Estimation of activation energies for carbene/alkene additions

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ABSTRACT

Activation energies for the additions to alkenes of carbenes CXY can be estimated from the carbene selectivity indices, m_{CXY} , which are readily derived from the substituent constants (σ_I and σ_R^+) of X and Y.

Keywords: carbenes, compensation, reactivity

Laser flash photolysis has provided activation parameters for the additions of carbenes to alkenes.¹⁻⁴ Analysis of these parameters for arylhalocarbenes² and dihalocarbenes³ suggests the occurrence of “compensation” between the energies or enthalpies of activation and the corresponding entropies of activation. That is, $\Delta H^\ddagger$ (E_a) and $\Delta S^\ddagger$ appear to increase *in tandem* for the additions of carbenes of increasing stability to a set of alkenes of decreasing degree of alkylation (decreasing reactivity).⁵⁻⁷

This behavior is at odds with expectations based on the Hammond postulate as applied to carbene/alkene additions by Skell:⁸ *viz.* as carbenic stability increases, $\Delta H^\ddagger$ should increase; the addition transition state (TS) should occur later along the reaction coordinate; separation of reactants should decrease in the TS; steric interactions should become more important; and $\Delta S^\ddagger$ should become more negative (decrease).

We suggested that carbene/alkene additions with low activation energies ($E_a < 10$ kcal/mol) might be better analyzed by a consideration of dynamic effects and reaction trajectories, rather than classical Eyring-Hammond transition state theory.^{5,9} In this regard, we might inquire how large E_a (or $\Delta H^\ddagger$) would need to be before transition state

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theory would be the more apposite analytical method for carbene/alkene additions. Suppose, for instance, that we take $E_a \sim 15$ kcal/mol as a threshold activation energy. Will this barrier be reached in additions of “common” carbenes to alkylethenes? To provide a preliminary answer, it would be useful to have a “back-of-the-envelope” method to estimate activation energies for carbene/alkene additions, a method that bypasses both arduous experimental determinations and semi-lengthy computations.

Years ago, we developed an empirically based “carbene selectivity index,” m_{CXY} , which correlated the relative reactivities of carbenes CXY in additions to simple alkenes.¹⁰ Moreover, m_{CXY} could be readily calculated for any CXY according to eq. (1), where $\Sigma_{\text{X,Y}} \sigma_R^+$ represents the sum of the resonance substituent constants (σ_R^+) of carbene substituents X and Y, and $\Sigma_{\text{X,Y}} \sigma_I$ represents an analogous sum of the inductive substituent constants (σ_I).^{11,12}

$$m_{\text{CXY}} = -1.10 \Sigma_{\text{X,Y}} \sigma_R^+ + 0.53 \Sigma_{\text{X,Y}} \sigma_I - 0.31 \quad (1)$$

Subsequently, we proposed that m_{CXY} correlated with both $\epsilon_{\text{CXY}}^{\text{LU}}$, the computed LUMO energies of CXY, and ΔE_{stab} , the computed stabilization energies of CXY relative to singlet methylene.^{12,13} For CXY (where X and Y are donor groups) adding to (nucleophilic) alkylethenes, the stabilization energy of the addition transition state will be largely determined by the interaction of the carbene’s LUMO or p orbital with the alkene’s HOMO or π orbital.^{7,13,14} Given that the stabilization energy is related to the activation energy for the carbene/alkene addition, we might anticipate that E_a will also be correlated by m_{CXY} .

Here, we confirm this expectation. We then use values of m_{CXY} to estimate the activation energies of several as yet unexplored carbene/alkene addition reactions. Finally, predictions based on m_{CXY} are compared to calculated activation energies.

The carbenes we employ to test the correlation of m_{CXY} with experimentally-determined activation energies are CCl_2 , CClF , CF_2 , PhCCl , and $\text{C}_6\text{F}_5\text{CCl}$. The associated values of m_{CXY} are 0.97, 1.22, 1.47, 0.72, and 0.92, respectively.^{15,16} Figures 1-3 depict the m_{CXY}/E_a correlations for additions of CXY to tetramethylethylene (TME), cyclohexene, and 1-hexene. The relevant values of E_a are reported for CCl_2 and CClF in ref. 3a, for CF_2 in ref. 3b, and for PhCCl and $\text{C}_6\text{F}_5\text{CCl}$ in ref. 2.

The least-squares-determined correlation equations derived from Figures 1-3 are given in algebraic form in eqs. (2)-(4).

$$\text{TME:}^{17} E_a = 8.73 m_{\text{CXY}} - 9.21 \quad (r = 0.96, \text{ std. error} = 1.26 \text{ kcal/mol}) \quad (2)$$

$$\text{cyclohexene: } E_a = 8.40 m_{\text{CXY}} - 5.08 \quad (r = 0.97, \text{ std. error} = 1.12 \text{ kcal/mol}) \quad (3)$$

$$\text{1-hexene: } E_a = 8.96 m_{\text{CXY}} - 4.97 \quad (r = 0.97, \text{ std. error} = 1.19 \text{ kcal/mol}) \quad (4)$$

Figure 1. Experimental activation energy vs. m_{CXY} for the additions of carbenes CXY to tetramethylethylene (TME).

Figure 2. Experimental activation energy vs. m_{CXY} for the additions of carbenes CXY to cyclohexene.

Figure 3. Experimental activation energy vs. m_{CXY} for the additions of carbenes CXY to 1-hexene.

These correlations are significant at the 99% confidence level and exhibit standard errors of ~ 1.2 kcal/mol in E_a . We conclude that the anticipated correlation between E_a and m_{CXY} is experimentally verified for donor-substituted examples of CXY.

Using these equations, we estimated activation energies for the putative additions of MeOCF, (MeO)₂C, MeOCNMe₂, and (Me₂N)₂C to TME, cyclohexene, and 1-hexene.¹⁵ The results appear in Table 1. As we would expect, the estimated activation energies for CXY additions to alkylethenes increase as substituents X and Y become more effective (resonance) donors¹⁸ and CXY becomes less electrophilic (more nucleophilic) and more stabilized.¹⁵

Table 1

Estimated activation energies (E_a) for carbene/alkene additions

Carbene	m_{CXY}^a	ΔE_{stab}^b	E_a^c		
			TME	cyclohexene	1-hexene
MeOCF	1.85	84.1	6.94	10.5	11.6
(MeO) ₂ C	2.22	92.0	10.2	13.6	14.9
MeOCNMe ₂	2.92	95.7	16.2	19.4	21.1
(Me ₂ N) ₂ C	3.60	86.6	22.2	25.2	27.3

^aCarbene selectivity index, calculated from eq. (1); see references 11, 12, and 15. ^bIn kcal/mol. ΔE_{stab} is defined as the negative of the reaction energy for $\text{CH}_2 + \text{CH}_3\text{X} + \text{CH}_3\text{Y} \rightarrow \text{CXY} + 2\text{CH}_4$. Computed here at the B3LYP/6-311++G(2d,p) level; see ref 15.

^cIn kcal/mol. Calculated from eqs. (2)-(4).

We note, however, that the “training” set of carbenes used in the correlations of Figures 1-3, which generated eqs. (2) – (4), are all electrophilic. Their addition transition states with TME, cyclohexene, and 1-hexene will be governed by the carbene LUMO – alkene HOMO interaction. In contrast, (MeO)₂C, MeOCNMe₂, and (Me₂N)₂C are more nucleophilic;^{12,14} their addition transition states with these alkenes will largely reflect the carbene HOMO – alkene LUMO interaction.^{7,12-14} Therefore, we should regard the activation energies estimated for these carbenes in Table 1 as suggestive only.

If we take $E_a > 15$ kcal/mol as an arbitrary barrier value that is likely to position a carbene/alkene addition in a regime where transition state theory applies, then the estimates in Table 1 suggest that we focus on the addition reactions of MeOCNMe₂ and

(Me₂N)₂C. The data also imply that additions of the well-known MeOCF¹⁹ or (MeO)₂C²⁰ are less likely to fall in the desired regime.

Although reactions of MeOCNMe₂ appear to be largely unexplored,²¹ there is a significant body of work on bis(dialkylamino)carbenes.^{22,23} The alkyl groups include isopropyl,^{22e} piperidyl,^{22d} ethyl,^{22b} and methyl.^{22b} Given that we estimate $E_a \sim 22$ -27 kcal/mol for additions of (Me₂N)₂C to the alkenes of Table 1, we might question whether this carbene or other bis(dialkylamino)carbenes would eschew dimerization long enough to undergo alkene addition reactions. Surprisingly, in the absence of catalysts, dimerizations of bis(dialkylamino)carbenes are very slow;^{22a,b} bis(diethylamino)carbene is kinetically stable to dimerization in THF at ambient temperature.^{22b} It has been reported that the barrier to dimerization of bis(dimethylamino)carbene is 78 kJ/mol,²³ but this value likely reflects a catalyzed process.^{22a,b} Alkene additions of bis(dialkylamino)carbenes therefore merit investigation as reactions for which transition state theory should provide an appropriate analytical method.

How well do our estimates of E_a based on m_{CXY} accord with values obtained from electronic structure calculations? We have carried out DFT calculations with four density functionals (M06-2X,²⁴ MN12-SX,²⁵ B3LYP,²⁶ PBE²⁷) and 6-311+G(d) basis sets,²⁸ simulating idealized gas-phase or solution conditions.²⁹ Full details of the calculations are available in the Supplementary Data. As expected, E_a values differ appreciably among the functionals but trends extracted from the computational data are independent of the functional applied. Gas-phase E_a 's derived from application of all four functionals appear in the Supplementary Data. In Table 2, we compare E_a values estimated from eqs. (2)-(4) with those derived from M06-2X/6-311+G(d) calculations assuming dichloroethane (DCE) is the reaction solvent.³⁰ For the carbene/alkene additions of interest here, activation energies simulated in a moderately polar solvent such as DCE tend to be 1-3 kcal/mol larger than idealized gas-phase values.

Table 2Estimated and computed activation energies, E_a , for carbene/alkene additions.^a

Carbene	m_{CXY} ^b	TME			Cyclohexene			1-hexene		
		E_a^c	Q_{carb}^d		E_a^c	Q_{carb}^d		E_a^c	Q_{carb}^d	
MeOCF	1.85	(6.94)	9.30	-0.14	(10.5)	17.7	-0.13	(11.6)	15.9	-0.08
(MeO) ₂ C	2.22	(10.2)	18.1	-0.06	(13.6)	25.2	-0.11	(14.9)	18.6	-0.05
MeOCNMe ₂	2.92	(16.2)	23.5	0.01	(19.4)	27.9	-0.05	(21.1)	20.0	0.12
(Me ₂ N) ₂ C	3.60	(22.2)	24.5	0.01	(25.2)	27.2	0.06	(27.3)	18.7	0.23

^a $E_a = \Delta H^\ddagger + RT$. ^bCalculated from eq. (1); see Table 1. ^cIn kcal/mol. Estimated values of E_a , in parentheses, are calculated from eqs. (2)-(4). Computed values of E_a are the results of DFT calculations using the M06-2X density functional, 6-311+G(d) basis sets and continuum dielectric solvent corrections using dichloroethane as model solvent. ^dNet charge on carbene in the transition state for alkene addition. A *negative* value of Q_{carb} implies that electron density has been transferred *to* the carbene *from* the alkene in the TS.

Somewhat surprisingly, the computed activation energies are most often greater than the estimated values, suggesting additions of (MeO)₂C, MeOCNMe₂, and (Me₂N)₂C to alkylethenes could be energetically more demanding than estimated from eqs. (2)-(4), which are based on data derived from additions of electrophilic carbenes. Only in the extreme case of (Me₂N)₂C reacting with 1-hexene is the calculated E_a significantly lower (ca. 9 kcal/mol) than E_a estimated from eq (4). The calculations uniformly indicate that addition of a nucleophilic carbene to cyclohexene exhibits a larger barrier than to 1-hexene, opposite to the results predicted by eqs. (3) and (4). Overall, the E_a 's presented in Table 2 show only fair agreement between estimated and computed activation energies with an average unsigned discrepancy between estimated and calculated E_a 's of 5.6 kcal/mol.

Moreover, the calculations suggest that in additions of nominally nucleophilic carbenes to these electron-rich or electron-sufficient alkylethenes, rather than to electron-deficient alkenes, the carbene HOMO – alkene LUMO interaction is not strongly dominant; the carbene LUMO – alkene HOMO interaction retains significant influence. See the discussion of transition state charge transfer, below.

Whereas E_a 's estimated using eqs (2)-(4) keep steadily increasing with increasing values of the carbene selectivity index (m_{CXY}), this trend does not carry over fully to the results from the DFT calculations. For a given alkylethene, E_a always increases with

increasing carbene nucleophilicity in the anticipated order $\text{MeOCF} < (\text{MeO})_2\text{C} < \text{MeOCNMe}_2$; the differential increase going from MeOCF to $(\text{MeO})_2\text{C}$ is roughly twice that going from $(\text{MeO})_2\text{C}$ to MeOCNMe_2 . However, when comparing E_a 's for the addition of MeOCNMe_2 and $(\text{Me}_2\text{N})_2\text{C}$ to the alkylethene test set, the electronic structure calculations predict only a small increase of 1.0 kcal/mol for TME; slightly *lower* barriers are obtained for $(\text{Me}_2\text{N})_2\text{C}$ additions to cyclohexene and 1-hexene than MeOCNMe_2 additions, by 0.7 kcal/mol and 1.3 kcal/mol, respectively. The E_a 's computed using electronic structure methods thus display a 'leveling' effect with increasing nucleophilicity of the carbene (as judged by its m_{CXY} value).³¹ We tentatively suggest carbene stability as a factor contributing to this result.

Carbene stabilization energies (computed relative to singlet CH_2) are included in Table 1 and show the anticipated large increase from MeOCF ($\Delta E_{\text{stab}} = 84.1$ kcal/mol) to $(\text{MeO})_2\text{C}$ (92.0 kcal/mol); a further increase to MeOCNMe_2 ($\Delta E_{\text{stab}} = 95.7$ kcal/mol) is modest, however. $(\text{Me}_2\text{N})_2\text{C}$ is computed to have a carbene stabilization energy of only 86.6 kcal/mol, considerably less than that of MeOCNMe_2 and comparable to that of MeOCF . We find it plausible that the noted trend in the carbene stabilization energies (ΔE_{stab}) plays a role in the distinct 'leveling' of the E_a values computed using DFT; deploying a 'Hammond-type' analogy,^{8,32} less stabilized carbenes will tend to be more reactive and will likely traverse transition states of lower energy.

An examination of the computed net charge on the carbene moiety in the TS for alkene addition (Q_{carb} , Table 2) is revealing. If we use the sign of Q_{carb} to determine philicity, then both MeOCF and $(\text{MeO})_2\text{C}$ act as electrophiles (negative Q_{carb} values, implying that electron density has been transferred *to* the carbene *from* the alkene in the TS; cf. Table 2) when adding to the selected alkylethene set; MeOCNMe_2 appears also to behave as an electrophile when reacting with cyclohexene. In contrast, only $(\text{Me}_2\text{N})_2\text{C}$ shows clearly nucleophilic character when it adds to cyclohexene or, in particular, 1-hexene; the reactions of MeOCNMe_2 and $(\text{Me}_2\text{N})_2\text{C}$ with TME appear to be charge-transfer neutral.

In conclusion, the anticipated correlation between E_a and m_{CXY} is experimentally verified for donor-substituted examples of CXY. Activation energies for the additions to

alkenes of carbenes CXY can be roughly estimated from the carbene selectivity indices, m_{CXY} , which are readily derived from the substituent constants (σ_I and σ_R^+) of X and Y.

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References and Notes

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Graphical Abstract