## PAPER

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# Seeking the most stable isomer of azahomocubanes†

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This study examines the stability and protonation properties of four potential azahomocubanes. Through high-level *ab initio* computations, we find that 9-azahomocubane is the most stable isomer, closely followed by 5-azahomocubane, 1-azahomocubane, and 2-azahomocubane. However, understanding the stability of the systems with a nitrogen atom incorporated into a highly constrained polycyclic environment extends beyond mere bond angles or hybridization considerations. Strain energy analysis reveals that azahomocubanes experience less strain compared to their carbon congeners. An exploration of multiple solvents shows that their impact on relative energies and geometries is negligible. On the other hand, among the four isomers, 2-azahomocubane exhibits the highest tendency for protonation. Basicity, as assessed through the minimum electrostatic potential, correlates well with protonation affinities.

## Introduction

The origins of homocubane can be traced back to 1966, when it was independently synthesized by Dunn *et al.*[1] and Dauben *et al.*[2] In contrast, the history of azahomocubane is relatively short. Eaton *et al.* reported the rearrangements of cubyl azides in acidic media to produce 1-substituted 9-azahomocubanes,[3] while Williams and co-workers synthesized a derivative called *seco*-6-azahomocubane in 2022.[4] More recently, Fahrenhorst-Jones *et al.* successfully synthesized 1-azahomocubane, showing the feasibility of incorporating a nitrogen atom into a highly strained environment.[5] The synthetic approach uses azidyl cubane as an intermediate to introduce nitrogen into the strained ring framework, building upon previous reports of a substituted 9-azahomocubane. The process includes a series of catalyzed rearrangements in an acidic medium, followed by *N*-chlorination, resulting in nitrogen incorporation into the ring system. The synthesis is completed by manipulating functional groups and facilitating ring closure through *N*-alkylation to obtain 1-azahomocubane.[5,6] The overall yield is 17% over 16 steps, starting from dimethyl 1,4-cubanedicarboxylate. It is worth noting that this amine remains stable in solution for over a month at room temperature in the dark.[5]

Several questions arise, with one of the most apparent being the identification of the most stable isomer among the four potential azahomocubanes and the factors contributing to its stability. Concurrently, our focus is on determining the structure among the four isomers most susceptible to protonation and evaluating the degree of basicity shown by these amines.

## Computational details

Geometries were fully optimized using the M06-2X[7]-D3 [8]/def2-TZVP level. The corresponding harmonic frequencies were computed at the same level to characterize each stationary point as a minimum and to ascertain the zero-point vibrational energies (ZPEs). Subsequently, the M06-2X geometries were subjected to CCSD(T)/cc-pVTZ single-point energy computations to refine the energy values further. The computed electronic energies were then corrected by adding appropriate Gibbs energy corrections derived from harmonic frequency analysis. So, the entire energy discussion is based on free energies computed at the CCSD(T)/cc-pVTZ//M06-2X-D3/def2-TZVP level. Solvent effects were taken into account only at the M06-2X-D3/def2-TZVP level by employing the self-consistent reaction field method, particularly the polarizable continuum model (PCM). Natural population analysis (NPA) charges were determined at the M06-2X/def2-TZVP level to gain insight into the electronic distribution. Additionally, a T1 diagnostic was conducted using the CCSD/cc-PVTZ level of theory, serving as a diagnostic tool for determining the quality of single-reference

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electron correlation methods. T1 diagnostic values for all systems, including the protonated species, were found to be lower than 0.02 (see Table 1, ESI†), indicating the suitability of our single-reference electron correlation methods. The proton affinity (PA) of a neutral molecule was computed as the negative of the enthalpy change for the gas-phase reaction between a proton and the neutral molecule. All the computations were performed using Gaussian 16.[9]

## Results and discussion

Fig. 1 shows the four isomers under consideration. Our computations identify 9-azahomocubane (**1**) as the most energetically stable among them. The remaining forms, ordered by their stability according to the Gibbs free energies, include 5-azahomocubane (**2**, 1.9 kcal mol$^{-1}$), 1-azahomocubane (**3**, 3.2 kcal mol$^{-1}$), and 2-azahomocubane (**4**, 3.4 kcal mol$^{-1}$). Note that these structures are local minima on the $C_8H_9N$ potential energy surface. While we will not explore this landscape exhaustively, we can identify alternative forms that exhibit higher stability than **1**. For instance, 2,3-cyclopentenopyridine, indoline, 3-vinylaniline, or 2-[(1E)-1-propenyl]pyridine are predicted to be more stable than **1** by $-86.1$, $-84.6$, $-78.8$, and $-75.7$ kcal mol$^{-1}$, respectively.

Additionally, we scrutinized the impact of six different solvents used in the synthesis of **3** (water, methanol, acetic acid, benzene, chloroform, and dichloromethane) to assess their influence on relative energies and geometries. Nonetheless, our results show that the solvents had a negligible influence on these aspects, as summarized in Table 2, ESI.† Consequently, our emphasis will remain on the results obtained in the gas phase.

Among the isomers, **1** holds the least fascination for us due to its nitrogen atom residing in a conventional environment with a classical hybridization. Thus, one might reasonably anticipate it to be the most stable among the isomers owing to the lower strain experienced by the nitrogen atom. However, while strain often governs stability, it is crucial to recognize that the strain on the nitrogen atom alone does not determine the whole stability. The sum of the bond angles around N in **1** is 322°, which closely approximates the ideal sp$^3$ hybridization (328.5°). In contrast, isomers **2**, **3**, and **4** display bond angle sums of 264.4, 299.7, and 283.3°, respectively. Note that even though isomer **2**, with the "highest degree of strain", paradoxically shows the highest stability among the last three arrangements. Interestingly, the value for **2** is slightly lower than that computed for azacubane (267.8°). This implies that the stability of these systems cannot be adequately explained by solely considering the sum of bond angles.

A similar lack of correlation is observed between the HOMO–LUMO gap ($\Delta_{H-L}$) and stability, with **3** having the largest gap (9.5 eV), while **4** having the smallest (9.0 eV). For reference, the corresponding $\Delta_{H-L}$ value for azacubane is 9.1 eV.

So, relying only on the sum of bond angles or hybridization at a single atom falls short of providing a comprehensive understanding of the stability of the system. We estimated strain energy (at the M06-2X-D3/def2-TZVP level) through a series of hypohomodesmotic reactions (see the ESI†). This indicates that the strain energy for azahomocubane skeletons is approximately 110 kcal mol$^{-1}$. Notice that the azahomocubanes frameworks are at least 40 kcal mol$^{-1}$ less strained than azacubane (see Table 1). When comparing these values with the strain energies of cubane (162.9 kcal mol$^{-1}$) and homocubane (117.6 kcal mol$^{-1}$), it becomes apparent that their carbon congeners experience a strain approximately 7 kcal mol$^{-1}$ higher.
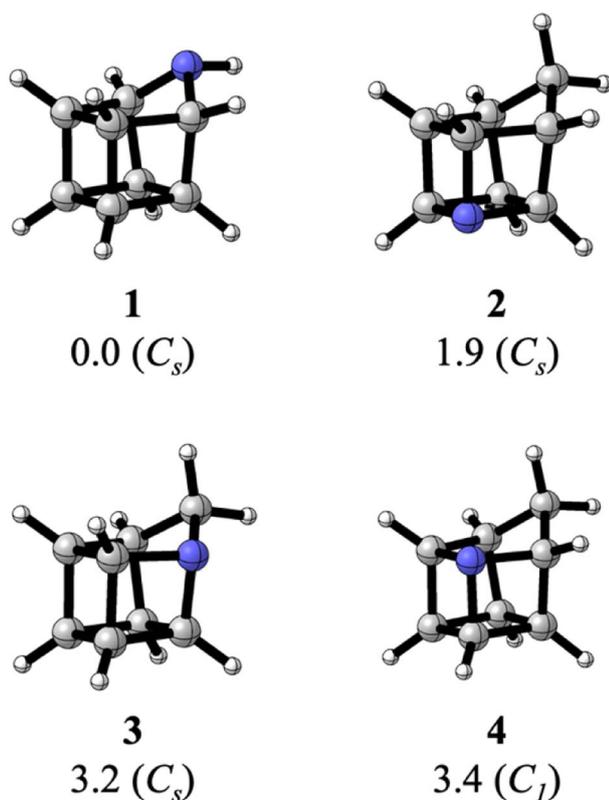


**Fig. 1** Geometries of azohomocubane isomers. Gibbs free energy differences (in kcal mol$^{-1}$) computed at the CCSD(T)/cc-pVTZ//M06-2X-D3/def2-TZVP level. The corresponding symmetry point group is indicated in parentheses.

**Table 1** The relative energies ($\Delta E$, in kcal mol$^{-1}$), the sum of the bond angles around the nitrogen atom ($\sum\theta$, in degrees), HOMO–LUMO gaps ($\Delta_{H-L}$, in eV), NPA charge on the nitrogen atom ($q(N)$, in $|e|$), the strain energies ($\Delta E_{strain}$, in kcal mol$^{-1}$), protonation affinities (PA, in kcal mol$^{-1}$), and the minimum electrostatic potential on the electron density surface ($V_{S,min}$, in kcal mol$^{-1}$) in azahomocubanes and azacubane

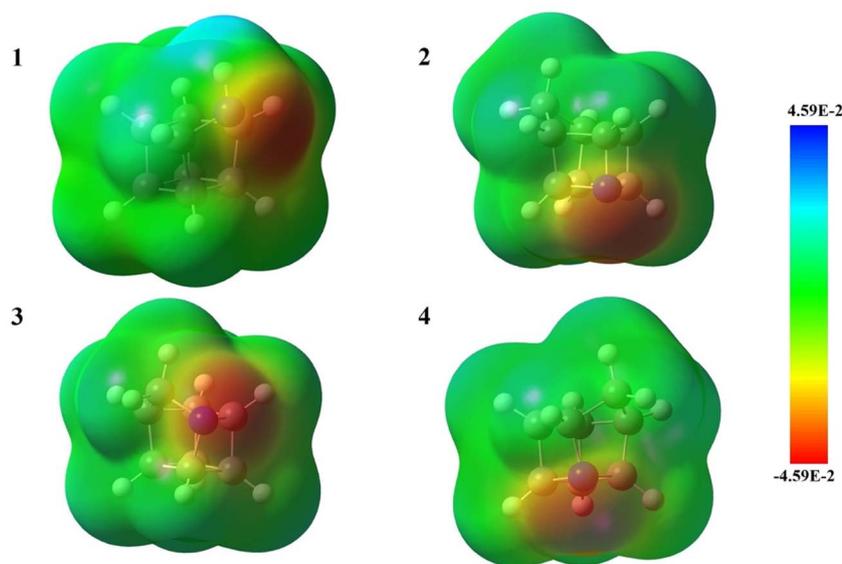|  | **1** | **2** | **3** | **4** | Azacubane |
|---|---|---|---|---|---|
| $\Delta E$ | 0.0 | 1.9 | 3.2 | 3.4 | — |
| $\sum\theta$ | 322.0 | 264.4 | 299.7 | 283.3 | 267.8 |
| $\Delta_{H-L}$ | 9.4 | 9.2 | 9.5 | 9.0 | 9.1 |
| $q(N)$ | −0.60 | −0.39 | −0.39 | −0.40 | −0.39 |
| $\Delta E_{strain}$ | 110.3 | 109.8 | 110.3 | 111.1 | 155.5 |
| PA | 238.7 | 246.3 | 243.2 | 246.4 | 233.2 |
| $V_{S,min}$ | −47.1 | −51.4 | −50.9 | −51.0 | −51.0 |

**Fig. 2** Electrostatic potential mapped onto the isodensity surface for compounds **1–4**.

Among these four species, which one exhibits the highest propensity for protonation? The protonation affinity of **1** is 226.1 kcal mol$^{-1}$, while the corresponding values for **2**, **3**, and **4** are 233.9, 230.8, and 234.0 kcal mol$^{-1}$, respectively. Notice that the value for **3** closely resembles that of azacubane (231.0 kcal mol$^{-1}$). The energy ranking of the protonated species undergoes a shift, with **4-H$^+$** emerging as the most stable and **1-H$^+$** lying 5.9 kcal mol$^{-1}$ higher in energy. In **1**, the NPA charge[10] on the nitrogen atom, $q(N)$, is $-0.60\ |e|$, whereas for the other three isomers, it is relatively consistent, approximately $-0.39\ |e|$, identical to that of azacubane. Thus, the charge significantly increases as the nitrogen atom experiences more strain. Based only on the charge, one might expect that compound **1** would show a higher susceptibility to protonation. However, there is no discernible correlation between PA and $q(N)$.

Previous studies have indicated that basicity has a stronger correlation with the minimum electrostatic potential on the electron density surface, $V_{S,min}$, rather than the atomic charges.[11] Fig. 2 depicts the electrostatic potential mapped onto the density isosurface, highlighting the negative electrostatic potential directed towards the inferred location of the lone pair on N. We also computed the $V_{S,min}$ values at the nitrogen atom for all four compounds, ranging from $-47.1$ to $-51.4$ kcal mol$^{-1}$. A clear linear correlation with the protonation energies exists (see Table 1).[12] Using these findings, we can infer that compound **1** would have the lowest $pK_b$ value, indicating relatively weak basicity. These results align with the strain on the nitrogen atom and are consistent with the protonation energy values mentioned earlier.

followed closely by 5-azahomocubane at only 1.9 kcal mol$^{-1}$. Interestingly, tertiary amines show increased susceptibility to protonation due to the strain despite having less negative charge. One important remark is that the stability of azahomocubanes does not depend solely on factors influencing a single atom; it is essential to assess whether such alterations have broader effects on the entire molecule. The strain values indicate that all variants of azahomocubane experience less strain than their carbon counterparts. The species most susceptible to protonation is 2-azahomocubane, the least stable azahomocubane. A linear correlation exists between proton affinity and the minimum electrostatic potential values. Several solvents were examined; nonetheless, their influence on relative energies and geometries was negligible. Finally, based on homocubyl fluxionality (and on other nonclassical carbocations[13–16]), rearrangements involving the generation of respective carbocations from the synthesized azahomocubanes could facilitate the formation of the remaining isomers -an avenue that we are exploring.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

## Conclusions

In summary, among the four potential azahomocubane structures, 9-azahomocubane exhibits the highest energy stability,

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