Molecular Clips Based on Propanediurea

Synthesis and Physical Properties

een wetenschappelijke proeve op het gebied van de Natuurwetenschappen, Wiskunde en Informatica

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Katholieke Universiteit Nijmegen, volgens besluit van het College van Decanen in het openbaar te verdedigen op dinsdag 15 januari 2002 des namiddags om 3.30 uur precies

door

Robertus Johannes Jansen

geboren op 29 maart 1971
te Luyksgestel

Promotor:	Prof. dr. R. J. M. Nolte
Copromotor:	Dr. J. W. Scheeren

Manuscriptcommissie:	Prof. dr. B. Zwanenburg
	Dr. R. J. M. Klein Gebbink (UU)
	Dr. J. N. H. Reek (UvA)

Omslag: 合成凹分子 (hé chéng au fen tž): 'Synthetische holtemoleculen'

Ontwerp en uitvoering: Lichen Kao en Rob J. Jansen

E-mail: rob.j.jansen@philips.com

ISBN 90-9015306-3

VLADIMIR: *That passed the time.*
ESTRAGON: *It would have passed in any case.*
VLADIMIR: *Yes, but not so rapidly.*

Samuel Beckett: *Waiting for Godot* (1955)

Voor mijn ouders

CONTENTS

1 General Introduction

1.1 Introduction

For many centuries, Nature has been an unlimited source of inspiration for scientists. Studying and mimicking Nature has been at the basis of a large number of scientific achievements. The Ancient Greek already recorded their dream of flying like the birds, but at the same time recognized man's inferiority to Nature.[1] The study of natural processes has gradually been scaled down from the macroscopic to the microscopic level, and more recently to the molecular level, and these processes continue to surprise and inspire scientists.

Nature has produced extremely complex structures that are perfectly suited to perform often highly complicated tasks. Evident but nonetheless beautiful examples include the action of enzymes, which are highly efficient and selective biocatalysts, the self-replicating properties incorporated in DNA, and the extremely efficient use of genetic material exhibited by viruses. Scientists are only just beginning to understand these processes. One abundantly cited and fairly well understood example is the Tobacco Mosaic Virus. This virus consists of 2130 identical protein subunits and a single RNA chain.[2] Under suitable conditions, the protein subunits assemble into discs, which then spontaneously organize themselves around the RNA chain to form a complete virus particle (see Figure 1).

A great challenge for the organic chemist is to design and prepare organic molecules that mimic these natural systems and processes. The examples that Nature provides us, show that most large biological systems consist of identical subunits that are held together by a large number of weak, non-covalent interactions. The assembly of these subunits takes place by molecular recognition events and is reversible, dynamic and self-correcting, and affords a product representing a thermodynamic minimum.[3] The use of identical subunits is Nature's way to reduce the amount of genetic material needed to perform the tasks required for life. This notion can be translated into organic chemistry terms as follows: the use of small molecules capable of self-association to prepare large structures reduces the amount of synthetic effort required. In other words: mimics of Nature consisting of one single molecule will usually be far too complex to prepare by conventional

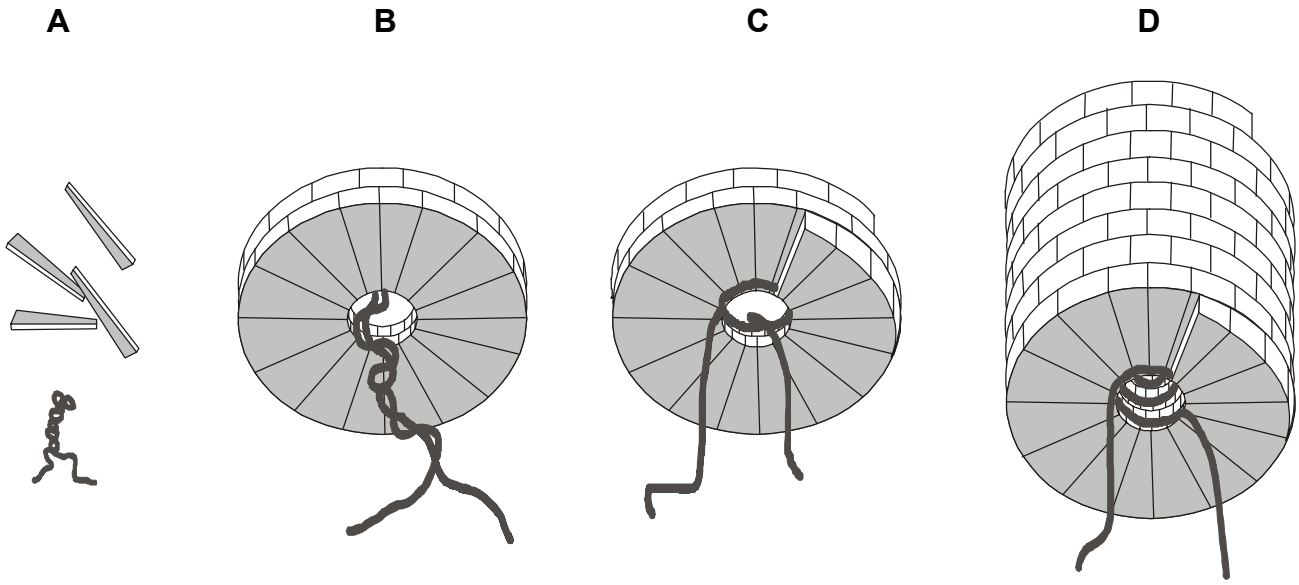


Figure 1 *Self-assembly of the Tobacco Mosaic Virus*

covalent organic synthesis. If large structures are to be prepared, the organic chemist needs to rely on supramolecular processes rather than covalent synthesis.

1.2 Supramolecular Chemistry[4]

Supramolecular chemistry is a branch of chemistry concerned with the assembly of molecules by non-covalent interactions: hydrogen bonding, π-π stacking, polar, and Van der Waals interactions. This assembly is based on molecular recognition, which relies upon complementarity of size, shape, and chemical functionalities. The first steps in the field of non-covalent interactions in synthetic systems were made by Pedersen in 1967.[5] In that year he published complexation studies of a large number of crown ethers with metal ions. Subsequent studies by Lehn,[6] and Cram,[7] gave rise to the

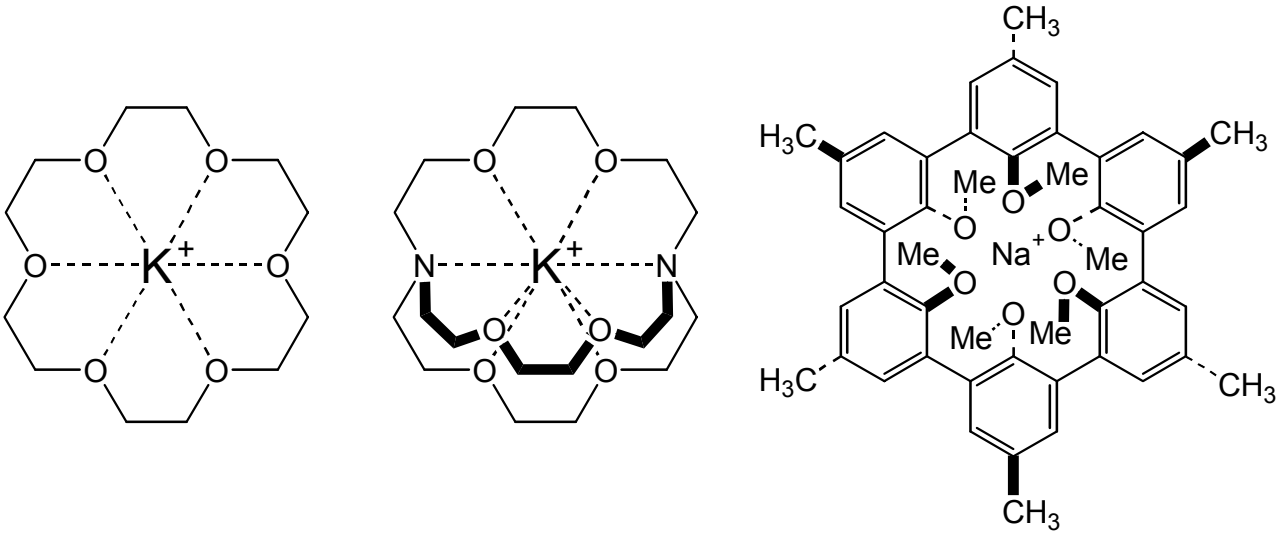


Figure 2 *Complexes of metal ions with a crown ether, a cryptand, and a spherand*

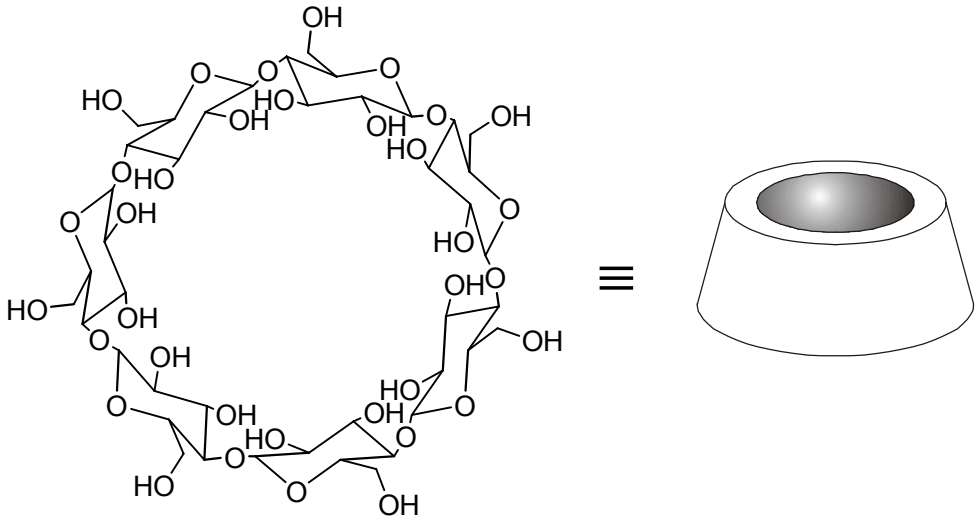


Figure 3 *The structure of β-cyclodextrin*

design and synthesis of cryptands and spherands (see Figure 2). All of these so-called host molecules are able to bind metal ions, using only ion-dipole interactions, as depicted in Figure 2.
Binding of neutral guests requires the use of other non-covalent interactions. In aqueous solution, cyclodextrins are often used as host molecules. Cyclodextrins are naturally occurring cyclic compounds consisting of six or more linked D-glucopyranose units. They have the shape of a bucket without a bottom, and possess a V-shaped cavity (Figure 3). Within this cavity, a variety of aromatic guests can be complexed in aqueous solution, using predominantly hydrophobic interactions.[8] Association constants are often large, but guest-selectivity generally is low.
In organic solvents, hydrogen bonding is often used for complex formation.[9] Whitesides and co-workers exploited the strong affinity of melamine towards barbituric acid. Using hydrogen bond

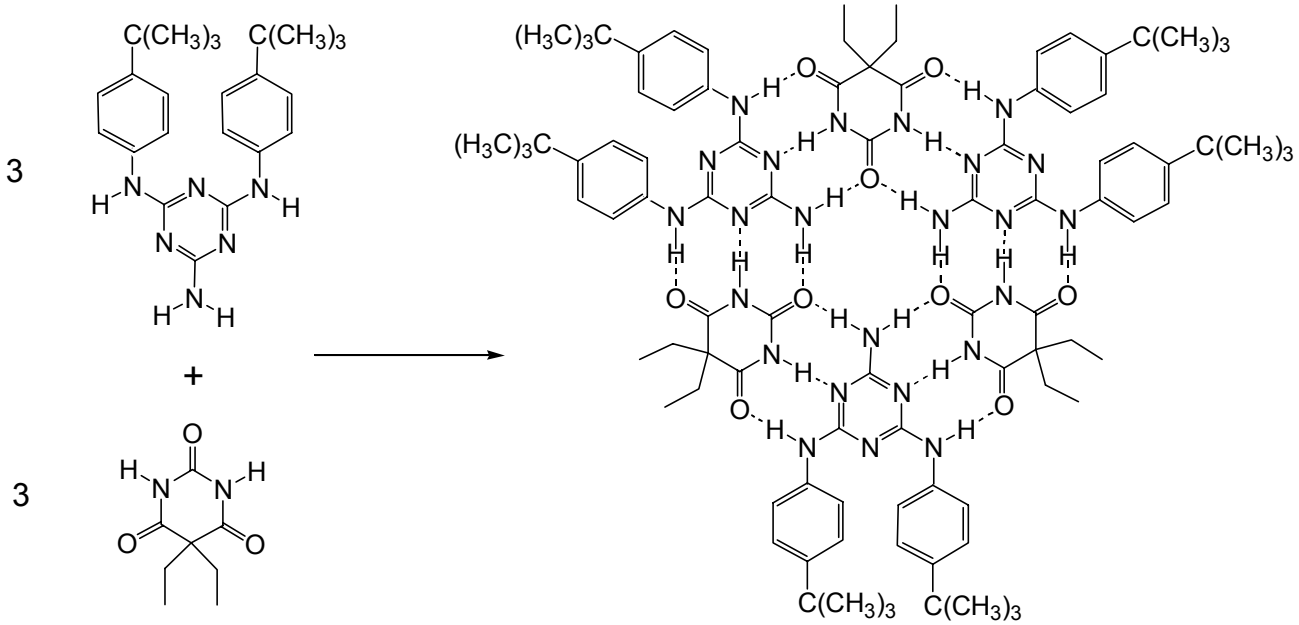


Figure 4 *A cyclic hexamer from melamine and barbituric acid derivatives*[9c,d]

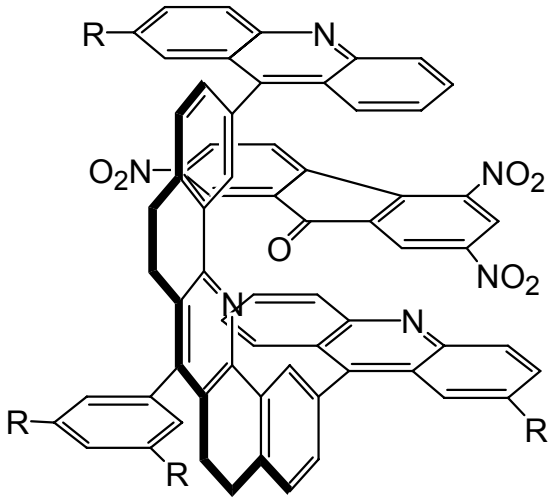


Figure 5 *Complexation of a guest by π-π stacking interactions according to Zimmerman*[11]

based interactions they prepared a variety of structural motifs (see Figure 4).[9c,d] Molecular recognition has also been effected by π-π stacking interactions. In these cases, usually two parallel aromatic surfaces are used, generating a cleft or tweezer-shaped host molecule.[10,9g,11] Zimmerman and co-workers prepared a diacridine that is able to complex 2,4,7-trinitrofluorenone (Figure 5).

1.3 Glycoluril in Supramolecular Chemistry

Glycoluril (Figure 6) is a small, concave molecule that has been known for well over a century. It was first prepared by Schiff in 1877,[12] by reacting urea with glyoxal, and research on this compound and its derivatives has continued until today. The importance of glycoluril in supramolecular chemistry is the subject of this paragraph.

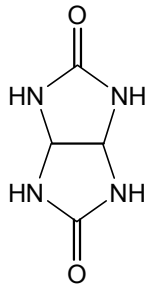


Figure 6 *Glycoluril*

1.3.1 Cucurbituril

Derivatives of glycoluril have found application in supramolecular chemistry since the crystal structure of cucurbituril (Figure 7), a cyclic hexamer of glycoluril, was elucidated in 1981 by Mock and co-workers.[13] They noted the bowl-shaped structure of the molecule and also that it was able to form host-guest complexes with a variety of alkylammonium ions.[13b,c] This notion was further explored by Kim and co-workers during the last years of the 20th century. The latter research group prepared, based on cucurbituril and quaternary ammonium salts, a large variety of supramolecular complexes, including rotaxanes, polyrotaxanes, catenanes, and molecular necklaces (Figure 7).[14] They also prepared cucurbituril homologues containing 5-11 glycoluril residues.[15]

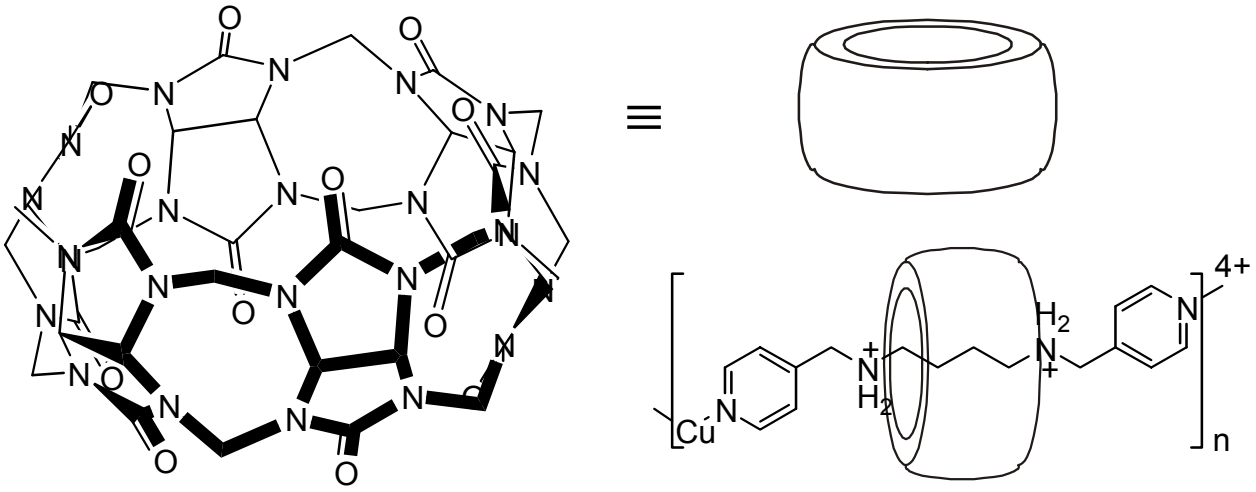


Figure 7 *Cucurbituril and a cucurbituril-based polyrotaxane*[16]

1.3.2 Self-assembling capsules

In 1993, Rebek, De Mendoza, and co-workers prepared a compound consisting of two diphenylglycoluril residues connected via an aromatic linkage.[17] This compound appeared to dimerize as depicted in Figure 8. The dimer is held together by eight strong hydrogen bonds. This dimer was named 'tennis ball' because it consists of two identical concave subunits that self-assemble into a ball-shaped structure. In a later paper, the authors reported encapsulation of small molecules like methane, ethane and ethylene within the cavity defined by the dimer.[18] The concept of self-complementarity was further explored, resulting in larger cavities, that were capable of encapsulating more and larger molecules,[19] and that could even act as a reaction chamber for a Diels-Alder reaction.[20]

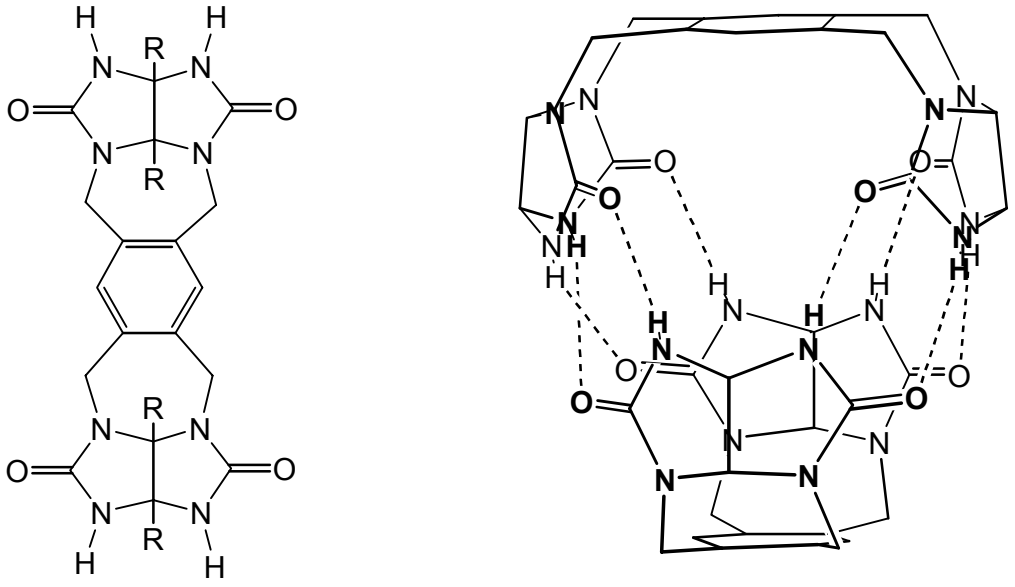


Figure 8 *Rebek's 'tennis ball': a glycoluril-based self-complementary molecule*

1.3.3 Molecular clips[21]

In the early 1980s a program of research was initiated on the preparation and study of glycoluril derivatives in the group of Nolte, with the hope that these molecules might be versatile building blocks for the construction of cage molecules. It was discovered that the reaction of diphenylglycoluril with formaldehyde and benzene gave a clip-shaped molecule (Figure 9).[22] This event initiated a large number of studies after molecules of this type, which are now known as molecular clips. It was found that the clips are excellent host molecules for a variety of aromatic guests, particularly phenols, resorcinol and other dihydroxybenzenes (Figure 10).[23] Binding is based on hydrogen bonding between the OH groups of the guest and the carbonyl oxygen atoms of the urea functions in the clip, and aromatic π-π stacking interactions between the host and the guest. The synthesis of this kind of molecules, as well as the binding affinities towards a variety of aromatic guests have been thoroughly explored. A large number of host molecules with different side walls and different convex sides have been prepared. The increased understanding of the structure and binding affinities of these molecules has stimulated research into their use in the construction of shape-selective catalysts and large supramolecular aggregates. These investigations

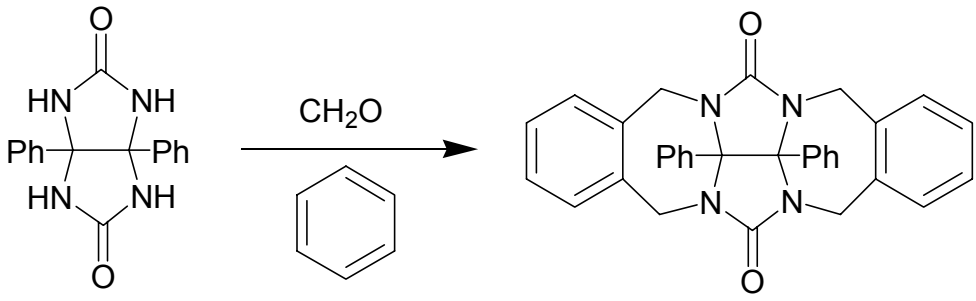


Figure 9 *Synthesis of a molecular clip*

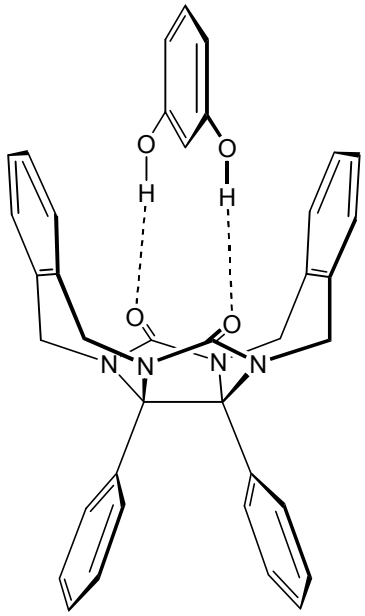


Figure 10 *Binding of resorcinol in a molecular clip*

have resulted, among others, in the preparation of supramolecular objects such as golf balls, cigars, and razor blades.

1.4 Outline of this thesis

In this thesis, the synthesis, characterization, and some applications of a new type of molecular clip are described. These clips are prepared from propanediurea, a glycoluril analogue.
In Chapter 2, a literature survey is presented of glycoluril-like molecules. Focus will be on molecules similar to glycoluril, which have a slightly different framework, and on propanediurea derivatives. In addition, a number of synthetic derivatizations are described.
In Chapter 3, synthetic efforts are described to prepare the parent propanediurea derivatives that are studied in this thesis.
Chapter 4 treats various synthetic routes towards molecular clips and half-clips from propanediurea derivatives. Furthermore, attempts are described to derivatize the clips, in order to obtain compounds with versatile handles that allow for further functionalization.
The structural features and binding properties of the new clip molecules are the subject of Chapter 5. By means of X-ray diffraction analysis, NMR and IR spectroscopy, and molecular modeling, the new clips are thoroughly studied. A comparison is made between clips derived from diphenylglycoluril and clips derived from propanediurea.
Applications of the new clips to construct large supramolecular aggregates are described in Chapters 6 and 7. Chapter 6 focuses on the preparation of porphyrin assemblies, using porphyrin functionalized clips and resorcinol functionalized porphyrins as components. In Chapter 7, attempts to prepare large supramolecular structures using a number of building blocks containing clips and guest residues are described.

1.5 References

1 *Daidalos and Ikaros*, a Greek myth.
2 Stryer, L. *Biochemistry*, 3rd ed., New York, **1988**.
3 Philp, D.; Stoddart, J.F. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154.
4 For an overview see: Lehn, J.-M. *Comprehensive Supramolecular Chemistry*, Elsevier Science Ltd., Oxford, **1996**, Vol. 2.
5 Pedersen, C.J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.
6 Lehn, J.-M. *Angew. Chem.* **1988**, *100*, 91, and references therein.
7 Cram, D.J. *Angew. Chem.* **1988**, *100*, 1041, and references therein.
8 Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, Berlin, **1978**.
9 See, for example: (a) Ducharme, Y.; Wuest, J.D. *J. Org. Chem.* **1988**, *53*, 5787; (b) Wilcox, C.S.; Adrian, J.C.; Webb, T.H.; Zawacki, F.J. *J. Am. Chem. Soc.* **1992**, *114*, 10189; (c) Seto, C.T.; Whitesides, G.M. *J. Am. Chem. Soc.* **1993**, *115*, 905; (d) Zerkowski, J.A.; Set, C.T.; Whitesides, G.M. *J. Am. Chem. Soc.* **1992**, *114*, 5473; (e) Jolliffe, K.A.; Crego Calama, M.; Fokkens, R.; Nibbering, N.M.M.; Timmerman, P.; Reinhoudt, D.N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1247; (f) Rebek, J., Jr.; Nemeth, D. *J. Am. Chem. Soc.* **1985**, *107*, 6738; (g) Sheridan, R.E.; Whitlock, H.W. *J. Am. Chem. Soc.* **1986**, *108*, 7120.

10 (a) Fleischhauer, J.; Harmata, M.; Kahraman, M.; Koslowski, A.; Welch, C.J. *Tetrahedron Lett.* **1997**, *38*, 8655; (b) Harmata, M.; Barnes, C.L.; Rao Karra, S.; Elahmad, S. *J. Am. Chem. Soc.* **1994**, *116*, 8392; (c) Kurebayashi, H.; Fukazawa, Y. *Chem. Lett.* **2000**, 530; (d) Klärner, F.-G.; Burkert, U.; Kamieth, M.; Boese, R.; Benet-Buchholz, J. *Chem. Eur. J.* **1999**, *5*, 1700; (e) Kamieth, M.; Burkert, U.; Corbin, P.S.; Dell, S.J.; Zimmerman, S.C.; Klärner, F.-G. *Eur. J. Org. Chem.* **1999**, 2741.
11 Zimmerman, S.C.; VanZyl, C.M. *J. Am. Chem. Soc.* **1987**, *109*, 7894.
12 Schiff, H. *Lieb. Ann. Chem.* **1877**, *189*, 157.
13 (a) Freeman, W.A.; Mock, W.L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367; (b) Mock, W.L.; Shih, N.-Y. *J. Org. Chem.* **1983**, *48*, 3618; (c) Mock, W.L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440.
14 Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 638, and references therein.
15 Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540.
16 Whang, D.; Jeon, Y.-M.; Heo, J.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 11333.
17 Wyler, R.; De Mendoza, J.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699.
18 Branda, N.; Wyler, R.; Rebek, J., Jr. *Science* **1994**, *263*, 1267.
19 For a review see: Conn, M.M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647.
20 Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50.
21 For reviews see: (a) Sijbesma, R.P.; Nolte, R.J.M. *Top. Curr. Chem.*, Ed. E. Weber, **1995**, *179*, 25; (b) Rowan, A.E.; Elemans, J.A.A.W.; Nolte, R.J.M. *Acc. Chem. Res.* **1999**, *32*, 995.
22 Smeets, J.W.H.; Sijbesma, R.P.; Niele, F.J.M.; Spek, A.L.; Smeets, W.J.J.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1987**, *109*, 928.
23 Sijbesma, R.P.; Kentgens, A.P.M.; Nolte, R.J.M. *J. Org. Chem.* **1991**, *56*, 3199.

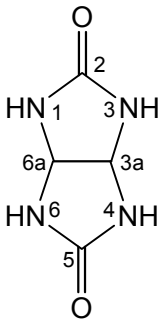
2 The Glycoluril Family

2.1 Introduction

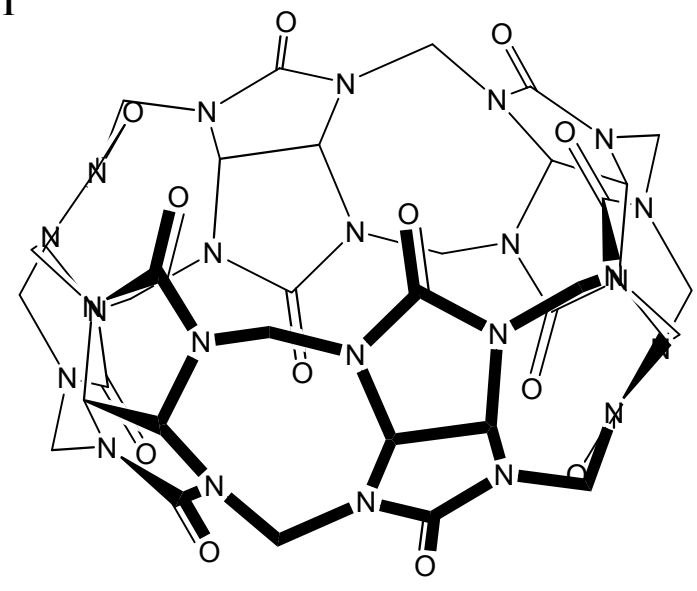
The use of glycoluril **1** as a building block in supramolecular chemistry dates back to the early days of this field. In 1981 its importance was recognized when the crystal structure of cucurbituril **2** was determined.[1] Cucurbituril is a methylene bridged cyclic hexamer of glycoluril. Mock and co-workers noted that it is able to bind a variety of molecules in its cavity.[1b,c] Since then, several groups have initiated research on glycoluril and its derivatives. Studies have been largely limited to glycoluril itself, *i.e.* to compounds consisting of two fused 2-imidazolidinone rings, and its substituted derivatives. Compounds with a related but different basic framework have remained relatively unexplored.

This chapter deals with glycolurils and glycoluril analogues from a synthetic point of view. Section 2.2 will focus on glycoluril itself. In view of the vast amount of data available, this overview will by

Chart 1



1



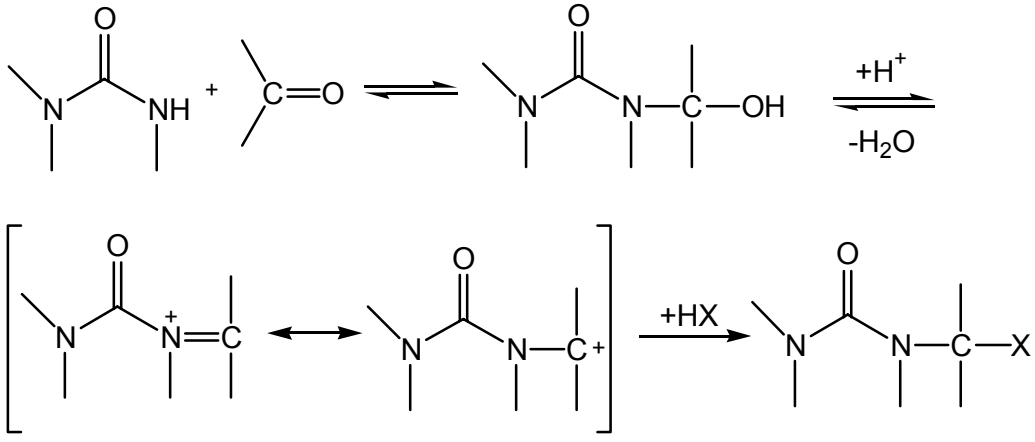
2

no means be exhaustive. In section 2.3 a complete overview will be given of glycoluril analogues that contain an extra methylene group. Compounds with this basic framework and their derivatives are the subject of the investigations described in this thesis. In section 2.4 glycoluril analogues containing thiourea and guanidine groups are discussed, as well as urea containing compounds with a structure similar to glycoluril that contain phosphorus and boron. Section 2.5 focuses on the modification of the different glycoluril analogues that have been discussed. In section 2.6 the structures of a series of glycoluril analogues will be compared on the basis of published crystallographic data.

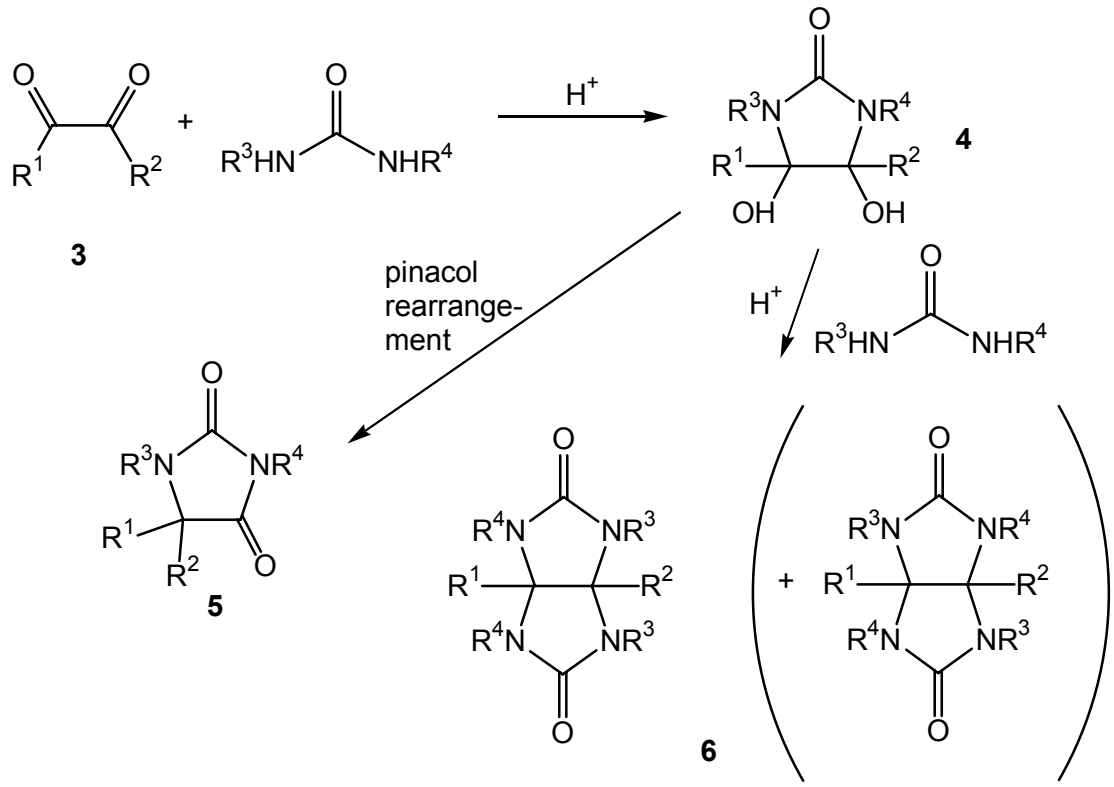
2.2 Synthesis of glycoluril derivatives

2.2.1 From glyoxal

Glycoluril was first prepared by Schiff in 1877.[2] Its synthesis involves the acid catalyzed condensation of glyoxal (**3**, $R^1 = R^2 = H$) with two equivalents of urea (Scheme 2). This reaction involves a so-called α-ureidoalkylation. This means that a nucleophilic substance is linked through the carbonyl carbon atom of an aldehyde or a ketone to the nitrogen atom of a urea. The primary step in this reaction consists of the addition of the urea NH group to the carbonyl group of an aldehyde or a ketone, giving rise to an α-alkylol compound. In the next step, which is generally acid catalyzed, water is eliminated and an α-ureidoalkylcarbenium ion, which is mesomeric with the α-ureidoalkylimonium ion, is generated. This ion can react with a nucleophile to give the condensation product (see Scheme 1). This type of reaction has been reviewed by Petersen.[3] Up till now, α-ureidoalkylation has proven to be the most versatile way of preparing glycolurils (Scheme 2). A large variety of glycoluril derivatives have been prepared. Glyoxal has been reported to react with several 1-substituted and 1,3-disubstituted urea derivatives to yield the corresponding *N*-substituted glycolurils.[4,5] Substituents on the starting ureas can be aromatic or aliphatic. Reaction of 1,3-diphenylurea or 1,3-dicyclohexylurea with glyoxal, however, does not yield the corresponding *N*,*N*′,*N*″,*N*‴-tetrasubstituted glycolurils.[4,5] In these cases the only isolated products are 1,3-



Scheme 1 *α-Ureidoalkylation, according to Petersen*[3]



Scheme 2 *Synthesis of glycoluril and derivatives*

disubstituted hydantoins **5**, which are formed from the intermediate **4** by a pinacol rearrangement (Scheme 2). Apparently, glycolurils cannot be formed from ureas with sterically demanding substituents. When ureas with one small and one large substituent are used as the starting material (*e.g.* 1-methyl-3-phenylurea) a mixture of glycolurils and hydantoins is obtained.[4]

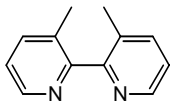
2.2.2 From 2-oxoaldehydes

2-Oxoaldehydes (**3**, R^1 = H; R^2 = alkyl, aryl) react with urea in similar ways as glyoxal, producing 3a-substituted glycolurils (**6**, R^1 = H; R^2 = alkyl, aryl; $R^3 = R^4$ = H). These reactions, however, have remained relatively unexplored. 3a-Methyl and 3a-ethylglycoluril have been synthesized,[6] but reactions of 2-oxoaldehydes with substituted ureas have not been reported.

2.2.3 From α-diketones

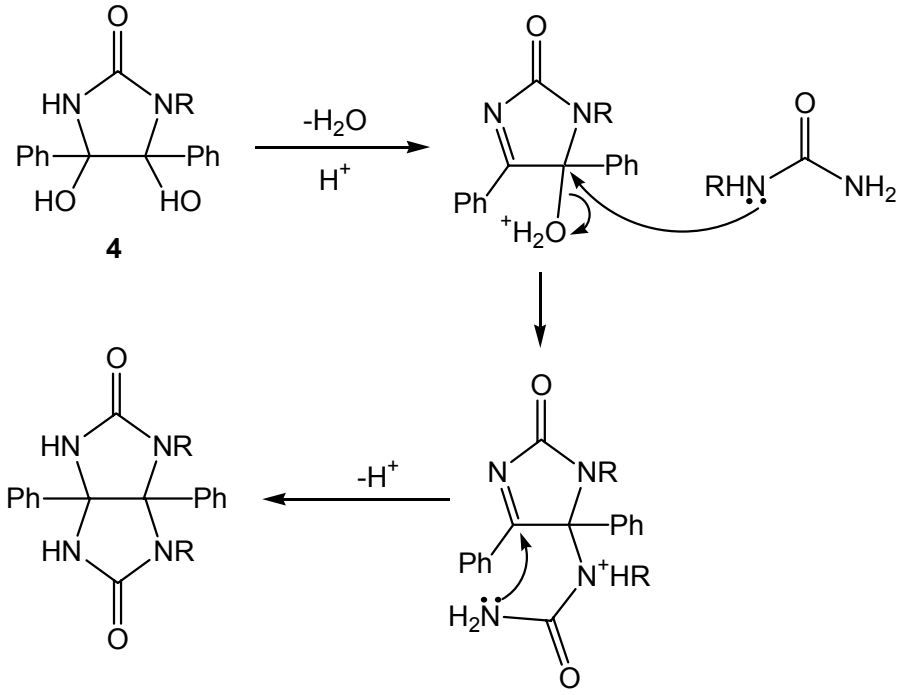
Reaction of α-diketones (**3**, R^1, $R^2 \neq$ H) with ureas yields 3a,6a-disubstituted glycolurils. Early preparations have been summarized by Biltz,[7] and include dimethyl, diphenyl (**6a**), and di(ethylcarboxylate) (**6d**) substituted glycolurils, generally prepared by heating the mixed starting compounds at high temperatures (170-220°C). Nowadays a procedure described by Butler and Leitch[8] is usually used, which involves refluxing the starting compounds in benzene or toluene with TFA as a catalyst, while removing the formed water azeotropically. The product precipitates from

Table 1 *3a,6a-Disubstituted glycolurils* ***6*** *($R^3 = R^4 = H$), with literature references*

Compound	R^1	R^2	Ref.
6a	Ph	Ph	7,8
6b	*p*-$C_6H_4OCH_2COOBn$	*p*-$C_6H_4OCH_2COOBn$	14
6c	*p*-$C_6H_4(CH_2)_6CH_3$	*p*-$C_6H_4(CH_2)_6CH_3$	10
6d	COOEt	COOEt	7,9
6e	C_5H_4N	C_5H_4N	11
6f	-$(CH_2)_n$- (n = 3-5)		12
6g			13

the reaction mixture, and can be isolated by filtration. This reaction generally proceeds in high yield. Instead of α-diketones also dihydrates of these compounds (*e.g.* dihydroxy diethyltartrate, $(C(OH)_2COOEt)_2$) can be used as starting compounds.[9] A large number of compounds of this series have been prepared (see ref. 3 and Table 1 for a selection). The ready availability of the starting α-diketones allows for the preparation of glycolurils with various functional groups R^1 and R^2 (Table 1).

Monosubstituted ureas react with α-diketones with formation of 1,6-disubstituted (*cis*) glycolurils as the main[14] or sole[8] product. The 1,4-disubstituted (*trans*) product is generally not found. The mechanism of this reaction has been investigated by Butler and Leitch and provides an explanation for the preferred formation of the *cis* compound.[8] First, water is eliminated from the intermediate **4**,



Scheme 3 *Preferential formation of 1,6-disubstituted glycolurils from benzil and monosubstituted ureas*

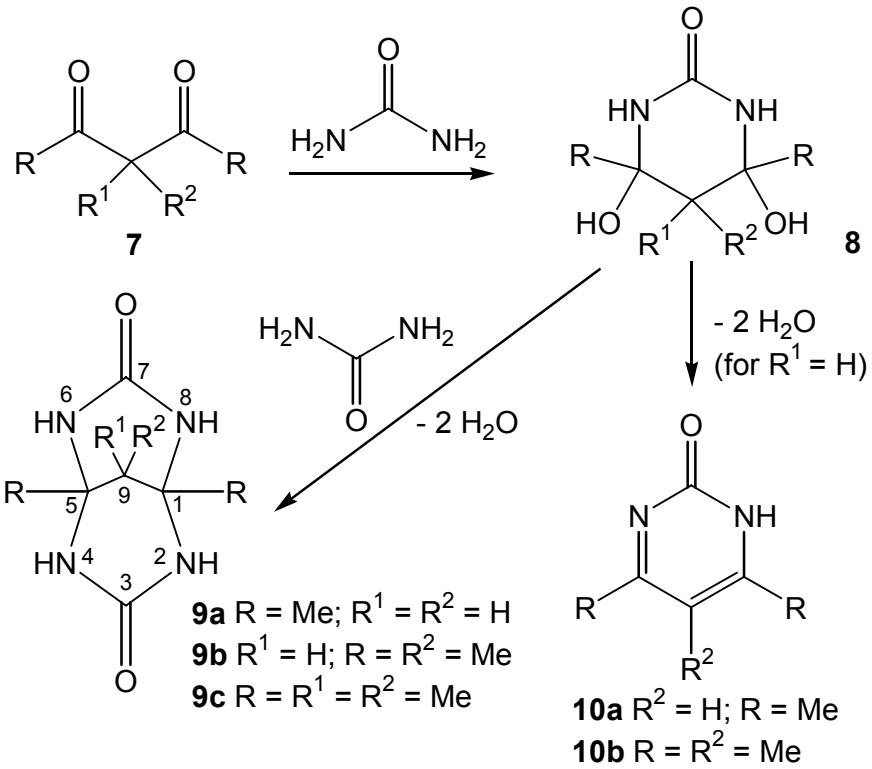
followed by protonation of the OH. Subsequent attack by a monosubstituted urea takes preferentially place via the alkylated urea nitrogen because this atom is more nucleophilic than the unsubstituted nitrogen, producing the 1,6-disubstituted glycoluril (Scheme 3).

Reaction of 1,3-disubstituted ureas with α-diketones does not yield glycolurils. The products from this reaction are 1,3,5,5-tetrasubstituted hydantoins **5**, which are formed when intermediate **4** (with R^1, $R^2 \neq H$) undergoes a pinacol rearrangement (Scheme 2).[8]

2.3 Synthesis of propanediurea[a] derivatives

2.3.1 From 2,4-pentanediones

In 1908 De Haan published the synthesis of three compounds (**9a-c**) with structures very similar to glycoluril.[15] These were prepared from urea and (methylated) 2,4-pentanedione in water at room temperature (**9a**,**b**) or without solvent at 140-160°C (**9c**). No yields were given, but the author indicated that only small amounts of the desired products were obtained, and other products were formed as well. Main products in these reactions were derivatives of the pyrimidinone series (**10**), which were formed by the elimination of two molecules of water from intermediates **8** (Scheme 4).



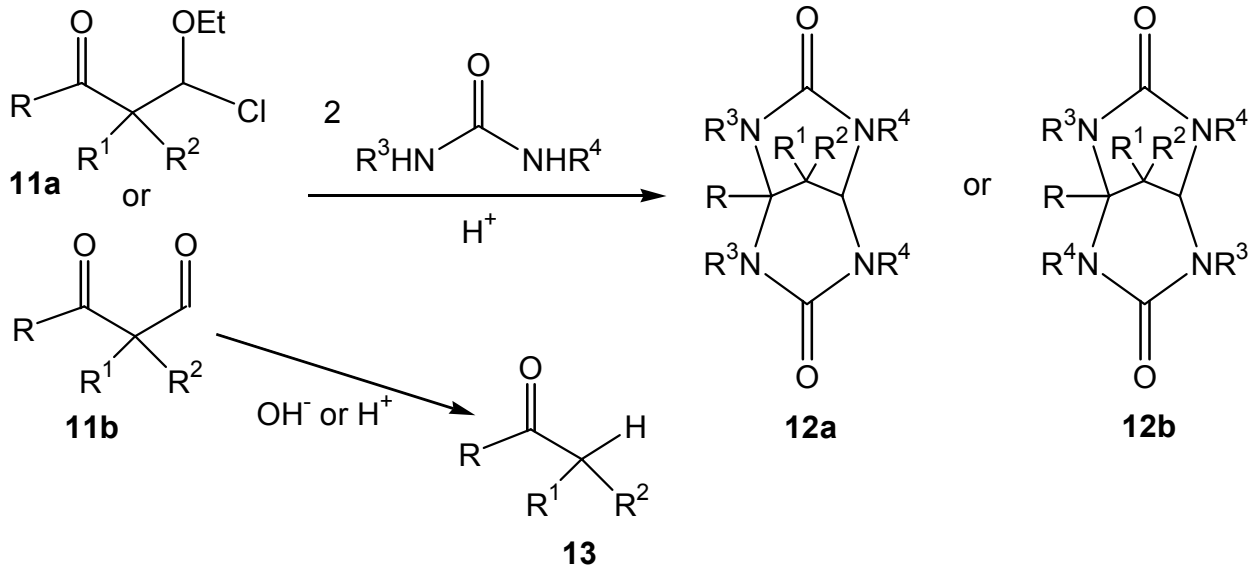
Scheme 4 *Synthesis of 1,5-dimethylpropanediureas*

[a] The name 'propanediurea' was introduced by Kobayashi (ref. 21) to simplify the naming of this series of compounds. The IUPAC name is: 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione.

Compound **9a** has been shown to convert to pyrimidinone **10a** upon standing in TFA.[16] Boyle and co-workers later prepared **9a** in 6% yield using water as the solvent and sulfuric acid as the catalyst at 50°C,[16] and we prepared **9c** in 34% yield in refluxing toluene, containing TFA as a catalyst.[17] There are no reports of differently substituted β-diketones or substituted ureas to undergo a similar reaction to produce other members of the 1,5-disubstituted propanediurea family.

2.3.2 From 3-oxoaldehydes

3-Oxoaldehydes (**11b**) react much more readily with urea than the β-diketones, producing 1-substituted propanediurea derivatives **12**. The only literature on this reaction is a 1964 patent.[18] As starting ureas unsubstituted, monosubstituted, and 1,3-disubstituted ureas can be used (Scheme 5). The patent does not report whether the *cis* (**12a**) or *trans* (**12b**) products are formed. Starting aldehydes cannot bear hydrogens at the 2-position, but this seems to be the only limiting factor in this reaction. Instead of aldehydes, their corresponding α-chloroethers (**11a**) can be used as well. The reaction takes place at temperatures higher than 80°C. When α-chloroethers are used, reaction temperatures of 40°C can be sufficient. The reaction allows for the presence of a large variety of functional groups, and the use of many solvents, including water, alcohols, ethers, esters, and halogenated hydrocarbons. The reaction conditions described in the patent do not mention the use of a catalyst. We found that this reaction proceeds very well with 3-oxoaldehydes and urea in refluxing toluene containing a catalytic amount of TFA, with azeotropic removal of water.[19] Yields are usually very high. The main side products are compounds of type **13**; they are the result of decarbonylation of the starting aldehyde (Scheme 5). House and co-workers found that aldehydes possessing a carbonyl group at the 3-position are quite easily decarbonylated under alkaline or acidic conditions.[20]



Scheme 5 *Synthesis of 1,9,9-trisubstituted propanediureas*

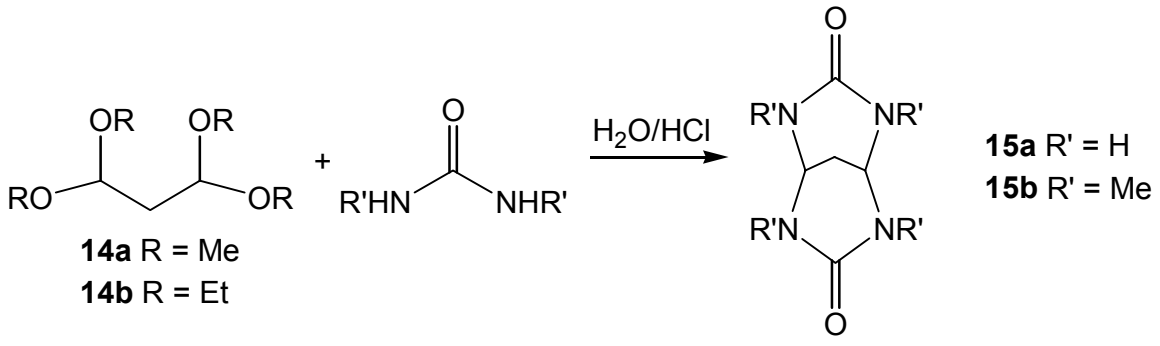
2.3.3 From 1,3-dialdehydes and their precursors

Logically, for the synthesis of propanediurea derivatives with hydrogens both at the 1- and 5-positions, the starting materials would be 1,3-dialdehydes (malonic dialdehydes). These compounds however are usually not stable. If they are to be used for the preparation of propanediurea derivatives, they have to be synthesized *in situ*. Kobayashi used the diacetal of malonic dialdehyde (1,1,3,3-tetramethoxypropane, **14a**) for the synthesis of unsubstituted propanediurea **15a**, in diluted hot hydrochloric acid (Scheme 6).[21] The yield of this reaction was quite low (35%). 1,1,3,3-Tetraethoxypropane (**14b**) has been reported to react with 1,3-dimethylurea in acidic water at 35°C to produce the tetramethylated propanediurea **15b** in 25% yield (Scheme 6).[22]

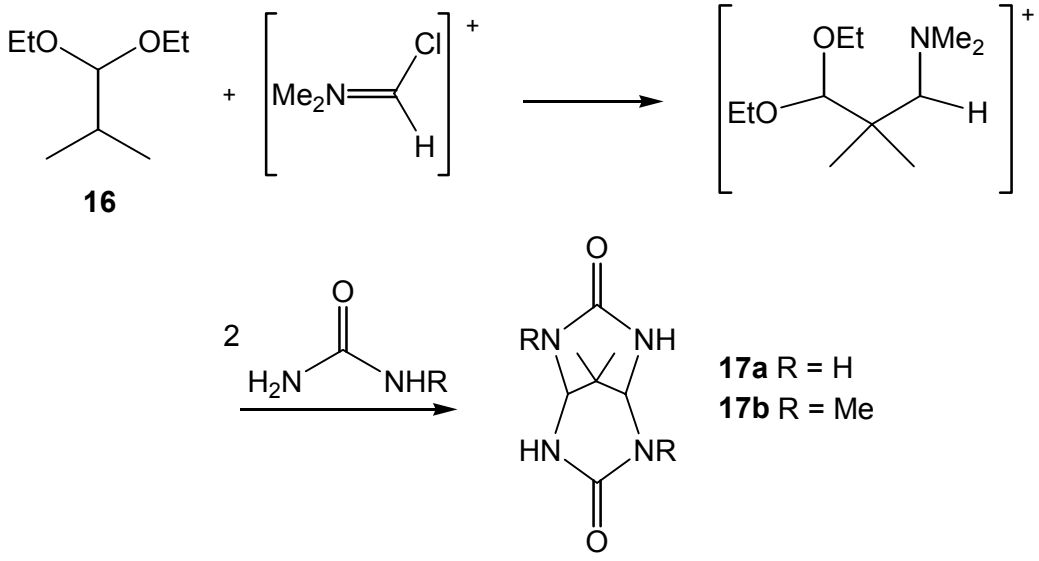
Malonic dialdehydes bearing only one hydrogen at the 2-position are stable compounds. Acid catalyzed reaction of these dialdehydes with urea yields mainly pyrimidinone derivatives (see also Scheme 4, compounds **10b**, with R = H).[23] There are no reports of reactions with urea to produce propanediurea derivatives. One report describes the reaction of 2-bromo-1,1,3,3-tetraethoxypropane with 1,3-dimethylurea in acidic water, yielding the corresponding 9-bromo-2,4,6,8-tetramethyl propanediurea in 7% yield.[22]

As is the case for the parent malonic dialdehyde, 2,2-disubstituted malonic dialdehydes are not stable either. Propanediurea derivatives of these compounds (**17**) have been synthesized from stable derivatives, or by preparation of the dialdehydes *in situ*. The first report on this type of preparation is a 1964 patent.[24] It describes a Vilsmeier formylation at the α-position of an acetal (**16**), α-chloroether, or enol ether, followed by reaction with urea or monosubstituted urea (Scheme 7). If water is used in the latter reaction, the malonic dialdehydes are supposed to be intermediates. The reaction generally proceeds in high yield. The proposed malonic dialdehyde derivatives have not been isolated.

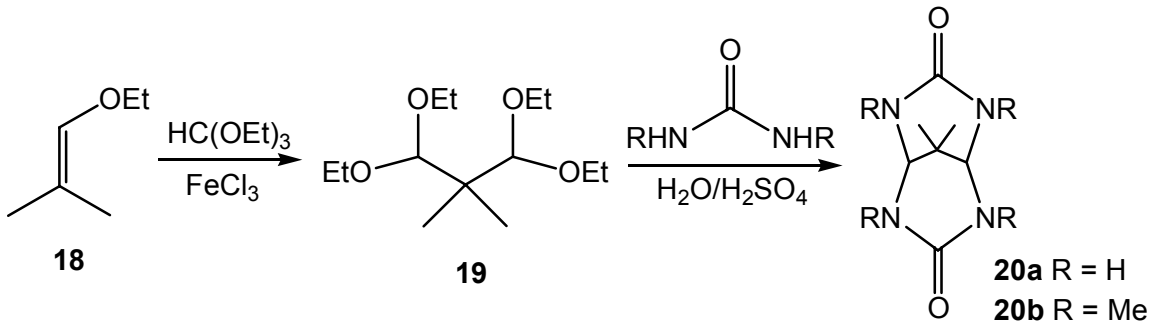
Diacetals of 2,2-disubstituted malonic dialdehydes, however, are known to be very stable compounds. They can be prepared by formylation of enol ethers with orthoformic esters in the presence of Lewis acid catalysts (Scheme 8).[25] 1,1,3,3-Tetraethoxy-2,2-dimethylpropane **19** prepared in this way has been reacted with urea in water in the presence of sulfuric acid at 90°C to produce 9,9-dimethylpropanediurea **20a** in 91% yield.[26] Reaction with 1,3-dimethylurea in diluted hydrochloric acid at 60°C has been reported to yield 92% of 2,4,6,8,9,9-hexamethyl propanediurea **20b**.[22]



Scheme 6 *Synthesis of propanediurea*



Scheme 7 *Synthesis of propanediurea derivatives by Vilsmeier formylation of acetals*



Scheme 8 *Synthesis of propanediurea derivatives from enol ethers*

It can be concluded that the preparation of derivatives of propanediurea from urea derivatives and the corresponding β-dicarbonyl compounds (or their acetals) only proceeds well if the carbon atom between the carbonyl groups does not bear any hydrogens. If it does, the reaction generally yields the very stable pyrimidinones (**10**, R = H), due to elimination of water.

2.4 Synthesis of glycoluril analogues containing heteroatoms

2.4.1 Thiourea and guanidine containing glycoluril analogues

The reaction of dicarbonyl compounds with thioureas or guanidines to yield glycoluril analogues has not been studied as thoroughly as their reaction with ureas. Of the propanediurea series only analogue **21** has been synthesized, from 2,4-pentanedione and thiourea in low yield.[27] Table 2 lists a number of guanidine and thiourea containing compounds of the glycoluril series.

Glyoxal has been reacted with thiourea in aqueous HCl to yield the thio analogue of glycoluril (**22a**) in low yield.[28] Diphenyldithioglycoluril **22b** has been prepared as early as 1891 by heating benzil (**3**, $R^1 = R^2 = Ph$) with thiourea at 200°C. When this reaction is performed in acidic solution,

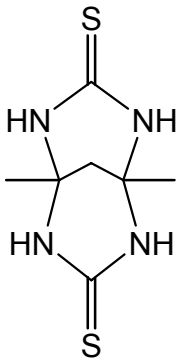
the only glycoluril analogue formed (in low yield) is **22c**, in which one sulfur atom is replaced by oxygen.[29] In basic solution (NaOH/butanol), diphenyldithioglycoluril **22b** can be obtained in good yield.[30] When substituted thioureas are used, no glycoluril analogue is formed. A series of 3a,6a-diaryldithioglycoluril derivatives have been prepared by Broan and co-workers.[30] These include methoxy (**22d**), methyl, chloro and nitro substituted derivatives. Sircar and co-workers prepared 3a,6a-difuryldithioglycoluril (**22e**) by heating furil with thiourea at 200°C.[31]

Takahashi and co-workers published the reaction of a series of glyoxal dialkylimines and diarylimines **24** with iso(thio)cyanato trimethylsilane **25** to yield 1,4-disubstituted (*trans*) (dithio)glycolurils **26** in low to moderate yields (Scheme 9).[32]

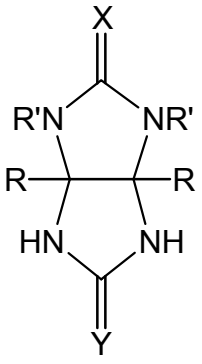
The base catalyzed reaction of benzil with guanidine derivatives to produce guanidine containing glycoluril analogues has been described in a few papers by Lempert and co-workers.[33] They prepared the 2,5-diimine **23a**, the 2,5-bis-*n*-butylimide **23b**, and a 2,5-bis-*n*-benzylimide derivative. They also noted that *S,S'*-dimethyl-3a,6a-diphenyl-2,5-dithioglycoluril (prepared from **22b** and methyl iodide) can be transformed into **23b** by reaction with *n*-butylimine. A similar reaction was later used to synthesize guanidine containing molecular clips from their thiourea containing analogues.[34]

Since it is known that the intermediates in the reaction of urea with α-dicarbonyl compounds to

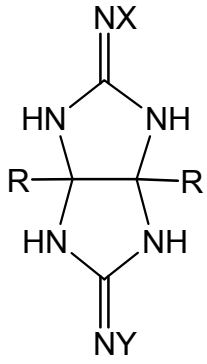
Chart 2



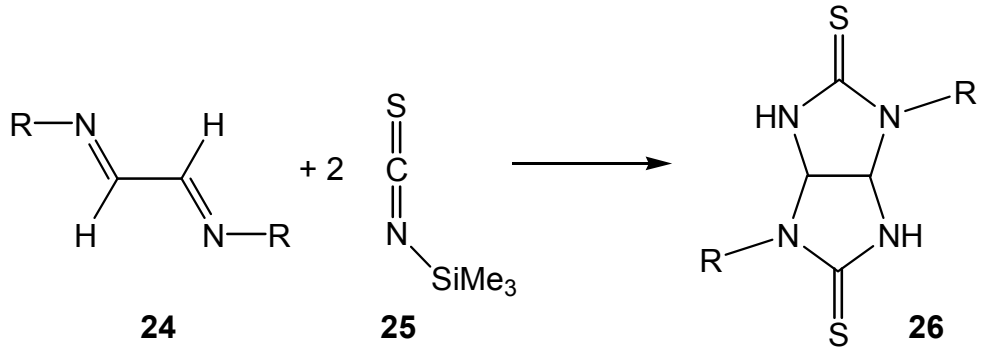
21



22a-j



23a-c



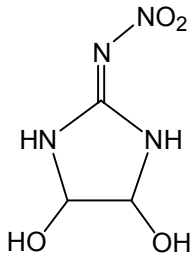
24 **25** **26**

Scheme 9 *Synthesis 1,4-disubstituted dithioglycolurils*[32]

Table 2 *Thiourea and guanidine containing glycoluril derivatives, with references*

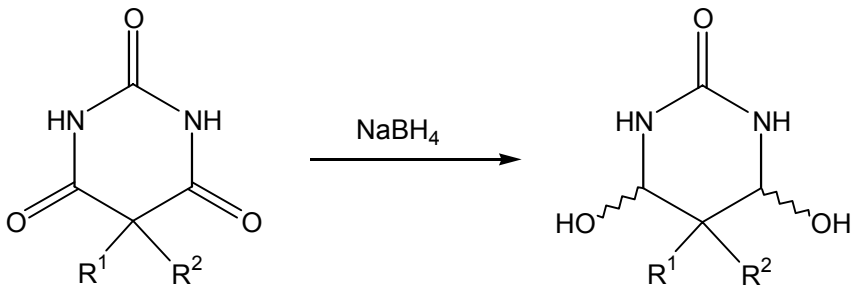
Compound	R	R'	X	Y	Reference
22a	H	H	S	S	28
22b	Ph	H	S	S	30
22c	Ph	H	O	S	29
22d	p-OMe-C_6H_4	H	S	S	30
22e		H	S	S	31
22f	H	H	O	S	35
22g	H	Me	O	S	35
22h	H	H	O	S	35
22i	Ph	Me	O	S	29
22j	Ph	H	O	S	29
23a	Ph	-	H	H	33
23b	Ph	-	*n*-C_4H_9	*n*-C_4H_9	33
23c	H	-	H	NO_2	36

form glycolurils are derivatives of 4,5-dihydroxy-2-imidazolidinone (**4**), attempts were made to synthesize asymmetric glycoluril derivatives from these intermediates. Eres'ko and co-workers prepared monothioglycoluril **22f** in very low yield by reacting 4,5-dihydroxy-2-imidazolidinone with thiourea in aqueous hydrochloric acid.[35] Reaction of urea or monosubstituted or 1,3-disubstituted ureas with 4,5-dihydroxy-2-imidazolidinethione (**4**, R^1-R^4 = H) in aqueous hydrochloric acid yielded a series of monothioglycoluril derivatives (**22g**, **22h**) in low yield.[35] High yields of 3a,6a-diphenylmonothioglycolurils (**22j** and its N-substituted derivatives) were obtained in an analogous fashion.[29] Guanidine containing glycoluril analogues have also been prepared in this manner. Guanidine was reacted with 4,5-dihydroxy-2-nitroiminoimidazolidine **27** to yield **23c**.[36]



27

The 4,6-dihydroxyhexahydro-2-pyrimidinones **8**, which are intermediates in the formation of propanediurea derivatives, have been prepared by treatment of



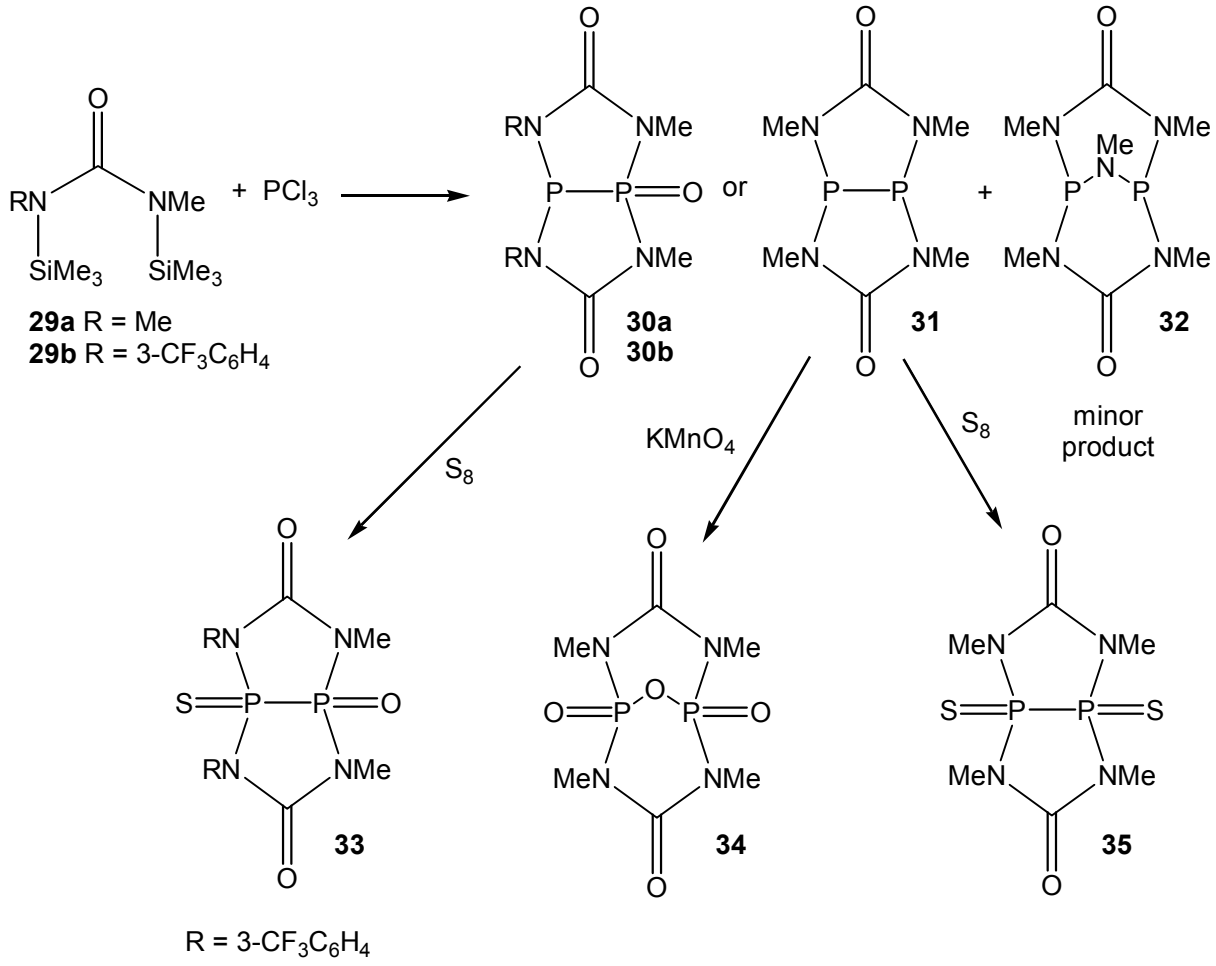
28 **8**

Scheme 10 *Reduction of barbiturates to yield 4,6-dihydroxyhexahydro-2-pyrimidinones*

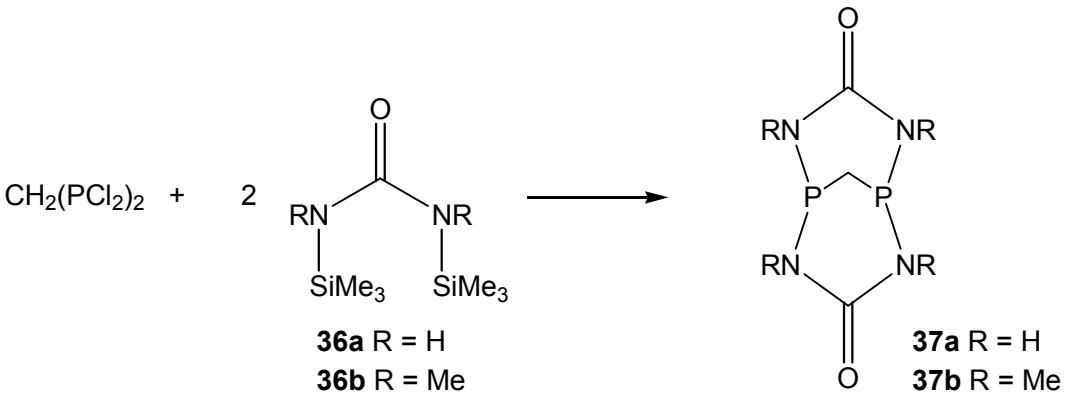
barbiturates with $NaBH_4$ (Scheme 10).[37] This reduction, however, is not very selective, and other preparations of **8** have not been reported, so these compounds are not very accessible. There are no reports on the formation of propanediurea derivatives from these intermediates.

2.4.2 Phosphorus and boron containing glycoluril analogues

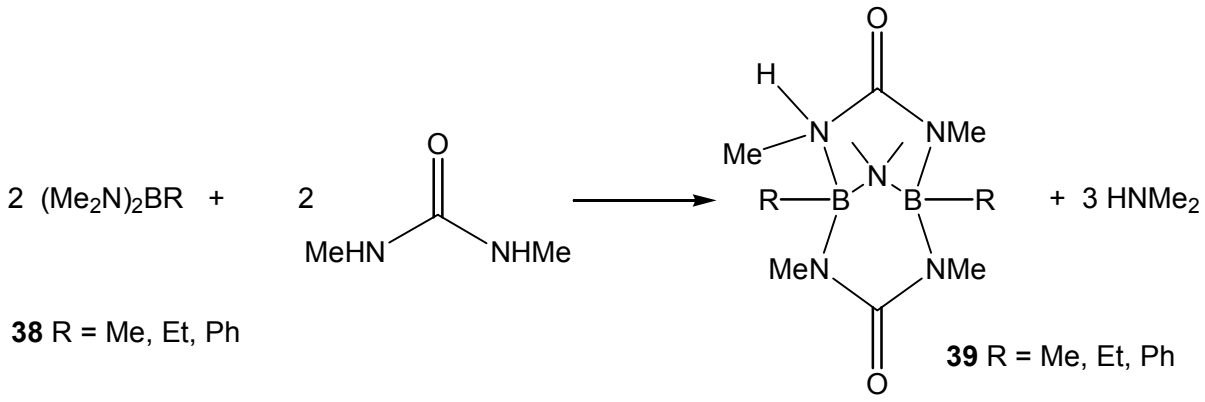
In a series of papers in the early 1980s, Roesky and co-workers studied the reaction between trimethylsilyl substituted ureas **29a**,**b** and PCl_3. By varying the reaction conditions and the substituents on the urea derivative, they were able to isolate four compounds (**30a**,**b**, **31**, **32**) with a glycoluril-like structure (Scheme 11).[38-41] Compounds **30b** and **31** were oxidized with sulfur or potassium permanganate to yield **33**, **34**, and **35** (Scheme 11).[40] Bicyclic products bearing a hydrogen atom at the urea nitrogen atoms were not reported by these authors. Extending this work, Neidlein and Degener reacted methylene bis(dichlorophosphane) with *N,N′*-bis(trimethylsilyl)urea derivatives **36a** and **36b** to produce methylene bridged glycoluril analogues **37a,b**.[42] The authors were able to synthesize both the unsubstituted (reaction at –70°C) and the tetramethyl substituted (reaction at room temperature) products (Scheme 12).



Scheme 11 *Synthesis of phosphorus containing glycoluril and propanediurea analogues*



Scheme 12 *Synthesis of phosphorus containing propanediurea analogues*



Scheme 13 *Synthesis of boron containing propanediurea analogues*

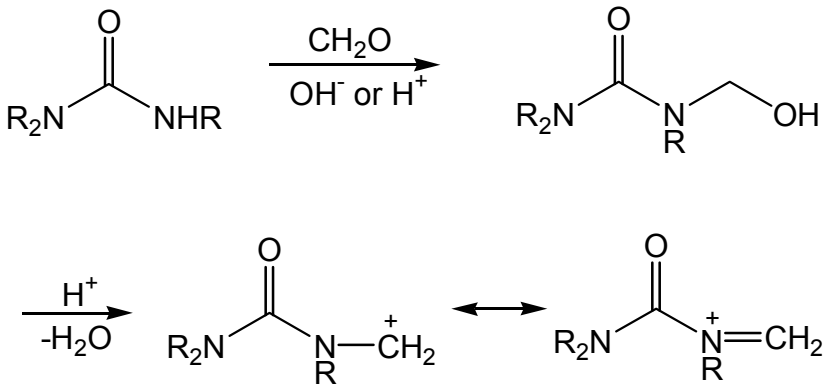
Compounds of type **32**, isolated as a minor product when **29a** was reacted with PCl_3,[41] were prepared in good yields by reaction of $MeN(PCl_2)_2$ with *N,N′*-disubstituted (thio)ureas at room temperature in pyridine.[43] Reactions were reported only with *N,N′*-disubstituted (thio)ureas. The substituents were methyl and phenyl groups, and the yields were between 45 and 84%.
Reaction of *N,N′*-dimethylurea with bis(dimethylamino)organylboranes **38** in refluxing toluene according to Scheme 13 was reported to yield the bicyclic compounds **39** in good yields.[44]

2.5 Derivatization of glycoluril analogues

Glycoluril analogues have been derivatized in a few different ways, which will be discussed below. First, the reaction with formaldehyde to yield *N*-methylol derivatives, and the use of these *N*-methylol derivatives as ureidoalkylating agents will be treated. Subsequently, *N*-alkylation with alkyl halides will be discussed. In the final section, a few scattered reports on other kinds of derivatizations are summarized.

2.5.1 Formylation

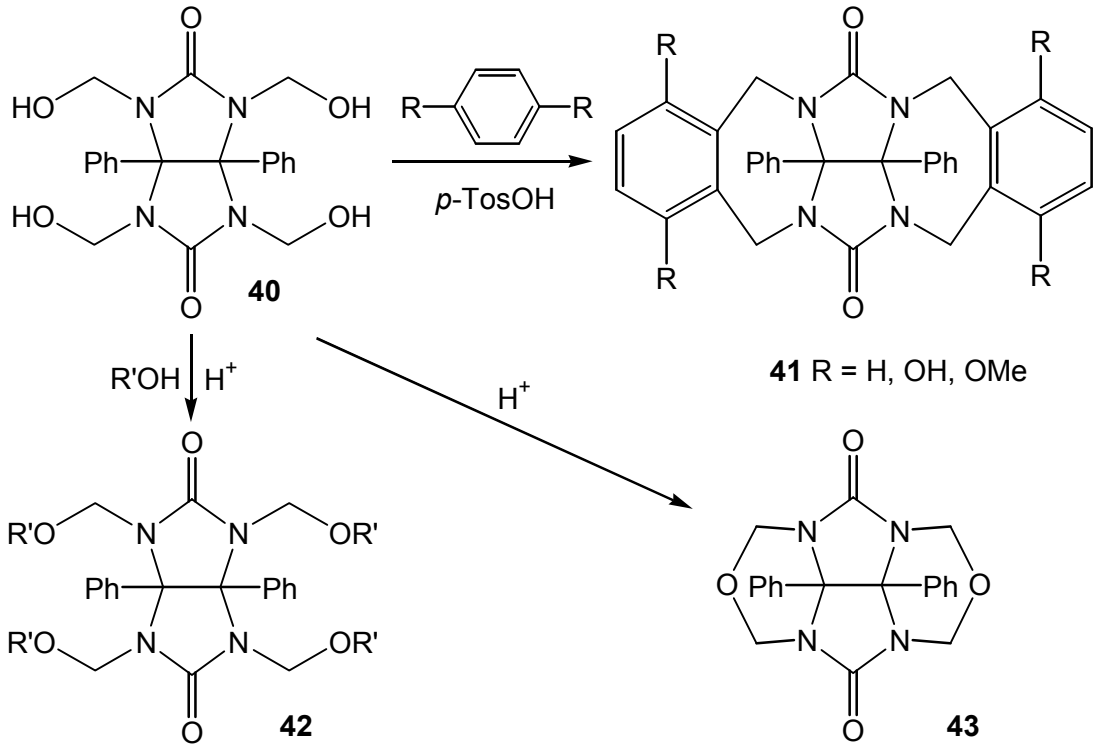
Formylation of urea derivatives has been used for a long time as a cheap and convenient method for functionalization of these compounds. The reaction is performed under alkaline or acidic



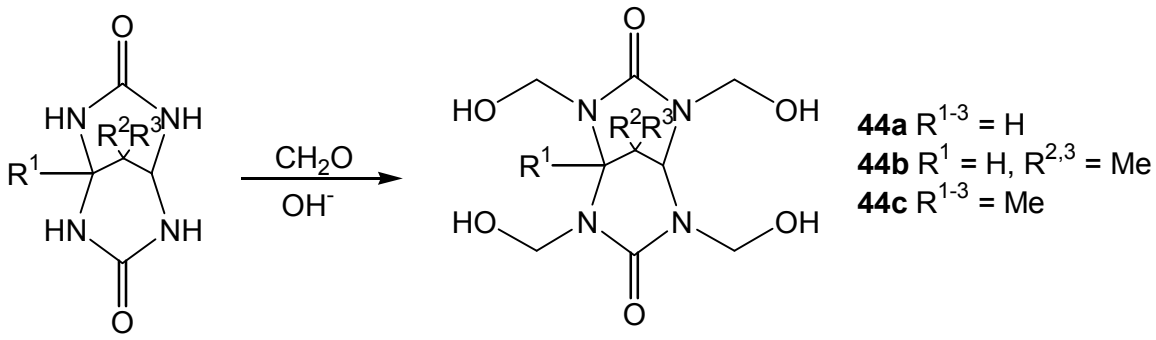
Scheme 14 *Formylation of urea derivatives, and the behavior of these compounds under acidic conditions*

conditions, and an *N*-methylol derivative is produced (Scheme 14). This product can serve as an ureidoalkylating agent under acidic conditions to yield a variety of products. Acid catalyzed reaction with alcohols yields ethers.[45] Intermediates in these reactions are carbiminium ions (Scheme 14).[46] As early as 1905, Behrend and co-workers applied this reaction to glycoluril and formaldehyde in acid solution, and obtained cucurbituril **2**.[47] This product, however, was not characterized until 1981, when Mock and co-workers solved its X-ray structure.[1a] Cucurbituril has been used as a catalyst,[1] and as the cyclic component of rotaxanes.[48]

N-methoxymethylene derivatives of glycoluril have been used as crosslinking agents for cellulosic fabrics.[49] The tetramethylol derivative of diphenylglycoluril (**40**) has been shown by our group to react with benzene, hydroquinone, and *p*-dimethoxybenzene in the presence of *p*-toluenesulfonic



Scheme 15 α-*Ureidoalkylation reaction applied to tetramethylol diphenylglycoluril*



Scheme 16 *Formylation of propanediurea derivatives*

acid to produce cavity-containing compounds **41**.[50] Compound **40** can be transformed in ethers **42** by an acid catalyzed reaction with alcohols with azeotropic removal of water, and in the cyclic ether **43** under acidic conditions.[51] This latter compound was reacted with acetic anhydride to give tetra(acetoxymethylene)diphenylglycoluril (**42**, R' = Ac), which was transformed into the tetra(chloromethylene) compound by reaction with thionyl chloride. All these compounds have been shown to be excellent ureidoalkylating reagents.[52]

The reaction of propanediurea derivatives with formaldehyde has been described in various patents. A Japanese patent reports the synthesis of the tetra(methylol) derivative of propanediurea (**44a**) (Scheme 16).[53] This compound, however, was not isolated, but obtained as an aqueous solution. The isolation of the tetra(methylol) derivative of 9,9-dimethylpropanediurea (**44b**) has been claimed in a patent (Scheme 16),[54] but this patent reports the preparation of the tetra(methylol) derivative of 1,9,9-trimethylpropanediurea (**44c**) in the form of an aqueous solution (Scheme 16). Of all these tetra(methylol) derivatives, only **44b** has been reported to react with alcohols in acidic solution to produce ethers in the same way as has been described for its diphenylglycoluril derived counterpart **40**.[54] It may be concluded that formylation of derivatives of the propanediurea series yields methylol compounds that are generally less stable than the methylol compounds of the glycoluril series.

2.5.2 Alkylation using alkyl halides

Suvorova and co-workers investigated alkylation of glycolurils and propanediureas.[55] They reacted these compounds with a variety of alkyl halides. The authors tried various solvents, including liquid ammonia, toluene, HMPTA, DMF, and nitrobenzene (but not DMSO). Reasonable yields (~50%) were obtained only when the reaction was performed in liquid ammonia with sodium amide as the base. It was noted that yields could be increased by the addition of potassium amide and alkali halides. Mono-, di-, and trialkylation products were not reported. In later papers, solvent-base combinations DMSO/NaOH,[56] DMSO/KOH,[57,58] DMF/NaH,[19] and DMSO/NaH[19] were shown to alkylate glycoluril and propanediurea derivatives, if the alkylating agent was a benzylic or allylic halide. This reaction has been used in Rebek's research group to synthesize cavity containing self-complementary molecules,[9,10,58] and by Nolte and co-workers to construct molecular clips (see Chapter 1).[19,57]

2.5.3 Other derivatizations (halogenation, nitration, and acylation)

Members of the glycoluril series (**1**, **6a**, 3a,6a-dimethylglycoluril) as well as 1,5-dimethylpropanediurea (**9a**) have been chlorinated and brominated at nitrogen by treatment with chlorine or bromine in aqueous sodium hydroxide.[59] The products of these reactions are strong bactericides and effective foliage protectants.

N-acylation of glycolurils and propanediureas has been accomplished by treatment with carboxylic anhydrides in the presence of bases or strong mineral acids, or by treatment with acid chlorides in the presence of bases. Depending on the reaction conditions 1,3- and 1,4-diacylated as well as 1,3,4,6-tetraacylated derivatives can be prepared.[60,61] Acylated glycolurils are good acylating agents.[60] Commercial applications of *N*-acylated glycolurils and propanediureas include their use as activators for inorganic percompounds (*e.g.* H_2O_2, H_2SO_5, perborates). In the presence of these activators, bleaching solutions containing peroxides bleach hair and textile faster or at lower temperatures than in their absence.[61]

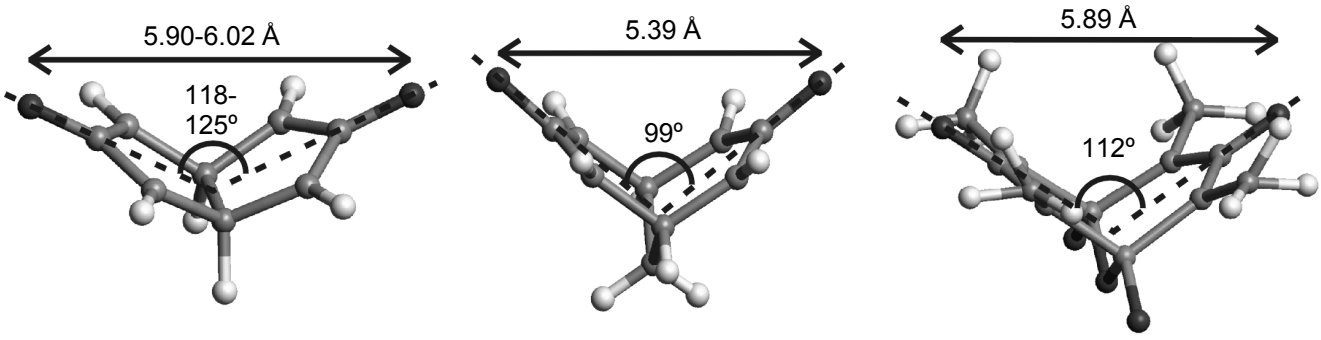
Glycoluril has been nitrated at nitrogen by treatment with nitric acid at slightly elevated temperatures, yielding 1,4-dinitroglycoluril in high yield. Treatment of glycoluril with HNO_3/N_2O_5 at 15°C yielded tetranitroglycoluril.[62] Not surprisingly, the latter compound is a very powerful explosive. By nitrolysis or nitration followed by hydrolysis of different *N*-acetylated glycolurils, a series of glycolurils with nitro (and acetyl) substituents has been prepared.[62]

Propanediurea has also been tetranitrated by treatment with concentrated nitric acid in acetic anhydride, and the product was shown to be a powerful explosive as well.[63]

2.6 Structural features

A number of crystal structures of glycoluril analogues described in this chapter have been solved. Their structures are all very similar. They are cup-shaped molecules, defining a shallow cavity with the urea carbonyl groups sticking out. The major difference is the angle between the carbonyl groups, which is directly related to the distance between the oxygen atoms. Several X-ray structures of glycoluril (**1**) have been reported.[64] The O-O distance in these structures is between 5.90 and 6.02 Å, with angles between the carbonyl groups ranging from 118 to 125°. 3a,6a-Dimethylglycoluril has a O-O distance of 5.75 Å, and the angle between the carbonyl groups is 113°.[65] This indicates that substituents on these positions push the carbonyl groups closer together. N-substitution of glycoluril generally does not have a large effect on the position of the carbonyl groups with respect to each other.[66] However, when 1 and 6 (or 3 and 4) nitrogens are linked, for example through a xylylene group (as is the case in Nolte's molecular clips and Rebek's molecular capsules), geometrical changes occur.[67] In these compounds, the O-O distance is between 5.51 and 5.70 Å, with angles between the carbonyl groups of 107 to 110°.

The structure of propanediurea (**15a**) is very similar to that of glycoluril (**1**) (Figure 1). The O-O distance and the angle between the carbonyl groups, however, are significantly smaller (5.39 Å and



1 **15a** **34**

Figure 1 *Crystal structures of glycoluril (**1**), propanediurea (**15a**) and phosphorus containing analogue **34**. The O-O distances and angles between the carbonyl groups are indicated*

99.4°, respectively).[68] Linking the N-atoms through a xylylene group decreases these values even further (5.19 Å and 94.8°, respectively).[19]

Four X-ray structures of phosphorus containing glycoluril analogues have been solved (**30b**,[39] **31**,[39] **34** (Figure 1),[40] **37b**[69]). The O-O distance in these molecules is between 5.89 and 5.95 Å, with angles between the carbonyl groups ranging from 107 to 112°. Since phosphorus is bigger than carbon, similar angles between the carbonyl groups of glycoluril derivatives and phosphorus containing analogues result in larger O-O distances in the latter molecules.

2.7 Conclusions

Glycoluril and its derivatives have been studied for well over a century. This research has led to a variety of commercial as well as academic applications, ranging from explosives and crosslinking agents for cellulose fabrics, to self-assembling molecular capsules and cucurbituril based rotaxanes. Phosphorus and boron containing glycoluril analogues have been synthesized as well, but applications of these compounds have not been reported. Propanediurea and its derivatives are compounds with structures similar to glycoluril; they are, however, less readily accessible. Research on these compounds has been rather limited, but a few commercial applications (many of which are similar to those of glycoluril), as well as a variety of synthetic methods have been described. In this thesis a study is made with regard to the synthesis and derivatization of these compounds and their application in the field of host-guest chemistry.

2.8 References

1 (a) Freeman, W.A.; Mock, W.L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367; (b) Mock, W.L.; Shih, N.-Y. *J. Org. Chem.* **1983**, *48*, 3618; (c) Mock, W.L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440.
2 Schiff, H. *Lieb. Ann. Chem.* **1877**, *189*, 157.
3 Petersen, H. *Synthesis* **1973**, 243.
4 Gautham, S.; Ketcham, R.; Nematollahi, J. *Synth. Commun.* **1979**, *10*, 863.

5 Nematollahi, J.; Ketcham, R. *J. Org. Chem.* **1963**, *28*, 2378.
6 (a) Seekles, L. *Recl. Trav. Chim. Pays-Bas* **1927**, *46*, 77; (b) Slezak, F.B.; Bluestone, H. *U.S. Patent* 3,187,004; C.A. **1965**, *63*, 13273g; (c) Mathew, C.T. *U.S. Patent* 3,767,669; C.A. **1974**, *80*, 82983m.
7 Biltz, H. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 4806.
8 Butler, A.R.; Leitch, E. *J. Chem. Soc. Perkin Trans. 2* **1980**, 103.
9 Branda, N.; Grotzfeld, R.M.; Valdés, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 85.
10 Kang, J.; Hilmersson, G.; Santamaria, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650.
11 Reek, J.N.H. *Thesis*, University of Nijmegen, **1996**.
12 Gompper, R.; Nöth, H.; Rattay, W.; Schwartzensteiner, M.-L.; Spes, P.; Wagner, H.-U. *Angew. Chem.* **1987**, *99*, 1071.
13 Elemans, J.A.A.W.; De Gelder, R.; Rowan, A.E.; Nolte, R.J.M. *Chem. Commun.* **1998**, 1553.
14 Pryor, K.E.; Rebek, J., Jr. *Org. Lett.* **1999**, *1*, 39.
15 De Haan, T. *Recl. Trav. Chim. Pays-Bas* **1908**, *27*, 162.
16 Boyle, P.H.; O'Brien, E. *Proc. R. Ir. Acad.* **1983**, *83B*, 13.
17 Jansen, R.J.; Scheeren, J.W.; Nolte, R.J.M. unpublished results.
18 Spänig, H.; Schönleben, W. *Belg. Pat.* 645094, **1964**.
19 Jansen, R.J.; Rowan, A.E.; De Gelder, R.; Scheeren, H.W.; Nolte, R.J.M. *Chem. Commun.* **1998**, 121.
20 House, H.O.; Wasson, R.L. *J. Am. Chem. Soc.* **1957**, *79*, 1488.
21 Kobayashi, E. *Yakugaku Zasshi* **1962**, *82*, 445.
22 Eres'ko, V.A.; Epishina, L.V.; Lebedev, O.V.; Khmel'nitskii, L.I.; Novikov, S.S.; Povstyanoi, M.V.; Kulik, A.F. *Bull. Acad. Sci. USSR, Chem. Ser.* **1979**, 1003.
23 (a) Reichardt, C.; Ferwanah, A.-R.; Pressler, W.; Yun, K.-Y. *Lieb. Ann. Chem.* **1984**, *4*, 649; (b) Rupe, H.; Knup, E. *Helv. Chim. Acta* **1927**, *10*, 299.
24 Spänig, H.; Schönleben, W. *Belg. Patent* 635,435, **1964**; C.A. **1964**, *62*, 13334b.
25 Nazarov, I.N.; Makin, S.M.; Kruptsov, B.K. *J. Gen. Chem. USSR* **1959**, *29*, 3641.
26 Khasapov, B.N.; Novikova, T.S.; Lebedev, O.V.; Khmel'nitskii, L.I.; Novikov, S.S. *J. Org. Chem. USSR* **1973**, *9*, 21.
27 Hale, W.J.; Williams, A.G. *J. Am. Chem. Soc.* **1915**, *37*, 594 and 1544.
28 Pauly, H.; Sauter, H. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 2063.
29 Broan, C.J.; Butler, A.R. *J. Chem. Soc. Perkin Trans. 2* **1991**, 1501.
30 Broan, C.J.; Butler, A.R.; Reed, D.; Sadler, I.H. *J. Chem. Soc. Perkin Trans. 2* **1989**, 731.
31 Sircar, A.C.; Guha, S.C. *J. Indian Chem. Soc.* **1936**, *13*, 704; C.A. **1937**, *31*, 3911-8.
32 Takahashi, M.; Miyadai, S. *Heterocycles* **1990**, *31*, 883.
33 (a) Lempert, K.; Lempert-Stréter, M. *Chem. Ber.* **1961**, *94*, 796; (b) Lempert-Stréter, M.; Stolt, V.; Lempert, K. *Chem. Ber.* **1963**, *96*, 170.
34 Gieling, G.T.W.; Scheeren, H.W.; Israël, R.; Nolte, R.J.M. *Chem. Commun.* **1996**, 241.
35 Eres'ko, V.A.; Epishina, L.V.; Lebedev, O.V.; Povstyanoi, M.V.; Khmel'nitskii, L.I.; Novikov, S.S. *Bull. Acad. Sci. USSR, Chem. Ser.* **1980**, *7*, 1138.
36 Kony, M.; Dagley, I.J. *Heterocycles* **1994**, *38*, 595.
37 Dudley, K.H.; Davis, I.J.; Kim, D.K.; Ross, F.T. *J. Org. Chem.* **1970**, *35*, 147.
38 Roesky, H.W.; Ambrosius, K.; Banek, M.; Sheldrick, W.S. *Chem. Ber.* **1980**, *113*, 1847.
39 Roesky, H.W.; Zamankhan, H.; Sheldrick, W.S.; Cowley, A.H.; Mehrotra, S.K. *Inorg. Chem.* **1981**, *20*, 2910.
40 Sheldrick, W.S.; Pohl, S.; Zamankhan, H.; Banek, M.; Amirzadeh-Asl, D.; Roesky, H.W. *Chem. Ber.* **1981**, *114*, 2132.

41 Roesky, H.W.; Amirzadeh-Asl, D. *Z. Naturforsch.* **1983**, *38b*, 460.
42 Neidlein, R.; Degener, H.J. *Arch. Pharm.* **1984**, *317*, 1053.
43 Wolf, G.-U.; Meisel, M. *Phosphorus, Sulfur, and Silicon* **1992**, *65*, 71.
44 Komorowski, L.; Niedenzu, K. *Inorg. Chem.* **1989**, *28*, 804.
45 Kadowaki, H. *Bull. Chem. Soc. Jpn.* **1936**, *11*, 248.
46 Zaugg, H.E. *Synthesis* **1970**, 49.
47 Behrend, R.; Meyer, E.; Rusche, F. *Lieb. Ann. Chem.* **1905**, *339*, 1.
48 Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 638, and references therein.
49 Petersen, H. *Textile Res. J.* **1971**, 239.
50 Smeets, J.W.H.; Sijbesma, R.P.; Niele, F.G.M; Spek, A.L.; Smeets, W.J.J.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1987**, *109*, 928.
51 Niele, F.G.M; Nolte, R.J.M. *J. Am. Chem. Soc.* **1988**, *110*, 172.
52 Sijbesma, R.P.; Nolte, R.J.M. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 643.
53 Kageyama, A.; Tada, K. *Jap. Patent* 21,743, **1961**; C.A. **1962**, *60*, 136271i.
54 Petersen, H.; Steimmig, A.; Schönleben, W.; Bille, H. *Ger. Patent* 2011703, **1971**; C.A. **1972**, *76*, 60867s.
55 Suvorova, L.I.; Eres'ko, V.A.; Epishina, L.V.; Lebedev, O.V.; Khmel'nitskii, L.I., Novikov, S.S.; Povstyanoi, M.B.; Lapshina, L.V.; Kulik, A.F. *Bull. Acad. Sci. USSR, Chem. Ser.* **1979**, *6*, 1222.
56 Dave, P.R.; Forohar, F.; Kaselj, M.; Gilardi, R.; Trivedi, N. *Tetrahedron Lett.* **1999**, *40*, 447.
57 Reek, J.N.H.; Kros, A.; Nolte, R.J.M. *Chem. Commun.* **1996**, 245.
58 Wyler, R.; De Mendoza, J.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699.
59 (a) Slezak, F.B.; Hirsch, A.; Rosen, I. *J. Org. Chem.* **1960**, *25*, 660; (b) Slezak, F.B.; Bluestone, H.; Magee, T.A.; Wotiz, J.H. *J. Org. Chem.* **1962**, *27*, 2181.
60 Kühling, D. *Lieb. Ann. Chem.* **1973**, 263.
61 Kühling, D.; Bloching, H. *U.S. Patent* 3,825,543, **1974**; C.A. **1974**, *83*, 58861.
62 Boileau, J.; Wimmer, E.; Carail, M.; Gallo, R. *Bull. Soc. Chim. Fr.* **1986**, 465.
63 Hong, G.; Zhu, C. *Proc. Int. Pyrotech. Semin.* **1991**, 17th, *1*, 193; C.A. **1992**, *112*, 197173.
64 (a) Li, N.; Maluendes, S.; Blessing, R.H.; Dupuis, M.; Moss, G.R.; DeTitta, G.T. *J. Am. Chem. Soc.* **1994**, *116,* 6494; (b) Xu, S.; Gantzel, P.K.; Clark, L.B. *Acta Cryst*. **1994**, *C50*, 1988.
65 Himes, V.L.; Hubbard, C.R.; Mighell, A.D.; Fatiadi, A.J. *Acta Cryst*. **1978**, *B34*, 3102.
66 (a) Dekaprilevich, M.O.; Suvorova, L.I.; Khmelnitskii, L.I.; Struchkov, Y.T. *Acta Cryst*. **1994**, *C50*, 2056; (b) Shamuratov, E.B.; Batsanov, A.S.; Struchkov, Y.T.; Tsivadze, A.Y.; Tsintsadze, M.G.; Khmel'nitskii, L.I.; Simonov, Y.A.; Dvorkin, A.A.; Lebedev, O.V.; Markova, T.B. *Khim. Get. Soedin. SSSR* **1991**, 937.
67 (a) Sijbesma, R.P.; Bosman, W.P.; Nolte, R.J.M. *Chem. Commun.* **1991**, 885; (b) Bosman, W.P.; Beurskens, P.T.; Admiraal, G.; Sijbesma, R.P.; Nolte, R.J.M. *Z. Kristallogr*. **1991**, *197*, 305; (c) Valdes, C.; Spitz, U.P.; Toledo, L.M.; Kubik, S.W.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 12733.
68 Piacenza, G.; Beguet, C.; Wimmer, E.; Gallo, R.; Giorgi, M. *Acta Cryst.* **1997**, *B53*, 1459.
69 Shevchenko, I.V.; Fischer, A.; Jones, P.G.; Schmutzler, R. *Chem. Ber.* **1994**, *127*, 1247.

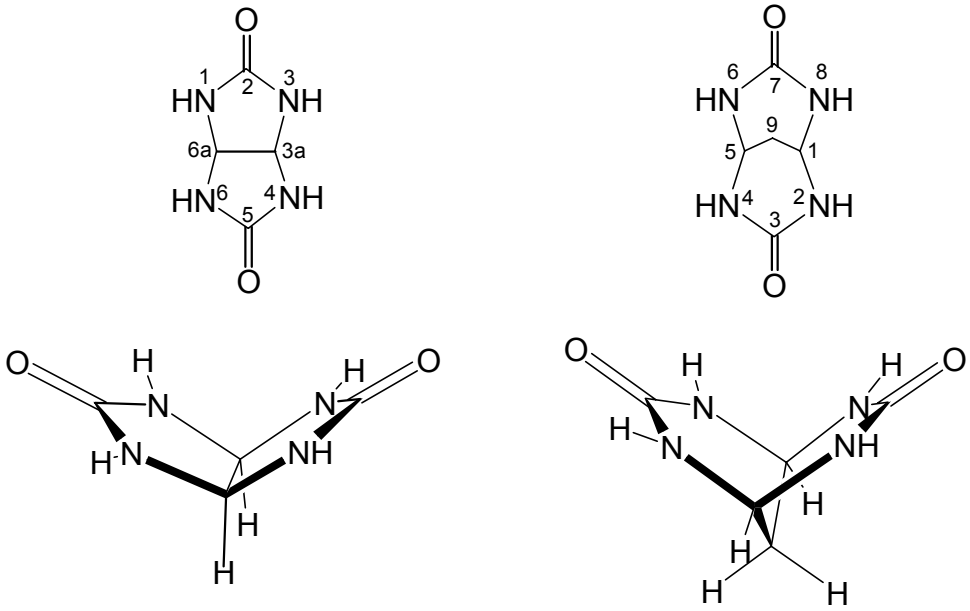
3

Synthesis of Bridged Glycoluril (Propanediurea) Analogues

3.1 Introduction

Glycoluril (**1a**) and its derivatives have been attracting a great deal of attention in recent years. Rebek's group has made extensive use of its hydrogen bonding properties in the construction of self-assembling molecular capsules.[1] Cucurbituril, a methylene bridged cyclic hexamer of glycoluril (see Chapter 2), has been studied by Mock and co-workers with respect to its complexation properties and its ability to catalyze reactions.[2] More recently Kim and co-workers utilized cucurbituril in the construction of rotaxanes and catenanes.[3] In our group derivatives of glycoluril are being used to build cavity-containing molecules that are excellent receptors for aromatic guests.[4] We, and recently also Isaacs and co-workers have used the self-complementarity of these

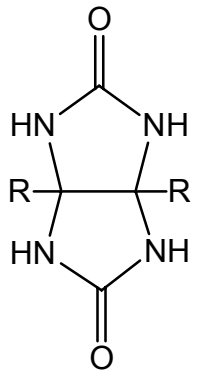
Chart 1



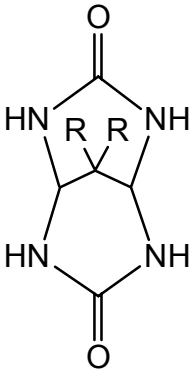
1a **2a**

molecules in an aqueous environment to construct nano-sized supramolecular structures.[5]
The methylene-bridged analogue of glycoluril, 2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (propanediurea, **2a**), has received hardly any attention. The history of molecules of this type dates back to 1908, when De Haan synthesized derivatives **4a-c**.[6] Some 60 years later, procedures were described for the preparation of derivatives **2b**[7] and **3a**.[8] Recently, the X-ray structure of **2a** has been solved[9] and it was noted that its structure is very similar to that of glycoluril.
In this chapter different procedures to prepare variously substituted 2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-diones are described. The synthesis involves reaction of two molecules of urea with a β-diketone, a β-ketoaldehyde, or a 1,3-dialdehyde analogue. These three approaches will be treated in sections 3.2, 3.3, and 3.4, respectively.

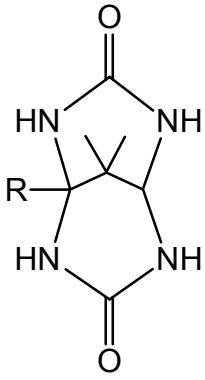
Chart 2



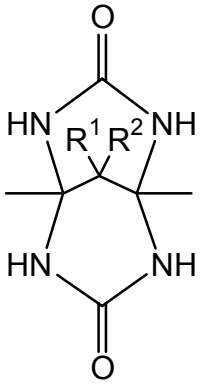
1a R = H
1b R = Ph



2a R = H
2b R = Me



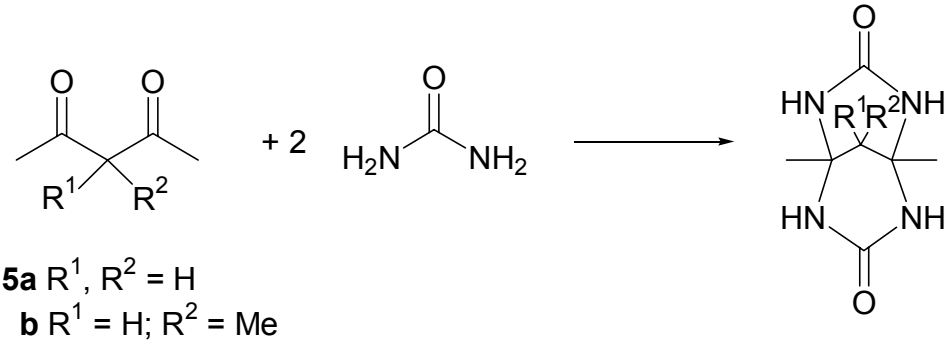
3a R = Me



4a R^1, R^2 = H
4b R^1 = H; R^2 = Me
4c R^1, R^2 = Me

3.2 Synthesis of propanediurea derivatives from β-diketones

Compounds **4a-c** have been prepared by reaction of urea with (methylated) acetylacetones **5a-c** at elevated temperatures (Scheme 1).[6] We attempted to react acetylacetone derivatives **5d**,**e**, which contain ethyl esters as functional groups with urea under similar reaction conditions. Neither reaction in refluxing toluene or mesitylene in the absence or presence of an acid catalyst (TFA, H_2SO_4), nor reaction without solvent yielded the desired products. Decomposition of the starting ketones took place. It was not possible to characterize the products. Similar negative results were obtained when dimethyl dibenzoylmethane was refluxed with urea in toluene with TFA as a catalyst.
It was concluded that β-diketones having electron withdrawing substituents at the α-position are generally not very reactive towards urea. At the high temperatures necessary for the reaction the functionalized β-diketones decompose. The reaction appears to be limited to simple alkyl



5a R^1, R^2 = H
b R^1 = H; R^2 = Me
c R^1, R^2 = Me
d R^1, R^2 = CH_2COOEt
e R^1 = Me; R^2 = CH_2COOEt

4a-c

Scheme 1 *Synthesis of propanediurea derivatives from β-diketones*

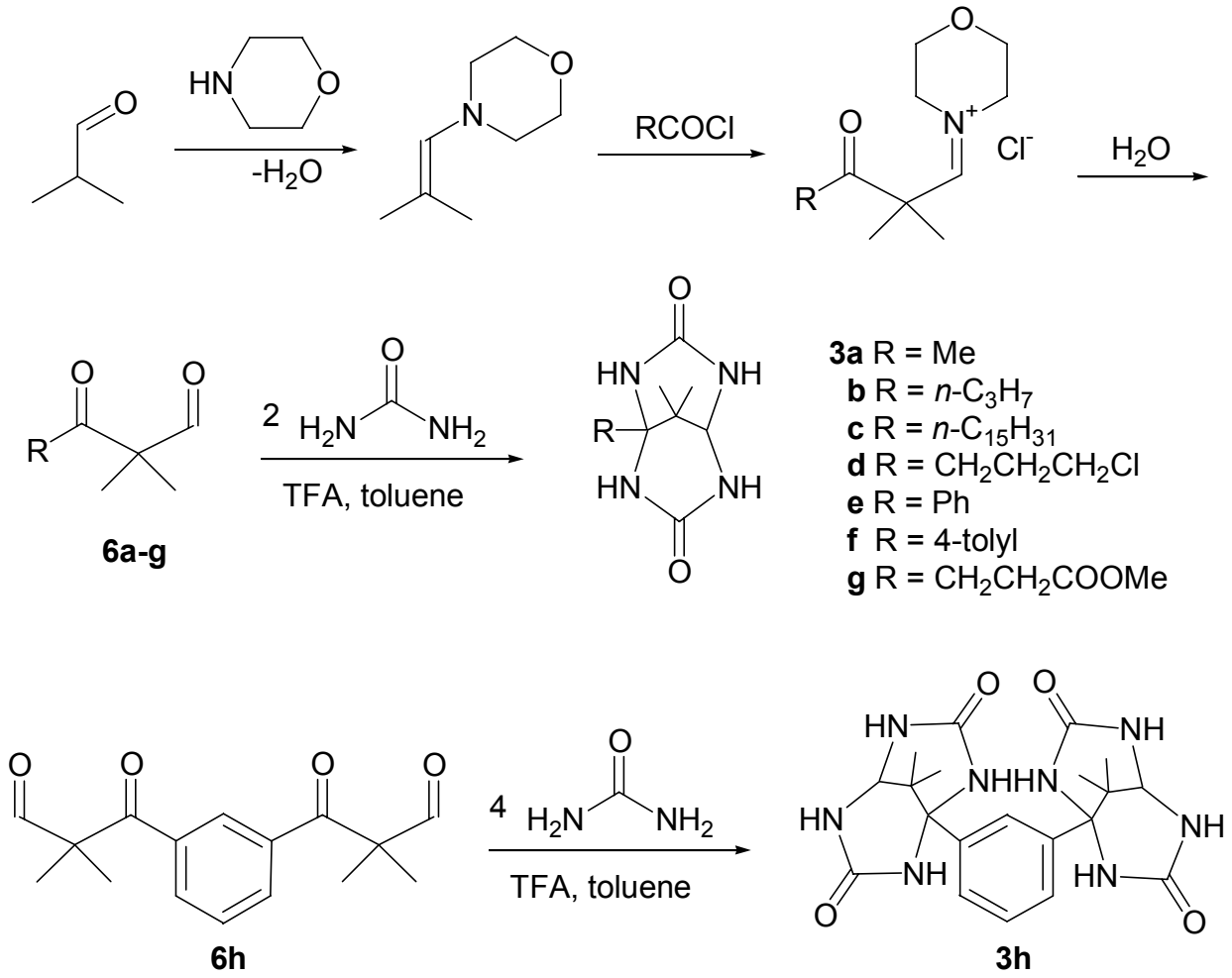
substituted acetylacetones. Therefore, the reaction of the more reactive 3-ketoaldehydes was investigated.

3.3 Synthesis of propanediurea derivatives from 3-ketoaldehydes

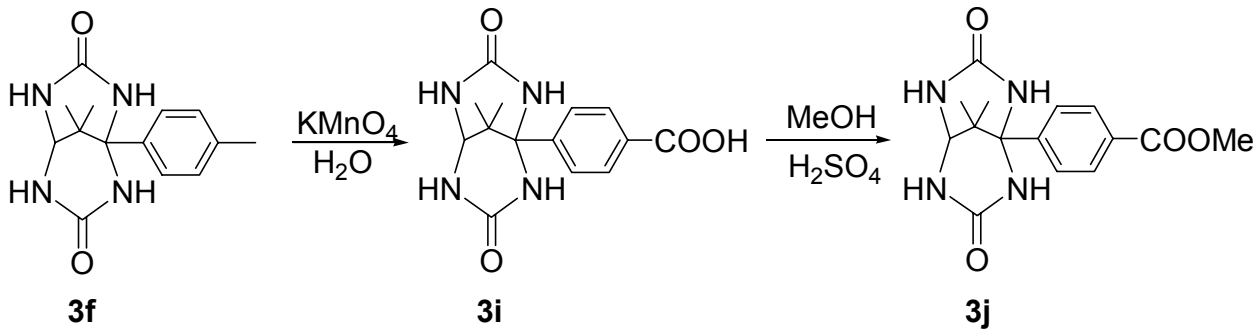
The preparation of 1,9,9-trisubstituted 2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione derivatives by heating 2,2-disubstituted-3-ketoaldehydes or 2,2-disubstituted-3-keto-α-chloro ethers with urea has been described in a patent.[8] We found that a convenient, high yield method for the preparation of these compounds was refluxing 2,2-disubstituted-3-ketoaldehydes **6** with two equivalents of urea in toluene with TFA as a catalyst (Scheme 2).

Compounds **3** precipitated from the reaction mixture and were isolated by filtration and washed with organic solvents and water. Yields were typically over 90%. Analytically pure samples could usually be obtained by recrystallization from water or diluted formic acid. The 2,2-dimethyl-3-ketoaldehydes were conveniently prepared by reaction of an acid chloride with the enamine of isobutyraldehyde, followed by mild hydrolysis of the product (Scheme 2).[10] Because of the ready accessibility of the 2,2-disubstituted-3-ketoaldehydes a large variety of compounds of type **3** can be prepared. The reaction of 3-ketoaldehydes with urea allows for the presence of various functional groups. The compounds that were prepared (Scheme 2) include alkyl (**3a**-**c**), chloroalkyl (**3d**), aryl (**3e**,**f**) and ester (**3g**) functionalized derivatives. From bis(ketoaldehyde) **6h** bis(glycoluril) derivative **3h** was obtained.

In a typical procedure 4-methylbenzoyl chloride was added to the enamine of morpholine and isobutyraldehyde. The two compounds were mixed and heated at 60°C for one hour. Hydrolysis yielded the ketoaldehyde **6f**. This ketoaldehyde was reacted with urea as described above to provide 1-(4-tolyl)-9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione **3f** in high yield. The benzylic methyl group was transformed into a carboxylic acid group by refluxing with $KMnO_4$ in water to yield **3i**. The methyl ester **3j** was obtained by refluxing in methanol in the presence of sulfuric acid (Scheme 3).



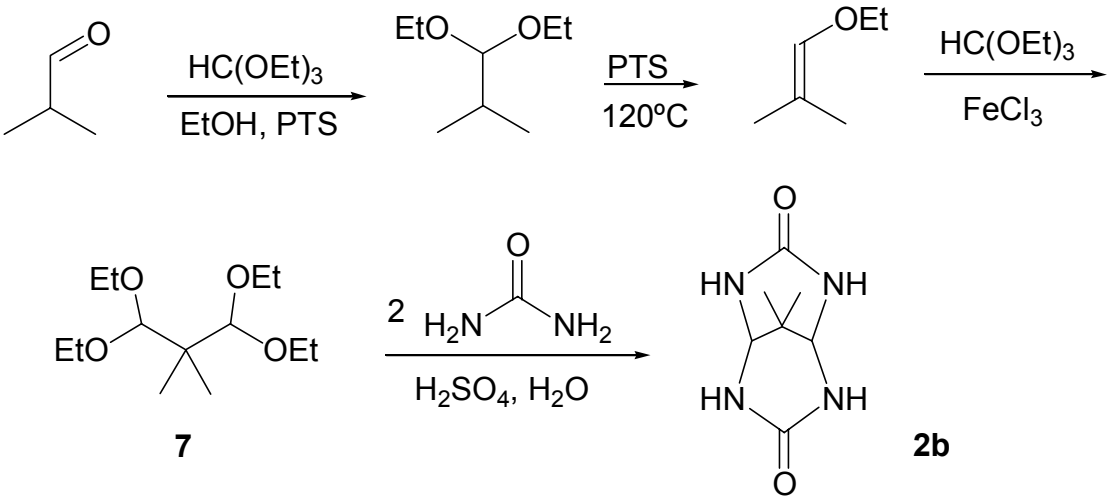
Scheme 2 *Synthesis of propanediurea derivatives from β-ketoaldehydes*



Scheme 3 *Preparation of a methyl ester functionalized propanediurea derivative*

3.4 Synthesis of propanediurea derivatives from acetals of 1,3-dialdehydes

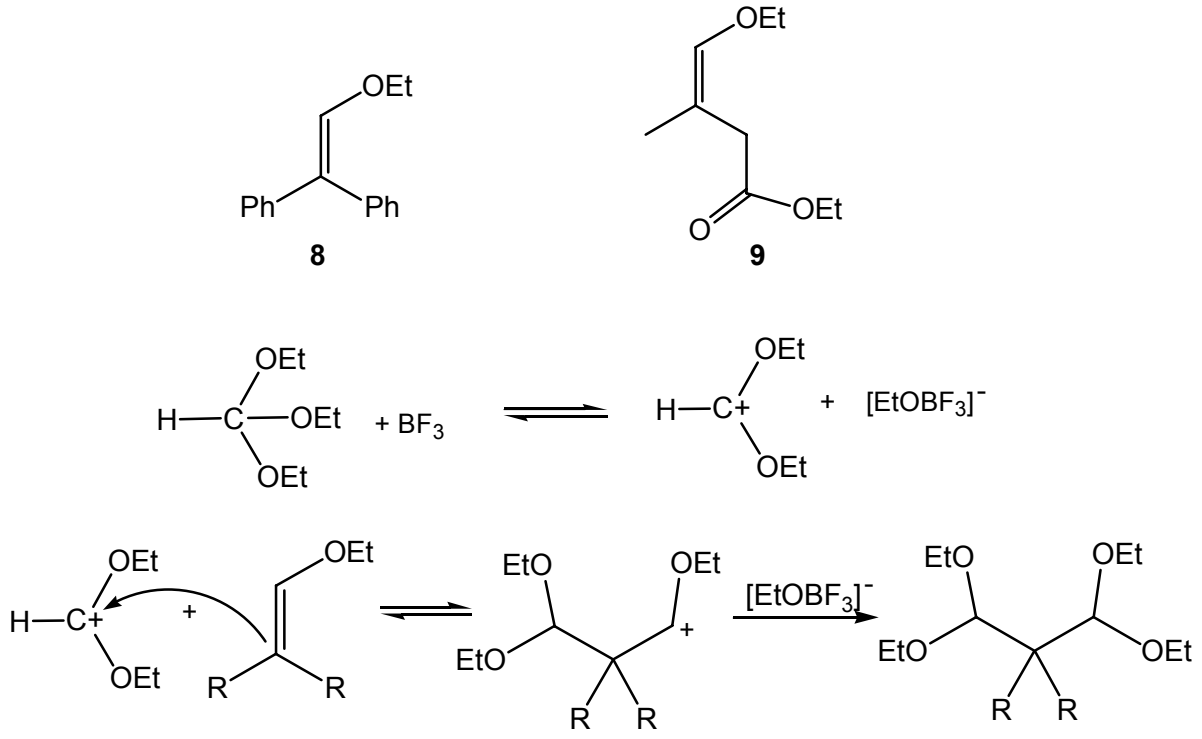
Derivatives of **2a** with hydrogens both on the 1 and 5 positions are much less accessible. The 9,9-dimethyl derivative **2b** has been prepared by heating dimethylmalonic dialdehyde with urea.[7] This route however is not very convenient due to the instability of malonic dialdehydes. The bisacetals of malonic dialdehyde on the contrary are quite stable compounds. They can be prepared by reaction of vinyl ethers with orthoformic esters in the presence of a Lewis acid catalyst at slightly



Scheme 4 *Synthesis of 9,9-dimethylpropanediurea*

elevated temperatures (~40°C).[11] When 2,2-dimethyl-1,1,3,3-tetraethoxypropane **7** is heated with two equivalents of urea in water in the presence of H_2SO_4 as a catalyst **2b** is formed in high yield (Scheme 4).[12]

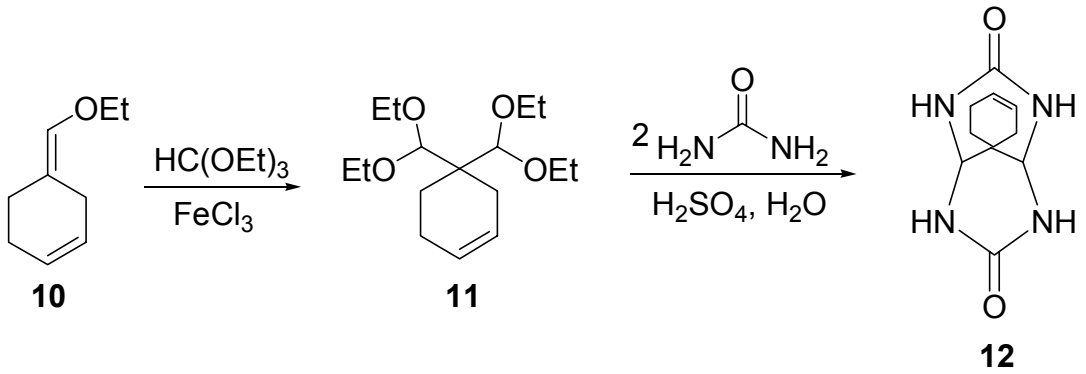
In our attempts to prepare functionalized derivatives of **2b** we tried to react functionalized vinyl ethers with triethyl orthoformate. However, ester and phenyl functionalized vinyl ethers **8** and **9** did not react under these conditions. Temperatures as high as 120°C as well as variation of the catalyst ($FeCl_3$, BF_3, $ZnCl_2$) did not result in detectable conversions and the starting compounds were recovered unchanged. The mechanism of this reaction provides an explanation for the dramatically decreased reactivity (Scheme 5).[13] The second step in the reaction is the addition of the diethoxymethyl cation to the vinyl ether double bond. This reaction proceeds smoothly when the R



Scheme 5 *Formation of a β-diacetal from an enol ether and triethyl orthoformate*

groups are electron donating alkyl functionalities. In the case of compounds **8** and **9** the double bond is stabilized by phenyl groups or an electron withdrawing ester group, and the intermediate carbocation is destabilized by the same substituents. An alternative explanation for the decreased reactivity of **9** is that the Lewis acid catalyst is deactivated by coordination to the ester carbonyl group.

Vinyl ether **10**, prepared from the commercially available cyclohexene aldehyde, did react with triethyl orthoformate to yield **11**. Subsequent reaction with urea yielded **12** in high yield (Scheme 6). The structure of **12** was confirmed by single-crystal X-ray diffraction (Figure 1).



Scheme 6 *Synthesis of a cyclohexene functionalized propanediurea*

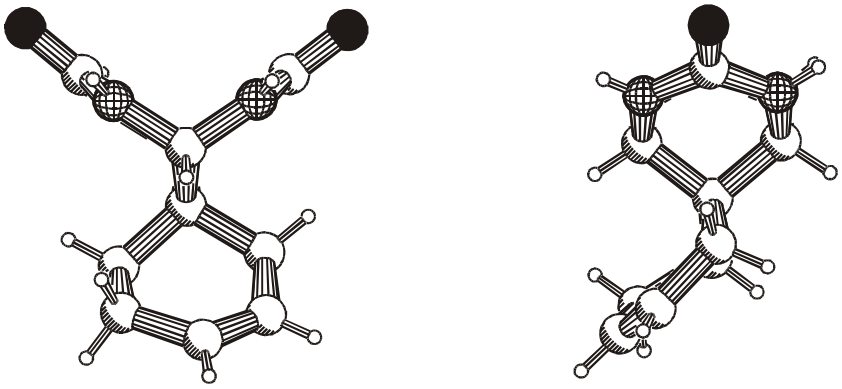


Figure 1 *Crystal structure of **12**, viewed from two sides. The drawings were made using the PLATON program*[14]

Preparation of propanediurea derivatives starting from 1,3-diols

Since both 2,2-disubstituted 1,3-dialdehydes and their bisacetals have been shown to react with urea to yield 9,9-disubstituted 2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-diones, we expected 2,2-disubstituted-3,3-dialkoxyaldehydes, previously reported to be stable compounds,[15] to undergo this reaction as well. Therefore we developed a general high yield route towards molecules of this type, starting from 1,3-diols. Pentaerithrytol (**13**) seemed an attractive starting material for this synthesis, for it is cheap and routes to protect two of its hydroxy groups are well described. Moreover, the use of doubly protected pentaerithrytols as starting compounds for the preparation of propanediurea derivatives provides compounds that possess two functionalities at their convex side.

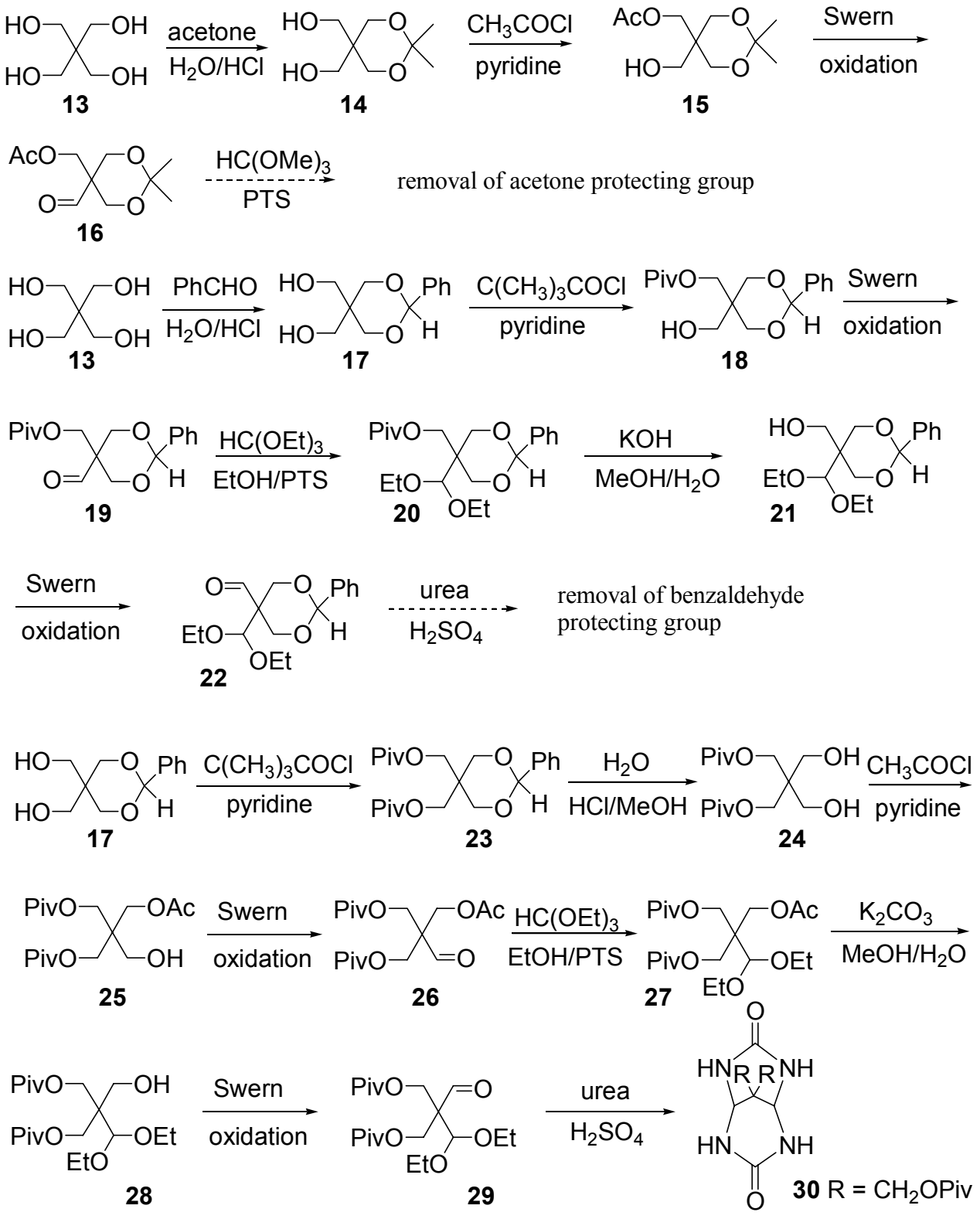
Synthetic strategy

Since 1,3-dialdehydes are not stable compounds, the two alcohol functions of a doubly protected pentaerithrytol derivative cannot be transformed into aldehydes in one step. A synthetic strategy that circumvents this problem was therefore developed. First, one of the alcohol groups is protected. Then, the remaining alcohol is oxidized to the aldehyde and immediately protected as the acetal. The other alcohol function is then deprotected and subsequently oxidized to yield the desired 3,3-dialkoxyaldehyde. It is clear that two different protecting groups are needed for the reaction sequence described above: one very stable group that is used to protect two of the four pentaerithrytol hydroxy groups and that will not be removed until the propanediurea framework has been formed, and one protecting group for temporary protection of one hydroxy group while the other one is being oxidized and acetalized. The various combinations of protecting groups that were tried are described below.

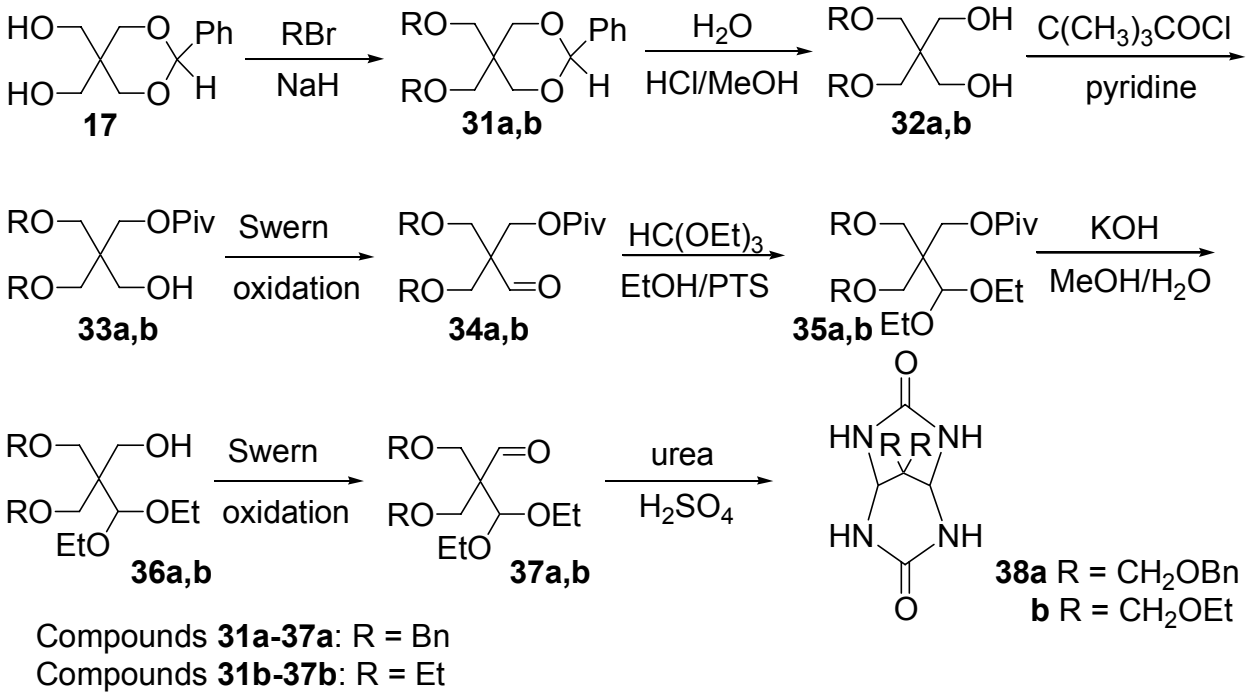
In a first attempt we started from pentaerithrytol protected as the acetone ketal **14**. The latter compound was reacted with one equivalent of acetyl chloride to yield **15**. Subsequent Swern oxidation yielded the aldehyde **16**. Unfortunately, attempted transformation of the aldehyde to the acetal with trimethyl orthoformate, methanol and an acid catalyst resulted in removal of the acetone protecting group (Scheme 7).

Apparently, a more acid stable protecting group for two of the four pentaerithrytol hydroxy groups was required. Therefore, we started from the monobenzal pentaerithrytol **17**. This compound was transformed into the pivaloic ester **18** by reaction with one equivalent of pivaloyl chloride. (The more bulky pivaloyl chloride was used instead of acetyl chloride in an attempt to prevent diacylation.) Swern oxidation of the product yielded the aldehyde **19**. In this case transformation of the aldehyde into the acetal **20** proceeded smoothly with triethyl orthoformate in the presence of catalytic amount of ethanol and *p*-toluenesulfonic acid (PTS). Deprotection of the pivaloic ester with KOH/methanol/water yielded the alcohol **21**, which was transformed into the aldehyde **22** by Swern oxidation. Reaction of **22** with urea in water containing H_2SO_4 resulted in removal of the benzaldehyde protecting group. It was not possible to isolate a propanediurea derivative having free hydroxy groups. When acetic acid was used as the solvent a small amount of a white product precipitated from the reaction mixture. Also in this case removal of the benzaldehyde protecting group took place. The precipitate was not soluble in water or organic solvents. Therefore, it was not possible to characterize the product (Scheme 7).

Since acetal protecting groups are not stable under the reaction conditions required for the formation of glycoluril derivatives we turned to more stable protecting groups. Protection of both alcohol functions of **17** as pivaloic esters was achieved by reaction with pivaloyl chloride, followed by acid hydrolysis of the acetal, yielding **24**. Essentially the same reaction conditions as described above now did provide glycoluril derivative **30** (Scheme 7), albeit not in a very high yield. Deprotection of acetate **27**, generally a high yield reaction, never produced over 70% of alcohol **28**, and the formation of the glycoluril derivative **30** was only achieved in a yield of 40-50%. This urged us to turn to the even more robust ethyl and benzyl ether protecting groups.



Scheme 7 *Preparation of 9,9-difunctionalized propanediurea derivatives*

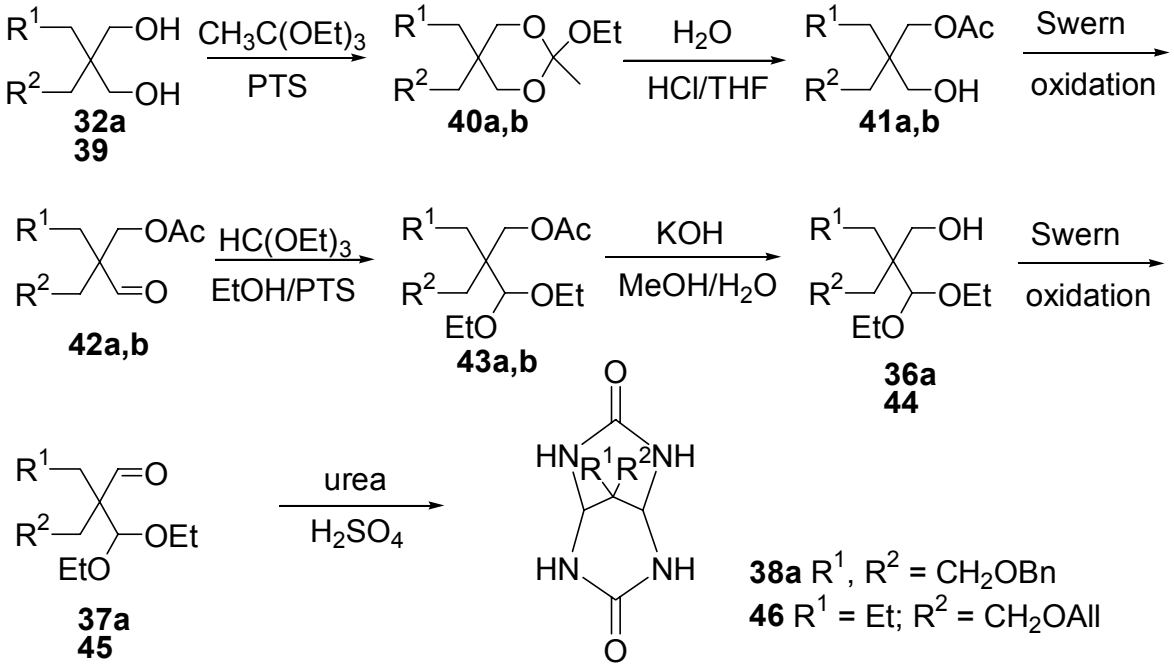


Scheme 8 *Synthesis of benzyl and ethyl ether functionalized propanediurea derivatives*

Dibenzyl and diethyl pentaerithrytol (**32a** and **32b**, respectively) were prepared by benzylation and ethylation of **17**, followed by acid hydrolysis of the acetal. Benzylation proceeded in 77% yield; ethylation in only 25% yield. Compounds **32a** and **32b** were transformed in five steps into the 3,3-diethoxyaldehydes **37a**,**b**. Diols **32a**,**b** were first protected as the monopivaloyl esters. Subsequent Swern oxidation, protection of the aldehydes as the diethyl acetals, ester hydrolysis, and a second Swern oxidation yielded compounds **37a**,**b** (Scheme 8). Reaction of these compounds with urea in acetic acid containing H_2SO_4 as a catalyst proceeded in 84% for the benzyl protected product **38a**, and in 50% yield for the ethyl protected product **38b** (Scheme 8).

Selective protection of one hydroxy group

The preparation of **38a** proceeded very smoothly. A tedious step in the synthesis, however, is the protection of the first hydroxy group of **32a** with pivaloyl chloride. Some esterification of both hydroxy groups cannot be avoided, and the separation of the two products is difficult. To circumvent this problem, **32a** was reacted with triethyl orthoacetate, yielding the mixed orthoester **40a**, which was immediately hydrolyzed by addition of diluted hydrochloric acid to the crude reaction mixture. The pure monoacetate **41a** was isolated from this mixture by extraction with diethyl ether. After transformation of **41a** to the aldehyde **42a** by Swern oxidation, and acetalizaton, **43a** was deprotected in high yield by stirring in KOH/methanol/water, yielding **36a** (Scheme 9). In this way, starting from 22.7 mmol of pure dibenzyl pentaerithrytol (**32a**), 15.9 mmol of uril derivative **38a** could be prepared, a 70% overall yield over 7 steps. Purification by distillation was advantageous only at the acetate-acetal stage (compound **43a**). Distillation of other intermediate products often led to severely decreased yields due to (trans)acetalization reactions at the high



Scheme 9 *High yield synthetic route towards allyl and benzyl ether functionalized propanediurea derivatives*

distillation temperatures required. The products of the Swern oxidations were purified by evaporation of the solvent and extraction of the salts with diethyl ether. Residual DMSO did not affect the subsequent reaction. The final product, glycoluril derivative **38a**, was purified by washing with water, ethanol and diethyl ether. All intermediate products were obtained reasonably pure without the use of chromatography.[a]

Since the synthetic procedures towards difunctionalized propanediurea derivatives were now well established, we searched for starting compounds that would allow for the synthesis of their monofunctionalized counterparts. Commercially available trimethylolpropane monoallylether (**39**) seemed an attractive candidate. It contains one allyl-protected hydroxy group, and a 1,3-diol functionality. Using the synthetic procedures established for compound **32a**, compound **39** was transformed into 9-ethyl-9-allyloxymethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**46**). The reactions all proceeded smoothly and the yields were comparably high (Scheme 9). However, unlike all other propanediurea derivatives described in this chapter, compound **46** is appreciably soluble in a variety of solvents, including acetic acid, water, DMSO, and methanol, and did not precipitate from the reaction mixture after its formation. It was therefore precipitated from the reaction mixture by addition of THF, isolated by filtration, and purified by recrystallization from ethanol.

[a] When the starting 1,3-diol **32a** was subjected to Swern oxidation no 1,3-dialdehyde could be isolated. However, when after the Swern oxidation was complete and the reaction mixture had reached room temperature, triethyl orthoformate and sufficient *p*-toluenesulfonic acid were added to make the mixture acidic, the 3,3-diethoxyaldehyde **37a** could be isolated in low yield. Reaction with urea yielded pure **38a** in an overall yield of ~10% (from **32a**).

3.5 Conclusions

It was possible to synthesize a large number of 9,9-disubstituted derivatives of 2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**2a**). Derivatives substituted at both the 1 and 5 positions are not generally accessible and limited to simple alkylated compounds. Derivatives substituted at only the 1-position are much more easily prepared. A number of these compounds with a variety of functional groups have been synthesized. It turned out to be difficult to extend the described synthesis of 9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione to compounds with different groups at the 9-position, since it was not possible to prepare the required 1,3-bisacetals. A cyclohexene functionalized compound was the only one that was synthesized. We therefore developed a new general synthetic route towards these molecules starting from 1,3-diols. With this route 2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione derivatives functionalized at the 9-position with benzyl and allyl protected alcohols have been prepared. In the following chapter the preparation of molecular clips from the newly synthesized glycoluril derivatives will be described.

3.6 Experimental section

General. Diethyl ether and toluene were distilled under nitrogen from sodium benzophenone ketyl. Methanol was distilled from calcium chloride. Dichloromethane was distilled from calcium hydride and kept on molecular sieves (4 Å) until it was used. All other solvents and chemicals were commercially available materials and were used as received. Merck silica gel (60H) was used for column chromatography. Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1720-X spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-100 and Bruker AM-300 instruments with $(CH_3)_4Si$ (δ 0.00 ppm) and DMSO-d_5 (δ 2.50 ppm) as the internal standards for the ^{1}H spectra, and $CDCl_3$ (δ 77.0 ppm), DMSO-d_6 (δ 39.5 ppm) or DMSO (in D_2O, δ 39.4 ppm) as the internal standard for the ^{13}C spectra. Abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; b, broad. MS spectra were recorded on a VG 7070E or a Finnigan MAT900S instrument. Elemental analyses were determined with a Carbo Erba EA 1108 instrument. Most intermediate alcohols, acetals, and aldehydes were isolated as high-boiling colorless oils, which often decomposed upon distillation. Impurities usually did not affect the following reaction steps. Therefore extensive purification was generally not attempted and the compounds were used directly in the next reaction.

Compounds: Compounds **6a**,**e**,[10a] **17**,[16] **14**,[17] **32a**,[18] **32b**,[19] and 4-(2-methyl-1-propenyl)morpholine[20] were synthesized according to literature procedures. The synthesis of compounds **3a** and **3e** has been published.[8] An improved synthetic procedure is described below.

1,9,9-Trimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**3a**): To toluene (90 mL) were added **6a** (2.41 g, 21.1 mmol), urea (2.54 g, 42.3 mmol), and TFA (2 mL). The mixture was

refluxed in an inert atmosphere for 4 h with azeotropic removal of water. Subsequently, it was cooled and filtered. The precipitate was washed with ethanol and dried *in vacuo*, yielding 3.93 g (94%) of **17a** as a white powder. Recrystallization from boiling water (~1 $g \cdot L^{-1}$) provided white crystals. M.p. > 350°C. ^{1}H NMR (DMSO-d_6): δ 1.03 (s, 6H, C(C*H*$_3$)$_2$), 1.14 (s, 3H, C(NH)$_2$C*H*$_3$), 3.88 (bs, 1H, C(NH)$_2$*H*), 6.87 (s, 2H, C(N*H*)$_2$CH$_3$), 6.94 (bs, 2H, CH(N*H*)$_2$).

1-Propyl-9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**3b**): Prepared as described for **3a** starting from **6b** (2.75 g, 19.4 mmol) and urea (2.40 g, 40.0 mmol). Yield: 4.35 g (99%) of **17c** as a white powder. Crystalline material was obtained by recrystallization from boiling water. M.p. 328-329°C (subl.). FAB MS (*m/z*) 227 ([M+H]$^+$), 154 (100%). ^{1}H NMR (DMSO-d_6): δ 0.84 (t, J = 6.3 Hz, 3H, CH$_2$C*H*$_3$), 1.06 (s, 6H, C(C*H*$_3$)$_2$), 1.40-1.55 (m, 4H, C*H*$_2$), 3.80 (t, J = 4.4 Hz, 1H, C(NH)$_2$*H*), 6.52 (s, 2H, C(N*H*)$_2$CH$_3$), 6.99 (bs, 2H, CH(N*H*)$_2$). IR (KBr): ν = 1654 cm^{-1} (C=O). Anal. Calcd. for $C_{10}H_{18}O_2N_4$: C: 53.08, H: 8.02, N: 24.76. Found: C: 53.31, H: 8.08, N: 24.47.

1-Pentadecyl-9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**3c**): Prepared as described for **3a** starting from **6c** (1.00 g, 3.22 mmol) and urea (0.396 g, 6.60 mmol). Yield: 0.840 g (66%) of **3c** as a white powder. M.p. 270°C. EI MS (*m/z*) 394 (M$^+$), 151 (100%). ^{1}H NMR (DMSO-d_6): δ 0.85 (t, J = 6.9 Hz, 3H, CH$_2$C*H*$_3$), 1.05 (s, 6H, C(C*H*$_3$)$_2$), 1.20-1.50 (m, 28H, C*H*$_2$), 3.79 (t, J = 4.4 Hz, 1H, C(NH)$_2$*H*), 6.52 (s, 2H, C(N*H*)$_2$CH$_3$), 6.99 (bs, 2H, CH(N*H*)$_2$). IR (KBr): ν = 1653, 1667, 1695 cm^{-1} (C=O). Anal. Calcd. for $C_{22}H_{42}N_4O_2$: C: 66.96, H: 10.73, N: 14.20. Found: C: 66.97, H: 10.90, N: 14.11.

1-(3-Chloropropyl)-9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**3d**): Prepared as described for **3a** starting from **6d** (11.95 g, 67.7 mmol) and urea (8.13 g, 136 mmol). Yield: 16.34 g (93%) of **3d** as an off-white powder. M.p. 245°C. EI MS (*m/z*) 260 (M$^+$), 71 (100%). ^{1}H NMR (DMSO-d_6): δ 1.07 (s, 6H, C(C*H*$_3$)$_2$), 1.59-1.66 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 1.91-1.97 (m, 2H, C(O)C*H*$_2$CH$_2$), 3.59 (t, J = 6.5 Hz, 2H, C*H*$_2$Cl), 3.88 (t, J = 3.2 Hz, 1H, C(NH)$_2$*H*), 6.70 (s, 2H, C(N*H*)$_2$CH$_2$), 7.06 (d, J = 4.1 Hz, 2H, CH(N*H*)$_2$). Anal. Calcd. for $C_{10}H_{17}N_4ClO_2$: C: 46.07, H: 6.57, N: 21.49. Found: C: 47.19, H: 6.76, N: 19.52.

1-Phenyl-9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**3e**): Prepared as described for **3a** starting from **6e** (8.00 g, 48.8 mmol) and urea (5.86 g, 97.7 mmol). Yield: 11.8 g (93%) of **3e** as a white powder. Crystalline material was obtained by recrystallization from boiling water. M.p. >350°C. ^{1}H NMR (DMSO-d_6): δ 0.87 (s, 6H, C(C*H*$_3$)$_2$), 3.98 (t, J = 4.4 Hz, 1H, C(NH)$_2$*H*), 6.99 (s, 2H, C(N*H*)$_2$(CH$_2$), 7.27 (bs, 2H, C(N*H*)$_2$Ar), 7.36-7.48 (m, 5H, Ar*H*).

1-(4-Methylphenyl)-9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**3f**): Prepared as described for **3a** starting from **6f** (11.64 g, 65.4 mmol) and urea (8.60 g, 143 mmol). Yield: 15.1 g (88%) of **3f** as a white powder. M.p. >350°C. EI MS (*m/z*) 274 (M$^+$), 231 (100%). ^{1}H NMR

(DMSO-d_6): δ 0.86 (s, 6H, C(C*H*$_3$)$_2$), 2.31 (s, 3H, ArC*H*$_3$), 3.97 (bs, 1H, C(NH)$_2$*H*), 6.84 (s, 2H, C(N*H*)$_2$(CH$_2$), 7.15-7.25 (m, 4H, C(N*H*)$_2$Ar and Ar*H*), 7.33 (d, J = 8.3 Hz, 2H, Ar*H*). ^{13}C NMR (DMSO-d_6): δ 21.50 C(NH)$_2$(*C*H$_3$), 22.05 (Ar*C*H$_3$), 34.72 (*C*C$_4$), 66.11 (*C*(NH)$_2$H), 73.91 (*C*(NH)$_2$CH$_3$), 128.75 and 129.00 (*C*H (arom.)), 135.42 (*C*CN$_2$ (arom.)), 138.29 (*C*CH$_3$ (arom.)), 156.22 (*C*=O). Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C: 61.30, H: 6.61, N: 20.42. Found: C: 61.65, H: 6.92, N: 19.76.

Methyl 3-(9,9-dimethyl-3,7-dioxo-2,4,6,8-tetraaza[3.3.1]bicyclonon-1-yl)propanoate (**3g**):
Prepared as described for **3a** starting from **6g** (1.13 g, 6.08 mmol) and urea (0.75 g, 12.5 mmol). Yield: 1.27 g (77%) of **3g** as a white powder. Crystalline material was obtained by recrystallization from boiling water. M.p. 262°C. EI MS (*m/z*): 238 (M^+–MeOH), 43 (100%). ^{1}H NMR (DMSO-d_6): δ 1.06 (s, 6H, C(C*H*$_3$)$_2$), 1.81 (dd, J = 8.0 Hz, 2H, C*H*$_2$COOMe), 2.64 (dd, J = 8.0 Hz, 2H, CH$_2$C*H*$_2$COOMe), 3.59 (3, 3H, OC*H*$_3$), 3.81 (bs, 1H, C(NH)$_2$*H*), 6.75 (s, 2H, C(N*H*)$_2$CH$_2$), 7.06 (d, J = 4.0 Hz, 2H, CH(N*H*)$_2$). Anal. Calcd. for $C_{11}H_{18}N_4O_4$: C: 48.88, H: 6.71, N: 20.73. Found: C: 48.78, H: 6.93, N: 20.60.

1-[3-(9,9-Dimethyl-3,7-dioxo-2,4,6,8-tetraaza[3.3.1]bicyclonon-1-yl)phenyl]-9,9-dimethyl-2,4,6,8-tetraaza[3.3.1]bicyclononane-3,7-dione (**3h**): Prepared as described for **3a** starting from **6h** (2.00 g, 7.29 mmol) and urea (1.76 g, 29.3 mmol). Yield: 2.75 g (85%) of **3h** as a white powder. M.p. >350°C. ^{1}H NMR (DMSO-d_6): δ 0.91 (s, 6H, C(C*H*$_3$)$_2$), 3.99 (t, J = 4.2 Hz, 1H, C(NH)$_2$*H*), 7.18 (s, 2H, C(N*H*)$_2$Ar, 7.23 (bs, 2H, CH(N*H*)$_2$), 7.45 (bs, 3H, Ar*H*), 7.57 (bs, J = 1H, Ar*H*). IR (KBr): ν = 1647, 1681 cm^{-1} (C=O).

4-(9,9-Dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.1]non-1-yl)benzoic acid (**3i**):
A suspension of **3f** (0.400 g, 1.46 mmol) and $KMnO_4$ (0.576 g, 3.65 mmol) in water (250 mL) was refluxed for 60 h. The mixture was cooled, filtered through infusorial earth and the pH was adjusted to 1 with aqueous 2.5 N sulfuric acid. Half of the solvent was removed *in vacuo*, and the mixture was cooled on an ice bath. The precipitate was collected by filtration, and washed with methanol and diethyl ether, yielding **3i** as a white solid. Yield: 0.49 g (77%). Recrystallization from water gave the analytically pure product. M.p. >350°C. FAB MS (*m/z*) 305 ($[M+H]^+$), 154 (100%). ^{1}H NMR (DMSO-d_6): δ 0.88 (s 6H, C(C*H*$_3$)$_2$), 3.99 (bs, 1H, NHC*H*NH), 7.04 (s, 2H, (*H*N)$_2$CAr), 7.26 (bs, 2H, (*H*N)$_2$CH), 7.55 and 7.94 (2×d, J = 7.7 Hz, 4H, Ar*H*). IR (KBr): ν = 1626, 1654, 1694, 1708 cm^{-1} (C=O). Anal. Calcd. for $C_{14}H_{19}O_{5.5}N_4$ (**3i**·1.5H$_2$O): C: 50.75, H: 5.78, N: 16.91. Found: C: 50.90, H: 5.44, N: 16.80.

Methyl 4-(9,9-dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.1]non-1-yl)benzoate (**3j**):
A suspension of **3i** (0.807 g, 2.65 mmol) and 8 drops of concentrated sulfuric acid in methanol (50 mL) was refluxed for 40 h. The mixture was cooled, and the precipitate was collected by filtration and washed with cold methanol and diethyl ether, yielding **3j** as a white solid (0.41 g, 49%). Crystalline material was obtained by recrystallization from water. M.p. 346°C (dec.). FAB MS

(*m/z*) 219 (M^+), 79 (100%). ^{1}H NMR (DMSO-d_6): δ 0.88 (s 6H, C(C*H*$_3$)$_2$), 3.88 (s, 3H, OC*H*$_3$), 4.00 (bs, 1H, NHC*H*NH), 7.08 (s, 2H, (*H*N)$_2$CAr), 7.27 (bs, 2H, (*H*N)$_2$CH), 7.61 and 7.98 (2×d, J = 8.2 Hz, 4H, Ar*H*). IR (KBr): ν = 1642, 1662, 1703, 1729 cm^{-1} (C=O). Anal. Calcd. for $C_{15}H_{20}O_5N_4$ (**3j**·H_2O): C: 53.57, H: 5.99, N: 16.66. Found: C: 53.69, H: 5.91, N: 16.62.

2,2-Dimethyl-3-oxohexanal (**6b**): To butyryl chloride (9.5 g, 89 mmol) in CH_2Cl_2 (35 mL) was added a solution of 4-(2-methyl-1-propenyl)morpholine (12.6 g, 89 mmol) in CH_2Cl_2 (35 mL). The mixture was refluxed for 2 h, cooled on an ice bath, and water (50 mL) was added. Then the pH was brought to 7 with a saturated solution of $NaHCO_3$, and the reaction mixture was stirred for 16 h. The CH_2Cl_2 layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. Distillation yielded **6b** (3.1 g, 25%). This material was used without further purification. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.33 (s, 6H, C(C*H*$_3$)$_2$), 1.53-1.66 (m, 2H, $CH_2CH_2CH_3$), 2.44 (t, J = 7.2 Hz, $CH_2CH_2CH_3$), 9.62 (s, 1H, C*H*O).

2,2-Dimethyl-3-oxooctadecanal (**6c**): To a solution of 4-(2-methyl-1-propenyl)morpholine (7.57 g, 53.7 mmol) in diethyl ether (75 mL) was a added solution of hexadecanoyl chloride (14.8 g, 54.3 mmol) in diethyl ether (75 mL). The mixture was refluxed for 8 days, cooled, and the precipitate was collected by filtration and washed with a small amount of dry diethyl ether. It was then dissolved in water (30 mL) and the solution was filtered. The filtrate was extracted with diethyl ether (50 mL). The ether layer was washed with water (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield **6c** (3.47 g, 21%). This material was used without further purification. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 6.6 Hz, 3H, CH_2CH_3), 1.25 (s, 24H, alkyl CH_2), 1.33 (s, 6H, C(C*H*$_3$)$_2$), 1.55 (t, J = 5.6 Hz, 2H, C(O)CH_2CH_2), 2.45 (t, J = 7.3 Hz, 2H, C(O)CH_2CH_2), 9.62 (s, 1H, C*H*O).

6-Chloro-2,2-dimethyl-3-oxohexanal (**6d**): To a cooled solution of 4-(2-methyl-1-propenyl)morpholine (41.5 g, 294 mmol) in CH_2Cl_2 (50 mL) was added during 45 min. a solution of 4-chlorobutyryl chloride (44.1 g, 313 mmol) in CH_2Cl_2 (50 mL). Then CH_2Cl_2 (100 mL) was added and the mixture was stirred for 3 h. and poured on crushed ice (250 g). The solution was neutralized with aqueous $NaHCO_3$, and stirred for 30 min. The organic layer was washed with water (2×100 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by distillation yielding **6d** (40 g, 77%). B.p. 101°C/7 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 6H, C(C*H*$_3$)$_2$), 1.99-2.12 (m, 2H, $CH_2CH_2CH_2$), 2.45 (t, J = 6.8 Hz, 2H, C(O)CH_2CH_2), 3.58 (t, J = 6.1 Hz, 2H, CH_2Cl), 9.62 (s, 1H, C*H*O).

2,2-Dimethyl-3-(4-methylphenyl)-3-oxopropanal (**6f**). 4-(2-Methyl-1-propenyl)morpholine (19.0 g, 135 mmol) was mixed with 4-methylbenzoyl chloride (20.9 g, 135 mmol) at room temperature and heated at 60°C for 1 h. Water (200 mL) and diethyl ether (150 mL) were added, and the mixture was neutralized with aqueous $NaHCO_3$. The organic layer was washed with water (2 × 100 mL), dried (Na_2SO_4), concentrated *in vacuo* and purified by distillation, yielding **6f** (16.5 g, 69%). B.p.

155°C/3 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 6H, C(C*H*$_3$)$_2$), 2.39 (s, 3H, ArC*H*$_3$), 7.22 and 7.67 (2×d, J = 8.3 Hz, 4H, Ar*H*), 9.75 (s, 1H, C*H*O).

Methyl 5,5-dimethyl-4,6-dioxohexanoate (**6g**): To a cooled solution of methyl 4-chloro-4-oxobutanoate (5.73 g, 38.1 mmol) in diethyl ether (12 mL) was added during 30 min. a solution of 4-(2-methyl-1-propenyl)morpholine (5.05 g, 35.8 mmol) in diethyl ether (12 mL). The reaction mixture was refluxed for 2 h and cooled on an ice bath. The precipitate was collected by filtration, washed with dry diethyl ether and dissolved in water (15 mL). Diethyl ether (15 mL) and sufficient aqueous $NaHCO_3$ was added to neutralize the mixture, which was stirred for 4 days. Extraction with diethyl ether (2 × 50 mL), washing of the combined organic layers with aqueous saturated $NaHCO_3$ (30 mL), drying ($MgSO_4$) and removal of the solvent *in vacuo* yielded the crude product. It was purified by distillation yielding **6g** (1.13 g, 17%). B.p. 120°C/10 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 6H, C(C*H*$_3$)$_2$), 2.60-2.85 (m, 4H, C*H*$_2$), 3.69 (s, 3H, OC*H*$_3$), 9.63 (s, 1H, C*H*O).

3- [3- (2,2- Dimethyl- 3-oxopropanoyl)phenyl] - 2,2 - dimethyl-3- oxopropanal (**6h**). Prepared as described for **6b**, from 4-(2-methyl-1-propenyl)morpholine (13.7 g, 97 mmol) and isophthaloyl dichloride (9.85 g, 48.5 mmol). The crude product was recrystallized from diethyl ether/hexane (4:1, v/v), yielding **6h**, (9.6 g, 72%) as a white crystalline solid. M.p. 52°C. ^{1}H NMR ($CDCl_3$): δ 1.51 (s, 6H, C(C*H*$_3$)$_2$), 7.54 (t, J = 7.8 Hz, 1H, *m*-Ar*H*), 7.94 (dd, J = 7.8 and 1.8 Hz, 2H, *p*-Ar*H*), 8.11 (t, J = 1.6 Hz, 1H, Ar*H*, ortho with respect to both substituents), 9.78 (s, 1H, C*H*O).

1-(2-Ethoxy-1-phenylvinyl)benzene (**8**): A mixture of diphenyl acetaldehyde (25.3 g, 129 mmol), triethyl orthoformate (19.1 g, 129 mmol) and a catalytic amount of *p*-toluenesulfonic acid was heated at 130ºC under reduced pressure (80 mm Hg). When the formation of ethanol had stopped, the reaction mixture was distilled under reduced pressure, yielding **8** (9.59 g, 33%) as a colorless oil. B.p. 135ºC/5 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J = 7.0 Hz, 3H, C*H*$_3$), 3.99 (q, J = 6.9 Hz, 2H, C*H*$_2$), 6.49 (s, 1H, C=C*H*), 7.15-7.40 (m, 5H, Ar*H*).

Ethyl (*E,Z*)-4-ethoxy-3-ethyl-3-butenoate (**9**): A solution of butyraldehyde (25 g, 0.35 mol) and diisopropylamine (45 g, 0.35 mol) in benzene (150 mL) was refluxed for 4 h with azeotropic removal of water. Then a solution of ethyl bromoacetate (89 g, 0.53 mol) in acetonitrile (100 mL) was added and refluxing was continued for 16 h. Aqueous acetic acid (25%, 70 mL) was added and the mixture was again refluxed for 4 h. The organic layer was washed with water (2 × 150 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (70 g) was purified by repeated distillation yielding ethyl 3-formylpentanoate as a colorless oil (19 g, 34%). B.p. 43-44ºC/3 mm Hg. ^{1}H NMR ($CDCl_3$): δ 0.98 (t, J = 7.5 Hz, 3H, C*H*$_3$CH$_2$C), 1.24 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.51-1.84 (m, 2H, CC*H*$_2$CH$_3$), 2.37 and 2.43 (2×d, J = 4.9 Hz, 1H, HC(O)C*H*), 2.66-2.81 (m, 2H, C*H*$_2$COOEt), 4.14 (q, J = 7.1 Hz, 2H, OC*H*$_2$CH$_3$). A mixture of ethyl 3-formylpentanoate (10.0 g, 63.3 mmol) and triethyl orthoformate (9.45 g, 63.8 mmol) and catalytic amounts of ethanol and *p*-toluenesulfonic acid was heated at 90ºC at 100 mm Hg until the formation of ethyl formate and

ethanol had stopped. Subsequent distillation gave **9** as a colorless oil (11.3 g, 96%). B.p. 52-54ºC/3 mm Hg. ^{1}H NMR ($CDCl_3$): δ 0.99 (t, J = 7.4 Hz, 3H, C*H*$_3$CH$_2$C), 1.15-1.28 (m, 6H, C*H*$_3$CH$_2$O), 1.96-2.22 (m, 2H, CC*H*$_2$CH$_3$), 3.11 (s, 2H, CC*H*$_2$C(O)), 4.09-4.16 (m, 4H, OC*H*$_2$CH$_3$), 5.92 and 5.97 (2×s, 1H, C=C*H*).

(*E*,*Z*)-3-cyclohexenylidenmethylethyl ether (**10**). A mixture of 3-cyclohexene-1-carbaldehyde (10 g, 91 mmol), triethyl orthoformate (13.5 g, 91 mmol) and a catalytic amount of *p*-toluenesulfonic acid was kept at 40ºC and 15 mm Hg until the evolution of ethyl formate had stopped. The temperature was then raised to 130ºC and the mixture was kept at this temperature until evolution of ethanol had stopped. The crude product was neutralized with CaH_2 and **10** was isolated by distillation as a colorless oil (9.04 g, 72%). B.p. 45ºC/6 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 5 Hz, 3H, C*H*$_3$CH$_2$O), 1.95-2.25 (m, 4H, C=CC*H*$_2$C*H*$_2$C=C), 2.50-2.90 (m, 2H, C=CC*H*$_2$C=C), 3.75 (q, J = 5 Hz, 2H, CH$_3$C*H*$_2$O), 5.60-5.75 (m, 2H, *H*C=C*H*), 5.87 and 5.96 (2×s, 1H, *H*C(OEt)=C, (*E*) and (*Z*)).

4,4-Di(diethoxymethyl)-1-cyclohexene (**11**): To a solution of $FeCl_3$ (72 mg, 0.39 mmol) in triethyl orthoformate (87.9 g, 593 mmol) was slowly added **10** (27.2 g, 197 mmol). The mixture was kept at 40ºC for 2 h, neutralized with CaH_2 (0.5 g) and purified by distillation. Product **11** was obtained as a colorless oil (36.2 g, 64%). B.p. 95ºC/7 mm Hg. EI MS (*m/z*) 103 (100%, $[CH(OEt)_2]^+$). ^{1}H NMR ($CDCl_3$): δ 1.16-1.23 (m, 12H, C*H*$_3$CH$_2$O), 1.70 (t, J = 7.5 Hz, 2H, C*H*$_2$CH$_2$C=C), 2.06-2.11 (m, 4H, C*H*$_2$C=C), 3.47-3.83 (m, 8H, CH$_3$C*H*$_2$O), 4.92 (s, 2H, *H*COEt), 5.63-5.67 (m, 2H, *H*C=C*H*). ^{13}C NMR ($CDCl_3$): δ 15.32 (*C*H$_3$), 22.59 (CH*C*H$_2$CH$_2$), 22.68 (CHCH$_2$*C*H$_2$), 25.63 (CH$_2$*C*HCH$_2$), 45.19 (CH*C*H$_2$CH=CH), 65.78 (O*C*H$_2$), 107.63 (*C*H(OEt)$_2$), 125.37 and 126.31 (C=C). Anal. Calcd. for $C_{16}H_{30}O_4$: C: 67.10, H: 10.56. Found: C: 67.82, H: 9.83.

(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.1]non-9-yl)-spiro-1'-(3'-cyclohexene) (**12**): A mixture of **11** (34.3 g, 120 mmol), urea (15.7 g, 253 mmol), sulfuric acid (0.5 mL) and water (45 mL) was refluxed for 4 h. During the reaction the pH was monitored and adjusted to ~3 with sulfuric acid if necessary. The mixture was cooled and the precipitate was collected by filtration, washed with water, acetone and diethyl ether, yielding **12** as a white powder (24.8 g, 91%). Single crystals suitable for X-ray analysis were prepared by slow diffusion of ethanol in a formic acid (85%) solution of **12**. M.p. 320°C (dec.). EI MS (*m/z*) 222 (M^+). ^{1}H NMR (DMSO-d_6): δ 1.51-1.75 (m, 2H, C*H*$_2$CH$_2$C=C), 1.90-2.12 (m, 4H, C*H*$_2$C=C), 3.90 (bs, 2H, NHC*H*NH), 5.63-5.71 (m, 2H, *H*C=C*H*), 7.00 (bs, 4H, N*H*). ^{13}C NMR (DMSO-d_6): δ 20.49, 24.81, and 28.75 (*C*H$_2$), 77.66 (N*C*HN), 123.29 and 124.80 (*C*=*C*), 152.42 and 152.66 (*C*=O), (*C*C$_4$ under DMSO peak). IR (KBr): ν = 1687, 1660, 1650, 1633 cm^{-1} (C=O, C=C). Anal. Calcd. for $C_{10}H_{14}O_2N_4$: C: 54.04, H: 6.35, N: 25.21. Found: C: 54.50, H: 6.34, N: 24.76.

[5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl]methyl acetate (**15**): Compound **14** (1.0 g, 5.7 mmol) was dissolved in dichloromethane (25 mL). Pyridine (0.49 g, 6.2 mmol) and acetyl chloride

(0.45 g, 5.7 mmol) were subsequently added and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo* and diethyl ether was added. The precipitate was removed by filtration; the filtrate was concentrated and purified by *Kugelrohr* distillation, yielding a 4:1 molar mixture of **15** and the corresponding diacetate. This mixture was not purified further, but directly used in the following step. B.p. 130ºC/0.5 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 6H, C(C*H*$_3$)), 2.04 (s, 3H, O*Ac*), 2.76 (bs, 1H, O*H*), 3.47 (s, 2H, C*H*$_2$OH), 3.67 (s, 4H, C*H*$_2$OC(CH$_3$)$_2$), 4.39 (C*H*$_2$OAc).

General procedure for Swern oxidation (procedure A): To a cooled (–60ºC) solution of oxalyl chloride (0.19 g, 1.5 mmol) in CH_2Cl_2 (4 mL) was dropwise added a solution of DMSO (0.235 g, 3.0 mmol) in CH_2Cl_2 (0.5 mL). After 5 min. a solution of the alcohol (1 mmol) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for 20 min. Then triethylamine (1 mL) was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed *in vacuo* and diethyl ether was added. The precipitate was removed by filtration and the filtrate was concentrated.

General procedure for the synthesis of an acetal from an aldehyde (procedure B): A mixture of the aldehyde (1.0 mmol), triethyl orthoformate (1.2 mmol), a drop of ethanol and a catalytic amount of *p*-toluenesulfonic acid was heated at 50ºC for 2 h. A few drops of triethylamine were added and the crude product was purified by *Kugelrohr* distillation.

(5-Formyl-2,2-dimethyl-1,3-dioxan-5-yl)methyl acetate (**16**): From **15** (2.3 g, containing ~25% of impurities, mainly diacetate), by Swern oxidation (procedure A). The crude product was purified by *Kugelrohr* distillation, yielding **16** (1.65 g, ~72%, containing ~25% of the diacetate). This mixture was used directly in the following reaction with trimethyl orthoformate. B.p. 110-120ºC/0.5 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 6H, C(C*H*$_3$)$_2$), 2.01 (s, 3H, O*Ac*), 3.82 and 3.98 (2×d, J = 12 Hz, 4H, C*H*$_2$OC(CH$_3$)$_2$), 4.24 (s, 2H, C*H*$_2$OAc), 9.71 (s, 1H, C*H*O).

[5-(Hydroxymethyl)-2-phenyl-1,3-dioxan-5-yl]methyl pivalate (**18**): To a solution of **17** (5.0 g, 22.3 mmol) and pyridin (2.1 g, 27 mmol) in CH_2Cl_2 (50 mL) was added pivaloyl chloride (2.67 g, 22.3 mmol). The mixture was stirred for 30 min. and concentrated *in vacuo*. Diethyl ether was added and the precipitate was removed by filtration. The filtrate was concentrated and purified by *Kugelrohr* distillation yielding **18** (3.7 g, containing ~12% of the dipivalate). The product was directly used in the following reaction. B.p. 200ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 9H, C(C*H*$_3$)$_3$), 2.31 (t, J = 4.4 Hz, 1H, O*H*), 3.73-4.20 (m, 8H, C*H*$_2$O), 5.43 (s, 1H, C*H*Ph), 7.20-7.50 (m, 5H, Ar*H*).

(5-Formyl-2-phenyl-1,3-dioxan-5-yl)methyl pivalate (**19**): From **18** (8.6 g, containing ~20% impurities, mainly the dipivalate) by Swern oxidation (procedure B). Yield: 6.65 g (~77%). Pure **19** was obtained by recrystallization from diisopropyl ether. M.p. 98-100ºC. ^{1}H NMR ($CDCl_3$): δ 1.19

(s, 9H, C(C*H*$_3$)$_3$), 3.96 and 4.60 (2×d, J = 12 Hz, 4H, C*H*$_2$OCHPh), 4.02 (s, 2H, C*H*$_2$OPiv), 5.49 (s, 1H, C*H*Ph), 7.33-7.45 (m, 5H, Ar*H*), 10.00 (s, 1H, C*H*O). Anal. Calcd. for $C_{17}H_{22}O_5$: C: 66.65, H: 7.24. Found: C: 66.73, H: 7.25.

[5-(Diethoxymethyl)-2-phenyl-1,3-dioxan-5-yl]methyl pivalate (**20**): From **19** (2.5 g, 9.5 mmol), by procedure B. Yield: 2.6 g (83%). B.p. 190-200ºC/0.5 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 9H, C(C*H*$_3$)$_3$), 1.17 (t, J = 7.0 Hz, 6H, C*H*$_3$CH$_2$O), 3.44-3.83 (m, 4H, OC*H*$_2$CH$_3$), 3.90 and 4.52 (2×d, J = 12 Hz, 4H, C*H*$_2$OCHPh), 3.99 (s, 2H, C*H*$_2$OPiv), 5.20 (s, 1H, C*H*(OEt)$_2$), 5.48 (s, 1H, C*H*Ph), 7.33-7.45 (m, 5H, Ar*H*).

[5-(Diethoxymethyl)-2-phenyl-1,3-dioxan-5-yl]methanol (**21**): A mixture of **20** (2.6 g, 6.8 mmol), ethanol (30 mL) and 30% aqueous KOH (10 mL) was refluxed for 2 h. The solution was concentrated *in vacuo* and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2CO_3) and concentrated, yielding **21** (1.7 g, 84%). B.p. 180ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J = 7.0 Hz, 6H, C*H*$_3$CH$_2$O), 3.16 (C*H*$_2$OH), 3.50-3.89 (m, 4H, OC*H*$_2$CH$_3$), 3.94 and 4.56 (2×d, J = 12 Hz, 4H, C*H*$_2$OCHPh), 5.18 (s, 1H, C*H*(OEt)$_2$), 5.44 (s, 1H, C*H*Ph), 7.35-7.51 (m, 5H, Ar*H*).

5-(Diethoxymethyl)-2-phenyl-1,3-dioxane-5-carbaldehyde (**22**): From **21** (2.4 g, 8.1 mmol) by Swern oxidation (procedure A). Yield: 1.95 g (81%). B.p. 160ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, J = 7.0 Hz, C*H*$_3$), 3.54-4.10 (m, 4H, C*H*$_2$CH$_3$), 4.00 and 4.48 (2×d, J = 12 Hz, 4H, C*H*$_2$OCHPh), 5.21 (s, 1H, C*H*(OEt)$_2$), 5.46 (s, 1H, C*H*Ph), 7.33-7.50 (m, 5H, Ar*H*), 9.78 (s, 1H, C*H*O).

3-(Pivaloyloxy)-2,2-di(hydroxymethyl)propyl pivalate (**24**): A mixture of **17** (10 g, 45 mmol), pyridin (8.8 g, 111 mmol), pivaloyl chloride (12.3 g, 102 mmol) and CH_2Cl_2 (100 mL) was stirred at room temperature for 16 h. The solvent was removed *in vacuo*, diethyl ether was added and the precipitate was removed by filtration. The filtrate was concentrated, dissolved in a mixture of methanol (150 mL), water (30 mL) and concentrated HCl (15 mL), and refluxed for 16 h. The hot mixture was poured onto solid Na_2CO_3 and subsequently concentrated *in vacuo*. The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Hexane was added to the oily residue and crystallization was induced by vigorous stirring. Filtration yielded **24** as white crystals (6.0 g, 44%). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 18H, C(C*H*$_3$)$_3$), 3.28 (bs, 2H, O*H*), 3.59 (bs, 4H, C*H*$_2$OH), 4.11 (s, 4H, C*H*$_2$OPiv).

3-(Acetyloxy)-2-[(pivaloyloxy)methyl]-2-(hydroxymethyl)propyl pivalate (**25**): Prepared as described for **15** from **24** (6.4 g, 21 mmol). Yield: 6.3 g (containing ~25% diacetate). The crude product was used directly in the following reaction. ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 18H, C(C*H*$_3$)$_3$), 2.09 (s, 3H, O*Ac*), 2.85 (bs, 1H, O*H*), 3.54 (d, J = 7.2 Hz, 2H, C*H*$_2$OH), 4.12 (s, 4H, C*H*$_2$OPiv).

3-(Acetyloxy)-2-formyl-2-[(pivaloyloxy)methyl]propyl pivalate (**26**): From **25** (6.3 g), by Swern oxidation (procedure A). Yield: 3.8 g (60%). B.p. 180ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.19 (s, 18H, C(C*H*$_3$)$_3$), 2.07 (s, 3H, O*Ac*), 4.32 (s, 6H, C*H*$_2$OAc and C*H*$_2$OPiv), 9.67 (s, 1H, C*H*O).

2-[(Acetyloxy)methyl]-3,3-diethoxy-2-[(pivaloyloxy)methyl]propyl pivalate (**27**): From **26** (0.70 g, 2.0 mmol) by procedure B. Yield: 0.68 g (80%). B.p. 170ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 18H, C(C*H*$_3$)$_3$), 1.21 (t, J = 7.0 Hz, 6H, CH$_2$C*H*$_3$), 2.05 (s, 3H, O*Ac*), 3.34-3.91 (m, 4H, C*H*$_2$CH$_3$), 4.21 (s, 4H, C*H*$_2$OPiv), 4.25 (s, 2H, C*H*$_2$OAc), 4.52 (s, 1H, C*H*(OEt)$_2$).

3,3-Diethoxy-2-(hydroxymethyl)-2-[(pivaloyloxy)methyl]propyl pivalate (**28**): A mixture of **27** (0.68 g, 1.6 mmol), methanol (30 mL) and saturated aqueous K_2CO_3 (20 mL) was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo*, extracted with CH_2Cl_2, dried (Na_2CO_3) and distilled (*Kugelrohr*). Yield: 0.40 g (60%). B.p. 170ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.20 (s, 18H, C(C*H*$_3$)$_3$), 1.23 (t, J = 7.3 Hz, 6H, CH$_2$C*H*$_3$), 2.90 (t, J = 6.3 Hz, 1H, O*H*), 3.38-4.03 (m, 4H, C*H*$_2$CH$_3$), 3.70 (s, 2H, C*H*$_2$OH), 4.14 (s, 4H, C*H*$_2$OPiv), 4.56 (s, 1H, C*H*(OEt)$_2$).

3,3-Diethoxy-2-formyl-2-[(pivaloyloxy)methyl]propyl pivalate (**29**): From **28** (0.89 g, 2.4 mmol) by Swern oxidation (procedure A). Yield: 0.60 g (67%). B.p. 170ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 18H, C(C*H*$_3$)$_3$), 1.23 (t, J = 6.9 Hz, 6H, CH$_2$C*H*$_3$), 3.38-4.00 (m, 4H, C*H*$_2$CH$_3$), 4.30 and 4.51 (2×d, J = 12 Hz, 4H, C*H*$_2$OPiv), 4.67 (s, 1H, C*H*(OEt)$_2$), 9.76 (s, 1H, C*H*O).

{9-[(Pivaloyloxy)methyl]-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.1]non-9-yl}methyl pivalate (**30**): A mixture of **29** (0.29 g, 0.78 mmol), urea (96 mg, 1.6 mmol), acetic anhydride (300 mg), and sulfuric acid (1 drop) was heated at 100ºC for 1 h. After cooling, the precipitate was collected by filtration and washed with water, acetone and diethyl ether. Yield: 150 mg (50%). M.p. >350°C. FAB MS (*m/z*) 385 ([M+H]$^+$), 170 (100%). ^{1}H NMR (DMSO-d$_6$): δ 1.14 (s, 18H, C(C*H*$_3$)$_3$), 4.09 (s, 4H, C*H*$_2$OPiv), 4.23 (t, J = 4.0 Hz, 2H NHC*H*NH), 7.35 (d, J = 4.1 Hz, 4H, N*H*). Anal. Calcd. for $C_{17}H_{28}N_4O_6$: C: 53.11, H: 7.34, N: 14.57. Found: C: 53.56, H: 7.33, N: 14.27.

3-(Benzyloxy)-2-[(benzyloxy)methyl]-2-(hydroxymethyl)propyl pivalate (**33a**): Prepared as described for **18** from **32a** (15 g, 47 mmol). Yield: 18.4 g, containing ~15% impurities, mainly dipivalate. ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 9H, C(C*H*$_3$)$_3$), 2.80 (bs, 1H, O*H*), 3.50 and 3.54 (2×d, J = 2.9 Hz, 4H, C*H*$_2$OBn), 3.68 (bs, 2H, C*H*$_2$OH), 4.15 (s, 2H, C*H*$_2$OPiv), 4.48 (s, 4H, C*H*$_2$Ph), 7.18-7.40 (m, 10H, Ar*H*).

3-Ethoxy-2-(ethoxymethyl)-2-(hydroxymethyl)propyl pivalate (**33b**): Prepared as described for **18** from **32b** (7.4 g, 38 mmol). Yield: 9.1 g, containing ~15% impurities, mainly dipivalate. ^{1}H NMR ($CDCl_3$): δ 1.08-1.26 (m, 15H, C(C*H*$_3$)$_3$ + CH$_2$C*H*$_3$), 3.07 (bs, 1H, O*H*), 3.25-3.57 (m, 8H, C*H*$_2$OC*H*$_2$), 3.66 (s, 2H, C*H*$_2$OH), 4.10 (s, 2H, C*H*$_2$OPiv).

3-(Benzyloxy)-2-[(benzyloxy)methyl]-2-formylpropyl pivalate (**34a**): From **33a** (18.4 g) by Swern oxidation (procedure A). The crude product was purified by *Kugelrohr* distillation followed by column chromatography (hexane/ethyl acetate (90/10, v/v)). Yield: 10 g (54%). B.p. 220ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 9H, C(C*H*$_3$)$_3$), 3.75 (s, 4H, C*H*$_2$OBn), 4.43 (s, 2H, C*H*$_2$OPiv), 4.54 (s, 4H, C*H*$_2$Ph), 7.18-7.45 (m, 10H, Ar*H*), 9.75 (s, 1H, C*H*O).

3-Ethoxy-2-(ethoxymethyl)-2-formylpropyl pivalate (**34b**): From **33b** (9.1 g) by Swern oxidation (procedure A). The crude product was purified by extraction with slightly basic water ($NaHCO_3$), followed by *Kugelrohr* distillation and column chromatography (hexane/ethyl acetate (92/8, v/v). Yield: 3.8 g (42%). B.p. 100-120ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.11 (t, J = 7.0 Hz, 6H, CH$_2$C*H*$_3$), 1.15 (s, 9H, C(C*H*$_3$)$_3$), 3.59 (s, 4H, C*H*$_2$OEt), 3.42 (q, J = 7.0 Hz, 4H, C*H*$_2$CH$_3$), 4.29 (s, 2H, C*H*$_2$OPiv), 9.65 (s, 1H, C*H*O).

2,2-Di[(benzyloxy)methyl]-3,3-diethoxypropyl pivalate (**35a**): From **34a** (7.9 g, 20 mmol) by procedure B. Yield: 7.55 g (80%). ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 9H, C(C*H*$_3$)$_3$), 1.17 (t, J = 7.0 Hz, 6H, CH$_2$C*H*$_3$), 3.44-3.83 (m, 4H, C*H*$_2$CH$_3$), 3.64 (s, 4H, C*H*$_2$OBn), 4.28 (s, 2H, C*H*$_2$OPiv), 4.46 (s, 4H, C*H*$_2$Ph), 4.62 (s, 1H, C*H*(OEt)$_2$), 7.20-7.35 (m, 10H, Ar*H*).

3,3-Diethoxy-2,2-di(ethoxymethyl)propyl pivalate (**35b**): From **34b** (0.95 g, 3.5 mmol) by procedure B. Yield: 1.0 g (83%). B.p. 120ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.07-1.27 (m, 21H, CH$_2$C*H*$_3$ + C(C*H*$_3$)$_3$), 3.31-3.95 (m, 12H, C*H*$_2$CH$_3$ + C*H*$_2$OEt), 4.21 (s, 2H, C*H*$_2$OPiv), 4.58 (s, 1H, C*H*(OEt)$_2$).

2,2-Di[(benzyloxy)methyl]-3,3-diethoxy-1-propanol (**36a**): *Method A*: from **35a**: A mixture of **35a** (4.3 g, 9.1 mmol), ethanol (30 mL), water (5 mL) and KOH (1.2 g) was refluxed for 24 h. The reaction mixture was then extracted with CH_2Cl_2, dried (Na_2CO_3), evaporated to dryness and purified by *Kugelrohr* distillation yielding **36a** (2.95 g, 84%). *Method B*: from **43a**: A mixture of **43a** (5.2 g, 12 mmol), methanol (40 mL), water (20 mL) and KOH (2.0 g) was stirred for 16 h at room temperature. Work-up as described for *method A* yielded **36a** (4.0 g, 86%). B.p. 200ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J = 7.0 Hz, 6H, CH$_2$C*H*$_3$), 3.09 (t, J = 6.1 Hz, O*H*), 3.45-3.84 (m, 4H, C*H*$_2$CH$_3$), 3.64 and 3.69 (2×d, J = 9 Hz, 4H, C*H*$_2$OBn), 3.83 (d, J = 6.2 Hz, 2H, C*H*$_2$OH), 4.49 (s, 4H, C*H*$_2$Ph), 4.66 (s, 1H, C*H*(OEt)$_2$), 7.20-7.35 (m, 10H, Ar*H*).

3,3-Diethoxy-2,2-di(ethoxymethyl)-1-propanol (**36b**): A mixture of **35b** (1.0 g, 2.9 mmol), ethanol (20 mL), water (3 mL) and KOH (1 g) was refluxed for 6 h. The reaction mixture was then extracted with CH_2Cl_2, dried (Na_2CO_3), evaporated to dryness and purified by *Kugelrohr* distillation, yielding **36b** (0.72 g, 95%). B.p. 100ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.17 and 1.22 (2×t, J = 7.0 and 7.0 Hz, 12H, CH$_2$C*H*$_3$), 3.17 (t, J = 6.0 Hz, 2H, C*H*$_2$OH), 3.36-3.97 (m, 12H, C*H*$_2$CH$_3$ + C*H*$_2$OEt), 4.62 (s, 1H, C*H*(OEt)$_2$).

2,2-Di[(benzyloxy)methyl]-3,3-diethoxypropanal (**37a**): From **36a** (3.3 g, 8.5 mmol) by Swern oxidation (procedure A). The crude product was purified by *Kugelrohr* distillation. Yield: 2.9 g (88%). B.p. 220ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.16 (t, J = 7.0 Hz, 6H, CH_2CH_3), 3.43-3.81 (m, 4H, CH_2CH_3), 3.79 and 3.90 (2×d, J = 9.2 Hz, 4H, CH_2OBn), 4.49 (s, 4H, CH_2Ph), 4.72 (s, 1H, $CH(OEt)_2$), 7.20-7.35 (m, 10H, Ar*H*), 9.77 (s, 1H, C*H*O).

3,3-Diethoxy-2,2-di(ethoxymethyl)propanal (**37b**): From **36b** (0.72 g, 2.7 mmol) by Swern oxidation (procedure A). The crude product was purified by *Kugelrohr* distillation. Yield: 0.58 g (81%). B.p. 100ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.15 and 1.21 (2×t, J = 7.0 and 7.0 Hz, 12H, CH_2CH_3), 3.37-3.95 (m, 12H, CH_2CH_3 + CH_2OEt), 4.70 (s, 1H, $CH(OEt)_2$), 9.75 (s, 1H, C*H*O).

9,9-Di[(benzyloxy)methyl]-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**38a**): A mixture of **37a** (300 mg, 0.78 mmol), urea (94 mg, 1.6 mmol), acetic acid (300 mg) and one drop of sulfuric acid was heated at 100ºC for 1 h. Then water (2 mL) was added and the product was collected by filtration, washed with water, acetone and diethyl ether. Yield: 210 mg (84%). Recrystallization from boiling water gave a white crystalline solid. M.p. 332°C (dec.). FAB MS (*m/z*) 397 ($[M+H]^+$), 91 (100%, $C_7H_7^+$). ^{1}H NMR (DMSO-d_6): δ 3.56 (s, 4H, CH_2OBn), 4.15 (bs, 2H, NHC*H*NH), 4.48 (s, 4H, OCH_2Ph), 7.18 (bs, 4H, N*H*), 7.20-7.40 (m, 10H, Ar*H*). IR (KBr): ν = 1643, 1665, 1701 cm^{-1} (C=O). Anal. Calcd. for $C_{21}H_{24}N_4O_4$: C: 63.62, H: 6.10, N: 14.13. Found: C: 63.81, H: 5.90, N: 13.93.

9,9-Di(ethoxymethyl)-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**38b**): Prepared from **37b** as described for **38a** (250 mg, 0.95 mmol). Yield: 145 mg (56%). M.p >350°C. FAB MS (*m/z*) 273 ($[M+H]^+$, 100%), 213 ($[M-CH_2OEt]^+$). ^{1}H NMR (DMSO-d_6): δ 1.11 (t, J = 6.9 Hz, 6H, CH_3CH_2), 3.43 (s, 4H, CH_2OEt), 3.44 (q, J = 6.9 Hz, 4H, CH_3CH_2O), 4.06 (t, J = 4.1 Hz, 2H, NHC*H*NH), 7.14 (d, J = 4.2 Hz, 4H, N*H*). Anal. Calcd. for $C_{11}H_{20}N_4O_4$: C: 48.52, H: 7.40, N: 20.58. Found: C: 48.68, H: 7.37, N: 20.09.

3-(Benzyloxy)-2-[(benzyloxy)methyl]-2-(hydroxymethyl)propyl acetate (**41a**): A solution of **32a** (5.0 g, 15.8 mmol), triethyl orthoacetate (3.85 g, 23.7 mmol), and a catalytic amount of *p*-toluenesulfonic acid in CH_2Cl_2 (20 mL) was stirred for 1 h at room temperature. Then the solvent was removed *in vacuo* on a 35°C water bath, and THF (20 mL) and aqueous 1 N HCl (20 mL) were added. The resulting mixture was stirred at room temperature for 1 h. Extraction of this mixture with CH_2Cl_2, drying (Na_2SO_4) of the extracts followed by *Kugelrohr* distillation yielded **41a** (4.8 g, 85%). B.p. 220ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.96 (s, 3H, O*Ac*), 2.77 (bs, 1H, O*H*), 3.49 (s, 4H, CH_2OBn), 3.67 (bs, 2H, CH_2OH), 4.16 (s, 2H, CH_2OAc), 4.46 (s, 4H, CH_2Ph), 7.20-7.40 (m, 10H, Ar*H*).

2-[(Allyloxy)methyl]-2-(hydroxymethyl)butyl acetate (**41b**): Prepared from **39** (26.3 g, 151 mmol) as described for **41a**. Yield: 31.1 g (95%). EI MS (*m/z*) 185 ($[M-CH_2OH]^+$). ^{1}H NMR

($CDCl_3$): δ 0.86 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.39 (q, J = 7.6 Hz, 4H, CH_2CH_3), 2.08 (s, 3H, O*Ac*), 2.64 (bs, 1H, O*H*), 3.38 and 3.42 (2×d, J = 9.1 Hz, 2H, CH_2OAll), 3.55 (s, 2H, CH_2OH), 3.96 (d, J = 4.2 Hz, 2H, CH_2C=C), 4.08 and 4.14 (2×d, J = 11 Hz, 2H, CH_2OAc), 5.16-5.30 (m, 2H, C=CH_2), 5.82-5.92 (m, 1H, C*H*=CH_2). ^{13}C NMR ($CDCl_3$): δ 7.19 (CH_2CH_3), 20.63 ($COCH_3$), 22.50 (CH_2CH_3), 42.06 ($C(CH_2)_4$), 64.31, 64.6, 65.35, 72.15 (4×CH_2O), 116.82 (C=CH_2), 134.21 (*C*=CH_2), 171.24 (*C*=O).

3-(Benzyloxy)-2-[(benzyloxy)methyl]-2-formylpropyl acetate (**42a**): From **41a** (4.8 g, 13.4 mmol) by Swern oxidation (procedure A). Yield: 4.6 g (96%). B.p. 220ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H, O*Ac*), 3.67 (s, 4H, CH_2OBn), 4.37 (s, 2H, CH_2OAc), 4.46 (s, 4H, CH_2Ph), 7.16-7.42 (m, 10H, Ar*H*), 9.67 (s, 1H, C*H*O).

2-[(Allyloxy)methyl]-2-formylbutyl acetate (**42b**): From **41b** (31.1 g, 144 mmol) by Swern oxidation (procedure A). Yield: 27.8 g (90%). The crude product was used directly in the following reaction.

2,2-Di[(benzyloxy)methyl]-3,3-diethoxypropyl acetate (**43a**): From **42a** (4.6 g, 12.9 mmol) by procedure B. Yield: 5.2 g (93%). B.p. 220ºC/0.8 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J = 7.0 Hz, 6H, CH_2CH_3), 1.96 (s, 3H O*Ac*), 3.34-3.93 (m, 4H, CH_2CH_3), 3.64 (s, 4H, CH_2OBn), 4.35 (s, 2H, CH_2OAc), 4.46 (s, 4H, CH_2Ph), 4.62 (s, 1H, C*H*$(OEt)_2$), 7.20-7.40 (m, 10H, Ar*H*).

2-[(Allyloxy)methyl]-2-(diethoxymethyl)butyl acetate (**43b**): From **42b** (27.8 g, 130 mmol) by procedure B. The crude product was purified by *Kugelrohr* distillation yielding **43b** (24.7 g, 66%). B.p. 110-120°C/1 mm Hg. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.7 Hz, 3H, CH_2CH_3), 1.25 (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.17-1.60 (m, 4H, CCH_2CH_3), 2.04 (s, 3H, O*Ac*), 3.38 and 3.43 (2×d, J = 9.0 Hz, 2H, CH_2OAll), 3.42-3.86 (m, 4H, OCH_2CH_3), 3.89-3.92 (m, 2H, CH_2C=C), 4.11 and 4.20 (2×d, J = 11 Hz, 2H, CH_2OAc), 4.47 (s, 1H, C*H*$(OEt)_2$), 5.12-5.27 (m, 2H, C=CH_2), 5.82-5.92 (m, 1H, C*H*=CH_2).

2-[(Allyloxy)methyl]-2-(diethoxymethyl)-1-butanol (**44**): Prepared as described for **36a**, method *B*, from **43b** (24.7 g, 85 mmol). Yield: 19.9 g (95%). EI MS (*m/z*) 103 ($[HC(OEt)_2]^+$, 100%), 187 ($[M\text{-}HC(OEt)_2]^+$). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.23 (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.40-1.60 (m, 4H, CCH_2CH_3), 3.10 (t, J = 6.0 Hz, 1H, O*H*), 3.43 (s, 2H, CH_2OAll), 3.52-3.87 (m, 6H, OCH_2CH_3, CH_2OH), 3.92-3.95 (m, 2H, CH_2C=C), 4.57 (s, 1H, C*H*$(OEt)_2$), 5.15-5.29 (m, 2H, C=CH_2), 5.82-5.92 (m, 1H, C*H*=CH_2).

2-[(Allyloxy)methyl]-2-(diethoxymethyl)butanal (**45**): Prepared from **44** (3.61 g, 14.7 mmol) by Swern oxidation (procedure A). Yield: 3.32 g (92%). ^{1}H NMR ($CDCl_3$): δ 0.85 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.20 and 1.22 (2×t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.68-1.92 (m, 4H, CCH_2CH_3), 3.63 (s,

2H, C*H*$_2$OAll), 3.45-3.88 (m, 4H, OC*H*$_2$CH$_3$), 3.94-3.97 (m, 2H, C*H*$_2$C=C), 4.65 (s, 1H, C*H*(OEt)$_2$), 5.15-5.29 (m, 2H, C=C*H*$_2$), 5.82-5.93 (m, 1H, C*H*=CH$_2$), 9.70 (s, 1H, C*H*O).

9-[(Allyloxy)methyl]-9-ethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**46**). A mixture of **45** (6.22 g, 25 mmol), urea (3.06 g, 51 mmol), acetic acid (15 mL) and sulfuric acid (15 drops) was kept at 110°C for 2 h. Then THF (80 mL) was added and the mixture was cooled to room temperature. The precipitate was collected by filtration and washed with THF and diethyl ether, yielding **46** (4.73 g, 74%) as a white solid. An analytically pure sample was obtained by recrystallization from ethanol. M.p. 311°C (dec.). FAB MS (*m/z*) 255 ([M+H]$^+$), 133 (100%). ^{1}H NMR (D$_2$O): δ 0.87 (t, J = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.57 (q, J = 7.4 Hz, 2H, CC*H*$_2$CH$_3$), 3.54 (s, 2H, C*H*$_2$OAll), 3.99 (d, J = 5.9, 2H, C*H*$_2$C=C), 4.41 (s, 2H, NHC*H*NH, 5.16-5.28 (m, 2H, C=C*H*$_2$), 5.82-5.93 (m, 1H, C*H*=CH$_2$). ^{13}C NMR (D$_2$O): δ 7.83 (*C*H$_3$), 21.81 (*C*H$_2$CH$_3$), 37.17 (*C*C$_4$), 59.86 (*C*H$_2$O), 68.07 (NHC*H*NH), 73.20 (*C*H$_2$C=C), 119.01 (C=*C*H$_2$), 134.46 (*C*H=CH$_2$), 157.84 (*C*=O). IR (KBr): ν = 1648, 1663, 1700 cm^{-1} (C=O). Anal. Calcd. for C$_{11}$H$_{18}$O$_3$N$_4$: C: 51.96, H: 7.13, N: 22.03. Found: C: 51.88, H: 7.09, N: 22.15.

X-ray analysis

Crystals of **12** suitable for X-ray diffraction studies were obtained by liquid diffusion of ethanol into a solution of the compound in formic acid (85%). A single crystal was mounted in air on a glass fiber. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Cu-Kα radiation, ω-2θ scan mode. Unit cell dimensions were determined from the angular setting of 18 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[21] was applied. The structure was solved by the program CRUNCH[22] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97[23]) with anisotropic parameters for the non-hydrogen atoms. All hydrogens, except the hydrogens attached to the cyclohexene ring, were initially placed at calculated positions and were freely refined subsequently. The hydrogens attached to the cyclohexene ring were placed at calculated positions. The cyclohexene ring is disordered over two positions. This disorder can be interpreted as a swap of the ring and can be described by a suitable disorder model. A structure determination summary is given in Table 1. A PLUTON drawing[14] is shown in Figure 1.

Table 1 *Crystal data and structure refinement for **12**.*

Crystal color	Transparent colorless
Crystal shape	Regular fragment
Crystal size	0.26 × 0.15 × 0.10 mm
Empirical formula	$C_{10}H_{14}N_4O_2$
Formula weight	222.25
Temperature	293(2) K
Radiation / Wavelength	CuKα (graphite mon.) / 1.54184 Å
Crystal system, space group	Orthorhombic, Pcab
Unit cell dimensions (18 reflections, 20.397 < θ < 44.187)	a = 11.4260(8) Å, α = 90° b = 12.0679(14) Å, β = 90° c = 14.9260(13) Å, γ = 90°
Volume	2058.1(3) $Å^3$
Z, Calculated density	8, 1.435 Mg/m^3
Absorption coefficient	0.858 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / ω-2θ
F(000)	944
θ range for data collection	5.93 to 69.99°
Index ranges	–13<=h<=0, –14<=k<=0, 0<=l<=18
Reflections collected / unique	1952 / 1952
Reflections observed	1200 ($[I_0>2\sigma(I_0)]$)
Absorption correction	Semi-empirical from ψ-scans
Range of relat. transm. factors	1.083 and 0.925
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1952 / 287 / 214
Goodness-of-fit on F^2	1.045
SHELXL-97 weight parameters	0.0653 0.5271
Final R indices [I>2σ(I)]	R_1 = 0.0535, wR_2 = 0.1189
R indices (all data)	R_1 = 0.1029, wR_2 = 0.1433
Largest diff. peak and hole	0.172 and –0.262 $e·Å^{-3}$

3.7 References

1 (a) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278; (b) Martin, T.; Obst, U.; Rebek, J., Jr. *Science* **1998**, *281*, 1842; (c) Kang, J.; Rebek, J., Jr. *Nature*, **1996**, *382*, 239; (d) Wyler, R.; De Mendoza, J.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699, and references therein.

2 (a) Freeman, W.A.; Mock, W.L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367;(b) Mock, W.L.; Shih, N.-Y. *J. Org. Chem.* **1983**, *48*, 3618; (c) Mock, W.L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440.

3 (a) Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 5; (b) Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1997**, *119*, 451; (c) Whang, D.; Yeon, Y.-M.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 11333.

4 For a recent review see: Rowan, A.E.; Elemans, J.A.A.W.; Nolte, R.J.M. *Acc. Chem. Res.* **1999**, *32*, 995.

5 Isaacs, L.; Witt, D.; Fettinger, J.C. *Chem. Commun.* **1999**, 2549.

6 De Haan, T. *Recl. Trav. Chim. Pays-Bas* **1908**, *27*, 162.
7 Spänig, H.; Schönleben, W. *Belg. Patent* 635,435, **1964**; C.A. **1964**, *62*, 13334b.
8 Spänig, H.; Schönleben, W. *Belg. Patent* 645,094, **1964**.
9 Piacenza, G.; Beguet, C.; Wimmer, E.; Gallo, R.; Giorgi, M.; *Acta Cryst.* **1997**, *B53*, 1459.
10 (a) Inukai, T.; Yoshizawa, R. *J. Org. Chem.*, **1967**, *32*, 404; (b) Spänig, H.; Schönleben, W. *Ger. Patent.* 1193028, **1965**.
11 Nazarov, I.N.; Makin, S.M.; Kruptsov, B.K. *J. Gen. Chem. USSR* **1959**, *29*, 3641.
12 Khasapov, B.N.; Novikova, T.S.; Lebedev, O.V.; Khmel'nitskii, L.I.; Novikov, S.S. *J. Org. Chem. USSR* **1973**, *9*, 21.
13 Hoaglin, R.J.; Hirsh, D.H. *J. Am. Chem. Soc.* **1949**, *71*, 3468.
14 Spek, A.L. PLATON. A Multipurpose Crystallographic Tool; *Utrecht University*, Utrecht, The Netherlands, **2001**.
15 Appelhans, D.; Reichardt, C. *Liebigs Ann./Recueil* **1997**, 2385.
16 Issidorides, C.H.; Gulen, R. *Org. Synth. Coll. IV* **1963**, 679.
17 Baldon, P.; Owen, L.N. *J. Chem. Soc.* **1950**, 585.
18 Weber, E. *J. Org. Chem.* **1982**, *47*, 3478.
19 Weber, E. *Lieb. Ann. Chem.* **1983**, *5*, 770.
20 Benzing, E. *Angew. Chem.* **1959**, *71*, 521.
21 North, A.C.T.; Philips, D.C.; Mathews, F.S. *Acta Crystallogr.* **1968**, *A24*, 351.
22 Gelder, R. de; Graaff, R.A.G. de; Schenk, H. *Acta Crystallogr.* **1993**, *A49*, 287.
23 Sheldrick, G.M. SHELXL-97. Program for the refinement of crystal structures; University of Gottingen: Germany, **1997**.

4 Synthesis of Molecular Clips from Propanediurea Derivatives

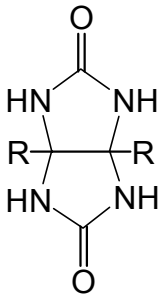
4.1 Introduction

The design and synthesis of host molecules for the binding of neutral guests continues to be an area of interest in supramolecular chemistry.[1] Research in our laboratory has for some time been focused on the development of receptors derived from the concave molecule diphenylglycoluril (See Chart 1, **1**, R = Ph). These 'U-shaped' clips bind dihydroxybenzenes by means of hydrogen bonding between the hydroxyl groups of the guest and the urea carbonyl groups of the host, and by π-π stacking interactions between the guest and the host side walls. Molecular clips with a large variety of side walls have been synthesized.[2] Some effort has been directed toward modifying the glycoluril framework **1** of the hosts. The urea functionalities in **1** have been replaced by thiourea and guanidine groups,[3] and clips have been synthesized starting from dimethylglycoluril (**1**, R = Me),[4] dipyridylglycoluril (**1**, R = 2-pyridyl)[5] and from ditolylglycoluril (**1**, R = 4-tolyl), with subsequent functionalization of the tolyl groups.[6,7] As could be expected, these modifications did not significantly alter the overall shape of the clips. More recently, clip molecules have been synthesized from bipyridylglycoluril, which displayed slightly 'squeezed' cavities, resulting in rather poor binding properties.[8]

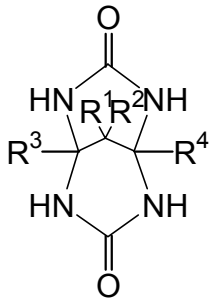
Molecules of type **2** (2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione, propanediurea, Chart 1) show strong similarities with glycoluril, and were first described in 1908 (**2b-d**).[9] Both **1** and **2** possess a shallow cavity with two strong hydrogen bond acceptor sites. The ureido nitrogen atoms allow for functionalization of the framework. The main difference between **1** and **2**, which triggered us to synthesize and study clip molecules from the latter type, is the slightly sharper angle between the carbonyl groups in **2**. This structural feature results in a cavity that is somewhat deeper with the carbonyl groups pointing further up and the carbonyl oxygen atoms being closer together.

In this chapter, we describe synthetic pathways towards molecular clips from derivatives of propanediurea. Section 4.2 will focus on the synthesis of clips using the well-known two-step procedure that involves a formylation of the NH-groups followed by a ureidoalkylation reaction with aromatic compounds. The synthetic route described in section 4.3 consists of deprotonation of

Chart 1



1



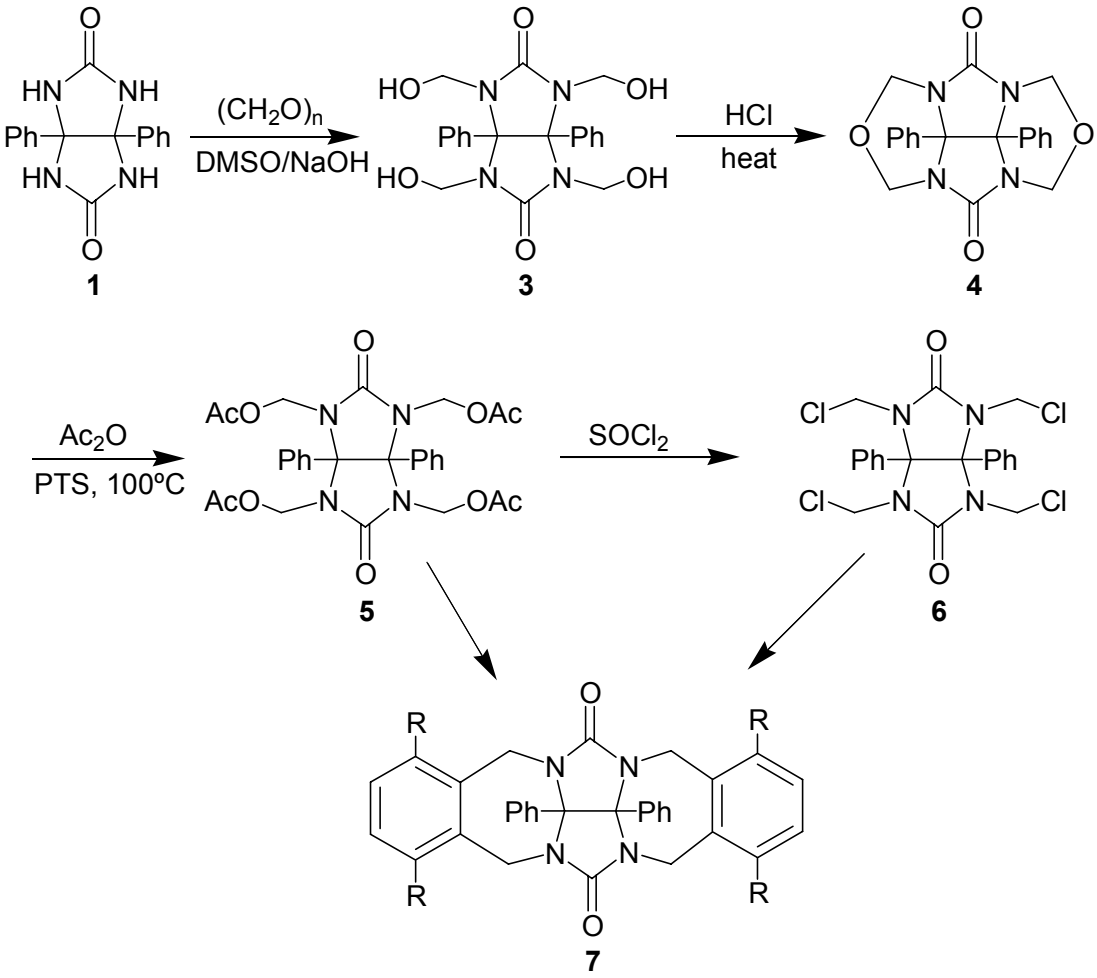
2

Propanediurea	R^1	R^2	R^3	R^4
2a	H	H	H	H
2b	H	H	Me	Me
2c	H	Me	Me	Me
2d	Me	Me	Me	Me
2e	Me	Me	H	H
2f	CH_2OPiv	CH_2OPiv	H	H
2g	CH_2OBn	CH_2OBn	H	H
2h	Et	CH_2OAll	H	H
2i	3-cyclohexene		H	H
2j	CH_2OEt	CH_2OEt	H	H
2k	Me	Me	Me	H
2l	Me	Me	n-propyl	H
2m	Me	Me	Ph	H
2n	Me	Me	*p*-C_6H_4COOMe	H
2o	Me	Me	CH_2CH_2COOMe	H

the NH-groups followed by a nucleophilic substitution reaction with a benzylic bromide. In section 4.4 attempts to further functionalize the new clips will be discussed, in order to obtain compounds with versatile handles that allow for extensive functionalization.

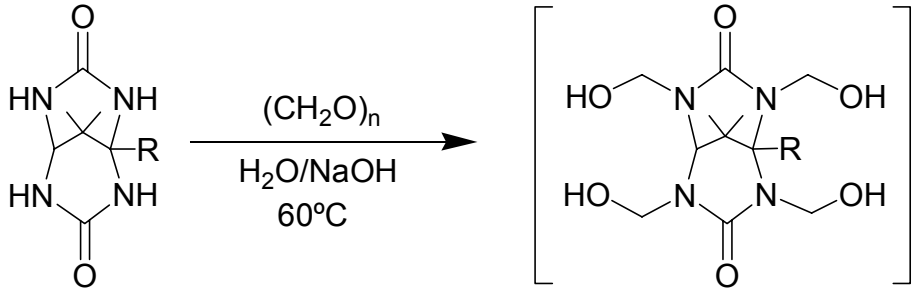
4.2 Molecular clips through ureidoalkylation of aromatic compounds

Clip molecules derived from diphenylglycoluril are usually synthesized from the cyclic ether **4**.[2] This compound is readily available from the base catalyzed reaction of **1** (R = Ph) with formaldehyde, yielding tetra(hydroxymethyl)diphenylglycoluril (**3**),[10] followed by acid catalyzed dehydration (Scheme 1).[2] The reaction of formaldehyde with 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**2e**) (Scheme 2) has been described in a patent.[11] Thus, **2e** was reacted with paraformaldehyde in slightly basic water to give the tetra(hydroxymethyl)



Scheme 1 *Synthesis of molecular clips from diphenylglycoluril*

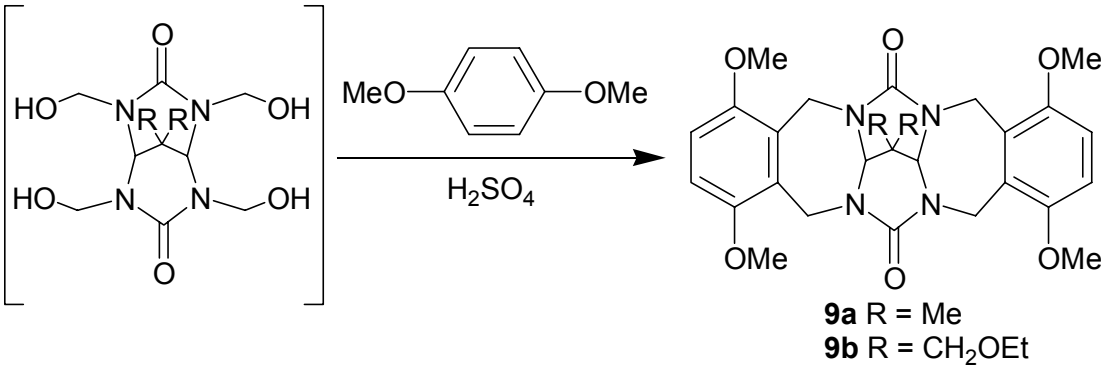
derivative **8** (Scheme 2). A ring-closed product comparable to **4** could not be obtained, neither by heating with acid nor by using dehydrating agents such as triethyl orthoformate or molecular sieves. Purification of **8** turned out to be difficult. The obtained product was a glassy mass, and ^{1}H NMR analysis indicated the presence of unreacted NH groups. Variation in reaction times and reaction temperature, as well as use of an excess of paraformaldehyde did not result in considerable



2e R = H
2k R = Me
2l R = *n*-Pr
2m R = Ph

8 R = H
16a R = Me
16b R = *n*-Pr
16c R = Ph

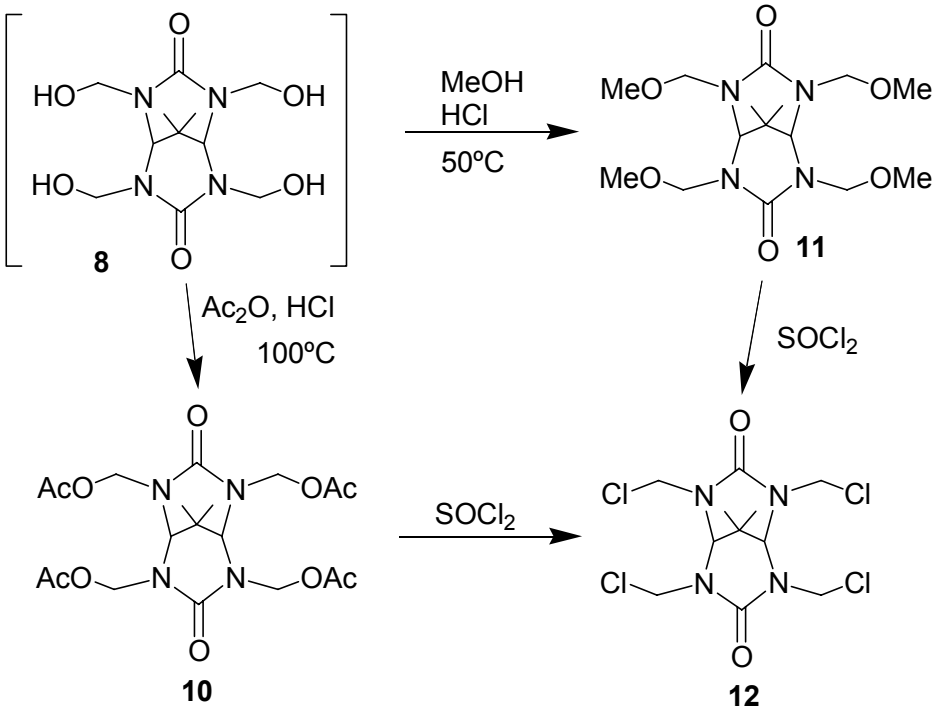
Scheme 2 *Formylation of substituted propanediureas*



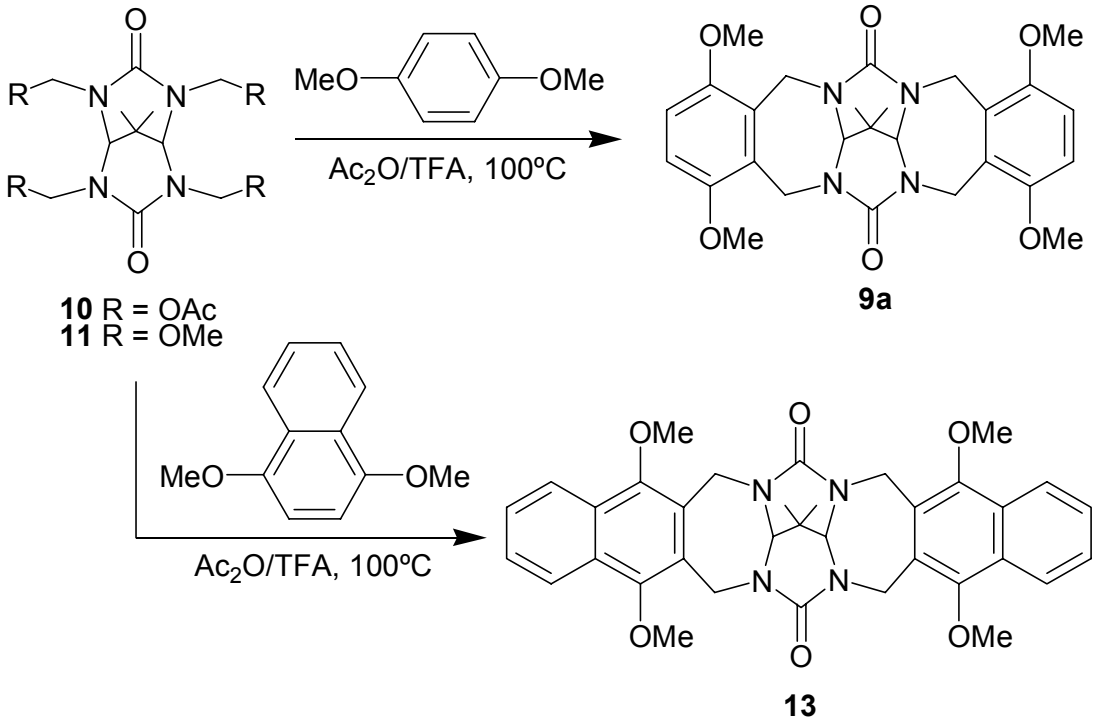
Scheme 3 *Synthesis of molecular clips through the Tscherniac-Einhorn reaction*

improvement. The impure compound was therefore used directly in the subsequent reaction with 1,4-dimethoxybenzene in sulfuric acid (Scheme 3). This so-called Tscherniac-Einhorn reaction[12] has been reported to proceed in high yield with the cyclic ether **4**.[13] In this way clip molecule **9a** was obtained in 23% yield. The rather harsh reaction conditions did not allow for the presence of various functional groups in the starting compounds. Propanediurea derivatives containing pivaloic esters (**2f**), benzyl ethers (**2g**), an allyl ether (**2h**) or a cyclohexene functionality (**2i**) were not stable under the reaction conditions. However, propanediurea derivative **2j**, containing ethyl ethers, did provide clip molecule **9b**.

Tetra(hydroxymethyl) derivative **8** can be transformed into the corresponding tetra(methoxymethyl) derivative **11** by stirring in methanol in the presence of HCl at 50°C (Scheme 4).[11] Compound **11** was reacted with 1,4-dimethoxybenzene in a ureidoalkylation reaction in acetic anhydride/TFA to give clip molecule **9a** in high yield (Scheme 5). The intermediate in this reaction is the



Scheme 4 *Synthesis of tetra(chloromethyl)propanediurea*



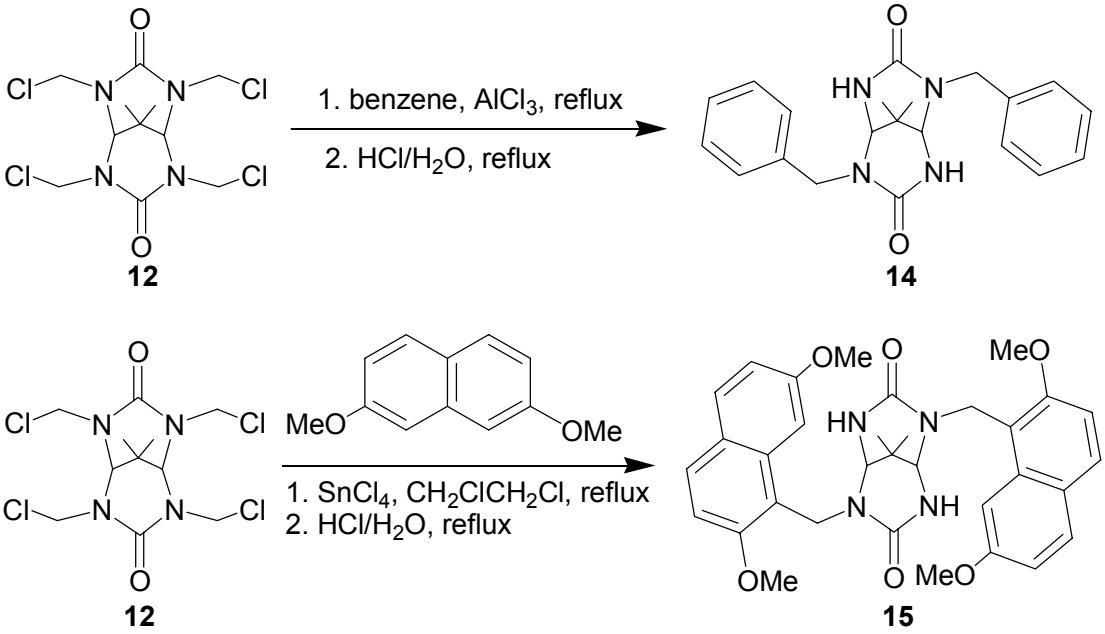
Scheme 5 *Ureidoalkylation of aromatic compounds yielding molecular clips **9a** and **13***

tetra(acetoxymethyl) derivative **10**. This compound could be obtained directly from **8** by heating with acetic anhydride/HCl (Scheme 4).[a] A clip molecule with 1,4-dimethoxynaphthalene walls (**13**) was prepared in reasonable yield by reaction of **11** with 1,4-dimethoxynaphthalene in acetic anhydride/TFA (Scheme 5).

The tetra(acetoxymethyl) and tetra(methoxymethyl) substituted propanediurea compounds **10** and **11** did not react with less activated aromatic molecules like benzene. In order to synthesize a clip molecule with benzene or 2,7-dimethoxynaphthalene side walls as has been described for clips of type **1**, we changed these substituents into chlorines, thus creating better leaving groups.[13,14] This was accomplished by reacting **10** or **11** with $SOCl_2$ at room temperature, giving the tetra(chloromethyl) derivative **12** in high yield (Scheme 4). The reaction of **12** with benzene in the presence of $AlCl_3$, as has been described for **6**,[13] afforded however 2,6-dibenzyl-9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione **14** as the sole product (Scheme 6). Reaction of **12** with 2,7-dimethoxynaphthalene using tin tetrachloride as a catalyst provided only 2,6-di[(2,7-dimethoxy-1-naphthyl)methyl]-9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione **15** in low yield (Scheme 6). Apparently, when one of the chloromethyl groups on one side of **12** has reacted, the remaining chloromethyl group is not reactive enough to give the bis-substituted derivative. In the subsequent hydrolytic work-up the remaining chloromethyl group is converted back to a hydroxymethyl group, which loses formaldehyde to give the free NH function.[15]

Compounds of type **2k-2o**, *i.e.* 1,9,9-trisubstituted 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-diones have been reported to react with formaldehyde to provide the tetra(hydroxymethyl) derivatives.[11] These products, however, have been prepared as aqueous solutions only, and have not been

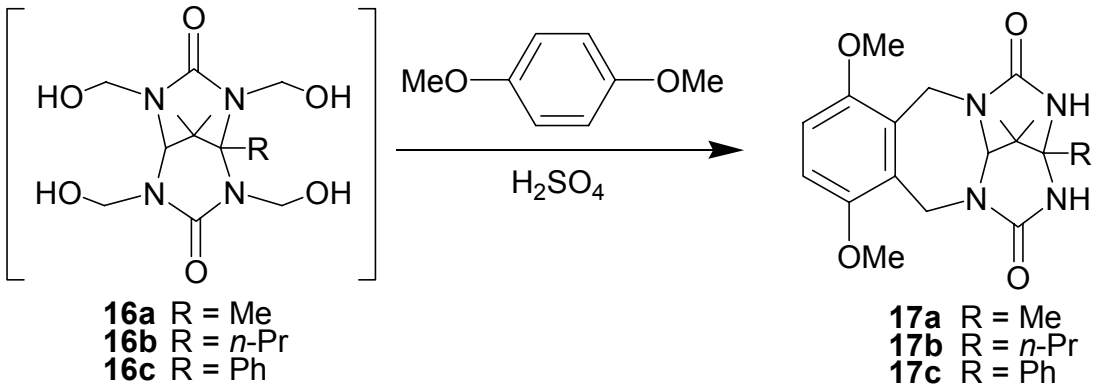
[a] It was possible to transform **10** into **11** in high yield by stirring in methanol containing a trace of HCl.



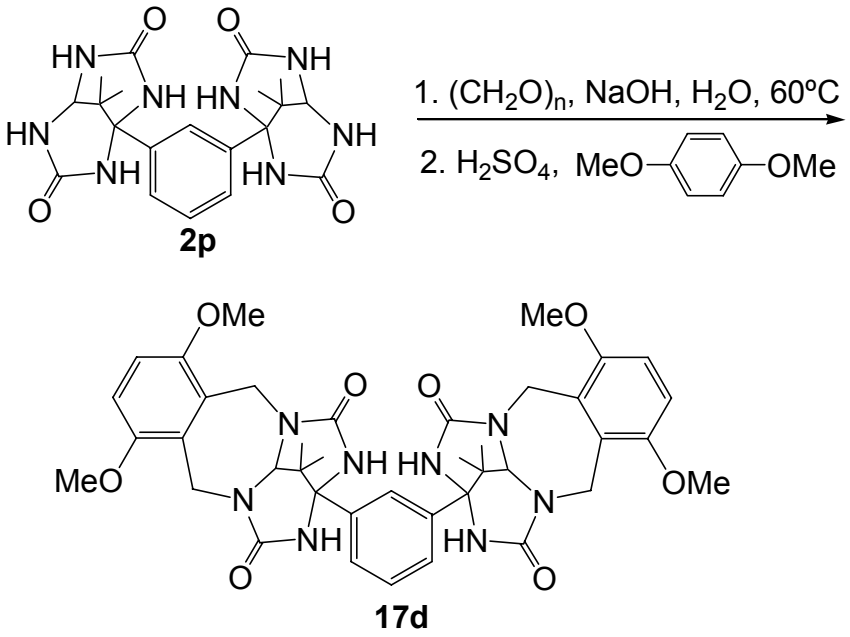
Scheme 6 *Ureidoalkylation of aromatic compounds yielding 2,6-disubstituted propanediurea derivatives **14** and **15***

isolated. Reaction of **2k**, **2l**, and **2m** with formaldehyde in slightly basic water, followed by neutralization and evaporation of the solvent provided impure **16a-c** (Scheme 2). Reaction of this crude product with 1,4-dimethoxybenzene in sulfuric acid, as described above, yielded exclusively 'half clip' compounds **17** in low yield (Scheme 7). Apparently, the hydroxymethyl groups at the side of **16** where R is located are either not sufficiently stable under the reaction conditions or are sterically blocked for reaction, leading to deformylation instead of substitution.[15] A variety of half clips has been prepared in this way (compounds **17a-c**). Reaction of the bis(propanediurea) **2p**, with formaldehyde and 1,4-dimethoxybenzene provided double half clip **17d** (Scheme 8).

When 1,5,9,9-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione **2d** was subjected to the reaction conditions described above, no clip molecule was isolated.



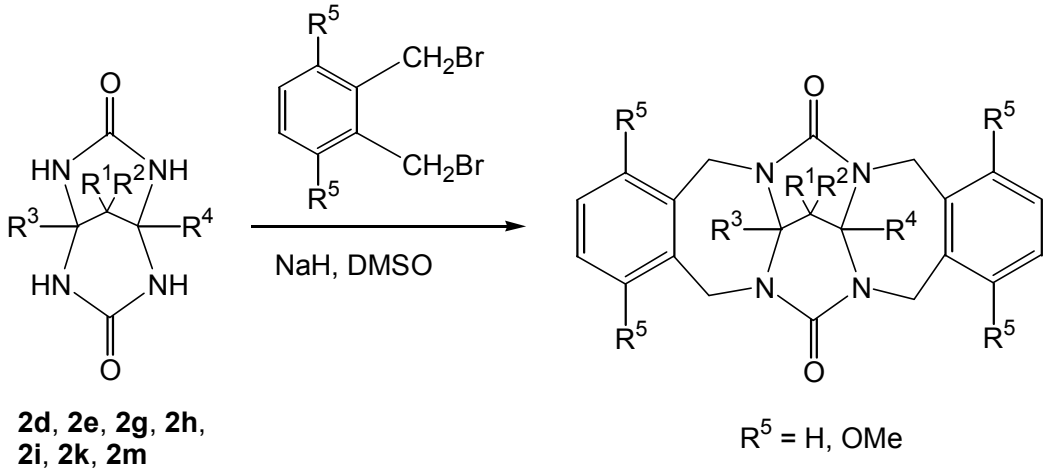
Scheme 7 *Synthesis of 'half clips'*



Scheme 8 *A double 'half clip'*

4.3 Molecular clips through nucleophilic substitution

In order to access clip molecules derived from 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-diones substituted at the 1 (and 5) positions of the skeleton (**2d**,**k**,**m**), and clip molecules with a larger variety of functional groups or with benzene side walls, we used a different synthetic route, which consist of a straightforward alkylation of the propanediurea skeleton (Scheme 9).[5,16] In a typical procedure, compound **2e** was suspended in DMSO and treated with 4.5 equivalents of NaH and 2.2 equivalents of α,α'-dibromo-*o*-xylene to give clip molecule **20** in 27% yield. It was also possible to use 1,4-dimethoxy-2,3-bis(bromomethyl)benzene (**18**) as the aromatic side wall.
Use of excess sodium hydride lowered the yield considerably, probably due to polymerization of



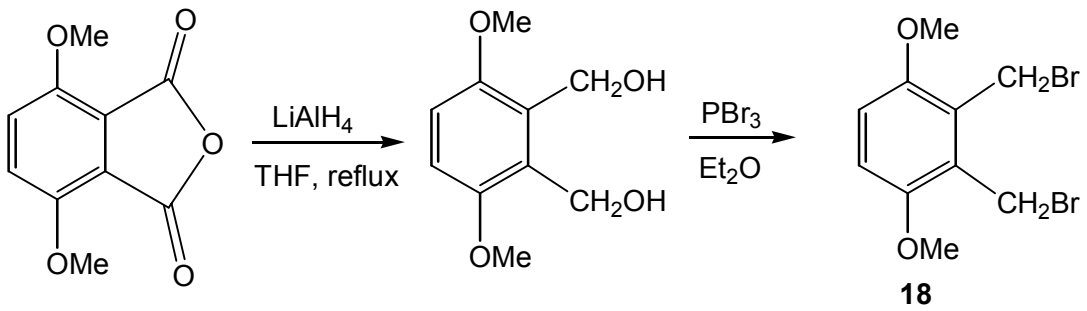
Scheme 9 *Molecular clips through nucleophilic substitution. Clips synthesized in this way are listed in Table 1*

Table 1 *Clip molecules synthesized according to Scheme 9*

Starting compound	R^1	R^2	R^3	R^4	R^5	Product	Yield(%)
2d	Me	Me	Me	Me	OMe	**19**	28
2e	Me	Me	H	H	H	**20**	26
2e	Me	Me	H	H	OMe	**9a**	20
2g	CH_2OBn	CH_2OBn	H	H	H	**21**	63
2g	CH_2OBn	CH_2OBn	H	H	OMe	**22**	50
2h	Et	CH_2OAll	H	H	OMe	**23**	49
2i	3-cyclohexene		H	H	H	**24**	26
2i	3-cyclohexene		H	H	OMe	**25**	63
2k	Me	Me	Me	H	H	**26**	26
2k	Me	Me	Me	H	OMe	**27**	25
2m	Me	Me	Ph	H	OMe	**28**	30

18. Other combinations of solvent and base (DMF/NaH, THF/NaH, DMSO/KO*t*Bu, *t*-BuOH/KO*t*Bu) did not produce any clip molecule. Reaction in DMSO with KOH as the base at temperatures between 100 and 150°C gave clip molecules in very low yield.

Using DMSO as the solvent and NaH as the base, a large variety of clip molecules was prepared (see Table 1). Propanediurea derivatives that contain ester groups (**2n**,**o**) did not give the desired clip molecules. These ester functionalities are apparently not stable under the strongly basic reaction conditions used. Reaction of the unsubstituted 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**2a**) with α,α'-dibromo-*o*-xylene did not produce a clip molecule either; ^{1}H NMR of the reaction product showed broad peaks, indicating that the product was probably a polymer. Compound **18** was obtained either by benzylic bromination of 1,4-dimethoxy-2,3-dimethyl benzene with NBS or in two steps by reduction of 3,6-dimethoxyphthalic anhydride with $LiAlH_4$ followed by treatment with PBr_3 (Scheme 10).



Scheme 10 *Synthesis of 2,3-di(bromomethyl)-1,4-dimethoxybenzene*

4.4 Derivatization of clip molecules

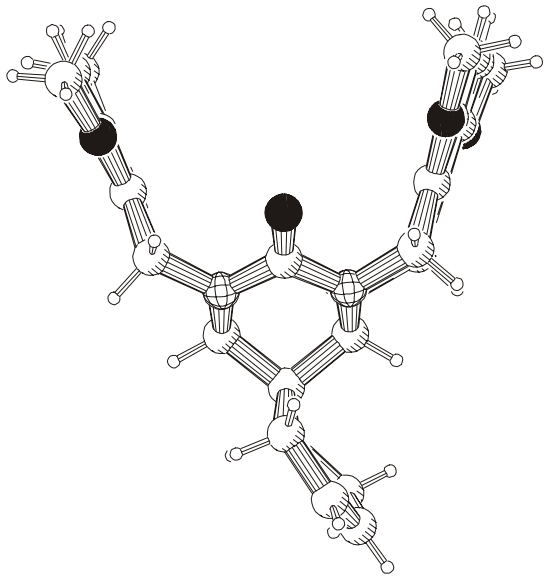
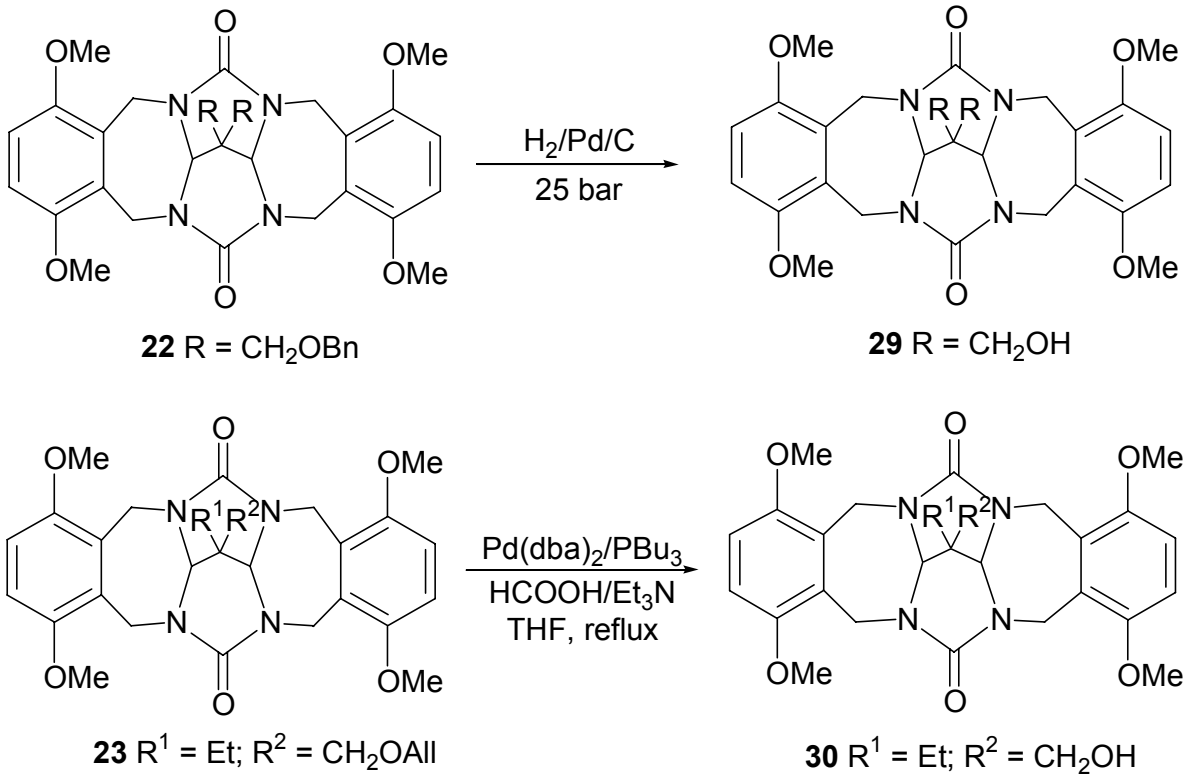


Figure 1 *Crystal structure of clip **25**. The drawing was made using the PLATON program*[17]

A few of the newly synthesized clip molecules contain groups that allow for further functionalization. Compounds **24** and **25** contain a cyclohexene functionality. Cyclohexene can be oxidatively transformed into hexanedioic acid, hexanedial or 1,2-cyclohexandiol by reaction with various transition metal oxides (OsO_4,[18] RuO_4,[19] cetyltrimethyl-ammonium permanganate,[20] $KMnO_4$[21]). These reagents however failed to react with clip molecules **24** and **25**, probably due to steric hindrance of the clip part of the molecule. It was therefore concluded that transition metal assisted oxidation of these clips was not a promising route toward functionalization. Oxidative ozonolysis with ozone[22] or ozone and *m*-CPBA[23] of **24** did not yield an identifiable product. Formation of the epoxide from **25** was possible in low yield using *m*-CPBA as the oxidant. Further functionalization of the epoxide was not attempted.

The crystal structure of cyclohexene functionalized clip (**25**) was solved in order to gain insight in the remarkably low reactivity of this molecule (Figure 1). However, the structure shows no features



Scheme 11 *Synthesis of alcohol functionalized clip molecules*

that can explain this behavior. The double bond of the cyclohexene group seems quite accessible. The overall structure of this clip is very similar to the structure of clip **9a**, which possesses methyl groups at its convex side. Chapter 5 will be devoted to the structural features of these clip molecules.
The benzyl protecting groups of **22** could be removed by Pd/C catalyzed hydrogenation, yielding a clip molecule with two alcohol functionalities (**29**) in high yield (Scheme 11). The allyl protecting group of **23** was removed using palladium bis(dibenzylidene acetonate)/tributyl phosphine ($Pd(dba)_2/PBu_3$) as the catalyst and Et_3N/HCOOH as the allyl group acceptor. Clip molecule **30**, containing one alcohol group, was thus obtained in high yield (Scheme 11).

4.5 Conclusions

A variety of clip molecules have been prepared from derivatives of propanediurea. The route generally followed in the synthesis of clip molecules from diphenylglycoluril, *i.e.* formylation followed by a ureidoalkylation reaction with aromatic compounds, gives in some cases good results for propanediurea derivatives. Tetra(acetoxymethyl) and tetra(methoxymethyl) functionalized dimethylpropanediureas are useful starting compounds for the synthesis of clips with 1,4-dimethoxybenzene and 1,4-dimethoxynaphthalene side walls. Tetra(chloromethyl) functionalized dimethylpropanediurea allows for the synthesis of 2,6-disubstituted propanediureas. Use of the Tscherniac-Einhorn reaction on unsubstituted and 1-substituted 2,4,6,8-tetra(hydroxymethyl) dimethylpropanediurea gives access to 1,4-dimethoxybenzene walled clips and half clips.
Since the ureidoalkylations described above require harsh reaction conditions, a different, straightforward route was investigated. This route involves deprotonation of the NH groups, followed by a substitution reaction with (a derivative of) α,α'-dibromo-*o*-xylene. This reaction allows for the presence of functional groups including allyl and benzyl protected alcohols. These protecting groups can be removed using standard deprotection techniques, providing clip molecules with one and two hydroxy groups. These functionalized clips (**29** and **30**) will be used in the following chapters as starting compounds in the construction of larger structures.

4.6 Experimental section

General. Thionyl chloride was distilled prior to use. Sodium hydride was a commercially available 60% suspension in mineral oil. Benzene, diethyl ether and THF were distilled under nitrogen from sodium benzophenone ketyl. Carbon tetrachloride was dried on molecular sieves (4 Å). 1,2-Dichloroethane was distilled from CaH_2. All other solvents and chemicals were commercially available materials and were used as received. Merck silica gel (60H) was used for column chromatography. Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1720-X spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument with $(CH_3)_4Si$ as the internal standard (δ 0.00 ppm) for the ^1H spectra, and $CDCl_3$ as the internal standard

(δ 77.0 ppm) for the ^{13}C spectra. Abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were recorded on a VG 7070E instrument. Elemental analyses were determined with a Carbo Erba EA 1108 instrument.

Compounds: The syntheses of compounds **2a**,[24] **2d**,[9] **2e**,[25] **11**,[11] and 3,6-dimethoxyphthalic anhydride[26] have been reported elsewhere. Compounds **2f-2p** were prepared as described in Chapter 3. 1,4-Dimethoxynaphthalene, 2,7-dimethoxynaphthalene, and 1,4-dimethoxy-2,3-dimethylbenzene were prepared by methylation of 1,4-dihydroxynaphthalene, 2,7-dihydroxynaphthalene, and 2,3-dimethylhydroquinone, respectively, using dimethyl sulfate and KOH as reagents.

4,7,15,18 - Tetramethoxy- 23,23- dimethyl- 1,10,12,21-tetraazahexacyclo [19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$. $0^{14,19}$]pentacosa-3,5,7,14(19),15,17-hexaene-11,25-dione (**9a**). *Method A*: from **2e**: A mixture of 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**2e**) (0.380 g, 2.07 mmol), water (0.9 mL), 3 drops of an aqueous 1 N NaOH solution, and paraformaldehyde (0.250 g, 8.33 mmol) was stirred at 60°C for 3 h. The resulting clear solution was neutralized by bubbling CO_2 through it for a few minutes. The solution was concentrated *in vacuo*, yielding impure **3** (0.602 g). A solution of 1,4-dimethoxybenzene (1.38 g, 10.0 mmol) in 16 mL of concentrated sulfuric acid was then added and the mixture was stirred for 16 h at room temperature. The resulting solution was poured onto 200 g of crushed ice, made basic with a concentrated aqueous NaOH solution, and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed once with water (50 mL) and dried (Na_2SO_4). The solution was concentrated *in vacuo* and the resulting yellowish powder was purified through a short column (EtOH/CH_2Cl_2, 2:98 v/v) yielding **9a** as a white powder (0.242 g, 23%). *Method B*: from **11**: To a mixture of TFA (1 mL) and acetic anhydride (1 mL) was added **11** (400 mg, 1.11 mmol). The resulting suspension was heated at 95°C for 30 min. Then 1,4-dimethoxybenzene (337 mg, 2.44 mmol) was added and the resulting solution was heated at 100°C for 30 min. The reaction mixture was cooled on ice and methanol (6 mL) was cautiously added. The precipitate was filtered off, washed with cold methanol and dried *in vacuo*, yielding **9a** as a white powder (439 mg, 78%). *Method C*: from **2e** and **18**: In 50 mL of degassed DMSO were suspended **2e** (331 mg, 1.80 mmol) and NaH (191 mg, 7.96 mmol) and the mixture was stirred under a nitrogen atmosphere at room temperature for 24 h. Then **18** (1.20 g, 3.70 mmol) was added and the reaction mixture was stirred for another 16 h at room temperature. The resulting solution was poured onto 150 g of crushed ice. The resulting precipitate was filtered off, washed with water, ethanol and diethyl ether and purified by column chromatography (EtOH/CH_2Cl_2, 2:98 v/v) yielding **9a** as a white powder (183 mg, 20%). An analytically pure sample was obtained by recrystallization from MeOH/$CHCl_3$. M.p. 348°C (subl.). EI MS (*m/z*) 508 (M^+, 100%). ^1H NMR ($CDCl_3$): δ 1.35 (s, 6H, C(CH_3)$_2$), 3.78 (s, 12H, OCH_3), 3.90 and 5.42 (2×d, J = 15.2 Hz, 8H, CH_2Ar), 4.32 (s, 2H, NC*H*N), 6.74 (s, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 23.04 (CH_3), 32.18 (CC_4), 44.73 (CH_2Ar), 57.44 (O*Me*), 79.10 (N*C*HN), 112.57 (*Ar*H), 128.31 (*Ar*C), 151.85 (*Ar*O), 154.42 (*C*(O)). IR (KBr): ν = 1638, 1659 cm^{-1} (C=O). Anal. Calcd. for $C_{28}H_{36}N_4O_7$ (**9a**·MeOH): C: 62.21, H: 6.71, N, 10.36. Found: C: 62.21, H: 6.66, N, 10.28.

23,23-Di(ethoxymethyl)-4,7,15,18-tetramethoxy-1,10,12,21-tetraazahexacyclo [19.3.1.0^{3,8}.0^{10,24}.0^{12,22}.0^{14,19}]pentacosa-3,5,7,14(19),15,17-hexaene-11,25-dione (**9b**). Prepared as described for **9a**, *method A*, from **2j** (46 mg, 0.17 mmol), paraformaldehyde (28 mg, 0.93 mmol), and 1,4-dimethoxybenzene (80 mg, 0.58 mmol). The crude product was purified by precipitation of a CH_2Cl_2 solution of the compound with diethyl ether. Yield: 36 mg (36%) of **9b** as a white powder. ^{1}H NMR ($CDCl_3$): δ 1.16 (t, J = 7.0 Hz, 6H, CH_2CH_3), 3.52 (q, J = 7.0 Hz, 4H, CH_2CH_3), 3.70 (s, 4H, CH_2OEt), 3.77 (s, 12H, OCH_3), 3.86 and 5.47 (2×d, J = 15 Hz, 8H, CH_2Ar), 4.66 (s, 2H, NC*H*N), 6.72 (s, 4H, Ar*H*).

{4,6,8-Tri [(acetyloxy)methyl]-9,9- dimethyl-3,7-dioxo-2,4,6,8-tetraaza bicyclo [3.3.1] non-2-yl} methyl acetate (**10**). Paraformaldehyde (1.86 g, 62.0 mmol) was dissolved by heating in 7.5 mL water containing 5 drops of an aqueous 2 N NaOH solution. Then 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**2e**) (2.85 g, 15.5 mmol) was added and the mixture was heated at 60°C until it became clear. The resulting solution was stirred for 30 min at room temperature and was neutralized by bubbling CO_2 through it for a few minutes. The solution was concentrated *in vacuo* and 25 mL of acetic anhydride and 5 drops of aqueous concentrated HCl were added. The mixture was stirred at 100°C for 30 min and poured onto 300 g of crushed ice. The solution was neutralized with aqueous NaOH and extracted with CH_2Cl_2 (2 × 200 mL). The organic layer was washed with water (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was passed through a short column (EtOH/CH_2Cl_2, 2:98 v/v). The first fraction was collected and recrystallized twice from 1-propanol, yielding white crystalline **10** (1.25 g, 17%). M.p. 164-166°C. EI MS (*m/z*) 267 (100%), 442 ([M – 2CH_3]$^+$). ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 6H, C(CH_3)$_2$), 2.09 (s, 12H, O*Ac*), 4.98 (s, 2H, NC*H*N), 5.44 and 5.54 (2×d, J = 10.8 Hz, 8H, CH_2OAc). ^{13}C NMR ($CDCl_3$): δ 21.27 and 21.82 (2×CH_3), 31.73 (CC_4), 72.02 (CH_2OAc), 77.85 (N*C*HN), 152.41 (N*C*(O)N), 171.61 (O*C*(O)CH_3). IR (KBr): ν = 1669, 1745 cm^{-1} (C=O). Anal. Calcd. for $C_{19}H_{28}N_4O_{10}$: C:48.30, H: 5.97, N, 11.86. Found: C:48.50, H: 5.94, N, 11.69.

2,4,6,8-Tetra(chloromethyl)-9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**12**). *Method A*: from **10**. A solution of **10** (321 mg, 0.680 mmol) in 2.5 mL of thionyl chloride was stirred under a nitrogen atmosphere for 16 h at room temperature. The solvent was removed *in vacuo* yielding **12** as a white, very hygroscopic powder (255 mg, 99%). *Method B*: from **11**. A solution of **11** (1.00 g, 2.78 mmol) in a mixture of CH_2Cl_2 (4 mL) and thionyl chloride (9 mL) and one drop of water was stirred under a nitrogen atmosphere for 16 h at room temperature. Diethyl ether (40 mL) was added and the reaction mixure was cooled to 0°C. The mixture was filtered and the residue was washed with dry diethyl ether. The resulting white solid was redissolved in dry CH_2Cl_2 and filtered. The solvent was removed *in vacuo* yielding **12** as a white powder (0.950 g, 90%): FAB MS (*m/z*) 329 ([M-CH_2Cl]$^+$, 100%). ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 6H, C(CH_3)$_2$), 4.65 (s, 2H, NC*H*N), 5.35 and 5.67 (2×d, J = 10.7 Hz, 8H, CH_2Cl). ^{13}C NMR ($CDCl_3$): δ 22.16 (CH_3), 31.73 (CC_4), 58.95 (CH_2Cl), 75.62 (N*C*HN), 149.66 (*C*(O)). Due to the instability of the compound no reproducible elemental analysis could be obtained.

4,11,19,26- Tetramethoxy-31,31- dimethyl-1,14,16,29- tetraazaoctacyclo [27.3.1.$0^{3,12}$.$0^{5,10}$.$0^{14,32}$.$0^{16,30}$.$0^{18,27}$.$0^{20,25}$]tritriaconta-3,5(10),6,8,11,18(27),19,21,23,25-decaene-15,33-dione (**13**):
Prepared as described for **9a**, *method* B, from **11** (116 mg, 0.322 mmol) and 1,4-dimethoxynaphthalene (140 mg, 0.745 mmol) yielding **13** as a white powder (113 mg, 58%). An analytically pure sample was obtained by slow diffusion of diethyl ether in a dichloromethane solution of the compound to give **13** as white needles. M.p. 326-328°C. EI MS (*m/z*) 608 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 6H, C(C*H*$_3$)$_2$), 4.03 (s, 12H, O*Me*), 4.05 and 5.77 (d, J = 15.6 Hz, 8H, *C*H$_2$Ar), 4.42 (s, 2H, NC*H*N), 7.43-7.47 (m, 4H, Ar*H*), 7.99-8.02 (m, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 23.01 (*C*H$_3$), 32.01 (*C*C$_4$), 46.47 (*C*H$_2$Ar), 62.64 (O*Me*), 79.80 (N*C*HN), 123.05, 126.28, 127.13, and 128.34 (*naphthalene)*, 150.38 (*Ar*OMe), 154.18 (*C*(O)). IR (KBr): ν = 1663 cm^{-1} (C=O). Anal. Calcd. for $C_{36}H_{38}N_4O_6Cl_2$ (**13**·CH_2Cl_2): C: 62.41, H: 5.53, N: 8.09. Found: C: 62.27, H: 5.48, N: 8.04.

(±)-2,6-Dibenzyl-9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**14**). A mixture of **12** (399 mg, 1.06 mmol), $AlCl_3$ (920 mg, 6.89 mmol) and 6 mL of dry benzene was refluxed under a nitrogen atmosphere for 16 h. The reaction mixture was allowed to cool to room temperature and an aqueous 6 N HCl solution (20 mL) was added. The resulting mixture was refluxed for 30 min, cooled, and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed with aqueous 2 N NaOH (50 mL) and water (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting brown powder was washed with diethyl ether to give (±)-**14** as a white powder (260 mg, 67%). A sample was recrystallized for elemental analysis by slow diffusion of diethyl ether in a CH_2Cl_2/MeOH solution of the compound, giving pure **14** as white crystals. M.p. 305-306°C. EI MS (*m/z*) 365 ($[M+H]^+$, 100%). ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 6H, C(C*H*$_3$)$_2$), 3.91 (d, J = 3.9 Hz, 2H, NC*H*N), 4.23 and 4.98 (2×d, J = 15.0 Hz, 4H, C*H*$_2$Ph), 5.63 (d, J = 3.6 Hz, 2H, N*H*), 7.27-7.37 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$): δ 22.55 (*C*H$_3$), 31.74 (*C*C$_4$), 48.76 (*C*H$_2$Ar), 68.74 (N*C*HN), 127.87, 128.51, 128.85, and 137.03 (*Ar*), 153.81 (*C*=O)). IR (KBr): ν = 1650, 1672 cm^{-1} (C=O). Anal. Calcd. for $C_{21}H_{24}N_4O_2$: C: 69.21, H: 6.64, N: 15.37. Found: C: 69.39, H: 6.60, N: 15.23.

(±) -2,6-Di [(2,7- dimethoxy- 1-naphthyl)methyl]-9,9- dimethyl- 2,4,6,8- tetraaza bicyclo [3.3.1] nonane-3,7-dione (**15**). A solution of **12** (120 mg, 0.317 mmol), 2,7-dimethoxynaphthalene (180 mg, 0.957 mmol) and $SnCl_4$ (0.4 mL) in 1,2-dichloroethane (20 mL) was refluxed in an inert atmosphere for 16 h. Then aqueous 6 M HCl (1 mL) was added and refluxing was continued for another 15 min. The mixture was cooled, diluted with CH_2Cl_2 (30 mL), washed with aqueous 1 M HCl, aqueous 1 M NaOH (twice), water, and dried (Na_2SO_4). The crude product was purified by column chromatography, yielding (±)-**15** as a white powder (20 mg, 11%). M.p. 276°C (subl.). EI MS (*m/z*) 584 (M^+), 32 (100%). ^{1}H NMR ($CDCl_3$): δ 0.63 (s, 6H, C(C*H*$_3$)$_2$), 3.68 (d, J = 3.7 Hz, 2H, NC*H*N), 3.87 and 4.00 (2×s, 12H, OC*H*$_3$), 4.79 and 5.43 (2×d, J = 14 Hz, 4H, *C*H$_2$Ar), 5.60 (bs, 2H, N*H*), 6.99 (dd, ^{4}J = 2.6 Hz, ^{3}J = 8.9 Hz, 2H, HCC(OMe)C*H*CH), 7.12 (d, J = 9.0 Hz, 2H, C(CH$_2$)C(OMe)C*H*), 7.51 (d, J = 2.3 Hz, 2H, *H*CC(OMe)CHCH), 7.64 and 7.74 (2×d, J = 9.0 Hz, C*H*C(C)C*H*).

4,7-Dimethoxy- 13,14,14- trimethyl-1,10,12,17- tetraazatetracyclo [11.2.2.0^{3,8}.0^{10,15}] heptadeca-3(8),4,6-triene-11,16-dione (**17a**): In a mixture of acetonitrile (7 mL) and water (2 mL) were suspended **2k** (213 mg, 1.08 mmol) and paraformaldehyde (230 mg, 7.67 mmol). Two drops of an aqueous 2N NaOH solution were added and the mixture was stirred for 16 h at 60°C. The resulting solution was cooled and CO_2 was bubbled through it for a few minutes. The solvent was removed *in vacuo* and a solution of 1,4-dimethoxybenzene (1.01 g, 7.31 mmol) in concentrated sulfuric acid (12 mL) was added. The reaction mixture was stirred for 16 h at room temperature. The resulting solution was poured onto 100 g of crushed ice, neutralized with a concentrated aqueous solution of NaOH and $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with water (2 × 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* yielding **17a** as a white powder (78 mg, 20%). M.p. 320-322°C (dec.). EI MS (*m/z*) 360 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.27 (s, 3H, C(NR)$_2$C*H*$_3$), 1.30 (s, 6H, C(C*H*$_3$)$_2$), 3.72 and 5.82 (2×d, J = 15.5 Hz, 2×2H, C*H*$_2$Ar), 3.86 (s, 6H, O*Me*), 4.41 (s, 1H, NC*H*N), 4.90 (bs, 2H, N*H*), 6.82 (s, 2H, Ar*H*). ^{13}C NMR ($CDCl_3$:MeOD-d$_4$, 4:1): δ 19.43 (C(*C*H$_3$)$_2$), 20.35 (C(NR)$_2$*C*H$_3$), 34.72 (*C*H$_2$Ar), 44.08 (*C*C$_4$), 56.77 (O*C*H$_3$), 69.08 (N*C*MeN), 81.25 (N*C*HN), 112.14 (*Ar*H), 128.05 (*Ar*CH$_2$), 151.40 (*Ar*OMe), 154.92 (*C*=O). IR (KBr): ν = 1631, 1676 cm^{-1} (C=O). Anal. Calcd. for $C_{19}H_{28}N_4O_5$ (**17a**·MeOH): C: 58.15, H: 7.19, N: 14.28. Found: C: 58.16, H: 7.13, N: 14.10.

4,7-Dimethoxy-14,14-dimethyl-13-propyl-1,10,12,17-tetraazatetracyclo[11.2.2.0^{3,8}.0^{10,15}] hepta-deca-3(8),4,6-triene-11,16-dione (**17b**): Prepared as described for **17a** from **2l** (501 mg, 2.22 mmol), paraformaldehyde (273 mg, 9.10 mmol) and 1,4-dimethoxybenzene (790 mg, 5.72 mmol). Yield: 210 mg (24%) of **17b** as a white powder. M.p. 322°C (dec.); EI MS (*m/z*) 388 (M^+, 100%); ^{1}H NMR ($CDCl_3$): δ 0.99 (t, J = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.23-1.34 (m, 8H, C(C*H*$_3$)$_2$ and C*H*$_2$CH$_3$), 1.57-1.63 (m, 2H, CC*H*$_2$CH$_2$CH$_3$), 3.72 and 5.82 (d, J = 15.4 Hz, 2×2H, C*H*$_2$Ar), 3.86 (s, 6H, O*Me*), 4.38 (s, 1H, NC*H*N), 5.04 (bs, 2H, N*H*), 6.82 (s, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 14.23 (*C*H$_3$), 14.44 (*C*H$_3$), 20.79 (*C*H$_2$CH$_3$), 34.65 (*C*H$_2$CH$_2$CH$_3$), 35.69 (*C*H$_2$Ar), 44.26 (*C*C$_4$), 57.34 (O*C*H$_3$), 70.71 (N*C*(CH$_2$)N), 81.69 (N*C*HN), 112.63 (*Ar*H), 128.38 (*Ar*CH$_2$), 151.68 (*Ar*OMe), 154.19 (*C*=O); IR (KBr): ν = 1646, 1675 cm^{-1} (C=O). Anal. Calcd. for $C_{21}H_{30}N_4O_4Cl_2$ (**17b**·CH_2Cl_2): C: 53.28, H: 6.39, N: 11.83. Found: C: 53.40, H: 6.21, N: 11.89.

4,7-Dimethoxy-14,14-dimethyl-13-phenyl-1,10,12,17-tetraazatetracyclo[11.2.2.0^{3,8}.0^{10,15}] hepta-deca-3(8),4,6-triene-11,16-dione (**17c**): Prepared as described for **17a** from **2m** (1.42 g, 5.46 mmol), paraformaldehyde (660 mg, 22 mmol), and 1,4-dimethoxybenzene (3.0 g, 22 mmol). The crude product was purified through a short column (EtOH/CH_2Cl_2, 5:95 v/v) yielding **17c** (580 mg, 26%). M.p. 333-334°C. EI MS (*m/z*) 422 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.15 (s, 6H, C(C*H*$_3$)$_2$), 3.78 and 5.80 (2×d, J = 15.4 Hz, 2×2H, C*H*$_2$Ar), 3.89 (s, 6H, O*Me*), 4.49 (s, 1H, NC*H*N), 5.20 (bs, 2H, N*H*), 6.85 (s, 2H, Ar*H*), 7.40-7.58 (m, 5H, C$_6$*H*$_5$). ^{13}C NMR ($CDCl_3$): δ 21.29 (C(*C*H$_3$)$_2$), 36.52 (*C*H$_2$Ar), 44.54 (*C*C$_4$), 57.38 (O*C*H$_3$), 74.88 (N*C*PhN), 81.90 (N*C*HN), 112.76 (MeOC(*C*H)$_2$COMe), 127.78, 128.35, 128.57, 129.32, (*Ar*H, *Ar*C), 151.79 (*Ar*OMe), 154.71

(*C*=O). IR (KBr): ν = 1636, 1644, 1674 cm^{-1} (C=O). Anal. Calcd. for $C_{24}H_{28}N_4O_4Cl_2$ (**17c**·CH_2Cl_2): C: 56.90, H: 5.58, N: 11.07. Found: C: 56.88, H: 5.48, N: 11.18.

13-3- [4,7-Dimethoxy- 14,14- dimethyl- 11,16- dioxo- 1,10,12,17- tetraazatetracyclo [11.2.2.$0^{3,8}$.$0^{10,15}$]heptadeca-3(8),4,6-trien-13-yl] phenyl-4,7-dimethoxy-14,14-dimethyl-1,10,12,17-tetraaza tetracyclo[11.2.2.$0^{3,8}$.$0^{10,15}$]heptadeca-3(8),4,6-triene-11,16-dione (**17d**). Prepared as described for **17a** from **2p** (500 mg, 1.13 mmol), paraformaldehyde (295 mg, 9.83 mmol) and 1,4-dimethoxybenzene (1.0 g, 7.25 mmol). The crude product was purified by column chromatography (EtOH/CH_2Cl_2, 5:95 - 15:85 v/v) yielding **17d** (60 mg, 6.9%). ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 6H, C*H*$_3$), 3.79 (OC*H*$_3$), 3.76 and 5.81 (2×d, J = 15.5 Hz, 8H, C*H*$_2$Ar), 4.46 (s, 2H, NC*H*N), 5.69 (bs, 4H, N*H*), 6.81 (s, 4H, wall Ar*H*), 7.49 (t, J = 7.7 Hz, 1H, Ar*H*, *meta*), 7.62 (d, J = 7.0 Hz, 2H, Ar*H*, *para*), 7.79 (bs, 1H, Ar*H*, *ortho*).

2,3-Di(hydroxymethyl)-1,4-dimethoxybenzene: To a cooled suspension of $LiAlH_4$ (4 g, 0.11 mol) in THF (250 mL) was slowly added a suspension of 3,6-dimethoxyphthalic anhydride (2.0 g, 9.6 mmol) in THF (300 mL). The reaction mixture was refluxed for 48 h in an inert atmosphere. The mixture was cooled on ice and water was added dropwise until evolution of hydrogen stopped. Water (200 mL) was added and the mixture was extracted with $CHCl_3$ (4 × 100 mL). The combined organic layers were washed with water (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*, yielding the crude product. Recrystallization from toluene/methanol gave a white crystalline solid (1.58 g, 83%). M.p. 145°C. EI MS (*m/z*) 198 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 2.87 (s, 2H, O*H*), 3.81 (s, 6H, O*Me*), 4.82 (s, 4H, C*H*$_2$), 6.83 (s, 2H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 56.15 (*C*H$_2$), 56.42 (O*Me*), 111.04 (*Ar*H), 129.45 (*Ar*CH_2), 151.81 (*Ar*OMe). Anal. Calcd. for $C_{10}H_{14}O_4$: C: 60.60, H: 7.12. Found: C: 60.70, H: 7.02.

2,3-Di(bromomethyl)-1,4-dimethoxybenzene (**18**). *Method A*: from 1,4-dimethoxy-2,3-dimethylbenzene. A mixture of N-bromosuccinimide (4.98 g, 28 mmol), 1,4-dimethoxy-2,3-dimethylbenzene (2.32 g, 14 mmol) and 50 mL of dry CCl_4 was irradiated with a 200 W lamp at reflux temperature in a nitrogen atmosphere for 1 h. The solution was cooled to room temperature, filtered and concentrated *in vacuo* yielding **18** as a white powder (4.36 g, 96%). *B*: from 2,3-di(hydroxymethyl)-1,4-dimethoxybenzene. To a cooled suspension of 2,3-di(hydroxymethyl)-1,4-dimethoxybenzene (6.26 g, 31.6 mmol) in 200 mL of dry diethyl ether was slowly added a solution of PBr_3 (20 g, 74 mmol) in diethyl ether (10 mL). The suspension was then refluxed for 2 h and allowed to cool to room temperature. The mixture was cautiously poured onto 200 g of crushed ice and extracted with diethyl ether (3 × 250 mL). The combined organic layers were washed with water (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* yielding **18** as a white powder (9.97 g, 97%). An analytically pure sample was prepared by crystallization from toluene. M.p. 149°C. EI MS (*m/z*) 164 ($[M–2Br]^+$, 100%), 324 (M^+). ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 6H, O*Me*), 4.74 (s, 4H, C*H*$_2$), 6.84 (s, 2H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 23.92 (*C*H$_2$), 56.24 (O*Me*), 112.12 (*Ar*H), 126.37

(*Ar*CH_2), 151.74 (*Ar*OMe). Anal. Calcd. for $C_{10}H_{12}O_2Br_2$: C: 37.19, H: 3.43. Found: C: 37.19, H: 3.58.

4,7,15,18-Tetramethoxy-22,23,23,24-tetramethyl-1,10,12,21-tetraazahexacyclo[19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$]pentacosa-3,5,7,14,16,18-hexaene-11,25-dione (**19**): Prepared as described for **9a** (*method C*) from **2d** (326 mg, 1.54 mmol) and **18** (1.02 g, 3.15 mmol). The crude product was recrystallized from $CHCl_3$/EtOH yielding **19** as a white crystalline solid (234 mg, 28%). M.p. 340-341°C (subl.). EI MS (*m/z*) 536 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 6H, C(C*H*$_3$)$_2$), 1.83 (s, 6H, C(NR)$_2$C*H*$_3$), 3.73 (s, 12H, O*Me*), 3.93 and 6.04 (2×d, J = 17.3 Hz, 2×4H, C*H*$_2$Ar), 6.59 (s, 4H, Ar*H*). ^{13}C NMR: δ 19.02 and 20.96 (*C*H$_3$), 39.21 (*C*H$_2$Ar), 40.06 (*C*C$_4$), 56.74, 74.22 (N*C*MeN), 110.20 (*Ar*H), 129.35 (*Ar*CH_2), 151.51 (*Ar*OMe), 154.44 (*C*=O). IR (KBr): ν = 1652 cm^{-1} (C=O). Anal. Calcd. for $C_{30}H_{37}N_4O_6Cl_3$ (**19**·$CHCl_3$): C: 54.93, H: 5.68, N: 8.54. Found: C: 54.98, H: 5.69, N: 8.48.

23,23-Dimethyl-1,10,12,21-tetraazahexacyclo[19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$]pentacosa-3,5,7,14,16,18-hexaene-11,25-dione (**20**). Prepared as described for **9a** (*method C*) from **2e** (656 mg, 3.57 mmol) and α,α'-dibromo-*o*-xylene (2.0 mg, 7.58 mmol). The crude product was purified by washing with a small amount of cold $CHCl_3$, yielding **20** as a white powder (428 mg, 26%). M.p. >350°C. EI MS (*m/z*) 388 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 6H, C*H*$_3$), 4.05 and 4.95 (2×d, J = 15 Hz, 8H, C*H*$_2$Ar), 4.45 (s, 2H, NC*H*N), 6.98-7.03 and 7.18-7.24 (2×m, 8H, Ar*H*). ^{13}C NMR (MeOD:$CDCl_3$, 1:4): δ 22.35 (*C*H$_3$), 32.09 (*C*C$_4$), 53.29 (*C*H$_2$Ar), 80.82 (N*C*HN), 126.90 and 129.72 (*Ar*H), 137.00 (*Ar*CH_2), 154.31 (*C*=O). IR (KBr): ν = 1654, 1665 cm^{-1} (C=O). Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C: 71.11, H: 6.23, N: 14.42. Found: C: 71.41, H: 6.21, N: 14.14.

23,23-Di[(benzyloxy)methyl]- 1,10,12,21- tetraazahexacyclo [19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$] pentacosa-3,5,7,14,16,18-hexaene-11,25-dione (**21**). Prepared as described for **9a** (*method C*) from **2g** (200 mg, 0.505 mmol) and α,α'-dibromo-*o*-xylene (390 mg, 1.48 mmol). Yield: 190 mg (63%) of **21** as a white powder. M.p. 249°C. EI MS (*m/z*) 600 (M^+), 91 ($C_7H_7^+$, 100%). ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 4H, C*H*$_2$OBn), 4.02 and 4.89 (2×d, J = 15 Hz, 8H, C*H*$_2$Ar), 4.56 (s, 4H, OC*H*$_2$Ph), 4.83 (s, 2H, NC*H*N), 6.98-7.03 and 7.16-7.21 (2×m, 8H, wall Ar*H*), 7.29-7.38 (m, 10H, benzyl Ar*H*).

23,23-Di[(benzyloxy)methyl]-4,7,15,18-tetramethoxy-1,10,12,21- tetraazahexacyclo [19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$]pentacosa-3,5,7,14,16,18-hexaene-11,25-dione (**22**). Prepared as described for **9a** (*method C*) from **2g** (3.00 g, 7.58 mmol) and **18** (5.40 g, 16.7 mmol). The crude product was dissolved in chloroform, filtered through infusorial earth, and precipitated in diethyl ether. Yield: 2.74 g (50%) of **22** as a white powder. M.p. 270°C. FAB MS (*m/z*) 721 ([M+H]$^+$), 154 (100%). ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 12H, OC*H*$_3$), 3.82 (s, 4H, C*H*$_2$OBn), 3.87 and 5.41 (2×d, J = 15 Hz, 8H, C*H*$_2$Ar), 4.52 (s, 4H, OC*H*$_2$Ph), 4.72 (s, 2H, NC*H*N), 6.72 (s, 4H, wall Ar*H*), 7.25-7.32 (m, 10H, benzyl Ar*H*). ^{13}C NMR ($CDCl_3$): δ 40.75 (*C*C$_4$), 44.85 (N*C*H$_2$Ar), 57.44 (O*Me*), 67.23 (O*C*H$_2$Ar),

73.21 and 73.54 (N*C*HN and *C*H_2OBn), 112.32 (*Ar*CH_2, side wall), 127.48, 127,70, 128.11, 128.40 (*Ar*H), 138.17 (OCH_2*Ar*), 151.63 (*Ar*O), 154.73 (*C*(O)). IR (KBr): ν = 1659, 1682 cm^{-1} (C=O). Anal. Calcd. for $C_{41}H_{44}N_4O_8$: C: 68.32, H: 6.15, N: 7.77. Found: C: 68.39, H: 6.15, N: 7.70.

23- [(Allyloxy)methyl]-23- ethyl-4,7,15,18- tetramethoxy-1,10,12,21- tetraazahexacyclo [19.3.1. $0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$]pentacosa-3,5,7,14,16,18-hexaene-11,25-dione (**23**). Prepared as described for **9a** (*method C*) from **2h** (565 mg, 2.22 mmol) and **18** (1.47 g, 4.54 mmol). Yield: 633 mg (49%) of **23** as a white powder. M.p. 260°C (dec.). FAB MS (*m/z*) 579 ($[M+H]^+$), 601 ($[M+Na]^+$, 100%). ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.87 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.62 (s, 2H, CH_2OAll), 3.77 (s, 12H, O*Me*), 3.87 (d, J = 15 Hz, 4H, CH_2Ar), 3.98 (d, J = 5.5 Hz, 2H, CH_2C=C), 4.53 (s, 2H, NC*H*N), 5.17-5.51 (m, 2H, C=CH_2), 5.44 and 5.48 (2×d, J = 15 Hz, 4H, CH_2Ar), 5.79-5.91 (m, 1H, C*H*=CH_2), 6.72 (s, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 7.95 (CH_2CH_3), 21.75 (CH_2CH_3), 38.76 (*C*C_4), 44.89 and 44.94 (CH_2Ar), 57.22 (O*Me*), 67.81 (CH_2C=C), 72.44 (CH_2OAll), 75.09 (N*C*HN), 112.35 (*Ar*H), 117.20 (C=*C*H_2), 128.16 and 128.26 (*Ar*CH_2), 134.47 (*C*H=CH_2), 154.63 and 154.82 (*C*=O). IR (KBr): ν = 1662, 1682 cm^{-1} (C=O). Anal. Calcd. for $C_{31}H_{38}N_4O_7$: C: 64.34, H: 6.62, N: 9.68. Found: C: 64.97, H: 6.65, N: 9.02.

11,25-Dioxo-1,10,12,21-tetraazahexacyclo[19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$] pentacosa-3,5,7,14,16,18-hexaene-23-yl-spiro-1'-(3'-cyclohexene) (**24**). Prepared as described for **9a** (*method C*) from **2i** (95 mg, 0.482 mmol) and α,α'-dibromo-*o*-xylene (258 mg, 0.977 mmol). The crude product was purified by column chromatography (MeOH/$CHCl_3$, 3:97 v/v) yielding **24** as a white powder (428 mg, 26%). M.p. 340°C (dec.). FAB MS (*m/z*) 428 ($[M+H]^+$, 100%). ^{1}H NMR ($CDCl_3$): δ 1.93-2.02, 2.15-2.22, and 2.32-2.38 (3×m, 6H, cyclohexene CH_2), 4.04, 4.06, 4.94, and 5.00 (4×d, J = 15 Hz, 8H, CH_2Ar), 4.48 (s, 2H, NC*H*N), 5.71-5.85 (m, 2H, *H*C=C*H*), 6.93-7.06 and 7.12-7.26 (2×m, 8H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 22.17 (CH_2CH_2C=C), 26.74 (CH_2CH_2C=C), 30.51 (CCH_2C=C), 33.78 (*C*C_4), 53.55 (CH_2Ar), 78.35 (N*C*HN), 124.04, 126.54, 126.92, and 129.94 (*Ar*H and *C*=*C*), 137.20 (*Ar*CH_2), 154.28 and 154.40 (*C*=O). IR (KBr): ν = 1653 cm^{-1} (C=C, C=O). Anal. Calcd. for $C_{26}H_{26}N_4O_2$: C: 73.22, H: 6.14, N: 13.14. Found: C: 74.48, H: 5.92, N: 12.11.

11,25-Dioxo-4,7,15,18- tetramethoxy-1,10,12,21- tetraazahexacyclo [19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$] pentacosa-3,5,7,14,16,18-hexaene-23-yl-spiro-1'-(3'-cyclohexene) (**25**). Prepared as described for **9a** (*method C*) from **2i** (1.24 g, 5.56 mmol) and **18** (3.97 g, 12.3 mmol). The crude product was purified by column chromatography (MeOH/$CHCl_3$, 2:98 v/v) yielding **25** as a white powder (1.91 g, 63%). Crystals suitable for X-ray analysis were obtained by slow diffusion of diethyl ether in a CH_2Cl_2 solution of the compound. M.p. >350°C. FAB MS (*m/z*) 547 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.85-1.94, 2.08-2.17, and 2.29-2.35 (3×m, 6H, cyclohexene CH_2), 3.77 (s, 12H, OCH_3), 3.85, 3.87, 5.48, and 5.48 (4×d, J = 15 Hz, 8H, CH_2Ar), 4.45 (s, 2H, NC*H*N), 5.65-5.80 (m, 2H, *H*C=C*H*), 6.72 (s, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 22.23 (CH_2CH_2C=C), 26.97 (CH_2CH_2C=C), 30.65 (CCH_2C=C), 33.45 (*C*C_4), 44.98 (O*Me*), 57.31 (CH_2Ar), 77.20 (N*C*HN), 112.40 (*Ar*H), 124.29 and 126.49 (*C*=*C*), 128.33 (*Ar*CH_2), 151.70 (*Ar*OMe), 154.17 and 154.45 (*C*=O). IR (KBr):

ν = 1651 and 1656 cm^{-1} (C=C, C=O). Anal. Calcd. for $C_{30}H_{34}N_4O_6$: C: 65.92, H: 6.27, N: 10.25. Found: C: 65.92, H: 6.22, N: 10.11.

22,23,23-Trimethyl- 1,10,12,21- tetraazahexacyclo [19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$] pentacosa-3,5,7, 14,16,18-hexaene-11,25-dione (**26**). Prepared as described for **9a** (*method C*) from **2k** (1.50 g, 7.58 mmol) and α,α'-dibromo-*o*-xylene (5.3 g, 20 mmol). The crude product was purified by column chromatography (MeOH/$CHCl_3$, 2:98 v/v) yielding **26** as a white powder (0.79 g, 26%). M.p. 283°C (subl.). EI MS (*m/z*) 402 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 6H, C(C*H*$_3$)$_2$), 1.77 (s, 3H, NC(C*H*$_3$)N), 4.04, 4.39, 4.91, and 4.95 (4×d, J = 15 Hz, 4×2H, C*H*$_2$Ar), 4.37 (s, 1H, NC*H*N), 6.91-7.02 (m, 4H, Ar*H*), 7.12-7.20 (m, 4H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 18.63 (NC(*C*H$_3$)N, 22.56 C(*C*H$_3$)$_2$, 35.78 (*C*C$_4$), 46.84 (*C*H$_2$Ar, methyl side), 53.64 (*C*H$_2$Ar, hydrogen side), 76.74 (N*C*(CH$_3$)N), 79.94 (N*C*HN), 126.50, 126.91, 129.99, and 130.19 (*Ar*H), 137.29 and 137.52 (*Ar*CH$_2$), 154.59 (*C*=O). IR (KBr): ν = 1649, 1658, 1697 cm^{-1} (C=O). Anal. Calcd. for $C_{24}H_{26}N_4O_2$: C: 71.62, H: 6.51, N: 13.92. Found: C: 73.04, H: 6.54, N: 12.48.

4,7,15,18-Tetramethoxy-23,23,24-trimethyl-1,10,12,21-tetraazahexacyclo[19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$. $0^{14,19}$]pentacosa-3,5,7,14(19),15,17-hexaene-11,25-dione (**27**): Prepared as described for **9a** (*method C*) from **2k** (554 mg, 2.80 mmol) and **18** (1.95 g, 6.02 mmol). The crude product was purified by column chromatography (EtOH/CH_2Cl_2, 2:98 v/v) yielding **27** as a white powder (366 mg, 25%). M.p. 352-353°C (subl.). EI MS (*m/z*) 522 (M^+, 100%). ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 6H, C(C*H*$_3$)$_2$), 1.71 (s, 3H, C(NR)$_2$C*H*$_3$), 3.74 (s, 6H, O*Me*), 3.77 (s, 6H, O*Me*), 3.85 and 5.55 (2×d, J = 15.2 Hz, 2×2H, C*H*$_2$Ar), 3.87 and 5.97 (2×d, J = 17.1 Hz, 2×2H, C*H*$_2$Ar), 4.27 (s, 1H, NC*H*N), 6.63 (s, 2H, Ar*H*), 6.72 (s, 2H, Ar*H*). ^{13}C NMR ($CDCl_3$): δ 18.30 (C(*C*H$_3$)$_2$), 22.62 (C(NR)$_2$*C*H$_3$), 35.23 and 39.35 (*C*H$_2$Ar), 45.24 (*C*C$_4$), 56.85 and 57.34 (O*C*H$_3$), 75.80 (N*C*MeN), 82.14 (N*C*HN), 110.38 and 112.36 (*Ar*H), 128.51 and 129.38 (*Ar*CH$_2$), 151.58 and 151.74 (*Ar*OMe), 154.29 (*C*=O). IR (KBr): ν = 1624, 1652 cm^{-1} (C=O). Anal. Calcd. for $C_{29}H_{35}N_4O_6Cl_3$ (**27**·$CHCl_3$): C: 54.26, H: 5.50, N: 8.73. Found: C: 54.44, H: 5.44, N: 8.62.

4,7,15,18- Tetramethoxy- 23,23-dimethyl-24- phenyl-1,10,12,21- tetraazahexacyclo [19.3.1.$0^{3,8}$. $0^{10,24}$.$0^{12,22}$.$0^{14,19}$]pentacosa-3,5,7,14(19),15,17-hexaene-11,25-dione (**28**): Prepared as described for **9a** (*method C*) from **2m** (350 mg, 1.35 mmol) and **18** (923 mg, 2.85 mmol). The crude product was purified through a short column (MeOH/CH_2Cl_2, 2:98 v/v) yielding **28** as a white powder (245 mg, 30%). An analytically pure sample was obtained by liquid diffusion using CH_2Cl_2 as the solvent and diethyl ether as the precipitant. M.p. >350°C. EI MS (*m/z*) 584 (M^+, 100%). ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 6H, C(C*H*$_3$)$_2$), 3.73 (s, 6H, O*Me*), 3.77 (s, 6H, O*Me*), 3.81 and 5.54 (2×d, J = 15.0 Hz, 2×2H, C*H*$_2$Ar), 3.89 and 5.42 (2×d, J = 15.2 Hz, 2×2H, C*H*$_2$Ar), 4.35 (s, 1H, NC*H*N), 6.53 (s, 2H, Ar*H*), 6.66 (s, 2H, Ar*H*), 7.27-7.43 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 23.03 (C(*C*H$_3$)$_2$), 36.63 and 41.76 (*C*H$_2$Ar), 45.00 (*C*C$_4$), 57.39 and 57.73 (O*C*H$_3$), 79.49 (N*C*PhN), 84.58 (N*C*HN), 112.00 and 112.84 (MeOC(*C*H)$_2$COMe), 127.84, 128.14, 128.59, 128.82, 129.61, 135.55 (*Ar*H,

*Ar*C), 151.92 (*Ar*OMe), 155.65 (*C*=O). IR (KBr): ν = 1654, 1675 cm^{-1} (C=O). Anal. Calcd. for $C_{33}H_{36}N_4O_6$: C: 67.79, H: 6.21, N: 9.58. Found: C: 67.91, H: 6.26, N: 9.42.

23,23 - Di (hydroxymethyl)- 4,7,15,18- tetramethoxy- 1,10,12,21- tetraazahexacyclo [19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$]pentacosa-3,5,7,14,16,18-hexaene-11,25-dione (**29**). In a mixture of CH_2Cl_2 (45 mL) and ethanol (5 mL) were suspended 10% Pd/C (100 mg) and 22 (350 mg, 0.49 mmol). The mixture was stirred for 16 h in a hydrogen atmosphere (10 bar). Then the mixture was heated and filtered hot through infusorial earth. Evaporation of the solvent produced **29** as a light gray solid in quantitative yield. The product was used in subsequent reactions without further purification. ^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.76 (s, 12H, O*Me*), 3.83 and 5.53 (2×d, J = 15.5 Hz, 2×4H, CH_2Ar), 4.72 (s, 2H, NC*H*N), 6.73 (s, 4H, Ar*H*).

23-(Hydroxymethyl)-23-ethyl-4,7,15,18-tetramethoxy-1,10,12,21-tetraazahexacyclo [19.3.1.$0^{3,8}$.$0^{10,24}$.$0^{12,22}$.$0^{14,19}$]pentacosa-3,5,7,14,16,18-hexaene-11,25-dione (**30**). Clip **23** (170 mg, 0.29 mmol) was suspended in THF (15 mL). This suspension was degassed by bubbling argon through it for 30 min. Then formic acid (27 mg, 0.6 mmol), triethyl amine (60 mg, 0.6 mmol), freshly distilled tributyl phosphine (7.3 µl, 29 µmol), and palladium bis(dibenzylidene acetonate) ($Pd(dba)_2$, 3.4 mg, 5.8 µmol) were added. The mixture was refluxed for 48 h in an argon atmosphere, cooled, after which the product was collected by filtration. Purification by column chromatography (CH_2Cl_2/EtOH, 98:2 v/v) yielded **30** as a white powder (100 mg, 63%). M.p. 291°C. FAB MS (*m/z*) 539 ($[M+H]^+$), 561 ($[M+Na]^+$), 154 (100%). ^{1}H NMR ($CDCl_3$): δ 0.99 (t, J = 7.8 Hz, 3H, CH_2CH_3), 1.88 (q, J = 7.8 Hz, 2H, CH_2CH_3), 3.77 (s, 12H, O*Me*), 3.81 (s, 2H, CH_2OH), 3.85 (d, J = 15 Hz, 4H, CH_2Ar), 4.55 (s, 2H, NC*H*N), 5.48 and 5.52 (2×d, J = 15 Hz, 4H, CH_2Ar), 6.73 (s, 4H, Ar*H*). Anal. Calcd. for $C_{28}H_{34}N_4O_7$: C: 62.44, H: 6.36, N: 10.40. Found: C: 62.83, H: 6.41, N: 9.97.

X-ray analysis

Crystals of **25** suitable for X-ray diffraction studies were obtained by slow diffusion of diethyl ether into a solution of the compound in dichloromethane. A single crystal was mounted in air on a glass fiber. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Cu-Kα radiation, ω-2θ scan mode. Unit cell dimensions were determined from the angular setting of 13 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[27] was applied. The structure was solved by the program CRUNCH[28] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97[29]) with anisotropic parameters for the nonhydrogen atoms. All hydrogens, except the hydrogens attached to the cyclohexene ring, were initially placed at calculated positions and were freely refined subsequently. The hydrogens attached to the cyclohexene ring were placed at calculated positions. The cyclohexene ring is disordered over two positions. This disorder can be interpreted as a swap of the ring and can be described by a suitable

disorder model. A structure determination summary is given in Table 2. A PLUTON[17] drawing is shown in Figure 1.

Table 2 *Crystal data and structure refinement for **25**.*

Crystal color	Transparent colorless
Crystal shape	Regular platelet
Crystal size	0.28 × 0.18 × 0.03 mm
Empirical formula	$C_{30}H_{34}N_4O_6$
Formula weight	546.61
Temperature	293(2) K
Radiation / Wavelength	CuKα (graphite mon.) / 1.54184 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions (13 reflections, 40.106 < θ < 46.846)	a = 9.7038(7) Å, α = 83.272(10)° b = 10.2836(11) Å, β = 87.583(8)° c = 13.4911(12) Å, γ = 75.212(10)°
Volume	1292.6(2) $Å^3$
Z, Calculated density	2, 1.404 Mg/m^3
Absorption coefficient	0.810 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / ω-2θ
F(000)	580
θ range for data collection	3.30 to 70.02°
Index ranges	–11<=h<=11, 0<=k<=12, –16<=l<=16
Reflections collected / unique	5215 / 4920 [R(int) = 0.0170]
Reflections observed	3152 ([I_0>2σ(I_0)])
Absorption correction	Semi-empirical from ψ-scans
Range of relat. transm. factors	1.110 and 0.912
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4920 / 33 / 508
Goodness-of-fit on F^2	1.050
SHELXL-97 weight parameters	0.049700 0.319200
Final R indices [I>2σ(I)]	R_1 = 0.0471, wR_2 = 0.1022
R indices (all data)	R_1 = 0.0888, wR_2 = 0.1199
Largest diff. peak and hole	0.159 and –0.212 e·$Å^{-3}$

4.7 References

1 For an overview see: Lehn, J.-M. *Comprehensive Supramolecular Chemistry*, Elsevier Science Ltd., Oxford, **1996**, Vol. 2.

2 (a) Sijbesma, R.P.; Nolte, R.J.M. *Top. Curr. Chem.*, Ed. E. Weber, **1995**, *179*, 25; (b) Rowan, A.E.; Elemans, J.A.A.W.; Nolte, R.J.M. *Acc. Chem. Res.* **1999**, *32*, 995.

3 Gieling, G.T.W.; Scheeren, H.W.; Israël, R.; Nolte R.J.M. *Chem. Commun.* **1996**, 245.

4 Van Nunen, J.L.M.; Nolte, R.J.M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1473.

5 Reek, J.N.H.; Kros, A.; Nolte, R.J.M. *Chem. Commun.* **1996**, 245.

6 Holder, S.J.; Elemans, J.A.A.W.; Barberá, J.; Rowan, A.E.; Nolte, R.J.M. *Chem. Commun.* **2000**, 355.

7 Rebek's group has synthesized glycoluril derivatives with various groups R which have been used for the construction of molecular capsules: (a) Conn, M.M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647; (b) Tokunaga, Y.; Rudkevich, D.M.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2656; (c) Szabo, T.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 6193.

8 Elemans, J.A.A.W.; De Gelder, R.; Rowan, A.E.; Nolte, R.J.M. *Chem. Commun.* **1998**, 1553.

9 De Haan, T. *Recl. Trav. Chim. Pays-Bas* **1908**, *27*, 162.

10 Smeets, J.W.H.; Sijbesma, R.P.; Van Dalen, L.; Spek, A.L.; Smeets, W.J.J.; Nolte, R.J.M. *J. Org. Chem.* **1989**, *54*, 3710.

11 Petersen, H.; Steimmig, A.; Schönleben, W.; Bille, H. *Ger. Pat.* 2011703, **1971** [*Chem. Abstr.* **1972**, *76*, 60867s].

12 Zaugg, H.E. *Synthesis* **1970**, *2*, 49.

13 Sijbesma, R.P.; Nolte, R.J.M. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 643.

14 Sijbesma, R.P.; Kentgens, A.P.M.; Nolte, R.J.M. *J. Org. Chem.* **1991**, *56*, 3199.

15 The acid hydrolysis of hydroxymethylene ureas to yield formaldehyde and the corresponding urea compound has been described: (a) Nordhøy, F.; Ugelstad, J. *Acta Chem. Scand.* **1959**, *13*, 864; (b) Petersen, H. *Textile Res. J.* **1971**, 239.

16 (a) Dave, P.R.; Forohar, F.; Kaselj, M.; Gilardi, R.; Trivedi, N. *Tetrahedron Lett.* **1999**, *40*, 447; (b) Wyler, R.; De Mendoza, J.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699.

17 Spek, A.L. PLATON. A Multipurpose Crystallographic Tool; *Utrecht University*, Utrecht, The Netherlands, **2001**.

18 Hurd, C.D.; Kelso, C.D. *J. Am. Chem. Soc.* **1948**, *70*, 1484.

19 Lemieux, R.U.; Van Rudloff, E. *Can. J. Chem.* **1955**, *33*, 1701.

20 Bhushan, V.; Rathore, R.; Chandesakaran, S. *Synthesis* **1984**, *5*, 431.

21 Cope, A.C.; Moon, S.; Park, C.H. *J. Am. Chem. Soc.* **1962**, *84*, 4843.

22 Neumeister, J.; Keul, H.; Saxena, M.P.; Griesbaum, K. *Angew. Chem.* **1978**, *12*, 999.

23 Wilms, H. *Lieb. Ann. Chem.* **1950**, *367*, 96.

24 Piacenza, G.; Beguet, C.; Wimmer, E.; Gallo, R.; Giorgi, M. *Acta Cryst.* **1997**, *B53*, 1459.

25 Khasapov, B.N.; Novikova, T.S.; Lebedev, O.V.; Khmel'nitskii, L.I.; Novikov, S.S. *J. Org. Chem. USSR* **1973**, *9*, 21.

26 Cardani, C.; Piozzi, F. *Lincei - Rend. Sc. Fis. Mat. Nat.* **1952**, *12*, 719.

27 North, A.C.T.; Philips, D.C.; Mathews, F.S. *Acta Crystallogr.* **1968**, *A24*, 351.

28 Gelder, R. de; Graaff, R.A.G. de; Schenk, H. *Acta Crystallogr.* **1993**, *A49*, 287.

29 Sheldrick, G.M. SHELXL-97. Program for the refinement of crystal structures; University of Gottingen: Germany, **1997**.

5 Propanediurea Based Clips: Structure and Binding Properties

5.1 Introduction

Within the growing field of synthetic receptors for neutral guest molecules,[1] research in our group has been focused for some time on the concave molecule diphenylglycoluril **1** (Chart 1). Hosts **2**-**5** derived from this molecule are receptors for hydroxybenzenes.[2] Binding of guest molecules **11** and **12** (Tables 1 and 2) in clips of type **4** is based on three factors (see Figure 1).[3] The most important interaction is the formation of hydrogen bonds between the hydroxy groups of the guest and the urea carbonyl groups of the host. A second interaction is π-π stacking of the guest with the cavity walls, and a third factor is a cavity effect. The latter effect displays two features. π-π Stacking interactions between a guest and one cavity wall are enthalpically favorable. This effect is, however, largely compensated for by the loss in translational and rotational entropy of the guest. Addition of a second wall and thus formation of a cavity is free from these entropy losses, and hence only the enthalpically favorable π-π stacking interactions contribute to the binding. The second feature is related to the fact that in chloroform the cavity is not completely filled; chloroform molecules are too large to fit very well within the cavity of the clip. When the cavity is filled with a guest molecule the resulting host is much better solvated than the free host.[3] In Figure 1 the mode of binding of a resorcinol guest in molecular clips is shown.

In recent years a large number of clip molecules of type **4** have been synthesized, and their supramolecular chemistry has been extensively studied.[2,3] Clip molecules have been constructed that exhibit induced fit and allosteric binding mechanisms, mimicking the processes seen in natural enzymes.[4] The glycoluril framework of these clips, however, has not been the subject of significant structural modifications that could influence the binding properties.

The newly synthesized clip molecules **8**-**10** based on propanediurea, which have been presented in Chapter 4 have a slightly altered geometry compared to the diphenylglycoluril derived clips. They can be prepared with various substituents, which can induce structural variations or which allow for subsequent functionalization in similar ways as reported for clips of type **4**.[5-7] In this chapter the structural features of propanediurea derived clips are presented, as studied by NMR, X-ray

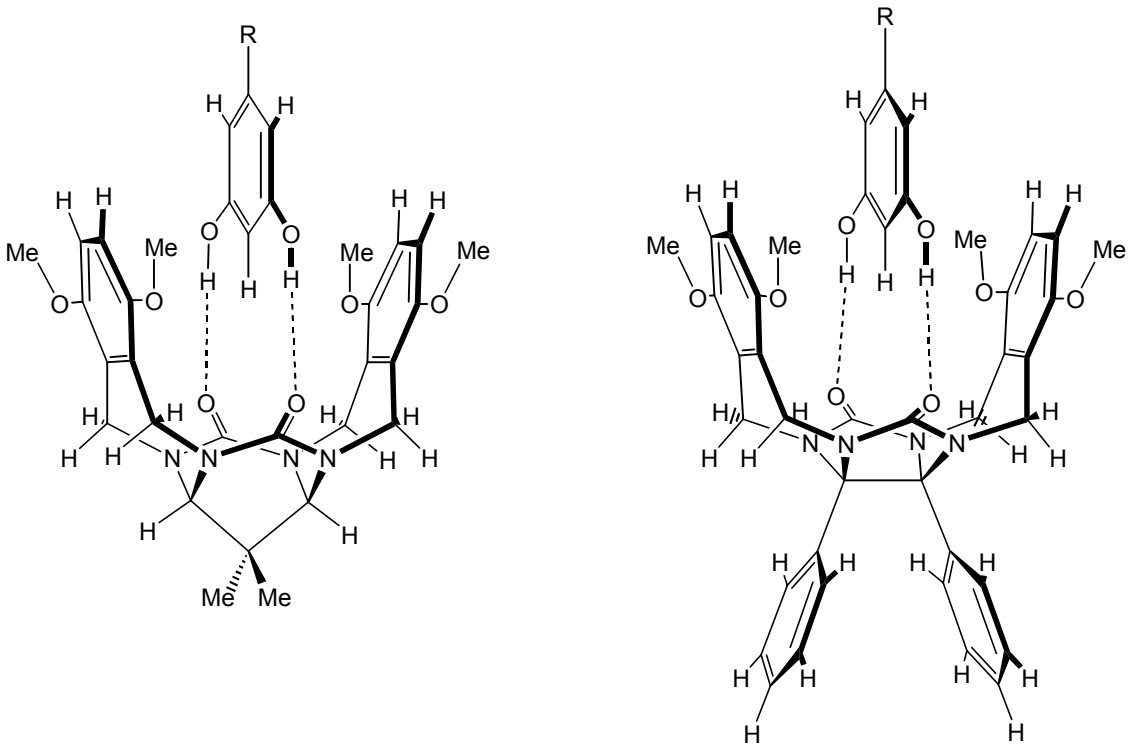


Figure 1 *Geometry of guest binding in propanediurea based clips (left) and in glycoluril based clips*

crystallography, and molecular modeling. The binding properties have been investigated using NMR titration experiments and IR measurements, and these are presented as well. A comparison is made between diphenylglycoluril derived clips and propanediurea derived clips.

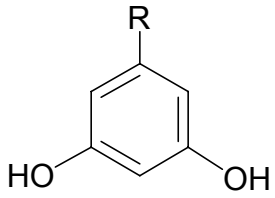
5.2 Binding properties

The binding affinities of the new host molecules **9a-f** for a number of hydroxybenzene derivatives (**11a-e**, Table 1, and **12a-e**, Table 2) were measured by NMR titration experiments in $CDCl_3$ using the aromatic wall protons of the host and the aromatic protons of the guest as probes.[8,9] We preferably used competition experiments as opposed to standard titration experiments to determine the association constants. With competition experiments binding constants can be measured that are too high to be measured by standard titrations. Moreover, these experiments allow for more reliable comparison of two association constants that have similar values.

Benzene walled clips

In Table 3 the binding constants K_a and free energies of association of propanediurea host **9a** and diphenylglycoluril host **4a** with resorcinol derivatives **11a-e** are listed. Clip **9a** binds these guests significantly stronger than clip **4a**. The difference in binding affinity between the two clips is dependent upon the type of guest. The binding free energies of guests **11a-e** in **9a** and **4a** are plotted as a function of the Hammett [σ_m(R)] parameter of the substituent R of the guest (Figure 2). For **11a**, a guest with a slightly electron releasing substituent, the difference in binding energy between

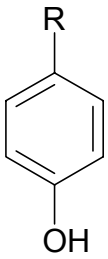
Table 1 *Substituted 1,3-dihydroxybenzene guest molecules **11a-e** and their Hammett substituent constants (σ_m(R))*



	R	[σ_m(R)][a]
11a	Me	–0.07
11b	H	0.00
11c	OMe	0.12
11d	Cl	0.37
11e	CN	0.56

a. Values are taken from ref. 11

Table 2 *Substituted phenol guest molecules **12a-e** and their Hammett substituent constants (σ_p(R))*



	R	[σ_p(R)][a]
12a	OMe	–0.27
12b	H	0.00
12c	Cl	0.23
12d	CN	0.66
12e	NO_2	0.78

a. Values are taken from ref. 11

clips **4a** and **9a** is relatively small (2.2 kJ·mol^{-1}). For guests with more strongly electron withdrawing substituents this difference is considerably larger (up to 3.8 kJ·mol^{-1}). Later in this chapter this phenomenon will be discussed in greater detail.[10]

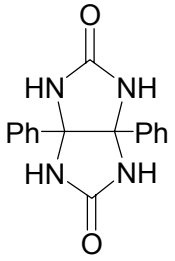
1,4-Dimethoxybenzene walled clips

As has been previously reported, diphenylglycoluril derived clips with dimethoxybenzene side walls exhibit much higher affinities for hydroxybenzene guests than clips with simple benzene walls.[3] As is clear from Table 4, this is also the case for the propanediurea derived clips. Of all the hosts studied compound **9c** has the highest affinity for resorcinol derivatives (K_a values up to 2.4 × 10^6 L·mol^{-1}). If a methyl substituent is present under one of the side walls of the clip (position-1) (**9d**) the association constants drop by approximately 10% ($\Delta\Delta G$ ~0.3 kJ·mol^{-1}). If methyl substituents are present at both the 1 and 5 positions (clip **9e**) the measured K_a values are approximately 30% ($\Delta\Delta G$ ~0.9 kJ·mol^{-1}) lower than those of the parent compound without these substituents (**9c**).[a] Molecular modeling indicates that the methyl substituents positioned directly under the side wall of the clip 'lock' the walls in a position which is slightly bent out due to Van der Waals contacts with the xylylene methylene protons (see Figure 3). Once a side wall is locked it is unable to alter its geometry in order to optimize the guest binding, which results in a lower binding constant. In the case of clip **9d** the decreased flexibility of one of the side walls can largely be

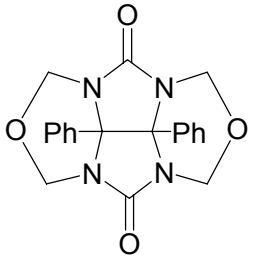
[a] Although the differences in association constants for clips **9c-e** with guests **11** as reported in Table 4 are small and are often negligible if the experimental errors are taken into consideration, we believe that the $\Delta\Delta G$ values of 0.3 and 0.9 kJ mol^{-1} are genuine since they are derived from direct competition experiments between two host molecules.

compensated for by the other side wall, which is still flexible. This results in only a relatively small decrease in binding affinity. When both side walls are 'locked', however, as is the case for clip **9e**, the binding constant decreases significantly because no 'induced fit' is possible.

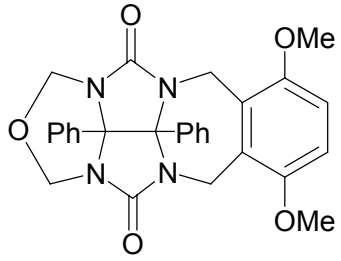
Chart 1



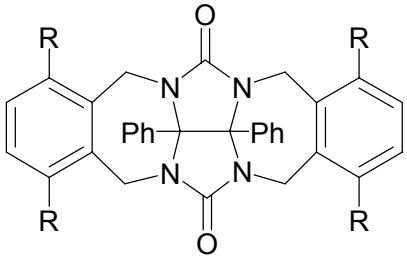
1



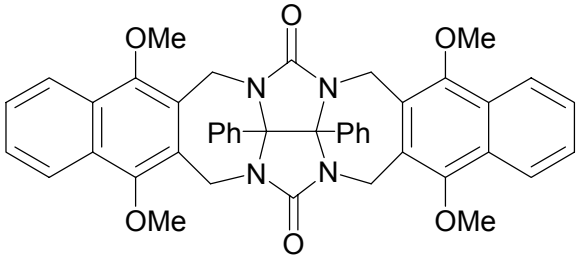
2



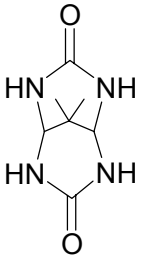
3



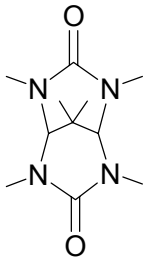
4a R = H
4b R = OMe



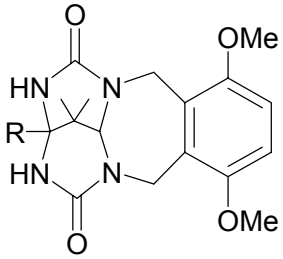
5



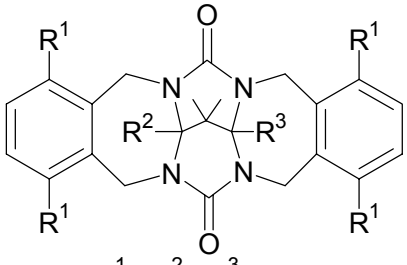
6



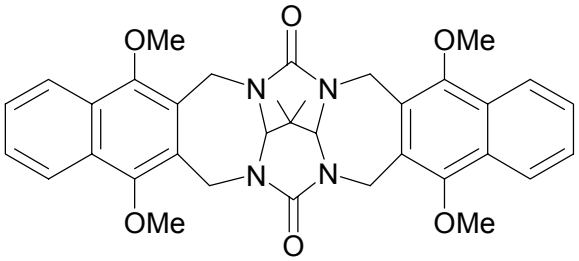
7



8a R = Me
8b R = Ph
8c R = *n*-propyl



9a R^1= R^2= R^3= H
9b R^1= R^2= H, R^3= Me
9c R^1= OMe, R^2= R^3= H
9d R^1= OMe, R^2= Me, R^3= H
9e R^1= OMe, R^2= R^3= Me
9f R^1= OMe, R^2= Ph, R^3= H



10

Table 3 *Association constants and binding free energies of clips **4a** and **9a** with various resorcinol derivatives in $CDCl_3$ at 298K*

	Clip **4a**		Clip **9a**			
Guest	K_a ($L \cdot mol^{-1}$)[a]	ΔG ($kJ \cdot mol^{-1}$)	K_a ($L \cdot mol^{-1}$)[a]	ΔG ($kJ \cdot mol^{-1}$)	K_{rel}[b]	$\Delta\Delta G$ ($kJ \cdot mol^{-1}$)
11a	85 (15)	–11.0	210 (20)	–13.2	2.5	2.2
11b	175 (15)	–12.8	490 (50)	–15.3	2.8	2.5
11c	190 (20)	–13.0	550 (50)	–15.6	2.9	2.6
11d	610 (70)	–15.9	2,100 (200)	–18.9	3.4	3.0
11e	3,500 (400)	–20.2	16,000 (1500)	–24.0	4.6	3.8

a. Error margins in brackets; b. ratio of association constants (K_{9a}/K_{4a})

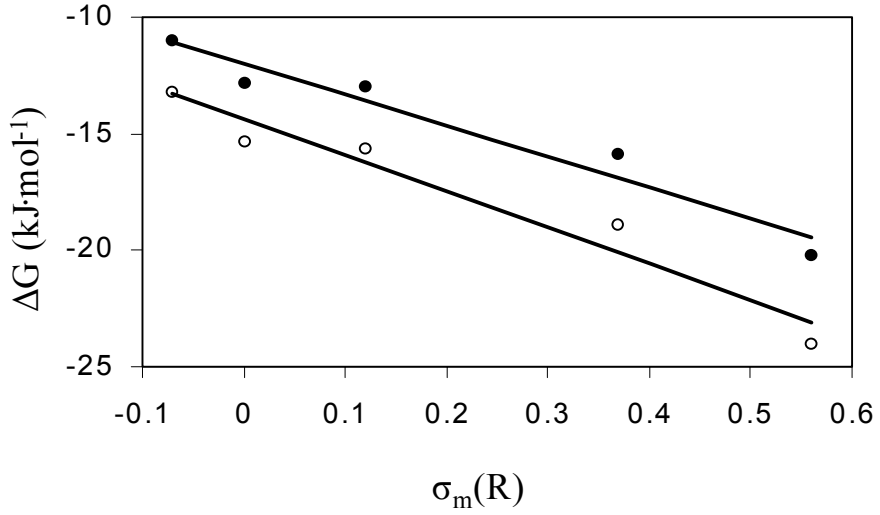


Figure 2 *Binding free energies of guests **11a-e** in clip molecules **4a** (•) and **9a** (o) plotted as a function of the Hammett parameter ($\sigma_m(R)$) of the substituent R in the guest*

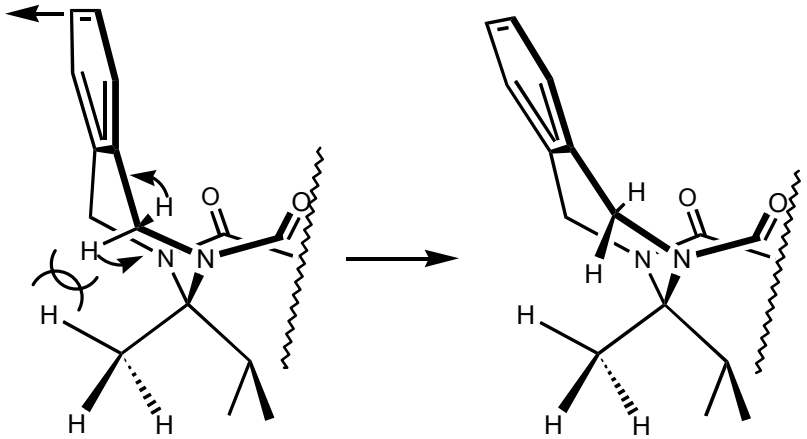


Figure 3 *Influence of a methyl group at position-1 on the orientation of the side wall in clip **9d***

Table 4 *Association constants (K_a, ($L \cdot mol^{-1}$)) and binding free energies (ΔG, ($kJ \cdot mol^{-1}$)) of dimethoxybenzene walled clips with resorcinol derivatives in $CDCl_3$ at 298K.*

	Clip **9c**		Clip **9d**		Clip **9e**		Clip **4b**	
Guest	K_a	ΔG	K_a	ΔG	K_a	ΔG	K_a	ΔG
11a[a]	13,000	–23.5	9,500	–22.7	8,800	–22.5	1,900	–18.7
11b[a]	31,000	–25.6	25,000	–25.1	22,600	–24.8	2,600	–19.5
11c[a]	34,000	–25.8	33,100	–25.8	23,500	–24.9	4,400	–20.8
11d[b]	280,000	–31.1	270,000	–31.0	200,000	–30.2	16,000	–24.0
11e[c]	2,400,000	–36.4	2,200,000	–36.2	1,600,000	–35.4	100,000	–28.5

a. Approximate error 20%; b. approximate error 30%; c. approximate error 40%

Additional evidence for this hypothesis comes from the NMR titration data. The resonances due to the *o*-xylylene protons (H^A, H^B) of the different clip molecules shift upon the addition of a guest molecule (see Table 5). Such a shift was not observed for host molecules of type **4**. The observed shifts indicate that the side walls of the clip undergo a conformational change upon binding of a guest (induced fit, see Figure 4). For clip **9c** these complexation induced shifts (CIS) were considerably larger than for clip **9e**. Due to its asymmetry, clip **9d** has two sets of signals for the *o*-xylylene protons: one set for the protons on the 'methyl side' and one set for the protons on the 'hydrogen side'. As expected, one set showed large shifts, as in clip **9c**, and one set relatively minor shifts, as in clip **9e**. The same trend was observed for the clip side wall protons. A large shift of $\Delta\delta$ –0.60 ppm was observed for the flexible clip **9c** and a smaller shift of $\Delta\delta$ –0.44 ppm for the rigid clip **9e**. Analysis of the NMR data revealed that the aromatic wall protons of clip **9d** also showed shifts, *viz*. of $\Delta\delta$ –0.53 and –0.49 ppm, respectively. These observed $\Delta\delta$'s reveal that upon binding of resorcinol the side walls of clip **9c** move closer to the guest. As a result of this change in geometry the aromatic protons of the host experience a shielding effect caused by the guest. This effect is more pronounced when the distance between the side wall protons and the aromatic ring of the guest is smaller. This leads to a shift of $\Delta\delta$ –0.60 ppm for **9c**, $\Delta\delta$ –0.44 ppm for **9e**, and two values between these extremes for **9d**.

The difference in binding affinity for resorcinol derivatives as found for clips **9c** and **9e**, is mainly due to a difference in flexibility of the cavity side walls. As can be seen in Table 4, the difference in ΔG^0 between binding to **9c** and **9e** is a constant 0.9 ± 0.1 $kJ \cdot mol^{-1}$ for all resorcinol derivatives. Since the position of the carbonyl groups with respect to the cavity walls is expected to be the same in **9c** and **9e**, differences in hydrogen bonding cannot account for the observed differences in binding affinities. This assumption has been validated by determining the binding affinities of clips **9c** and **9e** for a number of 4-substituted phenol derivatives (**12a-e**, Table 6). In this case only one hydrogen bond can be formed, which is optimal in all clip molecules. Any observed differences in binding energies must be the result of interactions with the cavity side walls. Since the binding affinities of **9c** and **9e** for **12** are relatively low, the $\Delta\Delta G^0$ values could not be determined as

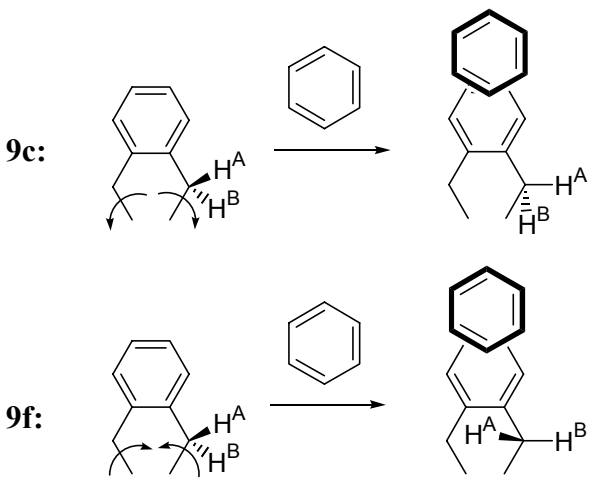
accurately as in the case of the resorcinol guests. The average difference in ΔG^0 values between **9c** and **9e** again was found to be approximately 0.9 $kJ \cdot mol^{-1}$. Noteworthy in this respect are also the CIS values of the aromatic wall protons of the clip molecules, which are a measure of the position of the guest with respect to the cavity side walls. These values are substantially higher for clip molecule **9c** than for clip **9e**. For example, with 4-nitrophenol (**12e**) as a guest the CIS values are –0.66 and –0.48 ppm for hosts **9c** and **9e**, respectively. This suggests that in the case of the former host the distance between the aromatic side walls and the guest in the complex is smaller than for the latter host.

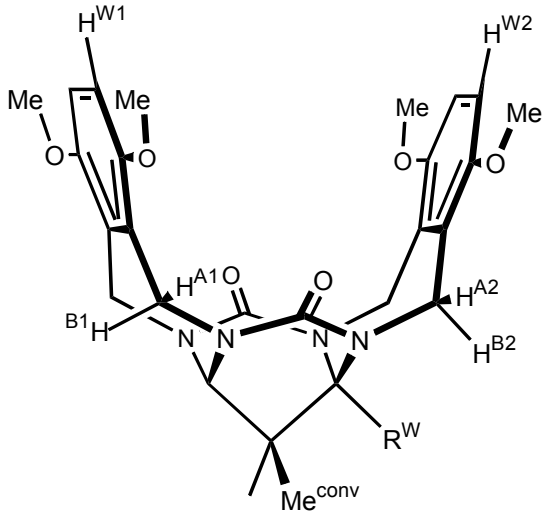
From the above data it is clear that binding of guests in clip molecules **9c** and **9d**, and to a much lesser extent in clip molecule **9e** takes place via an induced fit mechanism, mimicking processes seen in natural enzymes (see Figure 4). Increased flexibility of the host, and thus a greater ability to adopt its conformation to a guest bound in its cavity, results in a higher binding constant. With a

Table 5 *Chemical shifts (in ppm) of selected protons[a] in free clip molecules **9c-f**, and complexation induced shift (CIS) values (ppm, in parentheses) of these protons in host-guest complexes with resorcinol[b]*

	$H^{W1,2}$	$H^{A1,2}$	$H^{B1,2}$	Me^{W}	Me^{conv}
9c	6.74 (–0.60)	5.42 (+0.45)	3.91 (–0.28)[c]	-[d]	1.35 (+0.16)
9d	6.72 6.63 (–0.53) (–0.49)	5.55 5.95 (+0.31) (+0.06)	3.85 3.87 (–0.19) (+0.01)	1.71 (+0.09)	1.33 (+0.13)
9e	6.63 (–0.44)	6.05 (–0.04)	3.93 (+0.05)	1.82 (+0.10)	1.34 (+0.12)
9f	6.66 6.53 (–0.45) (–0.43)	5.54 5.42 (+0.43) (+0.14)	3.81 3.90 (–0.10) (+0.28)[c]	-[d]	1.06 (+0.15)

a. See structural depiction; b. a negative sign denotes an upfield shift and a positive sign denotes a downfield shift; c. on binding of a resorcinol guest molecule the xylylene protons H^{A2} and H^{B2} of clips **9c** and **9f** change positions in the following ways:





d. proton is not present in the molecule

Table 6 *Association constants (K_a, (L·mol^{-1})) and binding free energies (ΔG (kJ·mol^{-1})) of dimethoxybenzene walled clips with phenol derivatives in $CDCl_3$ at 298K*

	Clip **9c**		Clip **9e**		Clip **4b**	
Guest	K_a	ΔG	K_a	ΔG	K_a	ΔG
12a[a]	23	–7.8	16	–6.9	20	–7.4
12b[a]	22	–7.7	18	–7.2	29	–8.3
12c[a]	180	–12.9	160	–12.6	80	–10.9
12d[b]	2000	–18.8	1450	–18.0	415	–14.9
12e[b]	4400	–20.8	2000	–18.8	1200	–17.6

a. Approximate error 30%; b. approximate error 20%

strongly binding guest (5-cyanoresorcinol, **11e**) association constants of up to 2.4×10^6 L·mol^{-1} ($\Delta G = -36.4$ kJ·mol^{-1}) can be reached.

Clip molecule **9f** exhibits structural features and binding properties that cannot be easily explained using the mechanisms described above. Therefore, its properties will be discussed in the following paragraph, after presenting the X-ray structures of the clip molecules.

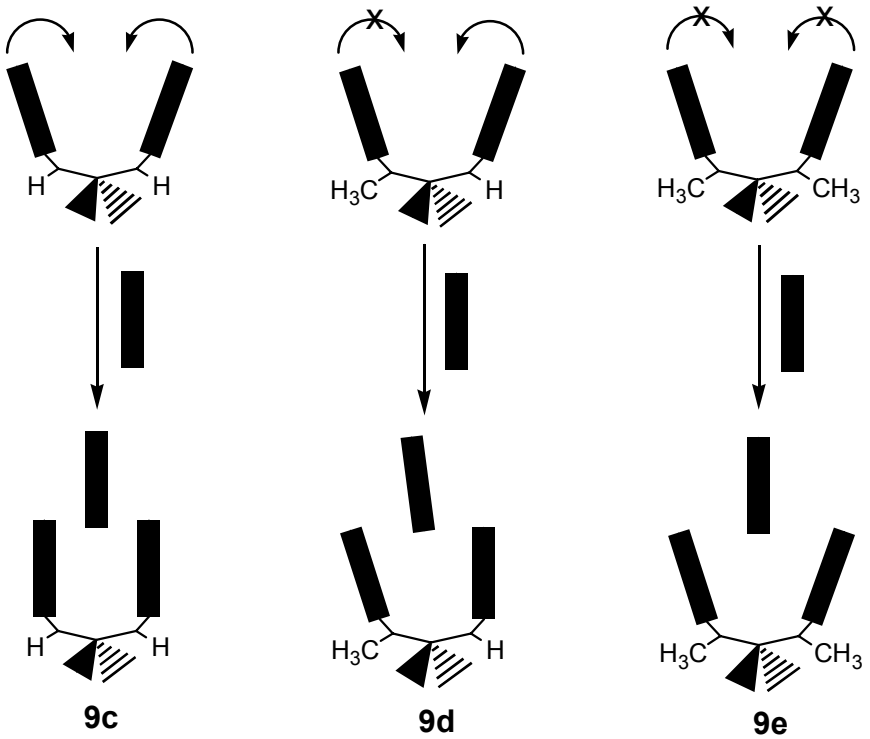


Figure 4 *Induced fit: on binding of a guest in clips **9c** and **d** the side walls adjust their position to optimize host-guest interactions. Such an adjustment does not occur in the case of **9e**.*

5.3 Structural features

To find additional support for the induced fit mechanism of guest binding the X-ray structures of clips **9a**, **9c**, **9d**, and **9f** were determined. In spite of repeated attempts it was not possible to obtain single crystals suitable for X-ray analysis for clip molecule **9e**. The structures of clips **9c** and **9d** are very similar (Figure 5). Both form dimers in the solid state, with the wall of one clip molecule being buried in the cavity of another clip. NMR dilution experiments of these clips showed that in $CDCl_3$ solution these molecules are not present as dimers ($K_{dim} < 2$ L·mol^{-1}), contrary to clips derived from

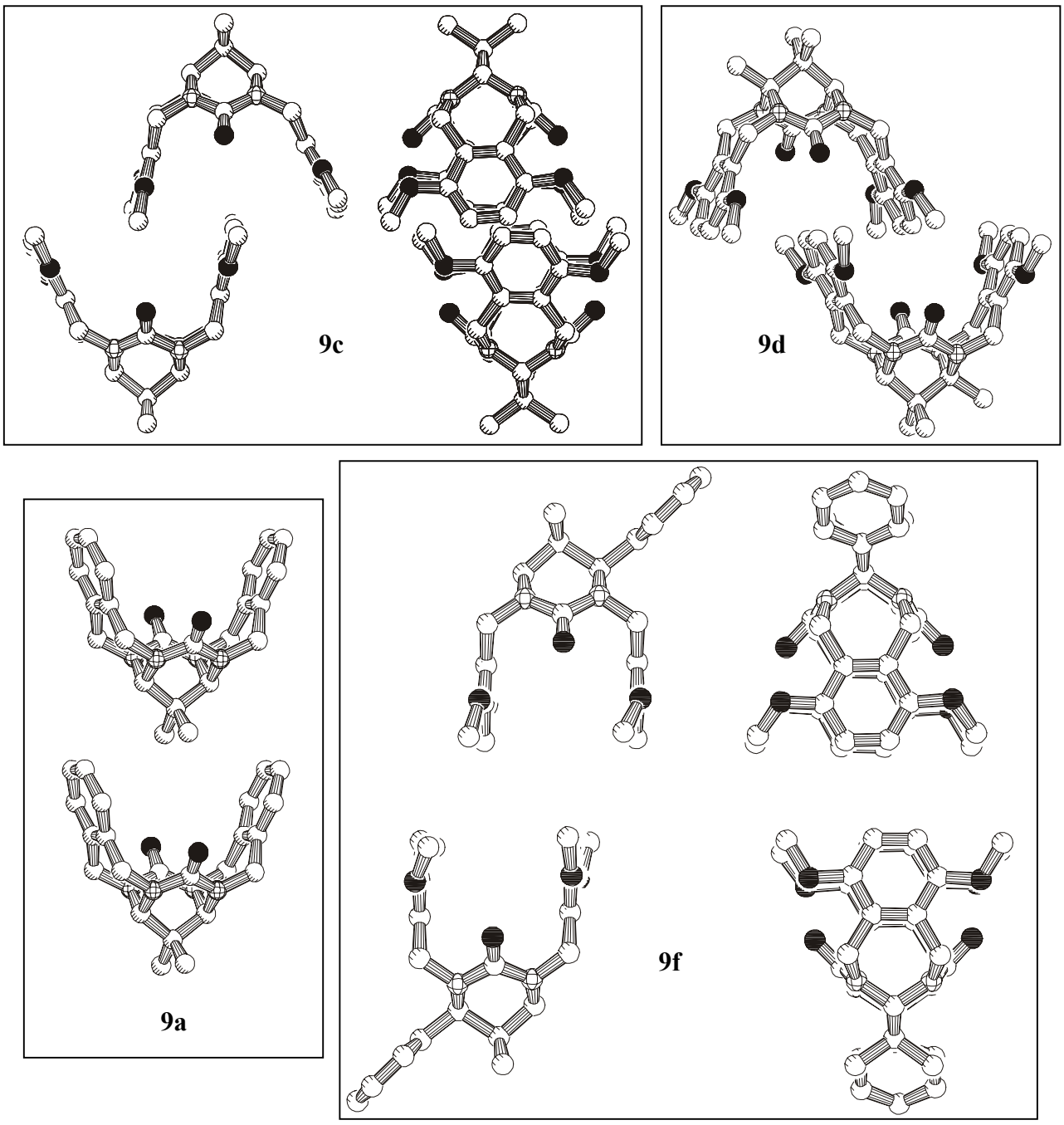


Figure 5 *Crystal structures of different host molecules:* ***9c*** *(two views),* ***9d***, ***9a***, ***9f*** *(two views). Hydrogens have been omitted for clarity. The drawings were made using the PLATON program*[12]

diphenylglycoluril.[2b] Clip molecule **9f** does not adopt a dimer geometry (Figure 5). This suggests that filling up the cavity of this clip molecule is energetically unfavorable.

Contrary to the other clips, clip molecule **9a** packs in a head-to-tail geometry. In the crystal it is present in the form of columns, in which the methyl groups at the convex side of the clips fill the cavities of other clips. Apparently, the head-to-head geometry, which is energetically favored for dimethoxybenzene-walled clips **9c** and **9d**, and also in the case of dimethoxybenzene-walled clips of the diphenylglycoluril type (**4b**), is significantly less favorable for the benzene-walled clip **9a**. The X-ray structure of **9f** indicates that the side walls of this clip are in a more parallel orientation than the side walls of clip **9c**. The distance between the centers of the aromatic side walls of clip **9f** is 4.84 Å, as opposed to 6.43 Å and 6.50 Å for clips **9c** and **9d**, respectively. Since the minimum energy contact distance between two parallel π systems is 3.42 Å, a cavity with a size two times this distance (6.84 Å) is ideal for binding of an aromatic guest.[9] It is therefore evident that on binding of a guest (or the side wall of a second clip molecule) the walls of **9f** are forced to bend outwards. This is hampered by the phenyl group under one of these side walls, resulting in a higher barrier for guest binding. This explanation is validated by the results of the binding experiments. The association constant of clip **9f** with resorcinol (**11b**) was measured to be 2800 $L \cdot mol^{-1}$, which is only 9% of the value measured for clip **9c** (K_a = 31,000 $L \cdot mol^{-1}$, Table 4). For 5-chlororesorcinol (**11d**) the binding constant was 25,000 $L \cdot mol^{-1}$, again 9% of the value measured for clip **9c** (K_a = 280,000 $L \cdot mol^{-1}$). The NMR spectra recorded during the determination of the binding constants of **9f** showed several interesting features. The pattern of the proton signals of the phenyl group under the cavity wall of **9f** changed considerably upon addition of a guest to the solution, in line with the idea that a guest bound in the cavity forces the side walls to bend outwards. When forced outward, the side wall directly above the phenyl group restricts the free rotation of this phenyl group, resulting in a splitting of the signals in the NMR spectrum. In Table 5 the CIS values of some of the protons of clip **9f** in the complex with resorcinol are listed, as well as the chemical shifts of these protons in the uncomplexed state. Upon complexation of the guest, the side walls bend away, pushing the xylylene CH_2 (B2) protons out of the shielding region of one of these side walls and the phenyl group. As a consequence a large downfield shift of +0.28 ppm results. In the case of clip molecule **9c** the side walls bend inwards upon complexation of a guest, moving the xylylene CH_2 B2 protons in their shielding zones. This results in a large upfield shift of –0.28 ppm (see also drawing in note c of Table 5).

Clip molecules of type **9** have a considerably higher affinity for resorcinol derivatives than clip molecules of type **4** (Tables 3 and 4). One of the reasons for this increased affinity is the flexibility of the side walls in the former molecules. Hosts **4** are quite rigid molecules; their xylylene CH_2 protons exhibit no CIS upon binding of a guest. The same rigidity is observed for the propanediurea derived clip molecule **9e**. However, this host still has a greater affinity for guest molecules than clips of type **4**. The CIS values of the side wall aromatic protons in the case of resorcinol as the guest are –0.60 ppm for the flexible clip **9c**, and –0.44 and –0.45 ppm for the rigid clips **9e** and **4b**, respectively. This indicates that **9e** and **4b** have a similar complexation geometry.

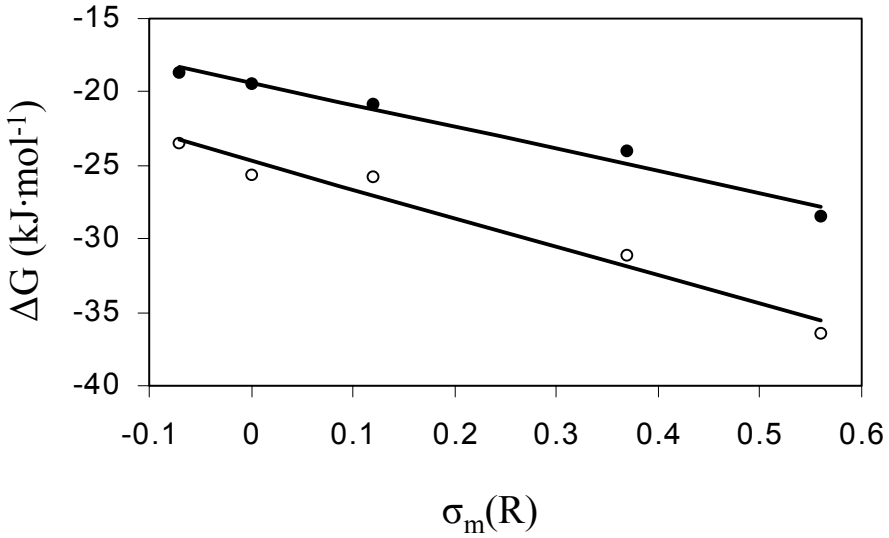


Figure 6 *Binding free energies of guests **11a-e** in clip molecules **4b** (•) and **9c** (o) plotted as a function of the Hammett parameter (σ_m(R)) of the substituent R on the guest*

For clips of type **4** it has been shown that the major contribution to guest binding comes from hydrogen bonding.[3] To investigate the relative importance of hydrogen bonding in clip **9c** we plotted the binding free energies of guests **11a-e** in **9c** and **4b** as a function of the Hammett [σ_m(R)] parameter of the substituent R of the guest (Figure 6). The plot reveals a linear correlation, for both clip **4b** and **9c**. The slopes of the plots indicate that binding of resorcinol derivatives in clip **9c** is slightly more sensitive to the substituent on the guest than binding in clip **4b**. The same observation was made in the case of clips **9a** and **4a** (Figure 2). This increase in binding as σ_m increases is the result of both an increase in the hydrogen bonding interaction and as well as an increase in the π-π stacking as the polarization of the guest increases. The increase in sensitivity of host **9c** over host **4b** (and **9a** over **4a**) can be attributed to two factors, namely a greater sensitivity of the hydrogen bonding in host **9c**,[3] and the induced fit mechanism that operates upon guest binding to **9c**. As a result of the induced fit mechanism the π-π interaction is stronger for the more polarized guests and hence the gradient is larger for **9c** than for **4b**.

Separation of the effects contributing to binding

The binding of resorcinol in the cavity molecules described here is due to three factors, namely hydrogen bonding between the phenolic OH groups and the urea carbonyl groups, π-π stacking interactions between the guest and the cavity walls, and a cavity effect.[3] By comparing the binding affinities of resorcinol for hosts **2**, **3**, **4b**, **7**, **8c**, and **9c** (Figure 7), the individual importance of these factors can be studied, both for the glycoluril based host-guest system (A), and for the propanediurea based system (B). Half clip **8c** was used instead of **8a** for solubility reasons; the binding affinities of the two half clips are assumed to be comparable.

The structures of hosts **8a** and **8b** were established by single crystal X-ray diffraction (Figure 8). The shapes of the different hosts are represented schematically in Figure 7.

Upon first glance at Figure 7, it can be seen that upon going from the hydrogen bonding receptors **2** and **7** to the monowalled hosts **3** and **8c** and then to the diwalled hosts **4b** and **9c** the ΔΔG observed for both the propanediurea host series and the diphenylglycoluril host series are very similar. This indicates that also the binding interactions in both systems are very similar. Receptors **2** and **7** can bind resorcinol on the basis of hydrogen bonding only (see Eqns. (1a) and (1b), respectively). In receptors **3** and **8c** the binding is a result of hydrogen bonding and π-π stacking interactions of one side wall with the resorcinol guest (see Eqns. (2a) and (2b), respectively). By subtracting the values in Eqns. (2a) and (2b) from the values in equations (1a) and (1b) the energies involved in π-π stacking interactions of one side wall with the resorcinol guests can be calculated (see Eqns. (4a) and (4b)). In the case of receptor molecules **4b** and **9c** the interaction energy is built up of hydrogen bonding, twice the π-π stacking interaction of the guest with one cavity wall and the cavity effect (see Eqns. (3a) and (3b)). The ΔG value attributable to the cavity effect can be calculated by subtracting twice the values in Eqns. (4a) and (4b) and the values in Eqns. (1a) and (1b) from the

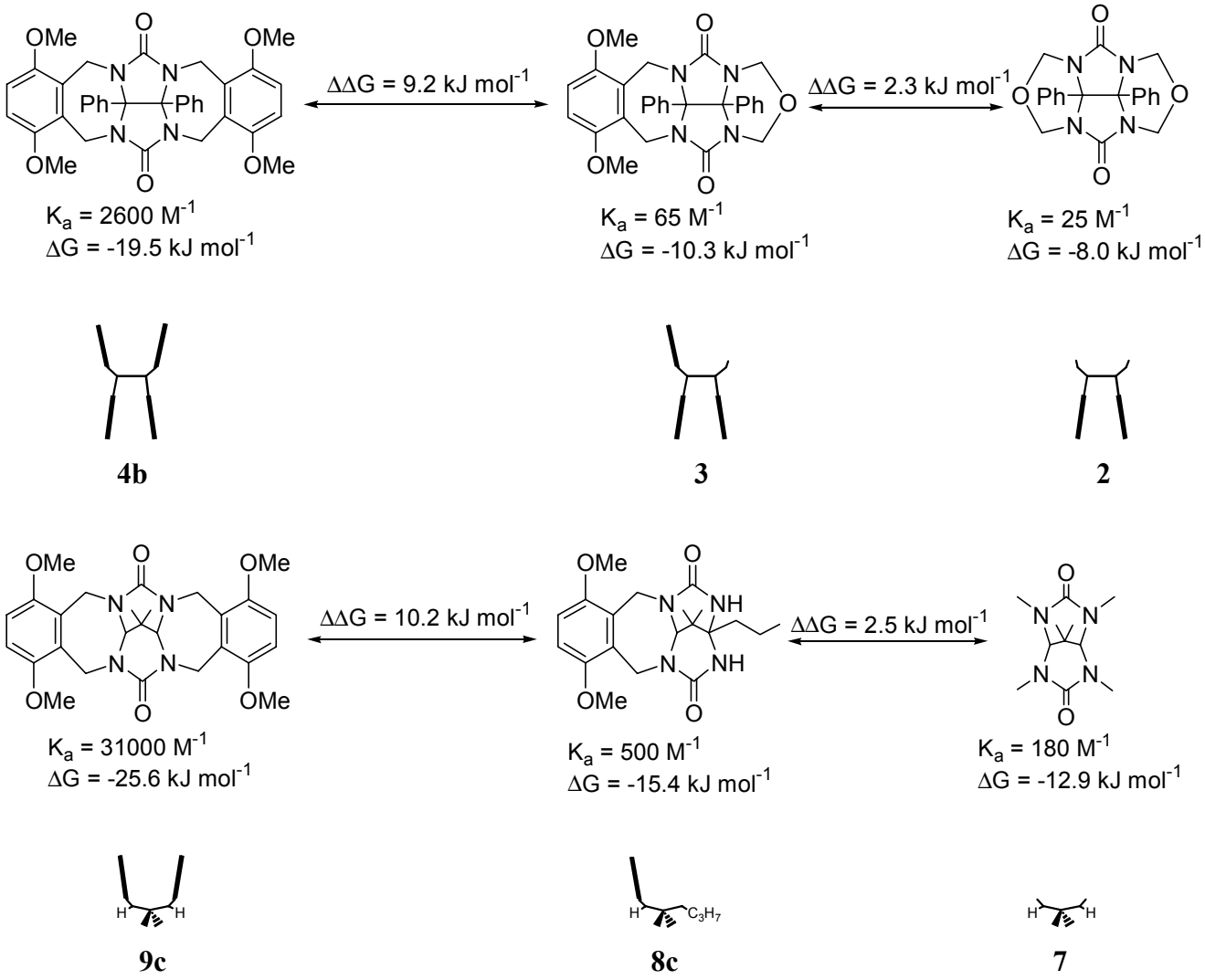


Figure 7 *Binding affinities of several host molecules for resorcinol. The shape of the hosts is indicated schematically*

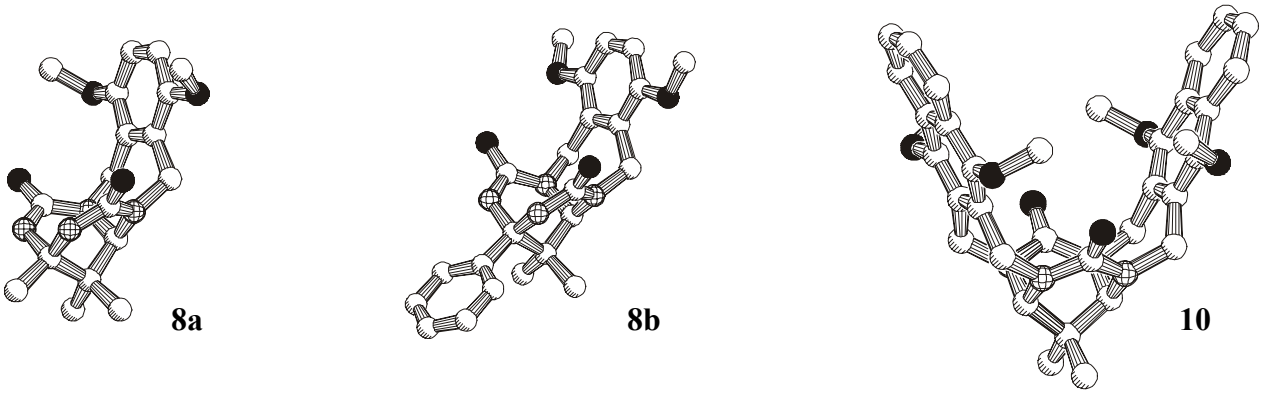


Figure 8 *Crystal structures of host molecules **8a, 8b, 10**. Hydrogens have been omitted for clarity. The drawings were made using the PLATON program*[12]

values in Eqns. (3a) and (3b) (see Eqns. (5a) and (5b)). It should be noted that the hydrogen bonding energy upon binding to **2** and **7** has a significant unfavorable entropic component. Hence subtracting equation (1) from (2) overestimates the contribution of one π-π interaction; the relative values are more an indication of the enthalpy of the π-π interaction, rather than the free energy. However, one can say that the relative effect of adding one wall and then a second one is the same for both cavities.

Equations (1a)-(5b):

Receptor **2**:	(hydrogen bonding)	$-\Delta G = 8.0$ kJ·mol^{-1}	(1a)
Receptor **7**:	(hydrogen bonding)	$-\Delta G = 12.9$ kJ·mol^{-1}	(1b)
Receptor **3**:	(hydrogen bonding + 1 × π-π interaction)	$-\Delta G = 10.3$ kJ·mol^{-1}	(2a)
Receptor **8c**:	(hydrogen bonding + 1 × π-π interaction)	$-\Delta G = 15.4$ kJ·mol^{-1}	(2b)
Receptor **4b**:	(hydrogen bonding + 2 × π-π interaction + cavity effect)	$-\Delta G = 19.5$ kJ·mol^{-1}	(3a)
Receptor **9c**:	(hydrogen bonding + 2 × π-π interaction + cavity effect)	$-\Delta G = 25.6$ kJ·mol^{-1}	(3b)
1 × π-π stacking interaction (host-guest system A)		$-\Delta G = 2.3$ kJ·mol^{-1}	(4a)
1 × π-π stacking interaction (host-guest system B)		$-\Delta G = 2.5$ kJ·mol^{-1}	(4b)
Cavity effect: (host-guest system A):		$-\Delta G = 6.9$ kJ·mol^{-1}	(5a)
Cavity effect: (host-guest system B):		$-\Delta G = 7.7$ kJ·mol^{-1}	(5b)

(Cavity effect = –ΔG for binding in clip molecule (Eqns. (3a) and (3b)) minus 2 × –ΔG for π-π interaction (Eqns. (4a) and (4b)) minus –ΔG for hydrogen bonding (Eqns. (1a) and (1b)).)

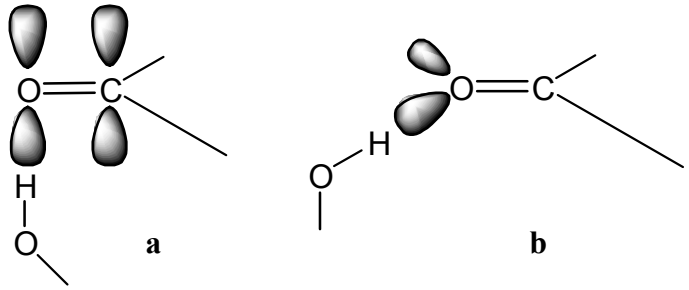


Figure 9 *Hydrogen bonding between a hydroxy group and a carbonyl group (**a**) to the π-electrons, (**b**) to the n-electrons*

By comparing Eqns. (1a)-(5a) with Eqns. (1b)-(5b) the following conclusions can be drawn with respect to the differences in binding affinity of resorcinol in clip molecules **4b** and **9c**:

(*i*) The difference in binding energies between clips of type **9** and type **4** is mainly due to hydrogen bonding interactions, which are stronger for the propanediurea hosts than for the glycoluril hosts ($\Delta\Delta G = 4.9$ kJ·mol^{-1}, see Eqns. (1a) and (1b)).

(*ii*) The π-π stacking interactions are approximately equal (see Eqns. (4a) and (4b)).

(*iii*) The cavity effects are approximately equal (see Eqns. (5a) and (5b)).

It is clear from the above analysis that the difference in hydrogen bonding is the major factor governing the increase in binding affinity for resorcinol derivatives of clip **9c** compared to clip **4b**. Therefore, we decided to investigate the differences in hydrogen bond geometry between the two host-guest complexes. A hydrogen bond with the oxygen atom of a carbonyl group can be formed with either the π-electrons (Figure 9a) or with the n-electrons (Figure 9b). Previously it was shown that in clip molecules derived from glycoluril, resorcinol forms hydrogen bonds with the π-electrons. The reason for this is that resorcinol, when bound in the cavity, forms hydrogen bonds with *both* carbonyl groups of the clip molecule, which leads to geometrical constraints.[8]

To investigate the importance of the hydrogen bonds in more detail we monitored the length of the hydrogen bonds between these clips and several guests by means of IR-spectroscopy. For compounds with comparable structural features the frequency difference between the OH vibration in the free state and in the hydrogen bonded state is a measure of the length of the hydrogen bond.[13] Experiments carried out with receptor **2** have shown that the length of the hydrogen bonds is independent of the guest and consequently of the energy involved in hydrogen bonding.[3] In the case of clip molecules of type **4b** the length is dependent on the type of guest because the binding geometry is a compromise between optimum hydrogen bonding and optimum π-π interactions: guests that form strong hydrogen bonds are pulled into the cavity in order to optimize hydrogen bonding, whereas guests that form weaker hydrogen bonds are pushed out in order to optimize π-π stacking. IR spectra of chloroform solutions of mixtures of guests and hosts showed two absorptions for the OH vibration: one for the free species and one for the hydrogen bonded complex. The measured OH vibration differences ($\Delta\nu$) were observed to be equal for clip molecules

4b and **9c** for each guest. For example, for resorcinol (**11b**) a $\Delta\nu$ = 233 cm^{-1} was measured for complexation with clip **4b**, and a $\Delta\nu$ = 239 cm^{-1} for complexation with clip **9c**. For cyanoresorcinol (**11e**) $\Delta\nu$ values of 301 cm^{-1} and 302 cm^{-1}, were measured, respectively. (The $\Delta\nu$ is larger for the latter guest because the hydrogen bond is shorter and stronger.) The very similar $\Delta\nu$ values observed for clips of type **4** and **9** indicate that for a specific guest the hydrogen bonds between the hydroxy groups and the carbonyl oxygen atoms of the clip have almost the same length in the complexes with both clip molecules. At a first glance this observed similarity seems to be contradictory to the observed differences in guest binding strength.

An additional important parameter in binding of resorcinol, however, is the distance between the oxygen atoms of the carbonyl groups of the host molecules which determines the geometry of the hydrogen bond. This distance, as determined from the X-ray structures, is 5.2 Å for clip **9c** and 5.5 Å for clip **4b**.[14] If one assumes that the hydrogen bonds are linear and have an O-H-O distance of 2.7 Å,[15] the optimal distance between the carbonyl oxygen atoms for binding of resorcinol is 3.9 Å (see Figure 10). Although both **9c** and **4b** do not approach this value the former clip molecule still is better suited for resorcinol binding than the latter clip molecule, in line with the measured binding constants.

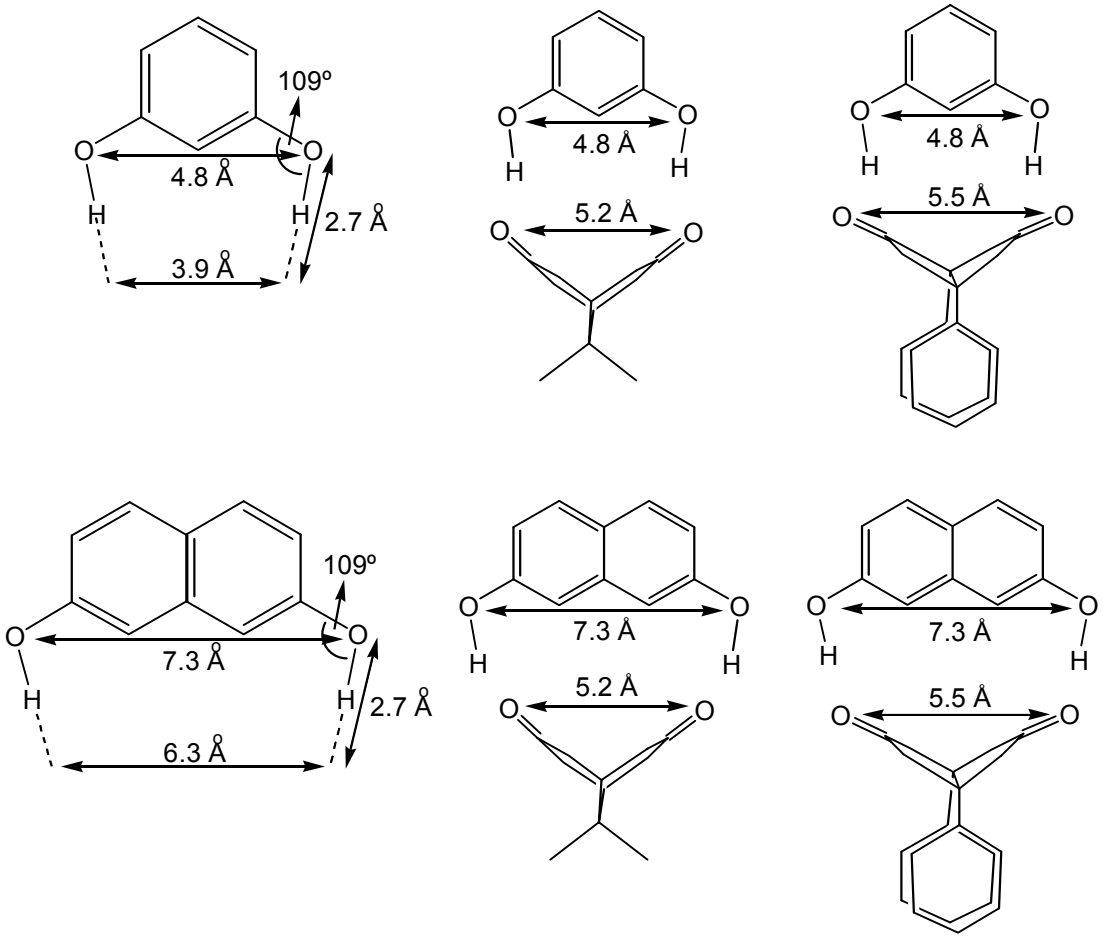
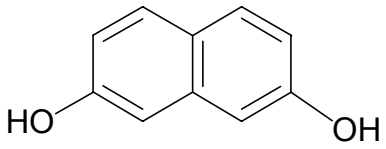


Figure 10 *Hydrogen bonding interactions between the guest molecules resorcinol (top) and 2,7-dihydroxynaphthalene (bottom) and host molecules of* ***9c*** *(middle) and* ***4b*** *(right). For clarity only the frameworks with the hydrogen bonding sites of the host molecules are shown*

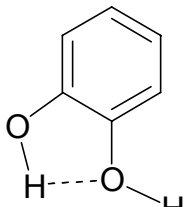
For 2,7-dihydroxynaphthalene **13**, however, the optimal distance between the carbonyl oxygen atoms is larger, *viz.* 6.3 Å. This means that host **4b** should have a higher affinity for this guest than host **9c** (see Figure 10). This could indeed be confirmed by NMR titration experiments. Host **9c** binds 2,7-dihydroxynaphthalene with an association constant of $K_a = 2300 \pm 200$ L·mol^{-1}, whereas for host **4b** the association constant is $K_a = 7100 \pm 500$ L·mol^{-1}.[8] We also measured the binding affinities of **9c** and **4b** for catechol (Chart 2). The association constants amounted to $K_a = 130 \pm 15$ L·mol^{-1} and $K_a = 60 \pm 10$ L·mol^{-1}, respectively. These low numbers indicate that the two clips are not very well equipped to complex this guest. Catechol forms an intramolecular hydrogen bond that needs to be broken to allow formation of two hydrogen bonds between this guest and the urea carbonyl groups of the clips. Nevertheless, clip **9c** is slightly better suited than clip **4b** for complexation of this guest.

It has been previously shown that resorcinol binds in an asymmetric geometry in a clip that possesses only one hydrogen bond acceptor group.[3] It is assumed that in clips with two hydrogen bond acceptor groups resorcinol cannot form two perfect hydrogen bonds simultaneously because of the geometry of the host carbonyl groups. We postulate given the experimental evidence that in hosts of type **9** the hydrogen bond geometry is closer to the optimum than for hosts of type **4** and hence stronger hydrogen bonding occurs. It is quite remarkable that such slight sub-atomic changes in geometry can induce such significant increases in binding.

Chart 2



13



14

5.4 Binding properties of a clip with 'high' naphthalene side walls

The association constant of the complex between naphthalene clip molecule **10** and resorcinol was found to be very low (<10 L·mol^{-1}) and could not be determined accurately. A more precise value of 80 ± 10 L·mol^{-1} was measured using 5-chlororesorcinol (**11d**) as the guest. These numbers are similar to those measured for the diphenylglycoluril derived counterpart **5**.[16] The dramatic decrease in binding affinities of a clip with 1,4-dimethoxynaphthalene side walls as compared to a clip with 1,4-dimethoxybenzene side walls has previously been explained and is the result of significantly reduced and even repulsive π-π interactions and the improper orientation of the methoxy groups by which the cavity is partly blocked.[3,16] The X-ray structure determination of **10** (Figure 8) showed that this molecule has the same structure with respect to the cavity side walls as its diphenylglycoluril derived counterpart.[16]

5.5 Co-crystallization of resorcinol with a propanediurea host

To gain more insight into the mode of binding of resorcinol in molecular clips we tried to grow crystals of host-guest complexes. We did not obtain crystals suitable for X-ray analysis of clips or half clips with resorcinol derivatives. It was nevertheless possible to co-crystallize resorcinol with the concave molecule 2,4,6,8,9,9-hexamethylpropanediurea (**7**) by slow evaporation of a chloroform solution containing the two compounds in a 1:1 ratio. The crystals, however, contained resorcinol and **7** in a 3:2 ratio. The unit cell contains eight molecules of **7** and twelve resorcinol molecules. One of the (symmetry independent) resorcinol molecules is lying on an inversion center. As a consequence this molecule is disordered over two positions. The two possible orientations could be refined using a disorder model. In both orientations there is a hydrogen bridge between the hydroxy groups and a carbonyl of two different molecules of **7**. The other (symmetry independent) resorcinol molecule is also disordered over two positions. The two possible orientations could also be refined using a disorder model. Also here, in both orientations there is a hydrogen bridge between the hydroxy groups and the carbonyl of two different molecules of **7**. In Figure 11 the two

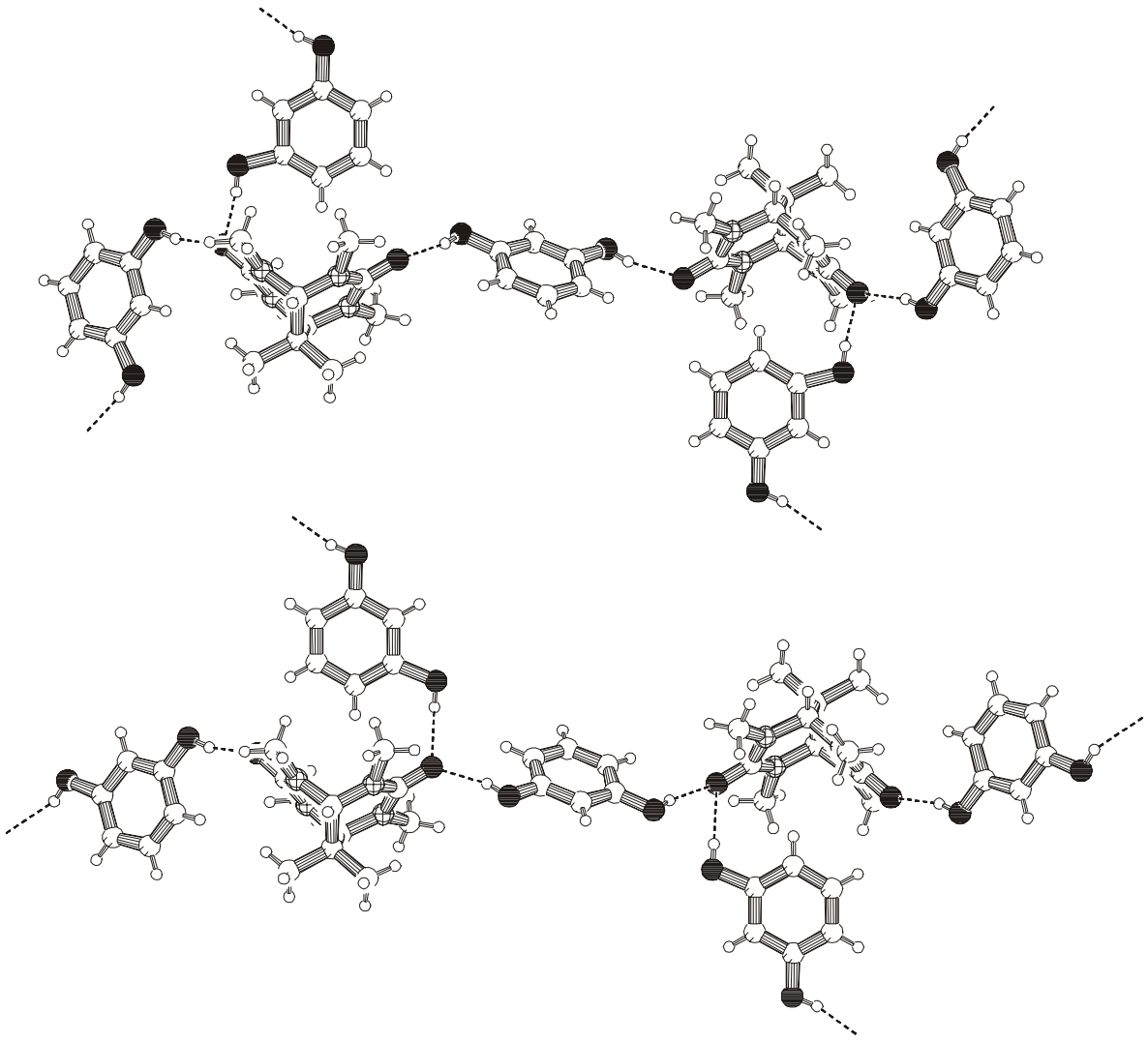


Figure 11 *Co-crystal of resorcinol and 7. The drawings were made using the PLATON program*[12]

possible situations for the stacking of **7** and resorcinol are shown together with the hydrogen bonding pattern. Interactions in the crystal include hydrogen bonds between both the carbonyl π-electrons and n-electrons and the resorcinol OH hydrogens (as opposed to complexation of resorcinol in clip molecules, in which case only the carbonyl π-electrons are involved in hydrogen bonding), but a resorcinol residue never forms two simultaneous hydrogen bonds with one propanediurea residue. This suggests that the geometry of **7** deviates from the ideal geometry for a 1:1 complex with resorcinol.

5.6 Conclusions

The binding properties of a series of new receptors derived from propanediurea have been studied in detail and have been compared to those of previously developed clip molecules derived from diphenylglycoluril. The enhanced binding properties of the new hosts can be accounted for by the smaller distance between the hydrogen bond acceptor sites in these clip molecules and an induced fit mechanism of binding. Although the differences in geometry between clips of type **4** and **9** are sub-ångstrøm (~0.3 Å), the effect on the binding properties is very large, highlighting the unexpected features one encounters in constructing an ideal host. It was found that the affinity of the propanediurea receptors for resorcinol could be fine-tuned by introducing substituents under the side walls of the molecules.
Host **9c** is able to bind guests by an induced fit mechanism, optimizing the host-guest interactions. The new propanediurea hosts clearly prove that a combination of flexibility and good host-guest complementarity results in host molecules that bind guests exceptionally strongly.

5.7 Experimental section

Compounds: Compounds **4a**,**b**[14b] and **7**[17] are accessible using literature procedures. Compounds **8a-c**, **9a-f**, and **10** were prepared as described in Chapter 4.

Determination of association constants by NMR:

In the equilibrium

$$H + G \rightleftharpoons HG \qquad (6)$$

the association constant K_a between host H and guest G is defined as:

$$K_a = \frac{[HG]}{[H][G]} \qquad (7)$$

in which [H], [G] and [HG] are the equilibrium concentrations of host, guest and 1:1 host-guest complex, respectively. (In this discussion the activity coefficients are assumed to be equal to unity. This means that the solutions are treated as if they were ideal solutions.)

If the exchange in Eqn. (6) is very slow on the NMR timescale and the separate observation of the signals for free and complexed compounds is possible, the association constant can in principle be determined from a single NMR experiment. If the exchange is fast, the observed chemical shift of a proton signal is the concentration-weighted average of the shift of this proton in the complexed and in the free state. For this case the following expression can be derived for the observed chemical shift δ_{obs}:

$$\delta_{obs} = \delta_{H0} + \frac{\Delta\delta_{H(lim)}}{2[H^0]}\left\{[H^0]+[G^0]+\frac{1}{K_a}-\left[\left([H^0]+[G^0]+\frac{1}{K_a}\right)^2-4[H^0][G^0]\right]^{\frac{1}{2}}\right\} \qquad (8)$$

in which $\Delta\delta_{H(lim)} = \delta_H0 - \delta_{HG}$; (the CIS value), δ_H0 is the chemical shift of the probe proton in the uncomplexed state, δ_{HG} is the chemical shift of the probe proton in the HG complex, $[H^0] = [H] + [HG]$, $[G^0] = [G] + [HG]$, and K_a is the association constant. A titration experiment gives a series of $[H^0]$, $[G^0]$, and δ_{obs}. The remaining unknown parameters $\Delta\delta_{H(lim)}$ and K_a can be determined using a nonlinear curve fitting method that is implemented in various software packages.

Titration experiments were carried out with 10 to 12 samples. A 0.5-1 mM stock solution A of the host in $CDCl_3$ was prepared. Half of this stock solution was used to prepare a second stock solution B containing 0.5-1 mM of the host and 5-10 mM of the guest. Different aliquots of the two stock solutions A and B were mixed to a total volume of 0.6 ml. The samples were measured on 200, 300 or 400 MHz spectrometers at 298 K. Indicated errors in the reported K_a values are estimations based on weighing errors in the sample preparations, which are generally larger than the errors from the fit procedure.

Monte Carlo simulations carried out by Granot[18] indicate that with the concentrations we used results become increasingly inaccurate for K_a values larger than 4000 $L \cdot mol^{-1}$. We found that titration curves of complexes with estimated K_a values over 10^5 $L \cdot mol^{-1}$ could not be fitted to Eqn. (8). Since the association constants for the clips described in this chapter with resorcinol derivatives are generally much larger than 10^4 $L \cdot mol^{-1}$ we used competition experiments for the determination of these K_a values, according to the method described by Alper.[19] This method consists of a three-component system in which two hosts compete for one guest. The relative association constant is defined as:

$$K_{rel} = \frac{K_a}{K_R} = \frac{[HG][R]}{[RG][H]} \qquad (9)$$

in which K_a is the association constant for the complex between host H and guest G, and K_R is the association constant between reference host R and guest G. For K_{rel} the following expression can be derived:[19]

$$K_{rel} = \left[\frac{\Delta\delta_H}{\Delta\delta_{H(lim)} - \Delta\delta_H} \right] \left[\frac{\Delta\delta_{R(lim)} - \Delta\delta_R}{\Delta\delta_R} \right] \qquad (10)$$

in which $\Delta\delta_H$ and $\Delta\delta_R$ are the observed chemical shifts of the probe protons of hosts H and R, respectively, and $\Delta\delta_{H(lim)}$ and $\Delta\delta_{R(lim)}$ the shifts of these protons in the fully complexed state (CIS values). This expression shows that from titration data obtained at various concentrations of H, R, and G, the relative association constant K_{rel} and the complexation induced shift $\Delta\delta_{H(lim)}$ can be determined if $\Delta\delta_{R(lim)}$ is known. We used a grid search in the (K_{rel}, $\Delta\delta_{H(lim)}$) plane to minimize the difference between observed and calculated shifts.

The method of determination of relative binding constants by means of a competition experiment has several advantages compared to the standard host-guest titration experiment described above. Most importantly, it allows for the determination of very high association constants that cannot be determined by standard NMR titrations. Secondly, the initial concentrations of the different components do not appear in Eqn. (10). This implies that it is not necessary to determine these concentrations. This method is therefore very fast. Related to this is the fact that a high degree of accuracy can be reached, since only δ values appear in the expression used to calculate K_{rel} and $\Delta\delta_{H(lim)}$ values. Consequently systematic and random uncertainties in these values represent the only sources of error in the output K_{rel} and $\Delta\delta_{H(lim)}$ values. These uncertainties are much smaller than the weighing errors in the concentration of the stock solutions used in the standard NMR titration experiment. Furthermore, Alper and co-workers showed that the K_{rel} obtained is not affected by the presence of impurities.[19] The hosts and guests that we use do not self-associate, so errors are not introduced by these factors either. Although the *absolute* association constant of a complex HG that is determined using this procedure logically has a lower degree of accuracy than the reference association constant of a complex RG, the *relative* association constant K_{rel} can be determined very accurately. This method is therefore very useful when comparing the affinity of two hosts for a certain guest molecule. If this affinity is similar, as is the case for clip molecules **9c**,**d**, and **e**, comparison of the binding constants determined by standard titrations is impossible because of the relatively large error margins. Direct competition experiments do allow for reliable comparison.

Competition experiments were carried out with 10 to 12 samples. A stock solution of the guest in $CDCl_3$ was prepared. From this stock solution two new stock solutions were prepared: one containing host H and one containing host R. The concentrations of all components of the stock solutions were approximately 1 mM. Different aliquots of these two stock solutions were mixed to a total volume of 0.6 ml and measured at 298 K on a 300 MHz spectrometer. Indicated errors in the

reported K_a values are estimations based on the fact that the error in an association constant determined by this method is always slightly larger than the error in the reference value.

X-ray analysis

Single crystals suitable for X-ray analysis were obtained in the following ways: **7**·(resorcinol)$_{1.5}$: slow evaporation of a chloroform solution containing **7** and resorcinol in a 1:1 ratio. **8a**: slow diffusion of diethyl ether in a MeOH/$CHCl_3$ solution of the compound. **8b**: slow diffusion of hexane in a MeOH/CH_2Cl_2 solution of the compound, followed by slow evaporation. **9a**: slow diffusion of hexane in a $CHCl_3$ solution of the compound. **9c**: slow diffusion of diethyl ether in a CH_2Cl_2 solution of the compound. **9d**: vapor diffusion using acetone/$CHCl_3$ as the solvent and diethyl ether as the precipitant. **9f**: slow diffusion of hexane/acetone in a CH_2Cl_2 solution of the compound. **10**: slow diffusion of hexane in a CH_2Cl_2 solution of the compound.
Single crystals were mounted in air on glass fibers. Intensity data were collected at room temperature, except for **9a**, **9f**, and the co-crystal of **7** with resorcinol, which were measured at –65ºC. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Cu-Kα radiation, ω-2θ scan mode (ω scan mode was used for **9a**). For **9c**, **9d**, **9f**, and **7**·(resorcinol)$_{1.5}$ unit cell dimensions were determined from the angular setting of 25 reflections. For **9a**, **10**, **8a** and **8b** the unit cell dimensions were determined from 23, 16, 17 and 15 reflections respectively. Intensity data were corrected for Lorentz and polarization effects and semi-empirical absorption correction (ψ-scans)[20] was applied, except for **9a** and **9c** for which no absorption correction was applied. The structures were solved by the program CRUNCH[21] and were refined with standard methods (refinement against F^2 of all reflections with SHELXL97[22]) with anisotropic parameters for the non-hydrogen atoms.
Treatment of the hydrogens and comments on the refinement:
9a: All hydrogens were placed at calculated positions. The reflection data proved to be of very low quality resulting in high R-factors.
9c: The hydrogen atoms of the methyl groups were refined as rigid rotors to match maximum electron density in a difference Fourier map. All other hydrogens were initially placed at calculated positions and were subsequently freely refined.
10: The hydrogen atoms of the methyl groups at the convex side were refined as rigid rotors to match maximum electron density in a difference Fourier map. The hydrogens of the dichloromethane molecule were placed at calculated positions and were refined riding on the parent atoms. All other hydrogens were initially placed at calculated positions and were freely refined subsequently. The solvent molecule (dichloromethane) is disordered over two positions.
8b/**9d**: The hydrogen atoms of the methyl groups were refined as rigid rotors to match maximum electron density in a difference Fourier map. All other hydrogens were placed at calculated positions and were refined riding on the parent atoms. The methyl group at the 1-position is disordered over two positions.
9f: All hydrogens were initially placed at calculated positions and were subsequently freely refined.

8a: The hydrogen atoms of the methoxy groups and the methyl group at the 1-position were refined as rigid rotors to match maximum electron density in a difference Fourier map. All other hydrogens were initially placed at calculated positions and were subsequently freely refined. The SQUEEZE procedure of the PLATON program[23] was used to correct for disordered solvent. A void at 0.192, 0.250, 0.877 with a volume of 64 $Å^3$ and an electron count of 16, indicated that a methanol molecule co-crystallized (methanol was one of the solvents used during the crystallization procedure).

7·(resorcinol)$_{1.5}$: All hydrogens were placed at calculated positions. The hydrogens of the hydroxy groups of the resorcinol molecules were placed in the plane of the aromatic ring and their position was determined by the best hydrogen bond that can be created.

Details of the data collection and structure determinations are collected in Tables 7a, 7b, and 7c.

Table 7a *Crystal data and structure refinement for* ***8a***, ***8b***, *and* ***9a***

Compound	**8a**	**8b**	**9a**
Crystal color	transparent colorless	transparent colorless	transparent colorless
Crystal shape	regular platelet	regular lump	regular thick needle
Crystal size (mm)	0.44 × 0.29 × 0.06	0.43 × 0.37 × 0.23	0.31 × 0.15 × 0.14
Empirical formula	$C_{19}H_{28}N_4O_5$	$C_{25}H_{34}N_4O_6$	$C_{23}H_{24}N_4O_2$
Formula weight	392.45	486.56	388.46
Temperature (K)	293(2)	293(2)	208(2)
Radiation (graphite mon.)	CuKα	CuKα	CuKα
Wavelength (Å)	1.54184	1.54184	1.54184
Crystal system, space group	Orthorhombic, Pcmn	Orthorhombic, Pbca	Monoclinic, P21/n
Unit cell # reflections, θ range (°)	17, 7.561 to 42.466	15, 15.530 to 22.664	23, 22.255 to 39.618
a (Å)	6.9032(4)	10.1709(9)	15.344(7)
b (Å)	11.0564(6)	21.756(2)	8.0896(10)
c (Å)	24.9579(11)	23.354(5)	15.416(6)
α (°)	90	90	90
β (°)	90	90	104.535(17)
γ (°)	90	90	90
Volume ($Å^3$)	1904.92(17)	5167.9(13)	1852.3(11)
Z, Calc. density ($Mg·m^{-3}$)	4, 1.368	8, 1.251	4, 1.393
Abs. coefficient (mm^{-1})	0.827	0.741	0.731
Scan	ω-2θ	ω-2θ	ω
F(000)	840	2080	824
θ range for data collection (°)	3.54 to 69.91	3.79 to 69.94	5.93 to 70.87
Index ranges	−8≤h≤0 −13≤k≤0 0≤l≤30	0≤h≤12 0≤k≤26 0≤l≤28	0≤h≤18 0≤k≤5 −18≤l≤18
Refl. collected / unique [R_{int}]	1911 / 1911	4900 / 4900	2205 / 2137 [0.1545]
Refl. observed ([Io>2σ(Io)])	1421	2391	922
Abs. corr.	Semi-emp. ψ-scan	Semi-emp. ψ-scan	None
Range of rel. transm. factors	1.277 and 0.938	1.416 and 0.797	-
Data / restraints / parameters	1911 / 9 / 157	4900 / 0 / 324	2137 / 466 / 263
Goodness-of-fit on F^2	1.071	1.020	2.341
SHELXL-97 weight param.	0.0722, 0.7694	0.1603, 1.1661	0.2000, 0.0000
Final R1, wR2 [I>2σ(I)]	0.0516, 0.1380	0.0951, 0.2433	0.2311, 0.5934
R1, wR2 (all data)	0.0690, 0.1479	0.1707, 0.2993	0.2988, 0.6240
Diff. peak and hole ($e·Å^{-3}$)	0.417 and −0.386	0.386 and −0.279	1.289 and −0.932

Table 7b *Crystal data and structure refinement for* ***9c****,* ***9d****, and* ***9f***

Compound	**9c**	**9d**	**9f**
Crystal color	transparent colorless	transparent colorless	transparent colorless
Crystal shape	regular	regular platelet	regular fragment
Crystal size (mm)	0.29 × 0.19 × 0.16	0.23 × 0.12 × 0.04	0.42 × 0.19 × 0.12
Empirical formula	$C_{27}H_{32}N_4O_6$	$C_{29}H_{35}Cl_3N_4O_6$	$C_{33}H_{36}N_4O_6$
Formula weight	508.57	641.96	584.66
Temperature (K)	293(2)	293(2)	208(2)
Radiation (graphite mon.)	CuKα	CuKα	CuKα
Wavelength (Å)	1.54184	1.54184	1.54184
Crystal system, space group	Monoclinic, $P2_1/a$	Triclinic, P-1	Monoclinic, $P2_1/a$
Unit cell # reflections, θ range (°)	25, 21.865 to 23.107	25, 13.285 to 23.864	25, 40.265 to 46.252
a (Å)	11.760(2)	10.3870(9)	10.73079(18)
b (Å)	15.300(3)	12.1100(12)	20.7040(4)
c (Å)	14.574(7)	13.7603(18)	13.2490(3)
α (°)	90	110.744(13)	90
β (°)	106.849(12)	110.217(15)	97.5144(18)
γ (°)	90	92.383(18)	90
Volume ($Å^3$)	2509.7(14)	1492.2(3)	2918.24(10)
Z, Calc. density ($Mg·m^{-3}$)	4, 1.346	2, 1.429	4, 1.331
Abs. coefficient (mm^{-1})	0.791	3.199	0.755
Scan	ω-2θ	ω-2θ	ω-2θ
F(000)	1080	672	1240
θ range for data collection (°)	3.17 to 62.19	3.72 to 70.13	3.36 to 69.97
Index ranges	0≤h≤13 0≤k≤17 −16≤l≤16	0≤h≤12 −14≤k≤14 −16≤l≤15	0≤h≤13 0≤k≤25 −16≤l≤16
Refl. collected / unique [R_{int}]	4186 / 3967 [0.0098]	5995 / 5661 [0.0768]	5830 / 5520 [0.0129]
Refl. observed ([Io>2σ(Io)])	3267	1296	4496
Abs. corr.	None	Semi-emp. ψ-scan	Semi-emp. ψ-scan
Range of rel. transm. factors	-	1.057 and 0.935	1.019 and 0.987
Data / restraints / parameters	3967 / 0 / 394	5661 / 0 / 397	5520 / 0 / 532
Goodness-of-fit on F^2	1.063	0.978	1.066
SHELXL-97 weight param.	0.1294, 1.2476	0.0717, 0.0000	0.0451, 1.0185
Final R1, wR2 [I>2σ(I)]	0.0549, 0.1863	0.1084, 0.1744	0.0412, 0.0989
R1, wR2 (all data)	0.0654, 0.1991	0.3727, 0.2698	0.0532, 0.1062
Diff. peak and hole ($e·Å^{-3}$)	0.377 and −0.238	0.294 and −0.248	0.228 and −0.233

Table 7c *Crystal data and structure refinement for **10** and **7**·(resorcinol)$_{1.5}$*

Compound	**10**	(**7**)·(resorcinol)$_{1.5}$
Crystal color	transparent colorless	transparent colorless
Crystal shape	regular rod	irregular fragment
Crystal size (mm)	$0.28 \times 0.11 \times 0.11$	$0.42 \times 0.25 \times 0.19$
Empirical formula	$C_{36}H_{38}Cl_2N_4O_6$	$C_{20}H_{29}N_4O_5$
Formula weight	693.60	405.47
Temperature (K)	293(2)	208(2)
Radiation (graphite mon.)	CuKα	CuKα
Wavelength (Å)	1.54184	1.54184
Crystal system, space group	Orthorhombic, Pnam	Orthorhombic, Pbca
Unit cell # reflections, θ range (°)	16, 20.429 to 44.283	25, 40.108 to 46.512
a (Å)	13.1145(18)	13.1240(3)
b (Å)	14.9866(11)	14.6840(4)
c (Å)	17.6524(8)	21.7886(5)
α (°)	90	90
β (°)	90	90
γ (°)	90	90
Volume (Å^3)	3469.4(6)	4198.97(17)
Z, Calc. density (Mg·m^{-3})	4, 1.328	8, 1.283
Abs. coefficient (mm^{-1})	2.105	0.768
Scan	ω-2θ	ω-2θ
F(000)	1456	1736
θ range for data collection (°)	3.87 to 69.96	4.06 to 70.00
Index ranges	−15≤h≤0 −18≤k≤0 −21≤l≤0	−15≤h≤0 −17≤k≤0 0≤l≤26
Refl. collected / unique [R_{int}]	3405 / 3405	3965 / 3965
Refl. observed ([Io>2σ(Io)])	1864	2983
Abs. corr.	Semi-emp. ψ-scan	Semi-emp. ψ-scan
Range of rel. transm. factors	1.053 and 0.948	1.026 and 0.942
Data / restraints / parameters	3405 / 18 / 297	3965 / 0 / 288
Goodness-of-fit on F^2	1.020	1.279
SHELXL-97 weight param.	0.0962, 1.3156	0.2000
Final R1, wR2 [I>2σ(I)]	0.0662, 0.1651	0.1104, 0.2852
R1, wR2 (all data)	0.1266, 0.2041	0.1288, 0.3150
Diff. peak and hole (e·Å^{-3})	0.358 and −0.445	1.086 and −0.551

5.8 References

1 (a) For an overview see: Lehn, J.-M. *Comprehensive Supramolecular Chemistry*, Elsevier Science Ltd., Oxford, **1996**, Vol. 2; for work on other cleft and tweezer-shaped molecules, see: (b) Harmata, M.; Barnes, C.L.; Rao Karra, S.; Elahmad, S. *J. Am. Chem. Soc.* **1994**, *116*, 8392; (c) Kurebayashi, H.; Fukazawa, Y. *Chem. Lett.* **2000**, 530; (d) Klärner, F.-G.;

Burkert, U.; Kamieth, M.; Boese, R.; Benet-Buchholz, J. *Chem. Eur. J.* **1999**, *5*, 1700; (e) Kamieth, M.; Burkert, U.; Corbin, P.S.; Dell, S.J.; Zimmerman, S.C.; Klärner, F.-G. *Eur. J. Org. Chem.* **1999**, 2741; (f) Fleischhauer, J.; Harmata, M.; Kahraman, M.; Koslowski, A.; Welch, C.J. *Tetrahedron Lett.* **1997**, *38*, 8655.

2 (a) Sijbesma, R.P.; Nolte, R.J.M. *Top. Curr. Chem.*, Ed. E. Weber, **1995**, *179*, 25; (b) Rowan, A.E.; Elemans, J.A.A.W.; Nolte, R.J.M. *Acc. Chem. Res.* **1999**, *32*, 995.

3 Reek, J.N.H.; Priem, A.H.; Engelkamp, H.; Rowan, A.E.; Elemans, J.A.A.W.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1997**, *119*, 9956

4 (a) Reek, J.N.H.; Engelkamp, H.; Rowan, A.E.; Elemans, J.A.A.W.; Nolte, R.J.M. *Chem. Eur. J.* **1998**, *4*, 716; (b) Sijbesma, R.P.; Wijmenga, S.S.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1992**, *114*, 9807; (c) Sijbesma, R.P.; Nolte, R.J.M. *J. Phys. Org. Chem.* **1992**, *5*, 649; (d) Sijbesma, R.P.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1991**, *113*, 6695.

5 Reek, J.N.H.; Kros, A.; Nolte, R.J.M. *Chem. Commun.* **1996**, 245.

6 Holder, S.J.; Elemans, J.A.A.W.; Barberá, J.; Rowan, A.E.; Nolte, R.J.M. *Chem. Commun.* **2000**, 355.

7 Elemans, J.A.A.W.; De Gelder, R.; Rowan, A.E.; Nolte, R.J.M. *Chem. Commun.* **1998**, 1553.

8 Sijbesma, R.P.; Kentgens, A.P.M.; Lutz, E.T.G.; Van der Maas, J.H.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1993**, *115*, 8999.

9 Whitlock, B.J.; Whitlock, H.W. *J. Am. Chem. Soc.* **1994**, *116*, 2301.

10 Within the experimental error, the association constants of the complexes between host **9b** and resorcinol derivatives are the same as those of the complexes between host **9a** and these guests.

11 Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* **1991**, *91*, 165.

12 Spek, A.L. PLATON. A Multipurpose Crystallographic Tool; *Utrecht University*, Utrecht, The Netherlands, **2001**.

13 Hadži, D.; Bratos, S. in *The Hydrogen Bond* (Eds.: P. Schuster, G. Zundel, C. Sandorfy), North Holland Publishing Company, Amsterdam, New York, Oxford, **1976**, Vol II, pp. 565-611.

14 (a) Sijbesma, R.P.; Kentgens, A.P.M.; Nolte, R.J.M. *J. Org. Chem.* **1991**, *56*, 3199; (b) Sijbesma, R.P.; Nolte, R.J.M. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 643.

15 Olovsson, I.; Jönsson P.-G. in *The Hydrogen Bond* (Eds.: Schuster, P.; Zundel, G.; Sandorfy, C.), North Holland Publishing Company, Amsterdam, New York, Oxford, **1976**, Vol II, pp. 393-456.

16 Sijbesma, R.P.; Bosman, W.P.; Nolte, R.J.M. *J. Chem. Soc., Chem. Commun.* **1991**, 885.

17 Eres'ko, V.A.; Epishina, L.V.; Lebedev, O.V.; Khmel'nitskii, L.I.; Novikov, S.S.; Povstyanoi, M.V.; Kulik, A.F. *Bull. Acad. Sci. USSR, Chem. Ser.* **1978**, *5*, 1073.

18 Granot, J. *J. Magn. Reson.* **1983**, *55*, 216.

19 Alper, J.S., Gelb, R.I., Laufer, D.A., Schwartz, L.M. *Anal. Chim. Acta* **1989**, *220*, 171.

20 North, A.C.T.; Philips, D.C.; Mathews, F.S. *Acta Crystallogr.* **1968**, *A24*, 351.

21 Gelder, R. de; Graaff, R.A.G. de; Schenk, H. *Acta Crystallogr.* **1993**, *A49*, 287.

22 Sheldrick, G.M. SHELXL-97. Program for the refinement of crystal structures; *University of Gottingen*: Germany, **1997**.

23 Spek, A.L. *Acta Crystallogr.* **1990**, *A46*, C-34.

6 Porphyrin Arrays from Molecular Clip Building Blocks

6.1 Introduction

Solar energy conversion in Nature, such as that effected by photosynthetic bacteria, is a process of both great importance and great complexity. It begins with the capture of a photon by a porphyrin array, followed by rapid and efficient transfer of the trapped energy to a reaction center.[1] Research towards the understanding of the factors governing these processes has been booming since the publication of the crystal structure of an integral membrane light-harvesting complex (LH2) from a photosynthetic bacterium.[2] This complex consists of two concentric cylinders of helical protein subunits and a ring of eighteen overlapping porphyrin (bacteriochlorophyll *a*) residues sandwiched between the helices. A further nine porphyrins are positioned between the outer helices (see Figure 1). This is the system that traps the sunlight, thus starting the cascade of events that ultimately leads to the conversion of water and CO_2 to glucose.[1,2]

The importance of these assemblies in Nature has inspired considerable interest in the synthesis of porphyrin arrays. Traditional synthetic methods of covalently linking porphyrins or multi-porphyrin building blocks have resulted in a variety of porphyrin oligomers. However, these synthetic strategies have proven to be quite limiting. They frequently involve large numbers of sequential steps, separation of statistical mixtures, and extensive chromatographic purification, resulting in low overall yields. Some relatively easy preparations include a porphyrin hexamer **3**, synthesized by the coupling of six porphyrins to a central benzene core via ether linkages (Chart 1),[3] and a porphyrin dimer, trimer, and tetramer **2**, synthesized by oxidative

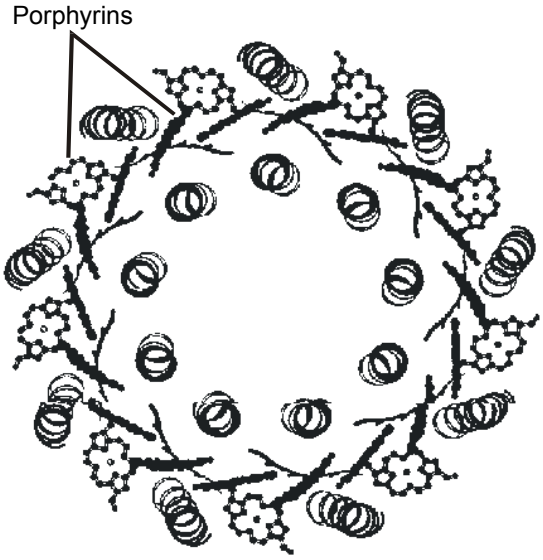
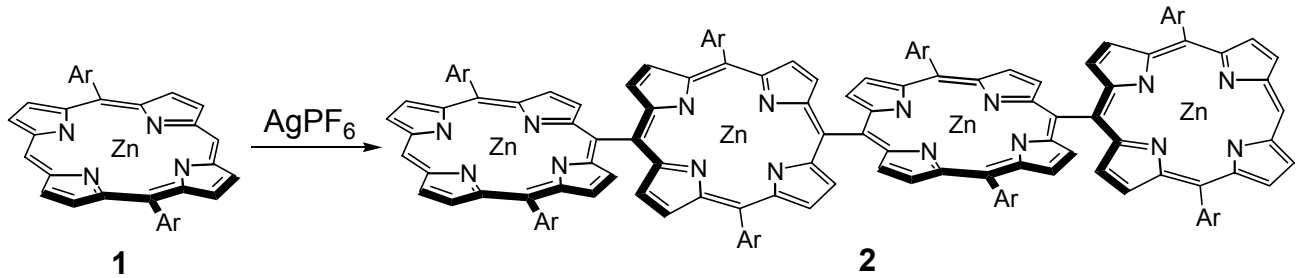


Figure 1 *Crystal structure of the LH2 complex*[2]



1 **2**

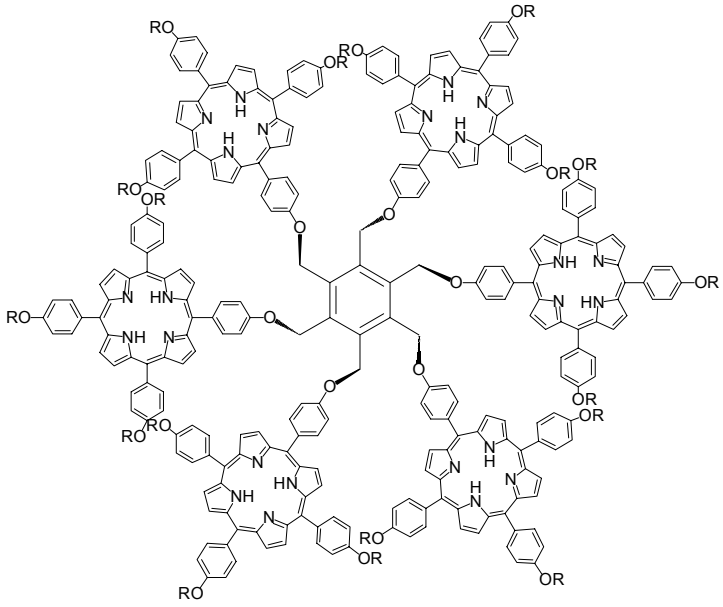
Scheme 1 *Meso,meso-linked porphyrin array*[4]

coupling of the monomer **1** using $AgPF_6$ (Scheme 1).[4] More recently, the latter approach was used to construct windmill and grid porphyrin arrays, containing up to 48 porphyrin residues.[5] Using a synthetically more demanding building block approach a porphyrin pentamer[6] and nonamer[6,7] have been prepared.

In order to allow for the construction of larger porphyrin arrays in high yields, a number of research groups have turned to the use of metal-ligand interactions. These interactions have proven to be especially useful because of their high directionality and their easy incorporation into porphyrin containing systems. Recently published examples include an octahedral array of six ruthenium porphyrins (**4**), synthesized by self-assembly of these porphyrins around a ruthenium or iron core, [8] and a planar self-assembled nonameric array of pyridyl porphyrins (**5**), synthesized by coordination of the pyridyl nitrogen atoms to palladium centers (Chart 2).[9]

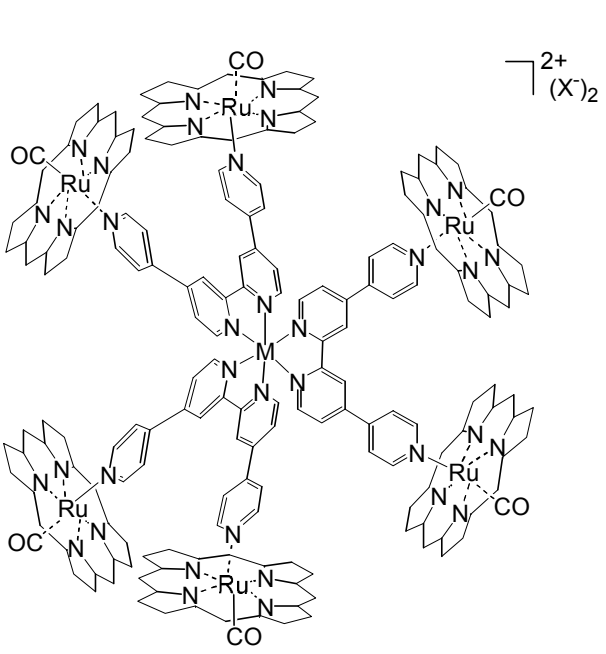
Hydrogen bonding has also been applied to construct porphyrin assemblies, albeit to a lesser extent than transition metal coordination. Sessler and co-workers used the self-assembling nucleobase-substituted porphyrins **6** and **7** that self-assemble to form rigid hydrogen-bonded complexes, within which energy transfer can take place (Chart 3).[10] Drain and co-workers constructed macrocycle **8**, which consists of three triaminotriazine units, each containing two porphyrins that self-assemble by means of hydrogen bonding with three dialkylbarbituric acids, yielding a macrocycle containing six

Chart 1

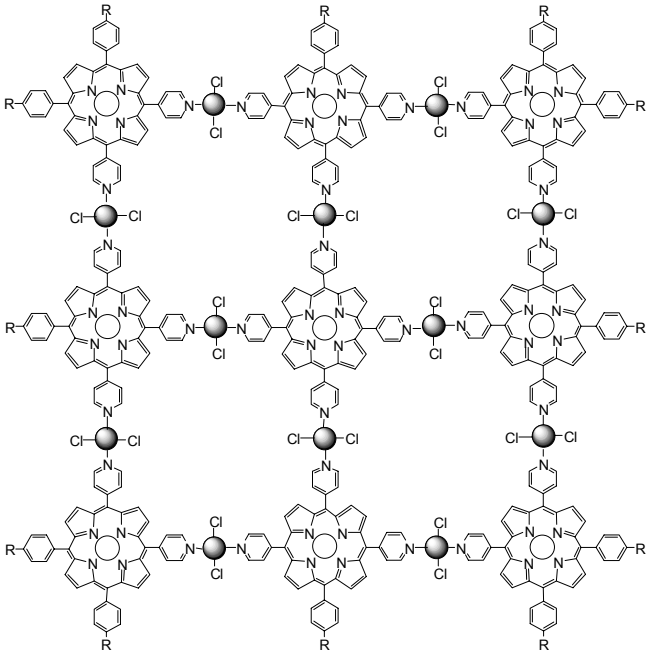


3

Chart 2



4

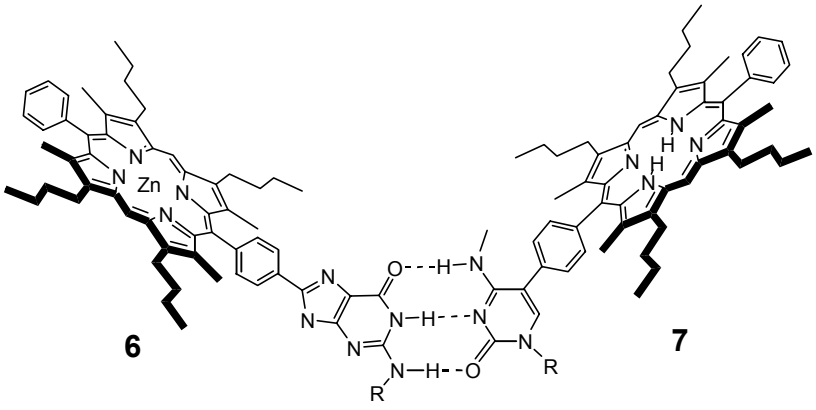


5

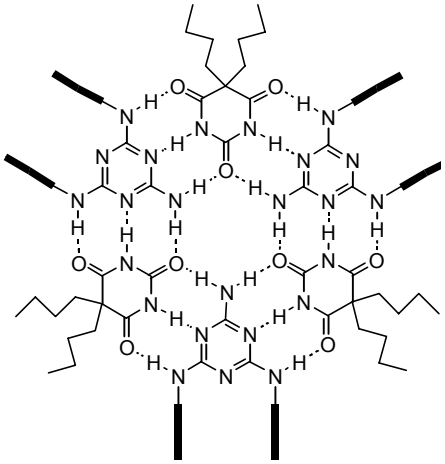
porphyrins (Chart 3).[11]

The above examples show that porphyrin assemblies can be prepared by making use of covalent, metal-ligand and hydrogen bonding interactions. In this chapter, attempts are described to construct multiporphyrin assemblies using host-guest interactions. As a host we use a propanediurea based molecular clip that is functionalized with two porphyrin residues at its convex side. This host is especially useful because of its high affinity towards resorcinol guest molecules. It is used in combination with a porphyrin based tetrafunctional guest or a styrene based polyfunctional guest to construct multi-porphyrin arrays.

Chart 3



6



7

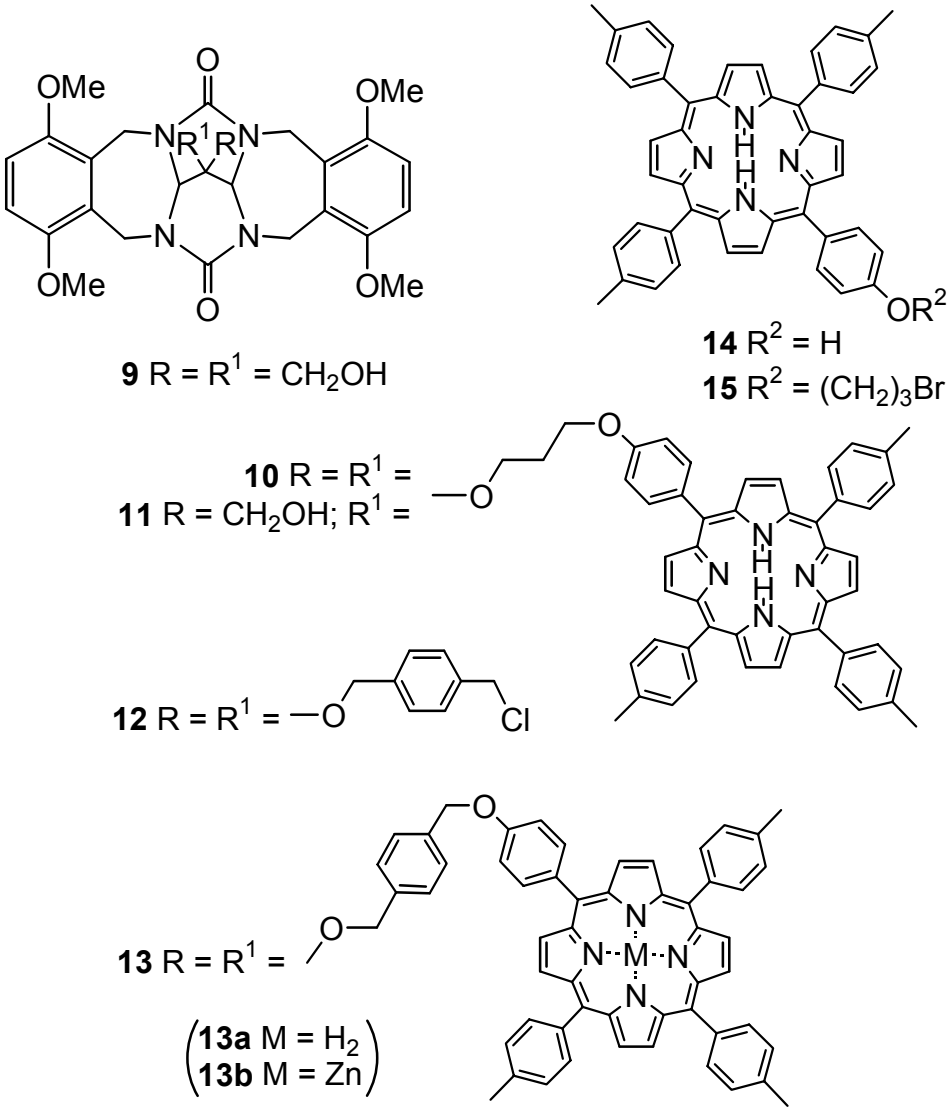
8 ▬ = porphyrin

6.2 Synthesis of the compounds

6.2.1 The porphyrin host

In order to prepare a porphyrin functionalized molecular clip we started from compound **9** (Chart 4), available in multigram quantities by the synthetic methods described in Chapter 4. This clip was reacted with bromopropyl functionalized porphyrin **15** (Chart 4) in DMF using sodium hydride as a base. After work-up and extensive column chromatography the desired product (**10**, Chart 4) was isolated in very low yield (~6%). Use of DMSO as the solvent and KOH as the base resulted in the formation of clip **11** (Chart 4), which contains only one porphyrin residue. The yield of this reaction again was very low. The probable cause of the low yields of these reactions is deprotonation of the porphyrin NH by the strong bases used, giving rise to a variety of side reactions.
Because of the disappointing results encountered in the synthesis of **10**, an attempt was made to link porphyrin **14** (Chart 4) directly to clip **9**. To this end, the hydroxy groups of **9** would have to be

Chart 4



transformed into leaving groups. Chlorine groups seemed attractive candidates for they are easily introduced and relatively small. (Larger groups, *e.g.* bromine, would increase the steric bulk of the clip part.) Clip **9** was therefore reacted with thionyl chloride at room temperature for 4 days. Identification of the product revealed that the reaction had not gone to completion. The reaction was then performed at 60°C for 16 hours. TLC analysis of the isolated product indicated that a complex mixture was formed, containing at least three products. NMR analysis showed that decomposition had taken place, probably through cleavage of the benzylic linkages. This decomposition reaction was surprising in view of the fact that clip molecules derived from diphenylglycoluril have been shown to be stable towards these reaction conditions.[12]

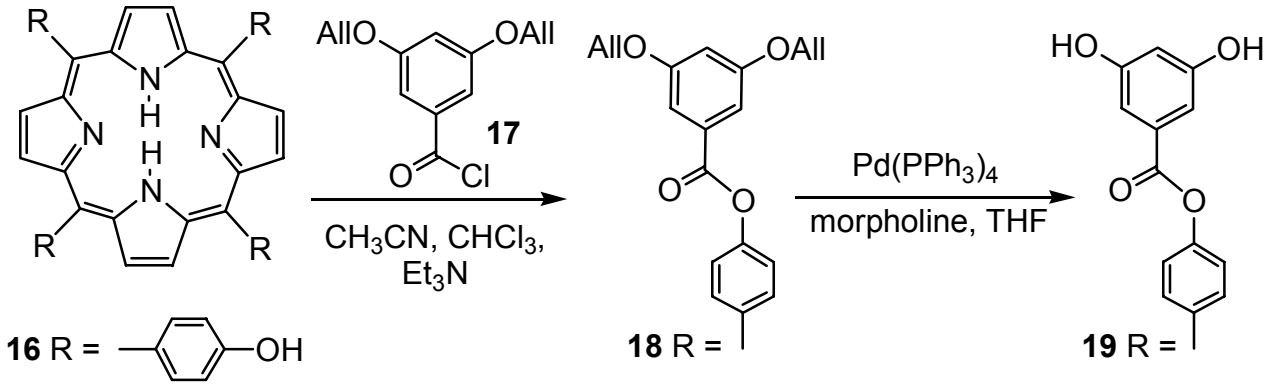
In a next attempt to further functionalize clip molecule **9**, it was deprotonated with sodium hydride in THF, followed by reaction with an excess of α,α'-dichloro-*p*-xylene, yielding clip molecule **12** (Chart 4). This reaction proceeded in variable yields, sometimes as high as 67%, but usually much lower (~30%). The reason for this low yield is the fact that α,α'-dichloro-*p*-xylene polymerizes under strongly basic conditions to yield poly(*p*-phenylene vinylene). This is visible from the color of the reaction mixture: it turns fluorescent yellow when the reaction proceeds. Nevertheless, yields of product **12** were judged to be sufficient. This clip molecule now possesses a very versatile handle that allows for straightforward functionalization.

Clip molecule **13a**, containing two porphyrin residues at its convex side (Chart 4), was obtained by reacting **12** with **14** in DMF at 80°C, using cesium carbonate as the base. The reaction proceeded smoothly, but purification of the product turned out to be difficult, since **13a** slowly decomposed during column chromatography. Use of neutral alumina instead of silica as the stationary phase or addition of triethyl amine to the eluent did not solve this problem. NMR analysis indicated that decomposition of the product probably took place by breaking of the benzylic ether linking the porphyrin to the clip residue. Therefore, impure **13a** was metallated with zinc acetate, yielding zinc porphyrin **13b**. This product was stable enough to be purified by column chromatography on silica.

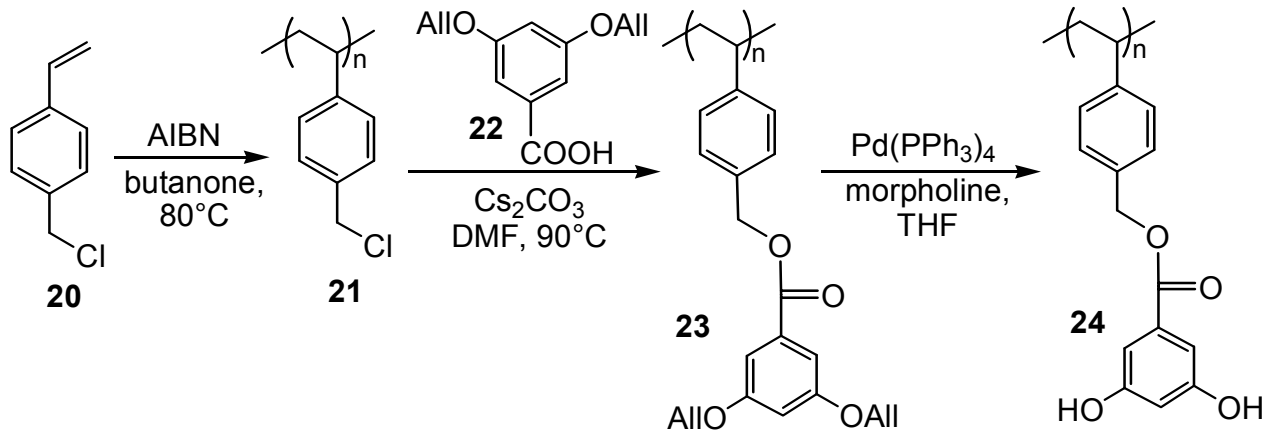
6.2.2 The guests

A tetrafunctional guest with a porphyrin core was synthesized from tetrakis-(4-hydroxyphenyl)-porphyrin **16** by esterification with 3,5-diallyloxybenzoyl chloride (**17**), yielding **18**. Acid chloride **17** was available in three steps from methyl 3,5-dihydroxybenzoate. Palladium catalyzed deprotection of **18** produced the tetrafunctional guest **19** (Scheme 2).

A polyfunctional guest was prepared in three steps according to Scheme 3. First, 4-vinylbenzyl chloride (**20**) was polymerized in butanone at 80°C, using AIBN as the initiator. The resulting polymer **21** was reacted with 3,5-diallyloxybenzoic acid in DMF at 90°C using cesium carbonate as the base, yielding the polymeric ester **23**. Deprotection as was described for **18** gave polyfunctional guest **24**. Purification of this polymer was attempted by washing with chloroform. It appeared impossible to remove all the morpholine from the product by this method. Even after Soxhlet filtration a trace of morpholine remained. Further purification was carried out by filtration of a suspension of the crude polymer in water over a 1000D ultra-filter. According to ^{1}H and ^{13}C NMR



Scheme 2 *Preparation of a tetrafunctional guest with a porphyrin core*



Scheme 3 *Synthesis of polyfunctional guest **24***

analysis approximately 10% of the residues in the polymer did contain a free benzylic alcohol instead of a resorcinol group. This could be the result of partial ester hydrolysis of **24** in the aqueous purification step. Alternatively, incomplete esterification in the second step of the synthesis, followed by hydrolysis of the remaining benzylic chloride during the purification of polymer **24** would also lead to a percentage of benzylic alcohol functions in **24**.

6.3 Study of the complexes

6.3.1 Complexation to tetrafunctional guest 19

The first complex that was studied is the 4:1 complex of host **13a** with guest **19** (Figure 2). The strongest complexation was expected to take place in chloroform. However, guest **19** is not soluble in this solvent. Therefore, a solution of this guest in acetonitrile was added to a solution of the porphyrin clip **13a** in chloroform. The solvents were allowed to evaporate slowly at room temperature and atmospheric pressure, thus allowing the complex to form. The resulting solid dissolved entirely in chloroform. This is a strong indication that complexation had taken place, since guest **19** cannot be dissolved in this solvent.

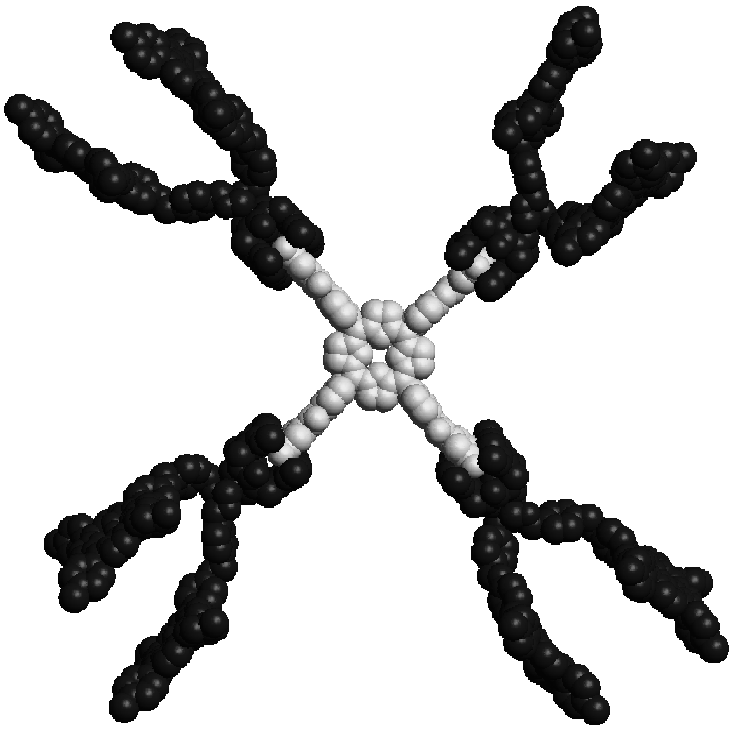


Figure 2 *Impression of the 4:1 complex of clip **13** (black) and guest **19** (grey)*

A very informative method to study complexation is ^{1}H NMR spectroscopy. When a resorcinol guest is bound inside the cavity of a clip, the aromatic protons on the cavity walls are in the shielding zone of the guest, and the guest protons are in the shielding zone of the cavity walls. As a result, these protons display shifts in the NMR spectra. Since the complexation-decomplexation rate is fast on the NMR timescale, it was not possible to separately see the protons in the complex and in the free state. The observed signal is the concentration-weighted average between these two positions. However, since the shift in the free state is known, and the shift in the complexed state can be calculated from titration experiments, the observed position of the signal is a measure of the complex formation. ^{1}H NMR spectra of the 4:1 host:guest mixture of **13a** and **19** with a guest concentration of 0.8 mM, revealed shifts indicative of complexation. The wall protons were shifted by 0.29 ppm upfield, and the downfield located AB doublet of the xylylene protons was shifted 0.24 ppm downfield. These values are indicative of a complexation ratio for the clip of approximately 50%. When the host:guest ratio was decreased to 1:1, the signals were shifted a little further. The total shift of the wall protons was –0.43 ppm, and the total shift of the AB doublet was +0.31 ppm. This is indicative of a complexation ratio for the clip of approximately 70%. Although the association constant for this particular complex has not been determined, the K_a of clip **13** and a resorcinol derivative with an ester group at the *meta*-position is expected to be approximately 10^5 M^{-1} (see Chapter 5).

Electronic interaction between porphyrins in solution can be investigated with UV-VIS spectroscopy. Uncomplexed porphyrins show a large absorption around 420 nm (the Soret band). Stacking of the porphyrins can lead to shifts in this absorption peak, referred to as exciton coupling (Figure 3).[13] Face to face stacking of the porphyrins causes a blue-shift in the UV-spectrum (Figure

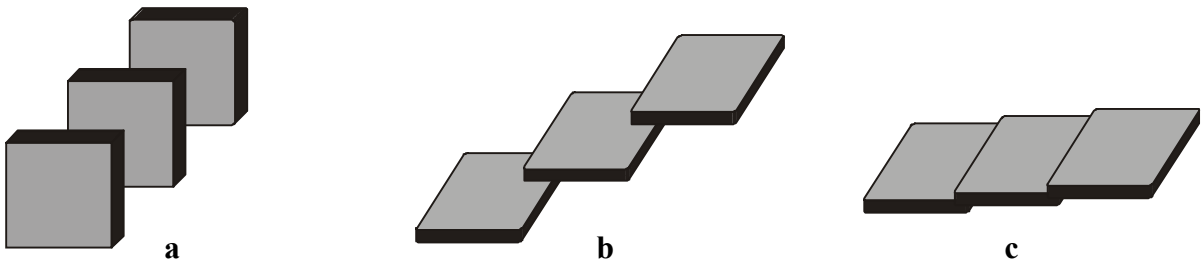


Figure 3 *Exciton theory: three modes of stacking lead to different changes in the Soret band. a: face-to-face stacking: blue shift of Soret band; b: head-to-tail stacking: red shift of Soret band; c: edge-to-edge stacking: splitting of Soret band*[13]

3a). Head to tail stacking leads to red-shift (Figure 3b), and edge-to-edge stacking results in a splitting of the Soret band (Figure 3c). The resorcinol porphyrins might stack in one of the ways shown in Figure 3, but it is also possible that the two porphyrins on the convex side of the clip are close enough together to show an exciton coupling.

The UV-VIS spectra that were recorded of the host-guest mixtures of **13b** and **19** (concentration of **19** approximately 2.5×10^{-6} M) all showed a Soret band at 420 nm. This indicates that the porphyrins are too far apart to show any significant exciton coupling, because UV-VIS spectroscopy can only detect coupling when the distance between the porphyrins is not larger than 4Å. Apparently, the porphyrins that are attached to the convex side of the clip are relatively far apart.

Energy transfer between two porphyrins can occur if one possesses a lower energy excited state than the other. In the 4:1 complex described above, this requirement can be met if the porphyrins

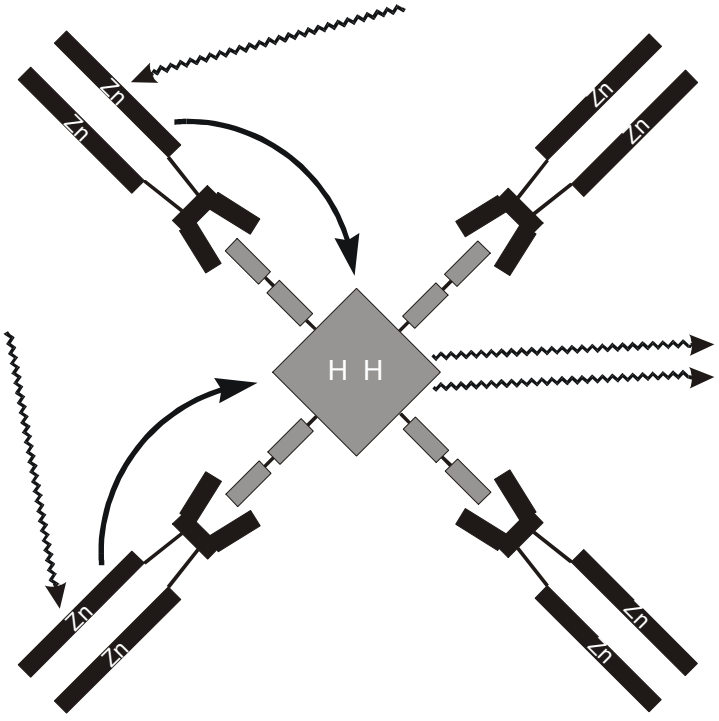


Figure 4 *Energy transfer in system* ***13b*** $_4$ ***19*** $_1$

attached to the clip are zinc porphyrins (high energy), and the central porphyrin with the resorcinol groups is a free base porphyrin (low energy). A free base porphyrin has a lower energy excited state than a zinc porphyrin. Using fluorescence spectroscopy, energy transfer between two porphyrins can be studied. This can be done by selectively exciting the zinc porphyrin. The excited state can now transfer to the central free base porphyrin, which will lose the energy by emitting a photon (see Figure 4). If energy transfer does not occur, the excited zinc porphyrin will fall back to the ground state by emitting a photon itself. Thus, by exciting the zinc porphyrin and recording the fluorescence spectrum one can measure if energy transfer takes place in this system. The 4:1 complex in chloroform was prepared using the procedure described above. It was diluted to a concentration of 10^{-5} M for clip **13b** and 2.5×10^{-6} M for central resorcinol porphyrin **19**. It was possible to excite the zinc porphyrins exclusively using a wavelength of 440 nm. However, fluorescence of the free base porphyrin was not detected.
It is possible that the concentration of the host-guest complex in solution is too low due to the high dilution conditions required for fluorescence measurements. Even if the association constant is very high, the complex concentration will be low in highly diluted solutions. A large portion of the porphyrin clip is then present in the uncomplexed state. Another explanation might be that the distance between the zinc porphyrin and the free base porphyrin is too large to allow energy transfer to occur. A third explanation is that energy transfer in fact does occur, but that the fluorescence of the free base porphyrin is not measured because it is quenched by solvent or solute molecules.

6.3.2 Complexation studies with polyfunctional guest 24

Complexation of porphyrin host **13** to polyfunctional guest **24** could lead to a column-like aggregate, which is schematically depicted in Figure 5. Since guest **24** is not soluble in chloroform, the complex was prepared using a procedure similar to the one described in section 6.3.1. One equivalent of clip **13a** was dissolved in chloroform and was added to a solution of **24** in acetone, containing one equivalent of resorcinol residues. The solvent was allowed to evaporate at room temperature and atmospheric pressure. The resulting complex was redissolved in chloroform to a concentration of 3 mM. ^{1}H NMR spectra of this solution showed broadening of the resonances of all cavity protons of **13a**. The signals due to the porphyrin protons were broadened as well, albeit to a lesser extent. The spectra further showed that the signals due to the side wall protons had shifted 0.30 ppm upfield, indicating that approximately 50% of the clip was present as a complex. Due to the extensive broadening of all signals, the shifts of other protons could not be determined. Addition of a few drops of acetonitrile to the solution led to decomplexation. This solvent competes with the carbonyl groups of the clip for hydrogen bonding with the hydroxy groups of the guest, thus greatly reducing the host-guest interaction. Moreover, acetonitrile fits inside the cavity, reducing the contribution of the cavity effect to binding (see Chapter 5). The decomplexation was immediately evident from the NMR spectrum: all signals sharpened up and the protons displayed chemical shifts similar to those of the clip in its uncomplexed state.

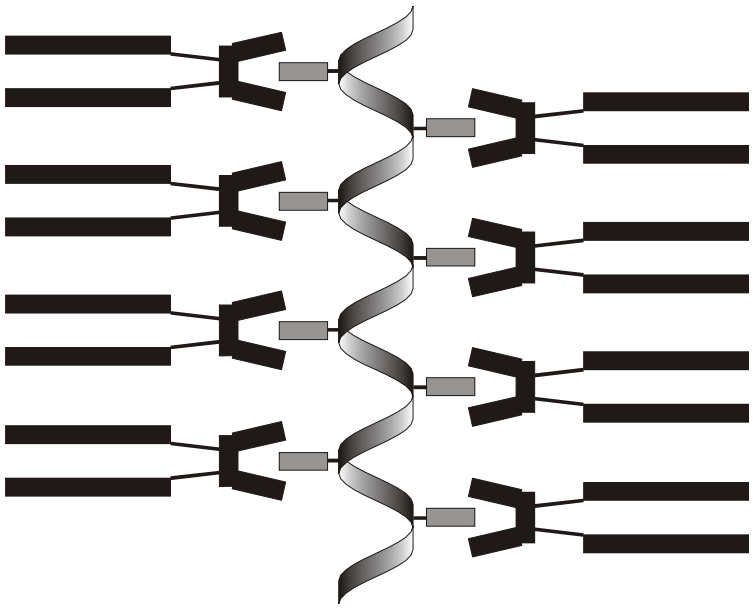


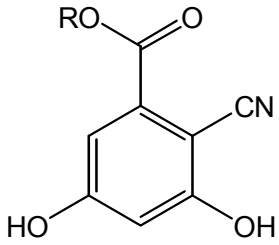
Figure 5 *Impression of the complex between polymer **24** and porphyrin clip **13a***

The UV-VIS spectrum of the complex did not reveal any changes with respect to the Soret band of the porphyrins, indicating that the porphyrin residues are relatively far apart in a solution of the complex.

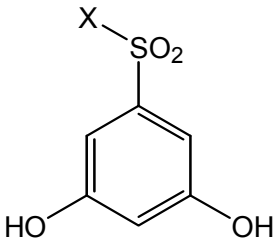
6.4 Conclusions and suggestions for further research

The importance of light-harvesting porphyrin assemblies in Nature has inspired considerable interest in the preparation of similar artificial structures. Covalent synthesis, metal-ligand interactions, as well as hydrogen bonding have been used to construct large porphyrin assemblies. The systems described in this chapter, are the first attempts in which host-guest binding is used to form porphyrin arrays. Evidence that a nona-porphyrin assembly can be constructed by self-assembly of four bis-porphyrin hosts around a tetrafunctional porphyrin guest has been presented. Furthermore, it is possible to construct a column-shaped multi-porphyrin array by self-assembly of the same hosts with a multi-functional polystyrene-based guest.
Solubility issues complicate the construction and study of the aggregates. The guests used are not soluble in halogenated hydrocarbons, the solvents needed for obtaining high association constants. An obvious but synthetically demanding solution to this problem is functionalization of these guests with hydrophobic hydrocarbon chains.
A second complication that we encountered is the fact that association constants in the range of 10^5 - 10^6 M^{-1}, which are typical for this system, still require relatively high concentrations ($> 10^{-5}$ - 10^{-4} M) of host and guest components to achieve near-complete complexation. These concentrations are too high to allow for study of the complexes by means of UV-VIS and fluorescence spectroscopy.
Higher association constants between these hosts and guests can be reached by introducing electron withdrawing substituents in the guests, such as cyano groups (**25**) or the very strongly electron

Chart 5



25



26 X = NHR, OR, R

withdrawing sulfone groups (**26**).[14] However, preparation of these compounds would require considerable synthetic effort.

6.5 Experimental section

General. All reactions were carried out in an inert argon atmosphere. Thionyl chloride and butanone were distilled prior to use. Sodium hydride was a commercially available 60% suspension in mineral oil. DMF was stirred with BaO for one week, decanted and distilled *in vacuo*. The first 30% of the distillate was discarded. THF was distilled under nitrogen from sodium benzophenone ketyl. DMSO and acetonitrile were distilled from CaH_2. Chloroform was distilled from $CaCl_2$. 4-Vinylbenzyl chloride was distilled *in vacuo*. AIBN was recrystallized from diethyl ether. All other solvents and chemicals were commercially available materials and were used as received. Merck silica gel (60H) was used for column chromatography, unless otherwise indicated. Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument with $(CH_3)_4Si$ (δ 0.00 ppm) and CHD_2OD (δ 3.48 ppm) as the internal standards for the ^1H spectra, and $CDCl_3$ (δ 77.0 ppm) and DMSO-d_6 (δ 39.5 ppm) as the internal standard for the ^{13}C spectra. Abbreviations used are as follows: bs, broad singlet; s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were recorded on a Finnigan MAT900S instrument. Elemental analyses were determined with a Carbo Erba EA 1108 instrument.

Compounds: Compound **9** was synthesized as described in Chapter 4 of this thesis. Porphyrins **14**[15] and **15**[16] were prepared according to literature procedures. Compound **22** was prepared according to a literature procedure.[17] Contrary to the described procedure it was purified by crystallization from *n*-hexane.

Diporphyrin clip with propyl spacer (**10**): Clip **9** (70 mg, 0.13 mmol) was suspended in DMF (5 mL) and the mixture was degassed. Sodium hydride (16 mg, 0.40 mmol) was added and the reaction mixture was stirred at room temperature for 5 hours. Porphyrin **15** (216 mg, 0.27 mmol) was added and the reaction mixture was stirred at room temperature for 5 days. Water was added and the reaction mixture was extracted with chloroform. The chloroform layer was washed with

water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 99:1 v/v), yielding nearly pure **10** as a purple solid (15.3 mg, 6%). Further purification was not attempted, because of the low yield of the reaction. ^{1}H NMR ($CDCl_3$): δ –2.79 (s, 4H, N*H*), 2.27 (t, J = 6.0 Hz, 2H, $OCH_2CH_2CH_2O$), 2.64 (s, 6H, $ArCH_3$), 2.69 (s, 3H, $ArCH_3$), 3.68 (s, 12H, OCH_3), 3.86-3.94 (m, 12H, NCH_2Ar, $OCH_2CH_2CH_2O$, and CH_2OCH_2Ar), 4.35 (t, J = 5.7 Hz, 4H, Porph-OCH_2), 4.81 (s, 4H, OCH_2Ar), 5.16 (s, 2H, NC*H*N), 5.30 (s, 4H, $ArCH_2O$-Porph), 5.58 (d, J = 15.2 Hz, 4H, NCH_2Ar), 6.61 (s, 4H, wall Ar*H*), 7.24-7.28 (m, 8H), 7.46-7.55 (m, 16H), 8.01-8.09 (m, 16H), 8.77-8.86 (m, 16H, pyrrolic-*H*).

Porphyrin clip with propyl spacer (**11**). Clip **9** (40 mg, 0.074 mmol) was suspended in DMSO (4 mL) and the mixture was degassed. Porphyrin **15** (120 mg, 0.15 mmol) and freshly powdered KOH (25 mg, 0.45 mmol) were added and the mixture was stirred for 4 days. Chloroform was added and the reaction mixture was washed with water. The chloroform layer was dried (Na_2SO_4), concentrated *in vacuo*, and the crude product was purified by column chromatography (CH_2Cl_2/MeOH, 99:1 v/v). Yield: 21 mg (14%) of nearly pure **11** as a purple powder. Further purification was not attempted, because of the low yield of the reaction. ^{1}H NMR ($CDCl_3$): δ –2.79 (s, 2H, N*H*), 2.26 (t, J = 5.8 Hz, 2H, $OCH_2CH_2CH_2O$), 2.70 (s, 9H, $ArCH_3$), 3.62-4.08 (m, NCH_2Ar, OCH_3, OCH_2), 4.34 (t, J = 5.8 Hz, 2H, Porph-OCH_2), 5.55-5.40 (m, 4H, NCH_2Ar), 6.71 (s, 4H, wall Ar*H*), 7.52-7.57 (m, 8H), 8.06-8.13 (m, 8H), 8.84 (s, 8H, pyrrolic-*H*).

Benzylic chloride clip 12. Clip **9** (260 mg, 0.48 mmol) was suspended in THF (20 mL) and the mixture was degassed. Sodium hydride (0.2 g, 5.0 mmol) was added and the reaction mixture was stirred for 30 min. Subsequently, α,α'-dichloro-*p*-xylene (13.1 g, 75 mmol) was added and the mixture was refluxed for 40 h. The reaction mixture was acidified with aqueous 6 M HCl and water (100 mL) was added. The mixture was extracted with $CHCl_3$, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was dissolved in chloroform, the solution was boiled with activated charcoal, filtered through infusorial earth, and concentrated again *in vacuo*. Diethyl ether was added to the residue and the resulting suspension was filtered. The residue was washed with diethyl ether to remove all unreacted α,α'-dichloro-*p*-xylene and then dried *in vacuo*, yielding a white solid (0.38 g, 67%). M.p. 229°C. FAB MS (*m/z*) 817 ($[M+H]^+$), 839 ($[M+Na]^+$), 154 (100%). ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 12H, OCH_3), 3.81 (s, 4H, CH_2OCH_2Ar), 3.87 and 5.41 (2×d, J = 15.2 Hz, 2×4H, NCH_2Ar), 4.51 (s, 4H, OCH_2Ar), 4.58 (s, 4H, $ArCH_2Cl$), 4.70 (s, 2H, NC*H*N), 6.71 (s, 4H, wall Ar*H*), 7.24 (d, J = 8.0 Hz, 4H, OCH_2ArH), 7.35 (d, J = 8.1 Hz, 4H, OCH_2ArH). Anal. Calcd. for $C_{43}H_{46}Cl_2N_4O_8$: C: 63.16, H: 5.67, N: 6.85. Found: C: 62.77, H: 5.62, N: 6.79.

Porphyrin clip 13a. Porphyrin **14** (258 mg, 0.383 mmol) was dissolved in DMF (6 mL) and the solution was degassed. Cesium carbonate (375 mg, 1.15 mmol) was added and the mixture was stirred for 5 h at 90°C. Clip **12** (78.3 mg, 0.096 mmol) was added and the reaction mixture was stirred at 90°C for 48 h. The mixture was filtered and the residue was redissolved in chloroform. The resulting solution was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*.

Purification was attempted by repeated column chromatography (silica, CH_2Cl_2/MeOH, 99:1 v/v; CH_2Cl_2/MeOH/Et_3N, 98:1:1 v/v/v; CH_2Cl_2/MeOH/Et_3N, 99:0.5:0.5 v/v/v, and neutral alumina, CH_2Cl_2). According to TLC, some impurity remained present. Yield: 79 mg (39%) of a purple solid. FAB MS (*m/z*) 2091 ([M+H]$^+$, 100%). ^{1}H NMR ($CDCl_3$): δ –2.78 (s, 4H, N*H*), 2.64 (s, 6H, ArCH_3), 2.69 (s, 3H, ArCH_3), 3.77 (s, 12H, OCH_3), 3.92 (s, 4H, CH_2OCH_2Ar), 3.93 and 5.46 (2×d, J = 15.2 Hz, 2×4H, NCH_2Ar, 4.63 (s, 4H, OCH_2Ar), 4.79 (s, 2H, NC*H*N), 5.32 (s, 4H, ArCH_2O-Porph), 6.72 (s, 4H, wall Ar*H*), 7.33 (d, J = 8.5 Hz, 4H), 7.42 (d, J = 7.9 Hz, 4H), 7.45 (d, J = 7.9 Hz, 8H), 7.52 (d, J = 8.2 Hz, 4H), 7.62 (d, J = 8.1 Hz, 4H), 8.02 (d, J = 7.9 Hz, 8H), 8.06 (d, J = 8.2 Hz, 4H), 8.09 (d, J = 8.5 Hz, 4H), 8.79-8.85 (m, 16H, pyrrolic-*H*).

Zinc porphyrin clip 13b: Porphyrin clip **13a** (51 mg, 0.024 mmol) was dissolved in a mixture of chloroform (6 mL) and methanol (3 mL). The solution was degassed and zinc acetate dihydrate (27 mg, 0.123 mmol) was added. The reaction mixture was refluxed for 3 h, cooled, and concentrated *in vacuo*. The residue was dissolved in dichloromethane and the solution was washed twice with water, concentrated *in vacuo*, and purified by column chromatography (CH_2Cl_2/MeOH, 99.5:0.5 v/v). Yield: 33 mg (62%) of **13b** as a purple solid. ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 6H, ArCH_3), 2.68 (s, 3H, ArCH_3), 3.00 (s, 12H, OCH_3), 3.06 and 4.69 (2×d, J = 15.3 Hz, 2×4H, NCH_2Ar), 3.73 (s, 4H, CH_2OCH_2Ar), 4.42 (s, 2H, NC*H*N), 4.55 (s, 4H, OCH_2Ar), 5.23 (s, 4H, ArCH_2OPorph), 5.74 (s, 4H, wall Ar*H*), 7.24 (d, J = 8.5 Hz, 4H), 7.44 (d, J = 7.8 Hz, 8H), 7.36 (d, J = 8.0 Hz, 4H), 7.50 (d, J = 7.8 Hz, 4H), 7.55 (d, J = 8.0 Hz, 4H), 7.97 (d, J = 7.8 Hz, 8H), 8.02 (d, J = 8.5 Hz, 4H), 8.03 (d, J = 7.8 Hz, 4H), 8.84-8.92 (m, 16H, pyrrolic-*H*). ^{13}C NMR ($CDCl_3$): δ 21.5, 40.6, 44.2, 56.9, 67.1, 70.2, 73.4, 112.1, 113.0, 120.4, 120.9, 127.2, 127.6, 127.8, 131.8, 134.3, 135.4, 135.7, 136.6, 136.9, 138.0, 140.0, 150.1, 150.2, 150.6, 154.1, 158.2.

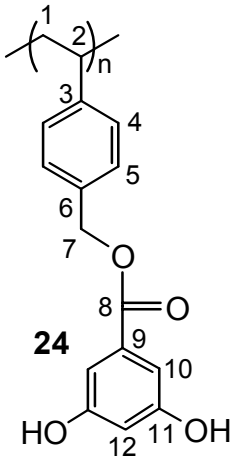
Allyl protected tetrafunctional guest 18. To a cooled suspension of 3,5-diallyloxybenzoic acid (**22**, 131 mg, 0.56 mmol) in chloroform (2 mL) were added one drop of DMF and 14 drops of oxalyl chloride. The mixture was stirred for 1 h at room temperature and concentrated *in vacuo*, yielding acid chloride **17** as a sticky solid. Subsequently acetonitrile (2 mL), chloroform (2 mL), triethyl amine (6 drops) and porphyrin **16** (67 mg, 0.10 mmol) were added, and the reaction mixture was stirred for 16 h. CH_2Cl_2 and water were added and the organic layer was separated, washed with water, and dried (Na_2SO_4). The crude product was purified by column chromatography (CH_2Cl_2), yielding **18** as a purple solid (80 mg, 53%). Yields of larger scale preparations were generally 35-40%. M.p. > 350°C. FAB MS (*m/z*) 1543 ([M+H]$^+$), 348 (100%). ^{1}H NMR ($CDCl_3$): δ –2.78 (s, 2H, N*H*), 4.69 (d, J = 5.3 Hz, 16H, OCH_2), 5.36-5.55 (m, 16H, C=CH_2), 6.07-6.20 (m, 8H, CC*H*=CH_2), 6.86 (t, J = 2.2 Hz, 4H, OCC*H*CO), 7.55 (d, J = 2.2 Hz, 8H, C(O)CC*H*), 7.65 (d, J = 8.4 Hz, 8H, Porph-Ar*H*), 8.29 (d, J = 8.4 Hz, 8H, Porph-Ar*H*), 8.95 (s, 8H, pyrrolic-*H*).

Tetrafunctional guest 19: The allyl protected tetrafunctional guest **18** (230 mg, 0.15 mmol) and morpholine (700 mg, 7.87 mmol) were dissolved in THF (15 mL) and the mixture was degassed. Subsequently, a catalytic amount of $Pd(PPh_3)_4$ was added and the reaction mixture was stirred at

room temperature for 4 days. The mixture was evaporated to dryness, washed with chloroform, and filtered. The crude product was dissolved in a small amount of THF and precipitated in hexane. Yield: 140 mg (77%) of **19** as a purple solid. M.p. >350°C. FAB MS (*m/z*) 1223 ($[M+H]^+$), 154 (dihydroxybenzoic acid$^+$, 100%) ^{1}H NMR (MeOD): δ 6.45 (d, J = 2.1 Hz, 8H, C(=O)CC*H*), 6.50 (t, J = 2.1 Hz, 4H, HOCC*H*COH), 7.40 (d, J = 8.3 Hz, 8H, Porph-Ar*H*), 8.20 (d, J = 8.3 Hz, 8H, Porph-Ar*H*), 9.04 (bs, 8H, pyrrolic-*H*). UV-vis (MeOH) λ/nm 418, 516, 553, 593, 651.

Benzylic chloride polymer 21: 4-Vinylbenzyl chloride (**20**, 610 mg, 4 mmol) was dissolved in butanone (4 mL) and the solution was degassed. 2,2'-Azobisisobutyronitril (AIBN, 4 mg) was added and the resulting mixture was refluxed for 16 h. The solution was concentrated *in vacuo* and methanol was added to the residue. The resulting precipitate was collected by filtration and rinsed with methanol to give a white powder. Yield: 580 mg (95%). ^{1}H NMR ($CDCl_3$): δ 1.38 (bs, 2H, C*H*$_2$CH(Ar)), 1.68 (bs, 1H, CH$_2$C*H*(Ar)), 4.52 (bs, 2H, C*H*$_2$Cl), 6.49 (bs, 2H, Ar*H*), 7.06 (bs, 2H, Ar*H*). From GPC: Mw ~13.000 (approximately 80 units), with a very broad weight distribution.

Allyl protected resorcinol functionalized polymer 23: Polymer **21** (100 mg, 0.656 mmol) was added to DMF (8 mL) and the mixture was degassed. Subsequently, cesium carbonate (428 mg, 1.31 mmol) and 3,5-di(allyloxy)benzoic acid (**22**, 307 mg, 1.31 mmol) were added, and the reaction mixture was stirred at 90°C for 16 h. The mixture was cooled, filtered and concentrated *in vacuo*. The residue was suspended in methanol, filtered off, and dissolved in a small amount of chloroform. The polymer was precipitated with the help of methanol. The precipitate was too fine to be isolated by filtration so it was collected by centrifugation. Yield: 328 mg (98%) of a brown sticky solid. ^{1}H NMR ($CDCl_3$): δ 1.32 (bs, 2H, H_1), 1.69 (bs, 1H, H_2), 4.36 (d, J = 5.2 Hz, 4H, CH$_2$=CHC*H*$_2$O), 4.42 (bs, 2H, H_7), 5.31-5.14 (m, 4H, C*H*$_2$=CHCH$_2$O), 5.95-5.82 (m, 2H, CH$_2$=C*H*CH$_2$O), 6.37 (s, 1H, H_{12}), 6.56 (bs, 2H, H_5), 6.92 (s, 2H, H_{10}), 7.13 (bs, 2H, H_4). For atom labels, see structural formula at polymer **24**.



Resorcinol functionalized polymer 24: Polymer **23** (800 mg, 2.29 mmol) and morpholine (2.39 g, 27.4 mmol) were dissolved in THF (25 mL) and the mixture was degassed. Then a catalytic amount of $Pd(PPh_3)_4$ was added and the reaction mixture was stirred at room temperature for 4 days. The solvent was removed *in vacuo* and the residue was washed with chloroform and diethyl ether. To remove the last traces of morpholine, the polymer was suspended in water, filtered over a 1000D ultra filter, and washed with water until morpholine could no longer be detected in the filtrate. The product was dried in vacuo to give a light-brown solid. Yield: 576 mg (93%). ^{1}H NMR (CD_3OD): δ 1.77 (bs, 3H, H_2 and H_1), 5.29 (bs, 2H, H_7), 6.65 (bs, 3H, H_5 and H_{12}), 7.15 (bs, 4H, H_4, and H_{10}). ^{13}C NMR (DMSO): δ 66.7 (C_7), 108.1 (C_{10}, C_{12}), 128.3 (C_4, C_5), 132.3 (C_9), 134.2 (C_6), 145.8 (C_3), 159.4 (C_{11}), 166.5 (C_8), C_1 and C_2 are obscured by the DMSO resonances.

6.6 References

1 Fleming, G.R.; Martin, J.-L.; Breton, J. *Nature* **1988**, *333*, 190.
2 McDermott, G.; Prince, S.M.; Freer, A.A.; Hawthorthwaite-Lawless, A.M.; Papiz, M.Z.; Cogdell, R.J.; Isaacs, N.W. *Nature* **1995**, *374*, 517.
3 Biemans, H.A.M.; Rowan, A.E.; Verhoeven, A.; Vanoppen, P.; Latterini, L.; Foekema, J.; Schenning, A.P.H.J.; Meijer, E.W.; De Schryver, F.C.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1998**, *120*, 11054.
4 Osuka, A.; Shimidzu, H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 135.
5 Nakano, A.; Yamazaki, T.; Nishimura, Y.; Yamazaki. I.; Osuka, A. *Chemistry, Eur. J.* **2000**, *6*, 3254.
6 Officer, D.L.; Burrell, A.K.; Reid, D.C.W. *Chem. Commun.* **1996**, 1657.
7 Mak, C.C.; Bampos, N.; Sanders, J.K.M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3020.
8 Chichak, K.; Branda, N.R. *Chem. Commun.* **2000**, 1211.
9 Drain, C.M.; Nifiatis, F.; Vasenko, A.; Batteas, J.D. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2344.
10 Sessler, J.L.; Wang, B.; Harriman, A. *J. Am. Chem. Soc.* **1995**, *117*, 704.
11 Drain, C.M.; Russell, K.C.; Lehn, J.-M. *Chem. Commun.* **1996**, 337.
12 Elemans, J.A.A.W. *Thesis*, University of Nijmegen, **2001**.
13 (a) McRae, E.G.; Kasha, M. *J. Chem. Phys.* **1958**, *28*, 721; (b) Kasha, M.; Rawls, H.R.; Ashraf El-Bayoumi, M. *J. Appl. Chem.* **1965**, *11*, 371.
14 For a comprehensive account of σ-values of different substituents, see: Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* **1991**, *91*, 165.
15 Etemad-Moghadam, G.; Ding, L.; Tadj, F.; Meunier, B. *Tetrahedron* **1989**, *45*, 2641.
16 Mehta, G.; Sambaiah, T.; Maiya, B.G.; Sirish, M.; Chatterjee, D. *J. Chem. Soc. Perkin Trans. 1* **1993**, *22*, 2667.
17 Van Nunen, J.L.M.; Folmer, B.F.B.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1997**, *119*, 283.

7 Supramolecular Hyperbranched Structures Based on Propanediurea Building Blocks

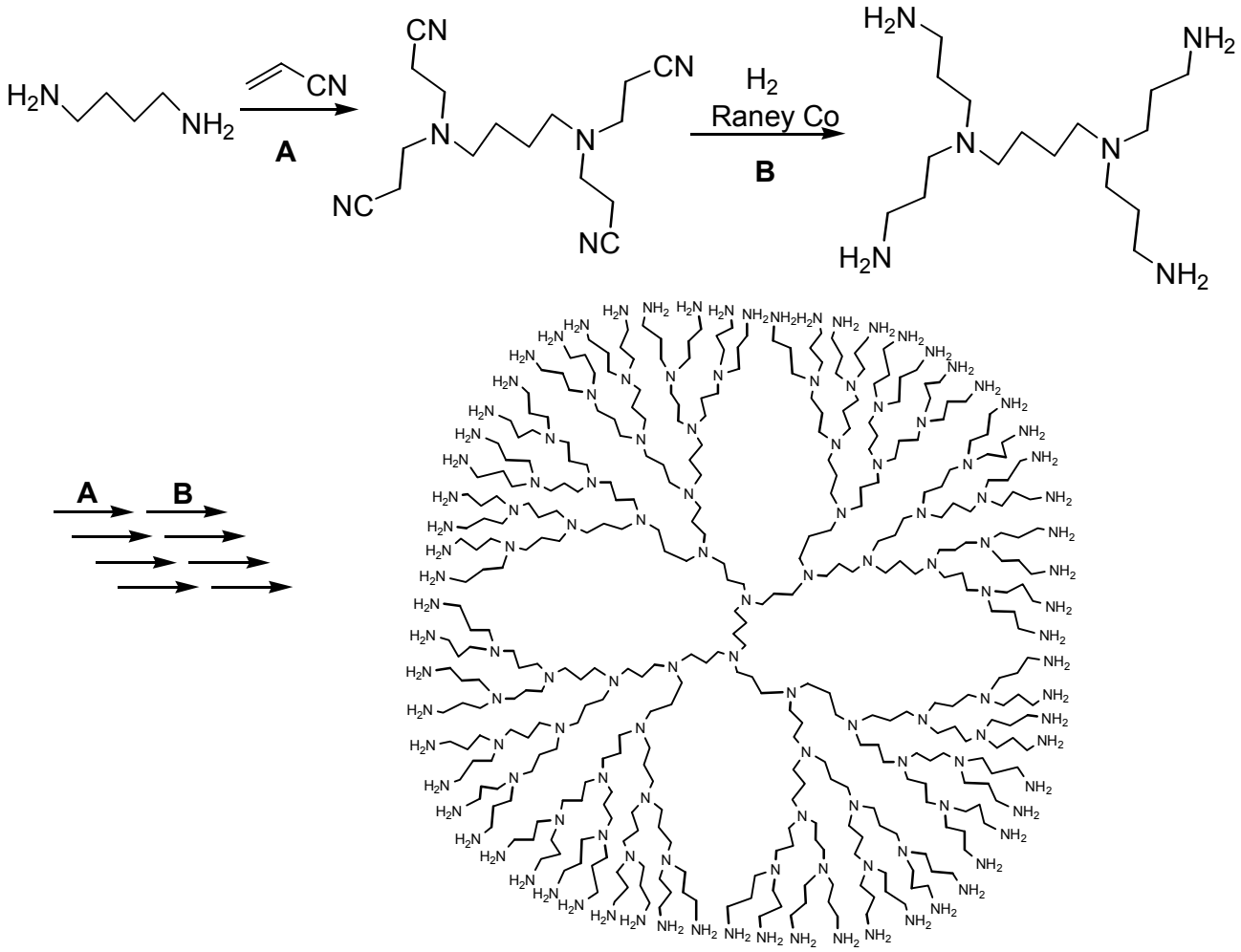
7.1 Introduction

Dendrimers are a class of macromolecules that have received a steadily growing attention during the past two decades. This attention is understandable in view of the unique structural and physical properties of these molecules. In recent years a series of excellent reviews have appeared, covering virtually all aspects of dendrimer chemistry.[1] Therefore, only a few typical examples from this vast field will be highlighted here.

Dendrimers are monodisperse macromolecules with a very regular and highly branched three-dimensional architecture. The first example of this type of molecules was reported by Vögtle in 1978.[2] The first dendritic structures that were thoroughly investigated are the poly(amidoamine) (PAMAM) dendrimers developed by Tomalia[3] and the 'arborol' systems developed by Newkome.[4]

Initially, dendrimers were prepared via a so-called divergent synthesis. In this method, synthesis is started from a multifunctional core molecule to which multifunctional units are attached. In this way, the dendritic molecule can be built up stepwise, until steric factors hamper further reaction on the end groups. Meijer's synthesis of poly(propylene imine) dendrimers, based on the early work of Vögtle,[2] nicely demonstrates this method (Scheme 1).[5] An obvious drawback of this divergent synthesis is the fact that chemical reactions do not proceed in 100% yield, which results in the occurrence of defects in the dendrimer. Because of the relatively small structural differences between the ideal dendrimer and the side products, purification is virtually impossible.[6]

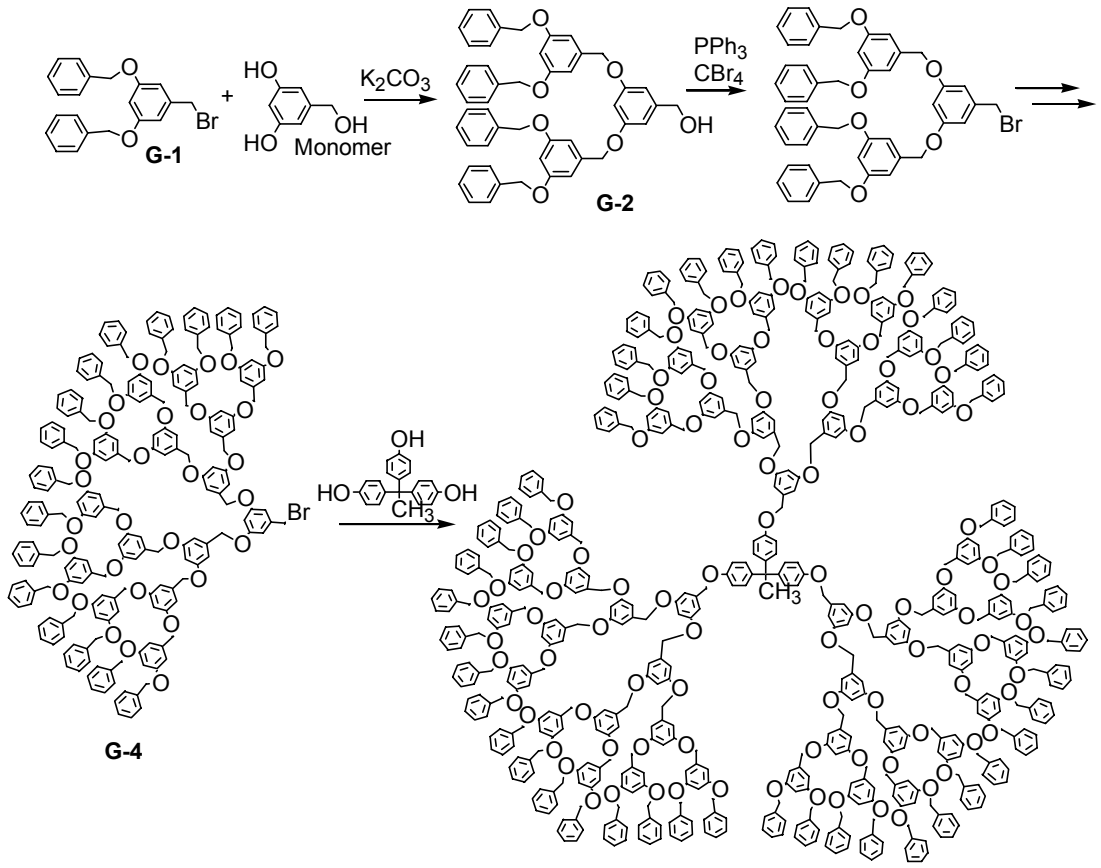
This drawback does not exist if dendrimers are synthesized convergently. In this method, introduced by Fréchet and co-workers,[7] the synthesis is started at the periphery, yielding so-called dendrons (see Scheme 2). These dendrons are attached to the core in the last step to produce the dendrimer. Structural differences between the main product and the side products of the reactions are now large enough to allow for purification of the intermediates. This implies that dendrimers without defects can be synthesized. A drawback however, is the fact that only relatively small dendrimers can be synthesized using this method, because of steric problems in the last reaction step, when very large molecules have to react with each other.



Scheme 1 *Divergent dendrimer synthesis according to Meijer and co-workers*[5]

More recently, supramolecular interactions have been set in to synthesize dendrimers. Zimmerman and co-workers attached Fréchet-type dendritic wedges to an isophthalic acid dimer molecule (see Scheme 3).[8] Isophthalic acids are known to self-assemble through dimerisation of the carboxylic acid functions, forming cyclic hexamers or polymers. Isophthalic acid dimers with large dendritic substituents were found to form stable hexameric structures. Thus, by attaching to a dendron a unit capable of self-assembly, a supramolecular dendrimer has been constructed.

The carbon-metal bond provides a versatile tool for the supramolecular chemist. It is often a very strong bond, so structures based on these bonds can be very stable. The bond often is also kinetically labile, providing the possibility of reorganizing the structures. Moreover, a carbon-metal bond is usually highly directional, so defined architectures can be formed. The use of metals in dendrimer chemistry has remained rather limited. Van Koten and co-workers prepared a silicon-based dendrimer with nickel centers at its periphery.[9] Vögtle, Balzani, and co-workers assembled three arylbenzyl ether dendrons around a Ru(II) core. Dendrimers with metal centers at each branching point have been prepared by Balzani and co-workers,[10] and more recently also by Reinhoudt and co-workers.[11] Reinhoudt's approach consists of a controlled divergent assembly of a metallodendrimer, taking advantage of the coordination chemistry of Pd(II) (see Scheme 4).

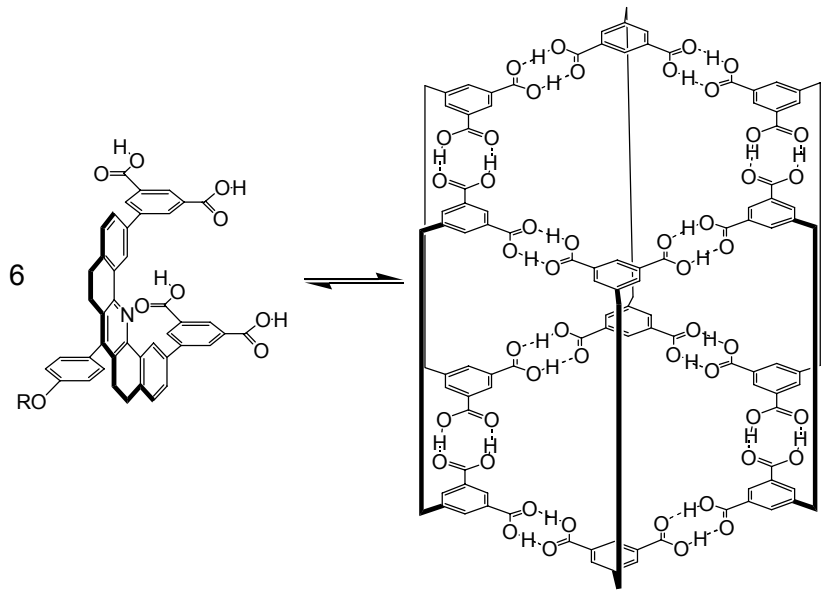


Scheme 2 *Convergent dendrimer synthesis according to Fréchet and co-workers*[7]

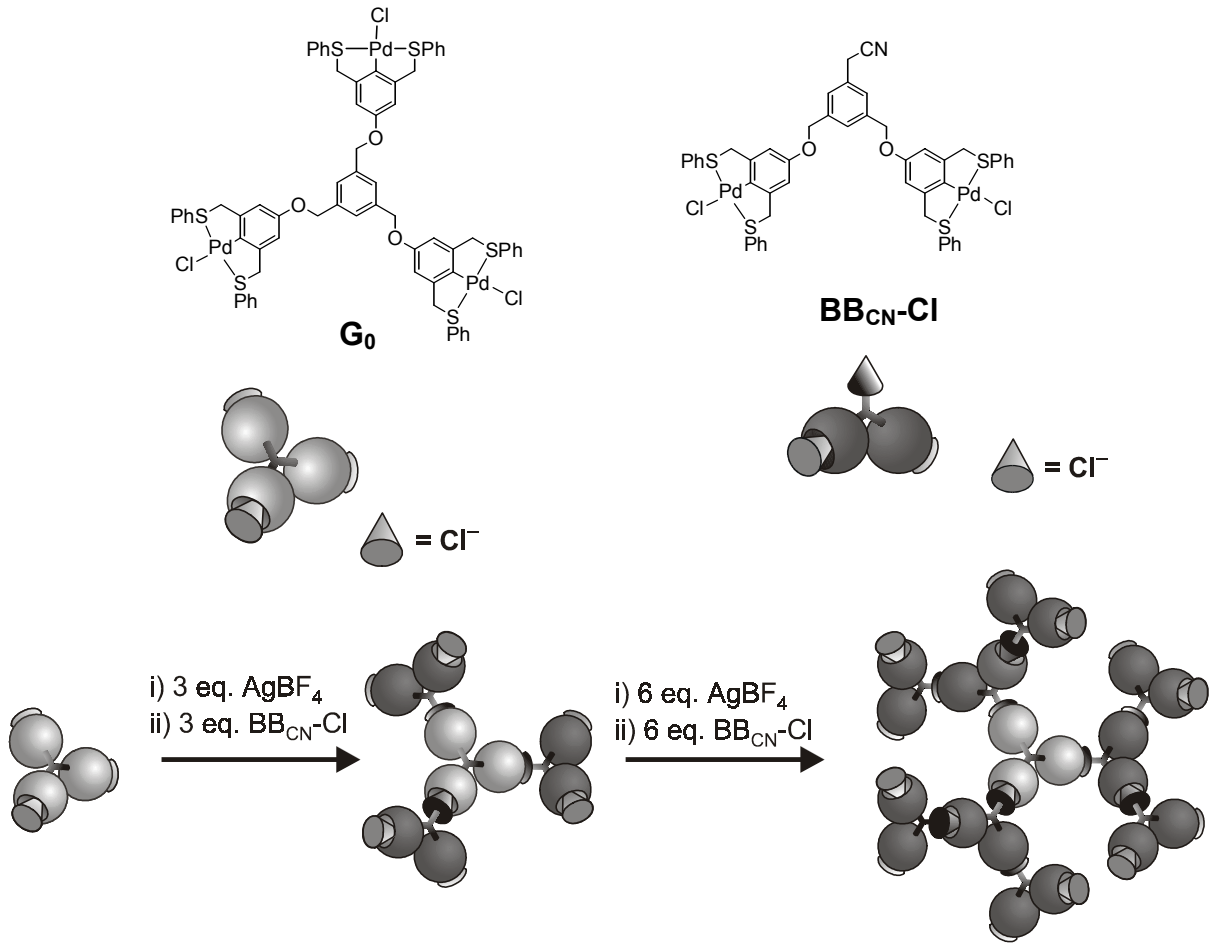
Building block **BB_{CN}-Cl** consist of two kinetically inert Pd-Cl centers and a cyano group, which is able to coordinate to palladium. The chloro group, however, can be removed with $AgBF_4$. In this way, using **G_0** as the core and **BB_{CN}-Cl** as dendrons, palladium dendrimers up to the fifth generation can be constructed by iterative treatment with $AgBF_4$ and **BB_{CN}-Cl**. A major advantage of this approach compared to covalent dendrimer synthesis, is the high yield of the complexation reaction. This greatly reduces the number of mismatches in the product.

Although the use of supramolecular interactions between neutral molecules has led to convergently synthesized dendrimers, in which the covalently synthesized dendrons are held together by hydrogen bonds,[8] dendritic structures based on supramolecular interactions *at every branching point* have not been prepared.[12]

The high association constants of the host-guest systems described in Chapter 5 of this thesis, seem to qualify these molecules for use as building blocks in the construction of stable supramolecular dendritic or hyperbranched structures in solution. In this chapter a system is described that uses strong, yet reversible host-guest interactions at every branching point for the formation of a dendritic structure. This system consists of a molecular clip (**4**, see Scheme 1) of the type described in Chapters 4 and 5 of this thesis (the host), with two resorcinol residues (the guests) attached to its convex side (see Scheme 5). The resorcinol residues are connected to the clip part via an ester



Scheme 3 *Self-assembly of six Fréchet-type dendrons (the R groups) by means of hydrogen bonds*[8]



Scheme 4 *Preparation of metallodendrimers according to Reinhoudt*[11]

linkage. This linkage was chosen because the ester group is strongly electron withdrawing, thus increasing the binding constant of the guest to the desirably high values of 10^5 to 10^6 M^{-1}.[13]

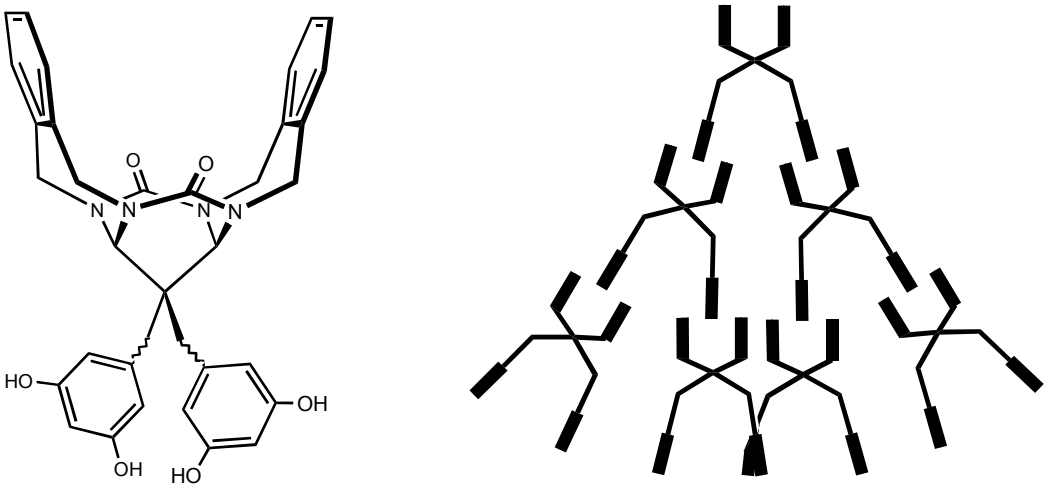
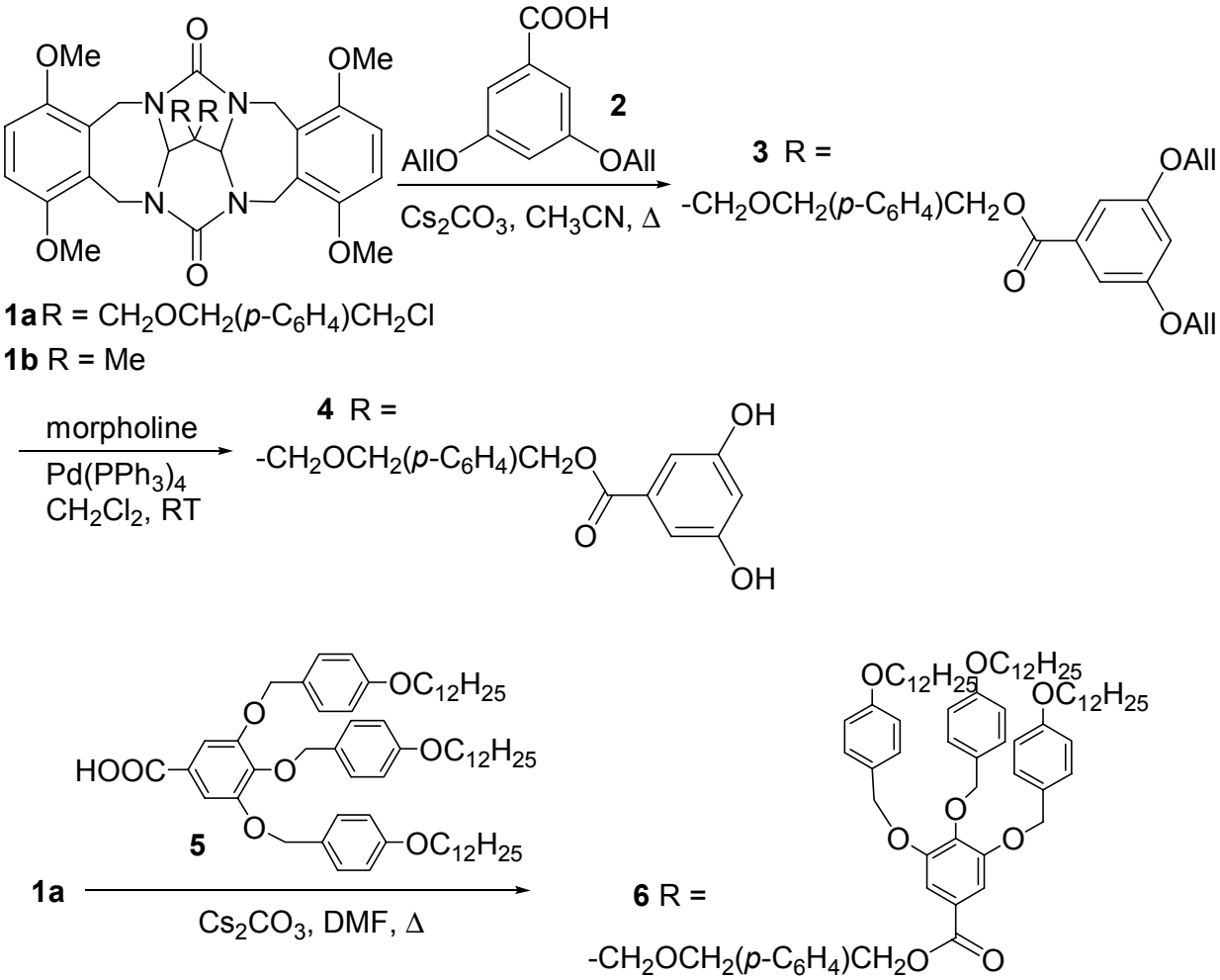


Figure 1 *Schematic representation of a clip with two guests connected to its convex side via a spacer, and its self-assembly into a dendritic structure*

An advantage of the use of non-covalent interactions instead of covalent ones is that only one molecule needs to be synthesized. It is expected to form a dendritic or hyperbranched structure by self-assembly in a suitable solvent, as pictured in Figure 1.
In section 7.2, the preparation and behavior of compound **4** is presented. This compound is studied by ^{1}H NMR and electron microscopy. In section 7.3, attempts are described to prepare a column-like aggregate of a multi-functional polymeric guest and clips with wedge-shaped tails. In section 7.4, the preparation of clip-functionalized polysiloxanes is discussed.

7.2 Results

The clip molecule that was used to prepare a self-assembling dendritic system based on host-guest interactions is molecule **4**. It was prepared in two steps from **1a** and **2** using standard procedures. Reaction of benzylic chloride **1a** with acid **2** in boiling acetonitrile using cesium carbonate as the base provided the ester **3** in high yield. Catalytic removal of the allyl groups with $Pd(PPh_3)_4$ and morpholine in CH_2Cl_2 gave **4** (see Scheme 5). This product precipitated from the reaction mixture and was isolated by filtration.
The interaction between a resorcinol guest and a molecular clip host is based on hydrogen bonding between the resorcinol hydroxy groups and the urea carbonyl groups of the clip, π-π interactions between the aromatic surfaces of host and guest, and a cavity effect, which can be considered as the enthalpically favorable filling of an empty space. From these interaction criteria it can be concluded that the interactions will be strongest in a solvent with following features: (*i*) it does not form competitive hydrogen bonds with the host or guest, (*ii*) it exhibits minimal π-π interaction, and (*iii*) it is too large to fit in the cavity. Suitable solvents are therefore mainly halogenated hydrocarbons such as chloroform and dichloro(m)ethane. Compound **4** appeared not to be soluble in these solvents, probably due to strong self-assembly based on host-guest interactions, which makes it



Scheme 5 *Preparation of clips with resorcinol residues or wedge-shaped tails at their convex sides*

very difficult to study its properties. Attempts to gain some insight in the behavior of this compound are described in the following section.

^{1}H NMR studies

Since NMR in pure $CDCl_3$ was not possible, we performed ^{1}H NMR studies on solutions containing different concentrations of **4** in $CDCl_3$ containing 20% of CD_3OD. If there is any host-guest interaction, increasing the concentration will lead to a higher concentration of the complexes, and probably also to a higher complexation rate, and consequently larger shifts of the protons near the complexating parts of the molecules. The aromatic proton situated between the hydroxy groups of the resorcinol residue was expected to show the largest shift upon complexation. Therefore, this proton was followed. At 0.5 mM, this proton appeared at δ 6.49 ppm, at 1 mM at 6.46 ppm, and at 2 mM at 6.41 ppm. It can therefore be concluded that, even in this highly competitive solvent mixture, significant complexation takes place. At lower methanol/chloroform ratios, the degree of complexation is expected to be higher. However, the solubility dropped dramatically when this ratio was decreased, rendering NMR experiments increasingly difficult.

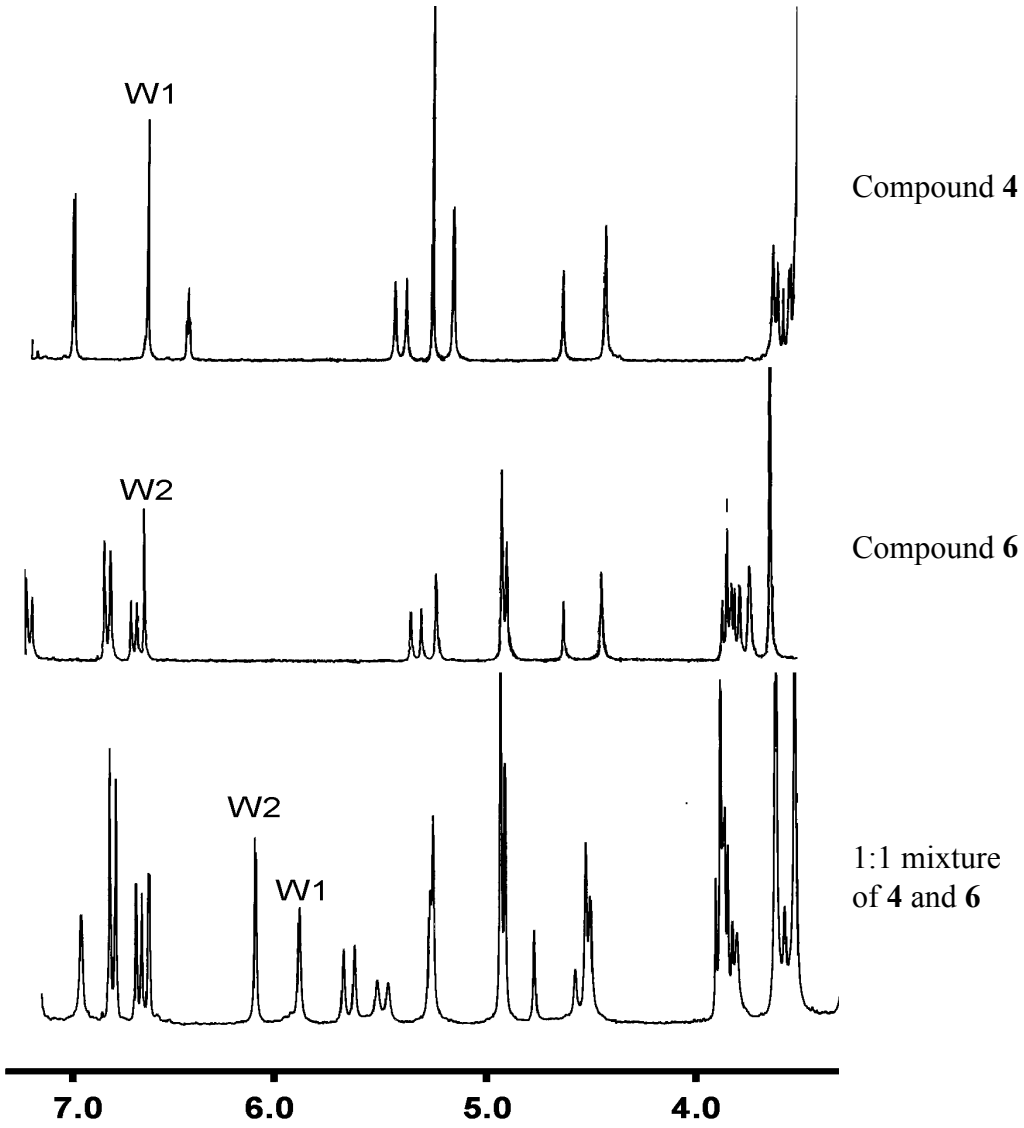


Figure 2 *^{1}H NMR spectra in $CDCl_3$ of compounds **4**, **6**, and the 1:1 mixture. The position of the side wall signal is indicated*

In chloroform, the high affinity of the cavities of **4** for resorcinol derivatives makes that a large number of these cavities will be occupied by guest residues, which are always present in excess. This will result in a structure in which the core, consisting of host-guest complexes is apolar, whereas the outside is covered with highly polar resorcinol hydroxy groups. This explains the virtual insolubility of **4** in the apolar solvent chloroform. Since we were interested in the behavior of **4** in solution, we attempted to overcome this solubility problem by coating the outside of the complex with clips containing aliphatic chains. For this purpose, we prepared clip **6**. This compound was prepared from **1a** and **5**, in a similar way as described for **4** (see Scheme 5). It was possible to prepare clear chloroform solutions containing clips **4** and **6** in a 1:1 ratio in the following way: the two compounds were dissolved in a mixture of chloroform and acetone, the solvents were allowed to evaporate at room temperature, and the resulting solid was redissolved in chloroform.

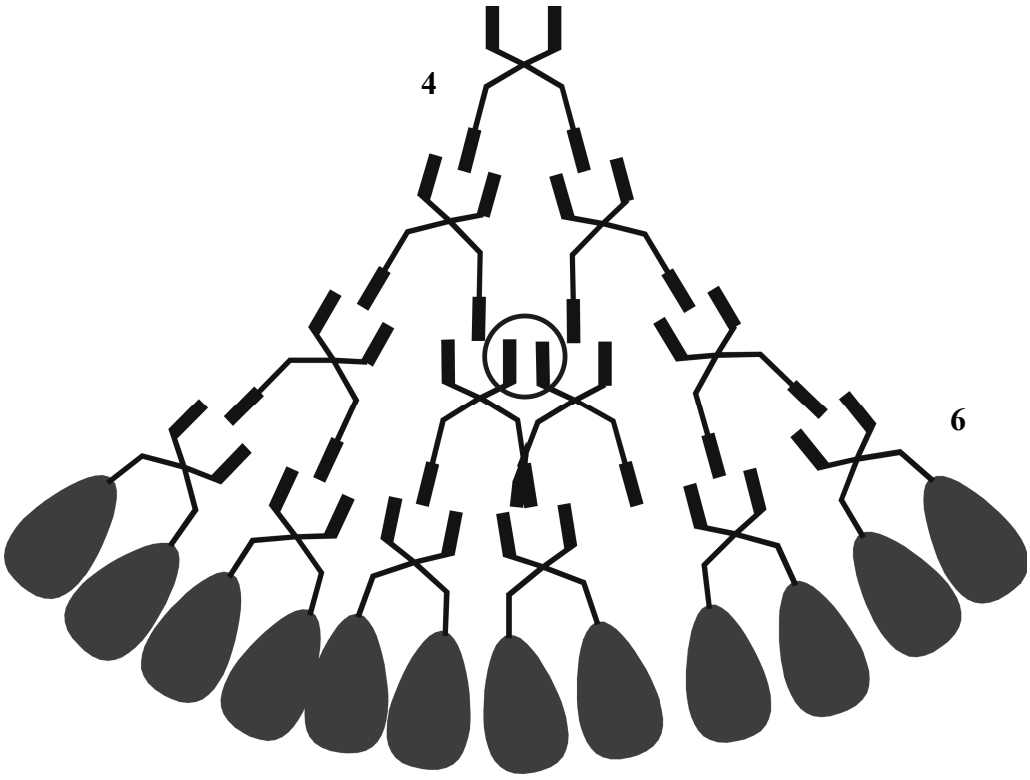


Figure 3 *Schematic representation of the self-assembly of clip molecules **4** and **6**. Interaction between two clip side walls is indicated with a circle.*

Figure 2 shows the ^{1}H NMR spectra of clip **4** (solubilized with a trace of DMSO-d_6)[a], clip **6**, and the 1:1 mixture of **4** and **6** in $CDCl_3$. The wall protons of clip **4** are shifted from δ 6.69 ppm in the uncomplexed state to 5.98 ppm in the 1:1 mixture with **6**. This shift of 0.71 ppm for the wall protons is higher than that of any other host-guest system studied in this thesis. It is significantly larger than the complexation induced shift (CIS) value of the unfunctionalized clip **1b** wall protons in a complex with the hexyl ester of 3,5-dihydroxybenzoic acid. This value, determined in a titration experiment, was 0.63 ppm. The remarkably large shift seen in the present experiment suggests that the cavities of clip **4** are not only occupied to a large extent by guest residues, but that secondary interactions also play a significant role. These secondary interactions probably include π-π stacking of neighboring cavity side walls, as indicated schematically in Figure 3.

A second feature of the side wall proton signals of **4** which deserves attention is the fact that these signals are slightly broadened in the 1:1 mixture. This broadening is not observed in a mixture of clip **1b** with the hexyl ester of 3,5-dihydroxybenzoic acid. It could indicate that the host-guest complex in the former system has a longer lifetime than in the latter. This is not unlikely because in a large supramolecular system some host-guest complexes are less susceptible to decomplexation because they are located in the core of the complex.

The signals due to the wall protons of clip **6**, on the contrary, are sharp, indicating that exchange is fast on the NMR time scale. They shift from δ 6.69 ppm in the uncomplexed state to 6.22 ppm in

[a] We assume that the NMR spectrum of **4** in $CDCl_3$/DMSO-d_6 shows reasonably accurate δ values for uncomplexed **4** in $CDCl_3$ since the shifts of the wall protons were the same as those of the allyl protected clip **3**.

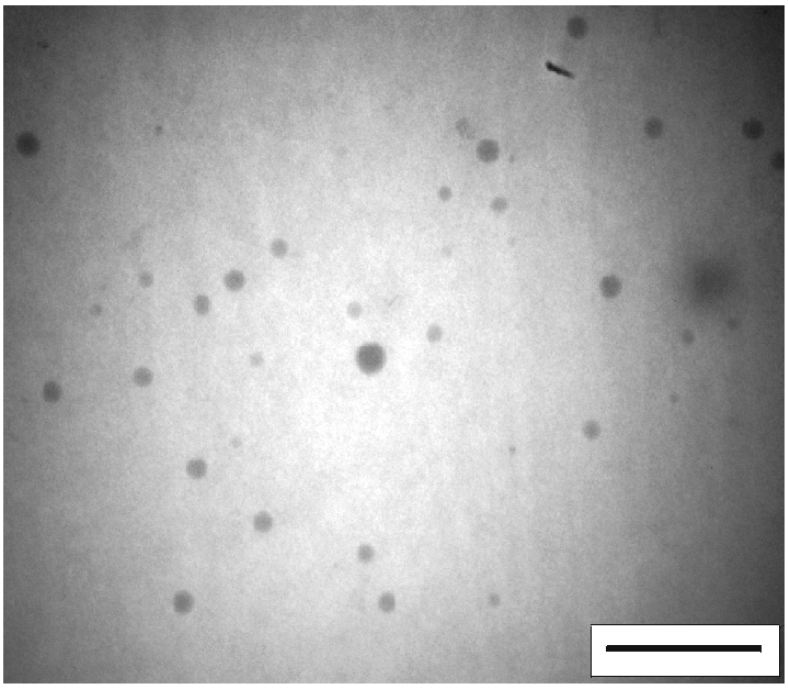


Figure 4 *TEM picture of aggregates of **4** and **6***

the 1:1 complex. This shift of 0.47 ppm indicates that approximately 25% of the clips in solution are present in the uncomplexed state. A possible reason for this relatively low complexation ratio (in view of the high association constant), is the crowdedness at the periphery of the complex, which, considering the size of **6**, might result in lower host-guest affinities. This is schematically represented in Figure 3.

TEM studies

If large supramolecular structures are present in 1:1 chloroform solutions of clips **4** and **6** it might be possible to visualize these structures with the help of transmission electron microscopy (TEM). We prepared a chloroform solution containing both clip **4** and clip **6** in a concentration of 0.4 mM using the procedure described for the NMR experiments. A drop of this solution was brought on a carbon coated copper grid, and the solvent was allowed to evaporate at room temperature. Figure 4 shows a TEM picture of this grid. It is covered with round structures with dimensions between 60 and 100 nm. A computer-generated model based on the host-guest chemistry of this system shows possible modes of aggregation of clips **4** and **6** (Figure 5). Formation of structure A consisting of two clips **6** and one clip **4** is very probable in view of the strong host-guest interactions present in this structure. Two of these complexes can subsequently bind to one molecule **4** to form a 3:4 complex of clips **4** and **6** in a dendrimer-like growth process (not shown).

Formation of larger complexes (7:8, 15:16, ..., $(2^n-1):2^n$) can also be envisaged. Built-up of complexes in this way will always result in an energetically unfavorable empty cavity at the starting point of the supramolecular dendron. Dimerization of two of these dendrons, as shown in Figure 5B for the 1:2 complex, would solve this problem. Although dimerization has not been seen for these clips in chloroform solution, they are generally present as dimers in the solid state (see Chapter 5).

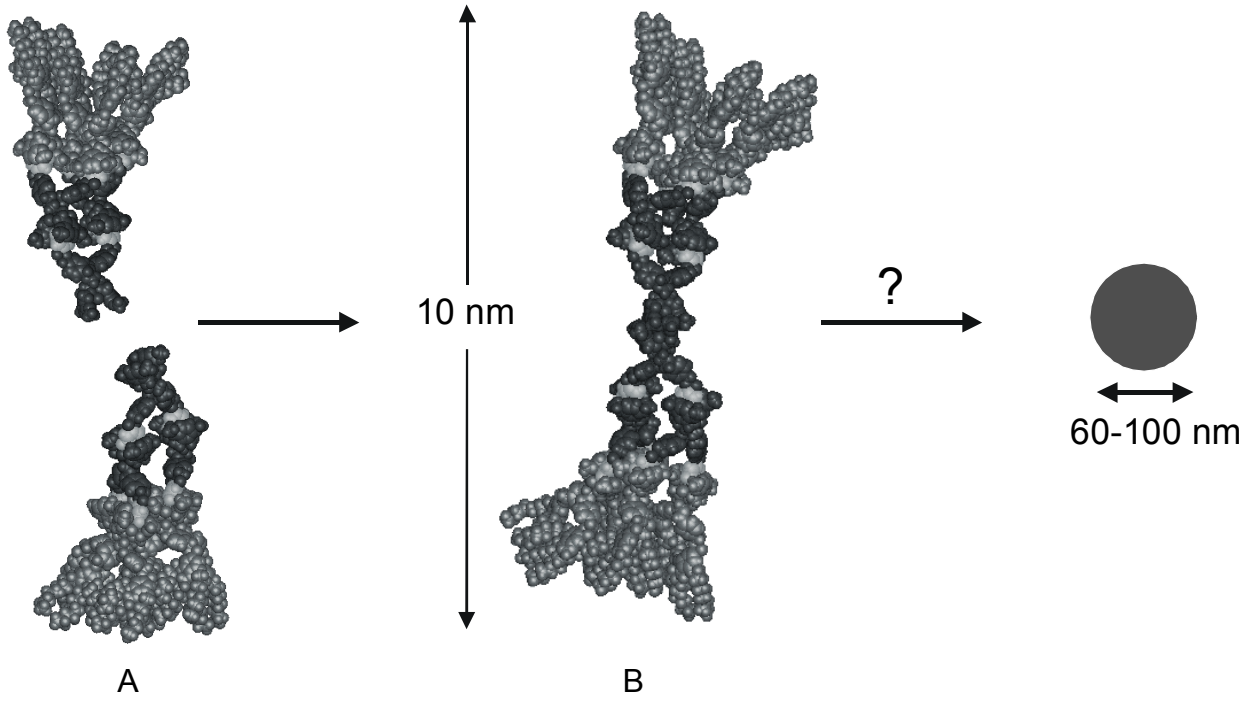


Figure 5 *Proposed self-assembly of clips **4** and **6***

A dimer of two 1:2 complexes has a length of approximately 10 nm. Dimers of structures with a higher degree of branching (*e.g.* 3:4, 7:8) will be slightly larger. Therefore, theoretically, these structures can grow to any dimension. It is presently unclear, however, how the round structures seen with the electron microscope are built up.

7.3 Aggregation of polymeric guest 7 with clip 6

The Tobacco Mosaic Virus (TMV) is a beautiful example of the way in which Nature uses supramolecular interactions and self-assembly to build up a complete virus particle. Under suitable conditions, this virus spontaneously assembles from its molecular components: one single RNA chain and 2130 identical protein subunits (see also Chapter 1).[14] For the supramolecular chemist it is a great challenge to construct a synthetic system that mimics this self-assembly process.
In an attempt to prepare a synthetic mimic of the TMV, Percec and co-workers used a linear synthetic polymer to which they covalently attached the wedge-shaped tails **5** introduced in the previous section.[15] The TMV mimic prepared in this way is actually a single molecule. A closer mimic however, would consist of two different components: a linear polymer and a molecule that binds to the subunits of this polymer sufficiently strongly and exhibits some self-assembling behavior. Polymer **7**, described in Chapter 6 of this thesis and the clip with the wedge-shaped tails **6** described in section 7.2 of this chapter seemed to be suitable candidates. The high association constants of the complexes between the resorcinol guest residues attached to the polymer and the clip molecules provide strong binding of the wedges to the core. In addition, the aromatic residues and the aliphatic tails in the wedges are expected to show some self-assembling behavior.

Similar to the system described in section 7.2, solubility problems complicated the study of the complexes of polymer **7** and clip **6**. The polymer is not soluble in halogenated hydrocarbons, which are the solvents of choice for complexation studies. We expected that it would be possible to solubilize polymer **7** by complexation of the hydrophilic resorcinol residues with the highly apolar clip **6**. To investigate the relative amount of clip necessary to solubilize the polymer a titration experiment was performed. Solutions of the polymer in acetone (4.4 μmol of resorcinol residues per gram) and the clip in chloroform (0.43 μmol per gram) were prepared. By mixing of 0.1 g of the polymer solution with different amounts of the clip solution, solutions were obtained containing the clip and the polymer in molar ratios of 1:1 to 1:10. These solutions were allowed to evaporate to dryness. The remaining solids were taken up in $CDCl_3$. Clear solutions were only obtained when 0.9 to 1 clip per guest residue was present.

The ^{1}H NMR spectra of the 1:1 solution and of free clip **6** are shown in Figure 6. As is evident from Figure 6, the signals of the protons of the cavity part of **6** are broadened in the mixture with polymer **7**. They are, however, hardly shifted with respect to the free clip signals. Moreover, no signals due to polymer **7** are visible in the spectrum. These observations can be explained by assuming that the signals of polymer and clips in the complex are severely broadened, to the extent

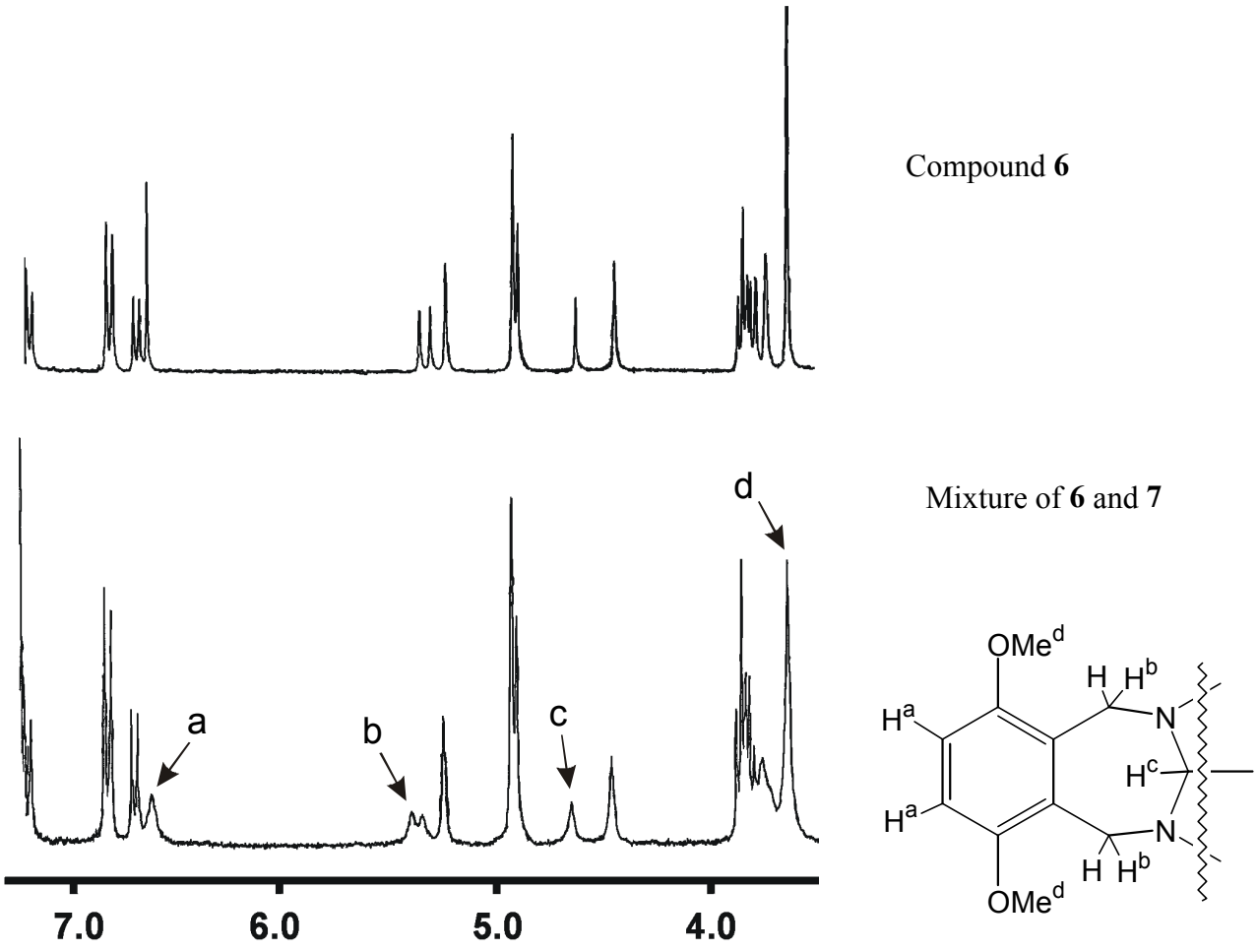


Figure 6 *^{1}H NMR spectra in $CDCl_3$ of compound **6** and a mixture of **6** and **7**. Broadened signals are indicated with arrows (see structural formula)*

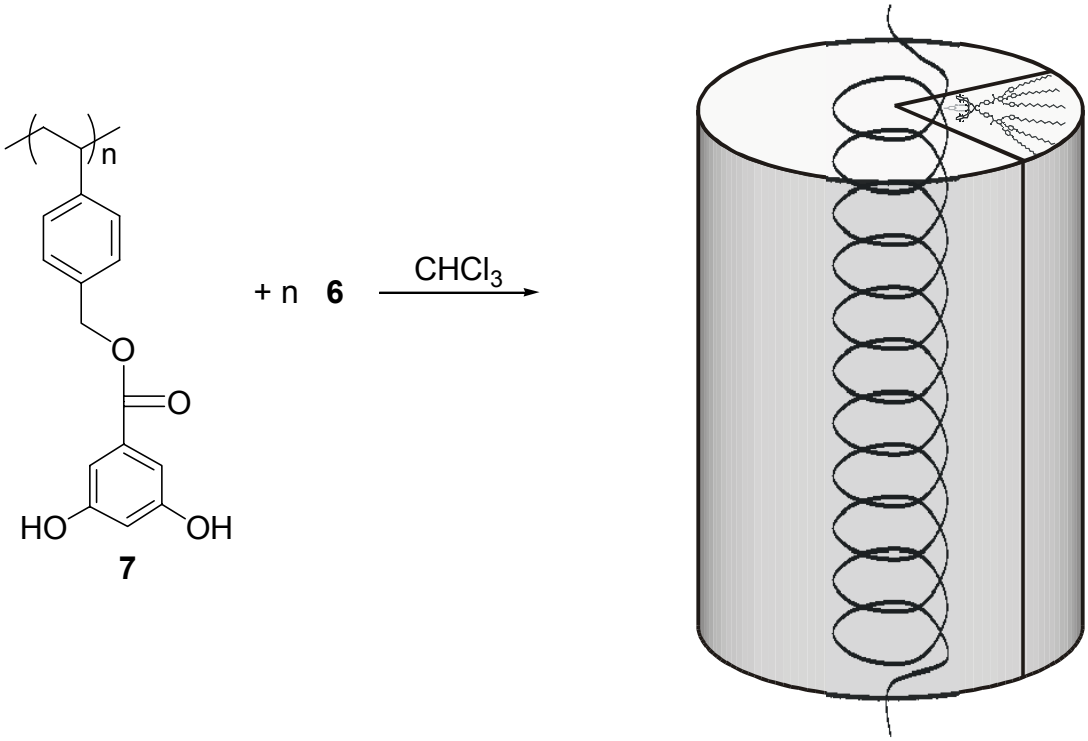


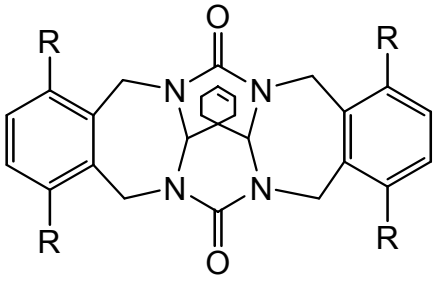
Figure 7 *Formation of a coated polymer by self-assembly*

that they are not visible any more in the spectrum. The signals that are visible are in fact due to free clip molecules in solution. Therefore, hardly any shifts due to host-guest complexation occur. Figure 7 shows how a column-like aggregate can form, by self-assembly of components **6** and **7**, in a way similar to the Tobacco Mosaic Virus.

Although the NMR data support the assumption that a complex is formed between polymer **7** and a number of clips **6**, additional data is required to describe the extent of complexation and the shape and structure of the aggregate. Initial TEM studies, similar to those described in section 7.2, did not show the presence of well-defined aggregates. Extensive proton, carbon and 2D NMR studies in combination with a thorough TEM investigation may provide the evidence needed to describe the structure of the polymer-clip complex in detail.

7.4 Grafting of polysiloxanes with molecular clips

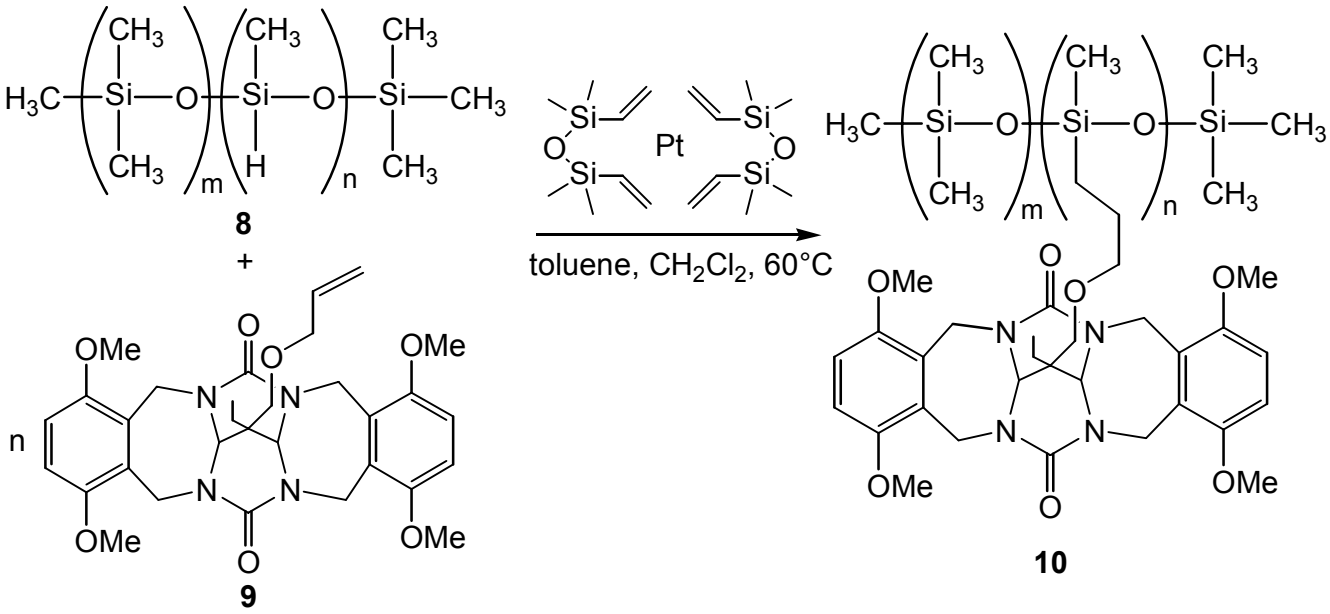
In the system described above a polymeric guest is used, to which wedge-shaped hosts are complexed. In a conceptually similar, but synthetically different approach, the host can be covalently attached to a polymer, followed by complexation with wedge-shaped guests. For this approach, we decided to use the commercially available polysiloxane **8** containing Si-H residues. Alkenes can be attached to Si-H bonds in a platinum catalyzed addition reaction.[16] Clip molecules **9** and **11a**,**b**, introduced in Chapter 4, were used as the alkenes.



11a R = H
11b R = OMe

Cyclohexene clips **11a**,**b** proved to be inert towards reaction with this polymer, even when boiling toluene was used. The inertness of these clip molecules in this reaction is in line with their behavior towards a number of other reagents, as described in Chapter 4. It was possible, however, to couple clip molecule **9**, containing an allyl group, to this siloxane polymer. The commercially available polysiloxane we used has a length of approximately 28 Si-O residues, of which on average seven or eight bear a Si-H function. The product was investigated by means of MALDI-TOF spectroscopy, and was shown to be a mixture of siloxane polymers with one, two, three, and four clip molecules attached. The fact that a maximum of four clips are attached to the polymer can be explained by steric factors: reaction of more clip molecules with the clip-grafted polymer will become increasingly difficult for these sterically demanding polymers. Moreover, side reactions may occur because the Si-H bond is susceptible to reaction with water, forming an inert Si-OH residue.

We may conclude that this approach is a promising way for grafting of polymers with host molecules.

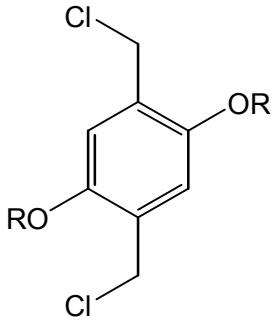


Scheme 6 *Grafting of a polysiloxane with molecular clips*

7.5 Conclusions and suggestions for further research

The search for dendrimers and other hyperbranched structures has resulted in various synthetic routes towards these types of compounds. In recent years non-covalent interactions and metal-ligand bonds have increasingly been used as synthetic tools in this field. The system described in this chapter is the first in which host-guest interactions are used to construct dendritic structures.

The host-guest complexation can take place at every branching point of the dendritic structure, rather than at a limited number of positions. The study of the behavior of these compounds turned out to be very difficult, mainly due to their limited solubilities in chloroform. Increasing the solubility of the complex without affecting its overall structure is in principle possible by the addition of aliphatic tails. In the future, these tails could be introduced at an early point in the synthesis, *e.g.* by using of clip side walls with octoxy instead of methoxy groups. Earlier work on clips with this kind of side walls has shown that the affinity for guests is not affected by these tails.[17]



12

Alternatively, the tails could be introduced at a later stage, *e.g.* by using alkoxy functionalized spacer groups (*e.g.* **12**) to connect the guests to the convex side of the clips of type **1a**.

7.6 Experimental section

General. Toluene was distilled from sodium benzophenone ketyl. Chloroform was distilled from $CaCl_2$. Acetonitrile and dichloromethane were distilled from CaH_2. DMF was stirred with BaO for one week, decanted, and distilled at reduced pressure. The first 30% of the distillate was discarded. All other solvents and chemicals were commercially available materials and were used as received. Reactions were carried out in an inert argon atmosphere. Merck silica gel (60H) was used for column chromatography. Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument with $(CH_3)_4Si$ as the internal standard (δ 0.00 ppm) for the ^1H spectra, and $CDCl_3$ as the internal standard (δ 77.0 ppm) for the ^{13}C spectra. Abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were recorded on a Finnigan MAT900S instrument. Elemental analyses were determined with a Carbo Erba EA 1108 instrument.

Compounds: Compounds **2**[18] and **5**[15] were prepared according to literature procedures. Compounds **1a** and **7** were prepared as described in Chapter 6, and compounds **1b**, **9**, **11a**, and **11b** were prepared as described in Chapter 4. Polymer **8** was an atactic methylhydrosiloxane-dimethylsiloxane copolymer with a molecular weight of 1900-2000 containing 25-30 molpercentage methylhydrosiloxane groups. It was obtained from ABCR. The platinum divinyltetramethyldisiloxane complex was obtained from Fluorochem.

Allyl protected resorcinol functionalized clip 3: Clip **1a** (100 mg, 0.12 mmol), 3,5-diallyloxybenzoic acid (**2**, 85.9 mg, 0.37 mmol), and cesium carbonate (159.5 mg, 0.49 mmol) were suspended in acetonitrile (10 mL). The mixture was refluxed for 1 h, cooled, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/EtOH, 99:1 v/v) yielding 0.13 mg of a white solid (90%). M.p. 145°C. FAB MS (*m/z*) 1213 ($[M+H]^+$), 1235 ($[M+Na]^+$), 391 (100%). ^1H NMR ($CDCl_3$): δ 3.75 (s, 12H, ArOC*H*$_3$), 3.83 (s, 4H,

C*H*$_2$OCH$_2$Ar), 3.88 (d, J = 15.6 Hz, 4H, NC*H*$_2$Ar), 4.52 (s, 4H, OC*H*$_2$ArCH$_2$OC(O)), 4.54 (d, J = 6.0 Hz, OC*H*$_2$CH=CH$_2$), 5.32 (s, 4H, ArC*H*$_2$OC(O)), 4.71 (s, 2H, NC*H*N), 5.33-5.26 (m, 8H, OCH$_2$CH=C*H*$_2$), 5.40 (d, J = 15.6 Hz, 4H, NC*H*$_2$Ar), 6.07-5.98 (m, 4H, OCH$_2$C*H*=CH$_2$), 6.68 (t, J = 2.1 Hz, 2H, C*H*(COAll)$_2$), 6.72 (s, 4H, Ar*H* clip wall), 7.22 (d, J = 2.1 Hz, 4H, C*H*CC(O)OCH$_2$), 7.27 (d, J = 7.8 Hz, 4H, OCH$_2$Ar*H*), 7.40 (d, J = 7.8 Hz, 4H, OCH$_2$Ar*H*). Anal. Cald. for $C_{69}H_{72}N_4O_{16}$: C: 68.30, H: 5.98, N: 4.62. Found: C: 68.44, H: 6.12, N: 4.35.

Resorcinol functionalized clip 4: Clip **3** (143 mg, 0.12 mmol) and morpholine (0.3 g, 2.9 mmol) were dissolved in dichloromethane (10 mL). The solution was degassed and a catalytic amount of Pd(PPh$_3$)$_4$ was added. The reaction mixture was stirred for 16 h at room temperature. The product was isolated by filtration and washed with dichloromethane and diethyl ether, yielding a white solid. Yield: 0.11 g (90%). M.p. 160°C. FAB MS (*m/z*) 1053 ([M+H]$^+$), 1075 ([M+Na]$^+$). ^{1}H NMR (CDCl$_3$/DMSO-d$_6$, 5:1): δ 3.69 (s, 12H, ArOC*H*$_3$), 3.75 (d, J = 15.3 Hz, 4H, NC*H*$_2$Ar), 3.79 (s, 4H, C*H*$_2$OCH$_2$Ar), 4.57 (s, 4H, OC*H*$_2$ArCH$_2$OC(O)), 4.77 (s, 2H, NC*H*N), 5.28 (s, 4H, ArC*H*$_2$OC(O)), 5.52 (d, J = 15.3 Hz, 4H, NC*H*$_2$Ar), 6.50 (t, J = 2.1 Hz, 2H, C*H*(COH)$_2$), 6.69 (s, 4H, Ar*H* clip wall), 7.03 (d, J = 2.1 Hz, 4H, C*H*CC(O)OCH$_2$), 7.32 (d, J = 7.8 Hz, 4H, OCH$_2$Ar*H*), 7.43 (d, J = 7.8 Hz, 4H, OCH$_2$Ar*H*). Anal. Cald. for $C_{57}H_{56}N_4O_{16}$: C: 65.01, H: 5.36, N: 5.32. Found: C: 64.75, H: 5.48, N: 5.46.

Clip with wedge-shaped tails 6: Clip **1a** (100 mg, 0.122 mmol), acid **5** (300 mg, 302 mmol), and cesium carbonate (270 mg, 828 mmol) were suspended in DMF (10 mL). The mixture was stirred at 85°C for 16 h, cooled, filtered, and extracted with CHCl$_3$. The organic layer was washed with water and purified by column chromatography (Et$_3$N/CH$_2$Cl$_2$, 1:99 v/v). Recrystallization from acetone yielded the pure product (185 mg, 55%). M.p. 131°C. FAB MS (*m/z*) 2754 ([M+Na]$^+$). ^{1}H NMR (CDCl$_3$): δ 0.88 (t, J = 6.7 Hz, 18H, CH$_2$C*H*$_3$), 1.26 (s, 108H, CH$_2$CH$_2$C*H*$_2$), 1.72-1.80 (m, 12H, OCH$_2$C*H*$_2$), 3.73 (s, 12H, O*Me*), 3.82-3.96 (m, 20H, OC*H*$_2$CH$_2$, NC*H*$_2$Ar, C*H*$_2$OCH$_2$Ar), 4.53 (s, 4H, CH$_2$OC*H*$_2$Ar), 4.71 (s, 2H, NC*H*N), 4.98 (s, 4H, ArOC*H*$_2$Ar (*para* with respect to ester)), 5.00 (s, 4H, ArOC*H*$_2$Ar (*meta* with respect to ester)), 5.31 (s, 4H, ArC*H*$_2$OC(O)Ar), 5.41 (d, J = 15 Hz, 4H, NC*H*$_2$Ar), 6.67 (s, 4H, Ar*H*, wall), 6.73 (d, J = 8.6 Hz, 4H, ArOCH$_2$Ar*H* (*para* with respect to ester, *ortho* with respect to CH$_2$)), 6.86 (d, J = 8.6 Hz, 8H, ArOCH$_2$Ar*H* (*meta* with respect to ester, *ortho* with respect to CH$_2$)), 7.23 (d, J = 8.6 Hz, 4H, ArOCH$_2$Ar*H* (*para* with respect to ester, *meta* with respect to CH$_2$)), 7.28 (d, J = 8.6 Hz, 4H, CH$_2$Ar*H*CH$_2$), 7.29 (d, J = 8.6 Hz, 8H, ArOCH$_2$Ar*H* (*meta* with respect to ester, *meta* with respect to CH$_2$)), 7.38 (s, 4H, Ar*H*, *ortho* with respect to ester), 7.39 (d, J = 8.6 Hz, 4H, CH$_2$Ar*H*CH$_2$). ^{13}C NMR (CDCl$_3$): δ 14.10 (*C*H$_3$CH$_2$), 22.67 (CH$_2$*C*H$_2$CH$_2$), 26.07, 29.31, 29.43, 29.61, and 31.91 (CH$_2$*C*H$_2$CH$_2$), 40.77 (*C*C$_4$), 44.81 (N*C*H$_2$Ar), 57.23 (O*C*H$_3$), 67.96 and 68.03 (O*C*H$_2$CH$_2$), 66.45, 67.24, 71.10, 72.99, 73.21, and 74.70 (other O*C*H$_2$ and N*C*HN), 109.33 (*C*H, *ortho* to ester), 112.40 (*C*H, wall), 114.07 and 114.41 (*C*H, *ortho* with respect to dodecoxy tail), 124.89, 127.68, 128.09, 128.29, 129.25, 129.42, 130.20, 135.67, and 138.18 (aromatic *C*H and *C*CH$_2$), 142.67 (aromatic *C*O, *para* with respect to ester), 151.72, 152.64, and 158.99 (other aromatic *C*O), 154.73 (urea *C*O), 166.04 (ester *C*O).

Clip grafted polysiloxane 10: Polymer **8** (45 mg) and clip **9** were dissolved in a mixture of toluene (12 mL) and CH_2Cl_2 (5 mL). Two drops of the platinum catalyst were added and the reaction mixture was stirred at 60°C in a closed vessel for 16 h. The solvent was removed *in vacuo* and the residue was dissolved in a minimal amount of CH_2Cl_2. The solution was slowly added to methanol, resulting in the precipitation of the product. The precipitate was further purified by two precipitation steps, resulting in a 23 mg of a gray solid. MALDI-TOF spectroscopy showed the presence of polymers with 1, 2, 3, and 4 clips attached. ^{1}H NMR ($CDCl_3$): δ 0.07 (bs, Si-*Me*), 0.50 (b, Si-C*H*$_2$), 0.94 (b, CH_2CH_3), 1.60 (b, CH_2CH_3), 1.90 (b, $CH_2CH_2CH_2$), 3.37 (b, OCH_2CH_2), 3.68 (b, O*Me*, ArCH_2, $CH_2OCH_2CH_2$), 4.52 (bs, NC*H*N), 5.58 (b, ArCH_2), 6.37 (b, Ar*H*).

7.7 References

1 (a) Bosman, A.W.; Janssen, H.M.; Meijer, E.W. *Chem. Rev.* **1999**, *99*, 1665; (b) Newkome, G.R.; He, E.; Moorefield, C.N. *Chem. Rev.* **1999**, *99*, 1689; (c) Smith, D.K.; Diederich, F. *Chem. Eur. J.* **1998**, *4*, 1353; (d) Zeng, F.; Zimmerman, S.C. *Chem. Rev.* **1997**, *97*, 1681; (e) Fischer, M.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 885.

2 Buhleier, E.W.; Wehner, W.; Vögtle, F. *Synthesis* **1978**, 155.

3 (a) Tomalia, D.A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117; (b) Tomalia, D.A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466; (c) Tomalia, D.A.; Naylor, A.M.; Goddard, W.A., III. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138.

4 (a) Newkome, G.R.; Yao, Z.; Baker, G.R.; Gupta, V.K. *J. Org. Chem.* **1985**, *50*, 2004; (b) Newkome, G.R.; Baker, G.R.; Saunders, M.J.; Russo, P.S.; Gupta, V.K. ; Yao, Z.; Bouillon, J.E. *J. Chem. Soc., Chem. Commun.* **1986**, 752; (c) Newkome, G.R.; Yao, Z.; Baker, G.R.; Gupta, V.K.; Russo, P.S.; Saunders, M.J. *J. Am. Chem. Soc.* **1986**, *108*, 849.

5 (a) De Brabander-van den Berg, E.M.M.; Meijer, E.W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1306; (b) Jansen, J.F.G.A.; De Brabander-van den Berg, E.M.M.; Meijer, E.W. *Science* **1994**, *266*, 1226.

6 Hummelen, J.C.; Van Dongen, J.L.J.; Meijer, E.W. *Chem. Eur. J.* **1997**, *3*, 1489.

7 Hawker, C.J.; Fréchet, J.M.J. *J. Am. Chem. Soc.* **1990**, *112*, 7639.

8 Zimmerman, S.C.; Zeng, F.W.; Reichert, D.E.C.; Kolotuchin, S.V. *Science* **1996**, *271*, 1098.

9 Knapen, J.W.J.; Van der Made, A.W.; De Wilde, J.C.; Van Leeuwen, P.W.N.M.; Wijkens, P.; Grove, D.M.; Van Koten, G. *Nature* **1994**, *372*, 659.

10 (a) Campagna, S.; Denti, G.; Serroni, S.; Juris, A.; Venturi, M.; Ricevuto, V.; Balzani, V. *Chem. Eur. J.* **1995**, *1*, 211; (b) Balzani, V.; Campagna, S.; Denti, G.; Juris, A.; Serroni, S.; Venturi, M. *Acc. Chem. Res.* **1998**, *31*, 26.

11 (a) Huck, W.T.S.; Roher, A.; Anilkumar, A.T.; Fokkens, R.H.; Nibbering, N.M.M.; Van Veggel, F.C.J.M.; Reinhoudt, D.N. *New J. Chem.* **1998**, 165; (b) Huisman, B.-H.; Schönherr, H.; Huck, W.T.S.; Friggeri, A.; Van Manen, H.-J.; Menozzi, E.; Vancso, G.J.; Van Veggel, F.C.J.M.; Reinhoudt, D.N. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2248; (c) Huck, W.T.S.; Hulst, R.; Timmerman, P.; Van Veggel, F.C.J.M.; Reinhoudt, D.N. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1006; (d) Huck, W.T.S.; Van Veggel, F.C.J.M.; Kropman, M.L.; Blank, D.H.A.; Keim, E.G.; Smithers, M.M.A.; Reinhoudt, D.N. *J. Am. Chem. Soc.* **1995**, *117*, 8293; (e) Huck, W.T.S.; Prins, L.J.; Fokkens, R.H.; Nibbering, N.M.M.; Van

Veggel, F.C.J.M.; Reinhoudt, D.N. *J. Am. Chem. Soc.* **1998**, *120*, 6240; (f) Huck, W.T.S.; Van Veggel, F.C.J.M.; Reinhoudt, D.N. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1213.

12 Linear supramolecular polymers based on complementary hydrogen bonding units or anion-crown ether complexation have been prepared (see, for example: (a) Fouquey, C.; Lehn, J.-M.; Levelut, A.-M. *Adv. Mater.* **1990**, *2*, 254; (b) Yamaguchi, N.; Gibson, H. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 143). Supramolecular polymers with an appreciably high degree of polymerization (also in dilute solution), have recently been prepared and studied by Meijer and co-workers (Sijbesma, R.P.; Beijer, F.H.; Brunsveld, L.; Folmer, B.J.B.; Hirschberg, J.H.K.K.; Lange, R.F.M.; Lowe, J.K.L.; Meijer, E.W. *Science* **1997**, *278*, 1601). They showed that high association constants ($K_a > 10^6$ M^{-1}) were needed in these systems.

13 Substituents with an electron withdrawing capacity that is comparable to or stronger than the ester group (*e.g.* Cl or CN, see Chapter 5) do not allow for further functionalization.

14 Stryer, L. *Biochemistry*, 3rd ed., New York, **1988**.

15 Percec, V.; Ahn, C.-H.; Cho, W.-D.; Jamieson, A.M.; Kim, J.; Leman, T.; Schmidt, M.; Gerle, M.; Möller, M.; Prokhorova, S.A.; Sheiko, S.S.; Cheng, S.Z.D.; Zhang, A.; Ungar, G.; Yeardley, D.J.P. *J. Am. Chem. Soc.* **1998**, *120*, 8619.

16 Miller, M.L.; West, R. *Chem. Commun.* **1999**, 1797.

17 Gieling, G.T.W.; Scheeren, H.W.; Israël, R.; Nolte, R.J.M. *Chem. Commun.* **1996**, 241.

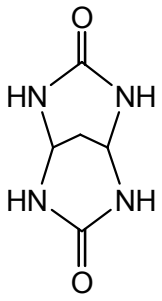
18 Van Nunen, J.L.M.; Folmer, B.F.B.; Nolte, R.J.M. *J. Am. Chem. Soc.* **1997**, *119*, 283.

Summary

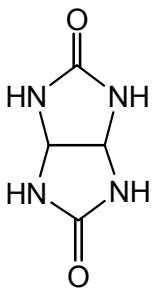
This thesis describes the synthesis and physical properties of a series of molecular clips derived from the concave molecule propanediurea (**1**). These molecular clips are cavity-containing receptors that can bind a variety of aromatic guests. This binding is a result of hydrogen bonding and π-π stacking interactions (see **4**). Previous work on molecular clips has been limited to compounds derived from substituted glycoluril (**2**). Propanediurea, the compound on which the clips described in this thesis are based, is a molecule that is very similar to glycoluril, the major difference being the presence of a methylene group in the former compound. This methylene group makes propanediurea slightly more concave, *i.e.* the angle between the urea carbonyl groups is sharper, and as a result, the oxygen atoms are positioned closer together. A second important difference between glycoluril and propanediurea is the relatively easy and well-documented synthesis of the former molecule and its derivatives, as opposed to the more laborious and much less extensively described synthesis of the latter compound and its derivatives.

In Chapter 2, a literature survey on the synthesis of glycoluril derivatives and its analogues is presented, with special focus on propanediurea derivatives.

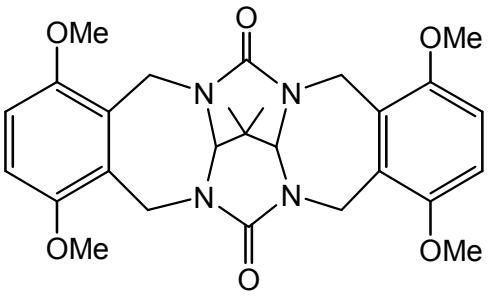
Synthetic efforts to prepare a variety of propanediurea derivatives, which constitute the basis of the rest of the work described in this thesis, are described in Chapter 3. Three different methods for the



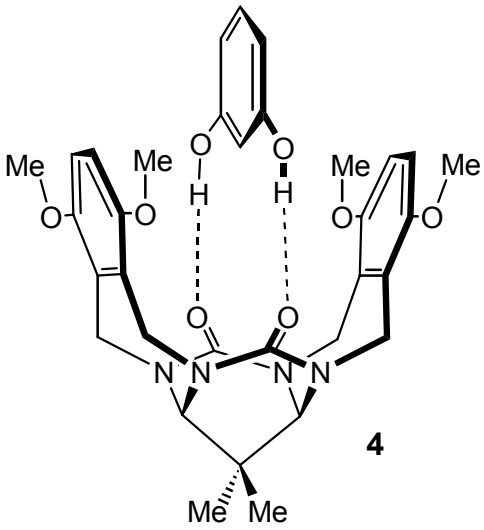
1



2



3



4

preparation of these compounds are treated, starting from (*i*) β-diketones, (*ii*) β-ketoaldehydes, and (*iii*) 1,3-dialdehyde analogues. The first method is straightforward and fast, but not very versatile. Using the second method, a large number of propanediurea derivatives can be prepared, with relatively few synthetic limitations. The third method, which is synthetically more demanding than the other two, provides a route towards propanediurea derivatives that can be functionalized relatively easily at a later stage.

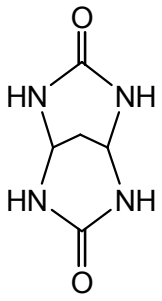
In Chapter 4, the synthesis of molecular clips from the propanediurea derivatives prepared according to the routes described in Chapter 3 is discussed. These clips are accessible through two conceptually different synthetic pathways. The first is a well-documented two-step procedure involving formylation of the propanediurea NH-groups, followed by a ureidoalkylation reaction with and aromatic compound. This procedure, which has also been used for the synthesis of clips from glycoluril derivatives, gives access to a clip with dimethoxybenzene side walls (**3**), a clip with 1,4-dimethoxynaphthalene side walls, and a series of half clips. The method, however, is far less versatile for propanediurea derivatives than for glycoluril derivatives. The second pathway involves deprotonation of the propanediurea NH-groups with a strong base, followed by reaction with benzylic bromides. A number of clips with benzene and 1,4-dimethoxybenzene side walls have been prepared using this procedure.

In Chapter 5 the binding properties of the propanediurea-derived clips are investigated. For these clips, it is shown that a higher flexibility of the side walls increases the affinity for guests. The binding properties of the clips can be fine-tuned by introducing substituents under the side walls of the molecules. A comparison is made between clips derived from propanediurea and clips derived from glycoluril. The former clips have a much higher affinity for resorcinol than the latter ones. Using NMR binding studies and X-ray diffraction analysis it is shown that this difference is due to a slightly smaller distance between the carbonyl binding sites in the propanediurea-derived clips. This geometrical feature makes these clips much better suited to accommodate resorcinol guests.

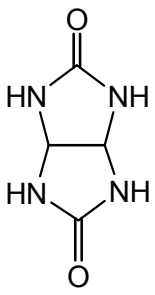
The last two chapters of this thesis focus on functionalizations of the propanediurea-derived clip molecules, with the ultimate goal of using their exceptional binding properties in the construction of large supramolecular aggregates. In Chapter 6, clips functionalized with porphyrin residues are described. Self-assembly of four bis-porphyrin hosts around a tetrafunctional porphyrin guest gives rise to a nona-porphyrin complex. A columnar aggregate is prepared by self-assembly of these bis-porphyrin hosts around polystyrene functionalized with resorcinol groups. The same polymer is used in Chapter 7 to form a columnar aggregate by self-assocation with clips functionalized at their convex sides with long aliphatic tails. In addition, a clip functionalized at its convex side with resorcinol residues is presented. This molecule can self-associate to form hyperbranched or dendrimer-like structures.

Samenvatting

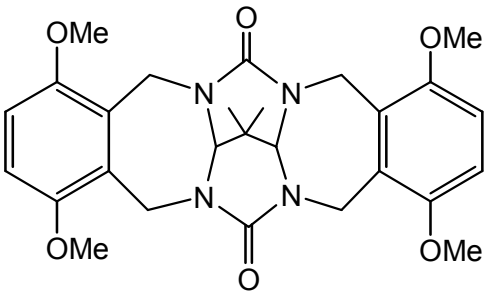
In dit proefschift worden de synthese en fysische eigenschappen beschreven van een aantal moleculaire clips die afgeleid zijn van het concave molecuul propaandiureum (**1**). Deze moleculaire clips zijn synthetische receptoren waarin een holte aanwezig is. Deze zogenaamde gastheermoleculen zijn in staat om in deze holte aromatische gastmoleculen te binden met behulp van waterstofbruggen en π-π interacties (zie **4**). Onderzoek naar deze clips is in het verleden beperkt gebleven tot verbindingen die afgeleid zijn van glycoluril (**2**). De clips die in dit proefschrift worden beschreven zijn afgeleid van propaandiureum, een verbinding die zeer sterk lijkt op glycoluril. Een belangrijk verschil tussen deze twee verbindingen is de aanwezigheid van een extra methyleen groep in propaandiureum, die er voor zorgt dat dit molecuul wat meer concaaf is. Dit houdt in dat de hoek tussen de carbonylgroepen wat scherper is, als gevolg waarvan de zuurstofatomen dichter bij elkaar staan. Een geheel ander, maar daarom niet minder belangrijk verschil, is het feit dat de synthese van glycolurilderivaten zeer goed beschreven is in de literatuur en bovendien eenvoudig is, terwijl het relatief kleine aantal gedocumenteerde propaandiureum-derivaten op een wat omslachtigere wijze gemaakt wordt.
Hoofdstuk 2 geeft een literatuuroverzicht van de synthese van glycolurilderivaten en –analoga, waarbij uitgebreid wordt ingegaan op derivaten van propaandiureum.



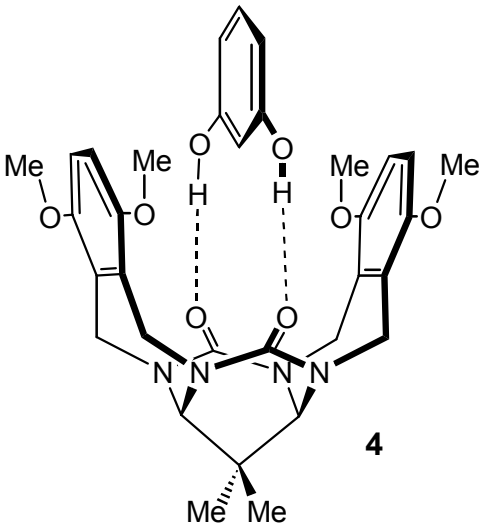
1



2



3



4

In hoofdstuk 3 worden de syntheses beschreven van de propaandiureumderivaten die de basis vormen van de overige studies in dit proefschrift. Drie verschillende syntheseroutes worden behandeld: de eerste gaat uit van β-diketonen, de tweede van β-ketoaldehydes en de derde van 1,3-dialdehyde-analoga. Met de eerste methode, die eenvoudig en snel is, kan slechts een beperkt aantal propaandiureumderivaten bereid worden. De tweede methode is ook niet erg bewerkelijk en kent bovendien veel minder synthetische beperkingen. Een groot aantal propaandiureumderivaten is dan ook volgens deze methode gemaakt. De derde methode vergt, in tegenstelling tot de andere twee, een relatief grote synthetische inspanning, maar geeft wel toegang tot propaandiureumderivaten die later gemakkelijk gefunctionaliseerd kunnen worden.
In hoofdstuk 4 wordt de synthese van moleculaire clips op basis van propaandiureumderivaten behandeld. Twee conceptueel verschillende routes worden beschreven. Allereerst wordt besproken in hoeverre de syntheseroute die gebruikt wordt voor de bereiding van clips uitgaande van glycolurilderivaten toepasbaar is op propaandiureumderivaten. De eerste stap in deze syntheseroute is formylering van de NH-groepen van propaandiureum die gevolgd wordt door een ureidoalkyleringsreactie met een aromatische verbinding. Volgens deze methode is een clip gemaakt met dimethoxybenzeenwanden (**3**) alsmede een clip met 1,4-dimethoxynaftaleenwanden. Daarnaast geeft deze methode ook toegang tot een aantal 'halve clips'. De synthese van clips volgens deze methode verloopt voor propaandiureumderivaten veel minder voorspoedig dan voor glycolurilderivaten. In de tweede syntheseroute worden de NH-groepen van propaandiureum eerst gedeprotoneerd met een sterke base en daarna in reactie gebracht met een benzylisch bromide. Enkele clips met benzeen– en 1,4-dimethoxybenzeenwanden zijn met behulp van deze methode bereid.
In hoofdstuk 5 worden de bindingseigenschappen van de clips op basis van propaandiureum beschreven. Er wordt aangetoond dat een hogere flexibiliteit van de zijwanden van de clips resulteert in een sterkere gastbinding. De bindingseigenschappen van de clips kunnen beïnvloed worden door het aanbrengen van sustituenten onder de zijwanden. Een uitgebreide vergelijking van clips gebaseerd op propaandiureum en clips gebaseerd op glycoluril laat zien dat de propaandiureum-clips resorcinol veel sterker binden dan de glycoluril-clips. Met behulp van kristalstructuuranalyse en bindingsstudies met NMR is aangetoond dat dit verschil het gevolg is van een kortere afstand tussen de carbonylgroepen van propaandiureumclips. Als gevolg van dit kleine structuurverschil past resorcinol veel beter in deze clips.
In de laatste twee hoofdstukken van dit proefschrift worden propaandiureum-clips beschreven die aan de achterzijde gefunctionaliseerd zijn, met als doel de zeer sterke affiniteit van deze clips voor resorcinolderivaten te gebruiken voor de constructie van grotere supramoleculaire structuren. In hoofdstuk 6 worden clips besproken die gefunctionaliseerd zijn met porfyrines. Een non-covalent gebonden nona-porfyrinecomplex is gesynthetiseerd door zelf-assemblage van vier bis-porfyrine gastheermoleculen rond een tetrafunctionele porfyrinegast. Op een soortgelijke wijze is een staafvormig porfyrineaggregaat gemaakt uit deze gastheermoleculen en een met resorcinolresiduen gefunctionaliseerd styreenpolymeer. Ditzelfde polymeer wordt in hoofdstuk 7 gebruikt voor de vorming van een ander staafvormig aggregaat, en wel één waarbij clips gefunctionaliseerd met

grote alifatische groepen aan dit polymeer worden gebonden. Verder worden in dit laatste hoofdstuk de synthese en eigenschappen beschreven van een clipmolecuul dat aan de achterzijde is voorzien van twee covalent gebonden resorcinolresiduen. Door middel van zelf-associatie kan dit molecuul sterk vertakte of zelfs dendrimeerachtige structuren vormen.

Dankwoord

Het dankwoord is voor mij het belangrijkste gedeelte van dit proefschrift. En dat is niet alleen omdat dit het meest gelezen deel is, maar vooral ook omdat ik hier kan laten zien dat dit boekje nooit vol had kunnen geraken zonder de hulp van een groot aantal mensen. En nu heb ik dus eindelijk de kans om hen allemaal officieel te bedanken.

Allereerst mijn promotor, Prof. dr. R. J. M. Nolte. Roeland, bedankt dat je mij de mogelijkheid hebt geboden om in jouw groep een promotieonderzoek te doen. Bedankt voor het vertrouwen dat je in mij hebt gehad en de daaruit voortvloeiende vrijheid die je mij hebt gegeven bij het opzetten en uitvoeren van het onderzoek. Jouw enthousiasme voor de nieuwe clips en hun hoge bindingsconstantes heeft me altijd gestimuleerd om door te gaan.
Minstens evenzoveel dank gaat uit naar mijn copromotor, Dr. J. W. Scheeren. Hans, bedankt dat je genoeg vertrouwen hebt gehad in mijn synthetische kwaliteiten om me aan te nemen voor een project waarbij de aloude clips eens goed door de synthetische mangel moesten. Van jou kwam het geweldige idee om clips te maken uit propaandiureum. Ongelooflijk dat je altijd een oplossing paraat had als ik weer eens vast zat met de syntheses. Ook heb ik je nuchtere kijk op de zaken altijd erg kunnen waarderen. Als ik me te hoog liet meevoeren door supramoleculaire fantasieën, wist jij me altijd weer snel met beide benen op de synthetische grond te zetten.

Als derde gaat een speciaal woord van dank natuurlijk naar René Aben. Na een verzoekje van Hans heb jij vol overgave je tanden gezet in de synthese van propaandiureumderivaten met een functionaliteit aan de achterzijde. De voor mij onbekende chemie van aldehydes, acetalen en allerlei beschermgroepen bleek aan jou goed besteed. Het grootste deel van hoofdstuk 3 van dit proefschrift is eigenlijk slechts een beknopte samenvatting van de onvoorstelbare hoeveelheid werk die je hebt verricht. Je hebt me een boel geleerd. Bovendien zouden hoofdstukken 6 en 7 nooit van de grond gekomen zijn zonder het benzylethergefunctionaliseerde propaandiureum dat je in elkaar hebt gezet. Bedankt!

Ik heb het genoegen gehad vier studenten te mogen begeleiden. Allereerst was daar Joost. Jouw project om een functionele groep in te bouwen in de propaandiureumclips, leidde al snel tot clips met een cyclohexeengroep aan de achterzijde. Deze clip bleek echter een harde noot om te kraken. Van de hardheid van deze noot had Jurry later ook last, toen hij probeerde om clipgefunctionaliseerd polysiloxaan te maken. Toen jij al lang en breed mijn collega-aio was, is het mij gelukt om, met de kennis die jij hebt opgebouwd, een veel reactievere clip aan polysiloxaan te zetten. Femke kwam binnen toen ik net van René het benzylethergefunctionaliseerde propaandiureum had gekregen. Jij zette daar in een handomdraai twee wandjes bovenop en twee resorcinolen onderaan. Alle reacties gingen als een zonnetje en je doelmolecuul stond snel op de plank. Dit molecuul was echter een taaie rakker, en het karakteriseren van de aggregaten bleek erg ingewikkeld. Linda pakte de clipchemie snel op en ging zeer doelgericht aan de slag om porfyrines

aan de clips te knopen. Je overwon heel zelfstandig alle clip- en porfyrinegerelateerde tegenslagen, en het doelmolecuul kwam er. Jammer dat er geen tijd meer was om de zaken goed door te meten. Alle vier, bedankt voor jullie bijdrage aan dit proefschrift, de gezelligheid en de wederzijdse leermomenten.
Het lag voor mij voor de hand uit dit groepje harde werkers twee paranimfen te kiezen om me bij te staan tijdens mijn promotie: Jurry en Femke alvast bedankt voor de steun!
Een woord van dank gaat ook naar Frank van der Reijden, die met zijn hoofdvakscriptie over glycolurilachtigen een stevige basis heeft gelegd voor hoofdstuk 2.

Nog iemand die mij enorm geholpen heeft is Dr. Alan Rowan. Alan, bedankt voor de nuttige tips over van alles en nog wat. Je stond altijd klaar om al die informatie en ideeën die in je hoofd zitten met me te delen, soms zelfs op synthetisch gebied! Ook bedankt voor het kritisch doornemen van mijn manuscript. Dr. René de Gelder heeft met het oplossen van maar liefst tien kristalstructuren een essentiële bijdrage geleverd aan dit proefschrift. Het inzicht in de structuur en bindingseigenschappen van clips heeft hiermee een stevige impuls gekregen. Zonder deze belangrijke kristallografische data zouden onze twee gezamenlijke artikelen nooit het daglicht hebben mogen aanschouwen. René, hartelijk bedankt voor de consciëntieuze wijze waarop je prachtige kristalstructuren toverde uit de brokjes clipmolecuul die ik naar je toebracht.

Verder zijn er natuurlijk nog de mensen die de verschillende labzalen bevolkten. Zij hebben er samen voor gezorgd dat ik geen enkele dag met tegenzin naar mijn werk ben gegaan. Toen ik net begon was een aantal van hen de biezen al aan het pakken, maar ik heb toch nog even kunnen profiteren van hun chemische kennis en levenservaring. Bert, Joost, Gerben en Albert, bedankt. Mijn collega's van een latere lichting wil ik graag bedanken voor de gezellige werksfeer en de stimulerende gesprekken over chemie en andere zaken. Allereerst de dames en heren die samen met mij een groot gedeelte van hun (aio-)tijd in prakticumzaal VII op de begane grond hebben gezeten: Alexander, Hans, Jantien, Edward, Vera, Simon, Bea, Simon, Peter, Marga, Gerald, Johan en Ruud. Verder nog de collega's van de eerste verdieping: Martin, Hans, Bastienne, Bart, Peter, Hans en Cristina. En natuurlijk de collega's van de overkant: Jeroen, Pieter, Jurry, Joan, Kelly en Dennis. Jongens, allemaal hartelijk bedankt, het was een leuke tijd!

Alle collega's van de derde verdieping wil ik bedanken voor het geduld waarmee ze mij geholpen hebben als ik langs kwam met een basaal synthetisch probleempje.
Met Bert Lutz en Prof. dr. J. H. van der Maas (UU) heb ik prettig samengewerkt bij het uitvoeren van enkele IR-metingen. Mijn hartelijke dank daarvoor.

Voor analytische en logistieke ondersteuning ben ik aan een heleboel mensen dank verschuldigd. Allereerst natuurlijk Chris Kroon, die altijd klaar stond om mij te voorzien van glaswerk en chemicaliën en Wim van Luyn, voor chemicaliën op bestelling. Ad Swolfs zorgde dat de NMR-apparaten bleven draaien, Peter van Galen en Heleen Amatdjais-Groenen zorgden voor de

massaspectra en de elementanalyses en Pieter van der Meer voor de computers. Huub Geurts wil ik bedanken voor niet-aflatende elektronenmicroscopieondersteuning, Roel Fokkens (UvA, UT) voor de MALDI-TOF-metingen en Joost van Dongen (TUE) voor de GPC-metingen. Sandra Tijdink, maar vooral Désirée van der Weij hebben op secretarieel gebied vanalles voor mij geregeld, hetgeen vooral in de afgelopen paar maanden flink wat werk heeft ingehouden. Hartelijk dank daarvoor!

De laatste bedankjes, maar wel de belangrijkste, gaan natuurlijk naar mijn familie. Pap en mam, bedankt dat jullie mij altijd hebben aangespoord om te studeren, en dat jullie er altijd voor mij waren. En natuurlijk bedankt dat jullie trots op mij zijn, want dat is altijd de belangrijkste stimulans voor mij geweest!
Lichen, je weet al dat je de belangrijkste persoon in mijn leven bent. Bedankt dat je mij steeds hebt gesteund en dat ik altijd tegen jou over mijn werk kon vertellen. Ook bedankt dat we over andere dingen konden praten als mijn hoofd niet naar scheikunde stond. En natuurlijk bedankt dat je bij mij wilt zijn, in dit koude land.

Curriculum Vitae

De schrijver van dit proefschrift werd geboren op 29 maart 1971 te Luyksgestel. In 1989 behaalde hij het Gymnasium-β diploma aan het Hertog Jan College te Valkenswaard. In datzelfde jaar begon hij aan de studie Scheikunde aan de Katholieke Universiteit te Nijmegen. In 1990 legde hij het propaedeutisch examen af. In dat jaar begon hij aan de studie Franse Taal- en Letterkunde, waarvan het propaedeutisch examen werd behaald in 1992. Hij volgde vervolgens een hoofdrichting Biochemie in Nijmegen. In 1993 werd hem de RUI Scholarship toegekend, die hem de mogelijkheid bood om een uitgebreide nevenrichting Organische Chemie te volgen aan de Rikkyo University (Prof. dr. C. A. Horiuchi) en de Jikei Medical University (Prof. dr. M. Tozawa, Prof. dr. T. T. Takahashi) in Tokyo, Japan, onder mede-begeleiding van Prof. dr. B. Zwanenburg in Nijmegen. In 1996 behaalde hij het doctoraaldiploma Scheikunde, waarna hij werd aangesteld als AiO in de vakgroep Organische Chemie van de Katholieke Universiteit te Nijmegen. Daar werkte hij onder begeleiding van Prof. dr. R. J. M. Nolte en Dr. J. W. Scheeren aan het werk dat beschreven is in dit proefschrift. Sinds 1 januari 2001 is de auteur in dienst van Philips Semiconductors te Nijmegen.

STELLINGEN

behorende bij het proefschrift

'Molecular Clips Based on Propanediurea - Synthesis and Physical Properties'

door

Rob J. Jansen

1. Een promotie is het omgekeerde van onderwijs: eerst komt de toets, achteraf pas de lessen.

2. Het gegeven dat accenten en trema's in de modernste softwarepakketten nog altijd moeten worden ingevoerd vóór de letter waar ze bijhoren is een tegennatuurlijk reliek uit het typemachinetijdperk en kan softwarematig eenvoudig worden aangepast.

3. Als milieubeschermingsorganisaties hun beleid van verkeerd, onvolledig en/of eenzijdig voorlichten van het publiek niet wijzigen, graven ze hun eigen graf en wellicht ook dat van het milieu.

4. Appels lijken op peren.

5. Op de wereldmarkt is uw euro een daalder waard.

6. De *ch* tussen *s* en *r* (s*ch*rijven) wordt door velen niet uitgesproken en zal bij een volgende taalhervorming hetzelfde lot moeten ondergaan als de *ch* tussen *s* en *e* (Nederlands*ch*e).

7. Het feit dat het Nederlands voor *to cook* hetzelfde woord gebruikt als voor *to boil* verklaart de kwaliteit van de Hollandse keuken voor een groot gedeelte.

8. Als van iedere 100 IT-specialisten op deze wereld er één bij Microsoft zou werken, dan konden 95 anderen op zoek naar een nieuwe baan.

9. "The past is over."
   George W. Bush