Structure and kinetics of novel cyclophane inclusion compounds

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A novel cyclophane host compound, 3, featuring a macrocyclic structure with two hydroquinone dimethyl ether and two 1,1-diphenylcyclohexane construction elements assembled *via* benzylic ether linkages has been synthesised and its inclusion compounds with toluene, 4, and cyclohexanone, 5, have been characterised by thermal analysis and X-ray crystallography. The conformation of the cyclophane is markedly different in the two inclusion compounds. The kinetics of desolvation of 5 are deceleratory and yield an activation energy of 182 kJ mol^{-1}.

Introduction

The pioneering work on cyclophanes as a class of molecular receptors was carried out by D. J. Cram[1,2] and their ability to form inclusion compounds in aqueous solution, as well as their selectivity of charged aromatic guests and their behaviour in organic solvents, has been reviewed recently.[3] These host frameworks are distinguished by a rather rigid cavity structure arising from the assembly of aromatic groups such as an angular diphenylmethane[4] or an analogous building block.[5]

Cyclophanes are versatile host compounds and there are copious examples of structures in which the guest is either entrapped in the cyclophane cavity or is sandwiched between host molecules in the crystal lattice. In the complex formed between 1′,1″-dimethyldispiro[1,6,20,25-tetraoxa[6.1.6.1]paracyclophane-13,4′:32,4″-bispiperidine] and *p*-xylene, the aromatic rings of the *p*-xylene are not found in the cavity but are located between two host molecules.[6] However, this host also forms an inclusion compound with benzene and water with stoichiometry 1:2:1, in which one benzene molecule is perfectly enclosed in the cavity of the cyclophane, while the second benzene and the water are located in channels in the crystal lattice.[6]

Similar effects have been reported for the structure of N^2,N^{11},N^{20},N^{29}-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane with dioxane,[7] in which the guests lie in channels formed by the stacking of the cyclophanes. This host also forms inclusion compounds with a variety of small molecules such as chloroform, acetonitrile and carbon dioxide, and they are located in the host cavity.[8] This host is interesting in that its inclusion compound with chloroform has been shown to undergo guest exchange with CH_2BrCl in the crystalline phase. This occurs in two steps, first slowly and then rapidly, and has been attributed to a change in crystal structure.[9]

Recently we reported a macrocyclic structure based on this design featuring two convergent carboxylic acid functions kept at a non-interactive distance.[10] These preorganised macrocycles were found to extract small alkaline earth metal ions in a liquid two-phase system with high selectivity. They also make possible selective inclusion of organic molecules.[11] Following this strategy, we substituted the benzoic acid groups of the macrocyclic host with hydroquinone dimethyl ether units in order to modify the size and polarity of the host interior. This lays the foundation for a possible redox-responsive[12] molecular receptor, or chromoacerand,[13] when the phenolic groups are deblocked.

We have studied the structure–reactivity relations of inclusion compounds which may be broadly classified as molecular complexes, whereby a guest is entrapped by a single host molecule, and lattice clathrates, where the guest fits into the intermolecular spaces created by the packing of host molecules. In particular we have concentrated on the kinetics of enclathration and desolvation of a number of inclusion compounds formed between bulky organic host compounds and volatile guest molecules, and we have also related their thermodynamic properties to their structure and the phase transformations which accompany the various dynamic processes.[14,15] We now present the synthesis of a novel cyclophane **3** and the structures of its inclusion compounds with toluene **4** and cyclohexanone **5**, and describe their thermal properties and kinetics of desolvation.

Experimental

IR spectral data were obtained on a Perkin-Elmer spectrometer and the ^{1}H NMR spectra were recorded on a Bruker MSL 300 spectrometer in $CDCl_3$ with $SiMe_4$ as an internal standard.

Host compound 3

A solution of 1,1-bis(4-hydroxyphenyl)cyclohexane, **1**,[16] (4.8 g, 15 mmol) in dry acetone (250 ml) and a solution of 1,4-dimethoxy-2,6-bis(bromomethyl)benzene, **2**,[17] (4.0 g, 15 mmol) were added dropwise simultaneously over 8 h to a suspension of caesium carbonate[18] (14.66 g, 45 mmol) in dry acetone (1 l) under reflux. The reaction mixture was filtered and the solvent was removed under reduced pressure. The extract was diluted with tetrahydrofuran, heated under reflux for 30 min and filtered. The solvent was removed again under reduced pressure and the extract was recrystallised in chloroform to give **3**, [see reaction (1)] (1.5 g, 23%); mp 265–267 °C; ν_{max}(KBr)/cm^{-1} 3043m, 2936s, 2859m, 1607w, 1509w, 1222s, 896m, 824w; δ_H 1.51 (m, CH_2), 2.18 (m, CH_2), 3.61 (s, CH_3), 3.71 (s, CH_3), 5.07 (s, Ar-CH_2), 6.80 (d, ArH), 6.93 (s, ArH), 7.05 (d, ArH) (Found: C, 78.3; H, 7.1. $C_{56}H_{60}O_8$ requires C, 78.11; H, 7.04%).

Host–guest compounds

The inclusion compounds were obtained by dissolving the host compound **3** in an excess of toluene and cyclohexanone. As all of the inclusion compounds proved extremely labile, becoming opaque within minutes in air, single crystals were sealed in

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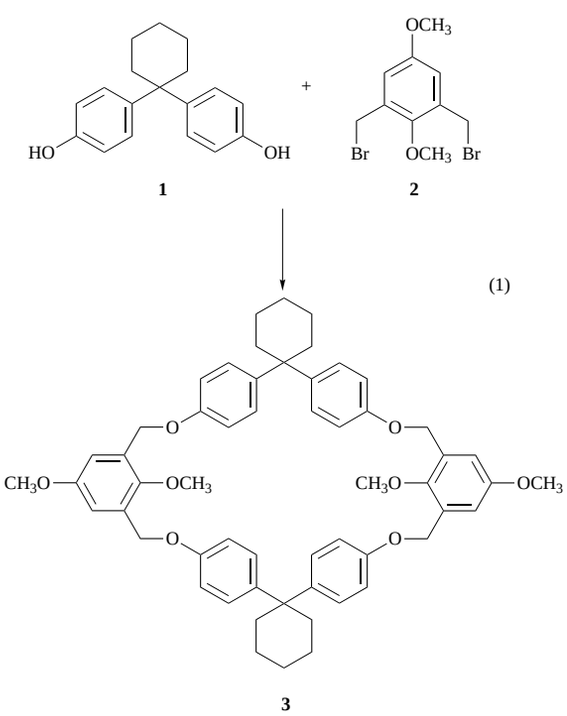
Table 1 Details of crystals, data collections and final refinements

Guest	Toluene	Cyclohexanone
Molecular formula	$C_{56}H_{60}O_8 \cdot 4C_7H_8$	$C_{56}H_{60}O_8 \cdot 2C_6H_{10}O$
M_r	1229.65	1057.32
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Z	1	1
a/Å	11.441(10)	10.0580(10)
b/Å	11.884(6)	10.252(2)
c/Å	14.716(6)	15.1090(10)
α/°	107.78(4)	99.300(10)
β/°	96.37(6)	99.921(10)
γ/°	103.36(6)	103.160(10)
Volume/Å^3	1818(2)	1461.2(3)
D_c/g cm^{-3}	1.123	1.202
μ(Mo-Kα)/cm^{-1}	0.55	0.72
F(000)	660	568
Crystal dimensions/mm	0.2 × 0.2 × 0.2	0.5 × 0.5 × 0.4
θ range scanned/°	3–75	1–25
Range of indices h, k, l	14, ±14, ±18	±11, ±12, 17
Temperature/K	143(2)	293(2)
No. of reflections collected	7331	5319
No. of unique reflections	6946	5106
R_{int}	0.0563	0.0217
No. of variables	400	357
R_1 [($I > 2\sigma(I)$)]	0.1314	0.0502
wR_2 (F^2)	0.3197	0.1431
S	2.138	1.094
$\Delta\rho_{max}$ final/e Å^{-3}	1.150	0.208
$\Delta\rho_{min}$ final/e Å^{-3}	−0.870	−0.218



Lindemann capillary tubes with mother liquor to prevent the desorption of the guest. X-Ray diffraction data were measured on a CAD4 diffractometer and during the data collection three reference reflections were monitored periodically to check crystal stability. The data reduction included correction for Lorentzian and polarisation effects. Crystal data and structural refinements are given in Table 1.‡ Both structures were solved by direct methods using SHELX-86[19] and refined by full-matrix least-squares with SHELX-93.[20] For both structures host non-hydrogen atoms were treated anisotropically. The hydrogen atoms were subjected to constrained refinement, with isotropic temperature factors given to hydrogen atoms of the same kind.

‡ Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/100.

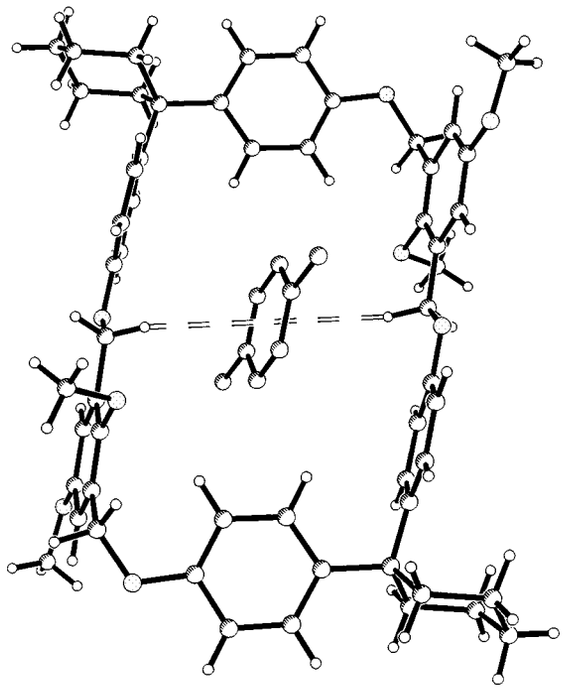


Fig. 1 Host with encapsulated disordered toluene

Differential scanning calorimetry (DSC) and thermal gravimetry (TG) were performed on a Perkin-Elmer PC7 series system. Finely powdered specimens, obtained from continuously stirred solutions, were blotted dry on filter paper and placed in open platinum pans for TG experiments and in crimped, but vented, aluminium pans for DSC experiments. The sample weight in each case was 2–5 mg. The temperature range was typically 30–300 °C at a heating rate of 20 °C min^{-1}. The samples were purged by a stream of nitrogen flowing at 40 cm^3 min^{-1}. Data for the kinetics of desolvation were obtained from isothermal TG experiments carried out at selected temperatures in the range of 80–100 °C.

Results and discussion

The toluene inclusion compound **4** has a host:guest ratio of 1:4 and crystallises in the space group $P\bar{1}$ with $Z = 1$. The host molecule is therefore located at a centre of inversion at Wyckoff position b. One of the toluene guests is located at the centre of the molecule and is disordered, making it appear like *p*-xylene, and its methyl groups were modelled with site occupancy factors of 0.5. Two of the remaining guest toluenes were located at Wyckoff positions a and c, while one was at a general position. All three of these toluenes exhibited considerable disorder. The host molecule with the entrapped toluene is shown in Fig. 1. Hydrogen atoms from the methylene bridges point directly towards the centre of the disordered toluene but the distances from the C-atoms of the macrocycle to the centroid of this toluene are between 3.25 and 4.13 Å and are therefore too large to propose the existence of C–H · · · π(Ar) hydrogen bonding. The packing of the toluene inclusion compound **4** is shown in Fig. 2 as a projection viewed along [010]. The unbound toluenes are located in channels running parallel to *a*.

The cyclohexanone inclusion compound **5** has a host:guest ratio of 1:2 and also crystallises in the space group $P\bar{1}$ with $Z = 1$. The host is again located at a centre of inversion, in Wyckoff position g, and the guests are in general positions. The packing of compound **5** is shown in Fig. 3 on a projection viewed along [010]. Here the host molecules are shown by the

Table 2 Torsion angles describing conformations of the host molecule

	Torsion angles	Host + Toluene	Host + Cyclohexanone
T_1	C(24)–C(23)–C(22)–O(21)	−177.4(3)	−93.6(3)
T_2	C(23)–C(22)–O(21)–C(18)	174.9(3)	−174.5(2)
T_3	C(22)–O(21)–C(18)–C(19)	10.4(5)	−3.3(4)
T_4	C(20)–C(15)–C(9)–C(14)	156.4(4)	24.1(4)
T_5	C(10)–C(9)–C(6)–C(5)	51.5(5)	12.9(3)
T_6	C(4)–C(3)–O(2)–C(1)	168.7(4)	19.1(4)
T_7	C(3)–O(2)–C(1)–C(27)*	78.8(5)[a]	143.1(2)[b]
T_8	O(2)–C(1)–C(27)*–C(24)**	−133.1(4)[a]	−82.0(3)[b]

Equivalent positions: [a] C(27)* and C(24)** (−x, −y, −z + 1); [b] C(27)* and C(24)** (−x, −y + 1, −z + 1).

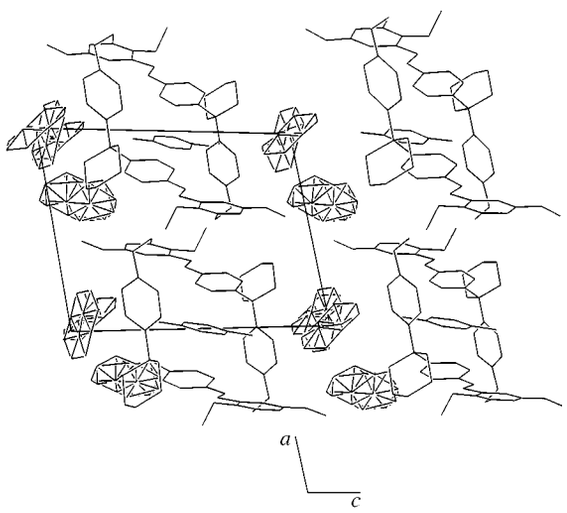


Fig. 2 Projection of **4** viewed along [010] showing the encapsulated and other disordered toluenes

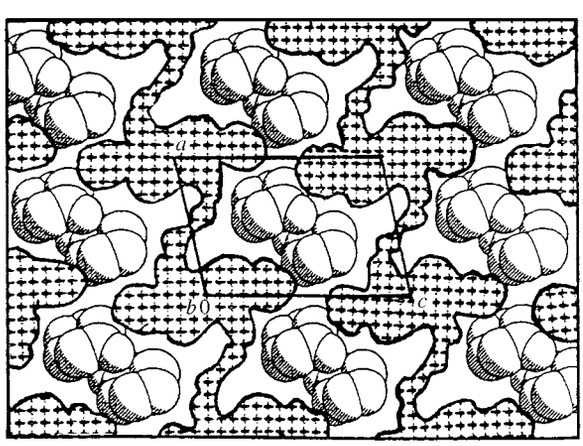


Fig. 3 Projected cross-section of the host molecules (hatched area) of **5** on [010] showing the guest molecules in highly constricted channels

hatched area, and the guest molecules lie in highly constricted channels running parallel to *a*. In contrast to **4**, the cyclohexanone inclusion compound has the host in a closed conformation with the endocyclic methoxy moieties pointing towards the centre of the host cavity.

The conformations of the host may be described by eight torsion angles of the asymmetric unit, comprising half the cyclic host molecule. These torsion angles are listed in Table 2 and are shown in Fig. 4. There are significant differences in the torsion angles, yielding dramatically different shapes to the cavity of the host. These are shown in Figs. 5 and 6, which give space-filling pictures of the host. In **4** the conformation of the host is such that the methoxy groups point outwards, yielding a rectangular cavity with dimensions of approximately 5.9 × 8.3 Å, which is able to accommodate a toluene guest (Fig. 5). This is in contrast to the conformation of the host in **5**, where opposite methoxy moieties point towards the centre of the cyclophane leaving insufficient space for the encapsulation of a guest (Fig. 6).

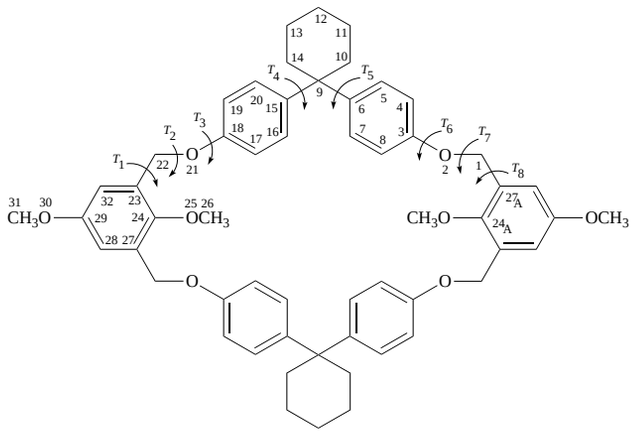


Fig. 4 Atomic nomenclature and torsion angles, *T*, of the host molecule

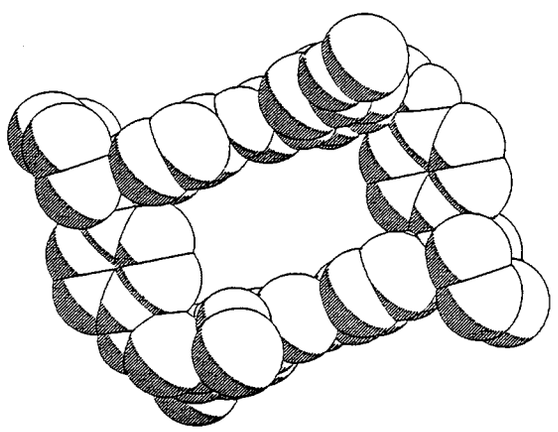


Fig. 5 Van der Waals representation of the host molecule in **4** showing rectangular cavity

The thermal gravimetry (TG) and differential scanning calorimetry (DSC) traces for both compounds are shown in Fig. 7. The toluene inclusion compound **4** decays in two distinct steps [Fig. 7(*a*)]. The first step corresponds to the loss of three toluenes (calc. 22.4%, found 20.5%) and the second step to the loss of one toluene (calc. 7.5%, found 9.8%) interpreted as the extra- and intra-cavity guests, respectively. Therefore the total loss of both steps represents four toluenes (calc. 29.9%, found 30.3%). The DSC trace shows one single endotherm due to the total guest loss, with an onset temperature at 83 °C, followed by a sharp endotherm due to melting of the host at 262.0 °C.

In contrast, the cyclohexanone inclusion compound **5** decays in a single step (calc. 18.6%, found 18.6%) and the DSC trace shows a broad endotherm, with $T_{OH} = 90$ °C [Fig. 7(*b*)]. The host melt exhibits two distinct endotherms with onset temperatures at 256.0 and 262.0 °C. This phenomenon is well-known and can be interpreted as a phase change in the host compound, followed by a final melting.[21]

In order to verify the existence of two different phases for the host compound we carefully desorbed both inclusion compounds **4** and **5** at 200 °C and obtained their powder diffraction patterns on a Debye–Scherrer goniometer. The photometric traces of these are quite different, thus establishing the two distinct phases α_1 (mp 262.0 °C) derived from **4** and α_2 (mp 256.0 °C) derived from **5**.

We measured the kinetics of desolvation of the cyclohexanone compound, **5**, by carrying out isothermal desorption runs by TG in the temperature range 80–100 °C. The inclusion compound used for the kinetic analysis was prepared as a fine

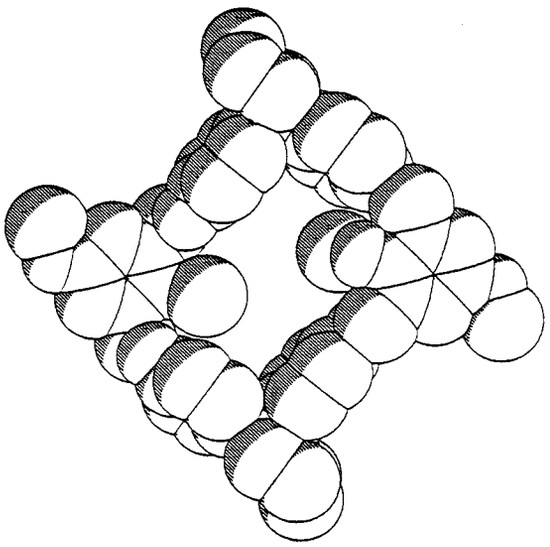


Fig. 6 Van der Waals representation of the host molecule in **5** showing the methoxy moieties pointing towards the centre of the cavity

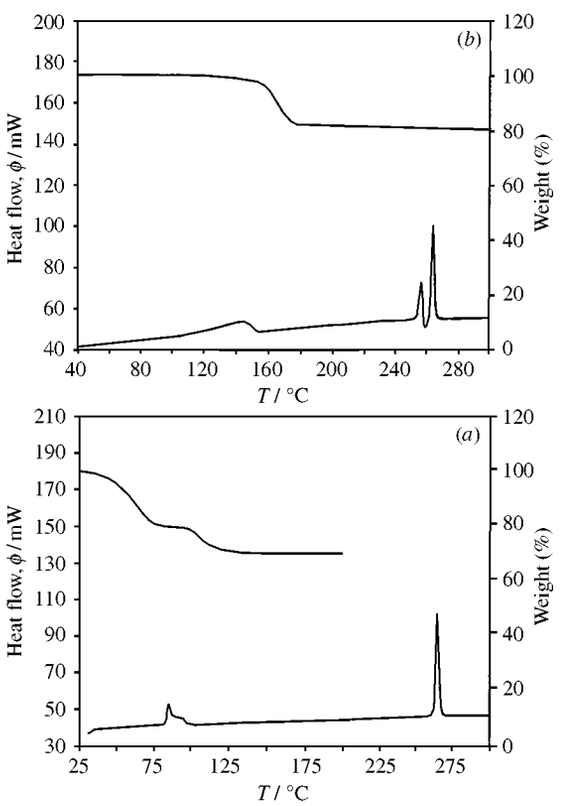


Fig. 7 Thermograms (TG and DSC) for (*a*) **4** and (*b*) **5**

powder by fast precipitation of a saturated solution of the host in cyclohexanone. We are cognisant of the fact that the phases and host : guest ratios of organic inclusion compounds are strongly dependent on their method of preparation. We therefore checked that the powdered compound formed had the same structure as that of the single crystal. This was achieved by comparing the measured X-ray powder diffraction pattern, obtained from the precipitated powder, with that generated from the atomic positions derived from the single crystal structure determination using the program LAZYPULVERIX.[22] This is shown in Fig. 8, where the match between measured and calculated peak positions is excellent, showing that the same host–guest compound had been formed.

Plots of the extent of reaction, α, *versus* time yielded decelerating curves. The contracting area mechanism (R2) fitted over the range of 0–0.7 for 90–100 °C. The reaction did not reach completion below 90 °C, but these curves were analysed over

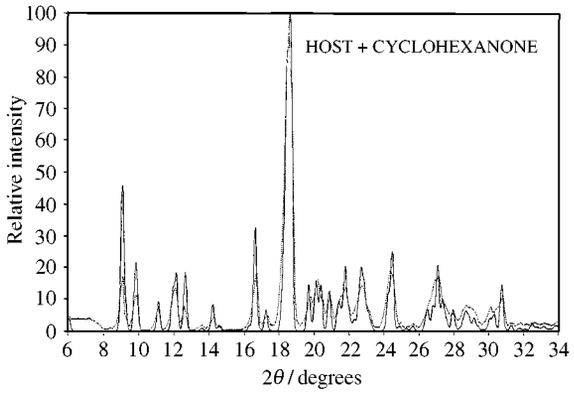


Fig. 8 Comparison of measured (– – –) and calculated (——) X-ray powder diagram for **5**

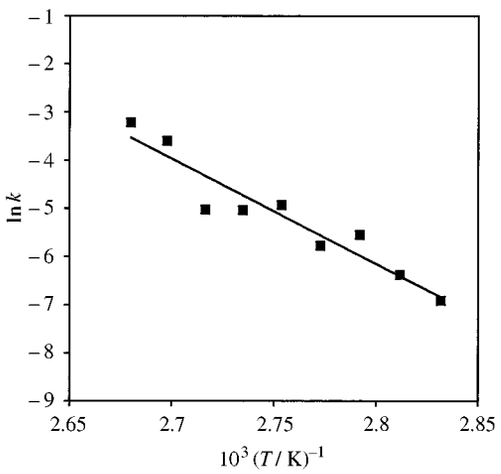


Fig. 9 Arrhenius plot for the desorption of **5**

the whole α range collected and were also found to follow the R2 model. The rate constants thus derived gave the Arrhenius plot shown in Fig. 9 which yielded an activation energy of 182 (20) kJ mol^{-1} for the range α = 0–0.5.

Activation energies for the desolvation of guests from inclusion compounds are generally low, and range from 40–130 kJ mol^{-1} in open channel structures. The inclusion compounds formed by the host 2,2′-bis(2,7-di-*tert*-butyl-9-hydroxyfluoren-9-yl)biphenyl with acetone and 1,4-dioxane both undergo desolvation reactions with activation energies of 147(4) and 150(6) kJ mol^{-1}.[22] The structures of both these compounds have the guest located in highly constricted channels, similar to the structure of compound **5**. Thus the high value of 182 kJ mol^{-1} obtained can be interpreted as arising from the disruption of the host framework which would be necessary for the cyclohexanone to escape.[23]

Conclusions

The novel cyclophane **3** has been synthesised and its inclusion compounds with toluene **4** and cyclohexanone **5** have been characterised. The conformations of the host molecule of the compounds **4** and **5** and their thermodynamic behaviour have been studied. Kinetics experiments on the desolvation of the inclusion compound **5** were carried out. Further work on related guests is continuing.

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