3**, **7**, **9** and **10** were prepared according to the literature procedures.[14,15]

25,25′,27,27′-*Bis*(1,3-*dioxypropane*)-*bis*(5,11,17,23-*tetra*-*tert*-*butylcalix*[4]*arene*-26,28-*diol*) (**4**)

To a 300 mL reactor, was charged **1** (1.95 g, 3 mmol), anhydrous potassium carbonate (0.83 g, 6 mmol), THF (150 mL) and DMF (50 mL). The system was refluxed under nitrogen for 5 h. Then, **2** (2.67 g, 3 mmol) was added to the reaction system and refluxed for 15 days under nitrogen atmosphere. The solvent was removed under reduced pressure. The solid residue was dissolved with CH_2Cl_2 (200 mL) and washed with water (3 × 100 mL), dried with anhydrous magnesium sulfate. After the solvent being removed under reduced pressure, the residue was purified with column chromatography (petroleum ether: CH_2Cl_2/2:1 *V*/*V*). 1.45 g (35.1%) of **4** was obtained. M. p. > 360℃ (toluene). ^1H NMR ($CDCl_3$) δ: 8.92(s, 4H, OH), 7.07(s, 8H, Ar-H), 7.00(s, 8H, Ar-H), 4.42(d, J = 12.5 Hz, 8H, $ArCH_2Ar$), 4.30(t, J = 7.8 Hz, 8H, OCH_2CH_2), 3.43(d, J = 12.5 Hz, 8H, $ArCH_2Ar$), 3.18—3.03(m, 4H, OCH_2CH_2), 1.21(s, 36H, *t*-Bu-H), 1.18(s, 36H, *t*-Bu-H). Anal. Calcd. for $C_{94}H_{120}O_8$: C 81.93, H 8.78. Found: C 82.04, H 9.04.

25,25',27,27'-*Bis*(1,4-*dioxybutane*)-*bis*(5,11,17,23-*tetra*-*tert*-*butylcalix*[4]*arene*-26,28-*diol*) (**5**)

Compound **5** was synthesized according the preparation of **4**. M.p. > 360℃ (toluene). ^{1}H NMR ($CDCl_3$) δ: 8.48(s, 4H, OH), 6.94(s, 8H, Ar-H), 6.86(s, 8H, Ar-H), 4.32(d, J = 12.6 Hz, 8H, $ArCH_2Ar$), 4.13(m, 8H, OCH_2CH_2), 3.18(d, J = 12.6 Hz, 8H, $ArCH_2Ar$), 2.73—2.56 (m, 8H, $OCH_2CH_2CH_2$), 1.19(s, 36H, *t*-Bu-H), 1.08(s, 36H, *t*-Bu-H). Anal. calcd. for $C_{96}H_{124}O_8$: C 82.01, H 8.89. Found: C 81.93, H 8.81.

25-(3-*Hydroxylproxyl*)-*calix*[4]*arene*-26,27,28-*triol* (**8**)

To a 100 mL reactor, was added **6** (427 mg, 0.7 mmol), **10** (467 mg, 0.7 mmol), K_2CO_3 (289 mg, 2.1 mmol) and DMF (70 mL). The suspension was stirred at 110℃ for 10 days under nitrogen atmosphere. The solvent was removed under reduced pressure. The brown solid residue was dissolved with CH_2Cl_2 (100 mL), and then washed with water (100 mL) and brine (100 mL) successfully. The organic layer was dried with sodium sulfate and filtered. The filtration was condensed to dryness. The brown residue was purified by column chromatography (petroleum ether: CH_2Cl_2/1:2, *V*/*V*). **8**·**DMF** (58 mg) was obtained as white foam in 15% yield, which was recrystallized from CH_2Cl_2-MeOH. **8**·**DMF** was obtained as a colorless crystal, mp 228—230℃. ^{1}H NMR ($CDCl_3$) δ: 7.05—6.64(m, 12H, Ar-H), 4.31—4.14 (m, 8H, OCH_2, $ArCH_2Ar$), 3.45(d, J = 13.0 Hz, 2H, $ArCH_2Ar$), 3.42(d, J = 12.7 Hz, 2H, $ArCH_2Ar$), 2.39—2.28 (m, 2H, OCH_2CH_2). Anal. calcd. for $C_{31}H_{30}O_5 \cdot C_3H_7NO$: C 73.50, H 6.71, N 2.52. Found: C 73.28, H 6.57, N 2.38.

Potassium selectivity evaluated by potentiometric selectivity coefficient and membrane electrode

The typical procedure for membrane preparation is as follows: Poly(vinylchloride) (PVC) (132 mg, 33%), dibutyl phosphate (DBP) (264 mg, 66%), benzothiazolyl functionallized calix[4]arene (4 mg, 1%), potassium tetrakis(*p*-chlorophenyl)borate (KTClPB) (100 mol% relative to the ionophore) were dissolved in 5 mL of THF. This solution was then poured into a flat-bottomed petri dish of 32 mm inner diameter and 50 mm height. Gradual evaporation of the solvent at room temperature gave a transparent, flexible membrane of about 0.3 mm in thickness. A disk of 7 mm in diameter was cut from the PVC membrane and incorporated into PVC tube tip with 5% THF solution in water. After injection of 0.01 mol/L aqueous solution of KNO_3 as the internal solution, the electrode was conditioned by soaking in 0.01 mol/L aqueous solution of KNO_3 for 2 h. The external reference electrode is a double junction type Ag/AgCl glass electrode. The composition of electrochemical cell is given as Ag·AgCl | int. soln. (0.01 mol/L KCl) | PVC membrane | sample | salt bridge (3 mol/L KCl) | saturated KCl | Hg_2Cl_2·Hg.

EMF *measurements*

All EMF (electromotive force) measurements were made at 25 ± 0.1℃, using a pH/mV meter. Sample solution was magnetically stirred and kept in a thermostated water bath. The EMF values were corrected by subtracting the liquid-junction potential between the external reference electrode and the sample solution in the high K^+ concentration.

Selectivity coefficients

The potentiometric selectivity coefficient $K^{pot}_{K,M}$ determined here is defined in the Nicolsky-Eisenman equation:

$$E = E_0 + \frac{2.303RT}{F}\log[\alpha_K + K^{pot}_{K,M}(\alpha_M)^{1/Z_M}] \quad (1)$$

where E represents the experimentally observed potential, R the gas constant, T the thermodynamic temperature in K, F the Faraday constant, α_K the K^+ activity, α_M the activity of the foreign cation, and Z_M the charge of the foreign cation. The selectivity coefficients were determined by a mixed-solution method. In order to evaluate the selectivity of the K^+ over other cations, the mixed-solution method was employed. According to this method, the potentiometric selectivity coefficients,

$K^{pot}_{K,M}$, can be evaluated from the potential measurements on solutions containing a fixed concentration of the interfering ions (M^{n+}) and varying amounts of K^+ ion concentration by using the equation:

$$K^{pot}_{K,M} = \alpha_K/(\alpha_M)^{1/Z_M} \quad (2)$$

The resulting $\log K^{pot}_{K,M}$ values are summerized in Table 1.

Crystallographic structural determination

Crystals of **4** suitable for X-ray crystallography were grown by slow evaporation from the CH_2Cl_2-1, 4-dimethylbenzene solution of **4**. Compound **5** was grown by slow evaporation from the CH_2Cl_2-toluene solution of **5**. Compound **8** was grown by slow evaporation from the CH_2Cl_2-MeOH solution of **8**. X-ray crystallographic data were obtained on Bruker Smart 1000 diffractometer. The data collection and refinement parameters are given in Table 2.

Table 2 Crystal data and data collection parameters

Data	**4**	**5**	**8**
Formula	$C_{94}H_{120}O_8 \cdot 6$ (1,4-dimethylbenzene)	$C_{96}H_{124}O_8 \cdot 4PhMe$	$C_{31}H_{30}O_5 \cdot DMF$
Formula wt. (g/mol)	2014.86	1774.49	555.65
T (K)	298(2)	298(2)	298(2)
wavelength (nm)	0.071073	0.071073	0.071073
crystal system	triclinic	orthorhombic	orthorhombic
space group	$P\bar{1}$	$Fdd2$	$Pna2(1)$
a (nm)	1.30012(15)	3.51443(16)	1.8580(6)
b (nm)	1.33561(2)	5.0269(2)	0.8907(3)
c (nm)	2.0003(2)	1.24740(6)	1.7532(5)
β (deg)	89.476(2)	90	90
V (nm^3)	3.1883(6)	22.0373(17)	2.9015(14)
Z	2	8	4
D_c (mg/mm^3)	1.049	1.070	1.272
μ (mm^{-1})	0.063	0.065	0.087
F (000)	1096	7712	1184
Cryst size (mm)	0.15 × 0.20 × 0.25	0.20 × 0.25 × 0.30	0.20 × 0.25 × 0.35
θ range (deg)	1.64 to 25.03	1.41 to 25.03	2.19 to 25.03
Reflns collected	13379	22809	5927
Independent reflns	11200	8795	3117
Data/restraints	11200/0	8795/1	3117/1
Parameters	703	595	360
GOOF	1.036	0.941	1.065
R_1	0.0744	0.0555	0.0661
wR_2	0.2209	0.1488	0.1994

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