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NON-COVALENT INTERACTIONS IN HOST–GUEST COMPLEXES WITH FLUORINATED PHENYL COMPOUNDS†

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Complexation constants with the macrocyclic azoniacyclophane CP44 and phenyl guest compounds with at least four fluorine atoms or alternatively protons at the ring were obtained by NMR shift titrations in water. The fluorinated compounds show free energies of complexation which are smaller by $\Delta\Delta G = 3{\cdot}4–7{\cdot}7$ kJ mol^{-1} in comparison with the protonated compounds. The NMR shifts induced upon 100% complexation (CIS values) were obtained simultaneously from non-linear least-squares fitting and indicate intra-cavity inclusion in all cases. The CIS values agree roughly with screening constants calculated from aromatic ring current and linear electric field effects, the latter resulting from the permanent charges at the host compound. Molecular mechanics calculations (CHARMm) indicate that intracavity inclusion is possible with all compounds with negligible strain induced (< 1 kJ mol^{-1}) in the macrocycle upon complexation. In contrast, α-cyclodextrin can accommodate fluorinated phenyl compounds only at the rim of the cavity without larger strain. Preliminary data with α-cyclodextrin, obtained by competitive UV–visible titration with methyl orange, indicate again a smaller association free energy ($\Delta\Delta G = 1{\cdot}{\cdot}7$ kJ mol^{-1}) for pentafluorphenol compared with normal phenol as guest. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Hydrophobic or lipophilic interactions in and with fluorinated compounds show puzzling behaviour. Thus, perfluorinated surfactants show lower critical micelle concentrations than the protonated analogues, but their sub-micellar aggregation numbers seem to be similar.[2] Protonated and fluorinated surfactants do not form mixed micelles, indicating less attractive C–H . . . F—C interactions.[3] With cyclodextrins (CDs) as host compounds, surface tension measurements show stronger association only with β-CD and only weak interactions with α-CD,[4,5] although the cavity of the latter is, in contrast to what was originally believed,[4,5a] not too small for intracavity inclusion (see computer-aided simulations below, Figure 3). Associations of fluorinated surfactants with β-CD have also been studied kinetically,[6] but the corresponding association constants are still difficult to assess.[7] Depending on the method used they are reported to be higher[5] than those of protonated analogues, or similar.[8] Information on the association modes or complex geometries is, to the best of our knowledge, virtually absent, as also is experimental insight into the relevant binding mechanism. Host–guest complexes with arene–fluorine interactions have not been studied hiterto, and were the main target of the present investigation. The importance for several applications[9] of non-covalent interactions with fluoro compounds has been stressed recently.

RESULTS AND DISCUSSION

As host compound we used the azoniacyclophane CP44 (Scheme 1), which was synthesized by a modification of the original protocol of Odashima *et al.*[10] The advantages of such water-soluble cyclophane hosts are that their complexes with a large variety of organic substrates in aqeous solution are experimentally well characterized by strong NMR shift changes,[11] and that the relevant binding mechanisms have been studied in detail.[1,12]

Molecular mechanics calculations with the aid of the CHARMm force field by Brünger and Karplus[13] indicated that the CP44 cavity is just wide enough to accommodate

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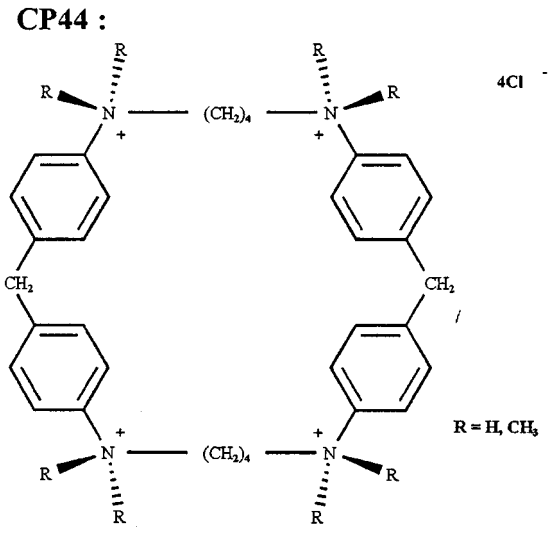
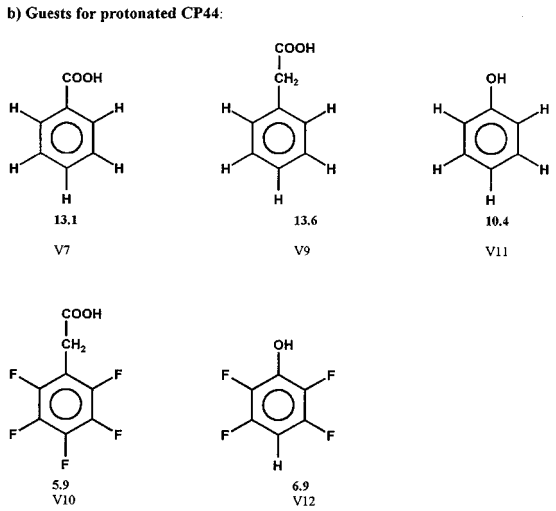


Scheme 1



Scheme 1 (cont.)

either a protonated or a fluorinated phenyl ring. The CHARMm/QUANTA-calculated molecular volumes of the fluorinated rings are about 10% larger than those of the protonated analogues, but for a tight fit do not require widening of the CP44 cavity (see appendix). Calculation of the total steric energy of the host CP44 alone before and after complexation, with both the free and the complex structure energy-minimized, showed the upper limit of the possible strain induced in the host to be on average below 1 kJ mol^{-1}.

The host compounds (Scheme 1) were chosen so that at least one proton was available for NMR shift measurements as a function of guest concentration and *vice versa*, which then were evaluated as described previously[14] to obtain from non-linear curve fitting reliable association constants *K* and also the NMR shifts of the totally complexed material (CIS values, Table 1). Only for the very lipophilic toluene and pentafluorotoluene was it necessary to add methanol to water (all solvents deuterated). The measurements with the latter and with the anionic host compounds **V1**–**V4** were performed with the permethylated host CP44 at pH 7.0 (pD 7.4), and those with the other electroneutral derivatives **V7**–**V12** with the protonated CP44 at pH 2·0 (pD 2·4) in order to secure protonation of the acidic groups. Measurements with related CP*nn* hosts have been shown previously[15] to lead to deviations of free complexation energies with protonated or permethylated cyclophanes of usually below 2 kJ mol^{-1}.

The experimentally observed complexation NMR shielding effects on the guest compounds (Table 1) are typical of many intracavity inclusion structures in such cyclophanes. After a recent reparametrization of aromatic ring current effects,[16] we were able to calculate the expected CIS values based on force field (CHARMm) optimized complex geometries of such complexes (Figures 1 and 2). As pointed out earlier, one needs to take into account the sizeable electric field effects exerted by the N^+ charges of the cyclophanes in order to obtain realistic NMR shielding variations.[11c] Although the deviations in the calculated complexes are sizeable (Table 2), the generally found approximate agreement is believed to be the first proof of intracavity inclusion of the kind illustrated in Figures 1 and 2. This is of particular significance as the alternative method of *inter*molecular NOE observations completely failed here. Even application of the ROESY spin-lock technique,[17] which can resolve the problem of unfavourable correlation times of complexes with molecular weights around 1000, did not lead to any usuable cross peaks, owing to too many rapidly exchanging symmetric protons with on average only

Table 1. Complexation constants K (mol l^{-1}) and CIS values (ppm)

Guest	*o*-H	*m*-H	*p*-H	CH_2	CH_3	K [mol/l]	K(H/F)[a]
V1	−0·60	−0·83	−0·51	–	–	768	
V2	–	–	−0·12	–	–	119	6·5
V3	−1·11	−1·19	−0·74	−0·46	–	886	
V4	–	–	–	−0·07	–	75	11·8
V5	−1·63	−1·42	−0·95	–	−0·77	59	
V6	–	–	–	–	−0·28	3·6	16
V7	−1·85	−1·45	−0·85	–	–	201	
V9	−1·90	−1·65	−1·00	−0·90	–	238	
V10	–	–	–	−0·52	–	11	22
V11	−1·66	−1·68	−0·95	–	–	66	
V12	–	–	−0·49	–	–	16	4

[a] K(H/F) = ratio of complexation constant of protonated for that of fluorinated guest compound

weak intermolecular contacts.

As is obvious from the association constants (Table 1) and the corresponding free enthalpies $\Delta\Delta G$ (Scheme 1), all the fluoro compounds show distinctly smaller interactions with the cyclophane. The $\Delta\Delta G$ for toluene, measured in the same solvent and with the same permethylated CP44 host, reaches nearly a difference of 10 kJ mol^{-1}. The smaller CIS value observed for the methyl signal of pentafluorotoluene **V6** (Table 1) points to a less deep immersion of the fluorinated compound in the cavity. Similarly, smaller CIS values with fluorinated derivatives are seen, e.g., with the *para*-protons of **V1**/**V2** and **V11**/**V121** as well as with the CH_2 signals of **V3**/**V4** and pf **V9**/**V10**. Obviously, in spite of the sufficiently wide cavity, the fluorinated compounds are less attracted into the π-electron-rich CP44 cavity. Inspection of the force field-generated geometries with the fluorinated compounds immersed in the cavity (Figures 1 and 2) illustrate that here all fluorine atoms would be in close contact at the centres of the π-moieties of the CP44 phenyl rings. The negative charges in all these locations must lead to electrostatic repulsions, explaining the reason for the lowered affinity (cf. the $\Delta\Delta G$ values) and the less pronounced intra-cavity inclusion (cf. the CIS values) with the fluorinated structures.

Another contribution to the diminished binding of the fluorinated compounds is expected from the induced dipole effect of the positively charged host ammonium centres on the aromatic moiety of the guest compounds, which has been shown earlier to provide most of the driving force in such complexations[12a, c, d, 18] Fluorine atoms in the guest molecules strongly deplete the electron density in the phenyl rings, and therefore also lower the stabilization by a cation π–effect between the host and guest. It should be noted that both the electrostatic effect from the permanent partial charges and the induced dipoles are not described in the force field used, which therefore cannot be expected to lead to completely realistic complex geometries. This is believed to be the major reason for the deviations between calculated and experimental NMR shieldings, as calculations with non-fluorinated compounds generally lead to better agreement.[11c]

With cyclodextrins only a preliminary study was carried out with α-cycloamylose (six glucose units) and phenol and pentafluorophenol as guests, using methyl orange (MO) in competitive titrations by UV–visible spectrophotometry. Measurements at eight different wavelengths between 480 and 550 nm yielded association constants for MO with only small deviations between 700 and 736 M^{-1}, in agreement with literature data.[19] Competitive titrations gave $K = 28\ M^{-1}$ or $\Delta\Delta G = 8{\cdot}3$ kJ mol^{-1} for phenol, and $K = 14\ M^{-1}$ or $\Delta\Delta G = 6{\cdot}55$ kJ mol^{-1} for pentafluorophenol. The lowered affinity of the fluorinated guest here is understandable in view of the narrow α-CD cavity, as visible in the CHARMm calculated geometry, which shows only partial immersion of the pentafluorphenol at the rim of the host (Figure 3). It should be noted, however, that the α-CD according to molecular mechanics calculations is just wide enough to accommodate an unfolded (all-*trans*) perfluoroalkane chain. The heptaamylose β-CD would be wide enough to accommodate also a perfluorophenyl host. Unfortunately, the formation of precipitates inhibited the determination of association constants with, e.g., pentafluorophenol and β-CD (at concentrations around 0.01 M for the phenol and 0·0035 M for β-CD). However, before precipitation the absorption of the added dye MO decreased markedly, indicating strong complexation.

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EXPERIMENTAL AND COMPUTATIONAL DETAILS

1,6,20,25-Tetra[6.1.6.1]paracyclophane (CP44)[10]. The cylophane in the amine form was obtained via reaction of *N*,*N*′-bis(*p*-tolylsuphonyl)-4,4′-diaminophenylmethane and 1,4-dibromobutane similarly to the literature procedure[10] in

35% yield after chromatography in the cyclization step, and 79% yield on detosylation with phenol–HBr.

Octamethyl-CP44 (permethylation). A mixture of 1.50 g (2.97 mmol) of CP44 (described above), 2·3 (23 mmol) $CaCO_3$ and 10 g (70 mmol) of methylodide was stirred under reflux in 30 ml methanol for 17 h. After removal of methanol and methyl iodide on a round evaporator, 8 ml of water were added and the solution was acidified with HCl. The resulting solid was filtered off, air-dried and stirred under reflux for 2 h with 80 ml of concentrated HCl and methanol. After removal of the solvent and HCl, the residue was dissolved in 40 ml of water and extracted with chloroform until the chloroform became colourless. The aqueous solution was concentrated to about 5 ml; after addition of excess ethanol and acetone, the precipitate formed was filtered off. The last procedure was repeated, and the last precipitate was dried in vacuum at 50 °C, yielding 2·11 g (93%) of NMR-pure material. ^{1}H NMR (D_2O), δ (ppm): 7·60 (d, *o*-ArH, 8 H), 7·36 (d, *m*-ArH, 8 H), 4·18 (s, $ArCH_2$, 4 H), 3·80 (broad, NCH_2, 8 H), 3·53 (s, NMe, 24 H), 1·34 (broad, NCH_2CH_2, 8 H).

NMR measurements. NMR measurements were carried out on a Bruker AM 400 system. To obtain association constants, 7–9 samples were measured at concentrations giving a complexation range between about 20 and 80%, as described previously.[14]

UV–visible titrations. The titrations were carried with methyl orange as described previously,[19] using a Kontron Uvikon instrument.

Molecular mechanics calculations. The calculations were performed on a Silicon Graphics workstation under QUANTA (Polygen/MSI) with the force field CHARMm[13] (version 22), with Gasteiger derived charges using $\varepsilon = 3{\cdot}0$ as

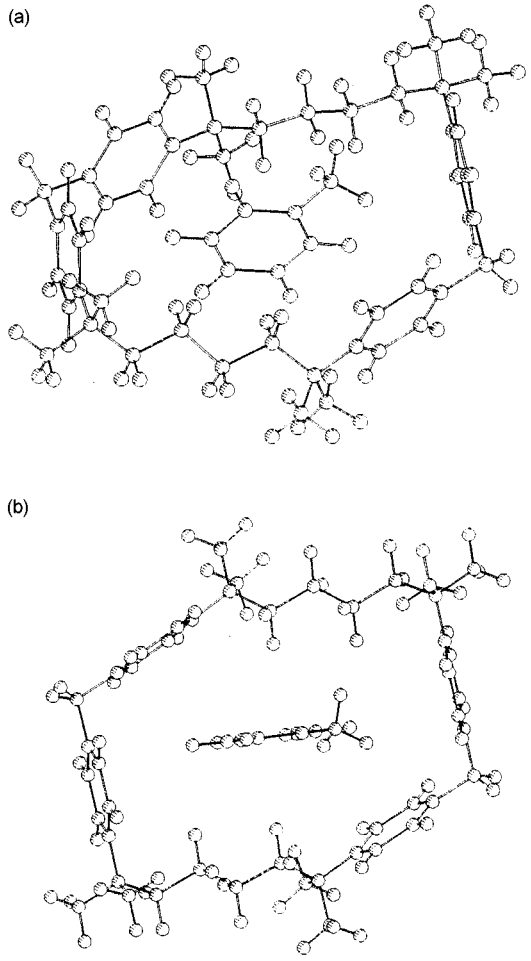

Figure 1. CHARMm simulations of host–guest structures: (a) CP44 (permethyl) + toluene (side view); (b) CP44 (permethyl) + toluene (top view)

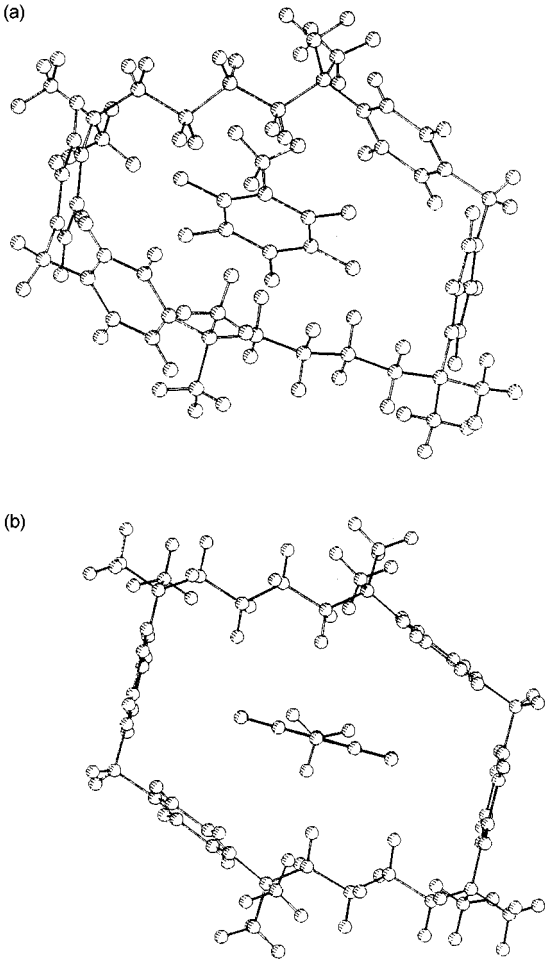

Figure 2. (a) CP44 (permethyl) + pentafluorotoluene (side view); (b) CP44 (permethyl) + pentafluorotoluene (top view)

Table 2. Calculated CIS values (ppm) for complexes with α-CD[a]

Guest	Proton No.	Δ_χ	LEF	$\Sigma(\Delta_\chi + \text{LEF})$	Exp. CIS	Difference (Σ − exp.)
V2	1	0·05	0·17	0·11	0·12	0·23
V9	1	1·98	0·06	1·92	1·90	0·02
	2	1·55	0·07	1·49	1·65	−0·16
	3	0·63	0·11	0·52	1·00	−0·48
	4	0·49	0·13	0·36	0·90	−0·54
V5	1	1·30	0·03	1·26	0·77	0·49
	2	1·68	0·08	1·59	1·63	−0·04
	3	1·74	0·13	1·61	1·42	0·19
	4	0·85	0·19	0·67	0·95	−0·28
V6	1	0·35	0·09	0·27	0·28	0·01
V12	1	0·28	0·12	0·17	0·49	−0·32

[a] Positive aromatic ring anistropic effects (Δ_χ) denote upfield shifts: positive linear electric field effects (LEF) denote downfield shifts; positive differences (between calculated and experimental shifts) denote upfield deviation.

the dielectric constant. Steepest decent minimization was used with stop criteria of 5000 steps of 0.001 kcal mol^{-1}, after which adopted basis set Newton Raphson minimizations were carried out under same conditions.

Strain energies of hosts calculated from energy-minimized structures of the free host and the host in the host–guest complex[11c] were as follows: of CP44 (permethylated) upon complexation with toluene, 0·33 kcal/mol^{-1}, with pentafluorotoluene, 0·19 kcal mol^{-1}; and of α-cyclodextrin with pentafluorophenol, 0·25 kcal-mol^{-1} (for structures see Figures 1–3).

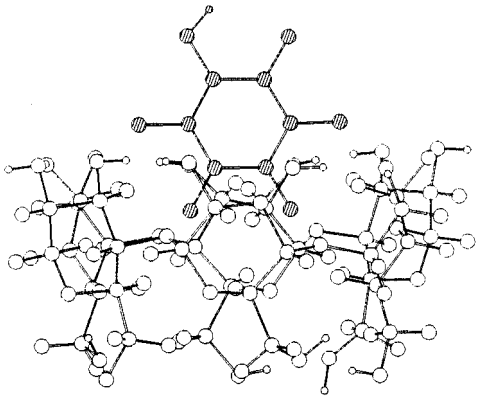

Figure 3. α-Cyclodextrin + pentafluorophenol (with electrostatics). Without electrostatics the same result is obtained: guest leaves the cavity upon energy minimization

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APPENDIX

Molar volumes of protonated and fluoroinated guest compounds

Compound RX	Volume (Å^3)	Rates of volumes, RF/RH
V1	401	1·07
V2	428	
V3	457	1·08
V4	495	
V5	382	1·12
V6	426	
V7	413	1·05
V8	433	
V9	462	1·08
V10	499	
V11	354	1·04
V12	368	
F/H alone		1·16