ORGANIC LETTERS

2009
Vol. 11, No. 9
1947−1950

Latent Nucleophilicity of Dichlorocarbene

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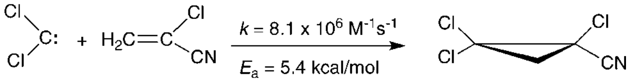
Received February 23, 2009

ABSTRACT



Rate constants and activation parameters are reported for additions of CCl_2 to methyl acrylate, acrylonitrile, and α-chloroacrylonitrile. The results reveal latent nucleophilicity in the addition of CCl_2 to α-chloroacrylonitrile, a conclusion supported by theoretical studies of the cyclopropanation reaction transition state.

Dichlorocarbene (CCl_2) has been *the* iconic carbene ever since Hine demonstrated its intermediacy in the hydrolysis of chloroform[1] and Doering trapped it by addition to alkenes.[2] Subsequent research revealed that CCl_2 discriminated between simple alkenes in an electrophilic fashion,[3] and it became the exemplar of electrophilic carbenes.[4]

In fact, a singlet carbene like CCl_2 is intrinsically *both* an electrophile and a nucleophile. In terms of frontier molecular orbital (FMO) theory, philicity depends on whether the “electrophilic” carbene-LUMO (p)/alkene-HOMO (π) or the “nucleophilic” carbene-HOMO (σ)/alkene-LUMO (π^*) orbital interaction dominates in the carbene/alkene cycloaddition transition state and governs the direction of charge transfer between the carbene and the alkene; cf. Figure 1.[4−6] Due to its relatively low-lying, readily accessible vacant p orbital (LUMO),[6] CCl_2 is an electrophilic carbene. Various other theoretical treatments concur in this characterization.[7]

However, if an alkene is made very electron poor (i.e., its π^* LUMO is sufficiently lowered), then even a normally electrophilic carbene like CCl_2 could add as a nucleophile. This occurs with phenylchlorocarbene (**1**), whose reactivity is generally similar to that of CCl_2.[4] Although **1** selects electrophilically across a “standard set” of alkenes,[5b,8] the absolute rate constants for its additions to such strongly electron-deficient alkenes as diethyl fumarate[9] or α-chloroacrylonitrile (**2**)[10] reveal nucleophilic character.

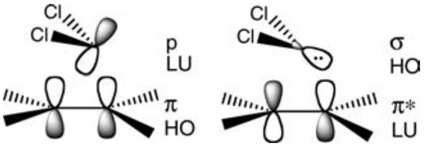
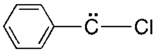


Figure 1. HOMO−LUMO interactions in CCl_2/alkene cycloadditions.



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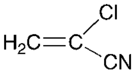

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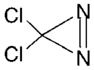

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Will a similar philicity reversal be manifested by CCl_2? The advent of a diazirine precursor for CCl_2, dichlorodiazirine (**3**),[11] now enables us to obtain absolute rate constants and activation parameters for CCl_2−alkene additions.[12] Moreover, the absence of trichloromethide anion (Cl_3C^-) when CCl_2 is generated by laser flash photolysis (LFP) of

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[1] Hine, J. *J. Am. Chem. Soc.* **1950**, *72*, 2438.
[2] Doering, W. v. E.; Hoffman, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162.
[3] Doering, W. v. E.; Henderson, W. A., Jr. *J. Am. Chem. Soc.* **1956**, *80*, 5274.
[4] Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58.
[5] (a) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15. (b) Moss, R. A. In *Carbene Chemistry: From Fleeting Intermediates to Powerful Reagents*; Bertrand, G., Ed.; Dekker: New York, 2002; p 57f.
[6] Rondan, N. G.; Houk, K. N.; Moss, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1770.

10.1021/ol900381r CCC: $40.75

3[11] ensures that additions of CCl_2 to very electron-deficient alkenes can be studied without mechanistic "contamination" by concomitant Cl_3C^- Michael addition cyclopropanation reactions.

Here, we report absolute rate constants and activation parameters for additions of CCl_2 to methyl acrylate (MeAcr), acrylonitrile (ACN), and α-chloroacrylonitrile (ClACN). The new results, coupled with previous data for additions to tetramethylethylene (TME), trimethylethylene, cyclohexene, and 1-hexene,[12,13] reveal latent nucleophilicity in the addition of CCl_2 to ClACN. This conclusion is supported by theoretical studies of the relevant cyclopropanation transition states.

We measured the kinetics and activation parameters for additions of CCl_2 to MeAcr, ACN, and ClACN *relative* to cyclohexene, for which the corresponding absolute rate constants and activation parameters were already available.[12] (Note that the Arrhenius correlation for the CCl_2−cyclohexene reaction is linear,[12] so that cyclohexene is an appropriate standard alkene.) Consider first MeAcr: CCl_2 was generated by photolysis of **3** ($A_{359} \sim 0.5$) in excess MeAcr and cyclohexene in pentane. The temperature was controlled by a circulating bath. After 3−4 h of photolysis with a focused UV lamp ($\lambda > 300$ nm), UV analysis indicated that **3** was gone. Then, capillary GC analysis of the known product cyclopropanes,[14,15] coupled with standard competition reaction product analysis,[16] gave the relative rate constants for addition of CCl_2 to MeAcr versus cyclohexene at various temperatures; cf., Table S-1 in the Supporting Information.

From $k_{\mathrm{MeAcr}}/k_{\mathrm{cyclohex}} = 1/107.7$ at 24.1 °C (Table S-1, note *e*) and $k_{\mathrm{cyclohex}} = 6.4 \times 10^7\ \mathrm{M^{-1}\ s^{-1}}$ at 25 °C,[13] we obtain $k_{\mathrm{MeAcr}} = 5.9 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$. This value appears in Table 1, together with analogous data for additions of MeOCCl.[17]

An Arrhenius plot of $\ln(k_{\mathrm{MeAcr}}/k_{\mathrm{cyclohex}})$ versus $1/T$ appears in Figure 2, where we find an excellent correlation ($r = -0.999$) for six relative rate constants measured at temperatures between −5.5 and 30.1 °C. Values of $\Delta E_a = 2.94$ kcal/mol, $\Delta\log A = 0.139\ \mathrm{M^{-1}\ s^{-1}}$, and $\Delta\Delta S^{\ddagger} = 0.63$ eu are obtained from the slope and intercept of the correlation. Combined with the absolute activation parameters for cyclohexene[12] (Table 2), we obtain for the addition of CCl_2 to MeAcr $E_a = 6.7$ kcal/mol, $\log A = 11.0\ \mathrm{M^{-1}\ s^{-1}}$, and $\Delta S^{\ddagger} = -9.9$ eu. These values appear in Table 2, together with derived values of $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$.

Table 1. Rate Constants for Additions of Carbenes to Alkenes

alkene	$k_{\mathrm{CCl2}}{}^{a}$ ($\mathrm{M^{-1}\ s^{-1}}$)	$k_{\mathrm{MeOCCl}}{}^{b}$ ($\mathrm{M^{-1}\ s^{-1}}$)
$Me_2C{=}CMe_2$	4.7×10^9	6.2×10^3
$Me_2C{=}CHMe$	2.5×10^9	
cyclohexene	6.4×10^7	
$CH_2{=}CHC_4H_9$	1.8×10^7	
$CH_2{=}CHE^{c}$	5.9×10^5	9.8×10^3
$CH_2{=}CHCN$	4.9×10^5	3.2×10^4
$CH_2{=}CClCN$	8.1×10^6	9.6×10^5

[a] In pentane at 24 °C. The first four entries are from ref 13; the last three entries are from this work. [b] In dichloroethane at 30 °C. Data are from ref 17 and its Supporting Information. [c] E = COOMe.

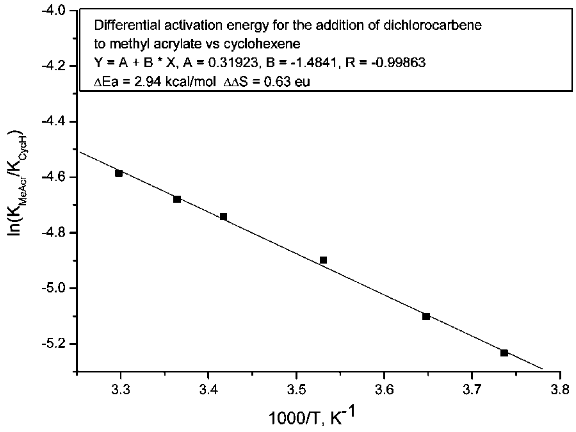

Figure 2. Differential activation energy for the competitive addition of CCl_2 to MeAcr versus cyclohexene: $\Delta E_a = 2.94$ kcal/mol; $\Delta\log A = 0.139\ \mathrm{M^{-1}\ s^{-1}}$, $r = -0.999$.

Similarly, we determined rate constants and activation parameters for additions of CCl_2 to ACN, relative to cyclohexene. At 24.1 °C, $k_{\mathrm{ACN}}/k_{\mathrm{cyclohex}} = 1/129.5$ (cf., Table S-2, Supporting Information). Together with $k_{\mathrm{cyclohex}} = 6.4 \times 10^7\ \mathrm{M^{-1}\ s^{-1}}$ at 25 °C,[13] we obtain $k_{\mathrm{ACN}} = 4.9 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$. This value appears in Table 1. An Arrhenius plot of $\ln(k_{\mathrm{ACN}}/k_{\mathrm{cyclohex}})$ versus $1/T$ appears in Figure S-1 (Supporting Information), which is based on the data of Table S-2. A satisfactory correlation ($r = -0.988$) is found for six k_{rel} measured at temperatures between −3.8 and 30.1 °C. The correlation affords $\Delta E_a = 3.09$ kcal/mol, $\Delta\log A = 0.154\ \mathrm{M^{-1}\ s^{-1}}$, and $\Delta\Delta S^{\ddagger} = 0.71$ eu. Combined with absolute activation parameters measured for CCl_2 addition to cyclo-

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(15) We prepared authentic samples of the CCl_2 adducts of MeAcr, ACN, and ClACN, generating the carbene from $PhHgCCl_3$ in refluxing benzene (48−72 h).[14] 7,7-Dichloronorcarane was prepared from cyclohexene, $CHCl_3$, and 50% aq NaOH by phase-transfer catalysis. The cyclopropanes were purified by preparative GC (SF-96). ^1H and ^{13}C NMR spectra of the adducts appear in the Supporting Information.

(16) Moss, R. A. In *Carbenes*; Jones, M., Jr., Moss, R. A., Eds.; Wiley: New York, 1973; Vol. 1, p 153f.

(17) Moss, R. A.; Zhang, M. *Org. Lett.* **2008**, *10*, 4045.

Table 2. Activation Parameters for CCl_2−Alkene Additions[a]

alkene[b]	E_a	log A	$\Delta H^‡$	$\Delta S^‡$	$-T\Delta S^‡$	$\Delta G^‡$
c-C_6H_{10}[c]	3.8	10.9	3.2	−10.5	3.1	6.4
1-hexene[c]	4.7	10.7	4.1	−11.5	3.4	7.5
MeAcr[d]	6.7	11.0	6.1	−9.9	2.9	9.0
ACN[d]	6.9	11.0	6.3	−9.8	2.9	9.2
ClACN[d]	5.4	11.2	4.8	−9.1	2.7	7.5

[a] Units are kcal/mol for E_a, $\Delta H^‡$, $-T\Delta S^‡$, and $\Delta G^‡$; $M^{-1}\ s^{-1}$ for log A; cal/(deg-mol) for $\Delta S^‡$. $\Delta H^‡$ is calculated at 283 K; $\Delta G^‡$ is calculated at 298 K. Errors in the data are estimated at 0.2−0.3 kcal/mol on the basis of previous studies.[12,17] [b] c-C_6H_{10} = cyclohexene; TME = tetramethylethylene; MeAcr = methyl acrylate; ACN = acrylonitrile; ClACN = α-chloroacrylonitrile. [c] In pentane; from ref 12. [d] In pentane; this work.

hexene,[12] we obtain $E_a = 6.9$ kcal/mol, log $A = 11.0\ M^{-1}\ s^{-1}$, and $\Delta S^‡ = -9.8$ eu for the addition of CCl_2 to ACN; cf. Table 2.

Lastly, rate constants and activation parameters were obtained for additions of CCl_2 to ClACN, relative to cyclohexene. Details and data appear in Table S-3 (Supporting Information), while an Arrhenius plot of $\ln(k_{ClACN}/k_{cyclohex})$ versus $1/T$ appears in Figure S-2 (Supporting Information). A good correlation ($r = -0.996$) obtained for five relative rate constants, determined at temperatures between −8.5 and 30.2 °C, affords $\Delta E_a = 1.63$ kcal/mol, $\Delta \log A = 0.305$, and $\Delta\Delta S^‡ = 1.39$ eu. Combined with the activation parameters for cyclohexene in Table 2, we obtain for ClACN $E_a = 5.4$ kcal/mol, log $A = 11.2\ M^{-1}\ s^{-1}$, and $\Delta S^‡ = -9.1$ eu. These values are shown in Table 2, together with derived values for $\Delta H^‡$ and $\Delta G^‡$.

Satisfactory cross-check kinetics experiments[16] link the relative reactivities of the MeAcr−ACN, cyclohexene−ACN, and ClACN−cyclohexene pairs; see the Supporting Information.

Inspection of the absolute rate constants for CCl_2−alkene additions to TME through ACN in Table 1 confirms that CCl_2 behaves as an electrophilic carbene. Rate constants decrease (and E_a increases; cf., Table 2) as electron-donating alkyl groups are removed from the alkenes. Rate constants also decrease as electron-withdrawing groups are imposed on the alkenes. However, the 16.5-fold *increase* in rate constant on passing from ACN to ClACN is striking and suggests nucleophilic CCl_2 addition. Very similar behavior was found for PhCCl (**1**) and was attributed to latent nucleophilic character.[10]

MeOCCl, a well-characterized ambiphile, exhibits electrophilic selectivity toward the alkyl-substituted olefins of Table 1 but nucleophilic selectivity toward the electron-poor olefins MeAcr, ACN, and ClACN.[4,5,18] However, the behavior of CCl_2 is more subtle; only with ClACN is nucleophilic behavior patent.

The activation parameters of Table 2 indicate that the rate increase observed for the CCl_2−ClACN addition is largely due to a reduction in E_a, which decreases by 1.5 kcal/mol for CCl_2 addition to ClACN relative to ACN and by 1.3 kcal/mol relative to MeAcr. Differences in $T\Delta S^‡$ are minimal for CCl_2 additions to these alkenes. Entropy is more important in MeOCCl additions, where $-T\Delta S^{+}$ contributes ~6−7 kcal/mol to $\Delta G^‡$.[17] Even here, however, the advantage of the highly electrophilic alkene ClACN is manifest: E_a for addition of MeOCCl to ClACN is 2.5 kcal/mol lower than for addition to ACN, 3.1 kcal/mol lower than for addition to MeAcr, and 1.9 kcal/mol lower than for addition to the highly nucleophilic alkene TME.[17]

Is nucleophilic selectivity of CCl_2 toward ClACN expected, and does theory support this characterization? In semiquantitative applications of FMO theory, we found that the carbene-LUMO/alkene-HOMO interaction dominated the additions of CCl_2 to *both* electron-rich alkenes (TME and $Me_2C{=}CHMe$) and electron-poor alkenes (MeAcr and ACN).[4,5] In contrast, with ambiphilic MeOCCl, the carbene-HOMO/alkene-LUMO interaction was dominant for additions to MeAcr and ACN, which were accordingly described as nucleophilic.[4,5]

What is the situation with ClACN as the substrate? We have carried out DFT electronic structure calculations at the B3LYP/6-311+G(d) level for the CCl_2−ACN and CCl_2−ClACN addition reactions (see the Supporting Information for computational details). Pertinent computed transition state (TS) parameters for both cycloadditions are listed in Table S-4 (Supporting Information); the TS for CCl_2−ClACN is displayed in Figure 3.

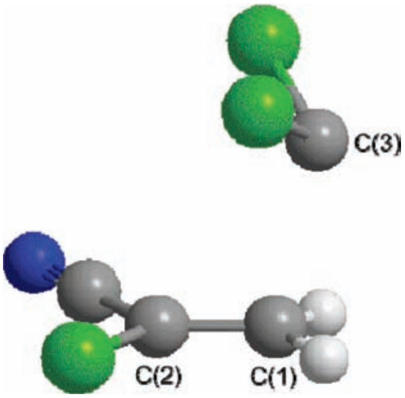

Figure 3. Transition state for CCl_2 addition to ClACN (B3LYP/6-311+G(d)).

As expected, the TS geometries are very similar for the two carbene−alkene combinations; a closer examination suggests significant nucleophilic character in the CCl_2−alkene interaction in each TS. Figure 3 and the data in Table S-4 show that the approaching dichlorocarbene is positioned on the "outside" of the unsubstituted alkene C-atom (angle C(3)−C(1)−C(2) ~ 100°) with significantly different C(carbene)−C(alkene) distances: C(1)−C(3) ~ 2.2−2.3 Å; C(2)−C(3) ~ 2.8−2.9 Å. Bond formation is thus

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(18) Moss, R. A.; Fedorynski, M.; Shieh, W.-C. *J. Am. Chem. Soc.* **1979**, *101*, 4736.

far more pronounced at the unsubstituted carbon, C(1).[19] The TS for CCl_2 addition to ClACN is "earlier" than that to ACN as shown by the larger C(carbene)−C(alkene) distances as well as a larger asymmetry in these distances; cf. Table S-4. Also, the increase in C═C double bond length from the free alkene to the respective TS is smaller in the case of ClACN (0.023 Å) than ACN (0.036 Å); in either TS, the local geometry of the carbene hardly changes from that of the free carbene. The carbene tilt angle, defined as the angle between the bisector of the carbene Cl−C−Cl angle and the alkene carbon−carbon bond, is very similar in both TS's, 49.6° for CCl_2−ClACN and 51.7° for CCl_2-ACN,[20] and the two carbene chlorine atoms are effectively positioned symmetrically with respect to the C═C bond. The puckering angle (α) at the unsubstituted carbon C(1) is 13.8° in the CCl_2-ACN TS and 13.3° for CCl_2−ClACN (Table S-4), with the CH_2 group bending away from the approaching carbene; the corresponding puckering angle at the substituted carbon C(2) is only 4° and bending is toward the carbene. The TS structural parameters just discussed,[6] namely the geometrical location of the carbene, the large value of the tilt angle, the distinct asymmetry in C(carbene)−C(alkene) distances, and the larger pyramidalization at C(1) than at C(2) all express a nucleophilic component in the cycloaddition TS for CCl_2−ACN and CCl_2−ClACN.

Charge-population analysis strongly supports the notion that CCl_2 acts predominantly as a nucleophile in these TS's. The net electron-transfer between CCl_2 and alkene (Mulliken population analysis)[21] is 0.03e for the CCl_2−ACN TS and 0.06e for the CCl_2−ClACN TS, *from* the carbene *to* the alkene.[22] The olefin polarizes so that, in the TS for CCl_2 addition to ClACN, partial negative charge is imposed on the C atom of the CN substituent and on Cl (relative to the free alkene; see Table S-5 (Supporting Information) for a more detailed list of atomic charges. Although theory indicates predominant nucleophilic character in CCl_2 additions to both ACN and ClACN, the experimental results (above) are less conclusive; only the addition to ClACN is obviously nucleophilic.

As noted previously,[12] when the carbene−alkene addition is treated as a one-step concerted reaction, decomposition of the activation free energy into its enthalpic and entropic components as computed by DFT methods differs significantly from the experimental determination. The computed difference in activation energies for CCl_2 additions to ACN and ClACN is 1.6 kcal/mol in favor of ClACN (Table S-6, Supporting Information), supporting the notion of this TS being "earlier" (Table S-4) and in excellent agreement with the experimentally measured difference (1.5 kcal/mol, Table 2). However, the individually computed E_a s are 1.1 and 2.7 kcal/mol for CCl_2−ClACN and CCl_2−ACN, respectively, values which are ca. 4 kcal/mol less than observed.[23] Perhaps more disturbing, although intriguing, the computed activation entropies are far more negative (ca. −31 eu) than observed (−9 to −10 eu, Table 2). Consequently, the computed activation free energies are strongly dominated by the entropy term and overall slightly larger (9.8 and 11.4 kcal/mol, Table S-6) than the experimental values (7.5 and 9.2 kcal/mol, Table 2). The intricate features of the potential energy surfaces, which may cause these discrepancies for carbene-alkene addition reactions, are under active investigation.[24]

Acknowledgment. We are grateful to the National Science Foundation and the Petroleum Research Foundation for financial support.

Supporting Information Available: Cross-check experiments; Figures S-1 and S-2; Tables S-1−S-7; NMR spectra; computational details; optimized geometries and energies for CCl_2, ACN, ClACN, transition states, and complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] Experimental evidence for unsymmetrical C−C bond formation in CCl_2−alkene addition is provided by: Keating, A. E.; Merrigan, S. R.; Singleton, D. A.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3933.

[20] For a purely electrophilic attack of a carbene, the tilt angle would be 0°. Large tilt angle values (>45°) signify substantial nucleophilic character;[6] e.g., at the B3LYP/6-311+G(d) level, the value of the tilt angle is only 42° in the CCl_2−propene TS, a distinctly electrophilic attack by the carbene.

[21] Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

[22] In contrast, the TS for CCl_2 adding to propene shows a net charge transfer of 0.07e in the opposite direction (B3LYP/6-311+G(d)).

[23] Most density functional combinations, including B3LYP, tend to systematically underestimate activation energy barriers; cf. Sousa, S. F.; Fernandes, P. A.; Ramos, M. J. *J. Phys. Chem. A* **2007**, *111*, 10439. At the CCSD/6-31G(d) level, the computed E_a s are approximately 1.5 kcal/mol less than observed (4.0 and 5.5 kcal/mol for CCl_2−ClACN and CCl_2−ACN, respectively; Krogh-Jespersen, K. Unpublished results.)

[24] Interestingly, the B3LYP/6-311+G(d) calculations locate very weakly bound precursor complexes between CCl_2 and ACN or ClACN on the potential energy surfaces. If we derive the activation parameters relative to these shallow local minima, then the computed activation entropies (−13 and −9 eu for ACN and ClACN, respectively) approach the experimental values, but the activation energies hardly change (see Tables S-6 and S-7, Supporting Information, for more details). We note that the B3LYP functionals underestimate intermolecular interactions[23] and also that the approximate variational transition state for CCl_2−ClACN obtained at the B3LYP/6-311+G(d) level does not differ significantly from the conventional TS presented in Figure 3 and Table S-4 (Supporting Information).