Molecular Machines

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A Ca^{2+}-, Mg^{2+}-, and Zn^{2+}-Based Dendritic Contractile Nanodevice with Two pH-Dependent Motional Functions

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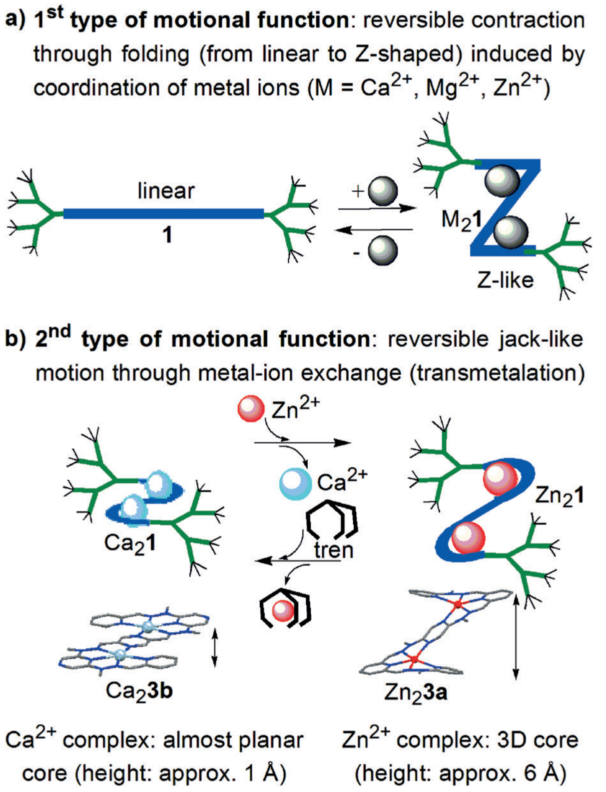
In memory of Areta Măcelaru

Abstract: *A contractile dendritic motional device is reported where metal ions with biological importance—Ca^{2+} (the main regulatory and signaling species of the natural muscles), Mg^{2+}, and Zn^{2+}—initiate two kinds of motional functions. The first motional function is the metal-ion-induced contraction of a linear strand into a Z-shaped dinuclear complex, and the second one is the change of the height of Z-shaped complexes via transmetalation. By means of the pH-dependent counter-ligand tren, the two motional features of the machine can depend on alternate additions of acid and base. An optical response is associated with the conversion of the linear form (which is yellow) into the metalated Z-shaped one (which is red).*

The contraction of muscle fibers is induced by Ca^{2+}, which is the main regulatory and signaling species in the machines of everyday life, the muscles.[1] Mg^{2+} also plays important biological roles[2] including formation of Mg-ATP and influencing muscle contraction. In parallel, much interest has been focused on artificial nanomachines, including chemical molecular machines.[3] Nevertheless, Ca^{2+}- and Mg^{2+}-based synthetic molecular machines are poorly represented to date. We report herein a pH-modulable contractile dendrimer, in which contraction/extension motions are induced, through a mechanism that differs from that of natural muscles, by metal ions of biological importance (Ca^{2+}, Mg^{2+}, and Zn^{2+}).

Moreover, while most molecular machines can perform (generally reversibly) only one type of controlled motion, the dynamic device reported herein can successively accomplish two[4] different kinds of controlled motional functions:

1) A metal-ion-induced reversible contraction[5] of a linear strand into a Z-like dinuclear complex, which includes the motion of one end with respect to another with significant amplitude, along with a shape change of the whole dendrimer (Figure 1 a).
2) A reversible jack-like motion between almost planar and three-dimensional Z-shaped units, consisting of a height change induced by the displacement of Ca^{2+} by Zn^{2+} (Figure 1 b).


a) 1st type of motional function: reversible contraction through folding (from linear to Z-shaped) induced by coordination of metal ions (M = Ca^{2+}, Mg^{2+}, Zn^{2+})

b) 2nd type of motional function: reversible jack-like motion through metal-ion exchange (transmetalation)

Ca^{2+} complex: almost planar core (height: approx. 1 Å)

Zn^{2+} complex: 3D core (height: approx. 6 Å)

Figure 1. Representation of the two types of motional functions of the molecular machine[3] reported herein. a) Type 1: reversible contraction; b) Type 2: reversible jack-like motion.

In this way the nature of the motional function is controlled. One can also control the occurrence of the motion by acid and base triggers, by means of a pH-dependent enveloping ligand that releases metal ions on protonation. This multiple modulation of the motion is of importance for functional nanomaterials with controllable mechanical properties. In addition, this device is amongst the few types of dendritic[6] mechanical molecular machines[3j,6a–f] reported to date.

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Ligand **1** (Figure 2) was synthesized in 16 steps (for an overview of the synthesis, see Scheme 1; for details see the Supporting Information (SI) pp. S2–S11, S47–S75) and it consists of a heterocyclic part and two second-generation Fréchet-type dendrons,[7] which amplify the heterocyclic core and improve the solubility. Due to its design based on the choice and placement of the hydrazone-connected[8a] 2,5- and 2,6-disubstituted pyrazine units, and to the *anti* orientation[4b,9] of N(sp^2) atoms, the core of dendrimer **1** adopts a linear conformation, as suggested by its ROESY NMR spectrum (SI p. S9) and by the X-ray structures (Figure 3 a) of model molecules **2a** and **2b** (SI pp. S1, S41–S46).

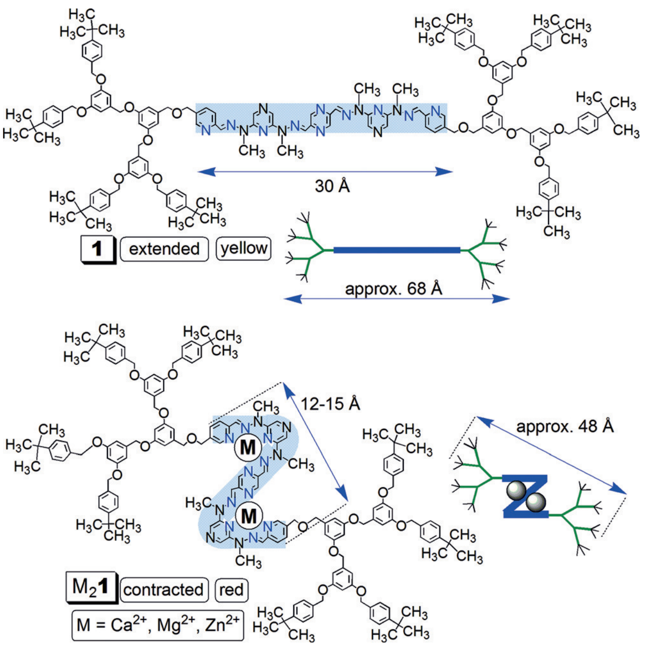
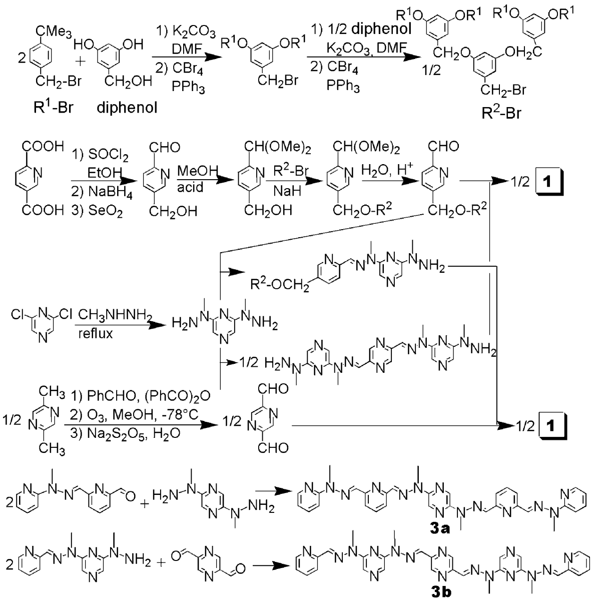


Figure 2. Structural formulae of ligand **1** and of the corresponding complexes M_2**1**. The 4+ charge of the complexes is not represented; distances noted on the formulae are rounded centroid-to-centroid C–C distances; the sizes of the whole dendrimers were estimated roughly. See also SI p. S40.



Scheme 1. Overview of the synthesis of compounds **1**, **3 a**, and **3 b** (see SI pp. S2–S11, S47–S80).

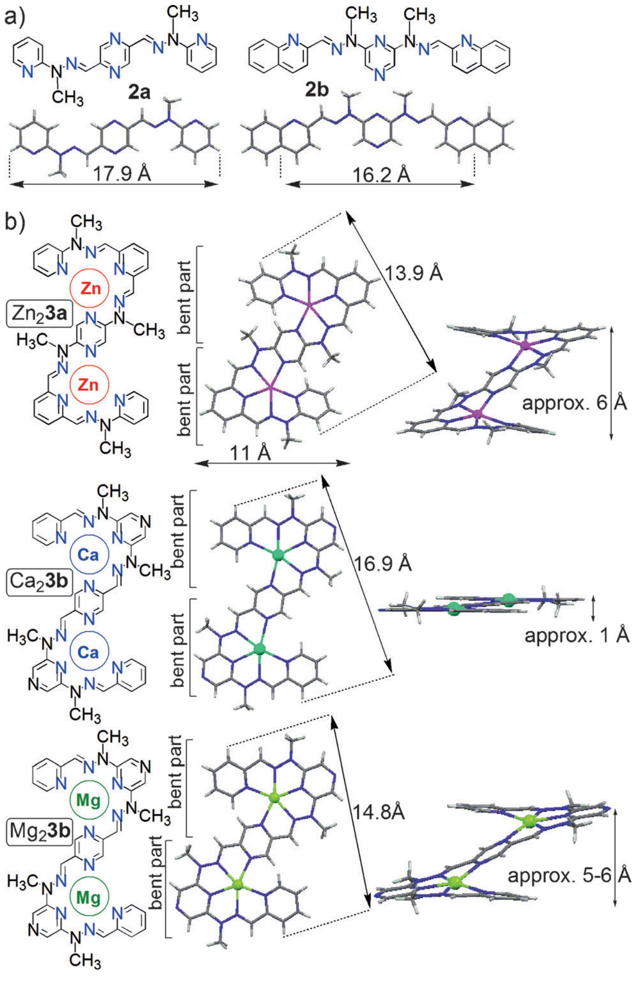


Figure 3. X-ray structures of a) molecules **2a** and **2b** (which are models for the linear part of ligand **1**) and b) complexes Zn_2**3a**, Ca_2**3b**, and Mg_2**3b** (which are models for the core of dendritic complexes M_2**1**). Anions and water and solvent molecules were omitted for clarity; distances are centroid-to-centroid distances; heights are approximate, rounded values. See also SI pp. S26–S34 and S41–S46.

On reaction with metal ions (Ca^{2+}, Mg^{2+}, Zn^{2+} as their triflates), the two 2,6-dihydrazonepyrazine units produce two bent or helical metalated[10] motifs that are connected, through the central 2,5-disubstituted pyrazine unit, like the two halves of the letter Z (Figure 3b). The Z-shape of the metalated ionic core is suggested by ROESY NMR spectra (SI pp. S14, S19, S22, S25) and by the X-ray structures of model compounds Zn_2**3a**, Ca_2**3b**, and Mg_2**3b** (charges are omitted for simplicity; see Figure 3b and SI pp. S26–S34). For the formation of Zn_2**1** complex 3–4 equiv of Zn triflate were added. While Ca_2**1** and Mg_2**1** form upon addition of 4–5 equiv of the metal ion, higher quantities (up to 12–18 equiv) were added to make sure the equilibrium was shifted. The complexation produces a color change from yellow (**1**) to red (M_2**1**). This metal-ion-induced linear-into-Z conversion corresponds to a motion of contraction of an average amplitude of about 17 Å.

A subsequent extension (M_2**1**→**1**; Figure 4) was performed via complexation of the M^{2+} ion by the tren ligand[4b] $N(CH_2CH_2NH_2)_3$, a competing ligand that coordinates more strongly than **1** (1.1–1.3 equiv tren per metal ion). At this stage, the pH-dependence of tren can render the molecular machine[3] responsive to pH changes. Indeed, addition of triflic acid (theoretically 3 equiv of acid per equiv of tren, but in practice one adds about 70–80 % of the required quantity of acid, and the final amount is determined by NMR titration) results in protonation of tren and formation of the complex M_2**1** (contraction, Figure 4). Addition of base (Et_3N, 1.1–1.5 equiv per equiv of acid) produces the free ligand **1** (extension). The process was followed by NMR spectroscopy (Figure 4 and SI pp. S35, S36, S38).

This first motional function is completed by a second one generated by transmetalation. The ionic radii[8b] (in Å) of the metal ions used herein are: 0.72 (Mg^{2+}), 0.74 (Zn^{2+}) and 1.00 (Ca^{2+}). The Z-shaped complexes induced by Mg^{2+} and Zn^{2+} have, according to X-ray structures of model complexes (Figure 3b), a height of about 5–6 Å, while that induced by Ca^{2+} has a height of about 1 Å. Here, the quantitative replacement of Ca^{2+} by Zn^{2+} (molar ratio Ca/Zn = 2–2.5) has an effect on the nanomechanical properties of the complex. Through this transmetalation, a jack-like motion occurs where the height of the heterocyclic core changes with an amplitude of about 4–5 Å (Figures 1b, 3b, and 5). After displacement of Ca^{2+} by Zn^{2+}, complex Ca_2**1** was restored by addition of tren. Subsequent addition of acid, then of base (Figure 5) as described before, modulated the second type of motional function. Zn^{2+} can also displace Mg^{2+} in the pH-modulable way (SI p. S39) but, according to X-ray structures of models (Figure 3b), without remarkable change of the height. In the mixtures containing Ca^{2+} or Mg^{2+}, degradation of ligand **1** occurs over time.

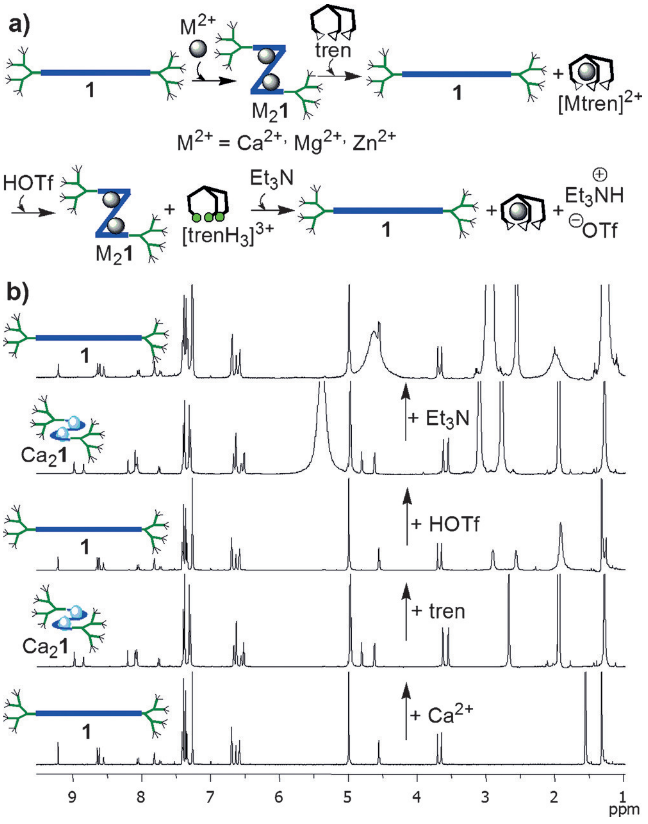


Figure 4. a) Sequence of reactions corresponding to reversible contraction/extension motions between **1** and M_2**1** ($M = Ca^{2+}, Mg^{2+}, Zn^{2+}$). Tren is used as competing pH-dependent ligand, and triflic acid and triethylamine are used as pH triggers. b) ^1H NMR spectra (400 MHz; $CDCl_3$ for ligand **1** and CD_3CN for complex Ca_2**1**) corresponding to the sequence from (a) for $M = Ca^{2+}$. See also SI pp. S35, S36, and S38.

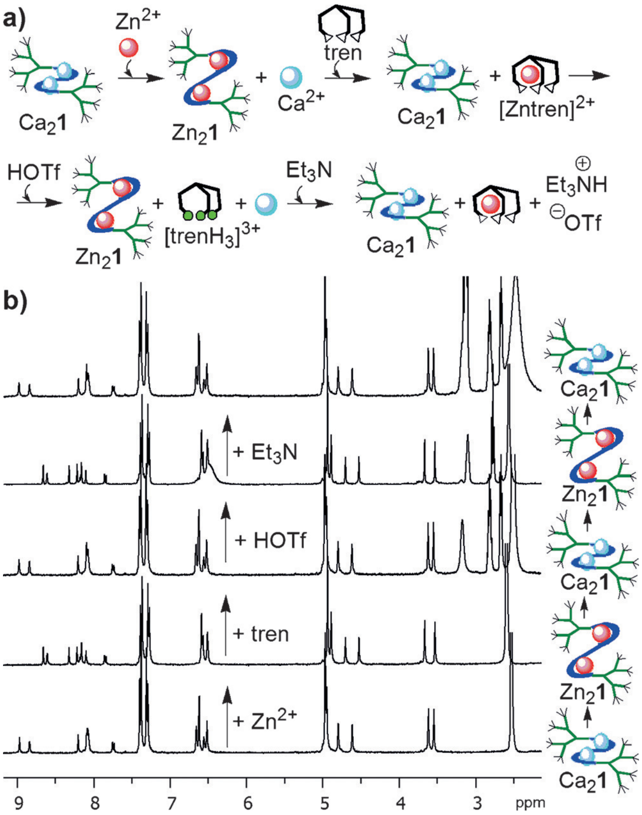


Figure 5. a) Sequence of reactions corresponding to the reversible jack-like motions between Ca_2**1** and Zn_2**1**. b) ^1H NMR spectra (400 MHz, CD_3CN) corresponding to the sequence from (a). See also SI p. S37.

In conclusion, we have developed an unprecedented nanomechanical Ca^{2+}-, Mg^{2+}-, and Zn^{2+}-based dendritic switch-type motional device[3] with two levels of control of the motional function. One level of control concerns the mode of motion: a) a change in length (average amplitude of about 17 Å) through reversible metal-ion-induced contraction of a linear to a Z-shaped structure accompanied by different optical responses associated with the extended (yellow) and contracted (red) states and b) a change in the height of the Z-shaped complexes (amplitude of about 4–5 Å) through transmetalation. The second level of control concerns the triggering of the motion, where the use of a pH-dependent counter-ligand (tren) makes both above motional functions responsive[11] to alternate additions of acid and base, that is, controllable via pH changes. This novel molecular device offers potential for the design of artificial molecular muscles[12] and other molecular machines.[3]

Experimental Section

The CIF files for this article have been deposited at the Cambridge Crystallographic Data Centre, and they have been assigned the following deposition numbers: CCDC 1041754 (**2a**), 1062153 (**2b**), 1041755 (Zn_2**3a**), 1047076 (Ca_2**3b**), and 1050603 (Mg_2**3b**).

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[1] a) M. W. Berchtold, H. Brinkmeier, M. Müntener, *Physiol. Rev.* **2000**, *80*, 1215–1265; b) M. Endo, *Physiol. Rev.* **2009**, *89*, 1153–1176; For calcium-depended spring-like motions of titin (a giant protein from skeletal and cardiac muscles), see: c) H. Granzier, S. Labeit, *J. Physiol.* **2002**, *541*, 335–342; d) C. A. Opitz, M. Kulke, M. C. Leake, C. Neagoe, H. Hinssen, R. J. Hajjar, W. A. Linke, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12688–12693; e) D. Labeit, K. Watanabe, C. Witt, H. Fujita, Y. Wu, S. Lahmers, T. Funck, S. Labeit, H. Granzier, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 13716–13721; f) M. M. LeWinter, Y. Wu, S. Labeit, H. Granzier, *Clin. Chim. Acta* **2007**, *375*, 1–9.

[2] a) W. J. Fawcett, E. J. Haxby, D. A. Male, *Br. J. Anaesth.* **1999**, *83*, 302–320; b) F. I. Wolf, A. Cittadini, *Mol. Aspects Med.* **2003**, *24*, 3–9; c) W. Jahnen-Dechent, M. Ketteler, *Clin. Kidney J.* **2012**, *5*, i3–i14.

[3] For a selection of reviews on molecular machines, see: a) V. Balzani, A. Credi, F. M. Raymo, J. F. Stoddart, *Angew. Chem. Int. Ed.* **2000**, *39*, 3348–3391; *Angew. Chem.* **2000**, *112*, 3484–3530; b) special issue on *molecular machines*, *Acc. Chem. Res.* **2001**, *34*, 409–522; c) G. S. Kottas, L. I. Clarke, D. Horinek, J. Michl, *Chem. Rev.* **2005**, *105*, 1281–1376; d) K. Kinbara, T. Aida, *Chem. Rev.* **2005**, *105*, 1377–1400; e) E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem. Int. Ed.* **2007**, *46*, 72–191; *Angew. Chem.* **2007**, *119*, 72–196; f) A. Coskun, M. Banaszak, R. D. Astumian, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.* **2012**, *41*, 19–30; g) J. M. Abendroth, O. S. Bushuyev, P. S. Weiss, C. J. Barrett, *ACS Nano* **2015**, *9*, 7746–7768; h) E. R. Kay, D. A. Leigh, *Angew. Chem. Int. Ed.* **2015**, *54*, 10080–10088; *Angew. Chem.* **2015**, *127*, 10218–10226; i) B. Champin, P. Mobian, J.-P. Sauvage, *Chem. Soc. Rev.* **2007**, *36*, 358–366; j) As used herein, "molecular machine" has a meaning that includes switches and molecular motors; see Ref. [3e], p. 74.

[4] For dual motion (rotation and twisting) in a double helicate, see: a) S. Yamamoto, H. Iida, E. Yashima, *Angew. Chem. Int. Ed.* **2013**, *52*, 6849–6853; *Angew. Chem.* **2013**, *125*, 6987–6991; For coupled motions of contraction and extension, see: b) A.-M. Stadler, J.-M. P. Lehn, *J. Am. Chem. Soc.* **2014**, *136*, 3400–3409; For simultaneous rotation and reversible contraction, see: c) H. Li, X. Li, Z.-Q. Cao, D.-H. Qu, H. Ågren, H. Tian, *ACS Appl. Mater. Interf.* **2014**, *6*, 18921–18929; For coupling of motions, see: d) T. Muraoka, K. Kinbara, T. Aida, *Nature* **2006**, *440*, 512–515.

[5] For examples of partial or total extension/contraction or contraction/extension motions, see: a) O.-S. Jung, Y. J. Kim, Y.-A. Lee, J. K. Park, H. K. Chae, *J. Am. Chem. Soc.* **2000**, *122*, 9921–9925; b) E. Yashima, K. Maeda, O. Sato, *J. Am. Chem. Soc.* **2001**, *123*, 8159–8160; c) M. Barboiu, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5201–5206; d) M. Barboiu, G. Vaughan, N. Kyritsakas, J.-M. Lehn, *Chem. Eur. J.* **2003**, *9*, 763–769; e) A.-M. Stadler, N. Kyritsakas, J.-M. Lehn, *Chem. Commun.* **2004**, 2024–2025; f) E. Berni, B. Kauffmann, C. Bao, J. Lefeuvre, D. M. Bassani, I. Huc, *Chem. Eur. J.* **2007**, *13*, 8463–8469; g) H.-J. Kim, E. Lee, H.-s. Park, M. Lee, *J. Am. Chem. Soc.* **2007**, *129*, 10994–10995; h) T. Hashimoto, T. Nishimura, J. M. Lim, D. Kim, H. Maeda, *Chem. Eur. J.* **2010**, *16*, 11653–11661; i) A.-M. Stadler, J. Ramirez, J. M. Lehn, *Chem. Eur. J.* **2010**, *16*, 5369–5378; j) Y. Ferrand, Q. Gan, B. Kauffmann, H. Jiang, I. Huc, *Angew. Chem. Int. Ed.* **2011**, *50*, 7572–7575; *Angew. Chem.* **2011**, *123*, 7714–7717; k) M. Numata, D. Kinoshita, N. Hirose, T. Kozawa, H. Tamiaki, Y. Kikkawa, M. Kanesato, *Chem. Eur. J.* **2013**, *19*, 1592–1598; l) M. Shibata, S. Tanaka, T. Ikeda, S. Shinkai, K. Kaneko, S. Ogi, M. Takeuchi, *Angew. Chem. Int. Ed.* **2013**, *52*, 397–400; *Angew. Chem.* **2013**, *125*, 415–418; m) D. Bléger, T. Liebig, R. Thiermann, M. Maskos, J. P. Rabe, S. Hecht, *Angew. Chem. Int. Ed.* **2011**, *50*, 12559–12563; *Angew. Chem.* **2011**, *123*, 12767–12771.

[6] a) C. J. Gabriel, J. R. Parquette, *J. Am. Chem. Soc.* **2006**, *128*, 13708–13709; b) K. C.-F. Leung, P. M. Mendes, S. N. Magonov, B. H. Northrop, S. Kim, K. Patel, A. H. Flood, H.-R. Tseng, J. F. Stoddart, *J. Am. Chem. Soc.* **2006**, *128*, 10707–10715; c) V. Percec, J. G. Rudick, M. Peterca, P. A. Heiney, *J. Am. Chem. Soc.* **2008**, *130*, 7503–7508; d) A. Ossenbach, H. Rüegger, A. Zhang, K. Fischer, A. D. Schlüter, M. Schmidt, *Macromolecules* **2009**, *42*, 8781–8793; e) V. Percec, M. R. Imam, M. Peterca, P. Leowanawat, *J. Am. Chem. Soc.* **2012**, *134*, 4408–4420; f) J. W. Lee, K. Kim, *Top. Curr. Chem.* **2003**, *228*, 111–140; g) D. Astruc, E. Boisselier, C. Ornelas, *Chem. Rev.* **2010**, *110*, 1857–1959.

[7] a) C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647; b) A. P. H. J. Schenning, J.-D. Arndt, M. Ito, A. Stoddart, M. Schreiber, P. Siemsen, R. E. Martin, C. Boudon, J.-P. Gisselbrecht, M. Gross, V. Gramlich, F. Diederich, *Helv. Chim. Acta* **2001**, *84*, 296–333.

[8] For molecular devices involving hydrazones, see: a) X. Su, I. Aprahamian, *Chem. Soc. Rev.* **2014**, *43*, 1963–1981; Radii values for hexacoordinated ions according to: b) R. D. Shannon, *Acta Cryst.* **1976**, *A32*, 751–767.

[9] a) K. M. Gardinier, R. G. Khoury, J.-M. Lehn, *Chem. Eur. J.* **2000**, *6*, 4124–4131; b) J.-L. Schmitt, A.-M. Stadler, N. Kyritsakas, J.-M. Lehn, *Helv. Chim. Acta* **2003**, *86*, 1598–1624.

[10] For reviews on metallofoldamers, see: a) G. Maayan, *Eur. J. Org. Chem.* **2009**, 5699–5710; b) *Metallofoldamers: Supramolecular Architectures from Helicates to Biomimetics* (Eds.: G. Maayan, M. Albrecht), Wiley, Hoboken, **2013**; For Ca^{2+}- and Mg^{2+}-induced folding, see: c) A. Ajayaghosh, E. Arunkumar, J. Daub, *Angew. Chem. Int. Ed.* **2002**, *41*, 1766–1769; *Angew. Chem.* **2002**, *114*, 1844–1847; d) A. Ajayaghosh, P. Chithra, E. Arunkumar, *J. Am. Chem. Soc.* **2004**, *126*, 6590–6598; e) E. Arunkumar, A. Ajayaghosh, J. Daub, *J. Am. Chem. Soc.* **2005**, *127*, 3156–3164; For reviews on folding, see, for example: f) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893–4011; g) C. M. Goodman, S. Choi, S. Shandler, W. F. DeGrado, *Nat. Chem. Biol.* **2007**, *3*, 252–262; h) H. Juwarker, J.-M. Suk, K.-S. Jeong, *Chem. Soc. Rev.* **2009**, *38*, 3316–3325; i) G. Guichard, I. Huc, *Chem. Commun.* **2011**, *47*,

5933–5941; For Ca^{2+} complexes with hydrazones, see: j) G. Vantomme, N. Hafezi, J.-M. Lehn, *Chem. Sci.* **2014**, *5*, 1475–1483.

[11] For reviews on stimuli-responsive dendrimers, see: a) R. Deloncle, A.-M. Caminade, *J. Photochem. Photobiol. C* **2010**, *11*, 25–45; b) A.-M Caminade in *Dendrimers: Towards Catalytic, Material and Biomedical Uses*, Wiley, Hoboken, **2011**; c) C. Kojima, *Expert Opin. Drug Delivery* **2010**, *7*, 307–319; For pH-controllable supramolecular systems, see: d) K. C.-F. Leung, C.-P. Chak, C.-M. Lo, W.-Y. Wong, S. Xuan, C. H. K. Cheng, *Chem. Asian J.* **2009**, *4*, 364–381; See also: e) A. J. McConnell, C. S. Wood, P. P. Neelakandan, J. R. Nitschke, *Chem. Rev.* **2015**, *115*, 7729–7793.

[12] a) M. C. Jiménez, C. Dietrich-Buchecker, J.-P. Sauvage, *Angew. Chem. Int. Ed.* **2000**, *39*, 3284–3287; *Angew. Chem.* **2000**, *112*, 3422–3425; b) M. C. Jimenez-Molero, C. Dietrich-Buchecker, J.-P. Sauvage, *Chem. Commun.* **2003**, 1613–1616; c) Y. Liu, A. H. Flood, P. A. Bonvallet, S. A. Vignon, B. H. Northrop, H.-R. Tseng, J. O. Jeppesen, T. J. Huang, B. Brough, M. Baller, S. Magonov, S. D. Solares, W. A. Goddard, C.-M. Ho, J. F. Stoddart, *J. Am. Chem. Soc.* **2005**, *127*, 9745–9759; d) F. Coutrot, C. Romuald, E. Busseron, *Org. Lett.* **2008**, *10*, 3741–3744; e) J. Wu, K. C.-F. Leung, D. Benítez, J.-Y. Han, S. J. Cantrill, L. Fang, J. F. Stoddart, *Angew. Chem. Int. Ed.* **2008**, *47*, 7470–7474; *Angew. Chem.* **2008**, *120*, 7580–7584; f) R. E. Dawson, S. F. Lincoln, C. J. Easton, *Chem. Commun.* **2008**, 3980–3982; g) C.-J. Chuang, W.-S. Li, C.-C. Lai, Y.-H. Liu, S.-M. Peng, I. Chao, S.-H. Chiu, *Org. Lett.* **2009**, *11*, 385–388; h) G. Du, E. Moulin, N. Jouault, E. Buhler, N. Giuseppone, *Angew. Chem. Int. Ed.* **2012**, *51*, 12504–12508; *Angew. Chem.* **2012**, *124*, 12672–12676; i) H. Li, X. Li, Y. Wu, H. Ågren, D.-H. Qu, *J. Org. Chem.* **2014**, *79*, 6996–7004; j) C. J. Bruns, J. F. Stoddart, *Acc. Chem. Res.* **2014**, *47*, 2186–2199; k) F. Niess, V. Duplan, J.-P. Sauvage, *Chem. Lett.* **2014**, *43*, 964–974; see also: l) F. Niess, V. Duplan, J.-P. Sauvage, *J. Am. Chem. Soc.* **2014**, *136*, 5876–5879.

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