3846 J. Org. Chem. 2000, 65, 3846−3849

Notes

On the Conformational Properties of [*n*]Cyclophanes. A New Application of the Ramachandran Plot Using Crystallographic Data

Frederik C. Krebs* and Mikkel Jørgensen

Condensed Matter Physics and Chemistry Department,
Materials Chemistry, RISØ National Laboratory,
P.O. Box 49, DK-4000 Roskilde, Denmark

Received February 7, 2000

Introduction

In the past 30 years, the area of organic chemistry pertaining to [*n*]cyclophanes has become extremely popular initially due to the work by Gutsche[1,2] but also because these molecules have shown promise as molecular sensors, molecular receptors, synthetic enzymes, and much more as shown by many important contributions by different groups[3−11] to mention only a few. One result is that a vast amount of synthetic and characterization work has been done on these molecules. Of interest here is the considerable number of crystal structures that have been solved for all these molecules, thus allowing for a statistical analysis. The most well studied [*n*]cyclophane (in a crystallographic sense) is by far the calix[4]arenes with more than 313 structures known. Following these, the resorcin[4]arenes and the cyclotriveratrylenes can be found with 50 and 23 structures known, respectively. Far less represented are the calix[5]-, calix[6]-, and calix[8]arenes.

The Ramachandran plot[12] is a very powerful way of correlating the conformational behavior of molecules provided that the conformation of the individual molecule or parts thereof can be given uniquely by two torsion angles or by sets of two torsion angles. The way the plot is presented is simply by plotting the two distinct torsion angles against each other.

In this paper, we present a conformational analysis of particularly the calix[4]arenes based on the presentation of crystallographic data in a Ramachandran-type plot and the relation to the unconstrained diphenylmethane system. A comparison with the other known [*n*]cyclophanes is also provided.

Experimental Section

Crystallographic information was retrieved from the CSD[13] for different search patterns corresponding to each of the macrocycles included in this study. The torsion angles defined in Figure 1 along with the search pattern were retrieved and tabulated for each of the series. Table 1 presents the number of structures retrieved for each series. Typical torsion angles for tetramethoxycalix[4]arene have been calculated using the program *InsightII*[14] and are presented in Table 2. This is in analogy with an earlier symbolic representation using only the sign of the torsion angle for calix[*n*]arenes.[15]

Results and Discussion

The most studied macrocycles are, as mentioned, the calix[4]arenes, and emphasis is therefore going to be on these molecules. This led us to consider a detailed study perhaps enabling the further distinction of different known conformers of the calix[4]arenes by organizing the large amount of information in a Ramachandran plot. The different conformers known for calix[4]arene are shown in Figure 2. Furthermore, the distinction between different phenol/aldehyde based macrocycles could be envisaged. While the computed conformational distribution had been studied earlier by van Hoorn et al.[16] the typical torsion angles for the different conformers of the calix[4]arene skeleton have to our knowledge not been presented anywhere and are for the purpose of this paper included (see Table 2). A Ramachandran plot of all the calix[4]arenes is presented in Figure 3. Each calix[4]arene as retrieved from the CSD gives rise to four sets of torsion angles, and therefore, four points appear for each on the plot. Visual inspection of Figure 3 reveals some symmetry. To make proper use of the plot, it is important to understand why this apparent symmetry emerges. In principle, the entire Ramachandran plot (the entire angular space) is unique provided that the absolute configuration is known and that the type of torsion angle (Φ or Ψ) is known. This is indeed the case for amino acids where nature has provided the absolute configuration, distinct and alternating torsion angles along the polypeptide chain which is directional (i.e., has two distinct ends, C-terminus and N-terminus). In the case of calix[4]arenes, this is not the case and there is some ambiguity

---

[1] Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; Royal Society of Chemistry: Cambridge, 1989.

[2] Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1999.

[3] Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713−1734.

[4] Vicens, J.; Böhmer, V. *Calixarenes, a versatile class of macrocyclic compounds*; Kluwer Academic Publishers: The Netherlands, 1991.

[5] Atwood, J. L.; Koutsantonis, G. A.; Raston, C. L. *Nature* **1994**, *368*, 229.

[6] Diamond, D.; McKervey, M. A. *Chem. Soc. Rev.* **1996**, 15−24.

[7] Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454−1457.

[8] Prins, L. J.; Huskens, J.; De Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498−502.

[9] Asfari, Z.; Harrowfield, J. M.; Ogden, M. I.; Vicens, J.; White, A. H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 854−856.

[10] Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403−12407.

[11] Danil de Namor, A. F.; Cleverley, R. M.; Zapata-Ormachea, M. L. *Chem. Rev.* **1998**, *98*, 2495−2525.

[12] Ramachandran, G. N.; Sasisekharan, V. *Adv. Protein Chem.* **1968**, *23*, 283−438.

[13] CSD, October release V5.16 1998. Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

[14] Computational results obtained using software programs from Molecular Simulations using the CFF91 force field.

[15] Ugozzoli, F.; Andreetti, G. D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 337−348.

[16] van Hoorn, W. P.; Briels, W. J.; van Duynhoven, J. P. M.; van Weggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1998**, *63*, 1299−1308.

10.1021/jo000166i CCC: $19.00

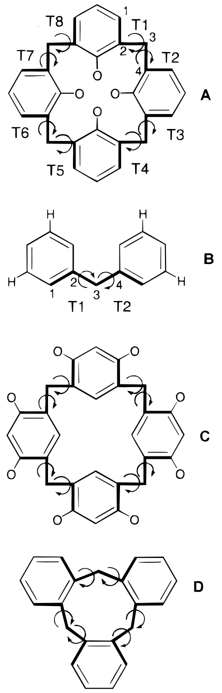

Figure 1. Search patterns used for the different searches along with a definition of the torsion angle pairs retrieved from each search. (A) The two hydrogen atoms for each methylene bridge of the calix[4]arene have been omitted for clarity but were included in the search fragment. Any substituent was allowed at the aromatic and phenolic positions (the higher calixarenes were defined similarly). (B) The diphenylmethane search fragment. The hydrogen atoms in the meta-positions were included to exclude the calixarenes from the search. Again the two hydrogen atoms at the methylene bridges have been omitted for clarity. (C) The resorcin[4]arene search fragment. Only one hydrogen atom was included for each methylene bridge (omitted for clarity). (D) The cyclotriveratrylene search fragment The two hydrogen atoms at each methylene bridge have been omitted for clarity.

Table 1. Number of Structures Retrieved from the CCD for Each Compound Type

compound type	no. of structures
calix[4]arenes, all	313
calix[4]arenes, cone	253
calix[4]arenes, not cone	58
calix[4]arenes, partial	25
calix[4]arenes, alkoxy cone	35
calix[5]arenes	9
calix[6]arenes	24
calix[8]arenes	26
cyclotriveratrylenes	23
resorcin[4]arenes	54
diphenylmethanes (excluding [4]cyclophanes)	458

Table 2. Torsion Angles for the Non-C_{4v} Conformers of 25,26,27,28-Tetramethoxycalix[4]arene and for the Pseudo-C_{4v} Conformer of 25,26,27,28-Tetrahydroxycalix[4]arene

torsion angle (deg)	cone	partial cone	1,3-alternate	1,2-alter nate	C_{4v}
T1	−118.08	+122.41	−125.37	+137.21	−91.13
T2	+63.49	−66.94	−126.54	+138.25	+82.89
T3	−61.65	+112.24	+125.64	−86.16	−82.95
T4	+113.50	+119.64	+125.41	+75.85	+90.93
T5	−115.13	−119.65	−125.45	−129.39	−91.13
T6	+63.77	−112.03	−125.11	−129.99	+82.89
T7	−62.10	+66.81	+125.18	+76.07	−82.95
T8	+116.62	−122.44	+125.28	−84.78	+90.93

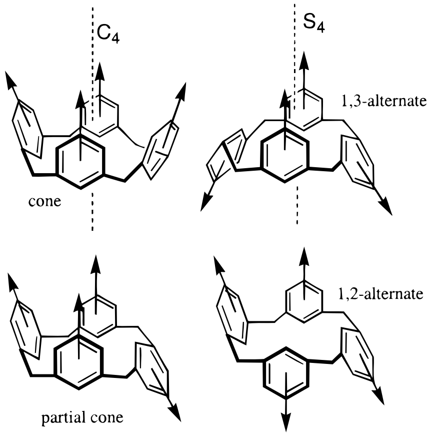

Figure 2. Structural drawings of the different conformers for the calix[4]arene system. The arrows indicate a directionality of the constituent phenyl rings. The axes denoted C_4 and S_4 represent molecular point group symmetry operators for the cone and the 1,3-alternate conformers, respectively.

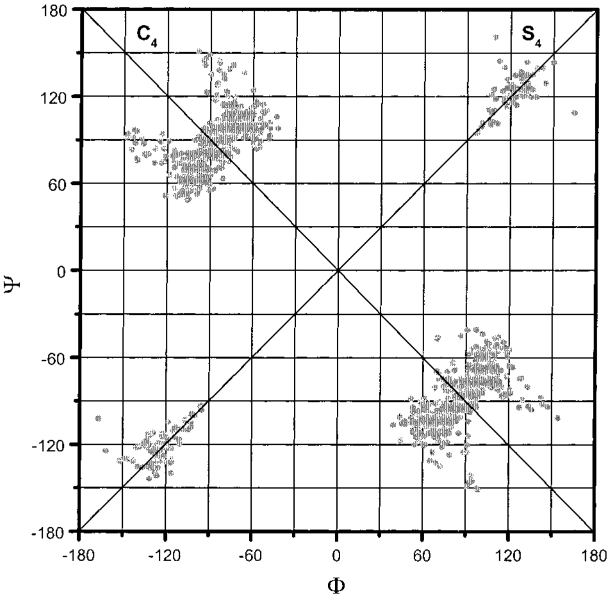

Figure 3. Ramachandran plot of all calix[4]arenes. The entire ΦΨ-space is shown and the residual symmetry is apparent. The diagonals of the plot are labeled C_4 and S_4, respectively.

which reduces the unique part of the plot to one-quarter of the angular space. To explain this it is important to acknowledge that the configuration of calixarenes retrieved from the CSD in general is not known and neither is the choice (made by the search engine) of starting torsion angle. In turn, the lack of knowledge of the absolute configuration makes the experimenter ignorant of the absolute sign of the torsion angles (but not the relative sign torsion angles between). In the plot of Figure 3, this corresponds to an inversion through the center of the plot (through $\Phi = 0$ and $\Psi = 0$). The lack of knowledge of the starting torsion angle makes the experimenter ignorant of the type of torsion angle (Φ or Ψ) since the torsion angles as defined in Figure 1 can be interconverted. Once a torsion angle has been chosen to be Φ, for instance, the others are given. In the plot of Figure 3, this corresponds to a reflection through the diagonals of the plot (labeled C_4 and S_4, respectively). From this it should be evident that the unique part of the plot is the angular space within either of the four

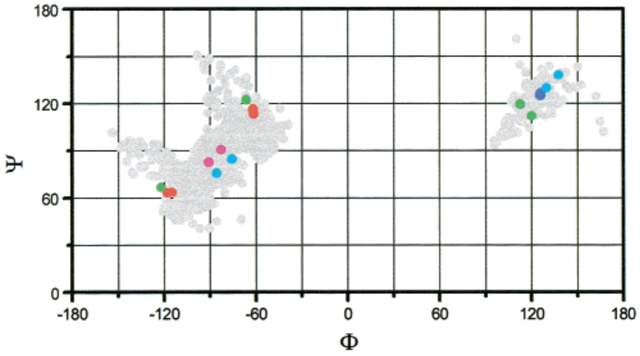

Figure 4. Reduced Ramachandran plot showing all the calix[4]arenes (gray shading) along with the calculated values of the torsion angle pairs for the different conformers (taken from Table 2) in different colors (cone = red, partial cone = green, 1,2-alternate = light blue, 1,3-alternate = blue, pseudo C_{4v} cone = pink).

triangles drawn by the diagonals on the plot. The presentation in a triangular plot is very unhandy. The most efficient way of presenting the data is by confining one of the variables, i.e., Ψ to positive values bearing in mind the residual mirror symmetry around the half C_4 and S_4 axis. Using this convention, it is now possible to plot the calculated values of the torsion angle pairs for calix[4]arenes. From Table 2 it should be clear that different conformers have different magnitudes of torsion angles but also different signs. Therefore, a distinction of the conformations of the calix[4]arenes can be made simply by plotting the values for the torsion angle pairs on the plot. It is perhaps evident that it should be this way, and it may be argued that the plot does not convey information on a given molecule that could not have been obtained by simple visual inspection of the individual molecular conformation. The plot does, however, give collective information on the general conformational behavior of calix[4]arenes and allows one to identify outliers and compare a given molecule to the typical molecule. This is analogous to the information gained from the original Ramachandran plot for proteins. In Figure 4, all calix[4]arenes are presented along with the calculated values of the different conformers. It is noteworthy that some conformers fall in one region only, namely the C_{4v} cone conformer, the C_{2v} pinched cone conformer, and the 1,3-alternate conformer, whereas two conformers fall in two regions, namely, the 1,2 alternate and the partial cone conformer. To test this hypothesis, the conformers of the calix[4]arenes were retrieved form the database in groups according to cone, alkoxycone, partial cone, and not cone conformers. The not cone conformers were the 1,2-alternate and 1,3-alternate conformations grouped together. Figure 5 presents a comparison between these four groups plotted individually. While different conformers fall in different regions of the plot, they are still confined to a small region compared to that available in the plot. This fact is inherently linked to the conformational energy of the calix[4]arene molecule, and it would in principle be possible to superimpose an energy plot on the Ramachandran plot, but only for one particular conformer at the time, making an energy plot impossible for the general Ramachandran plot of all calix[4]arenes. An indirect way to illustrate how the conformation of the calix[4]arenes is constrained is by comparing them to the in principle unconstrained diphenylmethanes. The CSD

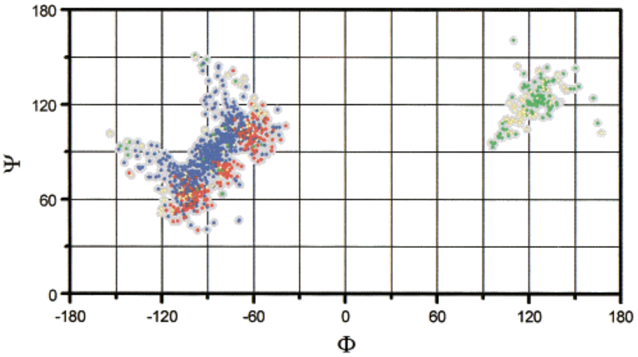

Figure 5. Reduced Ramachandran plot showing all calix[4]arenes (gray shading) along with the subsets of cone (blue), alkoxycone (red), not cone (green), and partial (yellow) as retrieved from the CCD.

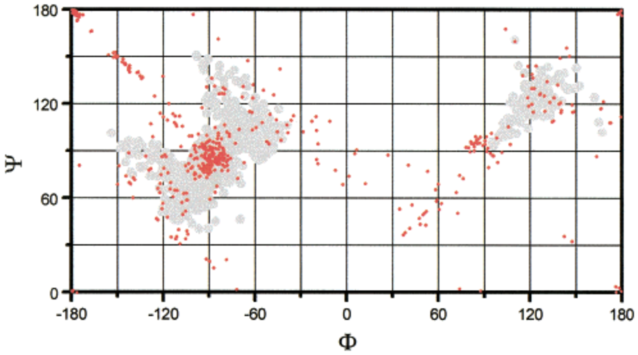

Figure 6. Comparison between the calix[4]arenes and the diphenylmethanes as retrieved from the CCD emphasizing the conformationally constrained nature of the calix[4]arenes with respect to the unconstrained diphenylmethane (it should be pointed out that some of the diphenylmethanes retrieved are substructures of otherwise constrained molecule, i.e., fluorene, dibenzopyrane, xanthone, anthrone, etc.).

was searched for all molecules containing the diphenylmethane substructure shown in Figure 1. In Figure 6, the calix[4]arenes and the diphenylmethanes are compared. From this plot, it can be seen that the diphenylmethanes are spread over a larger area of the plot, thus substantiating the idea that they have more conformational freedom. From the shape of the two distinct regions (termed domains) of the plot where the calix[4]arenes fall it can be inferred what types of conformational freedom particular conformers have. In Figure 7, the two domains have been labeled with Ξ occupying the first quadrant and Θ occupying the second quadrant. For [*n*]cyclophane torsion angle pairs for which the two phenyl rings point in opposite directions (the direction are defined in Figure 2) both torsion angles have like sign and fall in the Ξ domain. If the two phenyl rings point in the same direction, the torsion angle pairs have opposite sign and consequently fall in the Θ domain. For calix[4]arenes, this means that the 1,3-alternate conformer falls solely in the Ξ domain and cone conformers falls solely in the Θ domain. It is important to bear in mind that the partial cone and the 1,2-alternate conformers have structural features resembling both the cone and the 1,3-alternate conformation and they thus fall in both domains. Each of the domains have been divided into subregions labeled to signify distinct conformational trends. In the Ξ domain the region labeled Δ is where the 1,3-alternate conformer is typically found, whereas the region labeled Γ corre-

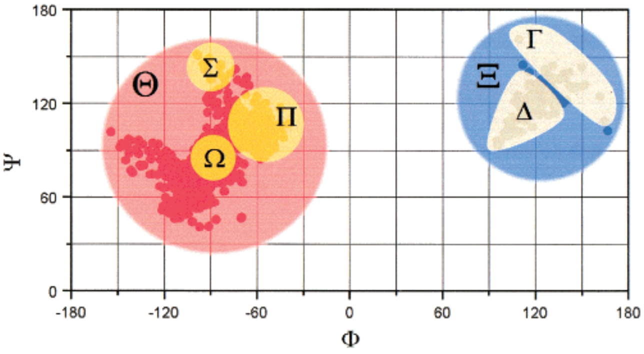

Figure 7. Schematic illustration of the two overall domains Ξ and Θ along with their subregions Δ (1,3-alternate), Γ (mainly partial), Σ (sheared pinched cone), Π (pinched cone), and Ω (C_{4v} cone) signifying conformational trends. Each subregion is shown with an inset drawing of the typical conformation of a calix[4]arene falling in that particular subregion.

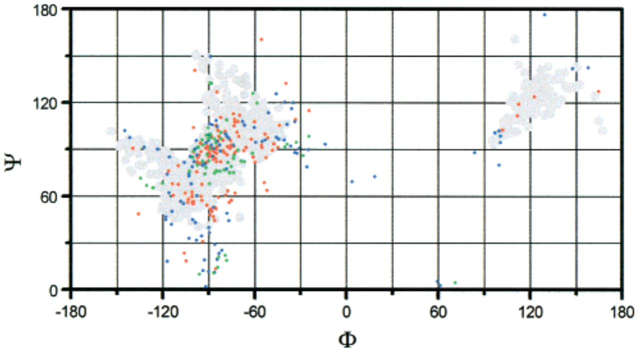

Figure 8. Comparison of the calix[4]arenes (gray) with the higher calix[*n*]arenes ($n = 5$ (red), 6 (blue), 8 (green)) as retrieved from the CCD. It is evident that the higher calix[*n*]arenes has more conformational freedom and can occupy a larger area of the plot.

sponds mainly to pinched 1,3-alternate and partial cone conformers. In the Θ domain, the region Σ thus corresponds to pinched cone conformers that have been sheared. The region Π is a relaxed pinched cone, and finally the region Ω corresponds to the C_{4v} cone conformers.

When comparing the calix[4]arenes with the higher calixarenes, the larger degree of conformational freedom becomes evident. Even though there are less data available the data for these higher calixarenes fall in a much larger area of the plot as seen in Figure 8. The extension of the analysis to the other well represented [*n*]cyclophanes (as mentioned in the beginning the cyclotriveratrylenes and the resorcin[4]arenes) yields not surprisingly that the cyclotriveratrylenes are very constrained (Figure 9) and that the resorcin[4]arenes (Figure 10) are constrained when compared to the prototypical the calix[4]arenes. The cyclotriveratrylenes fall in a very small region of the plot whereas the resorcin[4]arenes are more distributed. The present study have thus shown the use of crystallographic information to compare and contrast the conformational properties of complex macrocyclic molecules.

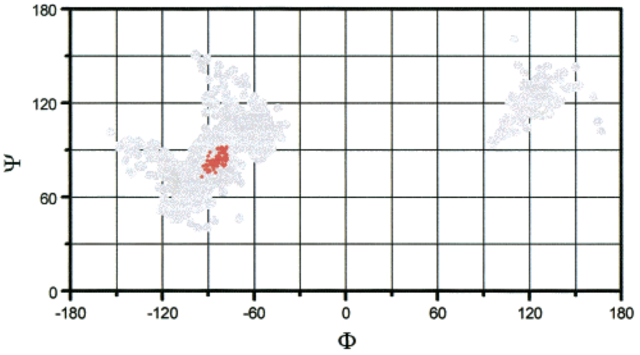

Figure 9. Comparison of the calix[4]arenes with the cyclotriveratrylenes. The cyclotriveratrylenes are much more constrained and confined to a very narrow region of the plot.

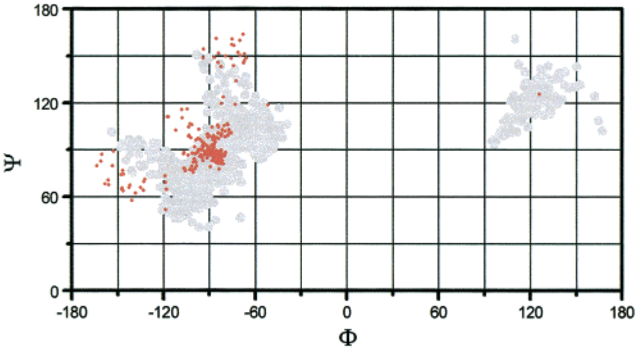

Figure 10. Comparison of the calix[4]arenes with the resorcin[4]arenes. The resorcin[4]arenes are more constrained than the calix[4]arenes and essentially found in two regions.

Acknowledgment. We deeply indebted to all the people who have made great contributions to this field enabling this study.

JO000166I