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Activation Parameters for Additions of Ambiphilic Methoxychlorocarbene to Alkenes

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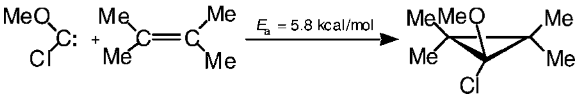
ABSTRACT



Activation parameters are determined for the additions of methoxychlorocarbene (MeOCCl) to four alkenes, including tetramethylethylene (TME). MeOCCl is the first carbene to exhibit appreciable activation energy in addition to TME (5.8 kcal/mol), although this reaction is still “dominated” by entropy ($-T\Delta S^\ddagger \approx 7$ kcal/mol).

The first applications of laser flash photolysis (LFP) to carbene−alkene additions afforded absolute rate constants[1,2] and activation parameters.[3,4] A striking feature of these early studies of phenylchlorocarbene (PhCCl)[3] and (singlet) fluorenylidene[4] was that the activation energies for additions of these carbenes to electron-rich alkenes such as tetramethylethylene (TME) and trimethylethylene were negative. A broader LFP study of the additions of five arylhalocarbenes to TME revealed that E_a ranged from −1.0 to −1.7 kcal/mol for *p*-CF_3PhCBr, PhCBr, PhCCl, and PhCF. Only with the more stabilized *p*-MeOPhCF was E_a (barely) positive at 0.2 kcal/mol.[5] Toward the less electron-rich substrate, 1-hexene, E_a was positive for all five carbenes, increasing from 0.4 kcal/mol with *p*-CF_3PhCBr to 3.1 kcal/mol with *p*-MeOPhCF.[5] For these carbenes and for fluorenylidene,[4] the free energies of activation for carbene-alkene additions ranged from 4−11 kcal/mol and were dominated by entropic rather than enthalpic contributions.[5,6]

The dominance of entropy in carbene−TME additions was not surprising: on the basis of measured *relative* activation parameters, Skell had already suggested that CCl_2 additions to highly substituted alkenes would be entropy-controlled.[7] Similar conclusions followed from computational studies by Houk[8] and Jorgensen[9] and from experimental work by Giese.[10] However, Giese[10] and Houk[8] predicted that enthalpic factors would dominate $\Delta G^\ddagger$ for alkene additions of the more stabilized CF_2.

In 1980, Rondan et al. provided a quantitative measure of carbene stability, ΔE_{stab}, defined as the negative of the computed 4-31G energies of the isodesmic reaction (eq 1).[11]

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ΔE_{stab} values (in kcal/mol) for several carbenes of interest here are $\mathrm{CCl_2}$, 26.5; CClF, 42.8; $\mathrm{CF_2}$, 62.8; and MeOCCl, 60.3.[11]

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

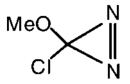
ΔE_{stab} reflects resonance electron donation from the carbene's substituents to its vacant p orbital, so that carbenic selectivity between alkenes, and presumably E_a for alkene addition, depend on the donor properties of the carbenic substituents.[11] Therefore, from either ΔE_{stab} of CXY, or $\Sigma\sigma^{+}{}_{\mathrm{R}}$ of X and Y, E_a for the addition of CXY to, e.g., TME should increase in the order $\mathrm{CCl_2} < \mathrm{CClF} < \mathrm{CF_2} \approx \mathrm{MeOCCl}$.

Recently, we measured activation parameters for the additions of PhCCl, $\mathrm{CCl_2}$, and CClF to TME, cyclohexene, and 1-hexene.[12] Additions of PhCCl to cyclohexene or 1-hexene were dominated by entropic contributions to $\Delta G^{\ddagger}$, additions of $\mathrm{CCl_2}$ displayed comparable contributions of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, and CClF additions featured dominant contributions of $\Delta H^{\ddagger}$ to $\Delta G^{\ddagger}$. However, entropy governed the additions of all three carbenes to the highly reactive TME.[12] Indeed, even for the moderately stabilized CClF, with $\Delta E_{\mathrm{stab}} = 42.8$ kcal/mol,[11] $\Delta H^{\ddagger}$ for addition to TME was only 0.3 kcal/mol.[12,13]

Both $\mathrm{CF_2}$ ($\Delta E_{\mathrm{stab}} = 62.8$ kcal/mol[11]) and MeOCCl ($\Delta E_{\mathrm{stab}} = 60.3$ kcal/mol[11]) are significantly more stabilized than CClF. Will these carbenes exhibit appreciable activation energies in additions to TME? Results for $\mathrm{CF_2}$ are not yet available, but we demonstrate here that MeOCCl does indeed display significant activation energy and enthalpy in this reaction.

MeOCCl is an ambiphile; the energies of its HOMO and LUMO orbitals are such that it reacts rapidly with either electron-rich alkenes (e.g., TME) or electron-poor alkenes (e.g., acrylonitrile), while reacting slowly with unexceptional alkenes such as *trans*-butene.[14] The absolute rate constant for its addition to the very electron-poor alkene chloroacrylonitrile (ClACN) was measured in pentane as 5.6×10^{5} $\mathrm{M^{-1}\ s^{-1}}$, following the decay of the carbene's weak absorbance at 310 nm as a function of alkene concentration.[15] However, the less reactive acrylonitrile or TME did not quench the MeOCCl absorbance, so that additional "absolute" rate constants were derived[15] by combining the ClACN absolute rate constant with *relative* rate constants obtained for other alkenes by classical competition experiments.[16] We thus derived k_{abs} ($\mathrm{M^{-1}\ s^{-1}}$) for additions of MeOCCl to TME (4.2×10^{3}), isobutene (1.8×10^{3}), *trans*-butene (3.3×10^{2}), methyl acrylate (9.8×10^{3}), and acrylonitrile (1.8×10^{4}).[15]

Here, we employ an analogous combination of absolute and relative kinetics to derive activation parameters for MeOCCl additions. We first redetermined k_{abs} for the MeOCCl−ClACN addition by LFP of methoxychlorodiazirine[17] (**1**) using the pyridine ylide method[18] because the absorbance of the MeOCCl-pyridine ylide at 472 nm[19] is considerably stronger than that of the MeOCCl signal at 310 nm.[15] LFP experiments were conducted with [pyridine] = 0.5 M in 1,2-dichloroethane (DCE), where the solubilities of pyridine and ClACN are greater than in pentane. The k_{abs} were determined at six concentrations of ClACN, varied between 0 and 2.5 M, and at approximate temperatures of −10, 0, 10, 25, and 30 °C. Precise temperatures (±0.1 °C) were ascertained at the instant of LFP via a thermocouple immersed in the reaction solution.



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Activation parameters were calculated from the rate constant−temperature data of two independent sets of measurements.[20] Figure 1 illustrates one of the two Arrhenius correlations. The Supporting Information contains graphical displays of the E_a correlations and of the primary kinetic data (Figures S-1 to S-12).

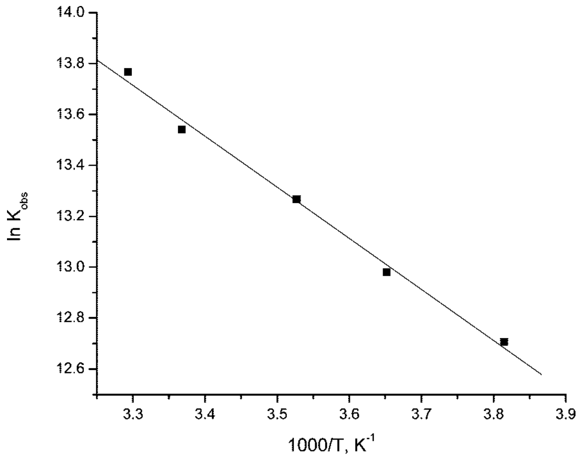

Figure 1. Activation energy for addition of MeOCCl to chloroacrylonitrile: $E_a = 3.98$ kcal/mol; $A = 6.76 \times 10^{8}$ $\mathrm{M^{-1}\ s^{-1}}$; $r = -0.997$.

From the Arrhenius correlations (Figures S-1 and S-7, Supporting Information), we find E_a for the addition of MeOCCl to ClACN to be 3.9 ± 0.06 kcal/mol, $\log A = 8.79 \pm 0.04$ $\mathrm{M^{-1}\ s^{-1}}$, and $\Delta S^{\ddagger} = -20.2 \pm 0.2$ eu. These values

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(13) Additions of PhCCl and $\mathrm{CCl_2}$ to TME exhibited negative values of $\Delta H^{\ddagger}$ (−2.3 and −1.8 kcal/mol, respectively).[12]

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(20) See, for example: Moss, R. A.; Tian, J.; Sauers, R. R.; Skalit, C.; Krogh-Jespersen, K. *Org. Lett.* **2007**, *9*, 4053.

Table 1. Activation Parameters for MeOCCl−Alkene Additions[a]

alkene[b]	E_a	log A	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$-T\Delta S^\ddagger$	$\Delta G^\ddagger$
ClACN	3.9 (0.06)	8.8(0.04)	3.4 (0.04)	−20.2 (0.2)	6.0 (0.2)	9.4 (0.2)
ACN	6.4	9.1	5.8	−18.9	5.6	11.4
TME	5.8	8.0	5.2	−24.0	7.2	12.4
MeAcr	7.0	9.0	6.4	−19.2	5.7	12.1

[a] In dichloroethane. 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; cal/(deg-mol) for $\Delta S^\ddagger$. $\Delta H^\ddagger$ is calculated at 283 K; $\Delta G^\ddagger$ is calculated at 298 K. Errors (in parentheses) are average deviations of two independent determinations. In all other cases, errors in the data are estimated at 10−15%. [b] ClACN = chloroacrylonitrile; ACN = acrylonitrile; TME = tetramethylethylene; MeAcr = methyl acrylate

and derived values for $\Delta H^\ddagger$ and $\Delta G^\ddagger$ appear in Table 1.

Next, we determined the kinetics and activation parameters for the addition of MeOCCl to acrylonitrile (ACN) *relative* to ClACN. MeOCCl was generated by photolysis of methoxychlorodiazirine ($A_{348} \approx 1.0$) in excess ClACN and ACN in DCE. The temperature was controlled by a circulating bath. After 3 h of photolysis[21] with a focused UV lamp ($\lambda > 300$ nm), capillary GC analysis of the known[14a,15] product cyclopropanes, coupled with standard competition reaction analysis,[16] gave the relative rate constants for addition of MeOCCl to ClACN versus ACN at various temperatures (cf. Table S-1 in Supporting Information).[22] Note that $k_{\mathrm{ClACN}}/k_{\mathrm{ACN}} = 33.1$ at 24.9 °C, in excellent agreement with the reported value of 33.7 at 25 °C.[15]

An Arrhenius plot of ln($k_{\mathrm{ACN}}/k_{\mathrm{ClACN}}$) versus $1/T$ is shown in Figure 2. A good correlation ($r = 0.997$) is found for eight relative rate contants measured at temperatures between −8.7 and 30.0 °C. Values of $\Delta E_a = 2.45$ kcal/mol, Δ log $A = 0.275$ M^{-1} s^{-1}, and $\Delta\Delta S^\ddagger = 1.26$ eu are obtained from the slope and intercept of the correlation. Combined with the absolute activation parameters measured for ClACN (Table 1), we obtain the following activation parameters for ACN: $E_a = 6.4$ kcal/mol, log $A = 9.1$ M^{-1} s^{-1}, and $\Delta S^\ddagger = -18.9$ eu. These data appear in Table 1, together with derived values of $\Delta H^\ddagger$ and $\Delta G^\ddagger$.

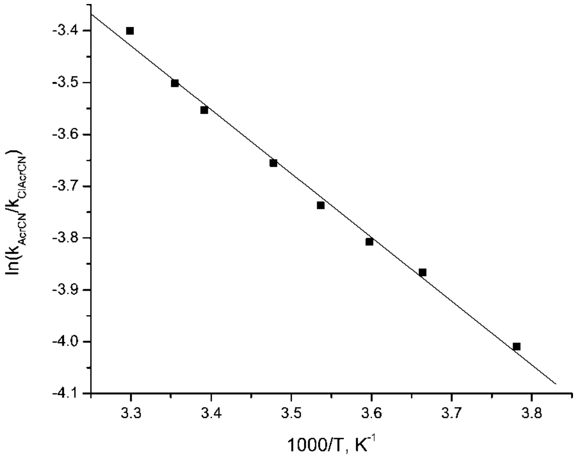

Figure 2. Differential activation energy for the competitive addition of MeOCCl to acrylonitrile versus chloroacrylonitrile: $\Delta E_a = 2.45$ kcal/mol; Δ log $A = 0.275$ M^{-1} s^{-1}; $r = -0.997$.

We similarly determined rate constants and activation parameters for additions of MeOCCl to TME, relative to ACN. We separately established that the MeOCCl−TME reaction product, 1-chloro-1-methoxy-2,2,3,3-tetramethylcyclopropane[14a] was stable to the reaction and analytical conditions. Both NMR and GC demonstrated its stability after 2 h at 80 °C in TME/pyridine. Relative rate constants, $k_{\mathrm{ACN}}/k_{\mathrm{TME}}$, determined at five temperatures between −8.9 and 30.0 °C, are collected in Table S-2 in Supporting Information.[22] Note that $k_{\mathrm{ACN}}/k_{\mathrm{TME}} = 4.84$ at 20.3 °C, in reasonable agreement with the value of 4.33 at 25 °C which can be calculated from literature data.[14a]

An Arrhenius plot of ln($k_{\mathrm{TME}}/k_{\mathrm{ACN}}$) versys $1/T$ appears in Figure S-13, based on the data of Table S-2 (Supporting Information). This satisfactory correlation ($r = 0.964$) affords $\Delta E_a = -0.57$ kcal/mol) Δ log $A = -1.12$ M^{-1} s^{-1}, and $\Delta\Delta S^\ddagger = -5.13$ eu. Combined with the “absolute” activation parameters derived from ACN (above and Table 1), the corresponding values for TME are $E_a = 5.8$ kcal/mol, log $A = 8.0$ M^{-1} s^{-1}, and $\Delta S^\ddagger = -24.0$ eu. These values appear in Table 1, together with derived values for $\Delta H^\ddagger$ and $\Delta G^\ddagger$.

Lastly, rate constants and activation parameters were determined for additions of MeOCCl to methyl acrylate (MeAcr), relatiave to ACN. Details and data appear in Table S-3 in Supporting Information.[22] An Arrhenius plot of ln($k_{\mathrm{MeAcr}}/k_{\mathrm{ACN}}$) versus $1/T$ appears in Figure S-14. A good correlation ($r = -0.988$), obtained for five relative rate constants determined at temperatures between −6.7 and 29.5 °C, affords $\Delta E_a = 0.62$ kcal/mol, Δ log $A = -0.0656$ M^{-1} s^{-1}, and $\Delta\Delta S^\ddagger = -0.30$ eu. Combined with the activation parameters for ACN in Table 1, we obtain for MeAcr: $E_a = 7.0$ kcal/mol, log $A = 9.0$ M^{-1} s^{-1}, and $\Delta S^\ddagger = -19.2$ eu. These values appear in Table 1, together with derived values for $\Delta H^\ddagger$ and $\Delta G^\ddagger$.

A satisfactory cross-check experiment[16] linked the relative reactivities of the ACN, MeAcr, and TME triad. A calculated value for $k_{\mathrm{MeAcr}}/k_{\mathrm{TME}}$ is given by ($k_{\mathrm{MeAcr}}/k_{\mathrm{ACN}}$) × ($k_{\mathrm{ACN}}/k_{\mathrm{TME}}$). Substituting the appropriate values from Tables S-3 and S-2 (at 19.3 and 20.3 °C) leads to $k_{\mathrm{MeAcr}}/k_{\mathrm{TME}} = 0.301 \times 4.84 =$

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(21) UV analysis indicated that the diazirine was absent after 3 h of photolysis.

(22) Analytical details appear in the table. The Supporting Information also includes GC traces and ^{1}H NMR spectra of these known[14a,15] cyclopropanes as indicators of identity and reaction efficiency.

1.46. A direct determination of this relative rate constant at 20.1 °C gives 1.52, in excellent agreement with the calculated value.

The following conclusions can be drawn: (1) As shown in Table 1, there is an appreciable positive activation energy of ~6 kcal/mol for addition of MeOCCl to TME. MeOCCl is the first carbene demonstrated to encounter a substantial energy barrier in addition to this reactive and nucleophilic alkene,[12] behavior in keeping with expectations based on the high ΔE_{stab} calculated for MeOCCl.[11] For the triad of carbenes CCl_2, CClF, and MeOCCl, E_a and $\Delta H^\ddagger$ for addition to TME increase with increasing ΔE_{stab}.[11,12]

(2) Table 1 also indicates that $\Delta S^\ddagger$ for the MeOCCl−TME addition exceeds $\Delta S^\ddagger$ for additions to the three other alkenes by 4−5 eu. Steric problems may be associated with this disparity; TME is tetrasubstituted, whereas the other three (electrophilic) alkenes each possess an unencumbered CH_2 double bond terminus. The data also reflects the ambiphilicity[14] of MeOCCl: E_a is lowest for addition of MeOCCl to the highly electrophilic ClACN, an alkene known to be an exceptional substrate for ambiphilic and nucleophilic carbenes.[23]

(3) The $\Delta G^\ddagger$ values in Table 1 accord with the observed alkene reactivities toward MeOCCl at ambient temperature,[14a,15] ClACN > ACN > MeAcr > TME. Considering the relative contributions of $\Delta H^\ddagger$ and $T\Delta S^\ddagger$ to $\Delta G^\ddagger$, MeOCCl addition to MeAcr is marginally controlled by enthalpy, its addition to ACN displays comparable enthalpic and entropic components, while its additions to TME and ClACN are dominated by entropy. Even though the MeOCCl/TME reaction manifests an appreciable $\Delta H^\ddagger$ (~5 kcal/mol), it remains an entropy-dominated addition with $-T\Delta S^\ddagger \approx 7$ kcal/mol.

We are continuing our studies of the dependence of activation parameters for carbene-alkene addition reactions on the structures of the carbenes and alkenes. A broad computational study of carbene-alkene addition reactions is ongoing; results will be reported in due course.[24]

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Supporting Information Available: Figures S-1−S-14, Tables S-1−S-3, and GC traces and NMR spectra of the cyclopropane products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[24] Krogh-Jespersen, K.; Moss, R. A. Work in progress. At this time, the computational and experimental results are not fully congruent. It therefore seems preferable to reserve a comparative discussion for the full paper.