On the Stability and Formation of Pillar\[n\]arenes: a DFT Study

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ABSTRACT: The increased use of both pillar[5]arenes and pillar[6]arenes, stimulated by increasingly efficient syntheses of both, has brought forward the question as to what drives the intermediates in this Friedel–Crafts ring formation to form a pillar[5]arene, a pillar[6]arene, or any other sized macrocycle. This study sets out to answer this question by studying both the thermodynamics and kinetics involved in the absence and presence of templating solvents using high-end wB97XD/6-311G(2p,2d) DFT calculations.

INTRODUCTION

The rapid rise of supramolecular chemistry has invoked a wide range of macrocyclic compounds,1 which increasingly make use of the precisely balanced covalent and non-covalent forces. This development has led to classical studies of crown ethers, cyclodextrins, and calixarenes but, more recently, also to a much wider variety, including cucurbiturils, heteroatom-containing macrocycles, and bis-paraquat-based macrocycles.2 Here, a central theme is relevant, namely, the intrinsic tendency of ring-closing reactions to form smaller rings or linear oligomers, rather than larger macrocycles. The balance between entropy (focusing on easy-to-form small rings or highly disordered oligomers) and enthalpy (often thought to dominate the formation of intermediate size rings) does in such cases tend to optimize specifically sized macrocycles.

A case in point is pillar[n]arenes [hereafter referred to as Pn]. Discovered by Ogoshi’s group in 2008, this class of macrocycles is dominated by the name-giving pillar[5]arenes [P5s].3 With this size, the para-substituted aryl rings are all oriented in the same direction (see Figure 1), giving rise to a unique hollow pillar shape. As a result of this structure and because of the ease to construct this macrocycle from intermediate oligomers, it has become one of the pillars of modern macrocyclic chemistry. This development hinges on possibilities for the precise functionalization of Pn, which after initial studies of especially mono- and difunctionalized P5s,5 has recently come to full fruition by the development of synthetic methods that allow the functionalization at will of rim-differentiated Ps,6 culminating in the formation of so-called tiara[5]arenes that are fully functional on one rim, while the other rim consists of C–H moieties.6 Such improved
syntheses have given rise to the development of a wide range of functional \( \text{P5} \)s that display tailor-made complexation—for example, biosensing—or structural features that allow for the formation of larger aggregates and even steered the discovery of novel phenomena, such as non-porous adaptive crystals, that selectively bind materials but without involvement of the macrocyclic pore. More recently, there is also an increasing focus on \( \text{P6} \)-based materials. The yield of \( \text{P6} \)s is characteristically only a few percent in this Friedel–Crafts-based cyclization reaction, but this can be optimized via a variety of synthetic approaches, explicitly including changes in the solvent and/or Lewis acid. As a result, more and more \( \text{P6} \)-based materials have shown up in literature. In contrast, no \( \text{P4} \) has been described, and the syntheses of larger \( \text{Pn} (\text{P7} - \text{P10}) \) have been marred by very low yields.11

There are three questions we aim to answer in this paper: (a) to which degree do the thermodynamics of the products determine the outcome of this ring-forming reaction? (b) Do the different sized \( \text{Pn} \)s display significant differences in their formation, that is, in the corresponding transition states (TSs)? (c) What is the role of the solvent? Given the Friedel–Crafts nature of this reaction, we focus for the latter two questions on the protonated species that actually form the macrocycle. We study these phenomena by high-end range-separated density-functional \( \text{wB97XD/6-311G(2d,2p)} \) calculations on per-methoxy substituted \( \text{Pn} \)s. This combination of a high-end density functional and extensive basis sets creates an approach that can give a proper description of both strain effects in products, intermediates, or TSs, and of the complexation of templating solvent molecules that have been described to play a crucial role in steering the reaction outcome.13 All DFT calculations were performed using the Gaussian 16 suite of programs, using the solvation model based on density

Figure 2. Conformations of different sized pillararenes \( (n = 4 - 8) \) and relative stability \( (E + ZPE) \) of these pillar[\( n \)]arenes per monomer compared to \( \text{P5} \) (in kcal/mol). Note: \( E + ZPE \) is calculated at the \( \text{wB97XD/6-311G(2d,2p)} \) level \textit{in vacuo} and in ACN (in brackets).
(SMD) model for generic solvent effects, with acetonitrile (ACN) as a standard solvent.\textsuperscript{15}

**RESULTS AND DISCUSSION**

Relative Energies of Pillar[n]arenes. To obtain detailed insights into the thermodynamics of Pillar formation, we calculated the structures and stability (here defined as the sum of electronic energy + zero-point energy \(E + ZPE\)) of the four- to eight-membered ring compounds of this family (see Figure 2). For all, a molecular mechanics-based conformational search was performed using the Merck molecular force field in Spartan.\textsuperscript{16} While it was not the goal to undertake an extensive conformational search, this approach confirmed that we did not miss any low-energy conformation. This was then followed by the wb97XD-based DFT calculations. Most of the P4 and P5 conformers found in the conformational search were not found as local minima when optimized at the wb97XD/6-311G(2d,2p) level of theory but rather merged into the characteristic symmetric structures, respectively, with \(C_2\) and \(C_2\) rotational axes for the P4 and P5 rings, respectively. One other conformer was found in both cases but for both at a higher energy than the name-giving symmetrical ones.

If a ring in the structure is rotated, the energy goes up. For P4, this yields (see Figure 2) an energy increase of ca. 1 kcal/mol per monomer, that is, 4 kcal/mol, in total. For P5, only one low-energy conformer is found (see Figure 2), as confirmed by a recent extensive study of the rotation of P5 rings.\textsuperscript{17} Analogous \(C_2\) and \(C_2\) symmetric structures are also found for P6 and P7, respectively, but therein the conformational freedom is larger, and the highly symmetric structures do not correspond to the lowest-energy minima: if one or two of the aryl rings are rotated, other conformational minima are also found, and these are even more stable than the more symmetric counterparts by several kcal/mol. The \(C_2\) symmetric structure of P7 also clarifies why that is the case (see Figure 2, bottom left): although the \(C_2\) structure is a certified minimum on the potential energy surface (i.e., it displays no imaginary vibrational frequencies), it is characterized clearly by a slight outward bending of the CH\(_2\)--aryl--CH\(_2\) fragments, giving rise to ring strain. In addition, upon changing the rotation of the rings, a more compact structure with increased intramolecular interactions is obtained. The attractiveness of such interactions becomes clear in P8, for which no \(C_8\) symmetric structure could be obtained. Three different structures were found: a “double cavity” structure that resembles a structure observed in crystals (Figure 2, bottom left);\textsuperscript{11c} a more compact, but still two-fold symmetric structure in which the increasing flexibility in the ring is used to obtain a variety of intramolecular stabilizing interactions, including a slightly tilted \(\pi--\pi\) stacking of the 1- and 5-aryl rings in this molecule (smallest C–C distance: 3.52 Å; full range: 3.52–3.93 Å; Figure 2, bottom, middle); and—as the lowest-energy conformation—a twisted “two-cavity” structure without obvious symmetry elements and significant intramolecular interactions.

Apart from the relative energy of various conformations, the most surprising result obtained from these calculations of various macrocycles actually is the relative stability per monomer. Such comparison reveals the relative stability of different Pillar members, that is, the relative enthalpy of formation. These data allow us to arrive at four conclusions: (1) P5 is by far the easiest member to synthesize, but it is not the most stable Pillar[n]arene. While it is, per monomer, indeed more stable than centrosymmetric P4 and P6 conformers, there are already other P6 conformers that are more stable per repeating unit. Also, P7 has a conformation that is more stable, and this is even more the case for P8. (2) The 2.29 kcal/mol per monomer, for example, the \(C_2\) symmetric structure of P8 actually refers to a large stability difference, as it means that when eight P5 molecules are rearranged to yield five P8 \(C_2\)-symmetric molecules, such a conversion has a reaction enthalpy of 40 X \(-2.29 = ca. -91\) kcal/mol. Thus, the enthalpy of the ring closure of diphenol moieties with formaldehyde (or derivatives thereof) itself cannot be the driver for the efficient reaction observed for P5 formation, and the near-complete lack thereof, for example, P8. (3) The name-giving pillar-like structure is a viable structure for the smaller members, but not for any larger ones and then non-pillar-like structures are actually more stable in line with experimental findings. This is perhaps no surprise for P7 and P8, but it is already calculated to be the case for P6. (4) While no reports of P4 have been published, these stability calculations suggest that the strain energy should not be prohibitive in achieving this goal—as already suggested by the successful syntheses of [1.1.1.1]paracyclophane and pillar[4]-pyridinium\textsuperscript{18}—although the role of the solvent in P4 formation may be a critical one (\textit{vide infra}).

Ease of Formation of Pillar[n]arenes without Templating Solvents. After concluding that the enthalpy of the ring closure of (formally) diphenol compounds and formaldehyde by itself cannot guide the macrocycle formation, we next focused on the barriers of formation, both in the absence and in the presence of any templating solvent molecules in the (forming) cavity. In the ring closure under Friedel–Crafts conditions, the TS without a templating solvent can be depicted as in Figure 3. In forming the TS, a delocalized benzyl cation approaches a neutral aryl group. This requires both the soon departing H atom and the H atoms of the CH\(_2\) moiety to bend away from planarity and forward (see Figure 3, top left). In the TS, the new ring-closing C–C bond is formed, and this leads to the protonated ring-closed intermediate (Figure 3, right bottom). In all the investigated cases, this is a real intermediate, as rapid proton transfer to and from, for
example, formaldehyde is taking place (e.g., $E_{act} = 4.7$ kcal/mol for proton transfer from $[P5 + H]^+$ to formaldehyde and $E_{act} = 3.5$ kcal/mol for proton transfer from protonated formaldehyde to $P5$). Our computational data shed light on three different facets of the reaction: the overall rate of reaction, the stability of any intermediates and the effects this has on the equilibrium, and the details of the ring formation itself.

To investigate the overall rate, we first calculated the barrier for a non-ring-forming $P3$ analogue, so as to remove any component of ring strain (see the Supporting Information for structure). This yielded an activation barrier ($E + ZPE$ correction) of 3.7 kcal/mol, and within the TS, a typical $r(C\cdots C) \approx 2.25$ Å. Only slightly higher values for the enthalpic barrier are found for $P4$, $P5$, and $P6$ formation: $E_{act} = 5.4$ kcal/mol for $P4$, 7.6 kcal/mol for $P5$, and 9.0 kcal/mol for $P6$ (see Figure 4, top). These low $E_a$ values are in line with experimental findings that show that the formation of pillararenes can be efficient at room temperature even without a templating solvent. The overall efficiency of the syntheses is, however, also determined by the stability of the product.

The exothermicity of the cyclization reaction was found to be $-14.1$ kcal/mol for $P4$, $-14.0$ kcal/mol for $P5$, and $-8.6$ kcal/mol for $P6$. Thus, the experimentally observed ease of formation of $P5$s and $P6$s is in line with these data, but—if this would be the whole story, which it is not (vide infra)—the experimental absence of $P4$ would still need to be explained.

Second, as a result, the energy barrier from the protonated product to the TS (i.e., the reverse reaction) becomes crucial for the overall yield in the syntheses. The enthalpy of activation for this back reaction was calculated to be $13.4$ kcal/mol for the unconstrained $P3$ model, $19.6$ kcal/mol for $P4$, $21.6$ kcal/mol for $P5$, and $17.6$ kcal/mol for $P6$. This confirms two things: (1) the ring-forming Friedel–Crafts reaction can indeed be considered as dynamic covalent chemistry with rapid exchange under the commonly used (Lewis) acid catalysis. (2) The (protonated) ring-closed product is thus significantly more stable than the benzylic cation intermediate, clearly driving the reaction in one direction. The low value of the energy barrier for both $P5$ and $P6$ formation does, however, not imply a simple reaction profile, in which only a
single path can be followed. For example, when the TS is first approximated by fixing the bond-forming carbon atoms at 2.25 Å (close to the maxima of the C–C bond-forming potential energy scans for nearly all structures under study) and optimizing the remainder of the structure, then—in the absence of a templating solvent molecule—a “nearly C₅-symmetric” TS to the protonated P₅ molecule has an activation barrier of 7.6 kcal/mol (Figure 5A). However, an alternative TS can be formed, in which the attacking benzylic cation is attacking “from the inside” with an only slightly higher energy barrier (Eact = 9.4 kcal/mol), as shown in Figure 5B. This TS yields a structure in which the H atoms of the bridging point inward, and these then rotate outward in moving from the TS to the protonated P₅ product. This attack “from the inside” proceeded under almost thermoneutral conditions (exothermicity of 2.4 kcal/mol). In other words, while the route indicated in Figure 3 is for P₅, which indeed is the lowest-energy mechanism, especially for larger macrocycles with increased flexibility, multiple analogous routes would be available.

**Ease of Formation of Pillar[n]arenes with Templating Solvents.** All the above energy barrier data only deal with the solvent effects via a continuum model that accounts for the polarity and polarizability of the medium surrounding the species, for which we—as a somewhat crude approximation of the evidently heterogeneous mixture of acidic organic solvents—take ACN as the polar organic solvent. However, in the formation of P₄s, often templating effects of solvents are invoked to explain the relative reactivity and/or product composition that was observed. Therefore, next, the effects of the most frequently used templating solvents [1,2-dichloroethane (DCE), chlorocyclohexane (CyCl), dichloromethane (CH₂Cl₂), and chloroform (CHCl₃)] were investigated.

The cyclization of P₄ with DCE inside the cavity gave a significantly higher barrier of 17.1 kcal/mol with a r(C–C) ~ 2.18 Å (compared to only 5.4 kcal/mol without DCE inside, vide supra), and the formation of the protonated product through a nearly thermoneutral reaction (~1.7 kcal/mol). In other words, if P₄ would have a DCE inside, it would lead to a significantly higher barrier than without DCE inside. In fact, a closer look at the TS and the protonated P₄ product reveals that the DCE lies half outside of the cavity, as it basically cannot fit in it. It is, however, not only the higher barrier imposed by the sterics of a DCE molecule in the cavity (i.e., product destabilization) that hamper the P₄ formation but DCE also stabilizes the reactant: in the ring-opened protonated P₄ intermediate, DCE can be nearly fully wrapped by the tetracyclic cation, yielding a complexation enthalpy of 18.7 kcal/mol. However, such stabilization is nearly given up by the pushing out of DCE from the forming cavity in the ring-closed protonated P₄ (with a complexation enthalpy of only 6.7 kcal/mol). As a result, in DCE and many other cation-stabilizing solvents, rather than helping out, the reactant stabilization effectively fully blocks the formation of P₄, which explains the near-absence of formation of any P₄. In addition, it seems likely that only in small-radius, weakly complexing solvents, any P₄ might be producible under such (Lewis) acid circumstances.

The situation for P₅ is more favorable in terms of TS barrier and stabilization of the formed macrocyclic structure. A “nearly C₅-symmetric” TS could also be obtained with a DCE molecule embedded in the cavity of the forming [P₅ + H⁺] macrocycle (Figure 5C). The role of DCE is frequently referred to as stabilizing the TS by a templating effect. As now the cavity is filled, only the larger TS can be formed. This yields a barrier of 5.6 kcal/mol, down from 7.6 kcal/mol without DCE in the cavity, and produces the protonated [P₅ + H⁺] macrocycle with an exothermicity of ~15.7 kcal/mol. Given the low activation barriers for the formation of the non-cyclic intermediates and for the ring-closure formation of protonated P₅, these TSs demonstrate that neither any of the non-cyclic intermediates nor the formation of P₅ requires a templating solvent molecule, although the formation is slightly catalyzed by a templating DCE. DCE does, however, also make the formation of ring-closed [P₅ + H⁺] more exothermic (from −14.0 to −17.7 kcal/mol) and thus helps to drive the reaction forward.

In addition, the enthalpy-driven wrapping around DCE by the ring-opened [P₅ + H⁺] implies that the entropic penalty of the ring-closure reaction is likely minimal, certainly compared

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**Figure 6.** TSs for ring closure to form protonated P₆ (C···C bond-forming distance is given in Å). (A,B) Different views of TSs for P₆ formation; (C–F) TS for P₆ formation with the solvent in cavity, namely, DCE (C), chlorocyclohexane (D), CHCl₃ (E), and CH₂Cl₂ (F).
to P5 with DCE in its cavity. Finally, with DCE as a template, the formation of P5 is strongly favored over both P4 and P6 (requiring 17.1 and 14.6 kcal/mol, respectively, see Figure 4B), explaining why it provides access to such smooth high-yielding synthesis.

In contrast, enforcing the reaction involving a templating molecule of CyCl in the cavity of P5 yielded a TS with an increased barrier of 10.1 kcal/mol and a reaction free energy of only −8.3 kcal/mol (Figure 5D). In other words, CyCl does not properly fit the P5 cavity and hampers rather than stimulates P5 formation. Its only positive effect may thus be on the stabilization of any intermediates from outside of the cavity.

The picture becomes more complicated when studying the formation of protonated P6. Here, the TS involving a molecule of DCE in the cavity has a barrier of 14.7 kcal/mol and thus 5.7 kcal/mol higher than that without DCE (Figure 6C). Since DCE does not fully fill the cavity, there is still a significant distortion from C6 symmetry in the TS and no proper activation entropy-lowering pre-organization, although only attack from the outside is observed to lead to the product. In contrast, CyCl really fills the cavity of [P6+H]+, leads to an ordered TS, displays a barrier of only 8.4 kcal/mol, and increases the exothermicity of the ring-closing step from −8.6 with DCE in the cavity to −15.0 kcal/mol with CyCl in the cavity (Figure 6D).

Similar studies were performed with CH2Cl2 and CHCl3 as templates. To validate the accuracy of our theoretical study, we finally compared the calculated barriers for P5 and P6 formation in these solvents with experimentally obtained yields of an analogous experimental study by Wang, Rathore, and co-workers, namely, the selective synthesis of P5 and/or P6 with methane-sulfonic acid as a catalyst (see Table 1).22 In Table 1. Comparison of Yields and Activation Energies for Pillar[n]arene Cyclization with Different Solvents in the Cavity

| solvent | P5 yield (%) | P6 yield (%) | Eact (ΔG) | Eact (ΔG) |
|---------|--------------|--------------|-----------|-----------|
| DCE     | 64           | trace        | 5.6 (−15.7) | 14.7 (−6.2) |
| CH2Cl2  | 71           | 8            | 7.2 (−12.2) | 11.8 (−8.7) |
| CHCl3   | 6            | 79           | 8.4 (−7.7)  | 4.5 (−13.4) |
| CyCl    | 5            | 56           | 10.4 (−8.3) | 8.4 (−15.0) |

*From ref 22. +Activation energies (Eact) and reaction free energies (ΔG) in kcal/mol.

the TSs for P5 formation, the solvents CyCl and CHCl3 are actually slightly too big for the cavity, and one and two Cl atoms are slightly above the ring formed by the aryl groups, respectively, thereby providing little stabilizing interactions. With both CH2Cl2 and DCE, both Cl atoms are more strongly involved in such stabilizing interactions. For P6 formation only for CyCl in the cavity, a nearly six-fold symmetric TS is observed. For the other three, the forming ring tries to reorganize in such a manner as to maximize the macrocycle-solvent interactions. For CHCl3, such distortion seems to be slightly less qualitatively, as it fills more of the cavity and two of its Cl atoms are directly pointing to an aryl ring. For both CH2Cl2 and DCE, such a fit requires more extensive conformational changes of the macrocycle. In all cases, the r(C·C) is a near-constant, thereby forming a strong limit as to what conformational changes are allowed. In summary, as observed experimentally, the preferential formation of P5 in DCE and CH2Cl2 and that of the cyclohexamer P6 in CyCl or CHCl3 is fully supported by the calculated differences in the activation barriers in each solvent, displaying the potential of our approach.

■ CONCLUSIONS

A detailed computational analysis of the process of pillar[n]arene formation shows four things: first, the predominance of P5 in the family of pillararenes is not caused by its intrinsic properties (stability and/or ease of formation)—without an active solvent, P4 requires a lower barrier to form, and P7 and P8 are evidently more stable. Second, while no templating solvents are needed, they do, however, help to slightly reduce the already low activation enthalpy, reduce the activation entropy by pre-wrapping the ring-opened structure around the solvent molecule, and help to drive the reaction forward by their significant complexation energies. Third, it is this solvent-macrocycle interaction that largely determines the relative ease of formation of various pillar[n]arenes in different solvents. Fourth, these findings precisely clarify why no P4 has been formed and also provide guidelines to further facilitate the formation of P6 and even larger Pn macrocycles. These results not only clarify the current—synthetically successful but conceptually partially vague—factors that drive the pillar[n]arene synthesis but also clearly point out the way to search for increased yields of, for example, P6s. Analogous analyses can also been made for other macrocycles. The rapidly growing interest in such more extended macrocycles for a variety of novel goals in supramolecular chemistry and materials science thus indicates the potential and experimental feasibility of such detailed mechanistic investigations.

■ EXPERIMENTAL SECTION

Computational Methods. All DFT geometry optimizations were performed with the dispersion-corrected wb97XD functional and the 6-311G(2d,2p) basis set as implemented within the Gaussian 16 series of programs. Solvent effects were included with the SMD continuum model to mimic ACN during both geometry optimizations and vibrational analysis. All of the energies and enthalpies presented for the reactant complex, TS, and product are given in hartree. All of the energies have been corrected with ZPEs. Vibrational frequency calculations were made at the same level of theory used for optimization. All TSs were verified to have only one negative eigenvalue in the Hessian matrix, describing the motion along the reaction coordinate. Furthermore, the calculated activation enthalpies and reaction enthalpies are given for every reaction in kcal/mol. Optimized structures were illustrated using CYLview20.3,23

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01679.

Full Gaussian 16 citation, various views for optimized pillar[n]arene structures, full results of conformational search, details on complexation energies for pillar[n]arenes, and the Cartesian coordinates of all structures in this paper (PDF)

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