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The Synthesis of 1,2-Bis(1,5,9-triazacyclododecyl)ethane: A Showcase for the Importance of the Linker Length within Bis(alkylating) Reagents

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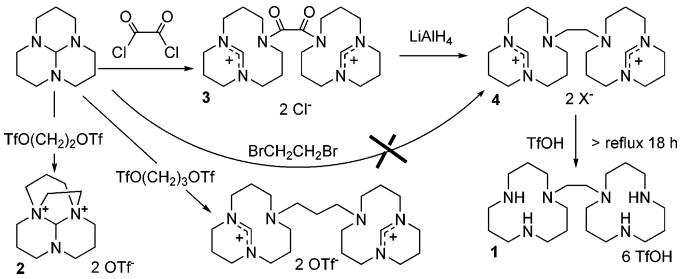
ABSTRACT



The synthesis of 1,2-bis(1,5,9-triazacyclododecyl)ethane (1) showcases how different bis(alkylating) reagents change the reaction from an intra- to an intermolecular pathway. The isolation of the intermediate hexahydro-3a,6a-ethano-1H,4H,7H,9bH-9a-aza-3a,6a-diazoniaphenalene-3a,6a-diium (2) explained why initially the synthesis of 1 was not possible. Both isomers of 2 were found in solution. DFT calculations revealed that isomer 2a is 4.6 kcal/mol lower in energy than 2b. Synthesis of 1 was finally achieved by using oxalyl chloride.

Synthetic azamacrocycles are widely used not only in chemistry[1] but also in biochemistry[2] and medicine.[3] Azamacrocycles have a strong tendency to form stable transition-metal complexes. The properties of these ligands can be tuned by varying the number and size of donor atoms, the size of the macrocycle, or the metal-to-metal distance in the case of dinuclear complexes.

Since selective alkylations in polyazamacrocycles are rarely possible,[4] several protection and deprotection steps in a long synthetic pathway are normally needed,[5] and as a consequence, often low overall yields are obtained. Bis-azamacrocycles, also called "earmuff ligands", have been described in the literature.[6] In particular, ethylene-bridged azamacrocycles have been synthesized by either reaction of ethylendiamine units with two equivalents of ditosylates[7] or simply reacting 1,2-dibromo[8]/ditosylate[9]-ethane with pre-

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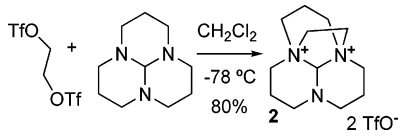
formed azamacrocycles. In this letter, we present the synthesis of 1,2-bis(1,5,9-triazacyclododecyl)ethane (**1**) in a straightforward synthetic route and discuss the reactivity of various bis(alkylating) reagents.

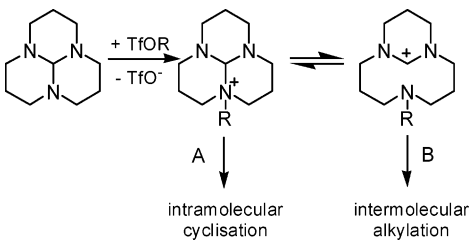
When we followed the Snodin method[10] in order to synthesize the novel 1,2-bis(1,5,9-triazacyclododecyl)ethane as a product, the unexpected tetracyclic compound **2** was obtained in 80% yield (see Scheme 1). Ethylene bistriflate

Scheme 1



had reacted as an intramolecular bisalkylating reagent. This is in remarkable contrast to the analogous reaction with propylene bistriflate. In that case, exclusively monoalkylation at one nitrogen atom of the two 1,5,9-triazatricyclo[7.3.1.0]-tridecane units was observed.[10] Scheme 2 shows the possible

Scheme 2

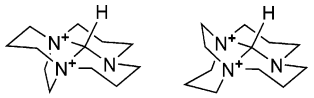


R= CH_2CH_2OTf (A) or $CH_2CH_2CH_2OTf$ (B)

reaction pathway following the first alkylation of 1,5,9-triazatricyclo[7.3.1.0]-tridecane. When R = CH_2CH_2OTf, the intramolecular ring closure is faster than the C−N breakage (case A in Scheme 2). However in the case of R = CH_2-CH_2CH_2OTf, the C−N bond breaks before the intramolecular alkylation can occur (case B in Scheme 2). As a consequence, the positive charge on the N−C−N acts as a protecting group, leading to a highly selective intermolecular dialkylation. Having an ethylene instead of a propylene linker changes the reaction from an inter- to an intramolecular pathway. The linker length within a dialkylating reagent seems to be crucial for the different reactivity observed.

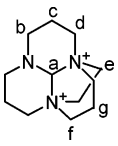
The dication of **2** can exist as two isomers that are not interconvertible without breaking a bond (Scheme 3). NMR

Scheme 3



integrals were used to determine the ratio between the two isomers, which was found to be 10:1. DFT calculations, at the mPW1PW91/6-31G(d) level of theory,[11] showed that **2a** was 4.6 kcal/mol lower in energy than **2b** (Scheme 3). The energetically more favored isomer **2a** has the propylene bridge across the two quaternary nitrogen atoms in an equatorial position and the ethylene bridge in the axial position. For **2b**, the substitution patterns are exactly opposite. The DFT calculations were further used to predict the ^{13}C NMR spectra for both isomers **2a** and **2b**.[12] The calculated ^{13}C NMR shifts were agreeing well with the experimental values (Table 1). The differences between the

Table 1. Experimental and Calculated ^{13}C NMR Shifts of Isomers **2a** and **2b** (See Supporting Information for Further Details)



	exptl		calcd		Δ exptl	Δ calcd
C atom	**2a**	**2b**	**2a**	**2b**	**2a,2b**	**2a,2b**
a	102.76	96.82	107.70	100.72	5.94	6.98
b	50.42	52.03	54.20	55.41	−1.61	−1.21
c	20.13	20.39	24.43	24.77	−0.26	−0.34
d	54.07	52.43	65.85	68.51	1.64	−2.66
e	60.61	63.47	57.37	60.82	−2.86	−3.45
f	64.17	57.92	67.05	55.71	6.25	11.34
g	18.48	18.11	22.93	22.67	0.37	0.26

two isomers for the experimental and calculated shifts respectively were coinciding even better. The main isomer of compound **2** crystallized by vapor diffusion of cyclohexane into a solution of **2** in ethanol (see Figure 1 and Supporting Information for further details).

As a consequence, a new synthetic pathway had to be found to obtain 1,2-bis(1,5,9-triazacyclododecyl)ethane. In a first attempt, $BrCH_2CH_2Br$ was used. However no reaction was observed, even when adding two equivalents of potassium iodide. Thus, a more reactive alkylating agent was chosen. Oxalyl chloride seemed the most appropriate due to the formation of two amides, which would reduce the possibility of an intramolecular bisalkylation. If R is an acyl

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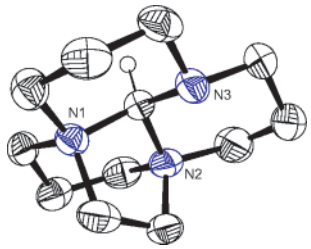
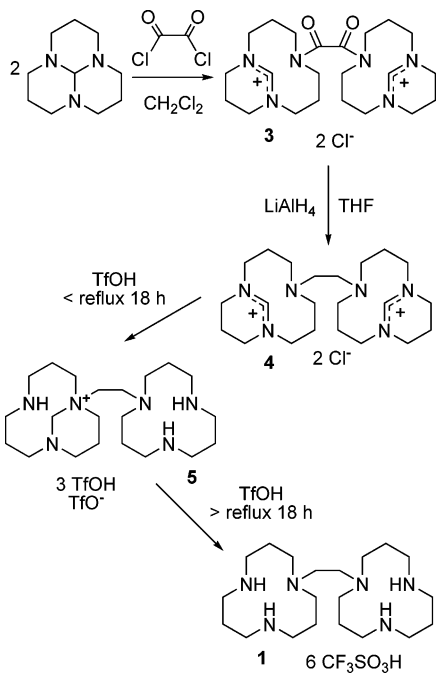


Figure 1. ORTEP presentation of the dication of **2** (ellipsoids drawn at 50% probability; most H atoms and the two triflate anions were omitted for clarity).

group (Scheme 2), the amide nitrogen would strongly prefer an sp^2 hybridization (B) rather than the sp^3 one (A). This synthetic strategy turned out to be successful:[13]

1,5,9-Triaza-tricyclo[7.3.1.0]tridecane[14] was first reacted with oxalyl chloride; thus, both rings were now linked by a diamide (see Scheme 4) which had to be reduced in order

Scheme 4



to further proceed with the normal synthetic path. The amides were reduced with $LiAlH_4$ to yield the corresponding amines (Scheme 4). Without further purification, compound **4** was then refluxed in triflic acid to form the hexaprotonated ligand **1** in a total yield of 43% based on the starting material 1,5,9-triaza- tricyclo[7.3.1.0]tridecane (Scheme 4). An interesting behavior was observed in this final reaction step. When compound **4** was refluxed for less than 18 h in triflic acid, an intermediate could be isolated (**5**). Only one of the two rings was fully hydrolyzed in this intermediate, whereas the other ring presented new features. The middle carbon had reorganized and now was linked to the former amide nitrogen to give a quaternary ammonium cation and leave a secondary amine in that ring (Scheme 4). It seems that even under these acidic conditions a preferential rearrangement of the central carbon atom to the most basic tertiary amine can take place. Suitable crystals for X-ray analysis could be grown by vapor diffusion of cyclohexane into ethanol for compound **5** (see Figure 2 and Supporting Information) and by vapor diffusion

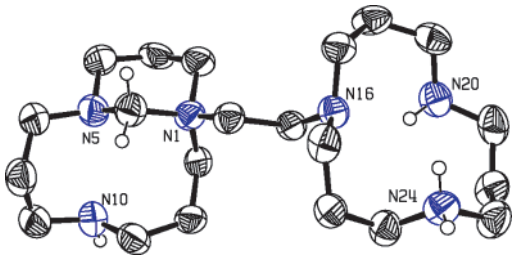


Figure 2. ORTEP presentation of compound **5**. (Ellipsoids drawn at 50% probability; hydrogen atoms, one methanol molecule, and four triflate groups were omitted for clarity).

of diethylether into ethanol for ligand **1** (see Supporting Information).

A highly efficient and selective synthetic route to the bis-(azamacrocycle) **1** has been reported. All reaction steps were very high yielding without the need for chromatographic purifications or any kind of protecting group. In addition, the interesting double ammonium salt **2** has been fully analyzed. This compound can exist in two noninterconvertible isomers, which could be identified by NMR. Its characterization allowed studying the influence of the linker length within bis(alkylating) reagents upon the second alkylation. Finally an unusual rearrangement during acidic hydrolysis could be observed. In both cases, crystal structures were essential in revealing reaction intermediates.

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Supporting Information Available: All experimental details and analyses, an ORTEP presentation of **1**, crystallographic data and CIF files for the crystal structures of **1**, **2**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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