ORGANIC LETTERS
2011
Vol. 13, No. 13
3292–3295

Unique Inclusion Properties of Crystalline Powder *p-tert*-Butylthiacalix[4]arene toward Alcohols and Carboxylic Acids

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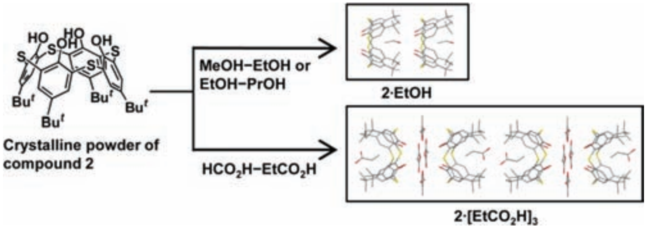
Received February 28, 2011

ABSTRACT



Powdery crystals of *p-tert*-butylthiacalix[4]arene (2) selectively include EtOH from 1:1 mixtures of MeOH–EtOH and EtOH–PrOH, and $EtCO_2H$ from HCO_2H–$EtCO_2H$. On the other hand, no acid is included from HCO_2H–$MeCO_2H$, even though $MeCO_2H$ is included from the neat acid. The origins of these phenomena are discussed based on X-ray analysis of inclusion crystals prepared separately by crystallization.

The development of host molecules that can strictly discriminate guest molecules of similar sizes and geometry is challenging and applicable to the design of precise separation materials, highly sensitive sensors, and so on. Calixarenes (e.g., **1**)[1] and thiacalixarenes (e.g., **2**)[2] have been used as artificial hosts for molecular recognition. Since Andreetti et al.'s report on the X-ray structure of a 1:1 complex between *p-tert*-butylcalix[4]arene (**1**) and toluene, in which compound **1** adopts cone conformation and the methyl group of toluene is included into the cavity,[3] a considerable number of studies have focused on inclusion phenomena of calixarenes. Many host–guest complexes have been prepared by crystallizing calixarenes from neat guests or solutions including guest molecules.[4] Complexation behavior of calixarenes has been investigated in solution[5] as well as in the gas phase.[6] Molecular capsules have been constructed by connecting more than two calixarenes to accommodate the intended guest molecules.[7] Certain molecules have been reported to get into the crystals of calixarenes,[8] as is sometimes the case

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(1) Reviews: (a) Gutsche, C. D. In *Calixarenes Revisited*, *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998. (b) *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000. (c) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J. M., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.

(2) Reviews: (a) Lhoták, P. *Eur. J. Org. Chem.* **2004**, 1675. (b) Parola, S.; Desroches, C. *Collect. Czech. Chem. Commun.* **2004**, *69*, 966. (c) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291.

(3) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.

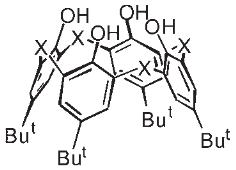
(4) For example, see: (a) Reference 1c, pp 457–475. (b) Ohba, Y.; Moriya, K.; Sone, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 576. (c) Iki, N.; Kabuto, C.; Fukushima, T.; Kumagai, H.; Takeya, H.; Miyanari, S.; Miyashi, T.; Miyano, S. *Tetrahedron* **2000**, *56*, 1437. (d) Ripmeester, J. A.; Enright, G. D.; Ratcliffe, C. I.; Udachin, K. A.; Moudrakovski, I. L. *Chem. Commun.* **2006**, 4986.

(5) For example, see: (a) Reference 1b, pp 37–61. (b) Yoshimura, K.; Fukazawa, Y. *Tetrahedron Lett.* **1996**, *37*, 1435. (c) Arena, G.; Contino, A.; Gulino, F. G.; Magri, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **2000**, *41*, 9327. (d) Kon, N.; Iki, N.; Miyano, S. *Org. Biomol. Chem.* **2003**, *1*, 751. (e) Arena, G.; Contino, A.; Longo, E.; Spoto, G.; Arduini, A.; Pochini, A.; Secchi, A.; Massera, C.; Ugozzoli, F. *New. J. Chem.* **2004**, *28*, 56.

(6) (a) Reference 1b, pp 37–61. (b) Wong, P. S. H.; Yu, X.-J.; Dearden, D. V. *Inorg. Chim. Acta* **1996**, *246*, 259. (c) Vincenti, M.; Irico, A. *Int. J. Mass Spectrom.* **2002**, *214*, 23.

10.1021/ol200506p

with other kinds of host molecules.[9] For example, Atwood et al. reported that a crystalline sample of compound **1** absorbed small molecules from the gas or liquid phase, accompanied by phase transition, turning into inclusion crystals with a different crystal lattice compared with the original.[8b,e,i] To the best of our knowledge, however, there is no report in which a calixarene selectively captured molecules into inclusion crystals by discriminating the size and geometry of small molecules under competitive conditions.[10] In this context, the research groups of Shinkai[11] and Atwood[12] independently reported that C_{60} could be isolated from carbon soot containing C_{60} and C_{70} by fractional precipitation with *p-tert*-butylcalix[8]arene, which provided facile access to C_{60} with high purity on a preparative scale. One might suspect that calixarenes are so conformationally mobile that their cavities can accommodate guest molecules of different sizes and geometries and, therefore, Shinkai and Atwood's method is not applicable to the precise discrimination of small molecules. However, we have found that a crystalline powder of thiacalixarene **2** selectively absorbs EtOH from 1:1 mixtures of MeOH–EtOH and EtOH–PrOH, even though compound **2** forms inclusion crystals of similar three-dimensional structures upon crystallization from the three alcohols. Herein, we report the inclusion behavior of powdery compound **2** toward alcohols compared with that toward carboxylic acids.



1: X = CH_2
2: X = S

The inclusion capability of compound **2** toward alcohols (MeOH, EtOH, and PrOH) was investigated as follows. A crystalline powder of compound **2** was placed in a screw-cap vial equipped with a stir bar and suspended by addition of an alcohol or an equimolar mixture of two kinds of alcohols. The suspension was stirred at a fixed temperature until equilibrium was reached (1–8 d), and the resulting powder was collected by filtration, dried in vacuo (0.5–1.0 kPa) at room temperature for 2 h, and analyzed by ^1H NMR spectroscopy. Table 1 lists the average number of guest molecules included into a host molecule ($\bar{n}$). A crystalline powder of compound **2** absorbed only EtOH when soaked in neat alcohols (entries 1–3), in contrast to the 1:1 inclusion crystals formed with all alcohols by crystallization (vide infra). Furthermore, the crystalline powder selectively absorbed EtOH from MeOH–EtOH and EtOH–PrOH at room temperature, although the selectivity was not perfect (entries 5 and 6). This may indicate that some EtOH molecules in an inclusion crystal can be replaced with MeOH or PrOH molecules; this is supported by the fact that the latter two alcohols cannot get into a crystal by themselves (entries 1 and 3). Lowering the temperature prolonged the operation time to reach a good inclusion ratio $\bar{n}$ but improved the selectivity for EtOH (entries 7 and 8); note that complete EtOH selectivity was achieved against MeOH with a good $\bar{n}$ value at −40 °C for 8 h (entry 8).

Table 1. Inclusion Ratios of Guest Molecules in Inclusion Crystals of Compound **2**[a]

entry	guest A–guest B	temp (°C)	time (d)	$\bar{n}_A$	$\bar{n}_B$
1	MeOH	rt	1	–[b]	
2	EtOH	rt	1	0.92	
3	PrOH	rt	1	–[b]	
4	MeOH–PrOH	rt	1	–[b]	–[b]
5	EtOH–PrOH	rt	1	0.90	0.11
6	MeOH–EtOH	rt	1	0.07	0.78
7	MeOH–EtOH	−20	2	0.02	0.70
8	MeOH–EtOH	−40	8	–[b]	0.71
9	HCO_2H	rt	1	–[b]	
10	$MeCO_2H$	rt	1	0.91	
11	$EtCO_2H$	rt	1	2.59	
12	$MeCO_2H$–$EtCO_2H$	0	1	0.53	1.96
13	HCO_2H–$EtCO_2H$	0	1	–[b]	2.45
14	HCO_2H–$MeCO_2H$	0	1	–[b]	–[b]

[a] Average value of measurements repeated more than three times. [b] Inclusion was not detected.

The inclusion experiments of carboxylic acids (HCO_2H, $MeCO_2H$, and $EtCO_2H$) were carried out using the same procedure, except compound **2** was suspended in carboxylic acid(s) in a glovebox to avoid water contamination,[13] and the filtered crystals were washed with water before drying

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(7) For example, see: (a) Reference 1b, pp 203–240. (b) Reference 1c, pp 130–180. (c) Rebek, J. *Chem. Commun.* **2000**, 637. (d) Vysotsky, M. O.; Pop, A.; Broda, F.; Thondorf, I.; Böhmer, V. *Chem.—Eur. J.* **2001**, *7*, 4403. (e) Corbellini, F.; Knegtel, R. M. A.; Grootenhuis, P. D. J.; C.-Calama, M.; Reijhoudt, D. N. *Chem.—Eur. J.* **2005**, *11*, 298. (f) Baldini, L.; Sansone, F.; Faimani, G.; Massera, C.; Casnati, A.; Ungaro, R. *Eur. J. Org. Chem.* **2008**, 869.

(8) (a) Gorbatchuk, V. V.; Tsifarkin, A. G.; Antipin, I. S.; Solomonov, B. N.; Konovalov, A. I.; Seidel, J.; Baitalov, F. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2287. (b) Atwood, J. L.; Barbour, L. J.; Jerga, A.; Schottel, B. L. *Science* **2002**, *298*, 1000. (c) Gorbatchuk, V. V.; Tsifarkin, A. G.; Antipin, I. S.; Solomonov, B. N.; Konovalov, A. I.; Lhoták, P.; Stibor, I. *J. Phys. Chem. B* **2002**, *106*, 5845. (d) Endo, K.; Kondo, Y.; Aoyama, Y.; Hamada, F. *Tetrahedron Lett.* **2003**, *44*, 1355. (e) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2948. (f) Kondo, Y.; Endo, K.; Hamada, F. *Chem. Commun.* **2005**, 711. (g) Ziganshin, M. A.; Yakimov, A. V.; Safina, G. D.; Solovieva, S. E.; Antipin, I. S.; Gorbatchuk, V. V. *Org. Biomol. Chem.* **2007**, *5*, 1472. (h) Ishii, Y.; Nakayama, N.; Konishi, K. *Chem. Lett.* **2007**, *36*, 246. (i) Thallapally, P. K.; Mcgrail., B. P.; Dalgarno, S. J.; Schaef, H. T.; Tian, J.; Atwood, J. L. *Nat. Mater.* **2008**, *7*, 146. (j) Yamada, M.; Kondo, Y.; Iki, N.; Kabuto, C.; Hamada, F. *Tetrahedron Lett.* **2008**, *49*, 3906.

(9) For example, see: (a) Toda, F.; Mori, K.; Akai, H. *J. Chem. Soc., Chem. Commun.* **1990**, 1591. (b) Dewal, M. B.; Lufaso, M. W.; Hughes, A. D.; Samuel, S. A.; Pellechia, P.; Shimizu, L. S. *Chem . Mater.* **2006**, *18*, 4855. (c) Kobayashi, Y.; Kodama, S. K.; Saigo, K. *Tetrahedron: Asymmetry* **2008**, *19*, 295.

(10) For the preferential crystallization of inclusion crystals of L-leucine with *p*-sulfonatocalix[6]arene, see: Atwood, J. L.; Dalgarno, S. J.; Hardie, M. J.; Raston, C. L. *Chem. Commun.* **2005**, 337.

(11) Suzuki, T.; Nakashima, K.; Shinkai, S. *Chem. Lett.* **1994**, 699.

(12) Atwood, J. L.; Koutsantonis, G. A.; Raston, C. L. *Nature* **1994**, *368*, 229.

(13) Inclusion of $MeCO_2H$ was inhibited also with a small amount of water.

to remove acid molecules on the crystal surface. A crystalline powder of compound **2** absorbed $MeCO_2H$ and $EtCO_2H$ from the neat acids (entries 9–11); the $\overline{n}$ values suggest the formation of 1:1 (compound **2**/$MeCO_2H$) and 1:3 (compound **2**/$EtCO_2H$) complexes. From a 1:1 mixture of $MeCO_2H$ and $EtCO_2H$, compound **2** included both acids with $\overline{n}$ values of 0.53 and 1.96, respectively, at 0 °C (entry 12). However, the $\overline{n}$ values varied with each run under the same conditions when the temperature was raised to room temperature (15–25 °C). This was attributed to a drastic temperature-dependent change in the complexation capability of compound **2** toward $MeCO_2H-EtCO_2H$ mixtures of ~1:1 composition. Figure 1 shows the dependence of the inclusion ratios of $MeCO_2H$ and $EtCO_2H$ on the mixing ratio of the two acids, observed at different temperatures. In experiments carried out at 17 ± 2 °C, the crystals collected from acid mixtures with mole fractions of $EtCO_2H$ (x) greater than 0.40 included both acids. The inclusion ratio of each acid varied depending on the x value, but the sum of the inclusion ratios of the two acids fell within a range of 2.56 ± 0.10, which is approximately equal to the inclusion ratio of $EtCO_2H$ (2.59) observed in the single guest experiment (entry 11). The powder X-ray diffraction (PXRD) pattern of the crystals taken from a mixture with $x = 0.5$ agreed with that of the crystals taken from neat $EtCO_2H$ (Figure S1). In addition, these PXRD patterns were nicely simulated from the single-crystal X-ray diffraction (XRD) data for a crystal, $\mathbf{2}\cdot[EtCO_2H]_3$, prepared separately by the crystallization of compound **2** from $EtCO_2H$ (vide infra). These observations indicate that the acid-absorbed powder formed in this x region has the same crystal lattice as that of $\mathbf{2}\cdot[EtCO_2H]_3$. The powder taken from a mixture with $x = 0.4$ exhibited an $\overline{n}$ value for $EtCO_2H$ (1.61–1.64) more than two times larger than that for $MeCO_2H$ (0.71). This strongly suggests that only one of the three $EtCO_2H$ molecules in $\mathbf{2}\cdot[EtCO_2H]_3$ can be replaced with $MeCO_2H$. When $x \leq 0.03$, a crystalline powder of compound **2** absorbed $MeCO_2H$ to form a 1:1 inclusion crystal. PXRD analysis revealed that it has the same crystal lattice as that of a single crystal, $\mathbf{2}\cdot MeCO_2H$, prepared by the crystallization of compound **2** from $CHCl_3-MeCO_2H$ (vide infra; Figure S1). Interestingly, no inclusion was observed between the two regions ($0.03 < x < 0.40$). A plausible explanation for this is that a small amount of $EtCO_2H$ ($x \approx 0.05$) disturbs the formation of $\mathbf{2}\cdot MeCO_2H$, whereas the low mole fraction of $EtCO_2H$ ($x < 0.40$) does not allow compound **2** to preferentially include $EtCO_2H$ rather than $MeCO_2H$ in a ratio greater than 2:1, which seems necessary to construct crystals with a $\mathbf{2}\cdot[EtCO_2H]_3$-type crystal lattice (vide supra). Decreasing the temperature to 0 °C shifted the lower limit of x for the construction of $\mathbf{2}\cdot[EtCO_2H]_3$-type crystals to 0.3, which ensures the reproducibility of $\overline{n}$ values in the inclusion experiments carried out at this temperature using a 1:1 mixture of $MeCO_2H$ and $EtCO_2H$ (vide supra). As expected from the single guest experiments (entries 9 and 11), $EtCO_2H$ was included with perfect selectivity from a 1:1 mixture of HCO_2H and $EtCO_2H$ at 0 °C (entry 13). On the other hand, $MeCO_2H$ was not included from a 1:1 mixture of HCO_2H and $MeCO_2H$ (entry 14). Again, the incorporation of another acid seemed to disturb the formation of $\mathbf{2}\cdot MeCO_2H$, as observed in the $MeCO_2H-EtCO_2H$ system (Figure 1).[13]

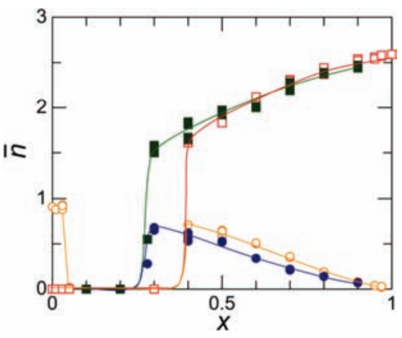

Figure 1. Dependence of the inclusion ratios of $MeCO_2H$ [● (0 °C) and ○ (17 ± 2 °C)] and $EtCO_2H$ [■ (0 °C) and □ (17 ± 2 °C)] on the mole fraction of $EtCO_2H$ in $MeCO_2H-EtCO_2H$ mixture.

To gain insight into the origin of the selective inclusion of EtOH with compound **2**, inclusion crystals of the three alcohols were prepared, and their structures were compared. The crystallization of compound **2** from each alcohol–toluene mixture gave single crystals formulated as **2**·alcohol. The XRD analysis of these crystals, carried out at a low temperature (223 K), revealed that they have a similar crystal packing;[14] they belong to the tetragonal system with a *P*4/*nmm* space group. The XRD data of **2**·EtOH nicely simulated the PXRD pattern of the EtOH-absorbed powder obtained in the inclusion experiment (Figure S1), indicating that both have the same crystal lattice. In **2**·alcohol, compound **2** adopts a cone conformation to form a cavity, in which an alcohol molecule is included, directing the alkyl group inside the cavity (Figure 2a–c). The EtOH and PrOH molecules are disordered with C_4 symmetry. The distance between the terminal carbon atom of the alcohol molecule and the centroid of each aromatic ring of compound **2** is 3.918 Å (**2**·MeOH), 3.694 Å (**2**·EtOH), and 3.725 Å (**2**·PrOH). This indicates the presence of a weak CH–π interaction between the host and guest,[15] which is most effective for **2**·EtOH. On the other hand, intermolecular hydrogen bonds are observed between the hydroxy group of an alcohol molecule and the four phenolic hydroxy groups of an adjacent host molecule in **2**·MeOH and **2**·EtOH; the O–O distances between the alcoholic and phenolic hydroxy groups are 3.548 and 3.018 Å, respectively, indicating that the hydrogen bonds in **2**·EtOH are stronger than those in **2**·MeOH (Figure 2a and 2b). On the other hand, for **2**·PrOH, only two hydroxy

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[14] Hosseini *et al.* previously reported the X-ray structure of 2·MeOH measured at 300 K. See: Akdas, H.; Bringel, L.; Graf, E.; Hosseini, M. W.; Mislin, G.; Pansanel, J.; Cian, A. D.; Fisher, J. *Tetrahedron Lett*. **1998**, *39*, 2311.

[15] (a) Reference 1c, pp 457–475. (b) Nishio, M. *CrystEngComm* **2004**, *6*, 130.

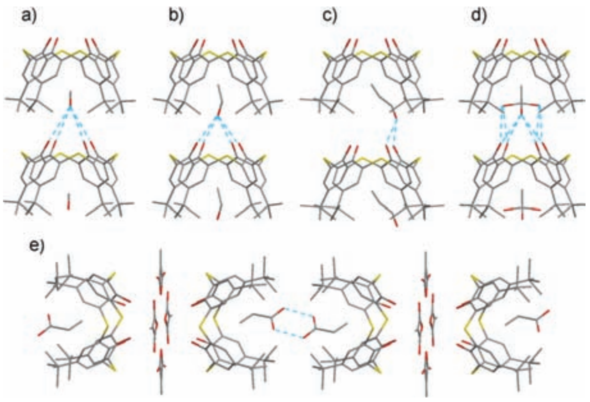

Figure 2. X-ray structures of **2**·MeOH (a), **2**·EtOH (b), **2**·PrOH (c), **2**·$MeCO_2H$ (d), and **2**·$[EtCO_2H]_3$ (e). Hydrogen atoms and some disordered atoms are omitted for clarity. Blue dotted line represents intermolecular hydrogen bond.

groups of a host molecule simultaneously participate in intermolecular hydrogen bonds (2.664 Å; Figure 2c). Through the CH−π interaction and hydrogen bonds, an alcohol molecule joins two neighboring host molecules in a head-to-tail manner to construct an infinite columnar structure along the *c*-axis. The intervals between two host molecules, which were calculated from the distance between the mean planes defined by the four sulfur atoms of compound **2**, are 8.236 Å (**2**·MeOH), 8.287 Å (**2**·EtOH), and 8.547 Å (**2**·PrOH). Although the intermolecular distance is longest in **2**·PrOH, it is too short for a PrOH molecule to form hydrogen bonds with four hydroxy groups of an adjacent host molecule. These observations suggest that compound **2** can accommodate EtOH in its cavity most stably among the three alcohols. In fact, EtOH required a higher temperature range (140−190 °C) for release from **2**·alcohol than MeOH (30−160 °C) and PrOH (120−140 °C), as evidenced by thermogravimetric analysis (TGA; Figure S2). Therefore, it was concluded that the subtle difference in crystal structure caused the high inclusion selectivity for EtOH.

The inclusion crystal **2**·$MeCO_2H$ has a similar packing structure to **2**·alcohol (Figure 2d); a CH−π interaction is observed between the aromatic rings of a host molecule and the methyl group of $MeCO_2H$ in that molecule, while intermolecular hydrogen bonds are formed between each oxygen atom of the carboxy group of a $MeCO_2H$ molecule and two adjacent hydroxy groups of a neighboring host molecule. On the other hand, the crystal structure of **2**·$[EtCO_2H]_3$ is quite different from the others (Figure 2e); it belongs to the tetragonal system with an *I*4/*mmm* space group. Two host molecules gather in a head-to-head manner to form a capsule, in which a dimer of $EtCO_2H$ is included. The dimer is disordered with C_4 symmetry. The distance between the terminal methyl carbon of $EtCO_2H$ and the centroids of the benzene rings of compound **2** is 3.716 Å, indicating the presence of a CH−π interaction. Four $EtCO_2H$ molecules are linked together through hydrogen bonds, and the resulting aggregate lies between two capsules. There are also intermolecular hydrogen bonds between the aggregate of $EtCO_2H$ and the two capsules. However, it was difficult to analyze the structure of the aggregate in detail, as well as the hydrogen bonds between the aggregate and the capsules, due to the severe disorder of the $EtCO_2H$ molecules. As mentioned earlier, the $EtCO_2H$ molecules in **2**·$[EtCO_2H]_3$ could be replaced with $MeCO_2H$ but not with HCO_2H. It seems that the crystal lattice cannot stably accommodate HCO_2H because the acid has no alkyl group, which is necessary for the CH−π interaction with benzene rings of the host molecule and for filling space in the crystal lattice. On the other hand, the crystal structure of **2**·$MeCO_2H$ may have made another acid disturb the inclusion of $MeCO_2H$ (vide supra).[13] It is well-known that carboxylic acid molecules strongly associate in solution. Therefore, during the course of the inclusion, the dissociation energy must be supplied by the formation of the inclusion complex, which is stabilized by the CH−π interaction and hydrogen bonds. The addition of another acid changes this energy balance by interfering with the association between $MeCO_2H$ molecules and/or by getting into the inclusion crystal to decrease its stability. This shows a distinct contrast to the formation of **2**·$[EtCO_2H]_3$, which contains aggregates of $EtCO_2H$ molecules.

In conclusion, we have shown that a crystalline powder of compound **2** exhibits precise molecular-recognition capabilities toward alcohols in inclusion complex formation and unique inclusion behavior toward carboxylic acids, depending on the kind of acid, as well as the mixing ratio. Further studies to improve the scope and selectivity of this inclusion method are underway.

Acknowledgment. The authors wish to thank Prof. K. Itaya and Prof. T. Yoshioka (Tohoku University) for courteous permission to use their instruments.

Supporting Information Available. TGA, PXRD, and XRD (CIF) data for complexes of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.