"Cascade"- and "Nonskid-Chain-like" Syntheses of Molecular Cavity Topologies

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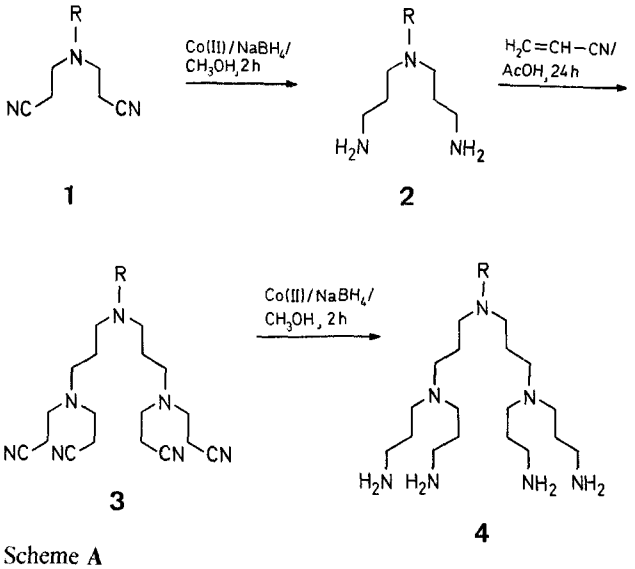
For the construction of *large* molecular cavities and pseudo-cavities that are capable of binding ionic guests or molecules (as complex or inclusion compounds) in a Host-Guest interaction[1], synthetic pathways allowing a frequent repetition of similar steps would be advantageous. Neutral ligand syntheses carried out so far[2], have not taken due advantage of this principle. We made use of this repeating-step principle in order to annex successive arms or rings in the synthesis of noncyclic and cyclic polyaza compounds *with increasingly growing cavity size*. Starting from monoamines (Scheme **A**), diamines (Scheme **B**), or else from a diaza-monocyclic ring such as **8** and adopting the now described "cascade-like" (Schemes **A** and **B**) or "nonskid-chain-like" (Scheme **C**) pathway for bond-formation, we succeeded in synthesizing noncyclic polyaza compounds, e.g. **4**, **7** and novel multicyclic medium- or large-sized ring systems such as **11–15**. Owing to the particular properties of the synthesized polyamines (basicity, extreme water-solubility, salt-complexation), all the synthetic steps mentioned above had to be modified with respect to those involved in the usual reactions of monofunctional aza-compounds. This particularly applies for the decomplexation following the cobalt(II) ion-catalyzed reduction.



Scheme **A**

Reaction of mono- or diamines (cf. Table) with acrylonitrile leads to the annexation of a pair of "arms" per amino group[3] (compounds **1** or **5** in Schemes **A** or **B**). After reducing the nitrile groups, to amine functions, repetition of the acrylonitrile addition yields the lengthened "cascade" molecule[4] **3** or **7**, which upon reduction as polyamines[6] or hydrolysis as polycarboxylic acids[7] should give novel complexones.

Polycycles enlarged in the "nonskid-chain" form are obtained by reacting monocycles of type **8** with glycolic acid nitrile or acrylonitrile[3] to form dinitriles **9** (step *a*), which are then reduced to the "two-armed" amines **10** (step *b*). Reaction with a dicarboxylic acid dichloride under high dilution conditions[8] (step *c*) gives the bicyclic system **11** (cf. Table). Subjecting **12** (obtained by reduction of **11** – step *d*) to the synthetic sequence: steps $a \rightarrow b \rightarrow c$ again leads to the tricyclic system **15**; that with m = o = 6, q = 4 (Table) represents a new type of oxygen-free hexaaza-cryptands possessing a large cavity. There is, in principle, no barrier to the annexation of more rings via the reaction sequence $a \cdots d$; the chain length can be varied in the reaction step *c* (Scheme **C**).

From the synthetic point of view, it is worth noting that the smooth, glacial acetic acid-catalyzed bis-cyanoethylation of primary aliphatic oligoamines as well as the bis-cyanoethylation of bifunctional secondary amines takes place in a

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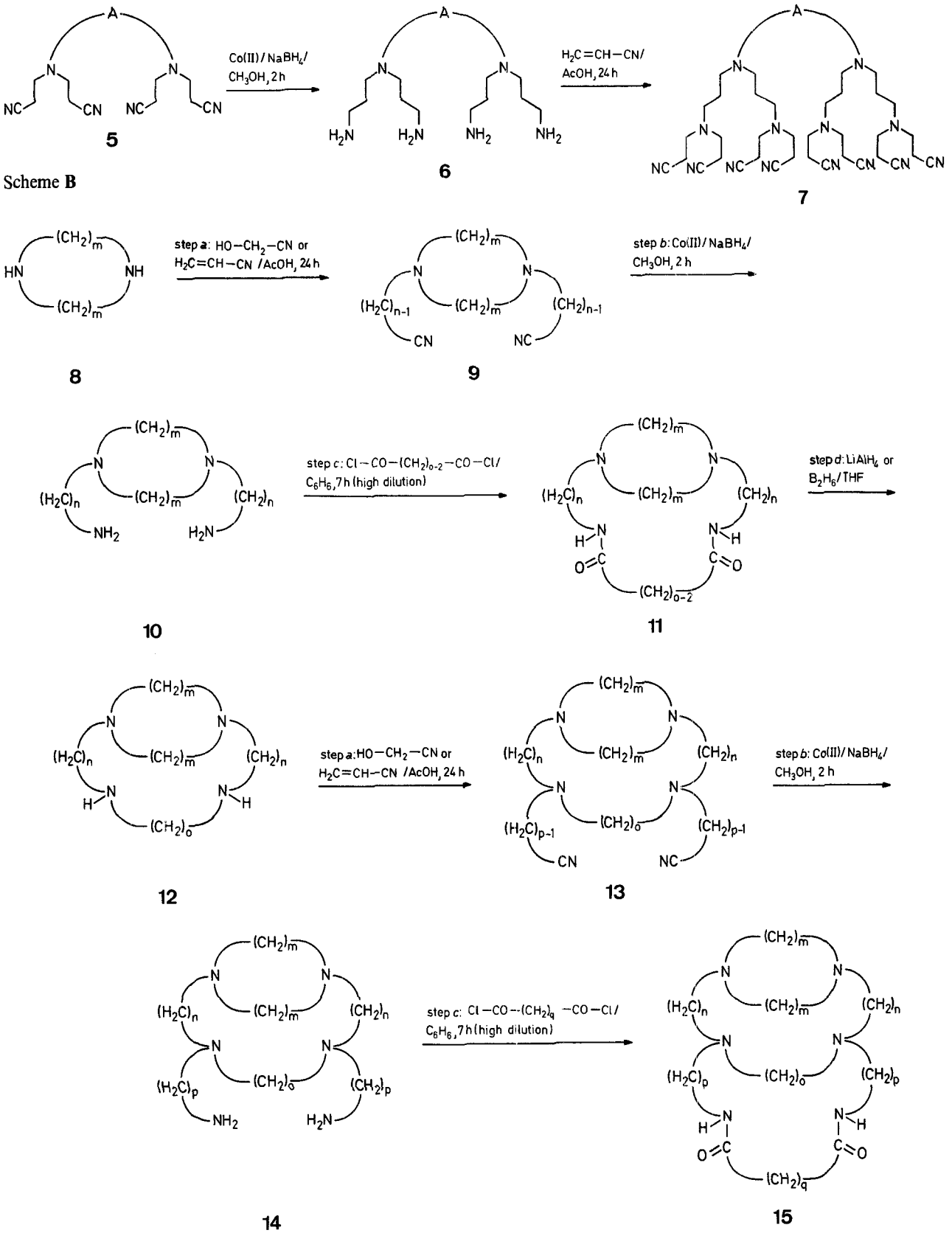


Scheme B

Scheme C

remarkably shorter time compared with other methods employed so far[3c,d]. Reduction of nitriles **9**, **13** proved to be a difficult step in the preparative synthesis with sodium borohydride and other borohydrides, cleavage of aminoethyl or aminopropyl side-chains occurs as a side-reaction. Reduction with cobalt(II)/sodium borohydride[9] proved to be the best choice.

For the isolation of the polyaza compounds after reduction, the following procedure was time-sparing and led to better yields; removal of the cobalt salts as ammine complex and subsequent extraction of the ammoniacal solution with chloroform[9b]. A further obstacle resided in the characterization of the high molecular weight and usually liquid tricyclic diamides **15**, since it is difficult to get abundant molecular peaks in the mass spectra.

With the use of known monocyclic diaza-oligooxaalkanes and following the "nonskid chain-synthesis principle", it is possible to synthesize novel, tailored cavity topologies containing strategically arranged heteroatoms.

Preparation of Oligonitriles 9a and 13a via Cyanomethylation; General Procedure:

70% Hydroxyacetonitrile solution (26 ml, 0.32 mol) is added dropwise to the diamine **8** or **12** (0.02 mol) in water (50 ml) at room temperature. The mixture is stirred for 4 h, the nitrile formed is filtered off, the aqueous solution is extracted with chloroform (3 × 25 ml), and the extract dried with sodium sulfate. The solvent is removed under vacuum and the residue is recrystallized. Product **13a** does not form as a solid and is extracted from the reaction mixture with chloroform (5 × 25 ml). Removal of the solvent in vacuum leaves an oily crude product which is chromatographed on neutral alumina with chloroform.

Preparation of Oligonitriles 1, 3, 5, 7, 9b, 13b, and 13c via Cyanoethylation; General Procedure:

The amine **2**, **6**, **8**, or **12** (10 mmol) is dissolved at room temperature in acrylonitrile (50 ml). Glacial acetic acid (20 mmol per primary amino function) is added and the solution is heated under reflux for 24 h. Excess acrylonitrile is distilled off under vacuum, the residue is extracted with chloroform (30 ml), and added to concentrated ammonia solution (10 ml). The organic phase is separated, washed with water, and dried with sodium sulfate. Solid products are recrystallized; oils are chromatographed on neutral alumina with chloroform.

Preparation of Primary Amines 2, 4, 6, 10, and 14 via Reduction with Cobalt(II)/Sodium Borohydride; General Procedure:

The nitrile **1**, **3**, **5**, **9**, or **13** (50 mmol) is dissolved in methanol (400 ml) and cobalt(II) chloride hexahydrate (23.8 g, 100 mmol per cyano group) is added. Sodium borohydride (75.6 g, 2.0 mol for dinitriles, 151.2 g, 4.0 mol for tetranitriles) is added in portions (violent gas evolution). The resultant mixture is stirred for 2 h at room temperature and then cautiously acidified with concentrated hydrochloric acid (400 ml). The solvents are removed under vacuum and the deep-blue, solid residue is taken up in concentrated ammonia solution (500 ml) and chloroform (370 ml). The flesh-colored precipitate is filtered off, the aqueous phase is extracted with chloroform (6 × 150 ml), and the extracts are dried with magnesium sulfate. The oily crude product is taken up in anhydrous benzene and dried with molecular sieve (3 Å, Merck) for 10 h.

Preparation of Bicyclic Diamides 11 and Tricyclic Diamide 15 under High Dilution; General Procedure:

Adipic acid dichloride (0.92 g, 5 mmol) dissolved in anhydrous benzene (250 ml) and the amine **10** or **14** (10 mmol) in anhydrous benzene (250 ml) are added simultaneously dropwise under nitrogen to anhydrous benzene (1000 ml) stirred at room temperature (yields are increased by rapid stirring). When the addition is complete, stirring is continued for 1 h, the precipitated hydrochloride is filtered off and the benzene phase concentrated. Solid products are recrystallized, oils are chromatographed on neutral alumina with chloroform.

Reduction of Cyclic Diamide 11 with Lithium Tetrahydroaluminate; General Procedure:

To a solution of lithium tetrahydroaluminate (3.7 g, 100 mmol) in tetrahydrofuran (100 ml) is added continuously under nitrogen through a hot-extracting soxhlet over a period of 48 h the diamide **11** (10 mmol). The mixture is then hydrolyzed with aqueous tetrahydrofuran, the precipitated aluminium hydroxide is filtered off, and the residue is extracted with tetrahydrofuran (3 × 100 ml). The combined filtrates are concentrated, the product is taken

Table. Compounds prepared

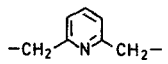
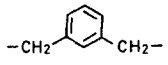
Product	R in **1–4** or A in **5–7**	Yield [%]	m.p. (solvent) or b.p./torr	Molecular formula[a]	Mass spectra *m/e* for M^+ (calc.)	T.L.C.[b] R_f (solvent)
1a	$C_6H_5-CH_2$	76	170–175°/0.5	$C_{13}H_{15}N_3$ (213.3)*	—	—
1b	*cyclo*-C_6H_{11}	69	152–156°/0.5	$C_{12}H_{19}N_3$ (205.3)*	205.1580 (205.1579)	—
2a	$C_6H_5-CH_2$	66	oil	$C_{13}H_{23}N_3$ (221.3)*,[c]	—	—
2b	*cyclo*-C_6H_{11}	44	110–115°/0.5	$C_{12}H_{27}N_3$ (213.3)*	—	—
3a	$C_6H_5-CH_2$	66	oil	$C_{25}H_{35}N_7$ (433.6)	433.2933 (433.2953)	0.73 (methanol)
4a	$C_6H_5-CH_2$	35	oil	$C_{25}H_{51}N_7$ (449.7)	—[d]	0.65 (methanol/acetic acid/water, 10:1:1)
5a		74	103° (acetone)	$C_{19}H_{23}N_7$ (349.4)*	—	—
5b	$-CH_2-CH_2-$	70	62° (acetone/ether)	$C_{14}H_{20}N_6$ (272.2)*	—	—
5c		86	76–77° (acetone/ether)	$C_{20}H_{24}N_6$ (348.4)*	—	—
6a	substituents as for **5a–c**	63	oil	$C_{19}H_{39}N_7$ (365.5)	365.3260 (365.3266)	0.51 (methanol/acetic acid/water, 10:1:1)
6b		24	oil	$C_{14}H_{36}N_6$ (288.3)	—[d]	0.50 (methanol/acetic acid/water, 10:1:1)
6c		57	oil	$C_{20}H_{40}N_6$ (364.5)	364.3320 (364.3314)	0.46 (methanol/acetic acid/water, 10:1:1)
7a		42	oil	$C_{43}H_{63}N_{15}$ (790.0)	790[e] (790)	0.73 (methanol)
7b		64	oil	$C_{38}H_{60}N_{14}$ (712.0)	713 ($M^+ + H$)[e] (713)	0.56 (methanol)

Table. (Continued)

Product	m	n	o	p	q	Yield [%]	m.p. (solvent) or b.p./torr	Molecular formula[a]	Mass Spectra *m/e* for M^+ (calc.)	T.L.C.[b] R_f (solvent)
9a	6	2	—	—	—	92	162° (acetone)	$C_{16}H_{28}N_4$ (276.4)*	—	—
9b	6	3	—	—	—	76	97° (methanol)	$C_{18}H_{32}N_4$ (304.3)*	304.2622 (304.2627)	—
10a	6	2	—	—	—	83	oil	$C_{16}H_{36}N_4$ (284.4)	—[f]	0.43 (methanol/acetic acid/water, 10:1:1)
10b	6	3	—	—	—	58	oil	$C_{18}H_{40}N_4$ (312.9)	312.3252 (312.3257)	0.48 (methanol/acetic acid/water, 10:1:1)
11a	6	2	6	—	—	19	200° (acetone/methanol)	$C_{22}H_{42}N_4O_2$ (394.3)*	394.3309 (394.3307)	—
11b	6	3	6	—	—	18	295° (acetone)	$C_{24}H_{46}N_4O_2$ (422.4)*	422.3620 (422.3621)	—
11c	2	3	6	—	—	43	209° (acetone)	$C_{16}H_{30}N_4O_2$ (310.5)*	—	—
12a	6	2	6	—	—	79	oil	$C_{22}H_{46}N_4$ (366.4)	366.3713 (366.3722)	0.68 (methanol)
12c	2	3	6	—	—	84	oil	$C_{16}H_{34}N_4$ (282.5)	282.2781 (282.2783)	0.49 (methanol)
13a	6	2	6	2	—	85	oil	$C_{26}H_{48}N_6$ (444.4)	444.3953 (444.3940)	0.67 (methanol)
13b	6	2	6	3	—	74	oil	$C_{28}H_{52}N_6$ (472.4)	472.4243 (472.4254)	0.71 (methanol)
13c	2	3	6	3	—	63	oil	$C_{22}H_{40}N_6$ (388.4)	388.3307 (388.3314)	0.52 (methanol)
14	6	2	6	3	—	61	oil	$C_{28}H_{60}N_6$ (480.5)	480.4885 (480.4879)	0.50 (methanol/acetic acid/water, 10:1:1)
15	6	2	6	3	4	12	oil	$C_{34}H_{66}N_6O_2$ (590.5)	590.5236 (590.5247)	0.48 (methanol)

[a] Products indicated with an asterix (*) gave satisfactory microanalyses [C ±0.42% (except **1b** +0.69%), H ±0.22%, N ±0.30%].

[b] All substances are pure as shown by T.L.C. Al_2O_3-precoated plastic sheets for T.L.C., layer: 0.2 mm, A 20 X N/UV 254, Macherey, Nagel & Co., Düren.

[c] Tripicrate.

[d] These liquid compounds do not give any molecular-ion peak (M^+) in their electron-impact mass spectra. Their structures could be characterized by the appearance of typical fragment-ions. Neither crystalline picrates, imines nor complexes could be prepared.

[e] The field desorption mass spectra of the compounds **7a,b** show (M^+)- respectively ($M+H^+$)-peaks. Their structures are confirmed by typical fragmentation patterns.

[f] Characterized as diamide **11a**.

up in chloroform, and the chloroform solution is dried with sodium sulfate. Concentration of the chloroform solution gives spectroscopically pure product which is not purified further.

Reduction of Diamide 11c with Diborane; Preparation of Cyclic Amine 12c:

To a solution of sodium borohydride (7.6 g, 200 mmol) and boron trifluoride etherate (26.0 ml, 200 mmol) in tetrahydrofuran (100 ml) is added powdered diamide **11c** (3.10 g, 10 mmol). The mixture is heated under reflux for 4 h. Excess diborane is decomposed by water and the solvent distilled off in vacuum. Concentrated hydrochloric acid (25 ml) and water (25 ml) are added to the colorless, amorphous residue and the mixture is heated under reflux for 2 h. The acidic solution is neutralized with sodium hydroxide solution and extracted with cold chloroform (3 × 150 ml). The extract is dried with sodium sulfate and the solvent removed in vacuum to give a colorless oil.

We thank Dr. H. R. Schulten and H. B. Linden (Institute of Physical Chemistry) and Dr. G. Eckhardt for their kind assistance in recording and assigning the field desorption and electron impact mass spectra.

Received: July 12, 1977
(Revised form: September 14, 1977)

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[4] The "cascade" and "nonskid chain" topology was chosen, in analogy to macroscopic systems, just like the design of octopus molecules[5] with respect to biological models. By "cascade syntheses" we mean reaction sequences which can be carried out repeatingly, whereby as in Schemes **A** and **B**, a functional group is made to react in such a way as to appear twice in the subsequent molecule. By "nonskid syntheses", we mean the stepwise construction of polycyclic ring compounds by repeatingly occuring reaction sequences; thus, a ring system is connected by a new bridge, which possesses functional groups for the annexation of further bridges as in Scheme **C**.

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(b) The procedure for the working-up is not given in detail in this preliminary communication.