Cavities, Layers, and Channels in the Hosting Framework of Molecular Complexes Derived From Cephradine

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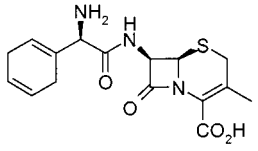
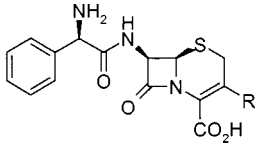
The cephalosporin-type antibiotics Cephradine, Cephalexin, and Cefaclor form clathrate-type complexes with a variety of naphthalene derivatives. The crystal structures of these complexes are isomorphous. Interestingly, the hosting framework formed by these cephalosporins can adapt to the guest molecule. This phenomenon of induced-fit appears to have a much larger potential, with the consequence that a series of smaller compounds (such as benzene derivatives) as well as bulkier compounds can also be hosted by Cephradine. When benzene derivatives were used as guests, pronounced deviations in the antibiotic framework were observed, and it is possible to induce deviations strikingly different from those found for the complexes with the naphthalene derivatives. Evidently, the hosting structure formed by Cephradine is highly flexible. Hosting frameworks containing layers, channels, and various other types of cavities can be obtained by selection of an appropriate guest molecule. Remarkably, a number of structural features and interactions remain unaffected in all these antibiotic frameworks. These persistent features seem to delineate the boundaries of framework formation for these antibiotics, thus defining the scope of complex formation.

Introduction

Crystal engineering is receiving rapidly growing attention from chemists and physicists. It is not only solid-state chemists and material scientists that are active within this field; supramolecular chemists and synthetic chemists are also often inspired and challenged by phenomena exhibited by molecules in the solid state. Clathrates receive special attention from synthetic chemists, since they can be used to isolate organic compounds in a chemoselective or enantioselective manner.[1−3] There is, however, no general theory available with the aid of which clathrates can be systematically designed. Supramolecular synthons have been postulated as a tool with which to understand and predict crystal structures of organic molecules and their complexes,[4] and one approach to the design of clathrates is to construct a framework from supramolecular synthons built up from host molecules, containing cavities that can be occupied by guest molecules. This approach is often hampered by the lack of robust supramolecular synthons that are not distorted by the guest molecules, or put another way, it requires that the host molecules form a supramolecular synthon built on strong intermolecular interactions. An example of an extremely robust supramolecular synthon is the basis of the molecular framework present in clathrates formed by the cephalosporin antibiotics **1**−**3** and a variety of guest molecules.[5]



1 Cephradine



2 Cephalexin (R = CH_3)
3 Cefaclor (R = Cl)

In these clathrates the cephalosporin molecules form bilayers held together by strong hydrogen bonding and electrostatic interactions. When these bilayers are packed to form a three-dimensional structure, channels remain and are filled by water and guest molecules. Effectively, the guest molecules are present in discrete cavities. Some remarkable induced-fit phenomena have been observed in clathrates formed by cephalosporins **1**−**3** and a series of naphthalene derivatives.[5] The cephalosporins are able to adapt their hosting framework to the size and the shape of the included guest. This adaptability arises from a slipping mechanism, in which the bilayers move with respect to each other, as a result of which the range of suitable guest molecules is significantly enlarged. In contrast, the cephalosporin Cefadroxil, which forms clathrates of a different structure type, lacks this adaptability.[5] The principle of induced-fit has been reported previously for inclusion compounds consisting of layered hosting frameworks formed by the dipeptide (*R*)-phenylglycyl-(*R*)-phenylglycine[6] and by guanidin-

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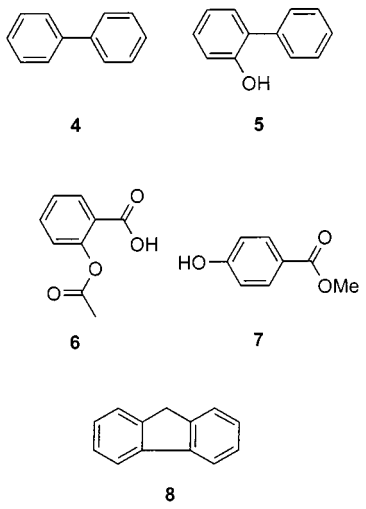
ium and disulfonate ions.[7] In these molecular frameworks, pillaring with guest molecules can alter the interlayer distance.

Selective complexation of cephalosporins can be a valuable technique for isolation of these important antibiotics from aqueous solutions.[8,9] A drawback associated with currently known guest molecules, all of which are naphthalene derivatives, is their toxicity and the inherent environmental image problem associated with these compounds. Hence, working on the assumption of an extended adaptability of cephalosporins **1**−**3**, the search for novel complexing agents was directed towards benzene derivatives. Unlike naphthalenes, many benzene derivatives have more acceptable characteristics with regard to toxicity and environmental image. Examples are biphenyl (**4**) (preservative E230), 2-hydroxybiphenyl (**5**) (preservative E231), acetylsalicylic acid (**6**) (Aspirin), and methyl 4-hydroxybenzoate (**7**) (preservative E218). From a fundamental point of view, it is also interesting to study cephalosporin complexation with tricyclic guest molecules larger than naphthalene, such as fluorene (**8**). In this way the boundaries of the adaptability of the hosting framework formed by the cephalosporins **1**−**3** can be explored. The results of this exploration in the case of Cephradine are described in this paper.



Results and Discussion

Preparation and Characterization of the Complexes

A series of benzene derivatives and several molecules larger than naphthalene, such as fluorene and benzilic acid, were subjected to complexation experiments with Cephradine. Crystalline complexes were analyzed by X-ray powder diffraction in order to establish whether the structures had the *C*2 cavity structures observed for complexes of cephalosporins **1**−**3** with naphthalenes.[10] The powder diffraction technique proved to be very valuable for this study, as nonisomorphous structure types could readily be recognized. This is illustrated in Figure 1 for two different structure types formed by Cephradine by variation of the complexing agents. In a number of cases, the deviations caused by the induced-fit processes are so large that the resulting structure no longer displays the typical X-ray powder pattern of the *C*2 cavity structure observed for complexes of **1**−**3** with naphthalenes. In these cases, the crystal structures of the complexes were elucidated by single-crystal X-ray diffraction, in order to establish the nature of the hosting framework.

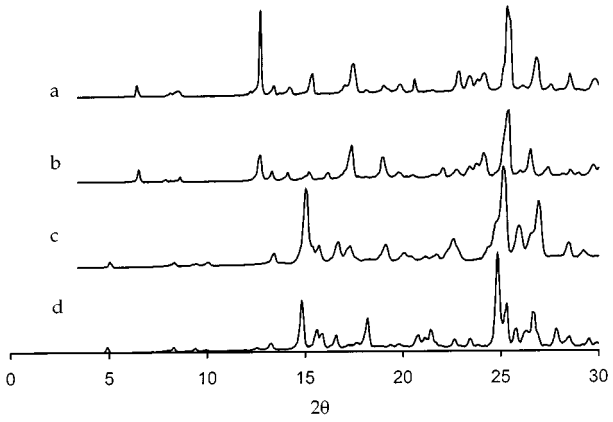
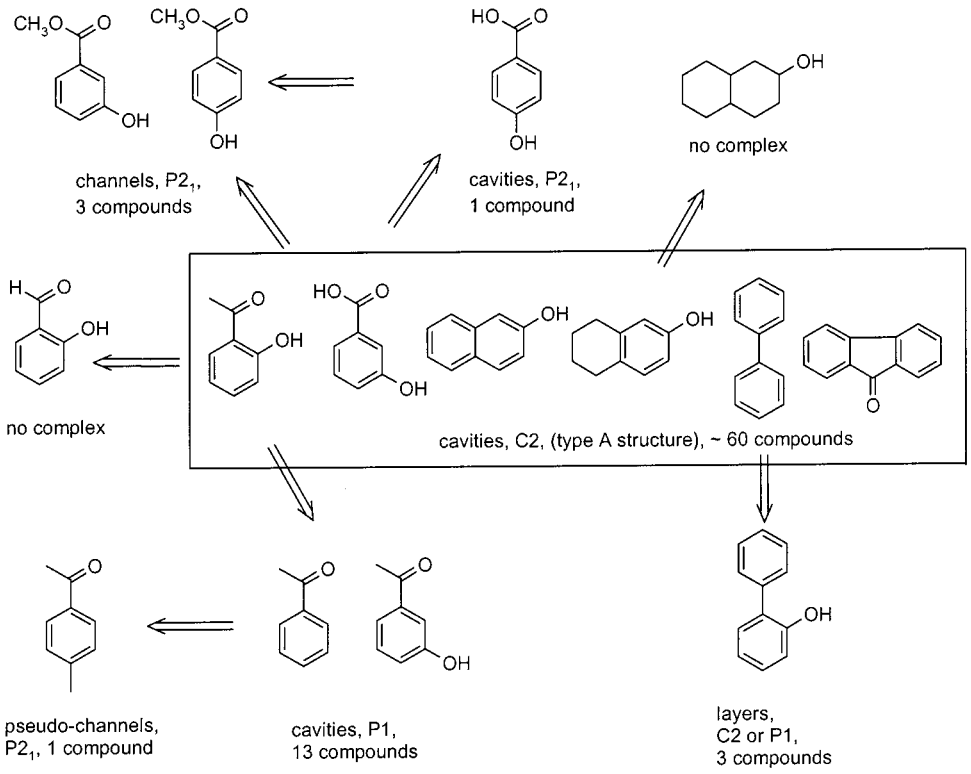


Figure 1. Powder diffraction patterns of complexes of Cephradine with 2-hydroxyacetophenone (a) and methyl benzoate (b) (type A, *C*2 cavity) and with 2,2′-biphenol (c) and 2-phenylphenol (d) (*C*2 layers)

It was possible to identify a large series of new guest molecules that form complexes with Cephradine. Most of these complexes were shown to have the *C*2 cavity type structure, but several other structure types were also found. The adaptability of the hosting framework of this structure type appeared to be high, as both benzene derivatives (benzoic acid, for example) and much larger molecules (such as fluorene and carbazole) can be hosted in it. Like the naphthalene complexes, some of the new structure types are clathrates containing discrete cavities. For certain guest molecules, however, layered and channel-type structures could also be created. The various types of complexes that have been prepared and characterized are summarized in Scheme 1, classified by space group and structure type: cavity-, layer-, or channel-type. The complexing behavior of the guest molecules is rather capricious, as subtle structural changes in the guest molecule can result in substantial changes in the overall structure of the Cephradine complexes, as is evident from Scheme 1. A complete list of newly discovered guest molecules and the structures of their corresponding Cephradine complexes is given in the Exp. Sect.

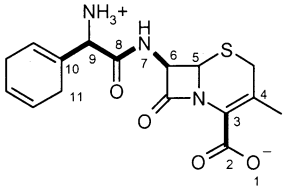
Structural Features of the Complexes

In order to quantify the conformational changes undergone by the Cephradine molecule in the new structures (relative to the known *C*2 cavity structure), five torsion angles were analyzed. These torsion angles are compiled in Table 1. To provide reference points for the *C*2 cavity structure obtained with the majority of guest molecules, Cephra-



Scheme 1. Complexants studied in the complexation with Cephradine and the type of complexes derived thereof; for each structure type the number of compounds that form that type of complex with Cephradine is shown

Table 1. Five torsion angles of Cephradine, measured in the corresponding complexes for all the structure types observed; torsion angles [°]: T_1 = 1−2−3−4, T_2 = 5−6−7−8, T_3 = 6−7−8−9, T_4 = 7−8−9−10, T_5 = 8−9−10−11



Complexing agent	Structure type	N[a]	T_1	T_2	T_3	T_4	T_5
β-Naphthol	$C2$ cavity	1	44	115	179	−169	50
2,2′-Bipyridyl	$C2$ cavity	1	45	106	178	−169	46
Fluorenone	$C2$ cavity	1	40	106	177	−161	44
4-Hydroxybenzoic acid	$P2_1$ cavity	2	74	104	179	−159	37
			94.3	87	−179	−136	100
Hydroquinone	$P1$ cavity	2	85	124	177	−176	42.0
			80.3	125	−180	−175	41
2-Hydroxybiphenyl	$C2$ layers	1	38.0	110	−175	−163	49
Benzilic acid	$P1$ layers	4	56	106	−172	−158	68.1
			49	104	−169	−159	50
			39	106	−170	−139	77
			55	112	−167	−152	56
4-Methylacetophenone	$P2_1$ pseudo channels	2	50	94	−176	−147	27
			31	101	−178	−157	40
Methyl 3-hydroxybenzoate	$P2_1$ channels	1	60	−73	−179	−139	52
Dimethylformamide	$P2_1$ channels	1	70	−71	−177	−155	50

[a] The number of independent Cephradine molecules per unit cell. The torsion angles in the table are specified above.

dine complexes with β-naphthol, 2,2′-bipyridyl, and fluorenone were taken.

The information compiled in Scheme 1 and Table 2 (Exp. Sect.) reveals that the majority of guest molecules form Cephradine complexes with the *C*2 cavity structure. Remarkably, the complexants here display considerable variation in structure, with benzene, naphthalene, and fluorene derivatives all belonging to this category, implying a substantial adaptability of this structure type. This adaptability can be accounted for by the bilayer slipping mechanism previously observed when naphthalene derivatives were used as the guest molecules.[5] It is of interest, however, to compare details of variations in the cavities produced by the various complexants, to shed light on the extent of the flexibility and, accordingly, on the limitations of the adaptability of this slipping mechanism.

The Cephradine hosting framework with the *C*2 cavity structure, which consists of bilayers of cephalosporin molecules, is depicted in Figure 2. It is conceivable that assemblage of this structure is from a supramolecular synthon (marked with circles in Figure 2), containing two carboxylate and two ammonium groups, provided by four individual Cephradine molecules. The adaptability of the *C*2 cavity structure can largely be attributed to the slipping mechanism along the crystallographic *a* axis. However, two other modes of induced-fit can be envisaged for the bilayer structure shown in Figure 2. These other modes of induced-fit are slippage along the *b* axis and variation in the interlayer distance. Although these induced-fit mechanisms have not been observed for the *C*2 cavity structures,[11] they may well be important for understanding of the formation of the new types of structures. In addition to the extra induced-fit modes, the new structures may also be accompanied by conformational changes in the cephalosporin molecules and may show a completely different motif of interactions in the repetitive unit of the hosting framework.

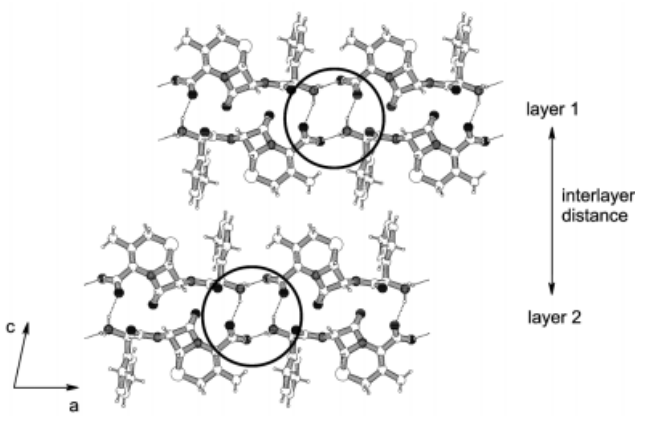


Figure 2. Three modes of induced-fit can be envisaged: slippage of the bilayers along the *a* axis and the *b* axis and variation in the interlayer distance

For 4-hydroxybenzoic acid, the complex with Cephradine has a $P2_1$ cavity type structure, as may be inferred from Scheme 1 and Table 2. This structure can readily be distinguished from the *C*2 cavity structure by X-ray powder diffraction. Remarkably, benzoic acid and 2- and 3-hydroxybenzoic acids (Scheme 1, Table 2) all form *C*2 cavity structures with Cephradine, whereas 4-hydroxybenzoic acid produces a very different structure, as shown in Figure 3. The following differences are notable:

the Cephradine molecules adapt two different conformations, which are present in a 1:1 ratio,

the main difference between the two conformations resides in the torsion $CH_{2,ring}-C-C-NH_3$ (T_5 in Table 1),

the pattern of intermolecular interactions between the Cephradine molecules, which is the basis for the formation of bilayers, is virtually identical to that in Figure 2.

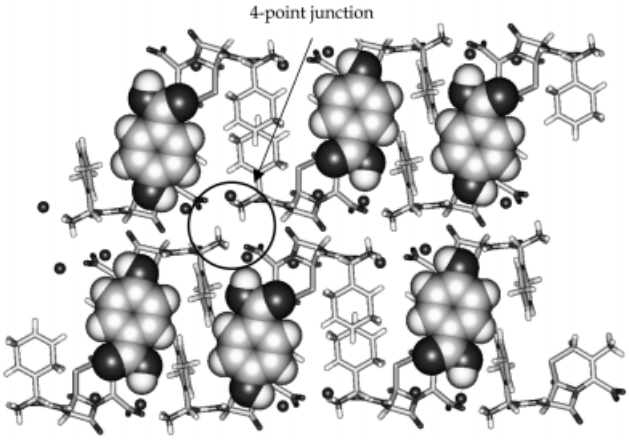


Figure 3. The complex formed by Cephradine and 4-hydroxybenzoic acid, viewed along the *b* axis; the host/guest/water ratio is 2:1:4

With 2-hydroxybiphenyl, 2,2′-dihydroxybiphenyl, and benzilic acid, Cephradine forms layer-type complexes. These three complexing agents have non-planar molecular structures, implying that these molecules would not easily fit into the cavities available in the *C*2 cavity type structures, which only tolerate flat substrates. The accommodation of planar guest molecules in the *C*2 cavity structure has already been demonstrated previously.[5] The phenomenon is further demonstrated by the observation that 2-decalinol forms no complex with Cephradine, while β-naphthol and 5,6,7,8-tetrahydro-2-naphthol do so. Apparently, induced-fit processes in the bilayers can achieve sufficient space for the inclusion of the hydroxybiphenyls as the guest molecules. The structure of the complex between Cephradine and 2-hydroxybiphenyl, depicted in Figure 4 (**a**), shows that the layered structures formed by Cephradine molecules are identical to those in the *C*2 cavity type complex. The conformation of the Cephradine molecule is also very similar, as can be seen from the torsional data shown in Table 1. The key dissimilarity between the *C*2 cavity structure and the structure shown in Figure 4 (**a**, **b**) is the enormous difference in the interlayer distance, amounting to an elongation of the *c* axis of 3.7 Å. This complex is hence not a clathrate with discrete cavities, but an intercalate formed by layers of cephalosporin molecules and layers of guest molecules, as is evident from Figure 4 (**b**). Accordingly, accom-

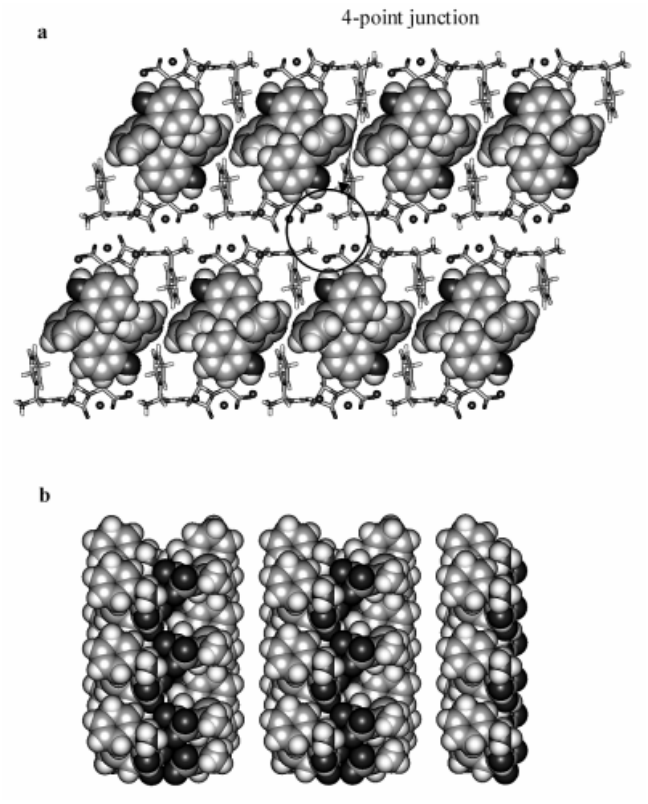


Figure 4. The complex of Cephradine and 2-hydroxybiphenyl, viewed along the *b*-axis (**a**); the complex of Cephradine and 2-hydroxybiphenyl, viewed along the *a* axis (**b**); for purposes of visualization of the intercalate structure the guest molecules are omitted

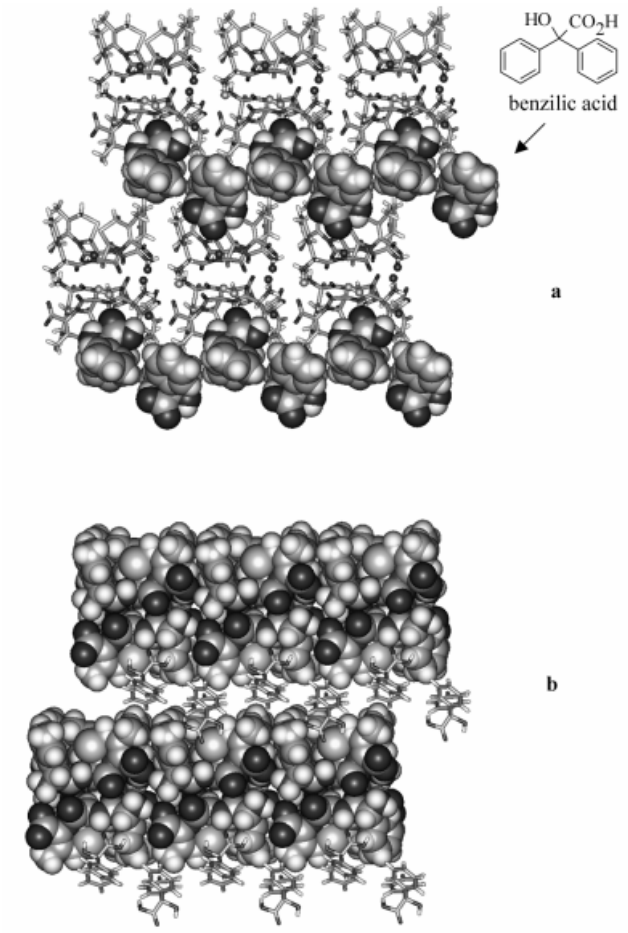


Figure 5. The complex of Cephradine (sticks) and benzilic acid (space-filling), viewed along the *a* axis (**a**); the complex of Cephradine (space-filling) and benzilic acid (sticks), viewed along the *a* axis (**b**)

modation in the guest molecule is not restricted by the shape of the cavity in the hosting framework of this type.

The structure of the complex between Cephradine and benzilic acid, shown in Figure 5, shows that the benzilic acid molecules also form two-dimensional layers. In this complex, the guest molecules have a pillaring effect on the layers formed by the Cephradine molecules.

After the *C*2 cavity type structure, the *P*1 cavity structure is most abundant, having been observed for 13 guest molecules (Table 2). The *P*1 cavity structure in the complex between Cephradine and hydroquinone was solved by X-ray diffraction and is depicted in Figure 6. The same motif of intermolecular interactions can be recognized in this structure, but it is, however, highly distorted in comparison with that in the *C*2 cavity structure. The cavities present in the *P*1 cavity structure are smaller than those present in the *C*2 cavity structure. In addition, the cavities are tilted, due to slippage of the bilayers in the direction of the *b* axis (Figure 6, **b**). This induced-fit mode, which is a combination of slips in two independent directions, had not been encountered previously. Moreover, the cephalosporin molecules have undergone conformational changes from their *C*2 cavity structures, as can be deduced from the torsional angles in Table 1.

Many of the *P*1 cavity complexes were initially isolated as needles, which underwent spontaneous transformation into powders during drying. In the cases of 2-aminophenol, aniline, and methyl 3-aminobenzoate, stable complexes both of the *C*2 cavity structure and of the *P*1 cavity structure could be isolated and characterized. So far, these are the only examples in which pseudo-polymorphs of cephalosporin complexes have been isolated. Interestingly, the *C*2-type complex could be converted into the *P*1 cavity structure by subjection of the crystals to low pressures. This transition was accompanied by powdering of the crystals, and presumably by the loss of one water molecule per antibiotic molecule. The crystal structure of the resulting powders could be established by X-ray powder diffraction. It is probable that a number of the complexes that initially gave needles but subsequently turned into powders underwent a similar but spontaneous transformation of the *C*2 cavity structure into the *P*1 cavity structure.

The complex between Cephradine and 4-methylacetophenone is depicted in Figure 7. Here, the bilayers are rather undulating, but the pattern of the intermolecular interactions between the Cephradine molecules is very much the same as that shown in Figure 2. Together with conformational changes in the Cephradine molecule, the major difference between the *C*2 cavity structure and the structure shown in Figure 7 is the enormous slip of the bilayers along

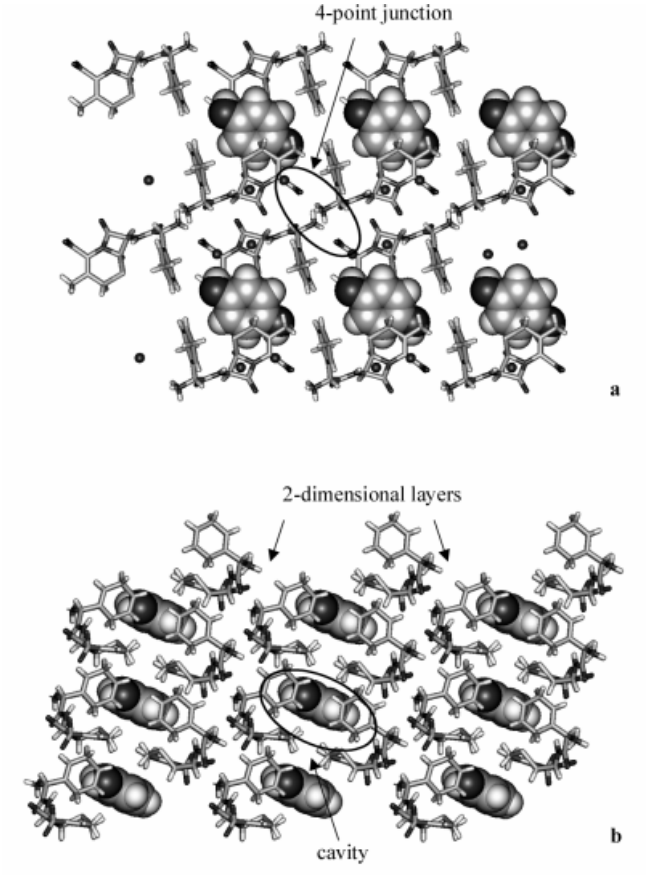


Figure 6. The structure of the complex of Cephradine and hydroquinone, viewed along the *a* axis (**a**); the host/guest/water ratio is 2:1:4; the complex of Cephradine and hydroquinone, viewed along the *b* axis (**b**)

the *a* axis, which is much more pronounced than in the case of naphthalenes as the complexants. This arrangement of the Cephradine molecules results in the inclusion of two guest molecules per cavity, instead of the one guest molecule common for the *C*2 cavity structure. Accordingly, the host/guest ratio amounts to 1:1. Moreover, two neighboring cavities have merged, which results in the formation of pseudo-channels winding through the hosting framework. In these pseudo-channels the complexant molecules adopt two different orientations.

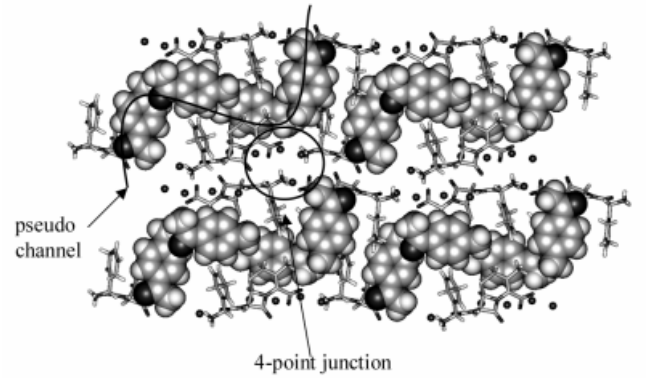


Figure 7. The complex of Cephradine and 4-methylacetophenone, viewed along the *b* axis

The structure deviating most strongly from the most abundant *C*2 cavity type structure was found in complexes between Cephradine and methyl 3-hydroxybenzoate, methyl

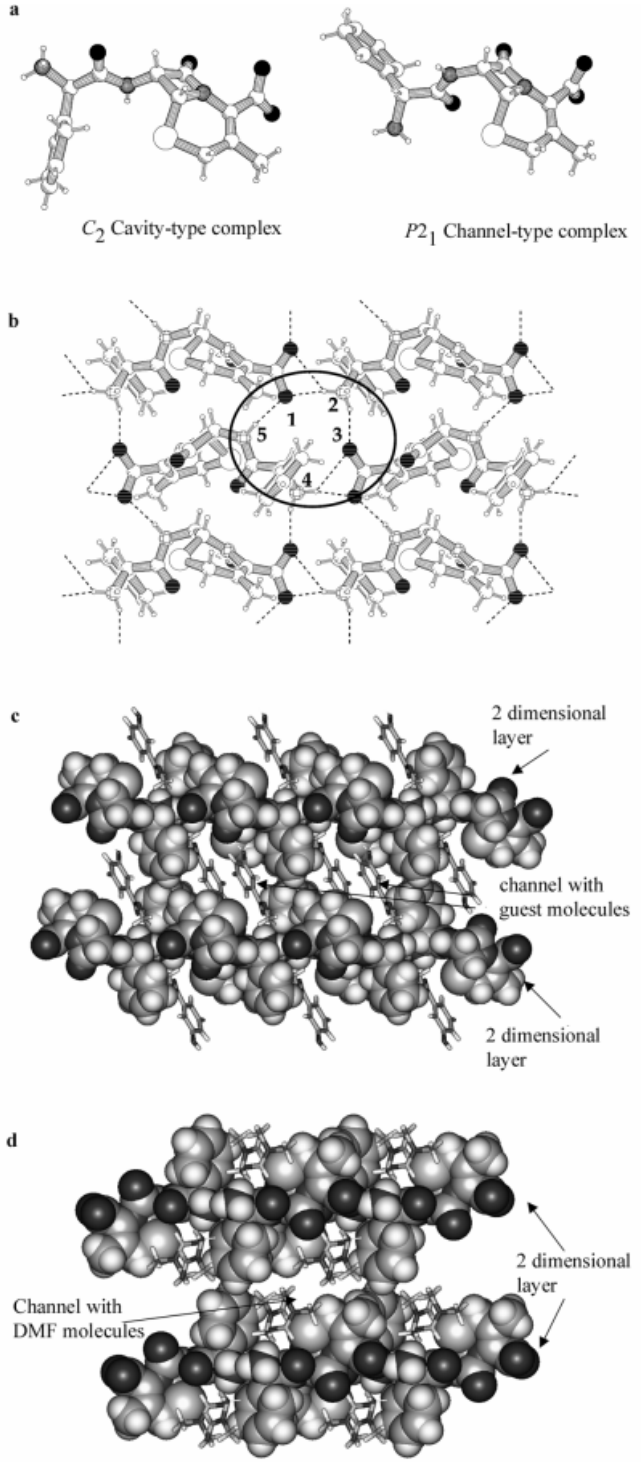


Figure 8. Platon drawings of the conformation of Cephradine in the *C*2 cavity type and the $P2_1$ channel-type complexes, respectively (**a**); the intermolecular interactions within the hosting framework of the $P2_1$ channel-type structure, viewed along the *c* axis (**b**); the complex of Cephradine and methyl 3-hydroxybenzoate, viewed along the *b* axis (**c**); the complex of Cephradine and dimethylformamide, viewed along the *b* axis (**d**)

4-hydroxybenzoate, and dimethylformamide. It is highly remarkable that subtle changes in the guest molecule (Scheme 1) have such enormous consequences for the structure of their complexes with Cephradine. The structures of these complexes with the complexants just mentioned involve a hosting framework containing genuine non-interrupted channels, which are directed along the *b* axis and do not contain any water molecules. Although the Cephradine network has features similar to the *C*2 cavity structure, the complex as a whole has an entirely different structure. This is accompanied by an enormous change in the conformation of the Cephradine molecules, as is evident from the torsional angles compiled in Table 1. Figure 8 (**a**) presents the conformations of Cephradine in the abundant *C*2 cavity structure and in the $P2_1$ channel type structure, clearly demonstrating the enormous difference. As the result of this alternative conformation, one of the four intermolecular bonds of the four-point junction, which is present in all other structure types, is disrupted. A Cephradine amide NH serves as a substitute for this disrupted bond, resulting in a cyclic array of hydrogen bonding and electrostatic interactions consisting of five interaction points, as pictured in Figure 8 (**b**). When the resulting bilayers are packed, a hosting framework with channels along the *b* axis is formed. In contrast to all other structure types, the guest molecules in these channel-type complexes are not surrounded by water. Figure 8 (**c**, **d**) shows the complexes between Cephradine and methyl 3-hydroxybenzoate and dimethylformamide, respectively, clearly revealing the channels.

Conclusion

Molecular complexes of the cephalosporin antibiotics Cephradine, Cephalexin, and Cefaclor with a variety of complexants all feature bilayers of the antibiotic molecule with weak van der Waals interactions between the layers, thus allowing them to move relative to one another with relative ease. This layer arrangement endows the hosting skeleton with considerable adaptability in accommodating guest molecules of different sizes, by three modes of induced-fit to adjust the size of the cavities for the complexing compound. This adaptability considerably expands the range of guest molecules, which is clearly not restricted to the initially discovered group of naphthalene derivatives as suitable complexants. It has been found that a series of benzene derivatives can serve as effective complexing agents for Cephradine, which was taken as the representative antibiotic in this study. These complexants are potential candidates for isolation of Cephradine from aqueous solutions, in, for example, an industrial production of this antibiotic during which an enzymatic coupling of the Cephradine nucleus with an appropriate side chain is performed in aqueous media. Among the benzene derivatives there are several compounds with fully acceptable environmental and toxicological profiles, much better than those of the previously reported naphthalene derivatives.

This study also found that subtle variations in the structure of the guest molecules can have an enormous impact on the structures of molecular complexes with Cephradine.

Table 2. Cephradine complexes prepared and characterized, classified by their structure type

Structure type	Guest molecules
*C*2 Cavities (Type A)	benzoic acid, salicylic acid, 3-hydroxybenzoic acid, methyl benzoate, methyl salicylate, *o*-methoxybenzoic acid, *o*-toluic acid, *m*-toluic acid, methyl *p*-methylbenzoate, benzamide, 2-aminobenzoic acid, methyl 2-aminobenzoate, 2-aminobenzamide, 4-aminosalicylic acid, methyl *N*-methyl-2-aminobenzoate, methyl 3-aminobenzoate,[a] 2,4-dihydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 3,5-dihydroxybenzoic acid, gallic acid, methyl gallate, methyl 2,4-dihydroxybenzoate, methyl 3,5-dihydroxybenzoate, 2-methoxybenzaldehyde, vanillin, 2-hydroxyacetophenone, 2-methoxyacetophenone, 2-methylacetophenone, catechol, pyrogallol, phlorogucinol, anisole, *m*-anisidine, aniline,[a] 2-aminophenol,[a] toluene, benzene, 4-hydroxybiphenyl, fluorene, fluorenone, carbazole, methyl 4-aminobenzoate
$P2_1$ Cavities	*p*-hydroxybenzoic acid
*C*2 Layers	2-hydroxybiphenyl, 2,2′-dihydroxybiphenyl
*P*1 Layers	benzilic acid
*P*1 Cavities	acetophenone, 3-hydroxyacetophenone, 4-aminoacetophenone, 1-indanone, phenol, resorcinol, hydroquinone, 4-methoxyphenol, *p*-cresol, 2-aminophenol,[a] 3-aminophenol, aniline,[a] methyl 3-aminobenzoate[a]
$P2_1$4-methylacetophenone	
$P2_1$ Channels	methyl 3-hydroxybenzoate, methyl 4-hydroxybenzoate, dimethylformamide

[a] Two pseudo-polymorphs have been isolated and characterized.

Table 3. Crystal data of the complexes Cephradine/4-hydroxybenzoic acid (**1a**), Cephradine/2-hydroxybiphenyl (**1b**), Cephradine/benzilic acid (**1c**), andCephradine/hydroquinone (**1d**)

	1a	**1b**	**1c**	**1d**
Crystal color	colorless	colorless	colorless	colorless
Crystal shape	regular thick needle	regular flat needle	regular rod	large regular platelet
Size [mm]	0.46 × 0.20 × 0.11	0.53 × 0.20 × 0.09	0.23 × 0.10 × 0.09	1.20 × 0.50 × 0.20
Formula	$C_{39}H_{52}N_6O_{15}S_2$	$C_{56}H_{70}N_6O_{16}S_2$	$C_{46}H_{50}N_6O_{11}S_2$	$C_{38}H_{52}N_6O_{14}S_2$
M_w	908.99	1147.30	927.04	880.98
T [K]	293(2)	293(2)	293(2)	208(2) K
Crystal system	monoclinic	monoclinic	triclinic	triclinic
Space group	$P2_1$	$C2$	$P1$	$P1$
a [Å]	14.917(5)	23.5642(6)	11.7069(13)	7.07185(19)
b [Å]	7.382(3)	7.1320(2)	11.8689(10)	10.7031(2)
c [Å]	20.503(9)	18.6893(9)	19.0047(17)	14.2342(5)
α [°]	90	90	75.064(9)	87.154(3)
β [°]	105.77(6)	109.380(3)	74.695(14)	78.999(3)
γ [°]	90	90	85.408(16)	89.743(2)
Reflections	15	25	24	25
θ range [°]	21.927−22.942	40.229−46.835	15.383−23.563	39.912−45.180
V [Å^3]	2172.7(15)	2962.96(19)	2460.8(4)	1056.28(5)
Z	2	2	2	1
D_c [Mg/m^3]	1.389	1.286	1.251	1.385
Abs. coeff. [mm^{-1}]	1.756	1.412	1.503	1.769
F(000)	960	1216	976	466
θ-rang. coll. [°]	3.08−69.96	3.94−69.98	3.85−70.30	3.17−69.86
Index range				
h	−17 to 18	−28 to 26	−14 to 14	−8 to 8
k	0 to 8	0 to 8	−14 to 0	−13 to 13
l	−24 to 0	0 to 22	−23 to 22	−17 to 0
Refl. coll./uniq.	4570/4441	3143/3046	9805/9805	4162/4162
R(int.)	0.0195	0.0605		0.0000
Refl.obs. [$I_o > 2\sigma(I_o)$]	4235	2788	4073	3897
Range of rel. transm. fact.	−	1.152/0.939	1.017 /0.986	1.175/ 0.907
Data/restr./param.	4441/1/567	3046/1/363	9805/375/1272	4162/3/545
g.o.f. on F^2	1.049	1.098	1.073	1.725
SHELXL-97	0.087800	0.132100	0.064500	0.200000
weight param.	0.392400	1.880800	5.013600	0.000000
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0423	$R1$ = 0.0555	$R1$ = 0.0883	$R1$ = 0.1218
	$wR2$ = 0.1187	$wR2$ = 0.1755	$wR2$ = 0.1727	$wR2$ = 0.3341
R indices (all data)	$R1$ = 0.0442,	$R1$ = 0.0616	$R1$ = 0.2256	$R1$ = 0.1218
	$wR2$ = 0.1213	$wR2$ = 0.1888	$wR2$ = 0.2285	$wR2$ = 0.3341
$\Delta\rho_{max/min}$ [e·Å^{-3}]	0.347/−0.279	0.428/−0.389	0.412/−0.390	1.086/−1.110

In all the Cephradine complex variants, the head-to-tail interactions of the zwitterionic Cephradine molecules, present in the majority of cases as 4-point junctions, remained unaffected. This adaptability in the inclusion of guest molecules is governed solely by slippage of antibiotic layers and variation in the interlayer distance. Evidently, the head-to-tail interactions determine the boundaries of the adaptability of the hosting framework for the accommodation of guest molecules.

Experimental Section

General Remarks: Cephradine monohydrate was a generous gift of DSM Life Sciences Group (Geleen, The Netherlands). All complexing agents used are commercially available and were purchased from either Acros or Aldrich. X-ray powder patterns were recorded with a Philips PW1820 Automatic Powder Diffractometer equipped with a Philips PW1830 High Voltage Generator.

Complexation Experiments: Cephradine monohydrate (525 mg, 1.5 mmol) was dissolved in water (50−100 mL). The complexing agent was dissolved in methanol (2 mL) and subsequently added to the Cephradine solution. Crystalline complexes were filtered off and dried under a flow of nitrogen. The complexes were analyzed by X-ray powder diffraction, and in some cases also by single-crystal X-ray diffraction. When the complexing agent was only poorly soluble in water, the complexes were crystallized from water/methanol mixtures. The results of the complexation experiments are compiled in Table 2.

Crystal Structure Determination: Crystals were mounted on glass fibers, and intensity data were collected with a Nonius CAD4 diffractometer. The radiation used was Cu-K_α (graphite-monochromated) with λ = 1.54184 Å. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption corrections (ψ-scan) were applied.[12] The structures were solved using the DIRDIF program system.[13] Structure refinement was performed by full-matrix, least squares on F^2 (SHELXL program).[14] Details of all structure determinations are given in Tables 3 and 4. Crystal-

Table 4. Crystal data of the complexes Cephradine/4-methylacetophenone (**1e**), Cephradine/methyl 3-hydroxybenzoate (**1f**), Cephradine/dimethylformamide (**1g**), and Cephradine/fluorenone (**1h**)

	1e	**1f**	**1g**	**1h**
Crystal color	colorless	colorless	colorless	colorless
Crystal shape	regular rod	regular platelet	regular platelet	regular needle
Size [mm]	0.44 × 0.16 × 0.06	0.34 × 0.18 × 0.08	0.33 × 0.25 × 0.07	0.49 × 0.12 × 0.06
Formula	$C_{25}H_{34}N_3O_{7.5}S$	$C_{24}H_{27}N_3O_7S$	$C_{22}H_{33}N_5O_6S$	$C_{45}H_{58}N_6O_{15}S_2$
M_w	528.61	501.55	495.59	987.09
T [K]	208(2)	208(2)	208(2)	293(2)
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$C2$
a [Å]	15.4038(6)	10.9073(3)	10.8747(4)	23.331(3)
b [Å]	7.2983(4)	9.40654(19)	9.5114(3)	7.287(3) A
c [Å]	23.5735(12)	12.1992(3)	12.3904(3)	14.7137(18)
α [°]	90	90	90	90
β [°]	99.354(4)	98.533(2)	98.705(3)	105.559(14)
γ [°]	90	90	90	90
Reflections	25	25	25	25
θ range [°]	22.865−46.103	40.666−45.763	40.203−45.994	8.889−12.444
V [Å^3]	2614.9(2)	1237.79(5)	1266.82(7)	2409.9(11)
Z	4	2	2	2
D_c [Mg/m^3]	1.343	1.346	1.299	1.360
Abs. coeff. [mm^{-1}]	1.536	1.582	1.525	0.184
F(000)	1124	528	528	1044
θ-rang. col.[°]	2.91−69.97	3.66−69.89	3.61−69.99	3.16−27.46
Index range				
h	0 to 8	−13 to 0	−13 to 13	0 to 30,
k	−8 to 0	−11 to 0	0 to 11	0 to 9
l	−28 to 28	−14 to 14	0 to 15	−19 to18
Refl. coll./uniq	5570/5365	2639/2504	2687/2566	3042/2970
R(int.)	0.0577	0.0896	0.0181	0.0483
Refl. obs. [$I_o > 2\sigma(I_o)$]	4871	2349	2474	1033
Range of rel. transm. fact.	1.317/0.864	1.583/0.766	1.176/0.917	1.179/0.881
Data/restr./param.	5365/1/666	2504/1/110	2566/1/377	2970/289/381
g.o.f. on F^2	4.010	5.308	1.055	1.023
SHELXL-97	0.100000	0.100000	0.087500	0.074000
weight param.	0.000000	0.000000	0.169400	0.000000
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.2095	$R1$ = 0.2492	$R1$ = 0.0373	$R1$ = 0.0920
	$wR2$ = 0.4176	$wR2$ = 0.5187	$wR2$ = 0.1060	$wR2$ = 0.1564
R indices (all data)	$R1$ = 0.2183	$R1$ = 0.2580	$R1$ = 0.0387	$R1$ = 0.2779
	$wR2$ = 0.4329	$wR2$ = 0.5318	$wR2$ = 0.1078	$wR2$ = 0.2188
$\Delta\rho_{max/min}$ [e·Å^{-3}]	3.651/−2.717	4.361/−2.739	0.427/−0.206	0.261/−0.304

lographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-160840 (Cephradine/4-hydroxybenzoic acid, **1a**), -160839 (Cephradine/2-hydroxybiphenyl, **1b**), -160833 (Cephradine/benzilic acid **1c**), -160838 (Cephradine/hydroquinone, **1d**), -160837 (Cephradine/4-methylacetophenone, **1e**), -160836 (Cephradine/methyl 4-hydroxybenzoate, **1f**), -160835 (Cephradine/*N*,*N*-dimethylformamide, **1g**), -160834 (Cephradine/fluorenone, **1h**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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framework (e.g., cavity structure, layer structure, or channel structure). The *C*2 cavity structure corresponds to the type A structure referred to in ref.[5]
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