Tetrahedron Letters 52 (2011) 136–138

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of a new calix[*n*]pyrrole: meso-pentaspirocyclohexyl calix[5]pyrrole

Mercedes Bedolla-Medrano, Luis Chacón-García *, Claudia A. Contreras-Celedón, Jesús Campos-García

Laboratorio de Diseño Molecular, Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Edificio B-1 Ciudad Universitaria, Morelia, Michoacán C.P. 58030, Mexico

ARTICLE INFO

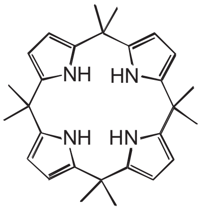
Article history:
Received 7 July 2010
Revised 31 October 2010
Accepted 1 November 2010
Available online 5 November 2010

Keywords:
Supramolecular chemistry
Calixpyrrols
Bismuth nitrate
Anion binding

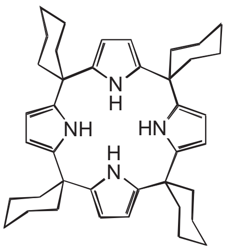
ABSTRACT

We describe the first synthesis of the novel meso-pentaspirocyclohexyl calix[5]pyrrole **2b**. Anion–guest properties of the new compound were evaluated with respect to fluoride, chloride, and bromide tetrabutylammonium salts by ^{1}H NMR titration techniques in deuterated dichloromethane at 22 °C by following the induced shifts in the NH resonances upon complexation.

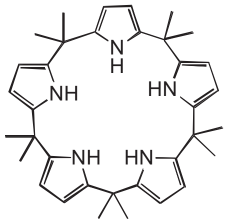
Calix[*n*]pyrroles are oligopyrrolic macrocycles produced by the condensation of a pyrrole and a ketone (*n* represents the number of pyrrole units in the molecule).[1,2] The reaction is traditionally catalyzed by a variety of protic acids, although in recent years Lewis acids have been successfully introduced in the synthesis of these compounds.[3,4] These macrocycles are of interest for their ability to recognize anions, cations, and neutral species. To date, they continue to provide fertile grounds for research in the area of supramolecular chemistry.[1] Typical and widely studied examples are compounds **1a** and **1b**.



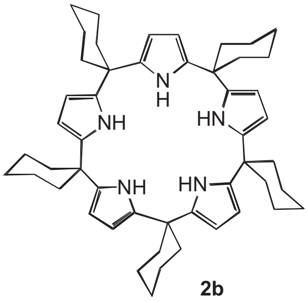
1a



1b



2a



2b

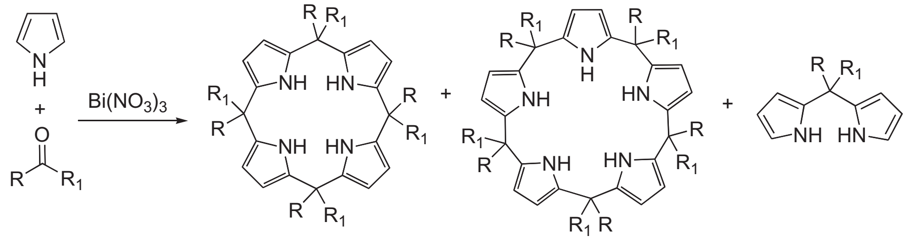
The synthesis and anion recognition properties of calix[4]pyrroles have been widely studied. However, the synthesis of the expanded calix[5]pyrroles is relatively new, with only two reported examples of the 'free' macrocycle (the β-difluoro substituted cycle and **2a**, the β-unsubstituted meso-decamethyl derivative).[5,6] As a consequence, the study of their anion binding potentials has been limited. The difficulty in obtaining calix[5]pyrroles may be due to the ease with which a pyrrole-isopropyl fragment can be lost to give the more stable four-membered analog calix[4]pyrrole. The problem of macrocycle contraction has been previously reported to be partially solved by the condensation of the less reactive 3,4-difluoropyrrole with acetone to give the β-fluorosubstituted meso-decamethylcalix[5]pyrrole.[5] Compound **1a** was captured after a three-step synthesis via conversion of the corresponding β-unsubstituted meso-decamethylcalix[5]furane into the corresponding calix[5]pyrrole **2a** by an opening process of the five-membered heterocycle. This process involved the selective reduction of the double bond and a Paal–Knorr condensation with ammonium acetate in 1% yield.[6]

---

* Corresponding author. Tel.: +52 443 326 5790; fax: +52 443 326 5788.
E-mail address: lchacon@umich.mx (L. Chacón-García).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.11.007

Table 1
Pyrrole conversion (%) and relative proportions of **1**, **2**, and **3**, as detected in the ^{1}H NMR of the crude reaction



1
a; R,R$_1$ = -CH$_3$
b; R,R$_1$ = -(CH$_2$)$_5$-
c; R,R$_1$ = -(CH$_2$)$_4$-
d; R = R$_1$ = -CH$_2$CH$_3$

2
a; R,R$_1$ = -CH$_3$
b; R,R$_1$ = -(CH$_2$)$_5$-
c; R,R$_1$ = -(CH$_2$)$_4$-
d; R = R$_1$ = -CH$_2$CH$_3$

3
a; R,R$_1$ = -CH$_3$
b; R,R$_1$ = -(CH$_2$)$_5$-
c; R,R$_1$ = -(CH$_2$)$_4$-
d; R = R$_1$ = -CH$_2$CH$_3$

Entry	R, R$_1$	Bi(NO$_3$)$_3$ (mol %)	Time (h)	1	2	3	Others	Pyrrole conversion (%)
1	–(CH$_2$)$_5$–	25	2	>99	–	–	<1	100
2	–(CH$_2$)$_5$–	1.2	2	53	46	–	<1	100
3	–(CH$_2$)$_5$–	0.6	2	30	70	–	–	100
4	–(CH$_2$)$_5$–	0.3	2	27	60	–	13	87
5	–(CH$_2$)$_4$–	0.6	2	39	–	8	27	61
6	–(CH$_2$)$_4$–	0.6	24	–	–	99	<1	9
7	–CH$_2$–CH$_3$	0.6	2	–	–	–	–	0
8	–CH$_2$–CH$_3$	0.6	4	31	–	19	45	95

We reported the synthesis of calix[4]pyrroles by the direct condensation of open or cyclic ketones with pyrrole catalyzed by bismuth nitrate, with yields that ranged from moderate to good. This work used a Lewis acid instead of a protic acid.[3] Extension of the study to other Lewis acids, such as Al, Mg, Cu, Zn, or other bismuth salts, such as iodide, chloride, phosphate, or triflate, demonstrated that low catalyst concentrations of the bismuth salts produced the calix[5]pyrrole, as detected by NMR, in the crude reaction mixture. Compound **2a** proved to be relatively stable and was isolated by HPLC with 20% yield.[7]

The synthesis of **2a** permitted to carry out initial investigations of the host–guest chemistry of the unsubstituted calix[5]pyrrole. Additionally, Kohnke and co-workers compared this compound with its analogs, calix[4] and calix[6]pyrroles,[8] in terms of their affinities toward chloride and fluoride by titrations followed by ^{1}H NMR in CD$_2$Cl$_2$ at 22 °C. Contrary to the expectations, **2a** exhibited a poor affinity for chloride ($K_a = 35\ M^{-1}$) when competing with **1a** ($K_a = 350\ M^{-1}$). Unfortunately, the association constant K_a of **2a** for fluoride in dry CD$_2$Cl$_2$ could not be accurately determined, although a saturated solution of D$_2$O showed less affinity for the anion than **1a** under the same conditions.[6]

Research in the field of expanded calix[n]pyrroles ($n > 4$), particularly with respect to their practical applications (i.e., effective and selective anion and neutral binding agents), is severely limited because the direct synthesis of these larger macrocycles from pyrrole and ketones is hampered by the predominant formation of cyclic tetramers. Hence, a synthetic method for the preparation of β-unsubstituted calix[5]pyrrole (one of the most elusive members of this family of compounds) is of considerable interest in the area of supramolecular chemistry. In this context, we extended the study of the condensation of acetone with pyrrole catalyzed by Bi(NO$_3$)$_3$, which yielded **2a**,[7] with the aim of obtaining β-unsubstituted calix[5]pyrroles derived from ketones other than acetone, and of studying the anion–guest properties of this molecule. In this Letter, we describe the first synthesis of the novel meso-pentaspirocyclohexyl calix[5]pyrrole **2b** and its anion–guest affinity toward fluoride, chloride, and bromide anions in CD$_2$Cl$_2$.

The condensation of pyrrole with an excess of cyclohexanone in the presence of 0.6 mol % Bi(NO$_3$)$_3$ as a catalyst at room temperature gave, after 2 h, the best conditions for obtaining **2b** with 100% conversion of pyrrole and a ratio of **1b**:**2b** of 30:70, as detected by ^{1}H NMR. It is noteworthy that the proton signals belonging to **1b** and **2b** were clearly distinguished by ^{1}H NMR by the beta protons of the pyrrole, at 5.89 and at 5.79 ppm, respectively. When the catalyst concentration was increased, the **1b**:**2b** ratio decreased to yield only **1b** for 25 mol % catalyst used. However, if less than 0.3 mol % catalyst were used, the pyrrole was not converted and a poor yield of the calixpyrroles was observed. Compound **2b** showed decomposition after column chromatography (SiO$_2$), and only calix[4]pyrrole was recovered. Purification was possible by washing the solid with ethyl ether, followed by acetone and dissolved in dichloromethane. It should be noted that ethyl ether was strongly trapped by the macrocycle, and it was not possible to remove it under high vacuum; therefore, the dissolution of dichloromethane was absolutely necessary. After purification, compound **2b** was obtained with 28% yield. This new compound was characterized by ^{1}H and ^{13}C NMR spectroscopy and by low resolution and high resolution mass spectrometry (LRMS and HRMS, respectively).[9]

The condensation of the pyrrole and cyclopentanone resulted in the formation of **1c**, **3c**, and other products after 2 and 24 h of reaction. The possibility that calix[5]pyrrole was present was not ruled out, but it was not isolated because purification attempts yielded only **1c** and **3c**. Reaction with 3-pentanone (Table 1, entries 7 and 8) gave only **1d** and **3d** with low pyrrole conversion after 4 h reaction time, which produced the 'best' conditions. The results, summarized in Table 1, correlated with the yields obtained under the conditions used to obtain compounds **1a**–**d** (Bi(NO$_3$)$_3$, 25 mol %), in which the relative yields were **1b** > **1a** > **1c** $\gg$ **1d** after 0.5, 5, 5, and 120 h, respectively.[3] These yields indicated that steric restrictions governed the yields of both macrocycles.

In an attempt to explore alternative green synthetic methods, the reaction was attempted under microwave radiation. The best conditions for the reaction of pyrrole with cyclohexanone were identified as 120 W irradiation at 40 °C to give **1b** and **2b** after 10 min reaction, although several impurities were obtained which were difficult to eliminate. The reaction with acetone gave mainly **1a** and **3a**, and the reaction with 2-pentanone gave only **3d**.

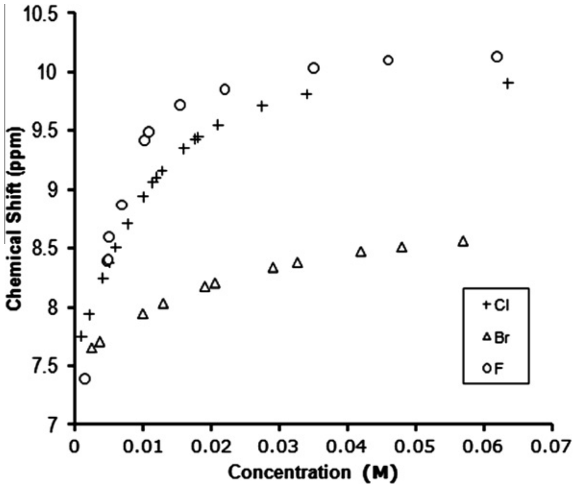


Figure 1. ^{1}H NMR titration plot of calix[5]pyrrole NH resonance upon addition of tetrabutylammonium fluoride, chloride, or bromide in dichloromethane-d_2 at 298 K.

Table 2
Comparison of anion stability constants (M^{-1}) for **1a**, **1b**, **2a**, and **2b** determined in deuterated dichloromethane anhydrous at 298 K[12,13]

Anion	1a	1b	2a	2b
F^-	17,170	3600	1400[14]	1130
Cl^-	350	117	35	225
Br^-	10	N.D.	N.D.	61

Anion–guest properties of **2b** were evaluated with respect to fluoride, chloride, and bromide tetrabutylammonium salts by ^{1}H NMR titration techniques in deuterated dichloromethane at 298 K by following the induced shifts in the NH resonances upon complexation.[10] Upon addition of the anions, a maximum NH proton shift was observed at 10.1 ppm for the fluoride, 9.9 ppm for the chloride, and 8.5 ppm for the bromide. Titration plots are shown in Figure 1.

Association constants (K_as) were obtained by assuming a 1:1 anion binding model using the WinEQNMR least-squares fitting program.[11] Table 2 shows the binding constants for the novel calix[5]pyrrole. Also included in Table 2 are the previously reported fluoride, chloride, and bromide anion affinities for the analogous calix[4] and calix[5]pyrroles **1a**, **1b**, and **2a**.

The results presented in Table 2 reveal that **2b** behaved similarly to **2a** in the sense that both compounds showed lower affinity toward anions than the corresponding calix[4]pyrrole compounds. However, the relative preference for the fluoride anion was maintained.

Our work demonstrated that **2b** could be synthesized by direct condensation. Although the affinity constants were low toward F, Cl, and Br, it may be interesting to probe other anions, such as the organic salts, which could interact with the extended cavity and improve the anion affinity through chemical modification of the macrocycle.

Acknowledgment

We thank CIC-UMSNH for financial support.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectroscopy, HPLC and LR-MS of compound **2b** and titration curves) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.007.

References and notes

1. Gale, P. A.; Sessler, J. L.; Kral, V. *Chem. Commun.* **1998**, 1–8.
2. Gale, P. A.; Anzenbacher, P.; Sessler, J. L. *Coord. Chem. Rev.* **2001**, *222*, 57–110.
3. Mejía-Farfán, I.; Contreras-Celedón, C.; Avina-Verduzco, J.; Chacón-García, L. *Lett. Org. Chem.* **2008**, *5*, 237–239.
4. Kumar, A.; Ahmad, I.; Rao, M. S. *Can. J. Chem.* **2008**, *86*, 899–902.
5. Sessler, J. L.; Anzenbacher, P., Jr.; Shriver, J. A.; Jursikova, K.; Lynch, V. M.; Marquez, M. *J. Am. Chem. Soc.* **2000**, *122*, 12061–12062.
6. Cafeo, G.; Kohnke, F. H.; Parisi, M. F.; Nascone, R. P.; La Torre, G. L.; Williams, D. J. *Org. Lett.* **2002**, *4*, 2695–2697.
7. Chacón-García, L.; Chávez, L.; Cacho, D. R.; Altamirano-Hernández, J. *Beilstein J. Org. Chem.* **2009**, *5*, 2.
8. Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1496–1498.
9. 1.29×10^{-2} mol of distilled pyrrole were mixed with 1.93×10^{-1} mol of cyclohexanone, and later 8.29×10^{-2} mol of pulverized bismuth nitrate were added. The mixture was stirred at room temperature during two hours and then neutralized with distilled water. The organic layer was washed with distilled water (4×15 ml) and dried with anhydrous sodium sulfate, filtered, and dried with vacuum. The solid was washed with cold ethylic ether (10×6 ml) obtaining a light brown precipitate, which was filtered and left to dry. The resulting material was washed out with 25 ml of acetone; when dried, it was dissolved in 10 ml of dichloromethane, which was evaporated with vacuum at room temperature. The final yield of pentaspirocyclohexyl calix[5]pyrrole **2b** was 28% of a light brown solid that in TLC can be identified with a $R_f = 0.37$ using a system hexane/ethyl acetate (95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (br s, 5H, NH), 5.80 (d, 10H, $J = 3.2$ Hz, CH), 1.86 (br s, 20H, CH_2), 1.43 (br s, 30H, CH_2), ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4 (β-C pyrrole), 104.3 (α-C pyrrole), 40.4 ($C(C_6H_{10})$), 37.6 (CH_2), 26.1 (CH_2), 23.1 (CH_2). LR-MS (EI): *m*/*z* (rel int.): 736 ([M+1]+, 3), 589 (45), 588 (62), 220 (100). HR-MS (EI): obsd 735.5251 (calcd for $C_{50}H_{65}N_5$, 735.5240).
10. Solutions 0.01 M of **2b** in CD_2Cl_2 anhydrous were prepared and mixed with various equivalents of tetrabutylammonium salts (F^-, Cl^-, Br^-). The respective chemical shifts were determined by ^{1}H NMR (400 MHz). The data obtained were corrected by the least-squares non linear fitting method and introduced to WinEQNMR to calculate the affinity constants reported. (For further details see Supplementary data).
11. Hynes, M. *J. Chem. Soc., Dalton Trans.* **1993**, 311–312. We thank Professor M. J. Hynes for providing us with the updated version of EQNMR for Windows..
12. Gale, P. A.; Sessler, J. L.; Kŕal, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141.
13. K_as for **1b** were measured in CD_2Cl_2 saturated with water as described in Ref. 6.
14. Measured in dichloromethane-d_2 saturated with D_2O 0.18% v/v.