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Characterization and Application of a New Diprotected Cyclam : a Novel Two-Step Synthesis of Linked Tetraazamacrocycles

Bernard Boitrel, Bruno Andrioletti, Mohammed Lachkar, Roger Guilard*

Laboratoire de Synthèse et d'Electrosynthèse Organométalliques
Unité de Recherches Associée au CNRS, 6, Boulevard Gabriel, 21100 - Dijon, France.

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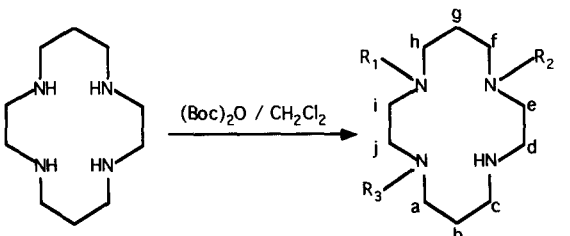
Abstract *:* The synthesis and separation of the 1,8-di-(tertbutyloxycarbonyl) cyclam (1,8-diboc cyclam) among other isomers allow the facile obtention of singly or doubly linked, and bridged tetraazamacrocycles within a two-step synthesis in a very convenient way. This strategy can be applied to a large scale preparation of several types of dioxygen carriers or activators.

In a previous communication, [1] we have described a model of cytochrome *C* oxidase prepared by reacting the 1,8-ditosyl cyclam (initially reported by Parker *et al.* [2]) with a properly functionalized porphyrin. For such a model containing amide linkages, the tosyl deprotection becomes a crucial step because the cleavage reagents [3] can induce side reactions. Curiously, the tertbutyloxycarbonyl group (Boc), widely used for the selective protection of amino functions (polyamines, amino-acids, peptidic chains...), has never been employed in the cyclam series. Only some precursors of cyclam derivatives have been synthesized using this protective group. [4-6] Here, we report the preparation of various diprotected cyclams by the Boc group, their NMR characterization, and one of the possible applications of the 1,8-diboc cyclam in a rapid and convenient synthesis of a bridged cyclam. The same synthesis also leads to a bis-macrocycle and a macrotricycle, analogs of those described in aza-crown ethers series [7,8] for which no protection is requested.

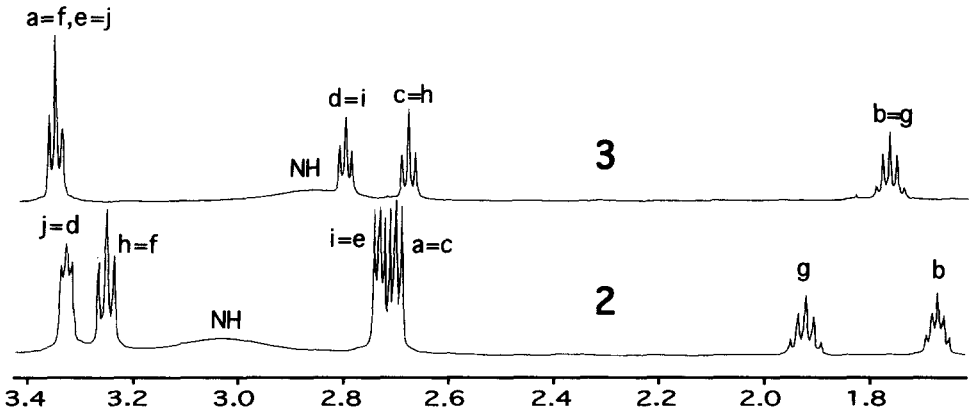
Scheme 1 : Protection of the cyclam by the Boc group.



1	$R_1=R_2=R_3=Boc$		(19.2%)
2	$R_1=R_2=Boc$	$R_3=H$	(38.8%)
3	$R_2=R_3=Boc$	$R_1=H$	(25.2%)
4	$R_1=R_3=Boc$	$R_2=H$	(0%)

By reaction of 1.8 equivalents of ditertbutyl dicarbonate with one equivalent of cyclam, a mixture of four products was obtained. The most polar was the starting material and was recovered by precipitation in diethylic ether (about 15%); the resulting filtrate was purified by flash chromatography on 15 μm silica gel. Three compounds were then eluted with increasing amounts of methanol in methylene chloride and their ^1H NMR spectra recorded. The tris-*t*-butyl carbamate **1**,[9] obviously characterized by the integration of the Boc resonance, is the less polar, then the compounds **2** and **3** [10] were collected. Among the three possible isomers, the "cis" diprotected cyclam **2** exhibits two quintuplets (2 x 2H) for the $-CH_2-$ b and g (figure 1, lower trace) whereas the isomers **3** and **4** should both exhibit one quintuplet (4H). Their structure can be established considering the signals of the protons e, d, i and j. In the case of **3**, one should observe two triplets due to e and j which are magnetically different of d and i (figure 1, upper trace); in the case of the non-isolated compound **4**, the protons i and e are expected magnetically equivalent to j and d respectively giving two singlets. The definitive assignments of the two quintuplets at 1.65 and 1.9 ppm for the dicarbamate **2** cannot be performed only by considering the electronic effects. However, the existence of a cross peak on the NOESY map of **2** between the Boc signal and the triplet of $-CH_2-$ (i=e) allowed us to assign the triplet and the two different quintuplets using the COSY map.

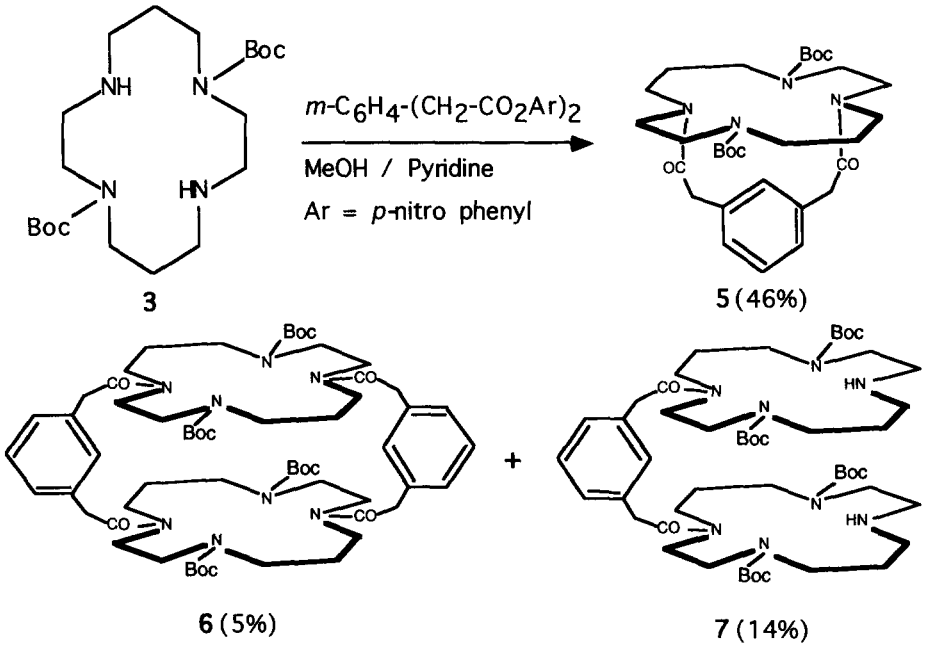
Figure 1 : Methylenic ^1H NMR domain of compounds **2** and **3** at 50°C ($CDCl_3$, 500MHz, scale in ppm).



The desired isomer **3** was then used in a condensation reaction with a diester linker (scheme 2). Three compounds resulting from different arrangements of the two building blocks were obtained when the reaction mixture of the diester and **3** was refluxed overnight in methanol. After cooling, the solution was evaporated and purified by flash silica gel chromatography. Finally, the macrobicycle **5** [11] (46%) and the macrotricycle **6** [12] (5%) were obtained by a simple reaction in which neither high dilution nor special care concerning the dryness of the solvents were required. It is worthy to note that the bis-macrocycle **7** [13] could be converted into **6** by a second coupling reaction with the same diester. At this step, a different spacer group could also be reacted with **7** to lead to an unsymmetrical macrotricycle.

The FAB mass spectra of **5** and **6** reveal the association of one molecule of methanol (M+1+32) whereas only the M+1 signal is observed in the case of **7**. Although the face-to-face conformation for **7** is not probable, the "cage" structure [14] of **5** and **6** is predictible and may explain this association. We plan to apply the properties of these macrocycles to coordinate various metal ions for different purposes.

Scheme 2 : Two-step synthesis of bridged cyclams.



- For clarity reasons, the bis-macrocycle **7** is drawn in a cofacial conformation, which is certainly not representative of its real conformation in solution.
- The cofacial macrotricycle **6** exists formally as a mixture of two isomers.

In this work, we have been able to demonstrate that it is possible to isolate and characterize different isomers of the cyclam protected by the Boc group. In contrast to the tosyl method, the latter one should allow the preparation of macrocycles containing amide bonds, either directly bonded to the macrocycle or in some appended groups. Indeed, no preliminary reduction is necessary before the deprotection step. Furthermore, the two macropolycycles **5** and **6** have been easily synthesized from the 1,8-diboc cyclam, in a convenient one-pot reaction. The tuning of the distance between the two cyclams in model **6** and their relative orientation can be achieved by a judicious variation of the linker. In the case of **5**, a coordinating ligand can replace the *m*-C_6H_4-(CH_2-CO)$_2$- unit to stabilize a coordinated metal. The shortness of this synthesis scheme is particularly advantageous compared to previous methods; work is in progress to extend this strategy for the preparation of other azacycles or unsymmetrical bimacrocycles.

Acknowledgments

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9 1,5,8-tris-(tertbutyloxycarbonyl) cyclam **1**: δ_H ($CDCl_3$, 323K) : 1.74 (2H, quint, 5.5); 1.96 (2H, quint, 6.5); 2.66 (2H, t, 5.5); 2.82 (2H, t, 5.5); 3.33 (4H, mult); 3.34 (2H, mult); 3.37 (2H, mult); 3.43 (4H; mult).

10 1,5-bis-(tertbutyloxycarbonyl) cyclam **2**: δ_H ($CDCl_3$, 323K) : 1.73 (2H, quint, 6); 1.92 (2H, quint, 7.5); 2.69 (4H, t, 5.5); 2.79 (4H, t, 5), 3.29 (4H, t, 7.5); 3.36 (4H, t, 5).
1,8-bis-(tertbutyloxycarbonyl) cyclam **3**: δ_H ($CDCl_3$, 323K) : 1.76 (4H, quint, 6.5); 2.67 (4H, t, 6.5); 2.79 (4H, t, 5.5); 3.33 (8H, t, 6.5).

11 macrobicycle **5**: δ_H ($C_6D_5CD_3$, 373K) : 1.66 (18H, mult); 2.09 (2H, quint); 2.55 (2H, sing); 2.71 (2H, sing); 3.31 (4H, mult); 3.46 (2H, mult); 3.60 (MeOH signal); 3.84 (2H, mult); 7.3 (mult); 7.5 (mult) ; Found: C. 63.45: H. 8.69: N. 8.91. $C_{30}H_{46}N_4O_6$, 1 MeOH requires C. 63.02: H. 8.53: N. 9.48.

12 macrotricycle **6**: Found: C. 62.04 H. 8.47: N. 8.44. $C_{60}H_{92}N_8O_{12}$, 3 MeOH requires C. 62.35: H. 8.63: N. 9.23.

13 bis-macrocycle **7**: Found: C. 62.75: H. 9.17: N. 10.52. $C_{50}H_{86}N_8O_{10}$ requires C. 62.60: H. 9.04: N. 11.17.

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