# Conformational Switching of Resorcin[4]arene Cavitands by Protonation

Preliminary Communication

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The synthesis of the quinoxaline-bridged resorcin[4]arene cavitand **1** was accomplished from 2-[3,5-di(*tert*-butyl)phenyl]acetaldehyde *via* formation of the intermediate octol **2**. Such cavitands are known to occur in an open 'kite' conformation at low temperature (< 213 K) but to adopt a 'vase' conformation at elevated temperatures (> 318 K). We discovered that protonation of cavitand **1** at room temperature by common acids, such as $CF_3COOH$, also causes reversible switching from 'vase' to 'kite', and that this conformational change can be conveniently monitored by both $^1$H-NMR and UV/VIS spectroscopy.

Recent advances in chemical switching have focused on the development of systems whereby large changes in molecular or supramolecular geometry are induced by redox processes, irradiation, or guest complexation. Examples are the shuttling rotaxanes and catenanes [1–4] or calixarene ionophores, which undergo a large conformational shift upon cation complexation [5]. Such molecular devices have significant potential in future applications especially in the fields of sensors, molecular motors, and information storage [6]. Among the most fascinating systems featuring two dramatically different, reversibly switchable geometries are a family of cavitands, consisting of a resorcin[4]arene bowl bridged by four quinoxaline moieties, which had been introduced by *Cram* and co-workers in 1982 [7]. These molecules were found by variable temperature (VT) $^1$H-NMR spectroscopy to exist in an open 'kite' conformation at low temperatures (< 213 K) but to adopt a 'vase' conformation, capable of guest inclusion [8], at elevated temperatures (> 318 K) (*Fig. 1*)[1]). The profound change in molecular geometry in solution was attributed to solvation effects: at low temperature, solvation of the larger, solvent-exposed surface favors the 'kite' conformation, whereas, at higher temperature, the entropic term $T\Delta S_{solv}$ for solvation of the larger kite surface becomes unfavorable. Several interesting applications of dynamic resorcin[4]arene-based cavitands in molecular recognition have been described [8][9] (for a review of resorcinarenes, see [10]); however, full exploitation of these compounds as conformational switches has so far been limited by the twin constraints of the need for solvent and temperature control.

Recently, we became interested in developing derivatives of the dynamic cavitands with suitable legs for adsorption onto metal surfaces (for the immobilization of

[1]) We thank Dr. *Yoko Yamakoshi* for generating the computer models shown in *Fig. 1*.

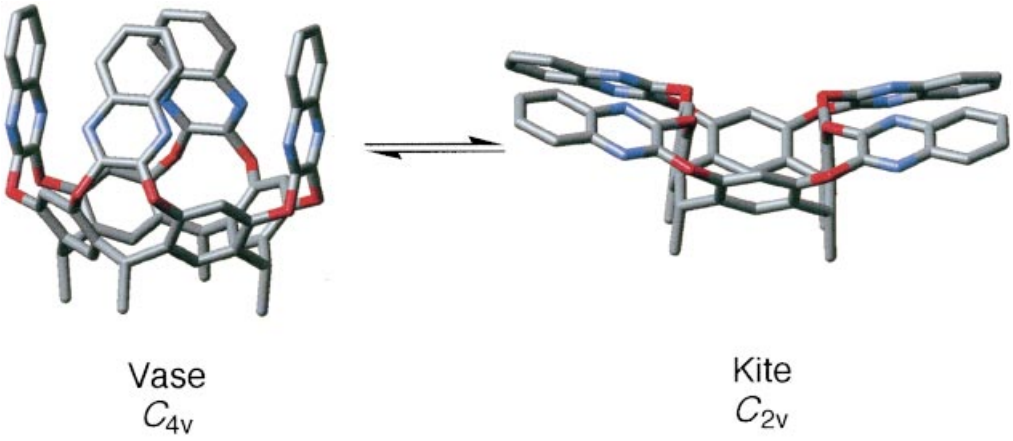



Fig. 1. *Molecular models* [11] *of the 'vase' and 'kite' conformers of quinoxaline-bridged resorcin[4]arene cavitands derived from acetaldehyde.* H-Atoms are omitted for clarity.

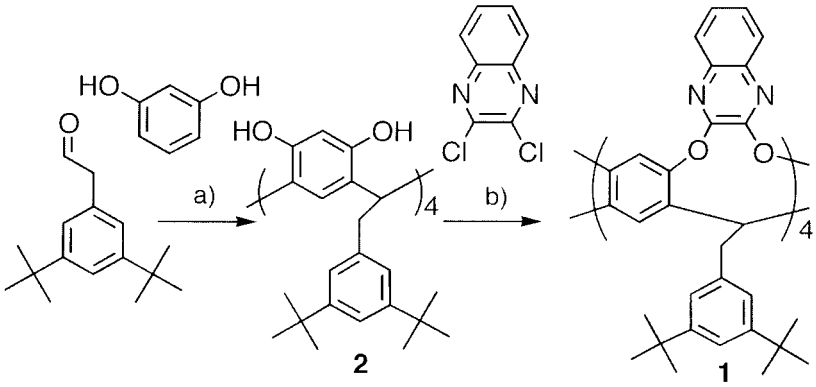
resorcinarene cavitands on surfaces, see [12]) to allow observation and manipulation by scanning tunneling microscopy (STM) and for use as potential molecular grippers [13]. Such investigations, in the absence of solvent, potentially require an alternative stimulus to induce switching between 'vase' and 'kite' forms. During that work, we discovered that protonation with common acids promotes, at room temperature, the reversible conformational change from 'vase' to 'kite', and that this change can be conveniently followed not only by $^1$H-NMR spectroscopy but also by optical methods.

We prepared cavitand **1** with four 3,5-di(*tert*-butyl)phenyl residues attached to the lower rim, since these legs had previously been shown to provide good adsorption of a porphyrin molecule on Cu surfaces for STM imaging [13b]. The synthesis started from octol **2**, which was obtained in 35% yield by acid-catalyzed condensation [12a][14] of 2-[3,5-di(*tert*-butyl)phenyl]acetaldehyde [15] with resorcinol (*Scheme*). Bridging octol **2** by nucleophilic substitution of 2,3-dichloroquinoxaline gave **1** in 65% yield.

Crystallization of **1** by slow evaporation of a solution in MeCN/$CHCl_3$ gave single crystals suitable for X-ray diffraction (*Fig. 2*). The crystal structure shows the cavitand in the 'vase' conformation, with the quinoxaline moieties shaping a large cavity, and with the distance between two parallel chromophores at the top of the cavity amounting to 8.97 Å. The cavity contains highly disordered solvent that could not be identified; some disorder that could be resolved is also apparent within the di(*tert*-butyl)phenyl legs.

VT $^1$H-NMR Spectroscopy showed that, in $CD_2Cl_2$, cavitand **1** freely interconverts between 'vase' (only conformer above 313 K) and 'kite' (only conformer below 213 K) forms. This information was conveniently obtained by monitoring the resonance of the methine H-atom in the skeleton of the octol bowl (*Fig. 3*). As described by *Cram* and co-workers for similar systems [7], the resonance of this proton in **1** is highly conformation-dependent, with a difference in chemical shift of more than 2 ppm

Scheme. *Synthesis of Cavitand* **1**




*a*) EtOH, conc. HCl, 5 d, 60°; 35%. *b*) $Cs_2CO_3$, anh. DMF, 2 d, 60°; 68%.

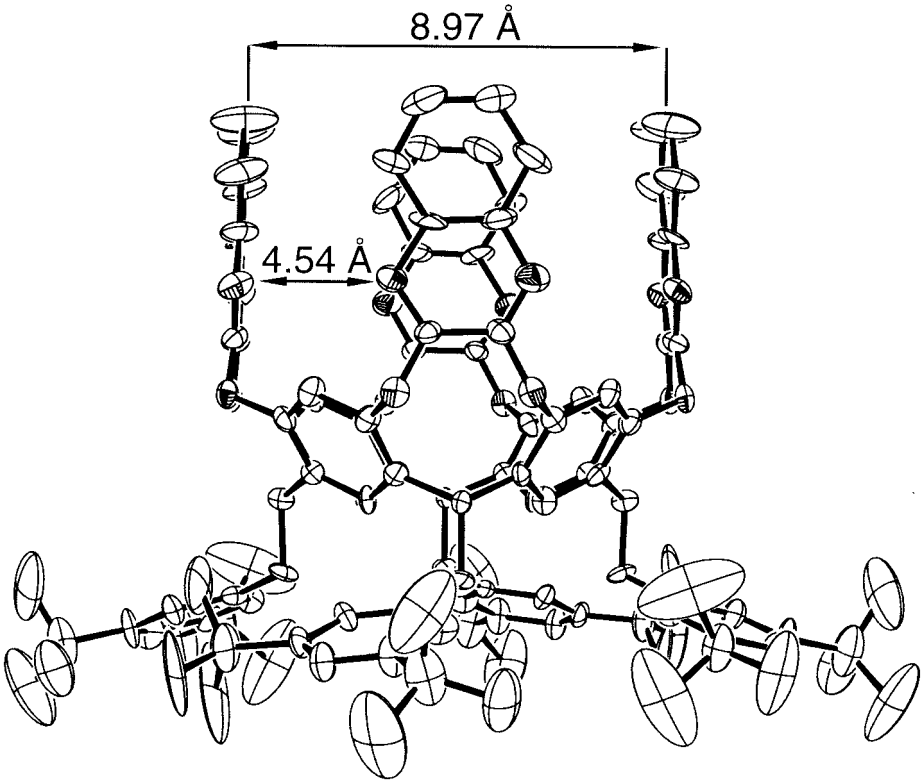



Fig. 2. *ORTEP Representation of* **1** *with vibrational ellipsoids at the 30% probability level highlighting the interatomic distances between adjacent quinoxaline N-atoms.* The cavity diameter at the upper rim is also shown. H-Atoms and unresolved solvent included within the cavity have been omitted for clarity.

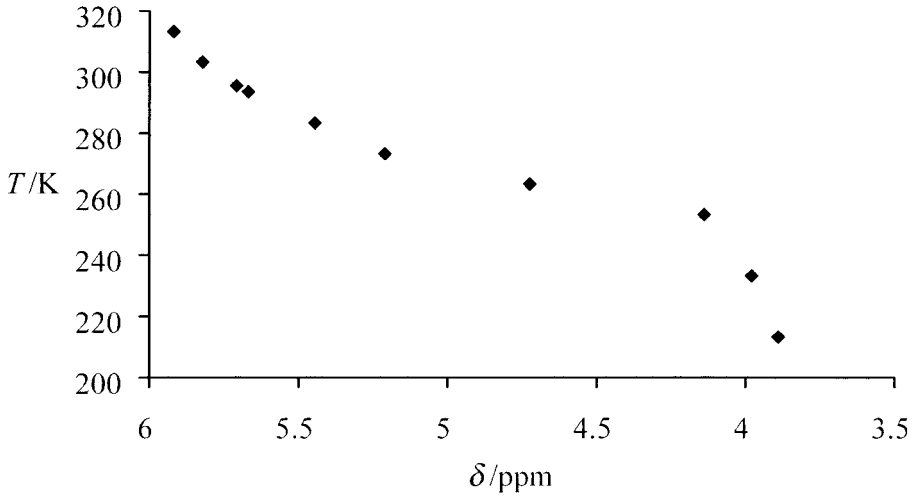



Fig. 3. *Temperature-dependent change in $^1$H-NMR chemical shift of the methine proton resonance of* **1** *in $CD_2Cl_2$*

between 'vase' ($\delta \approx 5.9$ ppm) and 'kite' ($\delta \approx 3.8$ ppm) conformations. From the temperature dependence of the chemical shift, $\Delta S$ and $\Delta H$ for the 'vase' → 'kite' equilibration were calculated as $+11.7\ \text{cal}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ and $+3.1\ \text{kcal}\cdot\text{mol}^{-1}$, respectively[2]), whereas the free enthalpy of activation $\Delta G_c^{\neq}$ at the coalescence temperature $T_c$ of 265 K was estimated as $11.6\ \text{kcal}\cdot\text{mol}^{-1}$ [3]).

The 'vase'-'kite' interconversion was also observed for the first time by variable-temperature UV/VIS spectroscopy (*Fig. 4*). At 293.3 K in $CH_2Cl_2$, **1** displayed maxima at $\lambda_{max} = 316$ and 328 nm, and a shoulder at 344 nm. Upon lowering the temperature stepwise to 203.2 K, an increase of the molar extinction coefficient $\varepsilon$ of the peak at 328 nm from 34700 to 49900 $\text{M}^{-1}\cdot\text{cm}^{-1}$ was measured. Moreover, the shoulder at 344 nm changed into an intense resolved band with a raise in $\varepsilon$ from 18300 to $51500\ \text{M}^{-1}\cdot\text{cm}^{-1}$. Isobestic points at 288 and 308 nm were also observed.

Addition of aliquots of trifluoroacetic acid (TFA) to a solution of **1** ($c = 1\cdot10^{-5}$ M) in $CHCl_3$ at 298 K led to changes in the UV/VIS spectra similar to those observed with decreasing temperature, albeit with increased vibrational broadening (*Fig. 5*)[4]). This is consistent with equilibration to the 'kite' conformer upon addition of the acid, and such

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[2]) The thermodynamic quantities were calculated according to the equation: $\ln(\{\delta\nu/\nu\} - 1) = (-\Delta H + T\Delta S)/RT$, where $\delta\nu$ [Hz] is the chemical-shift difference between the methine resonance in the pure 'vase' and 'kite' forms and $\nu$ [Hz] is the chemical shift difference of this resonance observed at a given temperature and in the pure 'vase' form.

[3]) An estimate of $\Delta G_c^{\neq}$ can be obtained from the equation given by *Sandström* [16]. This treatment assumes that the chemical shifts of the methine resonance in the pure 'vase' and 'kite' forms do not significantly differ from those that time-average to give the observed shift at the coalescence temperature. We thank Prof. Dr. *B. Jaun*, ETHZ, for valuable discussions.

[4]) We thank Prof. *A. Ludi* (University of Bern) for the inspiration behind this investigation.

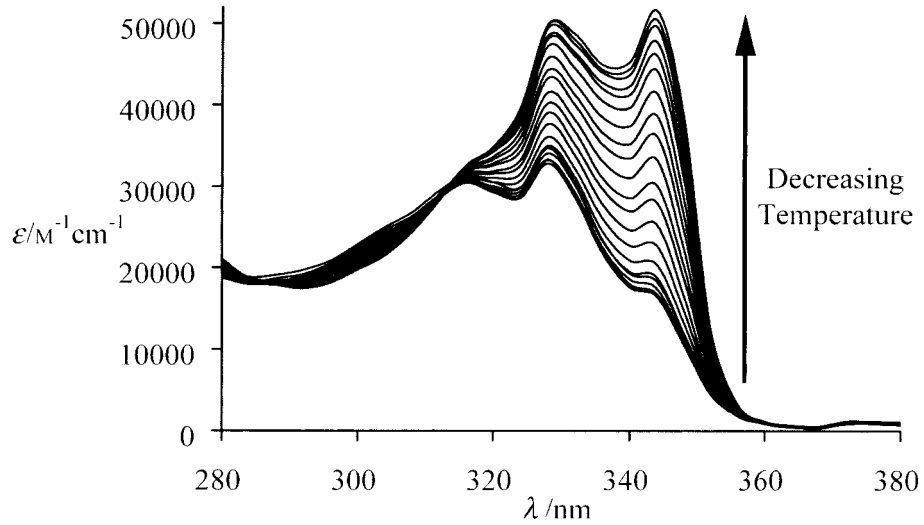


Fig. 4. *Temperature-dependent* (293 – 203 K) *UV/VIS spectra of* **1** *in* $CH_2Cl_2$ ($c = 1 \cdot 10^{-5}$ M)

a change in molecular geometry can be attributed to protonation of the mildly basic quinoxaline N-atoms[5]) and subsequent electrostatic repulsion of the resulting cationic cavitand walls in the 'vase' form (N ··· N distance: 4.54 Å; see *Fig. 2*). Saturation was achieved at a concentration of 0.4M TFA. Addition of trifluoromethanesulfonic acid, dichloroacetic acid, or HCl (2M in $Et_2O$) to **1** also gave rise to similar spectral changes, with longer p$K_a$ values of the added acid leading to lower saturation concentrations. Addition of AcOH or 2,2,2-trifluoroethanol led to no significant change in UV/VIS absorption, demonstrating that the effect is due to protonation rather than to a change in solvent polarity. The spectral (and conformational) changes were observed to be reversible upon addition of $Et_3N$.

The equilibration from 'vase' to 'kite' upon addition of TFA was unambiguously confirmed by $^1$H-NMR spectroscopy (*Fig. 6*). Addition of aliquots of TFA to a $CDCl_3$ solution of **1** at 298 K led to a characteristic broadening and large upfield shift (*ca.* 1.7 ppm) of the *triplet* for the methine H-atom resonance. Saturation was again achieved at *ca.* 0.4M concentrations of TFA, whereby the methine resonance was fully

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5) Addition of TFA to 2,3-dimethoxyquinoxaline in $CHCl_3$ also leads to a significant shift to longer wavelength, increased broadening of the quinoxaline absorption, and development of a new shoulder at 344 nm. The overall maximum extinction coefficient does not increase however (2,3-dimethoxyquinoxaline: $\lambda_{max}$ ($\varepsilon$/M$^{-1}\cdot$cm$^{-1}$) = 299 (6230), 305 (7020), 312 (10600), 318 (7570), 326 (10300) nm; 2,3-dimethoxyquinoxalinium cation: $\lambda_{max}$ ($\varepsilon$/M$^{-1}\cdot$cm$^{-1}$) = 331 (10600), 344 (9310) nm)), showing that the absorption changes observed upon addition of TFA to **1** result from both a combination of the changes expected upon protonation of the quinoxaline moieties and the conformational change to the kite conformer. The p$K_a$ value of the 2,3-dimethoxyquinoxalinium monocation has been reported as $-1.15 \pm 0.06$ [17].

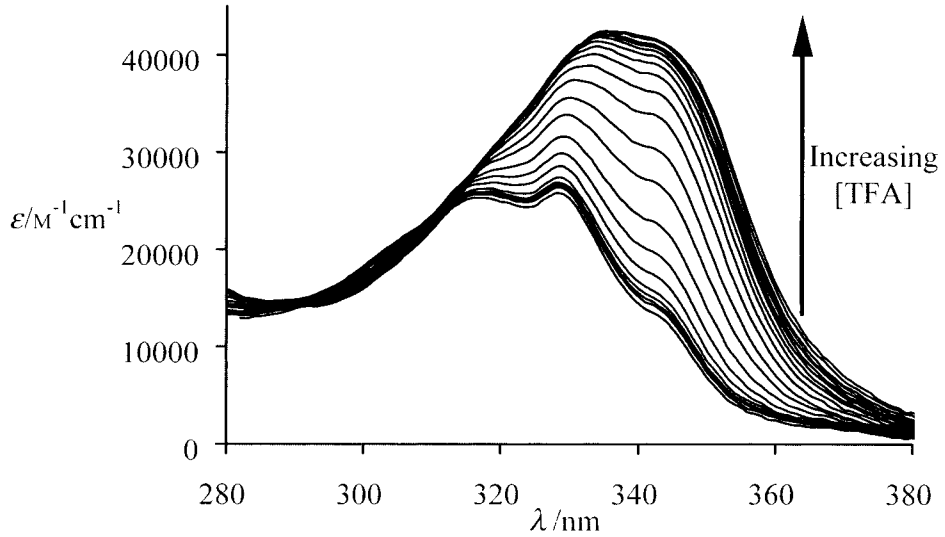


Fig. 5. *Changes of the UV/VIS absorptions of* **1** ($c = 1 \cdot 10^{-5}$ M) *in* $CHCl_3$ *upon addition of TFA* (0–0.65 M). $T =$ 298 K.

resolved into a *triplet*, showing complete conversion to the 'kite' conformer[6]). Reversibility to the 'vase' conformer was achieved by neutralization with $K_2CO_3$.

It is clear that the use of UV/VIS spectroscopy to monitor 'vase'-'kite' equilibrations and the ability to reversibly stimulate the conformational shift by pH change greatly expands the utility of the *Cram* cavitand systems. STM Investigations of **1** at the single molecule level will be reported in due course.

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## Experimental Part

*Low Temperature UV/VIS.* Spectra were acquired in cells held in an optical cryostat (*Oxford Instruments DN-704)* and collected *via* a *Perkin-Elmer LS50B* luminescence spectrometer. Temps. were maintained at 203–298 ± 0.1 K with an *Oxford Instruments ITC-6* temp. controller. Data was corrected to a constant averaged baseline (400–450 nm). We thank Mr. *S. FitzGerald* (Durham University) for help with this experiment.

*X-Ray Crystal Data of* **1**: $C_{60}H_{60}N_4O_4 \cdot CHCl_3$, $M_r = 2041$, tetragonal space group $P4/n$, $\rho = 1.12$, $Z = 2$, $a =$ 20.93(3), $b = 20.93(3)$, $c = 13.79(2)$ Å, $V = 6039(14)$ Å$^3$, $T = 293$ K. *Picker-Stoe* diffractometer, Cu$K_\alpha$ radiation, $\lambda = 1.5418$ Å. Prismatic crystals (linear dimensions approximately $0.08 \cdot 0.03 \cdot 0.02$ mm) were obtained by slow evaporation from MeCN/$CHCl_3$. The structure was solved by direct methods (SHELXTL). Disorder within the *t*-Bu groups could be resolved, but the $CHCl_3$ molecules disordered along the fourfold rotational axis in the

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[6]) Protonation of 2,3-dimethoxyquinoxaline by TFA in $CDCl_3$ leads to a downfield shift of +0.18 and + 0.31 ppm shift of the H–C(5) and H–C(6) resonances, respectively. Similar shifts (+0.19 and +0.20 ppm, resp.) of the comparable quinoxaline resonances were also observed upon addition of TFA to **1** ($CDCl_3$), whereas much smaller shifts (+0.04 and +0.08 ppm, resp.) are observed upon cooling (313 → 213 K). These data, combined with the observed shift of the methine resonance, confirm that *both* protonation and conformational change to the 'kite' isomer are occurring. The pH-dependent conformational switching was also observed for quinoxaline-bridged resorcinarenes formed by condensation with hexanal.

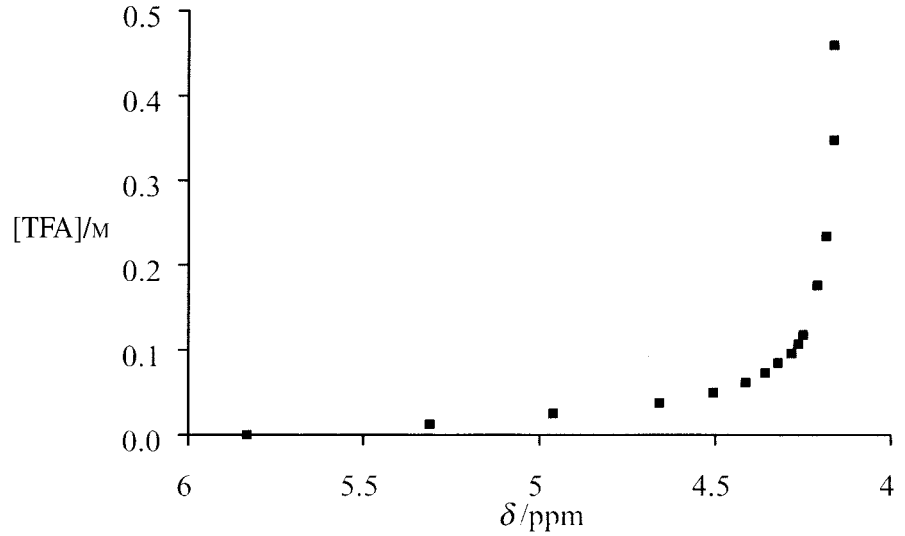


Fig. 6. *Change in $^1$H-NMR chemical shift of the methine proton resonance of* **1** ($c = 1 \cdot 10^{-3}$ M) *in $CDCl_3$ upon addition of TFA* (0–0.4 M). $T = 298$ K.

cavity could not be identified. All heavy atoms were refined anisotropically, H-atoms fixed isotropic with atomic positions based on stereochemical considerations. Final $R(F) = 0.088$ for 851 reflections with $I > 2\,\sigma(I)$, $wR(F^2) = 0.231$ for all 2135 data and 357 parameters. Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication no. CCDC-162859. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB 21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

*2,8,14,20-Tetrakis{[3,5-di(*tert*-butyl)phenyl]methyl}pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol* (**2**). White solid. M.p. 160–165° (dec). UV/VIS (MeOH): $\lambda_{max} = 288$ nm ($\varepsilon = 15100$ M$^{-1}$ cm$^{-1}$). IR ($CHCl_3$): 3678, 3620, 3433 (br., OH), 3011, 2967, 2889, 2400, 1522, 1478, 1422, 1217 (OH), 1044, 928, 750, 672, 622 cm$^{-1}$. $^1$H-NMR (500 MHz, $CD_3OD$): 7.67 (*s*, 4 H); 7.17 (*t*, $J = 1.7$, 4 H); 7.10 (*d*, $J = 1.7$, 8 H); 6.20 (*s*, 4 H); 4.76 (*t*, $J = 7.8$, 4 H); 3.66 (*d*, $J = 7.8$, 8 H); 1.23 (*m*, 72 H). $^{13}$C-NMR (125 MHz, $CD_3OD$): 152.4; 150.5; 140.6; 125.5; 124.8; 123.6; 119.8; 103.4; 41.0; 35.5; 35.0; 31.4. HR-MALDI (2,5-dihydroxybenzoic acid (DHB)): 1319.823 ($C_{88}H_{112}O_8$; calc. 1319.825). Anal. calc. for $C_{88}H_{112}O_8 \cdot MeCN \cdot 4\,H_2O$ (1410.98): C 76.61, H 8.79, N 0.99; found: C 76.70, H 8.68, N 0.95.

*2,3:2′,3′:2″,3″:2‴,3‴-(2,8,14,20-Tetrakis{[3,5-di(*tert*-butyl)phenyl]methyl}pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,24:6,10:12,16:18,22-octayloctaoxy)tetraquinoxaline* (**1**). Off-white solid. M.p. >300°. UV/VIS ($CHCl_3$): $\lambda_{max} = 316$ nm ($\varepsilon = 28900$ M$^{-1}$ cm$^{-1}$). IR ($CH_2Cl_2$): 3679, 3611, 3444 (br.), 3011, 2978, 2889, 2400, 1522, 1479, 1422, 1333, 1217, 1039, 928, 750, 672, 622 cm$^{-1}$. $^1$H-NMR (500 MHz, $CDCl_3$): 8.04 (*s*, 4 H); 7.82 (*dd*, $J = 6.4$, 3.4, 8 H); 7.54–7.50 (*m*, 4 H); 7.49 (*dd*, $J = 6.4$, 3.4, 8 H); 7.22 (*t*, $J = 1.8$, 4 H); 7.10 (*d*, $J = 1.8$, 8 H); 5.92 (br. *s*, 4 H); 3.66 (*d*, $J = 8.2$, 8 H); 1.25 (*s*, 72 H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 152.6; 151.8; 150.9; 139.6; 138.0; 135.2; 129.2; 127.9; 124.3; 123.0; 120.4; 118.3; 38.7; 36.0; 34.9; 31.6. HR-MALDI (DHB): 1823.9128 ($C_{120}H_{120}NaN_8O_8$; calc. 1823.9126). Anal. calc. for $C_{120}H_{120}N_8O_8 \cdot 4\,H_2O$ (1874.40): C 76.9, H 6.88, N 5.98; found: C 77.0, H 7.10, N 6.04. X-Ray crystal-structure: see *Fig. 2*.

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