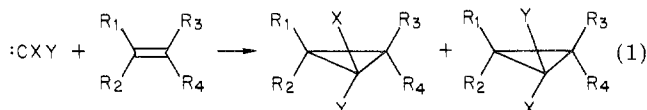# Carbenic Selectivity in Cyclopropanation Reactions

ROBERT A. MOSS

Wright and Rieman Laboratories, Department of Chemistry, Rutgers University, The State University of New Jersey, New Brunswick, New Jersey 08903

A quarter century has passed since Doering and Hoffmann reported that dichloro- and dibromocarbenes could be added to simple alkenes with the formation of cyclopropanes.[1] Fascination with this simplest of cycloaddition reactions (eq 1) was evident at once, and

$$:CXY + \underset{R_2}{\overset{R_1}{>}}=\underset{R_4}{\overset{R_3}{<}} \longrightarrow \underset{R_2}{\overset{R_1}{>}}\underset{Y}{\overset{X}{\triangle}}\underset{R_4}{\overset{R_3}{<}} + \underset{R_2}{\overset{R_1}{>}}\underset{X}{\overset{Y}{\triangle}}\underset{R_4}{\overset{R_3}{<}} \quad (1)$$
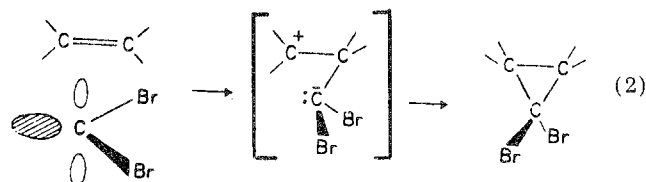
continued strongly.[2] Efforts were made early to experimentally and theoretically characterize carbenic addition reactions.

Experimental characterization of a reactive intermediate typically relies on kinetic and stereochemical studies. Both of these approaches were productive. Although carbene additions were too rapid for simple absolute kinetic studies, Skell[3] and Doering[4] carried out relative reactivity measurements: two alkenes (i and j) were allowed to compete for an insufficiency of carbene; from the product mole ratio of the corresponding cyclopropanes, corrected for the initial mole ratio of alkenes, one obtained the relative reactivity ($\approx$relative rate constant ratio, k_i/k_j) of the carbene toward the particular alkene pair. CBr_2[3] and CCl_2[4] were thus found to be *electrophilic* toward simple alkenes, reacting most rapidly with the most highly alkylated olefins. In this, they resembled the reactive intermediates of alkene bromination ("Br^+") and epoxidation ("OH^+") reactions.[3,4] Moreover, the additions of CBr_2 and CH_2 to cis- or trans-butene were shown to be cisstereospecific;[5] i.e., in eq 1, the cis relationships of R_1 to R_3 and R_2 to R_4 in the substrate alkene were preserved in the product cyclopropanes.

The key observations of electrophilic and stereospecific carbenic additions led to tentative theoretical formulation[3-5] of eq 1 "in terms of the simultaneous formation of both bonds of the ultimate cyclopropane ring and therefore in terms of a paired, singlet structure for dichloro- and dibromocarbene".[4] Dibromocarbene, for instance, was represented as planar, sp^2 hybridized, and possessing a vacant carbenic p orbital.[5b] The electrophilicity of its addition to alkenes was represented by imposition of a positive charge on the alkenic carbons in the addition reaction "intermediate complex" or transition state (cf. eq 2).[3]

Subsequent investigation refined this view of singlet carbenic cyclopropanation,[6,7] adding theoretical underpinning. The collection of a substantial, coherent body of experimental selectivity data for further

$$\underset{O}{\overset{O}{\underset{C}{\overset{Br}{\underset{Br}{>}}}}} \overset{\diagup}{\underset{\diagdown}{C}}=C\overset{\diagup}{\underset{\diagdown}{}} \longrightarrow \left[\overset{\diagup}{\underset{\diagdown}{C}}\overset{+}{\underset{:C}{\underset{Br}{\overset{Br}{-}}}}C\overset{\diagup}{\underset{\diagdown}{}} \right] \longrightarrow \underset{\diagdown}{\overset{\diagup}{C}}\underset{Br}{\overset{Br}{\underset{C}{\triangle}}}C\overset{\diagup}{\underset{\diagdown}{}} \quad (2)$$

analysis then became necessary. Doering indicated how this might be done:[4] one could define the "relative response", or selectivity, of carbene CXY to changes in alkene structures by plotting the logarithms of the relative reactivities for CXY against comparable data for CCl_2 (with relative reactivities all adjusted to a standard alkene, $k_0 = 1.00$), and then determining the slope of the correlation line. The magnitude of the slope would define CXY's ability to discriminate between alkenes and its "internal stabilization"[4] relative to CCl_2.

Intrinsically, this is a powerful experimental approach to the characterization of carbenic selectivity. If enough alkenes were included in the substrate set and "relative responses" were determined for many carbenes, much could be said about the response of eq 1 to the variation of olefinic substituents, R_i, and carbenic substituents, X and Y. Indeed, this use of linear free energy correlations became popular; by 1969 the olefinic selectivities of CF_2, CFCl, CBr_2, Me_2C=C=C, "CHCl", and CH_2 had been compared with that of CCl_2.[8] However, the relative reactivities of the carbenes had not been measured under comparable conditions of substrate set, temperature, and generative method; comparisons of carbenic selectivities were necessarily qualitative.

We set out to develop a *general, empirical, correlation* of carbenic selectivity toward alkenes.[9] While this enterprise was in course, the development of frontier molecular orbital (FMO) theory, particularly its application to carbene chemistry,[10] provided the tools for a parallel analysis of the experimental work. In this

(1) W. v. E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 76, 6162 (1954).

(2) (a) R. A. Moss and M. Jones, Jr., in "Reactive Intermediates", Vol. 1, M. Jones, Jr., and R. A. Moss, Ed., Wiley-Interscience, New York, 1978, pp 69 ff; (b) R. A. Moss and M. Jones, Jr., Ed., "Carbenes", Vol. II, Wiley-Interscience, New York, 1975; (c) M. Jones, Jr., and R. A. Moss, Ed., "Carbenes", Vol. I, Wiley-Interscience, New York, 1973; (d) W. Kirmse, "Carbene Chemistry", 2nd ed., Academic Press, New York, 1971; (e) J. Hine, "Divalent Carbon", Ronald Press, New York, 1964.

(3) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, 78, 5430 (1956).

(4) W. v. E. Doering and W. A. Henderson, Jr., *J. Am. Chem. Soc.*, 80, 5274 (1958).

(5) (a) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, 78, 3409 (1956); (b) P. S. Skell and R. C. Woodworth, *ibid.*, 78, 4496 (1956); (c) W. v. E. Doering and P. LaFlamme, *ibid.*, 78, 5447 (1956).

(6) W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, 28, 2200 (1963).

(7) R. Hoffmann, *J. Am. Chem. Soc.*, 90, 1475 (1968); R. Hoffmann, D. M. Hayes, and P. S. Skell, *J. Phys. Chem.*, 76, 664 (1972).

(8) Cf. P. S. Skell and M. S. Cholod, *J. Am. Chem. Soc.*, 91, 7131 (1969).

(9) R. A. Moss and A. Mamantov, *J. Am. Chem. Soc.*, 92, 6951 (1970).

(10) Review: W. M. Jones and U. H. Brinker in "Pericyclic Reactions", Vol. 1, A. P. Marchand and R. E. Lehr, Eds., Academic Press, New York, 1977, p 109 ff.

Robert A. Moss joined the chemistry faculty at Rutgers University in 1964 after doctoral study with Professor G. L. Closs at the University of Chicago and a postdoctoral year with Professor Ronald Breslow at Columbia University. He has been Visiting Scientist at M.I.T. and at the University of Oxford and a Fellow of the A. P. Sloan Foundation. He is also affiliated with the Baker Street Irregulars. In addition to the chemistry of carbenes, Dr. Moss is actively interested in micellar organic chemistry.
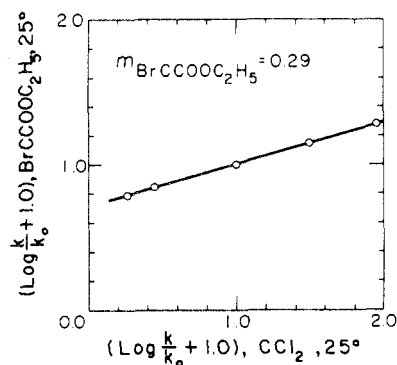
Carbenic Selectivity

Figure 1. Log $(k_i/k_0)_{BrCCOOC_2H_5}$ vs. log $(k_i/k_0)_{CCl_2}$ at 25 °C. The slope of the regression line is 0.29, and the correlation coefficient is 0.9999.

Table I
Observed and Calculated Carbene Selectivity Indexes

carbene	m_{CXY} (obsd)	m_{CXY} (calcd)^a	$\lvert \Delta m \rvert^b$
CF_2	1.48	1.47	0.01
CFCl	1.28	1.22	0.06
CCl_2	1.00^c	0.97	0.03
CH_3SCCl	0.91	d	d
PhCF	0.89	0.96	0.07
PhCCl	0.83	0.71	0.12
PhCBr	0.70	0.64	0.06
CBr_2	0.65	0.82	0.17
CH_3CCl	0.50	0.58	0.08
$BrCCOOC_2H_5$	0.29	0.26	0.03

^{a} Calculated from eq 3. ^{b} $\lvert m_{CXY}(\text{obsd}) - m_{CXY}(\text{calcd})\rvert$. ^{c} By definition. ^{d} See below, ref 21.

Account, we shall trace the development of the empirical correlation, then examine the FMO formulation of carbenic selectivity, and finally inspect the relatively satisfying picture which emerges from a *synthesis* of the two lines of inquiry.

The Empirical Correlation

Consider the general case of a carbenic addition, eq 1. We wish to derive a quantitative measure of the dependence on carbenic substituents X and Y and alkenic substituents R_i. To simplify matters, we shall consider only singlet carbenes (i.e., those which add stereospecifically to *cis*- and *trans*-butene) and ignore the question of stereoselectivity (i.e., the factors which determine the product isomer ratio in eq 1).[11] We must also be concerned with the method of carbene generation, making certain that only free carbenes are included in our set; see below.

The following conventions[9] are adopted: a standard set of alkene substrates ($Me_2C=CMe_2$, $Me_2C=CHMe$, $Me_2C=CH_2$, c-$MeCH=CHMe$, and t-$MeCH=CHMe$), with $Me_2C=CH_2$ as the reference alkene ($k_0 = 1.00$); and a standard carbene, CCl_2. Relative reactivities are measured for CXY and for CCl_2 at 25 °C, and the "carbene selectivity index", m_{CXY}, is *defined* as the least-squares slope of log $(k_i/k_0)_{CXY}$ vs. log $(k_i/k_0)_{CCl_2}$.

Numerous studies of carbenic relative reactivities have been reported,[12] but few adhere to our conventions. An example of the determination of $m_{BrCCOOC_2H_5}$ appears in Figure 1.[13] Taken by itself, the observation that $m_{BrCCOOC_2H_5(\text{obsd})} = 0.29$ means that bromocarboethoxycarbene is about one-third as selective as CCl_2 among the alkenes of the standard set. To progress beyond this rudimentary insight, we require m_{CXY} for other carbenes. The gradual accumulation of data[9,13,14] finally affords Table I.

Of the carbenes in Table I, CF_2,[15] PhCCl, PhCBr, CH_3CCl, and $BrCCOOC_2H_5$ were generated from diazoalkane or diazirine precursors; the remaining species

diazoalkane   diazirine

were generated by KO-t-Bu-mediated α eliminations of HCl or HBr. How do we know that "free" carbenes were the discriminating intermediates in all cases? We demonstrated that PhCBr and PhCCl could be generated as free carbenes from KO-t-Bu and the appropriate benzal halide if the macrocyclic polyether, 18-crown-6, was added to preclude carbenoid formation.[16] The crown ether–base-generated species had selectivities identical with those of the corresponding diazirine-photogenerated carbenes. Equivalence between thermally (KX leaving group) and photolytically (N_2 leaving group) generated species implicated a common intermediate, the free, nonexcited, singlet carbene.

Moreover, we could determine whether other base-induced α eliminations gave carbenes or carbenoids by measuring their selectivities in the presence or absence of crown ether; the use of a complex of KOR and the crown ether could make free carbenes available from halide precursors when diazoalkane or diazirine precursors were unavailable. These considerations were exemplified in determinations of m_{CXY} for PhCF,[17] CH_3SCCl,[17] and CBr_2.[18]

CBr_2 was particularly interesting: no steric discontinuity[19] was observed in the log–log plot of its relative reactivities vs. those of CCl_2, and a good correlation ($m_{CBr_2}(\text{obsd}) = 0.65$) was obtained.[18] The absence of a discontinuous steric effect does not preclude the operation of a significant, continuous differential steric effect in CBr_2 vs. CCl_2 additions to alkenes. In fact, when relative reactivities for CX_2 additions to $RCH=CH_2$ ($R = Et$, i-Pr, t-Bu) are correlated by the log $(k/k_0) = \delta E_S$ (Taft)[20] relation, it appears that CBr_2 encounters about 11% more steric hindrance in addition to 1-alkenes than does CCl_2 (i.e., $\delta_{CBr_2}/\delta_{CCl_2} = 0.98/0.88 = 1.11$).[18] Further consideration of this appears below.

Multiple linear regression analysis[21] of the dependence of $m_{CXY}(\text{obsd})$ on σ_R^+ and σ_I afforded the dual substituent parameter correlation, eq 3, in which $\sum_{X,Y}$

(11) Review: R. A. Moss in "Selective Organic Transformations", Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1970, p 35 ff.

(12) Review: R. A. Moss in ref 2c, p 153 ff.

(13) R. A. Moss, C. B. Mallon, and C-T. Ho, *J. Am. Chem. Soc.*, **99**, 4105 (1977).

(14) R. A. Moss and C. B. Mallon, *J. Am. Chem. Soc.*, **97**, 344 (1975).

(15) R. A. Mitsch and A. S. Rodgers, *Int. J. Chem. Kinet.*, **1**, 439 (1969).

(16) R. A. Moss and F. G. Pilkiewicz, *J. Am. Chem. Soc.*, **96**, 5632 (1974).

(17) R. A. Moss, M. A. Joyce, and F. G. Pilkiewicz, *Tetrahedron Lett.*, 2425 (1975).

(18) R. A. Moss, M. A. Joyce, and J. K. Huselton, *Tetrahedron Lett.*, 4621 (1975).

(19) Such a discontinuity had previously been reported; cf. ref 4.

(20) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, 1956, p 556 ff.

(21) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973). $m_{CH_3SCCl}(\text{calcd})$ is not obtainable from eq 3 because $(\sigma_R^+)_{SCH_3}$ is not well behaved.

$$m_{CXY} = -1.10 \sum_{X,Y} \sigma_R^+ + 0.53 \sum_{X,Y} \sigma_I - 0.31 \quad (3)$$

represents the sum of the appropriate σ constants[21] for the substituents of CXY.[13] The internal consistency of this correlation is apparent from Table I, in which are shown calculated values of m_{CXY}, and differences between m_{CXY}(obsd) and m_{CXY}(calcd). Figure 2 graphically presents the correlation between m_{CXY}(obsd) and m_{CXY}(calcd).[22]

Equation 3 is central to empirical analysis of carbene selectivity. It (a) correlates the selectivities of known carbenes, (b) is related to prevalent qualitative concepts of the carbene–alkene cycloaddition, (c) bears direct relation to quantitative indicators of carbenic stability derived from ab initio calculations, (d) may be used to estimate selectivities of unknown carbenes, and (e) leads to the discovery of *ambiphilic* carbenes. Let us consider these features in turn.

(a) Figure 2 indicates that eq 3 correlates the m's of the "extreme" carbenes, CF_2 and $BrCCOOC_2H_5$, very well. The selectivity index, m_{CBr_2}(obsd), deviates most seriously from the regression line ($\Delta m = 0.17$), but this is certainly a steric effect which can be at least partly compensated by multiplying m_{CBr_2}(obsd) by $\delta_{CBr_2}/\delta_{CCl_2}$.[18] Interestingly, inclusion of a steric term in eq 3, e.g., $c_S \sum_{X,Y} v$,[23] does not lead to significantly improved correlations of m_{CXY}(obsd) and m_{CXY}(calcd), suggesting that the equation mainly reflects differential electronic effects among its basis carbenes and need not include an explicit steric term.

(b) In qualitative terms, eq 3 indicates that increasing π-electron donation and increasing inductive withdrawal by X and Y *both* augment the selectivity of CXY; the coefficients of σ_R^+ and σ_I are negative and positive, respectively. The classical transition state, 1,[4,5a,6,7,14] is in accord with eq 3: electrophilic selectivity

1
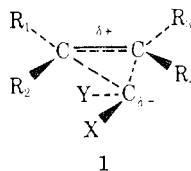
is greatest when strong resonance interactions of X and Y with the carbenic center necessitate correspondingly strong π-electron donation by the olefin; electron-releasing alkyl substituents moderate the resulting accumulation of positive charge on the olefinic centers, while inductively withdrawing carbenic substituents mitigate the accumulation of negative charge on the carbenic center.

(c) Professor K. N. Houk and Nelson G. Rondan at Louisiana State University have carried out extensive ab initio molecular orbital calculations on singlet carbenes and carbene cycloadditions in collaboration with the author. The geometries of a series of CXY were partially optimized[24a] by calculations at the STO-
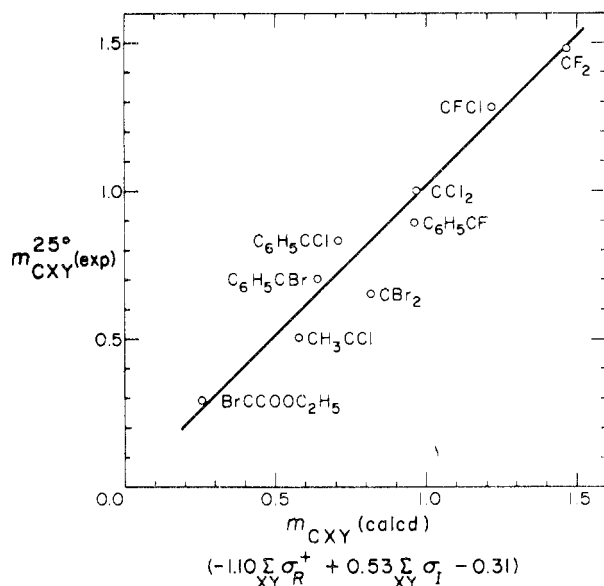

Figure 2. Slopes (m_{CXY}) of log (k_i/k_0) for CXY vs. log (k_i/k_0) for CCl_2 vs. σ_R^+ and σ_I; see eq 3.

Table II
Orbital Energies, Stabilization Energies, and Selectivities of Disubstituted Singlet Carbenes (from ref 25)

entry	carbene	LUMO (p), eV	HOMO (σ), eV	ΔE_{stab}, kcal/mol[a]	m_{CXY} (calcd)[b]
1	$ClCCH_3$	1.61	−10.28	29.3	0.58
2	FCPh	1.51	−10.23	45.7	0.96
3	$ClCSCH_3$	1.65	−10.23	38.7	0.91[c]
4	CCl_2	0.31	−11.44	26.5	0.97
5	FCCl	1.03	−11.98	42.8	1.22
6	CF_2	1.89	−13.38	62.8	1.47
7	$ClCOCH_3$	2.46	−10.82	60.3	1.59
8	$FCOCH_3$	3.19	−11.81	74.2	1.85
9	FCOH	3.05	−12.05	74.4	2.09[d]
10	$C(OCH_3)_2$	4.09	−10.81	79.8	2.22
11	$C(OH)_2$	3.99	−11.00	83.0	2.71[d]
12	$CH_3OCN(CH_3)_2$	5.41	−9.53	93.4	2.91

[a] Defined as the negative of the energy of eq 4. [b] Calculated from eq 3, using substituent constants from ref 21. [c] Experimental value; cf. ref 13 and 21. [d] $\sigma_R^+(OH) = -1.24$; $\sigma_I(OH) = 0.28$: O. Exner in "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Eds., Plenum, New York, 1972.
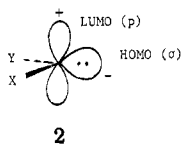
3G level;[24b] further calculations were then performed on these geometries with the split-valence 4-31G basis set.[24b,25] In Table II, we tabulate the 4-31G orbital energies of the carbenes' lowest unoccupied molecular orbitals (LUMO or p) and highest occupied molecular orbitals (HOMO or σ); cf. 2. Also included in Table II are values of m_{CXY}(calcd) from eq 3 and *carbene*

(22) The standard deviation of the Δm's (Table I) is 0.084. In Figure 2, the slope of the least-squares regression line is 1.00, $r = 0.971$, significant at the 99.9% confidence level. Additional statistical discussion appears in ref 13.

(23) M. Charton, *J. Am. Chem. Soc.*, **97**, 1552 (1975).

(24) (a) Values of r_{CX}, r_{CY}, and $\angle XCY$ were optimized; standard substituent geometries were used for polyatomic substituents save for $\angle COC$ and $\angle COH$, which were optimized. (b) For descriptions of STO-3G and 4-31G calculational methods, cf. W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4796 (1970). The first method employs a minimal basis set of orbitals which simulates a minimal basis set of Slater-type orbitals; a single function for hydrogen (1s) and five functions for each heavy atom (1s, 2s, 2p) are used. The 4-31G method employs an extended basis set, containing more than the minimal number of functions; H 1s and heavy atom 2s and 2p functions are described by inner and outer parts which are sums of three and one Gaussian functions, respectively. (c) Isodesmic reactions are "examples of chemical changes in which there is retention of the number of bonds of a given formal type, but with a change in their relation to each other".[24b]

(25) N. G. Rondan, K. N. Houk, and R. A. Moss, *J. Am. Chem. Soc.*, in press.

2

stabilization energies, ΔE_{stab}. The latter are the negatives of the 4-31G energies of the isodesmic reaction (eq 4)[24c] and reflect the stabilization of CXY relative

$$CH_2 + CH_3X + CH_3Y \rightarrow CXY + 2CH_4 - \Delta E_{stab} \quad (4)$$

to the corresponding substituted methanes.[25]

The m_{CXY}(calcd) values correlated linearly (99.9% confidence level) with ϵ_{LUMO}; electron-donating substituents on the carbene raised the LUMO energy and increased the carbene's selectivity, whereas electron-withdrawing groups lowered ϵ_{LUMO} and decreased selectivity. Further considerations,[25] however, suggested that *both* selectivity (m_{CXY}) and ϵ_{LUMO} were related to a common property, the exothermicity of the carbene–alkene addition. Figure 3 reveals the excellent correlation (significant at the 99.9% confidence level) between m_{CXY}(calcd) and ΔE_{stab} (which is inversely related to the exothermicity of carbene/alkene addition). The most stable carbenes, those which react least exothermically, exhibit the greatest selectivity. Presumably, this is due to the relative "lateness" of their addition transition states.[26] Indeed, 4-31G calculations carried out on ground states, transition states, and products of the additions of CXY to ethene gave the following values of E_a and ΔE_{rx} (kcal/mol):[25] CCl_2, 8, –70; CF_2, 27, –46; FCOH, 37, –31; C(OH)$_2$, 45, –18. As selectivity (m_{CXY}(calcd)) increases, E_a increases, while ΔH_{rx} decreases. The direct calculations thus support our qualitative analysis of the m_{CXY}(calcd)/ΔE_{stab} correlation.

The latter correlation also has applications to the selectivity of cyclopropylchlorocarbene (3).[27a] From the
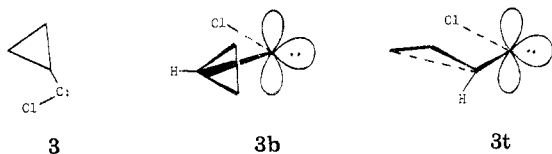
observed selectivities of **3**, m_3(obsd) = 0.41;[27b] but correlation eq 3, with appropriate σ constants, affords m_3(calcd) = 0.73.[27b] Why is **3** so much *less* selective than predicted by eq 3?

Carbene **3** prefers *bisected* conformation **3b**, in which cyclopropyl σ bonds favorably interact with the carbenic p orbital: calculated (4-31G) values of ΔE_{stab} for **3b** (35.9 kcal/mol) and its 90° "twisted" conformer, **3t** (26.4 kcal/mol), reveal the former to be more stable by ~9.5 kcal/mol.[27b] Molecular models, however, indicate that bisected **3b** would encounter substantial steric hindrance in electrophilic addition to alkenes. For the vacant p orbital to adequately overlap with the olefinic π orbital, a cyclopropyl carbon and its pair of H atoms must project down and onto the substrate's olefinic carbons or substituents. *Twisting* the cyclopropyl ring about the σ bond to the carbenic center relieves these adverse steric interactions. Accordingly, **3** should add
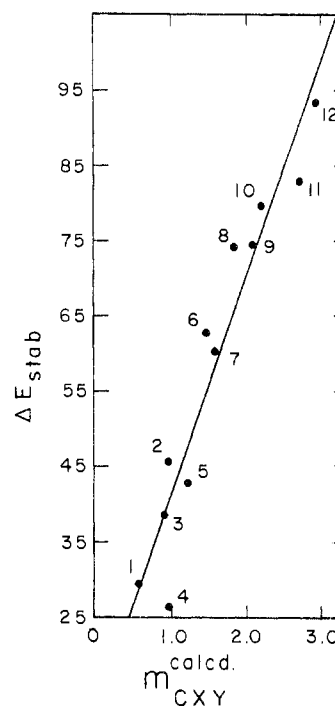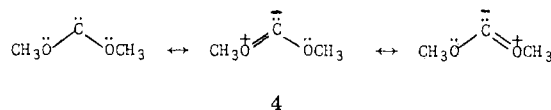
(26) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 384 (1955).

(27) (a) R. A. Moss and M. E. Fantina, *J. Am. Chem. Soc.*, **100**, 6788 (1978); (b) R. A. Moss, M. Vezza, W. Guo, R. C. Munjal, K. N. Houk, and N. G. Rondan, *ibid.*, **101**, 5088 (1979).

Figure 3. Calculated stabilization energies (ΔE_{stab}) vs. selectivities (m_{CXY}(calcd)) for CXY; see eq 3 and 4 and Table II. The carbene numbering key appears in Table II.

to alkenes via a *twisted* conformation (in the limit **3t**), which is largely unstabilized by cyclopropyl "conjugation", and should be much less selective than **3b**. This hypothesis explains the discrepancy between m_3(obsd) and m_3(calcd), because the latter is based on σ_p^+ for a "bisected" p-cyclopropyl-*tert*-cumyl cation; σ_R^+ (and m_3(calcd)) would be substantially *reduced* for a "twisted" p-cyclopropyl-*tert*-cumyl cation.

These considerations find support in the correlation of Figure 3. In explicit form, $\Delta E_{stab} = 28.6 m_{CXY}$(calcd) + 12.8, which translates the calculated ΔE_{stab} values of **3b** and **3t** (see above) to m_{3b}(calcd) = 0.81 and m_{3t}(calcd) = 0.48. Clearly, m_3(calcd) from eq 3, 0.73, is appropriate to bisected carbene **3b**, whereas m_3(obsd), 0.41, is equally appropriate to twisted carbene **3t**, resolving the "conflict" between m_3(obsd) and m_3(calcd).

(d) Correlation eq 3 permits estimation of m_{CXY} for carbenes yet unknown. Suppose we wish to identify a very selective CXY. Clearly, X and Y must be strong resonance-donating groups; $N(CH_3)_2$, OCH_3, F, and Cl ($\sigma_R^+ = -1.75, -1.02, -0.57,$ and -0.36, respectively[21]) are reasonable choices. From eq 3 and appropriate σ constants,[21] we find m_{CXY}(calcd) = 2.91, 2.22, 1.85, and 1.59 for $CH_3OCN(CH_3)_2$, $(CH_3O)_2C$, CH_3OCF, and CH_3OC-Cl, respectively. Each carbene is predicted to be more selective than CF_2, m_{CXY}(obsd) = 1.48, experimentally the most selective electrophilic carbene.

An interesting situation arises immediately. (CH_3-O)$_2$C is so strongly stabilized by resonance (4) that it

4

does not add to the alkenes of our standard set. It prefers addition to styrene, diethyl maleate or fumarate, and ethyl cinnamate; it is the archetypal nucleophilic carbene.[28] $CH_3OCN(CH_3)_2$ is even more resonance
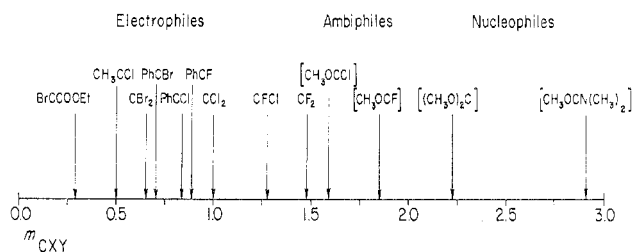
CARBENE SELECTIVITY SPECTRUM

Figure 4. A "carbene selectivity spectrum" in which carbenes are positioned according to experimental or calculated (from eq 3) m_{CXY} values. Carbenes sited according to calculated m_{CXY} appear in brackets. (Reprinted with permission from ref 33. Copyright 1979, Pergamon Press.)

Table III
Relative Reactivities of Carbenes

	k_{rel} for CXY		
alkene	CH_3OCCl (25 °C)^a	CH_3CCl (25 °C)^b	CCl_2 (80 °C)^b
$Me_2C=CMe_2$	12.6	7.44	78.4
$Me_2C=CH_2$	5.43	1.92	4.89
$t\text{-}MeCH=CHMe^c$	1.00	1.00	1.00
$CH_2=CHCOOMe$	29.7	0.078	0.060
$CH_2=CHCN$	54.6	0.074	0.047

^{a} From ref 31. ^{b} From ref 33. ^{c} Standard olefin.

The selectivity of CH_3OCCl is clearly indicative of its ambiphilic character: the k_{rel} sequence $Me_2C=CMe_2$ > $Me_2C=CH_2$ > $t\text{-}MeCH=CHMe$ is common to electrophilic carbenes,[12] whereas the high reactivities toward $CH_2=CHCOOMe$ and $CH_2=CHCN$ are appropriate to a nucleophilic carbene. This dramatic selectivity pattern differs remarkably from the clearly expressed electrophilicity of CCl_2 and CH_3CCl; cf. Table III.[34] Demonstration of CH_3OCCl ambiphilicity serves to unify the carbene selectivity spectrum of electrophiles, ambiphiles, and nucleophiles (Figure 4).

The FMO Formulation of Carbenic Reactivity[35a]

Frontier molecular orbital theory has been applied successfully to the rationalization and prediction of electrophilic, nucleophilic, and ambiphilic behavior in 1,3-dipolar cycloadditions and Diels–Alder reactions.[35b] The Houk/Rondan calculations of orbital energies for a variety of substituted carbenes[25] lend themselves to a similar rationalization of carbenic selectivity. The addition of a singlet carbene, 2, to an alkene involves simultaneous interactions of the vacant carbenic p orbital (LUMO) with the filled alkene π orbital (HOMO) and of the filled carbenic σ orbital (HOMO) with the vacant alkene π* orbital (LUMO).[10,35c] Although a singlet carbene is inherently *both* an electrophile and a nucleophile, behaviorally decisive is whether, in the transition state for addition, it is the $LUMO_{carbene}$/$HOMO_{alkene}$ or $HOMO_{carbene}$/$LUMO_{alkene}$ interaction which is stronger and determines the electronic distribution in the transition state. The dominant orbital interaction is determined *both* by the differential energies of the "competitive" interactions[36] and by the comparative extents of orbital overlaps. The orbital overlaps can be estimated as overlap integrals derived from calculated geometries and orbital coefficients for CXY/alkene transition states. Several examples will be given below. For the moment, however, we will ignore overlap and concentrate on the easily visualized

stabilized than $(CH_3O)_2C$, and also highly nucleophilic, adding to electron-deficient aryl isothiocyanates.[29]

Equation 3 is an empirical correlation with parameters normalized to the electrophilic carbene, CCl_2. This electrophilic heritage means that m_{CXY}(calcd) values can serve only as guides when applied to nucleophilic species such as $(CH_3O)_2C$, for which $m_{(CH_3O)_2C}$(calcd) is an "imaginary" selectivity index. Nevertheless, eq 3 helps define the m_{CXY} region in which nucleophilic carbenes reside. This categorizing ability of eq 3 is conveniently displayed in Figure 4, where experimental and calculated (from eq 3) m_{CXY}'s are displayed in a "carbene selectivity spectrum". Regions inhabited by electrophilic and nucleophilic carbenes are broadly indicated, based on available literature reports.[12]

(e) Because CF_2 (m(obsd) = 1.48)[13] is electrophilic toward the standard alkenes,[15] whereas $(CH_3O)_2C$ (m(calcd) = 2.22) is a nucleophile,[28] carbenes with 1.48 < m_{CXY}(calcd) < 2.22 are of immediate interest. If there is not to be a discontinuity between electrophilic and nucleophilic behavior, there must exist *ambiphilic carbenes*. Initially, we define these species operationally: an ambiphilic carbene acts as an electrophile toward electron-rich alkenes and as a nucleophile toward electron-poor alkenes. Inspection of the last column of Table II and Figure 4 suggests that the realm of the ambiphile might include CH_3OCCl (m(calcd) = 1.59) and CH_3OCF (m(calcd) = 1.85). The prediction for CH_3OCCl has now been dramatically confirmed.

CH_3OCCl is readily generated by thermolysis of the corresponding diazirine at 25 °C.[30] Although the carbene adds to a wide variety of alkenes, the absolute rate constants for diazirine decomposition and nitrogen evolution are essentially equal and effectively solvent independent, indicating that carbene formation is the rate-determining step of methoxychlorodiazirine thermolysis. The *selectivity* of CH_3OCCl[31] at 25 °C is shown in Table III, together with analogous data for the electrophiles[12] CCl_2[32,33] and CH_3CCl.[9,33]

(28) R. W. Hoffmann, W. Lillienblum, and B. Dittrich, *Chem. Ber.*, 107, 3395 (1974); R. W. Hoffmann and M. Reiffen, *ibid.*, 109, 2565 (1976).
(29) M. Reiffen and R. W. Hoffmann, *Chem. Ber.*, 110, 37 (1977).
(30) R. A. Moss and W.-C. Shieh, *Tetrahedron Lett.*, 1935 (1978); N. P. Smith and I. D. R. Stevens, *ibid.*, 1931 (1978).
(31) R. A. Moss, M. Fedorynski, and W.-C. Shieh, *J. Am. Chem. Soc.*, 101, 4736 (1979).
(32) CCl_2 was thermally generated from $PhHgCCl_2Br$ at 80 °C, a procedure which appears to involve direct carbene extrusion: D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Am. Chem. Soc.*, 87, 4259 (1965).
(33) R. A. Moss and R. C. Munjal, *Tetrahedron Lett.*, 4721 (1979). CH_3CCl was generated by photolysis (25 °C) of the corresponding diazirine.[9]

(34) Geometry optimized STO-3G calculations place triplet CH_3OCCl *at least* 18 kcal/mol *higher* in energy than the singlet (N. G. Rondan and K. N. Houk, private communication), so that the triplet is unlikely to be thermally accessible from the singlet at 25 °C. Triplet intervention is therefore not responsible for selectivity differences between CH_3OCCl and CCl_2 or CH_3CCl. Additions of CH_3OCCl to *cis*- or *trans*-butene are stereospecific,[31] as expected for a singlet carbene.
(35) (a) For an introduction to frontier molecular orbital theory, see I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley-Interscience, New York, 1976. (b) R. Sustmann, *Tetrahedron Lett.*, 2717, 2721 (1971); K. N. Houk, *Acc. Chem. Res.*, 8, 361 (1975). (c) W. M. Jones, R. A. LaBar, U. H. Brinker, and P. H. Gebert, *J. Am. Chem. Soc.*, 99, 6379 (1977), note 27.
(36) The differential energies appear in the denominators of the expression for ΔE, the stabilization energy gained when the FMO's of the reactants interact at the transition state; hence the *smaller* differential orbital energy makes the *larger* contribution to ΔE.

Table IV
Differential Orbital Energies for Carbene/Alkene Additions

| | carbene and differential orbital energies, eV[a] | | | | | | | |
| | CCl$_2$ | | CF$_2$ | | CH$_3$OCCl | | C(OCH$_3$)$_2$ | |
alkene	p-π	π*-σ	p-π	π*-σ	p-π	π*-σ	p-π	π*-σ
Me$_2$C=CMe$_2$[b]	*8.58*	13.71	*10.16*	15.65	*10.73*	13.09	*12.36*	13.08
Me$_2$C=CH$_2$[c]	*9.55*	13.63	*11.13*	15.57	*11.70*	13.01	13.33	*13.00*
t-MeCH=CHMe[d]	*9.43*	13.54	*11.01*	15.48	*11.28*	12.92	13.21	*12.91*
CH$_2$=CHCOOMe[e]	11.03	*12.24*	*12.61*	14.18	13.18	*11.62*	14.81	*11.61*
CH$_2$=CHCN[f]	11.23	*11.65*	*12.81*	13.59	13.38	*11.03*	15.01	*11.02*
CH$_2$=CH$_2$[g,h]	10.82	13.22	*12.40*	15.16	12.97	*12.60*	14.60	*12.59*

[a] (p-π) = ($\epsilon_{CXY}^{LUMO} - \epsilon_{alkene}^{HOMO}$); (π*-σ) = ($\epsilon_{alkene}^{LUMO} - \epsilon_{CXY}^{HOMO}$). For CXY orbital energies, see Table II. The smaller, dominant differential orbital energy is listed in *italics* in each case. [b] $\epsilon_\pi^* = 2.27,$[39] $\epsilon_\pi = -8.27.$[40] [c] $\epsilon_\pi^* = 2.19,$[39] $\epsilon_\pi = -9.24.$[40] [d] $\epsilon_\pi^* = 2.10,$[39] $\epsilon_\pi = -9.12.$[40] [e] $\epsilon_\pi^* = 0.80,$[41] $\epsilon_\pi = -10.72.$[42] [f] $\epsilon_\pi^* = 0.21,$[39] $\epsilon_\pi = -10.92.$[42] [g] $\epsilon_\pi^* = 1.78,$[39] $\epsilon_\pi = -10.51.$[40] [h] See Table V.

differential orbital energies. Consequences of this neglect of overlap turn out not to be crucial in the most interesting region of Figure 4, but they are important elsewhere and will have to be considered.

Consider the FMO differential energies for CCl$_2$ (or CF$_2$) in addition to common alkenes. The proximate, dominant interaction is LUMO$_{CXY}$–HOMO$_{alkene}$, **5**,[10,37]
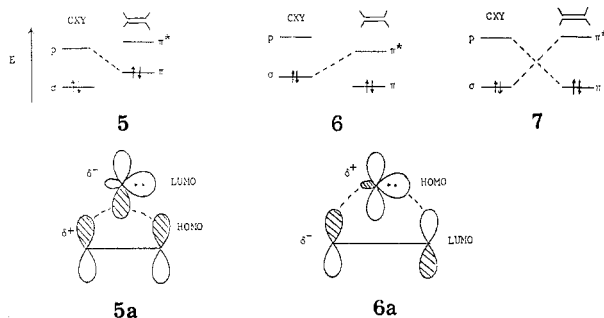
affording the transition-state charge distribution **5a** and electrophilic addition. Alternatively, for (CH$_3$O)$_2$C, the LUMO$_{alkene}$–HOMO$_{carbene}$ differential orbital energy is dominant, **6**; charge distribution **6a** is obtained, and nucleophilic addition is observed.[28] Finally, if the HOMO's and LUMO's of a carbene and a simple alkene are such as to afford comparable differential energies for both sets of orbital interactions, **7** (with similar overlap integrals), then ambiphilic carbene reactivity should obtain; substitution of strongly electron-donating or -withdrawing substituents on the alkene should convert **7** to **5** or **6**, respectively.

The FMO formulation naturally generates a continuum of carbenic selectivity ranging from electrophilicity through ambiphilicity to nucleophilicity. Indeed, the charge distributions of **5a** and **6a** are reflected in 4-31G calculations of appropriate CXY + CH$_2$=CH$_2$ transition states.[25] From Mulliken atomic charges, the net electron transfers at the transition states are 0.29, 0.20, and 0.10 electron in the pattern of **5a** for CCl$_2$, CF$_2$, and CFOH, respectively, but 0.06 electron in the pattern of **6a** for C(OH)$_2$.[25] Thus, we obtain electrophilic transition states for CCl$_2$ and CF$_2$ which reside in the electrophilic region of Figure 4; net electron density is transferred from alkene to carbene, and addition will be facilitated by increasing the number of electron-donating alkyl groups on the alkene's sp^2 carbons. In contrast, we obtain a nucleophilic transition state for

addition of C(OH)$_2$ (m_{CXY}(calcd) = 2.71); net electron density is transferred from carbene to alkene and addition would be facilitated by placing electron-attracting groups on the alkene.[38] Moreover, the electrophilic/nucleophilic balance of the charge distributions, measured by the calculated net electron transfers, *decreases* with *increasing* m_{CXY}(calcd), in accord with expectation.

Superficial FMO analysis permits rapid "quantitative" characterization of the olefinic selectivity of any CXY by using orbital energies to estimate the LUMO$_{carbene}$/HOMO$_{alkene}$ and LUMO$_{alkene}$/HOMO$_{carbene}$ differential energies for a series of CXY/alkene reactions. If a given CXY interacts with a spectrum of alkenes (cf. Table IV) so that the LUMO$_{CXY}$–HOMO$_{alkene}$ is always smaller than the LUMO$_{alkene}$–HOMO$_{CXY}$ differential energy, then that CXY can be considered electrophilic toward the accessible set of substrate alkenes. The inverse ordering of differential orbital energies would characterize a nucleophilic carbene. An ambiphilic carbene would exhibit a crossing of differential orbital energies over the examined substrate set.

Calculated CXY LUMO and HOMO energies appear in Table II.[25] Analogous energies have been experimentally determined for the alkenes of Table III,[39–42] so that we can readily estimate ($\epsilon_{CXY}^{LUMO} - \epsilon_{alkene}^{HOMO}$) and ($\epsilon_{alkene}^{LUMO} - \epsilon_{CXY}^{HOMO}$) for many situations. The resultant differential energies appear in Table IV. Note, however, that these data must be treated cautiously: the ϵ_{CXY}^{LUMO} values are actually virtual orbital energies and there are difficulties in equating them with experimental alkene orbital energies. Moreover, we have temporarily neglected the question of overlap in drawing conclusions solely on the basis of differential orbital energies.

Nevertheless, this admittedly incomplete treatment works very well in the most interesting region of the carbene selectivity spectrum; cf. Figure 4, where electrophiles and nucleophiles overlap with ambiphiles. Thus (Table IV) for CCl$_2$ and CF$_2$, ($\epsilon_{CXY}^{LUMO} - \epsilon_{alkene}^{HOMO}$) is uniformly less than ($\epsilon_{alkene}^{LUMO} -$

(37) See, also, R. R. Kostikov, A. P. Molchanov, G. V. Golovanova, and I. G. Zenkevich, *J. Org. Chem. USSR*, 13, 1846 (1977).

(38) On the basis of differential orbital energies, FCOH (m_{CXY}(calcd) = 2.09) would "react" ambiphilically with the alkene set of Table III, but it is predicted to be electrophilic toward ethene.

(39) K. D. Jordan and P. D. Burrow, *Acc. Chem. Res.*, 11, 341 (1978).

(40) G. Bieri, F. Burger, E. Heilbronner, and J. P. Maier, *Helv. Chim. Acta*, 60, 2213 (1977).

(41) K. N. Houk, J. Sims, R. E. Duke, Jr., and R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, 95, 7287 (1973).

(42) K. N. Houk and L. L. Munchausen, *J. Am. Chem. Soc.*, 98, 937 (1976).

Table V
Some Calculated Transition-State Parameters
for CXY + Ethene[a]

carbene	overlap integrals		α, deg[b]
	$CXY^{LUMO}/$ alkene^{HOMO}	$CXY^{HOMO}/$ alkene^{LUMO}	
CCl$_2$	0.131	0.095	36
CF$_2$	0.130	0.163	43
FCOH			48
C(OH)$_2$	0.138	0.175	58

[a] From ref 25. [b] Angle of tilt of CXY plane with respect to the original ethene plane; cf. 8.

ϵ_{CXY}^{HOMO}) across the substrate spectrum; these carbenes should be electrophilic in most accessible experimental situations, as is indeed the case for CCl$_2$ (Table III). CH$_3$OCCl, on the other hand, is clearly predicted by Table IV to be an ambiphile, and this too is supported by the data of Table III.

(CH$_3$O)$_2$C is predicted by Table IV to be nucleophilic toward most alkenes, but its addition to Me$_2$C=CMe$_2$ would be characterized as electrophilic *if it occurred*. In fact, even the smaller differential orbital energy (12.36 eV) is here quite large (as it also is with Me$_2$C=CH$_2$ and *t*-MeCH=CHMe). Consequently, these three addition reactions may not derive enough transition-state stabilization to become energetically competitive with alternative carbene reaction pathways.[28] Not shown in Table IV are the differential orbital energies for reactions of FCCl, FCOCH$_3$, and CH$_3$OCN(CH$_3$)$_2$. These are, however, in complete accord with expectation: FCCl is predicted to be electrophilic, FCOCH$_3$ ambiphilic, and CH$_3$OCN(CH$_3$)$_2$ nucleophilic toward the alkenes of the table.

This satisfying picture is not general, however. ClCCH$_3$, FCPh, and ClCSCH$_3$, carbenes which are well within the electrophilic realm of Figure 4, are predicted by differential orbital energies alone to be ambiphilic toward the alkenes of Table III. As reported there, however, CH$_3$CCl is certainly not an ambiphile. A more complete predictive rationale for carbene "philicity" thus requires consideration of *both* the comparative overlaps as well as the differential energies of the principal frontier orbital interactions, 5a and 6a.

Some useful information can be obtained in the following way. Using Slater orbitals for carbenic and ethene carbon atoms and the geometries and orbital coefficients obtained from STO-3G calculations for CXY–ethene transition states, we can obtain the pertinent transition state data of Table V.[25] There it is seen that a selective electrophile (CF$_2$) and a model nucleophile [C(OH)$_2$] actually have calculated dominant HOMO$_{carbene}$/LUMO$_{alkene}$ orbital overlaps (6a), at least in additions to ethene. Considered alone, this would mitigate for nucleophilic addition; but CF$_2$ is prevented from such addition by its extraordinarily low HOMO orbital energy (-13.38 eV, Table II), which makes CF$_2$ LUMO$_{carbene}$/HOMO$_{alkene}$ orbital interaction strongly preferred over HOMO$_{carbene}$/LUMO$_{alkene}$ interaction in terms of differential energies (Table IV). This outweighs directionally opposed overlap factors and accords with the apparent electrophilicity of CF$_2$.

With CCl$_2$, on the other hand, LUMO$_{carbene}$/HOMO$_{alkene}$ overlap is dominant, reinforcing the parallel energy-based orbital interaction preference (Tables IV and V). Carbenes which are *less* selective than CCl$_2$ presumably have *earlier* transition states (e.g., CH$_3$CCl) in which the overlap dominance of the LUMO$_{carbene}$/HOMO$_{alkene}$ interaction should be even more marked, determining the character of the addition reactions despite the opposed orbital energy factors encountered with electron-deficient alkenes.

These trends are also reflected in the behavior of α, the calculated angle of tilt of the CXY plane with respect to the original ethene plane at the addition transition state (calculated by Rondan and Houk using the STO-3G basis set); cf. 8 and Table V.[25] For a
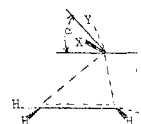
8

"pure" electrophilic approach, α would be 0°; a "pure" nucleophilic approach would have $\alpha = 90°$. In fact, α is 36° for CCl$_2$ and increases smoothly to 58° for C(OH)$_2$. The limited data indicate that α increases with increasing HOMO$_{carbene}$/LUMO$_{alkene}$ overlap, increasing addition activation energy, increasing carbene ΔE_{stab}, and decreasing reaction exothermicity. Naively, α may be taken as an indicator of carbene philicity: for electrophiles $\alpha < 45°$, whereas for nucelophiles $\alpha > 50°$. Of course, ambiphiles should display intermediate values of α.

A more detailed consideration can quantitatively link comparative transition-state overlap and differential orbital energies to the relative degree of electrophilicity or nucleophilicity for many CXY–ethene reactions.[25] Predictions of carbenic philicity made in this way fully accord with the more qualitative conclusions drawn above.

Conclusion

Chemistry is an open-ended endeavor, and the microcosm of carbene chemistry is no exception. New experiments may demand better, more complete, or even completely different analyses of carbenic selectivity. But to assume a measure of optimism, we now possess both a workable, predictive, semiquantitative theory and a parallel body of congruent experimental results. In at least one sense, therefore, the problem of carbenic selectivity is "solved". In a larger sense, however, we must be ready for extensive modification in the face of new calculational and experimental data, particularly the advent of absolute rate constants for CXY/alkene additions.