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Supramolecular Chemistry

Publication details, including instructions for authors and subscription information:

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To cite this Article Hishikawa, Yukio , Sada, Kazuki and Miyata, Mikiji(1999) 'Extremely Specific Recognition of Ethylene Glycol in Three-leaved Building Blocks of *N*-Methyldeoxycholamide', *Supramolecular Chemistry*, 11: 2, 101 – 108

To link to this Article: DOI: 10.1080/10610279908048721

URL: <http://dx.doi.org/10.1080/10610279908048721>

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Extremely Specific Recognition of Ethylene Glycol in Three-leaved Building Blocks of *N*-Methyldeoxycholamide

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(Received 30 November 1998; In final form 20 May 1999)

***N*-Methyldeoxycholamide (1) was recrystallized from over one hundred organic substances in a search for inclusion compounds. Only ethylene glycol (EG) was included into host assemblies together with water. Other solvents gave hemihydrate crystals without organic guests. X-ray structural analysis revealed that the former inclusion crystal has a three-leaved building block similar to that of glycodeoxycholic acid (2). Tomographical analysis of both the assemblies gave an insight about such an extremely specific inclusion behavior from the viewpoint of steric and hydrogen-bonding terms.**

Keywords: *N*-Methyldeoxycholamide, X-ray structural analysis, Specific recognition, Ethylene glycol, Three-leaved assembly, hydrogen bond

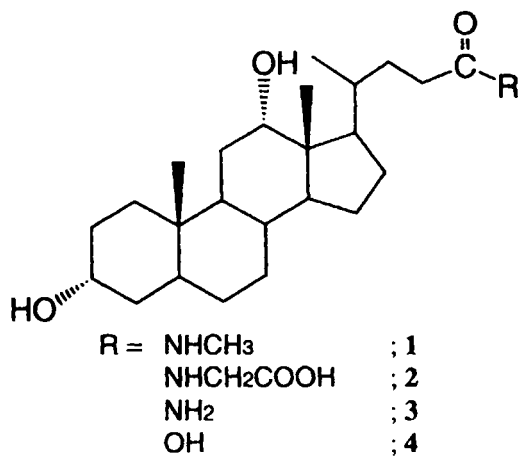
INTRODUCTION

Much attention has been devoted to design of self-assembly processes involving non-covalent interactions, such as hydrogen bonds [1]. Successful design lies in controlling the dimensionality of the building blocks, such as brick [2],

sheets [3], ribbons [4], helices [5] and tubes [6]. These architectures can afford some vacant space in which to include guests. In principle, the inclusion behavior will vary from case to case. However, extremely specific inclusion, meaning the inclusion of only a few organic compounds among many guest candidates, still remains rare.

In a series of our research for steroidal inclusion compounds, we encountered an extremely specific inclusion behavior. That is, *N*-methyldeoxycholamide (1) has been found to include only ethylene glycol. This is in contrast with the previous studies on a limited inclusion behavior of glycodeoxycholic acid (2) [7], as well as the extensive inclusion behavior of deoxycholamide (3) [8] and deoxycholic acid (4) [9]. The inclusion crystal of 1 with EG presents a three-leaved building block similar to that of 2. A comparative study of the crystal structures of 1 and 2 has enabled us to consider a mechanism of such an extremely specific inclusion ability of 1. This paper deals with the crystal structures and the mechanism for the recognition.

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SCHEME 1 Host compounds.

RESULTS AND DISCUSSION

Several research groups performed detailed structural analyses on inclusion compounds of deoxycholic acid (**4**) and related compounds, clarifying that the hosts commonly form building blocks of a bilayered fashion [9, 10]. For example, **4** yields a robust bilayered assembly, resulting in channel-like spaces for accommodating guest molecules [9]. However, some guests force the hosts to employ helical columns. For example, **4** includes ethanol or DMSO together with water in hexagonal columns [11].

Our previous report concerns the fact that **1** forms hemihydrate crystals upon recrystallization from organic guests [12]. Table I lists organic substances employed for the inclusion experiments. This represents over one hundred kinds of substances. The resulting crystals had prism-like shape, but the one obtained from EG had exceptional triangular shape. Further experiments made clear that **1** selectively included both EG and water by recrystallization from an equimolar mixture of EG with 1,2-propanediol, 1,3-propanediol, 1,2-butanediol, 1,3-butanediol, 1,4-butanediol or 2,3-butanediol. The triangular crystals were shown to include EG together with an equimolar amount of water, as described below.

The crystals gave three endothermic peaks (ca. 116, 132 and 190°C) in the DTA diagram. The one peak at the highest temperature corresponds to the melting point of **1** itself. The other two peaks at lower temperatures are based on release of the guest components from the host lattices, as indicated by mass losses in the simultaneous TG measurement. In the IR spectrum, the inclusion compound exhibited a clear absorption peak at 1100 cm^{-1} in the C—O stretching region, indicating the existence of EG. The guest component EG was isolated by means of evaporation, by heating the crystals, and identified by $^1\text{H-NMR}$ spectroscopy.

Direct evidence for the existence of water was obtained from a X-ray single crystal structural analysis. Slow evaporation of a mixed solution of EG and 2-butanol containing **1** at room temperature yielded triangular crystals suitable for the X-ray analysis. The crystal belongs to space group $R\bar{3}$, indicating that it is similar to an inclusion crystal of **2** with THF [9]. Table II shows the similarity of the two crystals.

Figure 1 shows an ORTEP drawing of the molecule **1**. It can be seen that its tail is folded back to the lipophilic face of the steroidal skeleton, which is similar to **2**. The two dihedral angles of $[C(20)-C(22)-C(23)-C(24) = 78.3(8)^\circ(1); 75.5(6)^\circ(2)]$ and $[C(22)-C(23)-C(24)-N(1) = -119.9(8)^\circ(1); -116.9(5)^\circ(2)]$ are very similar to each other. It is assumed that large thermal motion of water molecules prevents the lowering of the R -value.

Figures 2a and 2c show the crystal packing diagrams viewed along the crystallographic c -axis. Figures 2b and 2d represent side-views of the column. It can be seen that the host molecules form a three-leaved disk as a building block. The disks are stacked on each other along the crystallographic c -axis to yield a column with a lipophilic core and a hydrophilic surface. EG and THF molecules are located in similar positions.

Figures 3a to 3c display hydrogen-bonding networks among **1** and EG. One hydroxy group of EG connects to a 3-positioned hydroxy group

TABLE I Organic compounds as guest candidates for 1

Methanol	Ethylene glycol	Ethyl formate
Ethanol	Propylene glycol	Methyl acetate
1-Propanol	Trimethylene glycol	Ethyl acetate
2-Propanol	1,2-Butanediol	<i>n</i> -Propyl acetate
2-Methyl-1-propanol	1,3-Butanediol	Phenyl acetate
1-Butanol	1,4-Butanediol	Methyl benzoate
2-Butanol	1,2-Pentanediol	Ethyl benzoate
1,1-Dimethyl-1-propanol	1,5-Pentanediol	Isopropyl benzoate
2,2-Dimethyl-1-propanol	2,4-Pentanediol	<i>n</i> -Butyl benzoate
2-Methyl-1-butanol	1,2-Hexanediol	γ -Valerolactone
2-Methyl-2-butanol	2,3-Butanediol	Acetonitrile
3-Methyl-2-butanol	Acetone	Chloroacetonitrile
1-Pentanol	2-Butanone	Propionitrile
2-Pentanol	3-Methyl-2-butanone	<i>n</i> -Butyronitrile
2-Ethyl-1-butanol	2-Pentanone	2-Methyl-3-butenitrile
3,3-Dimethyl-2-butanol	3-Pentanone	Diethyl ether
2-Methyl-1-pentanol	3,3-Dimethyl-2-butanone	<i>n</i> -Propyl ether
3-Methyl-1-pentanol	3-Methyl-2-pentanone	Tetrahydrofuran
4-Methyl-1-pentanol	4-Methyl-2-pentanone	Tetrahydropyran
3-Methyl-2-pentanol	2-Methyl-3-pentanone	Diphenyl ether
4-Methyl-2-pentanol	2-Hexanone	Cyclohexane
3-Methyl-3-pentanol	3-Hexanone	Benzene
1-Hexanol	2-Methylcyclohexanone	Toluene
2-Hexanol	3-Methylcyclohexanone	2-Ethyltoluene
3-Hexanol	4-Methylcyclohexanone	3-Ethyltoluene
Cyclohexanol	Acetophenone	4-Ethyltoluene
2-Heptanol	<i>o</i> -Methylacetophenone	<i>n</i> -Butylbenzene
2-Methylcyclohexanol	<i>m</i> -Methylacetophenone	<i>m</i> -Diethylbenzene
3-Methylcyclohexanol	<i>p</i> -Methylacetophenone	<i>p</i> -Diethylbenzene
4-Methylcyclohexanol	Propiophenone	Dichloromethane
<i>trans</i> -4-Methylcyclohexanol	<i>n</i> -Butyrophenone	1,2-Dichloroethane
Benzyl alcohol	Isobutyrophenone	
1-Octanol	Valerophenone	
1-Decanol	2,4-Pentanedione	

TABLE II Crystallographic data for 1•EG•water and 2•THF

Compound	1•EG•water	2•THF
Host-Guest ratio	1:1:1	1:1
Formula	C ₂₆ H ₄₇ O ₆ N ₁	C ₃₀ H ₅₁ O ₆ N ₁
Formula Weight	485.70	521.74
Crystal System	Trigonal	Trigonal
Space Group	R3	R3
<i>a</i> /Å	32.021(6)	32.116(1)
<i>b</i> /Å	32.021(6)	32.116(1)
<i>c</i> /Å	7.0683(9)	7.267(2)
<i>V</i> /Å ³	6276(1)	6491(1)
<i>Z</i>	9	9
<i>D</i> _{calc} /g•cm ⁻³	1.156	1.201
<i>R</i>	0.083	0.042
Reference	This work	7

of a neighboring host (OH[C(3)] • • • OH [C(27)EG], 2.75(1) Å), while another hydroxy group of EG bonds to a carbonyl group of

another neighboring host which constitutes the identical disk (OH[C(26)EG] • • • O = C [C(24)''], 2.747(8) Å). In this way an EG molecule

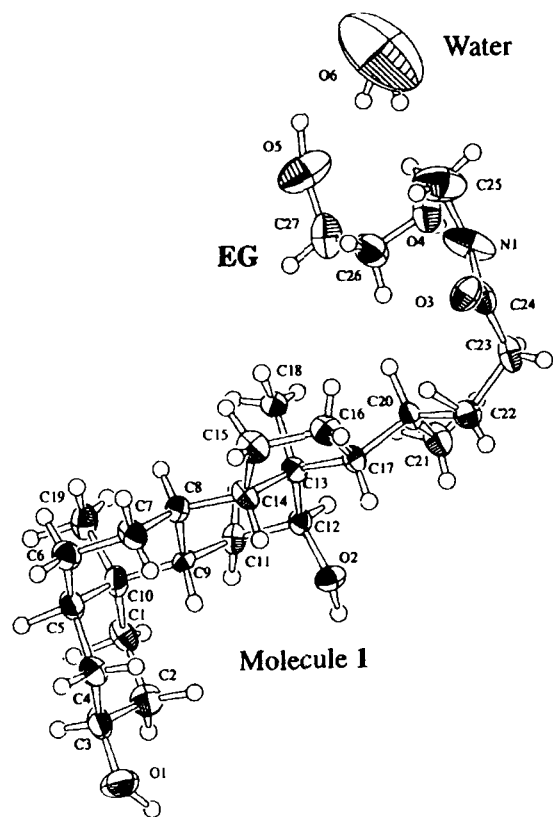


FIGURE 1 ORTEP drawing of molecule 1, EG and water in the crystal structure of $1 \cdot \text{EG} \cdot \text{water}$.

acts as a hydrogen-bonding linker between the host molecules to yield the three-leaved disk.

Accumulation of the three-leaved disks is achieved by hydrogen-bonds between N—H groups of the side chain and hydroxy groups of EG ($\text{N—H}[\text{C}(24)'''] \cdots \text{O—H}[\text{C}(26)\text{EG}]$, $3.030(8)\text{Å}$). The resulting columns are connected to each other by hydrogen-bonding contacts between a 12-positioned hydroxy group and a carbonyl group of 1 ($\text{O—H}[\text{C}(12)] \cdots \text{O}=\text{C}[\text{C}(24)']$, $2.799(7)\text{Å}$). Water molecules act as linkers among the columns.

Analysis of the crystal structures provides an explanation of the extremely specific recognition of EG. Figures 4b and 4c show cross-sectional drawings (0.5 Å thickness) for the space-filling model of the assembly in $1 \cdot \text{EG}$. It can be seen that four molecules of 1 leave a cage-like space,

where an EG molecule is accommodated (Fig. 4b). Two skeletons and two tails serve as a wall to yield deformed orthorhombic space, where a CH_2CH_2 part of EG is fixed (Fig. 4b). This prevents inclusion of other diols which have additional alkyl groups, such as 1,2-propanediol.

On the other hand, 2 included some organic compounds, such as acetone, 2-butanone, tetrahydrofuran, 1,4-dioxane, methyl *o*-toluate, cyclohexanone and so on, as demonstrated in the literature [9]. It seems that the inclusion ability of 1 is complementary to that of 2. Comparisons of the inclusion phenomena of 1 and 2 gave additional support for specific inclusion of 1.

The hydrogen-bonding networks for the inclusion crystal of 2 with THF are schematically shown in Figures 3d to 3f. A 3-positioned hydroxy group of 2 directly connects to a carboxyl group of a neighboring host which constitutes the disk, as in the case of 1. The resulting three-leaved disks stack along the crystallographic *c*-axis to generate a column. A THF molecule is located between the side chains and is linked to a 3-positioned hydroxy group of 2 through a hydrogen bond. The columns are connected to each other through a hydrogen bond between a 12-positioned hydroxy group and a carbonyl group of 2.

Furthermore, a tomographic drawing (0.5 Å thickness) for a cross-section of the inclusion space of $2 \cdot \text{THF}$ is depicted in Figures 4d to 4f. Two steroidal skeletons and two tails constitute walls of the inclusion space so as to leave cages suitable for THF. The cage can accommodate some molecules having hydrogen-bonding acceptors other than THF.

CONCLUSION

This study demonstrates that 1 exhibits extremely specific inclusion towards organic substances. Since there exists an infinite number of organic guest candidates, the question whether

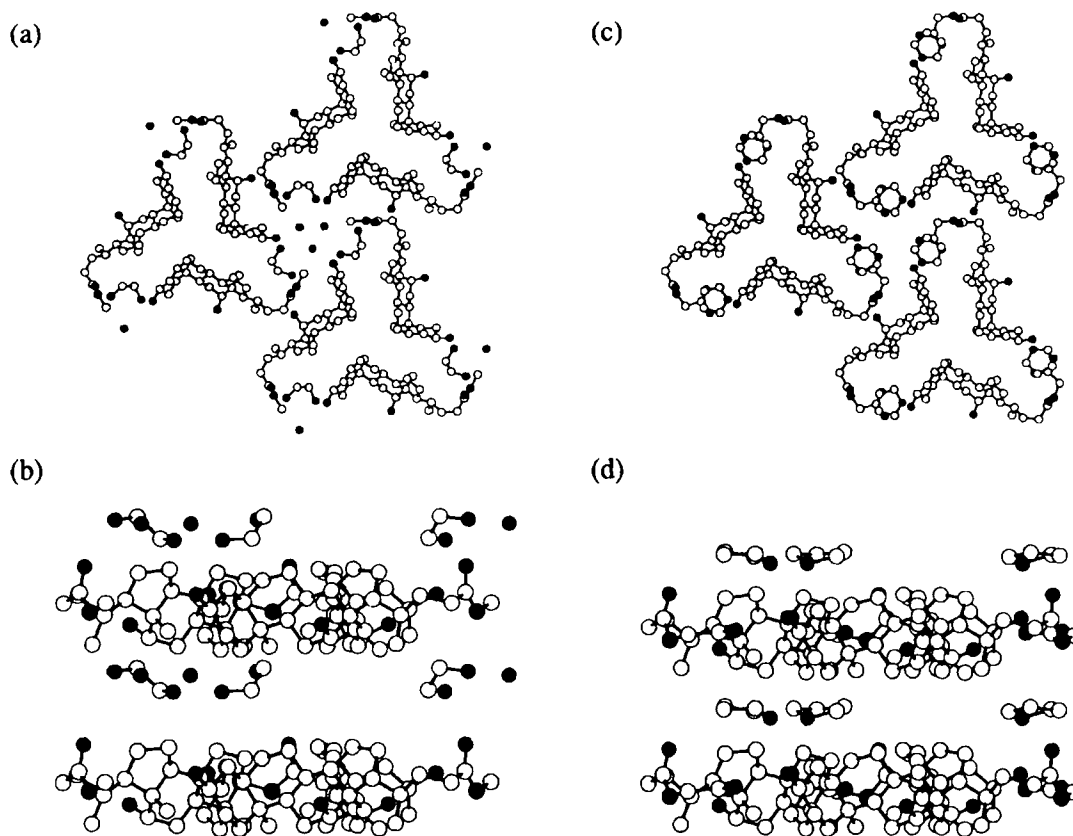


FIGURE 2 Crystal structures of $1 \cdot \text{EG} \cdot \text{water}$ (a) and $2 \cdot \text{THF}$ (c) as viewed down along the crystallographic c -axis. Side-views of the one column in the crystals of $1 \cdot \text{EG} \cdot \text{water}$ (b) and $2 \cdot \text{THF}$ (d). Hydrogen atoms are omitted for clarity. Empty, shaded and closed circles represent carbon, nitrogen and oxygen atoms, respectively.

other guests might be found by further study still remains. More attention may be paid to such an inclusion behavior, leading to the acquisition of simple models as compared with biopolymers, such as enzymes.

MATERIALS AND METHODS

Materials

Commercially available reagents and solvents were used without further purification. Compounds **1** were prepared from the parent acid **3** by the conventional mixed anhydride method in dried THF at -30°C as described in the literature [13].

Inclusion Crystals

The amide **1** was recrystallized from neat components or from 2-butanol solutions. The inclusion experiments were carried out by using over one hundred kinds of organic guest candidates, such as aromatic and aliphatic alcohols, ketones, esters, ethers, carboxylic acids, nitriles, hydrocarbons and so on, as shown in Table I. The resulting crystals were dried on filter paper and characterized by IR and $^1\text{H-NMR}$ spectroscopy, thermal analysis. Host-guest ratios were estimated by amounts of weight-loss in TG as well as integration of the corresponding peaks in $^1\text{H-NMR}$ spectra. The crystal structures were determined by X-ray diffraction methods of powders and/or single crystals.

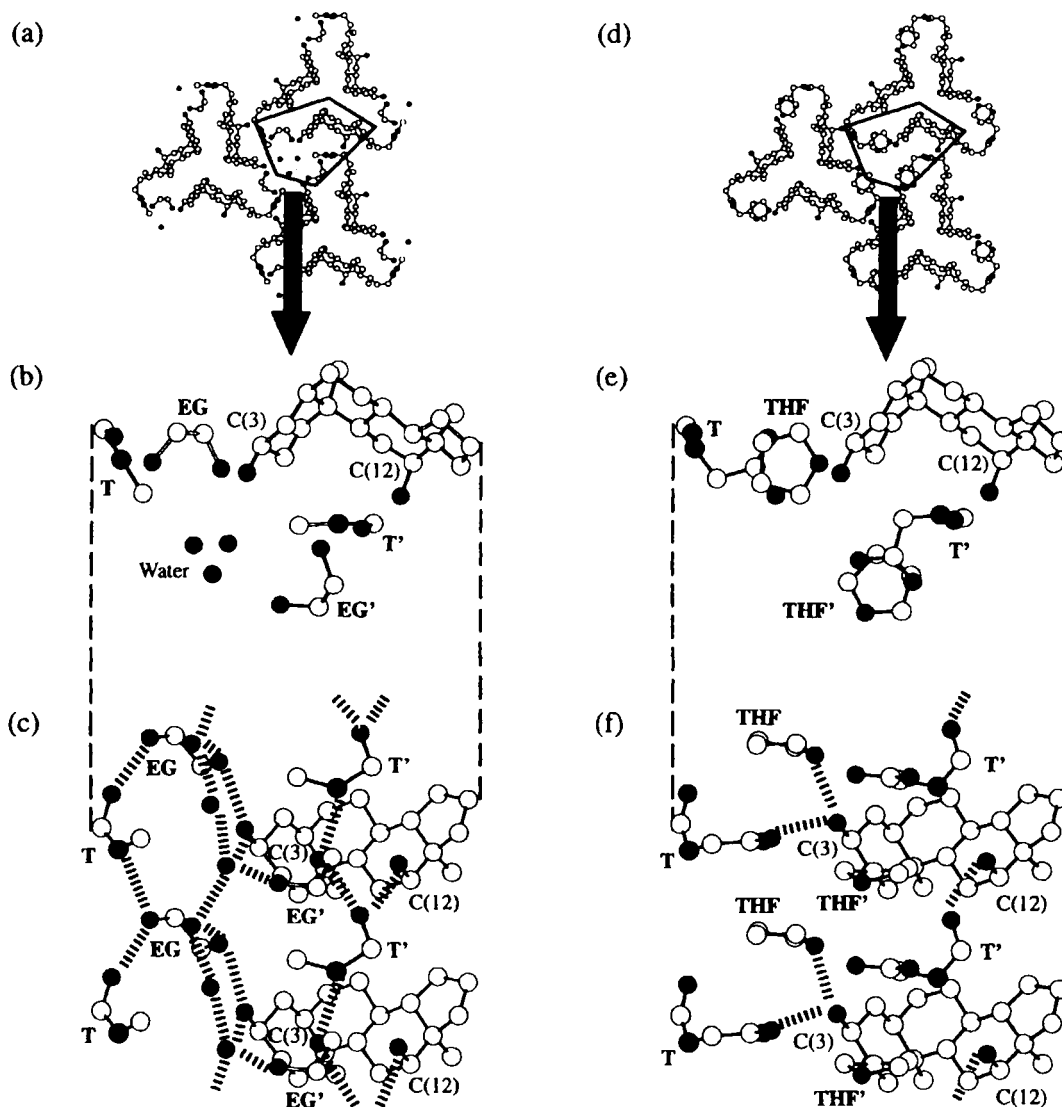


FIGURE 3 Packing diagrams and schematic representation of the hydrogen-bonding networks of the inclusion crystals of $1\bullet\text{EG}\bullet\text{water}$ (a–c), and the inclusion crystals of $2\bullet\text{THF}$ (d–f). Figures (a), (b), (d) and (e) are viewed along crystallographic c -axis. The shadowed parts in Figures (a) and (d) are magnified in the Figures (b) and (e), respectively. Figures (c) and (f) are side-views of Figures (b) and (e), respectively. T and T' mean tail parts of the host molecules. Dotted lines indicate hydrogen-bonding contacts. Hydrogen atoms are omitted for clarity. The atom coding is identical to that in Figure 2.

X-ray Crystallographic Study

Crystal structure data for $1\bullet\text{EG}\bullet\text{water}$ system ($\text{C}_{24}\text{H}_{41}\text{O}_3\text{N}_1\bullet\text{C}_2\text{H}_4\text{O}_2\bullet\text{H}_2\text{O}$) are as follows. The crystal belongs to trigonal crystal system, space group $R\bar{3}$. $a=b=32.021(6)$, $c=7.0683(9)$ Å, $V=6276(1)$ Å³, $\rho_{\text{calc}}=1.156$ g•cm⁻³, $z=9$, $R=0.083$,

$R_w=0.100$. The single crystal structure was determined by using a Rigaku RAXIS-IV imaging plate with a two-dimensional area detector with graphite-monochromatized Mo- $K\alpha$ radiation ($\lambda=0.71069$ Å). The intensity data were collected at *ca.* 200 K. The crystal showed 2065 unique reflections ($2\theta_{\text{max}}=50.0^\circ$). Some 1758

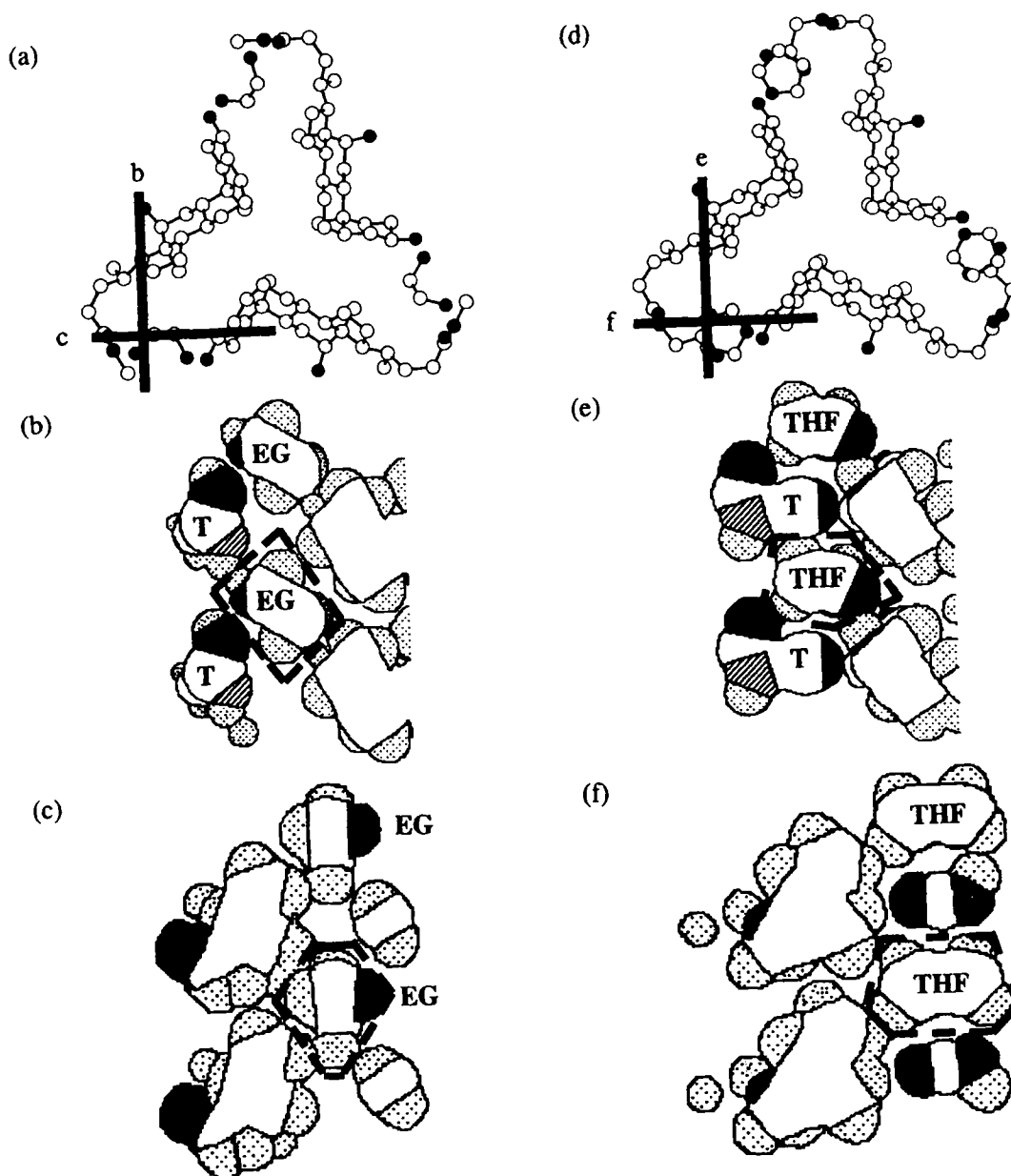


FIGURE 4 Tomographical drawings for cross-sections of the inclusion space (0.5 \AA thickness) using a space-filling model; (a–c) inclusion crystal of $1 \cdot \text{EG} \cdot \text{water}$ and (d–f) $2 \cdot \text{THF}$. T and T' mean tail parts of the host molecules. The dotted boundaries in the figures show inclusion cavities. Empty, shadowed, closed, dotted areas represent carbon, nitrogen, oxygen and hydrogen atoms, respectively.

$[|F_0| > 3\sigma|F_0|]$ reflections were used for further calculations after Lorenz and polarization corrections. The structure was solved by direct methods (SIR92) and refined by full-matrix least-squares. All non-hydrogen atoms were refined

anisotropically. Hydrogen atoms attached to carbon atoms were located in the calculated positions. The positions of hydrogen atoms attached to oxygen and nitrogen atoms were obtained from difference Fourier syntheses. All hydrogen

atoms were refined. All calculations were performed by using TEXSAN crystallographic software package of the Molecular Structure Corporation. Atomic coordinates and other crystallographic data are available from the authors.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas, "New Polymers and Their Nano-Organized Systems" (No. 277/09232237) from the Ministry of Education, Science, Sports and Culture, Japan and by the Sasakawa Scientific Research Grant from the Japan Science Society.

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