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## 1-Azahomocubane†

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Highly strained cage hydrocarbons have long stood as fundamental molecules to explore the limits of chemical stability and reactivity, probe physical properties, and more recently as bioactive molecules and in materials discovery. Interestingly, the nitrogenous congeners have attracted much less attention. Previously absent from the literature, azahomocubanes, offer an opportunity to investigate the effects of a nitrogen atom when incorporated into a highly constrained polycyclic environment. Herein disclosed is the synthesis of 1-azahomocubane, accompanied by comprehensive structural characterization, physical property analysis and chemical reactivity. These data support the conclusion that nitrogen is remarkably well tolerated in a highly strained environment.

## Introduction

Homocubane (**1**) was synthesized by Dunn *et al.*<sup>1</sup> and then Dauben *et al.*<sup>2</sup> as simultaneous contributions in 1966, just two years after the Platonic solid mimic cubane (**2**) by Eaton and Cole in 1964.<sup>3</sup> Some 25 years later the nitrogen (aza) analogs of cubane became the subject of considerable theoretical and synthetic interest (*i.e.*, azacubane, **3**),<sup>4–6</sup> but no member of the azacubanes have to-date succumbed to synthesis due to the considerable synthetic challenge these molecules pose.<sup>7</sup> In addition, the corresponding homologues, azahomocubanes **4–6**, are unprecedented in the literature, although 1-azahomocubane-9-one (**7**) was suggested as a probable reactive intermediate in related studies by Eaton *et al.*<sup>5,8</sup> The closest relative is a seco-6-azahomocubane derivative (*i.e.*, **8**), which was only recently synthesized by Williams *et al.*<sup>9</sup> (Fig. 1). Therefore, with the prospect of gaining additional physical property insight on uniquely strained aza hydrocarbons,<sup>10</sup> combined with the formidable synthetic challenge, and the contemporary interest in exploring fundamental cage hydrocarbon scaffolds for bioactive molecule<sup>11,12</sup> and materials<sup>13</sup> discovery, avenues to accessing and isolating an azahomocubane were pursued as reported herein.

## Results and discussion

## Synthesis of 1-azahomocubane

1-Azahomocubane (**4**, Fig. 1) was the pinnacle target chosen for this endeavour given the parent status of this molecule class (*i.e.*, first in the series). From a retrosynthetic perspective, adopting a synthetic approach to 1-azahomocubane (**4**) *via* a cubyl azide (*e.g.*, **9**) was logical, because the majority of the target skeleton could be imported from a commercial cubane derivative *via* nitrene insertion chemistry. Although, the route

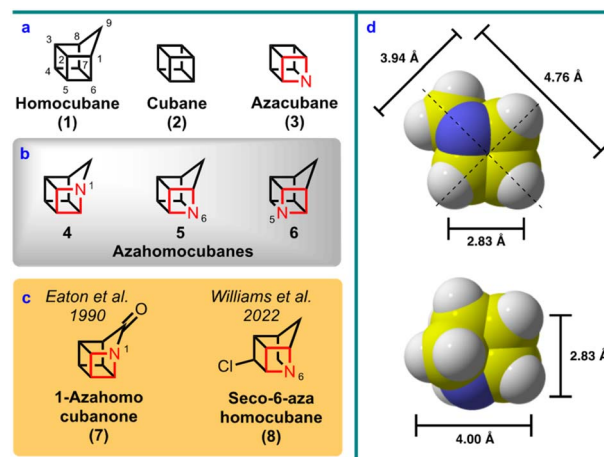


Fig. 1 (a) Parent homocubane and cubane skeletons, along with an example of the aza evolution (**3**). (b) The three possible azahomocubanes containing a tertiary nitrogen atom – positions 1/8, 2/7 (enantiomer 3/6) and 4/5 are interchangeable pairs. (c) Reported azahomocubanes – hypothesised **7** and synthesised **8**. (d) 1-Azahomocubane comparative bond distances given in Ångstroms [M062X-D3/Def2TZVPP] – nitrogen atom highlighted in blue, carbon in pale yellow, and hydrogen in white.

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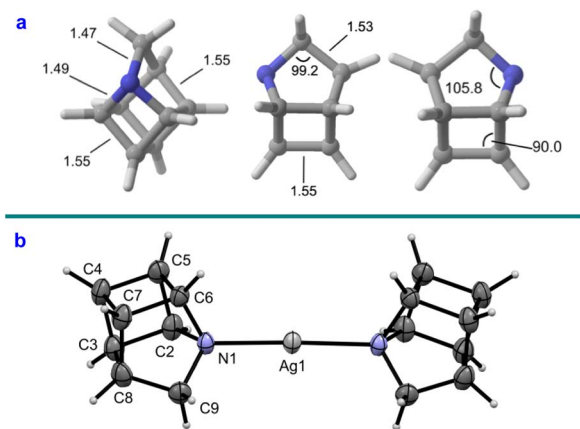


Fig. 2 (a) Calculated geometries of **4** in Ångströms. (b) X-ray crystal structure analysis of **4** as a 2:1 complex with silver perchlorate – ellipsoids shown at 50% probability.

### Structural analyses and physical properties of 1-azahomocubane

From Density Functional Theory (DFT) calculations, the sum of the bond angles around the nitrogen atom in azahomocubane (**4**) was found to be 299.6°, indicating significant deviation from ideal  $sp^3$  hybridization as expected (328.5°, Fig. 2a). Comparison to the conjugate acid (Fig. S14a†) predicted that protonation induces planarization of the nitrogen atom (e.g., C2–N–C9 increases from 105.8° to 108.3°), in addition to lengthening of the adjacent bonds: supporting the proposed mechanism for ring-opening of protonated azahomocubane (**21**) by chloride *via*  $S_N2$  displacement to give **24**. X-ray crystallographic data were obtained for **4** as a 2:1 silver perchlorate complex (Fig. 2b), which confirmed the structure ( $C_s$  point group). Gratifyingly,

the solid state geometries for the silver complex were close to the predicted bond lengths and angles computed for the free amine (e.g., C2–N–C9: 105.7°).

To gain wider physical property perspective, 1-azahomocubane was compared against the most relevant bridgehead azabicyclic systems available, 1-azabicyclo[2.2.1]heptane (**26**) and 1-azabicyclo[2.2.2]octane (i.e., quinuclidine, **27**) (Table 1). Firstly, aqueous acidity measurements ( $pK_a$ ) were undertaken (*via* the  $^1H$  NMR titration method),<sup>18</sup> which revealed a clear trend whereby increasing acidity of the conjugate acid (i.e.,  $pK_a$  11.5 to 9.7) correlated with increasing geometrical strain (i.e., **27** to **4**). This trend was supported by gas-phase proton affinity (PA) measurements,<sup>19</sup> which demonstrated that, even in the absence of solvent, the highly strained nitrogen bonding arrangement decreases the intrinsic basicity of **4** (PA = 975  $\text{kJ mol}^{-1}$ ) relative to other bridgehead amines (Table 1).<sup>20</sup>

Potential differences in skeletal hybridization were then assessed by measuring the  $^{13}C$ – $^1H$  coupling constants ( $^1J_{C-H}$ )<sup>21</sup> at the bridgehead positions opposite to the aza-bridgehead. Comparing these values with the corresponding hydrocarbons (Tables 1 and S8†) indicated little change had occurred within the aza series. This was reinforced by the calculated geometries for homocubane (**1**) (Fig. S14c†), which demonstrated that nitrogen substitution leads to slight shortening of the adjacent bonds (as expected due to the increased electronegativity), and enhanced pyramidalization around the nitrogen centre (e.g., C–N–C: 105.8° vs. 106.7°). To explore these effects further, natural abundance  $^{15}N$  NMR measurements (Table 1) were performed using long-range  $^1H$ – $^{15}N$  heteronuclear shift correlation methods (HMBC).<sup>24</sup> These measurements revealed that 1-azahomocubane (**4**) ( $\delta_N$  78.7 ppm) is less electron rich at the nitrogen centre (deshielding the nucleus) compared to the related azabicyclic systems, **26** ( $\delta_N$  58.7 ppm) and **27** ( $\delta_N$  15.0

Table 1 Physical property determinations of 1-azahomocubane (**4**)

Amine	$pK_a^a$	Proton affinity <sup>b,c</sup> (calcd <sup>d</sup> )	$^{15}N$ NMR <sup>f</sup> ( $C_6D_6$ )	Natural electron configuration <sup>g</sup> s (p) orbitals	Bridgehead $^1J_{C-H}^{h,i}$	$\sum$ bond angles for nitrogen <sup>l</sup>	Strain energy <sup>j</sup>
1-Azabicyclo[2.2.1]heptane ( <b>26</b> )	11.1 ( $\pm 0.1$ )	980 (973)	58.7	1.35 (4.03)	143.0 (140.1) <sup>k</sup>	309.5 (—)	15.7 (—)
1-Azabicyclo[2.2.2]octane ( <b>27</b> )	11.5 ( $\pm 0.1$ ) 11.3 (ref. 22)	983 (ref. 23) (978)	15.0	1.30 (4.09)	137.5 (134.3) <sup>k</sup>	327.6 (—)	10.6 (—)
1-Azahomocubane ( <b>4</b> )	9.7 ( $\pm 0.1$ )	975 (968)	78.7	1.38 (3.99)	146.7 (146) <sup>j</sup>	299.6 (300.6)	110.4 (117.6)
1-Azabicyclo[2.2.1]heptane ( <b>26</b> )	—	— [975 <sup>e</sup> (968)]	—	1.47 (3.89)	—	267.9 (270)	155.5 (162.8)

<sup>a</sup>  $pK_a$  values were determined using a  $H_2O/D_2O$  ratio of 9:1 [note: The  $K_a$  (acidity constant) values are the reciprocals of the protonation constants and converted to  $pK_a$ ]. <sup>b</sup> Gas-phase proton affinity determinations in  $\text{kJ mol}^{-1}$ . <sup>c</sup> Absolute uncertainty in PA values is considered to be  $\pm 8 \text{ kJ mol}^{-1}$  due to uncertainty in reference value while relative PA values have much lower uncertainties. <sup>d</sup> Calculated proton affinity (and ionization potential energies, Table S4) determined at the M06-2X(GD)/6-311++G(d,p) level of theory. <sup>e</sup> Empirical correction to calculated value, see Fig. S12. <sup>f</sup> Measured in ppm. <sup>g</sup> Number of electrons. <sup>h</sup> Measured in Hertz against the corresponding (all carbon) cage hydrocarbon. <sup>i</sup> For all bridgehead position  $^{13}C$ – $^1H$  coupling constants see Table S8 in the ESI. <sup>j</sup> Position 8. <sup>k</sup> Position 4. <sup>l</sup> Sum of all bond angles around the nitrogen atom expressed in degrees and strain energies expressed in  $\text{kcal mol}^{-1}$  as calculated at the M062X-D3/Def2TZVPP level of theory – corresponding hydrocarbon value in parentheses.



ppm). Combined with the  $^{13}\text{C}$ - $^1\text{H}$  coupling constant data suggested an upward trend in lone pair s-character, as supported by natural electronic configuration calculations, which is in line with the increasing  $\text{p}K_{\text{a}}$  and PA acidity trend *i.e.*, decreasing basicity (Table 1).

In order to obtain a deeper appreciation for the ring strain present in these systems, hypothetical atom exchange and hypohomodesmotic reactions<sup>25</sup> were conducted. For the conversion of cubane (2) to azacubane (3), and homocubane (1) into azahomocubane (4) (Fig. S13<sup>†</sup>), it was determined that 3 is more stable than 2 by 7.3 kcal mol<sup>-1</sup>, and 4 is similarly 7.2 kcal mol<sup>-1</sup> (strain energy, Table 1) more stable than 1. Overall, homologation of azacubane to azahomocubane lowers the strain energy by ~45 kcal mol<sup>-1</sup>, which can be rationalized by the inclusion of a more stable 5-membered ring. Interestingly, the azabicyclo[2.2.1] (26) and [2.2.2] (27) systems are approximately an order of magnitude less strained. To rationalize the unexpected stabilization observed for 1-azahomocubane, Second Order Perturbation Theory (SOPT, Table S6<sup>†</sup>)<sup>26</sup> analysis was also performed. Nitrogen lone pair – sigma\* interactions with the antiperiplanar carbon atoms were thus determined to be 5.8 kcal mol<sup>-1</sup> (“cubic” C–C bonds) and 4.6 kcal mol<sup>-1</sup> (“basket handle” C–C bond) respectively. A weaker interaction (2.9 kcal mol<sup>-1</sup>) was found for the nitrogen lone pair into the adjacent cyclobutyl C–H antibonding orbitals. This analysis suggested that the modest stabilization on introducing a nitrogen atom at the bridgehead of homocubane was due to hyperconjugative effects, though the minimal structural deformation (see above) indicated that this effect is minor. Orbital rehybridization effects, are also likely to be an additional contributor to the observed stabilization [*i.e.*, Bent’s rule and associated theories<sup>27</sup>] as evidenced by the observable change in s-character of the nitrogen lone pair orbital (*e.g.*,  $^{13}\text{C}$ - $^1\text{H}$  coupling constants and  $\text{p}K_{\text{a}}$ ).<sup>28</sup>

## Conclusions

The synthesis of 1-azahomocubane (4) has been achieved 56 years after the corresponding parent hydrocarbon was reported [*i.e.*, homocubane (1)]. Schmidt and aza-Favorskii type rearrangements were adopted, as the key steps, to achieve the synthesis. Access to 4 enabled a comprehensive experimental and computational analysis of a nitrogen atom positioned within a highly strained environment. In consideration of the compiled data set, this ring system not only displayed unexpected and remarkable stability as the free amine (and protonated CSA and triflate salts), but incorporation of a tertiary nitrogen atom into a small ring strained polycyclic framework yielded surprisingly small geometric changes relative to the all-carbon system. Finally, future investigations involving this ring system will aim to determine potential viability as a novel scaffold.

## Data availability

All experimental data are provided in the ESI.<sup>†</sup>

## Author contributions

T. F. J., G. P. S., P. E. E. and C. M. W. conceived the project. T. F. J., R. E. H. and A. M. F performed chemical synthesis. D. L. M. undertook proton affinity determinations. J. M. B. and S. J. B. carried out *in silico* calculations. G. K. P. obtained heteroatom coupling constants and nitrogen NMR data. T. F. J. and P. V. B. performed the acidity measures and analysis. P. V. B. acquired the X-ray crystallographic data and performed the analysis. C. M. W. coordinated the study, assisted in analysing and interpreting the data, and wrote the manuscript. All authors read and agreed on the content of the paper.

## Conflicts of interest

There are no conflicts to declare.

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