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Synthetic Strategies Toward *N*-Functionalized Cyclens

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Dedicated to Prof. Peter Kutschy on the occasion of his 55th birthday

Keywords: Cyclen derivatives / Lanthanide chelation / Contrast agents

Cyclen (1,4,7,10-tetraazadodecane) is a widely used building block in the synthesis of many important molecules with applications spanning MRI contrast agents, fluorescent probes and heavy metals sensors. This review describes the various synthetic methodologies employed for the preparation of *N*-functionalized cyclens such as: synthesis from acyclic precursors; alkylation or acylation of cyclen; and protecting group manipulations. Emphasis is given to synthetic strategies allowing for the selective, differential *N*-functionalization of cyclen which is particularly useful for many modern applications.

Introduction

The story of cyclen or 1,4,7,10-tetraazadodecane (**1**, Figure 1) begins in 1961, when its synthesis was first accomplished by the German chemists Stetter and Mayer.[1] Relatively few research reports dealing with cyclen and its derivatives appeared during the following two decades until the discovery of the ability of cyclen and its simple *N*-functionalized derivatives to chelate a wide variety of metal cations. This discovery resulted in a real boom in the chemistry, applications, and publications dealing with cyclen and its derivatives during the last two decades.

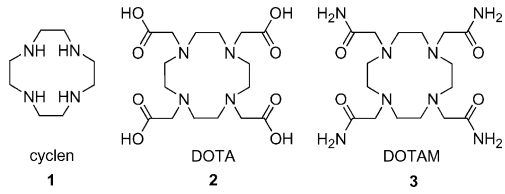

Figure 1. Structures of cyclen (**1**), DOTA (**2**) and DOTAM (**3**).

Among the simple derivatives, DOTA[2] (N^1,N^4,N^7,N^{10}-cyclentetraacetic acid, **2**) and DOTAM[3] (N^1,N^4,N^7,N^{10}-cyclentetraacetic acid amide, **3**) have received special attention, Figure 1. Nowadays, cyclen and its derivatives are be-

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Mojmír Suchý was born in 1974 in Martin, Czechoslovakia, now Slovakia. He studied chemistry at the Slovak Technical University in Bratislava (M.Sc. in 1997 with Prof. Katarína Špirková) and Pavol Jozef Šafárik University in Košice (Ph.D. in 2001 with Prof. Peter Kutschy). His graduate research was focused on the synthesis of indole phytoalexins and some related spirocyclic and fused indole derivatives. After graduation he worked for one year as a research associate in Prof. Kutschy's group and in 2002 he was awarded a prestigious NATO Postdoctoral Fellowship, which allowed him to move to Canada, to the research group of Prof. Maria Soledade C. Pedras at the University of Saskatchewan in Saskatoon. In 2006, he accepted a joint postdoctoral fellow position in research groups of Profs. Robert H. E. Hudson and Robert Bartha at the University of Western Ontario in London. His current research is devoted to the design and synthesis of temperature, pH and enzymatic activities responsive, DOTA and DOTAM based MRI contrast agents, mainly operating in PARACEST mode.

Robert Hudson is currently Associate Professor in the Department of Chemistry at the University of Western Ontario and holds a cross-appointment to the Department of Biochemistry, Faculty of Medicine and Dentistry. He arrived at UWO in 1997 by way of the California Institute of Technology where he tenured a NSERC Postdoctoral fellowship studying DNA minor groove-binding polyamides with the renown bioorganic chemist Prof. Peter Dervan. His prior training took place at the University of Toronto where he obtained an M.Sc. in the field of inorganic chemistry under the guidance of Prof. Anthony J. Poë and subsequently a Ph.D. studying nucleic acid chemistry under the mentorship of Prof. Masad J. Damha. Robert's research at Western is focused on synthetic and bio-organic chemistry of polyamides and oligonucleotides and he maintains a keen interest in the marriage of inorganic, synthetic and biological chemistries.

ing widely used in the construction of a wide variety of functional molecules such as MRI and PET contrast agents, fluorescent and luminescent probes, metal sensors, RNA cleavers, and antibacterial agents.

Various aspects of the chemistry related to cyclen and its derivatives, such as chemistry of DOTA-peptide conjugates,[4] PET imaging of biomolecules using metal-DOTA complexes,[5] use of transition-metal complexes of azamacrocycles in molecular recognition,[6] or responsive MRI contrast agents[7] have been recently reviewed. Moreover, some strategies for the regioselective *N*-functionalization of various tetraazacycloalkanes, including cyclen have been the subject of a review article,[8] however it is not as comprehensive as the present microreview.

The aim of this review is to summarize various synthetic approaches, including some protecting-group manipulations, towards *N*-functionalized cyclens. Special attention will be paid to the methodologies that permit the synthesis of selectively substituted cyclens, which are often times the key precursors in the preparation of a wide variety of cyclen conjugates exhibiting diverse and important functional properties.

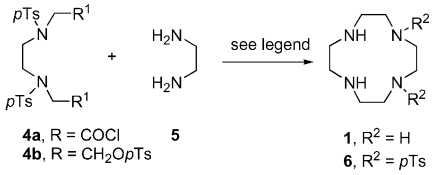
In principle, there are three general methodologies for the synthesis of *N*-functionalized cyclens: synthesis from acyclic precursors, alkylation of cyclen, and treatment of cyclen with acylation and sulfonylation reagents, or combinations thereof. While the final substitution pattern of the product in the synthesis of cyclens from acyclic precursors is determined by their structures, the later two approaches may be carried out in selective manner; that is, *N*-mono-, *N*-di-, *N*-tri- or *N*-persubstituted cyclens are formed either exclusively, or at least predominantly. The synthesis of cyclens from acyclic precursors is the oldest methodology and often requires protecting group manipulations in order to obtain the desired product. Because cyclen (**1**) is now commercially available, contemporary syntheses of *N*-functionalized cyclens are commonly achieved by its direct *N*-functionalization using a wide variety of alkylating, acylating and sulfonylating agents. Although there have been some advances in understanding the reactivity of cyclen, rationale design of syntheses based on the selective functionalization of cyclen is still a very challenging task. Thus, many of the trends in the reactivity of cyclen are gleaned through empirical observations, and thus the importance of a catalog of such reactivity.

Synthesis of *N*-Functionalized Cyclens from Acyclic Precursors

Three types of the cyclen ring formation from acyclic precursors can be found in the literature that may be categorized based on the number of nitrogen atoms contained in each precursor. In the rather rare 2+2 type cyclization, two acyclic precursors each contain two nitrogen atoms. The most prominent reported approach is the 3+1 type cyclization; as indicated by the description one precursor contains 3 nitrogen atoms and the remaining nitrogen is introduced by treatment with the second acyclic precursor. Finally, a 4+0 type cyclization involves a linear tetraamine (possessing all 4 nitrogen atoms) that undergoes ring closure to form a cyclen.

Type 2+2 Cyclization

The first synthesis of cyclen (**1**),[1] which was accomplished in 1961, belongs to the first type cyclization (2+2). Thus *N*,*N*′-ditosylethylenediamine-*N*,*N*′-diacetyl chloride (**4a**) was treated with ethylenediamine (**5**, Scheme 1) under the condition of high dilution resulting in the formation of cyclic diamide. Subsequent treatment of the diamide intermediate with $LiAlH_4$ resulted in reduction of amide functionalities with concomitant removal of protecting tosyl groups (Scheme 1). Cyclen (**1**) was obtained in 27% yield, based on the protected diamine **4a**.



4a, R = COCl **4b**, R = CH_2OpTs **5** **1**, R^2 = H **6**, R^2 = *p*Ts

Scheme 1. Examples of "2+2"-type cyclizations. Reagents and conditions: **4a** + **5** → **1**, *i*: THF, room temp., *ii*: $LiAlH_4$, THF, room temp. to reflux, 27% based on **4a**; **4b** + **5** → **6**, Na_2CO_3, MeCN, room temp. to reflux, 40%.

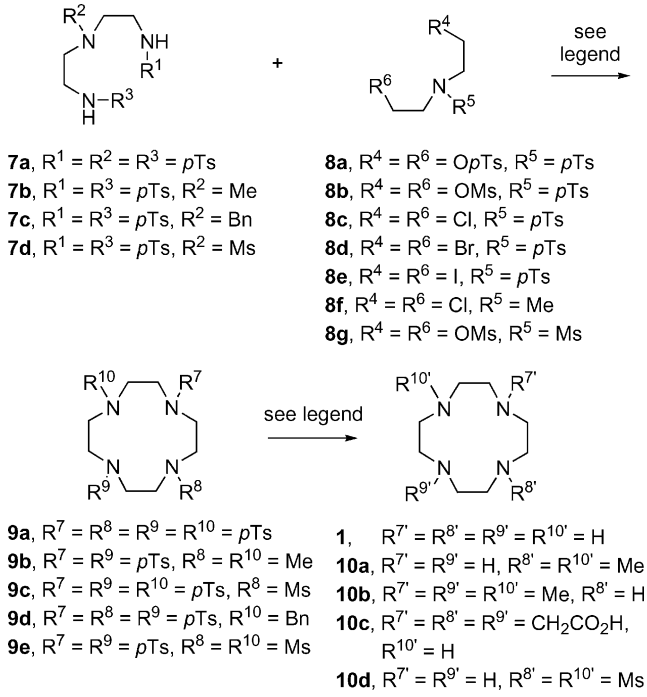
Another example of 2+2 cyclization was described in 1986, wherein the tetratosylated amino alcohol **4b** was refluxed with ethylenediamine in acetonitrile using Na_2CO_3 as a base (**5**, Scheme 1).[9] N^1,N^4-Ditosylcyclen (**6**) was isolated in 40% yield (Scheme 1).

Type 3+1 Cyclization

Among the methods for the preparation of cyclen and its derivatives from acyclic precursor, the second type (3+1) cyclization appears most prominently in the literature. The first example of such cyclization appeared in 1974,[10] when the 1,4-disodium salt of 1,4,7-tritosyl-1,4,7-triazaheptane (**7a**) was alkylated (in DMF, 110 °C) with 1,5-disubstituted 3-tosyl-3-azapentanes (**8a**–**8e**) bearing various leaving groups (OTs, OMs, Cl, Br, I) in good yields (ca. 80%) (Scheme 2). The resulting N^1,N^4,N^7,N^{10}-tetratosylcyclen (**9a**) underwent H_2SO_4-mediated detosylation to form cyclen (**1**) in 90% yield (Scheme 2). A modified procedure for the reaction of **7a** with **8a** using NaH in hot DMF (110 °C) as a base, followed by H_2SO_4-mediated detosylation and alkaline aqueous work-up afforded cyclen (**1**) in 60% overall yield (Scheme 2).[11]

A similar methodology was later used towards the synthesis of N^1,N^7-dimethylcyclen (**10a**)[12] from 1,4-disodium salt of 1,7-ditosyl-4-methyl-1,4,7-triazaheptane (**7b**) and 1,5-dichloro-3-methyl-3-azapentane (**8f**, Scheme 2). The macrocyclization (DMF, 110 °C) proceeded in 40% yield to give N^1,N^7-dimethyl-N^4,N^{10}-ditosylcyclen (**9b**). Detosyl-

ation was effected again by treatment with H_2SO_4 followed by alkaline aqueous work-up which then afforded N^1,N^7-dimethylcyclen (**10a**) in 90% yield (Scheme 2).[12]



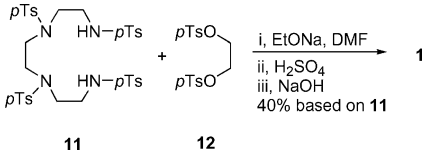
Scheme 2. "3+1"-type cyclizations. Reagents and conditions: **7a** + **8a**–**8e** → **9a**, **7b** + **8f** → **9b**, **7a** + **8g** → **9c**, **7c** + **8a** → **9d**, **7d** + **8g** → **9e**, DMF, 110 °C, 86% **9a**, **9b**, 90%, **9c**, 80%, **9d**, authors[14] claim low yield, no exact value reported, **9e**, 43%, **7a** + **8a** → **9a**, Cs_2CO_3, DMF, room temp., 79% or TBAB, LiOH, DMF, reflux, 71%; **9a** → **1**, **9b** → **10a**, **9e** → **10d**, H_2SO_4, room temp., 90%, ref.[15] or 70% ref.[11], **9a** → **1** in ref.[16] HBr, phenol, AcOH, reflux, 46%, **9c** → **10b**, *i*: HCOH, HCOOH, 110 °C, *ii*: Red-Al, $PhCH_3$, 100 °C, 10% (based on **9c**), **9d** → **10c**, *i*: Na, NH_3 (l), *ii*: $ClCH_2COOH$, NaOH, H_2O, *iii*: H_2, Pd/C, MeOH, authors[14] claim low yield, no exact value reported.

N^1,N^4,N^7-Trimethylcyclen (**10b**) was obtained from macrocylization (DMF, 110 °C, 80% yield) of precursors **7a** and **8g** (Scheme 2).[13] Intermediate **9c** underwent H_2SO_4-mediated detosylation (93% yield), followed by rather low yielding sequence (10%) involving the condensation with aqueous formaldehyde in formic acid and Red-Al-mediated reduction (Scheme 2).[13] A similar 3+1 cyclization strategy was reported in 1991 as an alternate route to N^1,N^4,N^7-cyclentriacetic acid (**10c**), known as DO3A.[14] Macrocyclization of the 4-benzyl precursor **7c** with **8a** led to the formation of N^1-benzyl-N^4,N^7,N^{10}-tritosylcyclen (**9d**, Scheme 2). The authors claim very low yields for the macrocyclization; however, the detailed experimental procedure is not provided.[14] Nonetheless, protected cyclen **9d**, which was prepared in larger quantities by selective *N*-tritosylation of cyclen and alkylation of remaining nitrogen atom with benzyl bromide, was converted to DO3A (**10c**, Scheme 2), by Na/NH_3-mediated reductive removal of the tosyl groups, followed by *N*-alkylation with chloroacetic acid and catalytic hydrogenolysis of the benzyl group (Scheme 2). The overall yield of the sequence was very low but neither the exact yield nor the experimental procedures have been reported.[14] The authors also describe a more straightforward and higher yielding procedure towards DO3A in the same paper;[14] it will be discussed in the section dealing with selective *N*-trialkylation of cyclen. Finally, treatment of **7d** with **8g** in hot DMF (110 °C) followed by H_2SO_4-mediated detosylation afforded N^1,N^7-dimesylcyclen (**10d**)[15] in 34% yield, based on **7d** (Scheme 2).

Considering that cyclen (**1**) is commercially available for a reasonable price from multiple suppliers it is rather surprising that the labor intensive 3+1 cyclization strategy to form cyclen is still in use.[16] Stirring (5 d) of the precursors **7a** and **8a** in DMF at room temperature in the presence of Cs_2CO_3 afforded N^1,N^4,N^7,N^{10}-tetratosylcyclen (**9a**) in 79% yield (Scheme 2). The authors also describe another procedure for the reaction of **7a** with **8a**, involving an overnight reflux (in DMF) of a mixture containing **7a**, **8a**, tetrabutylammonium bromide (TBAB) and LiOH. N^1,N^4,N^7,N^{10}-Tetratosylcyclen (**9a**) is obtained in slightly lower (71%) yield.[16] Two methods (HBr/phenol in AcOH or concentrated H_2SO_4) are described for detosylation, affording cyclen (**1**) in 46% (HBr/phenol in AcOH) or 88% (concentrated H_2SO_4) yield.[16]

Type 4+0 Cyclization

An isolated example of this type cyclization appeared in the literature in 1995.[17] Treatment of 1,4,7,10-tetratosyl-1,4,7,10-tetraazadecane (**11**) with *O*,*O'*-ditosylethanediol (**12**) in the presence of EtONa in DMF, followed by H_2SO_4-mediated detosylation and alkaline aqueous work-up afforded cyclen (**1**) in 40% overall yield (Scheme 3).[17]



Scheme 3. "4+0"-type cyclization. An alternate synthesis of cyclen (**1**).

Selective *N*-Monofunctionalization of Cyclen

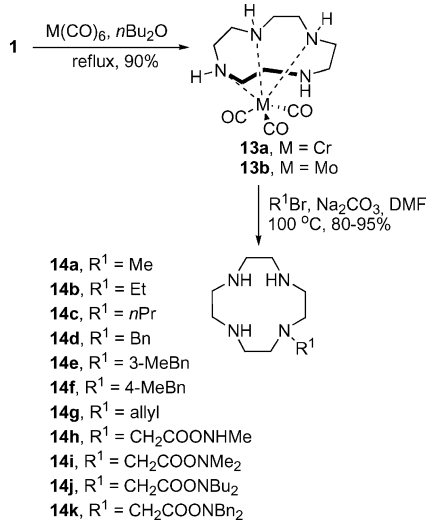
Given that the syntheses of *N*-functionalized cyclens from acyclic precursors are labor intensive and their yields are dependent on the nature of the substrates, it became apparent that other methods for selective *N*-functionalization of cyclen were required. These can be roughly divided into two groups: *N*-monofunctionalizations (mainly alkylations) via tri- or tetracyclic intermediates and selective *N*-monofunctionalizations (alkylations, acylations and sulfonylations) based on the differing basicity of four nitrogen atoms present in the cyclen ring.

Synthesis of *N*-Monofunctionalized Cyclens via Tri- or Tetracyclic Intermediates

Both transition metals (Cr, Mo) and some main-group elements (B, Si, P) have been used to complex cyclen offer-

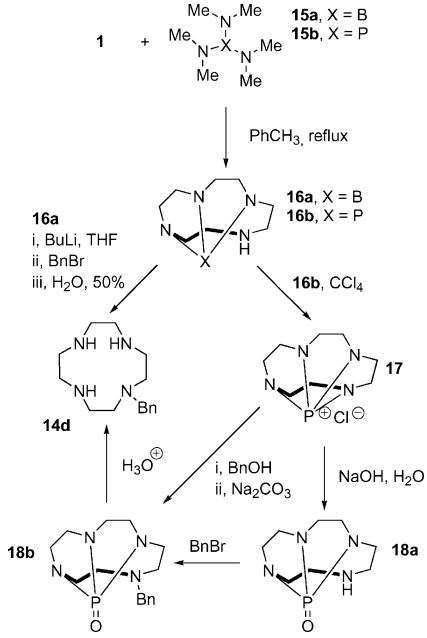
ing a route to *N*-monofunctionalized cyclens. As described later, tri- and tetracyclic intermediates formed upon treatment of cyclen with dimethylformamide diethyl acetal or glyoxal also resulted in the formation of *N*-monofunctionalized cyclens.

Handel, des Abbayes and co-workers appear to be the pioneers in the field of selective *N*-monofunctionalization of cyclen. They developed a methodology of wide scope for the formation and subsequent alkylation of tricarbonylchromium[18] or tricarbonylmolybdenum[19] complexes **13a** and **13b** (Scheme 4). Treatment of cyclen (**1**) with $Cr(CO)_6$ or $Mo(CO)_6$ in dry *n*-Bu ether under Ar atmosphere resulted in the formation of stable complexes **13a** and **13b** in high yields (90%). These were *N*-alkylated in good yields (Na_2CO_3, DMF, 80–95% yield) with simple alkyl bromides (compounds **14a**–**14c**), benzyl and allyl bromides (compounds **14d**–**14g**) (Scheme 4). Parker demonstrated the versatility of this methodology by using it towards the synthesis of cyclenacetamides **14h**–**14k** (Scheme 4).[20]



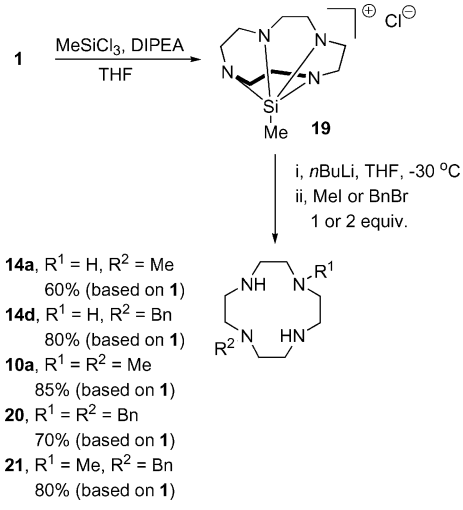
Scheme 4. *N*-Monoalkylation of cyclen (**1**) via chromium and molybdenum complexes **13a** and **13b**.

The major drawbacks associated with above described $M(CO)_6$-mediated *N*-monoalkylation were the use of highly toxic metal hexacarbonyls as well as requirement for strictly inert atmosphere during the synthesis. To circumvent these problems, complexes of cyclen with boron and phosphorus have been investigated. Reactions of cyclen (**1**) with tris(dimethylamino)borane (**15a**)[21] or tris(dimethylamino)phosphane (**15b**)[22] (Scheme 5) in refluxing toluene proceeded smoothly. The boron-derived complex **16a** was treated with *n*BuLi in THF (at –30 °C), followed by treatment with BnBr and aqueous alkaline work-up to afford *N*-benzylcyclen (**14d**) in 50% overall yield (Scheme 5).[21a] Addition of CCl_4 to the phosphorus-derived complex **16b** resulted in the formation of the phosphonium salt **17**, which can either be hydrolyzed ($NaOH/H_2O$, room temp.) and alkylated (BnBr, Na_2CO_3, DMF, 100 °C) or treated with BnOH in toluene, followed by heating (in DMF at 100 °C) with Na_2CO_3 (Scheme 5). Phosphane oxide **18b** bearing the desired substitution pattern is obtained in either case, followed by acidic aqueous work-up to give *N*-benzylcyclen (**14d**) in 80% (using BnOH) and 90% (using BnBr) overall yield (Scheme 5).[22]



Scheme 5. Synthesis of *N*-benzylcyclen (**14d**) via boron or phosphorus complexes **16a** and **16b**.

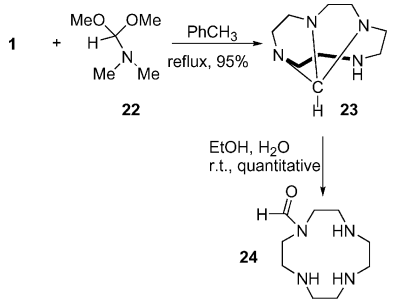
Handel and co-workers also investigated silicon-coordinated cyclen and its behavior in the presence of reactive electrophiles. The reaction of cyclen (**1**) with $MeSiCl_3$ in the presence of DIPEA in dry THF afforded the stable, although hygroscopic complex **19**, (Scheme 6).[23] Treatment of **19** with *n*BuLi, followed by quenching with reactive electrophiles resulted in the formation of *N*-mono- or N^1,N^7-disubstituted cyclens based on the stoichiometry of the reaction. When one equivalent of *n*BuLi and electrophile (MeI or BnBr) was used, *N*-monoalkylated cyclens **14a** or



Scheme 6. Silicon-derived complex **19** and its use in the formation of *N*-mono- and N^1,N^7-disubstituted cyclens.

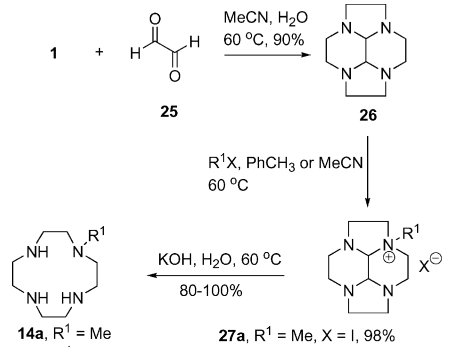
14d were obtained in reasonable yields (Scheme 6).[23] Use of two equivalents of *n*BuLi and electrophiles resulted in the formation of N^1,N^7-dialkylated cyclens **10a** and **20** (Scheme 6). N^1-Benzyl-N^7-methylcyclen (**21**, Scheme 6) can be obtained, when two equivalents of *n*BuLi are used, followed by immediate addition of 1 equivalent of benzyl bromide and 1 equiv. (after 1 h) of MeI.[23]

An important *N*-monofunctionalized cyclen derivative, *N*-formylcyclen (**24**, Scheme 7) can be obtained from cyclen (**1**) in two steps. Tricyclic intermediate **23** (Scheme 7) is obtained in almost quantitative yield by refluxing the mixture of cyclen (**1**) and dimethylformamide dimethyl acetal (**22**) in toluene (Scheme 7).[24] Tricyclic amine **23** undergoes the hydrolysis readily, leading to the formation of *N*-formylcyclen (**24**, Scheme 7) in quantitative yield.[14]



Scheme 7. Synthesis of *N*-formylcyclen (**24**) via tricyclic intermediate **23**.

Cyclen (**1**) was found to react with glyoxal[25] (**25**, Scheme 8) yielding the tetracyclic amine **26**, which upon treatment with various alkylating agents (in toluene or acetonitrile at 60 °C) afforded the quaternary ammonium salts **27a**–**27q** in good to excellent yields (Scheme 8).[26] These were hydrolyzed to *N*-monoalkylated cyclens **14a**–**14d**, **14g** and **28a**–**28l** in excellent yields (Scheme 8).[26a]



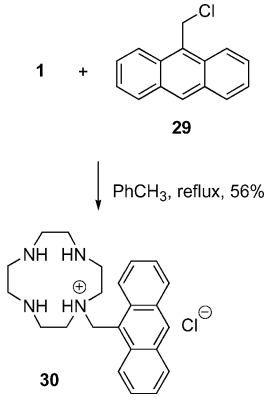
14a, R^1 = Me
14b, R^1 = Et
14c, R^1 = *n*Pr
14d, R^1 = Bn
14g, R^1 = allyl
28a, R^1 = *n*Bu
28b, R^1 = *n*pentyl
28c, R^1 = *n*hexyl
28d, R^1 = *n*octyl
28e, R^1 = *n*decyl
28f, R^1 = *n*dodecyl
28g, R^1 = *n*tetradecyl
28h, R^1 = *n*hexadecyl
28i, R^1 = *n*octadecyl
28j, R^1 = 4-NO_2-Bn
28k, R^1 = CH_2COOEt
28l, R^1 = CH_2CONH_2

27a, R^1 = Me, X = I, 98%
27b, R^1 = Et, X = I, 94%
27c, R^1 = *n*Pr, X = I, 90%
27d, R^1 = Bn, X = Br, 95%
27e, R^1 = allyl, X = I, 94%
27f, R^1 = *n*Bu, X = I, 84%
27g, R^1 = *n*pentyl, X = I, 76%
27h, R^1 = *n*hexyl, X = I, 79%
27i, R^1 = *n*octyl, X = I, 77%
27j, R^1 = *n*decyl, X = I, 72%
27k, R^1 = *n*dodecyl, X = I, 85%
27l, R^1 = *n*tetradecyl, X = I, 94%
27m, R^1 = *n*hexadecyl, X = I, 74%
27n, R^1 = *n*octadecyl, X = I, 77%
27o, R^1 = 4-NO_2-Bn, X = Br, 95%
27p, R^1 = CH_2COOEt, X = Br, 88%
27q, R^1 = CH_2CONH_2, X = I, 79%

Scheme 8. Preparation of tetracyclic amine **26** and its use in *N*-monoalkylation of cyclen (**1**).

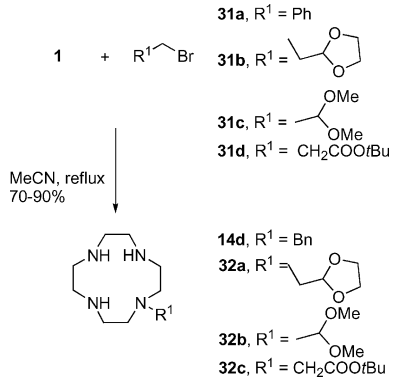
Selective *N*-Monoalkylation of Cyclen

The conjugate acids of the four nitrogen atoms present in the structure of cyclen (**1**) possess different pK_a values (10.5, 9.5, 1.6 and 0.8),[27] implying the possibility of selective *N*-monofunctionalization. One of the earliest examples of this approach towards *N*-monoalkylated cyclens is represented in the paper by Czarnik and co-workers.[28] Reaction of cyclen (**1**) with 9-(chloromethyl)anthracene (**29**) in boiling toluene afforded *N*-monosubstituted cyclen **30** as a hydrochloride salt in 56% yield (Scheme 9). No chromatographic purification was involved.



Scheme 9. Reaction of cyclen (**1**) with 9-(chloromethyl)anthracene (**29**).

A similar methodology was employed by Anelli and coworkers;[29] these authors have described the reaction of the large excess (5–10 equiv.) of cyclen (**1**) with alkylating agents **31a**–**31d** in refluxing acetonitrile (Scheme 10). Excess cyclen acted as a base and the *N*-monoalkylated cyclens **14d** and **32a**–**32c** were obtained in 70–90% yields after purification by simple crystallization (Scheme 10).[29]

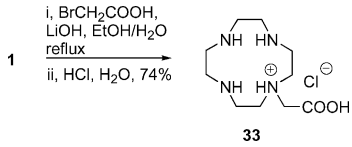


31a, R^1 = Ph
31b, R^1 =
31c, R^1 =
31d, R^1 = $CH_2COOtBu$

14d, R^1 = Bn
32a, R^1 =
32b, R^1 =
32c, R^1 = $CH_2COOtBu$

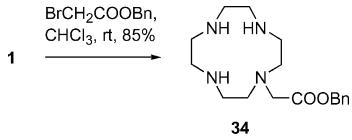
Scheme 10. Selective *N*-monoalkylation of cyclen (**1**) with the electrophiles **31a**–**31d**.

N-Cyclenacetic acid hydrochloride salt (**33**, Scheme 11) can be obtained in 74% yield by reaction of 5.5 equiv. of cyclen (**1**) with bromoacetic acid, using LiOH (2 equiv.) as a base, followed by aqueous acidic work-up (Scheme 11).[17]



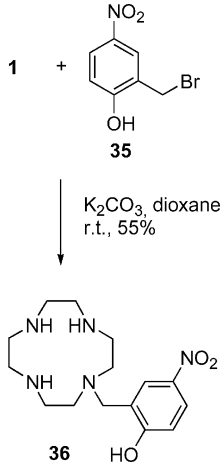
Scheme 11. Synthesis of *N*-cyclenacetic acid hydrochloride salt (**33**).

N-Benzyl cyclenacetate (**34**) was prepared (in 85% yield) by alkylation of cyclen (**1**, 2 equiv.) with benzyl bromoacetate in $CHCl_3$ (Scheme 12). The overall yield of the reaction remained high despite of the chromatographic isolation of the product.[30]



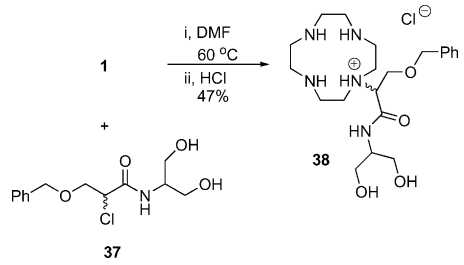
Scheme 12. Preparation of *N*-benzyl cyclenacetate (**34**).

The *N*-monosubstituted benzyl cyclen **36** can be obtained (55% yield, after chromatographic separation) upon stirring (at room temperature) the mixture of cyclen (**1**), 2-hydroxy-5-nitrobenzyl bromide (**35**) and K_2CO_3 in dioxane (Scheme 13).[31]



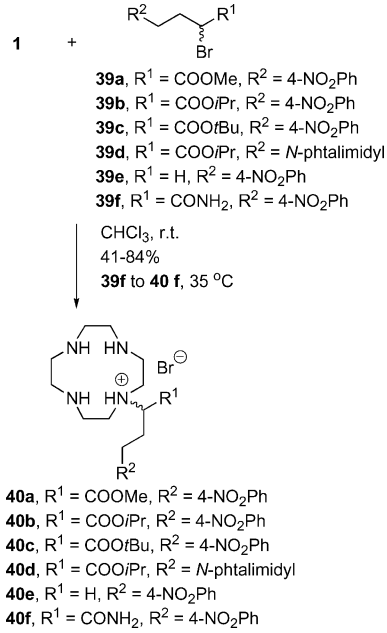
Scheme 13. Reaction of cyclen (**1**) with 2-hydroxy-5-nitrobenzyl bromide (**35**).

The useful properties associated with cyclen-derived molecules resulted in the development of *N*-monoalkylated cyclens with complicated side chains bearing multiple functional groups. One of the first examples is the synthesis of cyclen **38** bearing an aliphatic amide side chain.[32] Reaction of cyclen (**1**) with the chloroacetamide **37** (3 equiv.) in hot DMF (60 °C) followed by acidic aqueous work-up afforded the racemic cyclen **38** as hydrochloride salt in 47% yield (Scheme 14).[32]



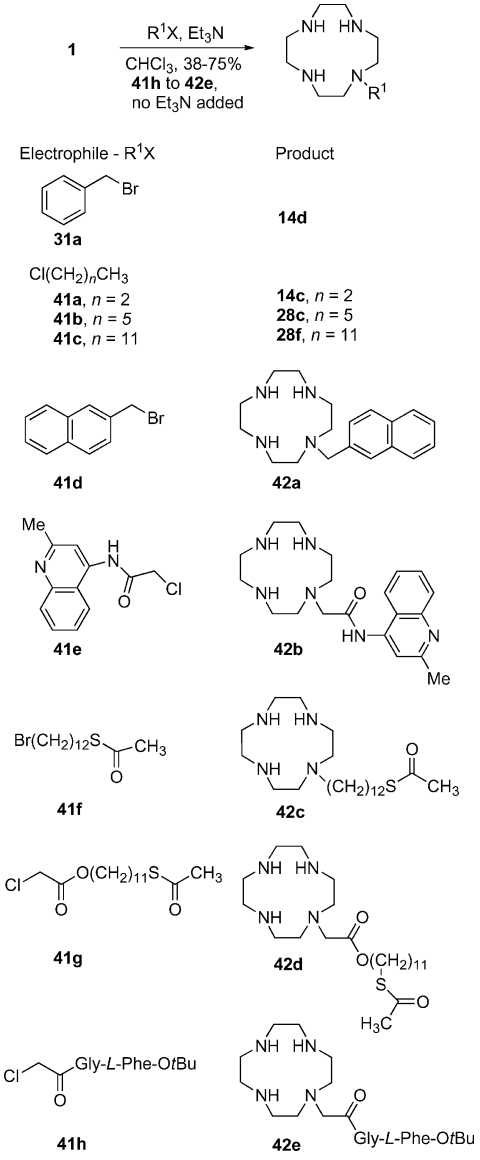
Scheme 14. Alkylation of cyclen (**1**) with racemic 2-chloropropionamide **37**.

An excellent study on *N*-monoalkylation of cyclen and other polyazamacrocycles, published by Kruper and coworkers[33] represents a milestone in the field of selective *N*-functionalizations of cyclen. These authors describe the highly selective *N*-monoalkylation (< 5% of both N^1,N^4- and N^1,N^7-dialkylated products observed by ^{1}H NMR) of cyclen (**1**) that proceeds at room temperature by use of equimolar amounts of cyclen and sterically hindered electrophiles. The proper choice of solvent appears to be important, as the selectivity is retained in non-polar solvents, such as chloroform or dichloromethane. Selectivity of *N*-monoalkylation, on the other hand drops significantly in polar, particularly in protic solvents. The authors rationalize these observations on the basis that nonpolar solvents favor the formation of the hydrobromide salt of the *N*-monoalkylated cyclen thereby reducing nucleophilicity of the remaining nitrogen atoms. Reaction of cyclen (**1**) with bromides **39a**–**39e** gives *N*-monoalkylated cyclens **40a**–**40e** as their hydrobromide salts (Scheme 15) in moderate to good yields (41–84%).[33] A slightly modified procedure (reaction temperature 35 °C) has been employed to promote *N*-alkylation of cyclen (**1**) with amide **39f** affording *N*-monosubstituted cyclen **40f** in 67% yield (Scheme 15).[34]



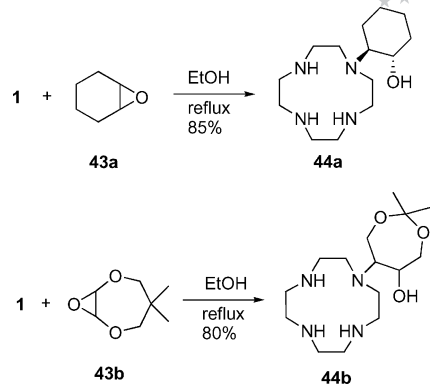
Scheme 15. Selective *N*-monoalkylation of cyclen (**1**) with bromides **39a**–**39f**.

N-Monoalkylation of cyclen (**1**) by a diverse set of electrophiles (**31a**, **41a**–**41g**) has been recently investigated.[35] Selective monoalkylation was achieved by refluxing four equivalents of cyclen in chloroform in the presence of Et_3N (1.2 equiv.) and appropriate electrophile (1 equiv.), (Scheme 16). The excess cyclen was conveniently removed by washing the chloroform solutions with 1 M NaOH and the *N*-monoalkylated cyclens **14c**, **14d**, **28c**, **28f** and **42a**–**42d** were isolated, without chromatography, in moderate to good yields (Scheme 16).[35]



Scheme 16. Selective *N*-monoalkylation of cyclen (**1**) with electrophiles **31a** and **41a**–**41h**.

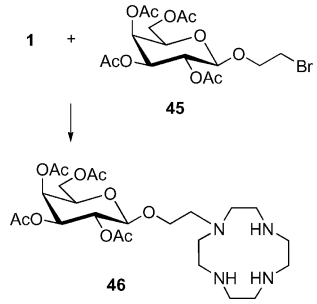
We have recently investigated the selective *N*-mono- and *N*-trialkylation of cyclen with different dipeptide sequences.[36] It was found that the reaction of cyclen (**1**) with *N*-chloroacetyl-Gly-L-Phe-O*t*Bu (**41h**, Scheme 17) carried out in chloroform (no Et_3N added) at room temperature gave *N*-monosubstituted cyclen **42e** in 48% yield. The moderate yield was ascribed to loss of material during isolation of **42e** by normal phase column chromatography.[36]



Scheme 17. Ring opening of epoxides **43a** and **43b** with cyclen (**1**).

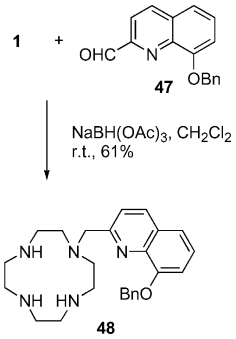
Cyclen (**1**) was found to effect epoxide ring opening resulting in high yields (> 80%) of *N*-monosubstituted cyclens (Scheme 17).[37] Reactions were easy to perform as were carried out simply by refluxing the components in EtOH. Ring opening of cyclohexene oxide (**43a**, 1–4 equiv.) takes place in stereoselective and chemoselective manner, leading to the *N*-monoalkylated cyclen **44a** (Scheme 17).[37a] When racemic epoxide **43b** was used in an equimolar amount, racemic *N*-monosubstituted cyclen **44b** was obtained (Scheme 17).[37b]

An interesting ethyl β-D-galactoside derived *N*-monoalkylated cyclen **46** has been prepared by treatment of 2,3,4,6-*O*-tetraacetyl-1-(2-bromoethoxy)-β-D-galactose (**45**) with cyclen (**1**, Scheme 18).[38] Unfortunately, neither the reaction conditions nor the yield for this particular transformation are reported. However, the reaction must proceed in good yield as **46** undergoes subsequent deacetylation and alkylation with bromoacetic acid in 37% overall yield (based on **45**).[38]



Scheme 18. Synthesis of an ethyl β-D-galactoside derived *N*-monoalkylated cyclen **46**.

Reductive amination [with $NaBH(OAc)_3$] of 8-benzyloxyquinoline-2-carboxaldehyde (**47**) with cyclen (**1**) (equimolar amounts) afforded the *N*-monoalkylated cyclen **48** in 61% yield (Scheme 19).[39] Small amounts of N^1,N^7-dialkylated side product and unreacted cyclen were removed by column chromatography. Potential of this methodology appears to be rather underestimated as there are, to the best of our knowledge, no other examples of selective *N*-monoalkylation of cyclen via reductive amination available in the literature.

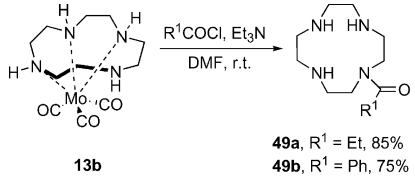


Scheme 19. Reductive amination of 8-benzyloxyquinoline-2-carboxaldehyde (**47**) with cyclen (**1**).

Selective *N*-Monoacylation, *N*-Monosulfonylalkylation and *N*-Monosulfonylarylation of Cyclen

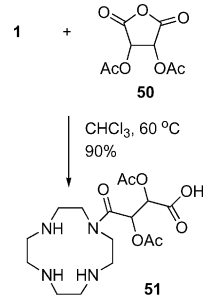
The vast majority of important cyclen-based transition- and lanthanide-metal chelators possess a -$CH_2C(O)$- linkage attached to the nitrogen atoms, which is introduced by alkylation. As a consequence, significantly less work has been done in the field of selective *N*-monoacylations and *N*-monosulfonylation of cyclen.

The molybdenum complex **13b** was found to be a suitable precursor of some aliphatic and aromatic *N*-acylcyclens (Scheme 18).[40] *N*-Propionyl- and *N*-benzoylcyclen (**49a** and **49b**) are obtained in good yields (Scheme 20) upon treatment of complex **13b** with corresponding carboxylic acid chlorides (1.1 equiv.) in DMF at room temperature.[40]



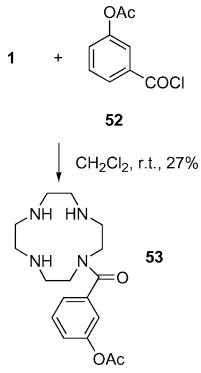
Scheme 20. Selective *N*-monoacylation of cyclen (**1**) via complex **13b**.

Racemic *O*,*O*′-diacetyl tartaric acid anhydride (**50**, 1 equiv.) was found to react in excellent yield (90%) with cyclen (**1**) in hot chloroform (60 °C) with the formation of densely functionalized cyclen **51** (Scheme 21).[37b]



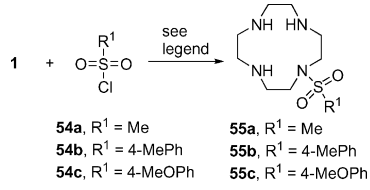
Scheme 21. Reaction of cyclen (**1**) with racemic *O*,*O*′-diacetyl tartaric acid anhydride (**50**).

Direct *N*-monoacylation of cyclen (**1**) with equimolar amount of acetylsalicylic acid chloride (**52**) in dichloromethane has been recently described.[41] The reaction to form *N*-monoaroylated cyclen **53** proceeded in rather low yield (27%) and extensive chromatographic purification of the product was required (Scheme 22).



Scheme 22. Reaction of cyclen (**1**) with acetylsalicylic acid chloride (**52**).

Direct *N*-monotosylation and *N*-monomesylation of cyclen (**1**) has been achieved by reaction of 1 with equimolar amount of corresponding sulfonyl chlorides **54a** and **54b** in pyridine (Scheme 23).[42] The authors used relatively small scale (up to 50 mg) and did not report the yields of *N*-monosulfonylated cyclens **55a** and **55b**.



Scheme 23. Reaction of cyclen (**1**) with alkyl- and arylsulfonyl chlorides **54a**–**54c**. Reagents and conditions: **1** + **54a**, **54b** → **55a**, **55b**, pyridine, room temp., no yield reported, ref.,[42] **1** + **54c** → **55c**, Et_3N, $CHCl_3$, 37 °C, 28%.

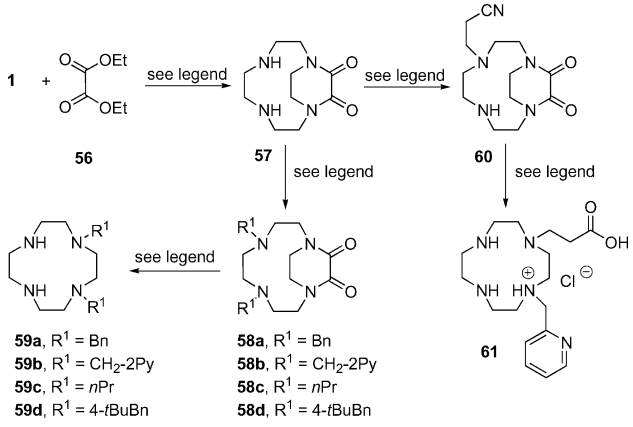
Slow addition of the chloroform solution of 4-methoxyphenylsulfonyl chloride (**54c**) to the warm (37 °C) solution of equimolar amount of cyclen (**1**) in chloroform/Et_3N resulted in the formation of *N*-monosulfonylated cyclen **55c** (Scheme 23). Extensive chromatographic purification was required resulting in rather low yield of 28%.[43]

Selective N^1,N^4- and N^1,N^7-Difunctionalization of Cyclen

Two isomeric (N^1,N^4 and N^1,N^7) structures can be obtained, when cyclen (**1**) undergoes a selective *N*-difunctionalization. N^1,N^4-Disubstituted cyclen is sometimes referred to as *N*,*N*′-*cis*-substituted, whereas N^1,N^7-disubstituted cyclen is denoted as *N*,*N*′-*trans*-substituted. The N^1,N^4 or *N*,*N*′-*cis* difunctionalization appears to be much more challenging compared to N^1,N^7 or *N*,*N*′-*trans* difunctionalization, considering the number of methods available for both types of transformation.

Direct N^1,N^4- or N,N'-*cis*-Difunctionalization of Cyclen

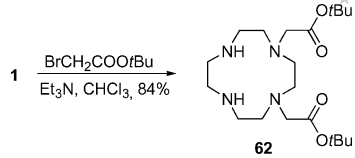
The first example of selective N^1,N^4-difunctionalization of cyclen appeared in the literature in 1999.[44a] Cyclen was refluxed (in EtOH) with an equimolar amount of ethyl dioxalate (**56**) to yield cyclenoxamide (**57**) in excellent yield (96%) (Scheme 24). Treatment of **57** with benzyl bromide, 2-chloromethylpyridine and *n*-propyl bromide afforded the disubstituted cyclenoxamides **58a**–**58c** (Scheme 24). Alkaline[44a] or acidic[44b] hydrolysis afforded N^1,N^4-dialkylated cyclens **59a**–**59c** in good overall yields. This methodology was later used by Welch and co-workers to prepare N^1,N^4-disubstituted cyclen **59d** and its *N*-peralkylated analogs (Scheme 24).[45]



Scheme 24. Synthesis of N^1,N^4-difunctionalized cyclens **59a**–**59d** and **61**. Reagents and conditions: **1** + **56** → **57**, EtOH, reflux, 96%, **57** → **58a**, BnBr, Na_2CO_3, DMF, 100 °C, 93%, **57** → **58b**, 2-chloromethylpyridine, Na_2CO_3, DMF, 100 °C, 94%, **57** → **58c**, *n*-PrBr, Na_2CO_3, DMF, 100 °C, 74%, **57** → **58d**, 4-*t*BuBnBr, DIPEA, MeCN, 76%, **58a** → **59a**, NaOH, H_2O, 90 °C, 81%, ref.[44a] **58a** → **59a**, HCl, H_2O, 90 °C, 81%, ref.[44b] **58b** → **59b**, NaOH, H_2O, 90 °C, 79%, **58c** → **59c**, NaOH, H_2O, 90 °C, 71%, **58d** → **59d**, NaOH, EtOH/H_2O, reflux, 90%, **57** → **60**, acrylonitrile, reflux, 67%, **60** → **61**, *i*: 2-chloromethylpyridine, Na_2CO_3, DMF, 100 °C, *ii*: HCl, H_2O, 90 °C, 49%.

An interesting transformation was discovered when cyclenoxamide (**57**) was refluxed in neat acrylonitrile. *N*-Monosubstituted cyclenoxamide **60** was isolated in 67% yield (Scheme 24) allowing for the subsequent *N*-alkylation with 2-chloromethylpyridine followed by hydrolysis to give N^1,N^4-difunctionalized cyclen **61**[44a] (Scheme 24) bearing two different side chains.

A high yielding and regioselective methodology for N^1,N^4-dialkylation of cyclen (**1**) with *tert*-butyl bromoacetate has been recently described (Scheme 25).[46] The authors found that the highest yield and regioselectivity of N^1,N^4-disubstituted cyclen **62** was achieved when the reaction of cyclen (**1**) with *tert*-butyl bromoacetate (2 equiv.) was carried out in a mixture of $CHCl_3$ and Et_3N (10 equiv.) at room temperature (Scheme 25). N^1,N^4-Disubstituted cyclen **62** was isolated in 84% yield and negligible amounts of *N*-mono- and *N*-trisubstitution products were readily removed by chromatography on Al_2O_3.[46a] Some other N^1,N^4-disubstituted cyclens have also been prepared in good yields (structures not shown).[46b]

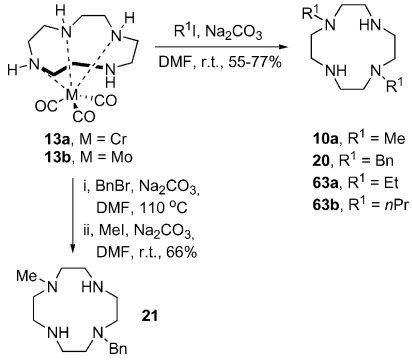


Scheme 25. Highly regioselective N^1,N^4-dialkylation of cyclen (**1**) with *tert*-butyl bromoacetate.

It is worth noting that N^1,N^4-ditosylcyclen can be obtained by reaction of cyclen (**1**) with tosyl chloride in chloroform/Et_3N mixture.[47] The product of *N*-monosulfonylarylation was removed by extraction into water and concentration of the organic extract and subsequent crystallization from MeOH, gave two different and very distinctive types of crystals, i.e. small needles vs. large cubes. The crystals were separated and each subjected to analysis in order to determine their structures. The small needles were found to correspond with N^1,N^7-ditosylcyclen, whereas large cubes have been subjected to X-ray analysis, which revealed their structure as N^1,N^4-ditosylcyclen (**6**).[47] Since the yield of N^1,N^4-ditosylcyclen (**6**) was very low (4%), this method cannot be considered synthetically useful (Scheme not provided).

N^1,N^7-Difunctionalization of Cyclen via Tri- or Tetracyclic Intermediates

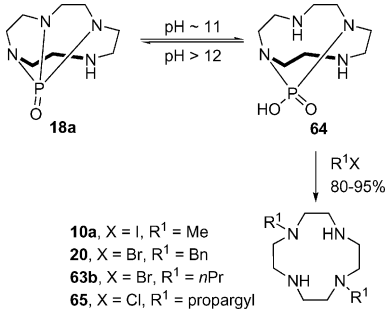
Some of the tri- and tetracyclic derivatives mentioned in section concerned with the selective *N*-monoalkylation of cyclen have also been used to achieve selective N^1,N^7-dialkylation. Tricarbonylchromium and tricarbonylmolybdenum complexes **13a** and **13b** have been used to achieve selective N^1,N^7-dialkylation of cyclen (**1**). Treatment of complexes **13a** and **13b** with various alkyl iodides resulted in the formation of dialkylated cyclens **10a**, **20**, **63a** and **63b** in good yields (Scheme 26).[19] This methodology was later extended to the synthesis of N^1,N^7-dialkylated cyclen **21** bearing one methyl and one benzyl group in 66% overall yield (Scheme 26).[48]



Scheme 26. Selective N^1,N^7-dialkylation of cyclen-derived complexes **13a** and **13b**.

An equilibrium between the phosphane oxide **18a** (see Scheme 5 for its preparation) and the diamidophosphoric acid (structure **64**, Scheme 27) can be shifted to the right

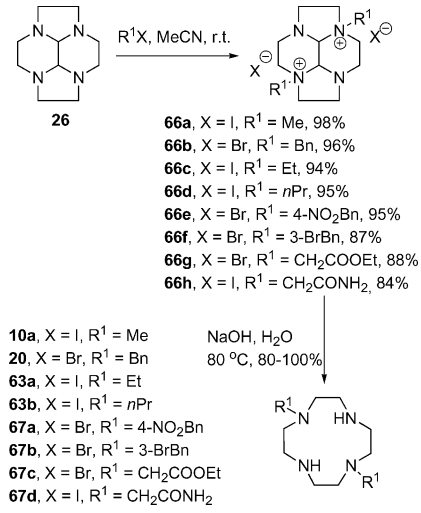
upon careful control of pH (pH ≈ 11).[49] Intermediate **64** revealed two unsubstituted nitrogen atoms and its alkylation was effected using various alkyl halides in aqueous medium (no experimental procedure reported) which led to the formation of N^1,N^7-dialkylated cyclens **10a**, **20**, **63b** and **65** in excellent yields (80–95%) (Scheme 27).[49]



Scheme 27. Selective N^1,N^7-dialkylation of cyclen-derived diamidophosphoric acid **64**.

The use of the complex **19**,[23] which was obtained upon treatment of cyclen with $MeSiCl_3$, for selective N^1,N^7-dialkylation of cyclen (**1**) has been already discussed (Scheme 6).

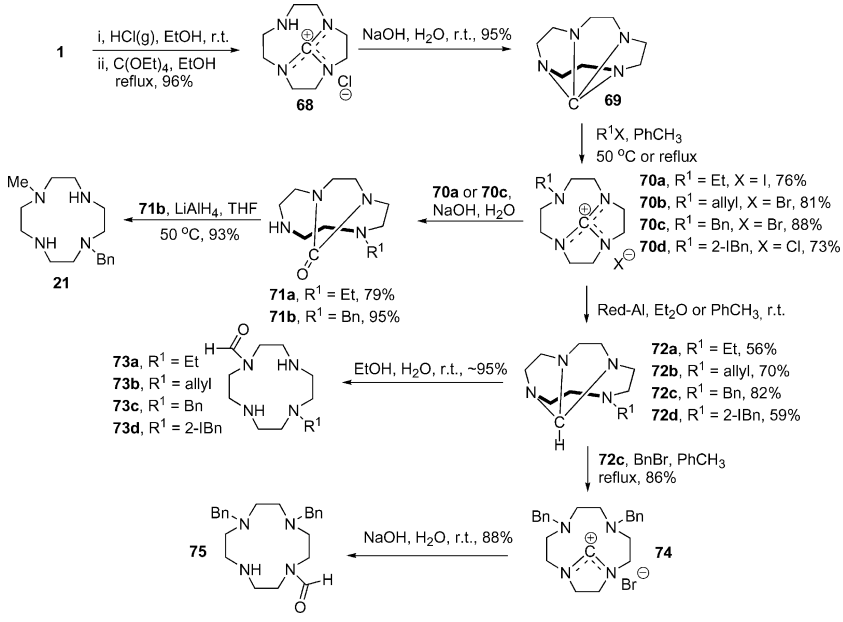
The tetracyclic amine **26** (preparation in Scheme 8) was converted to the diammonium quaternary salts **66a**–**66h** by treatment with 2 equiv. of alkyl halides in acetonitrile.[26b,50] It was found that the purity of the salts **66a**–**66h** strongly depends on the reaction conditions. Higher purity and better yields (84–98%) were achieved when the reactions were allowed to proceed for several days at room temp.; warming the reaction up to 60 °C resulted in the formation of undesirable side products, even though the reaction proceeded much faster. Alkaline hydrolysis of salts **66a**–**66h** (Scheme 28) resulted in the formation of N^1,N^7-dialkylated cyclens **10a**, **20**, **63a**, **63b** and **67a**–**67d** in good yields (80–100%) (Scheme 28).[26b,50]



Scheme 28. Synthesis of N^1,N^7-dialkylated cyclens **10a**, **20**, **63a**, **63b** and **67a**–**67d** by diammonium quaternary salts **66a**–**66h**.

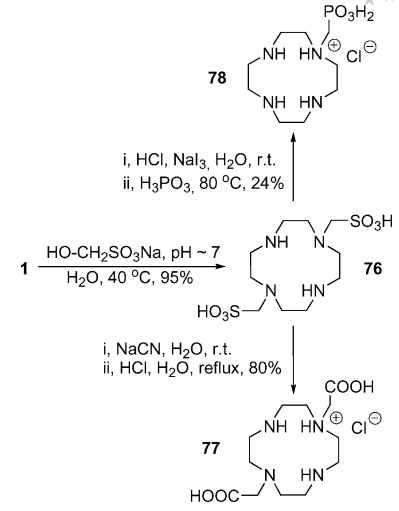
In an excellent piece of work by Li and Undheim,[51] the use of cyclen-derived guanidinium salts towards selective *N*-functionalizations of cyclen (**1**) was investigated. Guanidinium salt **68** was obtained (96% yield) by treatment of cyclen tetrahydrochloride salt with tetraethyl orthocarbonate in refluxing EtOH (Scheme 29).

Hydrolysis of **68** resulted in the formation of the tetracycle **69** (95% yield) and this intermediate was treated with various alkyl halides in hot toluene resulting in good yields of the *N*-monoalkylated guanidinium salts **70a**–**70d** (Scheme 29). Attempts to promote acidic hydrolysis of salts **70a**–**70d** failed and alkaline hydrolysis of **70a** and **70c** re-



Scheme 29. Cyclen-derived guanidinium salts and their use in the selective *N*-functionalizations of cyclen (**1**).

sulted in the formation of cyclic ureas **71a** and **71b** (Scheme 29). The urea **71b** was reduced by $LiAlH_4$ in warm THF to yield N^1-benzyl-N^7-methylcyclen (**21**) in 93% yield (Scheme 29). Reduction of the guanidinium salts **70a**–**70d** with Red-Al in Et_2O or toluene on the other hand afforded the *N*-monoalkylated tricyclic precursors **72a**–**72d** which underwent hydrolysis (in ≈ 95% yield) to give the N^7-monoalkylated *N*-formylcyclens **73a**–**73d** (Scheme 29). *N*-Alkylation of tricyclic intermediate **72c** with another equivalent of BnBr in refluxing toluene resulted in the formation of salt **74** (86% yield), which underwent subsequent alkaline hydrolysis to afford N^1-formyl-N^4,N^7-dibenzylcyclen (**75**) (88% yield, Scheme 29). Removal of formyl groups from **73a**–**73d** and **75** was achieved in hot aqueous HCl (structures not shown), leading to a new indirect method for *N*-mono- and N^1,N^4-dialkylation of cyclen.[51]



Scheme 30. Selective N^1,N^7-disulfomethylation of cyclen (**1**) and some subsequent transformations.

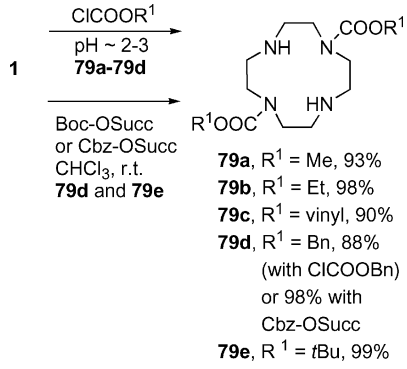
Direct N^1,N^7- or *N*,*N*′-*trans*-Difunctionalization of Cyclen

In the previous section we discussed the various methodologies that give N^1,N^7-difunctionalization of cyclen via tri- or tetracyclic intermediates. However, direct N^1,N^7-difunctionalization is more straightforward and several methods are currently known.

The Mannich-like reaction of cyclen (**1**) with sodium bisulfite adduct of formaldehyde under strict control of pH (pH ≈ 7–9) was found to result in the formation of N^1,N^7-disulfomethylated cyclen **76** in excellent (95%) yield (Scheme 30).[52] A negligible amount (< 5%) of N^1,N^4-disulfomethylated product was removed by crystallization. Nucleophilic displacement of the sulfonyl group by cyanide followed by acidic hydrolysis afforded N^1,N^7-cyclendiacetic acid (**77**) as corresponding hydrochloride salt in 80% yield (Scheme 30). It is worth mentioning, that **76** does not need to be isolated and the overall transformation of cyclen to N^1,N^7-cyclendiacetic acid (**77**, also known as DO2A) can be carried out as a one-pot reaction. An attempt to introduce the phosphinate moiety to structure **76** by oxidative hydrolysis with HCl/NaI_3 followed by heating in molten phosphorus acid resulted in degradation of **76**. Cyclen (**1**) was obtained as a main product along with small amount (24%) of *N*-monoalkylated methyl phosphinate **78** (Scheme 30).[52]

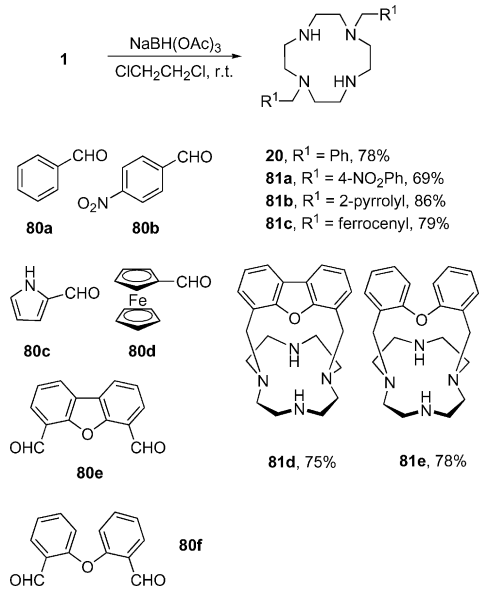
Sherry's group investigated other possibilities for the selective N^1,N^7-difunctionalization of cyclen and discovered that treatment of cyclen (**1**) with various chloroformates under acidic conditions (pH ≈ 2–3) resulted in the formation of the N^1,N^7-diacylated cyclens **79a**–**79d** in high yields (Scheme 31).[53a,53b,53c] Some other transformations of N^1,N^7-diacylated cyclens **79a**–**79d** are also described in the original paper,[53a] they are however not discussed here. The same methodology towards the N^1,N^7-diacylated cyclen **79d** has also been used by Welch and co-workers.[45b]

An extension of this methodology has been published recently using the reaction of cyclen (**1**) with commercially available benzyl- and *tert*-butyl-(oxycarbonyl) succinimides (Cbz-OSucc or Boc-OSucc) in chloroform at room temperature (Scheme 31).[53d] Both regioselectivity and yield have been found to be excellent using this methodology (Scheme 30) affording di-N^1,N^7-Cbz-cyclen (**79d**) in 98% and di-N^1,N^7-Boc-cyclen (**79e**) in quantitative yield. The observed selectivity hinged on taking advantage of a knowledge of the basicities of the ring nitrogen atoms, use of electrophiles with weakly basic leaving groups (OSucc anion) and use of a solvent in which the di-protonated form of the product is not soluble. One might envision using selectively substituted cyclens (particularly **79d** and **79e**) with easily removable protecting groups to prepare some other, less accessible N^1,N^7-disubstituted cyclens.



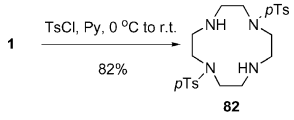
Scheme 31. Selective N^1,N^7-diacylation of cyclen (**1**) with chloroformates or oxycarbonyl succinimides.

Guilard and co-workers have recently expanded the scope of the reductive amination (see Scheme 19 for *N*-monoalkylation of cyclen via reductive amination) of various aromatic aldehydes with cyclen[54] (Scheme 32). Treatment of cyclen (**1**) with two equivalents of aromatic aldehydes **80a**–**80f** in the presence of excess of $NaBH(OAc)_3$ in 1,2-dichloroethane resulted in the formation of N^1,N^7-difunctionalized cyclens **20**, **81a**–**81e** in good yields (Scheme 32).



Scheme 32. Reductive amination of aromatic aldehydes **80a**–**80f** with cyclen (**1**). A route to N^1,N^7-difunctionalized cyclens **20**, **81a**–**81e**.

N^1,N^7-Ditosylcyclen (**82**) was obtained in high yield (82%) by treatment of cyclen (**1**) with two equivalents of tosyl chloride in pyridine (Scheme 33).[15,55] For comparison, recall that N^1,N^4-ditosylcyclen (**6**) was prepared in 40% by cyclization of linear precursors (Scheme 1).



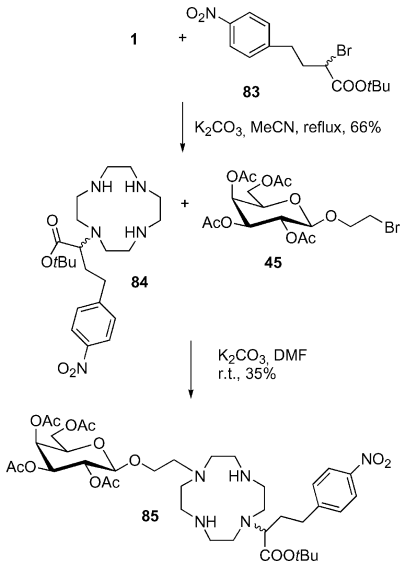
Scheme 33. Preparation of N^1,N^7-ditosylcyclen (**82**).

Synthesis of N^1,N^7-Difunctionalized Cyclens from *N*-Monofunctionalized Cyclens

Several reactions of *N*-monofunctionalized cyclens leading to N^1,N^7-difunctionalized cyclens have already been discussed. Examples for these types of transformations are found in Scheme 6, Scheme 26 and Scheme 29.

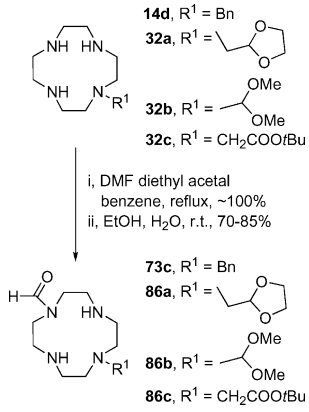
An interesting example of sequential *N*-dialkylation of cyclen, leading to N^1,N^7-dialkylated derivative has been described recently (Scheme 34).[56] *N*-Monoalkylation of cyclen (**1**) with racemic *tert*-butyl 2-bromo-4-(4-nitrophenyl) butanoate (**83**), followed by subsequent *N*-alkylation with the ethyl β-D-galactoside derived bromide **45** led to the formation of N^1,N^7-difunctionalized cyclen **85** in 23% overall yield (Scheme 34).[56]

The *N*-monofunctionalized cyclens **14d** and **32a**–**32c** (preparation in Scheme 10) have been treated with dimethylformamide diethyl acetal with the formation of corresponding tricyclic precursors in quantitative yields. These

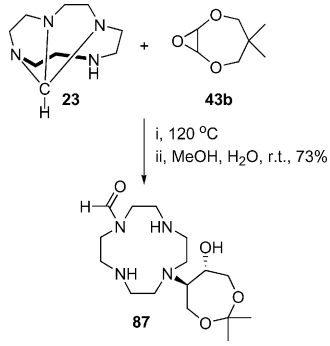


Scheme 34. Sequential *N*-alkylation of cyclen (**1**) with electrophiles **83** and **45**.

underwent hydrolysis smoothly leading to N^7-alkylated formyl cyclens **73c** and **86a**–**86c** in good yields (70–85%) (Scheme 35).[29]



Scheme 35. Preparation of N^7-alkylated *N*-formyl cyclens **73c** and **86a**–**86c** from *N*-monoalkylated cyclens **14d** and **32a**–**32c**.



Scheme 36. Epoxide **43b** nucleophilic ring opening with tricyclic amine **23**.

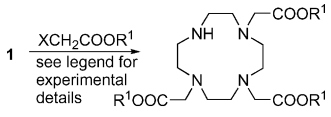
The tricyclic amine **23** (preparation in Scheme 7) has been used as a nucleophile in the ring opening of the epoxide **43b**.[24b] The reaction was carried out by heating the two components at 120 °C without any solvent (1.1 equiv. of **43b**, Scheme 36). After cooling the mixture to room temp. it was dissolved in aqueous MeOH and product of hydrolysis (structure **87**) was isolated in 73% yield, based on the tricyclic intermediate **23** (Scheme 36).

Selective *N*-Trifunctionalization of Cyclen

It has been pointed out previously,[8] that *N*-mono- and *N*-trifunctionalization of cyclen are closely related processes and both substitution patterns can be achieved via selective protection, functionalization and deprotection.

Selective *N*-Trialkylation of Cyclen

A discussion on the selective *N*-trialkylation of cyclen should start with the details of the preparation of some very important molecules – N^1,N^4,N^7-cyclentriacetic acid (**88a**) also known as DO3A and its trimethyl (structure **88b**), triethyl (structure **88c**), tri-*tert*-butyl (structure **88d**) and tribenzyl esters (structure **88e**). These molecules have been extensively used in the synthesis of MRI contrast agents as well as fluorescent and luminescent probes. Tweedle and coworkers described a direct alkylation of cyclen with chloroacetic acid (4 equiv. were found to be the optimum amount) in water at pH ≈ 9.[14] DO3A (**88a**) was obtained in 26% yield after extensive purification by ion exchange chromatography (Scheme 37). Later modification of the experimental conditions for the reaction of cyclen (**1**) with chloroacetic acid led to the formation of DO3A (**88a**) in 70% yield (Scheme 37).[57]

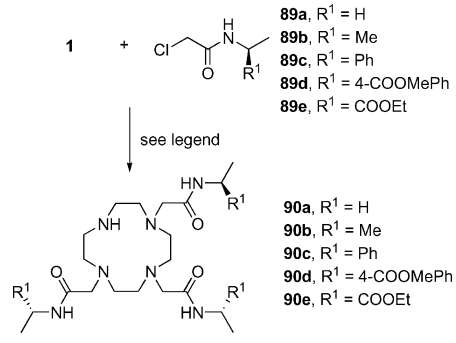


88a, X = Cl, R^1 = H
88b, X = Br, R^1 = Me
88c, X = Br, R^1 = Et
88d, X = Br, R^1 = *t*Bu
88e, X = Br, R^1 = Bn

Scheme 37. Synthesis of DO3A (**88a**) and its trimethyl- (**88b**) triethyl- (**88c**), tri-*tert*-butyl- (**88d**) and tribenzyl- (**88e**) esters. Reagents and conditions: **1** → **88a**, in ref.[14] KOH, H_2O, pH ≈ 9, 60 °C, 26%, **1** → **88a**, in ref.[57] NaOH, H_2O, pH ≈ 10, 4 °C to room temp., 70%, **1** → **88b**, Et_3N, MeOH, reflux, 54%, **1** → **88c**, CH_2Cl_2, room temp., 72%, **1** → **88d**, in ref.[60a] $NaHCO_3$, MeCN, 0 °C to room temp., 42%, **1** → **88d**, in ref.[46b] Et_3N, $CHCl_3$, room temp., 77%, **1** → **88e**, $NaHCO_3$, MeCN, room temp., 68%.

Various reaction conditions have been used to access the triacetate esters of cyclen. The trimethyl ester of DO3A (structure **88b**) was obtained by alkylation of cyclen (**1**) with methyl bromoacetate which was used in fourfold excess. This reaction was carried out in refluxing MeOH in the presence of Et_3N (3 equiv.) and afforded ester **88b** in ca. 50% yield after normal phase preparative TLC (Scheme 37).[58] The triethyl ester of DO3A (structure **88c**) was isolated in 72% yield after column chromatography (Scheme 37) when cyclen (**1**) was treated with 2.25 equiv. of ethyl bromoacetate in CH_2Cl_2 at room temp.[59] When cyclen (**1**) was alkylated with *tert*-butyl bromoacetate (3.3 equiv., MeCN, room temp.), DO3A tri-*tert*-butyl ester (**88d**) was obtained in 42% yield after crystallization from toluene (Scheme 37).[60] A more efficient procedure has been described recently (3.5 equiv. of *tert*-butyl bromoacetate, 10 equiv. of Et_3N in chloroform at room temp.) leading to DO3A tri-*tert*-butyl ester (**88d**) in 77% yield after chromatography on Al_2O_3 (Scheme 37).[46b] Finally, DO3A tribenzyl ester (**88e**) has been prepared by alkylation of cyclen (**1**) with benzyl bromoacetate (3 equiv., MeCN, room temp.) in the presence of $NaHCO_3$. The ester **88e** was isolated in 68% yield after column chromatography[61] (Scheme 37).

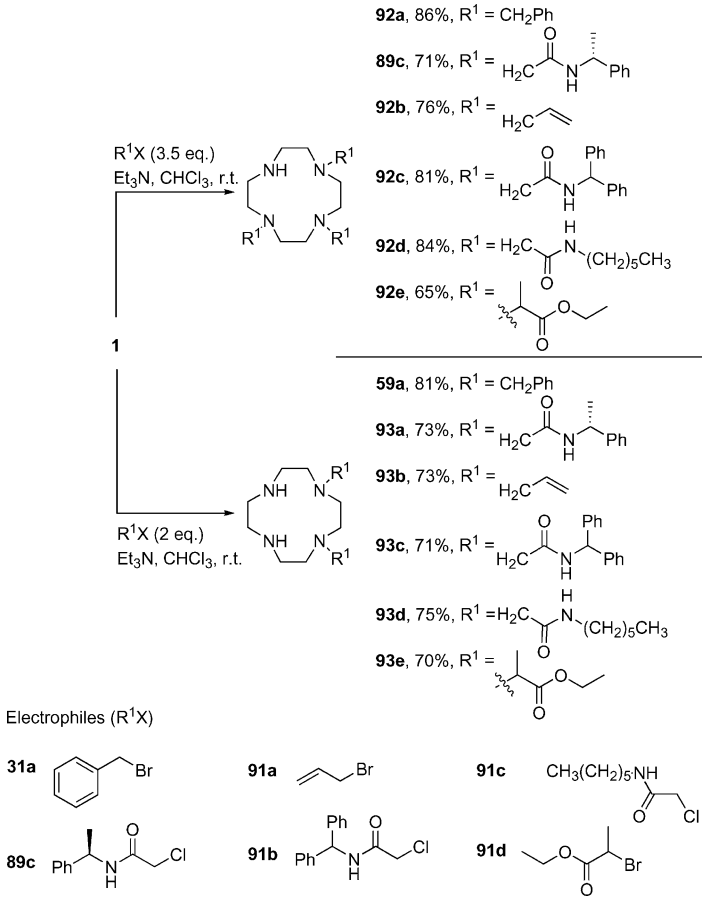
A general methodology for the *N*-trialkylation of cyclen (**1**) with the chiral chloroacetamides **89c**–**89e** has been developed by Parker and co-workers.[62] The dropwise addition of a solution of the amides **89c** and **89d** (3 equiv.) in EtOH, to the solution of cyclen (**1**) and Et_3N (3 equiv.) in EtOH, followed by refluxing the reaction mixture resulted in the formation of the *N*-trialkylated cyclens **90c** and **90d** (Scheme 38). The method suffered from rather poor regioselectivity and isolation of the desired products required an extensive chromatography on Al_2O_3 resulting in rather modest yields (29%). An alternate procedure has been used for the *N*-trialkylation of cyclen (**1**) with chloroacetamide **89e**.[62b] A mixture of cyclen, chloroacetamide **89e** (3 equiv.) and $NaHCO_3$ (3.1 equiv.) was stirred in acetonitrile at room temp. and the desired *N*-trialkylated cyclen **90e** was obtained after purification by chromatography on SiO_2 (Scheme 38). Unfortunately, the authors do not report the yield of this transformation. Heating (60 °C) a mixture of cyclen (**1**), chloroacetamides **89a** and **89b** (3 equiv.) and $NaHCO_3$ in acetonitrile followed by chromatography on Al_2O_3 afforded the *N*-trialkylated cyclens **90a** (52% yield) and **90b** (59% yield) in respectable yields[43] (Scheme 38).



89a, R^1 = H
89b, R^1 = Me
89c, R^1 = Ph
89d, R^1 = 4-COOMePh
89e, R^1 = COOEt

90a, R^1 = H
90b, R^1 = Me
90c, R^1 = Ph
90d, R^1 = 4-COOMePh
90e, R^1 = COOEt

Scheme 38. *N*-Trialkylation of cyclen (**1**) with chloroacetamides **89a**–**89e**. Reagents and conditions: **1** + **89a**, **89b** → **90a**, **90b**, $NaHCO_3$, MeCN, 60 °C, 52% (**90a**), 59% (**90b**), **1** + **89c**, **89d** → **90c**, **90d**, Et_3N, EtOH, reflux, 29%, **1** + **89e** → **90e**, $NaHCO_3$, MeCN, room temp., no yield is reported.[62b]



Scheme 39. *N*-Trialkylation and N^1,N^4-dialkylation of cyclen (**1**) with electrophiles **31a**, **90c**, **91a**–**91d**.

Various electrophiles (**31a**, **90c**, **91a**–**91d**) have been used to achieve selective *N*-trialkylation of cyclen. Treatment of cyclen (**1**) with above mentioned electrophiles (3.5 equiv.) in the presence of Et_3N (10 equiv. in $CHCl_3$) resulted in the formation of *N*-trialkylated cyclens **90c** and **92a**–**92e** in good yields[46b] (Scheme 39). Another example of this highly selective *N*-trialkylation leading to DO3A tri-*tert*-butyl ester (**88d**) has already been discussed (see Scheme 37).[46b]

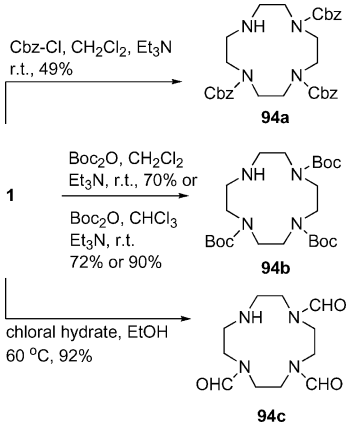
It is also interesting to point out, that N^1,N^4-dialkylated cyclens **59a** and **93a**–**93e** have been obtained in excellent regioselectivity and good yield,[46b] when 2 equiv. of electrophiles **31a**, **90c**, **91a**–**91d** have been used under identical reaction conditions (Scheme 39). An example of this highly regioselective N^1,N^4-dialkylation described in a preliminary communication[46a] has already been discussed (see Scheme 25).

Selective *N*-Triacylation and *N*-Trisulfonylarylation of Cyclen

The synthesis of *N*-triacylated cyclens has been very well studied, as *N*-triacylated cyclens can undergo further functionalization, followed by removal of acyl protecting groups usually under mild conditions. *N*-Monofunctionalized cyclens can be obtained in good yields therefore this methodology is still in use. This protocol represents a useful alternative to selective *N*-monofunctionalization of cyclen, which has already been discussed.

The first example of selective *N*-acylation of cyclen (**1**) was described in 1991. Cyclen (**1**) was treated with 3.2 equiv. of benzyl chloroformate (in the presence of Et_3N, 6.4 equiv.) in dichloromethane and tri-*N*-Cbz-cyclen (**94a**) was isolated in 49% yield after column chromatography[63a] (Scheme 40). The authors used the triprotected cyclen **94a** for *N*-alkylation of the remaining nitrogen atom (readers are referred to the original paper[63a] for details) and were able to remove Cbz protecting groups by catalytic hydrogenation. Some other transformations using tri-*N*-Cbz-cyclen (**94a**) as a starting material have also been described.[63b]

A superior intermediate among the *N*-triacylated cyclens appears to be tri-*N*-Boc-cyclen (**94b**). Its first synthesis was described in 1995[64a] and some variations of the original protocol appeared shortly afterwards. In the original procedure, cyclen (**1**) was treated with 2.4 equiv. of Boc_2O in dichloromethane.[64a] Tri-*N*-Boc-cyclen (**94b**) was isolated in 70% yield after column chromatography (Scheme 40). Some modified procedures have also appeared in the literature.[31,64b] Replacement of dichloromethane as solvent by

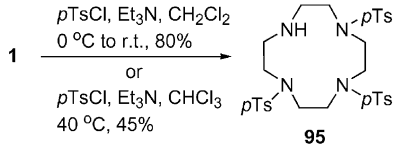


Scheme 40. Preparation of tri-*N*-Cbz-cyclen (**94a**), tri-*N*-Boc-cyclen (**94b**) and tri-*N*-formylcyclen (**94c**).

chloroform and performance of the reaction in the presence of Et_3N (3 equiv., Scheme 40) increased the yield of tri-*N*-Boc-cyclen (**94b**) to 90%. Details of *N*-functionalization of **94b** and acid-mediated removal of Boc groups are contained in the original papers.[31,64]

Reaction of cyclen (**1**) with an excess of chloral hydrate in hot (60 °C) EtOH was found to produce tri-*N*-formylcyclen (**94c**) in excellent yield of 92% (Scheme 40).[65a] The authors describe *N*-alkylation of the remaining nitrogen atom by various electrophiles followed by alkaline hydrolysis-mediated removal of formyl groups, see the original paper for details.[65a] Alkaline hydrolysis of various *N*-formylcyclens was found to be ineffective by our group[36] and by others,[45b] although the formyl group can be efficiently removed by acidic hydrolysis.[45b,51] Other methodologies investigated in our laboratory, such as oxidative[65b] or reductive[65c] removal of the formyl group proved to be rather troublesome, leading either to decomposition (oxidation) or recovery of the starting material (catalytic hydrogenation).[36]

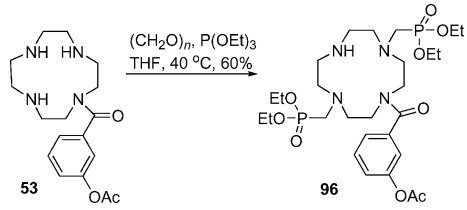
Tri-*N*-tosylcyclen (**95**) has been prepared in high yield (80%, purified by crystallization) by reacting cyclen (**1**) with tosyl chloride (3 equiv.) in dichloromethane with 3 equiv. of Et_3N (Scheme 41).[14] An alternative procedure appeared in 1994.[66] Dichloromethane was replaced with chloroform, only 2 equiv. of TsCl have been used and the reaction was carried out at 40 °C (Scheme 41). The yield of tri-*N*-tosylcyclen (**95**) was found to be 45% after crystallization.[66] Taking into account the yields of both procedures, the former one[14] appears to be more suitable.



Scheme 41. Preparation of tri-*N*-tosylcyclen (**95**).

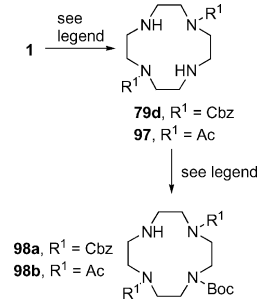
Synthesis of *N*-Trifunctionalized Cyclens from *N*-Monofunctionalized and N^1,N^7-Difunctionalized Cyclens

An interesting example of *N*-trifunctionalization of cyclen starting from *N*-monoacylcyclen **53** (see Scheme 22 for preparation) has been described recently.[41] Reaction of *N*-monoacylcyclen **53** with paraformaldehyde (3.3 equiv.) and triethyl phosphite (4 equiv.) in warm (40 °C) THF was found to produce *N*-trifunctionalized cyclen 96 in 60% yield (Scheme 42).[41]



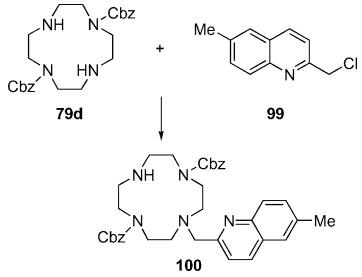
Scheme 42. Preparation of cyclen-derived phosphite **96**.

Di-N^1,N^7-(Cbz)-cyclen (**79d**) (see Scheme 31 for preparation) can be *N*-mono-Boc-protected in 65% yield upon treatment with Boc_2O in dichloromethane at room temp.[67] The protected cyclen **98a** is obtained in 65% yield (Scheme 43). Acetylation of cyclen (Ac_2O in AcOH at room temp.) led to the formation of di-N^1,N^7-acetylcyclen (**97**) in 88% yield (Scheme 43). Di-N^1,N^7-acetylcyclen (**97**) was then converted to *N*-mono-Boc-protected cyclen **98b** (in 41% yield) under above mentioned reaction conditions (Scheme 43).[67] Orthogonally protected cyclens **98a** and **98b** have been used for further transformations as described in the original paper.[67]



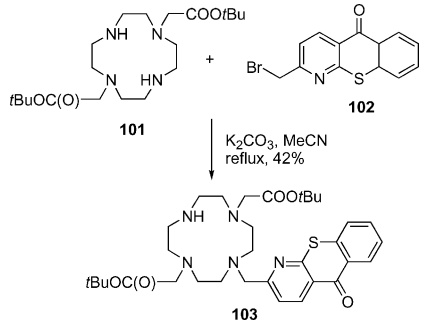
Scheme 43. *N*-Mono-Boc-protection of di-N^1,N^7-(Cbz)-cyclen (**79d**) and di-N^1,N^7-acetylcyclen (**97**). Reagents and conditions: **1** → **79d**, see Scheme 31, **1** → **97**, Ac_2O, AcOH, room temp., 88%, **79d** → **98a**, Boc_2O, CH_2Cl_2, room temp., 65%, **97** → **98b**, Boc_2O, CH_2Cl_2, room temp., 41%.

Alkylation of di-N^1,N^7-(Cbz)-cyclen (**79d**) with 2-chloromethyl-6-methylquinoline (**99**) afforded *N*-trifunctionalized cyclen **100** (Scheme 44) as a precursor to highly functionalized MRI contrast agent. Neither the experimental procedure, nor the chemical yield is reported in the original paper.[68]



Scheme 44. Alkylation of di-N^1,N^7-(Cbz)-cyclen (**79d**) with 2-chloromethyl-6-methylquinoline (**99**).

DO2A di-*tert*-butyl ester (**101**)[69] was refluxed (in acetonitrile) in the presence of K_2CO_3 (1 equiv.) with 2-bromomethyl-1-azathiaxanthone (**102**) (1.1 equiv.).[70] The *N*-trialkylated cyclen **103** was isolated in 42% yield after column chromatography (Scheme 45).

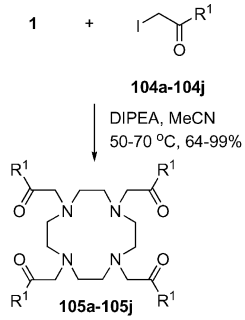


Scheme 45. *N*-Monoalkylation of the DO2A di-*tert*-butyl ester (**101**) with 2-bromomethyl-1-azathiaxanthone (**102**).

Synthesis of Fully Functionalized Cyclens

Substitution of all four cyclen nitrogen atoms of cyclen (**1**) with identical substituents is rather straightforward as indicated in a previous review.[8] The reaction of cyclen with various electrophiles should, in principle, lead to a fully substituted cyclen if sufficient amount of electrophile (at least 4 equiv.) is used. Numerous examples can be found in the literature and comprehensive treatment is beyond the scope of this microreview.

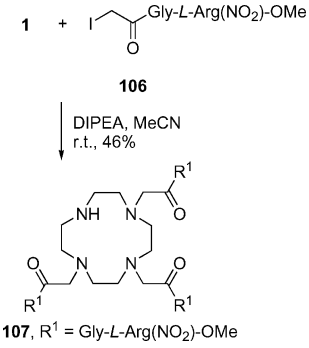
Recent work by our group can be used to provide an example for this type of transformation. One of the research topics currently under investigation in our laboratory is the development of temperature and pH responsive PARACEST MRI contrast agents based on the magnetic properties of various lanthanide(III) complexes of cyclen oligopeptide conjugates. *N*-Peralkylation of cyclen (**1**) with 4 equiv. of *N*-iodoacetyl mono-, di-, and tripeptides (structures **104a**–**104j**) was carried out in warm (50–70 °C) acetonitrile using ethyldiisopropylamine (DIPEA) as a base (Scheme 46).[71] Fully protected cyclen oligopeptide conjugates were obtained in good yields (64–99%). The removal of the protecting followed by metalation by different lanthanide(III) chlorides resulted in the formation of the desired complexes.[71] Among them the Eu^{3+} complex resulting from saponification and metalation of cyclen conjugate **105c** was found to be a sensitive temperature-responsive PARACEST MRI contrast agent.[72]



104a, **105a**, R^1 = *L*-Lys(Boc)-OMe
104b, **105b**, R^1 = *L*-Phe-OEt
104c, **105c**, R^1 = Gly-*L*-Phe-OEt
104d, **105d**, R^1 = Gly-*L*-Tyr(*t*Bu)-OMe
104e, **105e**, R^1 = Gly-*L*-Trp-OMe
104f, **105f**, R^1 = Gly-*L*-Lys(Boc)-OMe
104g, **105g**, R^1 = *L*-Asp(OMe)-*L*-Glu(OMe)-OMe
104h, **105h**, R^1 = *L*-Asp(OMe)-*L*-Phe-OEt
104i, **105i**, R^1 = *L*-Lys(Boc)-*L*-Phe-OEt
104j, **105j**, R^1 =Gly-*L*-Phe-*L*-Lys(Boc)-OMe

Scheme 46. *N*-Peralkylation of cyclen (**1**) with *N*-iodoacetyl mono-, di-, and tripeptides **104a**–**104j**.

A notable exception to the previous protocol was found when *N*-peralkylation of cyclen (**1**) with *N*-iodoacetyl-Gly-L-Arg(NO_2)-OMe (**106**, Scheme 47) was attempted.[71a] The *N*-trialkylated conjugate **107** precipitated out from the solution as a sole product (Scheme 47) despite of the reaction temperature (room temp. to reflux) and large excess of electrophile **106** (up to 10 equiv.).[71a]

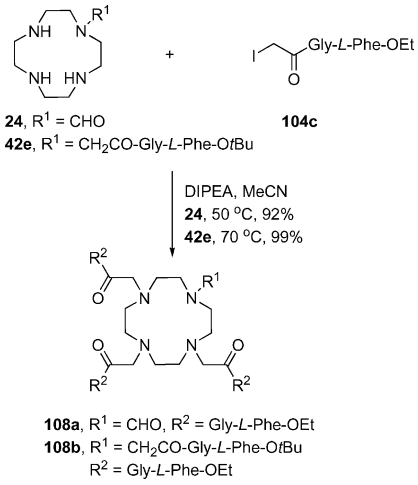


Scheme 47. Alkylation of cyclen (**1**) with *N*-iodoacetyl-Gly-L-Arg(NO_2)-OMe (**106**).

Similar to cyclen itself, *N*-peralkylation of *N*-monosubstituted cyclens can be achieved if sufficient amount of electrophile (at least 3 equiv.) is used. The same rule applies for both N^1,N^4- and N^1,N^7-disubstituted cyclens. At least 2 equiv. of electrophile are required in this case. Many examples can be found in the literature. We highlight yet another example from our laboratory to illustrate this type of transformation.

N-Formylcyclen (**24**) and *N*-monoacetyl-Gly-L-Phe-O*t*Bu cyclen (**42e**) have been *N*-peralkylated in very good yields (> 90%) with *N*-iodoacetyl-Gly-L-Phe-OEt (**104c**)

using DIPEA as a base and warm acetonitrile as a solvent (Scheme 48).[36] We did not meet with success, when we attempted to remove formyl protecting group from conjugate **108a**.[36] The orthogonally protected conjugate **108b** can undergo selective *t*Bu ester functionality acidolysis, followed by HBTU-mediated coupling with mono-Boc-cystamine to afford a close precursor (structure not shown) of new "conjugation ready" temperature sensitive PARACEST MRI contrast agent.[36]



Scheme 48. Peralkylation of *N*-formylcyclen (**24**) and *N*-monoacetyl-Gly-L-Phe-O*t*Bu cyclen (**42e**) with *N*-iodoacetyl-Gly-L-Phe-OEt (**104c**).

N-Functionalization of the remaining free nitrogen atom in *N*-trifunctionalized cyclens has been extremely well studied and many examples appear in the literature. A recent paper on functionalization of DO3A tri-*tert*-butyl ester by Aime and co-workers might serve as a good example.[73] DO3A tri-*tert*-butyl ester is often used as a starting material for the conjugation of cyclen-based metal chelators to large molecular entities such as peptides,[4a,74] proteins[61] or even viruses.[60e,75] Another important group of fully *N*-functionalized cyclens, which nowadays starts to receive an increased attention is based on the modification of *N*-trifunctionalized cyclens with a side chain possessing a terminal alkyne functional group.[76] Alkyne-modified cyclens have been used as precursors in Huisgen "click" cycloaddition with a variety of azides.[76]

Conclusions and Future Prospects

The present review surveyed the various methodologies towards *N*-functionalized cyclens with an emphasis on the chemistry and examples of selective mono-, di- and tri-*N*-functionalization. These examples highlight the complexity and subtleties in the chemistry of cyclen. Its reactivity is sensitive to the solvent, the amount and identity of the base, the electronic and steric nature of the electrophile as well as changes in its own conformation, pK_a and changes in solubility with increasing *N*-substitution. These factors impact the chemo- and regioselectivity and ultimately the chemical yield as do simple technical factors such as ease (or avoidance) of chromatography and other purification techniques.

The synthesis of *N*-functionalized cyclen from acyclic precursors is currently rarely used as cyclen itself and many of its important derivatives (e.g. DOTA, DOTAM, DO3A, DO3A tri-*tert*-butyl ester) are currently available from multiple commercial suppliers. Among the methodologies used for mono-, di- and tri-*N*-functionalization of cyclen, *N*-alkylation appears to be the most prominent. Synthetic methodologies have been developed to prepare *N*-monoalkylated, both N^1,N^4- and N^1,N^7-dialkylated as well as *N*-trialkylated cyclens in good yields and excellent regioselectivities. Various halogen derivatives are used as reactive electrophiles in most of the examples. Two methods for the alkylation of cyclen (**1**) have, in our opinion, been under utilized. Firstly, oxirane ring opening which can be performed both regio- and stereoselectively (see Schemes 17 and 36).[37] Only a very limited number of references using this methodology appears in the literature.[16,24b,37] It is quite easy to envision, that the scope of the nucleophilic small ring opening by cyclen can be expanded significantly, if some other strained reactive species such as aziridines, thiiranes or activated cyclopropanes are used. The other unexploited methodology is the reductive amination of aldehydes with cyclen (**1**) and its derivatives, which may also be done regioselectively and in high yield (see Schemes 19 and 32).[39,54]

N-Functionalization of cyclen by *N*-acylation, *N*-sulfonylalkyl and *N*-sulfonylarylation has also been well studied; however, these methods appear to be less prevalent in the current literature. Mainly carboxylic acid chlorides and anhydrides have been used as *N*-acylating agents and there is a wealth of example on which to design future syntheses. Surprisingly there are, to the best of our knowledge, only two reports describing the use of cyclens (naked cyclen as well as *N*-di- and *N*-trifunctionalized ones) as nucleophiles in reactions with isocyanates to form cyclen-derived ureas.[77] Some other cyclen-derived ureas are known, they have been, however not prepared by reactions of cyclens with isocyanates.[78] A sole example describing a reaction of cyclen with isothiocyanates to form cyclen-derived thiourea has appeared in the literature,[79] whereas reactions of cyclens with other cumulenes (allenes) or heterocumulenes (ketenes) have not been described to date. Reactions of cyclens with various cumulenes might provide the route to some new ligands, bearing interesting properties and being inaccessible by other methodologies.

"Conjugation ready" derivatives of cyclen (**1**) endowed with chemical functionality to permit conjugation with various macromolecules appear to be an important focus of many research groups involved in the development of MRI contrast agents or fluorescence and luminescence based optical probes. The classical method of conjugation involves peptide bond formation between the carboxylic group containing cyclen and reactive primary or secondary amino group of the peptide or protein.[4a] Among newer types of the "conjugation ready" cyclen derivatives, alkyne modified

molecules[76] are gaining their popularity as they can be used as substrates in Huisgen "click" cycloaddition with different azides. Our research group[36] and others[30b] have been involved in the development of primary sulfanyl group modified cyclen oligopeptide conjugates, which can be used for the conjugation with peptides (via disulfide bond formation), Michael acceptors or even nanoparticles.

Although there has been a very generous exploration of the chemistry for the preparation and applications of *N*-functionalized cyclens, this field is far from mature. During the recent past, there has been a significant increase in the number and type of applications that employ cyclen as an integral, functional part of the molecule. With the increasing sophistication of the applications for functionalized cyclens there is expected to be an increase in the synthesis of complex cyclen-containing molecules; indeed, the future of this field of endeavor will undoubtedly be very active, exciting and productive.

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