Driving *t*-Butyl Axial: The Effect of Small Spirocyclic Rings on A-Values

Anthony R. Izzotti and James L. Gleason*

Department of Chemistry, McGill University, 801 Sherbrooke W.,
Montreal, QC, Canada H3A 0B8.

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ABSTRACT: The presence of a small spirocyclic ring at an adjacent position alters the conformational preference for equatorial substitution in cyclohexane and piperidine rings. DFT and low-temperature ^{1}H NMR experiments demonstrate that alkyl groups larger than methyl possess negative A-values when geminal to a spirocyclohexane. Similar observations are made for halogen and other electron withdrawing substituents. For small groups such as methyl and hydroxy, the A-value is near zero, while for groups such as amino, acetamido and aryl, the A-values are positive, but significantly smaller than for simple cyclohexanes. Similar effects are observed for other strained rings (epoxide, cyclobutane, oxetane) and the concepts extend to acyclic models. 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 in medicinal chemistry has seen a significant increase in recent years.[1] 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 relevant disposition of pendant groups.[2, 3] Even more common is the use of cyclopropanes (Figure 1), which have been employed as isosteres for alkenes, isobutyl and tert-butyl groups and even aromatic rings.[4] While significant attention is paid to the directionality of groups directly attached to small rings, there is less information available on the conformation of bonds adjacent to strained rings.

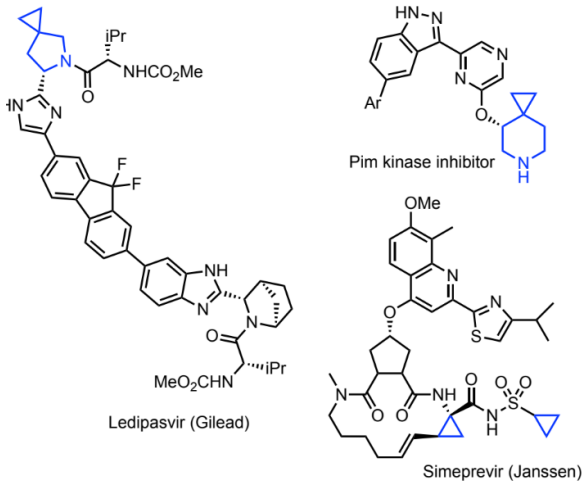

Figure 1. Structures of cyclopropane-containing drugs and drug candidates.

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The quintessential example of conformational analysis is the understanding of structure in cyclohexanes (Figure 2), where the preference for equatorial substitution is quantified in terms of A-values. In general, larger groups, when axial, incur larger gauche interactions with methylene groups at the 3- and 5-positions and thus significantly prefer the equatorial position.[5] Known exceptions to the preference for equatorial substitution do exist, with the most common example being the anomeric effect in carbohydrates and related acetals, and also hyperconjugative stabilization observed in 1,3,5-triazinanes.[6, 7] Other examples include α-halo-cyclohexanones and examples where hydrogen bonding stabilizes axial substitution.[8-10]

In the context of a methodology project, we observed anomalous behavior of groups adjacent to a cyclopropane in a chair-like transition state. A search of the literature turned up a single example of an aromatic ether adjacent to a spiro-cyclopropane which was found to be axial in an x-ray crystal structure of a Pim kinase inhibitor bound to its target (Figure 1), which was supported by a brief DFT study showing it was expected to prefer the axial conformation by 0.4 kcal/mol.[11] Intrigued by these observations, combined with the importance of small rings in medicinal chemistry, we initiated a full study of this phenomenon. Here we show that small rings, including cyclopropanes, cyclobutanes, oxetanes and epoxides can induce negative A-values for a wide range of substituents in a predictable way that can be used as a design element in molecule development.

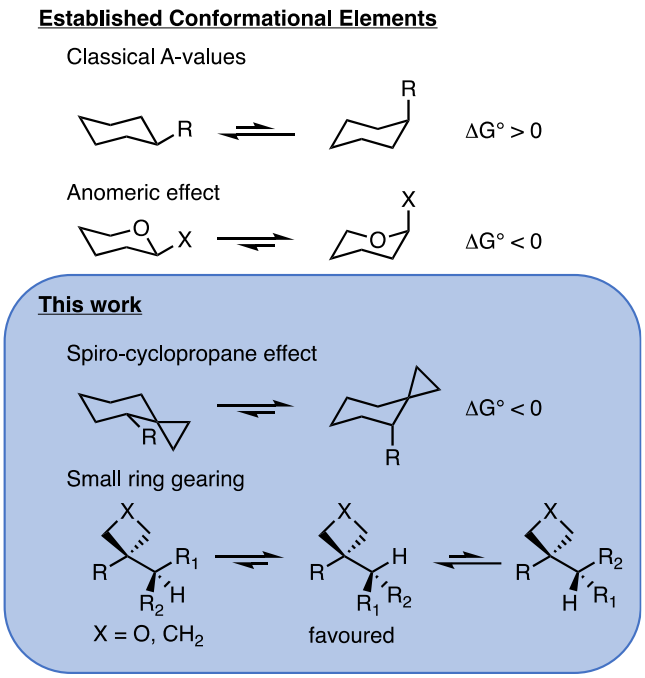

Figure 2. Conformational preferences can be influenced by small rings adjacent to methine positions.

Results

The study began with an assessment of A-values using DFT. The A-values of substituents on cyclohexanes are well established. Screening a series of functionals, we found the M06-2X functional, with a 6-311++G(2d, 2p) basis set, was superior to other functionals (B3LYP-D3, wB97XD) and MP2 in reproducing A-values for simple cyclohexanes (See SI for energy differences). Calculations were conducted with an SMD solvation model of acetone, as we intended to examine structures at low temperature by NMR.

We started with a comparison on the effect of a cyclopropane on the A-value of a variety of alkyl groups (Table 1). We contrasted the results with simple geminal dimethyl substitution to probe the specific effect of a small ring versus simple substitution. As can

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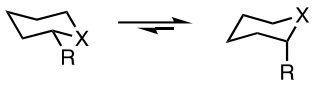
be seen in Table 1, the presence of a geminal dimethyl group had effect on A-values for most groups, with only tert-butyl (3.43 kcal/mol vs. 5.83 kcal/mol) and isopropyl (3.67 kcal/mol vs 2.78 kcal/mol) groups experiencing an absolute change greater than 1 kcal/mol. In stark contrast, for an adjacent cyclopropane the A-values decrease by a minimum of 2 kcal/mol, inverting to a negative value for all alkyl substituents. For instance, a simple methyl group drops from an A-value of 1.95 kcal/mol in a simple cyclohexane, to 1.76 kcal/mol in a system with geminal methyl substitution but when the two geminal substituents are connected in a cyclopropane, the A-value is –0.09 kcal/mol, slightly favoring the axial position, a change of –2.04 kcal/mol relative to the unsubstituted system and –1.85 kcal/mol relative to geminal dimethyl. Larger groups such as ethyl and isopropyl display more negative A-values (–0.56 kcal/mol and –2.73 kcal/mol), in contrast to the usual increase based on their larger size. Notably, even a *tert*-butyl group possesses a negative value of –2.08 kcal/mol, a change of nearly –8 kcal/mol from the normal equatorial preference in simple cyclohexanes. Importantly, unlike other simple systems such as cis-1,4-di-tert-butylcyclohexane, the twist boat was found to be significantly higher in energy (3.4 kcal/mol above the axial chair conformation) and thus would not be expected to be present to any significant extent.

We next examined the effects of cyclopropane on heteroatom substitution. Again, in all cases, we predicted a decrease in the A-value, with absolute changes ranging from –1.4 to –2.8 kcal/mol, and the axial conformation preferred for all substitution patterns, including small fluoro groups. Finally, we examined a range of π-conjugated

Table 1. A-value dependence on adjacent cyclopropanes.



	DFT (M06-2X/6-311++G(2d,2p))[a]			Change vs CH_2[b]	Expt.[c]
X =	CH_2	CMe_2	$C(CH_2CH_2)$		
R = Alkyl					
Me	1.95	1.76	–0.09	–2.04	0.04
Et	1.96	2.31	–0.56	–2.52	-0.71
iPr	2.78	3.67	–2.73	–5.51	<2.0
CH_2OH	1.80	1.88	–1.20	–3.00	–1.15
Bn	1.78	1.96	–0.85	–2.63	–1.15
tBu	5.83	3.43	–2.08	–7.88	<–2.0
R = Heteroatom					
OH	0.86	0.78	–0.72	–1.58	-0.03
NH_2	1.44	1.23	–0.17	–1.83	+0.76
NHAc	0.90	1.06	–1.04	–1.94	+0.32
N_3	0.33	0.30	–1.53	–1.88	–1.14
F	0.31	0.29	–1.05	–1.36	–1.28
Cl	0.63	1.16	–1.81	–2.44	n/a
Br	0.61	1.21	–2.23	–2.84	n/a
R = π and EWG					
Ph	3.58	3.76	1.02	–2.56	+1.47
CH=CH	1.69	1.66	0.31	–1.38	n/a
C≡CH	0.46	0.96	–0.23	–0.69	n/a
CO_2H	1.16	1.42	–0.63	–1.79	–0.59
CO_2Me	1.43	1.58	–0.42	–1.85	–0.47
CN	0.13	0.62	–0.69	–0.82	n/a
CF_3	2.50	1.66	–3.02	–5.53	n/a

a) ΔG° calculated at 25 °C (kcal/mol). b) ΔG°(cyclopropane) – ΔG°(CH_2). c) Measured by ^{1}H HMR at –78 °C in d_6-acetone.

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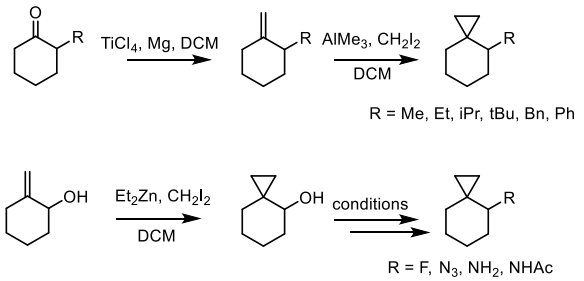
groups and electron withdrawing groups. Within this series, all substituents also displayed a shift towards a more negative A-value. For simple π-conjugating groups such as phenyl and vinyl, the shift was not sufficient to prefer the axial conformation, although the absolute change for phenyl is still significant (–2.5 kcal/mol). In contrast, all electron withdrawing groups were predicted to have a negative A-value, with the larger CF_3 group having the most significant change relative to a simple cyclohexane.

The computational results above strongly suggest a general trend toward preferred axial conformation next to spiro-cyclopropanes. To investigate experimentally, we synthesized a range of substituted spirocyclopropanes, the majority by via either Yamamoto or Simmons-smith cyclopropanation (see Scheme 1 for a general scheme and Supporting Information for details) and 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 peaks that were interconverting was achieved by saturation transfer in selective 1D NOE experiments. Notably, in the cyclopropyl system, the alpha equatorial protons are significantly shielded by anisotropy[12], which facilitated assignment.



Scheme 1. Synthesis of cyclopropane substrates.

As can be seen in Table 1, in most cases, there was good agreement between predicted and measured A-values. In particular, alkyl substituents including Me, 1°, 2° and 3° groups all showed a close correspondence between predicted and observed equilibria. We estimated our limit of detection to be roughly 2-5% of the major conformer, setting an upper limit for measuring the magnitude of A-values around 2 kcal/mol. This was the case for tert-butyl and isopropyl, where we only observed the axial form. Similarly, for phenyl and electron withdrawing groups, the observed A-values were consistent with the calculations. For heteroatoms, we found that the calculated A-value for a fluoro group reflected well the observed equilibrium concentrations. However, there were inconsistencies for groups bearing hydrogen bond donors. For OH, a very slight preference for axial was observed, while a –0.73 kcal/mol difference was expected. Larger discrepancies were observed for amine and amide substituents. We tentatively attribute the difference between calculation and experiment to potential hydrogen bonding to solvent (d_6-acetone).

We next examined whether the effect of a spirocyclopropane extends to N-substituted heterocycles[13] (Figure 3). N-Methyl and N-benzyl spiropiperidines **1** and **2** were easily prepared by Kulinkovich reaction on the corresponding lactams. DFT calculations on N-methyl substrate **1** demonstrated a predicted A-value of –1.2 kcal/mol while the N-benzyl substrate **2** was predicted to have an A-value of –2.1 kcal/mol. Experimentally, **2** exhibited only one conformer at –78 °C by ^{1}H NMR. The axial conformation was deduced by NOE; one benzylic methylene proton showed correlations to axial protons at C3 and C5, whereas irradiating the other methylene proton showed an NOE to only C3

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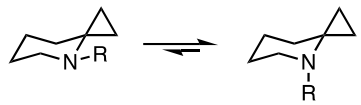
and one of the cyclopropyl protons. The strengths of these correlations fit well with the predicted structure which places the aromatic ring anti to the cyclopropane. Notably, in contrast to the corresponding cyclohexane, no equatorial conformer was observed indicating an A-value below –2.

A)



1 R = Me ΔG° = –1.2 kcal/mol
2 R = Bn ΔG° = –2.1 kcal/mol

B)

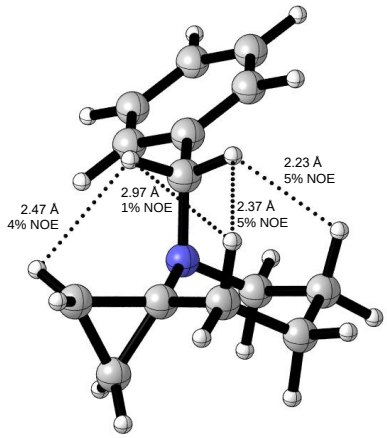
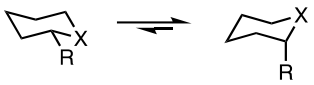
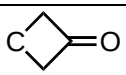


Figure 3. Conformational control in 2-spirocyclopropyl piperidines. **A)** Calculated piperidine A-values **B)** M06-2X/6-311++G(2d,2p) calculated structure and experimental 1D NOEs

Given the preference for axial orientation adjacent to a cyclopropane, we examined the effect of other small ring systems, probing these with small (Me, Et), medium (iPr) and large (tBu) substituents (Table 2). Spiro-epoxides demonstrated a similar decrease in A-values as cyclopropane, although the magnitude of the effect was reduced and varied depending on the relative stereochemistry of the epoxide; a *cis*-arrangement between the epoxide oxygen and the substituent had a larger decrease in A-value than the corresponding *trans*-isomer. For a small substituent, the equatorial isomers are often still preferred, though by a much smaller margin than for a regular cyclohexane. However, for larger groups such as isopropyl or tert-butyl, the axial conformers should prevail. We also examined cyclopropene and noted that while A-values were again diminished, it was not sufficient to favor the axial isomer for groups other than isopropyl.

Table 2. Conformational dependence on ring size.[a]



X	Me	Et	iPr	tBu
CH_2	1.95	1.96	2.78	5.83
CMe_2	1.76	2.31	3.67	3.43
	–0.09	–0.56	–2.73	–2.08 (<–2.0)
	1.47	1.10	–0.06	1.53
	0.69	–0.62	–1.99	–1.64 (<–2.0)
	0.24	0.30	–1.01	–0.59
	–0.11	–0.65	–1.71	–0.7 (<0)
	0.16	–0.04	–0.22	–0.48 (–0.47)
	0.17	–0.17	–1.61	–0.77

a) ΔG° calculated at 25 °C at M06-2X/6-311++(2g,2p), SMD=acetone and reported in kcal/mol. Experimental values in parentheses.

We also examined three examples of four-membered rings, cyclobutane, cyclobutanone and oxetane, the latter of which is a common isostere for carbonyl groups. Again, the

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small rings decreased the A-values relative to methylene or geminal-dimethyl substitution, with the cyclobutane having a larger effect for primary substituents and all three rings being sufficient to push groups larger than methyl axial to at least some extent.

We experimentally examined several different ring systems bearing tert-butyl groups (see Supporting Information for synthesis). The anti-epoxide heavily favored the axial conformer, as predicted, with no equatorial isomer observed. The syn-O epoxide was challenging to assess, as significant peak broadening was observed at –78 °C, suggesting that ring flip was still occurring. This was corroborated computationally; the syn-epoxide was predicted to have an 8.4 kcal/mol barrier to ring flip vs. 11.3 kcal/mol for the corresponding anti-epoxide. This difference is attributed to reduced eclipsing interactions between the epoxide ring and the tert-butyl in the syn isomer. The cyclobutanone was found to have a minor conformer, with a magnitude of 0.42 kcal/mol, though we were unable to assign the conformers with NOEs alone. Computational NMR prediction using the GIAO method[14] was performed and allowed us to conclude that the major conformer was indeed axial, indicating A = -0.42 kcal/mol (see Supporting Information). Due to overlapping signals, the cyclobutane substrate was not able to be quantified. However, based on chemical shifts by DFT and cross-peak intensity in low-temperature HSQC, the axial conformer was assigned as the major isomer.

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 in situations where the ring is 1,1-substituted. Given the recent importance of oxetanes, we examined the orientation of an isopropyl group situated on a 1-methyl oxetane. The preferred conformation, where the hydrogen was situated above the ring, was preferred by 2.1 kcal/mol (Figure 4). It would be expected that other similar substitutions, such as secondary stereocenters, would adopt a similar conformation. Importantly, the corresponding ketone would place one of the methyl groups eclipsed with the carbonyl group, and thus the oxetane represents a potentially useful gearing element in addition to its ability to act as an isostere. Notably, similar results were found for isopropyl adjacent to a cyclobutane (2.1 kcal/mol) and cyclopropane (1.6 kcal/mol).

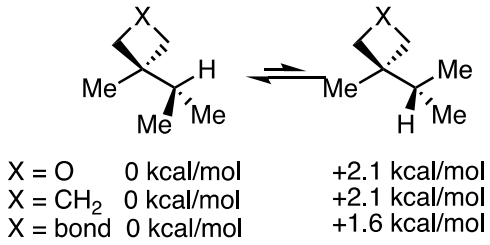

Figure 4. Acyclic gearing by small rings.

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. Important in the design and use of small rings is their ability to project groups into three-dimensional space in a way that reproduces the replaced functionality. Thus, BCP groups can be used to mimic *p*-benzenes due to their ability to mimic the size of an arene and project groups at 180°. More recent advancements have shown that 1,2-substituted BCPs can also mimic *o*- and *m*-substituted benzenes.[15] Similarly, the oxetane

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has seen significant use as a carbonyl mimic, with the slightly widened exocyclic bond angle mimicking that of the sp_2 carbon.[3] Cyclopropanes are also excellent mimics for multiple groups, particularly an alkene given frozen dihedral angles at 0° and ~140°.

In the examples above, we have demonstrated that small rings commonly used in isosteres can also be used for elements of conformational control in cyclohexanes and six-membered ring heterocycles. Compared to simple di-alkyl substitution, constraining groups within a small ring (cyclopropane, epoxide, cyclobutane, oxetane) shifts the equilibria towards axial conformers for most substituents.

The main origin of the effect can be explained by a change in torsional strain. In a simple geminal-disubstituted system, the dihedral angle between an equatorial substituent (e.g. methyl) and the two methyl groups is 60° ± 5° (Figure 5). The constraint of the cyclopropane ring significantly reduces this angle, resulting in increased torsional strain. In the case of groups larger than methyl, this is sufficient to outweigh the gauche interactions with C3/C5 in the axial conformation. This strain is alleviated somewhat in larger rings, or in groups lacking hydrogens on the ring (epoxide, cyclopropene).

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 may also contribute. For instance, both fluoro and chloro groups have smaller van der Waals radius than methyl[16, 17] 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. 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. 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 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.

Finally, we note that there is an approximate 1 kcal/mol decrease in A-value for N-heterocycles **1** and **2** relative to their cyclohexane counterparts. This change can be rationalized by the difference in bond length. The N-C(cyclopropane) bond length is predicted to be 1.45 Å, while the corresponding C-C bond is notably longer at 1.52 Å. The shorter bond exacerbates the torsional strain while having minimal effect on the gauche interactions with C3/C5 in the axial conformation, leading to a more negative A-value.

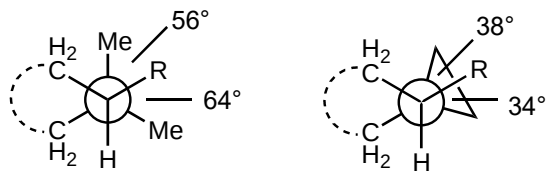

Figure 5. Increased torsional strain adjacent to cyclopropanes

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Conclusions

In summary, we have found that the presence of spirocyclic small rings on cyclohexane has a profound effect on the axial/equatorial orientation of adjacent groups. The effect of increased tortional 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 larger shift towards axial preference. The effect is observed most acutely with cyclopropane, but also extends to other three and four-membered rings. This observation has potential significance in medicinal chemistry, in that many of these small rings are common bioisosteres. The model also extends to adjacent nitrogen stereocenters, which benefit from increased torsional strain due to a shortened bond. Finally, the model is also relevant in acyclic systems where a methyl group is adjacent to a strained ring. Importantly, this affords the potential to alter directionality of groups when moving from ketones to bioisosteres such as oxetanes. The effects may also have relevance in catalyst development, as incorporation of small spirocyclic rings might be used to alter the conformation of catalysts and to project large groups (e.g. t-butyl) into chemical space that they normally do not occupy.

Additional Information

Supplementary Information is available for this paper. All data regarding the results described herein are available upon request.

Author Information

Corresponding Author: James L. Gleason (Jim.gleason@mcgill.ca)

Author Contributions

A.R.I. was responsible for all experimental results, both authors contributed to the DFT calculations, as well as the writing of the manuscript.

ORCID

James L. Gleason: 0000-0003-1687-3343

Competing Interests

The authors declare no competing interests.

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