

($[G_0 - Cl]^+$), 4783.5, ($[G_1 - Cl - 2 BF_4]^+$), 11 907.0 ($[G_2]^+$) and 24 030.2 ($[G_3 - 19 BF_4]^+$). The loss of anions takes place inside the mass spectrometer, generating the multiply charged ions needed for detection and calculation of the molecular weight.^[19]

Molecular mechanics calculations^[20] were performed on $G_0 - G_3$. The square-planar coordination environment of the Pd centers is well preserved. It is clear that after the second generation the structure of the dendrimer becomes quite entangled (Fig. 2).

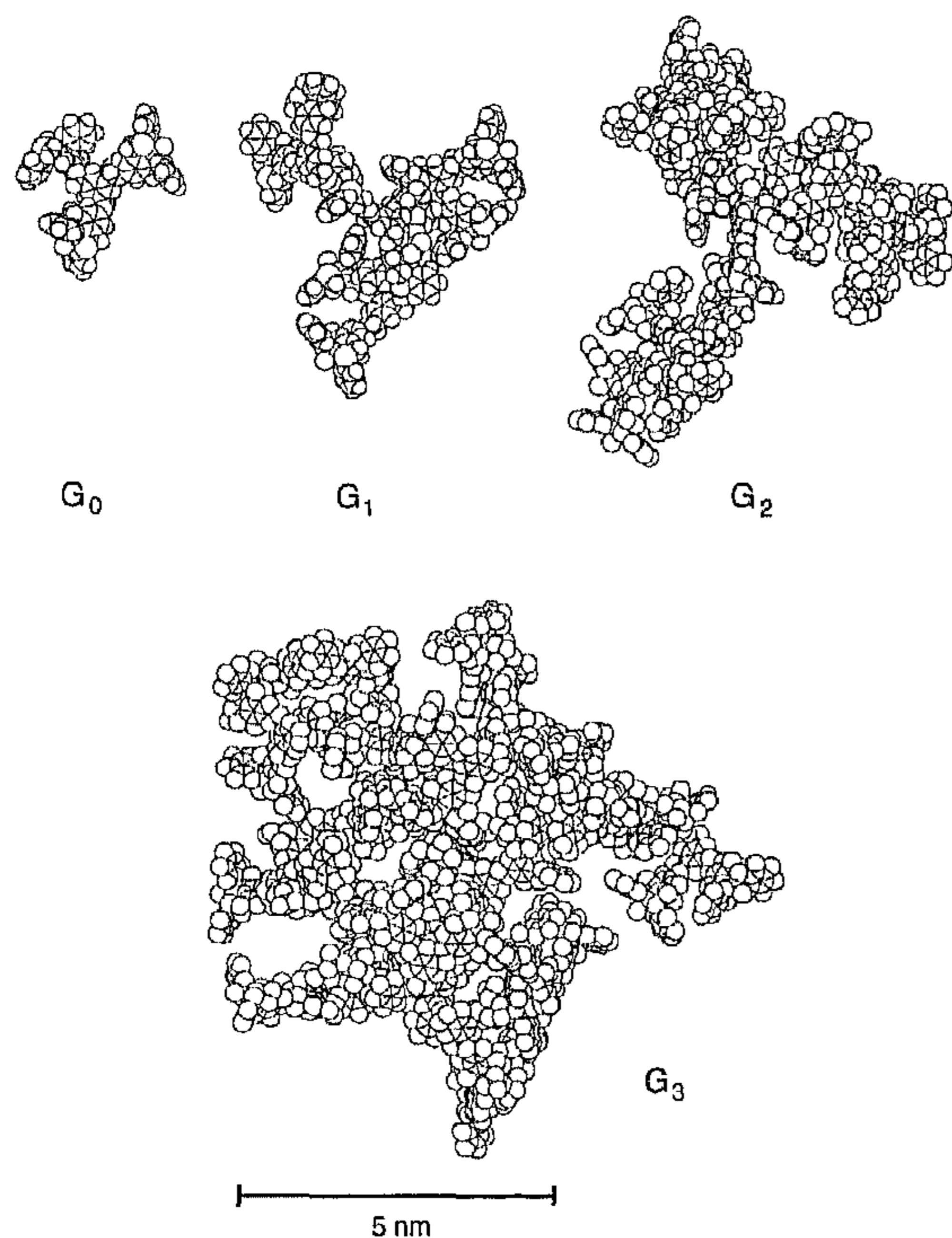


Fig. 2. Optimized structures of $G_0 - G_3$.

We have shown that organometallic structures of nanometer dimensions can now be constructed in a very simple and controlled way. This method of controlled assembly provides a new and versatile tool for dendrimer synthesis. The method allows large variation in the metal in each generation, the coordinating ligands, and the structure of the nucleus.

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Molecular Boxes Based on Calix[4]arene Double Rosettes**

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The construction of noncovalently bonded, well-defined aggregates has received increasing attention over the last few years. The study of molecular self-assembly is expected to provide information on how interactions between molecular functionalities lead to entities with new shapes and functions. The shapes of recently described ensembles range from boxes^[1, 2] and channels^[3] to more complex three-dimensional networks and other discrete aggregates.^[4–6] Reported molecular boxes based on noncovalent interactions all have rather small cavities, since they result from the dimerization of two molecules with concave structures.^[2] Recently we prepared receptors with large hydrophobic cavities by the covalent combination of calix[4]arenes and resorcin[4]arenes.^[7] The successful synthesis

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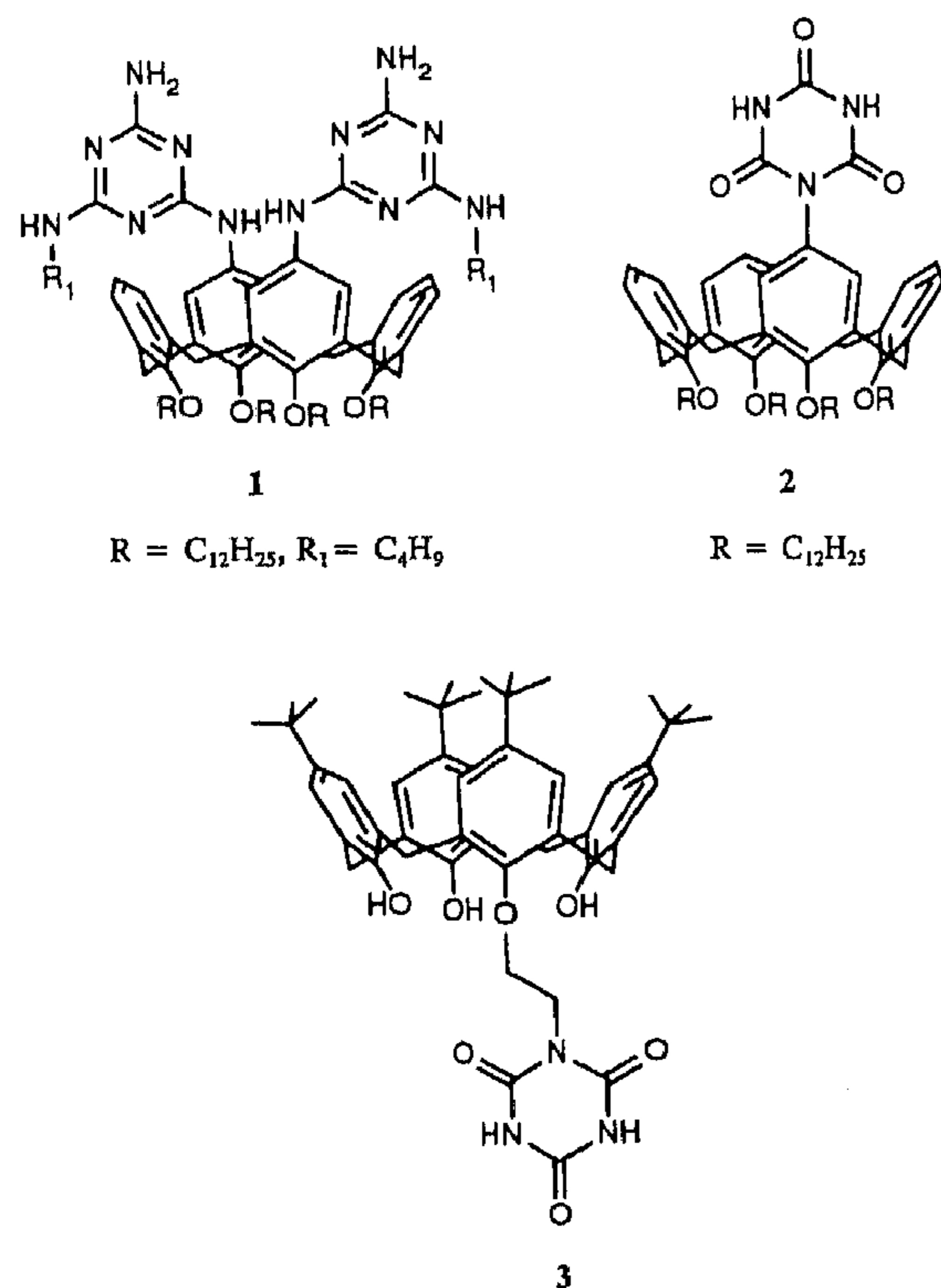
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of these molecules indicates that calix[4]arene^[8] is a suitable molecular building block for the construction of molecular boxes because it offers a rigid concave surface.

In this communication we describe the formation of large self-assembled boxes, which have a "double-rosette structure". The calix[4]arene skeleton^[9] serves as a spacer between the two rosettes and as molecular platform that preorganizes the hydrogen bonding groups. This spacer ensures that the centers of the two rosettes are separated by as much as 8.5 Å (based on CPK molecular models).^[10] The formation of the hydrogen-bonded rosette is the result of hydrogen bonding between melamine moieties and barbituric or cyanuric acid derivatives. This motif is being studied intensively by Whitesides et al.,^[11] and recently Lehn et al. have also used this motif for self-assembly.^[12]

We have used three different calix[4]arenes as components for the double rosettes: the dimelamine derivative **1**, upper-rim substituted isocyanuric acid derivative **2**, and the lower-rim substituted isocyanuric acid derivative **3**.^[13]



¹H NMR titration of **1** with diethylbarbituric acid (BA) in CDCl₃ showed several characteristic features (Fig. 1). Very interestingly, already at low concentrations of BA two signals (a, b) were evident at very low field. These resonances, which remain at $\delta = 14.10$ and 13.32 regardless of the 1:BA ratio, are assigned to the hydrogen-bonded NH protons of BA in the 1·BA complex. When the amount of barbituric acid is increased, the signal corresponding to the NH₂ protons of free **1** decreases in intensity but remains at the same position. At the same time, signals at $\delta = 8.37$ (c) and 7.43 (d) appear, which correspond to the two secondary amine protons of **1** in the hydrogen-bonded complex. At a ratio of 1:BA of 1:2 the spectrum is sharp, which indicates the absence of free **1**. The 1:2 ratio is consistent with the double-rosette structure schematically represented in Figure 2. Dilution of this solution did not give rise to changes in the ¹H NMR spectrum, indicating that the

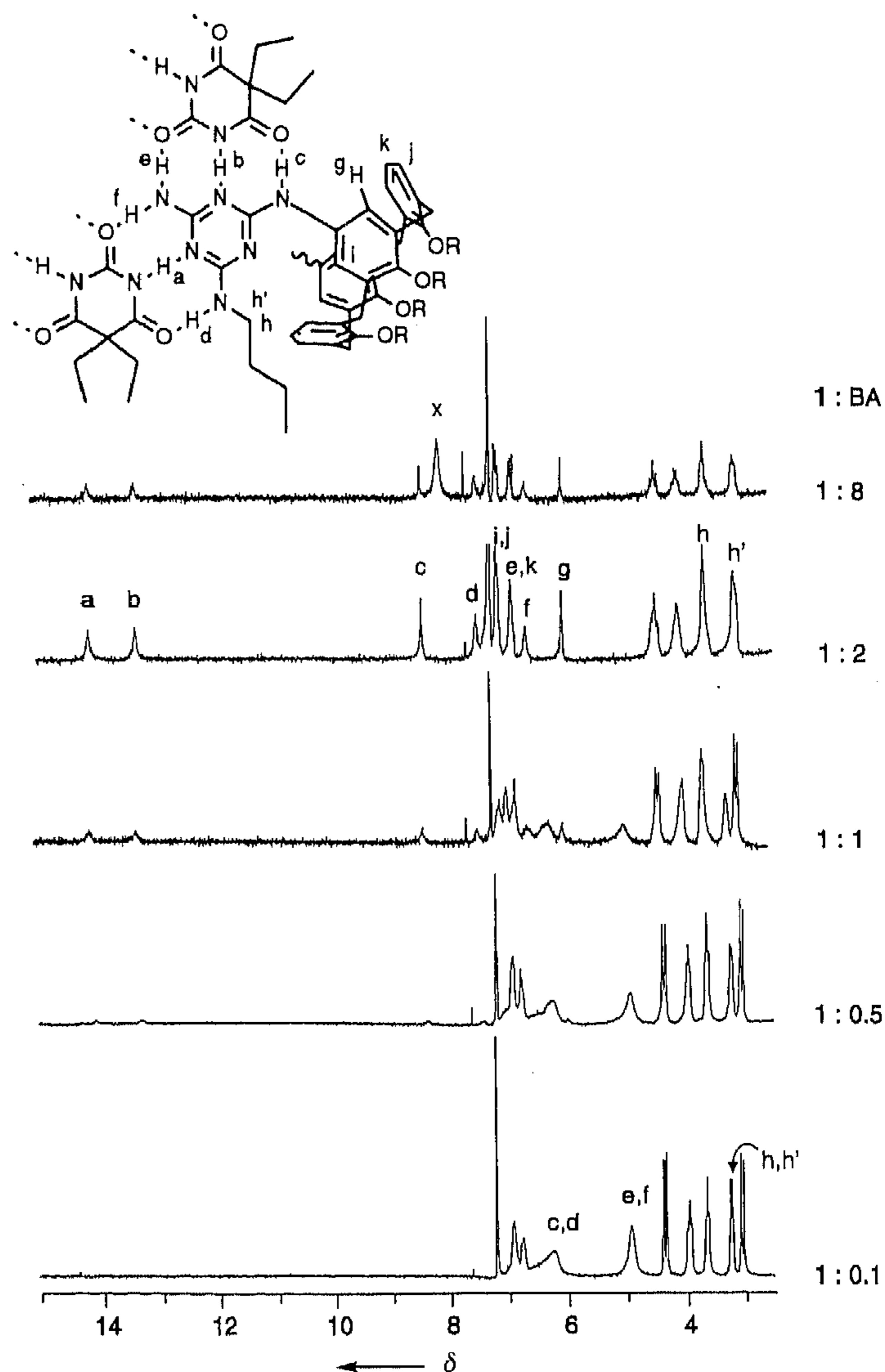


Fig. 1. ¹H NMR titration of **1** with BA measured at 400 MHz at ambient temperature. Separate 10 mM solutions of **1** and BA in CDCl₃ were mixed in various ratios. x = signal for the free acid.

presence of high-order aggregates is less probable. When more than two equivalents of barbituric acid are present, the signal for the NH protons in free BA is observed alongside the two for the hydrogen-bonded BA. This indicates that exchange between hydrogen-bonded and free BA is slow on the NMR time scale.^[15] In the rosette the two NH protons are observed at different chemical shifts as a result of the unsymmetrical substitution of the melamine units. Two signals are observed for both the two NH₂ protons (e, f) and for the two protons of the *n*-butyl chain next to the nitrogen (h, h'), indicating diastereotopicity.^[16]

The aromatic protons of the melamine-substituted aromatic ring of calix[4]arene **1** give rise to signals at $\delta = 7.15$ (i) and 6.03 (g). In free **1** these protons display broad signals at $\delta = 7.05$ – 6.70 and 6.65 – 6.05 , respectively. The resonance at $\delta = 6.03$ is in accordance with a pinched cone structure^[17] in which the two melamines approach each other.^[18]

Titration of **1** with **2** gave similar results. Large downfield shifts are observed for the NH protons ($\delta = 15.43$ and 14.15), free and hydrogen-bonded species do not exchange on the NMR time scale, and a 1:2 ratio is indicated. At ratios beyond 1:2 (i.e. excess **1**) only signals corresponding to the saturated double

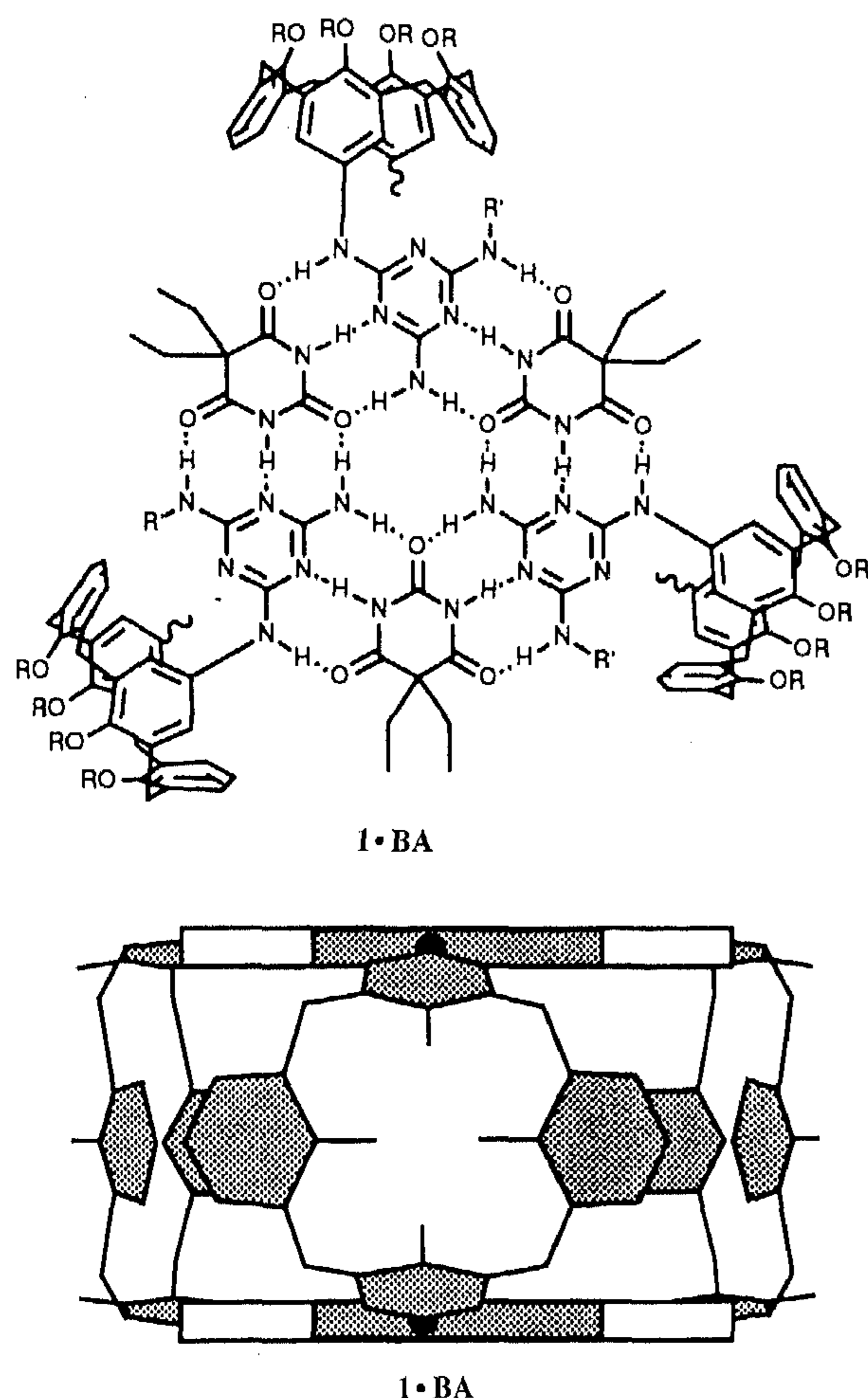


Fig. 2. Schematic representation of the proposed structure of a double rosette consisting of 1 and BA. Top: top view (for clarity only the upper rosette is shown). Bottom: side view.

rosette and free 1 are observed. No other signals are present at low field, in particular, which means that no intermediate structures such as partly filled double rosettes or linear aggregates exist. This suggests that rosette formation as depicted in Figure 3 is a cooperative process, in which the formation of one rosette preorganizes the remaining units, favoring the formation of the second rosette.

The ^1H NMR titration of 1 with 3 was, to a certain extent, similar to that of 1 with BA. The hydrogen-bonded NH protons were observed at slightly higher field ($\delta = 15.17$ and 14.47). At a 1:3 ratio of 1:2 the signals of free 1 disappear, indicating the formation of a double rosette.^[19]

The distances between the relevant protons in the three double-rosette structures were determined by 2D NOESY experiments (400 MHz) using the initial rate approximation (Table 1).^[20, 21] The distances are slightly larger than those obtained from CPK molecular models and molecular modeling of similar hydrogen-bonding motifs,^[22, 23] but provide sufficient evidence for the proposed rosette structure.

The above results strongly indicate the formation of rosettes.^[24] Further evidence for the formation of the rosettes was derived from build-up curves measured for the NOE interactions between the methylene bridge protons. From these data cross relaxation rates can be derived, the magnitude and sign of which relate to the rotation correlation time τ_c . If the random isotropic tumbling of a spherical molecule/aggregate and the absence of internal motion are assumed, τ_c can be related to the

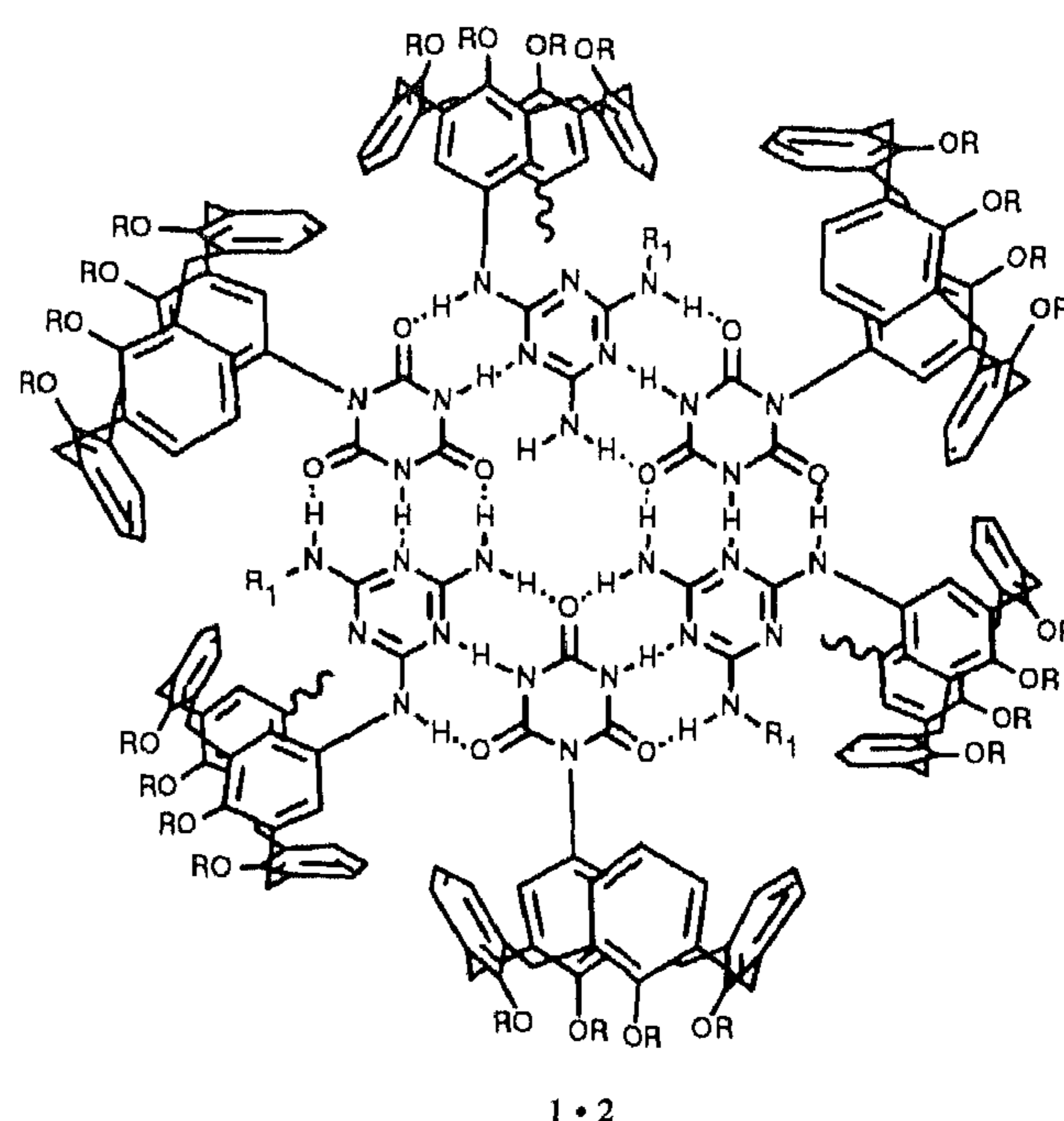
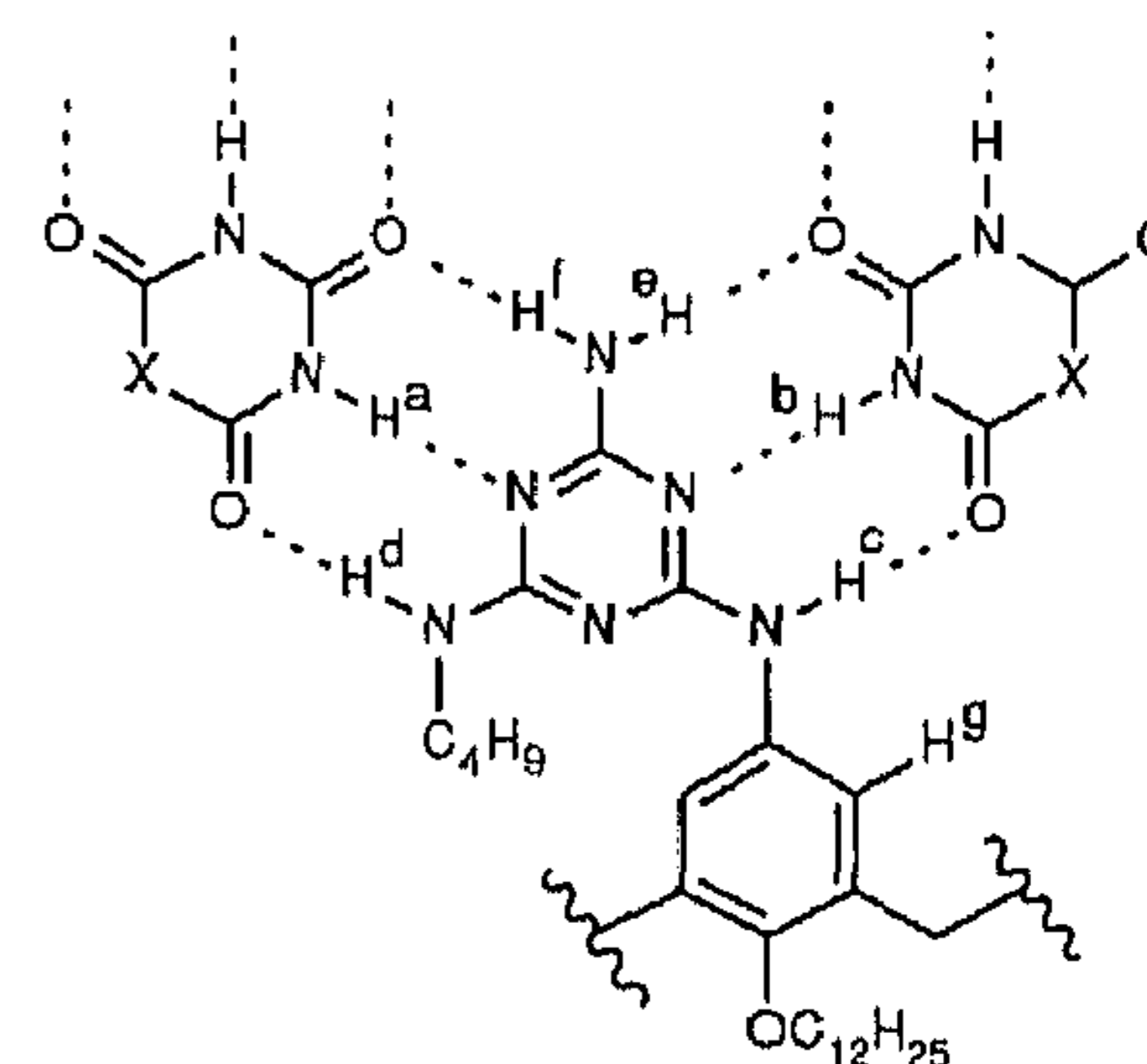


Fig. 3. Schematic representation of the proposed structure of a double rosette consisting of 1 and 2 (for clarity only the upper rosette is shown).

Table 1. Distances [\AA] between the H atoms in 1 · BA, 1 · 2, and 1 · 3 [a].

H Atoms	1 · BA	1 · 2	1 · 3
a-d	2.8	2.5	2.7
a-f	3.4	3.1	3.0
b-e	3.2	3.0	2.9
b-c	3.5	2.9	2.9
c-g	3.2	2.9	

[a] Deviation $\pm 0.1 \text{ \AA}$.



hydrodynamic volume.^[23, 25, 26] By using the initial rate approximation, the cross relaxation rates for the methylene bridge protons of the three aggregates together with those for the free 3 and 1 were determined, and from these values the corresponding τ_c values were calculated. Generally, the τ_c values increase as the expected molecular masses of the aggregates increase. Qualitatively a good correlation is present with the curve of the calculated τ_c values (Fig. 4).^[27]

The absolute deviations between the calculated and experimental values are most likely caused by the uncertain assumptions regarding density and shape. Assumptions regarding shape are not likely to hold for the somewhat flattened double rosettes. It is known that a greater ellipticity of a molecule leads to a larger effective correlation time, which correlates to a larger apparent molecular weight.^[28]

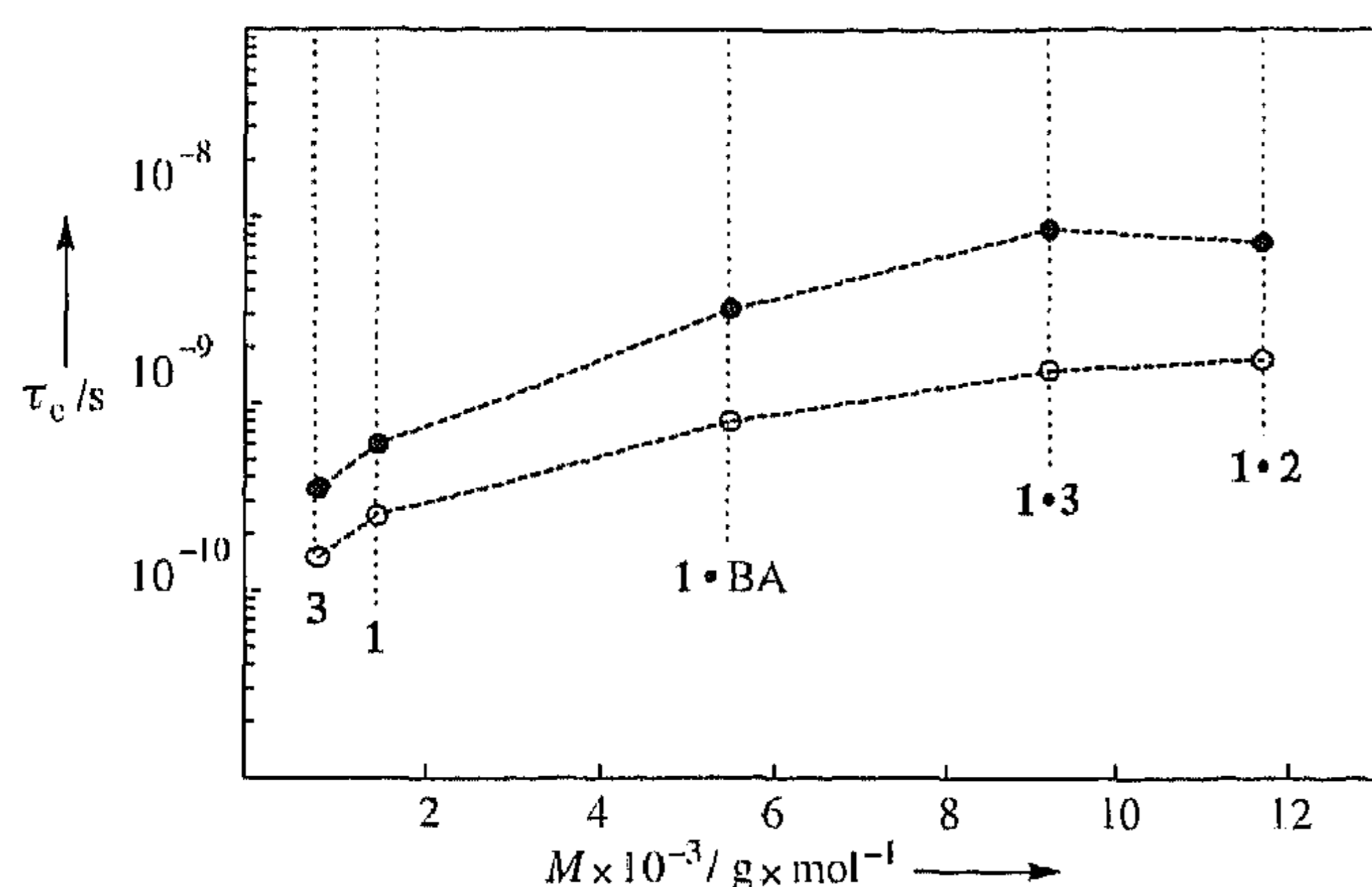


Fig. 4. Rotation correlation times τ_c determined from cross relaxation constants as a function of the molecular weights of the species in question. \bullet = experimental (400 MHz, 25 mM in CDCl_3); \circ = theoretical.

In conclusion, strong indications for the formation of the calix[4]arene-based double-rosette structure from three different combinations of bis(melamine)calix[4]arene and isocyanuric acid derivatives were obtained from ^1H NMR titrations and from the distances determined by NOE spectroscopy between the protons involved in hydrogen bonds. The results are in accordance with the expected 1:2 stoichiometry and suggest that the formation of the double rosettes is a highly cooperative process. In addition measurements of cross relaxation rates give further support for the formation of the large entities; the formation of aggregates is reflected by an increase in rotation correlation times. We feel that the determination of cross relaxation rates provides a valuable tool for the characterization of supramolecular structures in general. Future work will focus on complexation of guests, control of the cavity size and openings, and the introduction of chemical functionalities.

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[13] Calix[4]arene 1 was synthesized in five steps starting from de-*tert*-butylated calix[4]arene in an overall yield of 19%. The reactions include alkylation of the lower rim, selective nitration of the upper rim [14] followed by reduction to the diamine, and reaction with cyanuric chloride, ammonia, and finally *n*-butylamine. The first four steps of the synthesis of 2 are very similar to those of the synthesis of 1. Mononitrated de-*tert*-butylated calix[4]arene was reduced to the monoamine. Subsequent reaction with nitrobiuret gave the biuret derivative, which was converted to the isocyanuric acid by treatment with diethylcarbonate to give pure 2 in an overall yield of 22%. The synthesis of 3 started with monoalkylation of *p-tert*-butylcalix[4]arene with 2-bromoethylphthalimide. The resulting phthalimido derivative was quantitatively reduced to the monoamine, which was then reacted with nitrobiuret. Subsequent reaction with diethylcarbonate gave the pure monoisocyanuric acid 3. All new compounds were fully characterized by ^1H NMR and ^{13}C NMR spectroscopy, FAB mass spectrometry, and elemental analysis.

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[15] From the large difference in chemical shifts for free and complexed BA (Fig. 1) an upper limit for the dissociation rate constant of about 2000 s^{-1} can be estimated. Assuming that the formation rate constant is diffusion limited, an overall binding constant of $\geq 10^5\text{ M}^{-1}$ can be estimated.
[16] For the assignment of the signals of 1·BA and the other assemblies discussed in this paper NOE, ROE, and J-correlation spectroscopy were used.
[17] “Pinched” means that two opposite aromatic rings become almost parallel while the other two twist outward and “flatten” the calix.
[18] The rosette is also stable in acetonitrile and toluene; however, addition of >10% DMSO or MeOH to a CDCl_3 solution resulted in slow decomposition.
[19] In this case probably higher aggregates are formed as a result of hydrogen bonding between free 3 and the hydroxyl groups of 3 in the aggregate when more than two equivalents of 3 are present. This was concluded from the appearance of new signals in the ^1H NMR spectrum.
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[24] Rosette formation for the complexes 1·BA and 1·2 was also confirmed by electrospray MS: *m/z* values of 5770 (calcd for $M + 7\text{ MeCN}$ 5768) and 11727 (calcd for $M + 3\text{ H}$ 11727), respectively, were obtained. In the case of 1·2 complex VPO measurements in CHCl_3 at 29 °C gave a molecular weight of $10.0 \pm 1.8 \times 10^3\text{ g mol}^{-1}$ (calcd 9199).
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[26] The hydrodynamic volume is related to the molecular mass via the density ρ . Equation (a) is used to determine τ_c . This equation expresses the relationship

$$\sigma_{12} = \frac{1}{10} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{\gamma_1^4 \hbar^2}{r^6} \left\{ \frac{6\tau_c}{1 + 4\omega^2\tau_c^2} - \tau_c \right\} \quad (\text{a})$$

between τ_c and the cross relaxation constant, σ_{12} , for a two-spin system involving atoms 1 and 2. Isotropic tumbling and pure dipole-dipole relaxation are assumed. μ_0 = dielectric constant, γ = gyromagnetic constant, r = distance between atoms 1 and 2, ω = Larmor frequency.

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