

Enthalpy versus Entropy in Chlorocarbene/Alkene Addition Reactions

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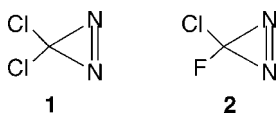
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More than fifty years ago, Doering and Hoffmann described the additions of CCl_2 and CBr_2 to cyclohexene and other alkenes,¹ initiating the widespread use of dihalocarbenes in organic synthesis.² The activation parameters for these dihalocarbene–alkene additions have never been measured, mainly because of a lack of appropriate carbene precursors for the necessary laser flash photolysis (LFP) experiments.^{3,4} Activation parameters for the alkene additions of arylhalocarbenes, such as PhCCl , have been measured and are characterized by very low or even negative activation energies and enthalpies.⁵ These reactions exhibit positive free energies of activation because they possess very negative entropies of activation (-25 to -29 eu).⁵

Are the additions of CCl_2 dominated by entropy or enthalpy? This question was the focus of much attention and speculation through 1989,^{5–7} but the absence of *absolute* activation parameters for dihalocarbene additions precluded definitive answers. Predictions, however, abounded. On the basis of *relative* activation parameters, Skell suggested that CCl_2 additions to monoalkylethylenes were enthalpy-controlled, whereas additions to more highly substituted alkenes would be entropy-controlled.^{6a} Giese concluded that entropy would dominate the additions of CBr_2 and CCl_2 , whereas enthalpy would control the reactions of CF_2 .^{6b–d} From computational studies at the HF and MP2 levels with 3-21G and 6-31G(d) basis sets, Houk predicted that CCl_2 additions would lack enthalpic barriers (even with ethene) and be entropy-dominated, whereas CF_2 additions would be enthalpy-controlled.^{7a–c} Houk formulated a variational transition state model, which emphasized that the free energy maximum differed from the maximum on the enthalpy surface, and that activation entropy played a major role in the additions of reactive carbenes to alkenes.^{7a–c} Jorgensen also predicted entropic control for CCl_2 additions but computed an enthalpic barrier of 1.1 kcal/mol for its addition to ethene, based on MP2/6-31G(d) calculations.^{7d}

Our syntheses of dichlorodiazirine⁸ (**1**) and chlorofluorodiazirine⁹ (**2**) afford spectroscopy-friendly precursors for CCl_2 and CClF which allow the LFP acquisition of kinetic data. Now, we report the first activation parameters for additions of these carbenes to alkenes, permitting us to evaluate some of the foregoing vintage predictions.



We focused on additions of CCl_2 and CClF to the moderately reactive alkenes cyclohexene and 1-hexene, but we also included the highly reactive substrate, tetramethylethylene (TME), in order

to link our findings to the early studies of PhCCl .⁵ Rate constants for the CCl_2 and CClF additions were obtained as previously described,⁹ by LFP of diazirines **1** and **2** in pentane solutions of the alkenes, using pyridine ylide visualization.¹⁰ For each carbene–alkene combination, rate constants were generally obtained at (ca.) 263, 273, 283, 297, and 303 K, with precise temperatures (± 0.1 K) ascertained at the instant of LFP via a thermocouple immersed in the target solution. Activation parameters were then calculated from the rate constant–temperature data, using two independent sets of measurements for each carbene–alkene combination. The Supporting Information contains graphical displays of all the primary kinetic data and the E_a correlations; activation parameters are collected in Table 1.

The following conclusions (valid over the temperature range of this study) can be drawn from the data and compared to the above predictions. (1) The addition of CCl_2 to TME, like that of PhCCl ,⁵ leads to a curved Arrhenius correlation of $\ln k$ vs $1/T$, and a negative E_a (Figures S-60, S-61, S-67, S-68); in contrast, the addition of CClF to TME features a small positive E_a (Figures S-74, S-80). (2) Additions of CCl_2 to cyclohexene or 1-hexene occur with discrete positive activation energies and enthalpies (Figures S-1, S-7, S-12, S-18), and the contributions of ΔH^\ddagger and $T\Delta S^\ddagger$ to ΔG^\ddagger are *comparable*. (3) Additions of the less reactive⁹ CClF to cyclohexene and 1-hexene exhibit activation enthalpies that are about twice as large as the entropic contributions to ΔG^\ddagger (Figures S-24, S-30, S-36, S-42). These reactions are under modest enthalpic control, although the addition of CClF to TME remains dominated by ΔS^\ddagger . (4) The slight ΔG^\ddagger advantage of cyclohexene over 1-hexene for CCl_2 or CClF addition is reflected in the observed relative reactivities: cyclohexene is about five times more reactive than 1-hexene toward either carbene.¹¹ (5) Across the triad of chlorocarbenes, XCCl , where $\text{X} = \text{Ph}, \text{Cl},$ or F , entropy dominates the additions of PhCCl to cyclohexene or 1-hexene, while enthalpy controls the analogous additions of CClF . CCl_2 is the “fulcrum,” where neither entropic nor enthalpic factors dominate. By extension, we would expect enthalpic control to characterize the additions of MeOCCl , CF_2 , or $(\text{MeO})_2\text{C}$, and experiments are planned to quantify these expectations. (6) Compensation may operate between the enthalpic and entropic components of ΔG^\ddagger in Table 1; as ΔH^\ddagger increases, $-T\Delta S^\ddagger$ decreases (and vice versa). This phenomenon is known in carbene additions.⁶

Are contemporary computational methods, such as DFT, capable of providing mechanistic insights to our present experimental results? We have carried out series of calculations with B3LYP, MPW1K, and MPW1PW91 density functionals and the 6-311+G(d) basis set on the carbene–alkene pairs listed in Table 1 (see Supporting Information for computational

Table 1. Activation Parameters for Carbene/Alkene Additions^a

carbene	alkene ^b	E_a	$\log A$	ΔH^\ddagger	ΔS^\ddagger	$-\Delta \Delta S^\ddagger$	ΔG^\ddagger
PhCCl ^{c,d}	TME	-1.7	7.2	-2.3	-28	8.3	6.0
PhCCl	<i>c</i> -C ₆ H ₁₀	1.24 (0.02)	7.4 (0.01)	0.68 (0.02)	-26 (0.01)	7.9 (0.02)	8.6 (0.03)
PhCCl ^c	1-hexene	1.1	7.4	0.5	-27	8.0	8.5
CCl ₂ ^d	TME	-1.2 (0.02)	8.8 (0.06)	-1.8 (0.02)	-20 (0.2)	6.0 (0.2)	4.2 (0.2)
CCl ₂	<i>c</i> -C ₆ H ₁₀	3.8 (0.2)	10.9 (0.3)	3.3 (0.2)	-10.5 (1.3)	3.1 (0.4)	6.4 (0.4)
CCl ₂	1-hexene	4.7 (0.3)	10.7 (0.2)	4.1 (0.3)	-11.5 (1.1)	3.4 (0.3)	7.5 (0.4)
CClF	TME	0.9 (0.02)	9.7 (0.02)	0.3 (0.02)	-16 (0.2)	4.7 (0.2)	5.0 (0.2)
CClF	<i>c</i> -C ₆ H ₁₀	5.6 (0.3)	11.5 (0.3)	5.0 (0.3)	-7.8 (1.1)	2.3 (0.3)	7.3 (0.4)
CClF	1-hexene	6.0 (0.06)	11.5 (0.04)	5.4 (0.06)	-7.8 (0.2)	2.3 (0.3)	7.7 (0.3)

^a Units are kcal/mol for E_a , ΔH^\ddagger , $-\Delta \Delta S^\ddagger$, and ΔG^\ddagger ; M⁻¹ s⁻¹ for $\log A$; cal/(deg·mol) for ΔS^\ddagger . ΔH^\ddagger is calculated at 283 K; ΔG^\ddagger is calculated at 298 K. Errors (in parentheses) are average deviations of two independent determinations. ^b TME = tetramethylethylene; *c*-C₆H₁₀ = cyclohexene. ^c From reference.^{5b} ^d Negative activation energies refer to 263 < T < 300 for PhCCl or 273 < T < 304 for CCl₂.

details). The calculated reaction parameters are functional dependent and, unfortunately, do not provide a unified picture. The B3LYP-based calculations identify distinct (gas phase) potential energy minima representing 1:1 carbene–alkene complexes, as well as TSs for cyclopropane formation, for all the species presented in Table 1. However, no CCl₂/TME complex or TS could be located when the MPW1K functionals were applied. When we employed the MPW1PW91 functionals, CCl₂/TME, CCl₂/1-hexene, as well as PhCCl/TME complexes and TSs were nonexistent.

Only the complexes of CCl₂ and CCIF with TME are bound on the B3LYP enthalpy surface. Applying MPW1K functionals, PhCCl/TME and CCIF/TME as well as CCl₂/cyclohexene complexes are bound, but just the latter two carbene–alkene pairs form enthalpy-bound complexes using MPW1PW91 functionals. Carbene–alkene complexes have been discussed,^{5,7} and mostly dismissed,⁷ in the literature. We note, however, in this context that we have recently detected a number of 1:1 halocarbene–arene complexes by fast UV spectroscopy.¹²

The calculations uniformly predict $\Delta S^\ddagger \approx -40$ eu ($P = 1$ atm, $T = 298$ K) for elementary one-step carbene–alkene addition reactions of the species investigated here (Tables S-1, S-3, and S-5; Supporting Information). However, less negative values for ΔS^\ddagger are anticipated, if the reaction proceeds with the intermediate formation of carbene–alkene complexes. Such “entropy-absorbing” complexes could also enjoy solvent cage stabilization.^{5b} Indeed, if the carbene–alkene complexes are used as reference, ΔS^\ddagger values computed for the additions are dramatically increased (less negative) relative to the computed bimolecular reaction values (Tables S-2, S-4, and S-6; Supporting Information), but neither quantitative nor qualitative agreement with the experimental ΔS^\ddagger data is observed, even for the reactant species where bound complexes have been located. Notably, the variational transition-state model developed by Houk does lead to activation entropies of reasonable magnitude for carbene–alkene model additions, which are analogous to the systems under investigation here.^{7a–c}

Calculated activation enthalpies also agree rather poorly with the experimental values and with expectations from variational transition state theory. Houk’s model predicts that the activation enthalpy calculated on the basis of a potential-surface maximum must be larger than the activation enthalpy derived from the variational transition state. Whereas we do calculate (B3LYP) activation enthalpies 3–5 kcal/mol larger than the experimental values for PhCCl, they are 1–2 kcal/mol less than the observed values for CCl₂ and CCIF. Thus, potential energy surface calculations based on some commonly employed DFT functionals do not well reproduce either the observed parameters or

the trends displayed in Table 1. More detailed calculations to characterize the variational transition states for some of the systems in Table 1 are planned.

In summary, we report the first measured activation parameters for the additions of CCl₂ and CCIF to simple alkenes and demonstrate the existence of enthalpic barriers for CCl₂ additions to cyclohexene and 1-hexene. With these two alkenes, additions of PhCCl are “dominated” by entropic contributions to ΔG^\ddagger and additions of CCl₂ display comparable contributions of ΔH^\ddagger and ΔS^\ddagger , while CCIF additions feature dominant ΔH^\ddagger contributions to ΔG^\ddagger . Entropic factors, however, control the additions of all three carbenes to the highly reactive alkene, tetramethylethylene.

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Supporting Information Available: Figures S-1–S-85; computational details, and Tables S-1–S-6. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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