Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

A New Anion Receptor with a Glycoluril Molecular Scaffold

Jongmin Kang[a]; Hyun-Kyoung Ju[a]; Jee-Hye Jo[a]
[a] Department of Applied Chemistry, Sejong University, Seoul, Korea

To cite this Article Kang, Jongmin , Ju, Hyun-Kyoung and Jo, Jee-Hye(2004) 'A New Anion Receptor with a Glycoluril Molecular Scaffold', Supramolecular Chemistry, 16: 3, 175 — 179
To link to this Article: DOI: 10.1080/10610270310001633754
URL: http://dx.doi.org/10.1080/10610270310001633754

Supramolecular Chemistry, April 2004, Vol. 16 (3), pp. 175–179

Taylor & Francis
Taylor & Francis Group

A New Anion Receptor with a Glycoluril Molecular Scaffold

JONGMIN KANG*, HYUN-KYOUNG JU and JEE-HYE JO

Department of Applied Chemistry, Sejong University, Seoul 143-747, Korea

Received (in Southampton, UK) 18 July 2003; Accepted 8 October 2003

The rational design and synthesis of a new anion receptor containing a glycoluril molecular scaffold are reported. This new receptor utilizes four amide hydrogen bonds arranged at the corner of the glycoluril unit. This new anion receptor binds spherically shaped halide ions in a 1:1 stoichiometry and has a high affinity for fluoride.

Keywords: Anion receptor; Hydrogen bond; Glycoluril

INTRODUCTION

The development of new artificial receptors for selective anion recognition is an area of intensive investigation owing to their importance in biomedicine and the environment [1–6]. Many successful positively charged receptors [7–11] and neutral receptors incorporating Lewis acids [12–14] have been reported. However, their selectivity is generally modest and limited as their interactions with anions are non-directional. Many anions have diverse geometries that require shape-selective recognition. Therefore, many researchers have used hydrogen bonds as the recognition element as they are directional. The correct orientation of hydrogen bonds can differentiate between anionic guests with different geometries. In nature, the neutral amide N–H group is most often used to achieve anion binding by proteins [15]. For synthetic receptors containing amides, the amide groups are arranged in space in a rigid and convergent manner. This has been achieved by incorporating the amide group into a macrocycle [16–26] or utilizing molecular scaffolds to arrange the amide groups. Benzene rings [27–29], pyrrole [30–32], cyclohexane [33], cholic acid [34–35], tris(aminoethylamine) [36] and calixarenes [37–38] have been utilized as molecular scaffolds to arrange amide bonds. To develop new anion receptors based on amide groups, we have designed the receptor **1**, which binds with fluoride and acetate with high affinity. Here we would like to report the synthesis and binding properties of receptor **1** with various anions.

EXPERIMENTAL

Synthesis and Characterization

Compound 1

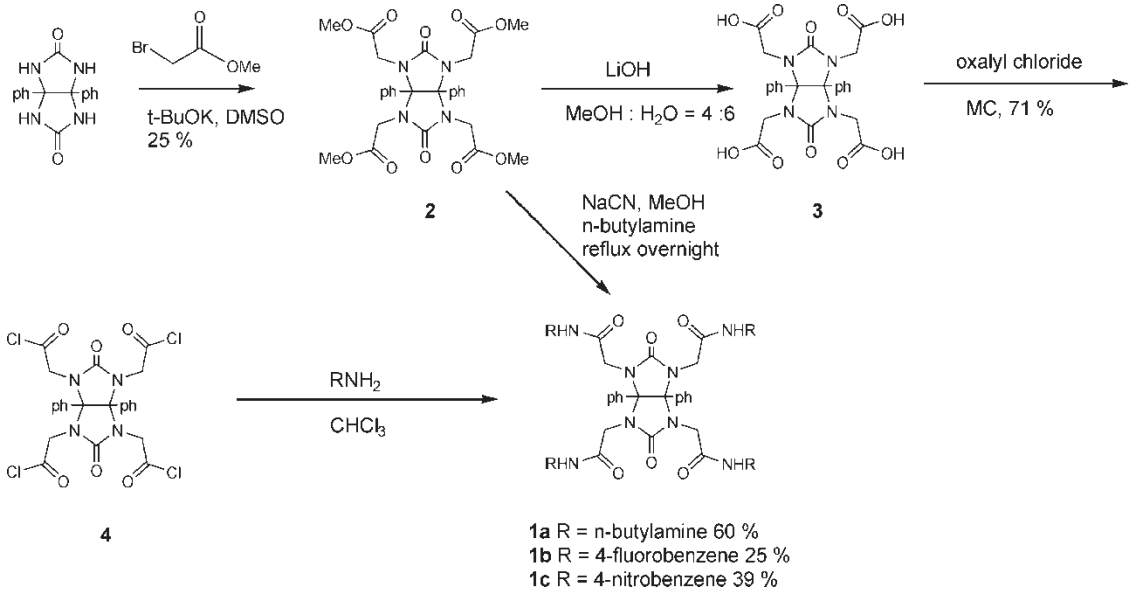
The synthesis of the compound **1** started from the reaction between diphenylglycoluril [39] and methyl bromoacetate with potassium *tert*-butoxide in DMSO to give compound **2** in 25% yield. Compound **2** was refluxed with *n*-butylamine and a catalytic amount of sodium cyanide in methanol to give the receptor **1a** in 60% yield. To obtain compounds **1b** and **1c**, compound **2** was hydrolysed with 20 equivalents of lithium hydroxide in 40% methanol in water to afford compound **3**. Then compound **3** was treated with oxalyl chloride to give tetraacyl chloride **4** in 71% yield. Reaction with 4-fluoroaniline or 4-nitroaniline gave the desired compounds **1b** and **1c** in 25 and 39% respectively (Scheme 1).

Compound 2

To a solution of 100 mg diphenylglycoluril in 4 ml DMSO was added 166 mg potassium *tert*-butoxide and the mixture was stirred for 30 min. Then 125 μl of methyl bromoacetate was added to the reaction mixture and stirred for 1 h at room temperature. The reaction mixture was poured into 50 ml of

*Corresponding author. Tel.: +82-2-3408-3213. Fax: +82-2462-9954. E-mail: kangjm@sejong.ac.kr

ISSN 1061-0278 print/ISSN 1029-0478 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10610270310001633754



SCHEME 1 The synthetic procedure for the anion receptors **1**.

chloroform and extracted with 50 ml of water 3 times to remove DMSO. The chloroform layer was dried with $MgSO_4$ and filtered. Evaporation of chloroform and silica gel chromatography with 1% methanol gave 37 mg of the oily product **2** in 25 yield. ^{1}H NMR ($CDCl_3$) 7.0 (10H, m), 4.0 (4H, d, $J = 17.6$ Hz), 3.7 (12H, s), 3.6 (4H, d, $J = 17.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.47, 158.32 131.74, 129.97, 129.29, 128.49, 88.19, 53.01, 43.60; HRMS (FAB) calculated for $C_{28}H_{30}N_4O_{10}H^+$: 583.2020; found: 583.2045.

Compound 3

To a solution of 150 mg of compound **2** in 10 ml of 40% methanol–water was added 206 mg of lithium hydroxide and the mixture was refluxed overnight. The solvent was removed from the reaction mixture *in vacuo* and the residue was dissolved in 10 ml of water. The undissolved solid was removed by filtration and the filtrate was treated with concentrated HCl until pH 2 was reached. Evaporation of the solvent gave the compound *3* in quantitative yield. ^{1}H NMR (D_2O) 6.8 (10H, m), 4.1 (4H, d, $J = 18.0$ Hz), 3.7 (4H, d, $J = 18.0$ Hz).

Compound 4

To a suspension of 200 mg of compound **3** in 20 ml of dichloromethane was added 7 ml of oxalyl chloride and 30 μl of 5% DMF in dichloromethane. The reaction mixture was stirred overnight. Evaporation of the solvent *in vacuo* gave 90 mg of compound **4** in 71% yield (yield from compound **2**). ^{1}H NMR ($CDCl_3$) 7.0 (10H, m), 4.5 (4H, d, $J = 18.3$ Hz), 4.1 (4H, d, $J = 18.3$ Hz).

Compound 1a

To a solution of 50 mg compound **2** in 10 ml of methanol was added 1 ml of *n*-butylamine and 4 mg of sodium cyanide. The reaction mixture was refluxed overnight. Evaporation of the solvent from the reaction mixture and silica gel chromatography with 2% methanol in dichloromethane gave 36 mg of the compound **1a** in 60% yield. Mp 250–252°C; ^{1}H NMR ($CDCl_3$) 7.0 (14H, m), 3.9 (4H, d, $J = 16.5$ Hz), 3.2 (8H, m), 1.5 (8H, m), 1.3 (8H, m), 0.8 (12H, t, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 172.88, 163.22, 135.24, 133.99, 132.98, 132.47, 92.64, 48.75, 43.77, 35.53, 24.31, 17.83; HRMS (FAB) calculated for $C_{40}H_{58}N_8O_6H^+$: 747.4537; found: 747.4558.

Compound 1b

To a solution of 40 mg of compound **4** in 5 ml of chloroform was added 63 μl of 4-fluoroaniline and the mixture was stirred for an hour at room temperature. Evaporation of the solvent from the reaction mixture and silica gel chromatography with 5% methanol in dichloromethane gave 15 mg of product **1b** in 25% yield. Mp 323–325°C; ^{1}H NMR ($CDCl_3$) 8.8 (4H, s), 7.1–6.7 (26H, m), 4.3 (4H, d, $J = 16.6$ Hz), 3.7 (4H, d, $J = 16.6$ Hz); ^{13}C NMR (50% CD_3OD in $CDCl_3$) δ 167.22, 161.04, 134.13, 131.37, 130.08, 129.22, 128.80,122.85, 115.67, 115.45, 89.24, 45.41; HRMS (FAB) calculated for $C_{48}H_{38}F_4N_8O_6H^+$: 899.2908; found: 899.2929.

Compound 1c

To a solution of 45 mg of compound **4** in 5 ml of chloroform was added 124 mg of 4-nitroaniline and the mixture was stirred for an hour at room

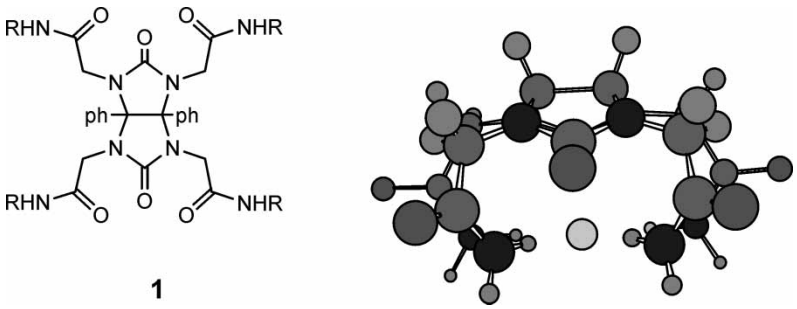


FIGURE 1 The energy-minimized structure of receptor **1** and fluoride (Cache 3.2 MOPAC calculation); aromatic rings are omitted for clarity.

temperature. Evaporation of the solvent from the reaction mixture and silica gel chromatography with 4% methanol in dichloromethane gave 29 mg of product **1c** in 25% yield. Mp 208–210°C; ^{1}H NMR ($CDCl_3$) 9.19 (4H, s), 8.09 (4H, d, $J = 9.1$ Hz), 7.71 (4H, d, $J = 9.1$ Hz), 4.3 (4H, d, $J = 17.1$ Hz), 3.8 (4H, d, $J = 17.1$ Hz); ^{13}C NMR (DMSO-d_6) δ 167.45, 157.85, 144.88, 142.05, 132.07, 128.94, 128.11, 127.98, 124.63, 119.25, 87.61, 45.17; HRMS (FAB) calculated for $C_{48}H_{38}N_{12}O_{14}H^+$: 1007.2709; found: 1007.2709.

RESULTS AND DISCUSSION

Modeling Studies

The structure of the receptor **1** is based on diphenylglycoluril, which has a concave structure. The concave structure of glycoluril has been used as an element of a molecular receptor by Nolte and Rebek [40]. We envisioned the structure such that the four amide groups are arranged at the corners of the glycoluril. The amide N–H hydrogen attached at the corner of glycoluril would form a cavity and point to the anion located at the center of the concave structure of the glycoluril. The shape of cavity seemed to be suitable for spherical halide ions and the size of the cavity seemed to be appropriate for the fluoride ion. The energy-minimized structure of receptor **1** and fluoride is shown in Fig. 1 (Cache 3.2 MOPAC calculation). From modeling, the distance between the amide N–H hydrogen and the fluoride fell in the range 1.75–1.77 Å. The four amides in receptor **1** are arranged symmetrically to bind to the fluoride ion. From a structural point of view, an anion is inserted within the closed cavity composed of four amides attached to the glycoluril.

NMR Studies

As the receptor **1c** was expected to have the strongest affinity to various anions, the association constants of **1c** to different anions were determined first. To determine the anion-binding abilities of the receptor **1c**, ^{1}H NMR titration experiments were performed in CD_3CN and the chemical shift data were analysed by EQNMR [41]. The addition of tetrabutylammonium anion salts to the solution of **1c** in CD_3CN resulted in downfield shifts in both the amide N–H hydrogen and CH_2 hydrogen next to the amides. In the case of the fluoride ion, the N–H hydrogen peak disappeared upon addition of fluoride. Therefore, the signals of the CH_2 protons located next to the amide groups were used to determine

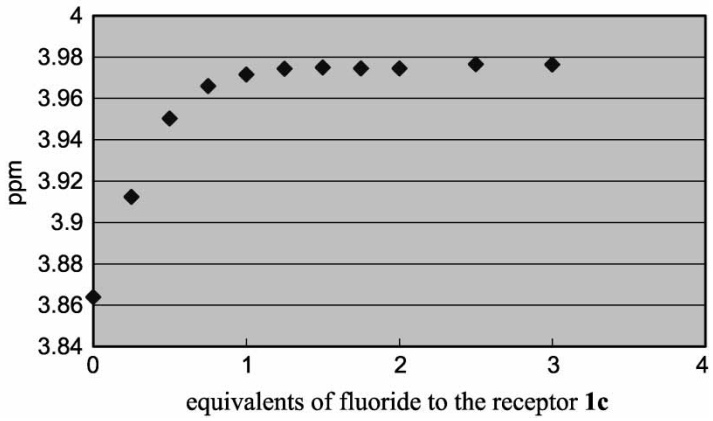


FIGURE 2 Changes in the CH_2 protons located next to amide groups in **1c** with increasing F^- concentrations.

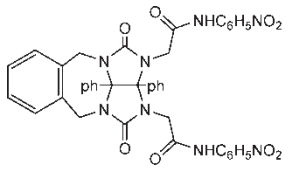
TABLE I Association constants (M^{-1}) of **1** with tetrabutylammonium anions in CD_3CN

Anion	**1a**	**1b**	**1c**
F^-	2263*	3801†	35900*
Cl^-	163*	653*	1584*
Br^-	57*	226*	776*
I^-	26*	31*	66†
NO_2^-	240*	691*	2637*
$CH_3CO_2^-$	1.8×10^{5}*	8.4×10^{5}†	2.7×10^{6}*

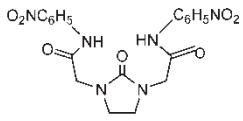
* Errors in K_a are estimated to be less than 10%. † Errors in K_a are estimated to be less than 20%.

the association constants for complex **1c** and anions. For **1c**, the CH_2 signals moved downfield by about 0.1 ppm for 1 equivalent fluoride ion and no further shift was observed, which indicates 1:1 binding, as shown in Fig. 2. The association constant was calculated as $35900\,M^{-1}$. Control experiments were performed to elucidate that the binding of **1c** with fluoride occurs by the cooperative action of four amide hydrogen bonds. Compounds **5** and **6** were synthesized and their binding to fluoride ion under the same conditions was investigated. The binding constant of fluoride ion to compound **5** in CD_3CN was calculated as $2770\,M^{-1}$. However, compound **6** was completely insoluble in CD_3CN and it was impossible to measure the binding constant between **6** and fluoride ion. Therefore, the binding constants of **1c**, **5** and **6** for fluoride ion were measured in DMSO-d_6. The binding constants in DMSO were calculated as $1028\,M^{-1}$ for **1c**, $159\,M^{-1}$ for compound **5** and $336\,M^{-1}$ for compound **6**. These control experiments indicate that at least three hydrogens or, more plausibly, all four amide hydrogens are involved in the binding event with fluoride ion. Assuming that the 1:1 stoichiometry applies to the association between spherically shaped halide ions and receptor **1c**, association constants between other halides and receptor **1c** were investigated. The results are summarized in Table I. From the table, it is clear that the association constants of receptor **1c** for halides follow the diameter and basicity of the halide ions. The smallest size and the largest basicity of the fluoride ion allowed a much better fit into the cavity and the formation of shorter and stronger hydrogen bonds. For **1c**, about a 550-fold selectivity for fluoride over iodide was observed. The acidity of the N–H bond also played a role in the association between the receptor **1** and halides. Receptors **1a** and **1b**, which have less acidic N–H than **1c**, showed a marked decrease in association constants for the same anion compared with **1c**. The association constant of receptor **1a**, which has the least acidic N–H, for iodide, which is the least basic and largest halide, was calculated as only 26.

We also investigated the binding of other anions with receptor **1**. Job plot experiments were performed between **1c** and various anions in CD_3CN. While the Job plot of nitrate ion and **1c** showed 1:1 binding stoichiometry (Fig. 3), the Job plot for acetate ion complexation by **1c** indicates that **1c** binds with acetate in a 1:2 host–guest stoichiometry. The calculated association constants of nitrate and acetate were $2637\,M^{-1}$ and $2.7 \times 10^{6}\,M^{-2}$ ($\beta_2 = K_1K_2$). The differences in basicity of the oxygens in nitrate and acetate seemed to be reflected in their binding constants.



5



6

In the cases of $H_2PO_4^-$, and CN^-, the Job plots were not symmetric and showed a maximum when the mole fraction of the host was 0.43 and 0.58, respectively, which indicates a mixed stoichiometry. Therefore, it was not possible to obtain accurate association constants for these anions.

In conclusion, we have synthesized an anion receptor based on a glycoluril molecular scaffold.

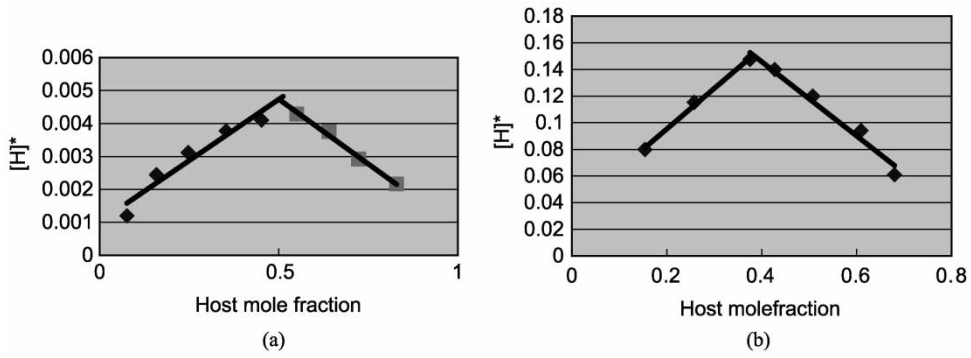


FIGURE 3 The Job plots of **1c** with (a) tetrabutylammonium nitrate; (b) tetrabutylammonium acetate.

Receptor **1** is selective for fluoride and acetate ions. Structural variation of receptor **1** would open more possibilities for designing new anion receptors. We are currently investigating this potential.

Acknowledgements

This study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (01-PJ1-PG3-21500-0017).

References

[1] Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486.
[2] Gale, P. A. *Coord. Chem. Rev.* **2000**, *199*, 181.
[3] Snowden, T. S.; Anslyn, E. V. *Curr. Opin. Chem. Biol.* **1999**, *3*, 740.
[4] Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443.
[5] Beer, P. D. *Acc. Chem. Res.* **1998**, *31*, 71.
[6] Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.
[7] Beer, P. D.; Drew, M. G. B.; Hesek, D.; Nam, K. C. *Chem. Commun.* **1997**, 107.
[8] Beer, P. D.; Drew, M. G. B.; Hodacova, J.; Stokes, S. E. *J. Chem. Soc., Dalton Trans.* **1995**, 3447.
[9] Beer, P. D.; Dent, S. W. *Chem. Commun.* **1998**, 825.
[10] Hossain, M. A. S.; Schneider, H. J. *Chem. Eur. J.* **1995**, *5*, 1284.
[11] Davis, A. P.; Lawless, L. J. *Chem. Commun.* **1999**, 2001.
[12] Kennedy, A. R.; Mulvey, R. E.; Rowlings, R. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 3180.
[13] Valerio, C.; Alonso, E.; Ruiz, J.; Blais, J. C.; Astruc, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1747.
[14] Schnebeck, R.-D.; Freisinger, E.; Lippert, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 168.
[15] Voet, D.; Voet, J. G.; Pratt, C. W. *Fundamentals of Biochemistry*; Wiley: New York, 1999.
[16] Szumna, A.; Jurczak, J. *Eur. J. Org. Chem.* **2001**, 4031.
[17] Hossain, M. A.; Liinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2001**, *40*, 2936.
[18] Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456.
[19] Hinzen, B.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1996**, *79*, 942.
[20] Davis, A. P.; Gilmer, J. F.; Perry, J. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1312.
[21] Sansone, F.; Baldini, L.; Casnati, A.; Lazzarotto, M.; Ugozzoli, F.; Ungaro, R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4842.
[22] Beer, P. D.; Gale, P. A.; Hesek, D. *Tetrahedron Lett.* **1995**, *36*, 767.
[23] Andrievsky, A.; Ahuis, F.; Sessler, J. L.; Vogtle, F.; Gudat, D.; Moini, M. *J. Am. Chem. Soc.* **1998**, *120*, 9712.
[24] Pascal, R. A.; Spergel, J.; Engbersen, D. V. *Tetrahedron Lett.* **1985**, *27*, 4099.
[25] Fujita, T.; Lehn, J.-M. *Tetrahedron Lett.* **1988**, *29*, 1709.
[26] Bisson, A. P.; Lynch, V. M.; Monahan, M.-K. C.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2340.
[27] Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675.
[28] Kavallieratos, K.; Gala, S. R. D.; Austin, D. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 2325.
[29] Beer, P. D.; Fletcher, N. C.; Grieve, A.; Wheller, J. W.; Moore, C. P.; Wear, T. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1545.
[30] Gale, P. A.; Camiolo, S.; Tizzard, G. J.; Chapman, C. P.; Light, M. E.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2001**, *66*, 7849.
[31] Gale, P. A.; Camiolo, S.; Chapman, C. P.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2001**, *42*, 5095.
[32] Camiolo, S.; Gale, P. A.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett* **2002**, *43*, 6995.
[33] Raposo, C.; Perez, N.; Almaraz, M.; Mussons, M. L.; Caballero, M. C.; Moran, J. R. *Tetrahedron Lett.* **1995**, *36*, 3255.
[34] Davis, A. P.; Perry, J. J.; Williams, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 1793.
[35] Ayling, A. J.; Perez-Payan, M. N.; Davis, A. P. *J. Am. Chem. Soc.* **2001**, *123*, 12716.
[36] Valiyaveetil, S.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 900.
[37] Beer, P. D.; Timoshenko, V.; Maestri, M.; Passaiti, P.; Balzani, V. *Chem. Commun.* **1999**, 1755.
[38] Cameron, B. R.; Loeb, S. J. *Chem. Commun.* **1997**, 573.
[39] Kang, J.; Meissner, R. S.; Wyler, R.; de Mendoza, J.; Rebek, J. Jr., *Bull. Korean Chem. Soc.* **2000**, *21*(2), 221.
[40] Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R.; J, M. *Acc. Chem. Res.* **1996**, *32*, 995.
[41] Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311.