CONSTRUCTION OF 1,4,6,10-TETRAAZAADAMANTANES *VIA* INTRAMOLECULAR OXIME/HYDRAZONE CYCLOTRIMERIZATION APPROACH

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Artem N. Semakin[a] and Alexey Yu. Sukhorukov[b]

[a]*Skolkovo Institute of Science and Technology (SKOLTECH University), Nobel str. 3, 143026 Moscow, Russian Federation*

[b]*N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences Leninsky prospect 47, 119991 Moscow, Russian Federation (e-mail: sukhorukov@ioc.ac.ru)*

Abstract. *The account is focused on the synthesis of 1,4,6,10-tetraazaadamantanes, a new class of heterocage scaffolds isomeric to urotropine (methenamine). The suggested strategy to the assembly of 1,4,6,10-tetraazaadamantane cage employs an intramolecular [2+2+2] cyclotrimerization reaction in a suitable tris-oxime or tris-hydrazone precursor. Various 1,4,6,10-tetraazaadamantane derivatives including unsymmetrically substituted ones are accessible by this route.*

Contents

1. Introduction

For more than 100 years, heteroadamantanes have been objects of high interest for pure and applied chemistry.[1,2] These cage polycyclic structures exhibit a wide range of useful properties[1-7] and, furthermore, are convenient models to study various fundamental problems dealing with structure and reactivity of organic compounds.[8-13]

Among various heteroadamantanes, 1,3,5,7-tetraazaadamantane (urotropine or methenamine) firstly obtained by Butlerow[14] in 1859 is the most important from the practical application point of view. Urotropine is widely used as a medication,[15] preservative in food industry,[16] formaldehyde equivalent in polymer synthesis,[17] precursor of high-energy materials[18] as well as a useful reagent in organic synthesis[19] and coordination chemistry.[20]

Until our recent studies, urotropine for 150 years had been the only representative of tetraazaadamantanes class known (Figure 1). Since not an any combination of heteroatoms in adamantane cage results in a stable structure,[12] the possibility of existence of other tetraazaadamantanes represents fundamental interest (Figure 1). Quantum-chemical calculations predict urotropine to be the least thermodynamically favored among four possible isomeric tetraazaadamantanes without nitrogen-nitrogen bonds.[21] This suggests that tetraazaadamantanes isomeric to urotropine or at least some of their derivatives may be stable.

Some years ago, we became interested in 1,4,6,10-tetraazaadmanatane **1**, a C_{3v}-symmetrical isomer of urotropine (Figure 1). Because of the presence of three bridge and one bridgehead nitrogen atoms, which can be easily modified by electrophilic addition reactions, 1,4,6,10-tetraazaadamantane can be viewed as an interesting multivalent (3+1) scaffold for the design of functional molecules and materials.[22] In such a way, 1,4,6,10-tetraazaadamantane may serve as a rigid three-dimentional matrix arranging an orthogonal orientation of functional units A and B (Figure 1). Thus, we aimed to accomplish the synthesis of 1,4,6,10-tetraazaadamantane **1** (so-called "isourotropine") and its derivatives.

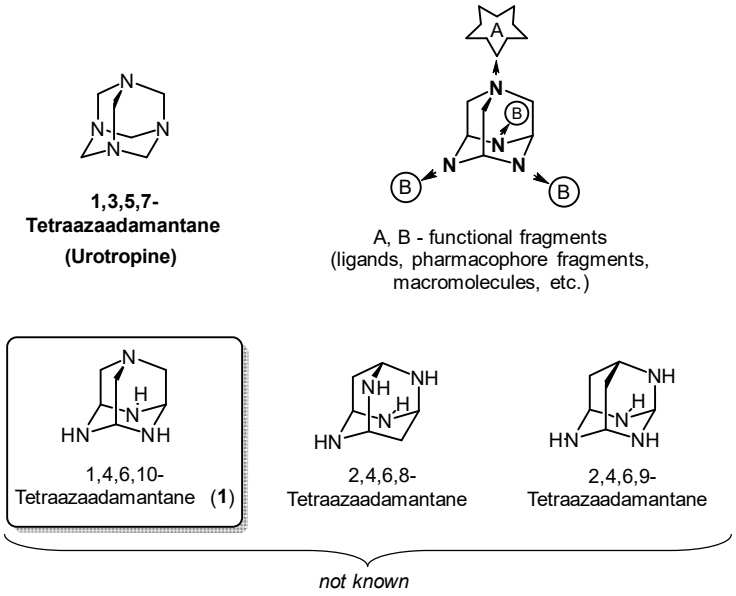


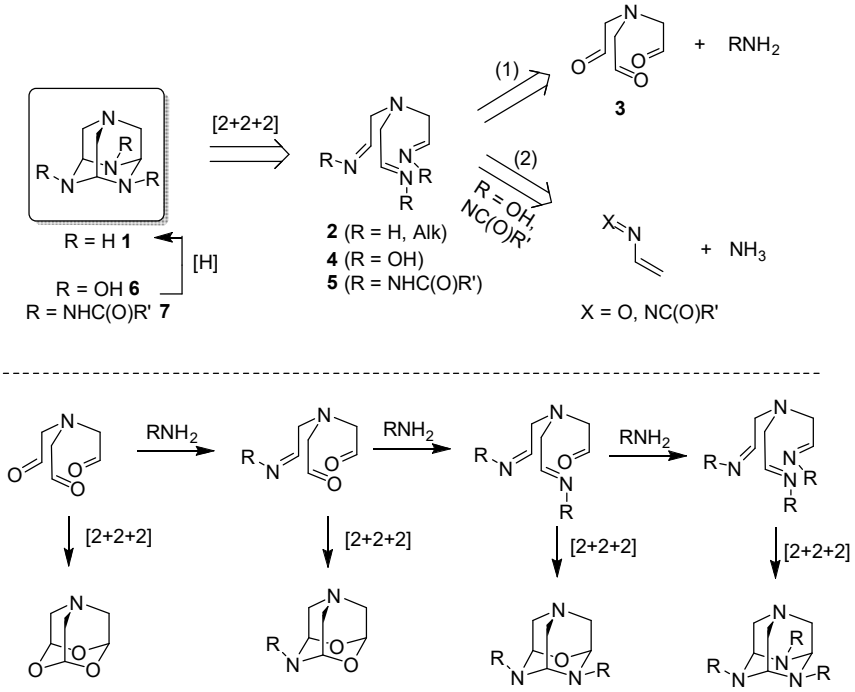
Figure 1. Urotropine and its isomers.

2. Synthetic strategy towards 1,4,6,10-tetraazaadamantane cage

The most logical approach to the construction of 1,4,6,10-tetraazaadamantane cage **1** is the intramolecular cyclotrimerization ([2+2+2]-annulation) of C=N bonds in a tris-imine precursor **2** (Scheme 1). Apparently, these intermediates can be generated from the corresponding trialdehyde **3** and ammonia or primary amine (route (1) in Scheme 1). A similar [2+2+2]-annulation of imines derived from tricarbonyl compounds has been previously applied for the synthesis of some heterocage structures such as triazawurtzitanes by Nielsen[23] and 2,4,9-triazadamantanes by Quast.[24] However, trialdehydes of type **3** as well as other tricarbonyl compounds easily undergo intramolecular cyclotrimerization to form trioxadamantanes and intramolecular aldol reactions.[25] This makes the synthesis of trialdehydes **3** quite problematic. Furthermore, intermediate iminoaldehydes generated on various stages of ammonia-trialdehyde condensation may also undergo intramolecular [2+2+2]-annulations to give mixed oxoazaadamantanes (see bottom part of Scheme 1, on the synthesis of mixed heteroadamantanes see ref.[24]).

A possible way to tackle this problem is the generation of tris(methylimino)amine intermediate by an alternative approach avoiding condensation of amines with a tricarbonyl precursor. To accomplish this, the Michael-type addition of ammonia to conjugated nitroso- or azoalkenes was suggested (Scheme 1, route (2), on the addition of amines to nitroso- and azoalkenes see refs[26-39]).

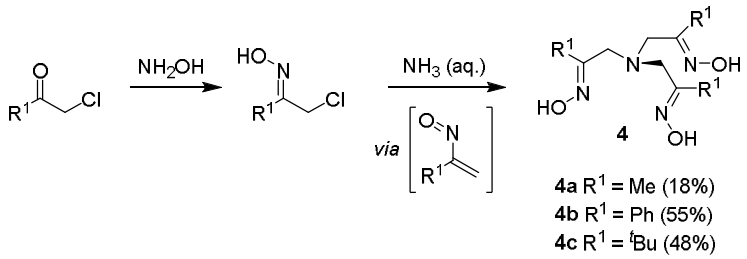
In this connection, tris-oximes **4** or tris-hydrazones **5** are likely to be the most reasonable precursors of target 1,4,6,10-tetraazaadamantanes **1**. However, the realization of this approach is not trivial. Firstly, although cyclotrimerization reactions are typical for azomethines, for oximes these processes are virtually undescribed[40] and very limited known for hydrazones.[41-43] Secondly, intramolecular cyclotrimerization of tris-oximes **4** and **5** would lead to *N*,*N'*,*N''*-substituted 1,4,6,10-tetraazaadamantanes **6** (R = OH) and **7** (R = NHC(O)R') in which N–O or N–N bonds have to be reduced. This may be difficult to accomplish, since aminal centers, which constitute a basis of 1,4,6,10-tetraazaadmantane cage, are also sensitive to reducing agents. Finally, considering the lability of aminals and the reversibility the imine cyclotrimerization, the stability of final 1,4,6,10-tetraazaadamantanes **1** was questionable.



Scheme 1. Suggested approach for construction of 1,4,6,10-tetraazaadamantane cage.

3. Synthesis of tris-oximes and tris-hydrazones as precursors of 1,4,6,10-tetraazaadamantanes

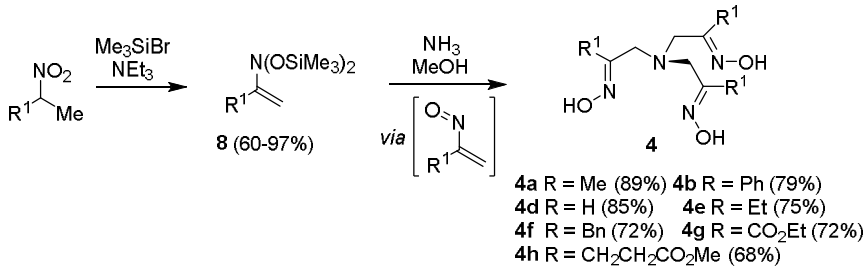
Only two tris-oximes **4** and no examples of tris-hydrazones **5** have been reported in literature prior our work. Both of tris-oximes **4a** and **4b** were firstly prepared in the end of 19th century by condensation of chloroacetone or chloloroacetophenone oximes with ammonia.[44,45] These reactions involve the generation of conjugated nitrosoalkenes as intermediates and their triple addition to ammonia.[27] This method provides tris-oximes **4** in low to moderate yields, yet it can be utilized for a multi-gram synthesis of simple symmetrical tris-oximes of type **4a-c** from readily available α-haloketones (Scheme 2). However, the synthesis of non-substituted tris-oxime **4d** (R = H, from chloroacetaldehyde oxime) as well as more complex tris-oximes **4** bearing functional groups cannot be accomplished by this route.



Scheme 2. Synthesis of tris-oximes **4** from α-chloroketones (yields are given for two steps).

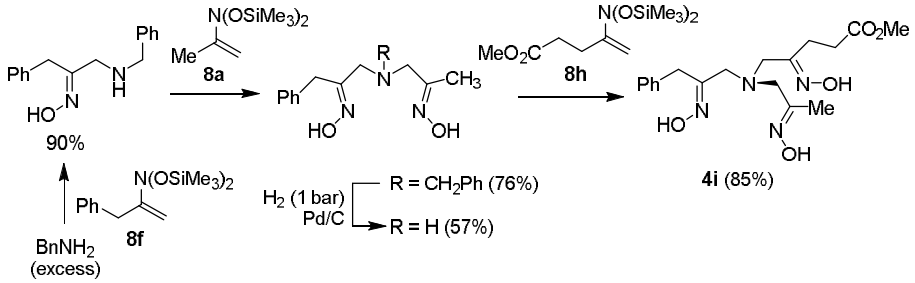
We have developed a more general approach to the synthesis of tris-oximes **4** employing nitrosoacetals of nitrosoalkenes (*N*,*N*-bis(siloxy)enamines **8**) as reagents instead of α-halooximes.[46] *N*,*N*-Bis(siloxy)enamines **8** are readily accessible by double silylation of aliphatic nitro compounds.[47] The key

advantage of enamines **8** is that highly reactive nitrosoalkenes are generated in a more controllable manner that prevents most of side processes, such as oligomerization (Scheme 3).[28,48] Alkylation of ammonia with *N*,*N*-bis(siloxy)enamines **8** provides tris-oximes **4** in high yields including the non-substituted tris-oxime **4d** (R = H)[49] as well as functionalized tris-oximes such as **4g** and **4h**.[49] Importantly, only triply alkylated products **4** are selectively formed in a wide range of **8**/ammonia ratios.



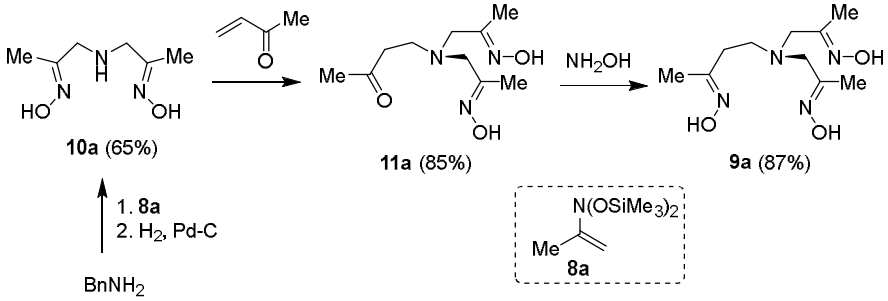
Scheme 3. Synthesis of tris-oximes **4** from aliphatic nitro compounds.

The high efficiency of oximinoalkylation of primary and secondary amines with *N*,*N*-bis(siloxy)enamines **8**[28] allowed to accomplish the synthesis unsymmetrically substituted tris-oximes **4** bearing two and even three different β-oximinoalkyl arms starting from benzylamine.[50] An example of such modular synthesis of unsymmetrical tris-oxime **4i** is shown in Scheme 4.



Scheme 4. Synthesis of tris-oxime **4i** possessing three different β-oximino-alkyl fragments.

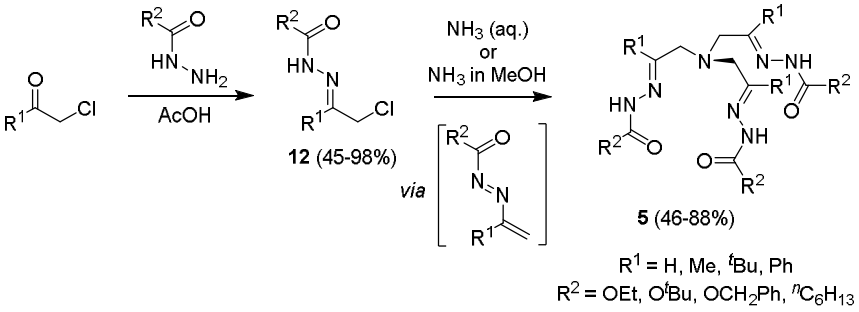
This approach was also adapted to the synthesis of tris-oximes of type **9**, bearing an additional methylene group in one of the oximinolalkyl fragment (Scheme 5).[51]



Scheme 5. Synthesis of tris-oxime **9a** with γ-oximinolalkyl fragment.

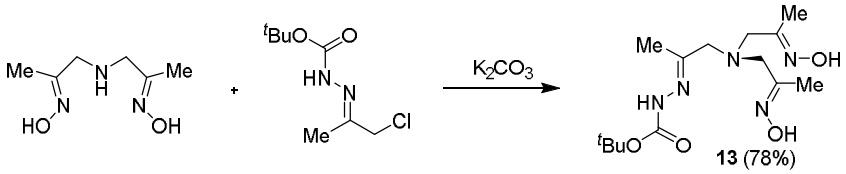
In this synthesis, β-oximinolalkyl fragments were introduced by double alkylation of benzylamine with *N*,*N*-bis(siloxy)enamine **8a**, while the γ-oximinolalkyl arm was constructed employing Michael addition of secondary amine **10a** to methyl vinyl ketone followed by oximation of the resulting ketone **11a**.

The synthesis of tris-hydrazones **5** was accomplished in a similar manner to tris-oximes **4** by the alkylation of ammonia with conjugated azoalkenes (Scheme 6).[52] The latter are more stable and selective Michael acceptors[29-39] than nitrosoalkenes, and thus can be efficiently generated from acylhydrazones of α-haloketones upon the action of bases. Reaction of acylhydrazones **12** with an excess of ammonia produces target tris-hydrazones **5** in high yields.



Scheme 6. Synthesis of tris-hydrazones **5**.

By combining nitrosoalkene and azaalkene approaches, mixed oxime-hydrazones of type **13** can be accessed (Scheme 7).

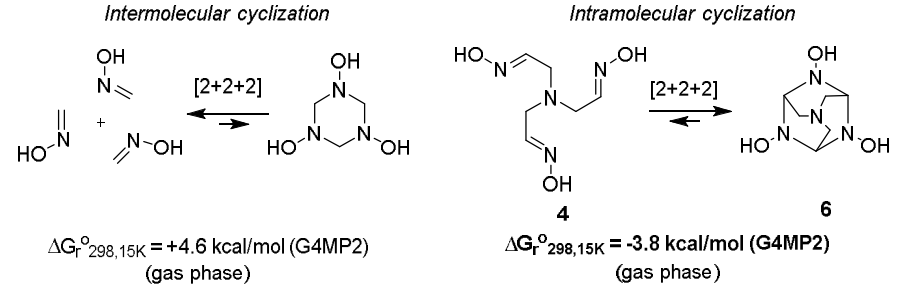


Scheme 7. Synthesis of mixed oxime-hydrazone **13**.

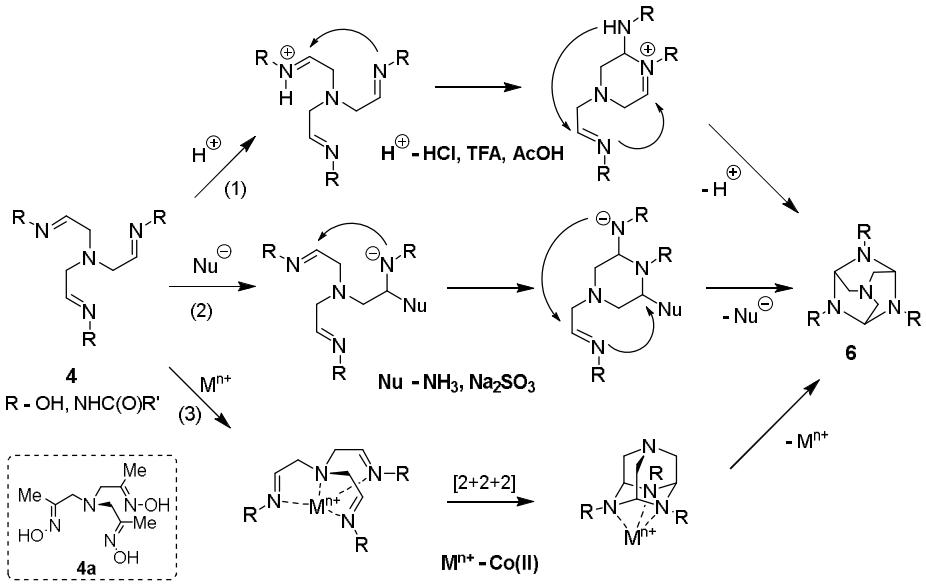
4. Studies of the intramolecular cyclotrimerization of C=N groups in tris-oximes and tris-hydrazones

The key issue in 1,4,6,10-tetraazaadamantane cage assembly strategy shown in Scheme 1 was the intramolecular cyclotrimerization of C=N bonds in tris-oximes **4** and tris-hydrazones **5**. Quantum-chemical calculations suggested that in contrast to intermolecular cyclotrimerization of oximes, a parent intramolecular [2+2+2]-annulation **4→6** is thermodynamically favored (Scheme 8). However, the majority of tris-oximes **4** (and tris-hydrazones **5**) are stable compounds and do not undergo spontaneous cyclization to target tetraazaadamantanes that may be caused by kinetic reasons. Therefore, our efforts were focused on a search for conditions and catalysts to facilitate transformation **4→6**.[49]

Based on the reactivity of oximes, several ways to promote C=N bond cyclotrimerization can be suggested, in particular catalysis by Brønsted acids, nucleophiles or d-metal ions (Scheme 9).[49] Brønsted acids by protonation of sp^2-nitrogen atom, should increase the electrophilicity of C=N bond thus promoting the nucleophilic attack by the nitrogen atom of the second oxime group (route (1), Scheme 9). Nucleophile addition to the C=N bond should increase the nucleophilicity of nitrogen atom thus inducing its nucleophilic attack on the second oxime group (route (2), Scheme 9). Transition metal compounds can be expected to facilitate the cyclotrimerization through a template effect (i.e. bringing oxime groups closer to each other through coordination, route (3) in Scheme 9) and/or Lewis acid enhancement of oxime group electrophilicity.



Scheme 8. Inter- and intramolecular cyclotrimerization.

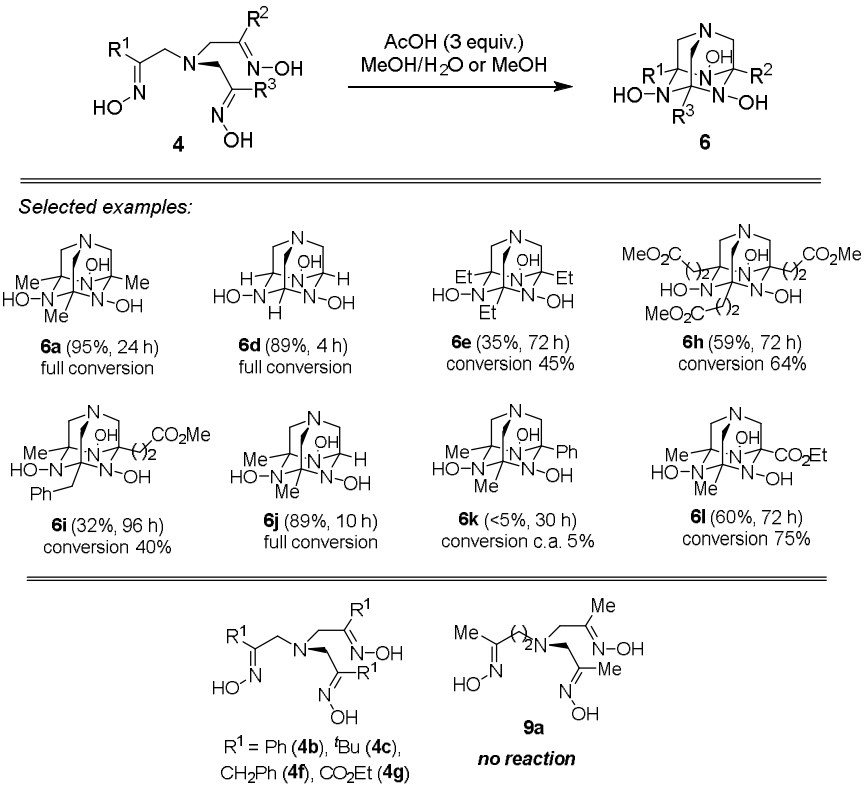


Scheme 9. Promotion of the intramolecular oxime cyclotrimerization in tris-oximes **4**.

A comprehensive study on the model tris-oxime **4a** revealed that all these approaches did promote the intramolecular cyclotrimerization process to some extent. [16] Thus, the action of strong and medium strong protic acids on tris-oxime **4a** caused the [2+2+2]-cyclization providing corresponding salts of adamantane **6a**. Nucleophilic catalysis with ammonia and sodium sulfite also furnished adamantane **6a**, though in lower yields. The metal-catalyzed assembly of adamantane cage from tris-oxime **4a** was also demonstrated with cobalt(II) salts. Interestingly, the action of other parent d-metal compounds (zinc (II), nickel (II), iron(III)) led to stable complexes of tris-oxime **4a**, which did not convert to adamantane **6a** (for the formation of tris-oxime complexes with transition metals see refs.[46,53,54]). The most efficient procedure to transform oxime **4a** into adamantane **6a** in terms of conversion and chemoselectivity proved to be the use of three equivalents of acetic acid as a promoter in aqueous methanol, which provided the desired product in 95% yield.

Subsequent substrate scope studies revealed an unexpectedly high sensitivity of oxime cyclotrimerization to the nature of substituents at C=N bonds (Scheme 10).[49,55] Thus, the unsubstituted tris-oxime **4d** underwent a rapid cyclization to the corresponding *N,N',N''*-trihydroxy-1,4,6,10-tetraazaadamantane **6a**, which is the direct precursor of target "isourotropine" (slow conversion of **4d** to **6d** was observed even without acetic acid). In contrast to **4a** and **4d**, complete conversion of tris-oximes **4e** and **4h** bearing ethyl and methylpropionate groups could not be achieved under same conditions. Tris-oximes

4b,**c**,**f**,**g** possessing three *tert*-butyl, phenyl, benzyl or ethyl carboxyethyl groups at C=N bonds did not enter the cyclization reaction at all. In a similar manner, no reaction was observed for tris-oxime **9a**, bearing an elongated oximinoalkyl arm. More detailed investigations demonstrated that oxime cyclotrimerization in **4** is reversible. In particular, heating of adamantane **6a** at 100°C led to its complete conversion to initial tris-oxime **4a**.[49]



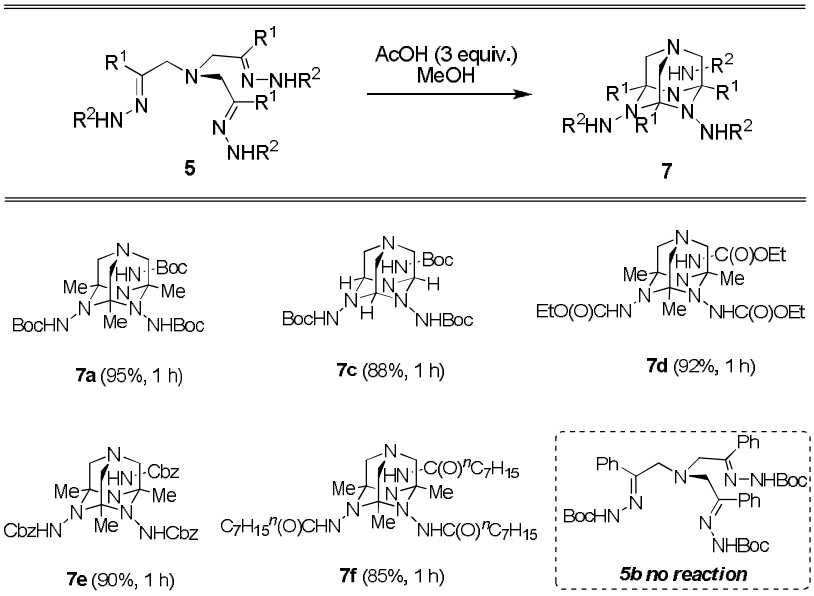
Scheme 10. Substrate scope of tris-oximes **4** cyclization to 1,4,6,10-tetrazaadamantanes **6**.

Tris-hydrazones **5** also underwent a Brønsted acid-promoted intramolecular [2+2+2]-annulation process resulting in *N*-amino-substituted 1,4,6,10-tetraazaadamantanes **7**.[52] Similarly to tris-oximes **4**, aldohydrazones entered the cyclization more smoothly than ketohydrazones. Also, the presence of three phenyl substituents completely blocked the formation of adamantane cage. In general, tris-hydrazones **5** were found to be more active towards intramolecular cyclization to tetraazaadamantanes as compared to parent tris-oximes **4**. For example, full conversion of tris-hydrazone **5a** to **7a** was achieved within 1 h, while 24 h were needed for the related tris-oxime **4a** to cyclize to **6a** (cf. data in Schemes 10 and 11). No significant effect of acyl (carbomoyl) group in hydrazones **5** on the intramolecular cyclotrimerization reaction was observed.

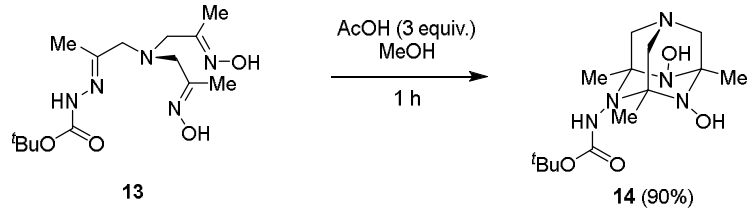
Upon the action of acetic acid on a mixed oxime-hydrazone **13**, an unsymmetrically substituted 1,4,6,10-tetraazaadamantane **14** was obtained in high yield (Scheme 12). It should be noted, that cyclization of **13** to **14** proceeded slowly even without acetic acid in DMSO solution.

Thus, the study of intramolecular oxime and hydrazone cyclotrimerization reaction revealed its reversible character and high dependence of the equilibrium position on the nature of substituents at C=N

bonds. Small groups favor the formation of adamantane form, while the open-chain tris-imine form is predominant for substrates bearing bulky substituents.



Scheme 11. Cyclization of tris-hydrazones **5** to 1,4,6,10-tetraazaadamantanes **7**.



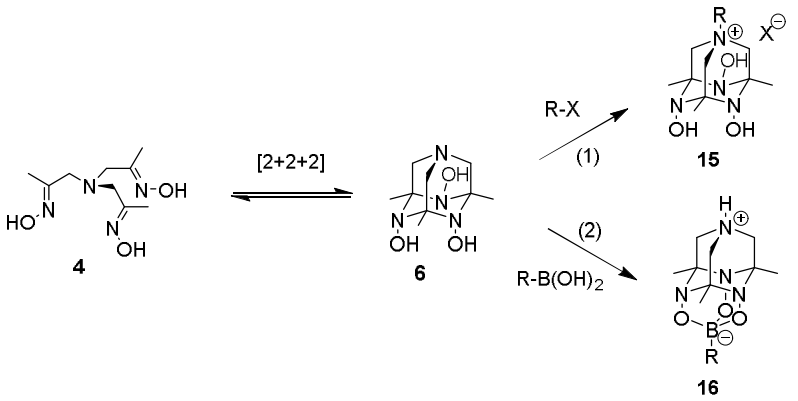
Scheme 12. Cyclization of mixed tris-imine **13** to 1,4,6,10-tetrazaadamantane **14**.

5. Stabilization of 1,4,6,10-tetraazaadamantane cage

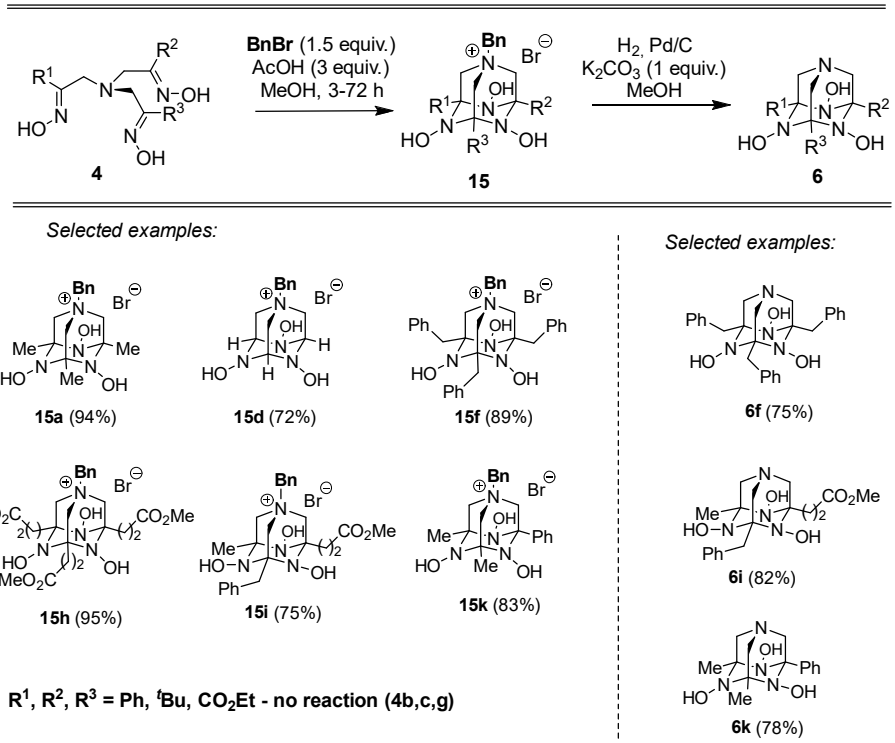
In order to shift the equilibrium between **4** and **6** to the desired adamantane form it is necessary to somehow stabilize its structure. We have suggested two plausible ways to increase the thermodynamic stability of 1,4,6,10-tetraazaadamantane cage (Scheme 13). The first way is the quaternization of bridge-head nitrogen forming 1,4,6,10-tetraazaadamantane salts **15** (Scheme 13, route (1)). According to quantum-chemical calculations, the cyclization of quaternary salts of tris-oximes to the corresponding adamantane derivatives **15** is much more thermodynamically preferable as compared to the cyclization of non-quaternized tris-oximes **4**.[56] The second approach is based on trapping *N*,*N*,*N*-trihydroxy-adamantanes **6** with boronic acids to form stable boron at-complexes **16** (Scheme 13, route (2)).

To explore the first route, the interaction of tris-oximes **4** with benzyl bromide as a quaternization reagent was studied. As can be seen from Scheme 14, upon treatment with benzyl bromide most of tris-oximes **4** were converted into corresponding *N*-benzyl salts of 1,4,6,10-tetraazaadamantanes **15** in high yields.[49,55,56] The presence of acetic acid facilitates the process. Even a sterically hindered tris-oxime **4f** bearing three benzyl groups (R^1, R^2, R^3 = Bn) cyclized into the corresponding adamantane salt **15f** in high yield. It should be noted, that without benzyl bromide, no conversion of **4f** to the isomeric adamantane **6f**

was observed (cf. with data in Scheme 10). This result demonstrates that for tris-oxime **4f** the equilibration concentration of cyclic form **6f** is very low (not detectable by NMR), yet the quaternization of nitrogen atom completely shifts the equilibrium to the adamantane salt **15f**.



Scheme 13. Approaches to stabilization of 1,4,6,10-tetraazaadamantane cage.



Scheme 14. Synthesis of quaternary salts **15** and their transformation to adamantanes **6**.

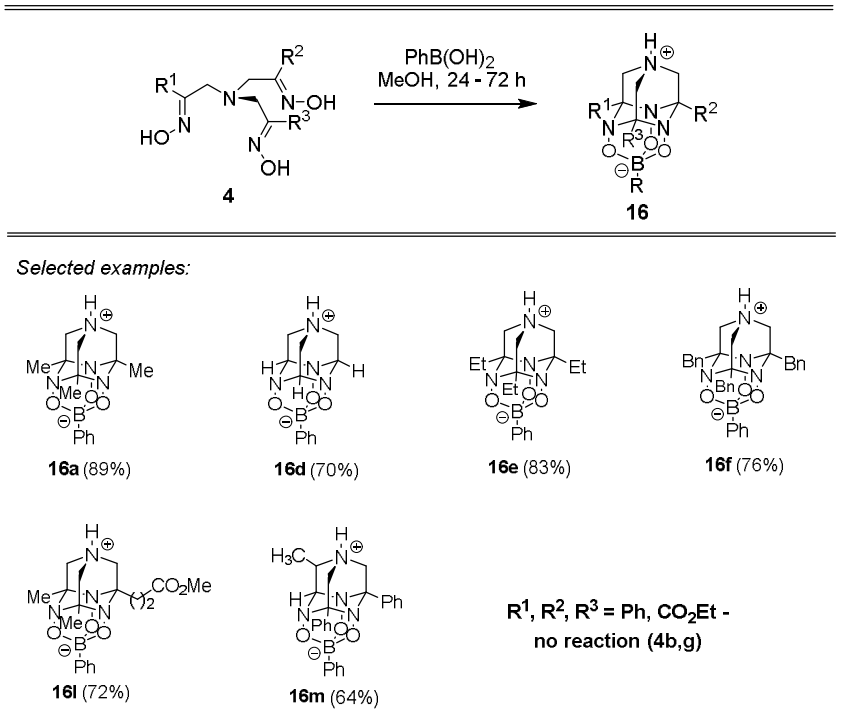
Even under these conditions, tris-oximes **4b**,**c**,**g** with three *tert*-butyl, phenyl or ethyl carboxyl groups at C=N bonds did not produce the corresponding 1,4,6,10-tetraazaadamantanes **15** demonstrating that, the

presence of these substituents completely hampers the cyclotrimerization. Yet, for unsymmetrical tris-oximes **4** containing combinations of these substituents and methyl groups intramolecular [2+2+2] process is possible (for example, see product **15k** in Scheme 14).[55]

Benzyl group at the quaternary nitrogen atom in 1,4,6,10-tetraazaadamantane salts **15** can be easily removed by catalytic hydrogenolysis in the presence of K_2CO_3 (Scheme 14).[55] Interestingly, free bases **6** formed by this route are relatively kinetically stable and transform into the open-chain tris-oximes **4** slowly. For example, the full conversion of unstable adamantane **6f** to tris-oxime **4f** was achieved within c.a. 2 days at ambient temperature in DMSO-d_6 solution. It should be specially noted, that adamantanes **6f** and **6k** cannot be prepared by direct cyclization of corresponding tris-oximes **4f** and **4k** (cf. with data in Scheme 10).

To check to applicability of the second approach towards stabilization of 1,4,6,10-tetraazaadamantane cage, the boronate-triol condensation was explored (Scheme 15). Reaction of boronic acids (e.g. $PhB(OH)_2$) with tris-oximes **4** gave in high yields unusual diamantanes **16** containing 1,4,6,10-tetraazaadamantane annulated with 3-boro-2,4,10-trioxa-1,5,7-triazaadamantane.[57] The presence of promoter (AcOH) was not needed in this case. As in reactions discussed above, no conversion was observed for tris-oximes **4b** and **4g**, thus demonstrating that the initial step is oxime group cyclotrimerization, which is sensitive to substitution. However, diamantane **16m** with two bulky phenyl groups was successfully prepared.

In contrast to free bases **6**, for none of products **15** or **16** the formation of an open-chain tris-oxime form was observed even upon heating. This demonstrates that quaternization as well as annulation with a second adamantane cage greatly stabilize the 1,4,6,10-tetrazaadamantane structure.



Scheme 15. Synthesis of diamantanes **16** by condensation of tris-oximes **4** with $PhB(OH)_2$.

6. Synthesis of unsubstituted 1,4,6,10-tetraazaadamantane ("isourotropine") and its derivatives

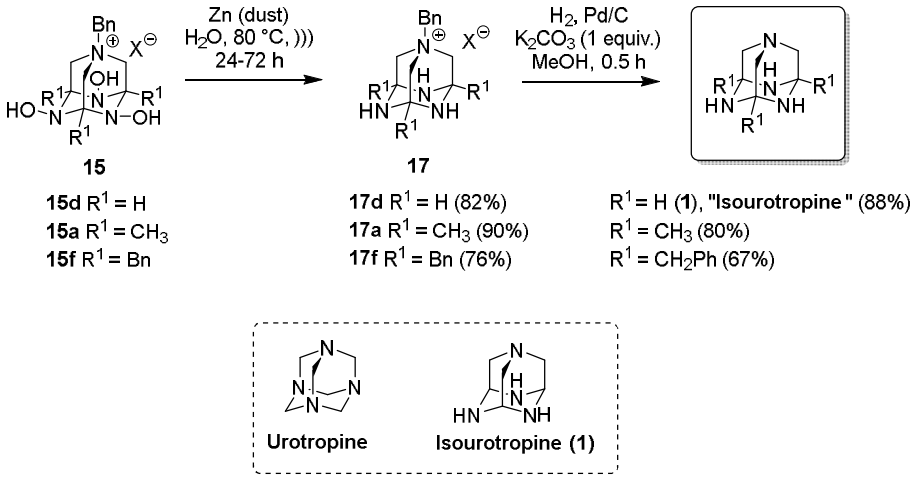
Having identified the structural factors governing the stability of 1,4,6,10-tetraazaadamantanes, our next efforts were focused on the synthesis of adamantanes unsubstituted at bridge nitrogen atoms, in

particular the parent compound "isourotropine".[21] We therefore, studied the reduction of N–OH fragments in stable quaternary salts **15** as a most reasonable way to accomplish this task.

Since aminal fragments in isourotropine derivatives are sensitive to reducing agents, most of strong reducing agents tested led to complex mixtures of overreduced products. After numerous attempts, we were lucky to find that zinc dust under prolonged ultrasound activation and heating selectively reduced three N–O bonds in 1,4,6,10-tetraazaadamantane salt **15a** leaving aminal fragments intact (Scheme 16).[21] This procedure allowed to prepare a series of 1,4,6,10-tetraazadamantane quaternary salts **17** unsubstituted at bridge nitrogen atoms. The latter proved to be highly stable compounds, which decomposed only upon melting (120-220 °C). Subsequent catalytic debenzylation of salts **17** gave free 1,4,6,10-teraazaadamantane bases, including the desired "isourotropine" **1**.[21]

The unsubstituted 1,4,6,10-tetraazaadamantane **1** proved to be a rather labile compound, which underwent resinification upon storage at ambient temperature. Apparently, such instability is associated with opening of adamantane cage *via* a retro-[2+2+2] process and oligomerization of reactive imine groups as well as hydride transfer from aminal to imine groups. The lability and tendency towards polymerization is characteristic for other cage compounds containing NH-aminal fragments such as triazawurtzitane,[23] 2,4,9-triazadamantane[24] and hexaazaisowurtzitane,[58] which despite of many efforts were not obtained in a free state.

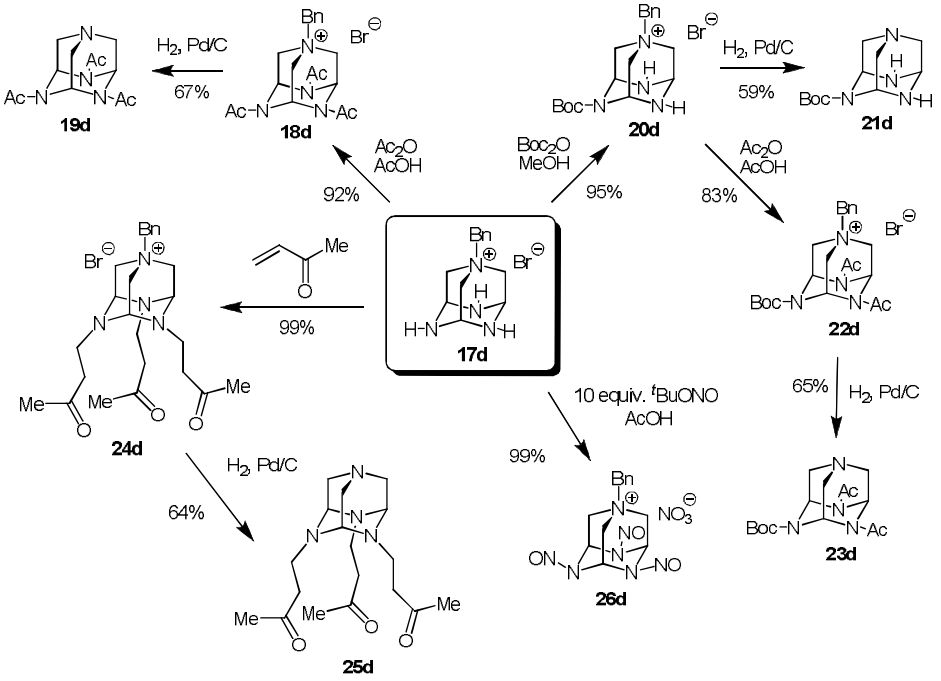
Interestingly, the C-substituted derivatives of "isourotropine" (R^1 = Me, CH_2Ph in Scheme 16) were found to be more stable than the parent compound. On the contrary, for urotropine, the presence of substituents at carbon atoms destabilize the adamantane structure (C-substituted derivatives of 1,3,5,7-tetraazaadamantane are virtually unknown[59]).



Scheme 16. Synthesis of "isourotropine" **1** and its C-substituted derivatives by reduction of quaternary salts **15**.

Considering the lability of 1,4,6,10-tetraazadamantane free base **1**, its *N*-benzyl salt **17d** is the most reasonable building block for a further functionalization at bridge nitrogen atoms.[21] As can be seen in Scheme 17, exhaustive acylation of **17d** to give **18d** can be easily achieved by treatment with acetic anhydride. Reaction with di(*tert*-butyl)dicarbonate selectively produced the mono-Boc product **20d**, apparently due to a steric hindrance of Boc-group. This can be further used in desymmetrization of bridge nitrogen atoms in 1,4,6,10-tetraazaadamantanes (for example, synthesis of product **22d**). Secondary amino groups in "isourotropine" salt **17d** were successfully involved in Michael addition with methyl vinyl ketone (product **24d**), yet other acceptors (methyl acrylate and acrylonitrile) were much less reactive. Reductive debenzylation of products **18d**, **20d**, **22d** and **24d** provided free 1,4,6,10-tetrazadamantane bases **19d**, **21d**, **23d** and **25d**, respectively. The latter are much more stable than the N–H unsubstituted "isourotropine" **1**.

Nitrosation of salt **17d** with an excess of *tert*-butylnitrite gave tris-nitroso compound **26d**.[21] Overall, despite of a somewhat reduced nucleophilicity of secondary amino-groups in *N*-benzyl salt **17d**, reactions with strong electrophiles can be used for a "chemical decoration" of 1,4,6,10-tetraazaadamantane cage.



Scheme 17. *N*-Functionalization of "isourotropine".

7. Comparison of urotropine and "isourotropine" structures

From the fundamental point of view, the comparison of urotropine (1,3,5,7-tetraazaadamantane) and "isourotropine" (1,4,6,10-tetraazaadamantane) structures is remarkable (Figure 2).[21] According to X-Ray diffraction analysis, a characteristic feature of 1,4,6,10-tetraazaadamantane cation in **17d** is flattening of the triazine cycle as compared to isomeric urotropinium cation. This is illustrated by greater N–C–N angles in triazine ring, which differ from tetrahedral as well as smaller deviation of bridge atoms from the mean plane created by three bridgehead atoms in triazine cycle (Figure 2). Another distinguishing feature of 1,4,6,10-tetraazaadamantane cation is a considerable shortening of C–N(4)$^+$ bonds as compared to 1,3,5,7-tetraazaadamantane.

The observed structural distinctions in 1,4,6,10- и 1,3,5,7-tetraazaadamantanes are likely to be due to different stereoelectronic interactions involving nitrogen atoms in these heterocage systems.[21] As demonstrated by NBO analysis, in 1,3,5,7-tetraazaadamantane cation two stereoelectronic interactions involving nitrogen lone pairs are realized, namely the electron donation to the σ* orbitals of C(1),(2),(3)–N(1),(2),(3) bonds, and donation to the σ* orbitals of C(4),(5),(6)–N(4)$^+$ bonds. In the 1,4,6,10-tetraazaadamantane cation, nitrogen lone electron pairs are involved in one anomeric interaction that is the donation to C(1),(2),(3)–N(1),(2),(3) bonds (lp(N_{eq})→σ*$_{C–N}$). It, thus, can be concluded that in "isourotropinium" cation lone electron pairs of nitrogen atoms more efficiently interact with σ* orbitals of C–N bonds in triazine ring than in urotropinium cation. This, in turn, should reduce the pyramidality of nitrogen atoms N(1),(2),(3) leading to the observed flattening of triazine ring. Furthermore, the abovementioned hyperconjugation effects should account for a reduced nucleophilicity of bridge nitrogen atoms in 1,4,6,10-tetraazaadamantane *N*-benzyl salt **17d**.

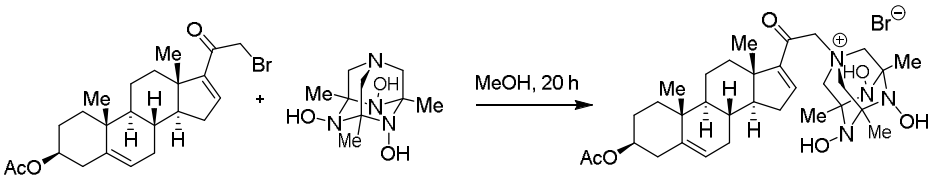
	1,4,6,10-teraazaadamantanium cation[21]	1,3,5,7-teraazaadamantanium cation[60]
Deviation*	0.607 Å	0.669 Å
∠N(1)-C(1)-N(2)	114°	111°
C-N(4)$^+$	1.51 Å	1.55 Å
lp(N_{eq})→ σ^*_{C-N}	10.7 kcal/mol	8.3 kcal/mol
lp(N_{eq})→ $\sigma^*_{C-N^+}$	-	14.4 kcal/mol

* Deviation of bridge atoms from the mean plane created by three bridgehead atoms in triazine cycle

Figure 2. Comparison of 1,4,6,10- and 1,3,5,7-tetraazaadamantanes structures.

8. Application of 1,4,6,10-tetraazaadamantanes for the design of water-soluble functional molecules

Quaternary salts of 1,4,6,10-tetraazaadamantanes are well-soluble in water (e.g., the solubility of salt **15a** is c.a. 200 mg/mL). Furthermore, preliminary biological studies both *in vitro* and *in vivo* demonstrated low toxicity of 1,4,6,10-tetraazaadamantane derivatives.[56] We therefore reasoned that the introduction of 1,4,6,10-tetraazaadamantane residue into lypophilic biomolecules can result in increasing of their water solubility and bioavailability. Conjugation of 1,4,6,10-tetraazaadamantane with a biomolecule can be achieved by a simple electrophilic addition to the bridgehead nitrogen atom of *N,N',N''*-trihydroxy-derivatives **6**. This was demonstrated by the synthesis of the modified steroid **27** by alkylation of adamantane **6a** with (3β)-21-bromo-20-oxopregna-5,16-dien-3-yl acetate (Scheme 18).[56] The resulting adduct is soluble in water at a concentration around 0.5 mg/mL.



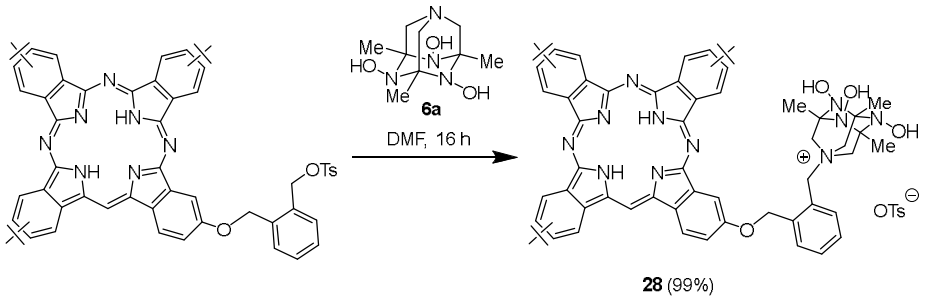
6a **27** (78%)

Scheme 18. Synthesis of water-soluble 1,4,6,10-tetraazaadamantane-modified steroid **27**.

In a similar way, introduction of 1,4,6,10-tetraazaadamantane unit into a phthalocyanine gave adduct **28**, which in contrast to normal phthalocyanines was soluble in polar solvents (alcohols and slightly in water).[61] The 1,4,6,10-tetraazaadamantane-modified phthalocyanine **28** exhibited marked activity against HIV-1_{BRU} virus (Scheme 19).[61]

9. Conclusions

Studies conducted by our group have led to the development of a straightforward approach to hitherto unknown 1,4,6,10-tetraazaadamantane system, which is isomeric to a well-known urotropine (1,3,5,7-tetraazaadaamantane).



Scheme 19. Synthesis of 1,4,6,10-tetraazaadamantane-modified phthalocyanine **28**.

1,4,6,10-Tetraazaadamantanes demonstrate marked distinctions from 1,3,5,7-terazaadaamantanes both in structure and chemical stability. In particular, the chemical space of 1,4,6,10-tetraazadamantanes is likely to be much broader than that of urotropine derivatives. Though unsubstituted 1,4,6,10-tetraazadamantane was found to be labile, its various C- and N-substituted derivatives were successfully prepared.

Because of the rigid structure, the ease of preparation and chemical modification, 1,4,6,10-tetraazaadamantane can be considered as a useful three-dimensional multivalent molecular platform for the design of various functional molecules, such as star-shape block copolymers, dendrimers, artificial enzymes, multivalent drugs etc. Furthermore, considering a privileged role of adamantane scaffold in pharmaceuticals, studies of biological activity of 1,4,6,10-tetraazadamantanes are of high expediency. Future research will definitely unlock growing points in chemistry and possible applications of "isourotropine" derivatives.

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