# Formation of Gel-Like Systems of an 2,6,8,12,14,18,20,24-Octahydroxypyridine[4]arene and an 2-Aminonaphthyridine

**Thorsten Gerkensmeier,[a] Björn Decker,[a] Marcus Schwertfeger,[b] Wolfgang Buchheim,[b] and Jochen Mattay*[a]**

*Dedicated to Professor Waldemar Adam on the occasion of his 65th birthday*

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2,6,8,12,14,18,20,24-Octahydroxypyridine[4]arenes are capable of forming complexes with suitable partner molecules. In apolar media the formation of gel-like aggregates of an octahydroxypyridine[4]arene and an 2-aminonaphthyridine at a ratio of 1:4 was observed. This viscous liquid was investigated by means of rheology and TEM techniques and was characterized as shear thinning and thermoreversible gel-like solution which is strongly affected by changes in the stoichiometry of the complex partners.

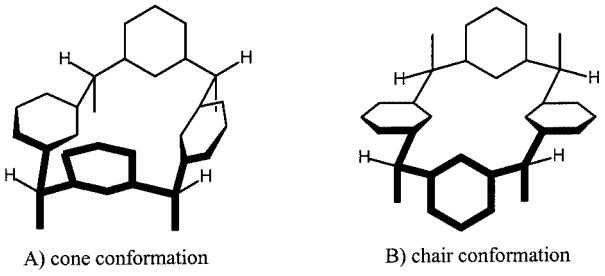


## Introduction

Calixarenes are still one of the important building blocks of supramolecular aggregates. Many projects within this field concern the complexation of both organic and inorganic compounds. The complexation of organic molecules is often controlled by molecular recognition phenomena and therefore the stoichiometry and the shape of the complex is crucial. One tool to achieve this selectivity is multivalent hydrogen bonding,[1a] and recently the groups of Hanabusa[1b] and McPherson[1c] have used this concept for designing novel organogel systems. The number and the stability of calixarene aggregates previously reported gives an idea of the importance of these macrocycles to this research area.[2–9] However, not all complexation phenomena lead to structurally well-defined aggregates but more likely result in less ordered structures of large size. Among these are micelles, layers, sticks and stripes. The microstructures often cause rheologic effects such as increased viscosity, which can be measured as a macroscopic material property. Other methods of determining the properties and the structural nature of viscous solutions and gels are various electron microscopy techniques,[10] light, small-angle X-ray or neutron scattering.

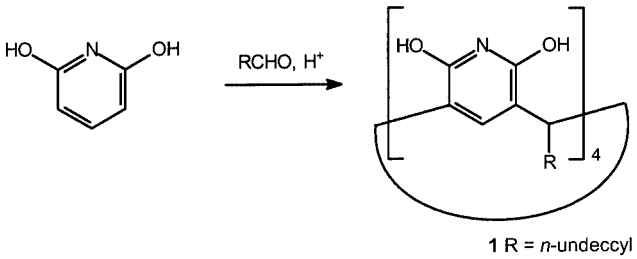
[a] Organische Chemie I, Fakultät für Chemie, Universität Bielefeld,
Postfach 100131, 33501 Bielefeld, Germany
E-mail: mattay@uni-bielefeld.de
[b] Bundesanstalt für Milchforschung,
Hermann-Weigmann-Straße 1, 24103 Kiel, Germany

Very recently the synthesis of a new member of the calixarene family derived from 2,6-dihydroxypyridine and aldehydes was developed.[11] In general, these compounds are accessible as *rccc*-configured, cone-shaped molecules in medium yields (Scheme 1).




Scheme 1. Cone conformation (A) of a *rccc*-configured and chair conformation (B) of an *rctt*-configured calix[4]arene isomer

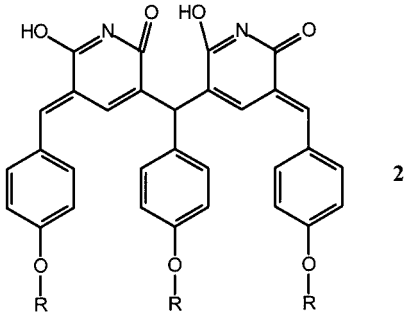
Only long-chain aldehydes, at least like hexanal, lead to highly soluble pyridine[4]arenes, that can be handled even in apolar solvents (Scheme 2). Short-chain aldehydes gener-




Scheme 2. Acid-catalysed synthesis of pyridine[4]arenes from 2,6-dihydroxypyridine and aliphatic aldehydes

ally yield nearly insoluble calixarenes which have to be acetylated or benzoylated to be analysed.

A number of aldehydes has been successfully applied in this reaction. However, some restrictions of the use of aldehydes are found. From alkenecarboxaldehydes only traces or no calixarene at all were isolated. Electron-deficient aromatic aldehydes mostly favour the *rctt*-configured isomer while electron-rich aromatic aldehydes lead to a methylidenepyridinone substructure **2**.

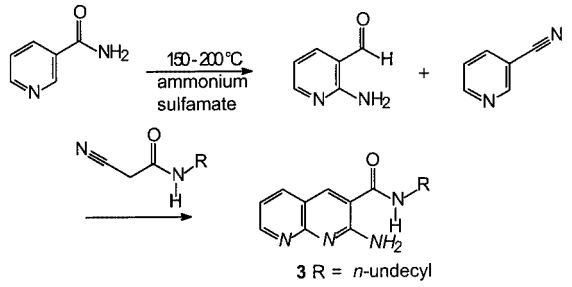


**2**

The motivation for the synthesis of this kind of calixarenes was to find a new building block for self-organizing systems. Since 2,6-dihydroxypyridines feature uracil mimics, a number of complementary molecules for multiple hydrogen bonding should be accessible for complexation studies.

## Results

The use of apolar media should support the formation of hydrogen bonds, therefore solutions of 2,6,8,12,14,18,20,24-octahydroxy-4,10,16,24-tetra-*n*-undecylpyridine[4]arene (**1**) as receptor molecule in toluene were applied for complexation studies. These conditions may also lead to homodimer formation, which has to be taken into consideration when discussing heteromolecular complexes. The first substrate checked, was 2,6-diaminopyridine. Upon mixing hot solutions of the calixarene and the diaminopyridine, a colourless, insoluble precipitate was obtained which turned black within a few hours. Attempts to analyse the precipitate by MS and NMR techniques were not successful. Whether the driving force of the formation of this insoluble precipitate is simply an acid-base interaction or the desired multivalent hydrogen bonding or both is not clear. In order to obtain more soluble complexes, we were looking for very apolar substituted partner molecules. Therefore we took a closer look at 2-aminonaphthyridine-3-carboxamides. These compounds have a hydrogen donor and two acceptor binding sites at the naphthyridine unit and should be complementary to the hydroxypyridone substructure of the pyridine[4]arenes, which is expected to be the dominant tautomer in the 2,6-dihydroxypyridine.[12−14] According to a procedure of Majewicz and Caluwe 2-aminopyridine-3-carboxaldehyde was prepared.[15,16] The reaction with malonamidonitriles according to the preparation of Fenlon affords the 2-aminonaphthyridine-3-carboxamides (Scheme 3).[17]




Scheme 3. Synthesis and binding sites (in italics) of the 2-amino-$N^3$-R-1,8-naphthyridin-3-carboxamide **3**

For our tests we chose *rccc*-octahydroxy-tetraundecylpyridine[4]arene **1** and 2-amino-$N^3$-undecylnaphthyridine-3-carboxamide (**3**). Both compounds are quite soluble in apolar media like toluene and dichloromethane. We mixed hot solutions of the pyridine[4]arene **1** and the naphthyridine **3** in toluene at a molar ratio of 1:2, 1:3 and 1:4 and tried to find evidence for complex formations by means of Maldi-MS and UV/Vis absorption spectroscopy. In all cases only the molecular mass of one of the components was detected by Maldi-MS. On the other hand UV/Vis spectroscopy showed a small decrease of absorption of the naphthyridine upon addition of the calixarene partner, however, too small to be used for a detailed analysis. We assume that there is no defined complex present due to the following observation. While 1:2 and 1:3 mixtures of **1** and **3** do not differ much, both presenting a clear, somewhat coloured solution of low viscosity, the 1:4 mixture forms a viscous solution upon cooling to at least 5 °C. Warming up to room temperature the solution becomes an easy moving fluid again. This process appeared to be reversible. In THF and 1,4-dioxane no thickening or gelation effect was observed for 1:4 mixtures. We decided to characterise the viscous solution by means of rheology and, if possible, by freeze fracture transmission electron microscopy. The rheologic experiments were carried out with the 1:3 and 1:4 mixtures.

### Rheology Studies

For reasons, that are going to be explained in the TEM part, 1,2-dichlorobenzene was applied as a solvent for the rheology experiments. Two solutions with given concentrations were prepared. The compounds were weighed and dissolved in hot 1,2-dichlorobenzene. Solution 1 contained the calixarene **1** and naphthyridine **3** in a molar ratio of 1:3 and was a clear liquid of low viscosity, whereas solution 2 contained **1** and **3** in a molar ratio of 1:4 and was a translucent fluid, that became viscous upon cooling to 5 °C. If this solution was stirred, the gel-like substance reversibly turned into a fluid. At first the results for the 1:3 ratio will be discussed. The temperature dependence is shown in Figure 1.

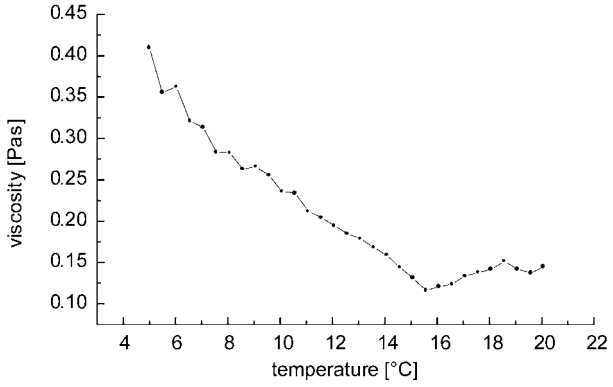



Figure 1. Temperature dependence of the 1:3 mixture of calixarene **1** and naphthyridine **3** at a shear rate of 0.2 [1/s]

Although the viscosity of the solution is comparatively low, a distinct decrease can be noted upon warming up to room temperature. Further interesting features of viscous liquids concern shear thinning or shear thickening. Shear thinning describes the decrease of viscosity upon mechanical stress whereas shear thickening describes just the opposite behaviour. The corresponding time-dependent effects are known as thixotropy and rheopexy. These effects take place, if special microstructures are present. Figure 2 shows the viscosity of the 1:3 mixture depending on the shear rate and time.

These experiments clearly revealed shear thinning and thixotropic features. The viscosity is dominantly controlled by the actual shear rate and by the time of shearing. On the other hand, the viscosity itself is relatively low. If the composition of the mixture changes from 1:3 to 1:4 viscosity of the solution drastically increases. The general features of thermoreversibility, shear thinning and thixotropy remain, i.e. the 1:4 mixture generally shows the same behaviour. However, especially for low shear rates the viscosity turns out to be high. The temperature as well as the shear rate takes strong influence on the viscosity of the solution (Figure 3).

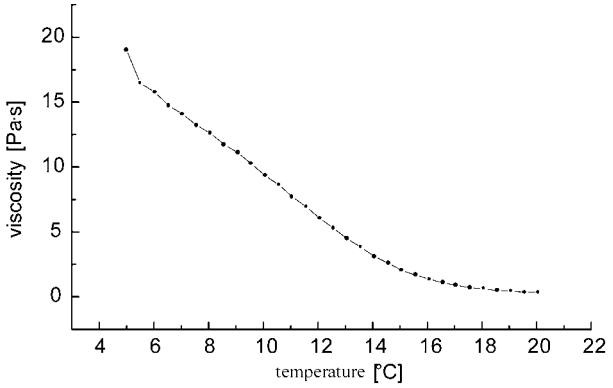



Figure 3. Temperature dependence of the 1:4 mixture of **1** and **3** at a shear rate of 0.2 [1/s]

Temperature changes have a strong influence on the viscosity of the viscous gel-like solution. Between 5 and 15 °C a nearly linear decrease is observed. This effect is reversible as well.

Figure 4 shows the shear rate dependence of the viscosity at 5 °C. Note the strong decrease of viscosity under mechanical stress and the fast recovering of the system if low shearing rates are applied. It is also important, that no viscoelasticity was observed and for that reason the gel-like mixture does not show a yield value.

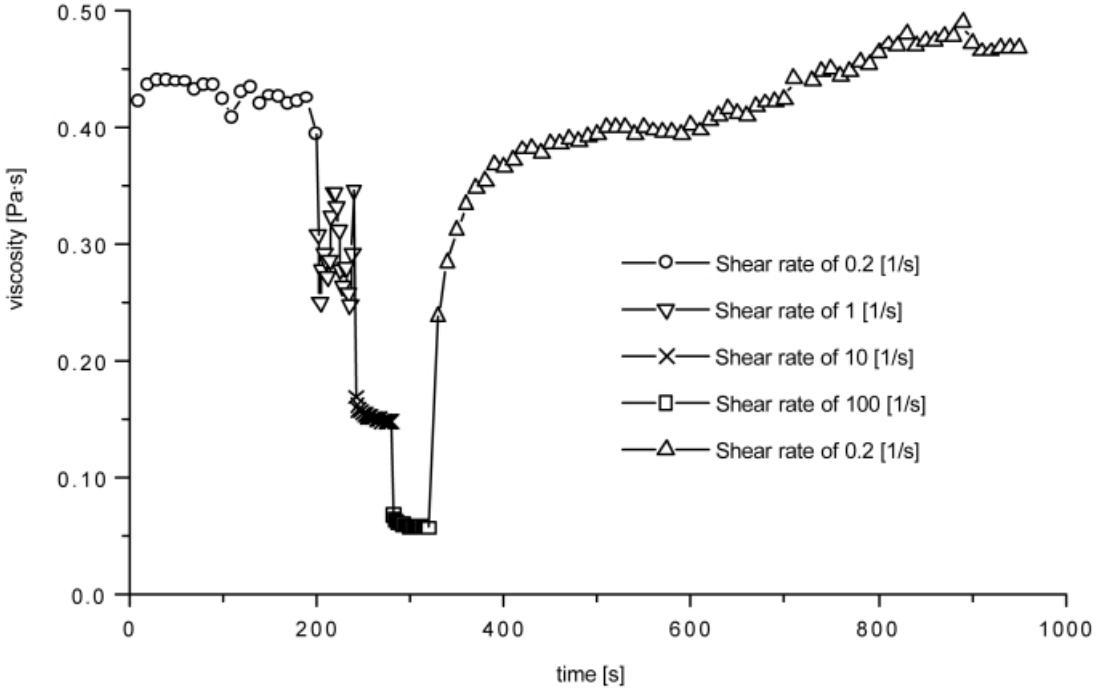



Figure 2. Shear-rate dependence of the viscosity of the 1:3 mixture of **1** and **3** at 5 °C

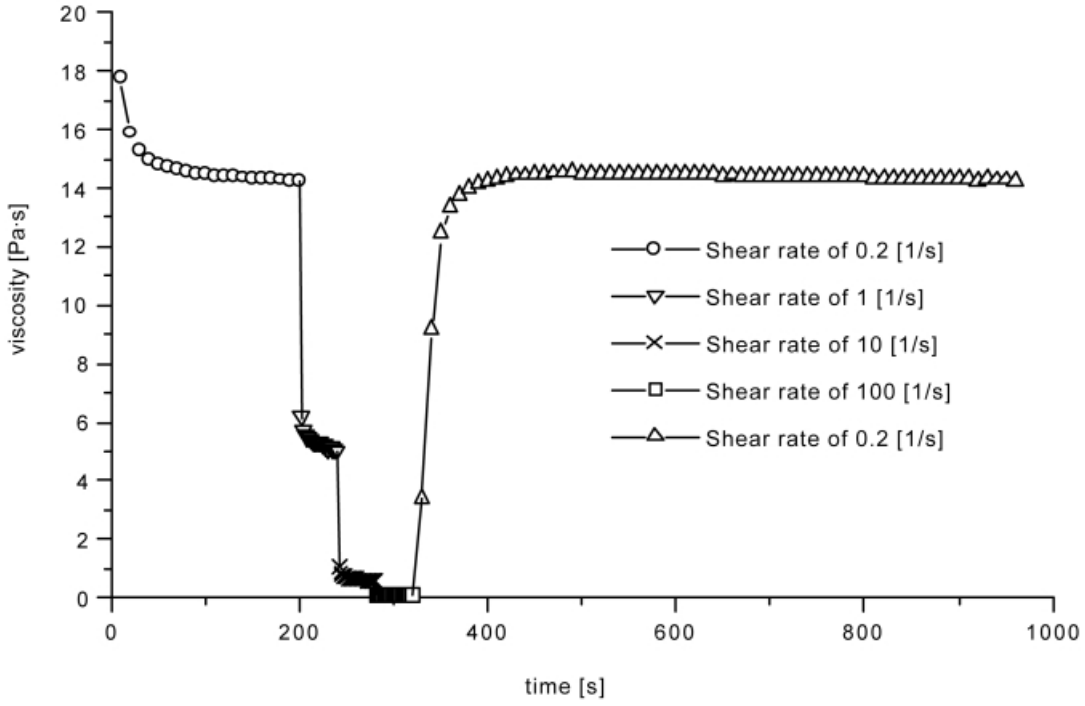



Figure 4. Shear rate dependence of the viscosity of **1** and **3** (1:4 ratio) at 5 °C

Rheologic experiments are important tools in characterising fluids. Yet, they only allow very limited insights into the structural details that are responsible for the rheologic behaviour. One method that has been successfully applied in the past is freeze fracture transmission electron microscopy.[18]

### Freeze Fracture Transmission Electron Microscopy

Freeze fracture TEM allows to display the topology of a surface generated by fracture and controlled sublimation of a matrix like water or suitable organic solvents from a solid specimen at adequate low temperatures. Since gels and similar systems are elastic or rather viscous fluids, they must be cryofixed in advance. Our first approach was a solution of the components in toluene, but unfortunately the viscous toluene solution is not well suited for the freeze fracture procedure. The quick freezing must allow the formation of an amorphous solid. Crystallization of the solvent leads to separation of the components and destruction or deformation of sensible microstructures. Toluene tends to crystallize upon freezing in melting freon.[18] Therefore we were looking for alternative solvents that allow the formation of the viscous gel-like solution and which are suitable for the freeze fracture procedure. We chose 1,2-dichlorobenzene because it allows the thickening effect and has a rather high melting point supporting amorphous freezing.

It is known, that various factors may affect the result of a freeze fracture preparation. One problem we faced was the separation phenomenon of the components upon cryofixation. The segregation of solvent and dissolved compounds may lead to the formation of an irregular network structure, that might be misinterpreted as an original structure. However, in our experiments we observed areas consisting of partly lamellar or partly hexagonal-like ordered planes (Figure 5). Careful examination of highly magnified electron micrographs showed periodical linear structures with unit distances of about 5 nm. Yet, the nature of the structure is unknown. It is not possible that these lamellar ordered aggregates are responsible for the rheologic effects, since their density is too high to be maintained throughout the solution at the actual molar concentration. However, they may be the reason for the degrading of the gel-like system. If most of the calixarene and naphthyridine needed to build up the thickening microstructure is concentrated in the dense but relatively small lamellar structures, the viscosity will be lowered.

The viscous solution is stable for many weeks if stored in the refrigerator at 5 °C or at lower temperature. At room temperature the shear thinning properties are irreversibly lost within one day and the system becomes an easy moving solution. No defined structures except one of the partner molecules are identified by Maldi-MS.

## Conclusions

The complexation experiment between the pyridine[4]arene **1** and the naphthyridine **3** in apolar solvents leads to aggregates of lesser order that has an impact on the rheologic properties of the solution. The gel-like viscous liquid shows shear thinning and thixotropic features and is thermoreversible. The ratio of the components plays an important role. No viscous solution formation is observed, if ratios other than 1:4 are applied. The viscosity is not stable at

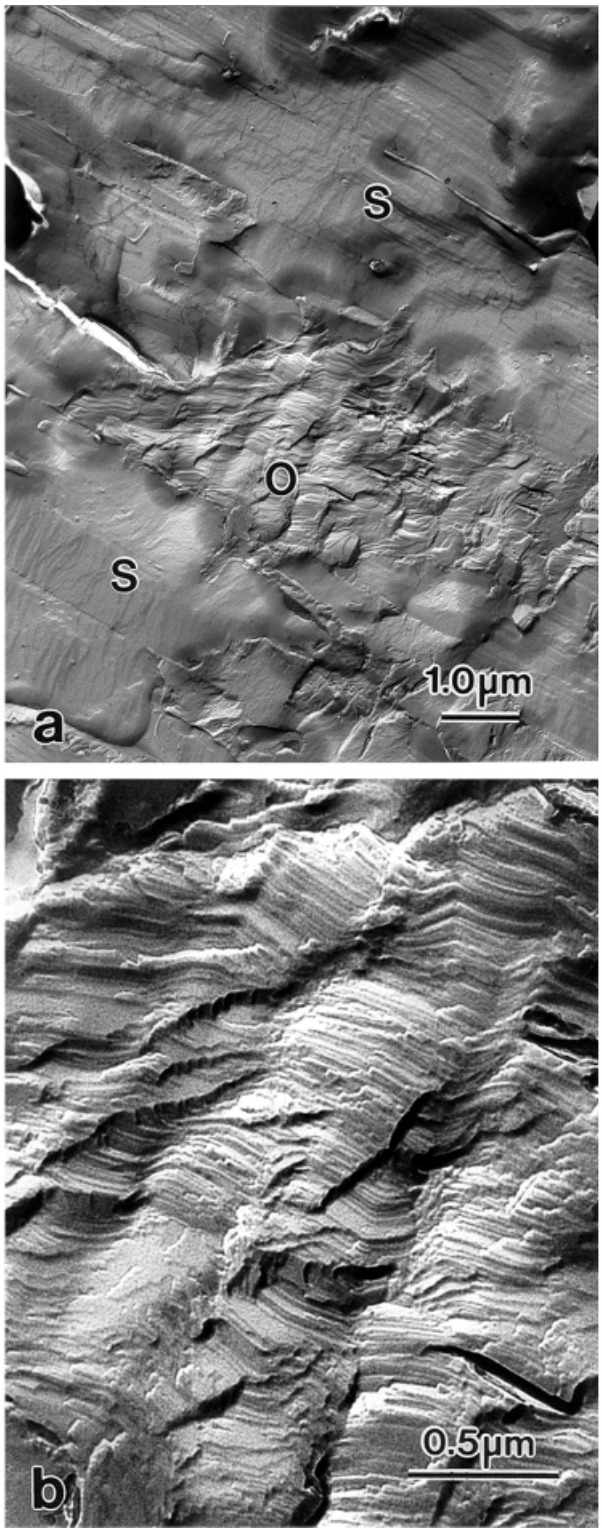



Figure 5. TEM electron micrograph of a freeze-etched 1:4 mixture of **1** and **3** in 1,2-dichlorobenzene: a: overview (O: area with ordered structure; S: solvent); b: detailed view of area O

room temperature. Eventually the thickening structure may rearrange into different aggregates which were observed by TEM. This aggregate contains dense layers of parallel molecular piles. The gel-like structure itself was not revealed in the TEM probably for reasons of segregation phenomena which covered most of the TEM records.

## Experimental Section

**General:** All chemicals and solvents were used in p.a. quality. The gel-like systems were prepared by the freeze fracture/freeze etch method:[19] Small particles (approx. 2 μL) were attached to gold specimen supports and immediately cryofixed by immersion into melting freon 22 (113 K), subsequently stored in liquid nitrogen. The freeze fracture preparation was carried out in a Balzers BA 360 M apparatus (cleavage temperature 173 K; etching time 10 min; shadowing the sample with 2 nm platinum at an angle of 45°, fortification of this layer with 20 nm of carbon). The cleaning of the replica film was achieved by repeated washing with chloroform. TEM was performed with a Philips EM 301 transmission electron microscope operating at 60 kV. Rheologic experiments were performed with a Physica UDS 200 apparatus; solvent 1,2-dichlorobenzene. Solution 1 contained 11.2 mg/ml calixarene ($1 \cdot 10^{-2}$ mol/L) and 10.7 mg/ml naphthyridine ($3 \cdot 10^{-2}$ mol/L). Solution 2 contained 5.5 mg/ml calixarene ($5 \cdot 10^{-3}$ mol/L) and 7.1 mg/ml naphthyridine ($2 \cdot 10^{-2}$ mol/L).

***rccc*-4,6,10,12,16,18,22,24-Octahydroxy-2,8,14,20-tetra-*n*-undecylpyridine[4]arene or *rccc*-2,8,14,20-Tetraundecyl-5,11,17,23-tetraazapentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15(26),16,18,21,23-dodecaen-4,6,10,12,16,18,22,24-octol (1):** A suspension of 2,6-dihydroxypyridine (8.0 g, 54.4 mmol) in glycol monoisopropyl ether (40 mL) and concd. hydrochloric acid (20 mL) was mixed with *n*-dodecanal (10.0 g, 54.4 mmol) and was heater to reflux under argon. After clearing of the solution, a wax-like yellow to red precipitate was formed within 5 h. Heating was continued for 7 d. After cooling, the raw product was filtered off, taken up in acetone (250 mL) and treated with ultrasound for 30 min. The resulting amorphous pale-yellow powder was separated and washed with acetone and ethanol. After drying and recrystallization from chloroform/ethanol, 7.15 g (6.4 mmol, 47%) of pale-yellow leafy crystals were obtained and identified as **1**. M.p. 170−172 °C. $^1$H NMR (500 MHz, $CDCl_3$ + $CF_3COOD$, 25 °C): δ = 0.89 (t, $^3J$ = 7.1 Hz, 12 H, $CH_3$), 1.10−1.50 (m, 72 H, $CH_2$), 2.14 (dt, $^3J$ = 8.0, 7.2 Hz, 8 H, $CHCH_2CH_2$), 4.27 (t, $^3J$ = 8.1 Hz, 4 H, $CH_{methine}$), 7.44 (s, 4 H, $CH_{pyridine}$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.1 ($CH_3$), 22.1 ($CH_2CH_3$), 27.7 ($CHCH_2$), 29.4, 29.55, 29.63, 29.70, 29.73, 29.75, 31.94 ($CH_2$, partial overlap), 109.8 (COHC), 117.0 ($CCOH_{pyridinediol\ tautomer}$), 136.1 ($CH_{pyridinediol\ tautomer}$), 124.0 (C=OC), 153.5 (COH), 157.8 ($COH_{pyridinediol\ tautomer}$), 163.3 (C=O) ppm. UV/Vis ($CH_2Cl_2$): λ (lg ε) = 240 (4.21), 328 (4.65) nm. IR: $\tilde{\nu}$ = 3458, 3116, 2923, 2851, 1633, 1593, 1466, 1400, 1370, 1303, 1211, 867, 608, 538 cm$^{-1}$. ESI-MS (toluene/methanol): *m*/*z* (%) = 1109.8 (100) [M$^+$], 1167.9 (8),1184.9 (5). MALDI-TOF-MS (matrix of 2,6-dihydroxybenzoic acid, ions positive): 1109 [M$^+$]. HMRMS for $C_{68}H_{109}N_4O_8$: calcd. 1109.8246; found 1109.8238.

**2-Amino-*N*$^3$-(*n*-undecyl)-1,8-naphthyridine-3-carboxamide (3):** *N*$^1$-Dodecylcyanoacetamide (1.85 g, 7.30 mmol) and pyridine (2 mL) were added to a suspension of 2-aminonicotinic aldehyde (1.00 g, 7.29 mmol) in ethanol (40 mL). Heating under reflux for 24 h followed by cooling to 5 °C yield a yellow precipitate which was recrystallised from chloroform/ethanol to give **3** (1.99 g, 62%) as yellow needles. M.p. 148−149 °C − $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.82 (dd, $^3J$ = 4.5, $^4J$ = 2.01, 1 H, 7-H), 8.17 (s, 1 H, 4-H), 7.87 (dd, $^3J$ = 8.0, $^3J$ = 2.0 Hz, 1 H, 5-H), 7.12 (dd, $^3J$ =

4.4, 7.9 Hz, 1 H, 6-H), 6.65−6.75 (br., 3 H, NH, $NH_2$), 3.45 (dt, $^3J$ = 5.5, $^2J$ = 7.3 Hz, 2 H, $NCH_2$), 1.6−1.75 (br., 2 H, $NCH_2CH_2$), 1.2−1.5 (m, 18 H, $CH_2$), 0.88 (t, $^3J$ = 6.9 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.0 (C=O), 158.5 (C-2), 157.0 (C-10), 154.6 (C-7), 137.2 (C-5), 137.1 (C-4), 118.5 (C-6), 116.7 (C-9), 116.4 (C-3), 40.2 ($NCH_2$), 31.9 ($NCH_2CH_2$), 29.7, 29.6, 29.59, 29.56, 29.53, 29.35, 29.32, 27.0 ($CH_2$, dodecyl residue), 22.7 ($CH_2CH_3$), 14.1 ($CH_3$) ppm. UV/Vis (acetone): λ (lg ε) = 238 (4.42), 268 (3.78), 363 (3.74) nm. IR: $\tilde{\nu}$ = 3389, 3150, 2920, 2847, 1643, 1558, 1516, 1479, 1432, 1208, 805.6 $cm^{-1}$. HRMS for $C_{21}H_{32}N_4O$: calcd. 356.25760; found 356.25670; for $C_{20}{}^{13}CH_{32}N_4O$: calcd. 357.26096; found 357.26030.

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