JOC The Journal of Organic Chemistry

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Reactivity of Chlorotrifluoromethylcarbene: Activation Parameters for Halocarbene−Alkene Addition Reactions

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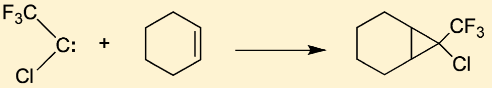
Supporting Information

ABSTRACT: Activation parameters are reported for $ClCCF_3$ additions to three alkenes (tetramethylethylene, cyclohexene, and 1-hexene). The results are compared to those for CCl_2, CClF, and CF_2. Activation enthalpies decrease as the carbene stability decreases and its electrophilicity increases, and also as alkene reactivity (degree of alkylation) increases. Activation entropies decrease in parallel with activation enthalpies, suggesting the operation of enthalpy−entropy compensation in these carbene additions.



E_a = 2.6 kcal/mol; $\Delta H^‡$ = 2.1 kcal/mol; $\Delta S^‡$ = -18 eu

1. INTRODUCTION

The archetypal dihalocarbenes CCl_2, CClF, and CF_2 manifest important relationships among structure, stability, and selectivity, as shown in Table 1.[1−7] Computed stabilization energies relative to CH_2 (ΔE_{stab})[4,8] decrease in the order CF_2 > CClF > CCl_2, spanning an energy range of approximately 25 kcal mol^{-1}. Simultaneously, the global electrophilicities (ω)[6,7] of these carbenes increase in the opposite order, driven by decreasing LUMO (ε_{LU}) and concurrently increasing HOMO (ε_{HO}) energies. In parallel, the carbenes become less discriminating toward alkenes, as measured by the carbene selectivity index, m_{CXY}.[5]

Table 1. Quantitative Measures of Carbene Reactivity

carbene	ε_{LU} [a]	ε_{HO} [a]	ΔE_{stab} [b]	ω [c]	m_{CXY} [d]
$ClCCF_3$	0.57	−11.30	21.3	1.21	0.31
CCl_2	1.00	−10.91	45.5	1.03	0.97
CClF	1.74	−11.71	56.1	0.92	1.22
CF_2	2.74	−12.85	70.9	0.82	1.47

[a] In eV. Calculated at the HF/6-31G(d,p)//MP2/6-31G(d,p) level; see ref 7. [b] In kcal mol^{-1}. Defined as the negative of the reaction energy for $CH_2 + CH_3X + CH_3Y \rightarrow CXY + 2CH_4$, computed here at the B3LYP/6-311++G(2d,p) level; see ref 4. [c] In eV. ω = global electrophilicity = $(\varepsilon_{LU} + \varepsilon_{HO})^2/[8(\varepsilon_{LU} - \varepsilon_{HO})]$, computed here at the HF/6-31G(d,p)//MP2/6-31G(d,p) level; see refs 6 and 7. [d] Calculated carbene selectivity index; see ref 5.

Most importantly, activation energies and enthalpies for additions of these dihalocarbenes to tetramethylethylene (TME), cyclohexene, and 1-hexene decrease in the same order (CF_2 > CClF > CCl_2).[1−4,9] Moreover, from the available data, there appears to be *compensation* between $\Delta H^‡$ and $\Delta S^‡$ in these carbene-alkene additions: as $\Delta H^‡$ decreases, $\Delta S^‡$ also decreases ($-T\Delta S^‡$ increases), thus mitigating the impact on $\Delta G^‡$. Activation enthalpy−entropy compensation might signify a mechanistically meaningful "extrathermodynamic" relation between $\Delta H^‡$ and $\Delta S^‡$,[10] or it might be an artifact.[11] More information is required to assess the extent, persistence, and possible significance of enthalpy−entropy compensation in carbene−alkene addition reactions.

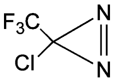
We chose to examine the reactions of chlorotrifluoromethylcarbene ($ClCCF_3$) for several reasons. (1) As shown in Table 1, $ClCCF_3$ is an extremum relative to the other carbenes. It is less stable than CCl_2 by a computed 24 kcal mol^{-1}, possesses a lower energy LUMO than CCl_2 by 0.4 eV, is more electrophilic on the ω scale, and is significantly less selective than CCl_2 by both calculated and experimental m_{CXY} values.[12,13] (2) $ClCCF_3$ is readily generated from the corresponding diazirine, and its addition reactions with alkenes are clean and well-characterized.[12] (3) $ClCCF_3$ is predicted to be a ground-state singlet with an adiabatic singlet−triplet energy separation of 4.6 kcal mol^{-1} according to calculations at the CCSD(T)/6-311+G(2df)//B3LYP/6-311+G(2df) level of theory; see the Supporting Information. This prediction agrees with experimental observations of stereospecific $ClCCF_3$ additions to *cis*- and *trans*-butene[12] and validates comparisons of $ClCCF_3$ to the other singlet halocarbenes of Table 1. (4) $ClCCF_3$ is also of interest in connection with synthetic studies of trifluoromethyl-substituted cyclopropanes.[14]

The results reported herein for the minimally stabilized, highly reactive, and strongly electrophilic $ClCCF_3$ significantly widen the breadth of $\Delta H^‡/\Delta S^‡$ interrogations of carbene-alkene addition reactions.

2. RESULTS AND DISCUSSION

We generated $ClCCF_3$ by laser flash photolysis (LFP) at 351 nm of 3-chloro-3-trifluoromethyldiazirine (**1**)[12,15] in pentane. The carbene was visualized by means of its isoquinoline ylide (**2**),[16] which absorbed strongly at 404 nm (major absorptions

Received: September 16, 2013
Published: October 8, 2013



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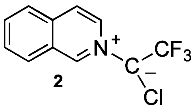

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predicted at 441 nm (f = oscillator strength = 0.09) and at 380 nm (f = 0.63) via a TD-B3LYP/6-311++G(2d,p)//B3LYP/6-311++G(2d,p) calculation with simulated pentane solvent (CPCM model). The LFP UV−vis spectrum of **2** appears in Figure 1.

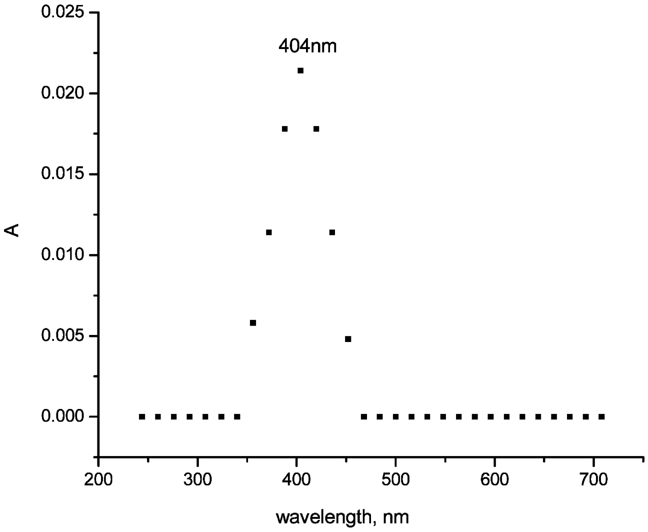

Figure 1. UV−vis spectrum of isoquinoline ylide of $ClCCF_3$ in pentane (404 nm): [isoquinoline] = 0.42 M; A(**1**) = 0.5, 120 ns after laser flash.

Absolute rate constants for the additions of $ClCCF_3$ to alkenes were measured by the ylide method,[16] wherein the apparent rate of formation of ylide **2** is accelerated by the addition of an alkene at a constant concentration (0.42 M) of isoquinoline. Correlation of the observed rate constants for the formation of **2** vs [alkene] produces a straight line, whose slope is k_{add} for the addition of $ClCCF_3$ to the alkene.[17] Figure 2 illustrates the determination of the rate constant for addition of $ClCCF_3$ to TME at 300 K. A very good linearity is observed between the apparent rate of formation of ylide **2** and the concentration of TME (r = 0.997). The slope of the correlation gives $k_{add} = 1.83 \times 10^9$ M^{-1} s^{-1}.

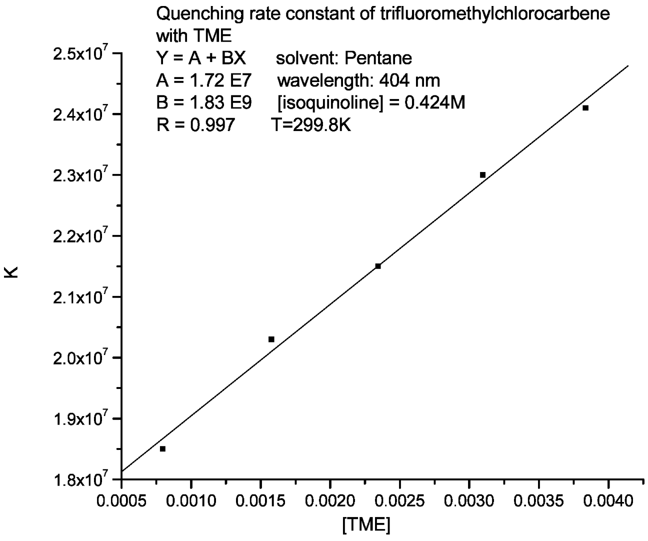

Figure 2. Determination of the rate constant for addition of $ClCCF_3$ to TME in pentane at 299.8 K: $k = 1.83 \times 10^9$ M^{-1} s^{-1}, r = 0.997.

Analogous correlations for determinations of k_{add} for $ClCCF_3$ with trimethylethylene, cyclohexene, and 1-hexene are shown in Figures S-1−S-3 in the Supporting Information. Rate constants for the additions of $ClCCF_3$ to the four alkenes appear in Table 2, where they are compared to analogous data for CCl_2,[18,19] CClF,[18] and CF_2.[2]

Table 2. Rate Constants for Carbene Additions[a]

alkene[b]	$ClCCF_3$	CCl_2[c]	CClF[d]	CF_2[e]
TME	1.8×10^9	4.7×10^9	1.2×10^9	6.4×10^8
Tri-Me	2.2×10^8	2.5×10^9	3.8×10^8	1.3×10^8
c-C_6H_{10}	2.6×10^7	6.4×10^7	2.7×10^7	1.4×10^7
1-hex	2.0×10^7	1.8×10^7	1.1×10^7	2.4×10^6

[a] From diazirine photolyses in pentane at 24 °C, except $ClCCF_3$ at 27 °C. Variation in rate constants (M^{-1} s^{-1}) is ≤10%; correlation coefficients are ≥0.994. [b] Alkenes: TME = tetramethylethylene; Tri-Me = trimethylethylene; c-C_6H_{10} = cyclohexene; 1-hex =1-hexene. [c] References 18 and 19. [d] Reference 18. [e] Reference 2.

As expected, $ClCCF_3$ is electrophilic; k_{add} increases as the alkene substrate becomes more heavily alkylated or nucleophilic. However, given its lower stability and greater electrophilicity relative to CCl_2 (Table 1), it is surprising that $ClCCF_3$ reacts more slowly than CCl_2 with the alkenes TME, trimethylethylene, and cyclohexene (Table 2; for 1-hexene, the rates of addition for $ClCCF_3$ and CCl_2 are comparable). It is tempting to ascribe this to "steric effects" originating at the larger CF_3 substituent present in $ClCCF_3$. It is known, however, that $ClCCF_3$ experiences *less* steric retardation than CCl_2 in additions to $RCH{=}CH_2$ (where R = Et, *i*-Pr, *t*-Bu): Taft steric susceptibility values (δ) are 0.41 for $ClCCF_3$ vs 0.88 for CCl_2.[12,20,21] A conventional rationalization of these results is that the destabilized, highly reactive $ClCCF_3$ adds to alkenes via earlier, more "open," less sterically demanding transition states than the more stabilized, less reactive CCl_2.[12] In reality, however, the lower reactivity of $ClCCF_3$ vs CCl_2 toward (e.g.) TME or cyclohexene is due to *very unfavorable entropies of activation* in the addition reactions (see below).

Activation parameters for $ClCCF_3$ additions to TME, cyclohexene, and 1-hexene in pentane were obtained from LFP determinations of k_{add} at five temperatures between 283 and 309 K.[17,22] Precise temperatures (±0.1 K) were determined at the instant of LFP via a thermocouple immersed in the reaction solution. The resulting Arrhenius correlations are shown in Figures 3−5, and the k_{add} determinations on which they are based appear in Figures S-4−S-17 in the Supporting Information.

The Arrhenius correlations are of good quality, with r ranging from 0.990 to 0.998. Values of E_a and A were obtained from the slope and intercept, respectively, of each correlation line, and converted to $\Delta H^\ddagger$ and $\Delta S^\ddagger$ by standard formulas.[23] Results for $ClCCF_3$, as well as for CCl_2, CClF, and CF_2, are collected in Table 3.[24]

Anticipated trends[25] in activation enthalpies $\Delta H^\ddagger$ are clearly expressed in Table 3. Values of E_a (and hence $\Delta H^\ddagger$) decrease with each alkene in the order of decreasing carbene stability: $ClCCF_3 < CCl_2 < CClF < CF_2$. $\Delta H^\ddagger$ is largest for each carbene with 1-hexene and smallest with TME. With TME, additions of

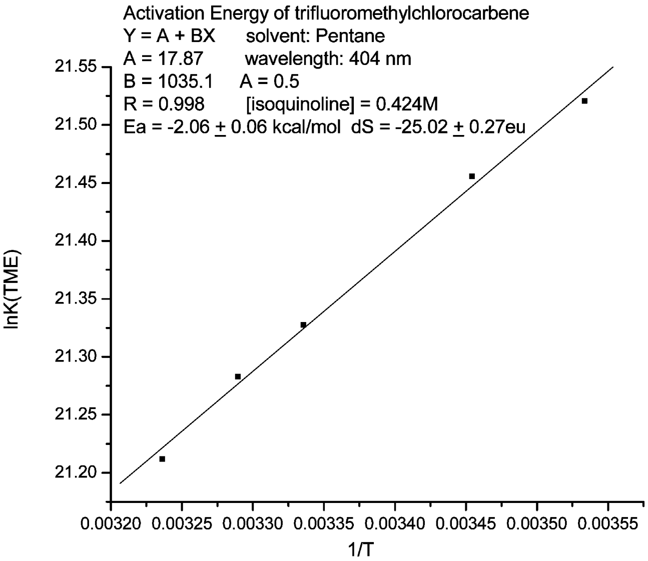

Figure 3. Determination of the activation energy for addition of $ClCCF_3$ to TME: $E_a = -2.06$ kcal mol^{-1}, log $A = 7.8$ M^{-1} s^{-1}, $r = 0.998$.

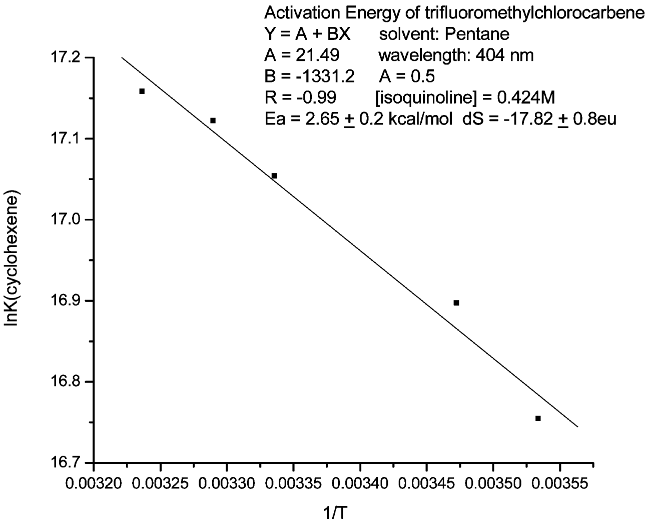

Figure 4. Determination of the activation energy for addition of $ClCCF_3$ to cyclohexene: $E_a = 2.65$ kcal mol^{-1}; log $A = 9.3$ M^{-1} s^{-1}, $r = -0.990$.

$ClCCF_3$ and CCl_2 exhibit negative values of $\Delta H^{\ddagger}$ (and E_a); barriers to these additions appear in $\Delta G^{\ddagger}$ and are a consequence of strongly negative $\Delta S^{\ddagger}$ values.[25b−d] Similar behavior is observed in the additions of phenylhalocarbenes to TME.[25e]

Indeed, $\Delta S^{\ddagger}$ is dominant in the additions of $ClCCF_3$ to all three alkenes; in each case, $-T\Delta S^{\ddagger}$ makes a larger contribution to $\Delta G^{\ddagger}$ than does $\Delta H^{\ddagger}$. (This is also true of the additions of CCl_2, CClF, and CF_2 to TME; cf. Table 3.)

Most intriguingly, compensation between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ persists upon extension of scrutiny to $ClCCF_3$: with each alkene, and for all four carbenes, $\Delta S^{\ddagger}$ decreases as $\Delta H^{\ddagger}$ decreases. From the pairing of the most stabilized carbene and least reactive alkene (CF_2 + 1-hexene) to that of the least stabilized carbene and most reactive alkene ($ClCCF_3$ + TME), $\Delta H^{\ddagger}$ decreases by 10 kcal mol^{-1} while $\Delta S^{\ddagger}$ decreases by 21 eu. Hence, $\Delta G^{\ddagger}$ decreases by only 4 kcal mol^{-1} across the full set of carbene−alkene combinations, because the decreasing $\Delta H^{\ddagger}$ value is offset by an increasing $-T\Delta S^{\ddagger}$ value. $\Delta H^{\ddagger}$ for $ClCCF_3$ addition to TME, cyclohexene, or 1-hexene is more favorable than for CCl_2 addition, but the decrease in $\Delta H^{\ddagger}$ is opposed by an even larger (or comparable, in the case of 1-hexene) change in $-T\Delta S^{\ddagger}$. Consequently, $ClCCF_3$ is less reactive than CCl_2 when adding to TME or cyclohexene.

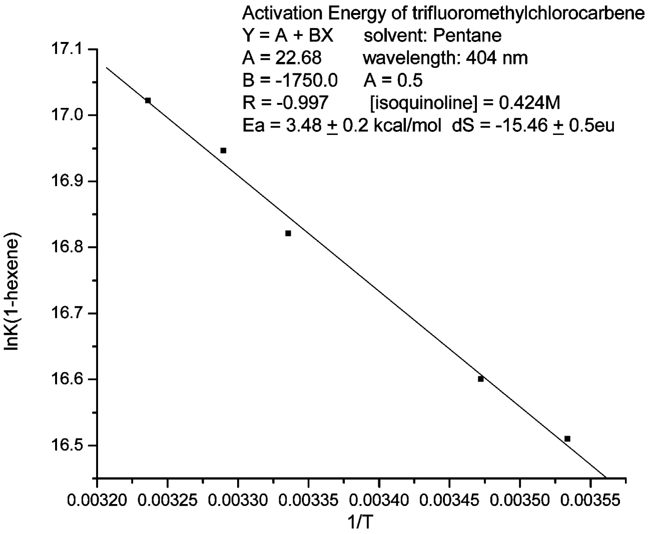

Figure 5. Determination of the activation energy for addition of $ClCCF_3$ to 1-hexene: $E_a = 3.48$ kcal mol^{-1}, log $A = 9.8$ M^{-1} s^{-1}, $r = -0.997$.

In the abstract, parallel decreases in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in a set of related reactions are not surprising: "for each mechanism of interaction between molecules...the maximum reduction in energy for the system is obtained only if certain geometrical conditions are met. The geometrical conditions of course constitute a constraint and mean that the decrease will be accompanied by some decrease in entropy."[10] Indeed, a linear correlation with a positive slope is frequently observed between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in a series of related reactions.[10] In the present case, we find fair $\Delta H^{\ddagger}/\Delta S^{\ddagger}$ correlations for the three alkene−carbene reaction sets of Table 3 (Figure 6). The slopes of these correlation lines (the isokinetic temperatures) range from 310 to 384 K, bracketing the "isoselective" temperature of 360 K observed for the competitive additions of various dihalocarbenes to trimethylethylene−isobutene.[26]

We caution that $\Delta H^{\ddagger}/\Delta S^{\ddagger}$ correlations are subject to substantial error propagation and are often spurious.[11] Even ignoring these correlations, however, the marked parallel decreases in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ between the CF_2 + 1-hexene and $ClCCF_3$ + TME pairings in Table 3 are far beyond experimental error, supporting some form of enthalpy−entropy compensation operating in these carbene−alkene additions. Such compensation appears contrary to Hammond-based conceptions of these reactions, in which $\Delta S^{\ddagger}$ should *increase* as the carbene's reactivity increases and its addition reaction transition state becomes earlier and more open.[25]

Currently available conventional electronic structure techniques (ab initio or DFT) are not adequate for the study of these halocarbene−alkene addition reactions, which feature very small (or even negative) enthalpy barriers.[1] Fundamental discrepancies exist between experimental and computed activation parameters. In particular, computed gas-phase activation entropies for halocarbene−olefin additions are

Table 3. Activation Parameters for Carbene Additions[a]

carbene	alkene[b]	E_a	log A	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$-T\Delta S^\ddagger$	$\Delta G^\ddagger$
$ClCCF_3$[c]	TME	−2.1	7.8	−2.6	−25	7.4	4.8 (0.1)
CCl_2[d]	TME	−1.2	8.8	−1.8	−20	6.0	4.2 (0.2)
CClF[d]	TME	0.9	9.7	0.3	−16	4.7	5.0 (0.2)
CF_2[e]	TME	3.0	11.0	2.5	−10	3.0	5.5 (0.3)
$ClCCF_3$[c]	c-C_6H_{10}	2.6	9.3	2.1	−17.8	5.3	7.4 (0.6)
CCl_2[d]	c-C_6H_{10}	3.8	10.9	3.3	−10.5	3.1	6.4 (0.4)
CClF[d]	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)
$ClCCF_3$[c]	1-hex	3.5	9.8	2.9	−15.5	4.6	7.5 (0.5)
CCl_2[d]	1-hex	4.7	10.7	4.1	−11.5	3.4	7.5 (0.4)
CClF[d]	1-hex	6.0	11.5	5.4	−7.8	2.3	7.7 (0.3)
CF_2[e]	1-hex	8.0	12.4	7.4	−3.9	1.1	8.6 (0.1)

[a] Units are kcal mol^{-1} for E_a, $\Delta H^\ddagger$, $-T\Delta S^\ddagger$, and $\Delta G^\ddagger$, M^{-1} s^{-1} for log A, and cal deg^{-1} mol^{-1} for $\Delta S^\ddagger$. $\Delta H^\ddagger$ is determined at 283 K; $\Delta G^\ddagger$ is calculated at 298 K. $E_a = \Delta H^\ddagger + RT$. Errors are 0.2−0.3 kcal mol^{-1} or less in E_a, and errors in $\Delta S^\ddagger$ are ~1 eu; errors are shown in parentheses for $\Delta G^\ddagger$. [b] Abbreviations: TME = tetramethylethylene, *c*-C_6H_{10} = cyclohexene, 1-hex = 1-hexene. [c] This work; correlation coefficients were ≥0.990. [d] From ref 1. [e] From ref 2.

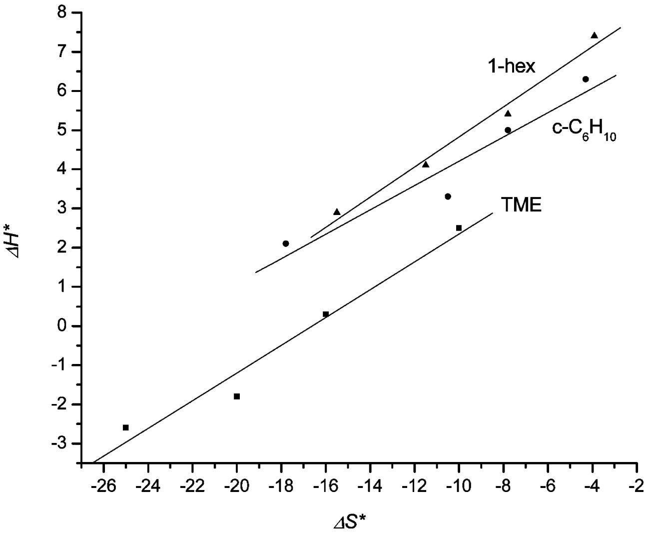

Figure 6. Plots of $\Delta H^\ddagger$ vs $\Delta S^\ddagger$ for the additions of $ClCCF_3$, CCl_2, CClF, and CF_2 to TME, cyclohexene, and 1-hexene. Data are taken from Table 3. Isokinetic temperatures (slopes) and correlation coefficients: TME, 354 K, $r = 0.983$; cyclohexene, 310 K, $r = 0.961$; 1-hexene, 384 K, $r = 0.992$.

consistently found to be considerably more negative than measured solution entropies.[1,4] We have proposed that for some carbene−olefin pairs precoordination may occur with the formation of weakly bound π complexes,[1] and we have clearly documented the formation of stable π complexes from carbenes interacting with a number of arenes.[27] However, we have not been able to detect analogous halocarbene−alkene complexes or provide truly compelling computational evidence for their existence. For the present carbene−alkene set, computational attempts at locating precursor π-type complexes or TS's for cycloaddition failed at both DFT (B3LYP and M06-2X functionals, 6-311+G(d) basis sets) and ab initio (MP2/6-311+G(d)) levels; only product cyclopropanes or loosely associated $ClCCF_3$−alkene species resulted from many searches of the potential energy surfaces, initiated at assorted trial geometries. Any specific role(s) of solvent influencing the activation parameters also needs to be elucidated. A carefully calibrated quantum mechanical (or QM/MM) molecular dynamics approach could be rewarding in highlighting the reasons behind, and possibly even resolving, these discrepancies,[28] although the need to evaluate both enthalpic and entropic contributions in solution makes daunting the prospect of studying the dynamic barriers present in formally barrierless reactions.

At the very least, however, the present results with $ClCCF_3$, in which the span of carbene stabilization energies has been broadened, reinforce the existence of an important and as yet unresolved conundrum in carbene−alkene additions.

3. CONCLUSION

Activation parameters are reported for $ClCCF_3$ additions to three alkenes (tetramethylethylene, cyclohexene, and 1-hexene). The results are compared to those for CCl_2, CClF, and CF_2. Activation enthalpies decrease (CF_2 > CClF > CCl_2) as the carbene stability decreases and also as alkene reactivity (TME > cyclohexene >1-hexene) increases. Activation entropies decrease in parallel with activation enthalpies, suggesting the operation of enthalpy−entropy compensation in these carbene additions.

4. EXPERIMENTAL SECTION

Preparative details have been published in full for 3-chloro-3-trifluoromethyldiazirine (**1**).[12,15] LFP experiments employed a Coherent Compex 120 excimer laser operating at 351 nm (XeF_2) emitting 42−56 ns light pulses with 55−65 mJ power. The detection system featured an Applied Photophysics #720 150 W pulsed xenon lamp with an ARC 620 lamp ignitor and an ARC 0-3-102 lamp pulser, a 1 in. Uniblitz shutter, and a Uniblitz 100-2B shutter drive control, an Instruments SA grating monochromator, and a RCA 4840 photomultiplier tube wired in a five-dynode configuration. Data collection and analysis utilized a Stanford Research Systems DG535 four-channel digital delay/pulse generator and a Tektronix TDA 520A two-channel digitizing oscilloscope. Data analysis used the Igor Pro 4.01 program (Wave Metrics, Inc.).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving kinetics and activation parameter data and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the National Science Foundation for financial support.

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(20) Even in the *syn*-CF_3 addition mode, δ for $ClCCF_3$ addition to $RCH{=}CH_2$ is less than δ for CCl_2: 0.47 vs 0.88.[12] (δ is 0.39 for $ClCCF_3$ addition in the *syn*-Cl mode.)

(21) $ClCCF_3$ manifests *syn*-Cl stereoselectivity toward alkenes: *syn*-Cl/*syn*-CF_3 ratios are 1.48 for trimethylethylene, 1.65 for *cis*-butene, 1.28 for 1-butene, 1.36 for isopropylethylene, and 1.66 for *tert*-butylethylene.[12] We did not determine the stereoselectivity for $ClCCF_3$ additions to 1-hexene or cyclohexene, but the previous results suggest that these selectivities will be small and similar those for 1-butene and *cis*-butene, respectively.

(22) The intercepts (A) of the rate constant correlations reflect the background rate constant for ylide formation at [alkene] = 0. Given the constant [isoquinoline], A values should all be similar. However, they vary by as much as a factor of 2. This has no effect on the determination of k_{add} (from the slope of the correlation), because each set of measurements uses the same stock solution. It does suggest, however, that [isoquinoline] is less accurate than the reported three places ("0.424 M"). We thank a reviewer for this observation.

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