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Catechol[4]arene: The Missing Chiral Member of the Calix[4]arene Family

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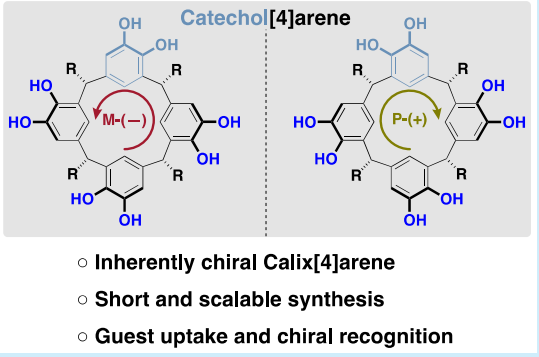
ABSTRACT: A missing, inherently chiral member of the calix[4]arene family denoted "catechol[4]arene" was synthesized. Its properties were studied and compared to the ones of its close relatives resorcin[4]arene and pyrogallol[4]arene. This novel supramolecular host exhibits binding capabilities that are superior to its sister molecules in polar media. The enantiomerically pure forms of the macrocycle display modest recognition of chiral ammonium salts.



In the broad field of supramolecular chemistry, macrocycles have always played a key role.[1] Phenol-based macrocycles have been explored intensively due to their facile preparation on large scale and the ease of functionalization. Important members of this class of macrocycles are calixarenes,[2] cyclotriveratrylenes,[3] and pillararenes[4] (Figure 1a). Among these synthetic macrocycles, the calix[4]arene family stands out as one of the most functional and versatile ones.[5] Calix[4]arene along with its sister molecules resorcin[4]arene (RS) and pyrogallol[4]arene (PG) are rigid, bowl-shaped, and easily derivatizable macrocyclic structures that enabled a variety of applications across the fields of material sciences, molecular sensing, and drug delivery.[6]

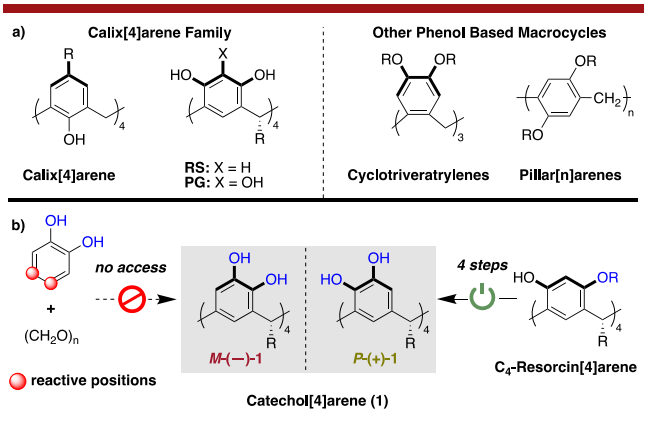


Figure 1. (a) Structures of important phenol-based macrocycles. (b) Inaccessible one-pot route toward catechol[4]arene and proposed stepwise approach from C_4-rersorcin[4]arene.

The latter two systems are of particular interest as they are known to self-assemble in apolar media, resulting in the formation of hexameric capsules held together by hydrogen bond networks.[7] The emerging enclosed space supplemented with its capability to take up neutral and cationic guests resembles enzymatic pockets to some extent.[8] In the case of RS, these properties have been successfully applied to the catalysis of a growing number of reaction classes.[9]

While there are examples of successful asymmetric catalysis employing achiral RS, these reactions exclusively rely on the presence of an optically active cocatalyst to carry the chiral information.[10] One way of overcoming this limitation would be the use of inherently chiral building blocks. In contrast to the inherently chiral pillararenes, the calix[4]arene family of macrocycles is achiral. Interestingly, a missing chiral relative (±)-**1** (Figure 1b) can be envisioned, we propose the name catechol[4]arene, which to the best of our knowledge has not been reported so far. This inherently chiral constitutional isomer of RS could potentially open access to a range of applications known from other inherently chiral macrocycles, such as asymmetric catalysis, chiral molecular recognition, and chiral self-assembly.[11]

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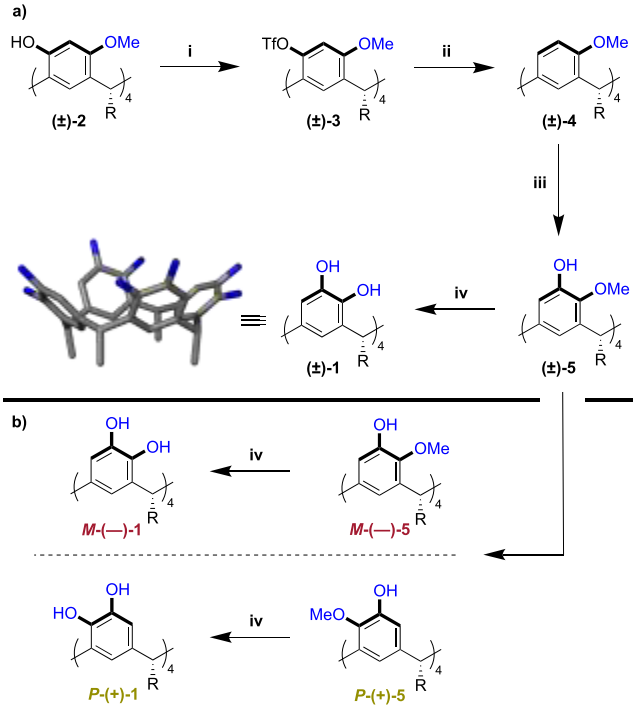
The known calix[4]arene family can be easily obtained through electrophilic aromatic substitution of the respective phenols with aldehydes.[12] However, the directing effects in catechol prevent the direct formation of **1**. Catechol derivatives reacting with formaldehyde under acidic conditions yield mainly the tricyclic cyclotriveratrylenes (Figure 1a), and no formation of catechol[4]arene has been reported.[3a] We here report the synthesis, characterization, and application of the new, inherently chiral, macrocyclic host **1** in its racemic and optically pure form.

It was decided to synthesize this elusive member through derivatization of the literature known compound (±)-**4** (Scheme 1).[13] The route toward tetramethoxy resorcin[4]arene

Scheme 1. Synthesis of Catechol[4]arene (1)[a]

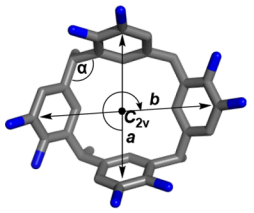


[a]R = $C_{11}H_{23}$. (a) Racemic synthesis and X-ray crystal structure of (±)-**1**. (b) Separation of enantiomers of 5 and synthesis of *M*-(−)-**1**/*P*-(+)-**1**. Reagents and conditions: (i) Tf_2O, pyridine, DCM, 0 °C to rt, 16 h, 94%; (ii) NEt_3, formic acid, $Pd_2[dba]_3$ (10 mol %), *rac*-BINAP (20 mol %), toluene, 120 °C, 40 h, 86%; (iii) *n*BuLi, TMEDA, Et_2O, −78° to rt, 16 h, then $B(OMe)_3$, −78° to rt, 8 h, then $NaOH/H_2O_2$, −78° to rt, 16 h, 47%; (iv) BBr_3, DCM, −78° to rt, 16 h, 91% (*M*-(−)-**1**, 96%; *P*-(+)-**1**, 97%).

(±)-**4** starts from the readily available racemic (±)-**2**, which can be prepared on the decagram scale in good yields from *O*-methylresorcinol and lauric aldehyde in the presence of the Lewis acid $BF_3{\cdot}Et_2O$ within a day.[14]

(±)-**2** is converted to the tetratriflate (±)-**3** in 94%, using literature conditions.[13] After optimization of the reported conditions,[13] it was possible to remove the triflates in high yield using $Pd_2[dba]_3$, *rac*-BINAP, and formic acid to give (±)-**4** (86%). The crucial step of the synthesis of (±)-**1** involved the tetrafunctionalization of (±)-**4**, which was achieved through ortho-lithiation. Ortho-lithiations of resorcin[4]arene derivatives are known[15] but typically require two *O*-alkylated directing groups per lithiation site. To achieve reasonable yields with the single methoxy directing group per aromatic moiety in (±)-**4**, a large excess of *n*BuLi and TMEDA, as well as long reaction times and a precise temperature program, were required. As a result of these optimizations, the yield for the tetrahydroxylated product (±)-**5**, obtained by subsequent borylation and oxidation to the phenol,[16] was increased to 47% while at the same time ensuring scalability of the reaction. At this stage, it was possible to readily separate the enantiomers by preparative, chiral HPLC to give optically pure *M*-(−)-**1** and *P*-(+)-**1** (Scheme 1b, Supporting Information (SI), Figure S12). In the final step, the methyl protecting groups were removed using boron tribromide, followed by a final purification by column chromatography to yield either (±)-**1** or enantiopure *M*-(−)-**1** and *P*-(+)-**1** in yields >90%. Catechol[4]arene was extensively characterized by ESI-HRMS, NMR- and IR-spectroscopy, as well as X-ray crystallography (Scheme 1a) to confirm the macrocyclic structure.

Single crystals suitable for X-ray crystallography were obtained from a solution of (±)-**1** in DMSO at room temperature. The crystal structure analysis of catechol[4]arene (space group: *P*-1) revealed a pseudoboat conformation (C_{2v} symmetry, Figure 2). While this deviation from ideal C_4-



Property	1	RS	PG
a/Å	7.73	7.81	7.75
b/Å	9.31	9.25	8.95
$\Delta\alpha_{max}$/°	4.7	1.4	0.7

Figure 2. X-ray crystal structure of (±)-**1** with the distances *a* and *b* and the tetrahedral angle *α*. Values for *a*, *b*, and the maximum variability of the tetrahedral angle $\Delta\alpha_{max}$ for **1**, RS, and PG.[17]

symmetric crown conformation is observed for its sister molecules RS and PG in the solid state, it is slightly more pronounced in the case of **1**.[17] This is reflected in the distances between the phenolic units of the macrocycle, for which **1** exhibits both the shortest (*a* = 7.73 Å) and longest (*b* = 9.31 Å) distance between two opposing aromatic faces across all three systems (Figure 2; SI, Figures S4, S9−S11 and Appendix B for details). Further structural differences between **1**, RS, and PG are observed for the distortion of the tetrahedral angles *α* at the bridging methane carbons. While for the latter two systems, these four angles vary by less than 1.5°, **1** shows considerable variability of $\Delta\alpha_{max}$ = 4.7°. These findings suggest a decreased rigidity of the framework that enables a more flexible conformation in comparison to its sister macrocycles.

To investigate the chiral properties of **1** in solution, its enantiomers were analyzed by CD-spectroscopy and optical rotation measurements. These characterization methods along with DFT calculations[18] allowed to assign the axial chirality and optical activity for *M*-(−)-**1** and *P*-(+)-**1** (Figure 3, SI, Chapter 2.5).[19]

After having confirmed the structure, its ability to self-assemble was explored. (±)-**1** turned out to be poorly soluble in chloroform, and no evidence for the formation of larger self-assembled structures was obtained by NMR spectroscopy (SI, Chapter 2.2). Also forcing conditions like prolonged heating, ultrasonication, templating, and ball-milling failed to induce any form of soluble higher structure.[20] The same was true for the optically active forms, *M*-(−)-**1** or *P*-(+)-**1**. We suspect that the

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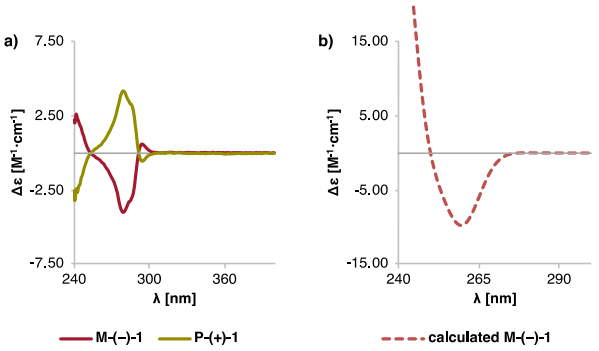

Figure 3. (a) Experimental CD spectra of enantiomers *M*-(−)-**1** and *P*-(+)-**1** in chloroform; (b) calculated CD spectrum for *M*-(−)-**1** (TD DFT B3LYP/6-31G(d,p)) in chloroform.

absence of hydrogen bonds between the aromatic units of the macrocycle, which stabilize the crown conformation in case of RS and PG, is detrimental to its aptitude for self-assembly. In polar solvents, such as acetone, diethyl ether, or methanol, **1** exhibited good solubility. The latter solvent is particularly interesting, as RS and PG are practically insoluble in alcoholic solvents, explaining their use for the recrystallization of these macrocycles.[21] The solvation of **1** is presumably facilitated through the increased flexibility of the macrocyclic framework.

The DFT calculations of **1** suggest a conformation with C_{2v} symmetry as major species in solution (SI, Figure S15, Table S3, and Appendix C). Nevertheless, the ^{1}H NMR spectra suggest a well-defined C_4 symmetric macrocycle, independent of the solvent and devoid of any signal splitting typically expected for C_{2v} symmetry. Consequently, it can be proposed that two rapidly interconverting pseudoboat conformers are present in solution (SI, Figure S3). Similar observations have been made for a related system.[22]

In light of the systematic differences between **1** and its sister macrocycles, the question arose to which extent their guest binding capability differs. We investigated the binding of organic ammonium guests. Acetone was chosen as solvent due to the good solubility of all three hosts (SI, Figure S5). Initial experiments with (±)-**1** and varying concentrations of methylpyridinium guests G1 and G2 showed considerable shifts of the host and guest signals indicating the formation of host–guest complexes in fast exchange on the NMR time scale (Figure 4; SI, Chapter 3.1).

Interestingly, binding of G1 and G2 was substantially higher than in RS and PG. A small library of five achiral guest molecules was investigated, comprising mono- and dicationic (G1, G2) methylpyridinium salts, as well as benzylic (G3) and phenylic (G4, G5) tri- and dimethylammonium salts. The hexafluorophosphate counterion ensured good solubility of these salts in acetone. As all three macrocycles were in fast exchange with their respective guests, the binding constants K_a for the host–guest complexes were determined by means of ^{1}H NMR titration in acetone-d_6 (Figure 5).[23]

While all host–guest complexes showed only weak to moderate binding affinities, (±)-**1** outperformed the other systems in every case tested. Surprisingly, RS demonstrated the weakest binding capabilities, which stands in stark contrast to its properties as a hexameric capsule in apolar solvents.[8a,e] The binding ability of (±)-**1** to G1 is comparable to the pillararenes.[24]

Upon assessing the achiral binding capabilities, we shifted our attention toward chiral recognition using enantiopure *M*-(−)-**1**

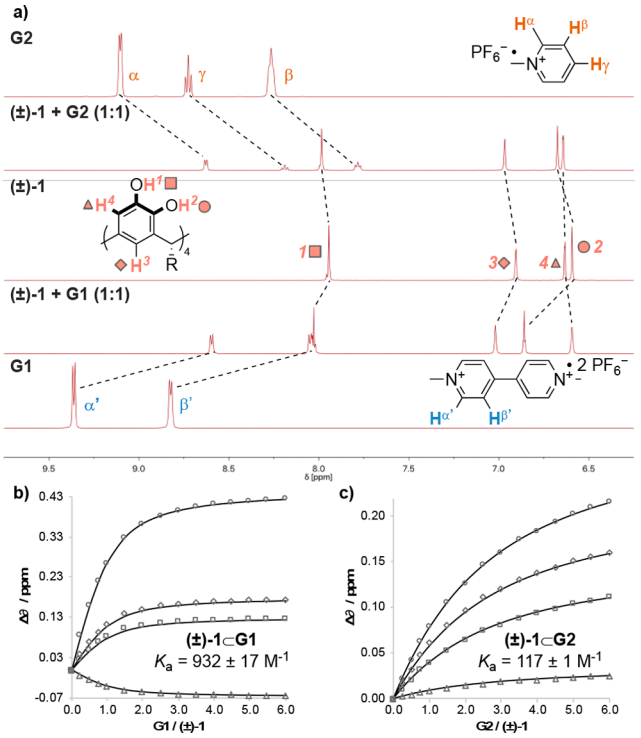

Figure 4. Host–guest interactions of (±)-**1** with guests G1 and G2. (a) Partial ^{1}H NMR spectra of G2; (±)-**1** + G2 (1:1, 4 mM); (±)-**1**; (±)-**1** + G1 (1:1, 4 mM); G1. (b,c) NMR shifts $\Delta\delta$ of (±)-**1** signals with increasing equivalents of G1 and G2 and their corresponding binding constants K_a for (±)-**1**⊂G1 and (±)-**1**⊂G2. All spectra were recorded in acetone-d_6.

G#	(±)-1 K_a/M^{-1}	RS K_a/M^{-1}	PG K_a/M^{-1}
G1	932 ± 17	47.2 ± 0.80	152 ± 3.2
G2	117 ± 0.80	10.5 ± 0.18	34.1 ± 0.10
G3	32.7 ± 0.22	n.d.	15.8 ± 0.045
G4	83.3 ± 1.3	12.5 ± 0.22	39.0 ± 0.51
G5	36.5 ± 0.19	6.75 ± 0.076	34.3 ± 0.33

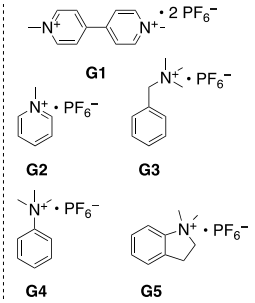

Figure 5. Binding constants K_a of (±)-**1**, RS, and PG and the corresponding guest (M^{-1}), determined by ^{1}H NMR titration in acetone-d_6. Titrations performed at 4 mM of host. n.d.: K_a could not be determined by means of NMR titration.

and *P*-(+)-**1**. Initial tests were performed with (*S*)-G6, a methylated derivative of 1-indamine, an important drug intermediate.[25] The ^{1}H NMR in acetone-d_6 of a 1:2 mixture of (±)-**1** and (*S*)-G6 demonstrated two distinguished sets of signals for each of the diastereomeric complexes *M*-(−)-**1**⊂(*S*)-G6 and *P*-(+)-**1**⊂(*S*)-G6 (Figure 6b). An exact assignment of the peaks was accomplished by comparison with spectra of pure *P*-(+)-**1** and (*S*)-G6 (Figure 6c).

To identify any form of enantioselective binding, a library of four chiral ammonium salts was compiled and the binding constants K_a for each host–guest pair were determined via ^{1}H NMR titration in acetone-d_6 (Figure 7; SI, Chapter 3.2).

For the structurally related guests (*S*)-G6, (*R*)-G7, and (*R*)-G8, a trend for selectivity of *M*-(−)-**1** toward *S* and *P*-(+)-**1** toward *R* configured guests was observed. In the case of the

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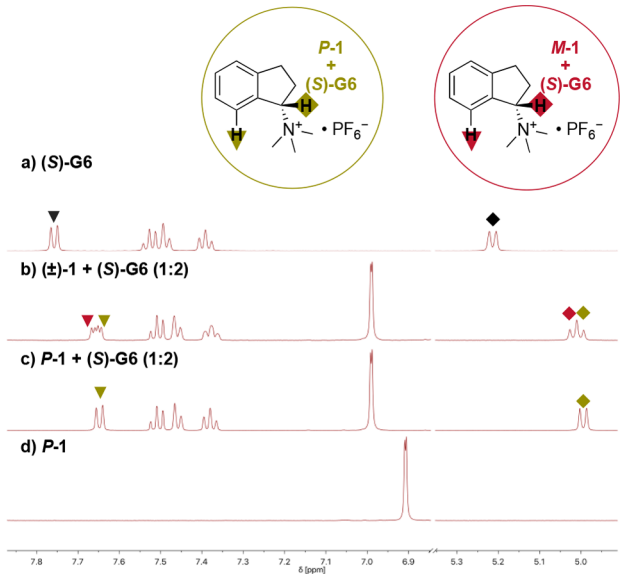

Figure 6. ^{1}H NMR spectra of (a) (*S*)-G6; (b) 4 mM (±)-**1** and 8 mM (*S*)-G6; (c) 4 mM *P*-(+)-**1** and 8 mM (*S*)-G6; (d) 4 mM *P*-(+)-**1**. All spectra were recorded in acetone-d_6.

G#	*M*-(—)-1 K_a/M^{-1}	*P*-(+)-1 K_a/M^{-1}	$K_a(M)/K_a(P)$
(*S*)-G6	58.4 ± 0.11	47.3 ± 0.085	1.23:1
(*R*)-G7	63.8 ± 0.14	79.4 ± 0.23	1:1.24
(*R*)-G8	37.7 ± 0.16	55.8 ± 0.26	1:1.48
(*S*)-G9	273 ± 0.95	268 ± 0.66	1.02:1

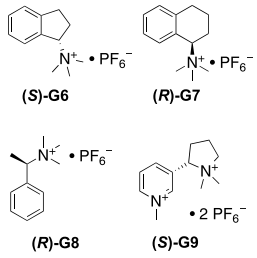

Figure 7. Binding constants K_a of *M*-(−)-**1** and *P*-(+)-**1** and the corresponding guest (M^{-1}), determined by ^{1}H NMR titration in acetone-d_6. Titrations performed at 4 mM of host.

structurally closely related guests (*S*)-G6 and (*R*)-G7, a chiral binding preference is detectable with $K_a(M)/K_a(P)$ values amounting to 1.23:1 and 1:1.24, respectively. The overall binding affinity increased with the dicationic guest (*S*)-G9 in accordance to our previous findings with G1. At the same time, binding selectivity with (*S*)-G9 became almost negligible. This observation may be explained by examining the binding motifs of this particular guest. While (*S*)-G9 possesses two cationic sites, our results from titration of the achiral guests G2 and G5 with racemic (±)-**1** suggest (*S*)-G9 to primarily bind via its methylpyridinium moiety. Because the chiral information, located on the pyrrolidinium moiety, points away from the chiral cavity of **1**, the selectivity might be lost. The strongest chiral recognition was observed for (*R*)-G8. In this case, the chiral center at the benzylic position displays a high degree of rotational freedom, which may be translated into an enhanced adaptability toward the chiral environment of the host, thus expressing the highest selectivity.

In summary, we have developed a short, high yielding (39% overall yield), and scalable synthesis of a missing member of the calix[4]arene family denoted "catechol[4]arene". This new, inherently chiral macrocycle was characterized in detail and compared to its sister molecules resorcin[4]arene and pyrogallol[4]arene. Macrocycle **1** is well soluble in alcohols while showing poor solubility in apolar solvents such as chloroform, which sets it apart from its close relatives RS and PG. In contrast to RS and PG, no evidence for the formation of larger self-assembled structures was found. However, (±)-**1** exhibited guest binding capabilities in polar solvents which exceeded those of RS and PG. This property may be attributed to its more flexible conformation that adapts to maximize the interaction with the individual guests. The enantiomers *M*-(−)-**1** and *P*-(+)-**1** were accessed by preparative, chiral HPLC, and their absolute configuration was assigned by CD spectroscopy and quantum mechanical calculations. The optically active macrocycles showed modest chiral recognition of optically active ammonium salts. We believe that **1** could serve as a readily available, inherently chiral macrocyclic platform for further derivatization and applications in chiral recognition, asymmetric catalysis and chiral self-assembly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01864.

Experimental details, NMR spectra of new compounds and computational and crystallographic data (PDF)

Accession Codes

CCDC 1999713 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

K.T. supervised the project. S.J.N. and K.T. conceived and planned the project. S.J.N. carried out all experimental work. H.J. and A.S. performed and interpreted the DFT calculations. A.P. performed the X-ray crystallography. The first draft of the manuscript was compiled by S.J.N. and K.T.

Notes

The authors declare no competing financial interest.

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