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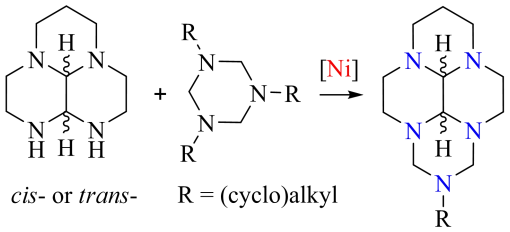
The first synthesis of *N*-substituted *cis*/*trans*-perhydropentaazapyrenes

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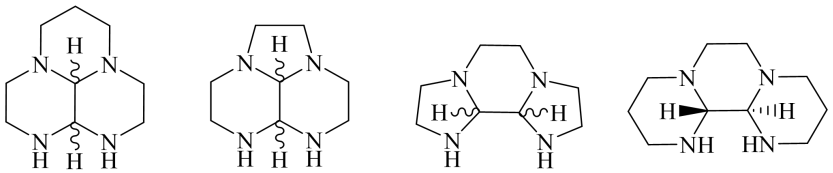
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The hitherto unknown *N*-(cyclo)alkyl substituted *cis*/*trans*-decahydro-1*H*,6*H*-2,3a,5a,8a,10a-pentaazapyrenes were synthesized by the reaction of isomeric perhydrotetraazaphenalenes with 1,3,5-tri(cyclo)alkyl-1,3,5-triazinanes in the presence of $NiCl_2 \cdot 6H_2O$ as a catalyst. The structures of the compounds were confirmed by NMR spectroscopy with coupled with quantum chemical calculations.



Keywords: catalysis, heterocyclization, bisaminals, 1,3,5-triazinanes, perhydropentaazapyrenes.

It is known[1–3] that the condensation of linear tetraamines with glyoxal affords *bis*-aminals **1–7** with various structures, both in the geminal and vicinal forms, with a *cis* or *trans* arrangement of the hydrogen atoms in the *bis*-aminal bridge.



Bis-aminal **1** in the *cis*-configuration is an effective building block in the syntheses of *cis*-tetraazacycloalkanes (Fig. 1).[4–9] *Bis*-aminals of linear tetraamines are used in the syntheses of *bis*-tetraamine ligands[10] and in the preparation of symmetric and asymmetric pentaamines.[11,12] In recent years, *bis*-aminals of cyclic and linear tetraamines have been extensively studied, enabling the synthesis of cyclene- and cyclam-type tetraazamacrocycles[13–18] that are effective chelating agents for many metal ions.[19,20]

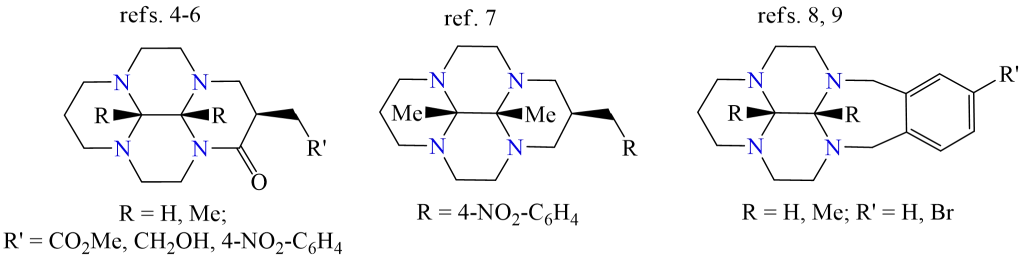
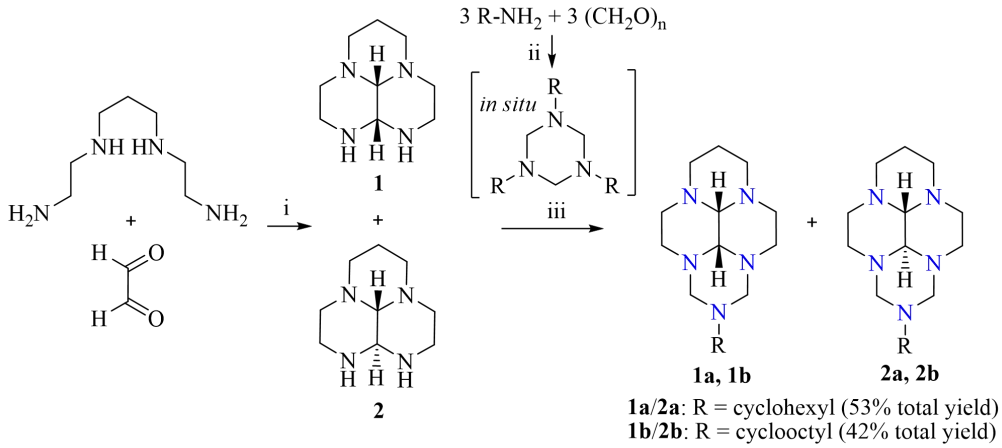


Figure 1 The structure of *cis*-tetraazacycloalkanes.

We believe that 1,3,5-trisubstituted 1,3,5-triazinanes are promising reagents for heterocyclization reactions because they can be used to synthesize various types of polyaza polycyclic systems.[21–28] Replacing a mixture of formaldehyde and a primary amine with the corresponding 1,3,5-triazinane substantially improves the selectivity of this reaction. In view of this, we sought to explore the possibilityof heterocyclization of perhydrotetraazaphenalenes (*bis*-aminals **1** and **2**) with 1,3,5-trisubstituted 1,3,5-triazinanes to synthesize previously unreported *N*-substituted pentaazacycloalkanes.

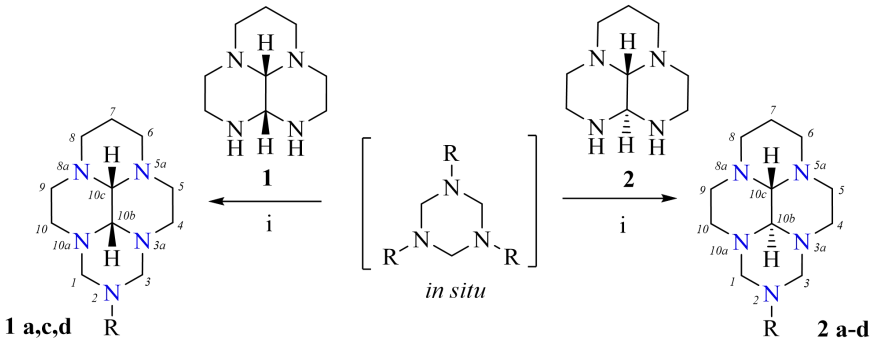
According to literature data,[1,2] the reaction of *N,N'*-bis(2-aminoethyl)propane-1,3-diamine with glyoxal gives a mixture of *cis/trans*-perhydrotetraazaphenalenes **1** and **2**, with the *cis* isomer generally being the major reaction product. Initially, we focused on studying the cyclocondensation of 1,3,5-triazinanes with a stereoisomeric mixture of perhydrotetraazaphenalenes **1** and **2** that served as starting "building blocks." Hexahydrated Ni(II) chloride was selected as the reaction catalyst since $NiCl_2 \cdot 6H_2O$ is known[29] to act as an "intermediate" Lewis acid that preferentially coordinates with *N*-donor ligands. It should be noted that 1,3,5-tri(cyclo)alkyl-1,3,5-triazinanes were prepared *in situ*, followed by the heterocyclization reaction without prior isolation. CH_3CN was selected as the reaction medium because of the good solubility of the starting reagents init. Our experiments showed (Scheme 1) that the reaction of 1,3,5-tricyclohexyl-1,3,5-triazinane prepared *in situ*[25] with a mixture of *cis/trans*-perhydrotetraazaphenalenes **1** and **2** in the presence of 5 mol % $NiCl_2 \cdot 6H_2O$ at 40°C in acetonitrile for 7 days afforded isomeric *cis/trans*-2-cyclohexyl-2,3a,5a,8a,10a-pentaazapyrenes **1a/2a**. The combined yield of compounds **1a/2a** was 53%. The *cis*-pentaazapyrene **1a** was the major reaction product; according to the ^{13}C NMR spectrum, the isomeric *cis/trans*-pentaazapyrenes **1a/2a** were present in a ~5:1 ratio. We found that under the optimal reaction conditions (5 mol % $NiCl_2 \cdot 6H_2O$, 40°C, CH_3CN, 7 days), 1,3,5-tricyclooctyl-1,3,5-triazinane is also capable of reacting with perhydrotetraazaphenalenes **1** and **2** to give a mixture of *cis/trans*-2-cyclooctyl-2,3a,5a,8a,10a-pentaazapyrenes **1b/2b** in 42% combined yield. We failed to separate the resulting *cis/trans*-pentaazapyrenes by column chromatography because their polarities were similar. In the NMR spectra of these compounds, we observed a double set of signals corresponding to the *cis/trans*-isomeric mixture of 2-cycloalkyl-2,3a,5a,8a,10a-pentaazapyrenes.



Scheme 1 *Reagents and conditions*: i. *N,N′-bis*(2-aminoethyl)propane-1,3-diamine (1 equiv.), glyoxal (40 wt% aq., 1 equiv.), EtOH, 0 °C, 2 h; ii. cycloalkylamine (3 equiv.), paraform (3 equiv.), MeOH, 60 °C, 3 h; iii. a mixture of *cis*/*trans*-perhydrotetraazaphenalenes (1 equiv.), 1,3,5-tricycloalkyl-1,3,5-triazinane (1 equiv.), 5 mol % $NiCl_2 \cdot 6H_2O$, CH_3CN, 40 °C, 7 days.

To synthesize stereoisomerically pure pentaazapyrenes, we continued studies on the catalytic heterocyclization of 1,3,5-triazinanes with individual *bis*-aminals **1** or **2**. To obtain the starting *cis*-perhydrotetraazaphenalene **1**, the condensation of *N,N′*-bis(2-aminoethyl)propane-1,3-diamine with glyoxal should be carried out in ethanol at −10°C for 3 h.[3] Our experiments showed that the reaction of 1,3,5-tricyclohexyl-1,3,5-triazinane with *cis*-perhydrotetraazaphenalene **1** at a 1:1 molar ratio of the starting reagents under the conditions (5 mol % $NiCl_2 \cdot 6H_2O$, 40°C, CH_3CN, 7 days) occurred selectively to give stereoisomerically pure *cis*-2-cyclohexyl-2,3a,5a,8a,10a-pentaazapyrene **1a** in 56% yield (Scheme 2). Similarly, replacing the cyclohexyl groups at the nitrogen atoms of the 1,3,5-triazinane molecule with cycloheptyl or *tert*-butyl substituents allowed us to obtain the corresponding stereoisomerically pure *cis*-2,3a,5a,8a,10a-pentaazapyrenes **1c** and **1d** in 46–53% yields. Increasing the concentration of the $NiCl_2 \cdot 6H_2O$ catalyst to 10 mol % did not increase the yields of the target polycycles considerably.

At the next stage of our study, we evaluated the possibility of synthesizing stereoisomerically pure *trans*-pentaazapyrenes from *trans*-perhydrotetraazaphenalene **2**. It should be noted that the addition of glacial acetic acid to the ethanol medium followed by refluxing the reaction mixture for 12 h is a prerequisite for synthesizing the starting *trans-bis*-aminal **2** by condensation of *N,N′*-bis(2-aminoethyl)propane-1,3-diamine with glyoxal.[3] We found that under the developed conditions (5 mol % $NiCl_2 \cdot 6H_2O$, 40°C, CH_3CN, 7 days), heterocyclization of the starting *trans*-perhydrotetraazaphenalene **2** with 1,3,5-tri(cyclo)alkyl-1,3,5-triazinanes afforded stereoisomerically pure *trans*-2-(cyclo)alkyl-2,3a,5a,8a,10a-pentaazapyrenes **2a–d** in 36–49% yields (Scheme 2).

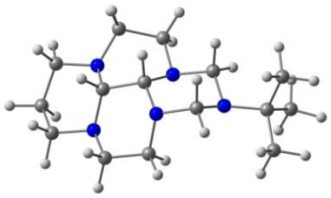


1a: R = cyclohexyl (56% yield) **1c**: R = cycloheptyl (53% yield)
1d: R = *tert*-butyl (46% yield)
2a: R = cyclohexyl (49% yield) **2b**: R = cyclooctyl (36% yield)
2c: R = cycloheptyl (44% yield) **2d**: R = *tert*-butyl (43% yield)

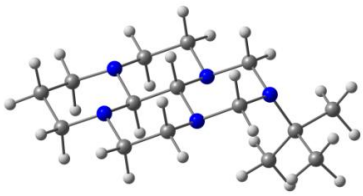
Scheme 2 *Reagents and conditions*: i. *cis*- or *trans*-perhydrotetraazaphenalene (1 equiv.), 1,3,5-tri(cyclo)alkyl-1,3,5-triazinane (1 equiv.), 5 mol % $NiCl_2 \cdot 6H_2O$, CH_3CN, 40 °C, 7 days.

Stereoisomerically pure *cis*-2,3a,5a,8a,10a-pentaazapyrenes **1a,c,d** and stereoisomerically pure *trans*-2,3a,5a,8a,10a-pentaazapyrenes **2a–d** were isolated as individual compounds. Their structures were determined by two-dimensional NMR experiments and high-resolution mass spectrometry. It should be noted that in the ^{1}H NMR spectra of the *cis* and *trans* stereoisomers, the vicinal coupling constant between the H^{10b} and H^{10c} protons of the *bis*-aminal bridge was 2.5 Hz and 7.0 Hz, respectively, similar to those observed for the starting *bis*-aminals.[30] Moreover, a distinctive feature of the ^{13}C NMR spectra of *cis*-2,3a,5a,8a,10a-pentaazapyrenes is the relatively large number of signals corresponding to the polycyclic framework. In fact, the ^{13}C NMR spectra of the *cisoid*-configured compounds **1a,c,d** exhibit eleven signals from the framework, whereas the ^{13}C NMR spectra of *trans*-2,3a,5a,8a,10a-pentaazapyrenes **2a–d** show only seven signals from the polycyclic framework due to the magnetic equivalence of the $C^{4,10}$, $C^{5,9}$, $C^{6,8}$, and $C^{1,3}$ carbon atoms. This spectral effect is evidently caused by the spatial symmetry found in *trans*-2,3a,5a,8a,10a-pentaazapyrenes with any *N*-substituent. To theoretically substantiate the assignments of the NMR signals for each stereoisomer, we determined all possible conformations using model compounds **1d** and **2d** as examples and identified the most energetically favorable structures based on DFT calculations at the PBE/3ζ level using the PRIRODA-20 program.

The calculated data (see the Online Supplementary Materials) indicate that the most energetically favorable structure of the *trans* stereoisomer **2d** corresponds to conformation K-16, in which all rings of the framework adopt the *chair* conformation. The optimized structure shown in Fig. 2 exhibits symmetry, which is consistent with the observation of pairs of magnetically equivalent carbon atoms in the ^{13}C NMR spectra. For the *cis* stereoisomer **1d**, the global minimum on the potential energy surface corresponds to conformation K-11, in which rings A, C, and D of the polycyclic system adopt *chair* conformations, whereas ring B adopts a *twist* conformation. These differences result in a doubling of several framework signals, as well as differences in the NMR parameters of the -N-CH_2-CH_2-N- moiety in compounds **1** and **2**. The ^{13}C NMR chemical shifts were calculated for these conformations and showed good agreement with the experimental values.



1d



2d

Figure 2 Optimized structures of the most advantageous conformers for *cis* and *trans* isomers.

Thus, heterocyclization of *cis/trans*-perhydrotetraazaphenalenes with 1,3,5-trisubstituted 1,3,5-triazinanes in the presence of nickel chloride provides access to previously unreported stereoisomerically pure *cis*-2,3a,5a,8a,10a-pentaazapyrenes and *trans*-2,3a,5a,8a,10a-pentaazapyrenes.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: *10.71267/mencom.___*

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