Pergamon

Tetrahedron 54 (1998) 12823–12828

TETRAHEDRON

Conformational Properties of Methylene Bridged Resorcarenes

Iris Thondorf*[a], Jörg Brenn[a], Volker Böhmer*[b]

[a]*Institut für Biochemie, Fachbereich Biochemie/Biotechnologie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 3,*
D-06099 Halle, Germany
[b]*Institut für Organische Chemie, Johannes-Gutenberg-Universität, J.-J.-Becher-Weg 34, SB1, D-55099 Mainz, Germany*

Received 22 July 1998; revised 3 August 1998; accepted 7 August 1998

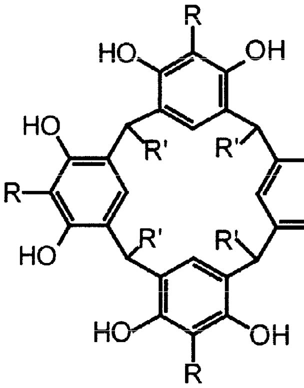
Abstract

Conformations and conformational interconversions of resorcarene **1c** have been studied by molecular mechanics calculations. As with calix[4]arenes the general stability of the four basic conformations is cone > partial cone > 1,2-alternate > 1,3-alternate. The lowest energy is calculated for a pinched cone conformer with C_{2v} symmetry stabilised by intramolecular hydrogen bonds of the two "parallel" resorcinol units as donors. The topomerisation of the cone conformation proceeds via the partial cone and 1,2-alternate intermediates with a calculated barrier of 9.9 kcal mol^{-1} which is in excellent agreement with the experimental value.

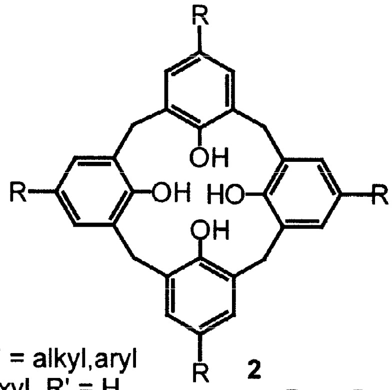
Keywords: Calixarenes; Molecular mechanics; Conformation

1. Introduction

Resorcinol-derived [1$_4$]-metacyclophanes („resorcarenes") [1] are of wide interest as macrocyclic hosts for a variety of organic guest molecules [2] or as building blocks for the construction of larger supramolecular systems [3-6]. Resorcarenes **1** with R' in an all-cis arrangement or with unsubstituted methylene bridges are found exclusively in the cone conformation, both in solution [7,8] and in the crystal [9-11]. The same is true for the related



1
a R = H, R' = alkyl,aryl
b R = *n*-hexyl, R' = H
c R = Me, R' = H



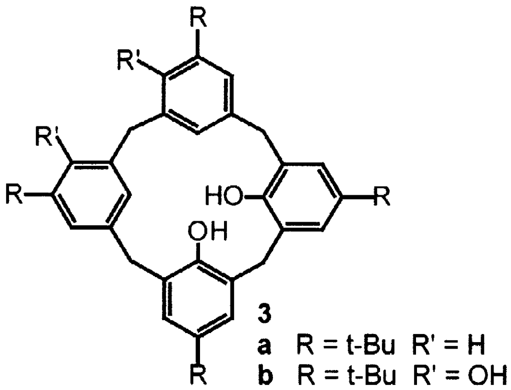
2
a R = t-Bu

---

*[a] Fax: 345-55 270 11, E-mail: thondorf@biochemtech.uni-halle.de; *[b] Fax: 6131-39 54 19, E-mail: vboehmer@mzdmza.zdv.uni-mainz.de

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00771-6

calix[4]arenes **2** [12]. In both cases this cone conformation is stabilised by four intramolecular hydrogen bonds either between pairs of *exo*-OH groups or by a circular array of the four *endo*-OH groups. Differences are observed for the flexibility of both $[1_4]$-metacyclophanes. While the resorcarenes **1a** exist exclusively in the cone conformation with axial disposition of the residues R' [7], **1b** interconverts between two identical cone conformations with a free activation energy $\Delta G^{\ddagger}_{298}$= 12.0 kcal mol^{-1} [8] in $CDCl_3$. This is lower than the barrier for the corresponding cone$\rightleftharpoons$cone inversion of **2a** ($\Delta G^{\ddagger}_{298}$ = 15.7 kcal mol^{-1} in $CDCl_3$ [13]). This difference has been interpreted [8] as weaker hydrogen bonding between *exo*-OH groups in comparison to *endo*-OH groups[1]. This assumption was supported by dynamic NMR studies on the calixarenes **3**, where the similarity of the free activation energies ($\Delta G^{\ddagger}_{c}$ = 10.6 and 10.8 kcal mol^{-1} for **3a** [14] and **3b** [15], respectively) indicates that the introduction of *exo*-OH groups has no significant influence on the flexibility of the macrocycle. On the other hand, the preferred conformation of **3a/b** is no longer exclusively the cone, since the 1,2-alternate allows the same number of intramolecular hydrogen bonds.



3
a R = t-Bu R' = H
b R = t-Bu R' = OH

As part of a program devoted to the influence of the substitution pattern on the conformational properties of $[1_4]$-metacyclophanes [15-18] we extend our calculations in the present paper to resorcarene **1c** in order to characterise the factors which govern the relative stability of different conformers and the energy barriers for their interconversion.

2. Results and Discussion

Table 1 lists the MM3 [19,20] calculated energies of the most stable basic conformers. Their geometries are shown in Fig. 1. The calculations indicate that the cone conformation should be exclusively present under experimental conditions due to the large energy differences to the other basic conformations. These energy differences are comparable to those obtained for **2a** (cone: 0.0, partial cone: 6.1, 1,2-alternate: 7.7, 1,3-alternate: 11.2 kcal mol^{-1} [16]) and suggest that the replacement of the *intra*annular OH groups by hydrogen and the introduction of eight *exo*-OH groups does not alter the exceptional stability of the cone structure. For both compounds the energetical stability of conformers parallels the number of possible hydrogen bonds: cone (4) > partial cone/1,2-alternate (2) > 1,3-alternate (none). The main difference

---

[1] The different strength of the hydrogen bonds is suggested also by the chemical shift of the OH protons but sterical factors cannot be ruled out for the passage of *endo*-OH groups through the annulus.

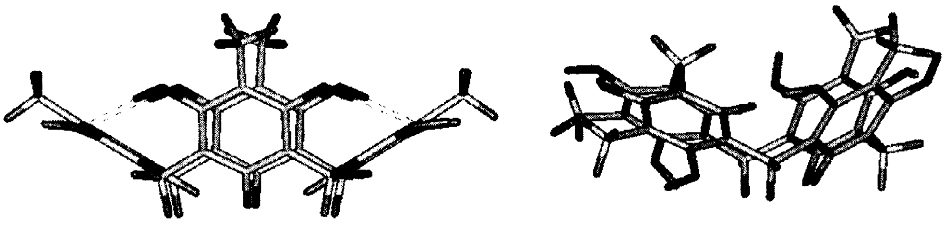
Table 1
MM3 calculated energies (in kcal mol^{-1}) of the basic conformations and of the transition states of interconversions of **1c**

	FSE[a]	ΔE	ΣE_{bnd}	ΣE_{nbnd}
cone	11.7	0.0	-25.5	37.2
paco	17.5	5.8	-23.3	40.8
1,2-alt	18.3	6.6	-25.1	43.4
1,3-alt	23.4	11.7	-21.2	44.6
cone ⇌ paco	21.6	9.9	-21.0	42.6
paco ⇌ 1,2-alt	19.8	8.1	-22.4	42.2
paco ⇌ 1,3-alt	28.9	17.2	-21.3	50.2

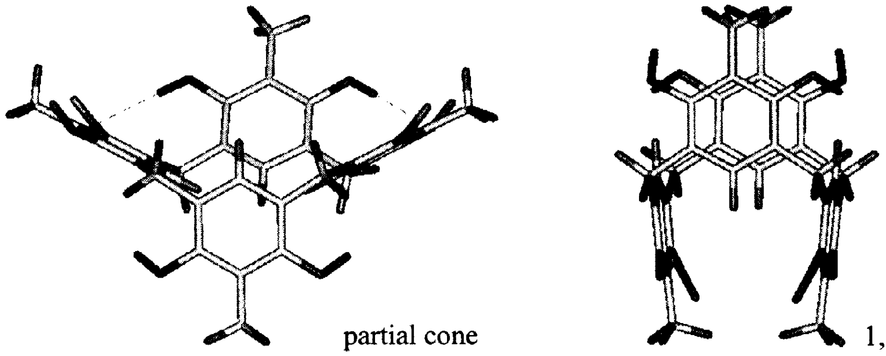
[a] FSE final steric energy, ΣE_{bnd} sum of all bonding energy contributions, ΣE_{nbnd} sum of all nonbonding energy contributions.

between **1c** and **2a** lies in the somewhat lower energy difference between the cone and the 1,2-alternate forms for the resorcarene **1c**. An inspection of the geometries of both 1,2-alternate conformers shows that in **1c** it adopts a „folded“ arrangement [21] which is energetically favoured over the typical 1,2-alternate structure with approximate C_i symmetry by 1.5 kcal mol^{-1}. This arrangement seems to be induced by the absence of at least two *endo*-OH groups [15,17,22]. Notably, the geometry of the partial cone conformer of **1c** also differs from typical partial cone structures [23] of substituted calix[4]arenes in which two opposite phenol rings pointing into the same direction assume an almost parallel arrangement.

The most stable conformer is a „pinched” cone in which both OH-groups of the two opposite resorcinol units oriented towards the cavity act as hydrogen bond donors (overall C_{2v} symmetry). Such a pattern was also found in the crystal for an all-cis resorcarene with R = H and R' = Me [9]. A cone form with homodirectional hydrogen bonding in which one OH-group



cone 1,2-alternate



partial cone 1,3-alternate

Figure 1. Lowest energy structures of the basic conformations of **1c**. Dashed lines indicate hydrogen bonding.

of each resorcinol ring serves as donor and one as acceptor „relaxes" also to a pinched conformation (C_2 symmetry, 0.8 kcal mol^{-1} above the global minimum). The „expected" C_4 symmetrical structure represents the transition state of the $C_2 \rightleftharpoons C_2$ pseudorotation for which a barrier of only 0.3 kcal mol^{-1} is calculated. This is comparable to the corresponding pseudorotation of **2a** (calculated barrier 0.8 kcal mol^{-1} [24]) but less than the experimentally determined barrier for the rotation about the C-O bond in phenol [25]. Therefore, it can be assumed that the $C_{2v} \rightleftharpoons C_{2v}$ pseudorotation of the most stable cone conformer which (in contrast to the $C_2 \rightleftharpoons C_2$ pseudorotation) requires a reorientation of the OH-groups is mainly determined by this rotation of the OH-groups.

Starting from the lowest energy cone conformation we have also simulated the pathways of its topomerisation which requires the stepwise rotation of all four resorcinol units through the macrocyclic annulus involving one of the alternate forms. The energies of the transition states which are also included in Table 1 indicate that the lowest energy pathway proceeds via the partial cone and 1,2-alternate intermediates with an overall activation energy of 9.9 kcal mol^{-1}. As shown in Figure 2 their geometries resemble those found for other $[1_4]$-metacyclophanes [17,18,26]. The calculated barrier is in excellent agreement with the activation enthalpy $\Delta H^{\ddagger}$ = 9.8 kcal mol^{-1} reported in [8] and it is 3.8 kcal mol^{-1} lower than the barrier calculated for the cone$\rightleftharpoons$cone interconversion of **2a** [16]. Since the similar energy gaps between the conformers of **1c** and **2a** point to similar hydrogen bonding strengths we ascribe the decrease in the calculated activation energies to the absence of *endo* substituents in **1c** which leads to a reduction of the sterical strain during ring inversion.

Investigations on the conformational properties of resorcarenes **1a** are in progress.

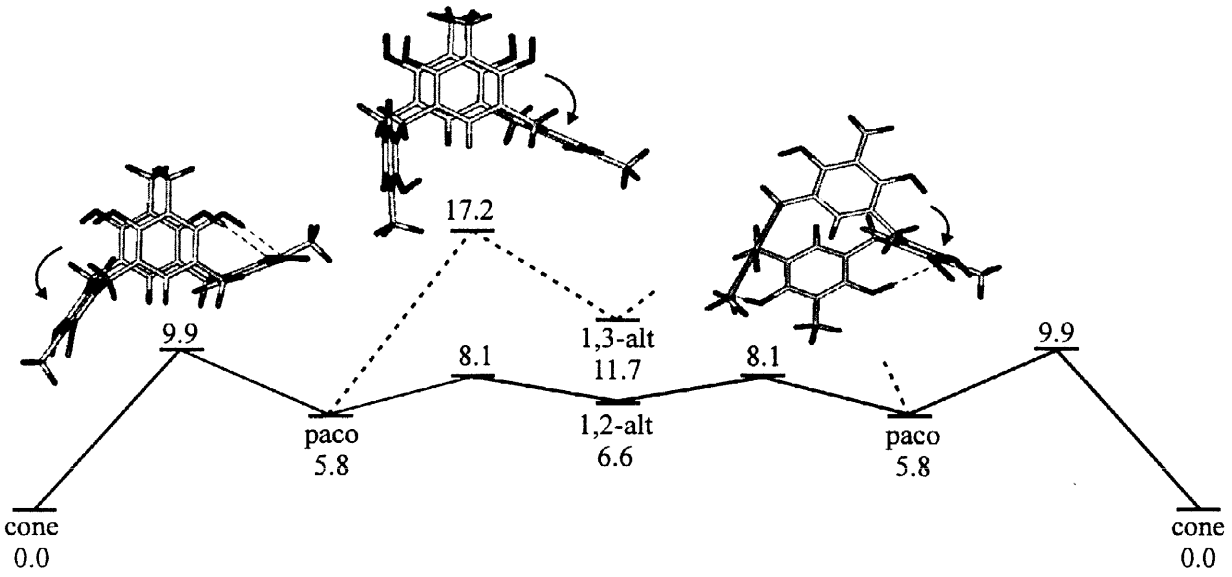


Figure 2. Pathways of conformational interconversions (all energies in kcal mol^{-1}) and transition state structures of **1c**.

3. Conclusion

Molecular mechanics calculations suggest that the cone conformation of resorcarene **1c** is of similar exceptional stability to that of *p-tert*-butylcalix[4]arene **2a**. The lower activation barrier calculated for the cone-to-cone topomerisation of **1c** which involves the rotation of all four aromatic rings through the macrocyclic annulus can be attributed to the absence of *intra*annular substituents.

4. Computational Details

The resorcarene **1c** was subjected to an extensive conformational search using the stochastic search routine of the standard MM3(94) force field using the default parameters except for the number of pushes which was set to 10000. The resulting structures were subsequently refined using the full matrix Newton-Raphson minimisation method and characterised as energy minima by means of the eigenvalues of the Hessian matrix. The $C_2 \rightleftharpoons C_2$ pseudorotation of the cone conformer and all possible rotational pathways of the cone-to-cone topomerisation were calculated by means of the coordinate driver method [16] which is based on the MM3 force field. Transition states were identified by a negative eigenvalue in the Hessian matrix. The analysis and visualisation of the calculated structures was carried out using the Sybyl [27] software.

Acknowledgements

The authors wish to thank Prof. Silvio E. Biali (The Hebrew University of Jerusalem) for valuable comments and critical reading of the manuscript. Financial support by the Deutsche Forschungsgemeinschaft (grant Th 520/2-2) is gratefully acknowledged.

References

[1] For a review on resorcarenes, see: Timmerman P, Verboom W, Reinhoudt DN. Tetrahedron 1996;52:2663-2704.

[2] Fujimoto T, Shimizu C, Hayashida O, Aoyama Y. J. Am. Chem. Soc. 1998;120:601-602 and references cited therein.

[3] Jacopozzi P, Dalcanale E. Angew. Chem. 1997;109:665-667. Yoon J, Cram DJ. Chem. Commun. 1997:2065-2066. Helgeson RC, Knobler CB, Cram DJ. J. Am. Chem. Soc. 1997;119:3229-3244.

[4] Cram DJ, Cram JM. Container Molecules and Their Guests. Monographs in Supramolecular Chemistry. Stoddard JF, editor. Cambridge: Royal Society of Chemistry: 1994.

[5] Soncini P, Bonsignore S, Dalcanale E, Ugozzoli F. J. Org. Chem. 1992;57:4608-4612. Gibb BC, Chapman RG, Sherman, JC. J. Org. Chem. 1996;61:1505-1509.

[6] Timmerman P, Verboom W, van Veggel FCJM, van Hoorn WP, Reinhoudt DN. Angew. Chem., Int. Ed. Engl. 1994;33:1292-1295. Chopra N, Sherman JC. Angew. Chem., Int. Ed. Eng. 1997;36:1727-1729.

[7] Abis L, Dalcanale E, Du vosel A, Spera S. J. Chem. Soc., Perkin Trans. II 1990:2075-2080.

[8] Konishi H, Morikawa, O. J. Chem. Soc., Chem. Commun. 1993:34-35.

[9] Zahn G, Sieler J, Müller K, Hennig L, Mann G. Z. Kristallogr. 1994;209:468-469. Mann G, Hennig L, Weinelt F, Müller K, Meusinger R, Zahn G, Lippmann T. Supramol. Chem. 1994;3:101-113.

[10] Adams H, Davis F, Stirling CJM. J. Chem. Soc., Chem. Commun. 1994:2527-2528.

[11] Leigh DA, Linnane P, Pritchard RG, Jackson G. J. Chem. Soc., Chem. Commun. 1994:389-390.

[12] For recent reviews on calixarenes, see: Böhmer V. Angew. Chem., Int. Ed. Engl. 1995;34:713-745. Pochini A, Ungaro R. Calixarenes and related hosts. In: Vögtle, F, editor. Compr. Supramol. Chem. Vol. 2. Oxford: Elsevier, 1996:143-194. Gutsche CD. Aldrichimica Acta 1995;28:3-9.

[13] Gutsche CD, Bauer L. J. Am. Chem. Soc. 1985;107:6052-6059.

[14] Aleksiuk O, Grynszpan F, Biali SE. J. Chem. Soc., Chem. Commun. 1993:11-13.

[15] Biali SE, Böhmer V, Brenn J, Frings M, Thondorf I, Vogt W, Wöhnert J. J. Org. Chem. 1997;62:8350-8360.

[16] Thondorf I, Brenn J. J. Mol. Struct. (Theochem) 1997;398-399:307-314.

[17] Thondorf I, Brenn J, Brandt W, Böhmer V. Tetrahedron Lett. 1995;36:6665-6668.

[18] Thondorf I. submitted.

[19] Allinger NL, Yuh YH, Lii J-H. J. Am. Chem. Soc. 1989;111:8551-8566,8566-8575,8576-8582.

[20] MM3(94) is available from Tripos Associates, 1699 South Hanley Road, St Louis, MO 63144, USA.

[21] A similar arrangement was also found in the crystal structure of the C-isopropoxycarbonylmethyl resorcarene octamethylether: Benedetti E, Pedone C, Iacovino R, Botta B, Monache GD, De Rosa MC, Botta M, Corelli F, Tafi A, Santini A. J. Chem. Res., Synop. 1994:476-477.

[22] A folded 1,2-alternate conformation was also found for some OH-depleted calix[4]arenes by molecular mechanics calculations: Harada T, Rudzinski JM, Osawa E, Shinkai S. Tetrahedron 1993;49:5941-5954. Harada T, Ohseto F, Shinkai S. Tetrahedron 1994;50:13377-13394.

[23] See for instance: Grootenhuis PDJ, Kollman PA, Groenen LC, Reinhoudt DN, van Hummel GJ, Ugozzoli F, Andreetti GD. J. Am. Chem. Soc. 1990;112:4165-4176.

[24] Brenn J, Thondorf I. unpublished results.

[25] Pedersen T, Larsen NW, Nygaard L. J. Mol. Struct. 1969;4:59-77.

[26] Fischer S, Grootenhuis PDJ, Groenen LC, van Hoorn WP, van Veggel FCJM, Reinhoudt DN, Karplus M. J. Am. Chem. Soc. 1995;117:1611-1620.

[27] Sybyl (version 6.4), is available from Tripos Associates, 1699 South Hanley Road, St Louis, MO 63144, USA.