each case, the largest portion of the negative ΔS is caused by the decrease in translational entropy (−35 eu). The smaller differences between the entropies of complexes, transition states, and products result from increasing vibrational frequencies primarily associated with the increasing force constants for CC stretching and CCC bending as bonds are formed. The experimental entropies of reaction of CH_2, CF_2, and CCl_2 with ethylene are all essentially identical (−42 ± 1 eu),[16a] so that the change in entropy is a function of the reaction coordinate but is independent of the identity of the carbene.

Even using the crude 3-21G values of ΔE, the ΔG values in Table II indicate that the complexes are not likely to be free energy minima at room temperature. Furthermore, the ether or halocarbon solvents often used for such reactions should be better Lewis basic coordinators than alkenes.[18] Complexes of CCl_2 or CF_2 with H_2O are calculated to be 23.6 and 9.7 kcal/mol, respectively, more stable than the separated species at the MP2/3-21G level. On the basis of these admittedly nondefinitive calculations, we conclude that no complexes, other then possible solvent "cage" complexes, are formed between the more reactive halocarbenes and alkenes in solution.

The following communication shows how this conclusion is compatible with the experimental observations of negative activation energies and entropy control of reactivity.

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Registry No. CCl_2, 1605-72-7; CF_2, 2154-59-8; ethylene, 74-85-1.

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[17] The vibrational frequencies obtained with a split-valence basis set are usually approximately 10% too large: Yamaguchi, Y.; Schaefer, H. F., III. *J. Chem. Phys.* **1980**, *73*, 2310.

[18] A variety of carbene complexes are known. For leading references, see: Lambert, J. B.; Larson, E. G.; Bosch, R. J. *Tetrahedron Lett.* **1983**, *24*, 3799.

Origin of Negative Activation Energies and Entropy Control of Halocarbene Cycloadditions and Related Fast Reactions

K. N. Houk* and Nelson G. Rondan

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

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The previous communication describes calculations which indicate that stable π-complexes are not formed in the reactions of relatively unstabilized carbenes with alkenes.[1] If stable complexes are not formed, how can negative activation energies and entropy control of selectivity be explained? We abandon calculations at this point and develop a new hypothesis to show how negative activation energies and entropy control of reactivity can arise in fast reactions having no inherent potential energy barrier. This hypothesis is based upon the well-known principle that the transition state of a reaction is the point where the free energy is a maximum separating reactants and products.[2] Both enthalpy and entropy changes contribute to the location of this maximum.[3]

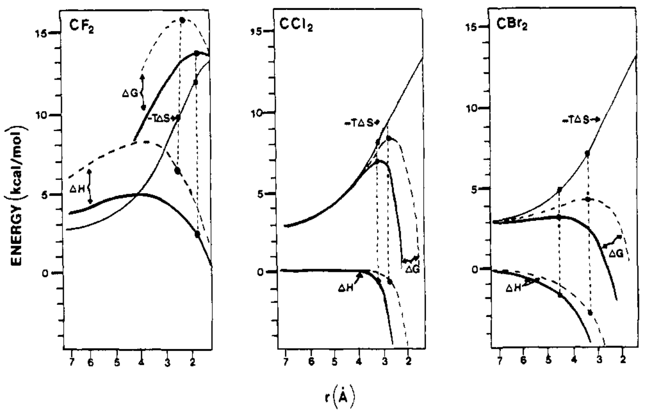

Figure 1. Model ΔH, $-T\Delta S$(298 K), and ΔG(298 K) profiles for the reactions of CF_2, CCl_2, and CBr_2 with isobutene (DME) and tetramethylethylene (TME). The $-T\Delta S$ curve is the same for both alkenes and all three carbenes. The full lines represent the TME potentials, and the dashed lines represent the DME potentials. The vertical dashed lines pass through the value of r at the transition states and intercept the ΔH and $-T\Delta S$ curves at the values of $\Delta H^{‡}$ and $-T\Delta S^{‡}$ at 298 K.

We have also constructed numerical model potential functions for the reactions of CF_2, CCl_2, and CBr_2. For conceptual simplicity, we have expressed these functions in terms of familiar transition-state theory quantities,[2] in spite of the limitations of this treatment.[4] The functions used to model ΔH are inverted Morse functions, $\Delta H = -\Delta H_{\max}(1 - e^{-\beta(r-r')})^2$, where r is the value of the reaction coordinate, r' is the value of r at the maximum value of ΔH, and $\Delta H_{\max}$ is the maximum of ΔH along the reaction coordinate. β controls the curvature of the function. $\Delta H_{\max}$ and r' were estimated using the information obtained from calculations or from calculated guesses.[5] Figure 1 shows plots of ΔH, $-T\Delta S$ (at 298 K), and ΔG for the reactions of three carbenes with two alkenes (DME = isobutene = 1,1-dimethylethylene; TME = tetramethylethylene). The $-T\Delta S$ functions were obtained from the linear correlation of 3-21G $-T\Delta S$ values vs. the reaction coordinate, r, in the region of r = 1.2–4 Å.[1] From 4 to 7 Å, $-T\Delta S$ is assumed to decay in a smooth fashion to a value of 2.7 kcal/mol at 7 Å. The quantity $-T\Delta S$ is assumed to be independent of the identity of the carbene or the alkene and becomes increasingly positive as the distance between the alkene and carbene decreases. This is a consequence of the increases in vibrational frequencies associated with forming bonds as r decreases. The ΔG $(=\Delta H - T\Delta S)$ curves show that the free energy maxima (vertical dashed lines) do not correspond to the ΔH maxima. The ΔG maximum is, however, the energy corresponding to the "transition state" (TS)[2] or, in dynamics terminology,[6] the critical point dividing the reactants from products. Each reaction has a "dynamical bottleneck", which becomes the primary determinant of the position of the TS when there is no enthalpic barrier. Because $-T\Delta S$ is linearly related to T, the position of the TS varies with temperature, becoming earlier (larger value of r) with lower temperature.

For CF_2, the TS for the less reactive alkene (DME) occurs earlier along the reaction coordinate than the TS for the more reactive alkene (TME), even though the ΔH maxima are assumed to be at the same value of r. This explains why $-T\Delta S^{‡}$ favors the less reactive alkene. By plotting $-\Delta G^{‡}/(2.303RT)$ (equivalent to log k(TME)/k(DME)), obtained from these functions, vs. $1/T$, we obtain values of $\Delta\Delta H^{‡}$(theor) and $\Delta\Delta S^{‡}$(theor) to compare

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[1] Houk, K. N.; Rondan, N. G.; Mareda, J. *J. Am. Chem. Soc.*, preceding paper in this issue.

[2] Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107.

[3] We thank Dr. Charles Doubleday, Jr., for enlightening discussions on this point. For a related case of entropy effects producing a free energy minimum, see: Doubleday, C., Jr.; Camp, R. N.; King, H. F.; McIver, J. W., Jr.; Mullaly, D.; Page, M. *J. Am. Chem. Soc.* **1984**, *106*, 447.

[4] For example, see: Menzinger, M.; Wolfgang, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 438.

[5] Details about these potential functions will be reported in detail: Houk, K. N.; Rondan, N. G.; Mareda, J. "Tetrahedron Symposium-In-Print"; Platz, M., Ed., in press.

[6] Truhlar, D. G.; Garrett, B. C. *Acc. Chem. Res.* **1980**, *13*, 440. Hase, W. B. *Ibid.* **1983**, *16*, 258, and references therein.

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with experimental data. For CF_2, these quantities are 3.8 kcal/mol and 6.0 eu, respectively. The experimental values obtained by Giese are $\Delta\Delta H^{\ddagger} = 3.4$ kcal/mol and $\Delta\Delta S^{\ddagger} = 5.0$ eu.[7]

For CCl_2, no significant ΔH barrier and no complex was assumed, but "entropy-controlled" behavior is reproduced, nevertheless. From the functions used to plot the curves for CCl_2 in Figure 1, $\Delta\Delta H^{\ddagger}$(theor) = −0.2 kcal/mol $\Delta\Delta S^{\ddagger}$(theor) = −5.0 eu. Giese's experimental values are $\Delta\Delta H^{\ddagger} = -0.3$ kcal/mol and $\Delta\Delta S^{\ddagger} = -5.3$ eu.[7] When variations in the curvature of the ΔH potential were tested, large variations in $-T\Delta\Delta S^{\ddagger}$ resulted, but $\Delta\Delta H^{\ddagger}$ always remained near zero, as long as $-T\Delta S$ increased linearly with decreasing r. Such behavior mimics the behavior of CCl_2 in cycloadditions to a wide variety of alkenes.[1,7] Even if there were a small enthalpic barrier for this reaction, the TS can occur at a point where ΔH is lower than ΔH of the reactants.

For CBr_2, $\Delta H^{\ddagger}$ at the TS is less favorable for the more electron-rich (more reactive) alkene, but $-T\Delta S^{\ddagger}$ is more favorable. From the functions shown in the figure, values of −1.3 kcal/mol and −7.7 eu are obtained for $\Delta\Delta H^{\ddagger}$(theor) and $\Delta\Delta S^{\ddagger}$(theor), respectively. The experimental values are −2.4 kcal/mol and −11.2 eu, respectively.[7] Negative activation enthalpies will be observed in such a case, and the value of $\Delta H^{\ddagger}$ will increase (become less negative) as the alkene becomes more electron rich. This is a general property of our model, as long as $-T\Delta S$ increases in essentially an exponential fashion in the region of the TS, as shown in the figure for CBr_2. The $-T\Delta S$ term controls reactivity only because of more favorable enthalpy of interaction at any given value of r for the more electron-rich alkene and the absence of a barrier. The more substituted alkene has a more favorable entropy because the transition state occurs earlier,[8] at the point where the rapidly decreasing enthalpy overcomes the unfavorable entropy. Since the enthalpy decreases faster for TME than for DME, the TS occurs earlier for TME.

For CCl_2 and more reactive carbenes, we postulate that no stable complexes are formed, nor will they be observed at low temperatures.[9] The Giese π-complex model predicts that carbene selectivities will reverse at low temperatures, with alkyl substitution eventually diminishing the rate of reaction. By contrast, we predict that reactions of CCl_2, CClBr, and CBr_2 will be unselective and diffusion controlled at low temperature. In general, diffusion-controlled reactions will occur when $\Delta G^{\ddagger}$(diffusion) exceeds the $\Delta G^{\ddagger}$ for reaction. Reactions that are diffusion controlled at some temperature should develop negative activation energies at higher temperatures, when the $\Delta G^{\ddagger}$ for reaction exceeds $\Delta G^{\ddagger}$ for diffusion. Put the other way, reactions in solution that increase in rate as the temperature is lowered ($E_{act} < 0$) will inevitably reach a rate mimimum at some lower temperature, after which diffusion-controlled behavior ($E_{act} > 0$) will be observed. Exactly such behavior has been observed for reactive carbene cycloadditions and for nitrile ylide cycloadditions.[1] Indeed, such behavior should be observed for all bimolecular reactions with negligible enthalpic barriers. For example, related descriptions have been given for the third-body-mediated recombination of radicals in the gas phase.[10]

The normal Bell–Evans–Polanyi-principle or Hammond-postulate reasoning about the relationship between reactivity, the position of the transition state, and reaction exothermicity holds, for example, when comparing the reactions of a single alkene with CF_2, CCl_2, and CBr_2. However, for the reaction of a single carbene with a series of alkenes, the reaction exothermicity does not change to any appreciable extent. Nevertheless, the position of the transition state does change appreciably when there are small or zero enthalpic barriers. In such cases, the more stabilizing the carbene–alkene interaction, the earlier the transition state.

In dynamics terminology, the temperature effects upon the kinetic behavior of reactive species such as carbenes are dictated by how fast the floor of the entrance channel slopes downward and by how fast the walls of the entrance channel narrow. The TS occurs at that point where the downward slope of ΔH equals the upward slope of $-T\Delta S$. For similar reactions with barriers that are large, the position of the TS is near the position of ΔH_{max}, and $\Delta H^{\ddagger}$ is a positive quantity. For reactions with no significant barriers, the TS occurs when the decrease in ΔH overcomes the unfavorable entropy effects, and $\Delta H^{\ddagger}$ is negative even when no complex is formed.

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Registry No. CF_2, 2154-59-8; CCl_2, 1605-72-7; CBr_2, 4371-77-1; DME, 115-11-7; TME, 563-79-1.

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(9) Our considerations do not prove the minima on the ΔH potential curves are absent but provide an explanation of the relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ that is independent of the nature of the ΔH potential before the transition state.

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High Threo Diastereoselectivity via Europium(III)-Catalyzed Cyclocondensation of a Silyloxy Diene with α-Alkoxy Aldehydes. Synthesis of (−)-Pestalotin

M. Mark Midland* and Richard S. Graham

Department of Chemistry, University of California
Riverside, California 92521

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Lewis acid catalyzed cyclocondensation of silyloxy dienes with dieneophiles has become a powerful method of constructing complex structures in a single step.[1] The cyclocondensation of the appropriately substituted diene with an aldehyde or ketone provides a potentially efficient and convergent method of synthesizing a variety of δ-lactones.[2] Since our research group is interested in the asymmetric synthesis of γ- and δ-lactones,[3] we chose to investigate the cyclocondensation of 1,3-dimethoxy-1-(silyloxy)butadiene with carbonyl compounds. Herein we report the use of this diene to prepare substituted δ-lactones and the stereochemical aspects of this cyclocondensation with substituted aldehydes.

Danishefsky and co-workers have clearly illustrated the usefulness of aldehydes as heterodieneophiles to provide γ-pyrones.[4] However, simple aryl and alkyl ketones have received very little attention as possible dieneophiles. In general, only highly elec-

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