Pergamon

Tetrahedron 57 (2001) 2385–2390

TETRAHEDRON

Stoichiometric mono *N*-functionalization of cyclen via a boron protected intermediate

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Received 13 November 2000; revised 16 January 2001; accepted 26 January 2001

Abstract—The temporary triprotection of cyclen by a boron atom performed in presence of sodium hydride offers a convenient solution for the mono *N*-alkylation of cyclen. Examples of mono *N*-alkylated cyclens and bis-cyclens are reported.

1. Introduction

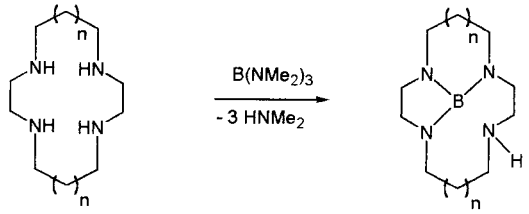
A lot of exploratory research about the complexation chemistry of functionalized tetraazamacrocycles has been reported over the last ten years.[1] The main reasons lie both in their strong ligating abilities towards a large range of cations, and in the high thermodynamic stability and kinetic inertness of their complexes. Hence, numerous efforts have been made to develop new *N*-functionalized cyclens which complex lanthanides to form MRI contrast agents[1–4] or luminescent probes.[5] At the same time, syntheses of mono *N*-modified 1,4,7,10-tetraazacyclotetradecane (cyclen), which binds to double-stranded DNA by either hydrogen bonding or $\pi-\pi$ stacking interactions, have been proposed.[6]

In the light of these examples, selective N-functionalization of the cyclen has to be controlled. Some direct mono *N*-alkylations were proposed, however the formation of bis and tris-*N*-alkylated adducts cannot be avoided[7] apart using an excess of cyclen.[8] A further purification step is then necessary, which makes this route tedious and time consuming, except in rare cases. The strategies based on the use of temporary nitrogen protecting groups[9–11] avoid the over-alkylation difficulties and thus are more general. They were successfully applied for the mono *N*-functionalization of cyclam and higher macrocycles. Among the described procedures, the use of a boron atom as protecting agent constitutes one of the most powerful methods: this technique is, indeed, easy to run and deprotection is performed under very mild conditions which allows the introduction of sensitive groups.[12,13] However, when it was applied to cyclen, this strategy failed. In this paper, we reinvestigate this reaction and report on the characterization of the boron intermediates before checking their reactivity towards various electrophiles such as alkyl halides, acid chlorides and tosylates.

2. Results and discussion

The cyclen protection was performed by transamination with tris-(dimethylamino)-borane under the experimental conditions previously established for cyclam (1,4,8,11-tetraazacyclotetradecane)[12] (Scheme 1). After alkylation with an electrophile such as benzyl bromide the reaction led, after hydrolysis, to a mixture containing the starting material, mono and poly *N*-alkylated cyclen derivatives. This result is indicative of an ineffective boron protection of cyclen.

Unlike cyclam, the transamination carried out in refluxing toluene appeared to be slow and not completed after five hours since three species were detected in the medium by NMR spectroscopy before the addition of the electrophile:



1a : n = 0 : cyclen

1b : n = 1 : cyclam

2 a - b

Scheme 1.

Keywords: cyclen; cyclam; mono *N*-alkylation; bis-cyclen.

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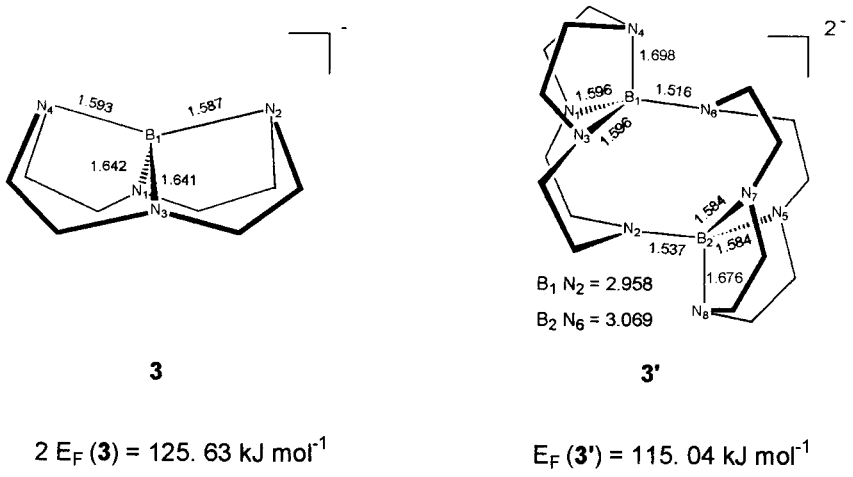
PII: S0040-4020(01)00115-6



Scheme 2. Relative stabilities and selected geometrical parameters calculated for the monomeric **3** and dimeric **3′** anionic forms of **2a** (bond lengths are in Å).

the starting materials and a reaction product which appeared to be different of the expected boron-cyclen **2a**.

To obtain quantitatively the boron-cyclen **2a**, the reaction time had to be significantly increased (24 h). This intermediate was characterized in ^{13}C NMR by two signals at 49.16 and 51.35 ppm along with a broad one at 55.44 ppm. This result is in agreement with a boron coordinated to three nitrogen atoms, which induces a partial loss of symmetry of the macrocycle. The third broad signal corresponds to two carbons involved in an intramolecular exchange process. In the ^{11}B NMR spectrum, the only signal detected at 29.52 ppm corresponds to a tri-coordinated boron atom.[14]

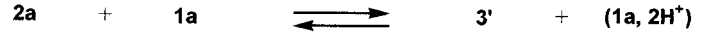
When pure **2a** is generated, a subsequent treatment by a base (BuLi or NaH) and addition of benzyl bromide lead to a clean mono *N*-alkylation indicating an effective protection of cyclen (vide infra).

When the transamination was performed at a lower temperature in refluxing benzene, the reaction did not proceed to completion. The NMR spectra show the presence of four products among which were found the two starting compounds (cyclen and $B(NMe_2)_3$), the boron-cyclen **2a** and a significant quantity of the fourth one already detected in the previous experiment in refluxing toluene. Its ^{13}C NMR spectrum exhibits two close signals around 42.03 and a third one at 49.22 ppm and its ^{11}B NMR spectrum is characterized by one signal at 27.09 ppm. Compared to **2a**, the upfield shift observed in ^{11}B NMR for this new compound is consistent with the formation of an anionic species and can be interpreted as an increase of the electronic charge on the boron atom[15] and a change in its coordination state to a BX_4^- sp^3 form. As a matter of fact, when **2a** obtained pure in toluene is treated with sodium hydride or when the exchange reaction is performed in presence of NaH in benzene or toluene, the reaction leads cleanly to this anionic compound as a sodium salt. The ^{13}C NMR spectrum at 100.62 MHz in benzene solution of the anion shows two peaks at 42.06 and 41.96 ppm and a third one, nearly two times higher, at 49.20 ppm, while ^{11}B NMR spectrum presents a single signal at 27.18 ppm.

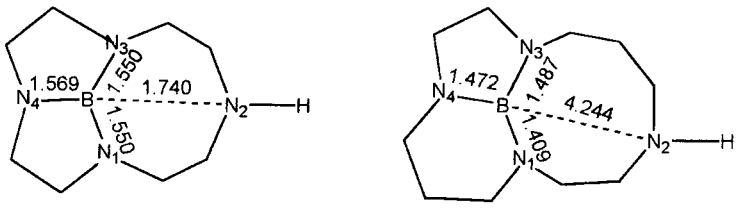
From a structural point of view, in an anionic BX_4^- structure like **3** (Scheme 2), the four nitrogen atoms around the tetrahedral sp^3 boron would occupy four identical positions and, consequently, all the carbon atoms would be equivalent and lead to a sole signal in the ^{13}C NMR spectrum. Apart an improbable distorted and locked up conformation, to interpret the multiplicity of the ^{13}C NMR spectrum one can suggest the formation of a dimeric structure that, first, allows a tetrahedral BX_4^- form and, secondly, minimises steric hindrance within the ring. Such structures were already proposed for boron derivatives of triazacyclononanes.[16] Unfortunately, as our intermediates are very moisture-sensitive, no mass spectrum can be recorded to confirm this hypothesis. However, molecular modelling using as models monomer boron-cyclen **3** and dimer boron-cyclen **3′** was carried out in order to test their respective stability (Scheme 2). It showed that the dimer **3′** was more stable than the two isolated monomers; in addition, the corresponding dimer geometry exhibited a centre of inversion and a mirror plane as suggested by the ^{13}C NMR spectrum. The two boron atoms occupy equivalent positions and the ^{13}C NMR spectrum should exhibit four different signals (three observed in 2:1:1 proportion).

The formation of this anion implicates the proton abstraction of the NH function of **2a**. As suggested by the relative intensity of the cyclen signal and the anion ones, two protons released by two boron-cyclen are trapped by a free cyclen molecule which possesses two basicities strong enough for this task.[17] This side-reaction significantly slows the formation of **2a**, the desired product of the reaction (Scheme 3).

The question raised now is the following one: which factor does control the autoprotolysis of boron-cyclen **2a**? Several works dealing with the electronic study of triprotected cyclens by phosphoryl or thiophosphoryl groups[18] have



Scheme 3.



	CYCLEN – BORE **2a**	CYCLAM – BORE **2b**
Sum of the angles around N_1	330.23	359.35
Sum of the angles around N_2	339.32	335.43
Sum of the angles around N_3	330.19	348.24
Sum of the angles around N_4	327.52	339.66
Sum of the angles around B	339.47	359.95

Scheme 4. Geometrical parameters calculated for **2a** and **b** (bond lengths are in Å and angles in degrees).

shown that transannular interaction between the nitrogen of the secondary amine and the phosphorus enhanced its proton acidity. Furthermore, it was shown that this interaction was not observed in cyclam analogues.[18] In order to test the lability of the proton and consequently the strength of the N→B interaction, pure **2a** and **b** were allowed to react with a strong base. The proton abstraction was then checked for the two boron intermediates with a slight excess of NaH, which usually does not remove the secondary amine hydrogen. The experiment was performed in refluxing THF, benzene and toluene: whatever the temperature conditions, we observed a rapid deprotonation of the secondary amine function of **2a** that led quantitatively to the anionic form. On the other hand, under the same conditions, **2b** remained unchanged. So, the energy of activation required to reach the anion of **2a** is lower than the one needed for **2b** as expected for a N–H cleavage monitored by the transannular interaction.

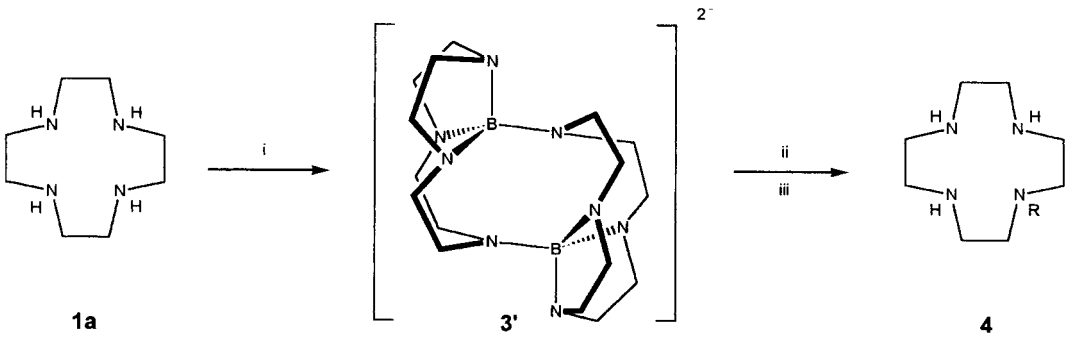
Table 1. Alkylation of **3′** with various electrophiles

Entry **4**	RX	Yield (%)
a	$C_6H_5CH_2Br$	98
b	C_6H_5COCl	80
c	$H_2C{=}CH{-}CH_2Br$	60
d	$CH_3(CH_2)_3I$	40
e	$(CH_3)_2CHI$	2
f	$Br{-}H_2C{-}C{\equiv}C{-}CH_3$	48
g	C_2H_5Ots	60

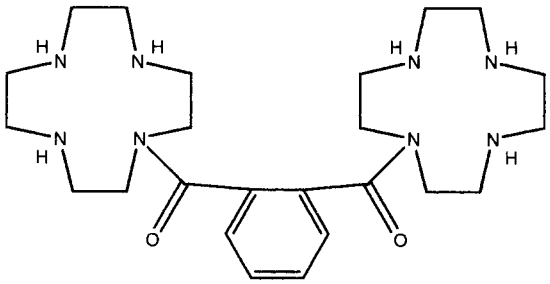
The modelling of **2a** and **b** gas phase geometries in AM1 formalism brings an additional indication of this interaction through the knowledge of the N→B distance (Scheme 4).

In fact, to be properly described this weak interaction needs higher level of theory excluded here because of the system size. Nevertheless, the optimized structures of **2a** and **b** showed in **2a**, a B···N_2(H) distance calculated at 1.74 Å and smaller than the corresponding one in **2b** (4.24 Å). Furthermore, in **2a** this distance is shorter than the sum of the Van der Waals radii estimated at 3.20 Å,[19] which is in agreement with a transannular interaction between the boron and the nitrogen N_2(H). This interaction was also pointed out in the phosphorylated analogues.[18]

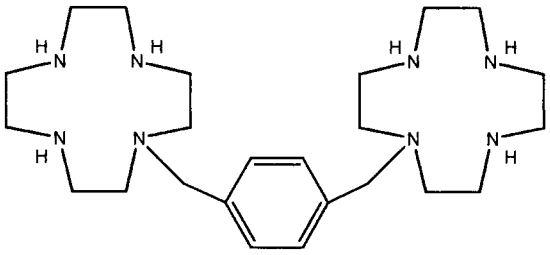
In respect to alkylation reaction, NaH did not play the same role towards boron-cyclen **2a** and boron-cyclam **2b**. Concerning **2b** it is noteworthy that NaH did not remove the secondary amine proton whereas, for **2a**, NaH drew the reaction towards the anionic form **3′**. This intermediate was then alkylated in situ in toluene and few typical examples illustrating its reactivity are reported in Table 1. The reaction kinetics are rather slow, except with reactive electrophiles such as benzyl bromide or benzyl chloride, probably because of the lowering of nitrogen nucleophilicity induced by the electronic delocalisation on the two monomeric moieties. Moreover, with a good leaving group such as iodide, the reaction is very sensitive to the steric hindrance on the electrophilic carbon as shown by the yields obtained for **4d** and **e**, respectively (Scheme 5). Nevertheless, the reaction is univocal and most of the mono



Scheme 5. (i) NaH, $B(NMe_2)_3$, Toluene; (ii) RX; (iii) MeOH.



4h



4i

Figure 1. 4h: 73% yield; **4i**: 88% yield.

N-alkylated cyclens were obtained in good yields after extraction and purification procedures. The boron protected macrocycles react readily with water;[12,13] we observed that deprotection rapidly occurred in very mild conditions with methanol or ethanol. The addition of methanol in excess to remove the boron moiety constitutes a particularly advantageous deprotection reaction, as volatile trimethoxyborate is formed. Finally, reactivity of **3′** towards bis-electrophiles, e.g. phtaloyl dichloride and 1,4-bis (bromomethyl) benzene, was checked (Fig. 1): the bismacrocycles **4h** and **i** were isolated in satisfactory yields; their ^{1}H and ^{13}C NMR spectra as well as microanalyses were in full agreement with previous data.[20]

3. Conclusion

In refluxing toluene, the transamination of cyclen with $B(NMe_2)_3$ is a slow process and the exchange reaction is limited by a side-reaction identified as the boron-cyclen autoprotolysis. This drawback can be avoided by adding a strong base such as NaH at the beginning of the process. Under these conditions, the reaction is shifted towards the formation of a dimeric anion, which can be alkylated in situ. Finally, this pathway constitutes an alternative method to the one proposed by Boldrini et al.[21] and allows the selective synthesis of several mono *N*-alkylated cyclen derivatives and bis-cyclens in good yields.

4. Experimental

4.1. General

All ^{1}H and ^{13}C spectra were recorded on Bruker AC300 and Bruker AMX400 spectrometers (75.47 and 100.62 MHz, respectively, for ^{13}C). Chemical shifts are given downfield from external TMS. ^{11}B NMR spectra were recorded on the AMX400 (160.46 MHz for ^{11}B). Elemental analyses were performed at the 'Centre de Microanalyses du CNRS' (Gif sur Yvette, France). All the reactions were run under nitrogen using freshly distilled and dry solvents. Molecular modelling was performed with the SPARTAN[22] software on a Silicon Graphics station. Trial structures of the compounds **2a**, **b**, **3**, **3′**, were generated and a conformational search was made to find the global minimum of each surface. Semi-empirical calculation was then accomplished, geometries were fully optimized and minima characterized by the number of negative eigenvalues (none) of the Hessian matrix.

4.2. Characterization of boron intermediates 2a and b

Either cyclen **1a** or cyclam **1b** (2 mmol) were dried prior to use by azeotropic distillation and then dissolved under nitrogen in freshly distilled and dried solvents (THF, benzene or toluene) and 2 mmol of $B(NMe_2)_3$ was added. The mixture was refluxed for 5 h (24 h for cyclen) and after cooling, the solution was introduced under nitrogen in the NMR tube equipped with a D_2O capillary.

4.2.1. Boron-cyclen 2a. ^{11}B NMR (toluene): 29.52 ppm. ^{13}C NMR (toluene): 49.16 ($2CH_2N$), 51.35 ($2CH_2N$), 55.44 ($4CH_2N$) ppm.

4.2.2. Boron-cyclam 2b. ^{11}B NMR (toluene): 24.18 ppm. ^{13}C NMR (toluene): 30.50 ($1CH_2$–CH_2N), 33.28 ($1CH_2$–CH_2N), 47.44, 46.16, 50.04, 51.38, 51.46, 52.14, 52.86, 54.76 ppm ($8CH_2N$).

4.2.3. Anion 3′. 3 mmol of oil-free sodium hydride were added to 2 mmol of boron-cyclen **2a** in toluene, benzene or THF and the mixture was refluxed for 1 h.

^{11}B NMR (benzene): 27.09 ppm. ^{13}C NMR (benzene): 42.06 ($4CH_2N$), 41.96 ($4CH_2N$), 49.20 ($8CH_2N$) ppm.

4.3. General procedure for cyclen alkylation

Cyclen **1a** (2 mmol, 344 mg) was dried by azeotropic distillation in 50 mL of toluene. After cooling, sodium hydride

(3 mmol, 140 mg) in dry toluene (30 mL) was added and stirred for 15 min $B(NMe_2)_3$ was then added (2.2 mmol, 410 μL) and refluxed for 4 h. Then, 1.1 equiv. of alkylating agent was introduced. The reaction mixture was allowed to react for 1 h at 110°C. After cooling, the excess of sodium hydride was carefully neutralized by addition of 10 mL of methanol; the boron complex was concomitantly destroyed. After solvent evaporation, the residue was dissolved in 10 mL of 4N NaOH solution (pH 14) and the product was extracted with dichloromethane. All the compounds were purified by chromatographic work-up on silica gel ($CHCl_3$–isopropylamine, 5:1) and precipitated as hydrochloride salt for elemental analysis (except for **4c** and **f**).

4.3.1. 1-Benzyl-1,4,7,10-tetraazacyclododecane 4a. Viscous colourless liquid: 513 mg (1.96 mmol, 98%). ^{1}H NMR δ ($CDCl_3$): 2.57 (m, 8H, NCH_2CH_2N), 2.67 (m, 4H, NCH_2CH_2N), 2.79 (m, 4H, NCH_2CH_2N), 3.61 (s, 2H, NCH_2Ph), 7.26 (m, 5H, Ph). ^{13}C NMR δ ($CDCl_3$): 44.76, 45.90, 46.83, 50.84 (NCH_2CH_2N), 58.92 (NCH_2Ph), 126.68, 127.94, 128.63, 138.51 (Ph). Anal. calcd for $C_{15}H_{26}N_4$, 3HCl (371.78): C 48.46, H 7.86, N 15.07, Cl 28.61. Found C 48.48, H 7.76, N 15.08, Cl 28.57.

4.3.2. 1-Benzoyl-1,4,7,10-tetraazacyclododecane 4b. Viscous colourless liquid: 442 mg (1.60 mmol, 80%). ^{1}H NMR δ ($CDCl_3$): 2.32 (m, 4H, NCH_2CH_2N), 2.83 (m, 8H, NCH_2CH_2N), 3.50 (m, 4H, NCH_2CH_2N), 7.26 (m, 5H, Ph). ^{13}C NMR (($CDCl_3$): 34.28, 38.55, 46.82, 47.23 (NCH_2CH_2N), 126.25, 127.39, 128.21, 135.53 (Ph), 170.43 (CO). Anal. calcd for $C_{15}H_{24}N_4O$, 3HCl (385.76): C 48.70, H 7.05, N 14.52, Cl 27.57, O 4.15. Found C 46.49, H 7.23, N 14.38, Cl 27.30, O 4.13.

4.3.3. 1-Allyl-1,4,7,10-tetraazacyclododecane 4c. Viscous colourless liquid: 225 mg (1.20 mmol, 60%). ^{1}H NMR δ ($CDCl_3$): 2.58 (m, 12H, NCH_2CH_2N), 2.64 (m, 4H, NCH_2CH_2N), 2.79 (m, 2H, NCH_2CH_2N), 3.11 (d, 2H, $NCH_2CH{=}$), 5.12 (m, 2H, $={CH_2}$), 5.81 (m, 1H, $NCH_2CH{=}$). ^{13}C NMR δ ($CDCl_3$): 44.32, 45.21, 45.98, 50.16 (NCH_2CH_2N), 56.84 ($NCH_2CH{=}$), 116.69 ($={CH_2}$), 134.72 ($={CH}$). Anal. calcd for $C_{11}H_{24}N_4$ (212.34): C 62.22, H 11.39, N 26.39. Found C 61.99, H 11.08, N 26.16.

4.3.4. 1-Butyl-1,4,7,10-tetraazacyclododecane 4d. Viscous colourless liquid: 183 mg (0.80 mmol, 40%). ^{1}H NMR δ ($CDCl_3$): 0.90 (t, 3H, CH_3), 1.30 (s, 2H, CH_2CH_3), 1.45 (q, 2H, $CH_2CH_2CH_3$), 2.38 (t, 2H, $NCH_2CH_2CH_2CH_3$), 2.52 (m, 4H, c), 2.65 (m, 12H, NCH_2CH_2N). ^{13}C NMR δ ($CDCl_3$): 13.50 (CH_3), 20.03 (CH_2CH_3), 28.98 ($CH_2CH_2CH_3$), 44.73, 45.49, 46.56, 51.01 (NCH_2CH_2N), 53.76 ($NCH_2CH_2CH_2CH_3$). Anal. calcd for $C_{12}H_{28}N_4$, 3HCl (377.76): C 42.67, H 9.25, N 16.59, Cl 31.49. Found C 42.62, H 9.37, N 16.99, Cl 31.19.

4.3.5. 1-Isopropyl-1,4,7,10-tetraazacyclododecane 4e. Viscous colourless liquid: 10 mg (0.04 mmol, 2%). ^{1}H NMR δ ($CDCl_3$): 1.06 (s, 6H, CH_3), 2.65 (m, 5H, CH and NCH_2CH_2N), 2.83 (m, 8H, NCH_2CH_2N), 3.00 (m, 4H, NCH_2CH_2N). ^{13}C NMR δ ($CDCl_3$): 17.54 ($2CH_3$), 45.10, 45.36, 46.79, 46.87 (NCH_2CH_2N), 49.26 ($C(CH_3)_2$). Anal. calcd for $C_{11}H_{26}N_4$, 3HCl (323.73): C 40.81, H 9.03, N 17.31, Cl 32.85. Found C 40.65, H 8.76, N 17.58, Cl 32.58.

4.3.6. 1-(2-Butynyl)-1,4,7,10-tetraazacyclododecane 4f. Viscous colourless liquid: 216 mg (0.96 mmol, 48%). ^{1}H NMR δ ($CDCl_3$): 1.81 (s, 3H, CH_3), 2.59 (m, 4H, NCH_2CH_2N), 2.70 (m, 12H, NCH_2CH_2N), 3.39 (s, 2H, $NCH_2C{\equiv}$). ^{13}C NMR δ ($CDCl_3$): 2.72 (CH_3), 42.80 ($NCH_2C{\equiv}$), 43.98, 45.41, 46.15, 49.29 (NCH_2CH_2N), 73.27 ($CH_2C{\equiv}$), 79.48 ($\equiv CCH_3$). Anal. calcd for $C_{12}H_{24}N_4$ (224.35): C 64.24, H 10.78, N 24.97. Found C 63.93, H 10.50, N 24.73.

4.3.7. 1-Ethyl-1,4,7,10-tetraazacyclododecane 4g. Viscous colourless liquid: 242 mg (1.20 mmol, 60%). ^{1}H NMR δ ($CDCl_3$): 0.89 (t, 3H, CH_3), 1.42 (sext, 2H, $CH_2CH_2CH_3$), 2.21 (m, 4H, NCH_2CH_2N), 2.50 (t, 2H, $CH_2CH_2CH_3$), 2.83 (m, 12H, NCH_2CH_2N). ^{13}C NMR δ ($CDCl_3$): 11.28 (CH_3), 44.65, 45.18, 46.45, 50.11 (NCH_2CH_2N), 50.71 (NCH_2CH_3). Anal. calcd for $C_{10}H_{24}N_4$, 3HCl (309.71): C 38.78, H 8.79, N 18.09, Cl 34.34. Found C 39.17, H 8.76, N 18.27, Cl 34.08.

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