Macrocycle Synthesis

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Molecular Waterwheel (Noria) from a Simple Condensation of Resorcinol and an Alkanedial**

Hiroto Kudo, Rieko Hayashi, Kouji Mitani,
Tsutomu Yokozawa, Noriko C. Kasuga, and
*Tadatomi Nishikubo**

The condensation reaction of phenols with aldehydes to afford bakelite was developed by Baekland in 1907,[1] and since then many papers and patents dealing with the synthesis and applications of phenolic resins have been reported.[2] About 40 years after the first report, it was found that oligomers could be similarly synthesized by reactions of phenols with formaldehydes.[3] Early structural studies[4] were brought to a successful conclusion more than 30 years later, when Erdtman, Gutsche, and their co-workers proved the oligomers to be large cyclic compounds by means of single-crystal X-ray analyses, and named them calixarenes.[5] Many applications of calixarenes have been reported in the field of host–guest chemistry.[6] Although the synthetic strategies for calixarenes have not basically changed since 1940, Gutsche et al. recently showed that dynamic covalent chemistry (DCC) systems could afford these compounds in high yield.[7] Furthermore, macromolecular capsule compounds, cavitands, and carcerands have been derived from calixarenes.[8]

Herein, we present the condensation reaction of resorcinol, as a difunctional compound, with 1,5-pentanedial [$(CH_2)_n(CHO)_2$] ($n = 3$), as a tetrafunctional compound, by using a similar approach to that employed for the synthesis of calixarenes to give a unique double-cyclic ladder-type oligomer with a central hole which resembles a waterwheel in structure (Scheme 1).

The reaction of resorcinol (2.2 g, 20 mmol) and 1,5-pentanedial (0.50 g, 5 mmol) was carried out in ethanol (4.5 mL) at 80 °C in the presence of concentrated HCl

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[*] Dr. H. Kudo, R. Hayashi, K. Mitani, Dr. T. Yokozawa, Dr. T. Nishikubo
Department of Material and Life Chemistry
Faculty of Engineering
Kanagawa University
3-27-1, Rokkakubashi, Kanagawa-ku, Yokohama, 221-8686 (Japan)
Fax: (+81) 45-413-9770
E-mail: nishikubot@kanagawa-u.ac.jp

Dr. N. C. Kasuga
Department of Chemistry
Faculty of Science
Kanagawa University
Tsuchiya, Hiratsuka, Kanagawa, 259-1293 (Japan)

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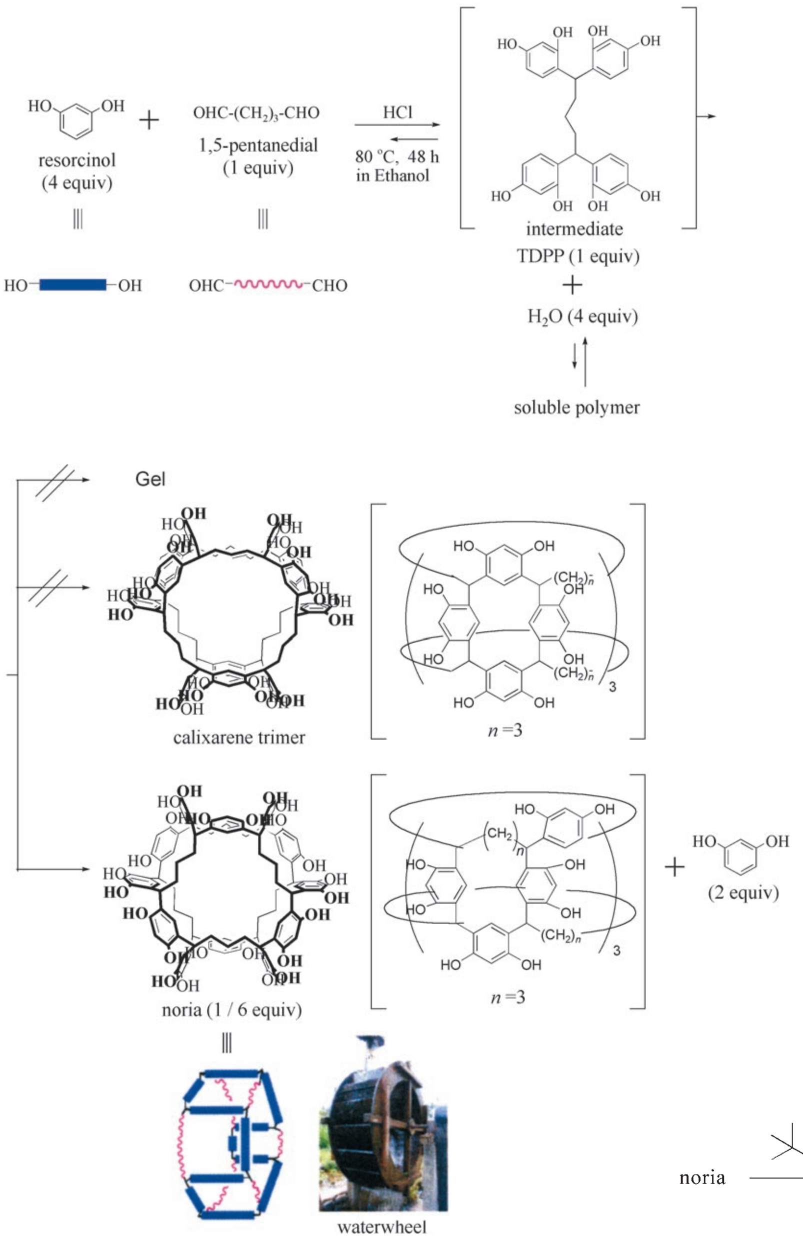
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

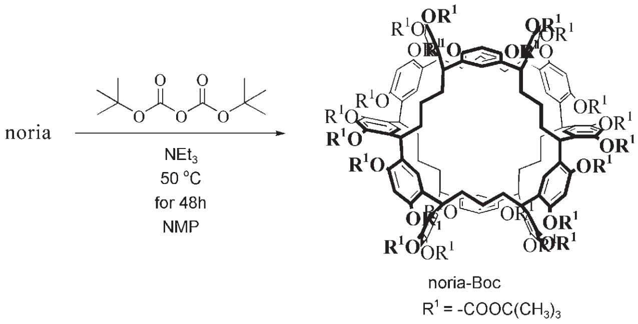


Scheme 1. The reaction of resorcinol with 1,5-pentanedial.

(3.0 mL). The initially homogenous reaction mixture afforded an insoluble product after 48 h. The reaction mixture was poured into methanol, and the precipitated product was washed with diethyl ether several times, then dried in vacuo at 60 °C for 12 h. The product (0.94 g) was soluble in aprotic, highly polar solvents, such as dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMAC), and 1-methyl-2-pyrrolidinone (NMP). The ^{1}H NMR spectrum showed that the product contained aromatic, methine, and methylene protons. The ratio of the units derived from resorcinol and 1,5-pentanedial was calculated to be 2:1 from the ratios of the signal integrals in the ^{1}H NMR spectrum. Furthermore, the MALDI-TOF mass spectrum of this product after doping with Na^+ ions showed parent ion signals at m/z 1705.86 and 1727.63, which correspond to the mass of a cyclic oligomer obtained by the condensation of two equivalents of resorcinol with one equivalent of 1,5-pentanedial, as shown in Scheme 1. It should be noted that only a soluble, large cyclic molecule was obtained, and there was no gel formation under the optimized conditions. On the basis of these data, we speculated that the product consisted of a calixarene-like trimer, as shown in Scheme 1.

We next determined the structure of this cyclic oligomer by single-crystal X-ray analysis. To increase the solubility, all the hydroxy groups were converted into *tert*-butoxycarbonyloxy groups by reaction with di-*tert*-butyl dicarbonate (Scheme 2).

A single platelike crystal of this derivative was obtained by recrystallization from chloroform/hexane. Surprisingly, the X-ray analysis showed that this derivative is not a calixarene trimer, but a double-cyclic ladder oligomer, in which each ring consists of alternating resorcinol and methylene units, and the two rings are connected through six resorcinol units (Figure 1).[9] It has 24 hydroxy groups, 6 cavities in the side, and a large hydrophobic hole through the center of the molecule, thus resembling a waterwheel in appearance (Scheme 1). We named it noria, which means waterwheel in Latin. It is noteworthy that such a complicated three-dimensional molecule was synthesized in one pot in high yield (83 %).



Scheme 2. The reaction of noria and di-*tert*-butyl dicarbonate.

The reaction conditions for the synthesis of the waterwheel-like product were examined by using various feed molar ratios of resorcinol and 1,5-pentanedial at temperatures between 0 and 80 °C. The amount of gel product decreased with increasing reaction temperature. The reaction at 0 °C for 24 h at a resorcinol/1,5-pentanedial feed ratio of 2/1 afforded the gel product in quantitative yield, while at 25, 40, and 60 °C the yields of gel decreased to 70, 52, and 12 %, respectively. At 80 °C, no gel was obtained and only noria was obtained in 7 % yield. No other product, such as polymer or oligomer, was produced, and starting materials were recovered under these reaction conditions.

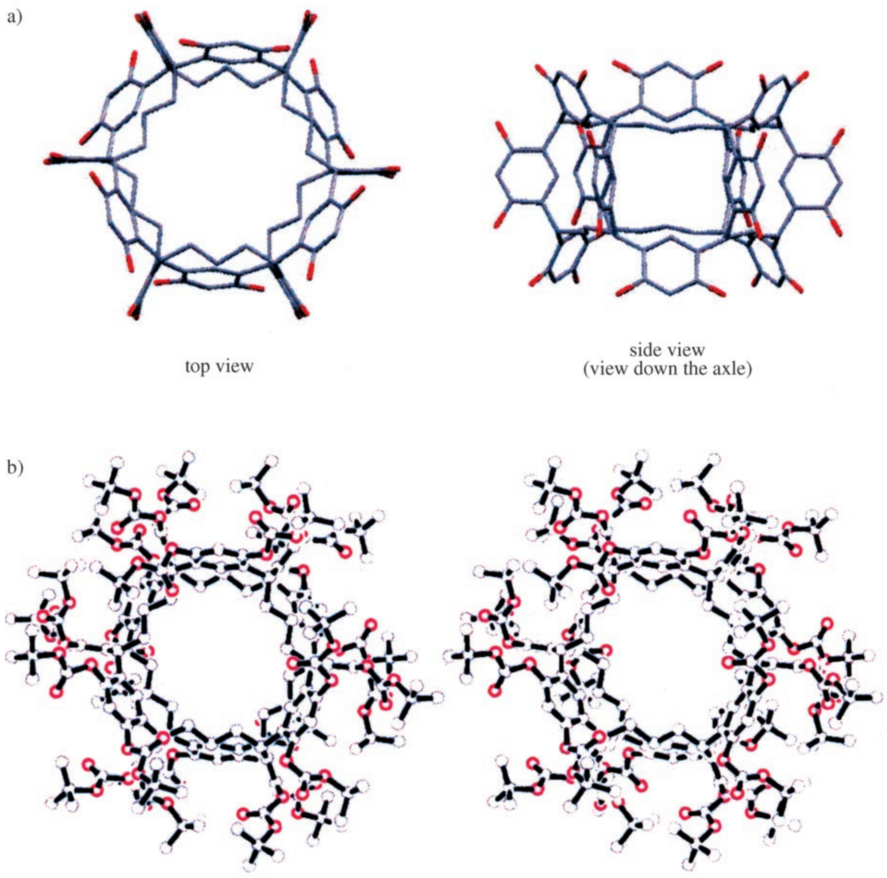


Figure 1. a) Top view and side view of synthetic noria. b) Stereoview of noria-Boc in the crystal. Boc = *tert*-butoxycarbonyl.

Resorcinol/1,5-pentanedial feed ratios of 2.6/1, 5/1, 6.8/1, and 10/1 at 80 °C afforded noria in yields of 56, 81, 76, and 68 %, respectively. Finally, we found that the use of a 4/1 ratio of resorcinol/1,5-pentanedial at 80 °C for 48 h afforded the highest yield of noria (83 %), with no gel formation.

To examine the mechanism of the reaction leading to noria, we examined the size-exclusion chromatography (SEC) profiles of the obtained products over time (Figure 2). After 5 minutes, peaks of polymer and oligomer were observed with retention times of 28 and 24 minutes, respectively. A decrease in the molecular weight of the polymer and an increase in the amount of noria were subsequently observed as the reaction time was increased. The retention time of the oligomer remained at 24 minutes for all the reaction times. This reaction behavior indicates that noria was constructed by a reversible reaction between polymer, oligomer, resorcinol, and 1,5-pentanedial. The oligomer with the retention time of 24 minutes appeared to be the key compound leading to noria.

This product was separated by column chromatography on silica gel, and was determined to be 1,1,5,5-tetra(2,4-dihydroxyphenyl)pentane (TDPP), which would have been formed by the condensation reaction of four equivalents of resorcinol with 1,5-pentanedial.

When TDPP was heated at 80 °C for 48 h in ethanol containing concentrated HCl noria was obtained in quantitative yield, accompanied by the formation of resorcinol. These results suggest that TDPP was formed by a reversible reaction between polymer, resorcinol, and 1,5-pentanedial, followed by the elimination reaction of resorcinol with TDPP in the presence of HCl as a catalyst to produce 1/6 equivalent of noria under complete thermodynamic control. That is, the condensation reaction for the synthesis of noria is related to the DCC system.[10] These reactions were accompanied by the formation of four equivalents of H_2O and two equivalents of resorcinol. This finding is consistent with the observation that noria was obtained in the highest yield at a resorcinol/1,5-pentanedial molar ratio of 4/1.

The structure of noria is similar to those of cavitands and carcerands, which are cyclic oligomers obtained from calixarenes through multiple synthetic steps. Therefore, noria, with its large central cavity, is expected to be useful as a new functional material in the field of host–guest chemistry. Several calixarene derivatives containing additional carboxylic ester moieties, such as a *para-tert*-butylcalix[8]arene derivative (BCA-COOEt) and a calix[4]resorcinarene derivative (CRA-COOEt), have been synthesized and their properties examined in solvent extraction experiments.[11] We therefore synthesized a noria derivative (noria-COOEt) containing carboxylic ester moieties by the reaction of noria with ethyl bromoacetate in the presence of potassium carbonate in NMP (Scheme 3).

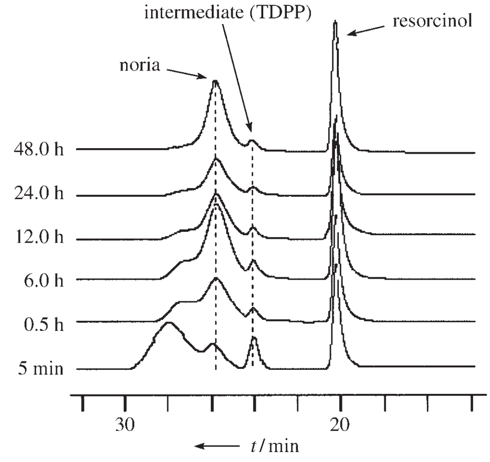
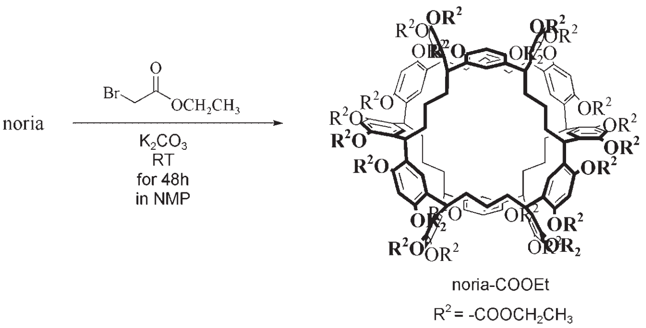


Figure 2. SEC profiles of the products obtained by the reaction of resorcinol (20 mmol) and 1,5-pentanedial (5 mmol) in the presence of conc. HCl (3 mL) in ethanol (4 × 5 mL) at 80 °C.

Its application in the liquid–liquid extraction of alkali metal cations were examined using picrate salts in water and dichloromethane. The results are summarized, together with those for BCA-COOEt and CRA-COOEt, in Table 1.[12]

The remarkable selectivity of BCA-COOEt suggests that the six oxygen atoms of pendant carbonyl groups of BCA-



Scheme 3. The reaction of noria and ethyl bromoacetate.

Table 1: Extraction of picrate salts with calixarene derivatives (BCA-COOEt, CRA-COOEt) and noria derivative (noria-COOEt).[a]

Ligand	Na^+ 2.04 Å[b]	K^+ 2.76 Å[b]	Rb^+ 2.98 Å[b]	Cs^+ 3.40 Å[b]
CRA[4]-COOEt	<1	<1	<1	<1
BCA[8]-COOEt	4.5	21.5	16.8	15.6
noria-COOEt	<1	<1	23.8	4.7

[a] Percentage cation extraction from an aqueous neutral alkali solution (2.5×10^{-4} mol dm^{-3}) into dichloromethane by the host (CRA[4]-COOEt, BCA[8]-COOEt, noria-COOEt; 2.5×10^{-4} mol dm^{-3}) at 25 °C. [b] Ionic diameter; see Reference [13].

COOEt can enclose metal ions within a sphere because of the rigid structure of the molecule. However, CRA-COOEt showed no significant ability to extract the metal ions, presumably because of its flexible structure. Noria-COOEt showed excellent selectivity for Rb^+ ions: the Rb^+ ion may be enclosed within the central hole of the molecule through interaction with the six oxygen atoms of the carbonyl groups.

In summary, we have synthesized in high yield a unique double-cyclic oligomer with ladderlike links between the two rings that resembles a waterwheel. This approach represents a new application of DCC. Single-crystal X-ray analysis of a derivative of this molecule, termed noria, confirmed it had a double-cyclic ladderlike structure with 24 hydroxy groups, 6 cavities in the side, and a large hydrophobic central hole. This molecule showed high selectivity for the complexation of a Rb^+ ion, which was presumably enclosed in the central hole in the molecule. We are currently examining the synthesis of other cyclic oligomers by using α,ω-dialdehydes.

Experimental Section

Synthesis of noria: A mixture of resorcinol (20 mmol) and 1,5-pentanedial (4.0 mmol) in ethanol was stirred at 80 °C for 48 h in the presence of conc. HCl (3.0 mL), then poured into a large amount of methanol to precipitate a white solid. The solid was washed with diethyl ether several times and dried in vacuo at 60 °C for 12 h. Yield 83 % (0.94 g). IR (film): $\tilde{\nu} = 3406$ (νO−H), 2931 (νC−H), 1621, 1505, and 1436 cm^{-1} (νC=C aromatic). ^{1}H NMR (600 MHz, [D$_6$]DMSO, tetramethylsilane): $\delta = 0.86$–2.35 (m, 36 H, $-CH_2CH_2CH_2-$), 3.98–4.22 (m, 12 H, >CH-), 6.09–7.42 (m, 24 H, Ar-H), 8.65–9.56 ppm (m, 24 H, OH); MALDI-TOF-MS: *m/z* $[M+H]^+$ calcd for ($C_{102}H_{96}O_{24}$+H): 1705.63, found: 1705.86; MALDI-TOF-MS: *m/z* $[M+Na]^+$ calcd for ($C_{102}H_{968}O_{24}$+Na): 1727.86, found: 1727.63.

Liquid–liquid extraction of alkali-metal cations: A mixture of solution (4.0 mL) of the noria-COOEt (2.5×10^{-4} mol dm^{-3}) in dichloromethane and an aqueous solution (4.0 mL) of a metal picrate (2.5×10^{-4} mol dm^{-3}) was stirred at 25 °C for 24 h and then allowed to stand for 1 h. The aqueous phase was examined by UV/Vis spectroscopy. The extraction ratio was calculated from the decrease in the intensity of the peak at $\lambda_{max} = 355$ nm.

The experimental procedures, ^{1}H, ^{13}C NMR, and IR spectroscopic analysis, MS data, and elemental analysis data of the noria derivative (noria-BOC, noria-COOEt), TDPP, and metal picrates are described in the Supportng Information.

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[1] L. H. Baekland, *J. Ind. Eng. Chem.* **1911**, *3*, 932.
[2] For example; C. C. Lin, *Ind. Eng. Chem. Res.* **2002**, *41*, 1986.
[3] a) J. B. Niederl, H. J. Vogel, *J. Am. Chem. Soc.* **1940**, *62*, 2512; b) A. Zinke, E. Ziegler, *Ber. Dtsch. Chem. Ges. B* **1941**, *74*, 1729.
[4] a) A. Zinke, R. Kretz, E. Legewie, K. Hossinger, *Monatsh. Chem.* **1952**, *83*, 1213; b) J. W. Cornforth, H. P. D'Arcy, G. A. Nicholls, R. J. W. Rees, J. Stock, *Br. J. Pharmacol.* **1955**, *10*, 73; c) B. T. Hayes, R. F. Hunter, *Chem. Ind.* **1956**, 193; d) B. T. Hayes, R. F. Hunter, *J. Appl. Chem.* **1958**, *8*, 743.
[5] a) H. Ertdman, S. Hogberg, S. Abrahamsson, B. Nilsson, *Tetrahedron Lett.* **1968**, 1679; b) C. D. Gutsche, B. Dhawan, K. H. No, R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, *103*, 3782; c) C. D. Gutsche, *Calixarenes*, *Monographs in Supramolecular Chemistry*, *Vol. 1* (Ed.: J. F. Stoddart), Royal Society of Chemistry, Cambridge, **1989**.
[6] For example: C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, **1989**.
[7] C. D. Gutsche, D. E. Johnston, Jr., D. R. Stewart, *J. Org. Chem.* **1999**, *64*, 3747.
[8] a) D. J. Cram, *Science* **1983**, *219*, 1177; b) for example: A. Jasat, J. Sherman, *Chem. Rev.* **1999**, *99*, 931; c) for example: P. Timmerman, W. Verboom, N. Reinhoudt, *Tetrahedron* **1996**, *52*, 2663; d) for example: R. Hooley, S. Biros, J. Rebek, *Angew. Chem.* **2006**, *45*, 3597; *Angew. Chem. Int. Ed.* **2006**, *45*, 3517.
[9] X-ray data for the noria derivative (noria-Boc·$CHCl_3$·H_2O·C_6H_{14}) ($C_{229}H_{305}O_{73}Cl_3$, $M_r = 4332.23$): $0.35\times0.20\times0.05$ mm, colorless plate, space group $P\bar{1}$(no. 2), $a = 17.4163(8)$, $b = 19.589(1)$, $c = 20.0063(9)$ Å, $\alpha = 107.992(3)$, $\beta = 106.857(3)$, $\gamma = 94.700(3)°$, $V = 6101.6(6)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.18$ mg m^{-3}, $F(000) = 2312$, radiation: $Cu_{K\alpha} = 1.5418$ Å, $T = 93$ K, reflections collected/unique 100073/21803 ($R_{int} = 0.0065$). Coordinates and anisotropic thermal parameters of non-hydrogen atoms except solvated molecules were refined. Hydrogen atoms were positioned geometrically. $R_1 = 0.1097$, $wR_2 = 0.3067$, GOF = 1.049. CCDC-279300 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. Elemental analysis data for (noria−Boc+$CHCl_3$+hexane) calcd for $C_{229}H_{303}O_{72}Cl_3$: C 63.70, H 7.02; found: C 63.96, H 7.14.
[10] Reviews: a) S. J. Rowan, S. J. Cantrill, G. R. L. Cousin, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 938; *Angew. Chem. Int. Ed.* **2002**, *41*, 898; Erratum: S. J. Rowan, S. J. Cantrill, G. R. L. Cousin, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 1528; *Angew. Chem. Int. Ed.* **2002**, *41*, 1460; b) O. Ramstrom, T. Bunyapaiboonsri, S. Lohmann, J.-M. Lehn, *Biochim. Biophys. Acta* **2002**, *1572*, 178.

[11] a) S. K. Chang, I. Cho, *J. Chem. Soc. Perkin Trans. 1* **1986**, 211; b) P. M. Marcos, S. Felix, J. R. Asceno, M. A. P. Segurado, J. L. C. Pereira, P. K. Parsa, V. H. Bruder, F. Arnaud-Neu, *New J. Chem.* **2004**, *28*, 748.

[12] The *para-tert*-butylcalix[8]arene derivative (BCA-COOEt) and calix[4]resorcinarene derivative (CRA-COOEt) were synthesized by the reactions of *para-tert*-butylcalix[8]arene (BCA) and calixresorcin[4]arene (CRA), respectively, with ethyl bromoacetate using K_2CO_3 in NMP.

[13] P. M. Marcos, J. R. Asceno, M. A. P. Segurado, J. L. C. Periera, *J. Phys. Org. Chem.* **1999**, *12*, 695.