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New Perspectives on Carbene Rearrangements: Migratory Aptitudes, Bystander Assistance, and Geminal Efficiency

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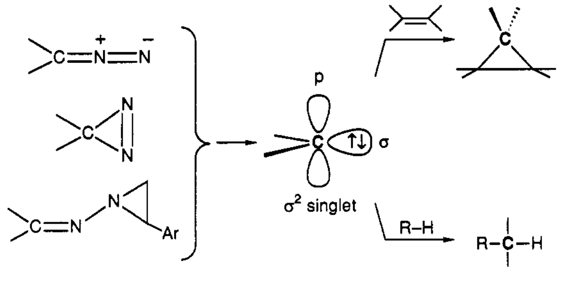
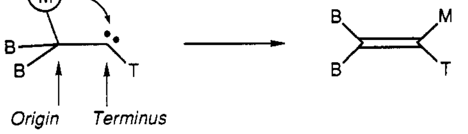
Singlet carbenes are commonly generated by thermolysis or direct photolysis of nitrogen-containing precursors such as diazo compounds, diazirines, and *N*-aziridinylimines.[1] (Because of innate instability, diazo species are often prepared and decomposed in situ.) Although carbenes can exist in three *singlet* electronic configurations (σ^2, σp, p^2), the σ^2 arrangement is favored energetically and in most cases is responsible for the chemistry of singlet carbenes, especially in condensed phases that allow rapid collisional decay of higher energy singlets. Typical reactions of singlet carbenes include stereospecific addition to alkenes to produce cyclopropanes and insertion into C–H bonds with retention of configuration. Since each of these processes can be either intermolecular or intramolecular, the product composition in any given case depends not only on intrinsic reaction rates but also on all factors that influence inter- vs intramolecular competitions.[1]



When singlet carbenes are generated next to saturated carbon, a 1,2-migration can take place to produce an alkene.[2] Because this rearrangement is intramolecular, it has an inherent advantage over intermolecular processes and is, in fact, often the major fate of a singlet carbene. If two or more different migrating groups compete for rearrangement, the ratios of alkene products provide information on relative rates of the competing migrations. Researchers have long recognized that the ease of shift can be influenced by nonmigrating (i.e., bystander) substituents,[2,3] so a quantitative scale of intrinsic migratory aptitudes for groups has not been feasible. Nevertheless, cumulated findings with mobile, open-chain carbenes has led to general acceptance that the qualitative ranking of inherent migratory ability is H > Ph > Me.[2,4] Indeed, alkenes derived from H shifts are often the major products, so the reaction has utility for synthesis.[1,2,5]



M = Migrating group; T = Group at Terminus;
B = Bystander groups (can be same or different)

Factor Analysis: Migratory Aptitude and Bystander Assistance

Additional insight can be gained from existing experimental data if we categorize structural factors that influence carbene rearrangements. For this "factor" analysis we adopt carbene 1 as the parent prototype and define the inherent migratory aptitude of hydrogen (symbolized *M*[H]) as the first-order, specific rate constant (k_H) for shift of a single designated H in this reference carbene.[6] (*Note*: Both bystander groups are

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[1] (a) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic: New York, 1971. (b) Jones, M., Jr., Moss, R. A., Eds. *Carbenes*; Academic: New York, 1973; Vol. 1. (c) Regitz, M.; Maas, G. *Diazo Compounds*; Academic: New York, 1986. (d) Doyle, M. P. *Chemistry of Diazirines*; CRC Press: Boca Raton, FL, 1987. (e) Felix, D.; Muller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 1276–1319.

[2] (a) Jones, W. M. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, pp 95–160. (b) Gaspar, P. P.; Hammond, G. S. In *Carbenes*; Moss, R. A., Jones, M., Jr., Eds.; Academic: New York, 1975; Vol. II, pp 207–362. (c) Reference 1a, pp 18–33. (d) Jones, M., Jr.; Moss, R. A. *Reactive Intermediates*; Wiley: New York, 1980; Vol. 2. (e) Reference 1d, Chapter 8. (f) Schaefer, H. F. *Acc. Chem. Res.* **1979**, *12*, 288–296. (g) Modarelli, D. A.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 8985–8986.

[3] (a) Moss, R. A.; Ho, G.-J. *Tetrahedron Lett.* **1990**, *31*, 1225–1228. (b) Bonneau, R.; Liu, M. T. H.; Rayez, M. T. *J. Am. Chem. Soc.* **1989**, *111*, 5973–5974. (c) Jackson, J. E.; Soundararajan, N.; White, W.; Liu, M. T. H.; Bonneau, R.; Platz, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 6875–6877. (d) Ho, G.-J.; Krogh-Jespersen, K.; Moss, R. A.; Shen, S.; Sheridan, R. S.; Subramanian, R. *J. Am. Chem. Soc.* **1989**, *111*, 6875–6877. (e) LaVilla, J. A.; Goodman, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 6877–6878. (f) Tomioka, H.; Hayashi, N.; Inoue, N.; Izawa, Y. *Tetrahedron Lett.* **1985**, *26*, 1651–1654. (g) Shechter, H. Personal communication. See: Gould, K. A. Ph.D. Thesis, The Ohio State University, 1975; *Diss. Abstr. Int.* **1975**, *36*, 2806-B. (h) Kirmse, W.; Buschoff, M. *Chem. Ber.* **1967**, *100*, 1491–1506.

[4] (a) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1961**, *83*, 3159–3160. (b) Philip, H.; Keating, J. *Tetrahedron Lett.* **1961**, 523–526. (c) Sargeant, P. B.; Shechter, H. *Tetrahedron Lett.* **1964**, 3957–3962. (d) Tomioka, H.; Ueda, H.; Kondo, S.; Izawa, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7818–7820. (e) Pomeranz, M.; Witherup, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 5977–5988.

[5] Pirrung, M. C.; Hwu, J. R. *Tetrahedron Lett.* **1983**, *24*, 565–568.

[6] When two or more H's are chemically equivalent, statistical corrections must be applied to the experimental data so that comparisons are on a "per H" basis.

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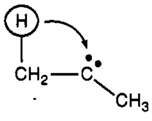
H.) Similarly, the inherent migratory aptitude of any group X (symbolized $M[X]$) is defined as the specific rate constant for shift of X in reference carbene **2** (in which both bystander substituents are again H).

Now consider shift of H_a in the same carbene (see **2B**). The k_{Ha} for this process is determined by the inherent migratory aptitude of hydrogen $M[H]$ and also by any influence exerted by the bystander X. We designate this influence as the *bystander assistance factor* of X and symbolize[7] it $B[X]$. This empirical, rate-multiplicative factor embodies all electronic and steric effects of X as well as any control it might have on rotamer populations, on competing 1,3-insertions, or on any other feature that could govern the outcome of intramolecular competitions.



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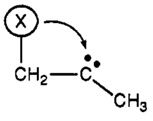
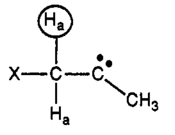
$k_H = M[H]$



2A

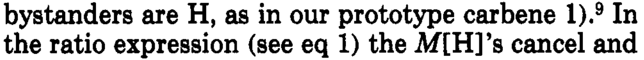
$k_X = M[X]$



2B

$k_{Ha} = M[H] \bullet B[X]$

We can evaluate B factors for different bystander X groups from alkene product ratios reported in the literature for carbenes of this type (redrawn as **3**). Such analysis is most meaningful when it pertains to carbenes generated under similar experimental conditions. Accordingly, we focused on published data for carbenes produced by *thermolysis* (usually at 150 ± 10 °C) of ketone tosylhydrazone salts (Bamford–Stevens reaction) under aprotic conditions.[1] For example, when X = Ph, carbene **3** gives alkene **4** (E and Z) and alkene **5** in the ratio 86/14.[8] After statistical correction ($2H_a$ vs $3H_b$) this experimental ratio amounts to a relative shift rate (per hydrogen) of $k_{Ha}/k_{Hb} = 9.2$. The rate constant for H_a corresponds to $(M[H])(B[Ph])$ (i.e., the inherent rate for H times the bystander assistance factor for Ph); and that for H_b should correspond *essentially* to the inherent rate $M[H]$ (because both bystanders are H, as in our prototype carbene **1**).[9] In the ratio expression (see eq 1) the $M[H]$'s cancel and we get $B[Ph] = 9.2$. Therefore, a bystander Ph accelerates H shift to a notable extent. By similar analysis of product data for other X substituents we obtain the B factors shown in the first numerical column of Table I.



$$\underset{a}{X-CH_2}-\ddot{C}-\underset{b}{CH_3} \longrightarrow X-CH=CHCH_3 + X-CH_2CH=CH_2$$

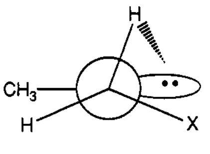
3 4 5

$$\frac{k_{Ha}}{k_{Hb}} = \frac{(M[H])(B[Ph])}{M[H]} = \frac{86/2}{14/3} = 9.2 \qquad (1)$$

Note that all the bystanders listed *promote* H shift (i.e., B values are greater than unity). Alkyls (Me, Et, allyl) exert appreciable activation and as a class are more effective than phenyl; methoxyl is the most powerful activator. Clearly, a bystander group plays a major role in the H rearrangement and, therefore, in the determination of regioselectivity.

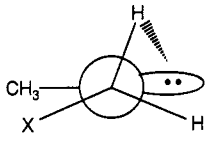
Anti and Syn B Values

Let us carry this approach further by considering the proportions of E and Z isomers produced in the conversion **3** → **4**. The (E)-alkene arises from a transition state in which X is anti-like to the terminus group (see **6**); and (Z)-alkene comes from a syn-like transition state (**7**).[13] By comparing the amounts of (E)-**4** and (Z)-**4** individually to the amount of alkene **5** we can extract individual $B[X]$ factors for the anti (**6**) and syn (**7**) transition states. For example, when X is Ph, alkene **4** (relative amount 86%) comprises 69% E isomer and 17% Z isomer.[8a] Relating the amount of E to the proportion of **5** (14%) and applying statistical correction ($2H_a$ vs $3H_b$) reveals that bystander assistance by anti-Ph (symbolized $B[Ph^A]$) is 7.4. For clarity, the derivation of this anti B number is shown in eq 2. A



ANTI

6



SYN

7

$$\frac{k_{Ha}}{k_{Hb}} = \frac{(M[H])(B[Ph^A])}{M[H]} = \frac{69/2}{14/3} = 7.4 \qquad (2)$$

corresponding expression for the Z component indicates that bystander assistance by syn-Ph (symbolized $B[Ph^S]$) is 1.8. The sum of these individual B's necessarily gives the composite $B[Ph]$ of 9.2 obtained earlier.

Similar analysis of published E/Z ratios for each of the other substrates gives the remaining listings in Table I, from which several insights emerge. For example, with the exception of MeO, all bystander groups benefit the anti transition state more than they benefit the syn. If a syn transition state is generally less favored because it is adversely affected by steric hindrance[11,14] between X and the terminus CH_3,[15] then the distinctly aberrant outcome in the case of MeO implies incursion

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(7) A subscript symbol outside the square bracket may be included to identify the migrating M group (e.g., $B[X]_M$). For economy, in acyclic systems omission of a subscript implies that the migrator is H.

(8) (a) Kaufmann, G. Ph.D. Thesis, The Ohio State University, 1967. Quoted in the following: Seghers, L.; Shechter, H. *Tetrahedron Lett.* **1976**, 1943–1946. (b) Su and Thornton (Su, D. T. T.; Thornton, E. R. *J. Am. Chem. Soc.* **1978**, *100*, 1872–1875) reported a ratio of ca. 90/10 when the carbene was generated from the diazo hydrocarbon at 25 °C. This higher selectivity at their lower temperature is reasonably expected.

(9) The presumption that the rate for migration of a methyl H in **3** (i.e., k_{Hb}) should correspond closely to that for a methyl H in reference carbene **1** seems reasonable for ordinary situations because the carbene center is insulated from X by a saturated carbon. This presumption might be less valid if X (through some unusual steric or electronic effect) significantly alters the geometry and/or stability of carbene **3** relative to the reference carbene **1**.

(10) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1959**, *81*, 5512–5513.

(11) Yamamoto, Y.; Moritani, I. *Tetrahedron* **1970**, *26*, 1235–1242.

(12) Stevens, I. D. R.; Liu, M. T. H.; Soundararajan, N.; Paike, N. *J. Chem. Soc., Perkin Trans. 2* **1990**, 661–667.

(13) Our transition-state drawings show a flattened, product-like disposition for bystander bonds in accord with recent theoretical calculations on carbene **1** (Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 9148–9156). However, our empirical treatment does not require, or rest on, any particular geometry in either the anti or the syn transition states.

(14) Shechter, H. Personal communication. See: Cherney, L. I. Ph.D. Thesis, The Ohio State University, 1971; *Diss. Abstr. Int.* **1971**, *32*, 1441-B. Slack, W. E. Ph.D. Thesis, The Ohio State University, 1974; *Diss. Abstr. Int.* **1974**, *35*, 2106-B.

Table I. Bystander Assistance Factors for Hydrogen Migration in Thermally Generated Carbenes[a]

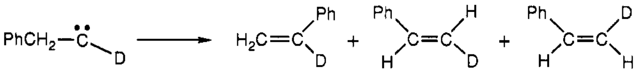
X	B[X]	$B[X^A]$	$B[X^S]$	data[b]
Ph	9.2	7.4	1.8	ref 8a
Me	28.5	20.1	8.4	ref 10
Et	32.3	26.6	5.7	ref 11
allyl	28.1	22.6	5.5	ref 12
MeO	73.5	20.3	53.3	ref 3g

[a] Via aprotic Bamford–Stevens reactions at 150 ± 10 °C except allyl, which involved diazirine thermolysis at 100 °C. Presumably, if a higher temperature were used for the allyl case, it would lower the regioselectivity and hence lower the allyl B values. [b] If one alkene is formed in very high proportion relative to another alkene, their ratio is appreciably sensitive to the reliability of measurement of the minor component. Because analytical accuracy and precision differ among laboratories, B factors should be viewed as approximate rather than quantitative.

by some additional overpowering interaction(s). An example of such an interaction might be destabilization of **6** through repulsion between unshared electrons on oxygen and the carbene free electrons.[3g,h,16] Note also that whereas bystander MeO is overall more powerful than bystander Me (cf. B[X] 73.5 vs 28.5), these substituents (coincidentally?) activate H comparably in the anti transition states (cf. 20.3 vs 20.1); their dissimilarity is manifested largely in the syn array (cf. 53.3 vs 8.4).

Whatever specific interactions are responsible,[17] bystander assistance in these H rearrangements is substantial and raises the possibility that the generally accepted migration order (H > Ph > Me) does not in fact express the inherent migratory abilities of these units but, instead, represents outcomes dictated in large part by *nonmigrating* groups. Indeed, the following reasoning suggests that H shift may not be favored intrinsically over Ph shift.

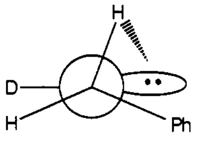
The alkene proportions from competitive Ph and H rearrangements in the deuterium-labeled carbene **8**, after statistical correction, correspond to a Ph/H shift ratio of approximately 1/6.2 at 160 °C.[18a] The expression that relates this ratio to M and B factors is shown in eq 3. [*Note*: A superscript symbol outside a square bracket identifies the *terminus* group whenever it is not our normal reference CH_3.] If we assume[19] for the moment that the anti and syn B factors for Ph in Table I (namely, 7.4 and 1.8) are extendable to carbene **8** (where the terminus group is D), eq 3 leads to $M[\mathrm{Ph}]^D/M[\mathrm{H}]^D = 1.5$ and to the realization that Ph shift is inherently about $1^1/_2$ times *faster* than H shift. We can mitigate the aforementioned assumption somewhat and also improve this numerical estimate by noting that the proportions of (*E*)-alkenes (**10**) and (*Z*)-alkenes (**11**) are the same and, therefore, that transition states **12** and **13** must be equally favored in terms of free energy.[17] Consequently, the syn arrangement of Ph and D in **13** does not diminish assistance by Ph (relative to anti) in contrast to the situation when Ph is syn to CH_3 in our comparison carbene (cf. **7**). Evidently, with a terminus group as small as deuterium, any steric disadvantage (that normally renders *syn*-Ph less beneficial than *anti*-Ph) is absent in **13**. It follows that the bystander factor 7.4 (for *anti*-Ph in **6** and, by extension, for *anti*-Ph in **12**) is very likely also a more accurate value for phenyl assistance in the "sterically comfortable" *syn*-Ph transition state **13**. And this use of 7.4 for *each* B factor in eq 3 leads to $M[\mathrm{Ph}]^D/M[\mathrm{H}]^D = 2.4$, which we believe to be an even better estimate of relative inherent migratory aptitude in **8**, again in favor of Ph over H.



8 **9** **10** **11**

7.5% 46.2% 46.2%

$$\frac{k_{\mathrm{Ph}}}{k_{\mathrm{H}}} = \frac{M[\mathrm{Ph}]^{D}}{(M[\mathrm{H}]^{D})(B[\mathrm{Ph}^{A}]^{D}) + (M[\mathrm{H}]^{D})(B[\mathrm{Ph}^{S}]^{D})} = \frac{7.5}{92.4/2} = \frac{1}{6.2} \quad (3)$$



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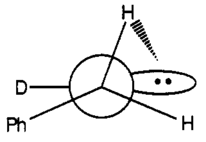

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Geminal Efficiency

Let us return to the concept of bystander assistance in carbene **3** and to our conclusions that a nonmigrating substituent strongly stimulates H shift and that this activating ability follows the order MeO > alkyl > Ph (Table I).[20] Recall also that the amount of bystander assistance differs according to whether X in the

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(15) If the syn transition state is disadvantaged *only* sterically (and not, for example, electronically as well), then a crude measure of the rate loss attributable to this steric (enthalpic and/or entropic) feature might be represented by the ratio $B[X^A]/B[X^S]$. Thus, for X = Ph this steric disadvantage diminishes the rate by a factor of 4.1 (i.e., 7.4/1.8); and for X = Me, Et, and allyl the corresponding retardations are 2.4, 4.7, and 4.1. Interestingly, the values do not differ much.

(16) Ojima, I.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1539–1545.

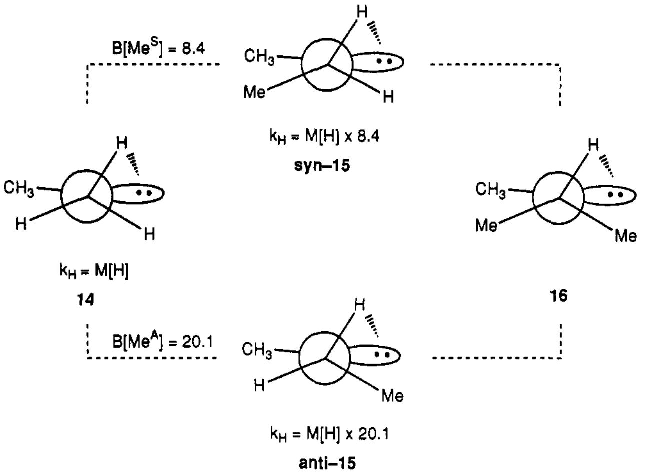
(17) *Entropy* of activation in the anti and syn transition states could also be involved. For entropy considerations in carbene rearrangements, see: Moss, R. A.; Ho, G.-J.; Liu, W. *J. Am. Chem. Soc.* **1992**, *114*, 959–963 and references cited therein.

(18) (a) Shechter, H. Personal communication. Kraska (Kraska, R. A. Ph.D. Thesis, The Ohio State University, 1971; *Diss. Abstr. Int.* **1972**, *32*, 3855-B) conducted the Bamford–Stevens reaction at 250 °C and found **9**/**10**/**11** = 10%/45%/45%. We adjusted these relative proportions to 160 °C by using the Arrhenius equation to estimate ΔE_a along with the presumption that preexponential factors for H and Ph shifts are comparable to each other at both temperatures. Without temperature correction Kraska's data would correspond to an even higher inherent Ph/H aptitude, namely, 3.3. (b) Shechter and Slack (ref 14) studied analogs of **8** with Ph replaced by mesityl and also by triisopropylphenyl and at temperatures that ranged from 120 to 250 °C. In all cases their *E*/*Z* ratios from H shift were likewise essentially 1/1.

(19) The B factors in Table I pertain to *thermally* generated carbenes of type **3**, where the terminus unit is CH_3 (the simplest alkyl group). These same values might not apply to carbenes generated *photically* or to carbenes with terminus groups (e.g., halogen, O, aryl) that can interact strongly with a carbene center. For example, the absolute rates of H (and alkyl) shifts in photochemically generated halo carbenes are known to depend on the nature of the halogen. For various flash photolysis studies, see refs 3a–f and also the following: (a) Modarelli, D. A.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 8985–8986. (b) Sugiyama, M. H.; Celebi, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 966–973. (c) Moss, R. A.; Ho, G.-J.; Liu, W. *J. Am. Chem. Soc.* **1992**, *114*, 959–963. (d) Moss, R. A.; Jang, E. G.; Fan, H.; Wlostowski, M.; Krogh-Jespersen, K. *J. Phys. Org. Chem.* **1992**, *5*, 104–107. For theoretical predictions of activation energies, see: Frenking, G.; Schmidt, J. *Tetrahedron* **1984**, *40*, 2123–2132. Evanseck, J. D.; Houk, K. N. *J. Phys. Chem.* **1990**, *94*, 5518–5523 and references cited therein.

(20) From our definitions of M[H] and M[X], it follows that whenever hydrogen is a *bystander* group (syn or anti), it can be regarded as always having a B value of unity.

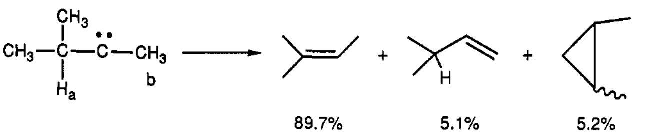
transition state is syn or anti to the terminus group (CH_3). For example, when X is Me, migration of H via transition state *syn*-**15** is 8.4 times faster than is the intrinsic rate *M*[H] in the parent reference carbene **1** (redrawn here as perspective **14**); whereas H shift via transition state *anti*-**15** is 20.1 times faster than in **14**.



Now imagine introduction of a second bystander Me (to give carbene **16**) and consider how the rate of the H shift might be influenced by the combined assistance of the two geminal Me bystanders. Conceptually, we can arrive at structure **16** by replacement of the bystander anti H in the *syn*-**15** transition state. If this newly-introduced anti Me were to exert assistance characteristic of a single anti Me (namely, a factor of 20.1), then H shift in **16** would be 20.1 times faster than in *syn*-**15** and would correspond to a 169-fold (i.e., 20.1 × 8.4) net acceleration relative to the original reference carbene **14**. In our terminology, k_H for **16** would then be expressed as $(M[H])(B[Me^S])(B[Me^A])$.

By similar reasoning, structure **16** can be thought of as arising by Me replacement of the bystander syn H in *anti*-**15**. If this new syn Me were to exert assistance typical of a single syn Me (namely, a factor of 8.4), the H shift rate in **16** should be 8.4 times greater than in *anti*-**15** and should again correspond to a net increase of 169-fold (8.4 × 20.1) relative to **14**, inasmuch as the conceptual order of introduction of the two bystander Me's is immaterial. Are these expectations borne out experimentally?

Carbene **16** (shown simply as **16A**) generated thermally by a Bamford–Stevens reaction has been reported to give **17**, **18**, and **19** in the relative proportions shown.[21]



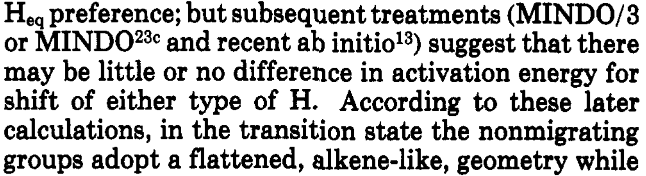
16A **17** **18** **19**

From the ratio **17**/**18** (after statistical correction) the rate of H_a shift (k_{Ha}) relative to H_b shift (k_{Hb}, which should be similar to k_H in reference carbene **14** ($\equiv 1$)) is 52.8. This acceleration is less than the 169-fold rate factor expected had each bystander Me afforded its assistance independent of the other. Therefore, when two bystander Me's act simultaneously, their combined effect is less efficient (by a factor of 52.8/169 = 0.31) than would be expected from their individual *B* values.

Any number of enthalpic and/or entropic features could contribute to a diminished efficiency when these two bystanders operate together. For example, one bystander might largely satisfy any electronic demand so that less is required of the second bystander. Or perhaps, two geminal Me's bring about changes in bond angles, in nonbonded interactions, in rotamer populations (if these are relevant), in competing side reactions, etc. Regardless of the underlying reasons, we accept the net efficiency of a geminal arrangement and define it empirically as the acceleration factor observed experimentally divided by what would have been expected on the basis of individual *B* values of the two bystander groups (i.e., $k_{obsd}/k_{expected}$). We term this ratio the *geminal* efficiency factor and symbolize it *G* or, more explicitly, $G[X^A,X^S]$, which identifies each bystander as well as its anti or syn relationship to the terminus moiety in the transition state.[22] Geminal efficiency is applicable only when *two* bystander substituents are present and reflects how much the experimental result deviates from expectations that hinge on *B* values. With inclusion of this new factor, we can express k_{obsd} for H_a in **16A** as $(M[H])(B[Me^S])(B[Me^A])(G[Me^A,Me^S])$. Evaluation and comparison of *G* factors in different substrates can alert us to unknown features that influence rearrangements, and later in this Account we shall illustrate the usefulness of *G* analysis when dealing with substituted cyclohexylidenes.

The H_{ax}/H_{eq} Migration Ratio

Any consideration of saturated 6-membered-ring carbenes necessarily involves axial and equatorial bonds, so first we must digress to discuss the fundamental question of relative migration rate of H_{ax} vs H_{eq} when a cyclohexylidene (**20**) rearranges to a cyclohexene (**21**). This issue is long-standing and, over the years, has been addressed theoretically by research teams led by Dewar,[23a] by K. Yates,[23b] by Kyba,[23c] and by Houk.[13] The early computations[23a,b] predicted a substantial H_{ax}/H_{eq} preference; but subsequent treatments (MINDO/3 or MINDO[23c] and recent ab initio[13]) suggest that there may be little or no difference in activation energy for shift of either type of H. According to these later calculations, in the transition state the nonmigrating groups adopt a flattened, alkene-like, geometry while other conformational adjustments allow the ring to position H_{ax} or H_{eq} about equally well for interaction with carbenic orbitals.



20 **21**

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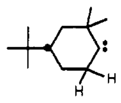
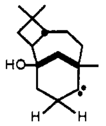
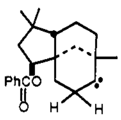
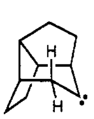
[21] Mansoor, A. M.; Stevens, I. D. R. *Tetrahedron Lett.* **1966**, 1733–1737.

[22] When the two geminal bystanders differ (e.g., X and Y) and when the substrate is acyclic (or a ring of large size), then (*Z*)- and (*E*)-alkenes are possible. If the *Z* and *E* proportions are known, and if all relevant *B* values were available, then individual *G* factors (namely, $G[X^A,Y^S]$ and $G(Y^A,X^S]$ could be evaluated for the *Z* and *E* transition states.

[23] (a) Bodor, N.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1972**, *94*, 9103–9106. (b) Altmann, J. A.; Tee, O. S.; Yates, K. *J. Am. Chem. Soc.* **1976**, *98*, 7132–7138. (c) Kyba, E. P. *J. Am. Chem. Soc.* **1977**, *99*, 8330–8332.

Table II. Hydrogen Migration in Cyclohexylidenes Generated Thermally by Bamford–Stevens Reactions

		Temp (C)	H/D Isotope Effect	Migration Ratio H_{ax}/H_{eq}	Ref.
22		155°	1.9	1.5	24a
23 (caryolane)		135°	1.8	ca. 1.0	24b
24 (clovane)		170°	2.1	ca. 0.7	24c
25 (homobrexane)		120-160°	2.3	1.7	24d

The H_{ax}/H_{eq} selectivity (involving only secondary and not tertiary H's) has also been probed experimentally; and Table II summarizes data from Kyba's group and also from three studies in our laboratory.[24] Kyba's team examined the *tert*-butyl-anchored monocycle **22**;[24a] and we investigated the polycycles **23**, **24**, and **25**, representing, respectively, the caryolane, clovane, and homobrexane ring skeletons.[24b–d] In all the cases listed, the carbenes were generated thermally by Bamford–Stevens reactions on deuterium-labeled precursors, according to a published general method.[25] The experimental results in Table II convincingly establish the absence of any appreciable H_{ax}/H_{eq} selectively in these diversely structured substrates.[26]

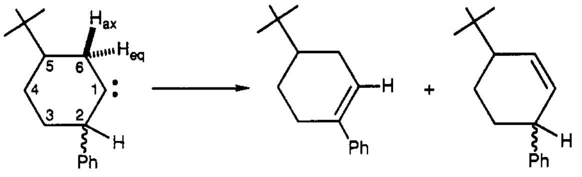
For *M*, *B*, and *G* analyses of cyclohexylidenes we need to adopt a single numerical value for the inherent H_{ax}/H_{eq} migration ratio. Rather than use an average of the four ratios listed in Table II, we select the ratio (i.e., 1.7) provided by the homobrexane skelton **25**, because that substrate is the only one in which the 6-membered carbenic ring is precluded (by the ethano bridges) from distorting to a boat-like shape. Chair–boat interconversions at any stage of the Bamford–Stevens reaction (tosylhydrazone salt, diazo hydrocarbon, or carbene) would change the alignments between C–H bonds and carbenic orbitals and thereby partially vitiate axial–equatorial integrity. Accordingly, we can relate the inherent migratory aptitude of an axial H (i.e., $M[H_{ax}]$) to that of an equatorial H (i.e., $M[H_{eq}]$) through either of the equivalent expressions shown in eqs 4a,b.[27] Let us now see how these expressions can be used in conjunction with the *B* and *G* concepts to analyze published data on rearrangements of cyclohexylidenes.

$$M[H_{ax}] = 1.7M[H_{eq}] \tag{4a}$$

$$M[H_{eq}] = 0.58M[H_{ax}] \tag{4b}$$

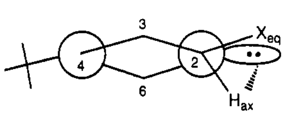
Geminal Efficiency in Cyclohexylidenes

Seghers and Shechter have investigated the Ph_{ax} and Ph_{eq} epimers of the *tert*-butyl-anchored cyclohexylidenes **26**, generated by thermal (160 °C) Bamford–Stevens reactions.[28] The major products are alkenes **27** and **28** from competitive H shifts, and their proportions are shown. To relate these alkene ratios to *M*, *B*, and *G* factors we note that H shift from C-2 (to give **27**) is assisted by two different bystanders, namely, Ph and ring alkyl unit C-3 (call it R_3); consequently geminal efficiency (*G*) and individual *B* factors are relevant here. On the other hand, shift of either H from C-6 (to give **28**) is assisted solely by ring alkyl unit C-5 (call it R_5), so only its *B* factor enters here.

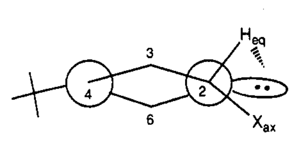


		26	27	28
a	eq Ph		77.1%	21.6%
b	ax Ph		52.3%	41.3%

A distinctive feature of these cyclic substrates is this: The tethered alkyl units R_3 and R_5 are constrained syn to each other. Consequently when the H at C-2 migrates, the bystander Ph must necessarily become anti to C-6 *whether the shifting H was initially axial or equatorial.* (See transition states **29** and **30**, respectively, with X = Ph.[29]) Accordingly, the relevant bystander assistance factors in such situations are the syn *B* values for R_3 and R_5 and the anti *B* value for Ph.



29



30

The rate ratio (and hence the observed product ratio **27**/**28**) from regiocompetitive H shifts can be expressed in terms of *M*, *B*, and *G* factors. For example, for epimer **26a** (Ph_{eq}, $t\text{-}Bu_{eq}$) the relationship is given in eq 5. (Note that alkene **27a** comes from shift of H_{2ax}; however, **28a** arises from shift of H_{ax} or H_{eq} from C-6, so their individual contributions are additive.) In the denom-

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(24) (a) Kyba, E. P.; John, A. M. *J. Am. Chem. Soc.* **1977**, *99*, 8329–8330. (b) Caryolane system: Experiments conducted by Dr. Haruhito Yagi. (c) Clovane system: Experiments conducted by Dr. John Morgan and Dr. Kohtaro Matsuo. (d) Homobrexane system: Experiments conducted by Dr. Alfred Stern. For synthetic methodology, see: Nickon, A.; Stern, A. G. *Tetrahedron Lett.* **1985**, *26*, 5915–5918. Stern, A. G.; Nickon, A. *J. Org. Chem.* **1992**, *57*, 5342–5352.

(25) Nickon, A.; Huang, F.-c.; Weglein, R.; Matsuo, K.; Yagi, H. *J. Am. Chem. Soc.* **1974**, *96*, 5264–5265.

(26) A cautionary note is appropriate here. To estimate (and thereby to correct for) the primary H/D isotope effect in these studies of d-labeled substrates it was necessary to assume that k_H/k_D isotope effects are the same for H_{ax} and H_{eq} migration. This assumption appears reasonable on the basis of zero-point energy consideration but, to our knowledge, has not been validated independently. The k_H/k_D issue merits attention particularly if quantum mechanical tunneling for H_{ax} and H_{eq} plays any role. See: Nickon, A.; Ilao, M. C.; Stern, A. G.; Summers, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 9230–9232.

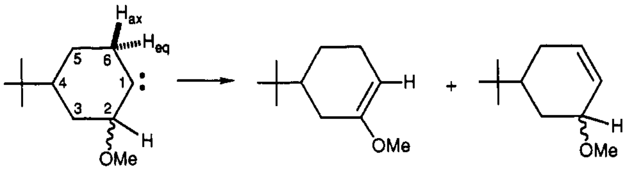
(27) Note that $M[H_{ax}]$ and $M[H_{eq}]$ are not the same as *M*[H] (defined earlier for acyclic carbene **1**), because H shift in a cyclohexylidene (**20**) always includes any effect of having a bystander ring unit and a terminus group connected to each other.

(28) (a) Seghers, L.; Shechter, H. *Tetrahedron Lett.* **1976**, 1943–1946. (b) Phenyl shift is a minor pathway (1.3% for **26a**; 6.5% for **26b**).

(29) These crude representations are for visual aid and do not imply any precise geometries. For H_{ax} or H_{eq} shift in cyclohexylidene itself, a flattened, product-like geometry for bystander bonds has been suggested by Evansek and Houk (ref 13).

$$\frac{k_{\mathrm{H2ax}}}{k_{\mathrm{H6}}} = \frac{\mathbf{27a}}{\mathbf{28a}} = \frac{(M[\mathrm{H_{ax}}])(B[\mathrm{R_3}^{\mathrm{S}}])(B[\mathrm{Ph}^{\mathrm{A}}])(G[\mathrm{Ph}^{\mathrm{A}},\mathrm{R_3}^{\mathrm{S}}]_{\mathrm{Hax}})}{(M[\mathrm{H_{ax}}])(B[\mathrm{R_5}^{\mathrm{S}}]) + (M[\mathrm{H_{eq}}])(B[\mathrm{R_5}^{\mathrm{S}}])} \quad (5)$$

inator we can express $M[\mathrm{H_{eq}}]$ in terms of $M[\mathrm{H_{ax}}]$ from their relationship in eq 4b and thereby allow cancellation of all M's. Furthermore, as R_3 and R_5 are ring alkyl units (generic, R), their B factors should be about equal and therefore also cancelable in the equation.[30] Then by insertion of the known $B[\mathrm{Ph^A}]$ value (Table I) and the experimental **27a**/**28a** ratio, eq 5 leads to $G[\mathrm{Ph^A},\mathrm{R^S}]_{\mathrm{Hax}} = 0.76$. Thus, $\mathrm{Ph_{eq}}$ acting together with its ring R provides 76% of the activation that would have been expected from B factors alone. A similar analysis applied to the data for the $\mathrm{Ph_{ax}}$, t-$\mathrm{Bu_{eq}}$ epimer (**26b**) gives $G[\mathrm{Ph^A},\mathrm{R^S}]_{\mathrm{Heq}} = 0.47$. Therefore, *on a cyclohexane ring*, axial Ph activates a geminal H less efficiently than does equatorial Ph. The disposition of atoms in transition state **29** (X = Ph) must possess some advantage over that in **30**. That this advantage is not unique to the Ph case and can be appreciable is strikingly demonstrated by similar analysis of data for the anchored (equatorial t-Bu) epimeric pair **31**, where the bystander substituent is OMe and the derived alkenes are **32** and **33**.[31]



31		32	33
a	eq OMe	95.1%	4.7%
b	ax OMe	58.4%	29.4%

In **31a** the geminal efficiency when equatorial OMe promotes $\mathrm{H_{ax}}$ shift (namely, $G[\mathrm{OMe^A},\mathrm{R^S}]_{\mathrm{Hax}}$) comes to 1.58; and in **31b** for axial OMe promoting $\mathrm{H_{eq}}$ shift the corresponding efficiency (namely, $G[\mathrm{OMe^A},\mathrm{R^S}]_{\mathrm{Heq}}$) is 0.068. For clarity, the expression that provided this last number is shown explicitly in eq 6, to be used in conjunction with eq 4a. Thus, when attached to a

$$\frac{k_{\mathrm{H2eq}}}{k_{\mathrm{H6}}} = \frac{\mathbf{32b}}{\mathbf{33b}} = \frac{(M[\mathrm{H_{eq}}])(B[\mathrm{R_3}^{\mathrm{S}}])(B[\mathrm{OMe}^{\mathrm{A}}])(G[\mathrm{OMe}^{\mathrm{A}},\mathrm{R_3}^{\mathrm{S}}]_{\mathrm{Heq}})}{(M[\mathrm{H_{ax}}])(B[\mathrm{R_5}^{\mathrm{S}}]) + (M[\mathrm{H_{eq}}])(B[\mathrm{R_5}^{\mathrm{S}}])} \quad (6)$$

cyclohexane ring, an equatorial OMe is moderately *more* activating than expected from B values, whereas an axial OMe is almost devoid of activating power![32] Again, transition state **29** (X = OMe) is favored over **30**; and in this case the preference is substantial.

In summary, evaluation of G factors for substituted cyclohexylidenes reveals that an equatorial Ph or OMe promotes H shift more effectively than does its axial epimer, and this phenomenon is especially pronounced for OMe.[33] The reasons for this unexpected stereochemical effect are not apparent and might be associated in part with rotameric geometry about the C–X bond, which could influence lone pair or π cloud orientations. Clearly, G analyses can unveil special features that modulate bystander assistance in ring compounds (and perhaps also in acyclic systems), so it would be desirable to determine G's for other substituents.[34] For example, an axial/equatorial CH_3 group, because of its 3-fold rotational symmetry and lack of lone pair or π electrons, would be a useful benchmark for comparison with the Ph and OMe cases.

Caveats

The "MBG" viewpoints have been developed for dialkyl carbenes generated by thermolysis.[19] In appropriate cases some of these considerations might be extendable to species produced by direct photolysis, although such carbenes can be more problematic mechanistically because they might involve higher energy states.[35] Also, several photolysis studies have revealed that some diazirines[36] (and perhaps also a diazoalkane[37]) can give products of "carbene" reactions (including rearrangements) directly from excited precursors or from species in which the departing nitrogens play some role. Whether diazo precursors can sometimes rearrange directly to alkenes on *thermal* treatment is not yet clear, but this possibility should be kept in mind.[38]

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(30) That the t-Bu anchoring group at C-5 exerts no influence in **26a** is supported by the fact that virtually the same alkene proportions (77% and 22%) are produced when the t-Bu is absent.[28a] Of course, B factors would not be cancelable if R_3 and R_5 differed substantially (for example, if either one were a ring heteroatom).

(31) Press, L. S.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 509–510. For **31b** the data are averages of closely-agreeing numbers from thermal Bamford–Stevens reactions conducted in diglyme and neat; also ca. 12.2% ring contraction (R_3 shift) was observed.

(32) Generalizing from equations like 5 and 6 we can see that when G comes out smaller than a certain "threshold" value (namely, $1/B[\mathrm{X^A}]$), the net effect of substituent X was to *deactivate*, rather than to activate, the migrating H. For example, since $B[\mathrm{Ph^A}] = 7.4$ and $B[\mathrm{OMe^A}] = 20.3$, the "threshold" G for Ph is 0.14, and for OMe it is 0.049. Our derived G value (0.068) for axial OMe is close to its threshold value, and this aspect likewise underscores the virtual absence of activating ability.

(33) This outcome is especially intriguing in view of the fact that when X = H (i.e., normal $\mathrm{H_{ax}}$ vs $\mathrm{H_{eq}}$ competition), transition states akin to **29** and **30** are about equal in energy. (Recall experimental data in Table II and theoretical calculations in refs 13 and 23c.)

(34) Press and Shechter also studied the analogs of **26** (as epimeric mixtures) with p-anisyl in place of Ph. (Personal communication from H. Shechter. See: Press, L. S. Ph.D. Thesis, The Ohio State University, 1977; *Diss. Abstr. Int.* **1977**, *38*, 696-B.) The observed alkene ratios (obtained by extrapolation) are similar to those from **26**; so even though we cannot evaluate G factors strictly until an anti B value for p-MeOPh becomes available, the outcomes will likely be comparable to those for Ph.

(35) Chang, K.-T.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 5082–5084.

(36) Modarelli, D. A.; Morgan, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7034–7041 and references cited therein.

(37) Seburg, R. A.; McMahon, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 7183–7189.

(38) (a) In connection with studies of 1,2-shifts on thermolysis of diazo compounds, Shechter's group reported kinetic evidence that N_2 loss precedes rearrangement. See: Robson, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1967**, *89*, 7112–7114. Recent studies of systems with a "terminus" phenyl group suggest that 1,2-shifts induced thermally might involve noncarbenic as well as carbenic pathways. See: Fox, J. M.; Scacheri, J. E. G.; Jones, K. G. L.; Jones, M., Jr.; Shevlin, P. B.; Armstrong, B.; Sztyrbicka, R. *Tetrahedron Lett.* **1992**, *33*, 5021–5024. (b) For relevant commentary on the issue of concertedness and nonconcertedness in intramolecular rearrangements, see: Carpenter, B. K. *Acc. Chem. Res.* **1992**, *25*, 520–528.