

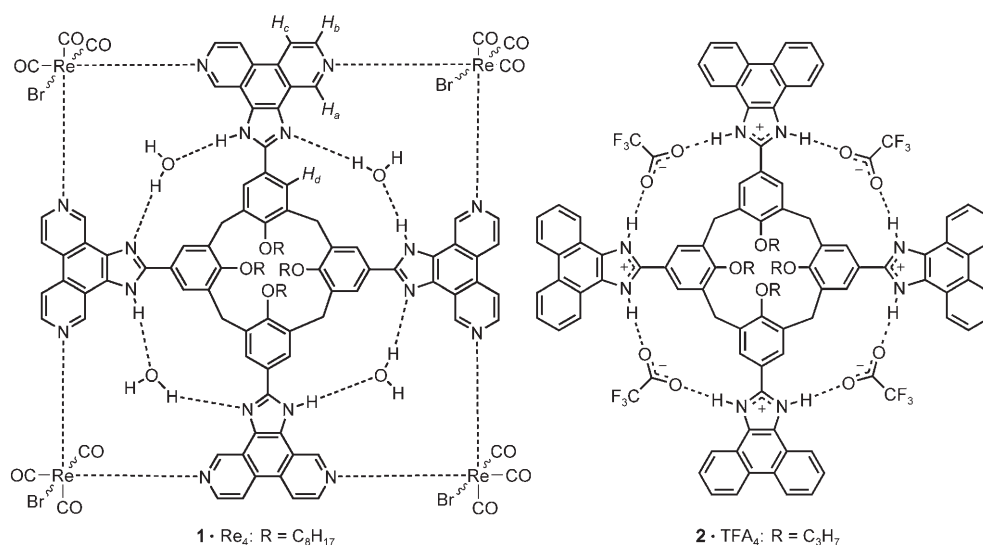
Inclusion of Cavitands and Calix[4]arenes into a Metallobridged *para*-(1*H*-Imidazo[4,5-*f*][3,8]phenanthrolin-2-yl)-Expanded Calix[4]arene**

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Since Cram and co-workers first introduced cavitands, namely bridged resorcin[4]arene hosts whose structure is preorganized in the absence of a guest,^[1] in 1982, many enforced cavities based on bowl-shaped resorcinarenes have been reported. The concave shapes of these constructs result from either covalent bonding^[2,3] or self-assembly mediated by hydrogen bonds,^[4] ion pairing,^[5] or metal coordination.^[6]

However, cavitand structures not based on resorcinarenes but on the related calixarenes instead are as yet unknown. Unlike resorcinarenes, calixarenes are difficult to bridge at the wider rim, although they benefit from the possibility of deepening the cavities, through the attachment of large, flat aromatic surfaces at the *p*-phenol positions, while keeping

their conical shapes.^[7] We report herein the synthesis of the deep calixarene **1** and its tetrarhenium complex **1**·Re₄—the first example of a metallobridged cavitand—and its binding properties towards cavitands and calix[4]arenes (Scheme 1).



Scheme 1. Structure of metallobridged cavitand **1**·Re₄ and of the previously described deep calix[4]arene **2**. TFA = trifluoroacetic acid.

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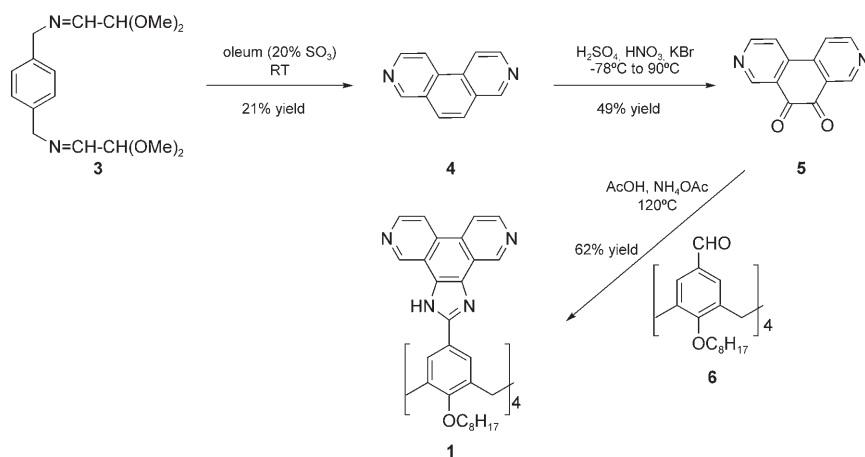
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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

We previously reported the synthesis of **2**, an expanded calix[4]arene bearing the wide, coplanar 1*H*-phenanthro[9,10-*d*]imidazol-2-yl aromatic surface at the *para* positions of the wider rim.^[8] It was shown that the overall conical shape of **2** can be partially stabilized by ion-paired bridges between the vicinal imidazole moieties (such as **2**·TFA₄), which prevent full collapse of the cavity (Scheme 1).^[8]

The use of a 3,8-phenanthroline instead of the phenanthrene moiety locates the heteroatoms at the corners of a square with the 90° angles required for bridging with metal ions with a preference for square planar or octahedral coordination.^[9] We selected {Re(CO)₃Br} as the metal bridges since highly stable tetranuclear square boxes based on porphyrins have been reported for this metal core.^[10]

The expanded 3,8-phenanthrolineimidazolylcalix[4]arene (**1**) was obtained in 62% yield by reaction of tetra-*O*-octyl *para*-formylcalix[4]arene (**6**)^[11] with eight equivalents of 3,8-phenanthroline-5,6-dione (**5**) in the presence of an excess of ammonium acetate in refluxing acetic acid (Scheme 2).^[8] The hitherto unknown quinone **5** was obtained in moderate yield by cyclization of bisimine **3** under strongly acidic conditions followed by oxidation of the resulting 2,7-diazaphenanthrene (**4**)^[12] under similar conditions as those reported for 1,10-



Scheme 2. Synthesis of calixarene **1**.

phenanthroline.^[13] Finally, the metallobridged cavitand **1**·Re₄ was formed in 80% yield from reaction of **1** with four equivalents of [Re(CO)₅Br] in refluxing tetrahydrofuran (THF). The neutral rhenium complex exchanges two equatorial CO ligands for two vicinal pyridine rings on the phenanthroline-imidazole subunits, with formation of a *fac*-[Re(CO)₃Br] bridge at each corner of the structure.

The ¹H NMR spectrum of **1** (in CDCl₃ containing 2% CH₃OH) showed broad signals, which likely arise from the slow interconversion of flexible conformers and prototropic tautomers. However, addition of a small amount of trifluoroacetic acid (TFA) to a suspension in [D₃]MeCN resulted in solubilization and a color change from yellow to red-orange. The ¹H NMR spectrum of the protonated ligand displayed well-resolved, sharp signals corresponding to a structured ligand conformation, probably caused by the formation of ionic TFA bridges between protonated imidazole and/or phenanthroline rings (see Supporting Information).

The metallocavitand **1**·Re₄ was fully characterized by ESI-MS as well as IR and NMR spectroscopy. The IR spectrum showed the characteristic strong CO absorption bands of *fac*-tricarbonylrhenium(I) complexes (at 2027, 1930, and 1879 cm⁻¹).^[14] The ¹H NMR spectrum (either recorded in CDCl₃ or [D₈]THF) gave two distinct sets of signals for the aromatic protons which were attributable to the presence of stereoisomers at the rhenium centers.^[15,16] The signals were unequivocally assigned by a full set of 2D NMR experiments (COSY, NOESY, and ROESY). Interestingly, water molecules were found to bridge the vicinal imidazole rings.^[17]

The proposed coordination of Re by phenanthroline heteroatoms in solution, as well as the bridging of the imidazole rings by water molecules, was fully confirmed in the solid state. In the crystal structure^[18,19] the four rhenium atoms were located at the corners of an almost perfect square (diagonal distances 16.0 and 16.7 Å; sides ca. 11.56 Å each) (Figure 1). The compound crystallizes as a mixture of stereoisomers about the apical positions of the bromine atoms attached to the rhenium atoms (up and down). This results in a positional disorder of the apical groups in the refined structure. The well-localized bridging water molecules are hydrogen bonded to the imidazole rings (O⋯N distances

ca. 2.8 Å). The remaining hydrogen atoms of the bridging water molecules contact the disordered atoms at the lower apical positions of the rhenium ligands (H⋯X distances ca. 2.5 Å). Additionally, these apical atoms interact with identical positions on neighboring molecules which are inverted in orientation (X⋯X contact distances ca. 3.5 Å). Overall, the cavity shows a local C₄ symmetry which is broken by a slight deformation in the pyramid shape by two concave and two convex opposite faces. In the hydrophobic region, the octyl chains display, as expected, large atomical displacement parameters (ADPs), although they could be clearly localized in their positions (Figure 1).

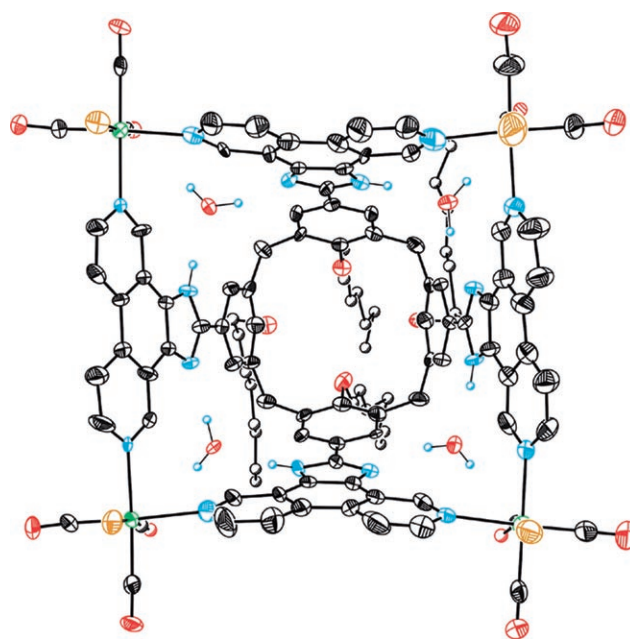


Figure 1. ORTEP plot (thermal ellipsoids shown at 50% probability level) of **1**·Re₄. Nonrelevant hydrogen atoms and solvent molecules have been omitted for clarity.

The deep metallocavitands pack in parallel 2D layers of alternating stacked pyramids (average distance between rings ca. 3.2 Å), with the octyl tails pointing into the interlayer space, in a membranelike arrangement (Figure 2). The tails interdigitate pairwise, leaving cavities between two molecules that are oriented in a face-to-face arrangement with respect to their wider rims and at a distance of about 10 Å. All the available space in these cavities is filled with partially disordered nitromethane molecules (not shown in Figure 2). In total, 9 different positions of solvent molecules could be localized and refined to give a total occupancy of 4.5 nitromethane molecules for each cavitand.

Simple molecular modeling studies^[20] suggest that the highly preorganized basketlike **1**·Re₄ molecule endowed with a nanosized, deep, square pyramidal cavity could be an almost

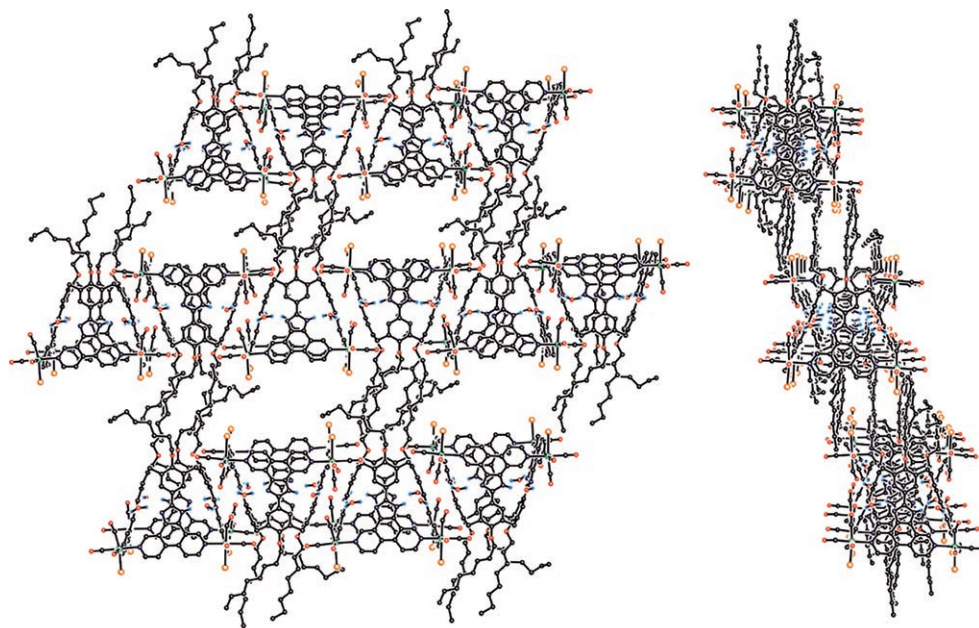


Figure 2. Structure model showing two different orientations of the molecular layers in the crystal packing of **1-Re₄**.

ideal receptor for the complexation of molecules of complementary shape and size, such as calix[4]arenes or cavitands, provided no steric hindrance is present at their lower rims. Accordingly, we explored the interaction of **1-Re₄** with several of these molecular structures by ¹H NMR spectroscopy. Thus, addition of one equivalent of calixarenes **7–9** or cavitand **12** to a 3.2 mM solution of **1-Re₄** in [D₈]THF caused dramatic changes in the line shape and chemical shift values of the proton signals of both the free host and the guest (Table 1). In contrast, addition of one equivalent of calixarenes **10** or **11**, endowed with *O*-propyl substituents at the lower rim, or of the methyl-substituted cavitand **13** to the host solution did not produce any observable change in the proton spectra.

Table 1: ¹H NMR chemical shifts $\Delta\delta$ (ppm, $\delta_{\text{complex}} - \delta_{\text{host/guest}}$) of the host **1-Re₄** and the guest (**7–9** and **12**) protons upon formation of a 1:1 complex.^[a,b]

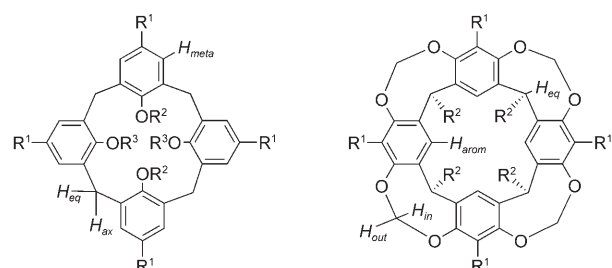
	7	8	9	12
Host ^[c]				
NH	+0.17	+0.20	+0.20	+0.18
H _c	−0.62	−0.79	−0.32	−0.84
Guest				
OH	−3.58	−3.20	n.d. ^[d]	
H _{meta}	−0.68	−0.80	−0.35	
R ¹	−0.28 (H _{para})	+0.02 (<i>t</i> Bu)	−0.21 (CHO)	−0.13 (Me)
H _{eq}	> −2.25	> −2.50	−0.60	−1.86
H _{ax}	> −2.25	> −2.50	−0.60	−4.45 (R ²)
H _{arom}				−3.11
H _{out}				−0.64
H _{in}				−0.24

[a] 1:1 **1-Re₄**:guest mixture in [D₈]THF. [b] No significant changes were observed for guests **10**, **11**, and **13**. [c] Some signals are split because of the presence of stereoisomers (See Supporting Information for details). [d] Signal not detected.

For the favorable cases (**7–9** and **12**) the fact that the proton chemical shifts of **1-Re₄** remain invariable after the addition of more than one equivalent of guest points to 1:1 stoichiometries and to stability constants for the complexes that are too high to be measured accurately by ¹H NMR spectroscopy. Consequently, binding affinities were established by luminescence spectroscopy. Addition of the guest (0 to 4.5×10^{-4} M) to a solution of **1-Re₄** in THF (1.0×10^{-5} M) resulted in a detectable modification of the luminescence spectra ($\lambda_{\text{exc}} = 340$ nm).^[21] The association constants were calculated from non-linear curve fitting of the dependence of the normalized luminescence intensity on the guest concentration by using a 1:1 binding model.^[22] The calculated K_a values (quoted under each formula in Figure 3) fully agree with the qualitative observations derived from the ¹H NMR spectra.

Calixarene guests **7–9**, which lack substituents at the lower rim, are strongly complexed by **1-Re₄**, whereas those endowed with four or just two propyl groups (**10** and **11**, respectively) did not show any binding or were only weakly bound. Cavitands behaved similarly: whereas the highly preorganized, sterically unhindered guest **12** showed the highest binding constant, the isomeric **13**, with methyl groups at the lower rim, was not recognized by the host.

The above data are consistent with the fitting of the guest inside the deep metallocavitand host, driven by face-to-face stacking interactions between the electron-rich guest and the



	K_a/M^{-1}		K_a/M^{-1}
7: R ¹ = H; R ² = R ³ = H	1.5×10^4	12: R ¹ = Me; R ² = H	1.5×10^5
8: R ¹ = <i>t</i> Bu; R ² = R ³ = H	2.0×10^3	13: R ¹ = H; R ² = Me	$<1.0 \times 10^2$
9: R ¹ = CHO; R ² = R ³ = H	n.d.		
10: R ¹ = CHO; R ² = R ³ = Pr	n.d.		
11: R ¹ = <i>t</i> Bu; R ² = Pr; R ³ = H	8.3×10^2		

Figure 3. Association constants K_a (M^{−1}) of guests **7–13** with **1-Re₄** in THF measured by luminescence ($\lambda_{\text{exc}} = 340$ nm, $\lambda_{\text{emission}}$ range = 475–650 nm). n.d.: not determined (changes in the luminescence of the host on binding were obscured by the luminescence of the added guest).

electron-deficient metallohost. This binding model was fully supported by computer calculations (Figure 4)^[20] and NMR data: protons pointing inside the host were dramatically shifted upfield (by more than 3 ppm for some of the inner protons at the bridging positions, Table 1).

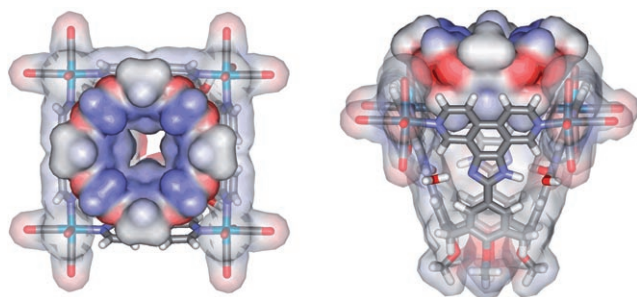


Figure 4. Top and side views of the optimized model of complex **12**@**1-Re₄**. Receptor **1-Re₄** is displayed in stick representation with a transparent van der Waals radii surface except for the front wall (side view). The octyl tails have been replaced by methyl groups for clarity. Cavitand **12** is shown with a van der Waals radii surface.

Intermolecular NOE contacts observed between protons H_b and H_c of the host and protons H_{meta} and H_{para} of guest **7**, or R^1 (Me) protons of **12**, also support the proposed geometry of the complex (see Scheme 1 and Figure 3 for proton assignment). Finally, the **7**@**1-Re₄** inclusion complex was stable enough to be detected by ESI-MS.

In summary, we have shown that a highly preorganized metallocavitand **1-Re₄** of nanoscopic dimensions can be readily synthesized from a simple formyl-substituted calix[4]-arene and 3,8-phenanthroquinone. Unsubstituted calix[4]-arenes and cavitands without substituents on the lower rim are ideal guests for such a structure. Thus, for the first time, a calixarene host becomes the guest. We are currently studying an O-unsubstituted derivative of **1-Re₄** that could self-assemble into a continuous pile of bowl molecules. Also, the use of the deep cavity of **1-Re₄** for recognition and catalysis studies is under active investigation.

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- [1] a) J. R. Moran, S. Karbach, D. J. Cram, *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828; b) D. J. Cram, *Science* **1983**, *219*, 1177–1183.
- [2] C. L. D. Gibb, E. D. Stevens, B. C. Gibb, *J. Am. Chem. Soc.* **2001**, *123*, 5849–5850.
- [3] E. S. Barret, J. L. Irwin, A. J. Edwards, M. S. Sherburn, *J. Am. Chem. Soc.* **2004**, *126*, 16747–16749.
- [4] L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469–472.

- [5] G. V. Oshovsky, D. N. Reinhoudt, W. Verboom, *J. Am. Chem. Soc.* **2006**, *128*, 5270–5278.
- [6] R. Pinalli, V. Cristini, V. Sottili, S. Geremia, M. Campagnolo, A. Caneschi, E. Dalcaneale, *J. Am. Chem. Soc.* **2004**, *126*, 6516–6517.
- [7] Resorcinarene cavitands with *o*-phenylene derivatives at the bridges result in cylindrical shapes: a) T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Nature* **1998**, *394*, 764–766; b) M. H. K. Ebbing, M. J. Villa, J. M. Valpuesta, P. Prados, J. de Mendoza, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4962–4966; c) F. Hof, L. Trembleau, E. C. Ullrich, J. Rebek, Jr., *Angew. Chem.* **2003**, *115*, 3258–3261; *Angew. Chem. Int. Ed.* **2003**, *42*, 3150–3153.
- [8] E. Botana, K. Nattinen, K. Risannen, J. de Mendoza, *Org. Lett.* **2004**, *6*, 1091–1094.
- [9] P. J. Stang, D. H. Cao, S. Saito, A. M. Arif, *J. Am. Chem. Soc.* **1995**, *117*, 6273–6283.
- [10] M. L. Merlau, M. P. Mejia, S. T. Nguyen, J. T. Hupp, *Angew. Chem.* **2001**, *113*, 4369–4372; *Angew. Chem. Int. Ed.* **2001**, *40*, 4239–4242.
- [11] R. H. Vreekamp, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1996**, *61*, 4282–4288.
- [12] a) T. J. Schwan, N. J. Miles, *J. Heterocycl. Chem.* **1982**, *19*, 1351–1353; b) E. W. Gill, A. W. Bracher, *J. Heterocycl. Chem.* **1983**, *20*, 1107–1109.
- [13] N. Margiotta, V. Bertolasi, F. Capitelli, L. Maresca, A. A. G. G. Moliterni, F. Vizza, G. Natile, *Inorg. Chim. Acta* **2004**, *357*, 149–158.
- [14] J. L. Smithback, J. B. Helms, E. Schutte, M. Woessner, B. P. Sullivan, *Inorg. Chem.* **2006**, *45*, 2163–2174.
- [15] Up to six stereoisomers (oooo, oooo, ooi, oioi, iiii, and iiii; i = inwards, o = outwards) can be predicted if it is assumed that the bromine atom is always located in an apical position relative to the plane containing the four metal centers.
- [16] No such mixtures were reported for porphyrin squares, since the stereoisomers averaged on the NMR time scale as a result of free rotation of the pyridine ligands: R. V. Slone, J. T. Hupp, *Inorg. Chem.* **1997**, *36*, 5422–5423.
- [17] This was clearly seen in the NOESY spectrum (contacts between the bulk water signal and the H_a and H_d cavitand signals).
- [18] CCDC-618949 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [19] Single crystals were grown by slow evaporation of a $CHCl_3$ /MeNO₂ solution at RT. Data for **1-Re₄** at 100 K: $C_{129}H_{135}Br_4N_{21}O_{30}Re_4$, 3524.02 g mol⁻¹, triclinic, space group $P\bar{1}$, $a = 16.1122(19)$ Å, $b = 23.443(3)$ Å, $c = 23.654(3)$ Å, $\alpha = 113.546(3)^\circ$, $\beta = 90.258(3)^\circ$, $\gamma = 99.928(3)^\circ$, $V = 8041.1(16)$ Å³, $Z = 2$, $\rho_{calcd} = 1.455$ Mg m⁻³, $R_1 = 0.1256$ (0.2172), $wR_2 = 0.3259$ (0.3960), for 20154 reflections with $I > 2\sigma(I)$ (for 40618 reflections ($R_{int} = 0.0966$) with a measured total number of 100297 reflections), GOF on $F^2 = 1.045$, largest diff. peak (hole) = 6.628 (–3.193) e Å⁻³.
- [20] CAChe WorkSystem Version 6.1.12.33. Fujitsu Limited.
- [21] The deep calixarene **1** and the metallocavitand **1-Re₄** are luminescent, as are the formyl-substituted calixarenes **9** and **10**, whereas the remaining calixarene and cavitand guests are not. Addition of increasing amounts of guest to a solution of **1-Re₄**, keeping its concentration constant, caused an increase in the intensity in the band at 550 nm.
- [22] *SPECFIT*, version 3.0.36, Spectrum Software Associates.