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Axial and Equatorial Hydrogen Shifts in Methyl Substituted Cyclohexylidenes. Stereochemically-dependent Isotope Effects and Bystander Assistance.

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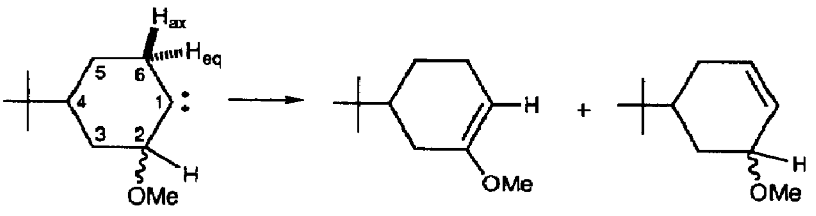
Abstract: Carbenes were generated from 4-*t*-butyl-*cis*-2-methylcyclohexanone (**4a**) and from 4-*t*-butyl-*cis*-2-*trans*-6-dimethylcyclohexanone (**8a**, and its corresponding 2,6-d_2 analog **8b**) by conventional Bamford-Stevens reactions. Product analysis revealed that an equatorial CH_3 assists migration of a geminal H more efficiently than does an axial CH_3 by a factor of about 4.6. The primary deuterium isotope effect (k_H/k_D) for axial shift (I_{ax}) is *ca.* 1.5 times greater than for equatorial shift (I_{eq}) in the anchored dimethyl substituted carbene **9**.

Regio- and stereoselectivity of 1,2-H migration in singlet carbenes to produce alkenes have received attention for over three decades.[1] The ease of H shift is known to be influenced strongly by nonmigrating (i.e. bystander) groups; but how they do so is little understood. A recent analysis[1c] of published data on 1,2-H migration in acyclic and cyclic carbenes distinguished factors such as: inherent migratory aptitude (termed M); assistance by a bystander group (B factor); and efficiency with which two geminal bystanders combine their activating effects (G factor). Evaluation of G factors in different substrates can reveal unrecognized structural features that influence carbene rearrangements.

Several experimental studies on cyclohexylidenes (particularly on homobrexylidene, which is free of twist boat ambiguities) have established that when epimeric ring H's compete with each other the H_{ax}/H_{eq} shift preference is small ("best" value *ca.* 1.7 for thermal processes).[1a] Theoretical calculations suggest that the H_{ax}/H_{eq} selectivity is low because the transition states for each migration are strikingly similar geometrically, even though each hydrogen starts off with a distinctly different alignment.[2]

Interestingly, when a tertiary H migrates in a substituted cyclohexylidene its ability to compete can be affected markedly by the stereochemistry of the geminal substituent. For example, the OMe_{ax} and OMe_{eq} epimers of the anchored cyclohexylidenes **1** (derived by thermal Bamford-Stevens reactions) produce alkenes **2** and **3** by

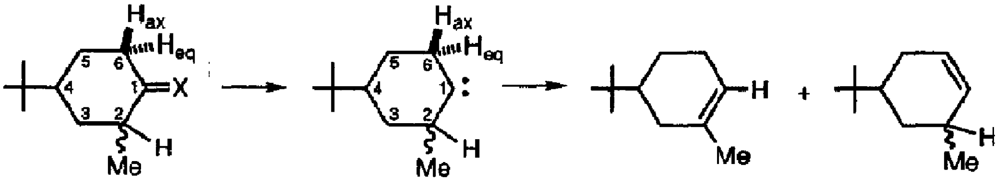


	1	2	3
a	eq OMe	95.1%	4.7%
b	ax OMe	29.4%	58.4%

competitive H shifts.[3] [Note that when the 3° H rearranges from C-2, the two bystanders are OMe and the C-3 ring residue (call it R); and when either H_{ax} or H_{eq} moves from C-6 only one bystander is present, namely ring residue C-5 (call it R).[1c]] Analysis of these alkene ratios in terms of competition among the three available H's revealed that eq OMe promotes geminal H shift more effectively than does ax OMe by a factor of 23.2. (This number arises from the ratios of their respectively derived G factors of 1.58 and 0.068.)[1c] In fact, the latter very low G value indicates that axial OMe on a cyclohexane ring is almost devoid of activating power. Geometry-dependent activation is not unique to OMe. Similar analysis[1c] of published results[4] for an epimeric pair where the bystander is a phenyl group revealed that Ph_{eq} promotes H shift better than does Ph_{ax} by a factor of *ca.* 1.6 (i.e. the respective G factors are 0.76 and 0.47).

The reasons why equatorial OMe and Ph accelerate H better than when these bystander groups are axial might be associated with interactions involving lone pair or π electrons, or rotameric geometry about the C—OMe and C—Ph bonds. Therefore, the behavior of CH_3 as a bystander group would be particularly informative, because CH_3 is rotationally symmetric and possesses only typical σ electrons.

In principle, product studies of the epimeric methyl substituted carbenes **5a** and **5b** (from precursors **4a** and **4b**) would disclose how effectively each Me promotes rearrangement of H-2. We prepared and examined the

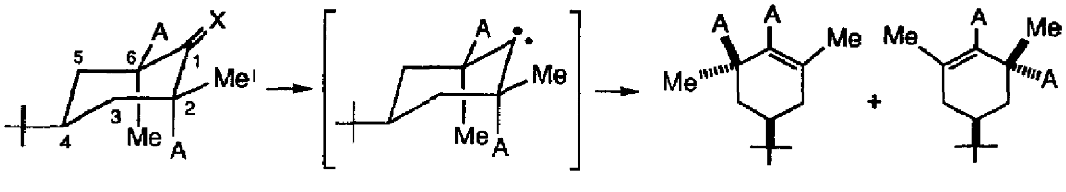


4 (X = O or NNHTs) 5 6 7

a eq Me

b ax Me

eq Me epimer **4a**; but in the ax Me series we were thwarted by substantial Me epimerization during attempted conversion of axial ketone **4b** to its tosylhydrazone, so this epimer could not be studied. However, we achieved our objective directly with substrate **8a**, which simultaneously possesses one eq Me and one ax Me.[5] The ratio of alkenes **10** and **11** produced from carbene **9** immediately reveals the H_{ax}/H_{eq} selectivity and hence the relative



8 (X = O or NNHTs) **9** **10** **11**

a A = H; **b** A = D

efficiencies of activation by ax Me and eq Me. Furthermore, a parallel investigation of the 2,6-d_2-analog **8b** provided valuable information about deuterium isotope effects.

Our synthesis of known ketones **4a** and **8a** (and d_2-analog **8b**) followed literature procedures[6] and are described elsewhere.[7] Tosylhydrazone **4a** (X=NNHTS) was converted with *n*-BuLi (1 equiv) to its Li salt, which was thoroughly dried and pyrolyzed (neat or in aprotic solvent). The predominant volatile products were alkenes **6** and **7**, in the ratios shown in Table 1. These data lead to a G factor of 0.31 for this epimer; and this value means that eq Me accelerates geminal H_{ax} migration to an extent that is 31% of the amount expected.[1c]

Table 1. Thermolysis of *p*-Tosylhydrazone Li Salt from 4a

Conditions (160 ± 3°)	Alkenes Rel (%)		G_{Hax} [a]
	6	7	
Neat (760 mm Hg)	79.7	20.3	0.31
Diglyme	79.5	20.5	0.30

[a] Full symbolism is $G[Me^A, R^S]_{Hax}$. The A and S indicate the Me and ring residue R are respectively Anti and Syn to the group at the migration terminus during migration of H_{ax}. The G_{Hax} values are computed by use of equations 4b and 5 in ref. 1c and the value $B[Me^A]$=20.1.

Thermolysis of the Li salt from **8a** gave alkenes **10a** and **11a**, and the Li salt from **8b** gave **10b** and **11b**, in the proportions summarized in Table 2. These proportions represent H_{ax}/H_{eq} selectivities of 6.9 - 8.7 (average 7.8), which are distinctly higher than those (*ca.* 1.7) reported[1c] for secondary hydrogens. Therefore eq Me activates geminal H more effectively than does ax Me by a factor of about 4.6 (i.e. 7.8/1.7).[8] This stereochemically - dependent assistance by Me parallels that displayed by OMe and Ph, so its basis cannot rest *entirely* on rotameric differences or on interactions associated with n or π electrons.

Isotope Effects. All published experimental studies on H_{ax}/H_{eq} selectivity used d-labeling to distinguish the two competing secondary H's. And, to estimate (and thereby to correct for) primary isotope effects (I),[9] researchers had to assume that k_H/k_D isotope effects are equal for the ax and eq trajectories (i.e. they assumed $I_{ax} = I_{eq}$).[1a,c,10] In fact, a similar assumption has to be invoked whenever conventional d-labeling is used to distinguish two epimeric H's in any intramolecular competition.[11] But, to our knowledge, this assumption has not been validated (or tested) experimentally.

By definition, $I_{ax} = k_{Hax}/k_{Dax}$; and $I_{eq} = k_{Heq}/k_{Deq}$. Therefore, the ratio I_{ax}/I_{eq} corresponds to $(k_{Hax}/k_{Heq})\bullet(k_{Deq}/k_{Dax})$; and this composite ratio should be unity if the two isotope effects are equal. However, the last column of Table 2 shows that the ratio is about 1.5. Clearly, I_{ax} and I_{eq} for 3° H shifts are not equal; and extension to 2° H shifts implies that numerical adjustments of published data on isotope effects, on H_{ax}/H_{eq} selectivities, and on G factors may be in order. For example, the "best" value for inherent H_{ax}/H_{eq} migration (1.7) would change to about 2.1. Such adjustments, which will be detailed in the full paper, do not alter any earlier conclusions about carbene behavior but are pertinent for quantitative discussions of stereoselectivity, isotope effects,[12] and bystander assistance.

Table 2. **Thermolysis of *p*-Tosylhydrazone Li Salts 8a and 8b**

Conditions (160 ± 3°)	Alkenes Rel (%)				Migration Ratio		$\frac{G_{Hax}}{G_{Heq}}$	I_{ax}/I_{eq}
	from **8a**		from **8b**		**10a/11a**	**10b/11b**		
	10a	**11a**	**10b**	**11b**	H_{ax}/H_{eq}	D_{ax}/D_{eq}		
Neat (760 mm Hg)	87.4	12.6	67.2	14.8	6.94	4.54	4.02[a]	1.53
Tetraglyme	89.7	10.3	65.4	11.7	8.71	5.59	5.10[a]	1.56

[a] Computed from the experimental **10a/11a** ratio and the inherent Hax/Heq=1.7 (ref. 1c).

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4. Seghers, L.; Shechter, H. *Tetrahedron Lett.* **1976**, 1943-1946.
5. The ax Me in **8** does not epimerize during tosylhydrazone formation presumably because of 1,3-allylic strain in the product. For a review see Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860.
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7. Kenar, J. A. Ph.D. Thesis, The Johns Hopkins University, **1994**. All details of synthesis, characterization, control reactions, etc. will be reported in a full paper.
8. The number 4.6 is also expressed by the G_{Hax}/G_{Heq} ratios shown in column eight of Table 2 (i.e. average of 4.02 and 5.10). Futhermore since $G_{Hax} = 0.31$ (Table 1), we can arrive at a G_{Heq} value of approximately 0.07 (i.e. 0.31/4.6) for an ax Me bystander on a cyclohexylidene.
9. Researchers disregard secondary isotope effects on the tacit or explicit grounds that these would be negligible. This belief is eminently reasonable for **9b**, where the non-involved C—D remains sp^3-type throughout the rearrangement.
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