



Research article

Modeling Nazarov cyclization inside a $[\text{Si}_4\text{L}_6]^{8-}$ nanocage: effects of charge and size[☆]Gantulga Norjmaa^{*}, Gregori Ujaque^{*}

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ABSTRACT

The Nazarov cyclization in a $[\text{Si}_4\text{L}_6]^{8-}$ tetrahedral nanocage is investigated by means of a combination of density functional theory (DFT) calculations and molecular dynamics (MD) simulations. Experimentally, the reaction is accelerated within the Si-cage relative to that in solution but slightly less accelerated compared to the $[\text{Ga}_4\text{L}_6]^{12-}$ analogue. In this work the following questions are addressed: how does $[\text{Si}_4\text{L}_6]^{8-}$ affect key steps of the reaction? What are the origins of the rate acceleration in the $[\text{Si}_4\text{L}_6]^{8-}$? Where does the difference in rate acceleration between these two cages stem from? To determine the relative stability of the protonated substrate within the cage compared to that in solution, the main step in the process, we establish a computational scheme involving the calculation of Gibbs binding energies of neutral and protonated species by means of MD simulations, along with computation of Gibbs energy of protonation at DFT level. The results are compared to that in solvent and within that of $[\text{Ga}_4\text{L}_6]^{12-}$ nanocage, revealing the influence of encapsulated solvent. Overall, the results are in good agreement with experiments, both in solution and for the two metallocages, thereby providing deeper understanding of the effects of charge and size in the supramolecular cage-catalyzed Nazarov cyclization.

1. Introduction

Supramolecular catalysis can be considered as a bridge between homogeneous catalysis and enzymatic catalysis. [1–3] In the last few decades, many nanocages have been employed successfully for supramolecular catalysis [4–8] such as Raymond's [9] Ga_4L_6 , Fujita's [10] Pd_6L_4 , Nitschke's [11] Fe_4L_6 , or Lusby's [12] Pd_2L_4 among others. [13].

Raymond's $[\text{Ga}_4\text{L}_6]^{12-}$ cage has been extensively investigated as a supramolecular host catalyst for several chemical reactions including the hydrolysis of orthoformates, [14] reductive elimination from Au(III) and Pt(IV) complexes, [15,16] the Nazarov cyclization, [17,18] the Prins cyclization, [19] hydroalkylation, [20] allyl alcohol isomerization, [21] and aza-Cope rearrangement, [22] among others. [23,24].

A Si-cage, $[\text{Si}_4\text{L}_6]^{8-}$, similar to the $[\text{Ga}_4\text{L}_6]^{12-}$ cage (Ga-cage), developed by Raymond, Bergman and Toste groups has also been demonstrated to accelerate the Nazarov cyclization by 3–4 orders of magnitude compared to the reaction in solution (Scheme 1). [25] The main difference between these two cages is the charge of the cage (33% reduction for the Si-cage, from -12 to -8). Interestingly, the Nazarov reaction was affected by this difference but cationic aza-Cope rearrangement was

not. The reason for this was originally attributed to the fact that a neutral substrate undergoes an increase in charge to access cationic transition states (TSs) in Nazarov cyclization whereas there is no change in charge of the substrate in net neutral aza-Cope rearrangement. [25] In order words, there is a proton-mediation process in Nazarov reaction but not in cationic aza-Cope rearrangement. Even though effects of charges have been highlighted in catalysis, [26] comparison between $[\text{Ga}_4\text{L}_6]^{12-}$ and $[\text{Si}_4\text{L}_6]^{8-}$ for Nazarov cyclization and cationic aza-Cope rearrangement represents the first experimental evidence of effects of synthetic supramolecular host charges in catalysis. [25] Both reactions have already been modeled in $[\text{Ga}_4\text{L}_6]^{12-}$, [27–29] however, comparison between the overall Nazarov reaction for $[\text{Ga}_4\text{L}_6]^{12-}$ and $[\text{Si}_4\text{L}_6]^{8-}$ was not previously performed; only the proton transfer step was investigated computationally [27] whereas the other steps of the cyclization within $[\text{Si}_4\text{L}_6]^{8-}$ were not considered, despite being rate-limiting steps (vide infra). Therefore, detailed computational investigations of Nazarov cyclization within $[\text{Si}_4\text{L}_6]^{8-}$ would lead to deeper understanding of the role of the host charge on these processes, since currently only carbon-carbon reductive elimination from an Au(III) complex have been studied computationally inside $[\text{Si}_4\text{L}_6]^{8-}$ in comparison with $[\text{Ga}_4\text{L}_6]^{12-}$. [30].

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In recent years, computational techniques have been employed successfully to study a number of reactions taking place in metal–organic cages (MOCs), elucidating origins of catalysis or rate accelerations. [27–35] In the present work, we investigate computationally the origins of a rate acceleration determined experimentally in Nazarov cyclization of 1,4-pentadien-3-ol within $[\text{Si}_4\text{L}_6]^{8-}$ (L represents the bidentate catechol ligand, 1,5-bis(2',3'-dihydroxy-benzamido) naphthalene) and evaluate the effects of the Si-cage on each key step of the reaction. The Nazarov cyclization is one of the fundamental processes to form five-membered rings in organic syntheses. We employ a combination of quantum chemical calculations, based on DFT, and molecular dynamics (MD) simulations to analyze the reaction in solution and inside the cages. The results are in good agreement with the experiments, elucidating the effects of $[\text{Si}_4\text{L}_6]^{8-}$ on different steps of the reaction and providing a deeper understanding of the origins of rate accelerations observed experimentally.

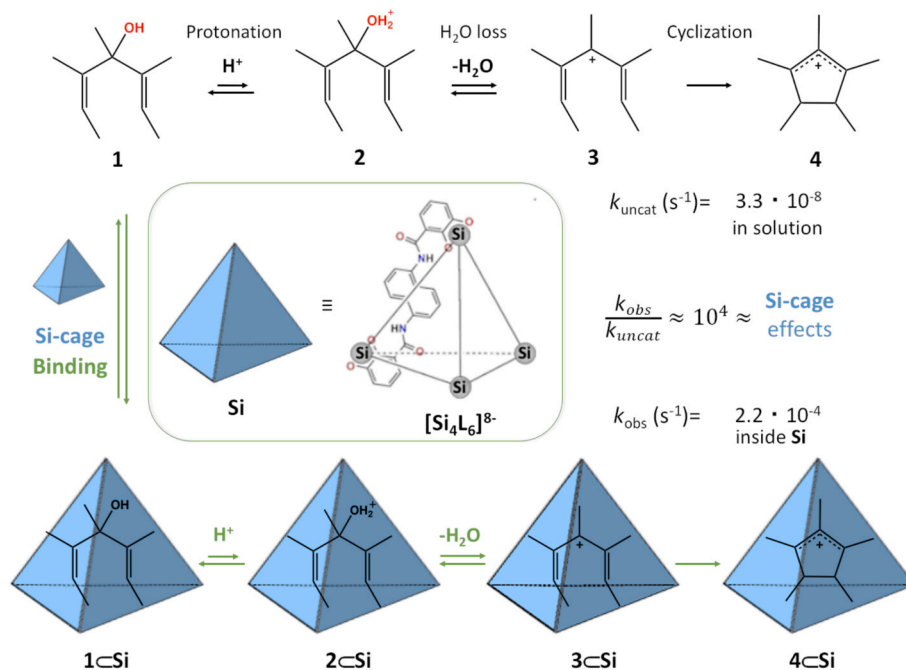
2. Computational details

All Gibbs energies were calculated at full DFT level except the binding of the neutral and protonated substrate in the Si-cage which were computed with molecular dynamics (MD) simulations.

All DFT calculations were performed using the Gaussian 16 software [36] with the B3LYP-D3 functional. [37–39] The SDD pseudopotential and related basis set was used for Si while the 6-31G(d) basis set was used for all other atoms. [40] The structures of the reactants, intermediates, transition states were optimized in water solvent by using the SMD continuum model. [41] The transition states were optimized at DFT level (i.e., B3LYP-D3/SMD) with the Gaussian16 program and the convergence criteria for the gradients were those by default in Gaussian16. The transition states were confirmed by frequency analysis with a single imaginary frequency corresponding to the vibrational motion of the breaking or forming bond. DFT calculations for Gibbs energies include two explicit water molecules along with the substrate in the cage. The most populated structure from MD simulation and additional starting structures constructed manually were used as initial structures for DFT geometry optimizations. These calculations involve systems with more than 300 atoms. The quasi-rigid-rotor-harmonic-

oscillator (quasi-RRHO) approach was used for thermal contributions to the Gibbs energies at 298.15 K with a cutoff of 100 cm^{-1} using the GoodVibes program. [42,43] The BSSE corrections for binding energies for the encapsulated neutral and protonated alcohol complexes were calculated with the Counterpoise method developed by Boys and Simon. [44,45] The standard state corrections are calculated in the 1 atm standard state. The reference state in solution is the 1 M state for all compounds and the correction term $RT \ln(1/24.5\text{ L/mol} \times 1\text{ mol/L}) = 1.9\text{ kcal/mol}$ was added to all compounds. [46]

MD simulations were performed with the AMBER 16 package [47] using the CUDA version of the pmemd program. The cage was solvated using Amber tleap solvatebox function by specifying the TIP3P water model. [48] no solvent water molecules were initially placed within the cavity. After minimization, heating and equilibration, the dynamic motion of water molecules entering and leaving is observed during MD simulation. The MD simulation box, of size $46 \times 49 \times 47\text{ Å}$ and treated under periodic boundary conditions, contains the Si-cage, the guest, and the needed number of potassium counterions reach neutrality (7 and 8 potassium counterions for the protonated and neutral alcohol substrates, respectively) and 2500 water molecules (TIP3P). [48] Force field parametrization procedure was described in our previous work. [49] The simulations were performed at constant temperature (298.15 K, using a Langevin thermostat) and pressure (1 bar, using a Monte Carlo barostat). A collision frequency of 2 ps^{-1} for Langevin dynamics and a time step of 2 fs were used in plain MD simulations, whereas for Gibbs energy calculations, a collision frequency of 1 ps^{-1} was used according to the APR method. [50] The binding Gibbs energies (ΔG_{bind}) were computed at DFT level ($\Delta G_{\text{bind,DFT}} = \Delta G_{\text{cage-substrate}} - \Delta G_{\text{cage}} - \Delta G_{\text{substrate}}$), and using the attach – pull – release (APR) method ($\Delta G_{\text{bind,MD}}$) [50–52]. The simulation details are: minimizing 50,000 cycles, running 1 ps NVT at 10 K, heating the system from 10 K to 298.15 K in 100 ps, equilibrating the system under constant pressure, 50 NPT cycle, and NPT production from 2.5 ns to 25 ns depending on the standard error of the mean (SEM) of the restraint forces; the SEM threshold is 0.100, analogous to the ones employed in our previous work. [49] The UCSF Chimera was used for clustering MD structures. [53].



Scheme 1. General schematic representation of the Nazarov cyclization of 1,4-pentadien-3-ol, 1, (black arrow) in solution and (green arrow) in Si-cage. Rate constants are taken from ref [18] and [25].

3. Results and discussion

Uncatalyzed Nazarov cyclization of 1,4-pentadien-3-ol (background reaction) in aqueous solution has several steps:[18] (i) protonation of the alcohol reactant, (ii) water loss from the protonated reactant, forming carbocation intermediate and (iii) cyclization of carbocation intermediate, forming a 5-member ring (black arrows in Scheme 1). For the Si-cage-catalyzed Nazarov cyclization, we will assume a similar encapsulated reaction thus involving an initial binding (i.e. encapsulation) of neutral substrate, followed by a protonation of the substrate within the Si-cage, water loss from the protonated substrate and an electrocyclization of the carbocation intermediate to form a 5-member ring; green arrows in Scheme 1.

The uncatalyzed reaction was investigated computationally in a previous study by us.[28] Since this is the background reaction for the Si-cage-catalyzed reaction, we first briefly discuss the results of the reaction in solution. In the next sections, we will discuss the results of the initial binding and protonation steps. The protonation of the substrate inside the Si-cage poses a challenge from the computational point of view since solvation Gibbs energies of the proton (employed for computing pKa values) are generally taken from experimental data; however, there is no experimental data for solvation of proton inside the Si-cage (i.e. inside any cage). We compare the energetics obtained for these steps using different computational approaches and discuss the importance of MD simulations to estimate the binding Gibbs energies for such host–guest complexation and protonation processes. Then, we present the results obtained for the following two key steps (water loss from the protonated substrate and electrocyclization of the carbocation intermediate) and discuss how these steps are affected by the Si-cage and the number of solvent molecules inside the Si-cage; the determination of the number of the encapsulated solvent molecules was based on MD simulations. Finally, we compare the effects of the Si-cage on each step of the reaction with those previously calculated for the Ga-cage in order to shed light on the charge role of these cages ($[\text{Si}_4\text{L}_6]^{8-}$ vs $[\text{Ga}_4\text{L}_6]^{12-}$).

3.1. Reaction in solution

A general schematic representation of the important intermediate structures for the mechanism are illustrated in Scheme 1 (black arrows for the uncatalyzed reaction and green arrows for the catalyzed one). As previously commented, the main reaction steps for the cyclization process are: (i) protonation of the alcohol group of the initial neutral substrate (1,4-pentadien-3-ol), **2**, (ii) water loss from the protonated substrate, forming a carbocation intermediate, **3**, and (iii) formation of the five-membered ring, **4**, by 4 π -electrocyclization.

The reaction in solution (uncatalyzed reaction) was previously investigated by our group employing DFT calculations,[28] and the overall Gibbs energy barrier was calculated to be 29.9 kcal/mol which is in excellent agreement with the experimental one of ca. 30 kcal/mol.[18] The rate-determining step of the reaction was calculated to be the cyclization, in concordance with the experimental results of the uncatalyzed (background) reaction.[18] The first step, protonation, was evaluated using a standard methodology for computational calculation of pKa,[18,54,55] and the protonated substrate, **2**, was calculated to be 19.5 kcal/mol higher in Gibbs energy than the initial neutral alcohol substrate. This was also in good agreement with the estimation reported based on experimental pKa values.[18] The next step is water loss from the protonated substrate and this step was calculated to have a Gibbs energy barrier of 26.6 kcal/mol, forming a high energy (24.8 kcal/mol relative to the initial neutral substrate) carbocation intermediate, **3**. The following step is cyclization with a transition state located 29.9 kcal/mol higher in Gibbs energy than the initial reactant, with the cyclized intermediate, **4**, at -3.1 kcal/mol. The Gibbs energy profile of the uncatalyzed reaction is shown in Fig. 2 along with that of the catalyzed reaction. In the subsequent sections, we will discuss the reaction within the cavity and how each of these steps is affected by the Si-cage.

3.2. Reaction within Si-cage

The reaction inside the Si-cage (catalyzed reaction) starts with the initial binding of the neutral substrate (1,4-pentadien-3-ol) to the Si-cage and proceeds with the same consecutive steps as those discussed in the previous section but within the Si-cage. We first discuss the initial binding and protonation steps within the Si-cage, and then the following steps.

3.3. Binding and protonation within Si-cage

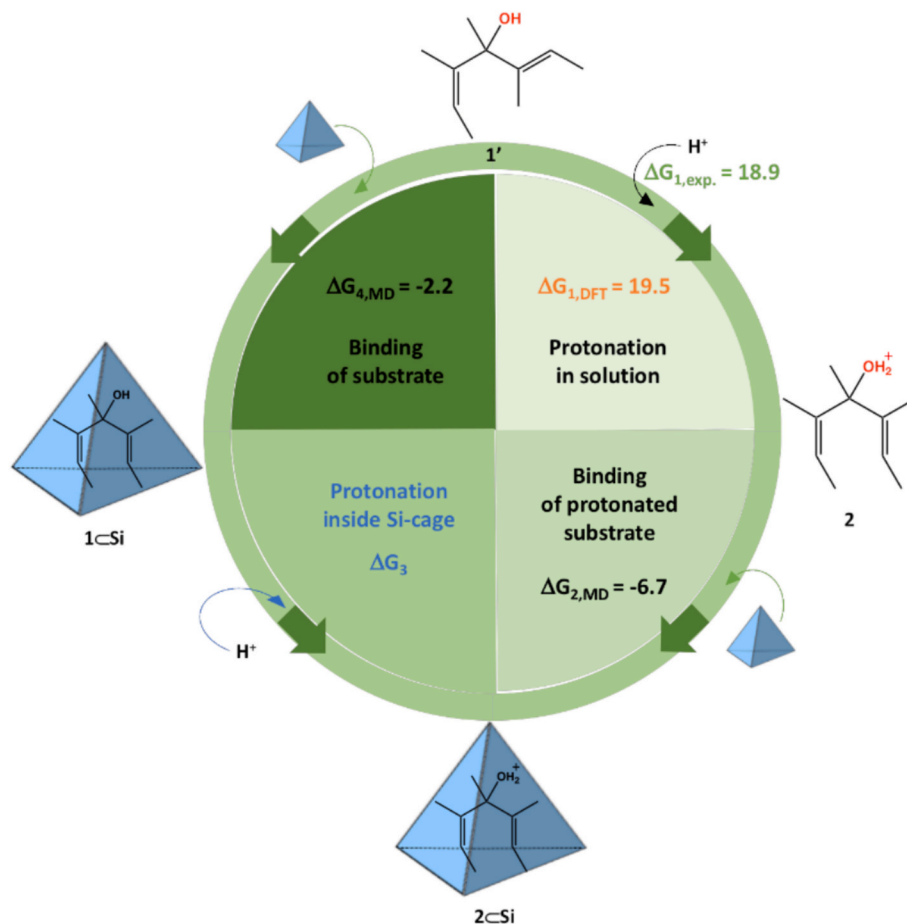
We first calculated the binding Gibbs energy of the initial neutral substrate (1,4-pentadien-3-ol) to the Si-cage. For this we employed two different schemes, one based on classical MD and umbrella sampling simulations ($\Delta G_{\text{bind,MD}}$) and another based on DFT calculations ($\Delta G_{\text{bind,DFT}}$); see computational details.

The calculated binding Gibbs energy at DFT level for neutral alcohol reactant **1**, $\Delta G_{4,\text{DFT}}$, is -0.5 kcal/mol. In turn, the calculated binding energy based on MD simulations, $\Delta G_{4,\text{MD}}$, is -2.2 kcal/mol, both in good agreement. Unfortunately, there are no experimental values for binding of 1,4-pentadien-3-ol to the Si-cage to compare with. Experimentally, encapsulation of the substrate is observed by NMR but the quantitative measure was not reported. [25].

The next step is protonation of the substrate within the Si-cage. Overall, the process involves encapsulation and protonation of the substrate leading to formation of the protonated substrate within the Si-cage (Scheme 2). In general, the Gibbs energy for the protonation is obtained using a standard protocol for pKa calculations in aqueous media; which relies on the experimental solvation Gibbs energy of the proton in water.[55] To apply this protocol in the present study the Gibbs energy for solvation of proton inside the Si-cage is required; however, no experimental data are available for this process. Consequently, from computational point of view, calculating the Gibbs energy for the protonation of the encapsulated reactant is more challenging than computing the binding Gibbs energy of the initial neutral reactant. To address this challenge, we derived a thermodynamic cycle consisting of two binding and two protonation processes as shown in Scheme 2.

The protonation of the substrate in solution was discussed in the previous section and it was calculated using a standard pKa calculation method.[28] The calculated Gibbs energy binding based on MD simulations for the protonated substrate ($\Delta G_{2,\text{MD}}$) is -6.7 kcal/mol. For the sake of completeness, we also computed the binding energy at DFT level, and it seems to be largely overestimated, $\Delta G_{2,\text{DFT}} = -13.0$ kcal/mol. In our previous study with the Ga-cage,[49] we calculated the binding Gibbs energy of tetraethyl ammonium based on both DFT calculations and molecular dynamics (MD) simulations. The results showed that DFT calculations with no explicit solvent overestimated significantly the value ($\Delta G_{\text{bind,DFT}} = -19.6$ kcal/mol), whereas MD simulations with explicit solvent ($\Delta G_{\text{bind,MD}} = -6.2$ kcal/mol) were in very good agreement with the experiment ($\Delta G_{\text{bind,exp}} = -6.3$ kcal/mol).[49] All these results indicate that computing the binding Gibbs is very challenging for these supramolecular host–guest complexes. Indeed, those methods based on MD simulations and conformational sampling with explicit solvent molecules appear to be more suitable approaches for these particular types of systems.

For obtaining the Gibbs energy for the protonation step within the Si-cage, ΔG_3 , we employed the thermodynamic cycle described in Scheme 2, using the calculations outlined in this subsection. The obtained value for ΔG_3 is 15.0 kcal/mol – based on the binding energies calculated with MD simulations. Compared to the process in solution, the energy required to protonate the reactant is diminished by 4.5 kcal/mol. This value, turns out to be crucial in the process, in agreement with previous studies.[27,28].



Scheme 2. Thermodynamic cycle to obtain the basicity (ΔG_3) of the encapsulated substrate (1) within Si-cage. Energies are given in kcal/mol.

3.4. Water loss and cyclization within Si-cage

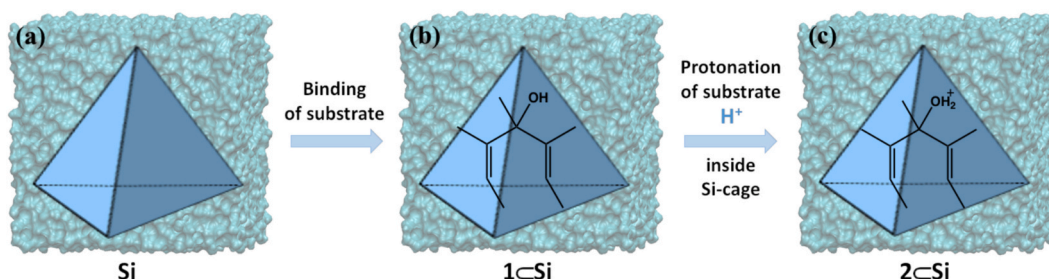
Once the substrate within the Si-cage is protonated, the following two steps involve water loss and cyclization inside the Si-cage (catalyzed reaction). We employed full DFT calculations to characterize these reaction steps. The importance of explicit consideration of solvent molecules has been highlighted in computational catalysis.[28,56,57] In order to know the number of solvent molecules encapsulated along with the protonated substrate within the Si-cage, we performed 200 ns MD simulations for the encapsulated protonated substrate (**2_{Si}**) in explicit water solvent (Scheme 3).

The simulation of **2_{Si}** show that the most populated structure along the simulation involves two solvent molecules encapsulated along with the protonated substrate within the Si-cage (see Supporting Information, Fig. S1). Therefore, we included two explicit solvent water molecules along with the protonated substrate within the Si-cage in the model systems (**2-w2_{Si}**) for DFT geometry optimizations. To identify the

most stable conformation of **2-w2_{Si}**, several arrangements including the most populated structure from MD simulation and other configurations constructed manually were used as initial geometry. The analysis was based on the most stable structure, whereas higher energy configurations are shown in the Supporting Information (Fig. S2).

The optimized geometries of intermediates and transition states for encapsulated substrate along with two explicit water molecules are shown in Fig. 1. The encapsulated protonated intermediate, **2-w2_{Si}**, as previously shown, has a relative Gibbs energy of 15.0 kcal/mol estimated using the thermodynamic cycle shown in Scheme 2. The transition state for the water loss from the protonated substrate inside the Si-cage, **TS_{2-w2_{Si}}**, has a relative Gibbs energy barrier of 8.3 kcal/mol, with a global barrier of 23.3 kcal/mol relative to **1-w2_{Si}** (Fig. 2). The distance of the protonated alcohol C-O bond (d_{C-Ow}) is elongated from 1.52 Å at the preceding intermediate (**2-w2_{Si}**) to 2.12 Å at the transition state (**TS_{2-w2_{Si}}**).

The water loss step in solution was calculated to be 7.1 kcal/mol



Scheme 3. Schematic representation of the systems investigated in the present study by means of molecular dynamics (MD) simulations inside a periodic box of H_2O .

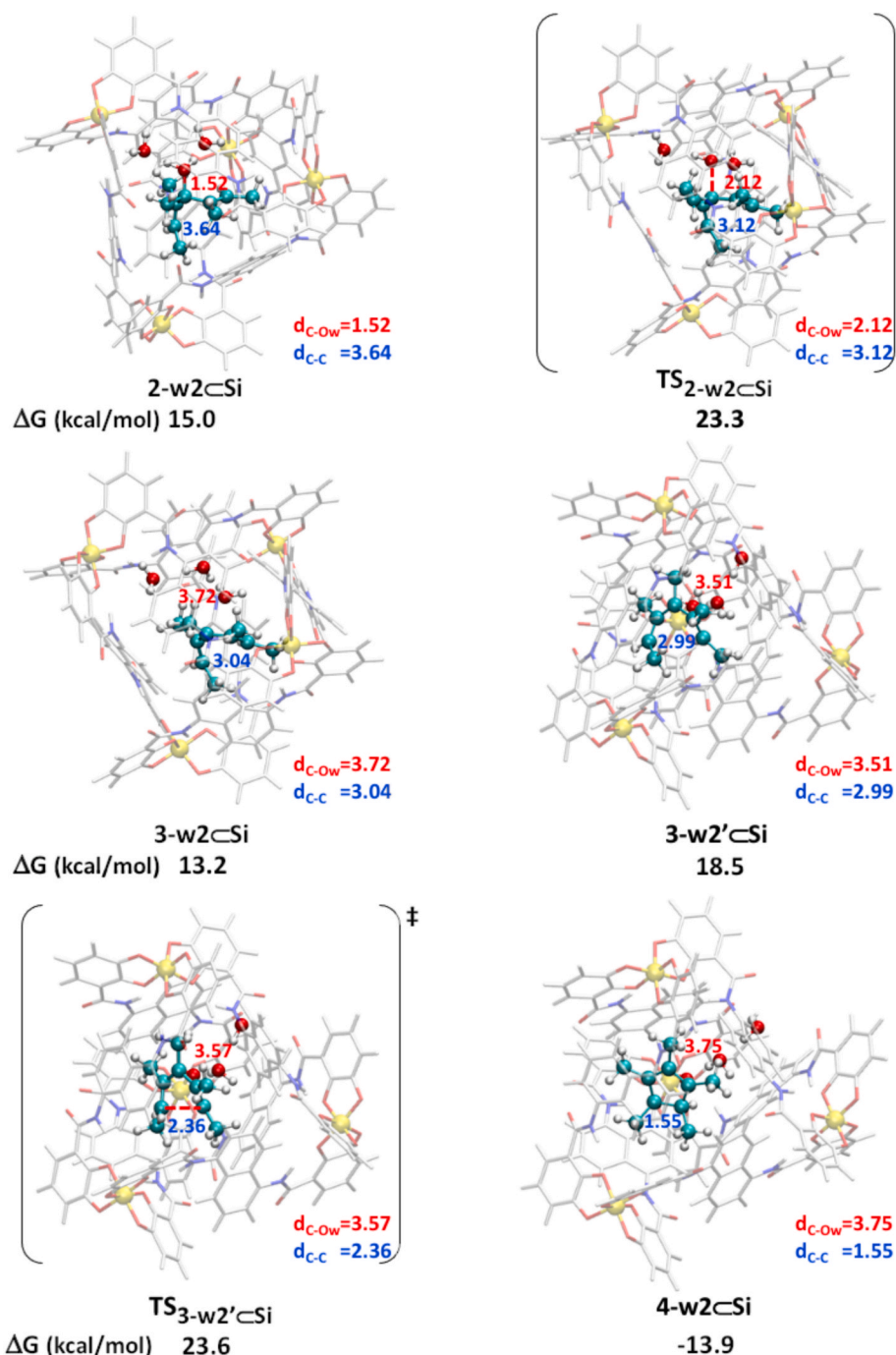


Fig. 1. Optimized geometries and relative Gibbs energies for the intermediates and TSs of the Nazarov cyclization inside the Si-cage, Si. Distances are given in Å.

higher than the protonated substrate. Therefore, performing the process inside Si-cage increases the barrier by 1.2 kcal/mol for this step. Even though the increase in the Gibbs energy barrier is minor, it is still relevant because it causes this step to become rate-limiting, together with the cyclization inside the Si cage (vide infra), in contrast to what occurs in solution.

The relative Gibbs energy of the encapsulated intermediate after the water loss, 3-w2 $\subset$ Si, is calculated to be at 13.2 kcal/mol relative to 1-w2 $\subset$ Si. At this point it is worth commenting how is affected the Gibbs energy barrier for the reversal process of water loss in solution and inside the Si-cage (3-w2 $\subset$ Si). In solution, the relative Gibbs energy barrier is 1.8 kcal/mol,[28] whereas the corresponding barrier inside the Si-cage (from 3-w2 $\subset$ Si to TS_{2-w2 $\subset$ Si}) increases up to 10.1 kcal/mol

(Fig. 2). For the case of the Ga-cage it was experimentally shown[17,18] and computationally confirmed[27,28] that the backward reaction step inside the cage is more energetically demanding than in solution. A similar effect, even much more pronounced, is observed for the Si-cage; this is because the 3-w2 $\subset$ Si intermediate is more strongly stabilized in the Si-cage.

The cyclization process, TS_{3-w2' $\subset$ Si}, is located at 23.6 kcal/mol from 1-w2 $\subset$ Si, (Fig. 2). The distance of the forming C-C bond (d_{C-C}) is 2.36 Å at the transition state, TS_{3-w2' $\subset$ Si} (Fig. 1).

The optimized geometry of the transition state keeping the same arrangement of water molecules than in 3-w2 $\subset$ Si is higher in energy by 2.5 kcal/mol (see Fig. S2 in Supporting Information). This indicates that solvent rearrangement should occur in the cage after the water loss step.

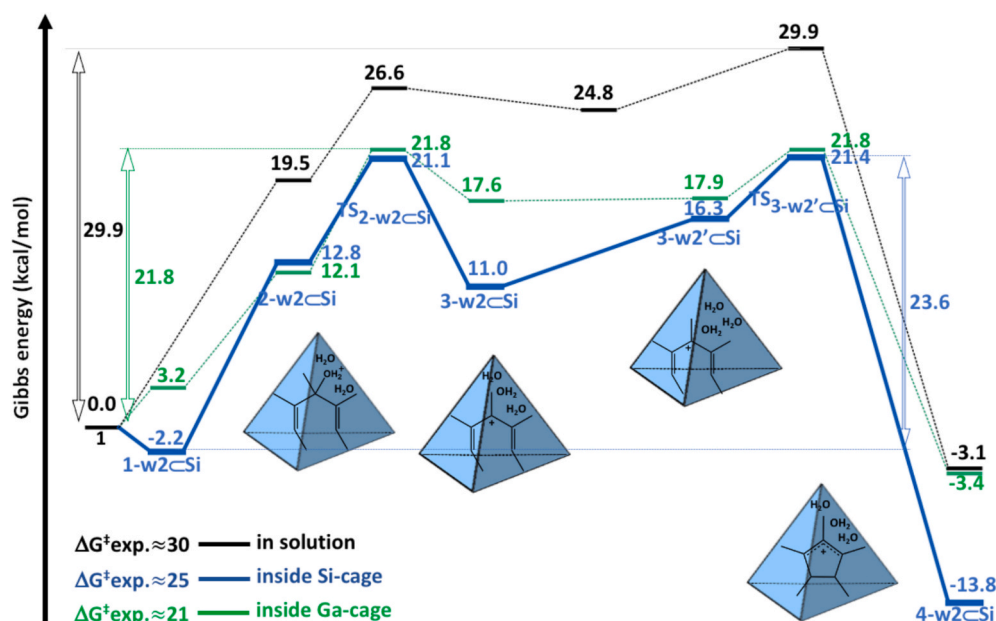


Fig. 2. Calculated Gibbs energy reaction profile for the Nazarov cyclization in solution and inside the $[\text{Si}_4\text{L}_6]^{8-}$ and $[\text{Ga}_4\text{L}_6]^{12-}$ nanocages. Data for the solution and Ga-cage profiles was taken from reference [28].

Indeed, the calculations show that the relative Gibbs energy of this encapsulated intermediate is affected by the solvent rearrangement inside the cage: the calculated relative Gibbs energies relative to **1** for **3-w2CSi** and **3-w2'CSi** are 13.2 and 18.5 kcal/mol, respectively (Fig. 2). These rearrangements of water molecules in the cage are illustrated in their optimized geometries (Fig. 1). The formation of the cyclic carbocation species, **4-w2CSi**, is highly exergonic with a Gibbs energy of -11.6 kcal/mol from **1-w2CSi**. Therefore, the reaction is irreversible once the cyclized species is formed.

The comparison between the cyclization step of the reaction in solution and inside the Si-cage is also interesting. The relative Gibbs energy barrier associated to the cyclization step in solution is 5.1 kcal/mol, whereas inside the Si-cage is 10.4 kcal/mol (from **3-w2CSi** to **TS_{3-w2'CSi}**); the energy barrier increases by 5.3 kcal/mol. These results denote that the carbocation intermediate, **3-w2CSi**, is significantly stabilized inside the Si-cage compared to solution.

Overall, the relative barriers for the water loss and cyclization are higher within the Si-cage compared to those in solution. Nevertheless, the overall barrier is lower because the protonated reactant is significantly stabilized within the Si-cage compared to solution. Indeed, all cationic intermediates are stabilized significantly within the cage. The calculated Gibbs energy barriers of 23.3 and 23.6 kcal/mol for the water loss and cyclization indicate that both are rate-determining steps, in good agreement with the estimated value of 25.0 kcal/mol.[25,58].

3.5. Comparison between Si-cage and Ga-cage

The main difference between the two cages lies in their overall

charge: -8 for the Si-cage and -12 for the Ga-cage, a decrease of 33% for the former. Computing the complete reaction mechanism in both cages allows us to identify how each cage affects the individual reaction steps. It is important to note that the cavity size is larger for the Ga-cage (Table S1). Although the number of solvent molecules encapsulated together with the substrate is comparable, it is not identical: three water molecules in the Ga-cage and two in the Si-cage. Therefore, the main differences between the two systems can be primarily attributed to the difference in cage charge, though the size by governing the encapsulated solvent may also play a role. The relative Gibbs energy values for each reaction step inside both cages, along with those for uncatalyzed reactions, are gathered in Table 1.[28] In the experimentally studied Nazarov cyclization, the cage charge plays a significant role, as the process is 680-fold faster for Ga-cage than for Si-cage, that correspond to a $\Delta\Delta G^\ddagger$ of 3.9 kcal/mol at 298 K.

The initial binding of the neutral substrate to the cage is -2.2 and $+3.2$ kcal/mol for the Si-cage and Ga-cage, respectively. According to these results, binding of a neutral substrate is more favorable in the cage with the lowest overall charge. This effect becomes relevant because for the Si-cage relative Gibbs energy barrier would be larger than for Ga-cage if the binding process was not favorable.

For the first step, namely the formation of the protonated intermediate, we found that the basicity of the encapsulated species is clearly enhanced in both cages. The results show that protonation is similar, slightly less favorable within the Si-cage than within the Ga-cage, with Gibbs energy changes of 12.8 and 12.1 kcal/mol, respectively. When comparing the full reaction profiles, this difference becomes a bit more pronounced (15.0 vs. 12.1 kcal/mol), owing to the more favorable initial

Table 1

Comparison of Gibbs energy values between Si-cage catalyzed and Ga-cage catalyzed Nazarov cyclization relative to the uncatalyzed reaction in solution.

	Cage + substrate	substrate binding	Protonated intermediate	Water loss – TS	Carbocation intermediate	Cyclization TS	Cyclic carbocation
Si-cage	0.0	-2.2 (0.0) ^a	12.8 (15.0) ^a	21.1 (23.3) ^a (22.2) ^b	11.0 (13.2) ^a (16.6) ^b	21.4 (23.6) ^a (23.7) ^b	-13.8 (-11.6) ^a (-8.1) ^b
Ga-cage		$+3.2$	12.1	21.8	17.6	21.8	-3.4
In solution	0.0	–	19.5	26.6	24.8	29.9	-3.1

^a Gibbs energy values considering encapsulated reactant as zero of energies; 2 water molecules encapsulated.

^b Gibbs energy values calculated considering 3 water molecules inside the Si-cage.

encapsulation in the Si cage. These results are in full agreement with those reported in the literature.[27] In particular, previous work by Tantillo and coworkers analyzed the protonation step in detail for both cages and found trends similar to those observed here. In addition, we computed the binding Gibbs energy of the protonated (charged) substrate to both cages. The resulting values are -6.7 kcal/mol and -7.4 kcal/mol for the Si-cage and the Ga-cage, respectively. These values are relatively similar between them, with binding being slightly more favorable in the cage with the larger negative charge, namely the Ga-cage. Overall, the protonation process is slightly favored for the Ga-cage compared to the Si-cage.

Comparing the processes in solution and inside the cages, the main difference comes by the fact that basicity (protonating the neutral substrate generating a charged species) is much more favored once the reactant is encapsulated. This means that modifying the charge of the substrate from 0 to +1 is much more favorable within both cages than in solution. This is a key difference with other processes like aza-Cope arrangement, where there is no change in the charge of the substrate along the reaction, and rate acceleration of both cages are very similar. [25].

In addition to the protonation step, we also examined the water loss and cyclization steps, which are rate-limiting for both cages, as these processes had not previously been investigated computationally. For the water-loss step, the relative Gibbs energy barriers are similar for both cages, with values of 21.1 kcal/mol for the Si-cage and 21.8 kcal/mol for the Ga-cage, respectively. However, the overall barrier is slightly higher for the Si-cage than for the Ga-cage (23.3 vs. 21.8 kcal/mol, respectively). A similar trend is observed for the other rate-limiting step, namely the cyclization step. The relative Gibbs free energy barriers are 21.4 and 21.8 kcal/mol for the Si-cage and the Ga-cage, respectively, while the overall barriers are again slightly higher for the Si cage (23.6 vs. 21.8 kcal/mol).

The main difference in the behavior of the two cages is observed in the relative stability of the carbocation intermediates. The carbocations formed after the water-loss step, **3-w2cSi** and **3-w2cGa**, have relative Gibbs energies of 11.0 and 17.6 kcal/mol, respectively. Surprisingly, the carbocation intermediate is more strongly stabilized in the cage with the lower overall charge, the Si-cage. A similar trend is observed when comparing the relative stability of the cyclized species **4-w2cSi** and **4-w2cGa**, which have relative Gibbs energies of -13.8 and -3.4 kcal/mol, respectively. Once again, the carbocation intermediate is significantly more stabilized by the less highly charged cage, namely the Si-cage. Consequently, formation of the cyclic carbocation is more exergonic in the Si-cage than in the Ga-cage. This trend is also consistent with reaction energies reported for a different system by Welborn and Head-Gordon, namely carbon-carbon reductive eliminations from an Au(III) complex, in which the effect of the same two cages was analyzed. In that case, the calculated reaction Gibbs energies were -25.4 and -17.5 kcal/mol for the Si-cage and the Ga-cage, respectively, thus observing a more exergonic reaction for the Si-cage.[30] This effect seems to be related to differences in the number of solvent molecules present within the cavity of each cage. Indeed, a related behavior was also observed in our previous study of reductive elimination forming a C-C bond from a Au(III) complex.[59] In that case, we found that removal of solvent molecules from the solvation sphere lowered the reaction barrier. For the sake of comparison, we also optimized the intermediates and transition states with three solvent molecules inside the Si cage (Table 1). This comparison shows that removal of solvent molecules (from three to two) stabilizes the relative Gibbs energies of the carbocations, whereas the Gibbs energy barriers are only marginally affected. Thus, although the overall energy barriers are not significantly influenced by the number of solvent molecules present in the cavity, the energy profile—specifically, the relative stability of the carbocation intermediate—is strongly affected. These results points out that the combination of DFT with MD simulation is needed to properly simulate the reaction steps for the process. Indeed, the solvation shell inside the

cage rearranges itself in the course of the reaction, thus suggesting that simulations that can directly account for such rearrangements, as AIMD simulations, could be even more appropriate.[30,33] However, this is out of the scope of this work.

In summary, the comparative analysis of the Si and Ga cages reveals that cage charge and solvation effects jointly govern reactivity. Neutral substrate binding is favored in the less negatively charged Si-cage, whereas binding of the protonated substrate is similar in both systems and slightly stronger in the more negatively charged Ga-cage. As far as the protonation step is concerned, encapsulation markedly enhances substrate basicity relative to solution, making protonation a key distinguishing feature of this reaction. For the rate-limiting steps, the relative barriers for the water-loss and cyclization steps are comparable in both cages, whereas the overall barriers are slightly higher in the Si cage, accounting for its slower reaction rate, in agreement with experiment. Notably, the most significant differences arise in the stability of carbocation intermediates, which are surprisingly more stabilized in the less charged Si-cage. This behavior might be related to differences in solvent occupancy within the cavities and is consistent with trends observed in related processes described in literature. Overall, these results highlight the interplay between cage charge, solvation, and intermediate stabilization in controlling catalytic outcomes.

4. Conclusions

The reaction mechanism for the Nazarov cyclization was analyzed inside the $[\text{Si}_4\text{L}_6]^{8-}$ nanocage by means of computational methods combining DFT calculations and molecular dynamics (MD) calculations and compared to the process inside the $[\text{Ga}_4\text{L}_6]^{12-}$ nanocage and in water solution. Even though the reaction has the same steps in solution and inside both nanocages, namely (i) protonation of the alcohol group of the substrate, (ii) water loss from the protonated substrate, forming a carbo-cationic species, and (iii) formation of the five-member ring by electrocyclization, the Gibbs energy barrier decreases significantly upon encapsulation.

Experimentally, the cyclization is accelerated in $[\text{Si}_4\text{L}_6]^{8-}$ relative to that in solution. The calculated Gibbs energies for the first step, protonation of the alcohol guest, are 19.5 kcal/mol and 15.0 kcal/mol in solution and inside $[\text{Si}_4\text{L}_6]^{8-}$, respectively. At this point, the combination of DFT and MD simulations was crucial for obtaining these energy values. The following two steps, water loss and cyclization, with overall barriers of 23.3 and 23.6 kcal/mol, respectively, are both affected moderately by encapsulation. These results indicate that the protonation process is the most important factor for accelerating the reaction rate.

The Nazarov cyclization process was also compared with the analogue $[\text{Ga}_4\text{L}_6]^{12-}$ (Ga-cage) since it is experimentally shown to be 680-fold faster than for $[\text{Si}_4\text{L}_6]^{8-}$ (Si-cage). The first step of the cage-catalyzed cyclization is the initial binding of the neutral alcohol guest. The associated Gibbs energies are -2.2 and $+3.2$ kcal/mol for $[\text{Si}_4\text{L}_6]^{8-}$ and $[\text{Ga}_4\text{L}_6]^{12-}$, respectively. This indicates that the neutral guest binding is more favored in the less negatively charged cage. The critical catalytic effect emerges in the subsequent protonation step, where encapsulation markedly enhances substrate basicity in both cages. This step is less favorable within the Si-cage ($\Delta G = 15.0$ kcal/mol) compared to the Ga-cage ($\Delta G = 12.1$ kcal/mol). This difference is the main contribution to the lower activity of the Si-cage. This is in concordance with a previously proposed explanation,[25] in which the difference was attributed to an increase in the charge of the guest (i.e. from a neutral reactant to cationic species) along the reaction pathway.

For the rate-limiting steps, water loss and cyclization steps, the intrinsic Gibbs energy barriers are similar for both cages (~ 21 – 22 kcal/mol). However, due to the less favorable initial substrate binding and protonation energetics, the overall effective barriers are consistently higher for the Si-cage (23.3 and 23.6 kcal/mol for water-loss and cyclization, respectively) versus the Ga-cage (21.8 kcal/mol). This accounts for the observed kinetic disparity, also in agreement with the

experimental results.

Another surprising finding concerns the stabilization of cationic intermediates. Carbocations formed after the water-loss and cyclization steps are more stable within the Si-cage than the Ga-cage (e.g., for cyclized carbocation the relative stabilities are -13.8 and -3.4 kcal/mol in both cages, respectively). This suggests that the lower-charge cavity provides larger stabilization for localized positive charges, a phenomenon potentially modulated by differential solvent organization within the cavity, in turn related to the cavity size. Thus, while the Ga-cage offers superior kinetics for this charge-generating reaction, the Si-cage provides greater thermodynamic stabilization of key cationic intermediates, highlighting a subtle interplay between global cage charge, substrate solvation, and specific reaction step requirements in supramolecular catalysis. Overall, these results should help the rational design of novel host–guest catalysis.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

CRediT authorship contribution statement

Gantulga Norjmaa: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gregori Ujaque:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The input/output files are available at the CORA repository: <https://doi.org/10.34810/data2867>. The information that will be published can be checked at: <https://dataverse.csuc.cat/previewurl.xhtml?token=5dbbf8fa-5867-443a-b5b3-acfb7c3c002d>.

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