Mechanism of Selective and Unselective Enclathration by a Host Compound Possessing Open, Flexible Host Frameworks

Kazunori Nakano,[a] Eiko Mochizuki,[b] Nobuyoshi Yasui,[b] Kyoichi Morioka,[b] Yukinori Yamauchi,[b] Nobuko Kanehisa,[b] Yasushi Kai,[b] Nungruethai Yoswathananont,[c] Norimitsu Tohnai,[c] Kazuki Sada,[c][†] and Mikiji Miyata*[c]

Keywords: Cholic acid / Inclusion compounds / Molecular recognition / Packing coefficients / Selectivity

Molecular recognition of *o*-, *m*-, and *p*-xylenes (**oX**, **mX**, and **pX**) through enclathration of cholic acid (**CA**) is described. All of the xylenes give lattice inclusion crystals with **CA**, and crystallographic studies reveal that they are included in different open host frameworks. In particular, **oX** has two polymorphs, depending on the recrystallization temperatures. Competitive recrystallization from mixtures of xylenes resulted in selective enclathrations and the formation of racemic mixed crystals. In the presence of an equimolar amount of **oX**, **CA** selectively includes **mX** or **pX** in the host frameworks, which are identical to those obtained from the pure **mX** or **pX**, respectively. The low affinity of **oX** is explained in terms of a lower stability of **CA·oX** than of the other two complexes, as judged from the low PC_{cavity}, the volume ratio of the guest compound to the host cavity. Meanwhile, mixtures of **mX** and **pX** yield inclusion crystals that accommodate both of the guests. These have the same open host framework as obtained from pure **mX**, and the guest components are disordered statically in the host cavity. The ratios of the xylene mixtures in the single crystals are similar to those in the original recrystallization mixtures, and also in the bulk crystals, indicating that **CA** forms mixed crystals of **mX** and **pX.** This non-selectivity is attributed to the similar stabilities of **CA·mX** and **CA·pX**, according to the moderate PC_{cavity}. The inclusion behavior of **CA** from mixtures of xylenes is quite similar to chiral recognition by diastereomer-salt methods.

Introduction

There has been growing interest in crystal engineering of nano-porous organic crystalline materials as an area of supramolecular chemistry.[1,2] Open host frameworks formed by self-assembly of host molecules often allow specific enclathration of a particular guest compound from guest mixtures. Selective guest recognition, including optical resolution of racemic neutral compounds, has been well documented,[3,4] and might be a promising separation method due to its high efficiency, saving of energy, production of less waste, and easy operation. However, screening for host−guest combinations with high specificity is still hard, due to difficulty in the prediction and control of crystal structures, and the above examples have mostly been found either by trial and error or by accident. Elucidation of molecular recognition from X-ray crystallographic studies might provide access to the design of selective enclathration, and might also offer insights into the natures of mixed crystals.

Recrystallization from mixtures of two guest compounds usually yields two types of inclusion phenomena: selective and nonselective. In the former case, the host−guest crystals formed by recrystallization selectively include one of the two guests, while the other acts only as a solvent. The crystal structure is identical to that of the authentic sample prepared from the pure included guest (I in Figure 1, part a) and the molecular recognition is explained by difference in stability between the two forms. In the latter case, both guest compounds are included in the host cavities, and this is sub-categorized by the following two mechanisms. The first is the formation of mixtures of the host−guest crystals that include one of the guest compounds selectively (II in Figure 1, part a), while the other is a homogeneous inclusion crystal that randomly includes both guest com-

[a] Nagoya Municipal Industrial Research Institute,
3-4-41 Rokuban, Atsuta-ku, Nagoya, Aichi 456-0058, Japan
Fax: (internat.) + 81-52/654-6788
E-mail: nakano.kazunori@nmiri.city.nagoya.jp
[b] Department of Materials Chemistry, Osaka University,
2-1 Yamadaoka, Suita, Osaka 565-0871, Japan
[c] Department of Material and Life Science, Graduate School of Engineering, Osaka University,
2-1 Yamadaoka, Suita, Osaka 565-0871, Japan
Fax: (internat.) + 81-6/6879-7404
E-mail: miyata@molrec.mls.eng.osaka-u.ac.jp
[†] Current Address: Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University,
6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

  DOI: 10.1002/ejoc.200200711

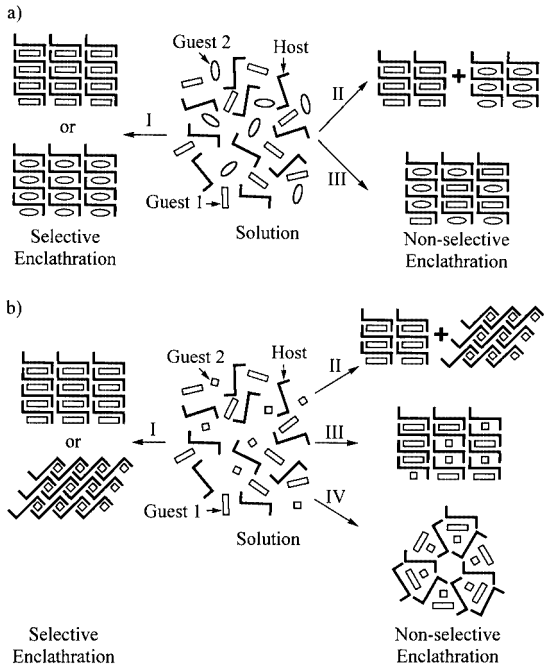


Figure 1. Mechanisms of selective and unselective enclathration under competitive conditions; (a) the guest compounds are included in the same host frameworks, (b) the guest compounds are included in different host frameworks

pounds in the host cavities (III in Figure 1, part a). These, however, are barely distinguishable because of the similarities of the host frameworks with slightly different guest compounds, so less attention has been paid to the elucidation of less efficient molecular recognition through the use of host−guest crystals.[5]

More recently, however, extensive structural studies of organic inclusion compounds have indicated that the host frameworks are modified by the functional groups and the steric dimensions of the included components.[6] In other words, the host compounds offer many types of open host frameworks, and these vary in response to the guest components through "induced-fit" mechanisms. In such cases, inclusion phenomena of mixed guest compounds are classified into the following four possible types, when the guests are included in the different host frameworks:

(1) One guest compound is selectively included, and the crystal structure is the same as that of an authentic crystal from the pure guest component. The other component is not included at all and acts only as a solvent (I in Figure 1, part b).

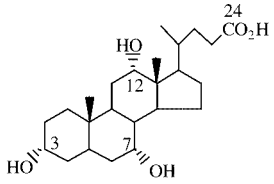
(2) Both guest compounds are included in the host cavities, and the crystals are mixtures of the individual inclusion crystals (II in Figure 1, part b). Each guest compound is included in each host framework, identically to those obtained from pure guest compound.

(3) The host compound includes both guest compounds without any selectivity. The host framework is the same as the authentic crystal formed from one of the two guests forms by recrystallization, and the guest compounds are statically disordered in the host cavities (III in Figure 1, part b).

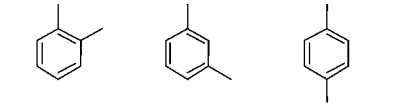
(4) Both of the guest compounds are included, and the host framework is completely different from those of the authentic inclusion crystals with both guest compounds (IV in Figure 1, part b).

The last three mechanisms provide unselective enclathration of guest compounds. X-ray crystallographic studies offer possible explanations of the mechanisms of either high or low selectivity and give the atomic coordinates of the host frameworks for comparisons of stabilities between them. To the best of our knowledge, however, there have been few reports about the mechanisms of selective and nonselective enclathration in relation to the isomerization of the flexible host frameworks.

CA, a commercially available steroidal bile acid, is known to form inclusion compounds with a variety of organic substances.[6i,7−14] X-ray crystallographic studies have revealed that **CA** can form at least nine open host frameworks, depending on the components included. More recently, we have found that the volumes of the guest components played a crucial role for isomerizations of the host frameworks and the host−guest ratios in **CA** inclusion crystals with monosubstituted benzenes.[6i] Furthermore, we revealed that selective enclathration of monosubstituted benzene compounds was dependent on the types of **CA** inclusion crystals.[7e] In particular, the **α**-*gauche*-type was preferred to other types because the phenyl ring of the guest molecule is suitably fitted to the square groove of the **α**-*gauche* host cavity. Since all the open host frameworks in the previous work have host cavity widths just suitable for a benzene ring, it is hard to estimate the effect of the guest shape for the host framework isomerization. Therefore, in order to clarify the role of the shapes of the guest components, we started to investigate the crystal structures of **CA** with disubstituted benzenes, in particular xylenes. In this report we describe the crystal structures of the inclusion crystals of **CA** with xylenes (Scheme 1). Crystallographic studies reveal that all xylenes are included in the different host frameworks. Further structural investigations from mixtures of xylenes give insights into the selective and unselective enclathration in the crystalline state. Moreover, we reveal that the packing coefficients of host cavities (PC_{cavity}),[6i,15] the volume ratios of host cavities to guest



Cholic Acid (**CA**)



o-Xylene (**oX**) *m*-Xylene (**mX**) *p*-Xylene (**pX**)

Scheme 1. Cholic acid (**CA**) and xylenes (**oX**, **mX**, and **pX**)

components, are useful for prediction of stability in solid state host−guest compounds.

Results and Discussion

Inclusion Complexes of CA with Pure Xylenes

CA formed inclusion crystals with **mX** and **pX** at host/guest ratios of 1:1, while **oX** gave two polymorphs with 2:1 host/guest stoichiometries. The crystal structures were characterized by X-ray structural analysis. The crystal data and packing diagrams are shown in Table 1 and Figure 2, respectively. The common structural feature is a bilayer structure, consisting of the alternative stacking of lipophilic layers and hydrophilic layers. In the hydrophilic layer, three hydroxy groups and one carboxylic acid group produce a two-dimensional extended hydrogen bond network. In the lipophilic layer, two methyl groups on the steroidal β-face are interdigitated and a host cavity runs between the layers, because of the anchored molecular structure of **CA**. Interestingly, the stacking mode of **CA·oX** (Form I)[7b] is different from those of the others. The crystal of Form I has an antiparallel stacking in the lipophilic layer and a parallel stacking in the hydrophilic layer, termed a DCA-type, because this arrangement is identical to those of inclusion crystals of deoxycholic acid.[7a,8] The other host frameworks have antiparallel stacking both in the lipophilic and in the hydrophilic layers, the characteristic host frameworks of **CA** inclusion crystals. They are finely classified into subgroups through the conformations of the side chain (*gauche* or *trans*) and the manner of interdigitation in the lipophilic layer (α or β).[7a] **CA·oX** (Form II), **CA·mX**, and **CA·pX** give α-*trans*, β-*trans*, and α-*gauche*-type host frameworks, respectively.

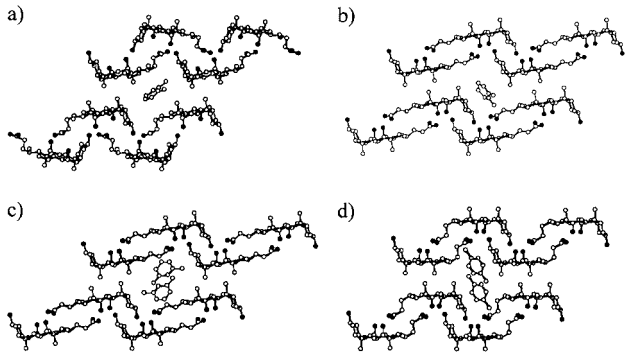


Figure 2. Molecular packing diagrams of **CA** with (a) **oX** (Form I), (b) **oX** (Form II), (c) **mX**, and (d) **pX**; the figures are viewed down along the crystallographic *b*-axis; in the case of **CA·oX** (Form II), one of the two sites of the disordered guest molecules is omitted for clarity; the carbon and oxygen atoms are represented by open and filled circles, respectively; the hydrogen atoms are omitted for clarity

Hydrogen bond networks are depicted in Figure 3. The DCA-type has linear hydrogen bond networks involving two hydroxy groups at OH (C3) and OH (C12) and the carboxylic acid along the *c*-axis. This linear hydrogen bond connects one host molecule with four adjacent host molecules to yield a two-dimensional sheet structure. The hydroxy group at the 7-position weakly connects to the hydrogen bond network. The other host frameworks yield a cyclic hydrogen-bonding network involving the sequence of OH (C3), OH (C7), OH (C12), and OH (C24). This cyclic hydrogen bonding connects one host molecule with the

Table 1. Crystallographic data for **CA** with xylenes

Compound	**CA·oX** (Form I)	**CA·oX** (Form II)	**CA·mX**	**CA·pX**
Host/guest ratio	2:1	2:1	1:1	1:1
Empirical formula	$C_{56}H_{90}O_{10}$	$C_{56}H_{90}O_{10}$	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$
Molecular mass	923.32	923.32	514.74	514.74
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
a [Å]	7.515(10)	12.331(3)	12.076(2)	13.584(2)
b [Å]	25.612(6)	7.9166(9)	8.165(1)	8.302(1)
c [Å]	13.827(9)	14.325(2)	15.973(5)	14.239(5)
β [deg]	90.99(8)	105.01(2)	109.25(2)	114.46(3)
V [Å^3]	2661(2)	1350.7(4)	1486.9(6)	1461.6(6)
Z	2	2	2	2
D_c [g/cm^3]	1.152	1.135	1.150	1.170
Number of unique reflections	5816	2762	2486	2568
Number of observed reflections	3796	2761	2485	2566
R_1,R_w	0.082/0.086[a]	0.101/0.259[a]	0.090/0.243[a]	0.084/0.222[a]
GOF	4.53	2.01	1.21	1.20
$2\theta_{max}$ [deg]	55	60.1	59.8	59.9
R/P	4.94	8.57	7.37	17.22
Temperature [°C]	25	−170	25	25
Host framework	DCA	α-*trans*	β-*trans*	α-*gauche*
Reference	[7b]	this work	this work	this work

[a] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$ (for all data).

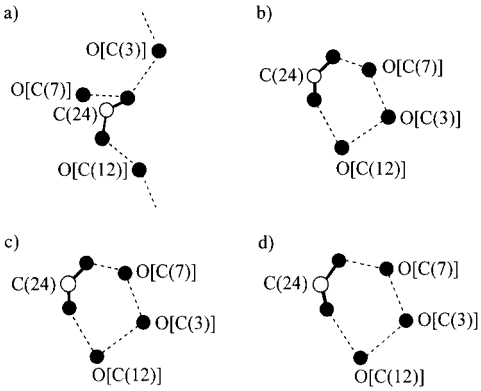


Figure 3. Hydrogen bond networks of **CA** with (a) **oX** (Form I), (b) **oX** (Form II), (c) **mX**, and (d) **pX**; the carbon and oxygen atoms are represented by open and filled circles, respectively

twelve surrounding host molecules. All hydrogen bond donors and acceptors take part in the network to yield the robust structural motif.

Shape-Dependent Isomerization of Host Framework

In order to estimate the size fit between the host cavities and the guest components, we calculated the PC_{cavity} values for the host−guest complexes in **CA** crystals. Table 2 shows volumes of the host cavities for one guest molecule and PC_{cavity}. Of the four types of host frameworks, the α-*gauche*-type has the smallest volume and the highest PC_{cavity}, indicating that the volume is the most suitable for xylenes. However, only **pX** forms the α-*gauche*-type framework, the other isomers producing other types. This indicates that the shape plays an important role for isomerization of the host frameworks. Figure 4 shows cross-sectional views sliced perpendicular to the axis of the channel. The shapes of the isomers are longer and narrower, in the order **pX** > **mX** > **oX**. The ellipse cavity of the α-*gauche*-type just fits the shape of *p*-substituted benzenes, but the cavity would be too narrow for other isomers. The wider cavity of the β-*trans* framework can incorporate the **mX** molecule, although the largest host cavity would be too narrow to accommodate **oX**. Consequently, **oX** cannot form the inclusion compounds with **CA** at a 1:1 host/guest ratio and so gives the DCA- or α-*trans*-type host framework, which has smaller host cavities at 2:1 host/guest ratios, reducing the number of the guest components in the unit cell in spite of the low packing coefficient. These results indicate that steric suitability of shape and volume between the guest molecule and the host cavity play an important role for the selection of host framework types by guest molecules.

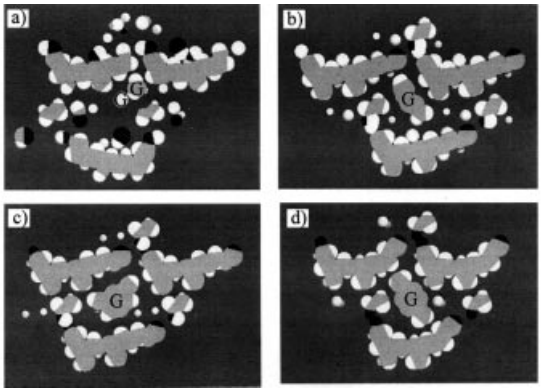


Figure 4. Cross sections of the host channels sliced perpendicular to the direction of the channel of **CA** with (a) **oX** (Form I), (b) **oX** (Form II), (c) **mX**, and (d) **pX**, respectively; the letter G stands for a guest molecule; in the case of **CA·oX** (Form II), one of the two sites of the disordered guest molecules is shown for clarity; carbon, hydrogen, and oxygen atoms are represented in gray, white, and black, respectively

Polymorphism of CA·oX Clathrates

It is noteworthy that **CA·oX** exhibits polymorphism dependent on the incubation temperature. Polymorphism of organic crystals arising through variation of recrystallization conditions has been well documented, and has attracted attention because chemical and physical properties depend on the crystal structures.[16] However, few examples of inclusion compounds with identical host−guest combinations and identical host−guest ratios have been reported.[6d][7c][7d] Recrystallization at 25 °C gave DCA-type crystals, while α-*trans*-type crystals were formed at higher temperatures (above 30 °C). In comparison with other inclusion crystals, both polymorphs have apparently low PC_{cavity} values, indicating no good steric match between the guest molecule and host cavity.[6i] The DCA-type crystal (PC_{cavity} = 48%) has a better steric match than the α-*trans*-type (PC_{cavity} = 41%), though the host framework is uncom-

Table 2. Molecular volumes, number of guests in a unit cell, cavity volumes of host cavity, PC_{cavity} and $PC_{crystal}$ for inclusion compounds of **CA** with xylenes.

Compound	Molecular volume [Å^3]	Number of guests in a unit cell	Volume of cavity[a] in a unit cell [Å^3]	Volume of cavity[a] per one guest molecule [Å^3]	PC_{cavity}[b] [%]	$PC_{crystal}$ [c] [%]
CA·oX (Form I)	118	2	497	248	48	70
CA·oX (Form II)	118	1	289	289	41	68
CA·mX	118	2	408	204	58	71
CA·pX	118	2	363	181	65	71

[a] Volumes of the cavity in unit cell calculated by use of a 0.7 Å radius probe. [b] PC_{cavity} is a packing coefficient of the guest components in the host cavity, given as the following Equation: PC_{cavity} [%] = (Molecular volume) × (Number of guests)/V_{cavity} × 100. [c] $PC_{crystal}$ is the packing coefficient of the whole crystal.

mon, due to the partial hydrogen bond at O[C(7)]···O=C(24)−O [Figure 3, (a)]. These facts suggest that the balance between steric fitness and the other factors involving hydrogen bonds cause the free energy differences between the polymorphs to be quite small.

Selective Inclusions from Mixed Xylenes

Competitive recrystallization with equimolar mixtures of xylenes results in characteristic molecular recognition. Recrystallization from 1:1 mixtures of **oX** and **mX**, or **oX** and **pX** exclusively afforded **CA·mX** or **CA·pX**, respectively. Crystallographic data for the inclusion crystals from xylene mixtures are shown in Table 3. A 1:1 mixture of **oX** and **mX** yields inclusion crystals with the β-*trans*-type host framework, and that of **oX** and **pX** the α-*gauche*-type. These frameworks are identical to those obtained from the corresponding pure **mX** and **pX** and are in good agreement with the results of the competitive recrystallization. Namely, **oX** acts as a solvent and is not included in **CA** host framework at all. As the result, these two cases yield selective enclathration by type I in Figure 1. This behavior can be understood in terms of the PC_{cavity} of the individual inclusion crystals; the values of PC_{cavity} for **mX** and **pX** crystals lie in the normal range,[6i] but those for polymorphic **oX** crystals are apparently low.

Unselective Inclusion from Mixtures of mX and pX

On the other hand, recrystallization from a 1:1 mixture of **mX** and **pX** yielded a crystal that included both guest components at a guest ratio similar to that in the bulk crys-

Table 3. Crystallographic data for **CA** with mixed xylenes

Guest mixture	**oX** + **mX** (1:1)	**oX** + **pX** (1:1)	**mX** + **pX** (3:1)	**mX** + **pX** (2:1)	**mX** + **pX** (1:1)
Guest ratios after refinement	0:1	0:1	0.65(2):0.34(2)	0.56(2):0.45(2)	0.38(3):0.62(3)
Empirical formula	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$
Molecular mass	514.74	514.74	514.74	514.74	514.74
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
a [Å]	12.096(2)	13.581(3)	12.013(3)	11.987(3)	11.964(4)
b [Å]	8.170(3)	8.304(5)	8.173(6)	8.173(3)	8.178(5)
c [Å]	15.968(2)	14.184(3)	16.025(3)	16.076(3)	16.131(3)
β [deg]	109.51(1)	114.25(2)	109.47(2)	109.68(1)	109.86(2)
V [Å^3]	1487.4(6)	1458.5(9)	1483.4(10)	1483.0(7)	1484.4(9)
Z	2	2	2	2	2
$D_{calcd.}$ [g/cm^3]	1.149	1.172	1.152	1.153	1.152
Number of unique reflections	3664	3589	3660	3832	3658
Number of observed reflections	1647	990	1777	3665	2166
R_1,R_w	0.082/0.090[a]	0.106/0.375[a]	0.083/0.238[a]	0.064/0.196[a]	0.078/0.427[a]
GOF	1.57	1.386	1.05	1.04	0.93
$2\theta_{max}$ [deg]	55.0	55.0	55.0	55.0	55
R/*P*	4.29	2.96	9.71	5.73	5.64
Temperature [°C]	23.0	23.0	23.0	23.0	23.0
Host framework	β-*trans*	α-*gauche*	β-*trans*	β-*trans*	β-*trans*

Guest mixture	**mX** + **pX** (1:2)	**mX** + **pX** (1:3)	**mX** + **pX** (1:4)	**mX** + **pX** (1:5)	**oX** + **mX** + **pX** (1:1:1)
Guest ratios after refinement	0.25(1):0.75(1)	0.20(1):0.79(2)	0.17(2):0.82(2)	0.12(1):0.87(1)	0:1:1
Empirical formula	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$	$C_{32}H_{50}O_5$
Molecular mass	514.74	514.74	514.74	514.74	514.74
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
a [Å]	11.928(10)	11.935(4)	11.932(4)	11.919(4)	11.92(1)
b [Å]	8.177(2)	8.282(5)	8.182(3)	8.186(5)	8.160(2)
c [Å]	16.127(4)	16.175(4)	16.178(3)	16.177(3)	16.082(4)
b [deg]	109.63(6)	109.95	109.97(2)	109.96(6)	109.56(6)
V [Å^3]	1481(1)	1484(1)	1484.3(7)	1483.6(9)	1474(1)
Z	2	2	2	2	2
$D_{calcd.}$ [g/cm^3]	1.154	1.152	1.152	1.152	1.152
Number of unique reflections	3623	3659	3660	3658	3755
Number of observed reflections	3614	1436	2428	2516	3754
R_1,R_w	0.051/0.141[a]	0.075/0.236[a]	0.072/0.236[a]	0.071/0.267[a]	0.047/0.139[a]
GOF	1.03	0.96	1.09	1.05	0.97
2θmax [deg]	59.9	55.0	55.0	55.0	60.1
R/*P*	8.86	3.50	5.95	6.17	9.20
Temperature [°C]	23.0	23.0	23.0	23.0	25.0
Host framework	β-*trans*	β-*trans*	β-*trans*	β-*trans*	β-*trans*

[a] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$ (for all data).

tals. A 1:1:1 mixture of all isomers also yielded a 1:1 mixture of **mX** and **pX**, without **oX**. In contrast to competitive experiments with **oX**, the inclusion crystals afforded only β-*trans*-type frameworks, the same as that of **CA** with **mX**. X-ray crystallography revealed that both **mX** and **pX** were found in the host cavity. They could be refined with partial occupancy factors, which were calculated as 0.38(3) for **mX** and 0.62(6) for **pX**. This indicates that both guests are included in the single crystals with static and location disorder in the host cavity. We then further investigated the crystal structures and the guest selectivities from the mixtures at various mixed ratios (**mX: pX** = 3:1, 2:1, 1:2, 1:3, 1:4, 1:5). These all gave the β-*trans*-type host frameworks irrespective of the isomer ratios of the recrystallization mixtures. The ratios between **mX** and **pX** in the single crystals were evaluated by refinement of the occupancy parameters of both isomers; Table 4 shows the occupancy ratios of guest compounds in the single crystals as determined by X-ray crystallography. These values are close to those of the recrystallization solvents, indicating that the single crystals include both of them and that the ratios are similar to those of starting mixed media.

Table 4. Occupancies of **mX** and **pX** in single crystals of **CA** inclusion crystals (occupancies are determined by X−ray crystallography)

X_i [a]	Occupancy of **mX**	Occupancy of **pX**
0.75	0.65(2)	0.34(2)
0.67	0.56(2)	0.45(2)
0.50	0.38(3)	0.62(3)
0.33	0.25(1)	0.75(1)
0.25	0.20(2)	0.79(2)
0.20	0.17(2)	0.82(2)
0.17	0.12(1)	0.87(1)

[a] X_i: Molar fractions of **mX** in the recrystallization mixtures.

In order to clarify the mechanism of the non-selective inclusion, we separately determined the guest ratios of the bulk crystals by gas liquid chromatography, as summarized in Table 5. Figure 5 illustrates the plots of the mol fractions (X) of **mX** in the single crystals against the feed ratios as well as those in the bulk crystals. It is noteworthy that the guest ratios in the single crystals are in a good agreement with those in the bulk crystals, and that they are similar to those of the recrystallization mixtures. This indicates that both **mX** and **pX** are included in the single crystals together and that the bulk crystals consist of homogeneous single crystals. Therefore, the non-selective enclathrations are attributed to type III in Figure 1, part b.

Table 5. Mole fractions (determined by GLC) of **mX** in the bulk crystals

X_i [a]	X_b [a]
0.91	0.88
0.83	0.78
0.80	0.73
0.75	0.66
0.67	0.54
0.50	0.35
0.33	0.16
0.25	0.09
0.20	0.07
0.17	0.07
0.09	0.04

[a] X_i: Molar fractions of **mX** in the recrystallization mixtures; X_b: Molar fractions of **mX** in the bulk crystals.

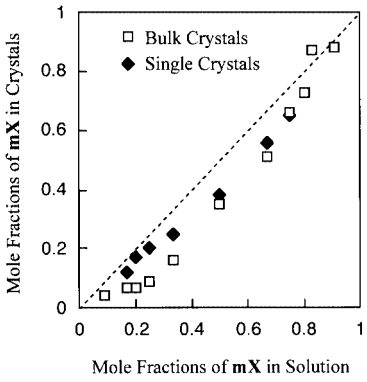


Figure 5. Mole fractions of **mX** in the single crystals and in the bulk crystals plotted against those of the starting mixed solvents of **mX** and **pX**

The presence of non-selective inclusion compounds (type III) is attributed to the similar stabilities of **mX** in β-*trans* and **pX** in α-*gauche*, judging from the same hydrogen bond networks and the PC_{cavity} in the normal range. In addition, the selection of the β-*trans* framework against α-*gauche* can be understood in terms of the differences between them in the size of the host cavities. The former host cavity has a suitable size and shape to accommodate both **mX** and **pX**, but the latter type can only accommodate **pX**. If the α-*gauche* host framework were formed, these crystals would accommodate **pX** selectively and **mX** should be separately included in the β-*trans*-type crystals. As the result, the crystals should be mixtures of the individual clathrates, as shown in Figure 1, part b, as type II. However, formation of the type II crystals is unfavorable to that of type III, because the latter would be expected to be more stable than the former at least by the term of mixing entropy (Rln2). Therefore, non-selective inclusion phenomena from **mX** and **pX** give the β-*trans* framework.

However, this result seems to be opposed to that of competitive recrystallization with monosubstituted benzenes.[7e] The order of selective enclathration with monosubstituted benzenes corresponds to the host framework types, and α-*gauche* is more favorable than the β-*trans*-type. This is due to the suitable shape, fitting between a square groove of the α-*gauche* framework and the phenyl ring of the monosubstituted benzenes. On the other hand, the **CA·pX** crystal does not have such a fitting, in spite of the α-*gauche* framework. Figure 6 illustrates typical cross-sections of the host cavity sliced parallel to the axis of the one-dimensional host cavity at the height that shows the cross-sections surrounded by

the side chains. In this cavity, **pX** molecules lie with their long molecular axes approximately perpendicular to the channel, and the phenyl rings of the **pX** molecules are located in the center of the channel and methyl groups in the square groove. The **CA·pX** crystal therefore does not have the suitable shape fitting observed in **CA** crystals with monosubstituted benzenes.

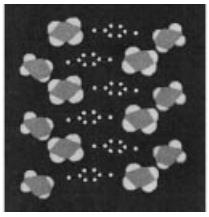


Figure 6. Cross sections of the host channels sliced parallel to the direction of the channel (carbon and hydrogen atoms are represented by gray and white, respectively) with arrays of included **pX** molecules (hydrogen atoms are omitted for clarity, and carbon atom is represented by open circle) in the **CA·pX** crystal

These results shed light on inclusion phenomena involving mixed guest compounds included in different open host frameworks. When the two inclusion crystals have different stabilities, the resulting crystals selectively include one of the guest compounds, and the host framework is same as that obtained from pure compounds. Similar stabilities of the inclusion crystals yield unselective enclathration. When one of the two host frameworks has a channel large enough to accommodate both of them, the host framework would be identical to the non-selectivity observed in the type III mechanism. On the other hand, when each guest compounds cannot be included in the other host framework, the resulting crystals are mixtures of the inclusion crystals, and the type II mechanism is attributed to non-selectivity. The inclusion phenomenon of less selective enclathration therefore depends on the accessibility of the guest compounds to the host cavities. The steric dimensions of the host cavities play an important role for non-selective recognition. In other words, inclusion crystals of mixed guest compounds without any selectivity may select the host frameworks with larger host cavities.

Finally, these results indicate that guest recognition by the host compounds with flexible host frameworks is similar to chiral recognition through diastereomeric salt formation. The four possible crystals in Figure 1, part b are the same as those of the diastereomeric salts.[17] Host compounds and guest mixtures correspond to chiral acids or amines and racemic mixtures to be resolved, respectively. When the difference in stabilities between the diastereomer salts is larger, one of the diastereomer salts forms selectively according to the type I mechanism. On the other hand, when they have similar stabilities, they display non-selective chiral recognition. Most less effective chiral recognition is attributable to the formation of diastereomer mixed crystals (diastereomer solid solution), and the diastereomer conglomerates are rarely formed.[17] The former corresponds to type III and the latter to type II.

Conclusion

We have demonstrated inclusion phenomena and crystal structures of **CA** with xylene isomers. The host frameworks and host/guest ratios depend on the shapes of the incorporated isomers. All xylenes are accommodated in the different host frameworks. This indicates that the shapes of guest components also play an important role for isomerization of the open host framework. Since the steric dimensions of the host channel are suitable for benzene rings, monosubstituted benzenes have good correlations between the guest volumes and the isomerizations. Interestingly, **CA** forms two types of **CA·oX** at the same host−guest stoichiometry at different incubation temperatures. This is new example of polymorphism of inclusion compounds of the same host/guest ratio and the host−guest combination.[6d,7c,7d] Competitive recrystallization from mixed xylenes revealed that **CA** exhibits both selective and unselective inclusion phenomena toward xylenes. The drastic changes in the guest selectivities are consistent with the differences in stabilities estimated from the PC_{cavity} values of the individual host−guest crystals. Moreover, in the unselective enclathration from **mX** and **pX**, X-ray diffraction studies revealed that the ratios of the guest components in the recrystallization mixtures are quite similar to those in the single crystals and in the bulk crystals. This indicates that unselective inclusion is attributable to the Type III mechanism, and not Type II.

To the best of our knowledge, this is the first report to describe mechanisms of selective and unselective enclathration of host compounds with flexible host frameworks. The molecular recognition mechanisms are the same as those involved in chiral recognition of diastereomer salts. The suggested mechanisms as shown in Figure 1, part b, should therefore be general for molecular recognition by crystalline materials consisting of three components. Finally, it is noteworthy that this principle of molecular recognition could also be applicable to guest-controlled interconversion of dynamic receptor libraries in solution.[18]

Experimental Section

Preparation of Inclusion Crystals: The inclusion crystals of **CA** with **oX** (Form I) were obtained by recrystallization from a solvent at room temperature. **CA** (100 mg) was dissolved with warming in 1-butanol (0.4 mL), and the xylene (2 mL) was added. The resulting solution was allowed to stand at room temperature. On the other hand, recrystallization at 30 °C gave the inclusion crystals of **CA** with **oX** (Form II). The inclusion crystals of **CA** with **mX** or **pX** were obtained by recrystallization in the presence of 1-butanol at room temperature. Competitive recrystallization from the mixture solution (host/guest ratios are 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5) was also carried out in a similar way. **CA** (100 mg) was dissolved with warming in 1-butanol (0.4 mL), and the prescribed mixed solution (2 mL) of two guest compounds was added. The resulting feed solution was allowed to settle overnight at room temperature to attain crystallization equilibrium.

X-ray Structural Analysis: X-ray diffraction data were collected with a Rigaku RAXIS-CS imaging plate two-dimensional area detector with use of graphite-monochromatized Mo-K_α radiation (λ = 0.71070Å). All the crystallographic calculations were performed by use of the TEXSAN[19] software package (Molecular Structure Corporation). Each crystal structure was solved by direct methods (MULTAN, SHEXL97), and refined by full-matrix, least-squares or SHEXL93. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to carbon atoms were located in calculated positions. The positions of hydrogen atoms attached to oxygen atoms were obtained from the difference Fourier syntheses. The crystal data for these crystals are shown in Table 1 and Table 3. CCDC-148957 to CCDC-148969 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.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].

Determination of Guest Ratios in Single Crystals: We confirmed the disorder of the guest molecules in the single crystals from the difference Fourier ($F_o - F_c$) map without guest components. The ratios between **mX** and **pX** in single crystals can be determined by refinement of the occupancy parameters of both sites under constraint.

Determination of Guest Ratios in Bulk Crystals: The typical procedure is as follows. All crystals formed in a glass vial of the mixed xylene were collected, dried on filter paper, and dissolved in methanol (0.4 mL). The solutions were analyzed by gas liquid chromatography (GLC) with a Shimadzu GC-14A instrument equipped with a ULBON HR-20M capillary column (PEG, 0.25mmφ × 50m). The retention times of **mX** and **pX** are 15.40 min and 14.97 min, respectively. The ratios of the guest compounds are calculated from the integration of the peaks after calibration.

Molecular Graphics and Calculations: Cross-sections of host channels were depicted by use of MODRASTE.[20] The atomic radii of hydrogen, carbon, and oxygen in the cross-sectional views are 1.20 Å, 1.60 Å, and 1.45 Å, respectively. The volumes of the host cavities were calculated from the atomic coordinates by use of the Free Volume program[21] in the Cerius[2] (version 4.0) software package.[22] The volumes of the **CA** cavities were calculated by use of a 0.7 Å radius probe.[5,6] The atomic radii were adopted as following values; hydrogen: 1.20 Å, carbon: 1.70 Å, and oxygen: 1.60 Å.

Acknowledgments

This work was supported by Grants-in Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan (Priority Area, Dynamic Control of Stereochemistry) and by TOKYO OHKA FOUNDATION for M. M.

[1] Reviews on lattice inclusion compounds: [1a] D. D. MacNicol, J. J. McKendrick, D. R. Wilson, *Chem. Soc., Rev.* **1978**, *7*, 66−87. [1b] J. E. D. Davies, W. Kemula, H. M. Powell, N. O. Smith, *J. Incl. Phenom.* **1983**, *1*, 3−44. [1c] *Top. Curr. Chem.*, vols. 140, 149 (Ed.: E. Weber), Springer-Verlag, London, UK, **1987**, **1988**. [1d] *Inclusion Compounds, Vol. 1−3* and *4−5*, (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol), Academic Press, London, **1984**, and Oxford Press, Oxford, **1991**. [1e] *Comprehensive Supramolecular Chemistry, Solid-State Supramolecular Chemistry: Crystal Engineering*; Vol. 6 (Eds.: D. D. MacNicol, F. Toda, R. Bishop), Pergamon, New York, **1996**. [1f] R. Bishop, *Chem. Soc., Rev.* **1996**, 311−319.

[2] For more recent examples of design of organic host compounds, see: [2a] P. Brunet, M. Simard, J. D. Wuest, *J. Am. Chem. Soc.* **1997**, *119*, 2737−2738. [2b] R. Bhyrappa, S. R. Wilson, K. S. Suslick, *J. Am. Chem. Soc.* **1997**, *119*, 8492−8502. [2c] K. Kobayashi, M. Koyanagi, K. Endo, Y. Aoyama, *Chem. Eur. J.* **1998**, *4*, 417−424. [2d] K. Biradha, D. Dennis, V. A. MacKinnon, C. V. K. Sharma, M. J. Zaworotko, *J. Am. Chem. Soc.* **1998**, *120*, 11894−11903. [2e] C. C. Evans, L. Sukarto, M. D. Ward, *J. Am. Chem. Soc.* **1999**, *121*, 320−325. [2f] K. Kobayashi, T. Shirasaka, A. Sato, E. Horn, N. Furukawa, *Angew. Chem. Int. Ed.* **1999**, *38*, 3483−3486. [2g] S. V. Kolotuchin, P. A. Thiessen, E. E. Fenlon, S. R. Wilson, C. J. Loweth, S. C. Zimmerman, *Chem. Eur. J.* **1999**, 2537−2547.

[3] Reviews and selected recent examples of enantioselective enclathration: [3a] F. Toda, in ref.[1c] pp. 43−69. [3b] F. Toda, in *Advances in Supramolecular Chemistry*, Vol. 2, (Ed.; G. W. Gokel), JAI Press, London, **1992**, pp. 141−191. [3c] G. Kaupp, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 728−729. [3d] A. Mravik, Z. Boscskei, K. Simon, F. Elekes, Z. Izsaki, *Chem. Eur. J.* **1998**, *4*, 1621−1627. [3e] M. Gdaniec, M. J. Milewska, T. Polonski, *Angew. Chem. Int. Ed.* **1999**, *38*, 392−395.

[4] [4a] A. D. U. Hardy, D. D. MacNicol, S. Swanson, D. R. Wilson, *J. Chem. Soc., Perkin II* **1980**, 999−1005. [4b] D. H. Brown, R. J. Cross, P. R. Mallinson, D. D. MacNicol, *J. Chem. Soc., Perkin II* **1980**, 993−998. [4c] Y. Aoyama, K. Endo, K. Kobayashi, H. Masuda, *Supramol. Chem.* **1995**, *4* 229−241. [4d] K. Endo, T. Sawaki, M. Koyanagi, K. Kobayashi, H. Masuda, Y. Aoyama, *J. Am. Chem. Soc.* **1995**, *117* 8341−8352. [4e] K. Endo, T. Ezuhara, M. Koyanagi, H. Masuda, Y. Aoyama, *J. Am. Chem. Soc.* **1997**, *119*, 499−505. [4f] M. Caira, A. Horne, L. R. Nassimbeni, F. Toda, *J. Mater. Chem.* **1998**, *8*, 1481−1484. [4g] E. Weber, I. Csoeregh, B. Stensland, M. Czugler, *J. Am. Chem. Soc.* **1984**, *106* 3297−3306. [4h] E. Weber, K. Skobridis, A. Wierig, L. J. Barbour, M. R. Caira, L. R. Nassimbeni, *Chem. Ber.* **1993**, *126*, 1141−1148. [4i] E. Weber, I. Csoeregh, J. Ahrendt, S. Finge, M. Czugler, *J. Org. Chem.* **1988**, 5831−5839. [4j] S. A. Bourne, L. R. Nassimbeni, F. Toda, *J. Chem. Soc., Perkin II* **1991**, 1335−1341. [4k] M. R. Caira, L. R. Nassimbeni, F. Toda, D. Vujovic, *J. Am. Chem. Soc.* **2000**, *122*, 9367−9372. [4l] A. M. Pivovar, K. T. Holman, M. D. Ward, *Chem. Mater.* **2001**, *13*, 3018−3031.

[5] [5a] J. Allemand, R. Gerdil, *Acta Crystallogr., Sect. B* **1982**, *38*, 1473−1476. [5b] J. Allemand, R. Gerdil, *Acta Crystallogr., Sect. B* **1982**, *38*, 2312−2315. [5c] Rina Arad-Yellin, B. S. Green, M. Knossow, G. Tsoucaris, *J. Am. Chem. Soc.* **1983**, *105*, 4561−4571. [5d] P. Briozzo, T. Kondo, K. Sada, M. Miyata, K. Miki, *Acta Crystallogr., Sect. B* **1996**, *52*, 728−733.

[6] [6a] D. Lawton, H. M. Powell, *J. Chem. Soc.* **1958**, 2339−2357. [6b] E. Weber, I. Csosregh, B. M. Czugler, *J. Am. Chem. Soc.* **1984**, *106*, 3297. [6c] M. P. Byrn, C. J. Curtis, Y. Hsiou, S. I. Khan, P. A. Sawin, S. K. Tendick, A. Terzis, C. E. Strouse, *J. Am. Chem. Soc.* **1993**, *115*, 9480−9497. [6d] M. D. Hollingsworth, D. B. Santarsiero, K. D. M. Harris, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 649−652. [6e] A. T. Ung, D. Gizachew, R. Bishop, M. L. Scudder, I. G. Dance, D. C. Craig, *J. Am. Chem. Soc.* **1995**, *117*, 8745−8756. [6f] J. A. Swift, A. M. Pivovar, A. M. Reynolds, M. D. Ward, *J. Am. Chem. Soc.* **1998**, *120*, 5887−5897. [6g] M. Gdaniec, B. T. Ibragimov, S. A. Talipov, in ref.[1e], pp. 117−145. [6h] R. Gerdil, in ref.[1e], pp. 239−280. [6i] K. Nakano, K. Sada, Y. Kurozumi, M. Miyata, *Chem. Eur. J.* **2001**, *7*, 209−220.

[7] [7a] M. Miyata, K. Sada, in ref.[1e], pp. 147−176. [7b] K. Nakano, K. Sada, M. Miyata, *J. Chem. Soc., Chem. Commun.* **1995**, 953−954. [7c] K. Nakano, K. Sada, M. Miyata, *Chem. Commun.* **1996**, 989−990. [7d] K. Nakano, K. Sada, M. Miyata, *Progr. Colloid Polym. Sci.* **1997**, *106*, 249−251. [7e] N. Yoswathananont, K. Sada, M. Miyata, S. Akita, K. Nakano, *Org. Biomol. Chem.* **2003**, *1*, 210−214.

[8] For a review of DCA inclusion crystals, see also E. Giglio, ref. [1d], Vol. 2, pp. 207−229.
[9] [9a] P. L. Johnson, J. P. Schaefer, *Acta Crystallogr., Sect. B* **1972**, *28*, 3083−3088. [9b] E. L. Jones, L. R. Nassimbeni, *Acta Crystallogr., Sect. B* **1990**, *46*, 399−405.
[10] [10a] M. Miyata, M. Shibakami, W. Goonewardena, K. Takemoto, *Chem. Lett.* **1987**, 605−608. [10b] K. Miki, A. Masui, N. Kasai, M. Miyata, M. Shibakami, K. Takemoto, *J. Am. Chem. Soc.* **1988**, *110*, 6594−6596. [10c] K. Miki, N. Kasai, M. Shibakami, K. Takemoto, M. Miyata, *J. Chem. Soc., Chem. Commun.* **1991**, 1757−1759. [10d] K. Nakano, K. Sada, M. Miyata, *Chem. Lett.* **1994**, 137−140. [10e] K. Nakano, K. Sada, M. Miyata, *J. Chem. Soc., Chem. Commun.* **1995**, 953−954. [10f] K. Nakano, K. Sada, M. Miyata, *Mol. Cryst. Liq. Cryst.* **1996**, *276*, 129−132.
[11] [11a] M. Shibakami, A. Sekiya, *J. Chem. Soc., Chem. Commun.* **1994**, 429−430. [11b] M. Shibakami, A. Sekiya, *J. Inclusion Phenomena* **1994**, *18*, 397−412. [11c] M. Shibakami, M. Tamura, A. Sekiya, *J. Inclusion Phenomena* **1995**, *22*, 155−168. [11d] M. Shibakami, M. Tamura, A. Sekiya, *J. Inclusion Phenomena* **1995**, *22*, 299−311. [11e] M. Shibakami, M. Tamura, A. Sekiya, *J. Am. Chem. Soc.* **1995**, *117*, 4499−4505.
[12] [12a] M. R. Caira, L. R. Nassimbeni, J. L. Scott, *J. Chem. Soc., Chem. Commun.* **1993**, 612−613. [12b] M. R. Caira, L. R. Nassimbeni, J. L. Scott, *J. Chem. Soc., Perkin Trans. 2* **1994**, 623−628. [12c] M. R. Caira, L. R. Nassimbeni, J. L. Scott, *J. Chem. Soc., Perkin Trans. 2* **1994**, 1403−1405. [12d] J. L. Scott, *J. Chem. Soc., Perkin Trans. 2* **1995**, 495−502. [12e] J. L. Scott, *Supramol. Chem.* **1996**, *7*, 201−207.
[13] [13a] M. Gdaniec, T. Polonski, *J. Am. Chem. Soc.* **1998**, *120*, 7353−7354. [13b] M. Gdaniec, M. Milewska, T. Polonski, *Angew. Chem. Int. Ed.* **1999**, *38*, 392−395.
[14] P. Dastidar, *CrystEngCommun.* **2000**, 8−11.
[15] S. Mecozzi, J. Rebek, Jr., *Chem. Eur. J.* **1998**, *4*, 1016−1022.
[16] For recent examples, see: [16a] A. Gavezzotti, G. Fillippini, *J. Am. Chem. Soc.* **1995**, *117*, 12299−12305. [16b] L. Yu, G. A. Stephenson, C. A. Mitchell, C. A. Bunnell, S. V. Snorek, J. J. Bowyer, T. B. Borchardt, J. G. Stowell, S. R. Byrn, *J. Am. Chem. Soc.* **2000**, *122*, 585−591.
[17] [17a] J. Jacques, A. Collet, S. H. Wilen, in *Enantiomers, Racemates and Resolutions*, Krieger Publishing Malabar **1994**. [17b] C. P. Brock, W. B. Schweizer, J. D. Dunitz, *J. Am. Chem. Soc.* **1991**, *113*, 9811−9820.
[18] For example, isomerization of guest-controlled cages in solution, see: K. Umemoto, K. Yamaguchi, M. Fujita, *J. Am. Chem. Soc.* **2000**, *122*, 7150−7151, and references cited therein.
[19] TEXSAN, X-ray Structure Analysis Package; Molecular Structure Corporation: The Woodlands, TX, **1985**.
[20] H. Nakano, *Molecular Graphics*, Science House, Tokyo, **1987**.
[21] R. Voorintholt, M. T. Kosters, G. Vegter, G. Vriend, W. G. J. Hol, *J. Mol. Graphics* **1989**, *7*, 243−245.
[22] Cerius^2, Molecular Simulation Software; Molecular Simulation Inc.

Received December 20, 2002

