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Inclusion Complexes

Tetrakis(dimethoxyphenyl)adamantane (TDA) and Its Inclusion Complexes in the Crystalline State: A Versatile Carrier for Small Molecules

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Dedicated to Prof. Dr. Alwin E. Goetz on the occasion of his 60th birthday

Abstract: Molecular storage solutions for incorporating small molecules in crystalline matrices are of interest in the context of structure elucidation, decontamination, and slow release of active ingredients. Here we report the syntheses of 1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane, 1,3,5,7-tetrakis(4-methoxyphenyl)adamantane, 1,3,5,7-tetrakis(4-methoxy-2-methylphenyl)adamantane, and 1,3,5,7-tetrakis(4-methoxy-2-ethylphenyl)adamantane, together with their X-ray crystal structures. All four compounds crystallize readily. Only the octaether shows an unusual level of (pseudo)polymorphism in its crystalline state, combined with the ability to include a number of different small molecules in its crystal lattices. A total of 20 different inclusion complexes with guest molecules as different as ethanol or trifluorobenzene were found. For nitromethane and benzene, schemes for uptake and release are presented.

Introduction

Developing molecular materials that form from organic molecules and that have the ability to act as host for small molecules is an interesting challenge.[1] The storage of guest molecules is usually made possible by the formation of networks of host molecules.[2,3] The assembly of host molecules into periodic lattices may be accompanied by chemical reactions, leading to covalent organic frameworks (COFs).[4,5] Examples of crystalline or amorphous organic materials that have the potential to incorporate guests include organic cages,[6a] porous aromatic frameworks (PAF),[6b] porous polymer networks (PPN),[6c] and porous organic frameworks (POF).[6d] Gases are frequently studied as guests, and the host structures are often rigid, being composed of aromatic and/or aliphatic rings.[7] The adamantane scaffold combines rigidity with the ability to induce formation of diamondoid structures.[8] Branched adamantane derivatives are known to form assemblies with the ability to act as hosts for small molecules.[9,10] As a consequence, tetrasubstituted adamantanes are valuable building blocks. But, their synthesis can be challenging, due to steric and electronic peculiarities.[11–13] Still, tetrasubstituted adamantanes find applications in medicine and materials sciences.[14,15]

We have become interested in using tetrasubstituted adamantanes as structuring elements in networks of oligonucleotide hybrids. In these hybrids, the adamantanes act as branching elements that preorganize short DNA arms, so that they can form three-dimensional networks via Watson–Crick base pairing.[16–18] So far, we have studied hybrids with tetrakis(hydroxybiphenyl)adamantane[19,20] or tetrakis(triazolylphenyl)adamantane[21] as core. Upon hybridization of short "CG zipper" DNA arms, the hybrids form nanoporous materials from aqueous solution when treated with divalent cations. The materials thus formed take up salts and intercalators, suggesting that they are nanoporous.[21–24] Crystals of the cores themselves have provided valuable insights.[21] This encouraged us to pursue the synthesis of a wider range of symmetrical molecules and to study their properties in the solid state. We focused on tetrasubstituted adamantanes because rigidity should be favourable for crystallization into porous materials.

Here we report the synthesis of four methoxy-substituted tetraphenyladamantanes, including derivatives with methyl or ethyl side chains on the phenyl rings. Among them, 1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane (TDA) showed an interesting propensity to act as host for guest molecules, incorporating a wide range of different small molecules in crystal structures of three different space groups. Neither of the other adamantanes showed the same behavior. The ability to crystallize in different forms and to capture and release different host molecules makes the octaether interesting for molecular storage applications.

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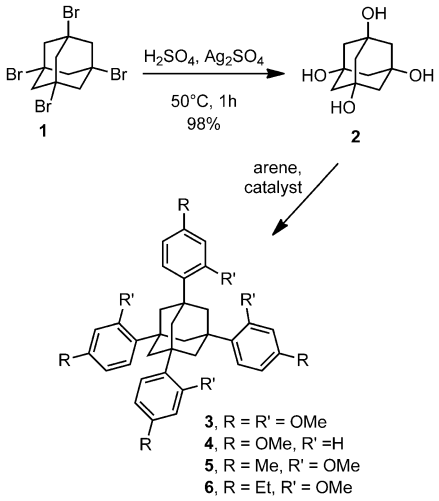
*Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201406568: ^{1}H and ^{13}C NMR spectra of new compounds and details of the crystal structures of compounds **3**, **4**, **5**, and **6**.*

Results

Syntheses

The synthesis of the tetraaryladamantes started from 1,3,5,7-tetrabromoadamantane (**1**, Scheme 1), accessible by four-fold bromination of adamantane under Stetter conditions.[25] The tetrabromide was hydrolyzed to tetraol **2**. Exhaustive Soxhlet extraction improved the yield to 98% over the 84% reported in the literature.[26] We selected phenyl rings as substituents for the desired tetraaryladamantanes, assuming that they will offer sites for molecular interactions with guest molecules in the final crystalline assemblies. Anisoles with an additional methoxy group (1,3-dimethoxybenzene) or alkyl group (3-methylanisole or 3-ethylanisole) were chosen as arenes, complementing the parent compound to be prepared with anisole itself. This led to tetrasubstituted adamantanes **3**–**6** as target molecules (Scheme 1).



Scheme 1. Synthesis of tetrasubstituted adamantanes **3**–**6**.

Introducing the phenyl substituents to the adamatane required alkylation of the anisoles. Friedel–Crafts alkylations often lead to overalkylation. Further, a high *ortho*-/*para*-selectivity can be difficult to achieve, making even single substitutions of adamantane substrates (be they alcohols or halides) a synthetic challenge.[27] The challenge is greater still, if tetrasubstitution is to be achieved, as in our case. It is therefore not surprising that there are a limited number of examples of successful four-fold substitutions via alkylation, starting from a tetrafunctionalized adamantane.[8,13] Stetter and coworkers had shown that anisole as an electron-rich arene can be introduced with a Brønsted acid as catalyst.[28]

We tested the catalysts and reaction conditions listed in Table 1 to obtain acceptable yields of either of the symmetrically tetrasubstituted adamantanes **3**–**6**. The best result was achieved for **5**, which was isolated in 41% yield after reacting **2** with 3-methylanisole in the presence of tosylic acid as catalyst for 72 h at 120 °C. For this and other alkylanisoles, long reaction times that favor thermodynamic control gave a more narrow product distribution than short reaction times, most probably because ortho/para isomers were slowly interconverting under these conditions.

Table 1. Results of substitution reactions involving **2** and different arenes.

Entry	Aromatic reactant	Catalyst	Reaction time [h]	Reaction temperature [°C]	Product	Yield [%]
1	1,3-dimethoxy-benzene	TsOH	48	140	3	21
2		TsOH	96	140	3	38
3		TMS-OTf	20	120	3	<1
4		TfOH	20	120	3	<1
5	anisole	TsOH	72	140	4	7
6		TMS-OTf	72	120	4	11
7		TfOH	20	120	4	39
8		TfOH [BMIM][OTf][a]	48	85	4	10
9	3-methylanisole	TsOH	72	130	5	41
10		TMS-OTf	72	130	5	11
11	3-ethylanisole	TsOH	24	120	6	20
12		TsOH	48	120	6	30

[a] Ionic liquid 1-butyl-3-methylimidazolium trifluoromethanesulfonate [BMIM][OTf] as solvent.

For **5**, Lewis acid TMS-OTf gave a lower yield than the Brønsted acid tested (tosylic acid). For the reaction with anisole that produced tetrakis(methoxyphenyl)adamantane (**4**), a yield of just 4% was obtained with pTsOH, compared to 10% for the reaction catalyzed by TMS-OTf, and over 39% for that catalyzed by triflic acid. The different optima found for different arenes might be a consequence of the equilibria leading to the active electrophile and the different propensities of the arene substrates to undergo side reactions, such as ether cleavage.

Crystal Structures

Anisole-containing parent compound **4** crystallized from *n*-hexane/dichloromethane. The X-ray crystal structure (Figure 1 and Table 2) showed no peculiarities, with four molecules per unit cell and an absence of solvent inclusions. Likewise, adamantanes **5** and **6** with their methyl or ethyl groups did not include solvent molecules in their crystal lattices. Both crystallized in a different space group.

Unlike **4**–**6**, adamantane **3** with its four dimethoxyphenyl substituents showed an unusual propensity to include guest molecules in its crystals. A total of 20 different inclusion complexes were found for this compound, along with two crystal structures that do not show any guest molecules, which were obtained when **3** was crystallized from acetic acid or aniline (Figure 2 and entries 4 and 22 in Table 2).

The inclusion complexes of **3** were obtained by crystallizing the octaether in the presence of different solvents. Figures 3

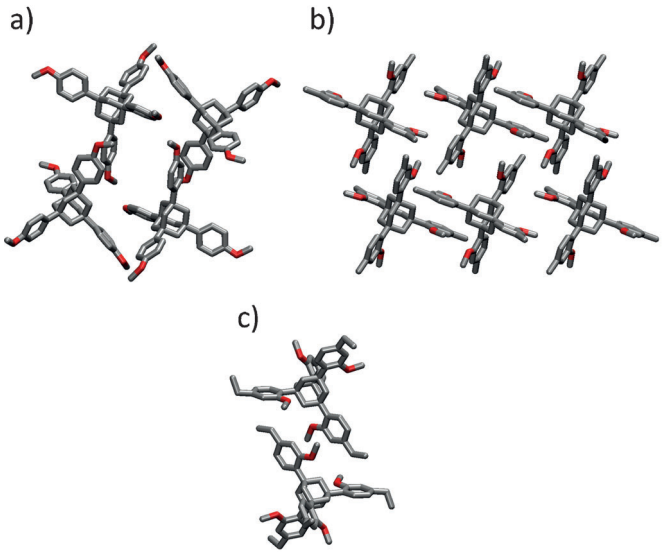


Figure 1. X-ray crystal structures of tetraaryladamanates **4** (a), **5** (b), and **6** (c). Color code: Carbon, grey; oxygen, red. Hydrogens were omitted for clarity. See entries 1–3 in Table 2 for details.

and 4 show details of the inclusion complexes as found in the crystals. Interestingly, fifteen of the structures of **3** were monoclinic (Figure 3), whereas eight were triclinic (Figure 2 and 4),

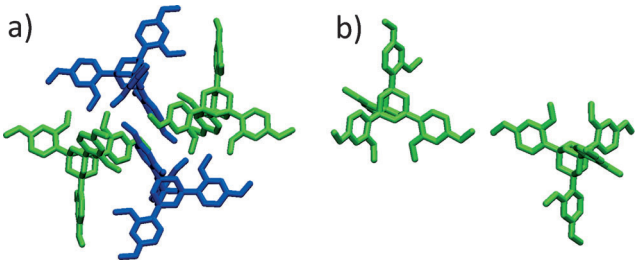


Figure 2. X-ray crystal structures of **3** without inclusion of a guest molecule, as obtained by crystallizing a) from glacial acetic acid, and b) from aniline. Non-equivalent molecules are shown in different colors. See Table 2, entry 4 and 22 for details.

including the structures lacking small molecules as guests. The monoclinic structures showed inclusion of molecules as different in size and polarity as dichloromethane, cyclohexane, nitrobenzene, acetonitrile, and acetone. In many instances, the guest molecules were well ordered (entries 5–7, 10–11, 13–20 and 23 in Table 2), whereas disordered guests were found in the crystals obtained from crystallization in solvents such as CH_2Cl_2 or $CHCl_3$ with EtOH, 2-propanol, or propanol as co-solvents (entries 8–9 and 12 in Table 2 and Supporting Information).

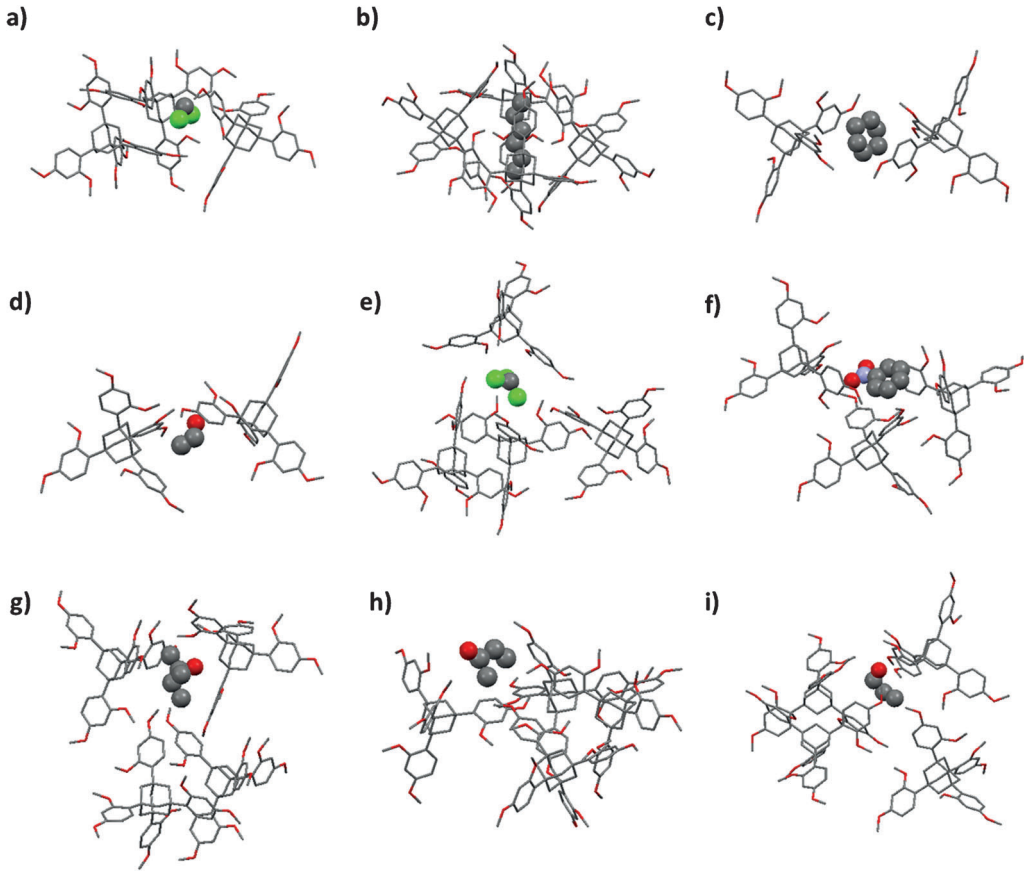


Figure 3. Molecular recognition of small molecule guests in inclusion complex of **3** with a) dichloromethane; b) *n*-hexane; c) cyclohexane; d) ethanol; e) chloroform; f) nitrobenzene; g) *rac*-2-methyl-2-butanol, h) 2-butanol, and i) *n*-propanol as guests. Hydrogen atoms were omitted for clarity. For further details, see entries 5, 6, 7, 10, 12, 13, 14, 15 and 18 of Table 2, respectively. Color code: Carbon, grey; oxygen, red; nitrogen, purple; chlorine, green.

Table 2. Structural parameters for crystals of tetraaryladamantanes with our without guest molecules.

Entry	Compound	Crystal system	Space group	Volume of u.c. [Å^3]	Z[a]	Density [Mg m^{-3}]	Solvent(s)	Inclusion guest	Calculated stoichiometry (host/guest)	$R1$[b]/$wR2$
1	**4**	monoclinic	$P2_1/n$	3009	4	1.238	CH_2Cl_2/C_6H_{12}	–	–	0.0377/ 0.0890
2	**5**	tetragonal	$I4_1/a$	3414	4	1,200	CH_2Cl_2/C_6H_{12}	–	–	0.0561/ 0.1480
3	**6**	triclinic	$P\bar{1}$	1866	2	1.198	CH_2Cl_2/C_6H_{12}	–	–	0.0551/ 0.0998
4	**3**	triclinic	$P\bar{1}$	3538	4	1.278	acetic acid	–	–	0.0424/ 0.1056
5	**3**	monoclinic	$C2/c$	15932	16	1.312	CH_2Cl_2	CH_2Cl_2	4:5	0.0841/ 0.2151
6	**3**	monoclinic	$P2_1/n$	7415	8	1.258	CH_2Cl_2/C_6H_{14}	C_6H_{14}	4:1	0.0453/0.1131
7	**3**	monoclinic	$C2/c$	16380	16	1.241	CH_2Cl_2/C_6H_{12}	C_6H_{12}	1:1	0.0358/ 0.0902
8	**3**	monoclinic	$P2_1/n$	7484	8	1.267	CH_2Cl_2/EtOH	CH_2Cl_2/EtOH	4:1:1	0.0546/ 0.1346
9	**3**	monoclinic	$P2_1/n$	7542	8	1.258	CH_2Cl_2/2-propanol	CH_2Cl_2/2-propanol	8:1:3	0.0580/ 0.1075
10	**3**	monoclinic	$P2_1/n$	7497	8	1.247	EtOH	EtOH	2:1	0.0461/0.1150
11	**3**	triclinic	$P\bar{1}$	7764	8	1.308	$CHCl_3$/*n*-propanol	$CHCl_3$/*n*-propanol	4:1:1	0.0669/ 0.1719
12	**3**	monoclinic	$P2_1/n$	7513	8	1.276	$CHCl_3$/EtOH	$CHCl_3$/EtOH	n.d.	0.0611/0.1575
13	**3**	monoclinic	$P2_1/c$	7445	8	1.325	nitrobenzene	nitrobenzene	2:1	0.0461/ 0.0918
14	**3**	monoclinic	$P2_1/n$	7650	8	1.259	2-methyl-2-butanol	2-methyl-2-butanol	2:1	0.0548/ 0.1310
15	**3**	monoclinic	$P2_1/n$	7572	8	1.259	2-butanol	2-butanol	2:1	0.0400/ 0.0967
16	**3**	triclinic	$P\bar{1}$	2066	2	1.306	trifluorobenzene	trifluorobenzene	1:1	0.0416/ 0.0771
17	**3**	monoclinic	$P2_1/n$	7511	8	1.279	CH_2Cl_2/*n*-propanol	CH_2Cl_2	2:1	0.0683/ 0.1816
18	**3**	monoclinic	$P2_1/n$	7577	8	1.246	$MeNO_2$/*n*-propanol	*n*-propanol	2:1	0.0861/ 0.1964
19	**3**	monoclinic	$P2_1/n$	15704	16	1.304	nitromethane	nitromethane	2:3	0.0641/ 0.1566
20	**3**	monoclinic	$C2/c$	15798	16	1.279	acetone	acetone	8:11	0.0739/ 0.1783
21	**3**	monoclinic	$C2/c$	15800	16	1.230	acetonitrile	acetonitrile	1:1.25	0.0927/ 0.2135
22	**3**	triclinic	$P\bar{1}$	1746	2	1.295	aniline	–	–	0.0461/ 0.0883
23	**3**	triclinic	$P\bar{1}$	2015	2	1.250	EtOH/C_6H_6	benzene	1:1	0.0442/ 0.1080
24	**3**	triclinic	$P\bar{1}$	4087	4	1.324	+ $CHCl_3$	benzene/$CHCl_3$	8:3:7	0.0731/ 0.1801
25	**3**	triclinic	$P\bar{1}$	1985	2	1.288	+ $CHCl_3$	$CHCl_3$	4:3	0.0656/ 0.1559

[a] Number of molecules in a unit cell, asymmetric unit. [b] Final R indices [$I > 2\,\sigma(I)$]. For binary solvent systems (Table 2, entries 8, 9, 11 and 12), an overlap model of both solvent components was used for better fitting the strongly disordered parts of the solvent electron densities. The unit cell dimensions are reported in the Supporting Information (Table S1).

Cyclohexane was incorporated in crystals of **3** at a molar ratio of 1:1 (Figure 3c and entry 7 of Table 2). Here, a large volume of the unit cell and a large asymmetric unit was found. Crystallization with *n*-hexane (Figure 3b and entry 6 in Table 2) showed inclusion of the acyclic alkane at a ratio of 4:1 (**3**: *n*-hexane), and the crystal structure contained unit cells with less than half the volume, showing the degree of variability in the crystal packing of **3**, and how differently the molecular recognition of small molecules is achieved.

The observations listed above suggested that **3** avidly takes up organic molecules, and that it does so by forming a rather promiscuous set of inclusion pockets. When a mixture of dichloromethane or chloroform with ethanol or propanol was used, crystals were found to contain a mixture of two solvents (Figures S17–20 and S23–26, Supporting Information). Crystallization attempts from toluene gave crystals of poor order, so that only the adamantane core could be observed in the X-ray diffraction patters, possibly because the phenyl arms and any

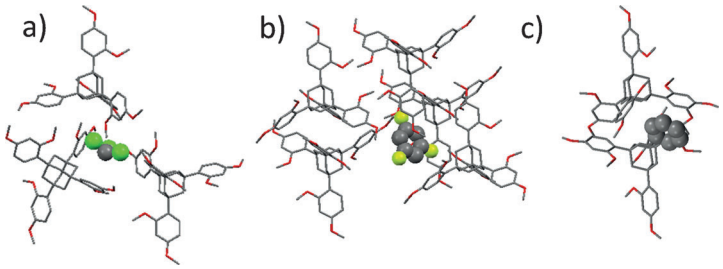


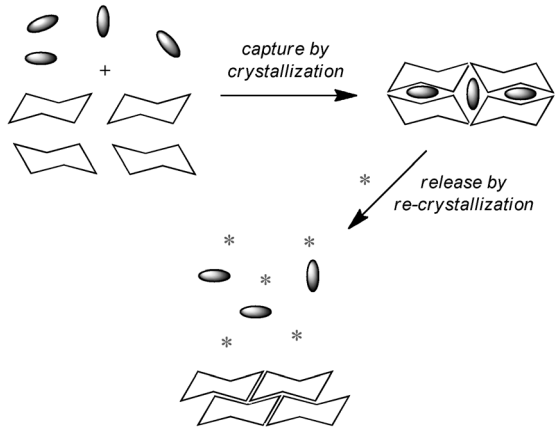
Figure 4. Structural details from inclusion complexes of **3** in triclinic crystal systems with a) chloroform (only one of the guest molecules is shown), b) 1,3,5-trifluorobenzene, and c) benzene as guests. Hydrogens were omitted for clarity. Color code: Carbon, grey; oxygen, red; chlorine, green; fluorine, light green. See Table 2, entries 11, 16, and 23 for further details.

included solvent showed too high a mobility. When crystallizing **3** from dichloromethane alone, crystals were obtained that appeared to lose solvent when exposed to air, leading to brittle and eventually unstable crystals. This suggested that for certain guests, a release of small molecules can be induced quite readily.

Uptake and Release

The detection[29,30] and removal[31] of combustible compounds and explosives are important challenges that require molecular solutions. Some unstable compounds, such as acetylene, have to be stored in porous materials to render them safe for transport and use. We were therefore encouraged to detect that the range of small molecules incorporated in the crystal lattices of **3** also included aromatic compounds with electron-withdrawing substituents, namely trifluorobenzene and nitrobenzene. Nitroarenes are a class of compounds, several members of which are explosives, and so are small aliphatic nitro compounds, such as nitromethane.[32]

Nitromethane is occasionally used as solvent,[33] making it a reasonable choice for studies on uptake by crystallization of



Scheme 2. Uptake of a hazardous or unstable small molecule into a crystalline phase of TDA and subsequent recovery of the TDA carrier material by addition of a volatile solvent in the form of recrystallization that leaves the small molecule in the solution with the solvent.

3. Nitromethane is also known for its role in the production of rocket propellants, explosive materials,[34] and as additive for high-performance fuel of combustion engines. We therefore studied uptake of nitromethane into TDA crystals and possible avenues for its controlled release. Scheme 2 shows the proposed regimen. First, the uptake of nitromethane by crystallization of **3** was studied. Figure 5 shows details of the X-ray crystal structure obtained when TDA was crystallized from nitromethane. It can be discerned that the tetraaryladamantane takes up the aliphatic nitro compound, and that the nitromethane guests are partially disordered in the crystal.

In order to identify conditions that allow for the recovery of **3** after serving as storage material for

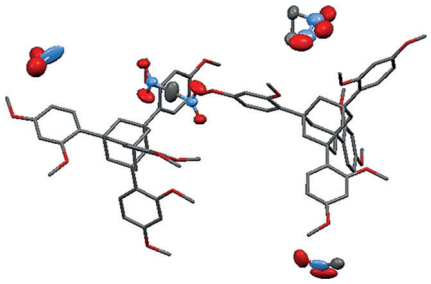


Figure 5. Crystal structure of **3** containing nitromethane. When a warm solution of TDA in nitromethane was allowed to cool, crystals of 0.1 cm length formed readily in less than 4 h. The graphic shows a portion of the X-ray crystal structure obtained from such crystals, containing the nitroalkane at a molar ratio of 2:3 (TDA:$MeNO_2$). Two well-ordered guest molecules and two inclusion sites with disordered nitromethane are shown, leading to a distorted appearance of the nitromethane molecules. Color code: Carbon, grey; oxygen, red; nitrogen, purple. See entry 19 of Table 2 for further details.

a small molecule compound, we then screened for a solvent that would have the potential to act as a release agent for nitromethane. For this, mixtures of nitromethane and various solvents (1:1, *v/v*) were screened for their ability to induce the crystallization of **3**. This included solvents such as methanol, ethanol, toluene, and 1,2-dichloroethane. After adding TDA, heating to obtain a clear solution, and cooling, the individual samples were examined for crystals. Toluene and 1,2-dichloroethane showed no crystals at the dilution chosen. In contrast, both methanol and ethanol induced the crystallization of TDA. When both the mother liquors and the crystals were examined by NMR, and the peak integrals were compared with those of the starting mixture of solvents, methanol showed itself as a promising release solvent for nitromethane (Figure 6). Whereas ethanol led to the incorporation of both nitromethane and the alcohol itself at a ratio of approximately 2:1, methanol induced the crystallization of **3** in largely guest-free form. Now, just 14 mol% of nitromethane was found in the crystals (Figure 6). Methanol was not detected in the NMR spectrum of the crystalline material dissolved in $CDCl_3$ (Figure 6b), and a modest loss of nitromethane detected in the mother liquor over the starting mixture confirmed the ability of methanol to

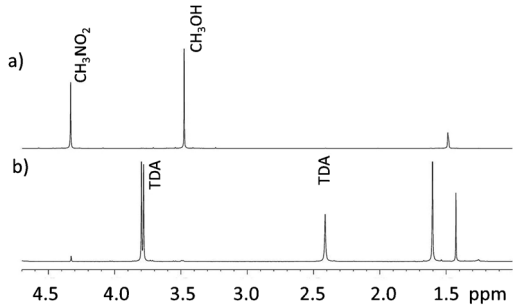


Figure 6. ^{1}H NMR spectra from crystallization studies with TDA (**3**) and a mixture of MeOH and nitromethane, recorded in $CDCl_3$ at 300 MHz. a) Spectrum the mother liquor of the crystallization of TDA from the 1:1 (*v/v*) mixture of the two solvents, and b) crystals obtained from the mixture after brief washing with water and cyclohexane, followed by dissolving in $CDCl_3$. Note that little nitromethane is found in the crystals of **3** formed under these conditions, making methanol suitable for release of the guest and recovery of the host material.

retain a large fraction of the explosive and to induce the crystallization of **3**.

Exploratory experiments were then performed with 1:1 mixtures of other solvents. A mixture of acetic acid and toluene gave crystals containing approx. 0.8 equivalents of toluene and traces of AcOH, again confirming that TDA does not readily include the carboxylic acid. A mixture of acetic acid and cyclohexane showed predominant inclusion of C_6H_{12}, whereas mixtures of both ethanol/benzene and methanol/benzene gave benzene as the only detectable guest molecule. At least one equivalent of benzene was taken up in either case. The crystal structure of the material obtained from the mixture of ethanol and benzene is listed as entry 23 in Table 2. The X-ray crystal structure obtained with a mixture of MeOH/C_6H_6 was almost identical (data not shown). The fact that, upon crystallization, benzene is taken up selectively from a mixture suggests that alcoholic solutions of TDA may become useful for decontaminating samples polluted with benzene.

An additional release mechanism was discovered for crystals containing benzene (Figure 7). It involved displacing benzene with chloroform at room temperature without loss of crystallinity. A sample of crystals obtained from a mixture of ethanol and benzene (1:1, *v/v*) that had given the crystal structure shown in Figure 7a was harvested, washed with water and cyclohexane, and immersed in chloroform. After one day, a crystal was collected, and the crystal structure shown in Figure 7b was obtained, which shows what appears to be an intermediate in the process of displacement. A combination of well-ordered benzene and chloroform molecules, as well as sites partially occupied by either of the two guests, are found in the unit cell. After one more day of exposure to chloroform, the crystal structure shown in Figure 7c was obtained from the same sample, which now shows two strongly disordered chloroform molecules only.

All three crystal structures were triclinic, space group $P\bar{1}$, but the volume of the unit cells was 2015, 4087, and 1985 Å^3, respectively. As mentioned above, the displacement of the benzene molecules occurred without macroscopically visible loss of crystallinity. Perhaps, a combination of porosity of the lattice and conformational flexibility in the TDA molecules allowed for the level of structural diversity found in the unit cells. The

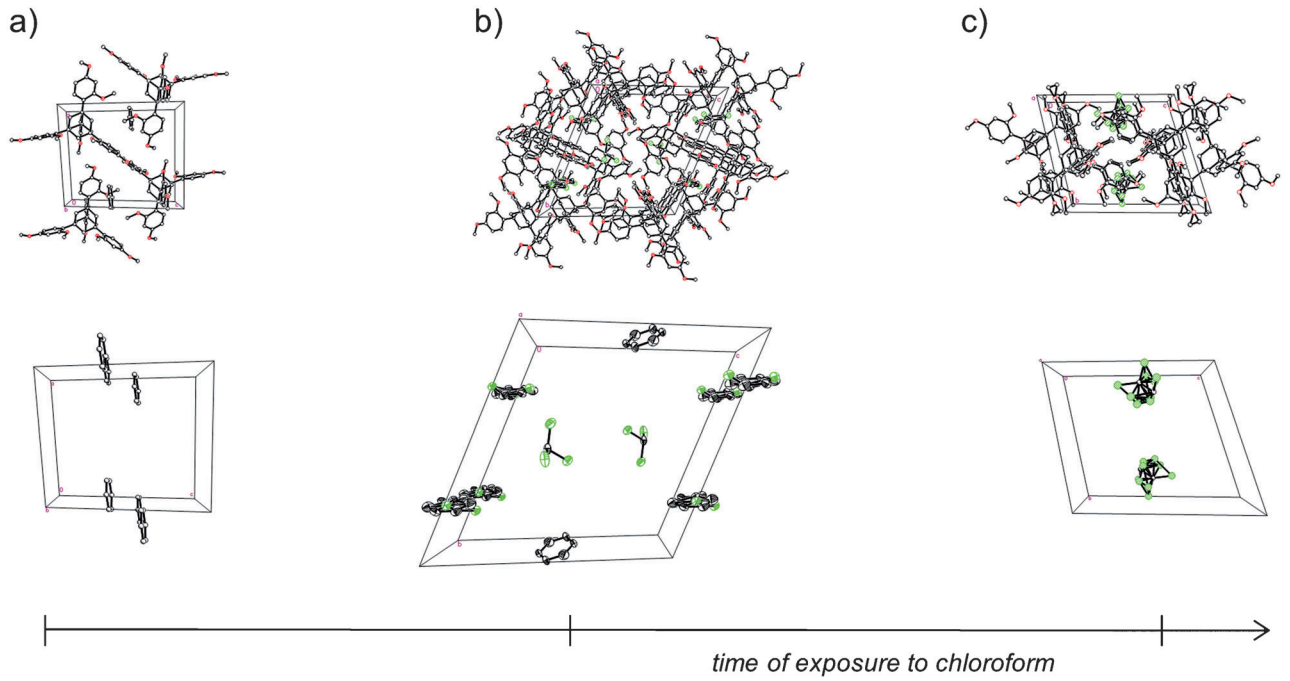


Figure 7. Release of benzene through displacement with chloroform at room temperature: a) X-ray structure of crystal obtained from a mixture of ethanol and benzene (1:1, *v/v*) with four benzene in the unit cell (lower part), b) Structure of crystal after exposure to $CHCl_3$ for 1 d, showing a mixture of both solvents in the unit cell, and c) X-ray structure of a crystal from the same sample after exposure to chloroform for two days, showing disordered $CHCl_3$ molecules as the only detectable guests. Color code: Carbon, grey; oxygen, red; chlorine, green. See entries 23–25 of Table 2 for further details.

chloroform molecules may have displaced the benzene guests without entirely breaking down crystalline order. The fact that the chloroform guests were less well ordered in the final structure than in the crystal structures obtained from chloroform as a crystallization solvents (e.g., Figure 3e) supports this hypothesis. Perhaps, the two chloroform molecules are filling voids left behind by the more spacious benzene rings. That what appears to be an intermediate was caught by X-ray crystallography also supports this view. Independent of the mechanism of release, the fact that benzene can be released from inclusion complexes of **3** at room temperature makes it likely that TDA will become useful as carrier for the capture and release of toxic aromatic compounds.

Discussion

The results presented above are noteworthy on different levels. One level is that of molecular recognition. Earlier X-ray crystal structures of other di- and other tetrarayladamantanes had shown inclusion complexes and a modest level of structural flexibility.[35–38] Unlike known inclusion complexes, though, in our case there is an absence of hydrogen bonds between the tetraaryladmantanes as host and small molecule guests. Further, the degree to which the guest molecules modulate the structure of the crystals formed by octaether **3** is unusual and so is the loading achieved for some guests, such as nitromethane.

It is difficult to predict crystal structures of organic molecules,[39] so any explanation for the unusual behavior of **3** in the crystalline state will necessarily be speculative. There are structural peculiarities that come to mind, though. One is that, compared to tetraether **4**, the inner sphere of aryl substituents (adjacent to the admantane) is more densely packed for **3**, due to the presence of the additional methoxy groups. As a consequence, a cogwheel-like arrangement of neighboring phenyladamantanes (Figure 8a) may be difficult to achieve. The more shallow indentations may be responsible for a flatter energy landscape, with more alternative packing arrangements and crystals structures, including structures with guest molecules (Figure 8b/c). Compared to unsubstituted tetraphenyladamantane, octaether **3** presents a more spherical shape, closer to that of truly spherical molecules, like fullerenes, which are known for their orientational disorder in the solid state.[40]

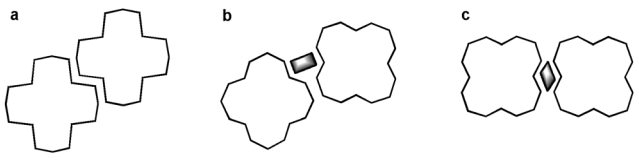


Figure 8. Simplified, two-dimensional model of packing for a less spherical (a) and a more spherical (b and c) four-fold substituted molecule. Guest molecules included in the packing are shown as dark objects.

Further, the eight methoxy groups of **3** are able to rotate. Thus, they are able to present a more polar (oxygen) or less polar face (methyl groups). This allows **3** to present oxygen lone pairs as interactions surface for hydrogen bond donors or dipoles in guest molecules, as in the structure with CH_2Cl_2 as guest. When rotating about their bonds to the phenyl rings, the methoxy groups can also present their lipophilic surfaces in order to bind lipophilic guests via van der Waals interactions, as in the inclusion complexes with *n*-hexane and cyclohexane. This Janus-like property may account for the ability to include such as broad range of different small molecules.

Figure 9 shows an overlay of different conformations of **3**, as found in its crystal structures. The structure of seven different conformations of TDA found in triclinic crystal systems, nine conformations found in space group *C*2/*c*, and 19 different conformations found in space group $P2_1/n$ were aligned. The overlays show that the phenyl rings rotate considerably when accommodating guest molecules, and so do the methoxy groups, particularly those at the *para*-position.

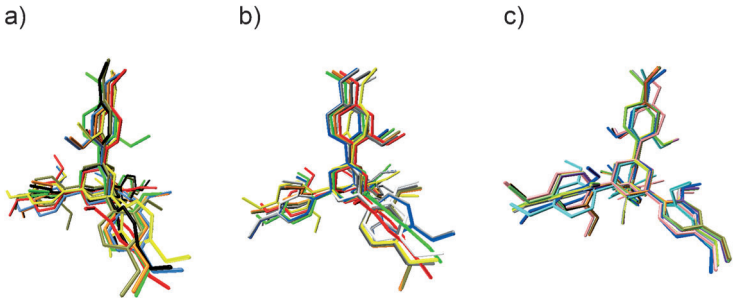


Figure 9. Overlay of the alignments of different conformations of TDA (**3**), as found in a) the triclinic crystal systems; b) the monoclinic crystal systems with the space group C 2/c; and c) the monoclinic crystal system with the space group $P2_1/n$. Each conformer is shown in a different color. In the triclinic crystal system, 19% of all neighboring methoxy groups on individual phenyl rings were found in a tweezer-like, *cisoid* orientation, and 81% were found in a *transoid* conformation. In monoclinic structures of space group C 2/c, the ratio was 39% *cisoid* and 61% *transoid*. Finally, in the structures of monoclinic system P 21/n, the ratio of the arrangements of the methoxy groups was 3% *cisoid* and 97% *transoid*.

On the level of possible applications, it is noteworthy how easily the uptake properties of **3** can be tuned by adding an alcohol as solvent and inducing recrystallization (Scheme 2 and Figure 6) or by adding a halogenated solvent and inducing displacement (Figure 7). This makes it reasonable to propose that TDA can be used to absorb and later release toxic or unstable small molecules. Thus, **3** may become useful as a material to safely ship and later release toxic or explosive compounds, such as nitromethane. Guest may be released by displacement at room temperature (Figure 7), by dissolving the material in a suitable solvent like methanol and recovering the TDA carrier compound upon cooling (Scheme 2), or possibly by thermal release through melting of crystals containing guests.

Conclusions

In conclusion, we report that tetrakis(2,4-dimethoxyphenyl)adamantane (**3**) shows a high degree of structural variation in its

crystalline state and forms inclusion complexes with a wide range of different guest molecules. The mode of interaction differs between guests and so does the mode in which the binding pocket is formed. Probably, the near-spherical shape of this eight-fold substituted tetraaryladamantane, combined with the tweezer-like positioning of the methoxy substituents favors inclusion complexes. The crystals thus formed are fascinating organic materials. Octaether **3** may be developed into molecular storage materials for small molecules that form by crystallizing readily (sometimes within minutes) and dissolve when heated with the proper release solvent. This compound may thus become useful for the absorption, safe transport, and controlled release of toxic, explosive or otherwise functional small molecules as well as for scientific studies that require the capture of a small molecule in a crystalline matrix.

Experimental Section

General: NMR spectra were recorded on a Bruker AVANCE 300 spectrometer. Chemical shifts (δ values) are in parts per million (ppm) relative to tetramethylsilane (TMS, 0 ppm) as internal standard or residual solvent peaks; coupling constants (J) are given in Hertz (Hz). Mass spectra were obtained on a Varian MS MAT 311 A spectrometer in EI mode. The following starting materials were synthesized according to literature procedures: 1,3,5,7-Tetrabromoadamantane (**1**) and 1,3,5,7-tetrahydroxyadamantane (**2**).[25,26] Intensity data were collected at low temperature (100 or 110 K) on a Bruker KAPPA APEXII DUO diffractometer using $Mo_{K\alpha}$ ($\lambda =$ 0.71073 Å) and, for small crystals, by a microsource $Cu_{K\alpha}$ ($\lambda =$ 1.54178 Å). Cell refinements and data reductions were performed by using the program package SAINT.[41] An absorption correction was performed by using the program SADABS.[41] Structures were solved by direct methods using SHELXS97 software.[42] Isotropic refinement of the structures by least-squares methods were also carried out by using SHELXL97,[42] followed by anisotropic refinements on F^2 of all non-hydrogen atoms. The H-atom positions were calculated geometrically using the relevant riding models. For binary solvent systems (Table 2, entries 8, 9, 11 and 12), an overlap model of both solvent components was used for better fitting of the strongly disordered parts in the solvent electron density.

CCDC-1040344 (**4**), 1040345 (**5**), 1040349 (**6**), 1040350 (**3**), 1040351 (**3**, entry 5, Table 2), 1040354 (**3**, entry 6, Table 2), 1040355 (**3**, entry 7, Table 2), 1040356 (**3**, entry 8, Table 2), 1040357 (**3**, entry 9, Table 2), 1040358 (**3**, entry 10, Table 2), 1040359 (**3**, entry 11, Table 2), 1040360 (**3**, entry 12, Table 2), 1040361 (**3**, entry 13, Table 2), 1040362 (**3**, entry 14, Table 2), 1040363 (**3**, entry 15, Table 2), 1040364 (**3**, entry 16, Table 2), 1040365 (**3**, entry 17, Table 2), 1040366 (**3**, entry 18, Table 2), 1040367 (**3**, entry 19, Table 2), 1049318 (**3**, entry 20, Table 2), 1049319 (**3**, entry 21, Table 2), 1049320 (**3**, entry 22, Table 2), 1049321 (**3**, entry 23, Table 2), 1049322 (**3**, entry 24, Table 2) and 1049323 (**3**, entry 25, Table 2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

1,3,5,7-Tetrakis(2,4-dimethoxyphenyl)adamantane (3): A mixture of **2** (20 mg, 0.1 mmol, 1 equiv), *p*-toluenesulfonic acid (9.5 mg, 0.05 mmol, 0.5 equiv), and 1,3-dimethoxybenzene (1.5 mL), was heated to 140 °C for 96 h in a Dean–Stark apparatus. Then, the solvent was evaporated in vacuo and the crude product was coevaporated four times with methanol (3–5 mL). The resulting residue was dissolved in CH_2Cl_2 (40 mL) and was successively washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), HCl (50 mL, 2 M) and H_2O (50 mL), dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The resulting dark brown crude product was taken up in CH_2Cl_2 and filtered through a short silica gel pad, by eluting first with petroleum ether (200 mL) and then with petroleum ether/CH_2Cl_2 (3:1, *v*/*v*, 300 mL). The second fraction was concentrated under reduced pressure. Purification via column chromatography (silica gel, petroleum ether/CH_2Cl_2 1:4, *v*/*v*) yielded **3** as a white solid (26 mg, 0.04 mmol, 38%). $R_f = 0.22$ (petroleum ether/CH_2Cl_2, 1:3, *v*/*v*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 8.4$ Hz, 4H), 6.48–6.44 (m, 8H), 3.78 (s, 12H), 3.77 (s, 12H), 2.41 ppm (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 159.8$, 158.8, 131.1, 127.2, 103.3, 99.7, 55.2, 55.0, 42.8, 39.0 ppm; MS (70 eV, EI): *m*/*z*: 680/681/682/683 [M^+]; HRMS *m*/*z* calcd for $C_{42}H_{48}O_8$ 680.335, found 680.334.

1,3,5,7-Tetrakis(4-methoxyphenyl)adamantane (4): A mixture of **2** (50 mg, 0.25 mmol, 1 equiv), TfOH (11 µL, 0.12 mmol, 0.5 equiv), and anisole (1 mL) was heated to 120 °C for 20 h in a Dean–Stark apparatus. After aqueous work up as described for compound **3**, purification via column chromatography (silica gel, petroleum ether/CH_2Cl_2 1:1, *v*/*v*) yielded **4** as a colorless solid (54 mg, 0.096 mmol, 39%). $R_f = 0.28$ (petroleum ether/CH_2Cl_2 1:1, *v*/*v*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$ (d, $J = 8.7$ Hz, 8H), 6.88 (d, $J =$ 9 Hz, 8H), 3.84 (s, 12H), 2.80 ppm (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 157.7$, 141.8, 126.0, 113.6, 55.2, 47.7, 38.6 ppm; MS (FAB, 3-NBA): *m*/*z*: 560, 561, 562 [M^+]; HRMS *m*/*z* calcd for $C_{38}H_{40}O_4$ 560.293, found 560.293.

1,3,5,7-Tetrakis(4-methoxy-2-methylphenyl)adamantane (5): A mixture of **2** (75 mg, 0.37 mmol, 1 equiv), *p*-toluenesulfonic acid (35.6 mg, 0.18 mmol, 0.5 equiv) and 3-methylanisole (3 mL) was heated to 130 °C for 72 h in a Dean–Stark apparatus. After aqueous work up as described for compound **3**, the resulting dark brown crude product was treated with MeOH (10 mL) in an ultrasonic bath, and the slurry was centrifuged. This procedure was repeated two times, and the title compound **5** was isolated as an off-white/gray solid (94.7 mg, 0.165 mmol, 41%). $R_f = 0.41$ (petroleum ether/CH_2Cl_2, 2:1, *v*/*v*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$ (d, $J = 7.9$ Hz, 4H), 6.76–6.70 (m, 8H), 3.77 (s, 12H), 2.45 (s, 12H), 2.32 ppm (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 158.7$, 136.6, 135.5, 126.7, 120.8, 112.5, 54.9, 42.4, 39.2, 21.1 ppm; MS (70 eV, EI): *m*/*z*: 616/617/618/619 [M^+]; HRMS *m*/*z* calcd for $C_{42}H_{48}O_4$ 616.355, found 616.356.

1,3,5,7-Tetrakis(4-methoxy-2-ethylphenyl)adamantane (6): A mixture of **2** (35 mg, 0.17 mmol, 1 equiv), *p*-toluenesulfonic acid (16.6 mg, 0.09 mmol, 0.5 equiv), and 3-ethylanisole (0.61 mL) was heated to 120 °C for 48 h in a Dean–Stark apparatus. After aqueous work up as described for compound **3**, MeOH (5 mL) was added to the resulting solid, and the slurry was treated in an ultrasonic bath. After centrifugation, the supernatant was removed and discarded. This washing procedure was repeated for two times. The title compound **6** was isolated a colorless solid (34 mg, 0.05 mmol, 30%). $R_f = 0.51$ (petroleum ether/CH_2Cl_2, 2:1, *v*/*v*); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.30$ (d, $J = 7.8$ Hz, 4H), 6.79–6.72 (m, 8H), 3.79 (s, 12H), 2.63 (q, $J = 7.6$ Hz, 8H,), 2.470 (s, 12H), 1.24 ppm (t, $J = 7.5$ Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.8$, 142.9, 135.7, 126.7, 119.4, 111.4, 54.9, 42.4, 39.3, 28.5, 15.3 ppm; MS (70 eV, EI): *m*/*z*: 672/673/674/675 [M^+]; HRMS *m*/*z* calcd for $C_{46}H_{56}O_4$ 672.418, found 672.418.

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Keywords: adamantane · controlled release · inclusion complexes · molecular storage · X-ray crystal structure

[1] J. D. Wuest, *Chem. Commun.* **2005**, 5830 – 5837.
[2] W. Lu, D. Yuan, D. Zhao, C. Schilling, O. Plietzsch, T. Muller, S. Bräse, J. Guenther, J. Blümel, R. Krishna, Z. Li, H.-C. Zhou, *Chem. Mater.* **2010**, *22*, 5964 – 5972.
[3] H. Zhao, Z. Jin, H. Su, J. Zhang, X. Yao, H. Zhao, G. Zhu, *Chem. Commun.* **2013**, *49*, 2780 – 2782.
[4] A. P. Côte, A. I. Benin, N. W. Ockwig, M. O'Keeffe, A. J. Matzger, O. M. Yaghi, *Science* **2005**, *310*, 1166 – 1170.
[5] H. A. Patel, S. H. Je, J. Park, Y. Jung, A. Coskun, C. T. Yavuz, *Chem. Eur. J.* **2014**, *20*, 772 – 780.
[6] a) M. Mastalerz, *Chem. Eur. J.* **2012**, *18*, 10082 – 10091; b) T. Ben, H. Ren, S. Ma, D. Cao, J. Lan, X. Jing, W. Wang, J. Xu, F. Deng, J. M. Simmons, S. Qiu, G. Zhu, *Angew. Chem. Int. Ed.* **2009**, *48*, 9457 – 9460; *Angew. Chem.* **2009**, *121*, 9621 – 9624; c) D. Yuan, W. Lu, D. Zhao, H.-C. Zhou, *Adv. Mater.* **2011**, *23*, 3723 – 3725; d) A. P. Katsoulidis, M. G. Kanatzidis, *Chem. Mater.* **2011**, *23*, 1818 – 1824.
[7] G. Zhang, M. Mastalerz, *Chem. Soc. Rev.* **2014**, *43*, 1934 – 1947.
[8] a) V. R. Reichert, L. J. Mathias, *Macromolecules* **1994**, *27*, 7030 – 7034; b) V. R. Reichert, L. J. Mathias, *Macromolecules* **1994**, *27*, 7015 – 7023.
[9] O. Ermer, *J. Am. Chem. Soc.* **1988**, *110*, 3747 – 3754.
[10] E. Galoppini, R. Gilardib, *Chem. Commun.* **1999**, 173 – 174.
[11] a) W. Maison, J. V. Frangioni, N. Pannier, *Org. Lett.* **2004**, *6*, 4567 – 4569; b) (C. Fleck, E. Franzmann, D. Claes, A. Rickert, W. Maison, *Synthesis* **2013**, *45*, 1452 – 1461.
[12] M. Saunders, H. A. Jiménez-Vázquez, *Chem. Rev.* **1991**, *91*, 375 – 397.
[13] N. Pannier, W. Maison, *Eur. J. Org. Chem.* **2008**, 1278 – 1284.
[14] a) J. G. Henkel, J. T. Hane, G. J. Gianutsos, *Med. Chem.* **1982**, *25*, 51 – 56; b) J. Zah, G. Terre'Blanche, E. Erasmus, S. F. Malan, *Bioorg. Med. Chem.* **2003**, *11*, 3569 – 3578.
[15] a) Q. Li, C. Jin, P. A. Petukhov, A. V. Rukavishnikov, T. O. Zaikova, A. Phadke, D. H. LaMunyon, M. D. Lee, J. F. Keana, *J. Org. Chem.* **2004**, *69*, 1010 – 1019; b) Q. Li, A. V. Rukavishnikov, P. A. Petukhov, T. O. Zaikova, C. Jin, J. F. W. Keana, *J. Org. Chem.* **2003**, *68*, 4862 – 4869; c) U. Radhakrishnan, M. Schweiger, P. J. Stang, *Org. Lett.* **2001**, *3*, 3141 – 3143.
[16] C. Richert, M. Meng, K. Müller, K. Heimann, *Small* **2008**, *4*, 1040 – 1042.
[17] C. Richert, M. Meng, A. Singh, *Small* **2009**, *5*, 2782 – 2783.
[18] M. Meng, C. Ahlborn, M. Bauer, O. Plietzsch, S. A. Soomro, A. Singh, T. Muller, W. Wenzel, S. Bräse, C. Richert, *ChemBioChem* **2009**, *10*, 1335 – 1339.
[19] C. I. Schilling, O. Plietzsch, M. Nieger, T. Muller, S. Bräse, *Eur. J. Org. Chem.* **2011**, 1743 – 1754.
[20] O. Plietzsch, C. I. Schilling, M. Tolev, M. Nieger, C. Richert, T. Muller, S. Bräse, *Org. Biomol. Chem.* **2009**, *7*, 4734 – 4743.
[21] A. Singh, M. Tolev, M. Meng, K. Klenin, O. Plietzsch, C. I. Schilling, T. Muller, M. Nieger, S. Bräse, W. Wenzel, C. Richert, *Angew. Chem. Int. Ed.* **2011**, *50*, 3227 – 3231; *Angew. Chem.* **2011**, *123*, 3285 – 3289.
[22] A. Singh, M. Tolev, C. I. Schilling, S. Bräse, H. Griesser, C. Richert, *J. Org. Chem.* **2012**, *77*, 2718 – 2728.
[23] H. Griesser, M. Tolev, A. Singh, T. Sabirov, C. Gerlach, C. Richert, *J. Org. Chem.* **2012**, *77*, 2703 – 2717.
[24] A. Schwenger, C. Gerlach, H. Griesser, C. Richert, *J. Org. Chem.* **2014**, *79*, 11558 – 11566.
[25] H. Stetter, C. Wulff, *Chem. Ber.* **1960**, *93*, 1366 – 1371.
[26] H. Stetter, M. Krause, *Liebigs Ann. Chem.* **1968**, *717*, 60 – 63.
[27] K. K. Laali, V. D. Sarca, T. Okazaki, A. Brock, P. Dera, *Org. Biomol. Chem.* **2005**, *3*, 1034 – 1042.
[28] H. Stetter, J. Gärtner, P. Tacke, *Chem. Ber.* **1965**, *98*, 3888 – 3891.
[29] Z. Takáts, I. Cotte-Rodriguez, N. Talaty, H. Chen, R. G. Cooks, *Chem. Commun.* **2005**, 1950 – 1952.
[30] T. Naddo, Y. Che, W. Zhang, K. Balakrishnan, X. Yang, M. Yen, J. Zhao, J. S. Moore, L. Zang, *J. Am. Chem. Soc.* **2007**, *129*, 6978 – 6979.
[31] J. D. Rodgersa, N. J. Bunce, *Water Res.* **2001**, *35*, 2101 – 2111.
[32] J. M. Schnorr, D. van der Zwaag, J. J. Walish, Y. Weizmann, T. M. Swager, *Adv. Funct. Mater.* **2013**, *23*, 5285 – 5291.
[33] W. Hofman, L. Stefaniak, T. Urbanski, M. Witanowski, *J. Am. Chem. Soc.* **1964**, *86*, 554 – 558.
[34] S. A. Koldunov, A. V. Ananin, V. A. Garanin, V. A. Sosikov, S. I. Torunov, *Cent. Eur. J. Energ. Mater.* **2009**, *6*, 7 – 14.
[35] M. Tominaga, K. Katagiri, I. Azumaya, *Cryst. Growth Des.* **2009**, *9*, 3692 – 3696.
[36] M. Tominaga, K. Katagiri, I. Azumaya, *CrystEngComm* **2010**, *12*, 1164 – 1170.
[37] M. Tominaga, H. Masu, I. Azumaya, *Cryst. Growth Des.* **2011**, *11*, 542 – 546.
[38] H. Masu, M. Tominaga, I. Azumaya, *Cryst. Growth Des.* **2013**, *13*, 752 – 758.
[39] S. L. Price, *Int. Rev. Phys. Chem.* **2008**, *27*, 541 – 568.
[40] a) L. Y. Chiang, J. W. Swirczewski, K. Liang, J. Millar, *Chem. Lett.* **1994**, 981 – 984; b) D. M. Eichhorn, S. Yang, W. Jarrell, T. F. Baumann, L. S. Beall, A. J. P. White, D. J. Williams, A. G. M. Barrett, B. M. Hoffmann, *Chem. Commun.* **1995**, 1703 – 1704; c) O. Ermer, *Helv. Chim. Acta* **1991**, *74*, 1339 – 1351; d) P. R. Birkett, C. Christides, P. B. Hitchcock, H. W. Kroto, K. Prassides, R. Taylor, D. R. M. Walton, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1407 – 1408; e) H.-B. Bürgi, E. Blanc, D. Schwarzenbach, S. Liu, Y. Lu, M. M. Kappes, J. A. Ibers, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 640 – 643; *Angew. Chem.* **1992**, *104*, 667 – 669.
[41] APEX2, SADABS and SAINT. Bruker AXS Inc. Madison, Wisconsin, USA.
[42] G. M. Sheldrick, *Acta Crystallogr. A* **2008**, *64*, 112 – 122.

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FULL PAPER

Inclusion Complexes

*A. Schwenger, W. Frey, C. Richert**

■■ – ■■

Tetrakis(dimethoxyphenyl)adamantane (TDA) and Its Inclusion Complexes in the Crystalline State: A Versatile Carrier for Small Molecules

Selective inclusion: A tetraaryladamantane octaether was shown to form 20 different inclusion complexes, absorbing toxic compounds such as benzene selectively, and releasing guests such as nitromethane upon recrystallizing from alcohols.

Organic crystals as molecular storage materials…
…are described in the Full Paper by C. Richert et al. on page ■■. Tetrakis(dimethoxyphenyl)adamantane (TDA) forms a dazzling array of crystalline inclusion complexes, with guest molecules ranging from nitromethane to trifluorobenzene. Molecules thus stored can be released by recrystallizing from an alcohol or by solvate displacement. Hazardous materials and explosives may be captured, and mixtures may be separated. The picture illustrates the process of adding toxic solutions to TDA, which then crystallizes.