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Evolution of Structure and Reactivity in a Series of Iconic Carbenes

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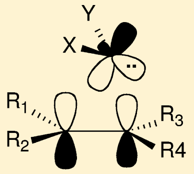
Ⓢ *Supporting Information*

ABSTRACT: We present experimental activation parameters for the reactions of six carbenes (CCl_2, CClF, CF_2, ClCOMe, FCOMe, and $(MeO)_2C$) with six alkenes (tetramethylethylene, cyclohexene, 1-hexene, methyl acrylate, acrylonitrile, and α-chloroacrylonitrile). Activation energies range from −1 kcal/mol for the addition of CCl_2 to tetramethylethylene to 11 kcal/mol for the addition of FCOMe to acrylonitrile. A generally satisfactory analysis of major trends in the evolution of carbenic structure and reactivity is afforded by qualitative applications of frontier molecular orbital theory, although the observed entropies of activation appear to fall in a counterintuitive pattern. An analysis of computed cyclopropanation transition state parameters reveals significant nucleophilic selectivity of $(MeO)_2C$ toward α-chloroacrylonitrile.

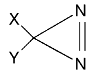


1. INTRODUCTION

The correlation of structure and reactivity has been central to the study of carbenes, since the early experiments of Hine,[1] Doering,[2] and Skell,[3] and the theoretical considerations of Hoffmann[4] and Houk.[5] Our efforts in this endeavor have been reviewed several times.[6,7] Of particular interest has been the [1 + 2] cycloaddition of singlet carbenes to alkenes, wherein the measurement and calculation of rates and activation parameters has continued to engage many investigators. Early studies of arylhalocarbene additions to alkenes by laser flash photolysis (LFP) revealed that activation energies and enthalpies were very low or even negative.[8−10] More generally, we may ask what are the magnitudes of these parameters and how do they evolve as functions of carbene and alkene structures? Prior to 2007, the absence of conveniently obtained and appropriate precursors for LFP studies of, e.g., the iconic dihalocarbenes precluded experimental answers to these questions, but many predictions were made.

On the basis of *relative* activation parameters, Skell concluded that CCl_2 additions to monoalkylethylenes were enthalpy-controlled but that entropic factors would dominate additions to more highly alkylated olefins.[11] Giese agreed that entropy would dominate CCl_2 additions but suggested that enthalpy would control CF_2 additions.[12] Houk offered a variational transition-state model that highlighted entropic factors in the additions of reactive carbenes.[13] His calculations supported the conclusions of Giese: CCl_2 additions should lack enthalpic barriers and be $\Delta S^{\ddagger}$-dominated, whereas CF_2 additions would be $\Delta H^{\ddagger}$-controlled.[13] Jorgensen also predicted entropic control of CCl_2 additions.[14]

Our recent syntheses of dichlorodiazirine (**1**),[15] chlorofluorodiazirine (**2**),[16] and difluorodiazirine (**3**),[17] coupled with the availability of chloromethoxydiazirine (**4**),[18] fluoromethoxydiazirine (**5**),[19] and dimethoxydiazirine (**6**),[20] provide LFP precursors for six key carbenes (CCl_2, ClCF, CF_2, ClCOMe, FCOMe, and $(MeO)_2C$), thus enabling a broad survey of activation parameters for carbene additions to alkenes. Our concerns include the dependence of $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ on carbenic structure and stability and alkene structure, as well as the possible operation of "compensation" between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, i.e. reciprocal behavior of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, a suspected phenomenon in carbene additions.[11]



1, X = Y = Cl
2, X= Cl, Y = F
3, X = Y = F
4, X = Cl, Y = MeO
5, X = F, Y = MeO
6, X = Y = MeO

We have published several letters and communications describing relevant data for CCl_2,[21] FCCl,[21] CF_2,[17] ClCOMe,[22] and FCOMe.[23] In this full paper, we integrate the prior information, add new experimental and computational results for $(MeO)_2C$, and provide a synoptic discussion of the addition reactions of all six carbenes. Our strategy focuses on the three "evolutionary" carbene sequences shown in Scheme 1, where the substituent changes modulate decreases in carbenic electrophilicity and concomitant increases in stability and nucleophilicity as one moves from left to right across each sequence.

Scheme 1. Three Evolutionary Carbene Sequences

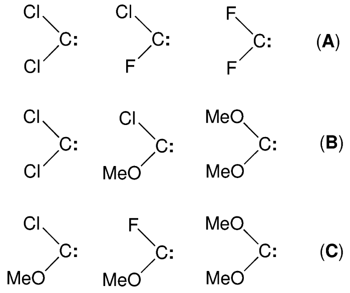


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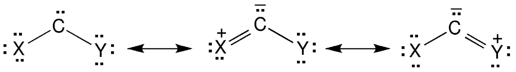
Table 1. Quantitative Measures of Carbenic Reactivity

carbene	$\varepsilon_{\text{LUMO}}$,[a,b] eV	$\varepsilon_{\text{HOMO}}$,[a,b] eV	ΔE_{stab},[a,c] kcal/mol	$m_{\text{CXY}}^{\text{calcd}}$[d]
CCl_2	0.31 (−3.74)	−11.44 (−7.50)	26.5 (45.5)	0.97
ClCF	1.03 (−3.39)	−11.98 (−8.09)	42.8 (56.1)	1.22
CF_2	1.89 (−2.83)	−13.38 (−8.77)	62.8 (70.9)	1.47
ClCOMe	2.46 (−1.91)	−10.82 (−6.97)	60.3 (72.7)	1.59
FCOMe	3.19 (−1.36)	−11.81 (−7.36)	74.2 (84.1)	1.85
$(MeO)_2C$	4.09 (−0.42)	−10.81 (−6.37)	79.8 (92.0)	2.22

[a] Data from ref 5. [b] HF/4-31G//STO-3G orbital energy. Orbital energies in parentheses are recalculated at the B3LYP/6-311++G(2d,p) level (this work). [c] Defined as the negative of the reaction energy of eq 1 computed at the HF/4-31G//STO-3G level.[5] Values in parentheses are computed at the B3LYP/6-311++G(2d,p) level (this work). [d] Calculated carbene selectivity index from ref 24.

2. THE CARBENES

The literature contains a number of parameters designed to "measure" carbenic reactivity, philicity, and stability; three of them are set out in Table 1 for the carbenes of Scheme 1.[5,24] The computed carbene LUMO energies, $\varepsilon_{\text{LUMO}}$, increase from CCl_2 to $(MeO)_2C$, reflecting increasingly potent electron donation by each carbene's substituents into its formally vacant p (LUMO) orbital; cf. resonance hybrid 7. This is accompanied by decreasing carbenic electrophilicity as π-electron donation from alkene reaction partners becomes energetically less competitive. The same trend in $\varepsilon_{\text{LUMO}}$ is manifested at both the HF/4-31G//STO-3G and the B3LYP/6-311++G(2d,p) levels. As anticipated, the LUMO energies are less positive (more negative) in the DFT than in the HF calculations.



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The carbene HOMO (σ) orbital energies in Table 1 are not as regular in their dependence on the carbenic substituents. In part, these orbital energies are influenced by the electronegativity of the carbenic substituents; viz. $\varepsilon_{\text{HOMO}}$ decreases as F replaces Cl ($\varepsilon_{\text{HOMO}}$ CCl_2 > ClCF > CF_2, and ClCOMe > FCOMe). The HOMO energies are less negative in the DFT than in the HF calculations, as expected.

The CCl_2 to $(MeO)_2C$ progression is accompanied by a general increase in ΔE_{stab}, a quantitative measure of carbenic stability relative to methylene, defined as the negative of the computed HF/4-31G//STO-3G [or B3LYP/6-311++G(2d,p)] energies of the isodesmic reactions defined in eq 1.[5] As the carbenes become more stable, we can anticipate an increase in the activation energies for their additions to alkenes. Note that the predicted B3LYP stabilization energies are uniformly larger than the HF/4-31G//STO-3G values. There are indications of additional stabilization (relative to the prior values), when the carbene contains a Cl atom. This most likely reflects the particular inadequacy of the 4-31G (and STO-3G) basis set for Cl.

$$:CH_2 + CH_3X + CH_3Y \xrightarrow{-\Delta E_{\text{stab}}} :CXY + 2CH_4 \qquad (1)$$

Table 1 also contains the carbene selectivity indices, m_{CXY}.[24] These are empirical reactivity indices that reflect the selectivity of the carbene toward a standard set of alkylethylenes, relative to the selectivity of CCl_2. The m_{CXY} index can be calculated for a given carbene from eq 2, where $\Sigma_{x,y}$ represents the sum of the appropriate σ constants for the X and Y substituents of CXY.[6,24] As m_{CXY} increases, the carbene's philicity changes from electrophilic (CCl_2, ClCF, CF_2) to ambiphilic (ClCOMe) to nucleophilic (FCOMe, $(MeO)_2C$).[6]

$$m_{\text{CXY}} = -1.10\Sigma_{\text{X,Y}}\sigma_{\text{R+}} + 0.53\Sigma_{\text{X,Y}}\sigma_{\text{I}} \qquad (2)$$

The literature also contains other parameters intended to characterize carbenic reactivity and philicity. Examples include ΔN, which tracks charge transfer between a carbene and an alkene;[25] the computed electron affinity and ionization potential of the carbene, which are related to the carbene's LUMO and HOMO orbital energies;[26] and ω, the global electrophilicity index of the carbene.[27a] Each of these parameters correlates reasonably well with m_{CXY}, leading to similar characterizations of carbenic philicity. We also note the newly introduced carbene stabilization energies (CSE), based on calculated heats of hydrogenation, as a measure of carbenic stability.[27b] The CSE tracks reasonably well with ΔE_{stab}.[5]

3. THE ALKENES

The six carbenes of Scheme 1 span a broad range of stability and philicity (Table 1), so that we require a set of alkene reaction partners with a comparably wide range of electronic properties. We chose three "electron rich" alkylethenes and three "electron deficient" alkenes substituted with electron withdrawing substituents. These substrates are shown in Table 2, together with their derived π (HOMO) and π* (LUMO) orbital energies from both experiment (i.e., valence ionization energies and vertical electron affinities, respectively)[28−33] and B3LYP/6-311++G(2d,p) computations (this work).

Table 2. Experimental and Computed Orbital Energies (eV) of Alkenes[a]

alkene	ε_{π} (HOMO)	ε_{π^*} (LUMO)
$Me_2C{=}CMe_2$	−8.27[b] (−6.19)	2.27[c] (−0.28)
cyclohexene	−8.94[b] (−6.66)	2.07[c] (−0.28)
$CH_2{=}CH\text{-}n\text{-}C_4H_9$	−9.48[d] (−7.78)	1.84[e] (−0.33)
$CH_2{=}CHCOOMe$	−10.72[f] (−7.85)	0.8[f] (−1.69)
$CH_2{=}CHCN$	−10.92[g] (−8.26)	0.21[c] (−1.99)
$CH_2{=}CClCN$	−10.58[g] (−8.15)	−0.35[h] (−2.31)

[a] Values in parentheses are *computed* orbital energies at the B3LYP/6-311++G(2d,p) level (this work). See the Supporting Information for details. [b] Reference 28. [c] Reference 29. [d] Reference 30. [e] Reference 31. [f] Reference 32. [g] Reference 33. [h] Estimated from HF/4-31G//STO-3G computed energies scaled to the measured value[29] for $CH_2{=}CHCN$.

Trends are readily apparent in Table 2. From tetramethylethylene (TME) to acrylonitrile (ACN), ε_{π} decreases as the alkene's π electrons become more strongly bound.[34] In this order, the alkenes become poorer electron donors, less nucleophilic, and poorer substrates for electrophilic carbenes like CCl_2.[6]

In contrast, as ε_{π^*} decreases from TME through α-chloroacrylonitrile (ClACN), the alkenes become better electron acceptors, more electrophilic, and better substrates for nucleophilic carbenes like $(MeO)_2C$.[6] These reactivity trends can be conveniently interpreted by frontier molecular orbital theory,[5,6,35] according to which stabilization of the cycloaddition transition state (TS) depends *inversely* on the magnitude of the differential energy ($\Delta\varepsilon$) of the principal interacting orbitals.[36] In the case of a carbene-alkene cycloaddition, these are the carbene p (LUMO) interacting with the alkene π (HOMO), and the carbene σ (HOMO) interacting with the alkene π^* (LUMO); cf. Figure 1.[5,6b,7] Orbital overlap is neglected in this qualitative analysis.

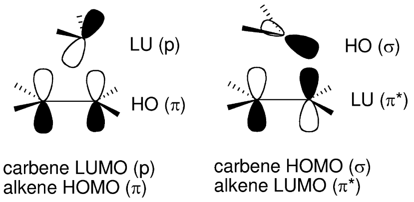


Figure 1. Frontier molecular orbital interactions in carbene/alkene additions. Reprinted with permission from ref 7.

A smaller $\Delta\varepsilon$ results in greater TS stabilization, lower E_a, and a faster addition reaction. The differential energies of the orbital interactions are expressed by eqs 3 and 4.[6b] If $\Delta\varepsilon_E < \Delta\varepsilon_N$, the carbene p/alkene π orbital interaction will dominate the TS, charge transfer will be directed from alkene to carbene, and the carbene will behave as an electrophile. If $\Delta\varepsilon_N < \Delta\varepsilon_E$, the carbene σ/alkene π^* orbital interaction will be dominant, charge will be transferred from the carbene to the alkene in the TS, and the carbene will behave as a nucleophile. If $\Delta\varepsilon_E \sim \Delta\varepsilon_N$, neither orbital interaction will dominate and the carbene will be an ambiphile, capable of strong interactions with either electron rich alkenes (as an electrophile) or electron poor alkenes (as a nucleophile).[6]

$$\Delta\varepsilon_E = {\varepsilon_{CXY}}^{LU} - {\varepsilon_{C=C}}^{HO} = p - \pi \tag{3}$$

$$\Delta\varepsilon_N = {\varepsilon_{C=C}}^{LU} - {\varepsilon_{CXY}}^{HO} = \pi^* - \sigma \tag{4}$$

In any given pairing of a carbene from Table 1 with an alkene from Table 2, a qualitative estimate of carbenic reactivity and philicity can be obtained by inserting the relevant orbital energies into eqs 3 and 4 and comparing the resultant $\Delta\varepsilon_E$ and $\Delta\varepsilon_N$, cf. Tables S-1–S-3 in the Supporting Information. We can thus rationalize the generally observed electrophilicity of CCl_2, nucleophilicity of $(MeO)_2C$, and ambiphilicity of ClCOMe.[5,6,24]

4. CARBENE–ALKENE ADDITIONS

Reactions of the six carbenes of Table 1 with the six alkenes of Table 2 would generate 36 sets of rate constants and activation parameters. However, not all of the carbene-alkene pairings lead to experimentally usable results. CCl_2, the least stabilized and most electrophilic of the carbenes, does afford quantitative results with all six alkenes,[16a,37] but the more stabilized and less electrophilic ClCF and CF_2 react well only with the most electron rich alkenes of Table 2 (TME, cyclohexene, and 1-hexene). Their reactions with the electron poor alkenes, methyl acrylate (MeAcr), ACN, and ClACN, are too slow to give good LFP data and too inefficient, compared to side reactions, to yield decent relative rate data.

Similarly, the three more stable and more nucleophilic carbenes (ClCOMe, FCOMe, and $(MeO)_2C$) react well only with the more electrophilic, electron-poor alkenes of Table 2 (MeAcr, ACN, and ClACN), while reacting poorly or not at all with the electron-rich alkenes TME, cyclohexene, and 1-hexene. Indeed, with $(MeO)_2C$, the most stable and most nucleophilic of our six carbenes, we could obtain usable data only with ClACN, the most electrophilic of the alkenes.[38,39]

Thus, of 36 potential sets of carbene–alkene addition reaction kinetics data, we could obtain only 19 usable data sets. Nevertheless, these results permit us to draw useful conclusions concerning the evolution of carbenic structure and reactivity across the six carbenes of Scheme 1 and Table 1.

5. DIMETHOXYCARBENE

We measured k_{abs} (k_{abs} = the *absolute* rate constant for the bimolecular addition reaction) for the addition of $(MeO)_2C$ to ClACN by LFP. LFP at 351 nm[40] of dimethoxydiazirine **6**[39] in pentane (A_{350} = 0.7) afforded $(MeO)_2C$, which absorbed as reported[39] at 255 nm. This $\sigma \rightarrow$ p absorption was calculated to appear at 262 and 275 nm, respectively, for the *cis*, *trans*, and *trans*, *trans* conformers of $(MeO)_2C$.[39] LFP at 25.1 °C gives $k_{abs} = 5.01 \times 10^5\ M^{-1}\ s^{-1}$ for the addition of $(MeO)_2C$ to ClACN, where k_{abs} derives from a correlation of the observed rate constants for the disappearance of the carbene's absorption at 255 nm vs the concentration of ClACN in pentane at five concentrations between 0.0 and 1.34 M ClACN; cf. Figure 2.

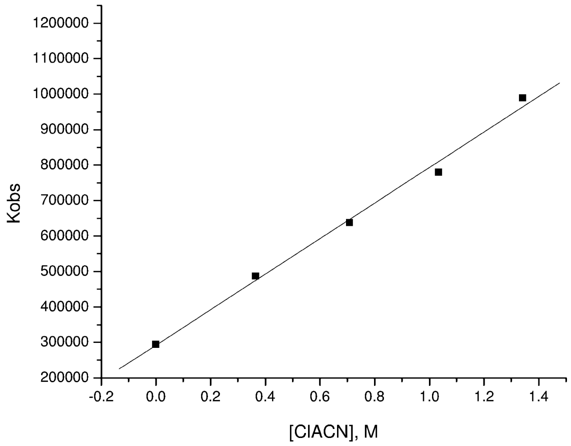


Figure 2. LFP determination of k_{abs} for the addition of $(MeO)_2C$ to ClACN at 298.2 K in pentane: k_{abs} for carbene decay at 255 nm vs [ClACN]. $k_{abs} = 5.01 \times 10^5\ M^{-1}\ s^{-1}$, $r = 0.997$.

We previously (1988) measured this rate constant as $5.0 \times 10^5\ M^{-1}\ s^{-1}$.[39]

Next, k_{abs} was similarly determined at an additional four temperatures between 272 and 303 K; cf. Figures S-1–S-4 in the Supporting Information. An Arrhenius plot of ln k_{abs} vs $1/T$ appears in Figure 3, where k_{abs} varies from 1.56×10^5 to $6.18 \times 10^5\ M^{-1}\ s^{-1}$ across a temperature range of 272.8–303.3 K. The slope and intercept of the least-squares correlation line afford E_a = 7.44 kcal/mol, log $A = 11.15\ M^{-1}\ s^{-1}$, and $\Delta S^{\ddagger} = -9.49$ eu.

A second, independent determination of these parameters is illustrated by Figures S-5–S-9 in the Supporting Information, leading to the Arrhenius correlation of Figure S-10, from which

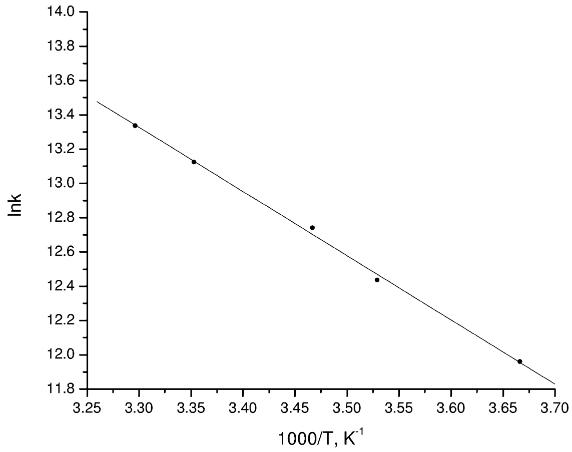
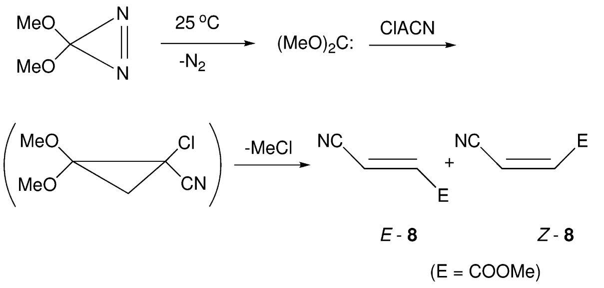


Figure 3. Determination of the activation parameters for the addition of $(MeO)_2C$ to ClACN, ln k vs $1/T$: $E_a = 7.44$ kcal/mol; $A = 1.41 \times 10^{11}$ M^{-1} s^{-1}, $\Delta S^{\ddagger} = -9.49$ eu, $r = -0.999$.

$E_a = 7.50$ kcal/mol, log $A = 11.19$ M^{-1} s^{-1}, and $\Delta S^{\ddagger} = -9.26$ eu. Average values of the activation parameters from the two determinations are $E_a = 7.47 \pm 0.03$ kcal/mol, log $A = 11.7 \pm 0.02$ M^{-1} s^{-1}, and $\Delta S^{\ddagger} = -9.38 \pm 0.12$ eu.

Unfortunately, we could not obtain a good linear fit for kinetics experiments of $(MeO)_2C$ with ACN. The addition rate constant at room temperature is ∼1.0×10^4 M^{-1} s^{-1}, but the carbene reacts too slowly to permit an adequate Arrhenius study.

Thermolysis of dimethoxydiazirine in ClACN gave a mixture of ring-opened[39] *Z* and *E*-α-cyanoacrylic acid methyl esters (**8**) with an *E*/*Z* ratio of ∼3:1, eq 5. The NMR spectrum of the mixture appears in the Supporting Information. Analogous reactions of $(MeO)_2C$ with MeAcr and ACN gave mixtures of the appropriate cyclopropanes and their ring-opened products. Stirring with small quantities of silica gel converted these mixtures to ring-opened derivatives **9** and **10**, respectively.[39]



(5)

$MeOOCCH_2CH_2COOMe$

9

$MeOOCCH_2CH_2CN$

10

We attempted to determine the reactivity of $(MeO)_2C$ toward MeACr and ACN, relative to ClACN, by competition reactions with binary alkene mixtures. However, the product mixtures contained many byproducts (as well as **8**, **9**, and **10**), and usable data could not be obtained.

6. DISCUSSION

The experimental activation parameters available to assess the "evolutionary" carbene sequences of Scheme 1 are set out in Tables 3−5.[7,17,21−23,37] Consider first Table 3 and sequence **A** of Scheme 1: CCl_2, ClCF, and CF_2. In the same order, ε_{LUMO}, ΔE_{stab}, and m_{CXY} increase (Table 1), and the carbenes become more stable and less reactive toward the electron rich alkenes of Table 2. These trends are "regular", in part, because all nine addition reactions of Table 3 are "electrophilic", i.e., $\Delta\varepsilon_E < \Delta\varepsilon_N$, and it is $\Delta\varepsilon_E$ that "controls" the activation energy. ε_{LUMO} of CXY increases in the order CCl_2 < ClCF < CF_2, so that for any given alkene $\Delta\varepsilon_E$ and E_a both increase in a parallel fashion; cf. Table 3 and Tables S-1−S-3 (Supporting Information).

E_a also increases in the substrate order TME < cyclohexene <1-hexene. As the alkene's ε_{HOMO} decreases (Table 2) and its π electrons become more tightly bound, $\Delta\varepsilon_E$ increases and E_a rises for any given carbene. These trends are the same for $\Delta H^{\ddagger}$ in Table 3 (since $\Delta H^{\ddagger} = E_a$ -RT), and similar for $\Delta G^{\ddagger}$, though mitigated by the behavior of $\Delta S^{\ddagger}$.

With the electron-rich alkenes in Table 3, $\Delta S^{\ddagger}$ becomes less negative and more favorable as the carbene's ΔE_{stab} and ε_{LUMO} increase. This apparent behavior is counterintuitive because the addition TS should become later, tighter, and more sterically demanding as the carbene becomes more stable. No satisfactory explanation for this apparent paradox has yet been offered.[7] Computational studies provide $\Delta S^{\ddagger}$ values that are considerably more negative than the experimental values.[21]

We next consider Table 4 and carbene sequence **B** of Scheme 1: CCl_2, ClCOMe, and $(MeO)_2C$. Here, the observed E_a's reflect a "competition" between $\Delta\varepsilon_E$ and $\Delta\varepsilon_N$ (eqs 3 and 4) for control of the TS. With CCl_2, additions to TME and (perhaps) MeAcr are controlled by $\Delta\varepsilon_E$. For additions of CCl_2 to ACN and ClACN, however, $\Delta\varepsilon_E$ and $\Delta\varepsilon_N$ are more comparable, and computational studies suggest that these are

Table 3. Activation Parameters for Carbene Additions: Sequence A[a]

carbene	alkene[b]	E_a	log A	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$-T\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$
CCl_2[c,d]	TME	−1.2	8.8	−1.8	−20	6.0	4.2
ClCF[c]	TME	0.9	9.7	0.3	−16	4.7	5.0
CF_2[e]	TME	3.0	11.0	2.5	−10	3.0	5.5
CCl_2[c]	c-C_6H_{10}	3.8	10.9	3.3	−10.5	3.1	6.4 (0.4)
ClCF[c]	c-C_6H_{10}	5.6	11.5	5.0	−7.8	2.3	7.3 (0.4)
CF_2[e]	c-C_6H_{10}	6.9	12.3	6.3	−4.3	1.3	7.6 (0.5)
CCl_2[c]	1-hex	4.7	10.7	4.1	−11.5	3.4	7.5 (0.4)
ClCF[c]	1-hex	6.0	11.5	5.4	−7.8	2.3	7.7
CF_2[f]	1-hex	8.0	12.4	7.4	−3.9	1.1	8.6

[a] Units are kcal/mol for E_a, $\Delta H^{\ddagger}$, $-T\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$; M^{-1} $s^{-1}$for log A, and cal(deg mol) for $\Delta S^{\ddagger}$. $\Delta H^{\ddagger}$ is calculated at 283K; $\Delta G^{\ddagger}$ is calculated at 298 K. Errors are 0.2−0.3 kcal/mol or less in E_a or $\Delta G^{\ddagger}$, except as shown in parentheses for $\Delta G^{\ddagger}$. [b] TME = tetramethylethylene, c-C_6H_{10} = cyclohexene, 1-hex =1-hexene, MeAcr = methyl acrylate, ACN = acrylonitrile, ClACN = α-chloroacrylonitrile. [c] From ref 21. [d] The negative E_a for CCl_2 refers to 273 K < T < 304 K. [e] From ref 17. [f] From ref 7.

Table 4. Activation Parameters for Carbene Additions: Sequence B[a]

carbene	alkene[b]	E_a	log A	$\Delta H^‡$	$\Delta S^‡$	$-T\Delta S^‡$	$\Delta G^‡$
CCl_2[c,d]	TME	−1.2	8.8	−1.8	−20	6.0	4.2
ClCOMe[e]	TME	5.8	8.0	5.2	−24	7.2	12.4
CCl_2[f]	MeAcr	6.7	11.0	6.1	−9.9	2.9	9.0
ClCOMe[e]	MeAcr	7.0	9.0	6.4	−19.2	5.7	12.1
CCl_2[f]	ACN	6.9	11.0	6.3	−9.8	2.9	9.2
ClCOMe[e]	ACN	6.4	9.1	5.8	−18.9	5.6	11.4
CCl_2[f]	ClACN	5.4	11.2	4.8	−9.1	2.7	7.5
ClCOMe[e]	ClACN	3.9	8.8	3.4	−20.2	6.0	9.4
$(MeO)_2C$[g]	ClACN	7.5	11.2	6.9	−9.4	2.8	9.7

[a] See footnote *a* in Table 3. [b] See footnote *b* in Table 3. [c] From ref 21. [d] The negative E_a for CCl_2 refers to 273 K < T < 304 K. [e] From ref 22. [f] From ref 37. [g] This work.

Table 5. Activation Parameters for Carbene Additions: Sequence C[a]

carbene	alkene[b]	E_a	log A	$\Delta H^‡$	$\Delta S^‡$	$-T\Delta S^‡$	$\Delta G^‡$
ClCOMe[c]	MeAcr	7.0	9.0	6.4	−19	5.7	12.1
FCOMe[d]	MeAcr	9.7	10.2	9.2	−14	4.1	13.2
ClCOMe[c]	ACN	6.4	9.1	5.8	−19	5.6	11.4
FCOMe[d]	ACN	11.1	11.3	10.5	−8.8	2.6	13.2
ClCOMe[c]	ClACN	3.9	8.8	3.4	−20	6.0	9.4
FCOMe[d]	ClACN	6.0	9.5	5.4	−17	5.1	10.5
$(MeO)_2C$[e]	ClACN	7.5	11.2	6.9	−9.4	2.8	9.7

[a] See note *a* in Table 3; $\Delta H^‡$ is calculated at 303 K for FCOMe. [b] See note *b* in Table 3. [c] From ref 22. [d] From ref 23. [e] This work.

"nucleophilic" additions in which the carbene HOMO−alkene LUMO (σ−π*) orbital interaction is dominant.[37]

With ClCOMe, addition to TME is controlled by $\Delta\varepsilon_E$; E_a will be greater for ClCOMe addition than for CCl_2 addition because ε_{LUMO} (ClCOMe) > ε_{LUMO} (CCl_2). In contrast, ClCOMe additions to MeAcr, ACN, and ClACN are all controlled by $\Delta\varepsilon_N$. Now, $\Delta\varepsilon_N$ for MeOCCl addition to ACN and ClACN is generally less than either $\Delta\varepsilon_E$ or $\Delta\varepsilon_N$ for CCl_2 addition, and E_a is either similar (MeAcr) or lower (ACN, ClACN) for MeOCCl addition than for CCl_2 addition. Note also that E_a for CCl_2 addition to ClACN is lower than for addition to ACN, suggesting that these are *nucleophilic* CCl_2 additions, a conclusion supported by computational studies.[37]

Despite these trends in E_a (and $\Delta H^‡$), $\Delta G^‡$ for CCl_2 additions to all four alkenes is lower than for the analogous ClCOMe additions. With TME, this is due to the 7 kcal/mol difference in E_a or $\Delta H^‡$ favoring CCl_2. For MeAcr, ACN, or ClACN, however, $\Delta G^‡$ is lower for CCl_2 addition because $\Delta S^‡$ favors CCl_2 over ClCOMe by ~9 − 11 eu (~3 kcal/mol in the $T\Delta S^‡$ contribution to $\Delta G^‡$), more than enough to overcome any small differences in E_a or $\Delta H^‡$ that favor ClCOMe. The origin of the unfavorable $\Delta S^‡$ attending the ClCOMe additions might reside in the need to restrict rotation of the methoxy group in the addition TS, and the significantly greater stability of ClCOMe vs CCl_2 (cf. ΔE_{stab} in Table 1). The latter point suggests that the TS for ClCOMe addition to a given alkene will be later, tighter, and more sterically demanding than the analogous CCl_2 TS.

Given the greater stability of $(MeO)_2C$ vs ClCOMe ($\Delta\Delta E_{stab}$ ~ 19 kcal/mol), the 3.6 kcal/mol E_a advantage for ClCOMe over $(MeO)_2C$ addition to ClACN is understandable. What is not clear is why $\Delta S^‡$ is 10−11 eu *more* favorable for the addition of the more stable, more sterically demanding $(MeO)_2C$. This entropy advantage makes $(MeO)_2C$ addition to ClACN only marginally less favorable in $\Delta G^‡$ than ClCOMe addition.

Lastly, we consider Table 5 and carbene sequence **C** of Scheme 1: ClCOMe, FCOMe, and $(MeO)_2C$. Our analysis here is similar to that of sequence **B**. FCOMe is more stable than ClCOMe by ~11−14 kcal/mol in ΔE_{stab}, and its (nucleophilic) additions to MeAcr, ACN, and ClACN all have higher E_a's than the comparable ClCOMe additions. On the other hand, $\Delta S^‡$ is more favorable for the FCOMe additions,[41] thus narrowing the differences in $\Delta G^‡$. The latter favors ClCOMe additions to the alkenes by ~1−2 kcal/mol. For additions to ClACN, E_a increases in the expected order: ClCOMe < FCOMe < $(MeO)_2C$, but $\Delta S^‡$ becomes less negative in the same order,[41] so that $\Delta G^‡$ for the addition of $(MeO)_2C$ is actually a bit more favorable than for the addition of FCOMe, and comparable to ClCOMe.

7. TS FOR ADDITION OF $(MeO)_2C$ TO ClACN

We have carried out electronic structure calculations (DFT B3LYP/6-311+G(d)) for the $(MeO)_2C$ + ClACN addition reaction (see Supporting Information for computational details). The computed TS is shown in Figure 4, and pertinent TS parameters are listed in Table 6. Also included in Table 6 are analogous computed data for the TS's involving ClACN reacting with CCl_2, ClCOMe, and FCOMe (previously available in the Supporting Information of ref 23). A closer examination of the structural parameters and the net carbene-alkene charge transfer suggests significant nucleophilic character for the $(MeO)_2C$−ClACN interaction in the TS.

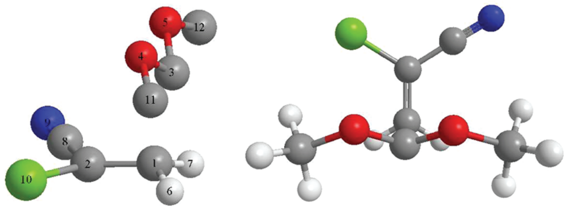


Figure 4. Transition state for $(MeO)_2C$ addition to ClACN (B3LYP/6-311+G(d)): side view (left, with Me hydrogens omitted for clarity) and top view (right, in perspective). Color code: gray = C; red = O; green = Cl; blue = N; white = H.

Figure 4 and the data in Table 6 show that in the $(MeO)_2C$ + ClACN TS, the approaching carbene is positioned on the "outside" of the unsubstituted alkene C1-atom (angle C3−C1−C2 = 105.9°) with significantly different C(carbene)−C(alkene) distances (C1−C3 = 1.989 Å; C2−C3 = 2.716 Å).

Table 6. Structural Parameters for the $(MeO)_2C$ + ClACN Transition State (B3LYP/6-311+G(d); Idealized Gas Phase)[a]

reacting species	C1−C3	C2−C3	C1−C2	δ[b]	C3−C1−C2	ζ[c]	α[d]	β[e]	Q_{net}[f]
$(MeO)_2C$ + ClACN	1.989	2.716	1.387	0.055	105.9	65.1	19.1	5.8	0.16
FCOMe + ClACN	1.963	2.682	1.385	0.053	105.1	60.9	30.2	8.5	0.09
ClCOMe + ClACN	2.030	2.740	1.379	0.047	105.4	61.4	27.7	6.4	0.09
CCl_2 + ClACN	2.294	2.890	1.355	0.023	101.6	49.6	13.3	3.7	0.06

[a] See Figure 4 for the Atom Numbering Scheme. Distances in Å, Angles in Degrees. [b] δ is the increase in C1−C2 double bond length from free alkene (1.332 Å) to the TS. [c] ζ is the (smaller) angle between the X4−C3−Y5 bisector of carbene CXY and the alkene C1−C2 bond. [d] α is the (smaller) angle between the H6−C1−H7 bisector of the alkene and the alkene C1−C2 bond. The CH_2 unit bends away from the approaching carbene. [e] β is the (smaller) angle between the C8−C2−Cl0 bisector of the alkene and the alkene C2−C1 bond. The substituents on C2 bend toward the approaching carbene. [f] Positive net charge means electrons have been transferred *from* carbene *to* olefin.

Incipient bond formation is thus far more pronounced at the unsubstituted carbon, in keeping with the TS possessing some nucleophilic Michael addition character. The increase in C1═C2 double bond length from the free alkene to the TS is significant (δ = 0.055 Å), whereas the local geometry of the carbene hardly changes from that of the free species. The carbene tilt angle, ζ, defined as the angle between the bisector of the X−C-Y carbene and the alkene C═C bond, is a qualitative indicator of the philicity of the carbene-alkene addition: for a purely electrophilic carbene attack, ζ would be 0°, whereas $\zeta > 45°$ indicates significant nucleophilic character.[5] We compute $\zeta = 65.1°$ for the $(MeO)_2C$-ClACN TS. The puckering angle (α) at the unsubstituted carbon C1 is 19.1°, with the CH_2 group bending away from the approaching carbene; the corresponding puckering angle (β) at the substituted carbon C2 is only about 6° and bending is toward the approaching carbene. The net electron-transfer between $(MeO)_2C$ and ClACN (Mulliken population analysis) is 0.16e, *from* the carbene *to* the alkene, and the olefin polarizes so that partial negative charge is imposed on the C atom bearing the CN substituent and on Cl (relative to the free alkene). The TS structural parameters just discussed, namely the geometrical relation of the carbene to the alkene, the large value of the tilt angle, the distinct asymmetry in C(carbene)−C(alkene) distances, and the larger pyramidalization at C1 than at C2, together with the direction of charge transfer, all point to a strong nucleophilic component in the TS for $(MeO)_2C$ adding to ClACN.[5]

According to data presented in Table 1, the order of stability for the carbenes considered in Table 6 is $(MeO)_2C$ > FCOMe > ClCOMe ≫ CCl_2. In keeping with the Hammond principle that a more stable and less reactive intermediate traverses a later and more product-like TS, the values of, in particular, the C−C and δ parameters in Table 6, clearly show that when ClACN is the alkene, the $(MeO)_2C$ and FCOMe TSs are later than that of the ClCOMe addition, which, in turn, is later than the TS for the CCl_2 addition. Making a distinction between FCOMe and $(MeO)_2C$ with respect to "lateness" and nucleophilicity on the basis of geometrical TS parameters is perhaps subtle. Thus, both the C1−C3 and C2−C3 distances, which represent the forming C−C bonds, are shorter (more product-like) in the FCOMe TS, suggesting that FCOMe is the more nucleophilic carbene. A slightly larger TS elongation toward the product C1−C2 cyclopropane single bond in the $(MeO)_2C$ addition than in the FCOMe addition may point toward $(MeO)_2C$ being the more nucleophilic species. However, the computed tilt angle (ζ) and net charge transfer are distinctly larger for the $(MeO)_2C$−ClACN TS and hence strongly favor greater nucleophilicity for $(MeO)_2C$. It appears that the relatively long C−C distances in the $(MeO)_2C$−ClACN TS reflect the steric influence of the two methyl groups in $(MeO)_2C$, which prevent this carbene from approaching the terminus of the alkene as closely as FCOMe.

Computed activation parameters for ClACN reacting with $(MeO)_2C$ are presented in Table 7. Also included in Table 7 are analogous data for the TSs for ClACN reacting with CCl_2, ClCOMe, and FCOMe (previously available in the Supporting Information of ref 23). The computed activation parameters for the most stable $(MeO)_2C$ conformer (*trans, trans*)[20] reacting with ClACN are E_a = 10.6 kcal/mol (corresponding to $\Delta H^‡$ = 10.0 kcal/mol) and $\Delta S^‡$ = −37.5 eu.[42] As we observed previously,[21,23] computed DFT activation parameters, particularly $\Delta S^‡$, differ significantly from the measured values: E_a = 7.5 kcal/mol and $\Delta S^‡$ = −9.4 eu for the $(MeO)_2C$/ClACN pair (Table 5). Although the experimental ordering of E_a ($\Delta H^‡$) is generally reproduced $(MeO)_2C$ > FCOMe > ClCOMe ≫ CCl_2) and supports the notion expressed above that $(MeO)_2C$ is a more nucleophilic carbene than FCOMe, the computed E_a value is too low for CCl_2 by ~4 kcal/mol, whereas with ClCOMe, FCOMe, and $(MeO)_2C$ the computed E_a's are too large by 3−4 kcal/mol, even though DFT generally tends to underestimate reaction barrier heights (including when B3LYP functionals are employed).[43] Inclusion of general solvation effects in the calculations via a dielectric continuum model lowers the activation energies only minimally (<1 kcal/mol),[23] because the hydrocarbon solvents used experimentally are of low dielectric constant. Also, approximate variational TS's on the free energy surfaces do not appear to differ significantly from the conventional TS's located on the potential energy surfaces.[37]

Table 7. Computed Activation Parameters for Carbene Additions[a]

carbene	alkene	E_a	$\Delta H^‡$	$\Delta S^‡$	$-T\Delta S^‡$	$\Delta G^‡$
$(MeO)_2C$	ClACN	10.6	10.0	−37	11.2	21.2
FCOMe	ClACN	9.6	9.0	−34	10.2	19.2
ClCOMe	ClACN	7.4	6.8	−35	10.4	17.2
CCl_2	ClACN	1.1	0.5	−31	9.3	9.8

[a] Units are kcal/mol for E_a, $\Delta H^‡$, $-T\Delta S^‡$, and $\Delta G^‡$; and cal(deg mol) for $\Delta S^‡$. $\Delta H^‡$, $\Delta S^‡$, and $\Delta G^‡$ are calculated at 298 K. $E_a = \Delta H^‡ + RT$; RT = 0.59 kcal/mol at T = 298.15 K. The standard state for computed $\Delta S^‡$ and $\Delta G^‡$ values was changed to better match the experimental reference state, i.e., T = 298.15 K and 1 M concentration (rather than 1 atm) for each species participating in the reaction. This reduces the computed $\Delta G^‡$ by 1.89 kcal/mol, corresponding to an increase in computed $\Delta S^‡$ of ~6.35 e.u.

Even more striking is the discrepancy between the computed and experimental values of $\Delta S^‡$. The computed values for the cyclopropanation reactions are always much more negative

(−31 to −37 e.u) than the measured values (−9 to −24 eu, Tables 4 and 5). As a result, the computed free energy barriers ($\Delta G^\ddagger$) tend to be dominated by their $-T\Delta S^\ddagger$ components, and are considerably larger than the experimental $\Delta G^\ddagger$ values. The different physical phases used as references for the calculations (idealized gas phase) and the experiments (condensed liquid phase) undoubtedly play a role in the discrepancy. The reduction in solution reaction entropies, relative to their (hypothetical) gas phase values, is presumably related at least partially to translational and rotational motions becoming more restricted in the condensed phase.[44] It appears from a simple comparison of computed and calculated values that the reduction in $\Delta S^\ddagger$ due to different reaction phases could amount to ~15−25 eu, but there does not appear to be a dependable way of applying a "condensed phase" correction to the computed results, and our current inability to rationalize the variability and trends in the measured $\Delta S^\ddagger$ values further complicates progress in this matter.

We have proposed that precoordination of the carbene to the alkene may occur in some cases with the formation of weakly bound precursor complexes, potentially promoting a change in the carbene-alkene resting state and influencing both activation energy and entropy parameters.[21] Unfortunately, as yet we have been unable to convincingly demonstrate the viability of this proposal by experiment or by computation for the present carbene-alkene sets, even though we have clearly documented the formation of stable complexes from carbenes interacting with, e.g., aromatic solvent molecules.[45] However, we would not anticipate significant complex formation to occur for a highly stabilized carbene such as $(MeO)_2C$.

We continue to actively investigate the fundamental reasons for the discrepancies between measured and calculated activation parameters in carbene reactions. Although the present discussion has focused on computations using the B3LYP set of hybrid functionals, the discrepancies between computed and measured activation parameters remain when other functionals[21] or even wave function-based methods are employed. In the Supporting Information (Table S-4) we briefly present additional results for the activation parameters pertaining to the $(MeO)_2C$/ClACN cycloaddition reaction, derived from computations with a number of different exchange-correlation functionals as well as MP2 and CCSD(T) techniques. Whereas the activation enthalpies obtained span approximately a 10 kcal/mol range, the activation entropies span a much narrower range of only 5 eu and are always much more negative than the observed value. Surely, the potential energy surfaces governing reactions of carbenes are exceedingly intricate.[46,47] Perhaps a resolution to most of the disagreements can be found from detailed considerations of the dynamics in these reactions[47] and studies of reaction trajectories instead of (or in addition to) classical transition state theory and potential energy surface calculations.[7]

8. CONCLUSION

In general, over the six carbenes of Table 1 and the six alkenes of Table 2, the evolutionary trends in E_a and $\Delta H^\ddagger$ expressed in Tables 3−5 parallel expectations based on consideration of ΔE_{stab}, $\Delta\varepsilon_E$, and $\Delta\varepsilon_N$. However, the evolutionary behavior of $\Delta S^\ddagger$ is neither as regular nor as predictable, resulting in some disorder to otherwise anticipated trends in $\Delta G^\ddagger$. In fact, there is some evidence of the operation of reciprocal behavior of $\Delta H^\ddagger$ and $\Delta S^\ddagger$. Compelling explanations for this counterintuitive pattern and the noted discrepancies between computed and measured activation parameters are currently lacking.

9. EXPERIMENTAL SECTION

Diazirines. Preparative details have been published in full for diazirines **1**−**6**. For 3,3-dichlorodiazirine (**1**), see ref 15b. For 3-chloro-3-fluorodiazirine (**2**), see the Supporting Information of ref 16a. For 3,3-difluorodiazirine (**3**), see the Supporting Information of ref 17. For 3-chloro-3-methoxydiazirine (**4**), see refs 18 and 48. For 3-fluoro-3-methoxydiazirine (**5**), see ref 19. For 3,3-dimethoxydiazirine (**6**), see ref 49.

Activation Parameters. Activation parameters are collected in Tables 3−5. The table notes provide references to the original data for CCl_2, ClCF, CF_2, ClCOMe, and FCOMe. The $(MeO)_2C$ data are described above.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures S-1−S-10, NMR spectrum of *E,Z*-**8**, Tables S-1−S-4, computational details, geometries, and energies of relevant species. This material is available free of charge via the Internet at http://pubs.acs.org.

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(41) It is unclear why, yet again, $\Delta S^\ddagger$ is more favorable for additions of the more stable carbene.

(42) The free energy difference between *trans, trans* and *cis, trans* $(MeO)_2C$ conformers is only 2.2 kcal/mol (B3LYP/6-311+G(d)), suggesting a *trans, trans/cis, trans* conformer ratio near 50 at ambient temperatures. However, the computed finding of a large barrier for interconversion of the two species ($\Delta G^\ddagger = 16.5$ kcal/mol) implies that the rate for (re)population of the *cis, trans* conformer is not competitive with the measured rate of cycloaddition product formation. It is interesting to note though, that the computed activation energy for the addition of *cis, trans* $(MeO)_2C$ to ClACN is only $E_a = 7.2$ kcal/mol ($\Delta H^\ddagger = 6.6$ kcal/mol; $\Delta S^\ddagger = -33.6$ kcal/mol).

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