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(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: C19H26NO3, calsd: C 34.86, H 2.69; found: C 34.69, H 2.72. IR (KBr): 3420, 2923, 1670, 1023 cm⁻¹. 2: 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 (0.033 g, 0.187 mmol) in acetone (5 mL) was layered over a solution of [Cu(acac)2]·(PF6). (0.064 g, 0.187 mmol) in acetone (5 mL) under a nitrogen atmosphere in a Schlenk tube. If the reaction mixture was left to stand for a few days, small multiformed colorless crystals of 2 formed. They were filtered off and dried (yield ca. 80%). The product is air stable for several weeks. Elemental analysis: C41H46Cu2C12O4, calsd: C 48.61, H 5.61, N 16.27; found: C 45.95, H 3.40, N 17.95. IR (Nujol): HCN 2258 (vav), 2321 (m), 2182 (s), COC (1724 (m), 1701 (s) cm⁻¹.

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9. The formation of 1 is somewhat surprising since the addition of acetone (or other ketones) to TCNE, to give the conjugated add 1H, is slow and was previously accomplished in the presence of catalytic amounts of HCl, BF₃ 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 plate-like colorless crystals of the novel heterocyclic compound, 2-methyl-[2(1H)-pyridone]-3,4-diamino-bis(3-sulfone) 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 disconnection of one equivalent of CN⁻ as AgCN and partial hydrolysis of the remaining nitride groups to amide groups, followed by ring closure by an internal oxime bond and elimination of hydrogen.

11. A single crystal of 2 was mounted under a coating of cryoanhydride glue on an Enraf-Nonius CAD-4 diffractometer. Crystal data: monoclinic, Cc (no. 9), a = 6.196(1) Å, b = 10.796(1) Å, c = 9.302(1) Å, β = 90.00(1), Z = 4, Dcalc = 1.885 g cm⁻³, MoKα radiation (λ = 0.71070 Å). The data collection was performed on 293 K on an Enraf-Nonius CAD4 diffractometer by the ω scan method, within the limits 5<ω<27°. The structure was solved by direct methods (SIR2) and refined by full-matrix least-squares against F² (SHELXL93). The final agreement index R was 0.0252 for the correct structure refinement, based on 105 independent significant F² > 2.2σ(F²) absorption corrected data. Anisotropic thermal factors were assigned to all the non-hydrogen atoms [25].

Solubilization of NaX salts in Chloroforom by Bip Elasticsearch Receptors**

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

Recently, we described bifurcational receptors that are capable of binding and transporting simple salts like K2PO4, CaCl2, and NaHPO4. In these bifurcational receptors the (isolated) receptor sites for the anion and cation are covalently linked. Cation complexation did not enhance the anion complexation or vice versa. Now, we report a class of simple, bifurcational receptors that can solubilize NaX salts (X = Cl, Br) in chloroform. In these bifurcational 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[4]arenes (n = 4, 6) yields receptors that are capable of binding halide anions exclusively through hydrogen bonding. It has also been established that functionalization of calix[4]arenes with four ethyl ester groups at the lower rim yields ionsophores with a high selectivity for Na⁺ ions. The combination of these two binding sites on the calix[4]arenec skeleton yields molecules that are potential receptors for NaX salts (X = halide). The synthesis of the bifurcational receptors having four ester groups at the lower rim and two or four urea groups at the upper rim is depicted in Scheme 1.

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Calix[4]arene 2 adopts a pinched cone conformation in CDCl₃ solution at room temperature due to intramolecular hydrogen bonding between the opposite aryl moieties. Recently, Rebeck and Shimizu reported that tetrakis(benzylxoy)tetra-(N-phenyleureido)calix[4]arenes form hydrogen-bonded dimers in CHCl₃ solution at room temperature.

Upon addition of Bu₄NCl or Bu₄NBr to a 5 mM solution of 2 in CDCl₃, 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⁺ 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 δ = 6.02 (Fig. 1a) to δ = 7.34 (Fig. 1b).

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


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**Fig. 1.** ¹H NMR spectra of 2 (CDCl₃, 5 mM). a) Uncomplexed, b) [2-Na]ClO₄, c) [2-NaClO]. For NH⁺ and NH₃⁺ see Scheme 1; for ArH and ArCH₂Ar see the text or ref. [14].
The addition of Bu₄NCl and Bu₄NBBr 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.[4] 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.[4] The addition of Bu₄NBBr or Bu₄NCl to a 5 mm solution of 5a,b in CDCl₃ does not result in anion complexation. When 5a,b is treated with NaClO₄, 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.[5] Now the addition of Bu₄NBBr or Bu₄NCl to a 5 mm solution of [5a-Na⁺]ClO₄ in CDCl₃ 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,b, with $K_{s} = 1.0 \times 10^{3} \text{M}^{-1}$ for Cl⁻ and $K_{s} = 1.3 \times 10^{3} \text{M}^{-1}$ 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 heterotopic allostery effect.[7] 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 complex 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⁺]ClO₄ 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 ester).[19] 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 M> MBr > MCI, 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 complex 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⁺]¹ (100%) signals are observed in the positive mode and [M + Cl⁻]¹ (100%) or [M + Br⁻]¹ (40%) signals in the negative mode. In addition also [M + Na⁺ + Cl⁻]² (20%) and [M + Na⁺ + Br⁻]² (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 CDCl₃ 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, Cs; 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]

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

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

<table>
<thead>
<tr>
<th></th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cs⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cs⁺</th>
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<td>Cl⁻</td>
<td>100</td>
<td>-</td>
<td>100</td>
<td>29</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Br⁻</td>
<td>100</td>
<td>16</td>
<td>100</td>
<td>62</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>I⁻</td>
<td>100</td>
<td>100</td>
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</tr>
</tbody>
</table>

[a] The concentration of 2 and 5a,b is 5 mm in CDCl₃. See also ref. [18].

[8] All new compounds gave correct elemental analyses and had spectral data in full accordance with their structures.
[14] NOESY experiments with 5a,b reveal through-space connectivities between the aromatic hydrogens of the calix[4]arene skeleton and the NH₃⁺CH₃CH₂NH₃⁺CH₃CH₂OH 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 (≥ 2000) are present.
The First Model of the Neocarzinostatin Chromophore with an Epoxide Ring and a Carbone Moiety**

Matthias Eckhardt* and Reinhard Brückner*

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

Neocarzinostatin is a chromoprotein with exceptionally high antitumor activity. 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. In parallel studies analogs of the enediyne anticancer antibiotics espermycin, calicheamicin, and dynemicin have been sought, in spite of the structural complexity of calicheamicin and dynemicin, their total synthesis 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(enzol trifluoromethanesulfonate) 2585(2) ("bisnol") 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 compounds 4a (six-ten-membered ring system) and 4b (six-eleven-membered ring system) of NCS (five-nine-membered ring system). The cyclized compounds were isolated in quite 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 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 2585(1) and a 1:1 diastereomeric mixture of the enantio-omERICALLY pure alcohols 258(1) were coupled in the presence of catalytic amounts of [PdCl2(dppe)2] and CuI to provide the monocoupling product 6 and nearly none of its regiosomer (Scheme 2). The technique and selectivity in this reaction parallel those of similar couplings which we described earlier. 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 pentyanol 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 furnished the bisscoupling product 7 in 73% yield. Produkt 7 is a 1:1 mixture of diastereomers since the precursor alcohol 5 was used as a 1:1 mixture of diastereomers.

Oxidation of dio! 7 with the Dess/Martin periodinane afforded ketoaldehyde 8 in 69% yield (Scheme 2). The 300 MHz 1H NMR spectrum of compound 8 revealed a minor broadened singlet at δ = 5.52 (imprunity) beside a dominant broadened singlet at δ = 5.45 (main product). Such signals are typical for the exocyclic olefinic methine protons of monocyclic Z-configurated dienediyne like compound 8. The minor signal indicates the presence of 4 mol% of the regiosomeric bisscoupling 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 regiosomer could no longer be detected by NMR spectroscopy.

The next transformation, a McMurry coupling, is the key step of our synthesis. In this reaction the monocyclic ketoaldehyde 8 was added by syringe pump to a suspensions of low-valent titanium freshly prepared from TiCl3, 1.5 MeOHCH2O Me (DME) and Zn/Cu couple (Scheme 2). This coupling leads chemoselectively to the bicyclic trienediyne 9 provided the

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