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# Stereoisomerism and complexation behaviour of functionalized *p-tert*-calix[6]-1,4-2,5-biscrown-4

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**Abstract**—*p-tert*-Calix[6]-1,4-2,5-biscrown-4 was subjected to functionalization by benzyl bromide or ethyl bromoacetate. Two pairs of disubstituted calix[6]biscrown stereoisomers were obtained. Their structures had been deduced from $^1$H NMR and ESI-MS (electrospray ionization mass spectroscopy). One of the bisethyloxycarbonylmethylated derivatives **3a** was further investigated by X-ray crystallographic analysis. Two-phase extraction experiments indicated that bisethyloxycarbonylmethylated derivatives exhibited high $Cs^+/Na^+$ selectivity. By ESI-MS and $^1$H NMR experiments it was confirmed that **3a** formed 1:1 complex with $Cs^+$.


Calixcrowns, which are constructed by incorporating crown ether segment into calixarene skeleton, play unique roles in the calixarene chemistry due to their outstanding selectivity towards alkali metal ions.[1,2] In 2000, two types of calix[6]biscrowns, namely 1,4-2,5 and 1,3-4,6 double bridged calix[6]biscrowns, had been reported for the first time.[3–6] The 2,5-diallyl derivative of calix[6]-1,3-4,6-biscrown-4 in the cone conformation showed a high $Cs^+/Na^+$ selectivity and exhibited a certain extent extraction ability towards $K^+$ ion.[3] Recently, we developed a convenient and simple method for the synthesis of *p-tert*-calix[6]-1,4-2,5-biscrown-4.[7] It is also well documented that the complexation ability of calixarene towards metal ions could be improved by incorporating additional ligands such as $CH_2COOC_2H_5$, $CH_2CONMe_2$, etc. Therefore, the derivatives, which are based on the *p-tert*-calix[6]-1,4-2,5-biscrown-4 framework could be a new candidate for ion receptors because of their more rigid conformation and polytopic binding sites. Besides, it is possible to give stereoisomers in such functionalized calixbiscrowns if the rotation of the functionalized phenolic groups is prohibited. To the best of our knowledge, little is known about the functionalization of calix[6]biscrowns.[8,9]

Herein we wish to report our work on functionalizing *p-tert*-butylcalix[6]-1,4-2,5-biscrown-4 (**2**), a new kind of stereoisomerism as well as the strengthened complexation ability and selectivity towards $Cs^+$ ion of some derivatives. The functionalization was performed as shown in Scheme 1.

The reaction of *p-tert*-calix[6]arene (**1**) with triethylene glycol ditosylates in xylene with $K_2CO_3$ as a base afforded *p-tert*-calix-1,4-2,5-biscrown-4 (**2**) in 52% yield conveniently.[10] Further treatment of *p-tert*-butylcalix[6]-1,4-2,5-crown-4 with 2 equiv benzyl bromide or ethyl bromoacetate in refluxing acetonitrile in the presence of 10 equiv $K_2CO_3$ for 12 h, gave two pairs of disubstituted derivatives, **3a** and **3b**, **4a** and **4b** in 65%, 23%, 52% and 34% yield, respectively. The structures of these compounds were characterized by ESI-MS spectra, elemental analyses and $^1$H NMR studies.[11] It is interesting to note that compounds **3a** and **3b**, or **4a** and **4b** both have the same molecular weight. This indicated that **3a** and **3b** should be a pair of stereoisomers. It was the same to **4a** and **4b**. From their constructed pattern, the only possibility was two benzyl or ethyloxycarbonylmethyl groups adopting different orientations (3,6-*syn* or 3,6-*anti*) and they were a pair of stereoisomers as shown in Figure 1.

As shown in Figure 1, the 3,6-*syn*-isomer has a $C_2$ symmetry axis passing through the centre of calix[6]arene cavity and the 3,6-*anti*-isomer has a horizontal $C_2$ symmetry axis through the plane of the molecule. It was in agreement with that the $^1$H NMR spectra where three singlets in a ratio of 1:1:1 for six *tert*-butyl groups were observed. The signals of *tert*-butyl of **3a** appeared at

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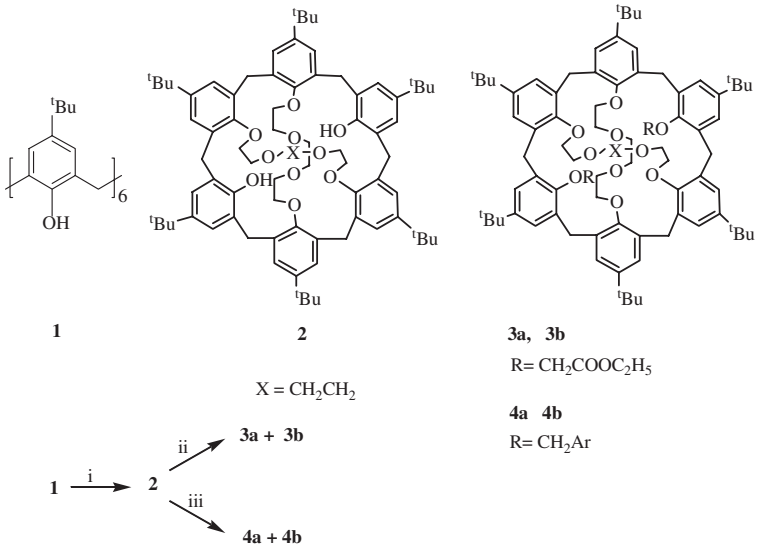


**Scheme 1.** Reagents and conditions: (i) $K_2CO_3$/xylene, triethylene glycol ditosylates, reflux, 12 h, 52%; (ii) $K_2CO_3$/MeCN, ethyl bromoacetate, reflux, 12 h, **3a**, 65%, **3b**, 23%; (iii) $K_2CO_3$/MeCN, benzyl bromide, reflux, 12 h, **4a**, 52%, **4b**, 34%.

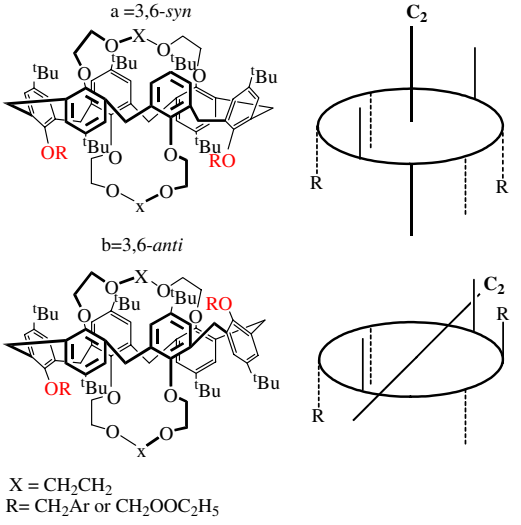


**Figure 1.** Stereoisomers of disubstituted derivatives.

1.36, 1.22 and 1.16 ppm, and those of **3b** appeared at 1.26, 1.23 and 1.18 ppm. It was remarkable that one of the signals in **3a** appeared at much lower field (1.36 ppm) as compared with the other *tert*-butyl (nearby 1.20 ppm). Secondly, there are six singlets (ratio of 1:1:1:1:1:1) for aromatic protons in the $^1$H NMR spectra of **3a**, and for **3b** the aromatic protons appeared as four doublets and one singlet in a ratio of 1:1:1:1:2. However, it could not be assigned whether it was 3,6-*syn*-isomer or 3,6-*anti*-isomer by $^1$H NMR data alone. The unambiguous proof was obtained by a single crystal X-ray analysis of **3a**, which confirmed **3a** with 3,6-*syn*-configuration (Fig. 2). Details are given in the Experimental section.[12]

Based on the above discussion, the structure of **4a** and **4b** were deduced from similarity of their $^1$H NMR spectra with **3a** and **3b**.

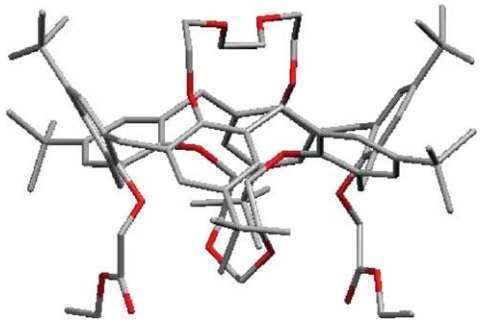

**Figure 2.** X-ray crystal structure of compound **3a**.

The alkali metal binding properties of *p*-*tert*-butylcalix[6]-1,4-2,5-crown-4 derivatives were investigated using the metal picrate extraction method, in which aqueous solutions of the picrate salts ($2.0 \times 10^{-3}$ M, 2 mL) were shaken with chloroform solutions of the hosts ($2.0 \times 10^{-3}$ M, 2 mL) at 25 °C.[13] The result of extraction studies was expressed as association constants listing in Table 1.

It was worthy to note that the ethoxycarbonylmethyl derivatives (**3a**,**b**) have higher extraction ability and selectivity towards $Cs^+$ comparing to the parent calixbiscrown (**2**) and the others. Especially, the $Cs^+/Na^+$ selectivity of compound **3a** (3,6-*syn*-isomer) is higher than that of compound **3b** (3,6-*anti*-isomer). It was proved again that the introduction of appropriate substituent onto special position could greatly increase the binding ability of *p*-*tert*-calix[6]-1,4-2,5-biscrown-4 towards certain metal ions.

Moreover, the stoichiometry of **3a** with $Cs^+$ was investigated. After 24 h precomplexation with 10 equiv of $Cs^+Pic^-$ in chloroform/methanol (3:1), electrospray mass spectrometry showed that only an intense peak

**Table 1.** Association constants ($K_a \times 10^{-5}$) for complexes of alkali metals with derivatives in $CHCl_3$ deduced from metal picrate extraction data

| | 2 | 3a | 3b | 4a | 4b |
|---|---|---|---|---|---|
| $Cs^+$ | 7.8 | 900.0 | 150.0 | 5.3 | 3.8 |
| $K^+$ | 9.2 | 130.0 | 24.1 | 11.0 | 5.5 |
| $Na^+$ | 12.2 | 3.8 | 2.6 | 10.2 | 9.4 |
| $Li^+$ | 6.5 | 5.0 | 3.0 | 6.0 | 8.0 |

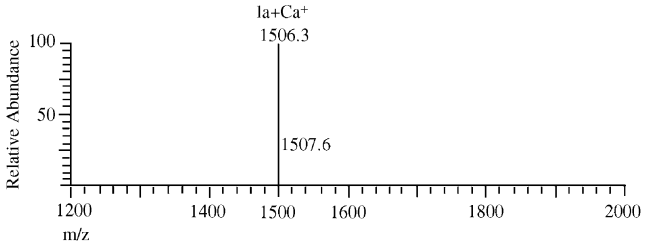


**Figure 3.** Electrospray ionization mass spectra for the complexation of compound **3a** with $Cs^+$.

at $m/z$ 1506.3 (Fig. 3) corresponding to the [**3a**+$Cs^+$] ion was observed. This indicated that only 1:1 complex was formed even in the presence of an excess of $Cs^+Pic^-$.

The result was also confirmed by $^1H$ NMR experiments. The changes of the chemical shifts of free ligand **3a** upon addition of $Cs^+Pic^-$ were observed. Among them, the change of one pair of *tert*-butyl protons was remarkable (Fig. 4). Its downfield shift reached maximum by $\Delta\delta = 0.17$ ppm when the molar ratio of $Cs^+Pic^-$ to ligand **3a** was equal to 1:1, and no further change could be observed by addition more $Cs^+Pic^-$.

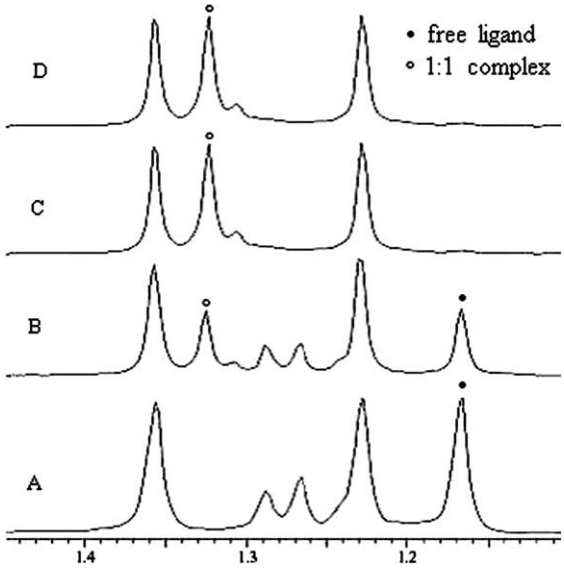


**Figure 4.** *tert*-Butyl region of $^1H$ NMR (300 MHz) spectra ($CDCl_3$/$CD_3OD$, v/v = 4:1, 298 K) of (A): free ligand **3a**; (B): **3a**+0.5 equiv of $Cs^+Pic^-$; (C): **3a**+1 equiv of $Cs^+Pic^-$; (D): **3a**+4 equiv of $Cs^+Pic^-$.

In conclusion, this paper described the synthesis of disubstituted *p-tert*-butylcalix[6]-1,4-2,5-crown-4 and the stereoisomerism of them. One of them (**3a**) was further investigated by single crystal X-ray analysis. We found that the ethyloxycarbonylmethylated derivatives, especially the 3,6-*syn*-isomer exhibited excellent complexation ability and high selectivity towards $Cs^+$ ions.

## Acknowledgements

Thank Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, for the single crystal X-ray analysis.

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10. A mixture of 4.89 g (5.0 mmol) **1**, 5.02 g (10.0 mmol) triethylene glycol ditosylate, 2.11 g (15.2 mmol) anhydrous $K_2CO_3$ and 500 mL xylene was stirred at reflux temperature for 12 h. After removal of solvent under reduced pressure, the residue was treated with HCl (10%, v/v) and extracted with $CHCl_3$. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. After recrystallization from mixture of chloroform and ethanol (2:8, v/v), 3.13 g **2** was obtained as colourless crystal in 52% yield; **2**: $^1H$ NMR (300 MHz, $CDCl_3$): 1.16 (36H, s, $ArC(CH_3)_3$), 1.33 (18H, s, $ArC(CH_3)_3$), 2.86 (4H, t, $J = 9.0$ Hz, $OCH_2$ $CH_2$), 3.25 (4H, q, $J = 10.5$ Hz, $OCH_2CH_2$), 3.34–3.50 (16H, m, $OCH_2CH_2$ and $ArCH_2Ar$), 3.8 (4H, q, $J = 10.5$ Hz, $OCH_2CH_2$), 4.07 (4H, s, $ArCH_2Ar$), 4.39 (4H, d, $J = 15$ Hz, $ArCH_2Ar$), 6.91 (4H, s, ArH), 7.03 (2H, s, ArOH), 7.04 (4H, s, ArH), 7.11 (4H, s, ArH). FAB-MS: $m/z = 1200$ ($M^+$, 100%). Anal. Calcd for $C_{78}H_{104}O_{10}$: C, 77.96; H, 8.72. Found: C, 78.10; H, 8.60.
11. *General*: Melting points were recorded on a Gallenkamp melting point apparatus in open capillaries without correction. $^1H$ NMR was recorded on a Varian Mercury VX300 instrument at ambient temperature with TMS as an internal standard. ESI-MS was recorded on Finnigan LCQ-Advantage instrument. All chemicals were A. R. grade and purified by standard procedure. The procedure for the synthesis of *p-tert*-butylcalix[6]-1,4-2,5-biscrown-4 derivatives: compound **2** (0.120 g, 0.1 mmol) was dissolved in $CH_3CN$ (100 mL) and $K_2CO_3$ (0.139 g, 1.0 mmol)

added under a nitrogen atmosphere. After stirring 1 h, ethyl bromoacetate (0.042 g, 0.25 mmol) or benzyl bromide (0.042 g, 0.25 mmol) was added and refluxed for 12 h. Then $CH_3CN$ was removed and the residue extracted with 50 mL of $CHCl_3$ and 50 mL of 10% HCl. The organic phase was separated, washed twice with water (100 mL) and the solvent was distilled off. The crude product was subjected to recrystallization or chromatography to afford pure products as described below: Compound **3a** was obtained by recrystallization of the crude product from $CH_2Cl_2$/MeOH (2:1. v/v) mixture in 65% (0.089 g) yield. The mother liquid was evaporated to dryness and the residue was subjected to column chromatography on silica gel using $CHCl_3$ as eluent to afford **3b** in 23% (0.032 g) yield; **3a**: mp > 270 °C; $^1$H NMR (300 MHz, $CDCl_3$): 1.16 (s, 18H, $C(CH_3)_3$), 1.22 (s, 18H, $C(CH_3)_3$), 1.25 (t, $J = 6.3$ Hz, 6H), 1.36 (s, 18H, $C(CH_3)_3$), 2.52–2.63 (m, 2H, $OCH_2CH_2$), 2.88–3.28 (m, 12H, $OCH_2CH_2$), 3.29–3.46 (m, 10H, $OCH_2CH_2$ and $ArCH_2Ar$), 3.59 (d, 2H, $J = 16.5$ Hz, $ArCH_2Ar$), 3.63–3.72 (m, 2H, $OCH_2CH_2$), 3.91–4.05 (m, 4H, $OCH_2CH_2$ and $ArCH_2Ar$), 4.07–4.22 (m, 6H, $OCH_2CH_2$, $ArCH_2Ar$ and $OCH_2CH_3$), 4.39 (s, 4H, $OCH_2CO$), 4.75 (d, $J = 14.4$ Hz, 2H, $ArCH_2$ AR), 6.74 (s, 2H, ArH), 6.96 (s, 2H, ArH), 7.06 (s, 2H, ArH), 7.12 (s, 2H, ArH), 7.17 (s, 2H, ArH), 7.24 (s, 2H, ArH); MS (ESI): $m/z = 1373.79$ ($M^+$). Anal. Calcd for $C_{86}H_{116}O_{14}$: C, 75.19; H, 8.51. Found: C, 75.33; H, 8.59; **3b**: mp > 270 °C; $^1$H NMR (300 MHz, $CDCl_3$): 1.18 (s, 18H, $C(CH_3)_3$), 1.23 (t, $J = 6.3$ Hz, 6H), 1.26 (s, 18H, $C(CH_3)_3$), 1.28 (s, 18H, $C(CH_3)_3$), 2.38–2.50 (m, 2H, $OCH_2CH_2$), 2.64–2.75 (m, 2H, $OCH_2CH_2$), 2.84–2.96 (m, 2H, $OCH_2CH_2$), 2.97–3.07 (m, 2H, $OCH_2CH_2$), 3.09–3.40 (m, 10H, $OCH_2CH_2$ and $ArCH_2Ar$), 3.54–3.79 (m, 6H, $OCH_2CH_2$ and $ArCH_2Ar$), 3.79–3.84 (m, 2H, $OCH_2CH_2$), 3.87–4.06 (m, 4H, $OCH_2CH_2$ and $ArCH_2Ar$), 4.08–4.32 (m, 10H, $OCH_2CH_2$, $ArCH_2Ar$ and $OCH_2CH_3$), 4.49 (d, $J = 15.6$ Hz, 2H, $ArCH_2Ar$), 4.66 (d, $J = 13.5$ Hz, 2H, $ArCH_2Ar$), 6.91 (d, $J = 2.4$ Hz, 2H, ArH), 6.93 (d, $J = 2.4$ Hz, 2H, ArH), 7.07 (d, $J = 2.4$ Hz, 2H, ArH), 7.11 (d, $J = 2.4$Hz, 2H, ArH), 7.23 (s, 4H, ArH). MS (ESI): $m/z = 1373.79$ ($M^+$). Anal. Calcd for $C_{86}H_{116}O_{14}$: C, 75.19; H, 8.51. Found: C, 75.41; H, 8.57; Compounds **4a** and **4b** were obtained by column chromatography of the crude product on silica gel using $CHCl_3$ as eluent. The yields were 52% (0.071 g) and 34% (0.047 g), respectively. **4a**: mp > 270 °C; $^1$H NMR (300 MHz, $CDCl_3$): 1.15 (s, 18H, $C(CH_3)_3$), 1.23 (s, 18H, $C(CH_3)_3$), 1.42 (s, 18H, $C(CH_3)_3$), 2.18–2.20 (m, 2H, $OCH_2CH_2$), 2.49 (t, $J = 10.5$ Hz, 2H, $OCH_2CH_2$), 2.60 (t, $J = 10.5$ Hz, 2H, $OCH_2CH_2$), 2.88–2.97 (m, 4H, $OCH_2CH_2$), 3.08–3.21 (m, 4H, –$OCH_2CH_2$ and $ArCH_2Ar$), 3.32 (d, $J = 15$ Hz, 2H, $ArCH_2Ar$), 3.39–3.49 (m, 4H, $OCH_2CH_2$ and $ArCH_2Ar$), 3.49 (s, 2H, $OCH_2Ar$) 3.58 (d, $J = 15$ Hz, 2H, $ArCH_2Ar$), 3.61 (d, $J = 15$ Hz, 2H, $ArCH_2Ar$), 3.90–4.08 (m, 6H, $OCH_2CH_2$, $ArCH_2Ar$ and $OCH_2Ar$), 4.29 (d, $J = 15.6$ Hz, 2H, $ArCH_2Ar$), 4.72 (d, $J = 15$ Hz, 2H, $ArCH_2Ar$), 4.73 (m, 4H, $ArCH_2Ar$ and $OCH_2Ar$), 6.70 (s, 2H, ArH), 7.04 (s, 2H, ArH), 7.05 (s, 2H, ArH), 7.08 (s, 2H, ArH), 7.18 (s, 10H, ArH), 7.25 (s, 2H, ArH), 7.28 (s, 2H, ArH). MS (ESI): $m/z = 1381.9$ ($M^+$). Anal. Calcd for $C_{92}H_{116}O_{10}$: C, 79.96; H, 8.46. Found: C, 79.92; H, 8.51; **4b**: mp > 270 °C; $^1$H NMR (300 MHz, $CDCl_3$): 1.18 (s, 18H, $C(CH_3)_3$), 1.20 (s, 18H, $C(CH_3)_3$), 1.22 (s, 18H, $C(CH_3)_3$), 2.37–2.50 (m, 2H, $OCH_2CH_2$), 2.57–2.70 (m, 2H, $OCH_2CH_2$), 2.70–3.02 (m, 12H, $OCH_2$ $CH_2$), 3.03–3.12 (m, 2H, $OCH_2CH_2$), 3.25 (d, $J = 13.5$Hz, 2H, $ArCH_2Ar$), 3.41–3.48 (m, 4H, $OCH_2CH_2$), 3.52–3.62 (m, 2H, $OCH_2CH_2$), 3.73 (s, 2H, $OCH_2Ar$), 3.91 (d, $J = 15.9$ Hz, 2H, $ArCH_2Ar$), 3.96 (s, 2H, $OCH_2Ar$), 4.14 (d, $J = 15.9$ Hz, 2H, $ArCH_2Ar$), 4.39 (d, $J = 13.5$ Hz, 2H, $ArCH_2Ar$), 4.59 (d, $J = 10.8$ Hz, 2H, $ArCH_2Ar$), 4.83 (d, $J = 10.8$ Hz, 2H, $ArCH_2Ar$), 6.87 (d, $J = 2.4$ Hz, 2H, ArH), 6.98 (d, $J = 2.4$ Hz, 2H, ArH), 7.00 (d, $J = 2.4$ Hz, 2H, ArH), 7.12 (s, 4H, ArH), 7.22 (s, 10H, ArH), 7.24 (d, $J = 2.4$ Hz, 2H, ArH). MS (ESI): $m/z = 1381.9$ ($M^+$). Anal. Calcd for $C_{92}H_{116}O_{10}$: C, 79.96; H, 8.46. Found: C, 80.11; H, 8.55.

12. Crystal data of **3a**: $C_{86}H_{116}O_{14}$, $M = 1373.79$, tetragonal, space group $P4(3)2(1)2$, $a = 13.1344(6)$, $b = 13.1344(6)$, $c = 47.415(3)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 8179.7(7)$ Å$^3$, $T = 293$ K, $Z = 4$, $\mu = 0.074$ mm$^{-1}$, $R1 = 0.0875$ for 4404 $F_0 > 4\sigma(F_0)$ and 0.2712 for all 7628 data. CCDC No. 24420 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: (internat.) +44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk].
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