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Urotropine Isomer (1,4,6,10-Tetraazaadamantane): Synthesis, Structure, and Chemistry

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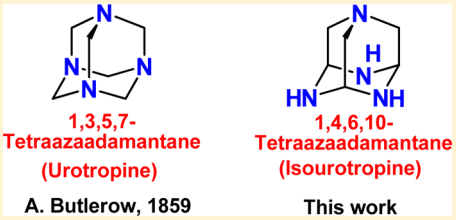
Supporting Information

ABSTRACT: The first synthesis of 1,4,6,10-tetraazaadamantane, the C_{3v}-symmetrical structural isomer of urotropine (1,3,5,7-tetraazaadamantane), and a series of its derivatives is reported. X-ray and quantum-chemical studies revealed remarkable distinctions in structures of urotropine and "isourotropine" cations, probably arising from different types of hyperconjugation between lone electron pairs of nitrogen atoms and σ^*_{C-N} orbitals in these heterocage systems. Since substitution at bridge and bridgehead nitrogen atoms can be easily introduced, 1,4,6,10-tetraazaadamantane may be considered as a new rigid multivalent (3 + 1) scaffold for the design of functional molecules and materials.



INTRODUCTION

For more than 100 years, heteroadamantanes have been objects of vast attention from fundamental and applied chemistry. These cage polycyclic systems represent interest not only due to their unique properties,[1] but also as convenient models for the study of basic problems dealing with structure and reactivity of organic compounds.[2]

Among many heteroadamantanes, 1,3,5,7-tetraazaadamantane (urotropine), which was first obtained by A. Butlerow in 1859, plays, probably, the most important role from an applied point of view.[3] Urotropine is used as a drug to treat bacterial infections,[4a,b] equivalent of formaldehyde in polymer production,[4a,c] intermediate in synthesis of high energy materials,[4d] food additive,[4e] as well as a valuable reagent in organic synthesis[4f] and ligand in coordination chemistry.[4g] Until recently urotropine was the only known representative of the class of tetraazaadamantanes (Figure 1).[5]

In this context the possibility of existence of other tetraazaadamantanes isomeric to urotropine represents considerable fundamental interest (Figure 1). According to quantum-chemical calculations at G3(MP2) level of theory urotropine ($\Delta H^\circ_{f,298}$(exp) = 47.5 kcal/mol, $\Delta H^\circ_{f,298}$(G3(MP2)) = 49.3 kcal/mol[6]) is the least thermodynamically stable of the four possible isomeric tetraazaadamantanes possessing no nitrogen−nitrogen bonds (Figure 1).[7] These results predict the stability of tetraazaadamantanes isomeric to urotropine or, for instance, some of their derivatives.

From the diversity-oriented molecular design standpoint the C_{3v}-symmetrical urotropine isomer, 1,4,6,10-tetraazaadamantane **1a** (Figure 1), is of special concern. Because of the presence of three bridge and one bridgehead nitrogen atoms, which can be modified employing reactions with electrophilic agents, molecule **1a** can be considered as a universal multivalent (3 + 1) scaffold for the construction of various functional

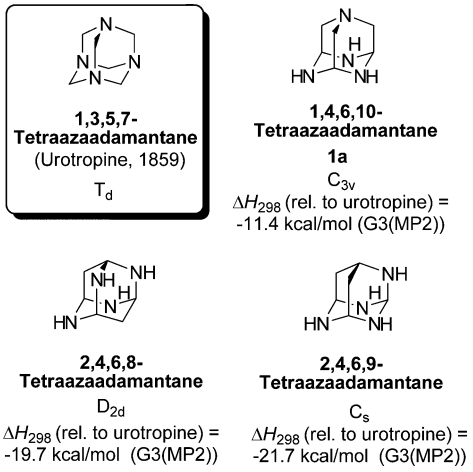


Figure 1. Urotropine and isomeric tetraazaadamantanes possessing no N−N bonds.

molecules and materials (bioconjugates, systems for molecular recognition and drug delivery, dendrimers, high energy materials).[8] 1,4,6,10-Tetraazaadamantane cage may serve as a rigid three-dimensional matrix providing tripodal arrangement of functional fragments E_1 with an orthogonal group E_2 (Figure 2). Substitution at bridgehead carbon atoms provides additional opportunities for the introduction of functional fragments (substituents R, Figure 2). In contrast to **1a**, urotropine cannot be used as a multivalent scaffold, since its derivatives possessing substituents at more then two nitrogen atoms are unstable.[9a,b]

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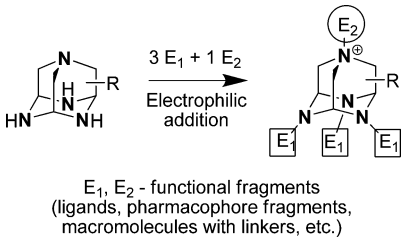


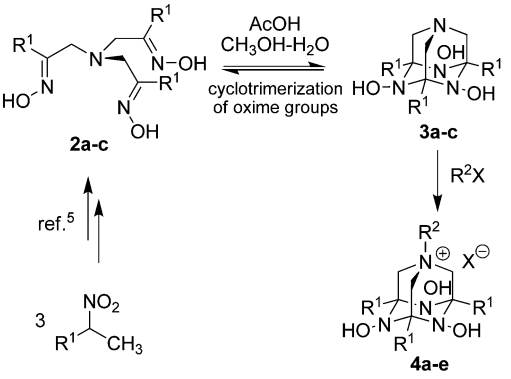
Figure 2. 1,4,6,10-Tetraazaadamantane as multivalent (3 + 1) scaffold.

In the present work, the synthesis of 1,4,6,10-tetraazaadamantane **1a** and a series of its C- and N-substituted derivatives was realized as well as their structure and reactivity were studied.

RESULTS AND DISCUSSION

Synthesis of 1,4,6,10-Tetraazaadamantanes. In our preliminarily communication[5] we reported the synthesis of *N*-hydroxy-substituted 1,4,6,10-tetraazaadamantanes **3** and their salts **4** employing an unprecedented intramolecular cyclotrimerization of oxime groups in tris(*β*-oximinoalkyl)amines **2** (Scheme 1). Using this simple approach a series of adamantanes **3a**–**c** and **4a**–**e** were prepared.

Scheme 1. Cyclotrimerization of Tris-Oximes 2 to 1,4,6,10-Tetraazaadamantane Derivatives 3 and 4



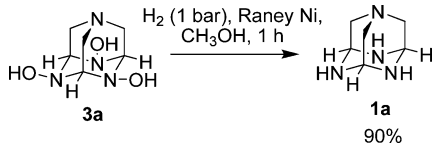
R1, R2, X = H, Bn, Br (**4a**, 72%); CH_3, Bn, Br (**4b**, 94%); Bn, Bn, Br (**4c**, 89%); H, CH_3, I (**4d**, 93%); CH_3, CH_3, I (**4e**, 97%)

For the synthesis of 1,4,6,10-tetraazaadamantanes **1** unsubstituted at nitrogen atoms selective reduction of *N*-hydroxy fragments in products **3** or their salts **4** is required without aminal groups being affected. Hydrogenolysis of N–O bond in the presence of labile aminal fragment is quite challenging and has very few precedents in literature.[10]

First, we investigated the interaction of trihydroxytetraazaadamantane **3a** (Scheme 1, R^1 = H) with a series of classical agents employed previously for the reduction of *N*,*N*-dialkylhydroxylamine fragment ($LiAlH_4$, Zn dust, Al/Hg and catalytic hydrogenation).[11] Typically, either no conversion of starting material was observed or indecipherable product mixtures were obtained. Fortunately, upon catalytic hydrogenation in the presence of Raney nickel at room temperature initial adamantane **3a** was rapidly converted (25–30 min) into target product **1a** in high yield (Scheme 2).

However, this procedure could not be extended to substituted trihydroxyadamantanes **3b** and **3c** (Scheme 1, R^1 = CH_3, Bn). Probably, difficulties in the reduction of these

Scheme 2. Synthesis of 1,4,6,10-Tetraazaadamantane 1a

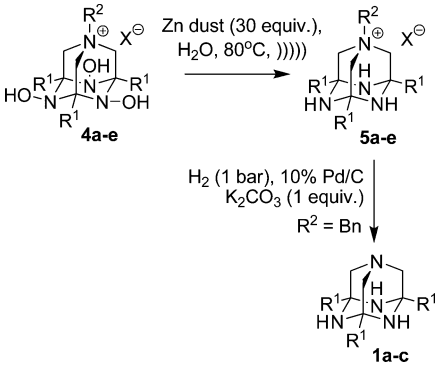


adamantanes are associated with larger steric hindrance of substituted hydroxylamine fragments. It is noteworthy, that increasing of temperature in reduction of **3b** and **3c** results in tetraazaadaamantane cage opening to give corresponding tris-oximes **2b** and **2c**.[5]

Product **1a** is the first member of 1,4,6,10-tetraazaadamantane family and the only up-to-date obtained structural isomer of urotropine. Unlike urotropine, "isourotropine" **1a** proved to be quite a labile compound, which easily underwent oligomerization at room temperature. It is likely that the instability of **1a** is associated with adamantane opening and subsequent polymerization of highly reactive imine groups. The lability and tendency toward polymerization are typical for some other heterocage compounds possessing N–H aminal fragments.[1c,12]

Previously we demonstrated that quaternization of bridgehead nitrogen in 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanes **3** to give *N*-benzyl salts **4** (R^2 = Bn, Scheme 1) results in remarkable stabilization of adamantane cage with respect to acyclic tris-oxime form.[5] We speculated that such a stabilization may also take place in case of 1,4,6,10-tetraazaadamantanes **1** unsubstituted at nitrogen atoms. To validate this hypothesis we studied the reduction of trihydroxytetraazaadamantane *N*-benzyl salt **4a** (Scheme 3, Table 1). Several different

Scheme 3. Synthesis of 1,4,6,10-Tetraazaadamantanes 1a–c



mechanism-based types of reducing agents were examined (H_2/Raney Ni or Pd/C,[11a,b] $Mo(CO)_6/H_2O$,[11c] Al/Hg,[11a] Na/Hg,[11a] Zn/NH_4Cl[11d]). In most of cases, except for the reduction with zinc, either starting material, or complex

Table 1. Reduction of Tetraazaadamantanes 4a–e

					4 → 5		5 → 1
entry	4	R^1	R^2	X	time, h	yield, %	yield, %
1	**4a**	H	Bn	Br	15	82	88
2	**4b**	CH_3	Bn	Br	6	90	80
3	**4c**	Bn	Bn	Br	15	76	67
4	**4d**	H	CH_3	I	8	90	–
5	**4e**	CH_3	CH_3	I	10	92	–

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mixtures of products were obtained. Zinc dust in water or methanol upon ultrasonic activation was found to be the reagent of choice for the reduction of *N*-benzyl adamantane **4a** to give products **5a**.[13] It is likely that the role of untrasound activation consists in depassivation of zinc particles by removing from their surface zinc hydroxide layer forming upon the reduction process (Scheme 3).[14]

With these reduction conditions in hand a series of *N*-methyl and *N*-benzyl quaternary salts of 1,4,6,10-tetraazaadamantanes **5a**–**e** unsubstituted at bridge nitrogen atoms were synthesized (Scheme 3, Table 1). All these tetraazaadamantanes are thermally stable and undergo decomposition only upon melting at temperatures around 130–220 °C.

Mild hydrogenolysis of benzylic C–N bond[15] in **5a-c** furnished free N–H adamantanes **1a**–**c** (Scheme 3). Tetraazaadamantanes **1b** and **1c** proved to be more stable than the unsubstituted "isourotropine" **1a**. On the contrary, the presence of substituents at carbon atoms of urotropine cage destabilizes its structure.[9c]

Structure of 1,4,6,10-Tetraazaadaamantanes. The identity and purity of tetraazaaadamantanes **1a**–**c** and **5a**–**e** were confirmed by ^{1}H and ^{13}C NMR, elemental analysis and high-resolution mass-spectrometry data. The structure of adamantane **5a** was established by X-ray crystallography (CCDC 966626, crystal solvate with methanol).

The cation of **5a** is a nearly C_{3v} symmetrical tetraazaadamantane (Figure 3). Carbon–nitrogen bonds in 1,3,5-triazine

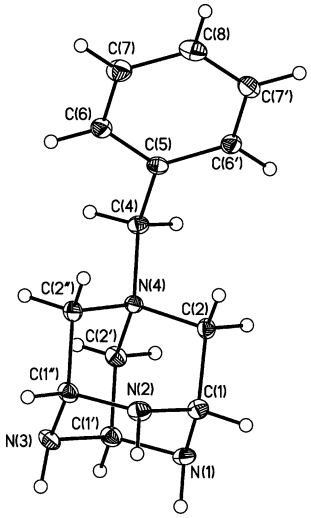

Figure 3. General view of the cation in a crystal **5a**·CH_3OH in representation of atoms via thermal ellipsoids (p = 50%).

ring fall in a narrow range of 1.469(2)–1.472(2) Å and thus are virtually equalized. In the same way, C–N bonds incorporating N(4) atom, as well as C–C bonds in **5a**, have very similar lengths (1.508(2)–1.517(2) Å and 1.517(3)–1.523(3) Å, respectively).

N–H fragments in triazine ring of 1,4,6,10-tetraazaadamantane cation **5a** are located in axial positions. This is in agreement with G3(MP2) calculations on four 1,4,6,10-tetraazaadamantane invertomers, which predict the all N–H axial isomer to be the most thermodynamically favored. The all N–H equatorial isomer is the least stable (ΔH = +11 kcal/mol as compared to all N–H axial isomer), probably due to the presence of three destabilizing 1,3-diaxial lone pair-lone pair interactions (cf. data in Table S1 in Supporting Information). In crystal of **5a**·CH_3OH N–H fragments form from weak to very weak hydrogen bonds with bromine anions; the corresponding distances N···Br vary from 3.4422(19) to 3.767(1) Å.

Comparison of the structures of *N*-benzyl 1,4,6,10-tetraazaadamantanium cation (**5a**) and isomeric *N*-benzyl 1,3,5,7-tetraazaadamantanium cation **5a**′ (for X-ray see ref 16) warrants special discussion (Figure 4). An intriguing feature

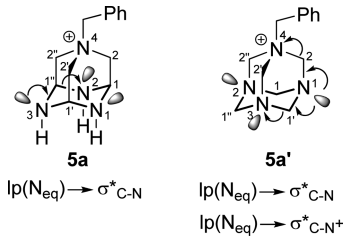

Figure 4. Anomeric effects in cations **5a** and **5a**′.

of cation **5a** is flattening of the triazine cycle as compared to urotropinium cation **5a**′. This is illustrated by smaller deviations of bridge atoms (N(1), N(2) and N(3)) from the mean plane of three bridgehead atoms (C(1)C(1′)C(1″)) in cation **5a**. Furthermore, bond angles N–C–N in triazine cycle of **5a** are larger than in cation **5a**′ and considerably deviate from tetrahedral angles (cf. data in Table 2). Another interesting feature of 1,4,6,10-tetraazaadamantane cage of **5a** is the shortening of C–N bonds between quaternary nitrogen atom N(4) and carbon atoms C(2), C(2′) and C(2″) as compared to 1,3,5,7-tetraazaadamantane **5a**′. On the other hand, C–N bonds in triazine cycle (C(1)N(1)C(1′)N(3)C(1″)N(2)) of **5a** and **5a**′ have virtually the same length (cf. data in Table 2).

We reasoned that the observed distinctions in 1,4,6,10- and 1,3,5,7-tetraazaadamantanes structures result from different stereoelectronic interactions involving nitrogen atoms N(1), N(2), N(3) and N(4) in these two molecules (Table 2, Figure 4). Thus, in 1,3,5,7-tetraazaadamantane cage of **5a**′ lone electron pairs of nitrogen atoms may interact with antibonding orbitals of six C–N bonds in triazine cycle (lp(N_{eq}) → σ^*_{C-N} donation) as well as with antibonding orbitals of three C–N(4)$^+$ bonds (lp(N_{eq}) → $\sigma^*_{C-N^+}$ donation, Figure 4). In 1,4,6,10-tetraazaadamantane cation (**5a**) only one type of such anomeric interactions (lp(N_{eq}) → σ^*_{C-N} donation) involving nitrogen atoms is possible (Figure 4). To estimate the energies of these interactions natural bold orbital analysis (NBO) was performed for cations **5a** and **5a**′. As can be seen from data in Table 2 theoretical models of 1,4,6,10- and 1,3,5,7-tetraazaadamantanium cations developed by quantum-chemical calculations at G3MP2 level of theory are in good agreement with X-ray data. According to NBO analysis the energy of lp(N_{eq}) → σ^*_{C-N} hyperconjugation in 1,4,6,10-tetraazaadamantanium cation is 2.5 kcal/mol greater than in 1,3,5,7-tetraazaadamantanium cation. The occupancies of C–N antibonding orbitals in **5a** and **5a**′ are 0.045 and 0.039 electrons, respectively. Accordingly, nitrogens lone electron pairs interact more efficiently with C–N antibonding orbitals in 1,4,6,10-tetraazaadamantanium cation than in urotropinium cation. Apparently, this is due to an additional hyperconjugation of nitrogens lone pairs with antibonding C–N(4)$^+$ orbitals (lp(N_{eq}) → $\sigma^*_{C-N^+}$) in urotropinium salt **5a**′, which results in experimentally observed elongation of C(2)–N(4)$^+$, C(2′)–N(4)$^+$ and C(2″)–N(4)$^+$ bonds (Table 2). Decrease of the

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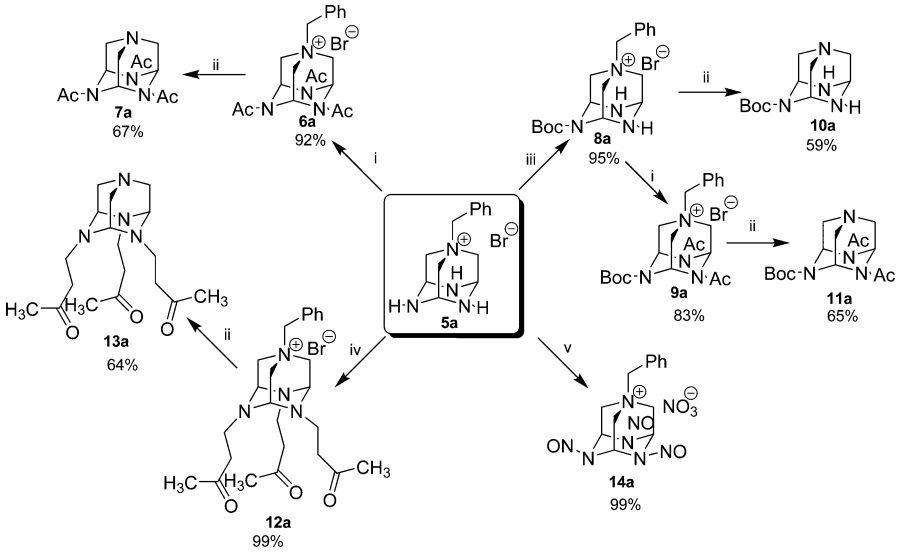
Table 2. Experimental (X-ray) and Calculated Characteristic Structural and Energetic Parameters of *N*-Benzyl 1,4,6,10-Tetraazaadamantanium (5a) and *N*-Benzyl 1,3,5,7-Tetraazaadamantanium Cations (5a′)

	4-benzyl 1,4,6,10-tetraazaadamantanium cation (**5a**)		1-benzyl 1,3,5,7-tetraazaadamantanium cation (**5a′**)	
parameter	experiment	theory[a]	experiment[16]	theory[a]
C−N$^+$, Å C(2)−N(4), C(2′)−N(4) C(2″)−N(4)	1.508(2)−1.517(2)	1.508−1.510	1.523(5)−1.550(4)	1.527
C−N, Å C(1)−N(1), C(1′)−N(1) C(1)−N(2), C(1″)−N(2), C(1′)−N(3), C(1″)−N(3)	1.469(2)−1.472(2)	1.463−1.464	1.467(5)−1.484(5)	1.460−1.461
∠N−C−N, deg ∠N(1)−C(1)−N(2) ∠N(1)−C(1′)−N(3), ∠N(2)−C(1″)−N(3)	114.36(15)−115.06(15)	115.91−116.05	110.6(3)−111.7(3)	110.09−110.12
deviation[b], Å	0.43(1)−0.44(1)	0.41−0.42	0.47−0.49	0.48
lp(N_{eq}) → σ^*_{C-N}, kcal/mol	–	10.7−10.8	–	8.3−8.4
lp(N_{eq}) → $\sigma^*_{C-N}{}^+$, kcal/mol	–	–	–	14.4−14.5

[a]Ab initio G3(MP2) method was used for geometry optimization, B3LYP/6-311+G** basis set for NBO analysis. [b]Deviation of bridge atoms (nitrogen in case of **5a** and carbon in case of **5a′**) from the mean plane created by three bridgehead atoms (C(1)C(2)C(3) in **5a** and N(1)N(2)N(3) in **5a′**) in triazine cycle.

Scheme 4. Modifications of 1,4,6,10-Tetraazaadaamantane *N*-Benzyl salt 5a



pyramidality of bridge nitrogen atoms N(1), N(2) and N(3) should account for the observed flattening of the triazine cycle and increasing of N−C−N bond angles in cation **5a** as compared to **5a′**.[17] Thus, key differences in structures of 1,4,6,10- and 1,3,5,7-tetraazaadamantanes are governed by stereoelectronic reasons.

Modifications of 1,4,6,10-Tetraazaadaamantanes. The presence of three secondary amino groups in combination with thermal stability and the relative ease of reductive debenzylation make quaternary *N*-benzyl salts **5** perspective precursors of various 1,4,6,10-tetraazaadamantanes functionalized at bridge nitrogen atoms. To demonstrate these possibilities, reactions of salt **5a** with different electrophilic (acetylating, alkylating and nitrosylating) agents were studied (Scheme 4).

Thus, treatment of adamantane **5a** with an excess of acetic anhydride in acetic acid led to the acylation of all three secondary amino groups forming triacetyl derivative **6a** in high yield (Scheme 4). Subsequent reductive debenzylation of product **6a** furnished the desired *N,N,N*-triacetyl-1,4,6,10-tetraazaadamantane **7a** in good yield.

Unexpectedly, reaction of benzyl salt **5a** with di(*tert*-butyl)dicarbonate (Boc_2O) resulted in the selective introduction of one Boc-group providing adamantane **8a** in 95% yield. The absence of products of double and triple addition is probably caused by steric hindrance created by the first Boc-group attached to adamantane skeleton.

This result allows to differentiate bridge nitrogen atoms in **5a** and thus to synthesize unsymmetrically substituted 1,4,6,10-tetraazaadamantanes. In particular, double acetylation of **8a** with acetic anhydride gave the unsymmetrically substituted adamantane **9a** (Scheme 4). Catalytic reductive debenzylation of **8a** and **9a** with hydrogen over Pd/C furnished free tertiary bases **10a** and **11a**, respectively.

Alkylation of adamantane **5a** was studied employing reactive alkyl halides (methyl iodide and benzyl bromide in the presence of potassium carbonate as a base) and Michael acceptors such as methyl acrylate, acrylonitrile and methyl vinyl ketone. However, no conversion of initial adamantane **5a** was observed in reaction with alkyl halides. Similarly, no reaction was detected between **5a** and acrylonitrile. Interaction of methyl

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acrylate with adamantane **5a** furnished an inseparable mixture of starting material and monoalkylation product (ratio ca. 5:3 according to ^{1}H NMR data). Full conversion of **5a** could not be reached neither with a large excess of methyl acrylate nor under prolongated reflux time. On the contrary, reaction of **5a** with an excess of methyl vinyl ketone in methanol led to a smooth formation of the tris-adduct **12a** (Scheme 4). The later was transformed into tertiary base **13a** by catalytic hydrogenation over Pd/C in the presence of potassium carbonate (Scheme 4).

Nitrosylation is a typical reaction of secondary amines leading to *N*-nitrosoamines. Accordingly, treatment of benzyl salt **5a** with an excess of *tert*-butyl nitrite furnished a *N,N,N*-tris(nitroso)adamantane **14a** in high yield. Interestingly, in the course of nitrosylation bromine anion was substituted for a nitrate. This may result from the action of nitric acid formed by oxidation of nitrogen oxides exposed from the excess of nitrosylation agent (examples of such oxidative bromine anion substitution for nitrate anion with nitric acids are precedent in literature[18]).

However, attempts to react the trimethyl substituted adamantane **5b** (R^1 = CH_3, R^2 = Bn, Table 1) with electrophilic agents failed. No reaction was observed with acetic anhydride and Boc_2O; interaction of **5b** with methyl vinyl ketone or *tert*-butyl nitrite furnished complex mixtures of unidentified products. It is likely that the lack of reactivity of adamantane **5b** is associated with a greater sterical hindrance of secondary amino groups in its structure.

Thus, *N*-benzyl salt **5a** may be considered as a stable equivalent of "isourotropine" in the construction of functional molecules based on 1,4,6,10-tetraazaadamantane scaffold.

■ CONCLUSIONS

Though much research was done in 1960−1990s, the chemistry and structure of heteroadamantanes still remains a matter of considerable scientific interest.[2a−h] In this work, 1,4,6,10-tetraazaadamantane, the structural isomer of urotropine, and a series of its derivatives substituted at carbon and nitrogen atoms have been synthesized for the first time. The suggested strategy utilizes available aliphatic nitro compounds as starting materials and involves an unusual intramolecular cyclotrimerization of oxime groups in tris-oximes **2**, reduction of N−OH fragments in the resulting adamantanes **3** or **4** and subsequent electrophilic addition to bridge nitrogen atoms.

1,4,6,10-Tetraazaadamantane structure demonstrates marked distinctions from the urotropine cage, which are governed by strong $lp(N_{eq}) \rightarrow \sigma^*_{C-N}$ hyperconjugation. Furthermore, C- and N-polysubstituted 1,4,6,10-tetraazaadamantanes proved to be more stable than the substituted urotropine derivatives. This implies that the chemical space of 1,4,6,10-tetraazaadamantanes is much greater than that of 1,3,5,7-tetraazaadamantanes.

As is demonstrated here, *N*-benzyl salt **5a** may serve as a universal and stable building-block for the molecular design of various 1,4,6,10-tetraazaadamantane derivatives possessing antiperiplanar or orthogonal oriented functional fragments. Because of the approach suggested by us, the class of 1,4,6,10-tetraazaadamantanes can be considered as available now.

■ EXPERIMENTAL SECTION

All reactions were performed in oven-dried (125 C) glass-ware. Reactions were monitored by analytical TLC using silica gel TLC plates with QF-254. Visualization was accomplished with UV light and the solution of ninhydrin in methanol. Methanol for reactions was distilled without drying agents. Catalytic hydrogenation was performed in round-bottom Schlenk-type flasks equipped with magnetic stirring bar using rubber balloon with hydrogen. In NMR spectra residual solvents peaks were used as an internal standard. Half-height widths of peaks (W in Hz) are reported for broad C−H signals. HRMS spectra were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer. Melting points (uncorrected) were determined on a hot-stage microscope. Commercial reagents were used without additional purification. Tris-oximes **2a−c**,[19] 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanes **3a−c**[5] and their *N*-benzyl salts **4a−c**[5] were prepared according to our previously reported procedures.

Synthesis of *N*-Methyl Quaternary Salts 4d,e. Acetic acid (860 μL, 15.0 mmol) and MeI (375 μL, 6.0 mmol) were added to a solution of tris-oxime **2a,b** (5.0 mmol) in MeOH (15 mL). The reaction mixture was kept overnight and volatile components were evaporated. The white solid residue was triturated with EtOAc−MeOH (3:1) and dried in a vacuum (0.25 Torr) until constant weight.

*4,6,10-Trihydroxy-1-methyl-1,4,6,10-tetraazaadamantan-1-ium iodide (**4d**).* 1.53 g (yield 93%). White crystals: mp 204−206 °C (with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.12 (s, 3 H), 3.72 (br s, W = 40 Hz, 6 H), 4.29 (s, 3 H), 8.8−9.3 (br, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 52.1, 53−57 (br, W = 165 Hz), 71−75 (br, W = 180 Hz); ESI-HRMS m/z $[M - I]^+$ Calcd for $C_7H_{15}N_4O_3$ m/z 203.1139, found 203.1137.

*1,3,5,7-Tetramethyl-4,6,10-trihydroxy-1,4,6,10-tetraazaadamantan-1-ium iodide (**4e**).* 1.80 g (yield 97%). White crystals: mp 193−199 °C (with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.22 (s, 9 H), 3.05 (s, 3 H), 3.42 (br, W = 17 Hz, 6 H), 8.1−8.7 (br, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 19.4, 52.8, 55−60 (br, W = 110 Hz), 74−77 (br, W = 55 Hz); ESI-HRMS m/z $[M - I]^+$ Calcd for $C_{10}H_{21}N_4O_3$ m/z 245.1608, found 245.1609.

Synthesis of 1,4,6,10-Tetraazaadamantane (1a). A suspension of Raney Nickel in MeOH (ca. 50 mg Ni) was added to a solution of 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantane **3a** (50 mg, 0.26 mmol) in MeOH (2.5 mL) the under argon atmosphere. The reaction vessel was evacuated and filled with hydrogen three times. Hydrogenation was performed at 1 atm H_2 until full conversion of **3a** (45−60 min, TLC control). Then the catalyst was separated by centrifugation, and the reaction mixture was evaporated at 40 Torr and 35 °C and then dried in a vacuum (0.25 Torr) until constant weight. 1,4,6,10-Tetraazaadamantane **1a** was obtained as a white foam (33 mg, yield 90%): ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.45 (s, 3 H), 3.17 (s, 6 H), 3.62 (s, 3 H); ^{13}C NMR (75 MHz, DEPT, DMSO-d_6) δ = 57.1 (CH_2), 61.5 (CH); ESI-HRMS m/z $[M + H]^+$ Calcd for $C_6H_{13}N_4$ 141.1135, found 141.1132.

Synthesis of 1,4,6,10-Tetraazaadamantan-1-ium Salts 5a−e. Zinc dust (10 g, 153 mmol) was added to a solution of 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanium salts **4a-e** (5 mmol) in distilled water (15 mL) under argon atmosphere. The reaction vessel was placed in ultrasonic cleaner and kept under ultrasonic irradiation (37 kHz, 150 W) at 80−85 °C until full consumption of starting material (NMR monitoring, 6−15 h, Table 1). The inorganic precipitate was centrifuged off and washed with MeOH. Combined solutions were evaporated in a vacuum (40 Torr) at 50−55 °C. The residue was triturated with EtOAc or EtOAc−MeOH mixture (5:1) and dried in vacuo (0.25 Torr) and then in a desiccator (P_2O_5) until constant weight.

*1-Benzyl-1,4,6,10-tetraazaadamantan-1-ium bromide (**5a**).* 1.27 g (yield 82%). White solid: mp 220−222 °C (with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.04 (s, 3 H), 3.63 (s, 6 H), 4.23 (s, 3 H,), 4.66 (s, 2 H), 7.50−7.61 (s, 5 H); ^{13}C NMR (75 MHz, DEPT, DMSO-d_6) δ = 59.5 (CH), 61.3 (CH_2), 68.1 (CH_2), 126.3 (C), 128.8 (CH), 130.3 (CH), 133.0 (CH); ESI-HRMS m/z $[M - Br]^+$ Calcd for $C_{13}H_{19}N_4$ 231.1604, found 231.1601. Anal. Calcd for $C_{13}H_{19}BrN_4$: C, 50.17; H, 6.15; N, 18.00. Found: C, 50.11; H, 6.35; N, 18.22.

*1-Benzyl-3,5,7-trimethyl-1,4,6,10-tetraazaadamantan-1-ium bromide (**5b**).* 1.59 g (yield 90%). White solid: mp 193−205 °C (with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.09 (s, 9 H), 2.41 (s, 3 H), 3.21 (s, 6 H), 4.61 (s, 2 H), 7.51−7.60 (m, 5 H); ^{13}C NMR (75 MHz, DEPT, DMSO-d_6) δ = 25.3 (CH_3), 62.9 (CH_2) and 63.6

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(CH_2), 67.9 (C), 126.1 (C), 128.8 (CH), 130.3 (CH) and 133.0 (CH); ESI-HRMS m/z $[M - Br]^+$ Calcd for $C_{16}H_{25}N_4$ 273.2074, found 273.2078. Anal. Calcd for $C_{16}H_{25}BrN_4$ calcd: C, 54.39; H, 7.13; N, 15.86. Found: C, 54.48; H, 7.30; N, 15.58.

*1,3,5,7-Tetrabenzyl-1,4,6,10-tetraazaadamantan-1-ium bromide (**5c**).* 2.20 g (yield 76%). White solid: mp 123−130 °C (with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.29 (s, 3 H), 2.73 (s, 6 H), 3.13 (s, 6 H), 4.54 (s, 2 H), 7.12−7.31 and 7.33−7.59 (2 m, 20 H); ^{13}C NMR (75 MHz, DEPT, DMSO-d_6) δ = 44.4 (CH_2), 62.2 (CH_2), 65.4 (C), 68.1 (CH_2), 126.0 (C), 126.7 (CH), 127.9 (CH), 128.8 (CH), 130.3 (CH), 130.6 (CH) and 133.8 (CH), 133.0 (C); ESI-HRMS m/z $[M - Br]^+$ Calcd for $C_{34}H_{37}N_4$ 501.3013, found 501.3007.

*1-Methyl-1,4,6,10-tetraazaadamantan-1-ium iodide (**5d**).* 1.27 g (yield 90%). White solid: mp 195−206 °C (with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.90−3.40 (br s, 3 H), 3.14 (s, 3 H), 3.68 (s, 6 H), 4.24 (s, 3 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ = 53.2, 59.4, 63.5; ESI-HRMS m/z $[M - I]^+$ Calcd for $C_7H_{15}N_4$ 155.1291, found 155.1290.

*1,3,5,7-Tetramethyl-1,4,6,10-tetraazaadamantan-1-ium iodide (**5e**).* 1.49 g (yield 92%). White solid: mp = 165−202 °C (melting with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.10 (s, 9 H), 2.25 (s, 3 H), 3.06 (s, 3 H), 3.25 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 25.2, 52.7, 63.5, 65.3; ESI-HRMS m/z $[M - I]^+$ Calcd for $C_{10}H_{21}N_4$ 197.1761, found 197.1782. Anal. Calcd for $C_{10}H_{21}N_4I$ calcd: C, 37.05; H, 6.53; N, 17.28. Found: C, 36.81; H, 6.75; N, 17.26.

Catalytic Debenzylation of 1-Benzyl-1,4,6,10-tetraazaadamantan-1-ium Salts 5a−c. K_2CO_3 (70 mg, 0.5 mmol) and Pd/C (10%, 20 mg) were added to a solution of **5a−c** (0.5 mmol) in MeOH (7.5 mL) under argon atmosphere. The reaction vessel was evacuated and filled with hydrogen, and the hydrogenation was performed for 30 min. Then the catalyst was removed by centrifugation, and the solution was evaporated in a vacuum (40 Torr) at 35 °C. Et_2O was added to the resulting solid, and the solution was filtered throw a short pad of Celite. The filtrate was evaporated, and the residue was dried in a vacuum (0.25 Torr) until constant weight to give adamantanes **1a−c**.

*3,5,7-Trimethyl-1,4,6,10-tetraazaadamantane (**1b**).* 73 mg (yield 80%). White foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.86 (s, 9 H), 1.46 (s, 3 H), 2.66 (s, 6 H); ^{13}C NMR (75 MHz, DEPT, DMSO-d_6) δ = 27.3 (CH_3), 60.6 (CH_2), 63.3 (C); ESI-HRMS m/z $[M + H]^+$ Calcd for $C_9H_{19}N_4$ 183.1604, found 183.1611.

*3,5,7-Tribenzyl-1,4,6,10-tetraazaadamantane (**1c**).* 137 mg (yield 67%). White foam: ^{1}H NMR (300 MHz, HSQC, DMSO-d_6) δ = 1.2 (br, 3 H), 2.45 (s, 6 H), 2.71 (s, 6 H), 7.06−7.25 (m, 15 H); ^{13}C NMR (75 MHz, HSQC, DMSO-d_6) δ = 45.4 (CH_2), 59.6 (CH_2), 64.0 (C), 126.2 (CH), 127.8 (CH) and 130.3 (CH), 135.0 (C); ESI-HRMS m/z $[M + H]^+$ Calcd for $C_{27}H_{31}N_4$ 411.2543, found 411.2541.

Synthesis of 4,6,10-Triacetyl-1-benzyl-1,4,6,10-tetraazaadamantan-1-ium bromide (6a). 1-Benzyl-1,4,6,10-tetraazaadamantan-1-ium bromide **5a** (110 mg, 0.354 mmol) was dissolved in AcOH (3 mL) and Ac_2O (500 μL, 5.3 mmol) was added, and reaction mixture was kept for 20 h with occasional stirring. The volatile components were evaporated, and residue was triturated with mixture EtOAc−MeOH (10:1) and dried in a vacuum (0.25 Torr) to give **6a** as white solid (142 mg, yield 92%): mp 230−235 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.14 (s, 9 H), 3.90 and 4.02 (2 br m, 6 H), 4.82 (s, 2 H), 6.68 (s, 3 H), 7.50−7.61 (m, 5 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 20.5, 56.6, 58.6, 67.5, 125.6, 129.1, 130.7, 133.0, 167.9; ESI-HRMS m/z $[M - Br]^+$ Calcd for $C_{19}H_{25}N_4O_3$ 357.1921, found 357.1921.

Synthesis of 1-Benzyl-4-[(*tert*-butoxy)carbonyl]-1,4,6,10-tetraazaadamantan-1-ium bromide (8a). Boc_2O (665 μL, 3.21 mmol) was added to a solution of **5a** (100 mg, 0.32 mmol) in MeOH (5 mL). The reaction was stirred for 3 h, and volatile components were evaporated in a vacuum. The residue was triturated with Et_2O and dried in a vacuum (0.25 Torr) until constant weight (125 mg, 95%). White solid: mp 210−214 °C; ^{1}H NMR (300 MHz, mixture of rotamers, DMSO-d_6) δ = 1.42 (s, 9 H), 3.48 (s, 2 H), 3.65 (s, 2 H), 3.70 (s, 4 H), 4.22 (br s, 1 H, W = 8.5 Hz), 4.74 (s, 2 H), 5.19 (br s, W = 8.5 Hz, 2 H), 7.49−7.60 (br s, W = 3.5 Hz, 5 H); ^{13}C NMR (75 MHz, mixture of rotamers, DMSO-d_6) δ = 27.8 and 27.9 (minor and major rotamers), 58.7, 59.6, 60.3, 67.8, 80.3, 126.0, 128.9, 130.5 and 133.1, 152.7; ESI-HRMS m/z $[M - Br]^+$ Calcd for $C_{18}H_{27}N_4O_2$ 331.2129, found 331.2131. Anal. Calcd for $C_{18}H_{27}N_4O_2Br$: C, 52.56; H, 6.62; N, 13.62. Found: C, 52.74; H, 6.89; N, 13.53.

Synthesis of 4,6-Diacetyl-1-benzyl-10-[(*tert*-butoxy)-carbonyl]-1,4,6,10-tetraazaadamantan-1-ium bromide (9a). Ac_2O (170 μL, 1.80 mmol) was added to a solution of **8a** (50 mg, 0.12 mmol) in AcOH (2 mL). The reaction mixture was stirred for 12 h, and volatile components were evaporated. The residue was triturated with EtOAc−MeOH (10:1) and dried in a vacuum (0.25 Torr) until constant weight (49 mg, yield 83%). White solid: mp 168−175 °C; ^{1}H NMR (300 MHz, mixture of rotamers, DMSO-d_6) δ = 1.41 (s, 9 H), 2.14 (s, 6 H), 3.85 and 3.97 (2 br m, W = 30 and 19 Hz, 6 H), 4.76 (s, 2 H), 6.40 and 6.61 (2 br m, W = 35 and 50 Hz, 2 and 1 H), 7.45−7.66 (m, 5 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 20.2, 27.5, 55.3 (br, W = 50 Hz), 58.3 (br, W = 45 Hz), 58.7 (br, W = 10 Hz), 59.7 (br, W = 30 Hz), 67.7, 82.2, 125.5, 129.0, 130.6, 133.0, 151.6, 166.3; ESI-HRMS m/z $[M - Br]^+$ Calcd for $C_{22}H_{31}N_4O_4$ 415.2340, found 415.2317.

Synthesis of 1-Benzyl-4,6,10-tris(3-oxobuthyl)-1,4,6,10-tetraazaadamantan-1-ium bromide (12a). Methyl vinyl ketone (800 μL, 9.6 mmol) was added to a solution of **5a** (100 mg, 0.32 mmol) in MeOH (5 mL). The reaction mixture was kept for 12 h, and volatile components were evaporated. The residue was washed with Et_2O and dried in a vacuum (0.25 Torr) until constant weight (165 mg, yield 99%). White solid: mp 185−192 °C (with dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.07 (s, 9 H), 2.53 (t, J = 6.4 Hz, 6 H), 2.93 (t, J = 6.4 Hz, 6 H), 3.45 (s, 6 H), 3.96 (s, 3 H), 4.60 (s, 2 H), 7.53 (s, 5 H); ^{13}C NMR (75 MHz, DEPT, DMSO-d_6) δ = 29.8 (CH_3), 42.0 (CH_2), 46.1 (CH_2), 56.4 (CH_2), 67.0 (CH), 67.8 (CH_2), 126.1 (C), 129.0 (CH), 130.5 (CH), 133.0 (CH), 207.7 (C); ESI-HRMS m/z $[M - Br]^+$ Calcd for $C_{25}H_{37}N_4O_3$ 441.2860, found 441.2858.

Synthesis of 1-Benzyl-4,6,10-trinitrozo-1,4,6,10-tetraazaadamantan-1-ium nitrate (14a). *Tert*-BuONO (420 μL, 3.6 mmol) was added to a solution of **5a** (75 mg, 0.24 mmol) in AcOH (2 mL) at ∼10 °C, and reaction mixture was kept at 0 °C for 12 h. Volatile components were evaporated, and the residue was triturated with EtOAc−MeOH (10:1) and dried in vacuo (0.25 Torr) until constant weight (91 mg, yield 99%). Yellow solid: T_d 140−149 °C; ^{1}H NMR (300 MHz, mixture of rotamers, DMSO-d_6) δ = 4.10, 4.27, 4.31, 4.44, and 4.64 (5 br m, 6 H), 4.90 (s, 2 H), 7.43−7.69 (m, 5 H), 8.05 (br m, 2 H), 8.60 (br m, 1 H); ^{13}C NMR (75 MHz, mixture of rotamers, DMSO-d_6) δ = 48.4, 57.0, 57.7, 58.1, 68.1, and 68.3 (major and minor rotamers), 125.3, 129.3, 131.0, 133.1; ESI-HRMS m/z $[M - NO_3]^+$ Calcd for $C_{13}H_{16}N_7O_3$ 318.1309, found 318.1314. Anal. Calcd for $C_{13}H_{16}N_8O_6$: C, 41.05; H, 4.24; N, 29.46. Found: C, 41.40; H, 4.77; N, 29.33.

Catalytic Debenzylation of 1-Benzyl-1,4,6,10-tetraazaadamantan-1-ium Salts 6a, 8a, 9a and 12a. K_2CO_3 (34 mg, 0.25 mmol) and palladium on charcoal (10%, 15 mg) were added to a solution of *N*-benzyl salts **6a**, **8a**, **9a** and **12a** (0.25 mmol) in MeOH (3 mL) under argon atmosphere. The reaction vessel was evacuated and filled with hydrogen 3 times. The hydrogenation was performed at 1 atm (120 min for **6a** and **9a**, 105 min for **8a**, 90 min for **12a**). The catalyst was separated by centrifugation, and the reaction mixture was evaporated in a vacuum. Et_2O or EtOAc−MeOH mixture (5:1) was added to the resulting solid, and the solution was filtered throw a short pad of Celite. The filtrate was evaporated, and the residue was dried in a vacuum (0.25 Torr) until constant weight.

*4,6,10-Triacetyl-1,4,6,10-tetraazaadamantane (**7a**).* 45 mg (yield 67%). White solid: mp 236−242 °C; ^{1}H NMR (300 MHz, HSQC, DMSO-d_6) δ = 2.09 (s, 9 H, 3 CH_3), 3.18 and 3.33 (2 d, J_1 = 13.5 Hz, J_2 = 13.5 Hz, 6 H, 3 CH_2), 6.05 (s, 3 H, 3 CH); ^{13}C NMR (75 MHz, HSQC, DMSO-d_6) δ = 20.6 (3 CH_3), 54.1 (3 CH_2), 57.4 (3 CH), 168.2 (C=O); ESI-HRMS m/z $[M + H]^+$ Calcd for $C_{12}H_{19}N_4O_3$ 267.1452, found 267.1460.

*4-[(tert-Butoxy)carbonyl]-1,4,6,10-tetraazaadamantane (**10a**).* 36 mg (yield 59%). White foam: ^{1}H NMR (300 MHz, HSQC, mixture of rotamers, DMSO-d_6) δ = 1.41 (s, 9 H), 2.98 and 3.24 (2 br, 2 H), 3.01 and 3.25 (2 d, J_1 = 12.6 Hz, J_2 = 12.6 Hz, 4 H), 3.18 (s, 2

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H), 3.55 (s, 1 H), 4.64 (s, 2 H); ^{13}C NMR (75 MHz, mixture of rotamers, HSQC, DMSO-d_6) δ = 27.9 and 28.1 ($C(CH_3)_3$, minor and major rotamers), 55.4 and 55.7 (3 CH_2), 59.4 (HN−CH−NH), 60.3 and 61.9 (2 br, W = 35 and 35 Hz, 2 HN−CH−NBoc), 78.8 and 79.4 ($C(CH_3)_3$), 152.7 (C═O); ESI-HRMS m/z [M + H]$^+$ Calcd for $C_{11}H_{21}N_4O_2$ 241.1659, found 241.1652.

*4,6-Diacetyl-10-[(tert-butoxy)carbonyl]-1,4,6,10-tetraazaadamantane (**11a**).* 53 mg (yield 65%). White foam: ^{1}H NMR (300 MHz, HSQC, mixture of rotamers, DMSO-d_6) δ = 1.39 and 1.42 (2 s, 9 H, $C(CH_3)_3$), 2.07, 2.10, and 2.14 (3 s, 6 H, 2 CH_3CO), 3.09−3.40 (m, 6 H, 3 CH_2), 5.69, 6.01, 6.13, and 6.51 (4 s, 3 H, 3 CH); ^{13}C NMR (75 MHz, mixture of rotamers, DEPT, HSQC, DMSO-d_6) δ = 20.3 and 20.6 (2 CH_3CO), 27.6 ($C(CH_3)_3$), 52.4, 53.7, 54.2, and 54.4 (3 CH_2), 55.8, 57.3, and 60.4 (3 CH), 80.6 ($C(CH_3)_3$), 153.1 (O−C═O), 166.3 and 168.0 (2 H_3CCO); ESI-HRMS m/z [M + K]$^+$ Calcd for $C_{15}H_{24}N_4O_4K$ m/z 363.1429, found 363.1426.

*4,6,10-Tris(3-oxobutyl)-1,4,6,10-tetraazaadamantane (**13a**).* 56 mg (yield 64%). Colorless oil: ^{1}H NMR (300 MHz, HSQC, DMSO-d_6) δ = 2.07 (s, 9 H, 3 CH_3), 2.46 (m, 6 H, 3 $CH_2CH_2COCH_3$), 2.94−3.06 (m, 12 H, 3 $CH_2CH_2COCH_3$ and 3 CH_2 in adamantane cage), 3.26 (s, 3 H, 3 CH); ^{13}C NMR (75 MHz, HSQC, DMSO-d_6) δ = 29.7 (3 CH_3), 42.5 (3 $CH_2CH_2COCH_3$), 47.5 and 52.5 (3 $CH_2CH_2COCH_3$ and 3 CH_2 in adamantane cage), 68.7 (3 CH), 208.2 (3 C═O); ESI-HRMS m/z [M + H]$^+$ Calcd for $C_{18}H_{31}N_4O_3$ m/z 351.2391, found 351.2374.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental information, analytical data, X-ray data for **5a**, Cartesian coordinates and absolute energies for all optimized geometries and NBO analysis summaries. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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(7) Relative ΔH_{298} values in Scheme 1 are given for the most stable isomer of each tetraazaadamantane with respect to positions of N−H hydrogens; for relative ΔH_{298} values for all 14 possible structures, see Supporting Information. All calculations were performed using Gaussian 09 package.

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