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Macrocyclic Hosts

Twisted Cucurbit[14]uril**

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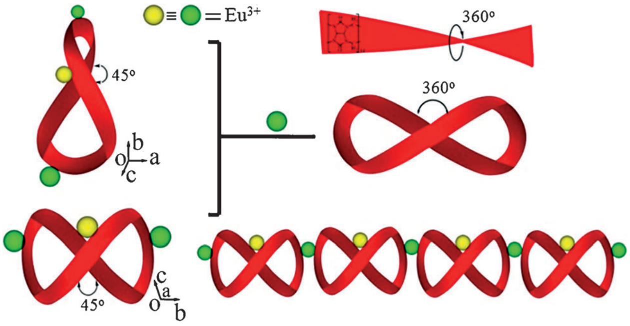
Since the structure of the cucurbituril (Q[6]), a cyclic oligomer of 6 units of glycoluril linked by 12 methylene bridges, was first determined by Mock and co-workers in 1981,[1] a series of its homologues and derivatives have been reported over the last three decades. The homologues (for example Q[5], Q[7], and Q[8]) were discovered by Day and Kim in 2000,[2] and cucurbit[10]uril (Q[10]), which includes a Q[5] molecule, was reported by Day in 2002.[3] The perhydroxylated (HO)2*n*Q[*n*] species were synthesized by direct oxidation of Q[*n*] species with $K_2S_2O_8$ and realized direct functionalization of the Q[*n*] species.[4] In recent years, Isaacs and co-workers reported the preparation of a series of oligomers of glycoluril[5] and cucurbit[*n*]uril derivatives with novel structures, such as the inverted cucurbit-[6]uril and inverted cucurbit[7]uril (*i*Q[6] and *i*Q[7]),[6] the chiral nor-seco-cucurbituril (±)-bis-ns-Q[6],[7] and the nor-seco-cucurbit[10]uril (ns-Q[10]), which results from formal extrusion of two CH_2 bridges from Q[10].[8] These new cucurbit[*n*]urils have inspired further intense interest in the chemistry of the enlarged cucurbit[n]uril family.[9] Interestingly, Q[*n*] ($n > 10$) was identified in reaction mixtures,[10] and these species have only been indicated in calculations by using the density functional theory.[11] Although Miyahara and co-workers have reported a large hemicucurbit[12]uril,[12] this does not show typical Q[*n*] properties.

Herein, we report a new member of the cucurbit[n]uril family, which we name tQ[14]. It is the largest cucurbit[*n*]uril with 14 normal glycoluril units linked by 28 methylene bridges. However, it consists of 14 units of the -glycoluril-$(CH_2)_2$- moiety with a 360° twist. As a consequence, it does not have a normal cavity like the most cucubit[*n*]urils, and has



Scheme 1. Representations of tQ[14] and the Eu^{3+}-tQ[14] complex.

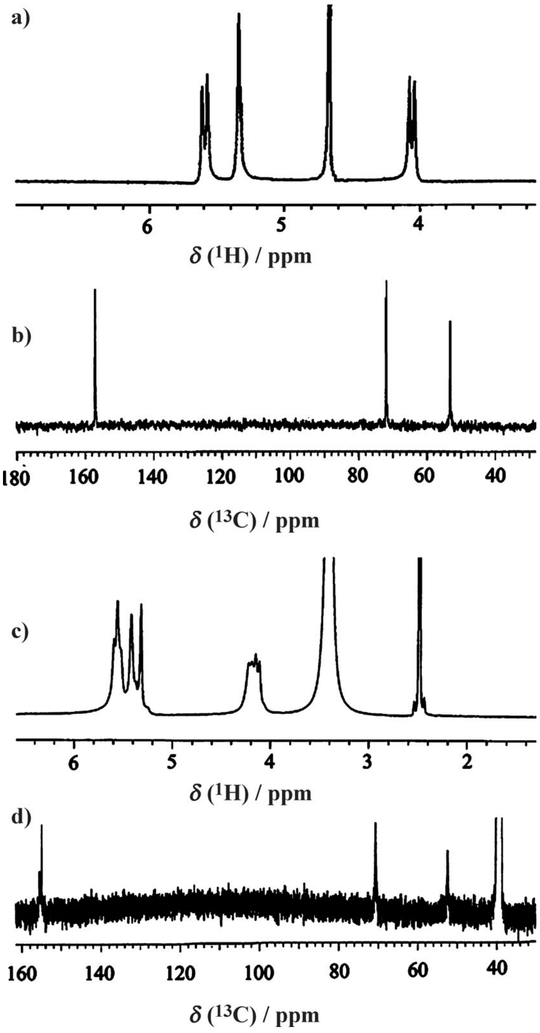


Figure 1. a, b) ^1H and ^{13}C NMR spectra of tQ[14] in D_2O; c, d) ^1H and ^{13}C NMR spectra of tQ[14] in $[D_6]DMSO$.

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the appearance of a folded, figure of-eight conformation (Scheme 1).

Using methods previously reported,[2a,b] a mixture of Q[*n*] species can be obtained by precipitating a reaction solution in methanol, and then washing the precipitate with hot water to give a water-soluble fraction that mainly consists of Q[5] and Q[7]. When we separated Q[5] and Q[7] by running a Dowex column, we obtained a white solid that was water-soluble.[13] The TLC analysis on a silica gel plate showed that this new species was different from any of the known unsubstituted Q[*n*] species (Supporting Information, Figure S1). The ^{1}H NMR spectra of this solid in D_2O is that of a typical symmetrical cucurbit[*n*]uril, having three groups of proton resonances with about 1:1:1 intensity, two doublet groups at $\delta \approx 4.0$ and $\delta \approx 5.6$, and a singlet at $\delta \approx 5.3$. Furthermore, the corresponding ^{13}C NMR spectra in D_2O shows three clear peaks, at $\delta = 53.23$, $\delta = 71.95$, and $\delta = 157.14$, (Figure 1 a,b). Generally, the cucurbit[n]urils with an odd number *n*, such as 5 and 7, are very water-soluble, while the cucurbit[n]urils with an even number *n*, such as 6, 8, and 10, are less water-soluble. Therefore, we speculated that the compound could be the missing Q[9]. By chance, we found that the new cucurbit[-*n*]uril can be dissolved in DMSO, and its ^{1}H and ^{13}C NMR spectra in [D$_6$]DMSO are quite different from those in D_2O (Figure 1 c,d). The ^{1}H NMR spectrum shows that all proton resonances are split, and the ^{13}C NMR spectrum shows two peaks from carbonyl carbon atoms, suggesting that this new Q[*n*] has an asymmetrical feature or there is a dynamic conformation process occurring around the ring in different solvents. ^{1}H NMR spectroscopy studies carried out in concentrated DCl (35 %) and NaOD (0.01 M) solutions at different temperatures revealed that this new compound is stable

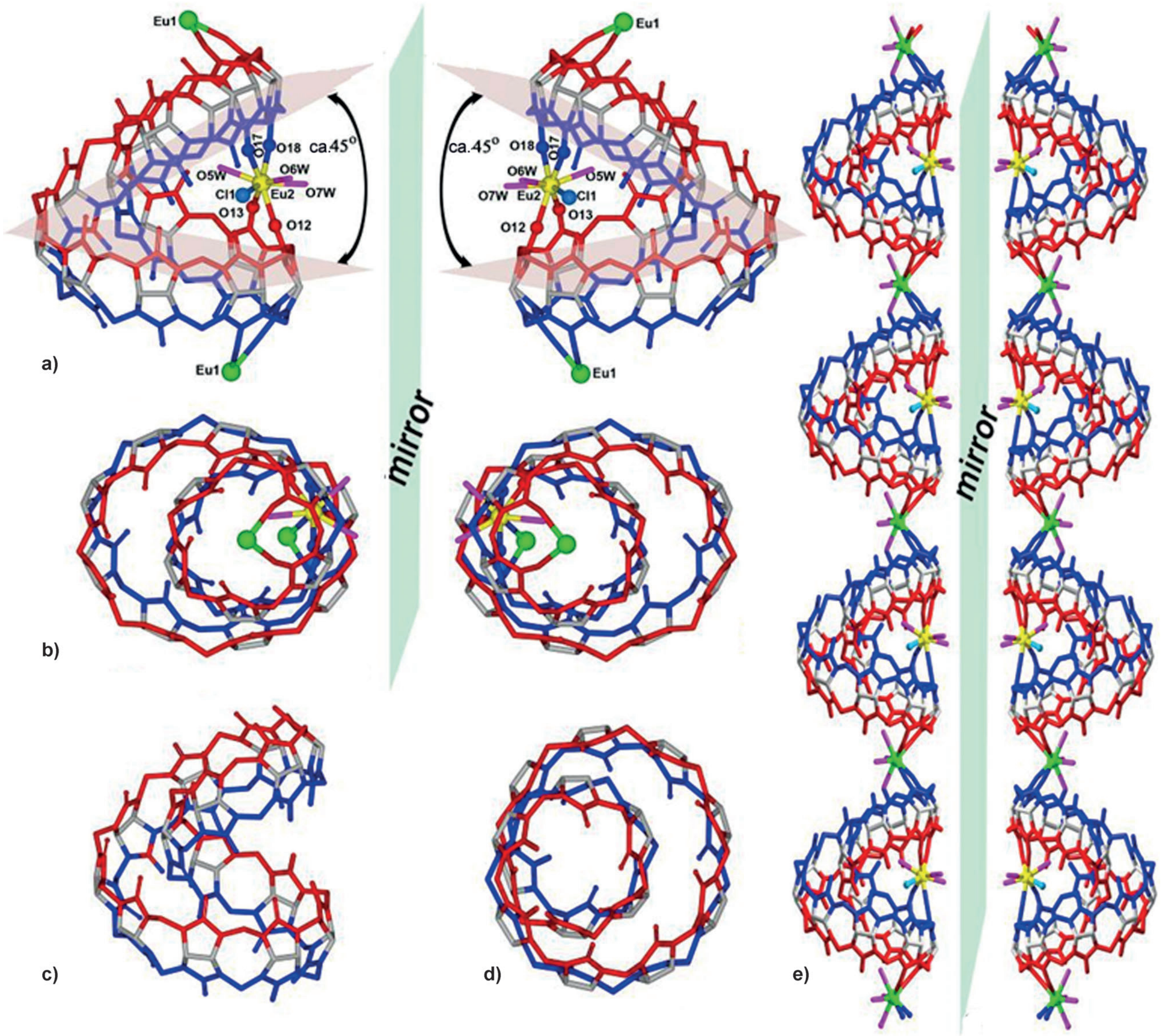

Figure 2. a) Side and b) top view of the two enantiomers of the Eu^{3+}-tQ[14] complex in the X-ray crystal structure; c) side and d) top view of tQ[14]; e) a pair of one-dimensional coordination polymers constructed by the Eu^{3+} cations and tQ[14] molecules (hydrogen atoms are omitted for clarity).

under the experimental conditions (Supporting Information, Figures S2–S5).

The host–guest interaction results reveal that the new Q[*n*] cannot include 1-aminopyrene or 1,10-phenanthroline, which can be included by Q[7] and Q[8].[14] The ^{1}H NMR spectra reveal that the resonances of these guest compounds show no change (or a slight downfield shift), suggesting at most a portal interaction between the new Q[*n*] and these guests (Supporting Information, Figures S6, S7). Further host–guest results show that the new Q[*n*] can bind guests with an alkyl chain, such as 1,12-diaminododecane, 1,ω-alkylenedi-4,4′-bipyridines, and 1,ω-alkylenedipydines (Supporting Information, Figures S8–S12). The alkyl chain, pyridine, or 4,4′-bipyridine moieties can be included in the cavities of the new Q[*n*], like Q[6],[15] suggesting that the portal size of the new Q[*n*] is larger than those of Q[5] and Q[6] but smaller than those of Q[7] and Q[8]. The related stability constant (K_a) of host–guest complexes involving with pyridine were determined to be in the range 5.98×10^3 L mol^{-1} to 1.20×10^6 L mol^{-1} (Supporting Information, Figure S13).

MALDI-TOF mass spectrometry of the new Q[*n*] gave an ion that was equivalent to a Q[14] species ($m/z = 2347$ for the Q[14]-Na ion and $m/z = 2363$ for the Q[14]-K ion; Supporting Information, Figure S14). Using a approach involving inorganic anion-induced coordination of metal ions to cucurbit[7]uril,[16] we were fortunate to obtain single crystals of the complex formed by Eu^{3+} metal ions with the new Q[14] in 6 M HCl in the presence of Eu^{3+} cation and $[CdCl_4]^{2-}$ anions. The X-ray crystal structure[17] unambiguously identifies this new Q[14] as having a twist, hence our naming as tQ[14] (Figure 2). A close inspection reveals that this Eu^{3+}-tQ[14] complex has chirality depending on the direction of the twist, there are two enantiomers of Eu^{3+}-tQ[14] in the crystal structure. The bulk sample of Eu^{3+}-tQ[14] should be a racemate of this two enantiomers, hence has no chirality (Figure 2a). Additionally, Figure 2e shows a pair of one-dimensional coordination polymers in which each tQ[14] is coordinated to three Eu^{3+} cations. Two of them (2 Eu1) are further coordinated to the two neighboring tQ[14] molecules, and interestingly, the remaining Eu2 cation coordinates to four carbonyl oxygen atoms of the two portals (O12, O13 and O17, O18) of a tQ[14] molecule (Figure 2a). This is the first observation of a metal ion coordinating to both portals of a cucurbit[*n*]uril molecule owing to the twisted connection in the tQ[14] molecule.

The single crystals of the Eu^{3+}-tQ[14] complex show a completely different ^{1}H NMR spectra from that free of metal ions, so that we thought tQ[14] might have changed into another form or decomposed during the initial stage of preparation of the single crystals in concentrated HCl (Figure 3a). However, adding $Eu(NO_3)_3$ to a D_2O solution of tQ[14] gave a similar ^{1}H NMR spectra to that of the single crystals of the Eu^{3+}-tQ[14] complex (Figure 3b,c), suggesting that interaction of the tQ[14] molecule with the metal ions is accompanied by a structural transformation, and that tQ[14] might be very flexible. The tQ[14] molecule seems to show a more symmetrical conformation when it interacts with an organic guest (Supporting Information, Figures S8–S12), but shows an asymmetrical conformation when it interacts with metal ions which have multiple positive charges, such as lanthanide metal ions (Supporting Information, Figure S15). When adding 1,12-diaminododecane HCl salt to a D_2O solution of tQ[14], it can be seen that the asymmetrical ^{1}H NMR spectra of the Eu^{3+}-tQ[14] complex changes gradually into a symmetrical ^{1}H NMR spectra, similar to the normal Q[*n*] (Supporting Information, Figure S16). More interestingly, tQ[14] seems to prefer to include the 4,4,-bispyridine moieties of the 1,6-di(4,4′-bipyridine) guest in [D$_6$]DMSO, while the 4,4,-bipyridine moieties are at the outside of the portals of tQ[14] in D_2O (Supporting Information, Figures S11, S12), suggesting that tQ[14] shows different binding properties in water and organic solvents. Since the discovery and the development of large-ring cyclodextrin molecules (LR-CDs),[18] many exciting results have been demonstrated and reported in the last two decades.[19] From a structural viewpoint, it is therefore believed that some unique supramolecular behavior by tQ[14] can be expected.

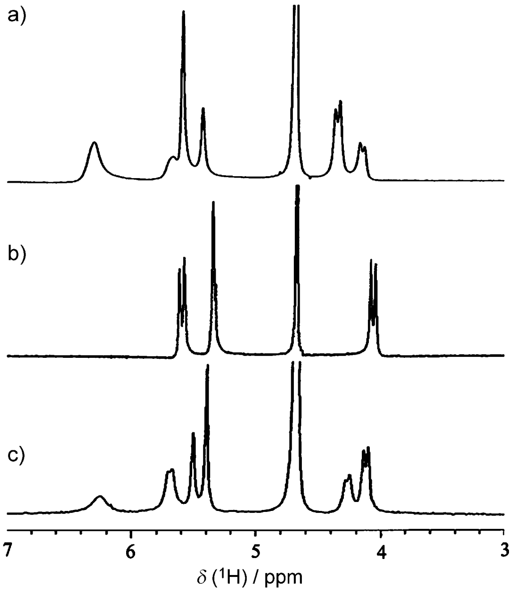

Figure 3. ^{1}H NMR spectra (400 MHz, D_2O, 25 °C) of a) the Eu^{3+}-tQ[14] complex; b) tQ[14]; and c) in the presence of about 2.0 equiv of $Eu(NO_3)_3$.

In summary, we have isolated and characterized the largest cucurbit[14]uril of the cucurbit[*n*]uril family. Although it does not have the largest portal sizes and cavity volume, which is due to the twisted connection in the twisted cucurbit[14]uril molecule, the discovery of tQ[14] provide the important information that larger oligomers and the corresponding cucurbit[n>10]urils could exist in processes of a normal Q[*n*]-synthesis. Moreover, the tQ[14] molecule shows many special properties, such as the structural flexibility, which could be adjusted by binding to organic molecules or metal ions; good solubility in water and organic solvents (DMSO, DMF); and chirality and different selectivity for the moieties of a guest in the different solvents. More detailed host–guest chemistry and coordination chemistry of tQ[14] are currently undergoing.

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[1] W. A. Freeman, W. L. Mock, N. Y. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 7367–7368.

[2] a) A. I. Day, A. P. Arnold, R. J. Blanch (Unisearch Limited, Australia), PCT Int. Appl., **2000**, WO2000–2000AU412 20000505, 112 (Priority: AU 99–232 19990507); b) J. Kim, I. S. Jung, S. Y. Kim, E. Lee, J. K. Kang, S. Sakamoto, K. Yamaguchi, K. Kim, *J. Am. Chem. Soc.* **2000**, *122*, 540–541.

[3] A. I. Day, R. J. Blanch, A. P. Arnold, S. Lorenzo, G. R. Lewis, I. Dance, *Angew. Chem.* **2002**, *114*, 285–287; *Angew. Chem. Int. Ed.* **2002**, *41*, 275–277.

[4] S. Y. Jon, N. Selvapalam, D. H. Oh, J.-K. Kang, S.-Y. Kim, Y. J. Jeon, J. W. Lee, K. Kim, *J. Am. Chem. Soc.* **2003**, *125*, 10186–10187.

[5] a) Y. J. Zhao, S. F. Xue, Q. J. Zhu, Z. Tao, J. X. Zhang, Z. B. Wei, L. S. Long, M. L. Hu, H. P. Xiao, A. I. Day, *Chin. Sci. Bull.* **2004**, *49*, 1111–1116; b) W. H. Huang, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2008**, *130*, 8446–8454.

[6] W. H. Huang, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2005**, *127*, 18000–18001.

[7] W. H. Huang, P. Y. Zavalij, L. Isaacs, *Angew. Chem.* **2007**, *119*, 7569–7571; *Angew. Chem. Int. Ed.* **2007**, *46*, 7425–7427.

[8] W. H. Huang, S. M. Liu, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2006**, *128*, 14744–14745.

[9] Reviews: a) I. Ghosh, W. M. Nau, *Adv. Drug Delivery Rev.* **2012**, *64*, 764–783; b) A. I. Day, J. G. Collins, *Supramol. Chem.* **2012**, *3*, 983–1000; c) E. Masson, X. X. Ling, R. Joseph, L. Kyeremeh-Mensah, X. Y. Lu, *RSC Adv.* **2012**, *2*, 1213–1247; d) A. Ayitou, B. C. Pemberton, E. Kumarasamy, N. Vallavoju, J. Sivaguru, *Chimia* **2011**, *65*, 202–209; e) V. Sindelar, S. Silvi, S. E. Parker, D. Sobransingh, A. E. Kaifer, *Adv. Funct. Mater.* **2007**, *17*, 694–701; f) K. Kim, N. Selvapalam, Y. H. Ko, K. M. Park, D. Kim, J. Kim, *Chem. Soc. Rev.* **2007**, *36*, 267–279; g) J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, *Angew. Chem.* **2005**, *117*, 4922–4949; *Angew. Chem. Int. Ed.* **2005**, *44*, 4844–4870; h) O. A. Gerasko, M. N. Sokolov, V. P. Fedin, *Pure Appl. Chem.* **2004**, *76*, 1633–1646; i) M. N. Sokolov, D. N. Dybtsev, V. P. Fedin, *Russ. Chem. Bull.* **2003**, *52*, 1041–1060; j) K. Kim, *Chem. Soc. Rev.* **2002**, *31*, 96–107; k) W. L. Mock, *Compr. Supramol. Chem.* **1996**, *2*, 477–493.

[10] a) N. J. Wheate, A. I. Day, R. J. Blanch, J. G. Collins, *PCT Int. Appl.* **2005**, *63*, 2005068469; b) K. Kim, D. Kim, J. W. Lee, Y. H. Ko, K. Kim, *Chem. Commun.* **2004**, 848–849; c) Q. An, G. T. Li, C. Tao, Y. Li, Y. Wu, W. Zhang, *Chem. Commun.* **2008**, 1989–1991; d) A. I. Day, A. P. Arnold, R. J. Blanch, B. Snushall, *J. Org. Chem.* **2001**, *66*, 8094–8100.

[11] S. R. Peerannawar, V. V. Gobre, S. P. Gejji, *Comput. Theor. Chem.* **2011**, *966*, 154–158.

[12] Y. Miyahara, K. Goto, M. Oka, T. Inazu, *Angew. Chem.* **2004**, *116*, 5129–5132; *Angew. Chem. Int. Ed.* **2004**, *43*, 5019–5022.

[13] A mixture of glycoluril (50 g, 0.35 mol), paraformaldehyde (26.2 g, 0.86 mol), and conc. HCl (100 mL) was stirred at room temperature for 1 h and then heated at 100 °C for 6 h. The resulting solution was cooled to room temperature and precipated by pouring into MeOH (700 mL) to yield a crude pale yellow solid. The residue was redissolved by boiling water 3 to 4 times (200 mL). The filtrate was collected by filtered and evaporated to give the crude solid, which contains Q[5] and Q[7] as major products, Q[5]@Q[10], tQ[14] and a small amount of unknown solid as minor products. Purification of the mixture was achieved by chromatography on a Dowex 50W × 2–400(H) column equilibrated with 1:1 acetic acid/water. The sample (ca. 27 g) was loaded onto the column (5 cm (Ø) × 75 cm), eluting with an eluent (1:1 acetic acid/water (v/v) with an increase of HCl from 0.01 to 2 M during the eluting process) to yield white solid tQ[14] (0.86 g, 1.2 %). It should be noted that the eluting period could last at least three months based on 12 h column running time per day. M.p.: > 300 °C. IR (KBr): $\tilde{\nu} = 1728, 1476, 1423, 1385, 1243, 1237\ \text{cm}^{-1}$. ^{1}H NMR (400 MHz, D_2O): $\delta = 5.62$ (d, $J = 9.2$, 28 H), 5.33 (s, 28 H), 4.03 ppm (d, $J = 9.2$, 28 H). ^{13}C NMR(100 MHz, D_2O): $\delta = 157.14, 71.95, 53.23$ ppm. MS *m*/*z*: 2347 $[M+\text{Na}]^+$. The solubility of tQ[14] in a solvent was determined by ^{1}H NMR spectra. Solubility of tQ[14]: $4.1 \times 10^{-2}\ \text{mol}\,\text{L}^{-1}$ in D_2O, $1.8 \times 10^{-2}\ \text{mol}\,\text{L}^{-1}$ in $[D_6]$DMSO.

[14] a) V. Sindelar, M. A. Cejas, F. M. Raymo, A. E. Kaifer, *New J. Chem.* **2005**, *29*, 280–282; b) H. Y. Fu, S. F. Xue, L. Mu, Y, Du, Q. J. Zhu, Z. Tao, J. X. Zhang, *Sci. China Ser. B* **2005**, *48*, 305–314.

[15] a) J. M. Yi, S. F. Xue, Z. Tao, *Chem. J. Chin. Univ.* **2012**, *9*, 1973–1977; b) X. Xiao, L. He, Z. Tao, S. F. Xue, Q. J. Zhu, A. I. Day, *Supramol. Chem.* **2010**, *22*, 194–201.

[16] L. L. Liang, X. L. Ni, K. Chen, Y. Q. Zhang, C. Redshaw, Q. J. Zhu, S. F. Xue, Z. Tao, *Inorg. Chem.* **2013**, *52*, 1909–1915.

[17] Crystal data: colorless parallelepipeds $0.30 \times 0.15 \times 0.15\ \text{mm}^3$, $[Eu_2(H_2O)_7{\cdot}Cl{\cdot}tQ[14]]{\cdot}5\,Cl\,66\,H_2O$, $M_r = 4157.70$, triclinic, space group $P\bar{1}$, $a = 15.378(2)$, $b = 18.510(3)$, $c = 29.066(4)$ Å, $\alpha = 96.448(5)$, $\beta = 96.450(6)$, $\gamma = 98.667(5)°$, $V = 8055.9(19)$ Å^3, $Z = 2$, $\rho_{\text{calcd}} = 1.714\ \text{g}\,\text{cm}^{-3}$, $T = 223$ K, Bruker-AXS SMART CCD diffractometer, $\text{Mo}_{K\alpha}$ ($\lambda = 0.71073$ Å), $\mu = 1.002\ \text{cm}^{-1}$, 95645 reflections measured for $\theta \leq 23°$, R_1 $(I > 2\sigma(I)) = 0.0792$. A number (66) of the water molecules in the unit cell have been taken into account to SQUEEZE option of the PLATON program, but the Eu^{3+}-tQ[14] complex is well-defined. CCDC 913620 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.

[18] a) J. Jacob, K. Gessler, D. Hoffmann, H. Sanbe, K. Koizumi, S. M. Smith, T. Takaha, W. Saenger, *Angew. Chem.* **1998**, *110*, 626–629; *Angew. Chem. Int. Ed.* **1998**, *37*, 605–609; b) K. Gessler, I. Uson, T. Takaha, N. Krauss, S. M. Smith, S. Okada, G. M. Sheldrick, W. Saenger, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4246–4251.

[19] a) K. L. Larsen, *J. Inclusion Phenom. Macrocyclic Chem.* **2002**, *43*, 1–13; b) M. E. Brewstera, T. Loftssonb, *Adv. Drug Delivery Rev.* **2007**, *59*, 645–666.