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Driving *tert*-butyl axial: the surprising cyclopropyl effect†

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The presence of a small spirocyclic ring at an adjacent position alters the conformational preference for equatorial substitution in six-membered rings. DFT calculations and low-temperature ^{1}H NMR experiments demonstrate that alkyl groups larger than methyl possess negative A-values when geminal to a spirocyclopropane, with larger groups such as isopropyl and *tert*-butyl being exclusively axial at −78 °C. Similar effects are found for heteroatoms, including halogens, and for a range of other electron-withdrawing substituents. Similar effects are observed for other strained rings (epoxide, cyclobutane, oxetane) and the concepts extend to acyclic models as well as heterocycles such as piperidines and piperazines. The origin of the effect is traced to an increase in torsional strain in combination with hyperconjugative effects in the case of electron-poor groups.

Introduction

The use of small ring structures as isosteres is a prominent technique for molecular design in medicinal chemistry.[1] In particular, in recent years the use of bicyclopentanes and oxetanes as replacements for aromatic and carbonyl groups has allowed medicinal chemists to increase the three-dimensionality of drug candidates while maintaining relative dispositions of pendant groups.[2,3] Even more common is the use of cyclopropanes (Fig. 1c) which have been widely employed as isosteres for alkenes, isopropyl (*e.g.* Pitavastatin, Fig. 1c) isobutyl and *tert*-butyl groups and even aromatic rings.[4,5] Notably, spiro-cyclopropanes are featured in many bioactive compounds, including Pim-kinase inhibitors,[6] ORL-1 antagonist MK-0911 (ref. 7) and the antitumor natural product illudins.[8] While significant attention is paid to the exit vectors for groups attached to small rings,[9,10] the conformational control elements adjacent to strained rings are less commonly examined.

The quintessential example of conformational analysis in organic chemistry is the understanding of structure in cyclohexanes (Fig. 1a), where the chair form is preferred over the twist-boat and substituents prefer equatorial positions over axial to minimize gauche interactions with C3 and C5. The equatorial preference is quantified in the form of A-values and in general, larger groups possess larger A-values.[11] Known exceptions to the preference for equatorial substitution do exist, with the most common examples resulting from stereoelectronic effects, including anomeric effects in carbohydrates and related acetals, hyperconjugative stabilization observed in 1,3,5-triazinanes,[12,13] vinylogous anomeric effects in 2-chlorocyclohexanone oximes,[14] and dipole minimization in α-halo-cyclohexanones,[15] as well as cases where hydrogen bonding stabilizes axial substitution.[16–18]

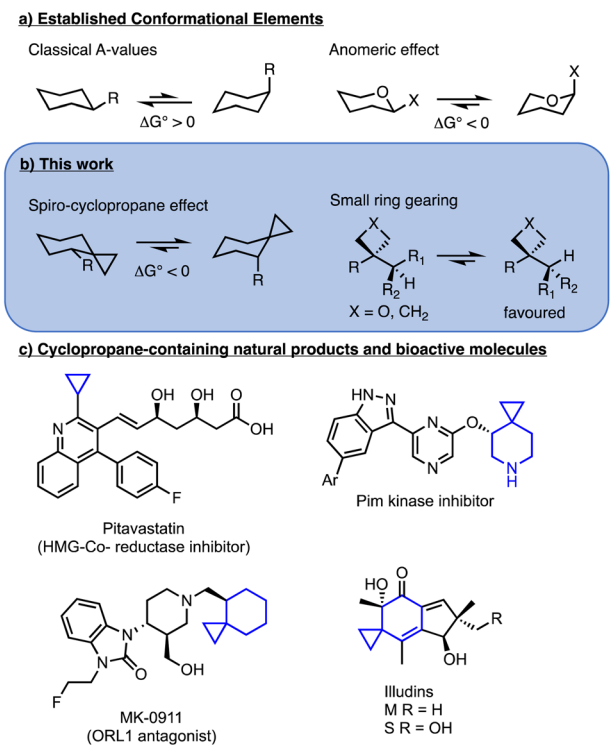

Fig. 1 Conformational elements in cyclohexanes and examples of cyclopropane-containing relevant molecules.

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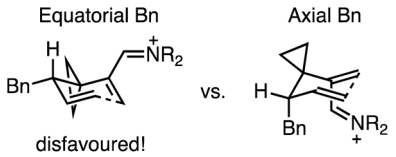


Fig. 2 Preference for axial orientation in a Cope-like transition state.

In the context of examining an organocatalytic Cope rearrangement,[19] we observed anomalous preference for axial orientation of alkyl groups adjacent to a cyclopropane in chair-like transition states (Fig. 2).[20] Modest preference for axial disposition of α-ethers and acetates adjacent to spirocyclopropanes had previously been noted and had been attributed mainly to stereoelectronic effects.[6,21] In addition, a spiro-oxetane was previously found to induce an N-alkyl group to adopt an axial conformation in a heterocycle in the solid state.[22] As our studies here will show, the effect is in fact broadly applicable to a range of groups and is more significant for large alkyl groups, such that isopropyl and *tert*-butyl are exclusively axial. In addition, we show that the effect is not limited to cyclopropanes, but is operative with other three- and four-membered rings and the effects can be generalized into heterocycles and acyclic systems. These conformational effects have potential for application in molecular design of catalysts and rational design in medicinal chemistry.

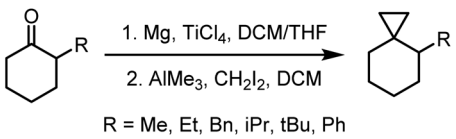
Results

We first examined, computationally and experimentally, the effect of an adjacent spirocyclopropane substitution on the A-values of a variety of simple alkyl groups. Comparisons were made to both simple cyclohexanes and those bearing geminal-dimethyl substitution adjacent to the group of interest to focus on the specific effect of a small ring. Density functional calculations were performed employing the M06-2X functional,[23] which has previously been employed in examining A-values,[24] with a 6-311++G(2d,2p) basis set. We employed an acetone solvation model (SMD[25]), as we intended to examine structures experimentally at low temperature by NMR. A-values were calculated from a Boltzmann population analysis of all stable conformers identified by conformational analysis.[26,27]

The effect of a spirocyclopropane on the A-value of a simple methyl group was significant (Table 1). While a geminal dimethyl group adjacent had, as previously observed,[28,29] little effect on the A-value, an adjacent cyclopropane resulted in a computed A-value of −0.09 kcal mol^{-1}, a change of −2.04 kcal mol^{-1} *vs.* the computed value for methylcyclohexane. Even more striking were the effects on groups larger than methyl. While the presence of a geminal dimethyl group generally had minimal effect, the A-values for groups adjacent to a spirocyclopropane were uniformly negative and generally shifted by −3 kcal mol^{-1} or greater. For instance, an ethyl group was predicted to have an A-value of −0.89 kcal mol^{-1}, indicating a clear preference for axial substitution and a change of −2.95 kcal mol^{-1} relative to ethylcyclohexane. Larger groups such as isopropyl and *tert*-butyl were predicted to have even larger preferences for the axial conformation. For *tert*-butyl the predicted A-value of −2.00 kcal mol^{-1} represents a change of nearly −8 kcal mol^{-1} from the normal equatorial preference in *tert*-butylcyclohexane.[30,31]

We examined these species experimentally to corroborate the computational results. We prepared the spirocyclopropane substrates by cyclopropanation[32] of the corresponding alkenes, themselves generated by olefination[33] of the corresponding ketones (Scheme 1 and ESI†). We measured the equilibrium ratios of axial and equatorial conformers by ^{1}H NMR at −78 °C in d_6-acetone. Axial and equatorial isomers were assigned from coupling constants while confirmation that specific protons were interconverting was achieved by saturation transfer in selective irradiation experiments.[34] Notably, in the spirocyclopropyl system, the α-equatorial protons are significantly shielded by anisotropy,[35] which facilitated the assignment.

The predicted effect of a spiro-cyclopropane was borne out experimentally. For the substrate bearing a methyl group, a 53 : 47 ratio of equatorial to axial conformers was observed.



Scheme 1 Synthesis of alkyl-susbstituted spirocyclopropanes.

Table 1 Effect of spirocyclopropane on A-values of alkyl groups

	Calculated A-value[a] (kcal mol^{-1})			Expt. A-value[b] (kcal mol^{-1})
R				
Me	+1.95	+1.76	−0.09 (δ = −2.04)	+0.05
Et	+2.06	+1.90	−0.89 (δ = −2.95)	−0.46
*i*Pr	+2.33	+3.27	−2.10 (δ = −4.43)	<−1.5
CH_2OH	+1.98	+1.71	−1.01 (δ = −2.99)	−0.72
Bn	+1.85	+1.78	−1.10 (δ = −2.95)	−0.75
*t*Bu	+5.83	+3.44	−2.00 (δ = −7.83)	<−1.5

[a] $\Delta G°$ calculated at 25 °C, M06-2X/6-311++G(2d,2p), SMD = acetone. [b] Experimental value determined by ^{1}H NMR at −78 °C in d_6-acetone.

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Although the equatorial isomer was very slightly preferred, the observed A-value of +0.05 kcal mol^{-1} was close to the predicted value and, importantly, the ratio was significantly different from the normal ~95 : 5 ratio in methylcyclohexane. Moreover, for all other isomers, the axial isomer was clearly preferred. For instance, for an ethyl group, the axial isomer predominated in a 77 : 23 ratio, indicating an A-value of −0.46 kcal mol^{-1}. Larger groups such as benzyl, isopropyl and *tert*-butyl more heavily favored the axial conformer – for the latter two substrates the equatorial isomers could not be observed at −78 °C. We estimated our limit of detection of the minor conformer to be roughly 2% of the major conformer, setting an upper limit for measuring the magnitude of A-values at 1.5 kcal mol^{-1} at −78 °C for these examples. We note that the DFT calculations slightly overestimated the effect of the cyclopropane by 0.1–0.4 kcal mol^{-1}, with the ethyl group having the largest error. Examination of other computational methods for ethyl substitution afforded either similar (B3LYP-D3 (ref. 36–40)) or more significant (WB97XD,[41,42] MP2 (refs. [43] and 44)) prediction errors (see ESI†) and thus the M06-2X functional was maintained for subsequent calculations.

We next examined the effects of spirocyclopropanes on heteroatom substitution (Table 2). As with alkyl substituents, in all cases, we predicted a decrease in the A-value with absolute changes ranging from −1.2 to −4.0 kcal mol^{-1} and the axial conformation preferred for all substitution patterns. Notably, even small groups such as fluoro were predicted to have significant negative A-values. We prepared all but the chloro and bromo substrates, as the latter were prone to ring-opening of the cyclopropane. The heteroatom substrates were prepared by Simmons–Smith cyclopropanation of 2-methylene-1-cyclohexanol followed by functional group interconversions (see ESI† for details). We found that the calculated A-value reflected well the observed equilibrium concentrations in almost all cases. A slightly larger discrepancy between predicted and observed values was observed with ammonium and acetamide groups, with the latter being the only incorrect prediction of axial preference. We tentatively attribute the difference in the latter case to potential hydrogen bonding (either to itself or to solvent d_6-acetone) which was not modeled explicitly by DFT, while the error in the former case may also reflect the difficulty in properly modelling solvation of the cation.

Finally, we examined a range of π- and electron withdrawing groups (Table 3). As with alkyl and heteroatom groups, all substituents also displayed a shift towards a more negative A-value. For phenyl the shift was not sufficient to prefer the axial conformation, although the absolute change is still significant (−2.04 kcal mol^{-1}) and for vinyl an equal population of axial and equatorial was predicted. In contrast, alkynes and all electron withdrawing groups were predicted to have a negative A-value, with the CF_3 group having the most significant change relative to a simple cyclohexane among this group and the largest predicted negative A-value among all substituents examined. We prepared four examples from this series; the phenyl substrate was indeed equatorial (92 : 8 ratio) as predicted, for ester and acid substrates the axial conformer was favored by roughly 70 : 30 ratios at −78 °C and for a cyano group the ratio was 80 : 20, again favoring axial.

An important question was whether this effect could be extended to other spiro ring systems. We probed this computationally with small (Me, Et), medium (*i*Pr) and large (*t*Bu) substituents with a variety of different ring sizes and rings incorporating oxygen (Table 4). Calculations showed that the effect was generally maintained with cyclobutane, albeit with a partial loss of expected axial preference. However, when the ring expands to a cyclopentane, the equatorial isomer is now preferred for all group sizes, though still less compared to a simple dimethyl substituted system. Examining other three-membered rings, we found that spiro-epoxides were predicted to have a decrease in A-values, although the magnitude of the effect was reduced and dependent on the relative stereochemistry. For small substituents, the equatorial isomers are often still preferred, though by a much smaller margin than for a regular cyclohexane. However, for larger groups such as

Table 2 Effect of spirocyclopropane on A-values of heteroatomic groups

	Calculated A-value[a] (kcal mol^{-1})			Expt. A-value[b] (kcal mol^{-1})
R				
OH	+0.89	+0.83	−0.37 (δ = −1.26)	−0.13
OMe	+0.87	+0.74	−0.67 (δ = −1.54)	−0.42
OAc	+0.74	+0.53	−0.54 (δ = −1.28)	−0.57
NH_2	+1.41	+1.36	−0.15 (δ = −1.56)	−0.24[c]
NH_3^+	+2.21	+0.84	−1.83 (δ = −4.04)	−1.23[c]
NHAc	+0.91	+0.84	−0.57 (δ = −1.48)	+0.19
N_3	+0.63	+0.86	−0.92 (δ = −1.55)	−0.72
F	+0.31	+0.29	−1.05 (δ = −1.36)	−0.82
Cl	+0.63	+1.16	−1.81 (δ = −2.44)	nd
Br	+0.61	+1.21	−2.23 (δ = −2.84)	nd

[a] $\Delta G°$ calculated at 25 °C, M06-2X/6-311++G(2d,2p), SMD = acetone. [b] Experimental value determined by ^{1}H NMR at −78 °C in d_6-acetone, except as note. [c] Determined in d_2-dichloromethane.

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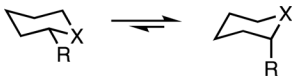
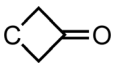
Table 3 Effect of spirocyclopropane on A-values of π- and electron withdrawing groups

	Calculated A-value[a] (kcal mol^{-1})			Expt. A-value[b] (kcal mol^{-1})
R				
Ph	3.03	3.76	0.99 ($\delta = -2.04$)	+0.95
CH═CH$_2$	1.80	1.74	−0.02 ($\delta = -1.82$)	nd
C≡CH	0.46	0.96	−0.23 ($\delta = -0.69$)	nd
CO$_2$H	1.16	1.52	−0.75 ($\delta = -1.31$)	−0.38
CO$_2$Me	1.34	1.59	−0.59 ($\delta = -1.93$)	−0.32
CN	0.13	0.62	−0.69 ($\delta = -0.82$)	−0.54
NO$_2$	1.02	1.31	−2.02 ($\delta = -3,04$)	nd
CF$_3$	2.50	1.66	−3.02 ($\delta = -5.52$)	nd

[a] $\Delta G°$ calculated at 25 °C, M06-2X/6-311++G(2d,2p), SMD = acetone. [b] Experimental value determined by ^{1}H NMR at −78 °C in d_6-acetone.

Table 4 Dependence of A-values on ring size[a]



X	Me	Et	iPr	*t*Bu
CH$_2$	+1.95	+2.06	+2.33	+5.83
CMe$_2$	+1.76	+1.90	+3.27	+3.44
	−0.09 (+0.3)	−0.89 (−0.46)	−2.10 (<−1.5)	−2.00 (<−1.5)
	+0.26	−0.25	−0.52	−0.72 (<0)
	+0.67	+0.66	+1.46	+0.11
	+0.69	0.00	−1.31	−1.64 (<−1.5)
	+0.24	−0.42	−0.98	−0.57 (−0.20)[b]
	+1.47	+1.07	+0.42	+1.14
	+0.17	+0.15	−1.80	−1.91
	+0.16	+0.18	−0.28	−0.27 (−0.23)

[a] $\Delta G°$ values calculated at 25 °C at M06-2X/6-311++(2g,2p), SMD = acetone and reported in kcal mol^{-1}. Experimental values determined at −78 °C in d_6-acetone in parentheses. [b] Determined at −98 °C.

isopropyl or *tert*-butyl, the axial conformers are again predicted to be dominant. We examined cyclopropene substitution and noted that while A-values were again diminished, it was not sufficient to favor the axial isomer for groups other than for isopropyl. We also examined cyclobutanone and oxetane units which have been extensively employed as isosteres. Oxetane had a significant effect on medium and large groups, though its effects on smaller groups was not sufficient to prefer the axial conformer and the effect of cyclobutanone was also muted even with large groups (Table 4).

We examined experimentally several different ring systems bearing *tert*-butyl groups (see ESI† for synthesis) and all were found to be generally in line with the calculations (see values in parentheses, Table 4). Due to overlapping signals, the ratio in the cyclobutane substrate could not be quantified. However, using computational NMR shift prediction with the GIAO

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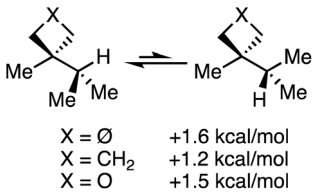


Fig. 3 Conformations in acyclic systems.

method[45] and cross-peak intensity in low-temperature HSQC, the axial conformer was assigned as the major isomer. The anti-epoxide[46] heavily favored the axial conformer, as predicted, with no equatorial isomer observed while the corresponding *syn*-epoxide had a lower preference for axial, again as predicted. The *tert*-butyl substituted spirocyclobutanone could be quantified and was found to have a 64 : 36 ratio. Although we were unable to assign the conformers with NOEs alone, again NMR chemical shift prediction allowed us to assign the major conformer as axial (see ESI†), indicating an A-value of -0.23 kcal mol^{-1} which was consistent with the computations.

Finally, the trends observed in cyclic frameworks were expected to have parallels in acyclic structures. Specifically, there should be an energetic penalty to place an alkyl group above a small ring, similar to the equatorial placement in the spiro systems above. We examined the orientation of an isopropyl group situated on a 1-methylcyclopropane, -cyclobutane and -oxetane. In all cases, the preferred conformation where the hydrogen of the isopropyl group was situated above the ring, was favored by 1.2–1.6 kcal mol^{-1} (Fig. 3). It would be expected that other similar substitutions, such as secondary stereocenters, would adopt a similar conformation. The acyclic directing effect of oxetanes has been previously noted[22] and is highly relevant in their use as bioisosteres, as it alters the normal preference for *syn*-periplanar orientation of alpha groups in ketones.[47]

Application

The surprising cyclopropane effect has potential as a simple but elegant way to influence conformation, particularly in cyclic systems. In medicinal chemistry, the ability of molecules to occupy specific chemical space is critical to ligand/target interactions. Heterocycles including piperidines and piperazines are common features of approved drugs, often adding an element of three-dimensionality to aromatic-rich structures. We considered whether the use of cyclopropanes could influence conformation about a heterocycle in similar fashion to the cyclohexanes above. We first examined a series of *N*-alkylpiperidines which, like cyclohexanes, display a preference for equatorial orientation of the *N*-alkyl group.[48] *N*-Methyl, *N*-benzyl and *N*-*tert*-butyl spiropiperidines **1–3** (Fig. 4) were easily prepared by Kulinkovich reaction on the corresponding lactams.[49] DFT calculations on all three substrates suggested the alkyl groups on nitrogen should assume an axial disposition, with predicted A-values of -1.16 kcal mol^{-1}, -1.83 kcal mol^{-1} and -2.37 kcal mol^{-1} for **1–3**, respectively. Notably, unlike in cyclohexanes, even the small methyl group is predicted to be

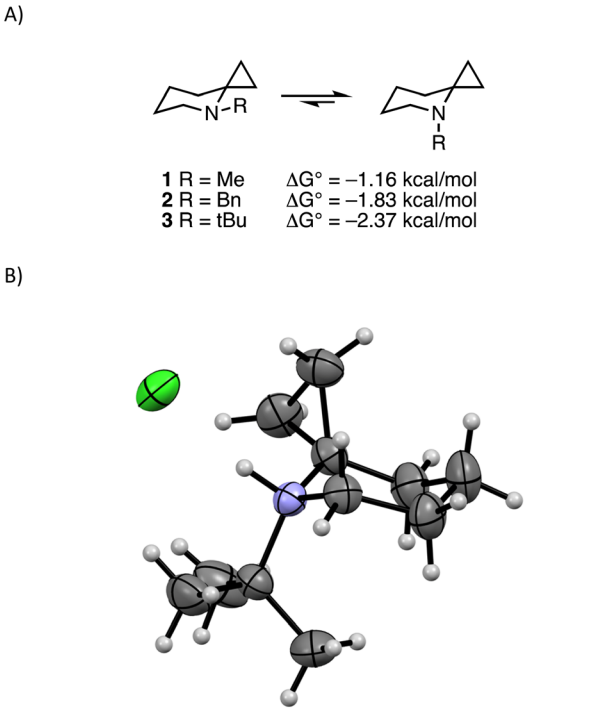
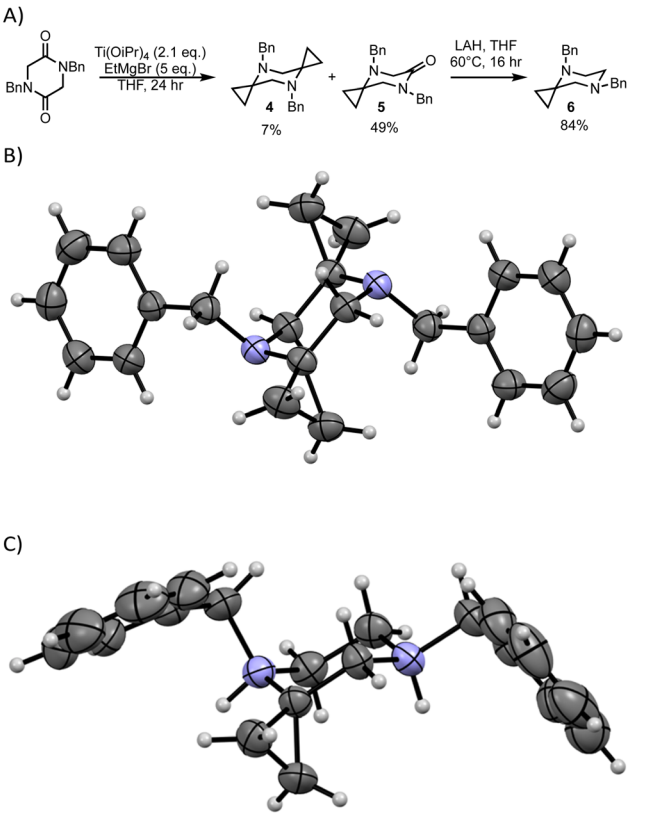


Fig. 4 Conformational control in 2-spirocyclopropyl piperidines. (A) Calculated piperidine A-values (B) X-ray crystal structure of **3**·HCl.



Scheme 2 (A) Synthesis and conformation of spirocyclopropylpiperazines (B) SCXRD of **4** (C) SCXRD of **6**·(TsOH)$_2$·H$_2$O (tosylates and water have been removed for clarity – see ESI† for full structure).

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mainly axial. Experimentally, all three exhibited only a single conformer at −78 °C.[50] For **2** and **3**, NOE studies clearly identified these as the axial conformer while for **1** the NOE data was inconclusive but DFT chemical shift analysis suggested the axial conformer (see ESI†). In the case of **3**, it was possible to crystallize the amine as its HCl salt (calculated A-value for **3**·HCl: −2.61 kcal mol^{-1}). X-Ray diffraction analysis confirmed the remarkable axial orientation of the *tert*-butyl group (Fig. 2b).

Piperazines are among the most common heterocycles in active pharmaceutical ingredients, being found in almost 10% of the top selling small-molecule drugs.[51] We prepared mono- and bis-cyclopropyl piperazines by Kulinkovich reaction of *N*,*N*′-dibenzyldiketopiperazine to afford a mixture of **4** and **5** (Scheme 2A). Lactam **5** could be further reduced with lithium aluminum hydride to afford mono-cyclopropyl piperazine **6**. All three piperazines (**4–6**) were found to display a single conformation at low temperature. While it was not possible to establish the conformations by NOE, the expected preference for diaxial conformation in **4** was observed in an X-ray crystal structure (Scheme 2b). Similarly, mono-cyclopropane **6** when crystallized as a hydrated bis-*p*-toluenesulfonic acid salt displayed an axial/equatorial conformation with the benzyl group adjacent to the cyclopropane selectively forced into the axial position (Scheme 2c). These studies establish the ability to modulate the conformation of 6-membered ring heterocycles by straightforward incorporation of spirocyclic cyclopropanes. Notably, comparing **4**, **5**, and **6**, it is possible to maintain one benzyl group axial while displaying the other axial, pseudo-equatorial, or equatorial, respectively, depending upon the identity of the adjacent group.

Discussion

The ability of small rings to act as isosteres, mimicking functionality such as alkenes, arenes, carbonyl and other groups is well recognized in medicinal chemistry. A key factor in the implementation of small rings is their ability to project groups into three-dimensional space in a way that reproduces the replaced functionality. Cyclopropanes are excellent mimics for multiple groups, including alkenes given their frozen torsion angles at 0° and ∼145°. Similarly, the oxetane has seen significant use as a carbonyl mimic, with the slightly widened exocyclic bond angle mimicking that of the sp^2 carbon.[3]

Our study has demonstrated that small rings commonly used as isosteres can also be used for elements of conformational control in cyclohexanes, six-membered ring heterocycles and in acyclic systems. Compared to simple di-alkyl substitution, small constrained rings shift the equilibria of adjacent groups towards axial conformers for most substituents.

The main origin of the effect for alkyl groups is a change in steric strain. In a simple geminal dimethyl system, the torsion angle between an equatorial substituent (*e.g.* methyl) and the two methyl groups is 60° ± 5° (Fig. 5A). The constraint of the cyclopropane ring significantly reduces this angle (34° and 38°), resulting in increased steric interactions. In addition, in the axial form, the torsion angle in the cyclopropane is opened significantly from 47° to 77°, suggesting a potential reduction of steric interactions. An NBO-STERIC calculation[52,53] indicated the relative difference between axial and equatorial conformers is reduced by 2.08 kcal mol^{-1} when comparing the dimethyl (2.72 kcal mol^{-1}) to cyclopropyl (0.64 kcal mol^{-1}) substituents. This 2 kcal mol^{-1} reduction in steric interactions is consistent with the change in A-value observed experimentally. To examine this effect in more depth, butane was used to model the steric interactions of individual torsion components. Freezing butane torsion angles at the equivalent angles from the cyclohexane system revealed that the smaller torsional angles in the equatorial form for the cyclopropane add 1.96 kcal mol^{-1} in steric interactions relative to the torsional angles in a dimethyl group (Fig. 5b). Conversely, in the axial form, the steric interactions

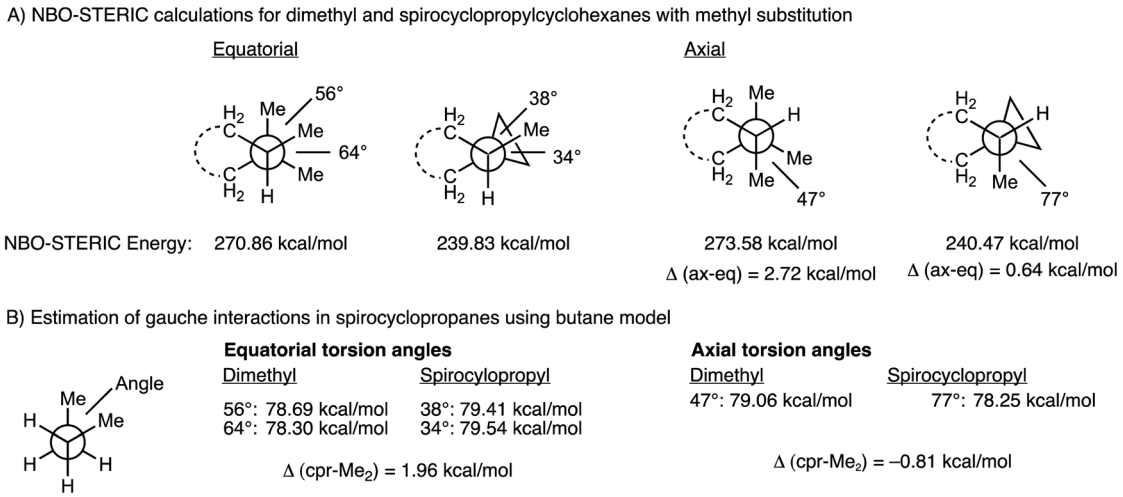

Fig. 5 Increased steric strain adjacent to cyclopropane. (A) NBO-STERIC calculations suggest a reduced difference between axial and equatorial epimers in the presence of a cyclopropane. (B) Modeling the effect of specific torsion angles using butane. NBO-STERIC energies were calculated fixing butane at angles found in the dimethyl and spirocyclopropyl systems. The sum of steric interactions are approximately 2 kcal mol^{-1} higher in the equatorial isomer with cyclopropyl substitution compared to dimethyl whereas in the axial isomer the cyclopropane interactions are 0.81 kcal mol^{-1} less.

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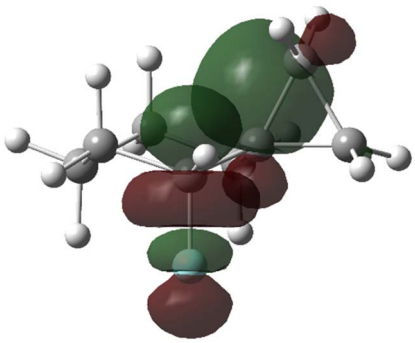

Fig. 6 NBO orbital overlap of cyclopropane C–C σ-bond with axial C–F σ*, calculated at the M06-2X/6-311++G(2d,2p) level.

are lower by −0.81 kcal mol^{-1} for the cyclopropane.[54] While only an approximation, these results are suggestive of a combination of destabilization of the equatorial form and a net stabilization (relative to dimethyl) in the axial form for spirocyclopropanes. These steric strain effects are presumably increased in N-heterocycles (*e.g.* **1–6**) due to reduced bond length along the torsion axis (1.45 *vs.* 1.52 Å) as well as with larger groups (*e.g.* *tert*-butyl).

While simple torsional strain arguments can be used to explain the preference in alkyl-substituted cyclohexanes, the trends with halides and other electron poor groups suggest that stereoelectronic factors also contribute. For instance, both fluoro and chloro groups have smaller van der Waals radius than methyl[55,56] but both clearly prefer the axial conformation whereas for methyl the axial and equatorial conformations are roughly equal in energy. One potential stabilizing factor may be hyperconjugative donation from the cyclopropyl group into the C–X antibonding orbitals.[21] While the C–C bond axis is not well aligned for donation, the electron density of the cyclopropane lies outside of the bond axis and is positioned appropriately to donate to σ* (Fig. 6). Notably, an NBO analysis revealed stronger donation into the C–X σ* from the cyclopropane *vs.* an axial methyl, on the order of 0.8–1 kcal mol^{-1} for both F and Cl. This hyperconjugative stabilization presumably stabilizes the axial form and, in combination with increased torsional strain in the equatorial isomer, results in a more significant preference for axial orientation. Notably, the hyperconjugation is significantly reduced in the corresponding cyclobutyl fluoride (predicted A-value: +0.15 kcal mol^{-1}, σ–σ* donation only 0.2 kcal mol^{-1} greater than methyl).

Conclusions

In summary, we have found that the presence of small spirocyclic rings on cyclohexane has a profound effect on the axial/equatorial orientation of adjacent groups. The effect of increased torsional strain and, in certain instances, hyperconjugation, results in a significant shift towards greater relative stability of the axial conformation. Effects are significant for a range of groups, with larger groups experiencing a more significant shift towards axial preference. The effect is observed most acutely with cyclopropane, but also extends to other three and four-membered rings as well as acyclic systems, and can be incorporated within heterocycles to control nitrogen stereochemistry. Importantly, these effects have significant potential for use as a design element in a wide range of applications. In medicinal chemistry, installation of a cyclopropane into a structure can allow the exploration of different chemical space. Similarly, small rings could be incorporated in cyclic catalysts to project large groups into specific areas to alter catalyst selectivity.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Both authors conceptualized the project, conducted computational studies and wrote the manuscript. ARI conducted all experimental work.

Conflicts of interest

There are no conflicts to declare.

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