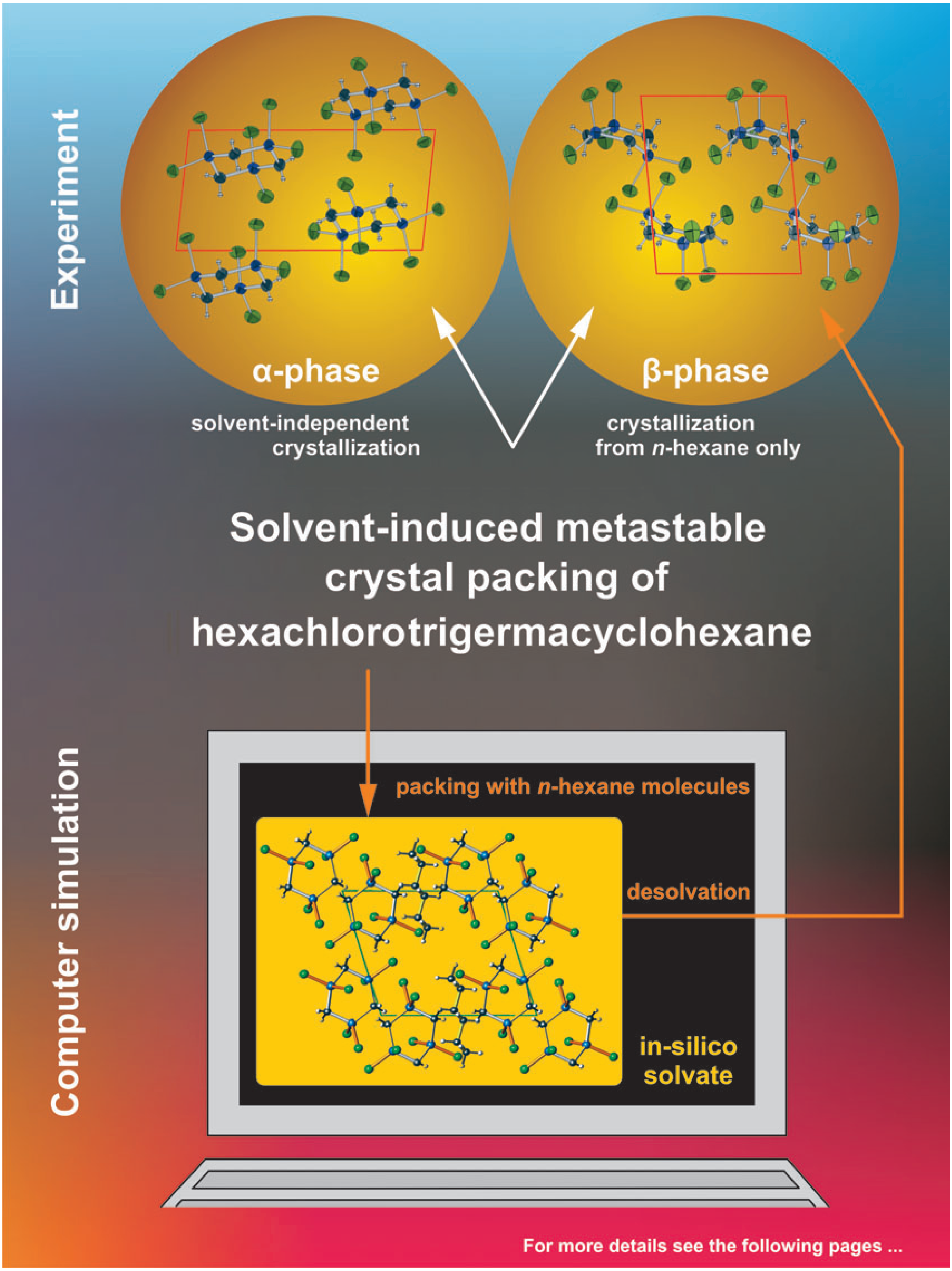

Solvent-induced metastable crystal packing of hexachlorotrigermacyclohexane

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Conformational Dimorphism of 1,1,3,3,5,5-Hexachloro-1,3,5-trigermacyclohexane: Solvent-Induced Crystallization of a Metastable Polymorph Containing Boat-Shaped Molecules

Vladislav Ischenko,[a] Ulli Englert,[b] and Martin Jansen*[a]

Abstract: Two crystalline modifications of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane have been experimentally obtained as phase pure products and studied by single-crystal X-ray diffraction. The six-membered heterocycles adopt a chair conformation in the α-phase; this polymorph is accessible by crystallisation from solution and from the melt. In contrast, the β-form is built up from boat-shaped molecules; it can exclusively be crystallised from *n*-hexane. At the molecular level, formation energies of the 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane conformers have been compared by using molecular mechanics, semiempirical and ab-initio quantum mechanical calculations. Possible reasons for the selective formation of the α- or β-phase in specific solvents have been considered. Formation of the metastable phase is suggested to occur via a hypothetical intermediate of composition $[(GeCl_2CH_2)_3]\cdot 0.5\,C_6H_{14}$. For such an in-silico solvate, a crystal structure of favourable lattice energy, closely related to the experimentally observed β-modification, has been found through global energy minimisation. Elimination of the *n*-hexane molecules from this computer-generated solid and subsequent simulated annealing resulted in a crystal structure that corresponds to the experimentally observed β-phase within the limits of the force field calculations. This scenario implies solvent directed crystallisation of a metastable polymorphic molecular crystal.

Keywords: conformational analysis · crystal engineering · heterocycles · polymorphism · solvent effects

Introduction

Isomerisation of a molecule within its conformational space plays a crucial role in determining the conditions of controlled preparation of organic and organometallic compounds and the probability of different transition states appearing in the course of their chemical transformations. Given sufficiently low activation barriers, or sufficiently high temperatures, all conformations of a molecule are accessible in gaseous or liquid media. Lowering the temperature would favour the lowest energy conformer, whereas other individual conformers may be fixed by various kinds of additional bonding interactions, such as specific donor–acceptor or crystal-field effects. Among these, design and control of molecular packing in crystals ("crystal engineering") continues to attract growing attention, since in this way basic properties of solid molecular materials can be modified.[1–3] Such options are especially important for electronic materials and for compounds with catalytic or physiological activity. To give just two examples, the electron mobility of a given molecular crystal significantly depends on packing, and the bio-availability of a solid drug can vary considerably from one polymorphic modification to the other. The term "conformational polymorphism"[4] has been coined for systems in which different crystalline modifications of the same compound are associated with different conformers of the same molecule. In favourable cases conformational polymorphs may be exploited to gain insight into the conformational space of the molecule under study.[5]

In this contribution we report on the molecular and crystal structures of two modifications of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane, combining experimental and theoretical methods in order to understand the interplay between crystal structures and molecular conformations in the polymorphs.

For cyclohexane, which is a prototype for the 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane under discussion, the

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existence of two different conformations—a "rigid" and a "flexible" isomer, which we now refer to as a chair and a boat form—was first pointed out by Sachse.[6] With the development of new analytical techniques and, especially, with the improvement and automation of force-field and quantum mechanics calculations, a number of conformational features of cyclohexane has been investigated and described.[7,8] The chair form is known to be the most stable conformation for unsubstituted cyclohexane, as well as for many of its derivatives, while the twist form represents a local minimum on the potential energy surface and is 4.7–6.2 kcal mol^{-1} higher in energy with respect to the chair form of cyclohexane. The twist form possesses higher entropy and has to be more abundant at higher temperatures. Due to a rather high potential-energy barrier (10.7–11.5 kcal mol^{-1}) for the chair–twist interconversion, only a small percentage of twist form of cyclohexane is found in equilibrium with chair at room temperature. Several first-order transition states have been reported for the interconversion of the cyclohexane ring.[9] One of them is the boat form, a saddle point on the potential-energy surface and a transition state for the twist–twist transitions (1–1.5 kcal mol^{-1} above the twist form). At higher temperatures such transitions represent a continuous twist–boat–twist pseudorotation of the cyclohexane molecule.

The conformational behaviours of various heterocyclic derivatives of cyclohexane, such as oxanes, sulfanes and azans, have been studied as well.[7] However, the information about those with carbon-group heteroatoms is relatively scarce, in spite of high potential and increasing importance of such compounds as precursors for the preparation of inorganic, polymeric organic and hybrid materials with interesting electronic properties. Applying quantum mechanical calculations and electron diffraction in the gas phase, Arnason and Oberhammer[10] investigated the conformations of 1,3,5-trisilacyclohexane and cyclohexasilane. They reported smaller energy differences between chair and twist conformations for these molecules (2.17 and 1.89 kcal mol^{-1}, respectively), compared to 6.49 kcal mol^{-1} for cyclohexane, the chair conformation still being the most stable. In comparison to homocyclic cyclohexane, the twist conformation is somewhat stabilised in 1,3,5-trisilacyclohexane and cyclohexasilane; this fact has been explained as being due to less pronounced interactions between partially eclipsed E–H bonds (i.e., those with small torsion angles) due to longer E–E distances (E = Si, C).

Results and Discussion

Crystallisation of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane: 1,1,3,3,5,5-Hexachloro-1,3,5-trigermacyclohexane (**1**) was synthesised by means of a Müller–Rochow type reaction, as previously published.[11] The interesting peculiarity of **1** not reported in the earlier literature is its ability to crystallise in two different modifications. The first one (in the following referred to as α-phase or α-**1**) crystallises from benzene, chlorobenzene and by solidification of molten **1** in the absence of any solvent. The second modification (in the following referred to as β-phase or β-**1**) is formed during crystallisation of **1** from its solution in *n*-hexane at room temperature (Figure 1); the isolated crystalline material does not contain solvent.

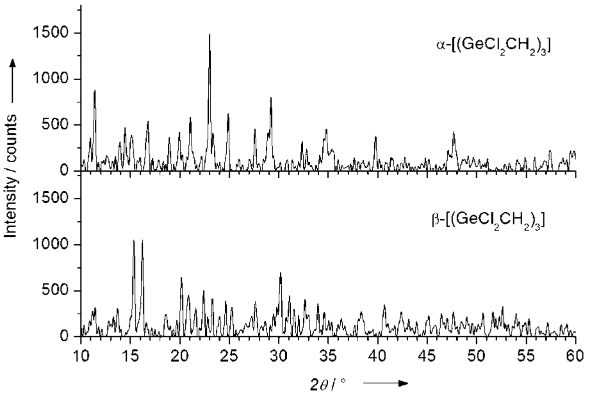

Figure 1. Powder X-ray diffraction data of α- and β-phase for 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane.

Crystal structures and molecular conformations in α- and β-1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane: The crystal structures of both α-**1** and β-**1**, determined from single-crystal X-ray diffraction data, are presented in Figures 2 and 3. Both modifications crystallise in the triclinic centrosymmetric space group ($P\bar{1}$) and differ in the molecules' ordering inside the crystal. The α-polymorph has slightly higher space filling (66.1 %) than the β-phase (65.5 %).

It is interesting to note, that the cyclic molecules in the two crystal modifications of **1** adopt completely different conformations: *chair* in α-**1** and *boat* in β-**1**. Deviations from the ideal symmetry are quite small: the molecules maintain C_{3v} symmetry in α-**1** (with a maximal atomic deviation of 0.152(3) Å) and C_s symmetry in β-**1** (with a maximal atomic deviation of 0.187(3) Å). The Ge2-Ge3-C3-C1 rectangle in the boat conformation of **1** remains planar with a maximum angle of 3.0(3)°, measured as the torsion angle between opposite edges. It is therefore legitimate to refer to this geometry as boat rather than twist conformation; for the latter nonplanarity of the above-mentioned rectangle would approach to 30°.

Crystal data, fractional coordinates and isotropic displacement parameters for α-**1** and β-**1**, determined from single-crystal X-ray diffraction analysis, are presented in Tables 1–3.[12] Bond lengths and angles agree very well with the expected values; no unusual deviations from the corresponding average values are observed. The ratio of molecular volumes of both conformations (determined as volumes of polyhedra with all terminal atoms as vertices) is 1.05, which is quite close to the ratio of the unit cell volumes (1.01). This confirms that β-**1** is free from solvent molecules.

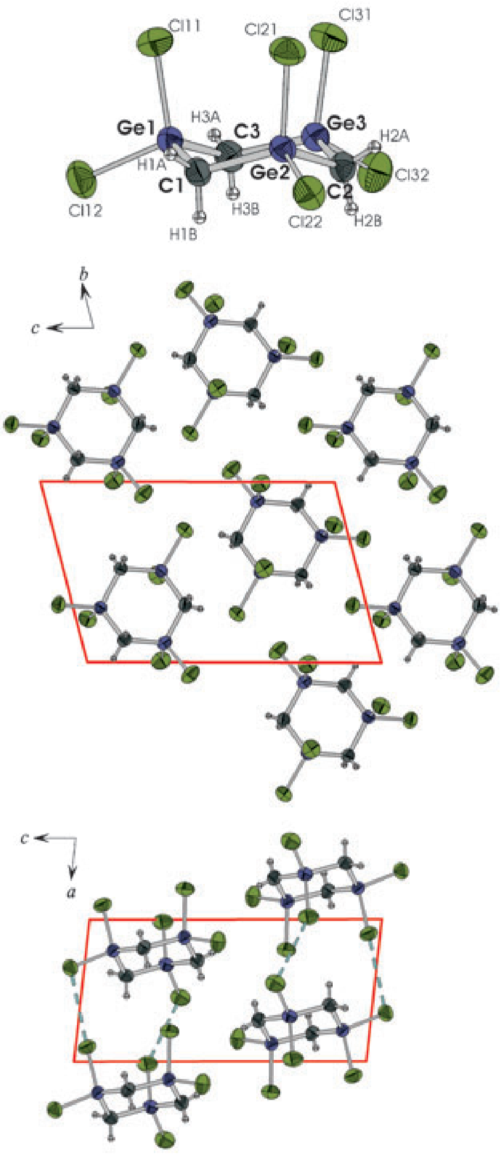

Figure 2. Crystal structure and molecular conformation of α-**1**. (The shortest intermolecular Cl···Cl contacts are depicted with dashed lines in the *ac* projection plane, see text for details).

Comparison between the molecular geometries of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane, 1,3,5-trigermacyclohexane and cyclohexane: We will compare the molecular geometry of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane (**1**) to that of its next homologues—cyclohexane and 1,3,5-trigermacyclohexane—as reference compounds. In contrast to our observations on **1**, for cyclohexane[13] and 1,3,5-trigermacyclohexane[14] only crystalline phases containing molecules in chair form have been reported so far.

Passing from homocyclic cyclohexane to heterocyclic rings with electronegative substituents such as chlorine, the polarisation of bonds increases significantly. This leads in turn to more pronounced electrostatic interactions between the atoms. Torsion angles between opposite bonds within the six-membered ring in chair conformation slightly increase in the series: cyclohexane < 1,3,5-trigermacyclohexane < **1**, being 0.0(4)/0.0(4)/0.0(4)°,[13] 0.0(2)/1.1(3)/1.2(3)°[14] and 1.04(13)/1.52(13)/2.66(13)°, respectively. This can be ascribed to the increasing role of steric effects, such as a repulsive interaction of substituents (axial chlorine atoms in **1**), and to possible intermolecular interactions in the crystal, which have to be much more significant in 1,3,5-trigermacyclohexane and especially in **1**, due to increasingly polarised bonds.

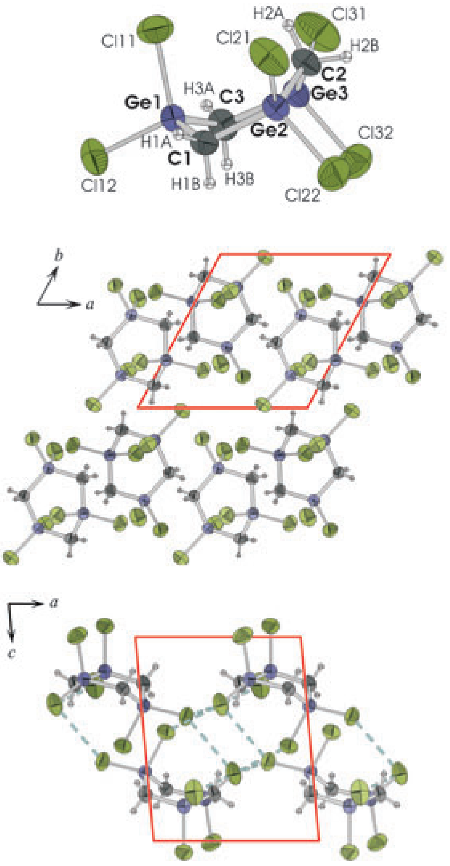

Figure 3. Crystal structure and molecular conformation of β-**1**. (The shortest intermolecular Cl···Cl contacts are depicted with dashed lines in the *ac* projection plane, see text for details).

The repulsion between axial chlorine atoms in the chair conformation of **1** is evidently also the reason for the ring flattening. Folding angles within the ring, as spanned by a plane through the rectangle and a second plane through the adjacent triangle in the ring, are very similar for cyclohexane (129.8(6)/129.8(6)/130.3(6)/130.3(6)/130.7(6)/130.7(6)°)[13] and 1,3,5-trigermacyclohexane (128.1(4)/128.5(3)/128.6(4)/129.7(3)/129.8(3)/131.1(3)°).[14] These folding angles are, however, notably increased in α-**1** (134.44(19)/135.40(18)/136.32(18)/138.20(19)/138.68(19)/139.19(19)°). Distances between the axial chlorine atoms in the chair form molecules of α-**1** (3.89, 3.74 and 3.75 Å) are quite close to the doubled nonpolarised van der Waals radius of chlorine (2 × 1.8 Å[15]), so that lower folding angles

Table 1. Crystal data for α-**1** and β-**1**.

	α-**1**	β-**1**
crystal system	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$
a [pm]	630.62(2)	886.7(2)
b [pm]	839.96(3)	911.5(2)
c [pm]	1316.87(5)	966.4(3)
α [°]	74.2050(10)	79.87(2)
β [°]	81.3640(10)	80.62(3)
γ [°]	80.3170(10)	60.64(2)
V [nm^3]	0.65762(4)	0.6674(3)
Z	2	2
ρ_{calcd} [g cm^{-3}]	2.386	2.351
crystal appearance	colourless	colourless
crystal dimensions [mm^3]	$0.8 \times 0.5 \times 0.4$	$1.0 \times 0.5 \times 0.5$
θ range [°]	2.54–37.53	3.75–37.21
scan mode	ω scans	ω scans
T [K]	293(2)	293(2)
μ [mm^{-1}]	7.982	7.865
index ranges	$-10 \leq h \leq 10$	$-13 \leq h \leq 11$
	$-14 \leq k \leq 13$	$-12 \leq k \leq 11$
	$-22 \leq l \leq 22$	$-15 \leq l \leq 14$
reflections collected	13291	6231
independent reflections	6784	3508
	[R(int) = 0.054]	[R(int) = 0.129]
data/restraints/parameters	6784/0/134	3508/0/110
goodness-of-fit	0.932	0.918
final R indices [$I > 2\sigma(I)$]	$R1 = 0.047$	$R1 = 0.048$
	$wR2 = 0.115$	$wR2 = 0.073$
R indices (all data)	$R1 = 0.069$	$R1 = 0.143$
	$wR2 = 0.127$	$wR2 = 0.097$
extinction coefficient	0.0038(9)	0.0040(10)
largest diff. peak/hole [e Å^{-3}]	1.272/−1.047	0.960/−1.071

Table 2. Atomic coordinates and isotropic displacement parameters [pm$^2 \times 10^{-4}$] for α-**1**.

	x	y	z	U_{iso}
Ge1	0.21765(4)	1.30151(4)	−0.09261(2)	0.03389(8)
Ge2	0.31696(5)	1.10749(4)	−0.27928(2)	0.03685(8)
Ge3	0.12530(5)	1.50206(4)	−0.33054(2)	0.03655(8)
Cl11	−0.10267(12)	1.24033(12)	−0.03941(7)	0.0533(2)
Cl12	0.33788(14)	1.31731(11)	0.04777(6)	0.04934(18)
Cl21	0.01703(14)	1.00842(13)	−0.25161(8)	0.0598(2)
Cl22	0.54908(15)	0.93253(13)	−0.34003(8)	0.0623(2)
Cl31	−0.21442(13)	1.48007(13)	−0.31528(7)	0.0574(2)
Cl32	0.15919(18)	1.73047(12)	−0.44790(7)	0.0599(2)
C1	0.3941(5)	1.1244(4)	−0.1459(2)	0.0380(5)
C2	0.2902(5)	1.3198(4)	−0.3835(2)	0.0425(6)
C3	0.1982(5)	1.5160(4)	−0.1958(2)	0.0376(5)
H1A	0.373(8)	1.019(7)	−0.092(4)	0.079(14)
H1B	0.539(8)	1.155(6)	−0.155(3)	0.068(13)
H2A	0.236(6)	1.296(5)	−0.431(3)	0.056(11)
H2B	0.406(9)	1.356(7)	−0.403(4)	0.092(17)
H3A	0.095(6)	1.578(5)	−0.178(3)	0.040(9)
H3B	0.322(6)	1.568(5)	−0.216(3)	0.057(11)

Table 3. Atomic coordinates and isotropic displacement parameters [pm$^2 \times 10^{-4}$] for β-**1**.

	x	y	z	U_{iso}
Ge1	0.01463(9)	0.31017(10)	0.33683(8)	0.0397(2)
Ge2	−0.33250(9)	0.60454(10)	0.20707(8)	0.0394(2)
Ge3	−0.20206(9)	0.21240(10)	0.17007(8)	0.0405(2)
Cl11	0.2641(3)	0.2456(3)	0.3891(2)	0.0640(6)
Cl12	−0.1330(3)	0.2980(3)	0.5351(2)	0.0690(7)
Cl21	−0.3493(3)	0.7144(4)	−0.0080(2)	0.0793(8)
Cl22	−0.5216(3)	0.7961(3)	0.3298(3)	0.0746(7)
Cl31	−0.2705(3)	0.0194(3)	0.2379(3)	0.0913(9)
Cl32	−0.1767(3)	0.2418(3)	−0.0554(2)	0.0688(6)
C1	−0.1027(8)	0.5398(9)	0.2546(7)	0.0395(17)
C2	−0.3897(9)	0.4243(10)	0.2303(8)	0.0448(18)
C3	0.0238(9)	0.1457(10)	0.2281(8)	0.0461(19)
H1A	−0.0342	0.5553	0.1698	0.047
H1B	−0.1122	0.6137	0.3202	0.047
H2A	−0.4881	0.4596	0.1772	0.054
H2B	−0.4254	0.4048	0.3291	0.054
H3A	0.0655	0.0364	0.2847	0.055
H3B	0.1052	0.1340	0.1452	0.055

of the ring would lead to shorter distances and consequently to increased repulsion between them.

Long-range 1,3-interactions between chlorine atoms may play a decisive role in fixing the conformation of **1**. This constitutes a principle difference between **1** and cyclohexane and 1,3,5-trigermacyclohexane, in which the 1,2-interactions of substituents (e.g., instability through eclipsed bonds in boat conformations or, in opposite, additional stabilisation due to a possible σ→σ* hyperconjugative effect between two neighbouring axial C–H bonds in chair cyclohexane[7]) are much more important.

Stability of the different conformations of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane: According to molecular mechanics calculations, the chair conformer of **1** is approximately 2.0 kcal mol^{-1} more favourable than the boat. In contrast, semiempirical and ab-initio calculations predict the boat conformation of **1** to be more stable with an associated difference between formation energies for boat and chair of 1.0 kcal mol^{-1} (AM1), 0.5 kcal mol^{-1} (PM3) and 0.3 kcal mol^{-1} (HF/TZVP). Due to the electron correlation considered in the MP2 scheme, the energy difference between boat and chair conformation is increased to 1.1 kcal mol^{-1}. DFT calculations give a value of 0.9 kcal mol^{-1} (B-LYP/SVP). The discrepancy in the relative stability of conformers predicted by molecular mechanics and quantum mechanics calculations arises because the standard force field does not account for the stabilisation due to nonclassical hydrogen bonds. In the present case only one such intramolecular interaction occurs: the H2A···Cl11 distance in the boat conformation (see Figure 3) amounts to 3.2 Å. Although quite weak, it may contribute to the stabilisation of this molecular geometry.

In general, our calculations show that the energy difference between chair and boat conformations is quite small (ca. 1 kcal mol^{-1} or less). Thus, at room temperature, the statistical numbers of molecules in either of both conformations are expected to be approximately the same, with the transitions among various conformations mediated by continuous pseudorotation. The crystallisation of **1** should then result in formation of either a mixture of different crystal polymorphs or only the thermodynamically most stable crystal modification, depending on the equilibrium conditions during crystallisation. The experimental observation that

Table 4. Shortest H···Cl distances and angles in α-**1** [pm and °].

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	$\sphericalangle\phi$ (D–H···A)	$\sphericalangle\theta$ (H···A–E)
C3–H3B···Cl31	93(4)	308(4)	379.7(3)	136(3)	149.0(7)
C3–H3A···Cl12	81(4)	313(4)	388.6(4)	157(4)	100.4(7)
C1–H1A···Cl12	99(5)	306(5)	377.2(4)	131(4)	98.2(10)
C1–H1A···Cl11	99(5)	299(5)	389.8(4)	153(4)	146.0(10)

Table 5. Shortest H···Cl distances and angles in β-**1** [pm and °].

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	$\sphericalangle\phi$ (D–H···A)	$\sphericalangle\theta$ (H···A–E)
C2–H2A···Cl32	97(2)	311(6)	396(8)	147.3(5)	111.59(8)
C3–H3B···Cl21	97(2)	311(3)	389(5)	138.0(5)	120.10(9)
C1–H1B···Cl11	97(2)	311(4)	397(5)	148.0(4)	91.65(7)
C3–H3A···Cl12	97(2)	306(4)	402(5)	170.1(5)	122.75(9)

both α-**1** and β-**1** crystal modifications can reproducibly be isolated in their pure form just by variation of solvent medium in the recrystallisation experiment, suggests that interactions between **1** and its solvents lead to different energetic behaviours or kinetics.

One possible reason for the selective formation of α-**1** or β-**1** in different crystallisation experiments may be attributed to screening effects, which could influence the coulomb interactions between substituents and could change, in turn, the relative thermodynamic stability of boat and chair molecules of **1** in solution. The simulation of screening caused by the solvent with the COSMO approximation in ab-initio calculations showed a decreasing energy difference between boat and chair conformations. This means that the pseudorotational transition of molecules of **1** between chair and boat conformations is evidently not suppressed by screening effects of the solvent medium.

The formation of metastable β-**1**, thus, cannot be adequately described on the basis of screening effects of the solvent medium alone, neglecting other possible interactions between **1** and solvent molecules. An alternative mechanism of the formation of the metastable polymorph might proceed through an intermediate solvate with favourable lattice energy and close structural relationship to β-**1**. Either desolvation or secondary nucleation at an early stage of crystal growth could then lead to the experimentally observed solid. Until now we have not been able to isolate such a solvate, but we decided to consider this hypothetical structure in our computer simulations.

Packing analysis and crystal structures of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane: Computer simulation of molecular crystals, based on the atom–atom potential method,[16] already has a long history; the subject has recently been reviewed.[17] According to lattice-energy minimisations based on van der Waals interactions, the crystal structure of α-**1** is found to be more stable than the β-polymorph (−19.31 and −17.86 kcal mol^{-1}, respectively). This result is in agreement with the observation that α-**1** may be obtained from the melt and shows the higher density. It might therefore be associated with crystallisation under thermodynamic control.[18,19]

Which intermolecular forces beyond van der Waals interactions may contribute to the lattice energy? Nonclassical C–H···Cl interactions occur in both modifications (see Tables 4 and 5). Generally, hydrogen bonds are dominated by electrostatic contributions. When coulomb interactions are taken into account and each atom is assigned a point charge, more favourable lattice energies result for both phases (α-**1**: −28.45 kcal mol^{-1}; β-**1**: −24.27 kcal mol^{-1}). Since the energy difference between the phases also increases, the polar interactions should evidently favour the formation of α-**1** rather than β-**1**.

Analysis of molecular packing[20] also shows the importance of interhalogen interactions. The shortest Cl···Cl contacts in **1** (Figures 2 and 3) are more frequent in the β-modification (see Table 6). A pure van der Waals model accounts best for this type of interaction, whereas the inclusion of charges tends to overestimate the energy difference in favour of α-**1**.[21,22]

Table 6. The shortest Cl···Cl distances in α-**1** and β-**1** [pm].

α-**1**	*d*(Cl···Cl)	β-**1**	*d*(Cl···Cl)
Cl11···Cl12	355.0(2)	Cl11···Cl21	363(3)
Cl21···Cl22	354.1(2)	Cl11···Cl22	368(5)
		Cl12···Cl22	356(4)
		Cl22···Cl31	361(3)

Neither modification contains significant voids if calculations with a 1.2 Å radius probe sphere are performed. Only if the probe radius is lowered to 0.8 Å, do interconnected areas of empty space show up. Under these conditions β-**1** contains a larger void (40 Å^3) than α-**1** (23 Å^3); the empty space in the crystal structure of β-**1** is centred around an inversion centre at (0.5, 0, 0.5).

This presence of small voids centred on special positions in β-**1**, general ideas about space filling and molecular packing and the fact that crystallisation from *n*-hexane represents the only access to the phase-pure β-modification inspired us to search by means of computer simulation for a solvate with the following properties: 1) the solid should contain boat-shaped molecules of **1** and *n*-hexane in a 2:1 stoichiometry, the latter residue in special position; 2) the hypothetical solvate crystal structure should exhibit reasonable lattice energy and space filling properties; and 3) the solvate should show an evident similarity to the β-modification. Ideally, "desolvation", that is, removal of the solvent from such an in-silico solvate, followed by energy minimisation in a computer experiment, should lead to β-**1**. As the largest void in this phase is located on an inversion centre and our simulations require residues in general positions, all solvate models were deduced for the non-centrosymmetric subgroup $P1$ rather than for $P\bar{1}$.

A 40 Å^3 void, such as that in β-**1**, is clearly too small to accommodate any organic solvent molecule. CSD data (refcodes HEXANE and HEXANE01) indicate that a molecule of *n*-hexane occupies a volume of 160 Å^3. It was therefore no surprise that positioning of either a complete hexane molecule or even a C_2 fragment, arbitrarily chosen as a minimum model for an organic solvent, followed by relaxation of the structure to the closest local lattice energy minimum did not result in a close-packed solid. After minimisation, the unit cell volume of such an unrealistic model for a hexane hemisolvate amounts to 868 Å^3. In view of the volume of the constituents (two molecules of **1** in boat conformation plus one *n*-hexane molecule, in total ca. 820 Å^3) and of the poor packing coefficient of only 0.619, this structure must be considered a dead end. A valid candidate for a solvate structure cannot be constructed by such a straightforward procedure; hence a larger part of the energy hypersurface has to be probed.

We reverted to the random generation of structures in space group $P1$ containing two boat-shaped molecules of **1** and one molecule of *n*-hexane in an all-*trans* conformation. A CSD search[23] also suggests this geometry as the most common conformation of the solvent molecule. We expected that the 2:1 stoichiometry and the solvent conformation should allow the transformation of promising candidates back to $P\bar{1}$ with the solvent on an inversion centre at a later stage of the computer simulation. A total of about 2000 random structures were subjected to a global energy minimisation with the simulated annealing technique.[24,25] The molecules of **1** in the experimentally observed boat conformation as well as the solvent were treated as rigid bodies. Under these approximations the energy hypersurface was subtended by a total of 24 variables, namely six lattice parameters of a presumed triclinic cell plus three translational and three orientation parameters for each of the three molecular residues. Candidate structures with high packing coefficients were subjected to a more accurate lattice-energy minimisation with PCK83. After metric reduction to conventional unit cells three trial structures converged to the same local minimum. This computer-generated structure was tested for inversion symmetry with the LePage algorithm,[26,27] as implemented in PLATON,[28] and transformed to the $P\bar{1}$ space group. The resulting hypothetical structure is shown in Figure 4A. It may be considered a serious candidate for a solvate: its final volume of 819 Å^3 is in agreement with the expectation, the final packing coefficient amounts to 0.663, and lattice energy of −47.94 kcal per two molecules of **1** plus one molecule of *n*-hexane is calculated.

Next, the *n*-hexane molecule was removed from the solvate structure described above, and the lattice energy of the remaining loosely packed structure (packing coefficient 0.535) was minimised in space group $P1$ by simulated annealing. This procedure was performed ten times. Among the minima obtained the structure associated with the most favourable energy was encountered twice. Local lattice-energy minimisation with PCK83 and subsequent transformation to $P\bar{1}$ resulted in the model shown in Figure 5A. This structure is very similar to the metastable modification crystallised from *n*-hexane (Figure 5B): the lattice energy per molecule of **1** amounts to $-17.82\,\mathrm{kcal\,mol^{-1}}$, and unit cell parameters are almost the same as those obtained from direct minimisation of the experimental β-**1** under the same conditions.

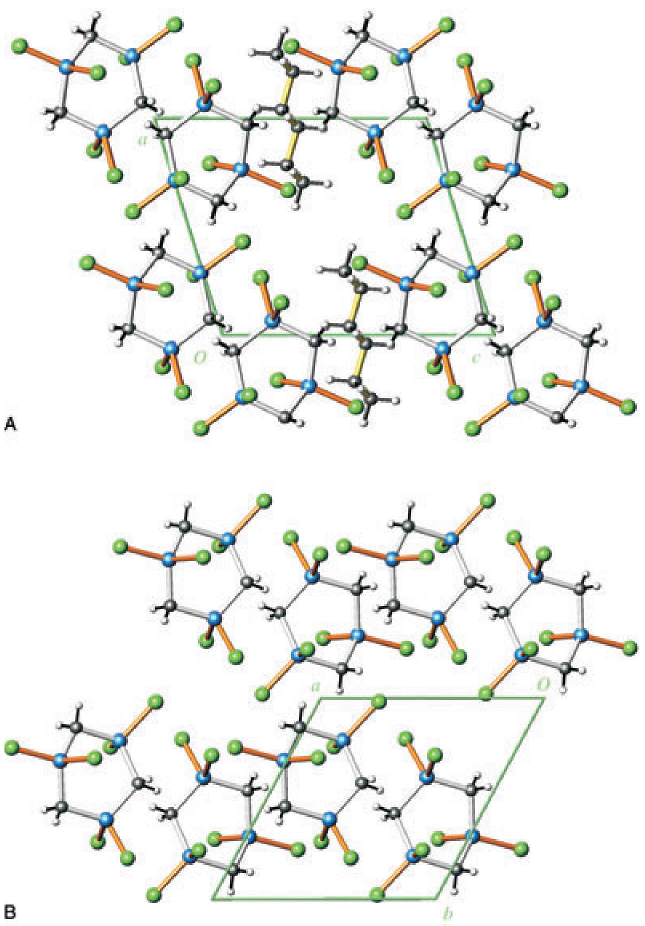

Figure 4. A) Projection of the hypothetical solvate obtained from simulating annealing. The unit cell contains a molecule of **1** in general position and an *n*-hexane molecule on a crystallographic inversion center. B) Experimentally obtained β-**1** modification in the same projection for comparison.

Energy minima are more abundant than "real" structures, and computer simulations cannot be regarded as a final proof as long as the hypothetical solids have not been synthesised. We have tried to understand the formation of a product under kinetic rather than thermodynamic control. In this context, the existence of reasonable energy minima for both, the solvated and desolvated product, as well as an easy conversion pathway from the former to the latter, offer an explanation for why β-**1** is obtained under these special conditions. Here we would like to mention that Braga, Grepioni and co-workers used pseudopolymorphs in seeding experiments for the growth of single crystals.[29,30] In one of their experiments, they could convert a solvate to a desol-

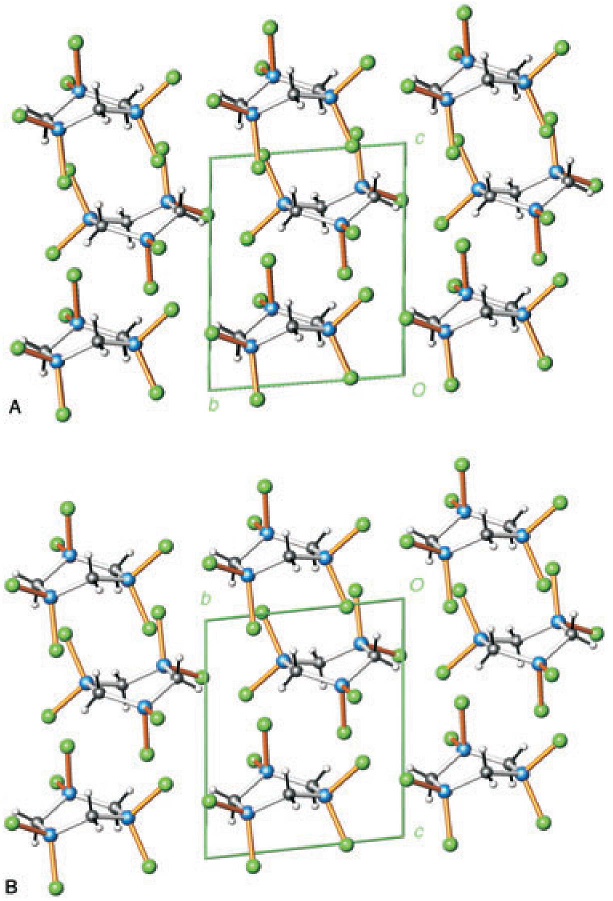

Figure 5. A) Projection of the "desolvated" structure (see text for details). B) Experimentally obtained β-**1** modification in the same projection for comparison.

vated powder, which in turn induced precipitation of solvent-free crystals from solution.[31] This experimental result provides an impressive example for the subtle balance between solvates and their desolvated derivatives.

Also, a significant contribution of Davey and co-workers on the comprehension of the solvent-induced effects on crystallisation of molecular crystal polymorphs has to be referred to at this point.[32–35] The active role of foreign molecules in crystallisation of molecular crystals is particularly emphasised by the observed influence that additive or solvent molecules exert on nucleation rate of different polymorph phases. Embedding the foreign molecules in the crystal structure may result in either inhibition or templating of further crystal assembly, mirroring the impact upon surface integration processes.

Conclusion

1,1,3,3,5,5-Hexachloro-1,3,5-trigermacyclohexane (**1**) shows conformational polymorphism: α-**1** is available from benzene and chlorobenzene and from the melt and contains chair-shaped molecules, whereas β-**1** crystallises from *n*-hexane and is composed of molecules in the boat conformation. The difference in formation energies between both molecular conformations is very small, and hence continuous pseudorotation at room temperature occurs.

Crystallisation of **1** from solution is directed by its interactions with solvent. Screening effects caused by the solvent medium cannot account for the selective formation of the metastable β-**1** phase. We suggest that the observed crystallisation of the metastable phase from *n*-hexane can occur as a result of the intermediate formation of a solvate $[(GeCl_2CH_2)_3]\cdot 0.5\,C_6H_{14}$. Intermolecular force-field-based computer simulations allowed the identification of a close-packed *n*-hexane solvate with this stoichiometry and suggestive similarity to β-**1**. Removal of the solvent from this in-silico structure and subsequent simulated annealing leads to the structure model experimentally obtained from *n*-hexane. In vitro, removal of the solvent may either correspond to desolvation at lower partial pressure of the solvent or to secondary nucleation. We expect that such a model of "solvent-aided" formation of the metastable phase of 1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane can be successfully applied for the directed preparation of less stable conformations of various molecular compounds.

Experimental Section

1,1,3,3,5,5-hexachloro-1,3,5-trigermacyclohexane (**1**) was synthesised in pure argon atmosphere by direct interaction of elemental germanium (Aldrich, −100 mesh, 99.99+%) with methylenechloride (Merck; dried over $CaCl_2$) in the presence of copper (Alfa Aesar, −100 mesh, 99.5%) as a catalyst (for the description of synthetic procedure see elsewhere[11,14]). The product **1** was separated from the other reaction products through repeated distillation under reduced pressure (125–130°C/0.5 mbar, lit.: 150–152°C/6.66 mbar,[11] 120°C/0.07 mbar[14]) and subsequently recrystallised from *n*-hexane. The final yield of **1** after purification corresponded to approximately 11% of the theoretical yield from Ge (lit.: 16%[11]). The melting point (m.p. 92°C) agreed well with the data given in the literature.[11]

Powder X-ray diffraction data were collected by using a STADI P diffractometer (Stoe & Cie) with $Cu_{K\alpha}$ radiation. Single-crystal X-ray diffraction measurements were performed by using a Bruker AXS Smart CCD X-ray diffractometer with graphite monochromator and $Mo_{K\alpha}$ radiation ($\lambda = 71.073$ pm). The diffraction data were corrected for absorption semi-empirically with the SADABS program.[36] Crystal structures discussed below were solved from single-crystal XRD data by using SHELXS-97[37] (direct and difmap) and refined by full-matrix least-squares on $|F^2|$ with SHELXL-97[38] software.

The optimised structures of **1** were obtained by applying the Hartree–Fock (HF) and the MP2 approach with SVP and TZVP basis sets,[39,40] as well as density functional theory (DFT) with SVP basis set and the gradient corrected B-LYP functional[41,42] by using TURBOMOLE software.[43] Semiempirical calculations were performed using parameterised Hamiltonian operators AM1[44] and PM3[45] with TURBOMOLE[43] and CAChe program suite.[46] Molecular mechanics calculations based on an enhanced MM2 force field[47] were performed with CAChe.[46] Local energy minima for crystal lattices were obtained with the help of the program PCK83.[48] Van der Waals interactions were modelled with a Buckingham potential using published parameters.[49] Chlorine interaction parameters had been derived to model a phase transition in $[MCl_3(thf)_3]$.[50] Point charges were obtained from Extended Hückel calculations followed by Mulliken population analysis.[46] The search for the solvate was performed with the program HARDPACK.[51]

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