(yield ca. 15%). The product is air and light stable. A few colorless crystals of **4** were separated successfully from the deep orange mother liquor [9]. Elemental analysis: $C_9H_5AgN_4O$, calcd: C 36.88, H 1.72, N 19.12; found: C 36.10, H 1.83, N 18.84. IR (Nujol): $\tilde{\nu}$(CN) 2251 (w), 2220 (m), 2153 (s), 2127 (s), $\tilde{\nu}$(CO) 1707 (m) cm^{-1}.

3: A solution of TCNE in acetone, acidified with dilute aqueous HCl, was stirred for 24 h. The product (**1**-H), isolated after evaporation of the solution to dryness, was used without further purification. A solution of **1**-H (0.0332 g, 0.178 mmol) in acetone (2 mL) was layered over a solution of $[Cu(MeCN)_4](PF_6)$ (0.0664 g, 0.178 mmol) in acetone (3 mL) under a nitrogen atmosphere in a Schlenk tube. If the reaction mixture was left to stand for a few days, small multifaced colorless crystals of **3** formed. They were filtered off and dried (yield ca. 80%). The product is air stable for days. Elemental analysis: $C_{12}H_{11}CuN_4O_2$, calcd. 46.98, H 3.61, N 18.27; found C 45.95, H 3.40, N 17.95. IR (Nujol): $\tilde{\nu}$(CN) 2258 (vw), 2213 (m), 2162 (s), $\tilde{\nu}$(CO) 1724 (m), 1701 (s) cm^{-1}.

Received: December 8, 1995 [Z 8624 IE]
German version: *Angew. Chem.* **1996**, *108*, 1170–1172

Keywords: complexes with nitrogen ligands · coordination polymers · copper compounds · silver compounds · tetracyanoethylene

[1] M. M. Olmstead, G. Speier, L. Szabo, *J. Chem. Soc. Chem. Commun.* **1994**, 541, and references therein.

[2] a) J. S. Miller, J. C. Calabrese, R. W. McLean, A. J. Epstein, *Adv. Mater.* **1992**, *4*, 498; b) V. J. Murphy, D. O'Hare, *Inorg. Chem.* **1994**, *33*, 1833, and references therein.

[3] a) A. G. Bunn, P. J. Carroll, B. B. Wayland, *Inorg. Chem.* **1992**, *31*, 1297, and references therein; b) F. A. Cotton, Y. Kim, J. Lu, *Inorg. Chim. Acta.* **1994**, *221*, 1.

[4] F. A. Cotton, Y. Kim, *J. Am. Chem. Soc.* **1993**, *115*, 8511.

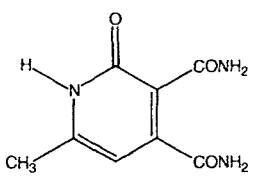
[5] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Chem. Soc. Chem. Commun.* **1994**, 2755.

[6] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Am. Chem. Soc.* **1995**, *117*, 4562.

[7] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *Angew. Chem.* **1995**, *107*, 2045; *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1895.

[8] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Am. Chem. Soc.* **1995**, *117*, 12861.

[9] The formation of **1** is somewhat surprising since the addition of acetone (or other ketones) to TCNE, to give the conjugated acid **1**H, is slow and was previously accomplished in the presence of catalysts like HCl, BF_3, or "molecular silver" [10]. The complexity of the overall process is, moreover, confirmed by the further reactions of **1**: we have observed the formation of some small platelike colorless crystals of the novel heterocyclic compound, 6-methyl-2(1H)-pyridone-3,4-dicarboxamide monohydrate (**4**) from the mother liquor. We have characterized **4** by a single-crystal X-ray analysis (see [25]). The formation of **4** from **1** presumably occurs by elimination of one equivalent of CN^- as AgCN and partial hydrolysis of the three remaining nitrile groups to amide groups, followed by ring closure by an internal oxime bond and migration of hydrogen.



4

[10] W. J. Middleton, R. E. Heckert, E. L. Little, C. G. Krespan, *J. Am. Chem. Soc.* **1958**, *80*, 2783.

[11] A single crystal of **2** was mounted under a coating of cyanoacrylic glue on an Enraf-Nonius CAD-4 diffractometer. Crystal data: monoclinic, *Cc* (no. 9), $a = 6.270(1)$, $b = 19.664(2)$, $c = 8.476(2)$ Å, $\beta = 98.91(1)^\circ$, $V = 1032.4(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.885$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å). The data collection was performed at 293 K on an Enraf-Nonius CAD4 diffractometer by the ω scan method, within the limits $3 < \theta < 27^\circ$. The structure was solved by direct methods (SIR92) and refined by full-matrix least-squares against F_o^2 (SHELX93). The final agreement index R was 0.0212 for the correct structure enantiomorph, based on 1034 independent significant $[F_o > 2\sigma(F_o)]$ absorption corrected data. Anisotropic thermal factors were assigned to all the non-hydrogen atoms [25].

[12] J. Konnert, D. Britton, *Inorg. Chem.* **1966**, *5*, 1193.

[13] M. Fujita, Y. J. Kwon, O. Sasaki, K. Yamaguchi, K. Ogura, *J. Am. Chem. Soc.* **1995**, *117*, 7287.

[14] a) T. Soma, T. Iwamoto, *Chem. Lett.* **1994**, 821; b) D. M. L. Goodgame, S. Menzer, A. M. Smith, D. J. Williams, *Angew. Chem.* **1995**, *107*, 605; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 574.

[15] a) L. R. McGillivray, S. Subramanian, M. J. Zaworotko, *J. Chem. Soc. Chem. Commun.* **1994**, 1325; b) O. M. Yaghi, G. Li, *Angew. Chem.* **1995**, *107*, 232; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 207 c) a similar structural motif is also present in a Mn^{II}/Cu^{II} polymer, but with cross-linking of the perpendicular 2D layers: H. O. Stumpf, L. Quahab, Y. Pei, D. Grandjean, O. Kahn, *Science* **1993**, *261*, 447.

[16] a) R. W. Gable, B. F. Hoskins, R. Robson, *J. Chem. Soc. Chem. Commun.* **1990**, 1677; b) T. Soma, T. Iwamoto, *Chem. Lett.* **1995**, 271.

[17] The reaction of **1**H with $Ag(CF_3SO_3)$ in H_2O/Me_2CO afforded a dark-brown microcrystalline mixture containing some crystals of **4** [9].

[18] Crystal data for **3**. The crystals are monoclinic, space group $P2_1/c$ (no. 14), $a = 7.314(2)$, $b = 15.332(4)$, $c = 12.758(3)$ Å, $\beta = 94.50(2)^\circ$, $V = 1426.2(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.429$ Mg m^{-3}. The data collection was performed within the limits $3 < \theta < 25^\circ$. The other experimental details are as for **2**. The final agreement index R was 0.0481 for 1523 independent significant $[F_o > 2\sigma(F_o)]$ absorption corrected data. Anisotropic thermal factors were assigned to all the non-hydrogen atoms [25].

[19] The bond parameters for the anion **1**, in both compounds **2** and **3**, are as expected, with mean bond lengths for $C(sp^2)-C(sp^3)$, $C(sp^2)-C(CN)$, and $C(sp^3)-C(CN)$ of 1.525, 1.384, and 1.489 Å, respectively. Note that as a consequence of the incomplete coordination the $C(sp^3)$ atom in **2** is chiral.

[20] A. F. Wells, *Further studies of Three-dimensional Nets*, ACA Monograph No.8, **1979**; this array is Net 8 in: A. F. Wells, *Three-dimensional Nets and Polyhedra*, Wiley, New York, **1977**.

[21] J. V. Smith, *Am. Mineral.* **1977**, *62*, 703.

[22] W. A. Dollase, *Z. Kristallogr.* **1965**, *121*, 369.

[23] K. H. Klaska, O. Jarchow, *Z. Kristallogr.* **1975**, *142*, 225.

[24] J. S. Kerr, *Z. Kristallogr.* **1974**, *139*, 186.

[25] Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-24. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code +(1223) 336-033; e-mail: teched(*a*) chemcrys.cam.ac.uk).

Solubilization of NaX Salts in Chloroform by Bifunctional Receptors**

Jurgen Scheerder, John P. M. van Duynhoven, Johan F. J. Engbersen, and David N. Reinhoudt*

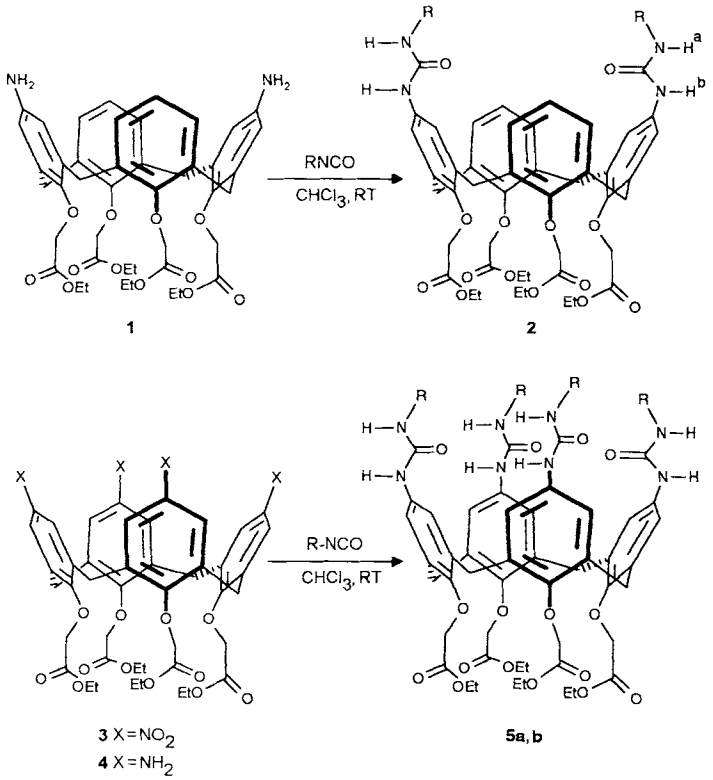
Recently, we described bifunctional receptors that are capable of binding and transporting simple salts like KH_2PO_4,[1] CsCl,[2] and NaH_2PO_4.[3] In these bifunctional receptors the (isolated) receptor sites for the anion and cation are covalently linked.[4] Cation complexation did not enhance the anion complexation or vice versa. Now, we report a class of simple, bifunctional receptors that can solubilize NaX salts (X = Cl, Br) in chloroform.[5] In these bifunctional receptors Na^+ complexation is essential for complexation of the anion (positive heterotropic allostery).

Previously we have shown that proper positioning of urea moieties on calix[*n*]arenes ($n = 4$, 6) yields receptors that are capable of binding halide anions exclusively through hydrogen bonding.[6] It has also been established that functionalization of calix[4]arenes with four ethyl ester groups at the lower rim yields ionophores with a high selectivity for Na^+ ions.[7] The combination of these two binding sites on the calix[4]arene skeleton yields molecules that are potential receptors for NaX salts (X = halide). The synthesis of the bifunctional receptors having four ester groups at the lower rim and two or four urea groups at the upper rim is depicted in Scheme 1.

[*] Prof. dr. ir. D. N. Reinhoudt, Dr. ir. J. Scheerder, Dr. J. F. J. Engbersen
Laboratory of Organic Chemistry, University of Twente
P. O. Box 217, NL-7500 AE Enschede (The Netherlands)
Fax: Int. code +(53)489-4645
e-mail: orgchem(*a*) ct.utwente.nl

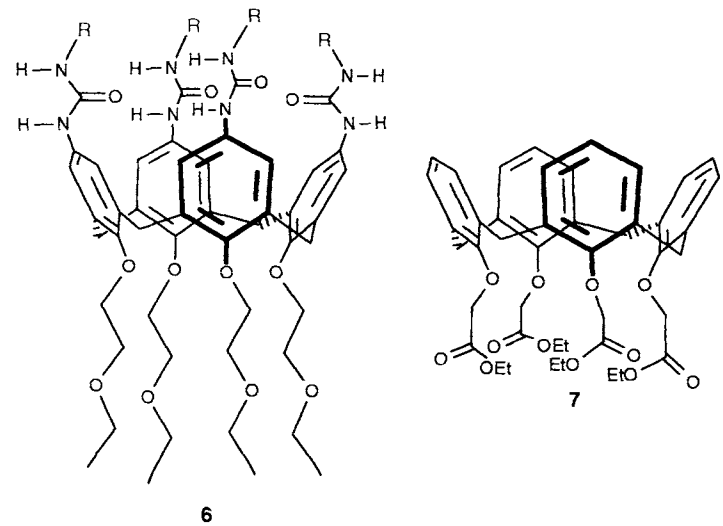
Dr. J. P. M. van Duynhoven
Laboratory of Chemical Analysis, University of Twente (The Netherlands)

[**] This work was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO). We thank D. M. Rudkevich for helpful discussions.



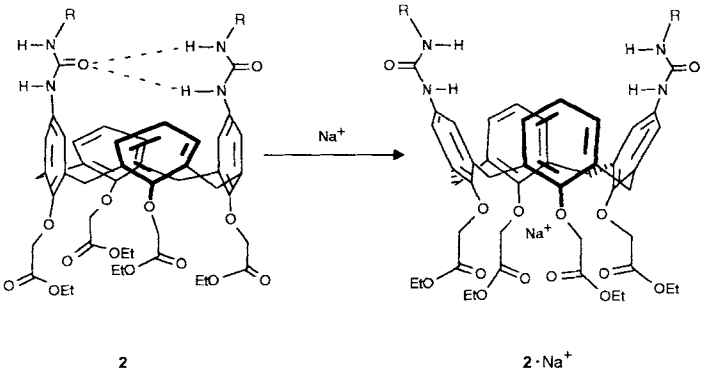
Scheme 1. Synthesis of **2** (R = *n*-octyl), **5a** (R = *n*-octyl), and **5b** (R = *tert*-butyl). The labels on the amide protons are used for the assignment of the NMR spectra in Figure 1. RT = room temperature.

Addition of *n*-octylisocyanate to a solution of 5,17-diaminocalix[4]arene tetra(ethyl ester) **1**[3] in $CHCl_3$ gave the di-(*n*-octylureido)calix[4]arene **2** in 44% yield.[8] Reduction of tetranitrocalix[4]arene **3**[9] (Scheme 1) with $NaBH_4/CoCl_2$ in MeOH at room temperature[10] gave the tetraaminocalix[4]arene **4** in 60% yield. Subsequent addition of the appropriate isocyanates to a solution of **4** in $CHCl_3$ at room temperature gave the tetra(ureido)calix[4]arenes **5a,b** in yields of 60 and 36%, respectively.[8] Calix[4]arene **6**, with only an anion binding site, and calix[4]arene **7**,[7] with only a cation binding site, were included as reference compounds (vide infra). Calix[4]arene **6** was synthesized in analogy to **5a,b**, starting from tetrakis-[(ethoxy(ethoxy)]tetranitrocalix[4]arene.[11]



Calix[4]arene **2** adopts a pinched *cone* conformation in $CDCl_3$ solution at room temperature due to intramolecular hydrogen bonding between the opposite urea moieties.[12] Recently, Rebek and Shimizu[13] reported that tetrakis(benzyloxy)tetra-(*N*-phenylureido)calix[4]arenes form hydrogen-bonded dimers in $CHCl_3$ solution at room temperature.

Upon addition of Bu_4NCl or Bu_4NBr to a 5 mM solution of **2** in $CDCl_3$, no complexation of halide anions was observed. Due to the pinched *cone* conformation of **2**, the anion binding site is blocked (Scheme 2, left). However, complexation of Na^+



Scheme 2. Complexation of Na^+ ions by **2** (R = *n*-octyl).

ions at the lower rim of **2** converts the pinched *cone* conformation into a symmetrical *cone* conformation. Intramolecular hydrogen bonding at the upper rim is not possible in this conformation due to the rigidification of the calix[4]arene skeleton (Scheme 2, right). This is evident from the large downfield shift of the ^1H NMR signal for the aromatic hydrogens of the substituted aromatic rings (ArH) from $\delta = 6.02$ (Fig. 1a) to $\delta = 7.34$ (Fig. 1b).

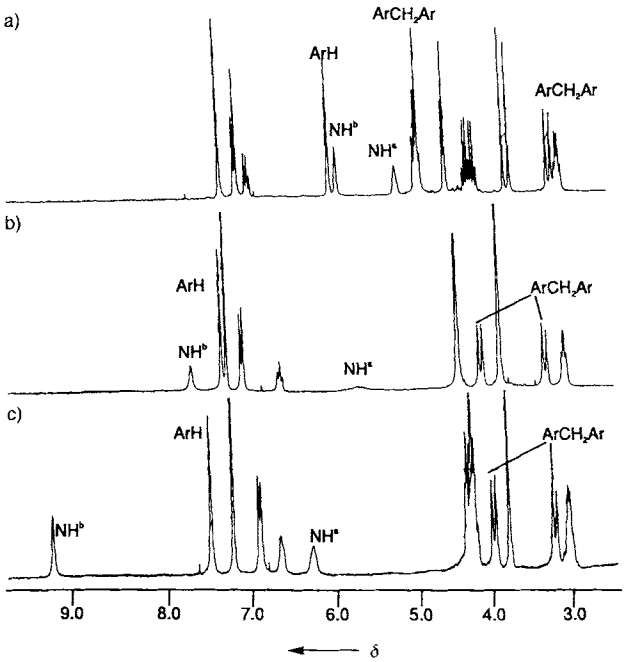


Fig. 1. ^1H NMR spectra of **2** ($CDCl_3$, 5 mM). a) Uncomplexed, b) [**2**·Na]ClO_4, c) [**2**·NaCl]. For NH^a and NH^b see Scheme 1; for ArH and $ArCH_2Ar$ see the text or ref. [14].

The addition of Bu_4NCl and Bu_4NBr to a 5 mM solution of the **2a**·Na^+ complex results in a clear downfield shift of the ^1H NMR signals of the urea hydrogens, indicating complexation of the anionic guests through hydrogen bonding.[6] In contrast, the urea hydrogens of **5a,b** are not available for anion complexation due to the formation of a hydrogen-bonded dimer in solution.[14] The addition of Bu_4NBr or Bu_4NCl to a 5 mM solution of **5a,b** in $CDCl_3$ does not result in anion complexation. When **5a,b** is treated with $NaClO_4$, the hydrogen bonding in the dimer is broken, as is evident from the disappearance of the two NMR signals for the aromatic hydrogens and the presence of one signal for these hydrogens.[15] Now the addition of Bu_4NBr or Bu_4NCl to a 5 mM solution of [**5a**·Na]ClO_4 in $CDCl_3$ results in a downfield shift of the signals of the urea hydrogens, indicating hydrogen bonding with the anions. A Job plot[16] indicates a 1:1 stoichiometry for the complex with **5a**, with $K_{ass} \geq 1.0 \times 10^4\ M^{-1}$ for Cl^- and $K_{ass} = 1.3 \times 10^3\ M^{-1}$ for Br^-. The preference for Cl^- ions can be explained by the preference of the "hard" urea hydrogen bond donor for the "harder" hydrogen bond acceptor Cl^-.

The results show that **2** and **5a,b** can simultaneously complex Na^+ and Cl^- or Br^- ions and that cation complexation induces a structural change that is prerequisite for anion complexation. This process resembles a heterotropic allosteric effect.[17] The Na^+ complexation by **5a,b** results in a dissociation of the dimer after which anion complexation can occur.

The bifunctional calix[4]arenes **2** and **5a,b** are capable of solubilizing simple alkali salts in chloroform. The results of the liquid–solid (L–S) extractions[18] of MX (M = Na, K, Cs; X = Cl, Br, I) by **2** and **5a,b** in chloroform are summarized in Table 1. A representative ^1H NMR spectrum of the NaCl com-

Table 1. Percentage of MX complex formed with **2** and **5a,b** after L–S extraction [a].

	2			**5a**			**5b**		
	Na^+	K^+	Cs^+	Na^+	K^+	Cs^+	Na^+	K^+	Cs^+
Cl^-	100	–	–	100	29	–	100	30	–
Br^-	100	16	–	100	62	–	100	75	–
I^-	100	100	–	100	100	–	100	100	–

[a] The concentration of **2** and **5a,b** is 5 mM in $CDCl_3$. See also ref. [18].

plex of **2** is depicted in Figure 1c. Comparison of this ^1H NMR spectrum with that of the free ligand **2** (Fig. 1a) and of [**2**·Na]ClO_4 reveals large downfield shifts of both urea hydrogens and the aromatic hydrogens of the substituted aromatic rings (ArH).

The strong complexation of the NaX salts indicates the strong preference of the receptors for Na^+ ions. Only partial complexation of KX salts is observed, in agreement with the weaker binding of K^+ ions by calix[4]arene tetra(ethyl esters).[7] No complexation of Cs^+ salts is observed, apparently because the Cs^+ ion is too large to fit in the cavity. Although the solubility of the free salts in chloroform is very low and decreases in the order MI > MBr > MCl, the preferential extraction of chloride salts indicates the higher affinity of the urea binding sites for Cl^- ions over Br^- and I^- ions.

Addition of an excess of **2** or **5a,b** to a solution of the salt complexes gives two sets of distinctly separate signals for the complex and the free receptor in the ^1H NMR spectrum. This means that the cation and anion are always complexed to the same molecule and that calix[4]arenes with only a cation or an anion are not present.

The complexation of the salts has also been confirmed by FAB mass spectrometry. When the chloroform solution obtained after L–S extraction of NaCl and NaBr by **5a** is concentrated and the FAB mass spectrum recorded, $[M + Na]^+$ (100%) signals are observed in the positive mode and $[M + Cl]^-$ (100%) or $[M + Br]^-$ (40%) signals in the negative mode. In addition also $[M + Na + Cl]$ (20%) and $[M + Na + Br]$ (20%) signals are present, which clearly proves the salt complexation.

Addition of NaCl or NaBr to a chloroform solution of calix[4]arene **7**, which lacks an anion binding site, did not result in any complexation of Na^+ ions. Addition of NaCl and NaBr to a chloroform solution of calix[4]arene **6**, which lacks the cation binding site, did not result in complexation of Cl^- or Br^- ions. The addition of NaCl or NaBr to a 1:1 mixture of **6** and **7** in $CDCl_3$ did not result in the complexation of Na^+ and Cl^- or Br^- ions. This shows clearly that both the cation binding site and the anion binding site are necessary for the complexation of NaCl or NaBr and that these must be within the same calix[4]arene skeleton.

In conclusion, bifunctional receptors are capable of binding hydrophilic salts MX (M = Na, K; X = Cl, Br, I) in apolar solvents, and the complexation of the cation is essential for anion complexation. Our receptors show a preference for sodium salts with hard anions.[1, 2]

Received: December 7, 1995 [Z86191E]
German version: *Angew. Chem.* **1996**, *108*, 1172–1175

Keywords: allosteric effects · calix[4]arenes · complexes with alkali metal halides · receptors · supramolecular chemistry

[1] a) D. M. Rudkevich, Z. Brzozka, M. Palys, H. C. Visser, W. Verboom, D. N. Reinhoudt, *Angew. Chem.* **1994**, *106*, 480; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 467–468; b) H. C. Visser, D. M. Rudkevich, F. de Jong, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1994**, *116*, 11554–11555.

[2] D. M. Rudkevich, J. D. Mercer-Chalmers, W. Verboom, R. Ungaro, F. de Jong, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, *117*, 6124–6125.

[3] D. M. Rudkevich, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1994**, *59*, 3683–3686.

[4] Recently we reported on a bifunctional receptor for NaSCN formed by self-assembly of a cation and an anion receptor. See D. M. Rudkevich, A. N. Shivanyuk, Z. Brzozka, W. Verboom, D. N. Reinhoudt, *Angew. Chem.* **1995**, *107*, 2300–2302; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2124–2126.

[5] Crown ethers having an arylboronic ester center have shown mono- or ditopic binding of potassium salts in organic solvents, depending on the anion. See M. T. Reetz, C. M. Niemeyer, K. Harms, *Angew. Chem.* **1991**, *103*, 1515; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1472–1474.

[6] a) J. Scheerder, M. Fochi, J. F. J. Engbersen, D. N. Reinhoudt, *J. Org. Chem.* **1994**, *59*, 7815–7820; b) J. Scheerder, J. F. J. Engbersen, A. Casnati, R. Ungaro, D. N. Reinhoudt, *J. Org. Chem.* **1995**, *60*, 6448–6454.

[7] F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill, E. M. Seward, *J. Am. Chem. Soc.* **1989**, *111*, 8681–8691.

[8] All new compounds gave correct elemental analyses and had spectral data in full accordance with their structures.

[9] W. Verboom, A. Durie, R. J. M. Egberink, Z. Asfari, D. N. Reinhoudt, *J. Org. Chem.* **1992**, *57*, 1313–1316.

[10] T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, Z. Imai, *Tetrahedron Lett.* **1969**, 4555–4558.

[11] J.-D. van Loon, J. F. Heida, W. Verboom, D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 353–359.

[12] J. Scheerder, R. Vreekamp, J. F. J. Engbersen, W. Verboom, J. P. M. van Duynhoven, D. N. Reinhoudt, *J. Org. Chem.* **1996**, in press.

[13] K. D. Shimizu, J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 12403–12407. We thank Prof. Rebek for providing us with his results on the behavior of the tetra(ureido)calix[4]arenes prior to publication.

[14] NOESY experiments with **5a,b** reveal through-space connectivities between the aromatic hydrogens of the calix[4]arene skeleton and the $NH^aCH_2CH_2$ and $NH^aCH_2CH_2$ hydrogens of **5a** and the *tert*-butyl hydrogens of **5b**. These connectivities cannot result from through-space interactions within a single molecule since in the same molecule these hydrogens are not close enough [14a]. Consequently, these NOE connectivities must result from intermolecular interactions. Furthermore, the sign of the NOE connectivities is positive, suggesting that slow-tumbling entities with increased molecular mass ($\geq$2000) are present

[14a]. Using the initial rate approximation [14b] and the distance between the equatorial and axial calix[4]arene bridging methylene hydrogens as a reference (1.79 Å) the cross relaxation constants (σ_{12}) for a two-spin system involving two atoms (1 and 2) were determined [14c]. The σ_{12} values are an indication of the degree of aggregation of the two atoms involved [14a]. The σ_{12} values for **5a** and **5b** are -0.7 and -0.2, respectively. The negative σ_{12} values suggest the presence of species with a higher molecular mass. These results support the dimeric structure for **5a,b** proposed by Rebek [13]. a) D. Neuhaus, W. P. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH, Weinheim, **1989**; b) R. R. Ernst, G. Bodenhausen, A. Wokaun, *Principles of Nuclear Magnetization Resonance in One and Two Dimensions*, Clarendon, Oxford, **1987**, pp. 490–538; c) Isotropic tumbling and pure dipole–dipole relaxation is assumed. See K. Wüttrich, *NMR of Proteins and Nucleic Acids*, Wiley, New York, **1986**, Chapter 6.

[15] According to Shimizu and Rebek, Jr. the presence of two signals for the aromatic hydrogens of tetra(ureido)calix[4]arenes **5a,b** results from hindered rotation of the urea moieties around the aryl–urea bond due to hydrogen bonding in the dimer [13]. The fact that upon the complexation of Na^+ by **5a,b** one signal for these hydrogens is present in the ^1H NMR spectra indicates that this hindered rotation is absent and that the dimer is no longer present.

[16] K. A. Conners, *Binding Constants*, 1st ed., Wiley, New York, **1987**, p. 24.

[17] J. Rebek, Jr., *Acc. Chem. Res.* **1984**, *17*, 258–264.

[18] A 5 mM solution (0.5 mL) of **2** or **5a,b** in $CDCl_3$ was stirred with an excess of MX for 24 h. The organic layer was separated and the relative amount of complex formed was determined on basis of the intensities of the ^1H NMR signals for the bridging calix[4]arene methylene hydrogens of the complex and the free ligand.

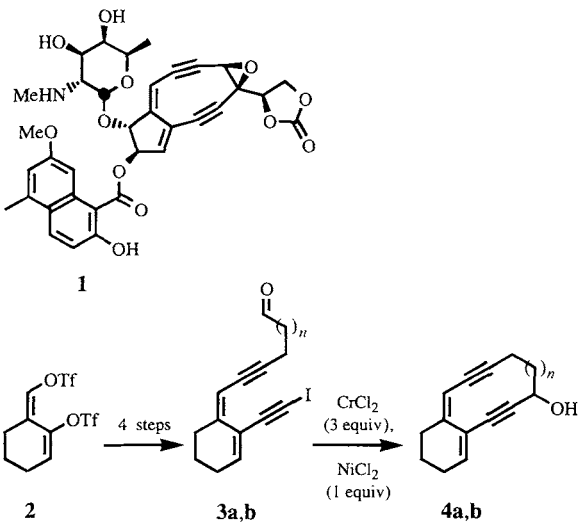
The First Model of the Neocarzinostatin Chromophore with an Epoxide Ring and a Carbonate Moiety**

Matthias Eckhardt* and Reinhard Brückner*

Dedicated to Professor Siegfried Hünig on the occasion of his 75th birthday

Neocarzinostatin is a chromoprotein with exceptionally high antitumor activity.[1] Its chromophore **1** ("NCS") has been established to be its pharmacophore. However, as soon as this compound is separated from the apoprotein, it becomes extremely sensitive towards heat (it is unstable even at room temperature), acid, base, and light. Accordingly, numerous attempts have been made to synthesize dienediyne analogs of **1** that have an in vitro DNA damaging activity comparable to that of the natural product but are hopefully much more stable.[1] In parallel studies analogs of the enediyne anticancer antibiotics esperamycin, calicheamicin, and dynemicin have been sought.[2] In spite of the structural complexity of calicheamicin[3] and dynemicin,[4] their total syntheses either as aglycons or as the fully equipped glycosides found in nature have been achieved. NCS, however, remains an elusive synthetic goal.

In our most recent efforts directed towards the synthesis of NCS analogs we have used bis(enol trifluoromethanesulfonate) **2**[5] ("bistriflate") as a starting material. We found that **2** can be converted into the iodinated dienediyne aldehydes **3a** and **3b** (Scheme 1), and that these compounds cyclize under modified Nozaki–Hiyama conditions to give the dienediyne model compounds **4a** (six-/ten-membered ring system) and **4b** (six-/eleven-membered ring system) of NCS (five-/nine-membered ring system).[6] The cyclized compounds were isolated in quite



Scheme 1. Tf = CF_3SO_2; **a**, $n = 1$; **b**, $n = 2$.

respectable yields of 51% (**4a**) and 54% (**4b**), indicating that the products are fairly stable. This encouraged us to attempt the synthesis of dienediyne models more closely resembling NCS. To limit ring strain we designed a target compound having the tested[6] unnatural six-/eleven-membered rings in the carbon skeleton, but we also incorporated both the epoxide and the carbonate substructure of the natural product in the correct configurations.

Bistriflate **2**[5] and a 1:1 diastereomeric mixture of the enantiomerically pure alcohols **5**[7] were coupled in the presence of catalytic amounts of $[PdCl_2(PPh_3)_2]$ and CuI to provide the monocoupling product **6** and nearly none of its regioisomer (Scheme 2). The technique and selectivity in this reaction parallel those of similar couplings which we described earlier.[5, 6] Although the monocoupling product **6** was isolable, it was usually used in situ in the next step. When the coupling reaction yielding **6** had gone to completion, we added pentynol to the reaction mixture, which still contained the catalytically active Cu and Pd species. A second coupling reaction occurred with cleavage of the remaining triflate moiety. Standard aqueous work-up and purification by flash chromatography on silica gel[8] furnished the biscoupling product **7** in 73% yield.[9] Product **7** is a 1:1 mixture of diastereomers since the precursor alcohol **5** was used as a 1:1 mixture of diastereomers.

Oxidation of diol **7** with the Dess/Martin periodinane[10] afforded ketoaldehyde **8** in 69% yield (Scheme 2).[9] The 300 MHz ^1H NMR spectrum of compound **8** revealed a minor broadened singlet at $\delta = 5.52$ (impurity) besides a dominant broadened singlet at $\delta = 5.45$ (main product). Such signals are typical for the exocyclic olefinic methine protons of monocyclic *Z*-configurated dienediynes like compound **8**.[5b, 6b] The minor signal indicates the presence of 4 mol% of the regioisomeric biscoupling product, a dienediyne ketoaldehyde in which the positions of the two alkyne arms are interchanged. Product **8** was used without further purification; after the next two steps the contaminating regioisomer could no longer be detected by NMR spectroscopy.

The next transformation, a McMurry coupling,[11] is the key step of our synthesis. In this reaction the monocyclic ketoaldehyde **8** was added by syringe pump to a suspension of low-valent titanium freshly prepared from $TiCl_3 \cdot 1.5\,MeOCH_2CH_2OMe$ (DME) and Zn/Cu couple (Scheme 2). This coupling leads chemoselectively to the bicyclic trienediyne **9**,[9] provided the

[*] Prof. Dr. R. Brückner, Dipl.-Chem. M. Eckhardt
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: Int. code +(551)392944

[**] This work was supported by the Volkswagen-Stiftung (Schwerpunktprogramm "Metallorganische Reaktionen für die Organische Synthese").