Investigation of the Solvent Enclathration Potentials of 5-Phenyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ol and Related Seven-membered Ring Alcohols

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ABSTRACT

Four previously reported tricyclic alcohols containing seven-membered central B-rings, 5-phenyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ol, 5-phenyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol, 11-phenyl-6,11-dihydrodibenzo[*b,e*]oxepin-11-ol and 11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol have been synthesized and their solvent enclathration (inclusion) properties investigated and compared by using ^{1}H-NMR and differential scanning calorimetry (DSC). The presence of an oxygen or a sulphur atom, respectively, in the B-ring of the latter two compounds had a detrimental effect on the solvent enclathration properties of the host compounds as compared to those containing an ethane or ethylene bridge. This suggests that, although enclathration is highly dependent on the hydrogen bonding ability of the host, rigidity of the structure plays a crucial role in the formation and stability of these complexes.

KEYWORDS

Enclathration, inclusion complexes, medium rings, seven-membered rings, 5-phenyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol, 11-phenyl-6,11-dihydrodibenzo[*b,e*]oxepine, 11-phenyl-6,11-dihydrodibenzo[*b,e*]thiepine.

1. Introduction

The enclathration chemistry of tricyclic heterocyclic compounds has been extensively investigated during recent years in view of the demonstrated solvent inclusion abilities of these compounds.[1,2] We are interested in the inclusion properties of xanthenyl and related tricyclic compounds with the ultimate aim of introducing chirality into suitable host molecules in order to effect chiral separations of enantiomers,[2,3] which is of particular importance to the pharmaceutical industry where the amounts of biologically inactive or harmful enantiomers of medicinal compounds have to be removed from racemic mixtures of synthesized medicinal compounds. As receptor sites are chiral and may bind to only one enantiomer in order to trigger a positive response, the other enantiomer may either enhance undesirable side-effects in the human body, or have no beneficial effect as a result of its inability to bind to the target receptor site. As chiral separation is both difficult and usually very expensive to achieve on a relatively large scale, the use of recyclable reagents such as inclusion host compounds seems to be a very useful way of achieving this goal, and the process would also be more environmentally friendly.

Our more specific interest was on the chiral separation of the enantiomers of menthol and menthone as part of a confidential industrial project, and, using our previously gained experience of the chemistry of alcohols and azides based on fluorenyl, xanthenyl, 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene, 5*H*-dibenzo[*a,d*]cycloheptene, 6,11-dihydro-11-dibenzo-[*b,e*]oxepine and 6,11-dihydro-11-dibenzo[*b,e*]thiepine and related cyclic modified trityl (triphenylmethyl) systems, it seemed appropriate to evaluate these compounds as potential enclathration compounds.[4]

Also, encouraged by our previous successes in our enclathration studies of solvents using xanthenyl and thioxanthenyl alcohols and amines,[5–7] we embarked on a systematic study and now disclose our recent results on the synthesis and enclathration properties of two alcohols **3** and **4**, as well as a re-investigation of two others **1** and **2**.

2. Results and Discussion

The previously reported alcohols **1–4** were synthesized by known methods and their enclathration potential assessed by recrystallization from a variety of solvents.[3,8–11] These results are summarized in Table 1 and Scheme 1.

The tricyclic alcohols **1–4**, containing seven-membered B-rings, were crystallized from a wide variety of solvents. None of methanol, ethanol, *i*-propanol, *t*-butanol, acetonitrile, nitromethane, THF, cyclohexane, ether, menthol and menthone were included by any of these host compounds.

Although the enclathration properties of **1** had been investigated extensively, discrepancies were found between our results and those reported.[3,11,12] In one case only, that of dioxane (entry 4, Table 1), did inclusion occur in the same ratio as reported. A 2:1 ratio was observed for three of the four inclusion compounds isolated (entries 3–5, Table 1), whereas DMF was included in a H:G ratio of 3:2 (entry 2).

The inclusion properties of **2** have also been reported previously.[3] However, our results showed that, contrary to those reported, *tert*-butanol, THF and piperidine were found not to be included by this host compound. Furthermore, the host:guest (H:G) ratios for the inclusion of acetone (entry 1), benzene (entry 8) and DMSO (entry 3) also differed from reported values, whereas the other inclusions and H:G ratios reported were confirmed.

These differences in H:G ratios are attributed to variations in the experimental conditions used in the crystallization methods.

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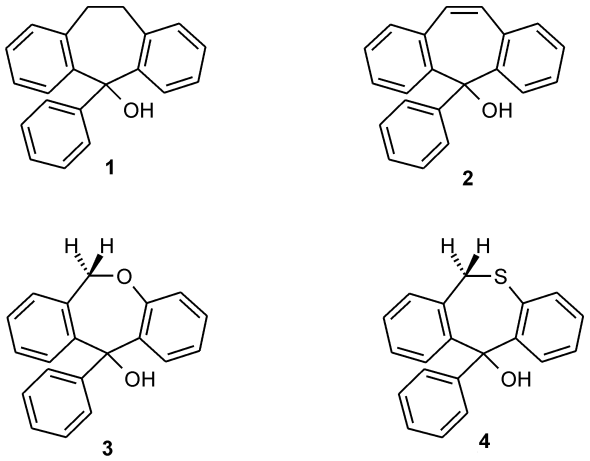
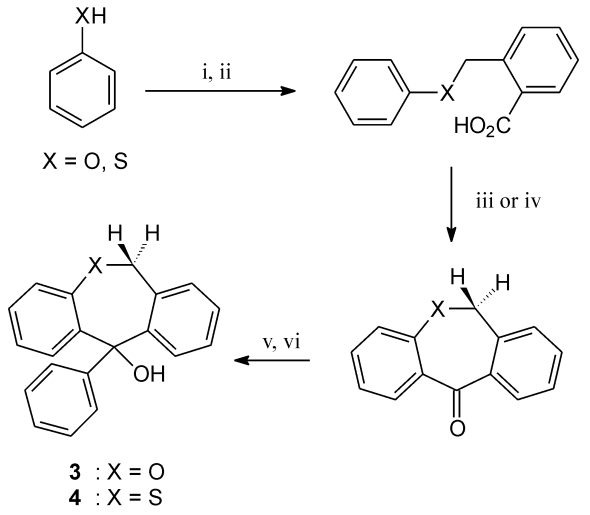
Table 1 Host:guest (H:G) ratios for inclusion complexes formed by alcohols **1–4**.

Entry no.	Guest	(**1**)	(**2**)	(**3**)	(**4**)
1	Acetone	–	2:1	–	–
2	DMF	3:2	1:1	–	2:1
3	DMSO	2:1	2:1	a	2:1
4	1,4-Dioxane	2:1	2:1	–	–
5	Morpholine	2:1	1:1	a	–
6	Piperidine	a	–	–	–
7	Pyridine	–	1:1	–	–
8	Benzene	–	3:1	–	–

a, Crystals dissolved on washing with ether or methanol.

However, it has also been confirmed that **2** is a more efficient host than **1**, ascribed to the more rigid structure of compound **2**. The B-ring double bond imparts more rigidity to the tricyclic system relative to the saturated ethylene bridging system, rendering the latter molecule conformationally more mobile. This trend for the inclusion abilities is not entirely unexpected, since rigidity in host molecules is known to be an important feature for effective enclathration.[13] Compound **2** gave predominantly H:G ratios of 1:1 and 2:1, respectively (Table 1).





Scheme 1
Synthesis of the tricyclic alcohols **3** and **4**.
Reagents: i, NaH, DMF; ii, phthalide, DMF, reflux; iii, BF_3 etherate (*X* = O); iv, PPA (X = S); v, PhMgBr; vi, aq. NH_4Cl.

The introduction of an oxygen atom in the ethylene bridge as in **3** proved to be highly detrimental to the inclusion ability of the system, as none of the solvents used was included (Table 1). Recrystallizations of **3** from DMSO and morpholine, respectively, gave crystals which, unfortunately, could not be characterized owing to their high solubility upon washing with methanol (see Experimental).

The presence of a sulphur atom in the ethylene bridge also significantly decreased the including ability of the system relative to that of **1** and **2**. Only DMF and DMSO were included by host **4**, both with a H:G ratio of 2:1. A similar trend has also been observed in the six-membered xanthenyl and thioxanthenyl systems, where the sulphur derivatives also displayed better host enclathration ability than their oxygen analogues.[5–7] DSC traces of the inclusion complexes formed by **4**, as well as the pure host are depicted in Figs 1–4.

The DSC trace for **4** (Fig. 1) shows a single endotherm with a leading tail and peaking at 201°C which corresponds to the melting point of the host. When the **4 · DMSO** inclusion complex was heated at 5 K min^{-1}, a single endotherm was observed – the guest release commencing at *ca.* 177°C (T_{on}, the onset temperature for guest release) with concomitant dissolution of the host (Fig. 2). In order to resolve the single endotherm of the trace, the complex was heated at a slower rate (2.5 K min^{-1}) (Fig. 3). Partial resolution of the peak was observed at this lower heating rate: the first peak may be assigned to the release of DMSO from the host cavities, while the second endotherm is probably due to the dissolution of the host in the released DMSO since it occurs at a temperature significantly below the pure host's melting point.

The DSC trace for the DMF complex showed two well-defined endotherms, the first with T_{on} = 119°C and peaking at 122°C is due to the guest release reaction, while the second starting at 192°C and peaking at 202°C is attributed to the melting of the

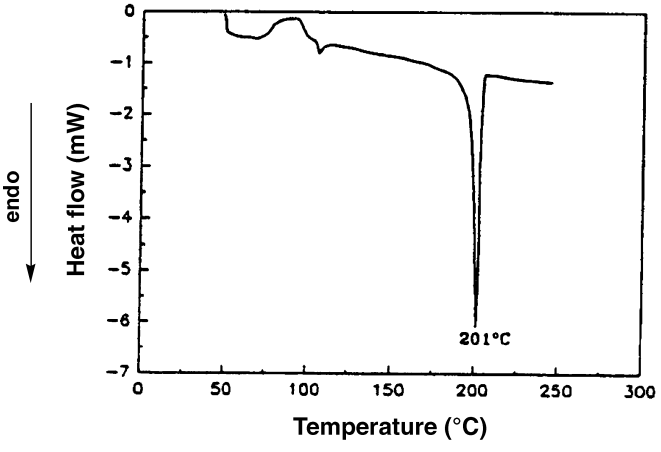


Figure 1 DSC trace of the pure alcohol host **4**.

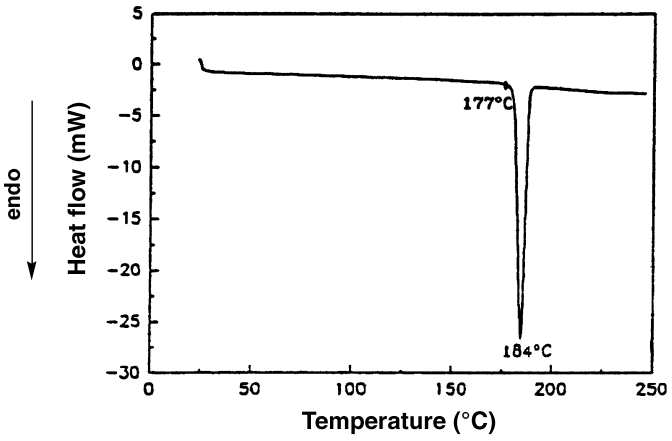


Figure 2 DSC trace for the **4 · DMSO** enclathration complex (heating rate: 5 K min^{-1}).

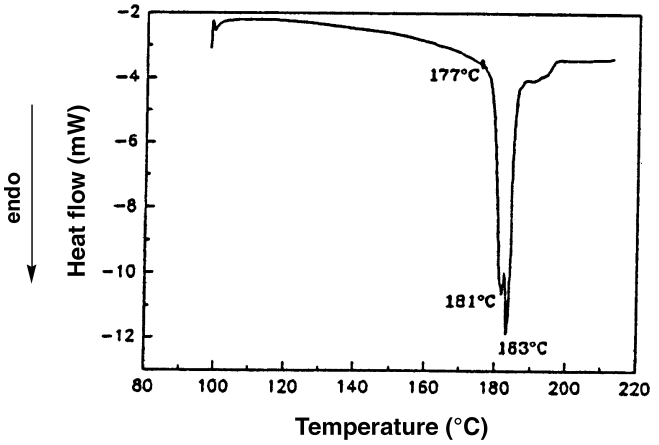


Figure 3 DSC trace for the **4 · DMSO** enclathration complex (heating rate: 2.5 K min^{-1}).

host compound (Fig. 4). By using the expression (T_{on}–T_b), where T_b is the boiling point of the pure guest compound, the relative thermal stabilities of these two compounds could be determined (Table 2).

Since (T_{on}–T_b) < 0 for both complexes, neither of the guests is strongly enclathrated in the crystal. That the DMF inclusion complex is thermally less stable than the DMSO clathrate is reflected by the larger magnitude obtained for (T_{on}–T_b) in the former case. Recrystallization of host **4** from a large excess of an equimolar mixture of DMSO and DMF (total guest:host ratio ≫20:1) resulted in the formation the **4 · DMSO** clathrate with a stoichiometric ratio of 2:1. The selective inclusion of DMSO is in accordance with the higher stability of the DMSO clathrate.

3. Conclusions

From the above results, it is evident that heteroatoms in the central seven-membered tricyclic systems have a detrimental effect on the enclathration properties of these alcohols. The oxygen-containing B-ring proved to be totally inefficient at any inclusions, whilst the sulphur analogue was slightly more successful in this respect, forming complexes with two of the solvents investigated. In addition, when comparing the ethane bridged system with that of the unsaturated ethene bridged system, the more rigid compound serves as the better host, possibly due to increased rigidity associated with the less saturated species. Furthermore, these seven-membered B-ring compounds are less efficient as hosts than their six-membered counterparts, suggesting that other factors such as conformation of the ring tricyclic systems, could also have an effect on inclusion processes.

4. Experimental

Melting points were determined on an Electrochemical IA9000 series digital melting point apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin Elmer 1600 series Fourier transform infrared spectrometer. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) were recorded on a Varian Gemini NMR spectrometer with TMS as internal standard and coupling constants (*J*) are expressed in Hz.

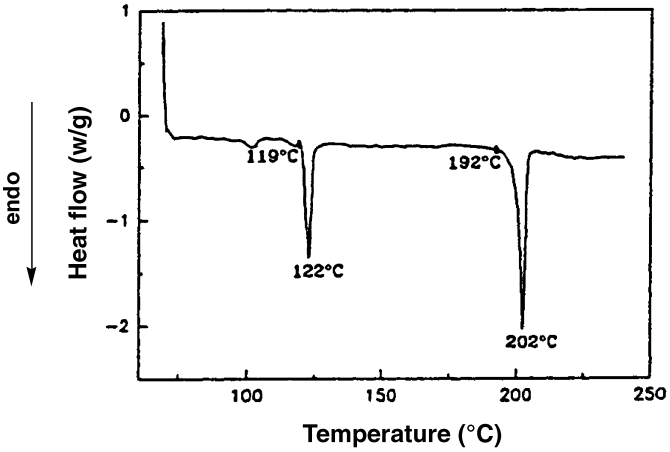


Figure 4 DSC trace for the **4 · DMF** enclathration complex.

Differential scanning (DSC) experiments were performed on a Du Pont 910 standard DSC module, linked to a Du Pont 9000 thermal analyser. High-purity dinitrogen was used as purging gas, at a heating rate of 5 K min^{-1}, unless otherwise stated. Samples were sealed in aluminium DSC pans with empty aluminium pans serving as a reference.

Mass spectra were recorded by Dr P. Boshoff at the Cape Technikon, Cape Town, South Africa, and analytical microanalyses performed at the CSIR (Division of Material Science and Technology), Pretoria, South Africa.

Preparative thin chromatography (PLC) was performed on silica gel layers (1.5–2.0 mm thickness) containing UV fluorescent indicator (254 nm).

Petroleum ether refers to the hydrocarbon fraction boiling at 40–60°C.

4.1. Synthesis of the Alcohols 1–2

4.1.1. General Method

A portion of bromobenzene in anhydrous THF was slowly added to a suspension of magnesium turnings in THF, contain-

Table 2 Thermal properties of clathrate complexes formed by host **4**.

Guest	T_o / °C	T_b / °C	(T_{on}–T_b) / °C	Host (**4**):m.p. / °C
DMSO	177	189	–12	Dissolves
DMF	119	153	–34	192

ing a crystal of iodine, and the mixture warmed to initiate the reaction. The remainder of aryl halide was then added at a rate that maintained a gentle reflux of the mixture. After complete addition of the bromobenzene, the mixture was stirred for a further 20 min. The ketone in THF, was then added slowly and the mixture heated under reflux for another 30 min, whereupon it was treated with 10% aqueous ammonium chloride (200 mL) and extracted with ether (3 × 100 mL). The organic phase was subsequently dried (Na_2SO_4) and the solvent distilled off under reduced pressure to give a residue which was purified by crystallization.

4.1.2. 5-Phenyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol **1**

Bromobenzene (15.08 g, 96.04 mmol), magnesium (2.40 g, 98.7 mmol) and 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-one (10.00 g, 48.0 mmol) in THF (100 mL), processed as outlined in the general procedure above, gave a residue which crystallized from chloroform – petroleum ether as white crystals of alcohol **1**, 10.75 g (78%); mp 149–150°C (lit.,[3] mp 153°C); ν_{max} ($CHCl_3$) / cm^{-1} 3603 (s), 3393 (br) and 1599; δ_H ($CDCl_3$) 2.42 (1H, s, O*H*, D_2O-exchangeable), 2.60–3.05 (4H, m, CH_2), 6.80–7.60 (11H, m, Ar*H*) and 8.11 (2H, d, J = 8.1, Ar*H*); δ_C ($CDCl_3$) 34.50 (*C*H_2), 81.44 (*C*OH), 127.63, 127.93 128.67, 129.63, 129.75, 130.69, 132.58, 139.82 (ArH and alkene carbon atoms), 145.59 and 150.58 (quaternary aryl carbons).

4.1.3. 5-Phenyldibenzo[a,d]cyclohepten-5-ol **2**

Bromobenzene (4.57 g, 29.1 mmol), magnesium (0.80 g 33 mmol) and 5*H*-dibenzo[*a,d*]cyclohepten-5-one (5.00 g, 24.2 mmol), treated according to the above method, yielded a residue which crystallized from dichloromethane as the alcohol **2**, 6.70 g (97%); mp 150–151°C (lit.,[3] mp 150–151°C); ν_{max} ($CHCl_3$) / cm^{-1} 3610 (s), 3500 (br) and 1597; δ_H ($CDCl_3$) 2.50 (1H, O*H*, D_2O exchangeable), 6.68–6.77 (4H, m, Ar*H*), 7.04–7.24 (3H, m, Ar*H*), 7.35–7.45 (4H, m, Ar*H*), 7.50–7.60 (2H, m, Ar*H*) and 8.26 (2H, d, J = 8.2, Ar*H*); δ_C ($CDCl_3$) 80.76 (*C*OH), 126.66, 128.71, 129.68, 130.13, 130.74, 133.33 (ArH and alkene carbon atoms), 135.31, 144.46 and 147.94 (quaternary aryl carbons).

4.2. Synthesis of 2-(Phenoxymethyl)- and 2-(Thiophenylmethyl)benzoic Acids

4.2.1. General Method

Phenol or thiophenol (300–400 mmol) was added to a stirred suspension of sodium hydride (500–600 mmol) in anhydrous DMF (500 mL). Upon cessation of dihydrogen evolution, phthalide (*ca.* 370 mmol), dissolved in the minimum amount of benzene (CAUTION) and the mixture heated under reflux for 24 h. The cooled solution was poured into ice water (1500 mL) and acidified with conc. HCl. The formed precipitate was filtered, washed with water and subsequently dissolved in dichloromethane (1500 mL). The organic layer was washed successively with 20% aq. Na_2CO_3 (3 × 500 mL) and water (3 × 500 mL), and dried (Na_2SO_4). The solvent was distilled off to give a residue which was recrystallized from an appropriate solvent.

4.2.2. 2-(Phenoxymethyl)benzoic Acid

Phenol (38.1 g, 404.8 mmol), NaH (14.6 g, 606 mmol) in anhydrous DMF (500 mL) and phthalide (50.0 g, 372.7 mmol) yielded a solid which crystallized from $CHCl_3$ – pet. ether as *2-(phenoxymethyl)benzoic acid*, 60.0 g (70.8%), mp 125–126°C (lit.,[14] mp 126°C) ; ν_{max} ($CHCl_3$) / cm^{-1} 2800–3200 (br), 1694 (s), 1599, 1495 and 1247 ; δ_H ($CDCl_3$) 5.58 (2H, s, CH_2) and 6.68–8.08 (10H, m, Ar-*H* and CO_2H), identical to an authentic sample.

4.2.3. 2-(Thiophenylmethyl)benzoic Acid

Thiophenol (40 g, 360 mmol), sodium hydride (13 g, 540 mmol) in DMF (500 mL) and phthalide (46.2 g, 340 mmol) gave a residue which was recrystallized from benzene (CAUTION) to give *2-(thiophenylmethyl)benzoic acid*, 60.7 g (69%), mp 109–111°C (lit.,[8] mp 106–109°C); ν_{max} ($CHCl_3$) / cm^{-1} 2536–3520 (br.) and 1693; δ_H (60 MHz) ($CDCl_3$) 4.55 (2H, s, CH_2), 7.10-7.60 (8H, m, 8.0–8.25 (1H, m, Ar*H*) and 11.25 (1H, s, COO*H*, D_2O exchangeable); δ_H (200 MHz) ($CDCl_3$) 4.6 (2H, d, CH_2), 7.1–7.5 (8H, m, Ar*H*) and 8.1 (1H, d, Ar*H*), the acid hydrogen atom could not be observed.

4.3. Synthesis of Ketones

4.3.1. 6,11-Dihydrodibenzo[b,e]oxepin-11-one

2-(Phenoxymethyl)benzoic acid (13.5 g, 59 mmol) and trifluoroacetic anhydride (TFAA) (12.5 g, 59.9 mmol) in CH_2Cl_2 (150 mL), were treated with boron trifluoride etherate (1.5 g, 10.5 mmol), the mixture stirred at ambient temperature for 1 h, cooled, poured into water (200 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers was washed successively with 20% NaOH (2 × 200 mL) and water (2 × 200 mL), and dried (Na_2SO_4). The solvent was distilled off under reduced pressure and the residue crystallized from $CHCl_3$ – pet. ether affording *6,11-dihydrodibenzo[b,e]oxepin-11-one*, 10.0 g (80.7%), mp 68–69°C (lit.,[9] mp 66–68°C); ν_{max} ($CHCl_3$) / cm^{-1} 1646; δ_H ($CDCl_3$) 5.23 (2H, s, CH_2), 7.05–7.70 (6H, m, Ar-*H*), 7.96 (1H, dd, J_1 = 7.5 Hz and J_2 = 1.5 Hz, Ar*H*) and 8.3 (1H, dd, J_1 = 8.1 and J_2 = 1.9 Hz, Ar*H*).

4.3.2. 6,11-Dihydrodibenzo[b,e]thiepin-11-one

2-(Thiophenylmethyl)benzoic acid (40 g; 162 mmol) was stirred with polyphosphoric acid (PPA) (500 mL) at 95°C for 6 h. The cooled mixture was poured into water (1500 mL), the formed precipitate filtered, dissolved in CH_2Cl_2 (500 mL) and the organic layer washed successively with 30% Na_2CO_3 (3 × 500 mL) and water (3 × 500 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue crystallized from CH_2Cl_2 – pet. ether affording *6,11-dihydrodibenzo[b,e]thiepin-11-one*, 55.7 g (76%), mp 85–86°C (lit.,[8] mp 86–88°C); ν_{max} ($CHCl_3$) / cm^{-1} 1643.2 (s, C=O), 1590.2 (s), 1424.4, 1299.9, 1151.7, 1115.1, 1068.1 and 928.1; δ_H ($CDCl_3$) (200 MHz) 4.05 (2H, s, CH_2-S,), 7.2–7.5 (7H, m, Ar*H*), 7.6 (1H, d, Ar*H*) and 8.2 (1H, d, Ar*H*).

4.4. Synthesis of Alcohols 3 and 4

4.4.1. 11-Phenyl-6,11-dihydrodibenzo[b,e]oxepin-11-ol **3**

By the general procedure outlined for the synthesis of **1** and **2** above, bromobenzene (5.6 g, 35.7 mmol) in anhydrous THF (100 mL), magnesium (2.5 g, 102.9 mmol) in anhydrous THF (100 mL) and 6,11-dihydrodibenzo[*b,e*]oxepin-11-one (5.0 g, 23.8 mmol) gave a solid, which crystallized from $CHCl_3$ – pet. ether as *11-phenyl-6,11-dihydrodibenzo[b,e]oxepin-11-ol* **3**, 85%, mp 143–143.5°C, (lit.,[10] mp not reported); ν_{max} ($CHCl_3$) / cm^{-1} 3602 and 3387; δ_H ($CDCl_3$) 2.49 (1H, s, O*H*, D_2O exchangeable), 4.67 (1H, d, J_1 = 14.0 Hz, CH_2), 5.13(1H, d, J_2 = 14.2 Hz, CH_2), 6.96 (1H, dd, J_3 = 7.9 Hz and J_4 = 1.1 Hz, Ar-*H*), 7.10–7.50 (10H, m, Ar-*H*, 7.96 (1H, dd, J_3 = 7.9 Hz and J_4 = 1.7 Hz, Ar-*H*) and 8.09 (1H, dd, J_5 = 7.8 Hz and J_6 = 1.2 Hz, Ar-*H*); δ_C ($CDCl_3$) 73.49 (*C*H_2), 80.63 (*C*-OH), 123.04 (Ar), 124.30 (Ar), 127.30 (Ar), 128.57, Ar), 128.57 (Ar), 128.88, 129.90, 129.90, 130.03, 130.03, 130.057, 150.57, 131.43, (Ar), 135.66 (quaternary Aryl C), 136.68 (quat. Ar), 146.19 (quat. Ar), 149.83 (quat. Ar) and 156.87 (quat. Ar); *m/z* 288 (M^+, 76 %), 271 (51.5), 211 (100), 183 (50.3), 165 (40.2) and 105 (39.7); HRMS: M^+,

288.1148. Calc. for $C_{20}H_{16}O_2$: M, 288.1150; (Found: C, 83.4; H, 5.7. Calc. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6 %.)

4.4.2. 11-Phenyl-6,11-Dihydrodibenzo[b,e]thiepin-11-ol **4**

Bromobenzene (31.2 g, 198.9 mmol) in THF (100 mL), magnesium (10 g, 420 mmol) and 6,11-dihydrodibenzo[*b,e*]thiepin-11-one (15 g, 66.3 mmol), gave a residue which crystallized from $CHCl_3$ – petroleum ether as *11-Phenyl-6,11-dihydrodibenzo [b,e]thiepin-11-ol* **4** (69%), mp 200–204.5°C (lit.,[10] mp 205–209°C); ν_{max} ($CHCl_3$) / cm^{-1} 3601 (s, OH), 3403 (br, OH) and 1588; δ_H ($CDCl_3$) 2.4 (1H, s, O*H*), 3.23 (1H, d, J = 13.6 Hz, CH_2S), 3.71 (1H, d, J = 13.6 Hz, CH_2S), 7.1–7.45 (11H, m, Ar*H*) and 8.1 (2H, m, Ar*H*); δ_C ($CDCl_3$) 36.1 ($\bar{C}H_2$S), 80.8 (quat. C, *C*-OH), 127.0 (Ar), 127.1 (Ar), 128.5 (Ar), 128.8 (Ar), 128.9 (Ar), 129.8 (Ar), 129.9(Ar), 130.4 (Ar), 130.7 (Ar), 131.0 (Ar), 131.1 (Ar), 131.5 (Ar), 133.6 (quat. Ar), 136.0 (quat. Ar), 140.8 (quat. Ar), 146.7 (quat. Ar), and 147.3 (quat. Ar); *m/z* 304 (M^+, 4%), 286 (M-18, 2%), 254 (M-50, 2%), 227 (M-77, 3%), 209 (M-95, 1%), 195 (M-195, 52%), 165 (M-139, 67%), 152 (M-152, 25%), 105 (58.7%), 91 (M-213, 52%) and 77 ($C_6H_5^+$, 100%); HRMS: Found: M^+, 304.0914. Calc. for $C_{20}H_{16}OS$: M, 304.0918.

4.5. Assessment of Host Potential of Compounds 1–4

The potential host compound was recrystallized from a range of organic solvents by dissolution in an excess of the solvent. The solvent was then allowed to evaporate slowly at ambient temperature. The crystals so obtained were filtered and washed with methanol and dried in the filter funnel at ambient temperature and pressure and subsequently analysed using ^{1}H-NMR spectroscopy to determine the extent of inclusion of the solvent (i.e. if inclusion had in fact occurred and, if so, also the stoichiometry of the complexes).[7] (None of the complexes washed with methanol included this solvent, nor did recrystallization experiments of the host compounds from methanol show any inclusion of this solvent.) The results and stoichiometries of the enclathration complexes are summarized in Tables 1 and 2. The complexes have been further characterized by differential scanning calorimetry (DSC) (Figs 1–4).

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