Synthesis and Solvent Inclusion Complexation Studies of Benzoyl Derivatives of Resorcinol-aldehyde Tetramers by ^{1}H NMR and Thermogravimetric Analysis

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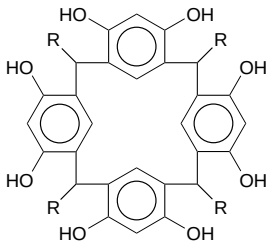
Benzoyl derivatives of resorcinol-aldehyde cyclophanes have been synthesized in order to observe their binding behaviour towards inclusion complex formation with solvent molecules using thermogravimeteric and ^{1}H NMR techniques.

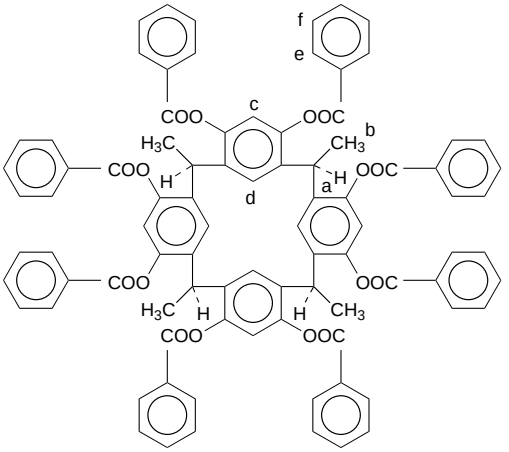
Tetrameric cyclophanes **1a–c**, obtained from the cyclization of resorcinol and acetaldehyde, benzaldehyde and *p*-hydroxybenzaldehyde respectively, have been used to synthesize **2–4** by the Schotten–Baumann reaction. The increased number of phenyl moieties is supposed to increase the size of the hydrophobic cavity of **1a–c**. The inclusion properties of **2** and **3** have been studied by ^{1}H NMR and thermogravimeteric analysis in order to understand the hydrophobic effect of the additional phenyl group. The results confirm that the size of the cavity is smaller in **3** than in **2**. Compound **3** does not form any inclusion complex with molecules containing bigger atoms, *e.g.* $CHCl_3$, and is therefore more selective, whereas **2** is more versatile. ^{1}H NMR spectroscopy showed maximum binding for smaller molecules like CH_3CN and $CHCl_3$ with host **2**. Complexation appears to involve the benzoyl groups, as indicated by the complexation-induced shift in the ^{1}H NMR signals of the host protons (Table 4).

The substituted cyclophanes **2–4** were characterized by elemental analysis and NMR spectroscopy. The resorcinol protons of the tetramer **1a** were overlapped by the benzoyl protons in **2–3** and **4** and integration favoured the formation of octabenzoates. There were no D_2O-exchangeable protons, indicating the absence of any free resorcinol OH. The ^{13}C NMR spectrum of **2** contained a quartet for C-1 at δ 19.8 which was replaced by a singlet in **3** and **4**. The carbonyl C-7 was at δ 164.39 while C-3, C-4 and C-5 gave signals at δ 130.2 (s), 151.67 (s) (due to attached O) and 116.89 (d) respectively. The C-2 doublet was present at δ 44.94 (s) in **2** and 30.3 (s) in **3**. C-3, C-6, C-8, C-9, C-10 and C-11 were very close to each other as overlapping signals at δ 130.2 (s), 129.44 (d), 136.2 (s), 128.2 (d), 128.35 (d) and 131.6.

As investigated by ^{1}H NMR[1,2] and X-ray crystallographic



1a R = Me
b R = Ph
c R = C_6H_4OH-*p*



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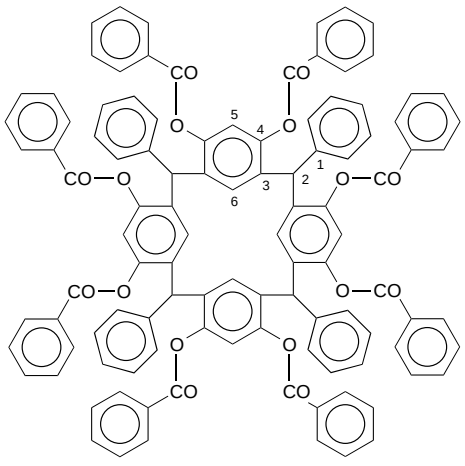

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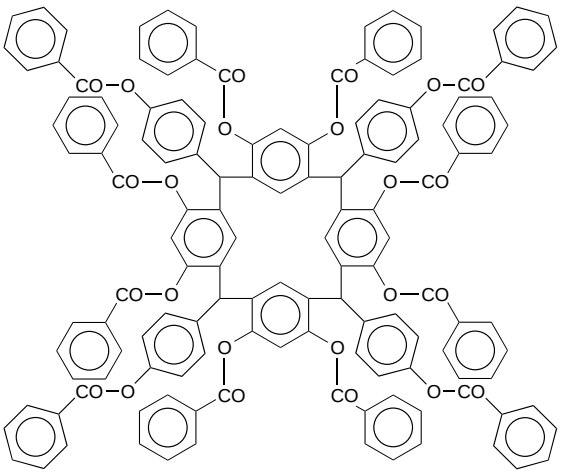

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studies,[3] the host **1a** forms inclusion complexes with small guests like the methyl group of quaternary amines, $CHCl_3$ and CH_3CN, as these fitted best in the cavity. It was thought that the cavity size should increase with the presence of benzoyl phenyls around the central bowl of the cyclophane **1**. As is clear from the present study the effective size of the cavity remains almost the same, although the benzoyl groups help in binding the guest, as supported by ^1H NMR studies.

Experiments were designed to check directly the loss of guest thermogravimetrically. The sample was weighed on a microbalance after recrystallization and drying at 25 °C by vacuum suction from the solvent guest. The same sample was also weighed after drying at 100 °C by vacuum suction. The difference in the weight gave the ratio of host to guest (Tables 1–3). Host **2** was found to accommodate small apolar molecules such as CH_2Cl_2, $CHCl_3$, C_6H_6 and ethyl acetate, forming 1:1 host–guest complexes, while with acetone and methanol **2** formed 1:2 complexes (Table 1). Host **3** forms a high complex ratio with methanol, *i.e.*, 1:4 (Table 2), and it was interesting that **3** did not form any inclusion complex with $CHCl_3$ because of the three large chlorine atoms, confirming the previously established fact[4] that **1b** is smaller than **1a** (from which **3** and **2** were synthesized).

To explore the effect of size in more detail, the more selective **3** was investigated further with regard to its binding with various alcohols (Table 3). It was clear from these studies that linear molecules were preferred over branched ones. *tert*-Butyl alcohol did not form any complex with **3** whereas *n*-butanol formed a 1:1 complex.

^1H NMR Complexation-induced Shifts of Solvent Guest Protons with Host **2**.—It was interesting to study the less selective host **2** for its size discrimination by ^1H NMR investigations. Compound **2**, with a large hydrophobic cavity encircled by twelve phenyl groups, was recrystallized from various solvents. The host–guest inclusion complexation was studied by the shifts in the host as well as the guest signals. The shift in signals indicates clearly the interaction of various guests with different sites of **2**. The H_a protons of host **2** were shifted upfield by δ 0.274–0.165 for various solvents, but the effect on H_b was negligible (except for benzene), signifying that the effect on H_a is due to strain in the cyclophane ring while binding the guest. The protons of the resorcinol units, *i.e.* H_c and H_d, are deeply buried under the benzoyl groups and did not interact with the guest, as indicated by negligible shifts in the signals for these protons (Table 4). The maximum shift of the benzoyl signals was from δ −0.463 to −0.297 for the H_e and δ 0.456 for the H_f protons. The H_e protons showed a downfield shift implying a decrease in electron density at the *ortho* position of the benzoyl groups in the inclusion complexes. That the H_f protons showed the maximum upfield shift of all the host **2** protons indicated quite clearly that the benzoyl groups are enclosing the guest. The trend of the complexation-induced shifts also shows that the basic cavity, lined by four resorcinol units in **1a**, is supplemented for its binding behaviour in **2** by the addition of eight benzoyl units which act as a source of lipophilic interactions.

The signal shifts for the guest also indicate clearly the role of the benzoyl groups in **2** in binding the guest. The CH_3OH groups show only a negligible shift (Table 4), indicating that in solution the cavity may be too hydrophobic after addition of the eight phenyls to attract hydrophilic molecules such as methanol. Shifts are maximal for apolar guests such as $CHCl_3$, CH_3CN and C_6H_6 (δ 0.19, 0.29 and 0.17 respectively) (Table 4).

Table 1 Inclusion complexes of **2** with various solvent guests

Solvent guest	Loss calculated for 1:1 complex (mg)	Loss observed (mg)	Host:guest ratio in complex
CH_2Cl_2	0.28	0.30	1:1
$CHCl_2$	0.18	0.18	1:1
C_6H_6	0.22	0.23	1:1
AcoEt	0.16	0.14	1:1
Me_2CO	0.29	0.58	1:2
MeOH	0.05	0.09	1:2
1,4-Dioxane	0.30	0.97	1:2
THF	0.32	0.53	2:3

Table 2 Inclusion complexes of **3** with various solvent guests

Solvent guest	Loss calculated for 1:1 complex (mg)	Loss observed (mg)	Host:guest ratio in complex
CH_2Cl_2	0.08	0.04	2:1
$CHCl_3$	0.20	0.06	1:0
C_6H_6	0.05	0.14	1:3
AcOEt	0.25	0.23	1:1
Me_2CO	0.14	0.08	2:1
MeOH	0.04	0.17	1:4
THF	0.20	0.19	1:1

Table 3 Inclusion complexes of **3** with various alcohols

Alcohol	Loss calculated for 1:1 complex (mg)	Loss observed (mg)	Host:guest ratio in complex
MeOH	0.04	0.17	1:4
Pr^iOH	0.17	0.24	2:3
Bu^iOH	0.15	0.17	1:0
Bu^nOH	0.15	0	1:1
EtOH	0.1	0.09	1:1

Table 4 ^1H NMR complexation-induced shifts of host **2** and guest solvents[a]

$\Delta\delta$ (shift for host protons)	MeOH	$CHCl_3$	MeCN	C_6H_6	EtOH	Et_2O
H_a	0.27	0.20	0.26	0.24	0.16	0.20
H_b	0.02	0.03	0.03	0.17	−0.02	0.03
H_c	0.09	0.09	0.06	0.06	0.03	0.03
H_d	0.06	0.05	0.00	0.06	0.03	0.05
H_e	−0.29	−0.36	−0.29	−0.29	−0.39	−0.46
H_f	0.54	0.48	0.51	0.61	0.45	0.048
Shift of guest signal	0.02	0.19	0.29	0.17	0.09[b]	0.07[b]

[a]Negative indicates a downfield shift. [b]Shift for CH_3.

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Techniques used: ^1H NMR, ^{13}C NMR, microanalysis, thermogravimetry

References: 15

Tables: 4

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