Pergamon

Tetrahedron 58 (2002) 4179–4183

TETRAHEDRON

Crystalline self-assembly induced by aromatic edge-to-face interactions: the crystal structure of 2,6,6,10-tetrabenzyl-2,10-diaza-6-azonia[11]paracyclophane bromide

M. Isabel Burguete,[a] Michael Bolte,[b] Juan C. Frías,[a] Enrique García-España,[c] Santiago V. Luis[a,*] and Juan F. Miravet[a]

[a]*Departamento de Química Inorgánica y Orgánica, Universitat Jaume I, 12080 Castellón, Spain*
[b]*Institut für Organische Chemie, J.W. Goethe-Universität Frankfurt, Marie-Curie-Str. 11, 60439 Frankfurt am Main, Germany*
[c]*Departamento de Química Inorgánica, Universitat de Valencia, 46100 Burjassot, Valencia, Spain*

Received 21 January 2002; revised 14 March 2002; accepted 3 April 2002

Abstract—The crystal structure of 2,6,6,10-tetrabenzyl-2,10-diaza-6-azonia[11]paracyclophane bromide reveals several intermolecular aromatic edge-to-face interactions which are important in the three-dimensional growing of the crystalline structure. Molecular dynamics and semiempirical studies indicate that the conformer found in the crystal is not the most stable in solution confirming the important role that edge-to-face interactions play in the structural arrangement found in the solid state. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The study of aromatic–aromatic interactions is of biological interest due to their role in the stabilization of the tertiary structure of proteins.[1] Following the seminal work of Burley and Petsko and considering their importance in living systems, different experimental and theoretical studies regarding this type of non-covalent interactions have been published in recent years.[2,3] Within this context, much work has been carried out in order to synthesize and study simple model molecules that could give place to this type of intermolecular or intramolecular interactions. In particular, it is of interest the study of molecules with a high number of phenyl rings that would be forced to accommodate these subunits in the most thermodynamically stable conformations when forming condensed phases, especially in crystalline solids. With this idea in mind we found that tetrabenzylated compound **1** could be an interesting model for this purpose. Here we report on the preparation and study of that compound placing special emphasis on the analysis of its crystal structure which provides interesting information regarding the mentioned aromatic–aromatic interactions.

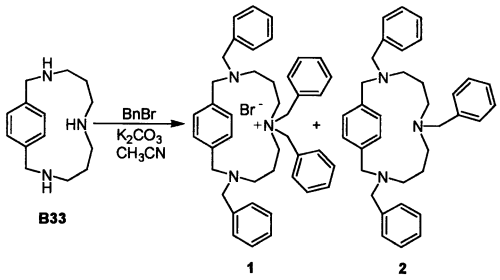
2. Results and discussion

Following our work on polyazamacrocycles[4] we found that the modification of the macrocycle **B33** by *N*-benzylation yielded as an important side product the tetra-*N*-benzylated macrocycle **1** (Scheme 1). It is worthy to note that this behaviour, in which the central nitrogen atoms are more reactive than the benzylic ones in free polyazacyclophanes, is opposite to that found in the presence of Zn(II) salts, which results in the selective functionalization in the benzylic nitrogen atoms.[4b,c] Compounds such as **1**, **2** and related perbenzylated macrocycles are poorly soluble in water due to their hydrophobic nature. This property permits their use as ligands able to solubilize metal cations in different organic solvents.[5] Compound **1**, for example, despite being ionic is soluble in organic solvents as chloroform.

The structure of **1** contains five aromatic rings in close proximity and so can be considered as a nice model for the study of both intramolecular and intermolecular aromatic–aromatic interactions. The use of other small-size molecules containing a large number of aromatic rings, for instance *cis*-1,4-dihydro-4-tritylbiphenyls, has been reported for the study of intramolecular aromatic edge-to-face interactions.[2d,6] On the other hand, theoretical calculations have suggested that the presence of electron-withdrawing substituents on the aromatic ring can favour edge-tilted-T conformations in which the substituent is in the phenyl ring interacting in the edge fashion (it can be also termed as the one acting as hydrogen donor), according to an electrostatic model of interaction (Fig. 1).[7] In this respect, the presence in **1** of two aromatic rings containing a methylammonium substituent can be considered as an additional interesting feature.

Keywords: edge-to-face interactions; molecular dynamics; aromatic–aromatic interactions.
* Corresponding author; e-mail: luiss@uji.es

0040–4020/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(02)00381-2



Scheme 1.

Initial studies on **1** by NMR were disappointing as no evidence was obtained for the presence of aromatic–aromatic interactions in solution. Under the different conditions studied, no significant upfield shifts could be detected for any of the aromatic protons. Nevertheless, a completely different situation was found in the solid state. Crystals of **1** suitable for X-ray structure determination were obtained from a chloroform solution by slow evaporation. The observed structure reveals the presence of bromide as the counteranion, located in the vicinity of the charged nitrogen atom (4.91 Å). It is noticeable the presence of three chloroform molecules surrounding the anion and that are hydrogen bonded to it, with hydrogen-bromide distances of 2.63, 2.52 and 2.41 Å. A similar situation has been reported in other organic crystal structures.[8] An analysis of the relative disposition of the tetrabenzylated macrocycles in the crystal structure highlights the importance of aromatic–aromatic edge-to-face interactions in the packing that takes place when the crystal is formed (Fig. 2). No intramolecular aromatic–aromatic interactions are observed in the structure, but all five aromatic rings of each molecule are involved in edge-to-face interactions with two other molecules. Three different aromatic–aromatic interactions were found in this system. The main structural parameters for those interring interactions, as defined in Fig. 3, are gathered in Table 1.

As can be seen in Fig. 2, for each molecule of **1**, one of the aromatic rings at the benzylic positions of the macrocycle (ring A) is located close to the two aryl rings bound to the ammonium site of a second molecule, giving place to the presence of two edge-to-face interactions. The first one, between rings A and B, presents a distance between phenyl ring centroids (d_1 in Fig. 3) of 5.00 Å and a dihedral angle between the two aryl rings(θ in Fig. 3) of 76.1°. Ring A acts as the hydrogen donor, in contrast with what has been described for related situations.[7] One of the hydrogen

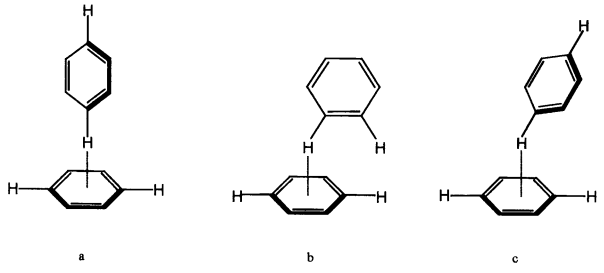


Figure 1. Limit structures possible for edge-to-face aromatic interactions: (a) T-shaped, (b) edge-tilted-T, and (c) face-tilted-T.[2d]

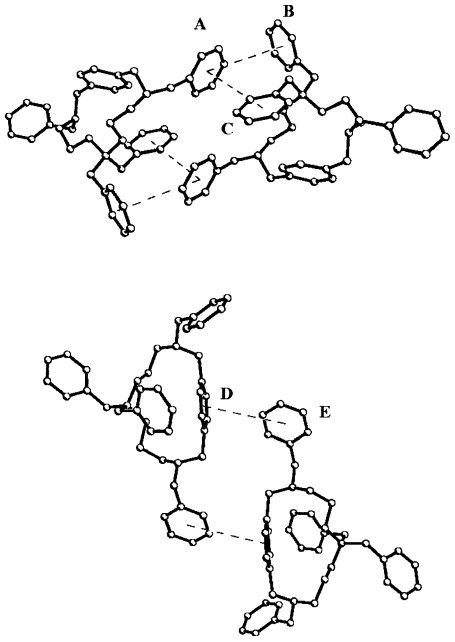


Figure 2. Selected pairs of molecules from the crystalline structure of **1**. Dotted lines indicate the edge-to-face interactions found.

atoms of A projects towards the plane of ring B at 2.69 Å (d_2 in Fig. 3) and offset by 0.74 Å (d_3 in Fig. 3) from the B ring centroid.

The second edge-to-face interaction, between rings A and C has a d_1 value of 4.92 Å and a θ value of 69.5°. In this case the ring C containing a methylammonium substituent is acting as the hydrogen donor as could be expected from theoretical calculations.[7] The perpendicular H-ring distance is, in this case, 2.56 Å and the offset is only 0.14 Å. The complementary situation is found between the two central aromatic rings (B and C) on the first molecule and ring A on the second molecule. Thus, a strong dimer is assembled through the presence of four edge-to-face interactions. The two remaining aromatic rings on each molecule, D and E, are involved in two additional edge-to-face interactions with a third and a fourth molecule located at opposite directions and allowing for the three-dimensional growing of the structure. In this case ring E is acting in the edge fashion, and the centroid-to-centroid distance (d_1) is 4.83 Å being the interring angle 76.5°. One of the hydrogens of E is located at 2.42 Å from the plane of D and is offset from the centroid by 0.65 Å.

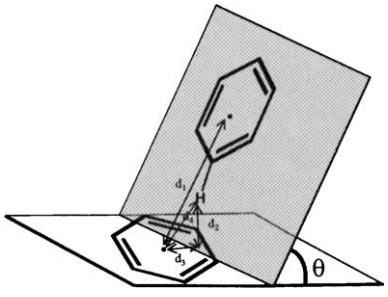


Figure 3. Schematic representation of the angle θ and distances d_1–d_4 used for describing edge-to-face interactions (Table 1).

Table 1. Geometry of edge to face interactions determined from X-ray data

Interaction[a]	d_1 (Å)[b]	d_2 (Å)[c]	d_3 (Å)[d]	d_4 (Å)[e]	θ (Å)[f]
A–B	5.00	2.69	0.74	2.76	76.1
C–A	4.92	2.56	0.14	2.56	69.5
E–D	4.83	2.42	0.65	2.47	76.5

[a] See Fig. 2. The first letter corresponds to the ring that acts as 'hydrogen donor'.
[b] Distance between ring centroides. (Fig. 3).
[c] Distance between hydrogen and ring plane (Fig. 3).
[d] Offset from the ring centroid (Fig. 3).
[e] Distance between ring centroid and hydrogen (Fig. 3).
[f] Angle formed by the planes that contain the rings (Fig. 3).

According to those data, aromatic edge-to-face interactions play a central role in the self-organization that results in crystal formation and in determining the nature of the crystal packing observed for **1**. Obviously, this should not be the only factor, and, for instance, ionic interactions must play a role, as corresponds to an ionic molecule. Nevertheless, hydrogen bonding interactions are limited to the interaction between the bromide anion and the hydrogen atoms of the three chloroform molecules surrounding it, and the presence of a three-dimensional hydrogen bonding network is not observed.

The values of the different parameters in Table 1 are in good agreement with those found experimentally and theoretically in other systems.[1–3] For example, in the work of Burley and Petsko mentioned previously, they found that in proteins there is a preference for edge-to-face type interactions between phenyl rings, with a predominance of structures which present a distance between phenyl ring centroids between 4.5 and 7 Å and a dihedral angle between 60 and 90°. Our results are also in accordance with the calculated optimal distance between centroids for edge to face interaction between benzene rings which is 5.5 Å.[9]

An important question that remains is to analyse if the conformation found for **1** in the crystalline structure represents the more stable one or if, on the contrary, this conformation is just adopted in order to optimize aromatic–aromatic interactions in the solid and to improve crystal packing. In order to do this, we performed molecular mechanics calculations with MACROMODEL 5.0 using

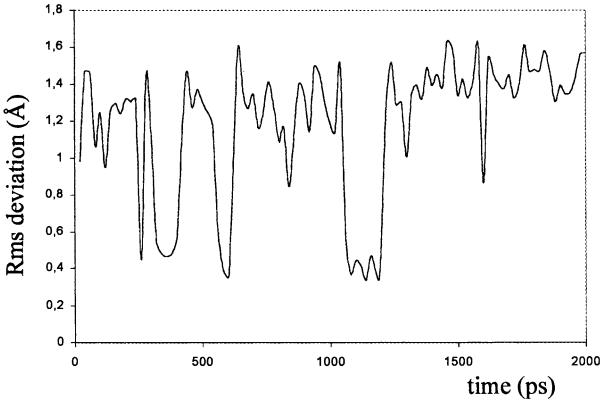


Figure 4. Representation of rms deviation calculated for the superimposition of the crystal conformer and the structures found in the MD simulation of **1**.

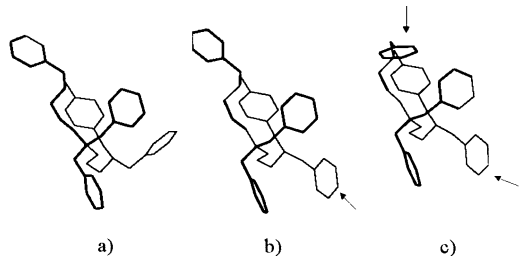


Figure 5. Structure of the calculated conformers of **1**. Arrows indicate benzyl groups whose disposition differs from that found in the crystalline state.

AMBER* force field and GB/SA simulation of chloroform as solvent.[10] We have shown previously that this force field reproduces well the conformations of related polyazacyclophanes.[11] To explore the conformational space in the vicinity of the conformation found in the crystalline state, molecular dynamics (MD) simulations were carried out, according to the general protocol described in Section 3. The analysis of the different structures sampled during the MD calculations (100 structures) revealed, basically, the presence of two families of conformers (a and b in Fig. 5). Upon structure superimposition, the conformers from the first family presented root-mean-square deviations (rms) from the crystal structure of around 0.5 Å while the second group of conformations presented a rms value between 1 and 1.5 Å (Fig. 4). It was found that the former family corresponded, essentially, to the conformation present in the solid crystalline state, while the second group of conformers was also very similar to the solid state structure but with one of the benzyl arms significantly twisted (see arrow in structure b of Fig. 5).

The higher number of conformers found in the group with rms≈1–1.5 Å indicates a thermodynamic preference for this structure. This preference is also found upon energy minimization of MD structures, which showed that the conformers of type b yielded a minimum energy structure 2.5 kJ/mol more stable than the one obtained from the family corresponding to the solid state structure (a in Fig. 5). Extensive conformational searching revealed that the global minimum found corresponds to the structure labelled as c in Fig. 5. This structure presents significant deviations from the X-ray structure in the relative position of both lateral benzyl groups and is 4.5 kJ/mol more stable than the structure a. PM3 semiempirical calculations[12] confirm that conformations like those in the crystalline state a are higher in energy than those related to b and c (5.0 and 3.3 kJ/mol, respectively).

Therefore, the calculations indicate that the conformation found in the solid state does not correspond to the minimum energy in solution. In particular, it is to note that the only significant difference comes from the disposition of benzyl arms while the polyamine chain shows, basically, the same arrangement in all the structures. These results support the hypothesis of the important role played by edge-to-face interactions in this system, which would compensate for the use of a high-energy conformer whose proportion in organic solvents would be low. Although it is widely accepted that conformations in the solid state can be different to those found in solution, this constitutes a clear

example that highlights how edge-to-face aromatic interactions can be responsible for those conformational differences and one of the main driving forces involved in crystal packing.

3. Experimental

3.1. General

3.1.1. Perbenzylation of 2,6,10-triaza[11]paracyclophane. Macrocycle **B33** (0.1 g, 0.43 mmol) was dissolved in dry CH_3CN (30 mL) containing anhydrous K_2CO_3 (0.6 g, 4.3 mmol). Benzyl bromide (160 μL, 1.30 mmol) was then added at 0 °C and the mixture was stirred at rt for 24 h. After this period the solution was filtered and the solvent was vacuum evaporated. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1) and products **1** and **2** were separated with a yield of 19 and 59%, respectively.

3.1.2. 2,6,6,10-Tetrabenzyl-2,10-diaza-6-azonia[11]paracyclophane bromide (1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (m, 4H), 2.54–2.70 (m, 8H), 3.44 (s, 4H), 3.72 (s, 4H), 4.69 (s, 4H), 6.94 (s, 4H), 7.20–7.56 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 53.1, 57.5, 60.5, 62.9, 63.5, 127.3, 127.4, 128.2, 128.9, 129.2, 129.7, 130.3, 133.0, 138.9, 139.6. ESI-MS: 594 (M^+). Anal. calcd for $C_{42}H_{48}BrN_3$: C, 74.7; H, 7.2; N, 6.2. Found: C, 74.9; H, 7.1; N, 6.3.

3.1.3. 2,6,10-Tribenzyl-2,6,10-triaza[11]paracyclophane (2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (m, 4H), 2.09 (m, 4H), 2.40 (m, 4H), 3.51 (s, 4H), 3.57 (s, 2H), 3.72 (s, 4H), 7.24–7.49 (m, 19H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 52.2, 52.4, 57.7, 60.5, 62.5, 126.9, 128.1, 128.2, 128.8, 129.7, 139.5, 139.8. ESI-MS: 504 ($M+H^+$). Anal. calcd for $C_{35}H_{41}N_3$: C, 83.5; H, 8.2; N, 8.3. Found: C, 83.7; H, 8.1; N, 8.3.

3.2. X-Ray crystallographic determination

Suitable crystals of **1** were obtained from chloroform. A colourless prism was mounted on top of a glass filament on a CCD diffractometer (Siemens, now Bruker AXS). Final lattice parameters were obtained by least-squares refinement of 72 reflections. Data were collected at 173 K, corrected for Lorentz and polarization effects and an empirical absorption correction[13b] was applied. The structure was solved by direct methods[13a] and refined against F^2 with full-matrix least-squares methods[13c] to $R1=0.0503$ for $4066F_{obs}>4\sigma(F_{obs})$ and $wR2=0.1160$ for all data. All H atoms were found and refined using a riding model. A total of 523 parameters were refined, 13.5 data per parameter. The highest peak and the deepest hole in the final difference electron density map are 0.675 and -0.594 eA^{-3}, respectively.

3.3. Molecular mechanics

Monte-Carlo conformational search and molecular dynamics studies for **1** were performed with MACROMODEL 5.0[10] using AMBER* as the force field and GB/SA simulation of chloroform as solvent. The Monte-Carlo conformational search involved the modification of the torsional angles automatically setup by the program and convergence was obtained after performing two cycles of 1000 steps departing from different conformers in each case. Molecular dynamics calculations were carried out using the following conditions: simulation temperature=300 K, length of simulation=1000 ps with 1.5 fs steps, SHAKE was used to constraint the length of bonds to hydrogen and 100 structures were sampled.

4. Supplementary material

Drawing of the crystalline packing. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 177642. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

Financial support has been provided by the CICYT (Project BQU2000-1424) and Bancaja (P1.1A2000-10).

References

1. (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. (b) Blundell, T.; Singh, J.; Thornton, J. M.; Burley, S. K.; Petsko, G. A. *Science* **1986**, *234*, 1005. (c) Singh, J.; Thornton, J. M. *J. Mol. Biol.* **1990**, *211*, 595. (d) Hunter, C. A.; Singh, J.; Thorton, J. M. *J. Mol. Biol.* **1991**, *218*, 837.
2. (a) Hunter, C. A. *Chem. Soc. Rev.* **1994**, 101. (b) Hobza, P.; Selzle, H. L.; Schlag, E. W. *Chem. Rev.* **1994**, *94*, 1767. (c) Hobza, P.; Havlas, Z. *Chem. Rev.* **2000**, *100*, 4253. (d) Jennings, W. B.; Farrell, B. M.; Malone, J. F. *Acc. Chem. Res.* **2001**, *34*, 885.
3. (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. (b) Linse, P. *J. Am. Chem. Soc.* **1992**, *114*, 4366. (c) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J. Am. Chem. Soc.* **1994**, *116*, 3500. (d) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J. Phys. Chem.* **1996**, *100*, 18790. (e) Chipot, C.; Jaffe, R.; Maigret, B.; Pearlman, D. A.; Kollman, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 11217. (f) Carver, F. J.; Hunter, C. A.; Seward, E. M. *Chem. Commun.* **1998**, 775. (g) Hobza, P.; Špiro, V.; Selzle, H. L.; Schlag, E. W. *J. Phys. Chem. A* **1998**, *102*, 2502. (h) Nakamura, K.; Houk, K. N. *Org. Lett.* **1999**, *1*, 2049. (i) Hong, B. H.; Lee, J. Y.; Cho, S. J.; Yun, S.; Kim, K. S. *J. Org. Chem.* **1999**, *64*, 5661. (j) Martin, C. B.; Mulla, H. R.; Willis, P. G.; Cammers-Goodwin, A. *J. Org. Chem.* **1999**, *64*, 7802. (k) Sindkhedkar, M. D.; Mulla, H. R.; Cammers-Goodwin, A. *J. Am. Chem. Soc.* **2000**, *122*, 9271. (l) Müller-Dethlefs, K.; Hobza, P. *Chem. Rev.* **2000**, *100*, 143.
4. (a) Bencini, A.; Burguete, M. I.; García-España, E.; Luis, S. V.; Miravet, J. F.; Soriano, C. *J. Org. Chem.* **1993**, *58*, 4749. (b) Burguete, M. I.; Escuder, B.; Frías, J. C.; Luis, S. V.; Miravet, J. F.; García-España, E. *Tetrahedron* **1997**, *53*, 16169. (c) Burguete, M. I.; Escuder, B.; Frías, J. C.; García-España, E.; Luis, S. V.; Miravet, J. F. *J. Org. Chem.* **1998**, *63*, 1810.

5. Frías, J. C. PhD Dissertation, University Jaume I, Castellón, Spain, 2000.
6. Grossel, M. C.; Cheetham, A. K.; Hope, A. O.; Weston, S. C. *J. Org. Chem.* **1993**, *58*, 6654.
7. Williams, V. E.; Lemieux, R. P.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 1927.
8. Steiner, T. *Acta Crystallogr.* **1998**, *B54*, 456.
9. (a) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J. Phys. Chem.* **1990**, *93*, 5893. (b) Arunan, E.; Gutowsky, H. S. *J. Chem. Phys.* **1993**, *98*, 4294. (c) Jaffe, R. L.; Smith, G. D. *J. Chem. Phys.* **1996**, *105*, 2780.
10. (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Chang, G.; Hendrickson, T.; Still, W. C. J. *Comput. Chem.* **1990**, *11*, 440. (b) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127.
11. Altava, B.; Bianchi, A.; Bazzicalupi, C.; Burguete, M. I.; García-España, E.; Luis, S. V.; Miravet, J. F. *Supramol. Chem.* **1997**, *8*, 287.
12. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
13. (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467. (b) Sheldrick, G. M. *SADABS: a program for empirical absorption correction of area detector data*; University of Göttingen: Germany, 1996. (c) Sheldrick, G. M. *SHELX-97: a program for the refinement of crystal structures*; University of Göttingen: Germany, 1997.