

## Thermal Polymorphic Transformation of *p*-*tert*-Butylcalix[4]arene Derivatives Bearing Amino Acid Substituents

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Studies were made on the polymorphism of *p*-*tert*-butylcalix[4]arene derivatives having amino acid groups on the lower rim to stabilize their hydrophilic pseudocavity by circular intramolecular hydrogen bonding. The calixarenes exhibit a polymorphic transformation upon heating in the solid state. This transformation is controlled by the thermal history of solids, accompanying the change on the conformation of the calixarene skeleton and also the change of hydrogen bonding in the hydrophilic pseudocavity.

### Introduction

Considerable attention has been paid to functionalized calixarenes from the view of their potential utility as molecular receptors and ionophores.<sup>1</sup> Their complexing ability and conformation have already been widely studied both in solution and in the solid state.<sup>1</sup> However, little attention has been focused on their polymorphism in the solid state, although Shinkai and co-workers have reported that *p*-hexanoylcalix[4]arene shows a phase transition accompanying a conformational change from a cone conformation to a partial cone conformation.<sup>1,2</sup> Therefore, the study of the polymorphism of calixarene derivatives may open up a new area in the field of calixarene chemistry. Polymorphs are chemically identical but exhibit different physical properties.

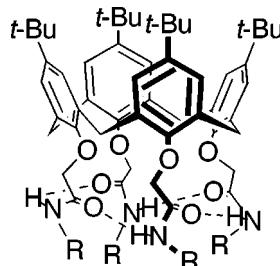
Previously, we reported the synthesis of the calixarenes **1a–d** and their binding ability toward metal ions.<sup>3</sup> The structural feature of these calixarenes is the amino acid substituents on the lower rim that serve to stabilize a binding site in their hydrophilic pseudocavity by circular intramolecular hydrogen bonding. In the course of this study, we found that some of these calixarenes exhibited a polymorphic transformation upon heating in the solid state.

This paper describes experimental evidence indicating that the calixarene derivatives manifest the polymorphic transformation. Evidence was obtained by means of differential scanning calorimetry (DSC), X-ray diffraction (XRD), <sup>13</sup>C cross polarization-magic angle spinning NMR (<sup>13</sup>C CP-MAS NMR), and FT-IR. It was found that the polymorphic transformation is affected by the thermal history of solids and is accompanied by the interconversion between the cone conformation having *C*<sub>4</sub> symmetry and the pinched cone conformation having *C*<sub>2</sub> symmetry<sup>4</sup>

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**1**

- a** : R=CH(CH<sub>3</sub>)COOBn
- b** : R=CH(CH<sub>3</sub>)COOMe
- c** : R=CH<sub>2</sub>COOBn
- d** : R=CH(CH(CH<sub>3</sub>)<sub>2</sub>)COOBn

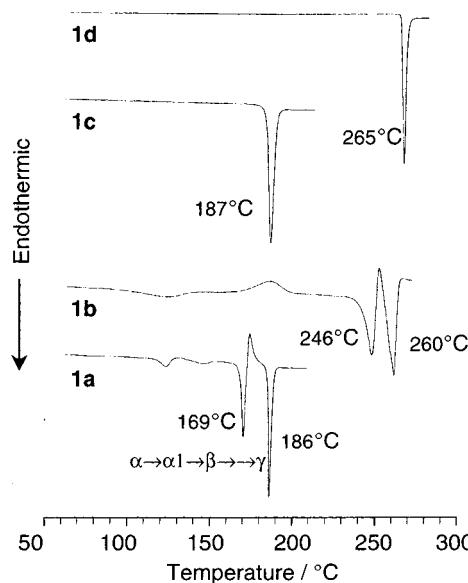
in the calixarene skeleton and also by the change of the hydrogen bonding capability in the hydrophilic pseudocavity.

### Results and Discussion

The calixarenes **1a–c** were recrystallized from dichloromethane/ether to afford needles. Crystals of **1d** were obtained by recrystallization from acetonitrile. The crystals were dried under reduced pressure at room temperature for 24 h, and they were found not to contain any of solvents.

Calorimetric measurements for **1a–d** were carried out by DSC. The first DSC heating runs are shown in Figure 1. The DSC thermograms were obtained by heating the samples at a scan rate of 10 °C min<sup>-1</sup>. The thermogram of **1a** showed two small endothermic peaks around 122 and 144 °C and a strong endothermic peak at 169 °C. The last peak was followed by an exothermic change and then the final melting at 186 °C. The exothermic change

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**Figure 1.** DSC curves of **1a–d** at a heating rate of  $10\text{ }^{\circ}\text{C min}^{-1}$ .

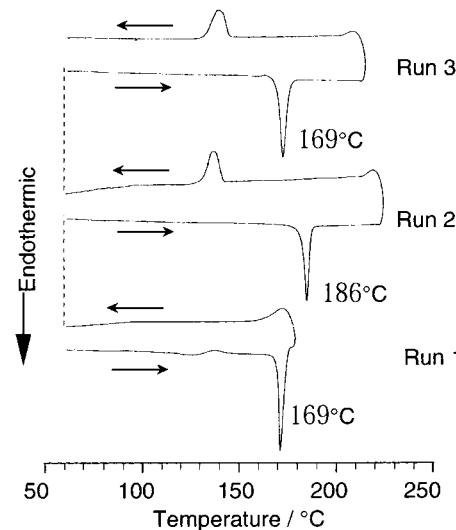
**Table 1. Transition Temperatures and Enthalpy Changes of **1a****

process	$T^a/{}^{\circ}\text{C}$	$\Delta H/\text{kJ mol}^{-1}$
$\alpha \rightarrow \alpha 1$	122 (115)	5.8
$\alpha 1 \rightarrow \beta$	144 (134)	3.5
$\beta \rightarrow \text{liquid}$	169 (167)	20.4
$\text{liquid} \rightarrow \gamma$	172	9.6
$\gamma \rightarrow \text{liquid}$	186 (184)	30.4

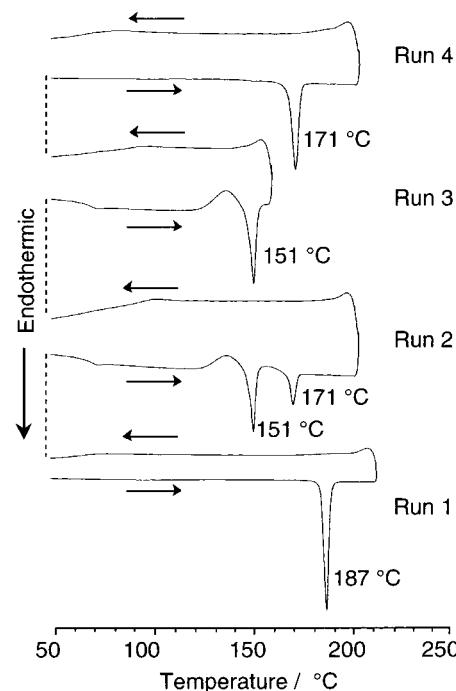
<sup>a</sup> Peak temperatures. The onset temperatures are shown in parentheses.

corresponded to recrystallization. The heating curves were affected by the scan rate. Slow heating scans of below  $10\text{ }^{\circ}\text{C min}^{-1}$  gave sharp endo- and exothermic peaks with a slight shift to lower temperature. At increasing scan rates of above  $50\text{ }^{\circ}\text{C min}^{-1}$ , the endothermic peaks became broad and the exothermic peaks disappeared. The transition temperatures and the transition enthalpies of **1a** at a scan rate of  $10\text{ }^{\circ}\text{C min}^{-1}$  are summarized in Table 1. The thermogram of **1b** showed also two strong endothermic peaks at 246 and 260 °C. The thermograms of **1c** and **1d** showed only endothermic peaks at their melting temperatures at 187 and 265 °C, respectively.

The DSC thermograms of **1a** were obtained continuously by heating and cooling the sample at a scan rate of  $10\text{ }^{\circ}\text{C min}^{-1}$  (Figure 2). The  $\gamma$ -form crystals, which had a higher melting peak at 186 °C, were prepared by heating to 175 °C and then cooling (run 1). Recrystallization of the sample finished at 175 °C, and no other exothermic peaks appeared during the cooling process. The  $\gamma$ -form crystals were able to be produced only by first heating of the original  $\alpha$ -form crystals that were recrystallized from dichloromethane/ether. The  $\beta$ -form crystals, which had a lower melting peak at 169 °C, were prepared by cooling after heating to 210 °C (run 2). During the cooling process, the exothermic peak due to recrystallization was observed at about 140 °C. The next heating curve (run 3) showed the endothermic peak at 169 °C, and their peak was reproducible by heating to 210 °C. These heating and cooling processes show that the phase transition of **1a** is controlled by its thermal history. The three crystalline forms ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) gave the same  $^1\text{H}$



**Figure 2.** DSC curves of **1a** upon continuous heating and cooling ( $10\text{ }^{\circ}\text{C min}^{-1}$ ).

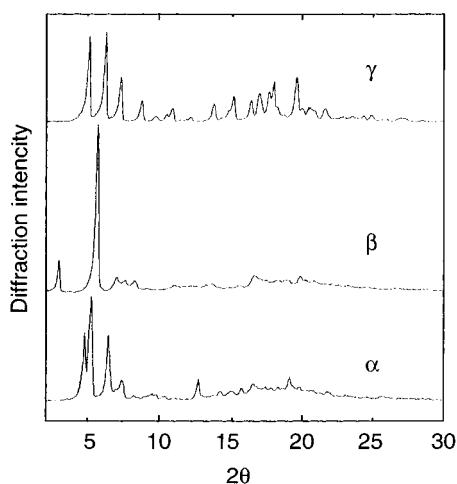


**Figure 3.** DSC curves of **1c** upon continuous heating and cooling ( $10\text{ }^{\circ}\text{C min}^{-1}$ ).

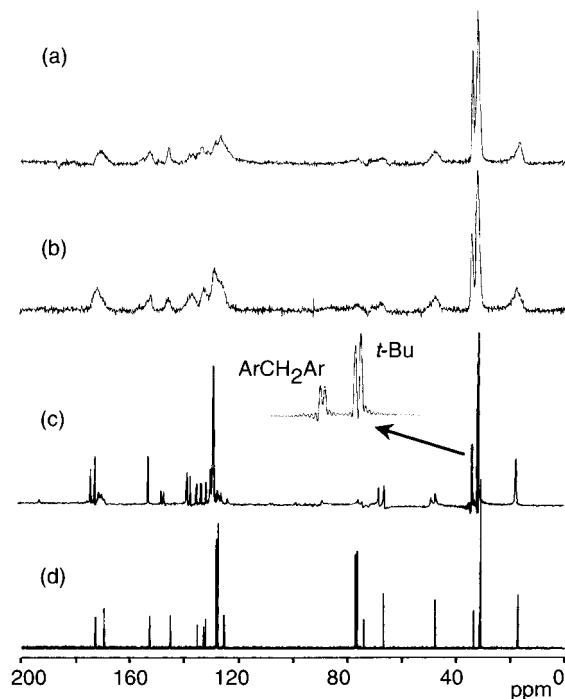
NMR and CD spectra in solution. This clearly indicates that no chemical change occurs by heating.

The thermal behavior of **1c** was slightly different from that of **1a** (Figure 3). Lower melting peaks for **1c** were observed at 151 and 171 °C during the second heating process of the original crystals that had a higher melting peak at 187 °C. During this process, the exothermic peak at about 135 °C due to recrystallization was observed. The crystals having melting peak at 171 °C were prepared by cooling after heating to 160 °C (run 3). For **1c**, the crystals having higher melting peak at 187 °C were obtained only recrystallization from dichloromethane/ether.

The XRD spectra of **1a** showed three different patterns according to the crystalline forms, indicating that **1a** had three different crystalline structures (Figure 4). In



**Figure 4.** X-ray diffraction intensities of the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -forms of **1a**.



**Figure 5.**  $^{13}\text{C}$  CP-MAS NMR spectra of (a)  $\alpha$ -form, (b)  $\beta$ -form, and (c)  $\gamma$ -form of **1a** at 20 °C. (d)  $^{13}\text{C}$  NMR spectra of **1a** in  $\text{CDCl}_3$  solution at 20 °C.

particular, the high angle peaks for the  $\gamma$ -form crystals indicated a highly ordered crystalline state.

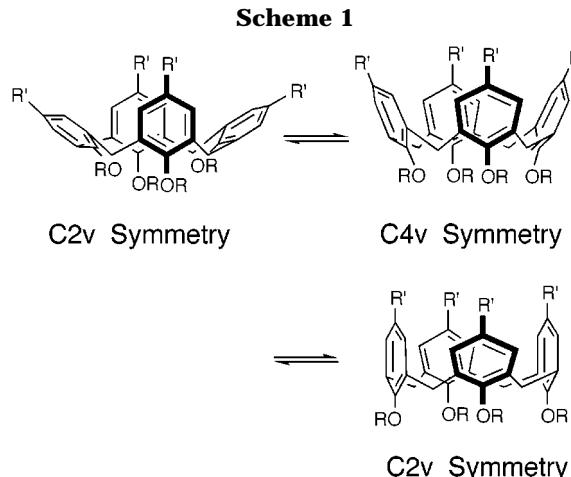
The  $^{13}\text{C}$  solid-state NMR technique provides information about crystal polymorphs and also about their structures through anisotropic chemical shifts.<sup>5-7</sup> The  $^{13}\text{C}$  CP-MAS NMR spectra of **1a** showed signals having chemical shifts close to those observed in solution (Figure 5), but the spectra exhibited different splitting patterns depending on the crystalline forms. The spectrum for the  $\gamma$ -form of **1a** gave sharp splitting signals (Figure 5c), but that for the  $\alpha$ - and  $\beta$ -forms gave broad signals in the

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whole region of spectra. The calixarene **1a** has a cone conformation in solution.<sup>3</sup> The conformational interconversion of **1a** is inhibited by introduction of a larger substituent on the phenolic oxygens.<sup>8</sup> Calix[4]arenes in a cone conformation still possess flexibility of the skeleton, and two pinched cone conformations having  $C_{2v}$  symmetry interconvert via the cone conformation having  $C_{4v}$  symmetry in solution (Scheme 1).<sup>4</sup> The conformation



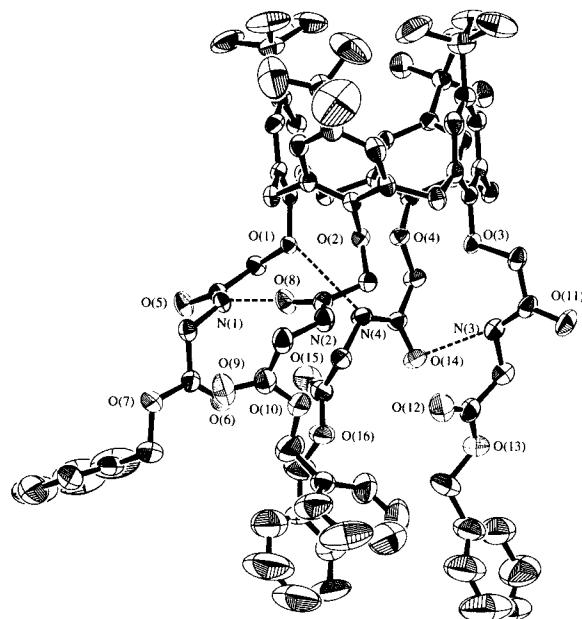
having  $C_{2v}$  symmetry is thermodynamically more stable than the conformation having  $C_{4v}$  symmetry.<sup>4,9</sup> In the  $^{13}\text{C}$  CP-MAS NMR spectrum of the  $\gamma$ -form of **1a**, the sharp splitting patterns for *tert*-butyl and aromatic ring carbons of the skeleton showed the pinched cone conformation having  $C_2$  symmetry (Figure 5c). The calixarene **1a** of the cone conformation has the hydrophilic pseudocavity by circular intramolecular hydrogen bonding in solution.<sup>3</sup> For polymorphism in a number of organic crystals, the conformational change accompanying a change in hydrogen bond networks is known to be significant.<sup>6,10</sup> Furthermore, the existence of two independent calixarene molecules in the same crystalline unit cell, in which molecules have different intramolecular hydrogen bonding, is known.<sup>11</sup> Hence, we examined the behavior of intramolecular hydrogen bonding among the amide groups of **1a** and **1c** by means of FT-IR measurements. The IR spectrum for the  $\alpha$ -form of **1a** exhibited the NHCO bands at 3285 and 1663  $\text{cm}^{-1}$ . The  $\beta$ -form of **1a** showed them at 3300 and 1670 (with shoulder at around 1690)  $\text{cm}^{-1}$ . The  $\gamma$ -form of **1a** showed them at 3302 and 1663  $\text{cm}^{-1}$ . For **1c**, the original crystals that had a higher melting peak at 187 °C showed the NHCO bands at 3429, 3368, 3317, and 1676  $\text{cm}^{-1}$ . On the other hand, the crystals of **1c** that had lower melting point at 171 °C showed them at 3308 (with small shoulder at around 3370) and 1676 (broad)  $\text{cm}^{-1}$ . These spectral changes indicate that crystals have different modes of hydrogen bonding, which are responsible for melting temperatures. The variation of

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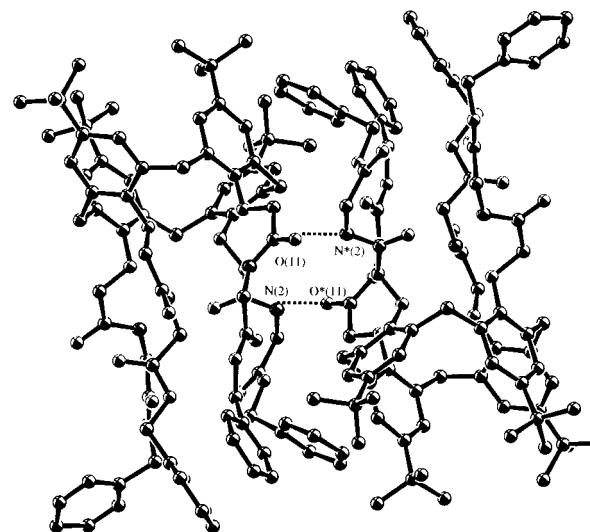


**Figure 6.** The X-ray crystallographic structure of **1c** (30% probability). Hydrogen atoms are omitted for clarity. Hydrogen bonding (Å): N(1)…O(8) 2.809(7); N(4)…O(1) 2.933(5); N(3)…O(14) 3.316(8).

the spectra for the crystals having higher melting temperatures can be explained by assuming that the intramolecular hydrogen bonding among the amide groups of the calixarenes is broken partially and followed by a conformational change to the stable pinched cone conformation having  $C_2$  symmetry.

We have tried to obtain data supporting the change of hydrogen bonding capability by a single-crystal X-ray diffraction. The determination of the crystal structures of the  $\beta$ - and  $\gamma$ -form of **1a** was difficult because the single crystals could not be obtained through thermal transformation. For the  $\alpha$ -form that is original crystals, the structure was not solved by the X-ray diffraction. The original crystals of **1c** that are recrystallized from dichloromethane/ether have a higher melting point. The  $^{13}\text{C}$  CP-MAS NMR and FT-IR spectra of the crystals of **1c** exhibited the same conformational behavior. Therefore, the crystal structure of **1c** was assumed to be similar to that of  $\gamma$ -form of **1a**. Fortunately, the crystal structure of **1c** was determined by the X-ray analysis and was shown in Figure 6. The calixarene **1c** was found to have a cone conformation with  $C_2$  symmetry in the calixarene skeleton. The two NH groups of the amide groups form intramolecular hydrogen bonds with the neighboring O atoms and the distance of N(1)…O(8) is 2.809(7) Å and that of N(4)…O(1) is 2.933(5) Å. One NH group forms a weak intramolecular hydrogen bond with the neighboring CO group and the distance of N(3)…O(14) is 3.316(8) Å. Furthermore, the residual NH group forms an intermolecular hydrogen bond with the CO group of the neighboring molecule each other (Figure 7) and the distance of N(2)…O\*(11) (O(11)…N\*(2)) is 2.849(7) Å. This result shows that for the crystals of **1c** having higher melting points, the intramolecular hydrogen bonding among the amide groups is broken partially.

In conclusion, the polymorphic transformation of the calixarene derivatives is controlled by the thermal history of solids accompanied by a conformational change to the stable pinched cone conformation having  $C_2$  symmetry



**Figure 7.** Portion of the X-ray structure of consecutive molecules of **1c**. Hydrogen atoms are omitted for clarity. Intermolecular hydrogen bonding (Å): N(2)…O\*(11) (O(11)…N\*(2)) 2.849(7).

in the calixarene skeleton and also by the change of hydrogen bonding in the hydrophilic pseudocavity.

## Experimental Section

**Materials.** The calixarenes **1a–d** were prepared by the method previously reported.<sup>3</sup> The calixarenes **1a–c** were recrystallized from dichloromethane/ether to afford needles. Crystals of **1d** were prepared by recrystallization from acetonitrile. These crystals were dried under reduced pressure at room temperature for 24 h.

**Calorimetric Measurements.** Calorimetric measurements were carried out with a differential scanning calorimeter. Nitrogen flux was used as a purge gas for furnace. Calibrations were made using indium at the same scan rates used in the same experiments. The measurements were run on sample weighing between 4.5 mg and 5.5 mg in aluminum pans. An empty aluminum pan was used as a reference.

**NMR Spectroscopy.**  $^{13}\text{C}$  NMR spectrum of **1a** in  $\text{CDCl}_3$  solution was recorded on a 100 MHz spectrometer using TMS as an internal standard. Cross polarization magic angle spinning (CP-MAS)  $^{13}\text{C}$  spectra of the polymorphs were obtained by the following conditions: rotor of outer diameter: 7 mm; recycle time: 10 s; 90° pulse: 4.5  $\mu\text{s}$ ; contact time: 5 ms. The NMR pulse sequence TOSS (total suppression sidebands)<sup>12</sup> was used to suppress spinning sidebands in MAS spectra. All  $^{13}\text{C}$  chemical shifts were reported using hexamethylbenzene as an external standard.

**Powder X-ray Diffraction.** X-ray diffraction patterns were obtained on samples placed on glass plate using a X-ray diffractometer at room temperature.  $\text{Cu K}\alpha$  radiation was obtained through a flat graphite crystal monochromator. The samples scanned in the range of 2–80° of  $2\theta$  at 4°  $\text{min}^{-1}$ .

**Single-Crystal X-ray Diffraction for 1c.** The single-crystal X-ray data was collected on a Rigaku R-AXIS RAPID Imaging plate diffractometer. All calculations were performed with the crystallographic software package teXsan (Molecular Structure Corp., 1985 and 1999). Crystal data for **1c**:  $\text{C}_{88}\text{H}_{100}\text{O}_{16}\text{N}_4$ ,  $M = 1469.78$ , triclinic, space group  $P\bar{1}$ ,  $\text{Cu K}\alpha$  radiation;  $T = 23^\circ\text{C}$ ,  $a = 18.8441(5)$  Å,  $b = 21.1457(5)$  Å,  $c = 11.6242(3)$  Å,  $\alpha = 100.932(1)^\circ$ ,  $\beta = 96.9570(7)^\circ$ ,  $\gamma = 67.154(1)^\circ$ ,  $U = 4185.3$  (2) Å $^3$ ,  $Z = 2$ ,  $D_c = 1.166$  g cm $^{-3}$ ,  $\mu$  ( $\text{Cu K}\alpha$ ) = 6.48 cm $^{-1}$ , 24338 reflections were collected and merged to give 14353 unique data ( $R_{\text{int}} = 0.027$ ). The structure was solved by direct method (SHELXS-97)<sup>13</sup> and expanded using Fourier techniques

(DIRDIF94).<sup>14</sup> Non-hydrogen atoms were refined anisotropically. Hydrogen atoms except NH groups were included at calculated positions. Full-matrix least-squares refinement was

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based on 7263 observed reflections ( $I > 2.00\sigma(I)$ ) and 974 variable parameters.  $R = 0.074$ ,  $R_w = 0.109$ , GOF = 1.34.

**Supporting Information Available:**  $^3\text{C}$  CP-MAS NMR spectra and  $^{13}\text{C}$  NMR spectrum of **1c**, FT-IR spectra of **1a** and **1c**, and X-ray crystallographic details for **1c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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