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Driving *tert*-Butyl Axial: The Surprising Cyclopropyl Effect
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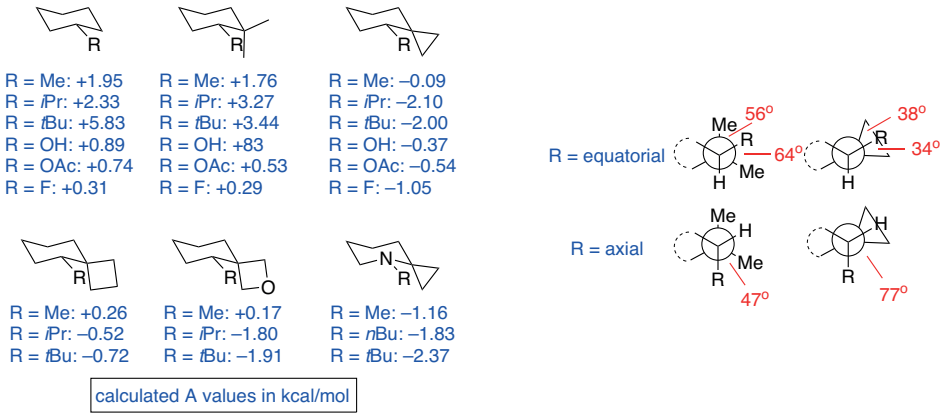
Spiro Cyclopropane Influences Axial Substituent Disposition in Cyclohexanes, Piperidines and Piperazines



Significance: Substituents on a cyclohexane ring generally adopt an equatorial disposition, with the preference increasing with the size of the substituent. Thus, a *tert*-butyl substituent strongly favors an equatorial conformation, captured energetically in the well-known A values. This study examined the effect of the introduction of a spirocyclopropyl moiety adjacent to the site of substitution and observed a significant change in the calculated A values by as much as 7.83 kcal/mol for a *t*Bu substituent. The phenomenon extended to polar substituents and also to piperidines and piperazines. These observations impinge on drug design principles where conformational preferences and molecular shape can be of critical importance in modulating ligand potency and selectivity. This phenomenon may also be of value in the design of organocatalysts where judicious deployment of substituent disposition may modulate catalyst selectivity and specificity.

Comment: DFT calculations were performed for a series of substituted cyclohexanes, 2-substituted *gem*-dimethyl and 2-substituted spirocyclopropyl cyclohexanes, and 2-spirocyclopropyl piperidines and piperazine. The predicted conformational effects were supported by ^{1}H NMR analysis of representative compounds at –78 °C in acetone. Whilst the presence of the *gem*-dimethyl substitution exerted only a small effect on the equatorial preference of adjacent substituents, a spirocyclopropyl moiety favored an axial disposition that increased with substituent size. A similar effect was observed with polar substituents, illustrated above by OH, OAc and F. In the cyclobutyl homologue, the effect was evident but muted, although more pronounced in the spiro-oxetane. The phenomenon was observed in piperidine and piperazine derivatives where the N-substituent preferred an axial disposition. The phenomenon was rationalized based on steric effects that are more acute in the spirocyclopropyl compounds, although a stereoelectronic effect was invoked in the disposition of polar substituents.

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