ORGANIC
LETTERS

1999
Vol. 1, No. 5
819−822

Remote Substituent Effects on Phenylchlorocarbene C–H Insertion Reactions

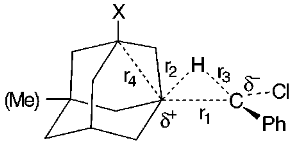
Robert A. Moss* and Shunqi Yan

*Department of Chemistry, Rutgers, The State University of New Jersey,
New Brunswick, New Jersey 08903*

moss@rutchem.rutgers.edu

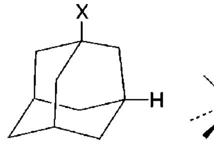
Received July 12, 1999

ABSTRACT

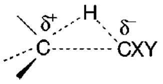


Phenylchlorocarbene inserts into the tertiary CH bonds of 1,3-dimethyladamantane and 1-X-adamantanes (X = H, OMe, COOMe, Cl, CN). There is a good correlation between the relative rate constants for these insertions and the inductive substituent constants, σ_I(X), with $\rho = -1.5$. Absolute rate constants for the insertions range from 2.5×10^5 M^{-1} s^{-1} for Ad-Me_2 to 2.5×10^4 M^{-1} s^{-1} for Ad-CN. B3LYP/6-31G* calculations give a good account of reactivity in these systems.

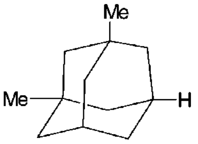
We recently described the absolute kinetics of phenylchlorocarbene (PhCCl) insertion reactions with a variety of substrates.[1] In benzene solution, for example, PhCCl inserted into a tertiary CH of adamantane (Ad-H; **1a**) with $k = 1.26 \times 10^5$ M^{-1} s^{-1} (per H atom) and with $E_a = 3.2$ kcal/mol and $\Delta S^\ddagger = -24$ eu.[1] The transition state (TS) for carbene C−H insertion can be schematically represented as **2**, where a hydride-like migration between the substrate and carbenic carbon atoms engenders charge separation, with positive charge on the former and negative charge on the latter.[2,3]



1 a, X=H; **b**, X=OMe;
c, X=COOMe; **d**, X=Cl;
e, X=CN



2



3

Insertions of (for example) CCl_2 into benzylic or α-ether C−H bonds are readily interpretable with TS **2**.[2,3] Thus, a Hammett study of CCl_2 insertions into the tertiary CH of substituted cumenes gave $\rho = -1.19$ (σ) or -0.89 (σ^+), consistent with the development of δ^+ on the cumyl carbon at the transition state.[2a] Analogous insertions into the Si−H bonds of silacumenes revealed ρ values ranging from -0.97[4] to -0.63.[5]

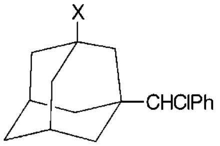
With the cumyl and silacumyl substrates, both inductive and resonance effects of the substituents act upon the reaction center. We imagined that a study of the *remote* substituent effects attending the efficient[1,6] carbene insertions into bridgehead adamantane C−H bonds could "isolate" the inductive effect, providing a direct estimate of its importance. Qualitative results for CCl_2 insertions (at C3−H) into 1-substituted adamantanes (**1**) demonstrate that electron-withdrawing substituents deactivate the substrate and lower product yields.[6] Here, we present quantitative data for the related PhCCl insertions: both kinetics and computational studies are in good accord with generalized TS **2** and implicate a surprisingly large inductive effect operating on these C−H insertion reactions.

---

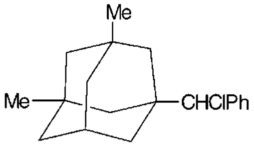
[1] Moss, R. A.; Yan, S. *Tetrahedron Lett.* **1998**, *39*, 9381.
[2] (a) Seyferth, D.; Cheng, Y. M. *J. Am. Chem. Soc.* **1973**, *95*, 6763. (b) Seyferth, D.; Mai, V. M.; Gordon, M. E. *J. Org. Chem.* **1970**, *35*, 1993.
[3] Pascal, R. A., Jr.; Mischke, S. *J. Org. Chem.* **1991**, *56*, 6954.
[4] Watanabe, H.; Ohsawa, N.; Sudo, T.; Hirakata, K.; Nagai, Y. *J. Organomet. Chem.* **1977**, *128*, 27.
[5] Seyferth, D.; Damrauer, R.; Mui, J. Y.-P.; Jula, T. F. *J. Am. Chem. Soc.* **1968**, *90*, 2944.
[6] Tabushi, I.; Yoshida, Z.; Takahashi, N. *J. Am. Chem. Soc.* **1970**, *92*, 6670.

10.1021/ol990161b CCC: $18.00

Substrates included adamantane (Ad-H, **1a**) and its 1-X derivatives Ad-OMe (**1b**), Ad-COOMe (**1c**), Ad-Cl (**1d**), and Ad-CN (**1e**), as well as the readily available (Aldrich) 1,3-dimethyladamantane (Ad-Me$_2$; **3**). For preparative and product identification purposes, PhCCl was generated either thermally (100−110 °C, 2−6 h) or photochemically (Ad-Cl, $\lambda > 320$ nm, 30 min) from phenylchlorodiazirine[7] in concentrated benzene solution ($A_{374} > 3.0$). The PhCCl reacted with 18−37 mmol of Ad-X in 2−6 mL of benzene to afford products **4a**−**e** and **5**, which were purified by silica gel chromatography and characterized by their NMR and GC-MS spectra, as well as elemental analysis or high-resolution mass spectrometry.



4 (**a**-**e** as in **1**)



5

Yields of insertion products ranged from 96% (**5**) and 90% (**1a,b**) to 60% (**4d**) and 35% (**4e**).[8] Carbene dimer and azine byproducts increased from 1% and 3% yields with substrate **3** to 15% and 25% with **1d**, and even higher with **le**.[8] Clearly, electron-withdrawing substituents adversely affect the reactivity of Ad-H.[6]

The absolute rate constant for PhCCl insertion into **1a** is 5.02×10^5 M^{-1} s^{-1} (in benzene[9] at 23 °C), corresponding to 1.26×10^5 M^{-1} s^{-1} per bridgehead C−H bond.[1] We determined *relative* rates for C−H insertions with substrates **1b**−**e** and **3** by competition reactions in which an insufficiency of PhCCl was allowed to compete with ~50-fold excesses of substrate pairs. PhCCl was generated by photolysis ($\lambda > 320$ nm) of the diazirine in benzene solution at 23 °C for 20 min, after which no diazirine was detectable by UV spectroscopy. Molar ratios of the derived insertion products, **4a**−**e** and **5**, were determined by capillary GC on a CP-Sil-5CB column, using a calibrated flame ionization detector and electronic integration. Relative rate constants were calculated from $k_A/k_B = (S_B/S_A)(P_A/P_B)$, where S_B/S_A is the initial molar ratio of substrates and P_A/P_B is the molar product ratio. Competitions were performed in duplicate, with GC analyses in triplicate, and the reproducibilities of k_A/k_B were better than ±4%.

Relative reactivities were determined for the following substrate pairs (k_A/k_B shown in parentheses): Ad-Cl/Ad-H (0.205), Ad-Me$_2$/Ad-Cl (5.12), Ad-OMe/Ad-H (0.44), Ad-COOMe/Ad-Cl (1.62), Ad-CN/Ad-H (0.150). Additional competitions were carried out between Ad-Me$_2$/Ad-Cl, Ad-OMe/Ad-Me$_2$, Ad-COOMe/Ad-OMe, and Ad-Cl/Ad-COOMe in order to demonstrate the internal consistency of the relative reactivities. Appropriate relative rate constants were averaged; the results, relative to Ad-H, are displayed in Table 1, where average deviations in k_{rel} are better than ±5%.

Table 1. Kinetics of PhCCl Insertion into the Adamantyl Tertiary CH Bond[a]

substrate	k_{rel} (tot)[b]	k_{rel} (per H)[c]	$10^5 k_{abs}$, M^{-1} s^{-1} [d]	σ_I[e]
Ad-Me$_2$ (**3**)	0.995	1.99	2.51	−0.02[f]
Ad-H (**1a**)	1.000[g]	1.00[g]	1.26[h]	0.00
Ad-OMe (**1b**)	0.420	0.56	0.70	0.30
Ad-COOMe (**1c**)	0.315	0.42	0.53	0.32
Ad-Cl (**1d**)	0.197	0.26	0.33	0.47
Ad-CN (**1e**)	0.150	0.20	0.25	0.57

[a] In benzene at 23 °C. [b] Reactivity relative to Ad-H, not statistically corrected. [c] Per-bond reactivity, relative to a single Ad-H tertiary CH bond. [d] Absolute rate constant, per C−H bond, derived from the absolute rate constant for PhCCl + Ad-H,[1] and k_{rel} (per CH). [e] Inductive substituent constant for X in Ad-X.[10a] [f] σ_I(Me) = −0.01; for 2 Me's we take $\sigma_I = -0.02$. [g] Standard substrate. [h] See ref 1.

The "spread" in k_{rel} is a factor of 10 from the most (Ad-Me$_2$) to the least reactive substrate (Ad-CN), while the corresponding absolute rate constants for C−H insertion range from 2.5×10^5 to 2.5×10^4 M^{-1} s^{-1} (per bridgehead H atom). There is a clear correlation between the reactivity of a substrate's tertiary CH bond and the electronic character of its substituent, X, as quantitated by the relation between log k_{rel} (per H) and σ_I(X), the inductive substituent constant[10] (see Figure 1). Here, $\rho = -1.50$, consistent with TS **2**, where an electron-withdrawing substituent destabilizes $\delta+$ on the Ad carbon atom and slows the insertion reaction, while an

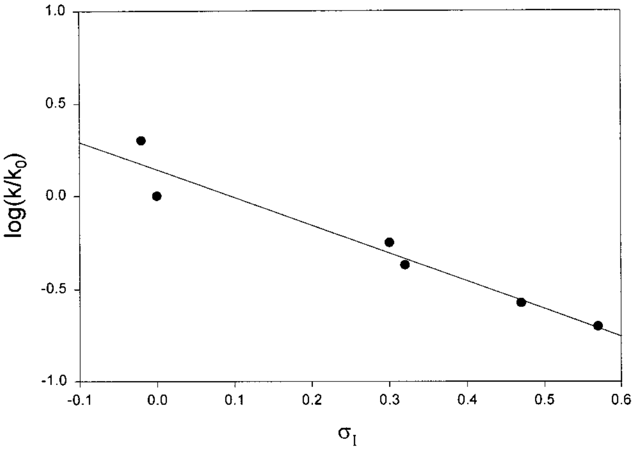


Figure 1. Correlation of log k/k_0 with σ_I for insertions of PhCCl into the tertiary CH bonds of substrates **3** and **1a**−**e**. See text for discussion.

---

(7) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

(8) Product **4e**, from Ad-CN, was accompanied by 15% of PhCCl dimer and 50% of (PhCCl=N)$_2$ azine. **4e** could not be separated from excess **1e** by chromatography and was identified in situ by GC-MS.

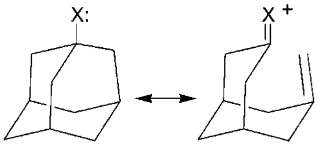
(9) The insertion is 2−3 times slower in benzene than in pentane; benzene "complexes" PhCCl and modulates its reactivity: Moss, R. A.; Yan, S.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1998**, *120*, 1088. Krogh-Jespersen, K.; Yan, S.; Moss, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6269.

(10) (a) Charton, M. Prog. *Phys. Org. Chem.* **1981**, *13*, 119. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

electron-releasing substituent has the opposite effect. For comparison, correlation of $\sigma_I(X)$ with k_{rel} for bridgehead H abstractions from **1** by the trichloromethyl radical at 40 °C gives $\rho = -0.90$.[11] Charge separation (in the sense of **2**) is less pronounced in the electrophilic radical abstraction by CCl_3 than in the PhCCl insertion.

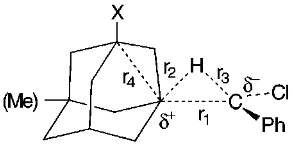
Although there is appreciable scatter for the X = Me and H points in Figure 1, the overall correlation is of good quality, with $r = 0.97$, significant at the 99% confidence level. The apparent scatter may be largely due to uncertainty in $\sigma_I(Me)$, given as −0.01 (±0.02).[10a] Using a more negative value (e.g. −0.05[10b]) improves the correlation ($r = 0.986$) and marginally trims the ρ value to −1.40.

The magnitude of ρ (∼−1.5) is rather large for "remote" substituents acting on the $\delta+$ of **2** only by an inductive effect; recall that for CCl_2 insertion into cumenes, where para substituents interact with the reaction center by both resonance and inductive effects, ρ ranges only from −0.89 to −1.19.[2a] Substantial contribution of a resonance component, originating at X, to the stabilization of $\delta+$ in TS **2** (illustrated for X-Ad$^+$ by the "frangomeric"[12] resonance structures **6**) is unlikely, because the k_{rel} of Ad-OMe is well-correlated by $\sigma_I(OMe)$; cf. Figure 1. Note that the electronic effect of X, here termed an "inductive effect," may be propagated through space, through the intervening σ bonds, or by a combination of modalities; partition of the transmission mode cannot be easily accomplished.[13]



6

The B3LYP hybrid density functional method, as contained in the Gaussian 94 package,[14] affords reasonable transition states and energetic trends for PhCCl/C−H insertion reactions.[1] B3LYP/6-31G* transition states, represented by **7**, were located for the reactions of PhCCl with **1a**−**e** and **3**, and confirmed by frequency calculations that gave only one negative frequency. Transition state **7** is "late," with the migrant hydride closer to the PhCCl terminus than the adamantyl origin.[15] Thus, $r_3 < r_2$ for all substrates, with these distances rather insensitive to substrate identity: for **3** through **1e**, r_2 varies from 1.374 to 1.387 Å, with bonding between H and the carbenic carbon well established. Distances r_1 (2.497−2.489 Å) and r_4 (2.491−2.474 Å) are also computed to be relatively substituent insensitive. The TS for the Ad-H/PhCCl insertion is illustrated in Figure 2.



7

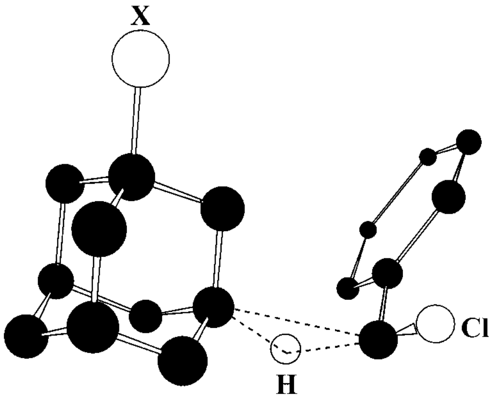


Figure 2. B3LYP/6-31G* transition state for insertion of PhCCl into the tertiary CH bond of substrate **1a**. Uninvolved H atoms are omitted for clarity.

As shown in Table 2, considerable positive charge is induced on the adamantyl carbon of TS **7**, with comparable negative charge buildup on the carbenic carbon (NBO analysis). These charges are slightly sensitive to the Ad substituents; both positive and negative charges decrease as the TS moves toward product with increasing electron-withdrawing character of the substituents. Substituent sensitivity is more strongly displayed by the computed activation energies (Table 2), which (uncorrected for zero point energy) range from 8.55 (Ad-Me$_2$) to 9.94 kcal/mol (Ad-CN). Although these values are too high,[1,16] their trend with substituent variation is appropriate. Indeed, there is a reasonable correlation ($r = 0.93$) between the computed E_a's and $\sigma_I(X)$, with $\rho = 1.86$; electron-withdrawing substituents destabilize the positive charge on the migration origin of **7**, raising both TS and activation energies.

Table 2. Computational Results[a]

substrate	E_a, kcal/mol[b]	$\delta+$ [c]	$\delta-$ [d]
Ad-Me$_2$ (**3**)	8.55	0.202	0.190
Ad-H (**1a**)	9.10	0.197	0.189
Ad-OMe (**1b**)	9.30	0.195	0.188
Ad-COOMe (**1c**)	9.46	0.193	0.188
Ad-Cl (**1d**)	9.64	0.185	0.183
Ad-CN (**1e**)	9.94	0.184	0.183

[a] B3LYP/6-31G*. [b] Uncorrected for zero-point energy. [c] Positive charge on adamantyl carbon in TS **7**. [d] Negative charge on carbenic carbon in TS **7**.

The B3LYP/6-31G* calculations thus provide a serviceable model for the PhCCl insertion reactions, sensitively

---

[11] Owens, P. H.; Gleicher, G. J.; Smith, L. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4122.

[12] Grob, C. A.; Fischer, W.; Katayama, H. *Tetrahedron Lett.* **1976**, 2183 and references therein.

[13] Exner, O.; Charton, M.; Galkin, V. *J. Phys. Org. Chem.* **1999**, *12*, 289 and accompanying papers.

[14] GAUSSIAN 94, Revision E.2; Gaussian, Inc., Pittsburgh, PA, 1995.

reproducing the observed substituent effects on carbenic reactivity. At the same time, the adamantane system furnishes an excellent scaffold on which to probe the electronics of this archetypal carbene reaction.

Acknowledgment. We are grateful to Professor Marvin Charton for helpful discussions and to the National Science Foundation for financial support. Access to the computational resources of the Center for Computational Neuroscience at Rutgers University (Newark) is much appreciated.

OL990161B

---

(15) A similar observation was made for the computed PhCCl/cyclohexane TS.[1]

(16) The computed E_a for the PhCCl/Ad-H insertion is 9.1 kcal/mol, whereas the experimental value is 3.2 kcal/mol.