

Conformational behaviour of tetramethoxythiacalix[4]arenes: solution versus solid-state study

Pavel Lhoták,^{a,*} Michal Himl,^a Ivan Stibor,^a Jan Sýkora,^b Hana Dvořáková,^c Jan Lang^c and Hana Petříčková^d

^aDepartment of Organic Chemistry, Prague Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic

^bInstitute of Chemical Process Fundamentals, Czech Academy of Sciences, Rozvojova 135, 165 02 Prague 6, Czech Republic

^cLaboratory of NMR Spectroscopy, Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic

^dDepartment of Solid State Chemistry, Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic

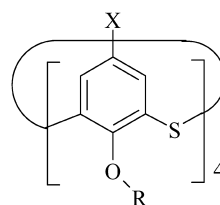
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Abstract—The conformational behaviour of simple thiacalix[4]arene derivatives was studied using a combination of NMR spectroscopy and X-ray diffraction analysis. The 25,26,27,28-tetramethoxythiacalix[4]arene was found to adopt an unprecedented solid-state structure, where the *cone* and *1,3-alternate* conformers co-exist in the crystal lattice in the 3:1 ratio. This phenomenon reflects the basically distinct conformational behaviour of thiacalix[4]arene skeleton as compared with classical calixarenes.

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1. Introduction

New members of the traditional calix[*n*]arene family,¹ so called thiacalixarenes,² represent very interesting molecules with many potential applications in supramolecular chemistry. The presence of four sulphur atoms instead of the methylene bridges imparts thiacalix[4]arenes **1a,1b** many novel features when compared with the chemistry of ‘classical’ calixarenes. Consequently, several reactions unknown from the chemistry of calix[4]arene have been described. Among them, the intramolecular formation of lactone derivatives³ or the introduction of amino groups into the lower rim⁴ of thiacalixarenes could be mentioned. Despite the recently increasing number of papers dealing with thiacalix[4]arenes, the full-scope utilisation of these compounds as building blocks in supramolecular chemistry is still restricted by the lack of knowledge regarding their chemistry and/or behaviour. During our ongoing research we have shown that thiacalixarenes exhibit higher flexibility in the solution⁵ and different conformational preferences in the solid-state⁶ as compared with classical calixarenes. In this paper we report on another example of unique conformational behaviour of simple thiacalix[4]arene derivatives revealed by the combination of NMR spectroscopy and single crystal X-ray diffraction.



1a, R = H, X = Bu^t;
1b, R = H, X = H;
2a, R = Me, X = Bu^t;
2b, R = Me, X = H,

2. Results and discussion

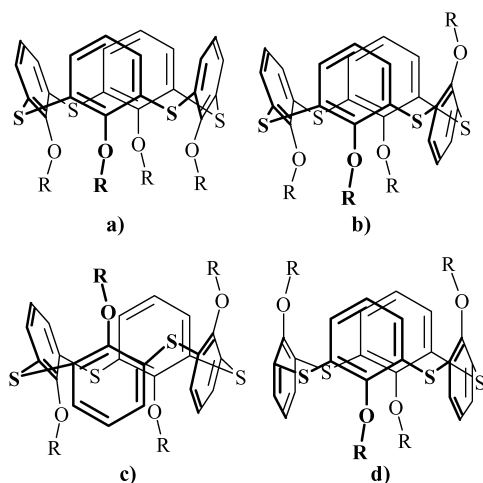
2.1. Synthesis and NMR study

Starting thiacalixarenes **1a** and **1b** were alkylated using methyl iodide/K₂CO₃ in boiling acetone to yield tetramethylated products **2a** and **2b** in high yields (95 and 85%, respectively).⁷ The conformational properties of **2a** were studied by means of temperature dependent ¹H NMR spectroscopy in the temperature range of 208–303 K in CDCl₃. The spectrum acquired at room temperature proved the presence of average signals caused by the fast chemical exchange of several conformers (Scheme 1). The spectral pattern at low temperature is consistent with the presence of partial *cone* and *1,3-alternate* conformers. However, the large line width of the resonances did not allow us to prove the presence of these conformers by more sophisticated methods.

The conformational behaviour of tetramethoxy derivative **2b** was studied similarly in the range of 183–336 K using

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* Corresponding author. Tel.: +420-2-2435-5048; fax: +420-2-2435-4288; e-mail: lhotakp@vscht.cz



Scheme 1. Conformers of thiacalix[4]arene: (a) *cone*, (b) *partial cone*, (c) *1,2-alternate*, (d) *1,3-alternate*.

CDCl_3 as a solvent. The temperature dependence showed rather complicated conformational dynamics. A simple set of three signals (doublet and triplet in the aromatic part of spectrum together with the methyl singlet at $\delta=3.8$ ppm) at 336 K is due to fast chemical exchange of various conformers. As demonstrated in Figure 1 the lowering of temperature leads to the appearance of new signals. At the ambient temperature (293 K) the resonances of *cone* conformer and average signals of the remaining conformers are distinguished (Fig. 1). The assignment of the conformers of **2b** (**2a**, respectively) was accomplished in analogy with spectral patterns of the less mobile tetraethoxy and tetrapropoxy derivatives described previously.^{5,8} Interestingly, signals of the *cone* conformation have almost disappeared at 271 K, reappearing again at lower temperature with doubled multiplicity. This indicates an additional dynamic process ascribed to the *pinched cone*–*pinched cone* interconversion (Fig. 2) between two identical

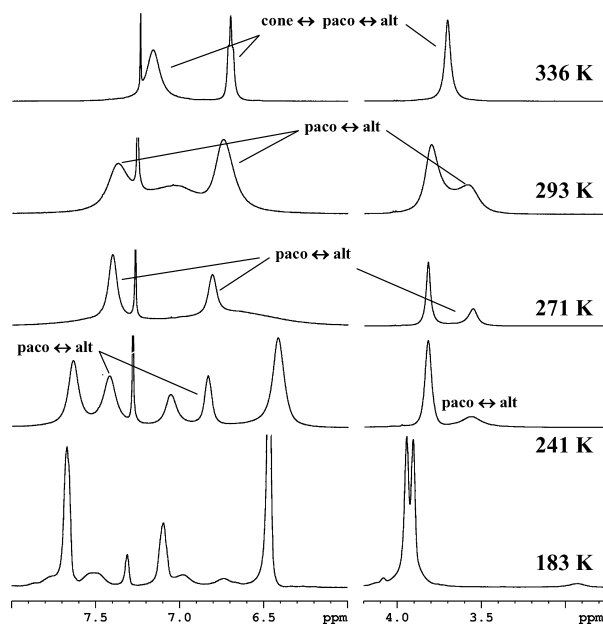


Figure 1. Temperature dependent ^1H NMR spectra of **2b** (CDCl_3 , 500 MHz, spectrum at 183–336 K). Assignment of the individual conformers is shown.

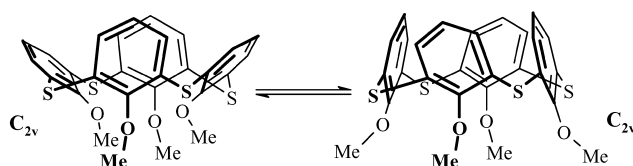


Figure 2. *Pinched cone*–*pinched cone* interconversion of **2b**.

conformers possessing lower C_{2v} symmetry. The C_{4v} symmetry commonly observed in the NMR spectra of calix[4]arene *cone* derivatives is, in fact, the time-averaged signal due to fast chemical exchange.^{1c} The coalescence temperature T_c of this exchange process can be used to calculate the activation free energy $\Delta G_0^*=52 \text{ kJ mol}^{-1}$ ($\pm 1 \text{ kJ mol}^{-1}$) by means of Eq. (1) (R is the gas constant, $\Delta\nu$ is the chemical shift difference of the exchanging resonances in the absence of chemical exchange)

$$\Delta G_0^* = RT_c[22.96 + \ln(T_c/\Delta\nu)] \quad (1)$$

The chemical shift difference $\Delta\nu$ between the exchanging aromatic doublets is 610 Hz, the coalescence temperature T_c is $283 \pm 5 \text{ K}$.

The coalescence phenomenon of this equilibrium is usually directly unobservable by means of ^1H NMR for ‘classical’ calix[4]arene derivatives because the interconversion is too fast (very low coalescence temperature).⁹

Hence, the introduction of sulphur atoms into a thiacalixarene moiety leads to a dramatic change in their conformational behaviour.¹⁰ Unfortunately, even at the lowest accessible temperature (183 K), besides the narrow resonances of the *pinched cone*, only several very broad *alternate* and *partial cone* signals appeared in the spectrum that could not be assigned more specifically.

2.2. Crystallographic study

The conformational preferences of **2a** in the solid-state were studied using the single crystal X-ray diffraction analysis. The crystallisation from dichloromethane yielded thiacalixarene **2a** in a *1,3-alternate* conformation.¹¹ Square box-shaped cavities of thiacalixarenes are packed parallel to each other and form infinite channels. The free space outside these channels (again a channel of approximately the same diameter) is occupied by dichloromethane guest molecules (Fig. 3). Interestingly, the carbon atoms of CH_2Cl_2 are situated exactly between the two centers of the aromatic subunits from the two neighbour calixarene molecules ($\text{C}\cdots\text{C}$ -plane distance=3.55 Å). The inner space of thiacalixarene cavity is filled by a water molecule being positioned between the *para* carbon atoms ($\text{O}\cdots\text{C}$ =3.51 Å) of two distal aromatic subunits (Fig. 4(a)). Almost identical crystal packing (space group $Pnmm$) with included molecules of solvent (but without water molecules) was also found for chloroform.

On the other hand, the crystallisation of **2a** from solvents which are too bulky (such as isopropanol or *p*-xylene) to be accommodated within the channel structures, led to dramatic changes in the conformational preferences. In these cases, the thiacalixarene skeleton

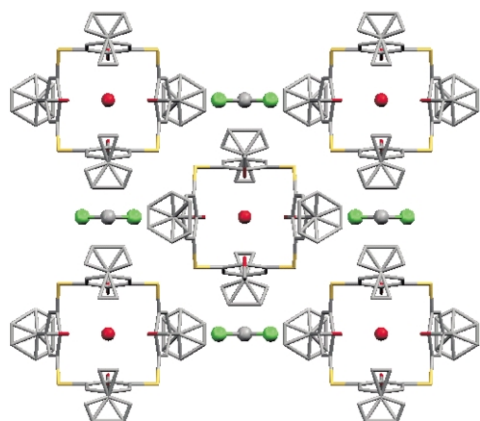


Figure 3. Crystal packing of **2a**·CCH₂Cl₂·H₂O complex (*1,3*-alternate conformations). Hydrogen atoms were omitted for better clarity.

adopts a *1,2*-alternate conformation (Fig. 4(b)). It is known, that the packing modes of calix[4]arenes in the cone conformation can vary depending on the guest molecule being included into the cavity.¹² On the other hand, the above described fact—the entire change of the solid-state conformation invoked by the change in crystallisation solvent—seems to be very unusual, and to the best of our knowledge, this phenomenon is without precedent in calixarene literature so far.

The single crystal X-ray diffraction analysis of **2b** (crystals obtained upon slow evaporation of the ethyl acetate solution) revealed unprecedented conformational behaviour of this compound in the solid-state. The independent part of the unit cell is created by the one complete and one-half of the *cone* conformers together with one-half of *1,3*-alternates. Consequently, the whole unit cell consists of 16 molecules of thiacalixarene **2b**, where 12 molecules adopt the *cone* conformation and the remaining four molecules are in the *1,3*-alternate conformation. To the best of our knowledge, this is the first example of a solid-state structure where two different calix[4]arene conformations (Fig. 5) co-exist at the same time in crystal lattice.

The whole arrangement is held together by a complicated array of CH– π and π – π interactions. Molecular packing along the *Y*-axis is characterised by infinite channels of calixareners with regularly alternating *cone* and *1,3*-alternate conformers (Fig. 6(a)). Pairs of molecules within the channel are coupled by strong CH– π interactions. Two

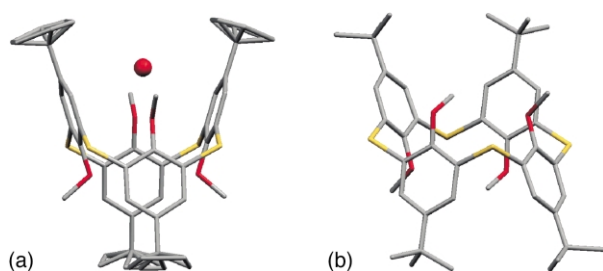


Figure 4. (a) Crystal structure of **2a** (*1,3*-alternate conformation) with included H₂O molecule; (b) crystal structure of **2a** (*1,2*-alternate). Hydrogen atoms were omitted for better clarity.

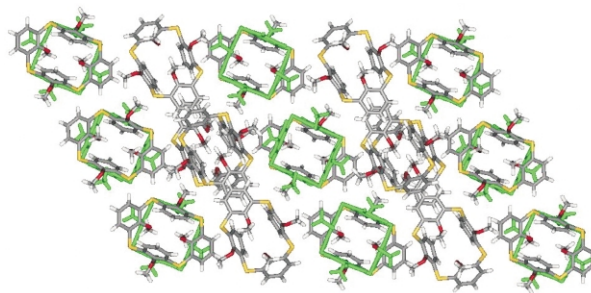


Figure 5. Crystal packing of tetramethoxy derivative **2b** (*1,3*-alternate conformers are in green colour).

hydrogens in the *1,3*-alternate's opposite *para* positions are oriented above the plane of the pinched aromatic subunits of neighbour *cone* conformer (distance=3.16(1) Å). The channels are separated from each other (along the *X*-axis direction) by wall-like structures comprising the *cone* conformers only arranged in the chains (*Z*-axis direction) by means of π – π interactions (Fig. 6(b)). Molecules within the chains are regularly staggered which enables the interaction of almost coplanar aromatic units (inter-planar angle=0.3(1)°, mutual distances 3.6(1) and 3.9(1) Å, respectively). Finally, the above-mentioned walls are interconnected via *cones* from infinite channels using the CH– π interactions of their aromatic parts with the methoxy groups of the *cone* in the wall (distance 2.98(1) Å). Moreover, the whole structure is held by additional CH– π interactions of the *cone* *p*-positions (distance 2.97(1) Å). This leads to the formation of tunnel-like structures (consisting exclusively of the *cone* conformers, Fig. 7(a)) filled with the *1,3*-alternate lines (Fig. 7(b)). There are no obvious interactions between the neighbour molecules of *1,3*-alternate conformations.

As mentioned above, all *cones* are in so called *pinched cone* conformation with dihedral angles 144–161° and 66–77° for corresponding opposite aromatic rings. The inner symmetry of *cones* in channels (Fig. 6(a)) is *C*_{2v}, while the *cone* conformers in the walls (Fig. 7(a)) possess lower *C*₁ symmetry. Symmetry of the *1,3*-alternate is almost *S*₄ with dihedral angles being in the interval 94–95°.

The above-described unprecedented conformational preferences of compound **2b** in the solid-state were found to be a

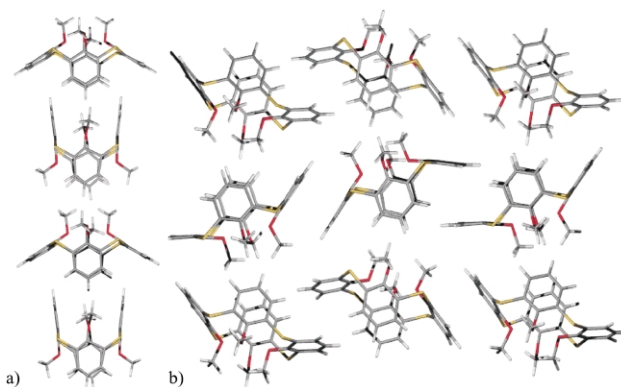


Figure 6. (a) Crystal packing of **2b** along the *Y*-axis; (b) wall-like assembly exhibiting the π – π interactions.

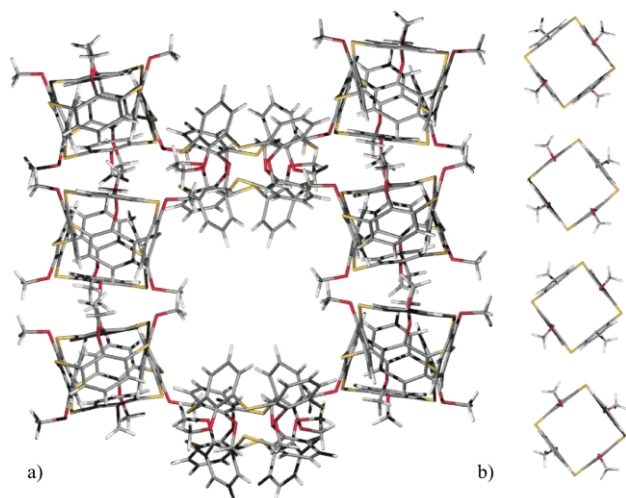


Figure 7. (a) Tunnel-like structures consisting of the *cone* conformers; (b) tunnel 'filling' represented by the *1,3-alternate* lines.

general phenomenon. The same results were obtained using acetone, acetonitrile, ethyl acetate or the mixtures of these solvents for the crystallisation.

In conclusion, the ^1H NMR study showed that thiacalix[4]arene **2b** exhibits thermodynamic equilibrium between at least three different conformations with the pronounced *cone* conformation undergoing the *pinched cone-pinched cone* interconversion. On the other hand, the X-ray diffraction of this compound revealed unique molecular packing, where a '3:1 mixture' of the *cone* and the *1,3-alternate* conformations is 'frozen' and held together by complicated arrays of π - π and CH- π interactions. This phenomenon reflects the basically distinct conformational behaviour of thiacalix[4]arene skeleton as compared with classical calixarenes.

3. Experimental

Melting points are uncorrected and were determined using a Boetius Block apparatus. ^1H NMR spectra were recorded on a Varian Gemini 300 and a Bruker DRX 500 Avance spectrometers using tetramethyl silane as an internal standard. ^1H NMR spectra were measured with a spectral width 7500 Hz, data size 32K, the recycle time 3.1 s, and 16 scans. FAB MS were measured on ZAB-EQ VG Analytical spectrometer.

Compounds **1a** and **1b** were prepared according to known procedures.

3.1. Synthesis of derivative **2a** and **2b**

The mixture of derivative **1a** or **1b** (1 mmol), potassium carbonate (10 mmol) and methyl iodide (20 mmol) was stirred under reflux in 20 ml of acetone overnight. The reaction mixture was poured into diluted aqueous hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried over MgSO_4 and evaporated to dryness. Pure products were obtained by reprecipitation from a chloroform-methanol mixture.

3.1.1. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-2,8,16,22-tetrathiacalix[4]arene (2a). Yield: 91%, white crystalline solid, mp: 313–315°C (ethyl acetate) [lit.¹³ mp 314–316°C]. ^1H NMR (CDCl_3 , 300 MHz, 298 K) δ 1,24 (s, 36H, *tert*-butyl), 3,44 (s, 12H, OCH_3), 7,43 (s, 8H, Ar-H). EA calcd for $\text{C}_{44}\text{H}_{56}\text{O}_4\text{S}_4$: C, 68.22; H, 7.26; S, 16.52%. Found C, 68.40; H, 7.71; S, 16.10%.

3.1.2. 25,26,27,28-Tetramethoxy-2,8,16,22-tetrathiacalix[4]arene (2b). Yield: 85%, white crystals, mp: 186–188°C (ethyl acetate). ^1H NMR (CDCl_3 , 300 MHz, 298 K) δ 3,83 (br s, 12H, OCH_3), 6,60 (2x br s, 12H, Ar-H). EA calcd for $\text{C}_{28}\text{H}_{24}\text{O}_4\text{S}_4$: C, 60.84; H, 4.38; S, 23.20%. Found C, 60.34; H, 4.54; S, 23.14%.

3.2. Crystallographic study

Data were measured at 293 K on an Enraf-Nonius CAD4 diffractometer with graphite monochromated $\text{Cu K}\alpha$ radiation. The structure was solved by direct methods.¹⁴ The whole structure was refined by the full matrix least-square analysis on F values.¹⁵

X-Ray data for **2a** (*1,3-alternate*, solvate with dichloromethane): $(\text{C}_{44}\text{H}_{56}\text{O}_4\text{S}_4)\cdot(\text{CH}_2\text{Cl}_2)\cdot 1/2(\text{H}_2\text{O})$, $M=871.104$, orthorhombic system, space group $Pnmm$, $a=12.1698(7)$ Å, $b=12.9042(8)$ Å, $c=15.2940(7)$ Å, $V=2401.8(2)$ Å³, $Z=2$, $D_c=1.2045$ g cm⁻³, $\mu(\text{Cu K}\alpha)=31.487$ cm⁻¹, crystal dimensions of $0.2\times 0.7\times 0.9$ mm³. $R=0.0808$, $R_w=0.0932$ and $S=1.0272$ with 156 parameters using 1634 independent reflections ($\theta_{\text{range}}=3.63$ – 69.96°). Hydrogen atoms linked to carbon atoms were located from expected geometry and were not refined. Hydrogen atoms linked to oxygen atom in molecule of water were found from Fourier difference electron density map and their positions were refined. Crystallographic data were deposited in CSD under CCDC registration number 209480.

X-Ray data for **2a** (*1,3-alternate*, chloroform solvate): $(\text{C}_{44}\text{H}_{56}\text{O}_4\text{S}_4)\cdot(\text{CHCl}_3)$, $M=896.542$, orthorhombic system, space group $Pnmm$, $a=12.1834(7)$ Å, $b=13.342(1)$ Å, $c=15.260(1)$ Å, $V=2480.4(3)$ Å³, $Z=2$, $D_c=1.2004$ g cm⁻³, $\mu(\text{Cu K}\alpha)=35.396$ cm⁻¹, crystal dimensions of $0.8\times 0.8\times 0.9$ mm³. $R=0.1022$, $R_w=0.1192$ and $S=1.0315$ with 159 parameters using 1601 independent reflections ($\theta_{\text{range}}=3.63$ – 69.92°). Hydrogen atoms linked to carbon atoms were located from expected geometry and were not refined. CCDC registration number 209481.

X-Ray data for **2a** (*1,2-alternate*): $\text{C}_{44}\text{H}_{56}\text{O}_4\text{S}_4$, $M=776.164$, triclinic system, space group $P-1$, $a=9.8209(4)$ Å, $b=9.8941(7)$ Å, $c=12.8700(8)$ Å, $\alpha=93.557(5)^\circ$, $\beta=111.939(4)^\circ$, $\gamma=112.583(5)^\circ$, $V=1039.8(2)$ Å³, $Z=1$, $D_c=1.2411$ g cm⁻³, $\mu(\text{Cu K}\alpha)=21.129$ cm⁻¹, crystal dimensions of $0.2\times 0.40\times 0.50$ mm³. $R=0.0522$, $R_w=0.0518$ and $S=1.1117$ with 236 parameters using 2743 independent reflections ($\theta_{\text{range}}=3.81$ – 67.91°). Hydrogen atoms linked to carbon atoms were located from expected geometry and were not refined. CCDC registration number 209482.

X-Ray data for **2b**: $\text{C}_{28}\text{H}_{24}\text{O}_4\text{S}_4$, $M=552.76$ g/mol, monoclinic system, space group $C2/c$, $a=39.475(1)$ Å,

$b=15.224(1)$ Å, $c=21.106(1)$ Å, $\beta=121.67(1)$, $Z=16$, $V=10795(1)$ Å³, $D_c=1.36$ g cm⁻³, $\mu(\text{Cu K}\alpha)=35.0$ cm⁻¹, crystal dimensions of $0.4\times 0.4\times 0.4$ mm³. All heavy atoms were refined anisotropically. Hydrogen atoms were located from expected geometry and were not refined. This model converged to final $R=0.0695$ and $R_w=0.0609$ using 7298 independent reflections ($\theta_{\text{max}}=68^\circ$). CCDC registration number 190892.

Copies of the corresponding data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

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